Network reset: a simplified overarching theory of locus coeruleus noradrenaline function

Sebastien Bouret and Susan J. Sara

Neuromodulation, Plasticité Neuronale et Cognition, CNRS UMR 7102, Université Pierre & Marie Curie, 9 Quai Saint Bernard, 75005 Paris, France

Unraveling the functional role of neuromodulatory systems has been a major challenge for cognitive neuroscience, giving rise to theories ranging from a simple role in vigilance to complex models concerning decision making, prediction errors or unexpected uncertainty. A new, simplified and overarching theory of noradrenaline function is inspired by an invertebrate model: neuromodulators in crustacea abruptly interrupt activity in neural networks and reorganize the elements into new functional networks determining the behavioral output. Analogously in mammals, phasic activation of noradrenergic neurons of the locus coeruleus in time with cognitive shifts could provoke or facilitate dynamic reorganization of target neural networks, permitting rapid behavioral adaptation to changing environmental imperatives. Detailed analysis and discussion of extensive electrophysiological data from the locus coeruleus of rats and monkeys in controlled behavioral situations is provided here to support this view. This simplified ‘new look’ at locus coeruleus noradrenaline function redirects the challenge of understanding neuromodulatory systems towards their target networks, particularly to the dynamics of their interactions and how they organize adaptive behavior.

Introduction
‘Pluralitas non est ponenda sine necessitate’ – William of Occam (1285–1349)

The law of parsimony attributed to Occam has long been an underlying principle in scientific theorizing. It simply means that one should not construct over-elaborate explanations when a simple one will account for the observed phenomena. Nevertheless, in the decades since Crow [1,2] and Kety [3] proposed that the noradrenergic system might be involved in learning and memory, there have been increasingly complex theories concerning the functional role of this system, beginning with vigilance, attention and memory processes, and culminating in complex models concerning prediction errors, decision making and unexpected uncertainty [4–9]. We believe that these theories have become unnecessarily complex for furthering understanding of the functional role of a system of simple origin, which projects to the whole brain and is remarkably conserved during evolution. We propose a new, overarching theory of function of the locus coeruleus (LC) noradrenergic system that can account for the available data. Inspired by a simple invertebrate model, the theory necessarily shifts the focus to the target networks that mediate cognitive function and behavioral output.

In crustacea, synchronized input from a small number of neuromodulatory cells can abruptly interrupt activity in neural networks and reorganize the elements into new functional networks. A single neuron can participate in several networks, and a single anatomical network can mediate multiple functions, depending on the state of the system [10]. This enables the organism to display rapid behavioral adaptation in response to changing environmental imperatives. Neuromodulators achieve such reconfiguration of anatomically defined networks into different functional circuits by action on both intrinsic properties of the neuron and on synaptic strengths. Evidence for this comes from extensive studies showing how amines and peptides can reconfigure the crab and lobster pyloric networks into different output patterns, determining behavior [11,12].

Although the noradrenergic system emerges evolutionarily only at the cephalochordate–vertebrate transition, the general characteristics of neuromodulatory systems are strikingly preserved throughout phylogeny. In most vertebrates, including amphibians, reptiles, fish and birds, noradrenergic neurons are concentrated in small nuclei having widespread projections to forebrain areas [13]. By contrast, in invertebrates neuromodulatory neurons are not organized into specific nuclei; nevertheless, their activity has simultaneous effects on widely dispersed target networks, acting on G-protein-coupled receptors to influence both cellular excitability and synaptic strengths [14,15]. Thus, one might speculate that the general function of neuromodulatory systems, such as promoting rapid network plasticity, would be common to vertebrate and invertebrate systems. In fact, our present thinking has been inspired by the exquisitely simple description of the principles governing behavioral adaptation in crustacea [12,14], and we promote the view that implication of neuromodulatory systems in cognitive functions might be accounted for by these common principles.
In mammals, neuromodulatory systems have been associated with cognition through diverse effects on complex processes, including attention, motivation, learning and memory. A re-evaluation of available data on the LC noradrenergic system in primates and rats has led us to propose a simplified, overarching theory of the functional role of this particular neuromodulatory system.

