
Role of Locus Coeruleus in Attention and Behavioral Flexibility

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Previous findings have implicated the noradrenergic locus coeruleus (LC) system in functions along the dimension of arousal or attention. It has remained uncertain what role this system has in attention, or what mechanisms may be involved. We review our recent work examining activity of LC neurons in monkeys performing a visual discrimination task that requires focused attention. Results indicate that LC cells exhibit phasic or tonic modes of activity, that closely correspond to good or poor performance on this task, respectively. A computational model was used to simulate these results. This model predicts that alterations in electrotonic coupling among LC cells may produce the different modes of activity and corresponding differences in performance. This model also indicates that the phasic mode of LC activity may promote focused or selective attention, whereas the tonic mode may produce a state of high behavioral flexibility or scanning attentiveness. The implications of these results for clinical disorders such as attention-deficit hyperactivity disorder, stress disorders, and emotional and affective disorders are discussed. Biol Psychiatry 1999;46:1309–1320 © 1999 Society of Biological Psychiatry

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Introduction

The ability to respond selectively to certain aspects of the environment, and filter out others that are irrelevant or disruptive to the current behavioral plan, is at the heart of the capacity for goal-directed behavior. At the same time, behavior must be flexible, so as to quickly adjust to new imperative, or unexpected events. Thus, successful behavior in both animals and humans requires the capacity for both selective responding in a stable environment, and rapid adaptive responding in a changing environment. This capacity represents a fundamental reg-

ulation of attention between two states: selective or focused attention vs. scanning or labile attentiveness. This interplay between focused versus flexible responding is a fundamental property of higher nervous systems that is poorly understood. Knowledge of the mechanisms that regulate this interplay would not only advance our understanding of normal behavior, but also of disruptions in behavior associated with a variety of psychopathological disorders—such as schizophrenia, attention deficit disorder, obsessive-compulsive disorder, and depression—in which overly focused or overly labile behavior are commonly observed.

Our recent work on the locus coeruleus-norepinephrine (LC-NE) system has led us to hypothesize that it plays a central role in regulating this balance between focused versus flexible responding, or selective versus scanning attention. The primary goal of the present paper is to review some of the most salient previous work on the LC system relevant to understanding its role in cognitive activity and attention, and then to review our recent neurophysiology in behaving monkeys and modeling work aimed at understanding the mechanisms by which this neuromodulatory brain system operates, and how it regulates behavior.

Background

Global Efferent Projections

LC-NE neurons give rise to an extensive set of efferent projections in rats and primates (Dahlstrom and Fuxe 1964; Freedman et al 1975; Morrison et al 1982; Ungerstedt 1971). Notably, the LC projects throughout the cerebral cortex, hippocampus, thalamus, midbrain, brainstem, cerebellum and spinal cord (Aston-Jones et al 1984; Foote et al 1983); in fact, this small nucleus innervates a greater variety of brain areas than any other single nucleus yet described. It is also noteworthy, however, that the LC exhibits substantial regional and laminar specificity in its efferent projections (Morrison et al 1982). In particular, brain areas that are associated with attentional processing (e.g., parietal cortex, pulvinar nucleus, superior colliculus) receive a particularly dense LC-NE innervation (Morrison

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and Foote 1986). Recent studies also reveal that LC terminals make conventional synapse-like appositions with postsynaptic specializations on target neurons rather than contacts onto blood vessels (Koda et al 1978; Olschowka et al 1981; Papadopoulos et al 1987; Papadopoulos et al 1989).

NE Modulates Activity of Neurons in LC Target Areas

Early studies (Hoffer et al 1973; Segal and Bloom 1974) found that iontophoretic NE inhibited basal activity of cerebellar and hippocampal neurons. Subsequent experiments by Foote, Segal and colleagues (Foote et al 1975; Segal and Bloom 1976) found that NE decreased spontaneous impulse activity to a greater extent than activity evoked by afferent or sensory stimulation. Furthermore, in many cases NE has been found to augment evoked activity (either excitatory or inhibitory) while decreasing spontaneous activity of the same neuron (Waterhouse et al 1980; Waterhouse et al 1984; Waterhouse and Woodward 1980). Such relative enhancement of responses to strong inputs relative to low-level or basal activity has been found in several LC target areas including cerebral cortex, hippocampus, midbrain, thalamus, and spinal cord (for review see Aston-Jones et al 1991; Foote et al 1983), and is consistent with recent neural modeling work hypothesizing that NE acts to enhance signal to noise ratios in target systems (Servan-Schreiber et al 1990). As seen below, this modulatory property of NE may be a key mechanism for its role in attentional state.

Tonic LC Activity Varies with Behavioral State

We found that spontaneous LC activity in rat covaried consistently with stages of the sleep-waking cycle, firing most rapidly during waking, more slowly during slow-wave sleep, and becoming virtually silent during paradoxical sleep (Aston-Jones and Bloom 1981a). These results are similar to findings from other labs for cat LC neurons (Hobson et al 1975; Rasmussen et al 1986), and we have observed similar discharge properties in monkeys (Foote et al 1980; Rajkowski et al 1998; Rajkowski et al 1997). We also found that LC activity is decreased during certain behaviors in aroused waking. During both grooming and consumption of a glucose solution, LC impulse activity in rat and monkey decreased compared to other epochs of similar EEG arousal (Aston-Jones et al 1988; Aston-Jones and Bloom 1981a; Grant et al 1988; Rajkowski et al 1994). These findings indicate that LC activity is reduced not only for periods of low arousal (drowsiness or sleep), but also moderately so during certain behaviors (grooming and consumption) when animals are in active waking, but

are engaged in automatic, vegetative activity and inattentive to most extrapersonal environmental stimuli.

