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Adaptive Gain and the Role of the Locus Coeruleus–Norepinephrine System in Optimal Performance

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ABSTRACT

Historically, the locus coeruleus–norepinephrine (LC-NE) system has been implicated in arousal, but recent findings suggest that this system plays a more complex and specific role in the control of behavior than investigators previously thought. We review neurophysiological, anatomical, and modeling studies in monkey that support a new theory of LC-NE function. LC neurons exhibit two modes of activity, phasic and tonic. Phasic LC activation is driven by the outcome of task-related decision processes and is proposed to facilitate ensuing behaviors and to help optimize task performance. When utility in the task wanes, LC neurons exhibit a tonic activity mode, associated with disengagement from the current task and a search for alternative behaviors. Monkey LC receives prominent, direct inputs from the anterior cingulate (ACC) and orbitofrontal cortices (OFC), both of which are thought to monitor task-related utility. We propose that these prefrontal areas produce the above patterns of LC activity to optimize the utility of performance on both short and long time scales. J. Comp. Neurol. 493:99–110, 2005.

Indexing terms: neuromodulation; decision making; utility; optimization; orbitofrontal cortex; anterior cingulate cortex

NEUROMODULATORY SYSTEMS AND THE REGULATION OF BEHAVIOR: A HISTORICAL PERSPECTIVE

The locus coeruleus–norepinephrine (LC-NE) system is one of several brainstem neuromodulatory nuclei with widely distributed, ascending projections to the neocortex (Aston-Jones, 2004). Traditionally, many have thought that this NE system mediates arousal (Jouvet, 1969; reviewed in Berridge and Waterhouse, 2003). However, arousal reflects a fundamental property of behavior that has proven difficult to define or to explain precisely with neurobiological mechanisms. The importance of arousal is undeniable: It is closely related to other phenomena such as sleep, attention, anxiety, stress, and motivation. Dampened arousal leads to drowsiness and, in the limit, sleep. Heightened arousal can facilitate behavior but in the limit can also lead to distractibility and anxiety. Traditional theories of LC-NE function, which have tied this structure to arousal, have not described specific mechanisms by which this system produces changes in arousal and have left important unanswered questions about the relationship between arousal and behavior. For example, performance on most tasks is best with an intermediate level of arousal and is worse with too little or too much arousal. This inverted U-shaped relationship is described by the classic Yerkes-Dodson curve. As we discuss below, a similar relationship has been observed between performance and LC-NE activity. This relationship could be interpreted as consistent with the view that the LC-NE system

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mediates arousal. In this review, however, we propose a theory of LC-NE function that, rather than addressing arousal per se, specifies a role for the LC-NE system in optimizing behavioral performance, which in turn may explain effects conventionally interpreted in terms of arousal.

EMPIRICAL AND MODELING STUDIES OF LC AND COGNITIVE FUNCTIONS

Classical findings concerning the neurobiology of the LC-NE system

NE can have different effects on target neurons, depending on the receptor that is activated (Foote et al., 1983; reviewed in Berridge and Waterhouse, 2003). Thus, alpha1 adrenoceptor activation is often associated with excitation, and alpha2 adrenoceptor activation (the dominant type within LC itself) is associated with inhibition (Rogawski and Aghajanian, 1982; Williams et al., 1985). However, modulatory effects that do not evoke simple excitatory or inhibitory effects are also frequently described. For example, NE increased the ratio of synaptically evoked activity to spontaneous activity in target neurons in early studies (Foote et al., 1975; Segal and Bloom, 1976). Later studies found that in many target areas NE augments evoked responses (either excitatory or inhibitory), while decreasing spontaneous activity of the same neuron (Waterhouse et al., 1980, 1984; Waterhouse and Woodward, 1980). Thus, modulation of neuronal responses to other inputs is a prominent effect of NE actions on target cells.