**The LC noradrenergic system**

The first ‘evidence for the existence of monoamine containing neurons in the central nervous system’ came from pioneering studies of Dahlstrom and Fuxe [16,17], and a first description of the cortical distribution of noradrenergic terminals was provided soon after by the same group [18]. This was followed by a wave of neuroanatomical studies using various methods, culminating in a definitive autoradiographic study by Jones and Moore [19] describing the extensive projections from a tiny pontine nucleus to the brainstem, cerebellum, diencephalon and a first description of the cortical distribution of noradrenaline from pioneering studies of Dahlstrom and Fuxe [16,17], (Figure 1). This noradrenergic projection from the LC to virtually all brain regions (with the exception of the basal ganglia) incited intense speculation concerning its functional role in perception, cognition and memory formation. Taking into consideration this widespread intrusion into the forebrain and the postsynaptic actions known at that time, Kety [3] attributed a dual role to noradrenergic activation associated with an aroused state. It ‘affects synapses throughout the central nervous system, suppressing most, but permitting or even accentuating activity in those that are transmitting novel or significant stimuli’ [3]. These speculations, clearly suggesting a role in information selection and processing, subsequently elicited much experimental interest.

A substantial literature was generated, mainly based on *in vivo* electrophysiological recording of the effects of noradrenaline in target regions. Many studies have shown that noradrenaline modulates the gain of evoked activity, especially in sensory areas. This has been described in terms of either improved selectivity or increased magnitude of neuronal responses to sensory stimulation [20]. Several *in vitro* studies point to enhancement of extracortical, relative to intracortical, inputs to cortical neurons [21,22]. In addition to these data emphasizing its short-term influence, many studies have shown that noradrenaline promotes long-term synaptic plasticity [23]. The functional significance of these multiple neuronal effects for cognitive functions, such as perception, attention, learning and memory, have been the focus of much speculation [5,20,21].

Studies of electrophysiological activity of LC neurons in cats, rats and primates have also contributed to a theory of the functional role of the LC noradrenergic system. LC activity varies first and foremost with the state of vigilance, as first reported in 1969 by Jouvet [24]. It was later shown in the rat that the rate of firing of LC units varies according to the level of arousal and attentiveness: LC neurons show low activity during low vigilance behavioral states such as grooming and eating, but respond phasically to stimuli in all sensory modalities when they are novel and salient [25–27]. Studies in primates showing that neurons respond selectively to target cues in a vigilance task led their authors to suggest that the LC is involved in maintaining ongoing focused attention [4,28].

An important feature of LC responses is their rapid habituation in the absence of reinforcement [6,29,30], sometimes observed within a few trials. However, when stimulus-reinforcement contingencies change abruptly, such as in pairing a stimulus with reinforcement (conditioning) or withholding of expected reinforcement (extinction), or when the predictive value of positive and negative stimuli is reversed, habituated LC neurons begin anew to respond, signaling the change. This new response occurs rapidly, many trials before overt behavioral adaptation can be measured, both in rats [6,31] and monkeys [32]. This has led to speculation that the released noradrenaline somehow permits or facilitates the subsequent behavioral adaptation [6,7,29,32]. Further support for the notion that this LC signal is important for learning and adapting to new contingencies comes from experiments showing that behavioral adaptation to extradimensional shift (a change in modality of the discriminative

![Figure 1. Anatomical interactions between the locus coeruleus (LC) and other brain structures. The LC sends projections to virtually all forebrain structures including the basolateral nucleus of the amygdala (BLA), the thalamus (Thal), the olfactory system (olfactory bulb, OB and piriform cortex, PCx), the neocortex (Cx), including the frontal cortex (FCx), and the hippocampus (Hipp). Compared with this highly divergent projection pattern, LC neurons receive projections from a relatively limited set of brain regions. In addition to excitatory inputs from the paragigantocellularis (PGi) brainstem nucleus, LC neurons receive projections from the frontal cortex and the central nucleus of the amygdala (CeA).](www.sciencedirect.com)
stimulus) can be facilitated by pharmacologically stimulating the noradrenergic system [33], and can be impaired by removing noradrenergic innervation from the medial frontal cortex (mFCx) [34].