LC Neurons Exhibit Polymodal Sensory Responsiveness

In addition to the above fluctuations in LC tonic activity, LC neurons in unanesthetized rats and monkeys were phasically responsive to conspicuous environmental stimuli of many modalities (Aston-Jones and Bloom 1981b; Foote et al 1980; Rasmussen et al 1986). Notably, stimuli that elicited large LC responses in either rats or monkeys also typically disrupted ongoing behavior and evoked a behavioral orienting response. The same stimuli that did not disrupt behavior elicited small LC responses. Thus, there was a strong correspondence in rat and monkey between sensory-evoked LC impulse activity and *behavioral disruption and reorientation* (Aston-Jones and Bloom 1981b; Foote et al 1980; Grant et al 1988).

Other studies have revealed strong phasic and tonic activation of LC neurons by stressors. Stimuli such as sciatic nerve activation or other painful events most potently activate LC cells (Chiang and Aston-Jones 1993; Ennis and Aston-Jones 1988). Other stressors such as air puff in the awake monkey (Grant et al 1988) or a variety of environmental (Abercrombie and Jacobs 1987a; Abercrombie and Jacobs 1987b) or physiological stressors (Morilak et al 1987a; Morilak et al 1987b; Morilak et al 1987c) also activate LC neurons. In addition, LC neurons are activated by the stress hormone corticotropin releasing hormone (CRH) (Valentino et al 1983), which mediates the response of LC cells to certain physiological stressors such as hypotension (Valentino et al 1991).

Recent Results Recording LC Neurons in Behavioral Monkeys

Although the above previous findings for LC neurons were consistent with a role in arousal and attention, they did not make clear specifically what such a role might be, and the mechanisms by which the LC might contribute. Therefore, we recorded LC neuronal activity in monkeys during performance of a visual discrimination task that demands focused attention for optimal performance. The results of our studies will be described below for changes in tonic activity and phasic responses, both of which vary in close relation to behavioral performance. We will then describe modeling studies that simulate the patterns of LC activity during task performance, and that indicate that altered electrotonic coupling may play a pivotal role in the function of this system. Finally, we will consider this new perspective for implications in clinical disorders, with focus on attention deficit-hyperactivity disorder, stress

disorders such as post-traumatic stress disorder, and in learning and memory.

Behavioral Task

The behavioral task was described in our recent publications (Aston-Jones et al 1997; Aston-Jones et al 1994a; Rajkowski et al 1994) and will be only briefly summarized here. Monkeys were trained to perform a visual discrimination (vigilance) task. During training and recording sessions, animals assumed a natural squatting position in a modified primate chair, facing a color video monitor.

Each monkey was trained to depress a lever to initiate the task, after which a small rectangular spot (fix spot) appeared in the center of the monitor. The animal was required to stably foveate this spot, after which the fix spot was extinguished and a conditioned stimulus was presented at the fix spot location. Conditioned stimuli were either a vertical or horizontal bar; one orientation was used as the target (CS+) stimulus and the other as the distractor (nontarget, or CS-) stimulus. The animal's task was to release the lever in response to a target stimulus within 650 msec to receive a juice reward (Tang). Incorrect releases to distractor stimuli resulted in a 3 sec time-out. Target stimuli occurred on 20% of trials, and were semi-randomly dispersed among distractor stimuli. Inter-trial intervals randomly varied from 1.1 to 2.4 sec, and averaged 1.6 sec. Performance was measured in terms of hits (correct releases to target stimuli), misses (incorrect nonreleases to target stimuli), rejections (correct nonreleases to distractor stimuli), and false alarms (incorrect releases to distractor stimuli).

Phasic Activation of LC Neurons by Meaningful Stimuli

Responses of LC neurons during this task were surprisingly selective. As illustrated for one example in Figure 1, nearly all of the 300+ LC neurons recorded to date were phasically activated preferentially by target stimuli (e.g., vertical bars) but only weakly or not at all by distractor stimuli (e.g., horizontal bars); lever release outside of the task or juice delivery elicited no response (Aston-Jones et al 1994a). Some LC neurons were weakly inhibited by distractor stimuli.

Contrary to some conceptions of the LC system as a non-specific, slowly acting system, the latencies of LC responses to targets were relatively short (~100 msec onset), and preceded behavioral responses by ~200 msec. Moreover, the latencies of response for LC neurons and lever releases were significantly correlated over trials, so that shorter LC responses were associated with shorter behavioral responses to the same cues (Aston-Jones et al