This modulatory action was captured in an early computational model of NE effects as an increase in the gain of the activation function of neural network units (Fig. 1), which was shown to mimic many of the physiologic effects of NE and could explain patterns of behavior associated with manipulations of NE (Servan-Schreiber et al., 1990). This computational model of NE's modulatory effects set the stage for further studies using more elaborate models involving LC neurons and their targets, as described in more detail below.

Tonic impulse activity of LC-NE neurons strongly covaries with stages of the sleep-waking cycle. These neurons fire most rapidly during waking, slowly during drowsiness and slow-wave/non-REM sleep, and become virtually silent during REM/paradoxical sleep (Hobson et al., 1975; Aston-Jones and Bloom, 1981a; Rasmussen et al., 1986; Rajkowski et al., 1998). These and related findings support the view that low levels of LC activity facilitate sleep and disengagement from the environment.

Further supporting the view that the LC-NE system plays a role in general arousal and environmental responsiveness, LC neurons in rats and monkeys activate robustly following salient stimuli in many modalities that elicit behavioral responses (Foote et al., 1980; Aston-Jones and Bloom, 1981b; Grant et al., 1988). For example, tapping the cage door around feeding time elicits LC activation accompanied by a behavioral orienting response and increased physiological signs of arousal. Conversely, stimuli that elicit no behavioral response typically do not evoke an LC response.

Recent neurophysiological findings also indicate that LC may play a specific role in information processing and

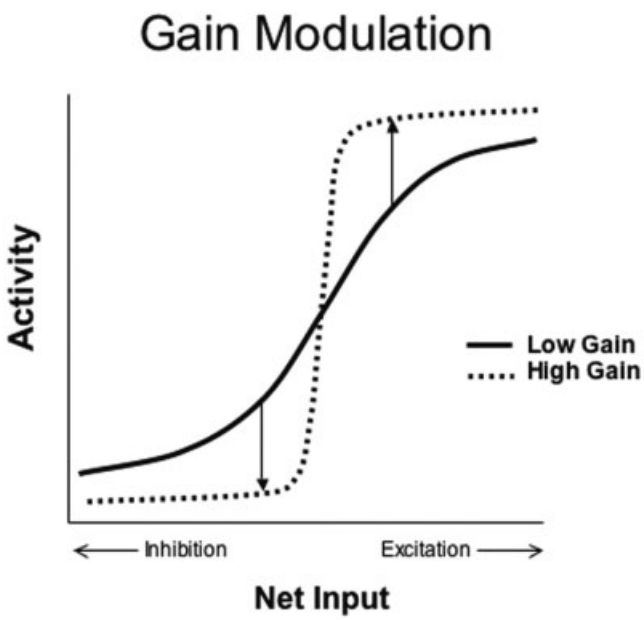

Fig. 1. Effect of gain modulation on nonlinear activation function. The activation (or transfer) function relates the net input of a unit to its activity state (e.g., the firing rate of a single neuron or the mean firing rate of a population). An increase in gain (dotted line) increases the activity of units receiving excitatory input (upward arrow on right) and decreases the activity of units receiving inhibitory input (downward arrow on left), thus increasing the contrast between activated and inhibited units and driving them toward more binary function. Adapted from Servan-Schreiber et al. (1990).

that it may interact closely with top-down influences from cortical systems.

Fluctuations in phasic and tonic LC activity in association with task performance

LC phasic responses. A number of studies have revealed that during accurate task performance reflecting focused attentiveness, LC neurons fire tonically at a moderate rate and respond phasically and selectively shortly following task-relevant target stimuli, but not after distractors. In one series of experiments LC activity was recorded while monkeys performed a simple signal-detection task in which they were required to respond by releasing a lever following a visual target (e.g., a small vertical bar of light—target cue, 20% of trials) but to withhold responding for a similar cue (e.g., a horizontal bar of light—distractor, 80% of trials). Correct responses were rewarded by the delivery of a small quantity of juice, whereas incorrect responses (target misses and false alarms to the distractor) were punished by a brief time-out. Monkeys perform this task with high accuracy, typically greater than 90%. Figure 2 shows a representative recording of LC neurons, demonstrating phasic activation shortly following target stimuli but only a weak (if any) response following distractors (Aston-Jones et al., 1994). Systematic examination of the LC phasic response following targets indicated that it is not specific to particular sensory attributes. Also, LC does not respond phasically to distractors even if they are infrequent and (in a forced-choice task) LC responses occur even when targets are