Based essentially on this body of evidence, Yu and Dayan proposed a model of noradrenaline function in which this neuromodulator is involved in reporting ‘unexpected uncertainty’ to the forebrain [9,35]. Noradrenaline would signal ‘gross changes in the environment that produce sensory information strongly violating top-down expectations’ and would, through an enhancement of ‘bottom-up’ information processing at the expense of irrelevant ‘top-down’ expectations, favor behavioral adjustment [35]. However, the model addresses only the slow (between-trial) action of noradrenaline and does not account for the persistent responses of LC neurons to the sequence of events occurring within trials observed in both rats and primates [8,31]. We propose a simpler model that also takes into account these rapid, within-trial changes in LC activity. The noradrenaline signal would have a general reset function, facilitating changes in widespread forebrain networks that are mediating specific cognitive functions. The two hypotheses are clearly complementary and overlapping in that they both emphasize the role of noradrenaline in promoting cognitive shifts, and they differ mostly in terms of timescale.

Task-related LC activity: what is it related to?
We have re-examined data on LC activity in behaving animals in the light of this ‘reset’ hypothesis and have found that activation of LC neurons within a trial is tightly related to cognitive shifts and precedes changes in neuronal activity in several forebrain structures (Figure 2). In ‘Go–NoGo’-type tasks, LC neurons of both rats and monkeys show a response to the conditioned stimulus (CS) associated with the reinforcement (CS+), with the activation being more tightly aligned with the subsequent behavioral response than with the preceding stimulus onset [31,36]. It should be noted that even though LC firing is aligned to the behavioral response, it is not related to the motor act *per se* because it is not observed for behavioral responses emitted between trials or after false alarms (CS–), where the animal does not

![Figure 2](image_url)
really expect the reward’. This phasic activation has been interpreted as reflecting either reward anticipation [31] or a decision process [8,36].

**Decision or reward anticipation?**

The ‘reward anticipation’ hypothesis is based on the consistent response of LC neurons to primary reward during early trials in three different learning situations: when new odor CSs were introduced, in reversal learning and when reward was reintroduced after extinction [31]. In all three cases, LC cells were activated at the time of reward delivery for the first few trials, after which the response shifted to the CS+ and continued to respond to the CS+ during ongoing performance trials (Figure 3). This is reminiscent of what has been described for dopaminergic neurons, interpreted as reflecting prediction (or prediction error) of reward delivery [37].

An alternative interpretation of the LC response to CS+ is that it is related to decision processes, based on a study where monkeys were forced to respond to unrewarded in addition to rewarded stimuli to obtain the reward [36]. Under these conditions, LC neurons were also activated before the behavioral response during unrewarded trials, supporting a role in decision rather than in reward anticipation [8].

A recent experiment in our laboratory clearly rules out both reward anticipation and decision as driving LC activation. Rats were trained in a simple operant task to press a lever to obtain a food-pellet reward. The task differs from the Go–NoGo task (Figure 2) only by the absence of external cue; a rat-initiated instrumental response delivers the reward. To mimic the response–reward interval used in the Go–NoGo task, rats were required to bar-press and maintain the pressure for 600 ms. There was no sign of LC activation before the behavioral response, and a decrease in firing rate was observed during the 600 ms period when the animal was holding the lever before reward delivery (Figure 4). Thus, in a situation where the animal initiates a reward-directed behavioral response in the absence of a discrete external cue (CS), LC neurons do not show any activation before the behavioral response. It is, therefore, unlikely that activation is related in any simple way to response initiation (decision) or reward anticipation in tasks where a discrete CS is present and LC activation is more tightly aligned with the behavioral response than with cue onset. We conclude from these results that LC activation probably reflects recognition of the CS+, when it is expected. Supporting this are data from an earlier Go–NoGo experiment that did not include a preparatory signal before the CS. The phasic response to CS+ appeared at the onset of a change in stimulus–reward contingency, but rapidly habituated after a few trials [6]. Thus, in recent experiments that do include a preparatory signal, the phasic activation of LC neurons seems to be triggered in parallel with the prepared behavioral response and both would reflect the recognition of an awaited stimulus.

