Function of Brain Noradrenergic Neurons in Behaving Primate: New data and a Computational Model

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Abstract

Noradrenergic neurons of the brain nucleus locus coeruleus (LC) were recorded in monkey during performance of a visual discrimination task. Results revealed that fluctuations in behavioral performance correlated closely with changes in LC activity. A computational model is presented that accounts for these data and describes how the LC may regulate behavior. The model explains changes in performance in terms of electrotonic coupling among LC neurons, and closely simulates the varying patterns of LC activity associated with fluctuations in task performance. It provides the first detailed mechanistic account of how LC regulates attentional states and behavioral performance, and predicts a major role for electrotonic coupling and synchronous neural discharge in this process.

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The locus coeruleus (LC) is thought to play an important role in vigilance and attention (1), but a precise characterization of its influence on behavior has remained elusive. Recently, Aston-Jones and colleagues found marked correlations between LC impulse activity in monkeys and the level of performance in a vigilance task (2, 3). Here, we report an inverse relationship between tonic (spontaneous) and phasic (synchronous, stimulus-locked) components of LC activity, and their relationship to task performance. In particular, we observed that periods of high tonic LC activity corresponded closely with poor performance, while periods of lower tonic activity but robust synchronous responses, corresponded closely with periods of improved performance. We describe a computational model that captures this relationship between the pattern of LC firing and behavioral performance. Our model reveals that electrotonic coupling among LC neurons (4), as well as previously reported modulatory effects of NE (5, 6), may critically regulate the activity and behavioral influence of LC neurons.

Monkey LC neurons were recorded during the performance of a vigilance task as described recently (2). This task required monkeys to respond to infrequent visual target stimuli but not to frequent nontarget visual distractors. In our experiment we identified 12 recordings during which behavioral performance vacillated substantially. As shown in Fig.1, tonic LC activity correlated closely with the level of behavioral performance. During periods of good performance (defined as epochs of at least 1 min containing less than 2% false alarms- FAs), LC neurons discharged at a moderate tonic rate, significantly lower than during periods of poor performance (epochs with more than 6% FAs) (3, 7). Moreover, as previously reported (2, 3), during periods of good performance and moderate tonic LC activity these cells were phasically activated selectively by target stimuli. They were not activated by distractor (nontarget) stimuli, even if the animal responded to them (Fig.1). Phasic responses occurred synchronously among LC neurons (8), and preceded the behavioral response by more than 100 msec. Thus, phasic LC activity accurately predicted responses to target but not to distractor stimuli. In contrast, during periods of poor performance (frequent FAs) when LC tonic discharge rate was high, LC phasic responses were much weaker and less synchronized, than during good performance. In addition, we found that during periods of good performance the distribution of response times (RTs) was significantly narrower than during periods of poor performance ($p < 0.001$; Fig. 1F).

Insert Figure 1 about here

Together with our earlier data, these results strongly suggest the involvement of LC in the regulation of behavioral performance. To specify LC's role in such behavioral regulation, we
have developed a computational model of LC and its influence on performance. The goals of our modeling effort were to: (i) Explain the phasic LC activity following target stimuli that elicit hit responses but not following distractor stimuli even when they elicit FA responses. (ii) Account for why phasic LC responses only occur during periods of moderate tonic LC activity and good performance. (iii) Account for the reduction in FAs, without a cost in misses or increased RT, during periods of low tonic and increased phasic LC activity (9).

The model we propose is a hybrid, with two basic components: a simple stimulus discrimination network that simulates performance in the signal detection task, and a more detailed simulation model of LC neuronal activity (Fig. 2A). The former represents the simplest network model capable of performing the behavioral task, while the latter is significantly more detailed.

Insert Figure 2 about here

**Task model.** This network consists of two input units (for target and distractor stimuli), two corresponding decision units, and one response unit (10). We assume that only the target unit (but not the non-target unit) is connected to the response unit and the LC (11), that connections between units in different processing layers are excitatory (providing information flow), that connections within a layer are inhibitory (allowing competition), and that the activity of units is subject to small random variations (noise) (12). In addition, we have assumed that LC influences the responsivity of units in the network via NE neuromodulation by changing the gain parameter of their activation function (13).