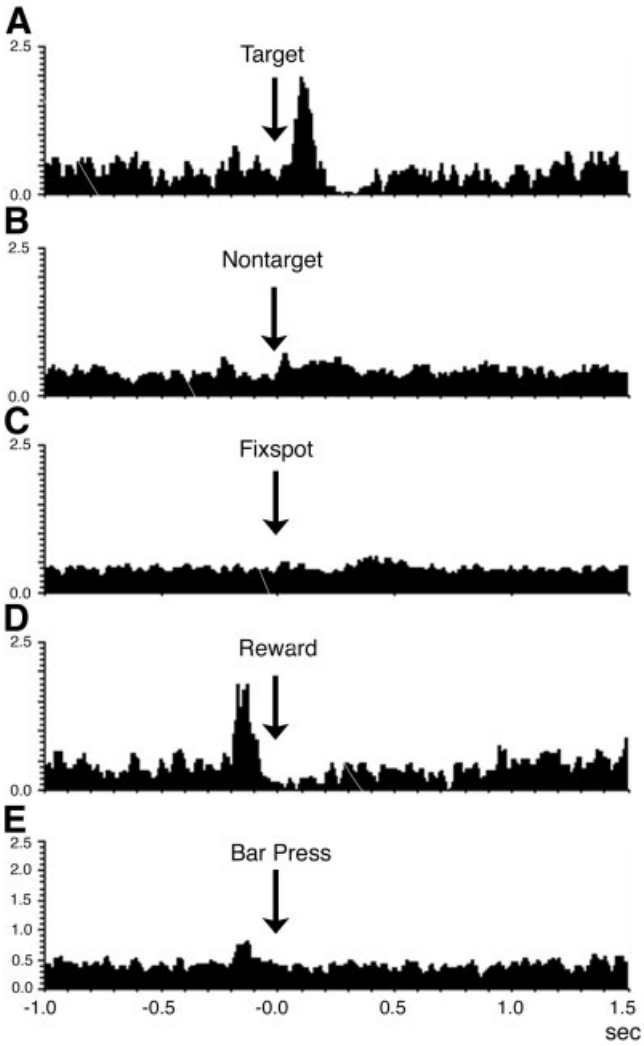

Fig. 2. Phasic activation of monkey LC neurons in a signal-detection task. Peri-event time histograms (PETHs) for a typical individual LC neuron in response to various events during performance of the signal detection task. PETHs are each accumulated for 100 sweeps of activity in this neuron synchronized with (**A**) target stimuli, (**B**) nontarget stimuli, (**C**) fix spot presentation, (**D**) juice solenoid activation, or (**E**) bar press and release performed between trials as well as during the task. Note the selective activation following target stimuli (A). The small tendency for a response in C may reflect activation after target stimuli that occur at short but somewhat variable times after fix spots. Similarly, the activation seen before reward presentation (D) is due to activation following target cues. From Aston-Jones et al. (1994).

presented on every trial (described below). The LC response also does not appear to be linked to a specific reward because similar responses are observed for different juice rewards or for water reward in fluid-restricted subjects. Furthermore, in reversal experiments in which the distractor becomes the target and vice versa, LC phasic responses are quickly acquired to the new target and extinguished for the new distractor. This reversal in LC response precedes stable behavioral reversal within a single testing session (Aston-Jones et al., 1997). These findings indicate that the LC response is highly plastic and that it is not rigidly linked to specific sensory attributes of a stimulus, but rather responds to events in a task-sensitive manner. These findings were recently replicated in a study of LC activity in behaving rats (Bouret and Sara, 2004).