Another element that seems to be required for LC neurons to respond to a salient signal is a relative uncertainty about that signal. This has been emphasized in work describing the LC sensitivity to novel stimuli or situations [29] or stimulus-reinforcement contingency [6]. Moreover, during behavioral protocols requiring discrimination, a selective LC response to a CS+ is observed and that response is stronger if the CS is infrequent (odd-ball) than if it is frequent [28]. Similarly, the LC response to primary reward is observed during only initial stages of learning situations, when the predictability of reward delivery following a behavioral response is relatively low. In stable conditions, when the reward can readily be predicted, the LC activation is observed only in response to the CS+ (Figure 3), which is usually delivered on 50% of the trials. Finally, this sensitivity of LC neurons to relatively unexpected signals is supported by earlier work showing a phasic response to sensory stimuli that elicit an orienting response [26]. In our Go–NoGo task, LC neurons readily respond to the light signaling trial onset when rats that are disengaged between trials display a conditioned orienting response and re-engage in the task (Figure 2). All these observations suggest that LC neurons respond to task-relevant stimuli when their occurrence (or their timing) cannot be fully predicted.

![Figure 3. Activity of a representative LC neuron around reward delivery when novel odors are introduced in the olfactory Go–NoGo task. The raster and PSTH represent both early and late trials; the solid line indicates reward delivery (time 0) and the broken line indicates the average time of entry in the reward port (Go response). In early trials, the rat finds the odor–reward contingency by trial and error; the LC cell is activated after reward delivery. In these early trials, the reward is unexpected and requires a shift to a consummatory behavior. The reward is obtained after a probe response that does not constitute a cognitive shift. After 15 trials, the animal has learned the odor–reward contingency and activation of LC occurs immediately before the reward-directed behavioral response, which is a cognitive shift from a state of response preparation and inhibition to one of ‘Go’ and reward anticipation. The reward delivery being expected, it does not constitute a cognitive shift and does not induce activation of LC. Using data from [31].](image-url)
Phasic LC responses and behavioral shifts

From these observations, it seems reasonable to propose that during behavioral tasks, LC neurons are activated following recognition of an awaited stimulus that is not predicted with much reliability. Most importantly, the activation of LC neurons is tightly related to stimulus-induced cognitive shifts. In the Go–NoGo task, the light indicating trial onset evokes a conditioned orienting response, which constitutes the first shift within each trial (Figure 2). In primates, the signal for trial onset (the fixation point) does not induce such a phasic activation, probably because the inter-trial period is shorter and monkeys remain engaged between trials. No clear behavioral shift occurs in such a situation. In rats, the light is analogous to the fixation point in primates, and acts as a preparatory signal for the ‘Go’ response, which must be actively inhibited before cue onset. The CS– tells the animal to continue to inhibit the prepared response until the end of the trial, so there is no behavioral shift (Figure 2). By contrast, recognition of the CS+ activates LC and triggers a shift from behavioral inhibition to a ‘Go’ response (Figure 2). The subsequent delivery of the reward, when it is reliably predicted by the CS+, does not require a cognitive shift. However, when the animal obtains the reward unexpectedly, as in early stages of learning, a shift to consummatory behavior is required and LC neurons are now activated by the reward itself (Figure 3). Thus, within trials, the phasic activation of LC neurons coincides with stimulus-induced cognitive shifts and might promote these shifts.