**LC neuronal model.** We model the LC by a population of 250 spiking neurons, each of which is a leaky integrate-and-fire cell (14) that exhibits temporal dynamics similar to those obtained in detailed compartmental models (15, 16). Each LC cell receives input from the target decision unit, as well as noise which is responsible for a spontaneous firing rate of about 1 Hz (as observed in vivo; (2, 3). LC cells interact with each other in two ways. First, lateral inhibition simulates the effect of local NE release (17, 18). Second, coupling among LC cells simulates the effects of electrotonic coupling among LC neurons, consistent with the observation of gap junctions and electrotonic coupling among LC neurons in neonatal rats (4, 19).

**Task simulation.** After a stimulus is presented, activation spreads to the competing units in the decision layer. Figure 2B displays characteristic dynamic responses of the target, non-target and response units after presentation of a target or non-target stimulus in the absence of modulation by LC. Presentation of a stimulus activates both the target and non-target
decision units, due to their overlapping connections with the input. However, these compete, and after approximately 100 msec the unit corresponding to the stimulus prevails, while the competing is suppressed. FAs occur due to noise in the response units or when these are combined with transient activation of the target unit by a distractor stimulus.

**LC simulation.** Figure 3A shows the simulated pattern of LC firing with and without electrotonic coupling, following target or non-target stimuli. Targets evoke a phasic, synchronized response in LC activity, which is due to input from the target unit to LC cells. The phasic response is terminated by NE-mediated collateral inhibition. Electrotonic coupling among LC neurons has two main effects. First, coupling causes a stronger, more synchronized (phasic) activation of the LC population by target inputs, as a result of the distribution of spike-induced depolarizations to the whole population. Second, coupling reduces the tonic (spontaneous) firing rate of LC cells by mutually shunting the effect of uncorrelated noise on each cell’s membrane potential (20). These simulation results closely resemble the pattern of monkey LC activity that corresponded with periods of good versus poor performance (Figs. 1,3)(21).

Insert Figure 3 about here

**Hybrid model simulation.** Next, we combined these two model components to directly examine whether these changes in the patterns of LC activity could be responsible for the observed changes in task performance. We compared output of the response unit under conditions of high and low coupling among LC neurons. The dominant effect of increased coupling among LC neurons is a reduction in FAs (from 12 to 2%), without an increase in misses. Thus, a change in coupling among LC neurons is able to simulate changes in errors that occur during good versus poor periods of task performance. We also examined the RT-distributions for simulated target responses in the hybrid model as a function of coupling among LC neurons (Figure 3E). The distribution is narrower with coupling among LC neurons, again simulating empirical results seen during good task performance. Thus, in the model, coupling reduced extremely fast responses (some of which may be anticipatory), but at the same time sped slower (hit) responses.

Why do changes in electrotonic coupling within our LC model produce the changes observed in simulated task performance? First, increased coupling reduced tonic LC activity which lowered the responsiveness of units within the behavioral network. For the response unit, this is equivalent to raising its threshold (6), which reduces the number of FAs. Alone, this effect would also lead to an increase in misses, as well as a lengthening of the average RT.
However, this is compensated for by the adventitously-timed phasic LC response that occurs in response to targets with increased coupling. This phasic response selectively potentiates processing of the target throughout the network, reducing RT (22). Thus, reduced tonic LC activity, together with an appropriately-timed LC-phasic response to target-stimuli, produces an improvement in performance by reducing FAs without increasing either misses or RT.