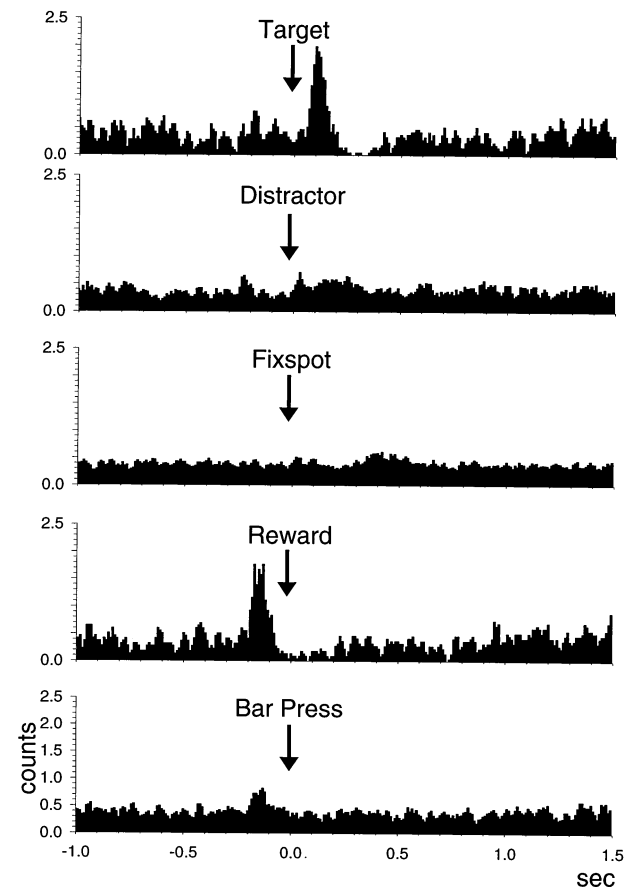


Figure 1. Peri-stimulus time histograms (PSTHs) for a typical individual LC neuron in response to various events during performance of the discrimination task. PSTHs are each accumulated for 100 sweeps of activity in this neuron synchronized with different task events, as indicated. Note the selective activation by target stimuli. The activation seen before reward presentation or bar release is due to activation by target cues.

1994a). These findings indicate that LC target responses might facilitate behavioral responses to target stimuli.

Recordings during reversal training indicated that these LC responses were independent of sensory attributes. Reversal of cue meaning caused LC cells to reverse responsiveness, and become selectively activated by the new target stimulus and lose responsiveness to the old target (Aston-Jones et al 1997). Thus, phasic LC activation in this task is specifically related to the *meaning* of the stimuli, not to their physical attributes.

An infrequent distractor stimulus (square) was included in additional experiments to test whether the activation of LC neurons by target stimuli was due to their infrequent presentation. Of the three distinct stimuli presented in these experiments (20% bar targets, 20% square distractors, and 60% bar distractors), only target stimuli elicited phasic excitatory responses in LC neurons (Aston-Jones et

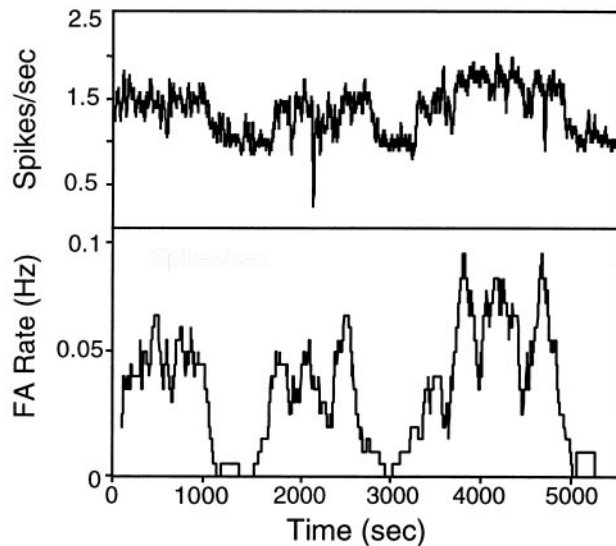


Figure 2. Representative data from a typical LC neuron recorded in a monkey during performance of the discrimination task. The rate of discharge for an LC cell (upper curve) and the number of FAs (lower curve), both integrated for a sliding window of 20 sec. Reprinted from Usher et al 1999, with permission. © 1999 American Association for the Advancement of Science.

al 1997). This indicates that frequency was not the determining factor for LC activation. Instead, responses of LC cells are specifically phasically activated by attended stimuli that signal the availability of reward (Rajkowski et al 1996).

Fluctuations in Tonic LC Activity during Task Performance

In addition to these phasic responses, we also noted that levels of tonic LC activity during alert task performance varied between intermediate and elevated discharge rates. In some of our recordings, LC neurons changed levels of tonic discharge several times (e.g., Figure 2). The difference between these tonic rates was small, in the range of 1–2 spikes/sec; however, similar changes in tonic LC activity have been demonstrated to have substantial functional effects (e.g., EEG activation; Berridge and Foote 1991).

Most importantly, these different levels of tonic LC discharge were closely associated with differences in performance on the visual discrimination task. As shown in Figure 2, periods of elevated tonic LC activity were consistently accompanied by more frequent false alarm errors but no changes in misses or hits (Kubiak et al 1992; Usher et al 1999). Analyses using signal detection measures revealed that during periods of elevated LC activity the animal's ability to discriminate targets from distractors (d' factor) and its criterion for responding (β factor) both

decreased (Aston-Jones et al 1994a; Rajkowski et al 1992). Thus, it appears that during elevated LC activity the animal is less focused on task stimuli (making it more difficult to discriminate target from nontarget stimuli), displaying increased distractibility and a greater tendency to respond to nontarget stimuli (lower response criterion).

This interpretation is supported by additional analyses of LC activity and attentional focus. In brief, decreased steady foveation of the fix spot at the onset of each trial, and increased "scanning" eye movements, were associated with epochs of elevated LC activity. Conversely, consistent visual fixation occurred during periods of intermediate tonic LC discharge (Rajkowski et al 1992; Rajkowski et al 1993; Rajkowski et al 1994). This inverse relationship between visual fixation and LC activity was highly significant. In contrast, there was no consistent relationship between LC activity and simple eye position or direction of eye movement. These results suggest that focused attention on this task is highest during periods of intermediate LC activity, and lower with elevated LC discharge.