Longer-lasting changes in firing rate of LC and behavioral shifts

In addition to the phasic responses to task-relevant, shift-inducing stimuli, LC neurons also display long-lasting changes in firing rate that correlate with attentional states and behavioral performance in a task [38]. Periods of high firing rate (tonic mode) are associated with higher distractibility, reflected in both decreased task performance and decreased foveation of the fixation spot at task onset [38]. If, as we have proposed here, LC activation promotes behavioral shifts, this distractibility would result from numerous shifts induced by task-irrelevant or environmental stimuli in the presence of a long-lasting increase in LC activity.

However, periods of relatively low LC firing rate (phasic mode) are observed when animals are actively engaged in a task. In the Go–NoGo experiment, LC neurons show a lasting decrease in firing rate when rats engage in the task at each trial onset, indicated by the light (Figure 2). In monkeys, the inter-trial interval is relatively short and the animals remain constantly engaged, with a concomitant ‘phasic mode’ of LC firing [38]. Thus, in both rats and monkeys showing correct task performance, LC activation is restricted to task-relevant stimuli that require a behavioral shift. When the animal is actively engaged and awaits the cues, the low LC activity would prevent spurious behavioral shifts and corresponding distraction by irrelevant stimuli. Such a state corresponds to the ‘expectancy’ mode of attention, as defined by Rougeul-Buser and Buser [39] in cats, when the animal awaits a ‘to-be-presented’ stimulus. It requires a low level of noradrenaline and is characterized by a specific electroencephalogram (EEG) oscillatory pattern and limited behavioral and neuronal flexibility [39–41]. The same EEG pattern in rats, within a similar cognitive context, was recently reported [42]. This expectancy situation perfectly describes the conditions in which LC firing rate is low: before onset of ‘to-be-presented’ stimuli, either in the Go–NoGo task (Figure 2) or before reward in the operant conditioning situation (Figure 4). Together, these observations suggest that engagement in the task, corresponding to the ‘expectancy’ mode of attention, is related to relatively low LC activity that prevents
Forebrain activity concomitant with LC activation

A theory of noradrenergic LC system function in terms of network dynamics must accommodate the firing patterns of neurons in regions afferent and efferent to the LC in relation to activity of LC noradrenergic neurons themselves. The mFCx of the rat has bidirectional interactions with the LC [43,44], and has a crucial role in cognitive functions that appear to overlap with those attributed to the LC, namely attention and response to changes in environmental contingencies [45–48]. The central nucleus of the amygdala (CeA) is a second region of interest for similar anatomical reasons [49–51]. Moreover, some functional attributes of the CeA derived from lesion studies resemble those of the LC [52].

We carried out simultaneous recordings from LC and mFCx, or from LC and CeA in the olfactory Go–NoGo task described in the previous section. A significant proportion of mFCx neurons (42/112) and CeA neurons (4/10) showed a tonic inhibition starting ~250 ms after light onset and lasting throughout the trial. This inhibition was clearly related to engagement in the task and was particularly evident during the pre-odor (preparatory) period. It should be noted that the latency of these inhibitory responses to light in the mFCx and CeA was always longer than that of excitatory responses of simultaneously recorded LC neurons (mean latency = 155 ms). In both the CeA and mFCx, a partially overlapping population of cells responded during the interval between behavioral response and reward delivery. This was observed only after the learning was established, when reward could be reliably predicted. This is in marked contrast to task-related LC responses: LC activation precedes the reward-directed behavioral response (Figure 2), and during learning it always appears in early training trials, before any behavioral expression of the learning (Figure 3). Thus, LC responses precede those of the mFCx both within and between trials [31], and our preliminary data from the CeA show a similar picture. These observations strongly support the idea that LC activation at transition periods could act as a reset signal to facilitate behavioral and underlying neuronal adaptation. Although too few cells were recorded simultaneously in the mFCx and amygdala for formal analysis of the neuronal interactions underlying network processes, the change in firing rate recorded for a significant proportion of neurons at similar latencies, around specific events, and lasting hundreds of milliseconds could be described as an event-related change in network state. In this case, the fact that the probability of a population of cells showing a change in firing rate increases after LC activation suggests that LC activation might promote that change. Moreover, during the period of LC inhibition preceding odor presentation (‘expectancy mode’), the activity of mFCx and CeA units did not show any significant change in firing rate. This supports the idea that if LC activation promotes behavioral and neuronal transitions, a decrease in LC firing rate helps in preventing such transitions.