The timing of LC phasic responses is also informative and contrasts with traditional concepts of a slowly acting, nonspecific system. The latency of LC phasic activation following targets is surprisingly short (~100 ms onset) and precedes lever-release responses by about 200 ms. Thus, the timing of impulse arrival in cortical targets makes it possible for the LC phasic response and NE release to influence the behavioral response on the same trial. Consistent with this possibility, the latency of LC neuron response and lever release are significantly correlated over trials; shorter LC response is associated with shorter behavioral response to the same cue (Aston-Jones et al., 1994).

LC recordings in monkeys performing two-alternative forced choice (2AFC) tasks strongly suggest that these phasic responses are associated with decision processes. In one such experiment with LC recordings, monkeys were rewarded for responding with the left lever for one stimulus and the right for another (Clayton et al., 2004). As in previous experiments, LC phasic responses were observed shortly following task cues and preceding lever responses. More detailed analysis revealed that LC activation was more tightly time-locked to the behavioral response than to presentation of the stimulus (Fig. 3). This analysis also showed that LC responses precede behavioral responses by about 230 ms regardless of trial type or behavioral response time (RT). Note in particular that, in stimulus-locked histograms, LC responses appear to be greater for correct trials than for error trials, whereas in the response-locked histograms LC activity is comparable for correct and error trials. This can be explained by the additional observation that RT variability was significantly greater for error than for correct trials, and LC activity is more tightly coupled to the behavioral response than to stimulus onset. LC activation did not occur on trials in which the animal made no response despite viewing the cue. In addition, there was no LC response associated with spurious lever responses that occasionally occurred between trials when no stimulus was present. Finally, note that the LC phasic response appears to be closely coupled with, and precedes, the task-related behavioral responses. Similar results were obtained in a recent study that recorded LC neurons in behaving rats (Bouret and Sara, 2004). These observations have been confirmed in a signal-detection task in which trial difficulty was manipulated to produce variable RTs. Once again, LC phasic activity was more tightly linked to the RT than to the sensory stimulus and preceded lever responses by ~200 ms (Rajkowski et al., 2004).

The pattern of results described above precludes the possibility that LC phasic activation is driven strictly by stimulus onset, response generation, or reward. As discussed in greater detail elsewhere (Aston-Jones and Cohen, 2005), these results have led us to hypothesize that LC phasic activity is driven by the outcome of internal decision processes that may vary in duration from trial to trial (accounting for RT variability) but precede response generation with a regular latency. Along these lines, an important observation is that stimulus-locked LC phasic responses are largest and most consistent when the ani-