Although the above results are intriguing, they do not establish whether these alterations in LC activity are causative of, are simply correlated with, or result from, the changes in attention. We have gathered preliminary evidence using microinfusions into the monkey LC that supports the view that the LC plays a causative role in these behaviors. In brief, we have found that microinfusion of clonidine into the LC of a monkey exhibiting hyperactive behavior and poor task performance significantly improved performance by decreasing false alarm and omission errors. In contrast, in monkeys performing the task well, activation of LC neurons by local microinjection of the cholinergic agonist pilocarpine interrupted task performance (Ivanova et al 1997).

RELATIONSHIP OF TONIC TO PHASIC LC ACTIVITY.

Periods of elevated tonic LC activity were also consistently associated with decreased phasic responsiveness of LC neurons to target stimuli in all 27 LC cells examined for this in 3 monkeys (Figure 3). In other words, the phasic activation of LC neurons typically seen for target stimuli (described above) was observed predominantly during epochs of intermediate tonic LC discharge and excellent behavioral performance. Conversely, elevated tonic LC discharge corresponds to both decreased attentional performance and decreased phasic activation of LC neurons by target stimuli. Moreover, phasic LC responses to target stimuli were also suppressed in the few instances when task performance continued during drowsiness and very low LC tonic activity. These findings indicate that phasic evoked responses are closely related to intermediate tonic discharge levels of monkey LC neurons and focused attentional performance.

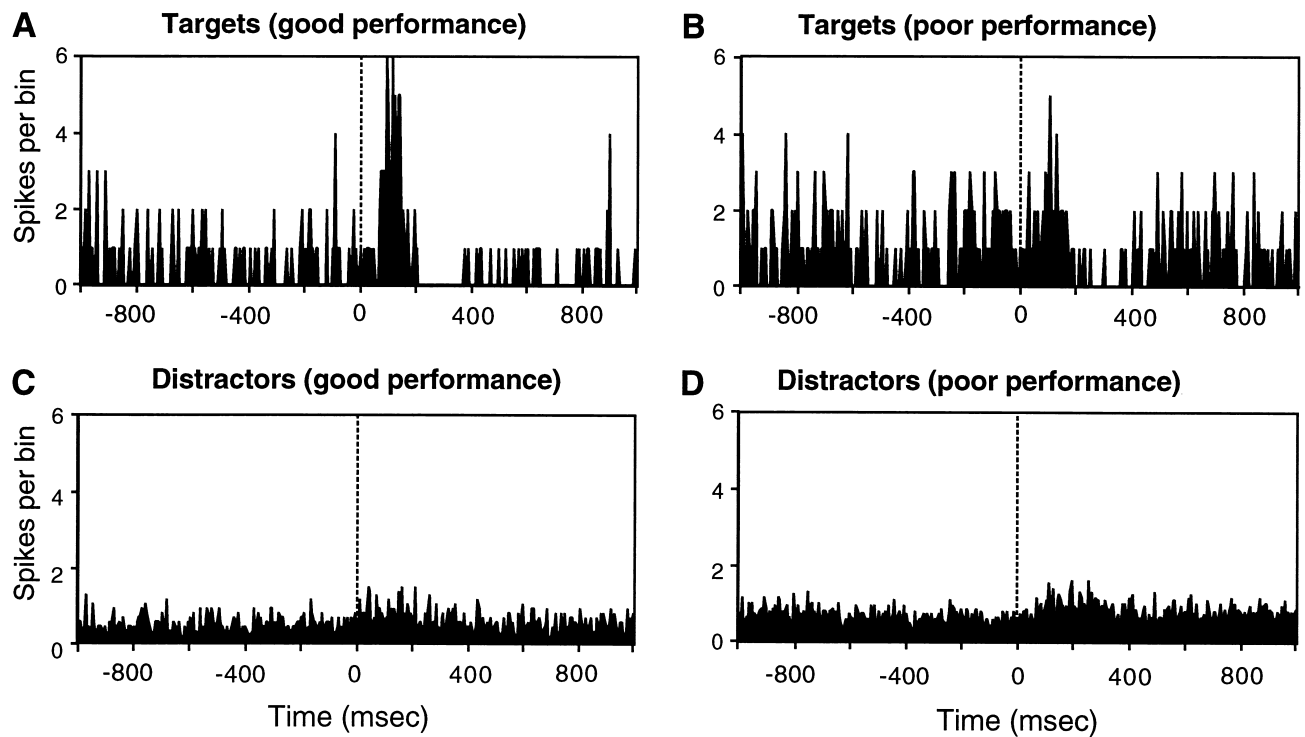


Figure 3. PSTHs for LC activity during the visual discrimination task. (A, B): response for targets; (C, D): response for distractors; (A, C): periods of good performance (phasic LC mode); and (B, D): poor behavioral performance (FA rate typically > 7%; tonic LC mode). Stimuli occur at time zero. All histograms are normalized to a standard of 100 trials. Note that the phasic LC mode is found during periods of good performance, and that the tonic mode corresponds to poor performance on this task. Reprinted from Usher et al 1999, with permission. © 1999 American Association for the Advancement of Science.