LC modulation of neuronal and behavioral adaptation

If the activation of the LC facilitates stimulus-induced cognitive shifts by promoting reset of functional networks, how could such an action account for implication of the noradrenergic system in cognitive processes? According to this view, the cognitive functions of the noradrenergic system would be defined by the behavioral conditions in which it is activated and the functional networks that receive its projections, rather than by its influence on individual neurons. A full account of noradrenergic effects on cognition and behavioral output would require a definition of the complex networks underlying related functions, all of which would receive projections from LC. In the case of rats and primates, such a definition remains elusive. By contrast, the relative simplicity of the invertebrate nervous system enables a clear characterization of neuromodulatory input to well-defined networks underlying specific behavioral outputs. The foregut of lobster and crab can display several stereotyped motor patterns, under the control of the stomatogastric nervous system. Each motor pattern is controlled by a specific functional network, defined as a dynamic assembly of neurons establishing specific spatiotemporal interactions. Through simultaneous modulation of synaptic and cellular properties of its numerous target neurons, the activation of a single neuromodulatory neuron rapidly induces complete reorganization of the functional interactions between these cells. This results in abrupt dissolution of the pre-existing functional network controlling a given motor pattern and in the emergence of a functional network controlling a different motor pattern [11]. Furthermore, a single neuron can participate in several of the networks, and a single anatomical network can mediate multiple functions, depending on the state of the system [10].

What is the relevance of such a simple system in understanding the role of neuromodulators in the vertebrate CNS and its higher-order cognitive functions? Several elements make the comparison viable. First and foremost, the activity pattern of noradrenergic neurons, and that of their target neurons, is compatible with such a function. Cognitive states such as focused attention, expectancy and response preparation correspond to specific electrophysiological patterns, reflecting specific functional networks [53–56]. As in invertebrates, behavioral transitions correspond to abrupt modifications of network activity, as reflected by oscillatory patterns that shift from one discrete state to another rather than showing progressive modification [53,56–58]. Abeles et al. [59] exquisitely illustrate this abrupt reorganization of neuronal interaction. Recording spike trains simultaneously from several single units in cortical regions of monkeys performing a visually guided spatial Go–NoGo task revealed rapid ‘flips’ in underlying organization of local cortical activity, from one state to another, within a discrete trial. Different behavioral modes and stimuli were reflected by different states of neuronal activity. These authors suggest that the recorded neurons are embedded in networks that are rapidly reconfigured as the monkey
performs the task [59]. Analysis of correlational dynamics of neuronal neighbors showed that interactions between pairs of neurons can be time-locked to a specific event such as the stimulus or response preparation. Moreover, a single neuron can change its coupling to nearby or distant neurons, participating, even within a trial, in different ensembles or functional networks related to different ‘computational tasks’ or behavioral outputs [60].

It is tempting to suggest that these rapid ‘flips’ in cortical network activity are promoted by neuromodulatory influences, analogous to the neuromodulation-dependent rapid plasticity in the lobster and crab pyloric network. This idea is especially compelling given that in both rats and monkeys, there is a clear stimulus-driven activation of LC neurons at crucial transitions within the trial. Furthermore, our experiments suggest that neuronal activation in the LC precedes forebrain network ‘flips’. Although the current data provide only an indirect argument for a mediating role of noradrenaline in this ‘flip’ function, a recent report by Harley’s group [61] furnishes more compelling evidence. In that study, phasic activation of the LC provoked abrupt changes in hippocampal state as reflected by predominant oscillation frequencies in the EEG.