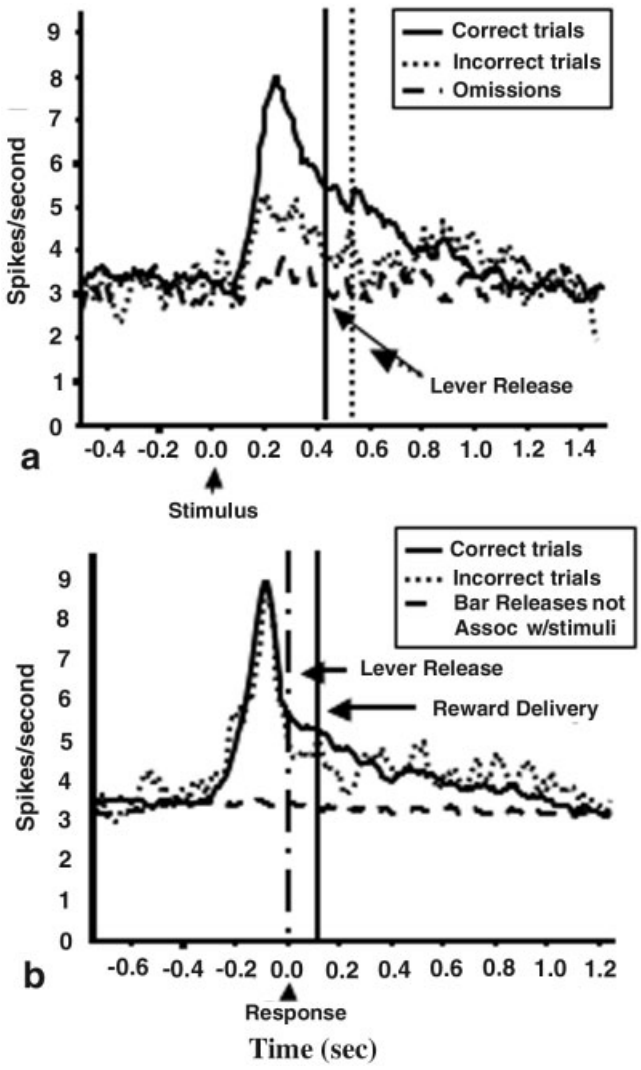

Fig. 3. Phasic activation of monkey LC neurons in a two-alternative forced choice (2AFC) task. Stimulus- and response-locked population PETHs showing LC responses for trials yielding correct and incorrect behavioral responses. **a:** Stimulus-locked population PETHs showing LC response to cues (presented at time 0) for trials yielding correct or incorrect behavioral responses. Note that the LC response peaks sooner and is less prolonged on correct compared with incorrect trials in this analysis (17,533 and 1,362 trials, respectively). No LC activation was detected on omission trials (dashed line, 1,128 trials). Vertical lines indicate the mean behavioral RTs. **b:** The difference in the phasic LC response between correct and incorrect trials was not evident in response-locked population PETHs. In addition, no LC activation occurred prior to or following lever releases not associated with stimulus presentation (dashed line; 3,381 trials). Vertical lines indicate the mean stimulus onset times. From Clayton et al. (2004).

mal is performing the task well. During epochs of poor performance, stimulus-locked LC phasic responses are considerably diminished or absent. These observations are consistent with our hypothesis that the LC phasic response plays a role in facilitating task-relevant behavioral responses.

LC tonic activity. In addition to LC phasic responses, levels of LC tonic (baseline) activity vary significantly in relation to measures of task performance. For example, during performance of a signal-detection task periods of elevated LC tonic activity were consistently accompanied by more frequent false-alarm errors (Kubiak et al., 1992; Aston-Jones et al., 1996; Usher et al., 1999). Analyses using standard signal-detection measures revealed that, during periods of elevated tonic LC activity, the animal's ability to discriminate targets from distractors (d-prime) and its threshold for responding to stimuli (beta) both decreased (Aston-Jones et al., 1994). RT distributions were also wider. Furthermore, the experimental paradigm required the animal to foveate the center of the computer display prior to stimulus presentation (as an indicator of task preparedness). Such foveations were less frequent during periods of elevated LC tonic activity, resulting in a significantly greater number of aborted trials (Aston-Jones et al., 1996, 1998). Collectively, these findings indicate that when baseline tonic LC activity is increased, the animal is less effectively engaged in task performance. Such periods are also consistently associated with a diminution or absence of the LC phasic responses seen during periods of best performance (Aston-Jones et al., 1994). These observations are consistent with the hypothesis that LC phasic activity facilitates behavioral responses engaged by task-related decision processes, and that a lack of phasic LC response helps to disengage from the task at hand. As described below, we propose that although the tonic LC mode is disadvantageous for performance on an ongoing specific task, it is important for sampling alternative behaviors and adaptively pursuing other tasks in a changing environment.