A direct prediction of the model is that electrotonic coupling (perhaps mediated by gap junctions) exists among LC neurons in the adult primate, and that changes in behavioral performance correspond closely with changes in coupling efficacy. In neonatal rats, the evidence for gap junctions and electrotonic coupling among LC neurons is strong (4). Although such coupling appears to decrease with age, recent studies indicate that coupling may persist in the adult LC (23). The present findings support this possibility, and indicate that such coupling may be modulated in accordance with, and produce potent effects upon, behavioral performance. This prediction can be tested using pharmacological agents that alter electrotonic coupling (23).

Increased coupling among LC neurons in our model produces a state of selective responding. This is beneficial in a stable environment where the source of reward is predictable, such as in our experimental task. However, in a changing environment, such selectivity may at times be deleterious, as unexpected but imperative stimuli require abandonment of current behaviors and re-evaluation of the current sensory environment (e.g., prey response). High tonic LC activity (as a result of low coupling) may increase behavioral responsiveness to unexpected stimuli, mediating a more labile, widely attentive state. Thus, a tension exists between optimizing performance in a stable environment and maintaining variability that is adaptive in a changing environment. Our model suggests that changes in the mode of LC functioning (mediated by alterations of coupling) may be a key element in brain circuits that regulate such important aspects of behavioral functioning.

References and Notes


8. Phasic LC responses to targets are characterized by a concentration of the spikes in the 80-150 msec window after stimulus presentation, as previously reported (2, 3). This response is compensated by post-activation inactivity, so that only the temporal alignment, but not the total number of spikes, differs after target stimuli. This is consistent with proposals that synchronous discharge may be important in guiding selective attention [E. Niebur, C. Koch, *J. Comp. Neurosci.*, 1: 141, (1994).]

9. One simple possibility is that low tonic LC activity raises the threshold for responding, reducing FAs. However, closer inspection of performance eliminates this possibility. First, there is no increase in misses as should occur with an increased response threshold. Second, an increased threshold should slow RT; however, average RT is is not slower during good compared to poor periods of performance. Finally, the distribution of RTs is much narrower during good vs. poor performance (Fig. 1E), a finding that cannot be explained by a simple change in threshold.

10. Cell assemblies supporting stimuli or response representations are simulated as single processing units, with a continuously valued activation level. This assumes that information is represented neurally as the average spike rate of a set of cells which exhibit ergodicity (allowing them to be treated as a single continuously valued unit [D. J. Amit, Modeling Brain Function, Cambridge Univ. Press. (1989)]. Recurrent self-connections simulate mutual excitatory synapses between cells that belong to a particular assembly. In addition, we assume that the stimuli used in the task have overlapping features, and therefore each partially activates the representation of the other.
11. This corresponds to the fact that the animal has been overtrained to respond to the target but not the distractor.

12. These assumptions are consistent with the GRAIN framework, described by McClelland [L. J. McClelland, “Towards a theory of information processing in graded, random and interactive networks”, in D. E. Meyer, Kornblum eds., *Attention and Performance, XIV*, 655 (1993)], which identifies a set of processing principles intended to capture the aspects of biological systems likely to be most relevant at the information processing level.

13. The strength of the connectivity between units was increased in proportion to the amount of NE released by spiking LC cells. This is motivated by previous work (6) demonstrating that this assumption captures a large body of data about the neurophysiological and behavioral effects of NE (5). A delay time of about 55-90 msec between NE release by LC cells, and its effect on target units was used, consistent with experimental data [S. L. Foote, F. E. Bloom, G. Aston-Jones, *Physiol. Rev.* 63, 844 (1983).]


16. Each LC cell integrates its input current (see below) and fires when it reaches threshold, after which its voltage is artificially reset to rest, and remains refractory until its voltage begins to rise again. We chose a refractory period of 10 msec, to mimic the afterhyperpolarization that follows individual LC spikes.


18. Lateral inhibition occurs with a rise time of about 25 msec following LC cell firing, and a decay of 250 msec [S. L. Foote, F. E. Bloom, G. Aston-Jones, *Physiol. Rev.* 63, 844 (1983).] This collateral NE release regulates the firing rate of the LC population: After each phasic, synchronized response of the population (see below), a slightly delayed but strong inhibitory effect appears (as reflected in the PSTH histograms; Fig. 1C).