Concluding remarks and perspectives
A survey of studies of the cognitive contexts governing activity of LC neurons reveals that, in both monkeys and rats, these neurons are activated within behavioral contexts that require a cognitive shift – that is, interruption of ongoing behavior and adaptation. This LC activation occurs whenever there is a change in environmental imperative, such as the appearance of a novel, unexpected event, or a change in stimulus-reinforcement contingencies within a formal learning situation. Within trials, LC neurons are driven by stimuli that require a rapid behavioral adjustment – a preparatory signal, a CS or an unexpected reward. Data available from simultaneous recording suggest that activation of LC neurons precedes task-related modifications of forebrain activity, at least in the case of the mFCx and amygdala.

Taking into consideration the anatomical data showing widespread distribution of noradrenergic terminals, along with well-documented effects of noradrenaline on intrinsic properties of target neurons and on their synaptic weights, we propose a theory of function for the LC noradrenergic system inspired by invertebrate studies (Figure 5). Release of noradrenaline in response to a particular sensory event will provoke or facilitate dynamic reorganization of neural networks, creating a completely new functional network. This functional reconfiguration will govern the adaptive behavioral output.

We have restricted our analysis to the noradrenergic system, because of the extensive data available from unit recordings of noradrenergic neurons in various cognitive situations. However, rapid reconfiguration of networks is probably achieved by a family of neuromodulators acting in concert. Adaptive behavioral output probably requires interaction or synergy among different neuromodulatory systems with overlapping neuronal targets but slight differences in the cognitive context in which they are activated. Simultaneous recording from LC and dopaminergic cells of the midbrain or cholinergic cells of the basal forebrain in behaving animals would contribute greatly to the understanding of this concerted action, keeping in mind that behavioral output would depend on the action of the neurons on target structures.

In conclusion, the role of neuromodulatory systems in the invertebrate model and the mammalian brain might be similar: to interrupt the activity of existing functional networks, and then to facilitate their reorganization to promote rapid behavioral adaptation. Interspecies differences would be found in the complexity of organization of the target areas. The challenge will be to delineate the networks, to understand the dynamics of their interactions and how they organize and control the behavioral output.

Acknowledgements
This research was funded by ACI ‘Neurosciences intégratives et computationnelles’ NIC0076 (S.J.S.) and by CNRS UMR 7102. S.B. was supported by a fellowship from Fondation pour la Recherche Medicale (FRM). We thank Peter Dayan, Satoru Otani and Oxana Yeschenko for critical comments on an earlier version of the manuscript and Yves Moricard for expert technical assistance and help in preparation of the manuscript.

References


Articles of interest in other Trends journals

Regulation of Na, channels in sensory neurons
Mohamed Chahine, Rahima Ziane, Kausalia Vijayaragavan and Yasushi Okamura
Trends in Pharmacological Sciences DOI: 10.1016/j.tips.2005.08.002

Adenosine receptor signaling in the brain immune system
György Haskó, Pál Pacher, E. Sylvester Vizi and Peter Illes
Trends in Pharmacological Sciences DOI: 10.1016/j.tips.2005.08.004

Emerging molecular mechanisms of general anesthetic action
Hugh C. Hemmings, Jr et al.
Trends in Pharmacological Sciences DOI: 10.1016/j.tips.2005.08.006

Neurophysiological markers of early language acquisition: from syllables to sentences
Angela D. Friederici
Trends in Cognitive Sciences DOI: 10.1016/j.tics.2005.08.008

Imitation: is cognitive neuroscience solving the correspondence problem?
Marcel Brass and Cecilia Heyes
Trends in Cognitive Sciences DOI: 10.1016/j.tics.2005.08.007

Chemokines, chemokine receptors and pain
Catherine Abbadie
Trends in Immunology DOI: 10.1016/j.it.2005.08.001

To be or not to be (inflamed) – is that the question in anti-inflammatory drug therapy of neurodegenerative disorders?
Bianca Marchetti and Maria P. Abbracchio
Trends in Pharmacological Sciences DOI: 10.1016/j.tips.2005.08.007

Gene-transfer technology: a preventive neurotherapy to curb obesity, ameliorate metabolic syndrome and extend life expectancy
Satya P. Kalra and Pushpa S. Kalra
Trends in Pharmacological Sciences DOI: 10.1016/j.tips.2005.08.008