Interpretation of Results—LC Neurophysiology Experiments

Overall, these results indicate that there are two modes of LC activity that correspond to different levels of performance on this task that requires focused attention. 1) In the *phasic mode*, LC cells exhibit phasic activation selectively for target stimuli but only a moderate level of tonic discharge. This mode of LC activity is consistently associated with excellent performance on the task with few errors and high visual fixation. 2) In the *tonic mode*, LC cells fail to phasically respond to any task stimuli, but exhibit higher levels of ongoing tonic activity. This mode corresponds to poor performance on this task, with many false alarm errors and less consistent fixation of fix spot stimuli, with more scanning eye movements.

The results of these studies, although corroborating certain aspects of the relationship we proposed between LC activity and vigilance, paint a more complex picture than our previous hypotheses suggested (Aston-Jones 1985; Aston-Jones and Bloom 1981b; Aston-Jones et al 1991). At very low levels of LC activity the animal failed to engage sufficiently to perform the task, apparently because of low arousal and drowsiness. At higher levels of

LC activity, arousal and performance increased. At the highest LC activities, however, performance *decreased*, inconsistent with earlier predictions. These new results resemble the classic Yerkes-Dodson (inverted U) relationship (Figure 4) that has frequently been observed between arousal and performance (Easterbrook 1959; Parasuraman 1984).

Computational Modeling: Simulation of LC Activity and Task Performance

The data described above pose several questions about the mechanisms underlying LC activity and its relationship to behavioral performance. Two in particular stand out: 1) What mechanisms explain the observation of different modes of LC firing? 2) What mechanisms explain the relationship between each of these modes and the pattern of behavioral performance with which it was associated? Embedded in these questions are more detailed ones. For example, how is it that a reduction of false alarms during periods of good performance was not accompanied by an increase in response latency, as might have been predicted by a simple increase in response threshold? And what might account for the narrowing of the response latency

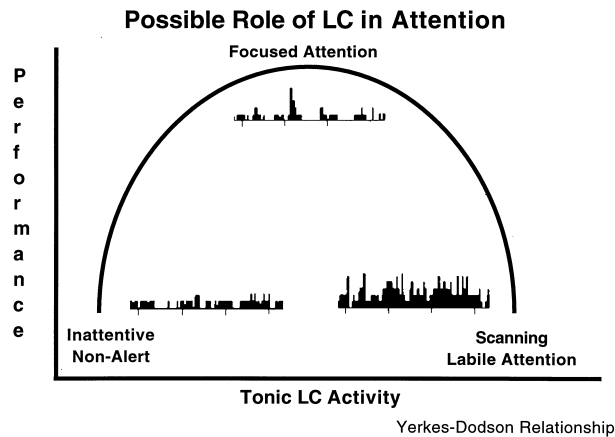


Figure 4. Inverted-U relationship between LC tonic activity and performance on the discrimination task. Performance is poor at very low levels of LC tonic discharge because animals are drowsy and nonalert (Aston-Jones and Bloom 1981a; Foote et al 1980). Performance on this task that requires focused attention is optimal with moderate LC tonic activity and phasic LC responses to target stimuli (phasic LC mode). Performance is poor at high levels of tonic LC activity (tonic mode) because of scanning, labile attentiveness which is incompatible with this task. Note that the tonic LC mode would be optimal for tasks (contexts) that require high behavioral flexibility rather than focused attention. In this view, the LC regulates the balance between focused and flexible behavior.

distribution during these periods of good performance? In order to address these questions, we developed a simulation model of LC function and its influence on performance in the vigilance task. The model is described in detail in (Usher et al 1999), and only outlined briefly below. The model is a hybrid, with two basic components: a simple stimulus discrimination network that simulated performance in the behavioral task, and a detailed model of LC neuronal activity. The former was the simplest network model capable of performing the behavioral task, and was used to examine the influence of LC activity on performance. The model of LC was significantly more elaborate and biologically realistic, permitting examination of the neural mechanisms that might be responsible for its different modes of functioning.

Stimulus Discrimination Network

This was composed of a small number of units, each of which represented cell assemblies supporting stimulus or response representations necessary for performing the task. Thus, there were two input units (for the target and distractor stimuli), two decision units, and one response unit (Figure 5). Only the target decision unit was connected to the response unit, based on the assumption that the animal was overtrained to respond to the target but not the distractor. Connections between units in different

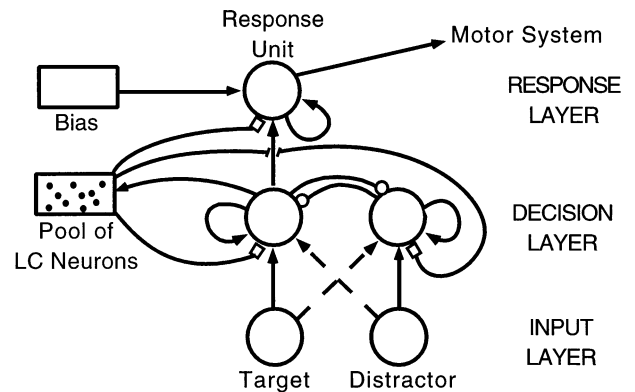


Figure 5. Architecture of the model of task performance. Arrows represent excitatory links, small circles represent inhibition, and the squares from LC projections represent the modulatory influence of NE on target units. See Usher et al 1999 for more details. Reprinted from Usher et al 1999. © 1999 American Association for the Advancement of Science.

processing layers were excitatory (information flow) whereas those within a layer were inhibitory (competition), and activity of units was subject to small random variations (noise). Finally, the physiological effect of NE was simulated as a change in the gain parameter of the activation function of processing units. Elsewhere (Servan-Schreiber et al 1990), we have argued that this is consistent with a large body of data concerning the neurophysiological and behavioral effects of NE (reviewed in Foote et al 1983; Freedman et al 1975; Segal and Bloom 1976; Waterhouse and Woodward 1980).