19. We assume that coupling produces a weak ohmic conductance between pairs of cells, which reaches a maximum of approximately 2.5% of the input current received by the cell, corresponding to the amount of current found in gap junctions identified in neonatal

20. In the simulations electrotonic coupling decreases LC spontaneous rate of discharge from .90 to .67 Hz. This reflects a similar decrease in the tonic discharge rate observed in LC cells from poor to good behavioral periods (Fig. 1).

21. We have also explored other schemes for simulating the variation of the LC pattern of firing with the behavioral modes, none of which could reproduce the change in the PSTH (Fig. 1B-E). For example, a decrease in the noise to LC cells, leads to some reduction in the tonic discharge and an increases in the synchronization of phasic responses but does not lead to the amplification of this response observed during good behavioral periods.

22. Note, however, that if it were to occur immediately, it would also potentiate processing in the distractor unit, which is transiently activated by the target stimulus (see Figure 3). This would lead to an increase in misses (through competition with the target unit) as well as an increase in FAs. However, the phasic LC response occurs about 100 msec following target presentation, which is after the period of transient activation of the distractor unit.


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Figure Captions

Fig 1. Representative data from a typical LC neuron recorded in a monkey during performance of the visual discrimination task. A) The firing rate of the cell (upper graph) and rate of FAs (lower curve). During ‘good’ behavioral periods (< 2% FAs), LC cells exhibited a decrease in tonic firing rate (2.1 ± 0.3 Hz versus 2.8 ± 0.3 Hz during poor performance epochs; p < 0.001, paired t-test). B-E) Post-stimulus time histograms (PSTHs) for LC activity during the visual discrimination task. Top (B, C): response for targets. Bottom (D, E): response for non-targets. Left (B, D): ‘good’ behavioral periods. Right (C, E): ‘poor’ behavioral periods (FA rate > 6%). Stimuli occur at time zero. The histograms are all normalized to a standard of 100 trials. Similar results were obtained in other 7 single cell and 3 multiunit recordings obtained in the LC. Phasic response magnitudes (number of spikes during the phasic response interval, greater than baseline (3)) were significantly larger during good than during poor performance epochs (30.9 ± 6.3 versus 7.1 ± 2.3; p<0.01, pair t-test). Compare to simulated data in Fig. 3A, F) Response time distributions for behavioral responses (lever releases) during ‘good’ periods (solid line) versus ‘poor’ periods (dashed line). Compare to simulated results in Fig. 3E.

Fig. 2. A) Architecture of the neural model. Arrows represent excitatory links and circles inhibition. There is a moderate positive bias on the response unit which captures the observation that monkeys in this task make many FAs but very few misses (2, 3). B) Dynamic trajectories of the target, non-target and response assemblies (as indicated), in response to targets (upper) or non-targets (lower) stimuli. Stimulus presentation is at time zero. Notice the initial activation of both cell assemblies, after which the incorrect response is suppressed. Solid lines: target unit, Dashed lines: non-target, dotted lines: response unit. A threshold is set for activation of the response unit (0.6) which, if exceeded, is recorded as a response.

Fig. 3. A-D) PSTHs for the simulated data. Top (A, B): response to targets. Bottom (C, D): response to non-targets. Left (A, C): Coupling among LC neurons. Right (B, D): No coupling among LC neurons. PSTHs are normalized for 100 trials, as for the empirical data (see Fig. 1). Note correspondence between these simulation results and the actual spike data (Fig. 1B). E: Response time distributions for model responses (response unit activations) following targets. Solid lines: Distribution during simulated coupling among LC neurons. Dashed lines: Distribution during no coupling among LC neurons. Notice the presence of anticipations without coupling, and a shorter tail (fewer long responses) with coupling. Compare to empirical results in Fig. 1C. The difference of about 150 msec between the latencies of empirical and simulated behavioral responses are consistent with a residual sensory and motor latency.