LC Model

This consisted of a population of 250 spiking neurons, each of which was a leaky integrate-and-fire cell (Knight 1972) that exhibited temporal dynamics similar to those obtained in detailed compartmental models (Bernander et al 1994). Each LC cell received input from the target decision unit, as well as noise that was responsible for a weak spontaneous firing rate of about 1 Hz (as observed in vivo; Aston-Jones et al 1994a; Foote et al 1980; Grant et al 1988). LC cells interacted with each other in two ways. First, lateral inhibition simulated the effect of local NE release (Aghajanian et al 1977; Ennis and Aston-Jones 1986). Second, we included electrotonic coupling among LC cells, that simulated such coupling found empirically (Christie and Jelinek 1993; Christie et al 1989; Ishimatsu and Williams 1996; Travaglini et al 1994; Travalgi et al 1995). As described below and illustrated in Figure 6, by modulating only electrotonic coupling among LC neurons our model was able to capture the full set of neurophysiological and behavioral findings observed in the monkey experiments above.

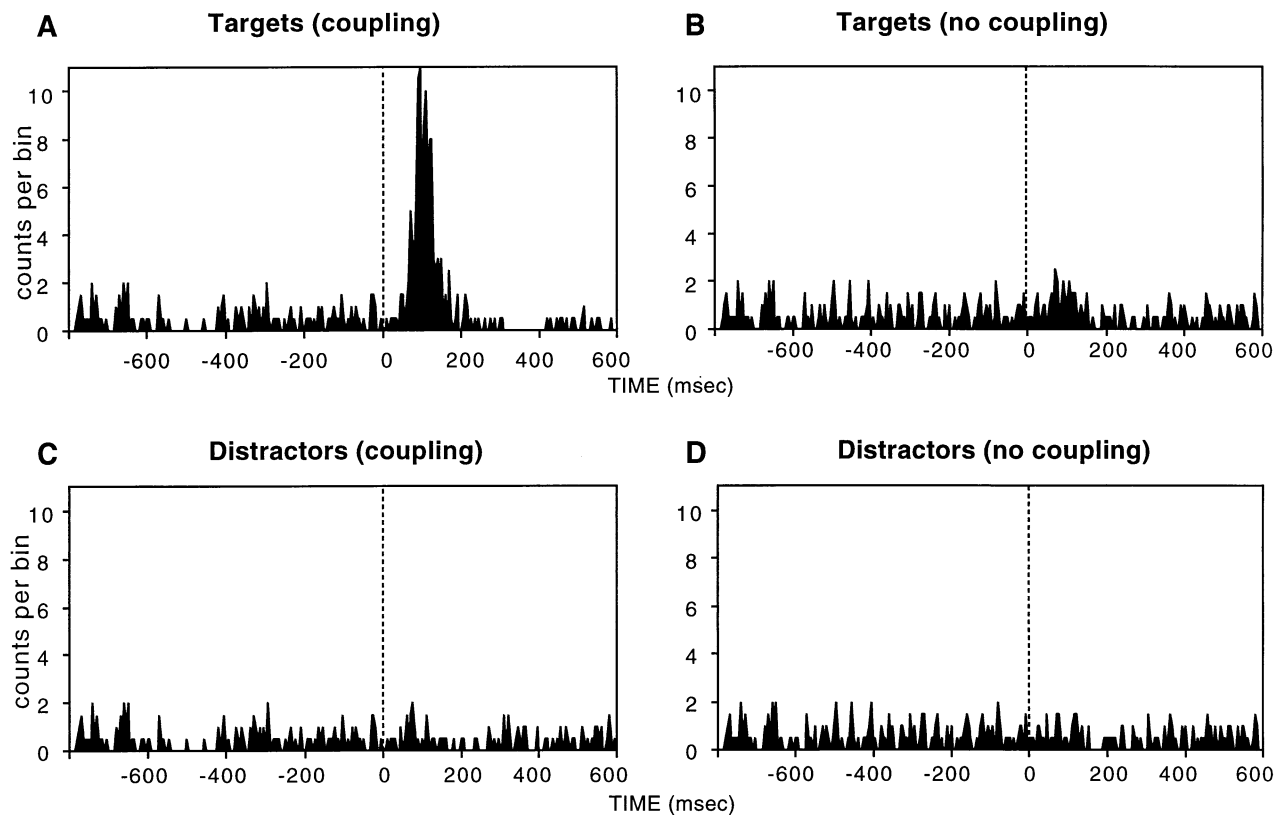


Figure 6. PSTHs for the simulated data. (A, B): response to targets; (C, D): response to distractors; (A, C): coupling among LC neurons; and (B, D): no coupling among LC neurons. PSTHs are normalized for 100 trials, as for the empirical data (see Figure 3). Note that coupling reduces tonic (baseline) LC activity but increases phasic (transient) response to target stimuli, capturing the phasic mode of LC neurons in our recordings (Figure 3). Reprinted from Usher et al 1999. © 1999 American Association for the Advancement of Science.

Simulation Results

The model explained the two modes of LC firing in terms of differences in the degree of electrotonic coupling within LC. High coupling caused stronger, more synchronized (phasic) activation of the LC in response to inputs due to the distribution of the voltage in spiking cells to the remainder of the population across electrotonic links (Figure 6). At the same time, coupling reduced spontaneous firing by averaging uncorrelated noise among the population (shunting the depolarizing effect of noise to other coupled neurons), resulting in an overall reduction in tonic activity. Thus, our model reveals that changes in phasic and tonic firing properties may be directly related to one another, and governed by the same mechanism: electrotonic coupling among LC units. The model also provides an explanation of the behavioral effects of LC. Recall that we simulated the physiological effect of the LC on targets by increasing the gain of the activation function of processing units in the task model (see above). Thus, reduced coupling which produces high tonic LC activity causes higher responsivity of units in the task model, and

thus a greater number of false alarms (triggered by intrinsic noise). Conversely, increased coupling leads to a reduction of tonic activity and an increase in phasic activity. The reduction in tonic activity produces a reduction of the responsivity of units in the task model, and therefore a concomitant reduction in false alarms. On target stimulus trials during high coupling, this reduced responsivity is compensated for by an increased phasic LC response to the target, which in turn produces a temporary increase in responsivity and therefore a quick response. Thus, an increase in electrotonic coupling is able to produce an increase in the accuracy of performance (reduced false alarms), without a cost in the response time to targets. These results are described in detail in our recent publication (Usher et al 1999).

Interpretation of Results—Modeling Experiments

Our model offers several new insights into LC function, and its influence on behavior. First, it predicts that the phasic and tonic properties of LC firing may be co-determined by a single parameter, electrotonic coupling,

and inversely related to one another. The model also predicts that an increase in tonic LC activity, and the concomitant reduction of phasic activity, will impair performance under certain circumstances. This is consistent with empirical observations in the vigilance task described above. Although this mode of LC function impaired performance in the vigilance task, we believe that, in fact, it may serve an important adaptive function under certain circumstances. By increasing responsivity to all stimuli, it may provide a mechanism for insuring behavioral flexibility. This suggests a general theory concerning the psychological function of the LC-NE system, as elaborated below.

Discussion

Electrotonic Coupling

A variety of evidence indicates that LC neurons may be coupled by low resistance electrotonic junctions. In neonatal rats Christie and colleagues (Christie and Jelinek 1993; Christie et al 1989) demonstrated robust electrotonic and dye coupling among LC neurons. Similar techniques in adult rat LC did not demonstrate coupling. Although it is possible that coupling is expressed only transiently in the LC during development, it is also possible that coupling persists but becomes weaker and more distributed over distant dendrites, and thus more difficult to demonstrate in adulthood. Evidence for weak coupling in adult LC has recently been reported by Williams and colleagues (Ishimatsu and Williams 1996; Travalgi et al 1995), and we have accumulated similar evidence in slice studies (Ivanov and Aston-Jones 1995). These results are consistent with the possibility that in adulthood coupling among LC neurons becomes ubiquitously located on distal dendrites, so that virtually all LC neurons may be weakly coupled to all other LC cells in a synticium-like arrangement. Our computational model of the LC (Usher et al 1999) predicts that weak, ubiquitous coupling among LC neurons is sufficient to substantially regulate LC tonic and phasic activity.

A New Theory of LC Function

These empirical and computational modeling studies have led us to a new hypothesis of LC function. At the neurophysiological level, we propose that the LC governs the responsivity of its target neuronal assemblies to their afferent inputs. This can manifest overtly as the likelihood that a stimulus will elicit a behavioral response, or have internal consequences, such as on attentional selection. Thus, the influence that LC-evoked changes in responsivity have on performance will depend upon the current task demands (e.g., whether they engage behavioral and/or

attentional responses). It will also depend on the magnitude and pattern of LC discharge. With lowest LC activity, systems modulated by LC input will be unresponsive, and this level of activity is important for facilitating sleep and unresponsiveness to external stimuli). In the phasic LC mode (intermediate tonic activity plus stimulus-evoked phasic activity), such systems will become responsive to specific task-relevant stimuli. As the levels of tonic activity increase further (tonic LC mode, with a concomitant reduction in phasic activity), increases in responsivity will occur to a broader class of stimuli, ultimately to the point that behavior (and attention) become relatively indiscriminate and labile. We argue that these different modes of LC activity each have adaptive advantages under different environmental circumstances. The phasic mode (intermediate tonic activity) may support cortically-driven behaviors optimized to specific stable environments (e.g., tasks requiring focused attention). Although the behavioral lability associated with the higher tonic LC activity would impair performance under such circumstances, it may be adaptive in changing, or unpredictable environments. That is, the variability associated with high tonic LC activity may be critical to behavioral flexibility, and responsiveness to unexpected events.

Relationship of LC Function to Attention

Our original hypothesis suggested that LC function was directly related to the vigilance component of attention. Our current hypothesis suggests that LC function is also closely related to selective attention. Thus, the increased accuracy of responding to task-relevant stimuli associated with the phasic mode of LC activity can be interpreted as a heightening of selective attention. Conversely, the increase in responses to task-irrelevant stimuli that occurs with high tonic activity can be interpreted as an increase in distractibility, or a reduction in selective attention. From a theoretical (and computational) perspective, however, we think it is important to distinguish between attentional selection (mediated by specific internal representations used to selectively identify and process task-relevant stimuli) and LC-induced modulations of responsivity (mediated by a distributed influence on a parameter of processing units throughout the system). Thus, we believe that LC-mediated changes in responsivity interact closely with attentional selection, just as they do with overt behavioral response mechanisms. In our previous work with the vigilance task, we have focused on the influence of LC on response systems. In this analysis, we broaden our scope to include the effects of LC on attentional selection. From the perspective of attentional function, the changes in responsivity evoked by the different modes of LC activity according to this model could be thought of as

facilitating either focused, selective attention (phasic LC mode) or scanning, labile attention (tonic LC mode).

Clinical Implications

ATTENTIONAL DISORDERS. The present analysis indicates that the LC system could play a role not only in the regulation of attentional stability and responsiveness, but also in disorders of attention. Our results indicate that attention-deficit/hyperactivity disorder (ADHD) may result, at least in part, from an overly tonic LC mode. That is, ADHD may occur in subjects whose LC neurons exhibit the tonic mode inappropriately in many contexts, and only infrequently transition to the phasic mode. As the tonic LC mode facilitates interactions with many stimuli rather than focusing on only a subset, this could produce an inability to focus attention. Consistent with this possibility, ADHD patients who perform a task similar to the one we used in our monkey studies (described above) exhibit many more false alarm errors than normal subjects (Solanto 1998), resembling performance that we obtained when LC neurons were in the tonic mode. In addition, drugs that treat ADHD including stimulants and clonidine improve performance of ADHD subjects in this task (Solanto 1998), and decrease tonic activity of LC neurons that may thereby facilitate transitions of these cells to the phasic mode.

STRESS DISORDERS. Two sources of clinical data support the connection between LC function and post-traumatic stress disorder (PTSD). Symptom patterns typical for PTSD have been seen as part of other conditions associated with LC function in animals and implicated in humans. These include sleep disturbances, difficulty with concentration, hypervigilance and modification of startle responses (Davidson et al 1985). In PTSD these symptoms are seen in the majority of cases and are associated with recall of the traumatic event or by "flashbacks" stimulated by new but reminiscent environmental stimuli. Our recent results for conditioned LC response to meaningful stimuli in waking primates suggests that such sensory and arousal disturbances of PTSD may be associated with heightened LC tonic activity or heightened LC responsiveness to conditioned stimuli. As we have reviewed elsewhere (Aston-Jones et al 1994b), drugs that decrease LC discharge rate, such as clonidine, phenelzine, and imipramine, improve PTSD symptom intensity and frequency of nightmares, flashbacks and intensive recollections.

EMOTION AND AFFECTIVE DISORDERS. As we have discussed recently (Aston-Jones et al 1996), the LC is strongly linked to the two major indices used to measure emotional responses, autonomic activity and EEG. The

link to autonomic activity is the strong projection to the LC from the nucleus paragigantocellularis (PGi), which is a major sympathoexcitatory brain region (Aston-Jones et al 1986). Emotionally charged stimuli that elicit sympathetic activation do so in part by activating PGi neurons. The parallel connections from the PGi to both spinal sympathetic areas and the LC may form the basis for the finding that stimuli that cause sympathetic activation typically also activate the LC. The activation of LC, with the consequent increase in responsivity of receiving units throughout the brain, may be a key element in promoting emotional activation.

The present analysis indicates that a chronically hyperactive LC system may give rise to some symptoms of manic-depressive disorder, including sleeplessness and impulsivity (Siever and Davis 1985). On the other hand, chronically decreased LC function may be associated with limited emotionality and flat affect, a common characteristic of a subpopulation of depressed patients. It is noteworthy in this regard that alterations in receptors and biochemical parameters of LC neurons have been reported in brains of suicide victims (Biegon and Fieldust 1992; Ordway et al 1994a, 1994b; Widdowson et al 1992). In addition, inappropriate LC hyper-responsiveness to stimuli may participate in the exaggerated stimulus-responsivity and emotionality seen in patients with stress or anxiety disorders (Aston-Jones et al 1994b). Thus, dysregulation of the LC system in a variety of ways may be associated with clinical manifestations with a substantial emotional component. Independent clinical work has indicated that the LC system may be dysregulated in depression and other disorders (Siever and Davis 1985). It is also noteworthy that several studies have found reduced numbers of LC neurons in patients suffering from dementia associated with Parkinson's or Alzheimer's Diseases (Chan-Palay 1991, 1993; German et al 1992; Hoogendijk et al 1995; Zweig et al 1993).

REGULATION OF ELECTROTONIC COUPLING IMPLICATIONS FOR NEW PHARMACOTHERAPIES. The present results indicate that modes of phasic versus tonic LC activity may participate in important behavioral functions as well as several mental dysfunctions. Our modeling and neurophysiology work in monkeys predicts that these modes may be produced by degrees of electrotonic coupling among LC neurons, and that such coupling may be modulated by inputs to LC cells. Such modulated coupling has been studied in the retina, where coupling between horizontal cells is reduced in response to a dopamine input in a cAMP-protein kinase A-dependent manner. These considerations suggest that sites may exist that could be pharmacologically targeted that selectively regulate coupling among central neurons such as the LC. New agents

that, for example, increase coupling among LC cells could be a new means of treating disorders such as ADHD. Coupling has been found commonly among many brain neurons during development, and recent evidence indicates that it persists in adulthood not only in the LC, but also in midbrain DA neurons and in the striatum, among other sites. Our results indicate that such coupling may regulate important functional properties of these brain neurons, and that this coupling therefore is a new potential target for drug development for a variety of mental disorders. Additional work exploring the prevalence of electrotonic coupling in the adult brain, and development of drugs that specifically modulate such coupling, may prove to be a useful avenue for developing new pharmacotherapeutics in the future.

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