The above results indicate an association of LC activity with task performance. However, they do not establish whether alterations in LC activity are causative of, correlated with, or result from other mechanisms responsible for changes in performance. In a recent study, the alpha2 adrenoceptor agonist clonidine was used to decrease tonic LC activity and the muscarinic cholinergic agonist pilocarpine was used to stimulate tonic LC discharge. Direct microinfusion of clonidine into the LC of a monkey exhibiting an unusual degree of distractibility (hyperactivity) and poor performance on the signal-detection task significantly decreased tonic LC activity, increased LC phasic responses to target stimuli, and improved performance by decreasing false-alarm and omission errors. In contrast, during error-free performance in other monkeys, local microinjection of the muscarinic cholinergic agonist pilocarpine caused tonic activation of LC neurons, decreased phasic responsiveness to task stimuli, and interfered with task performance (Ivanova et al., 1997).

Two modes of LC activity. The above results indicate that LC neurons may be viewed as having two patterns or modes of activity: a *phasic mode* in which the neurons fire tonically slowly but exhibit phasic activations following task stimuli and decision outcome, and a *tonic mode* when the neurons fire tonically more rapidly but do not exhibit phasic activation with task events. These two modes of activity appear to be mutually exclusive, as illustrated for one example recording in Figure 4. As described above, the phasic mode is closely associated with good performance in tasks that require selective attention, whereas the tonic mode is associated with poor performance on such tasks. However, as described below, we propose that this mode of activity is useful for behaving flexibly and disengaging

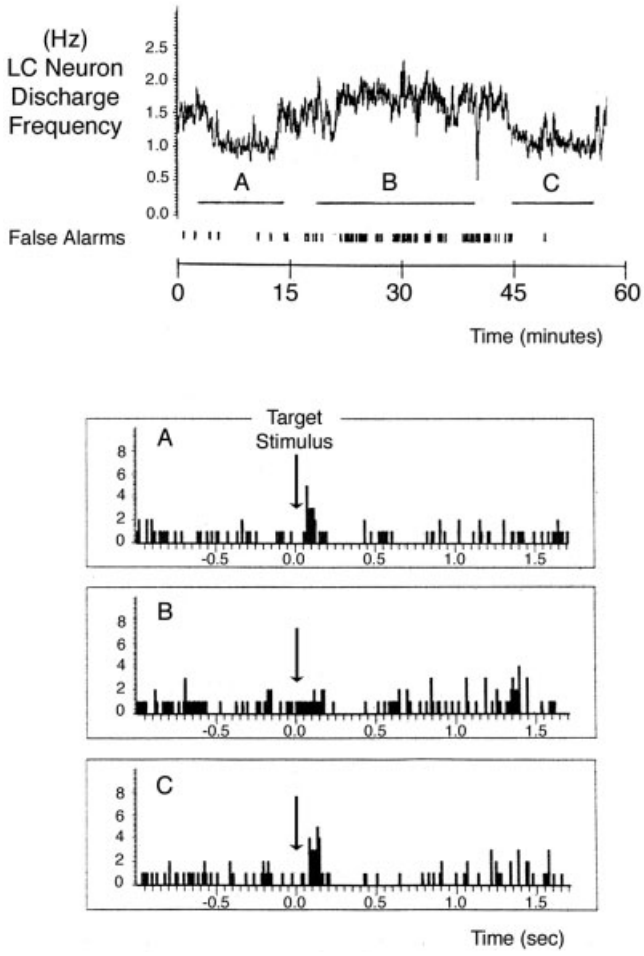

Fig. 4. Two modes of LC activity. Upper: Tonic level of impulse activity of a sample LC neuron during signal detection task performance. Note fluctuating levels of activity between epochs marked A, B, and C. Note also that errors (false alarms) are more frequent during the higher tonic LC activity (epoch B). Lower: Three peristimulus time histograms showing activity of this neuron accumulated over trials and synchronized with target stimulus onsets. Each histogram is from a particular epoch of tonic activity in the upper panel, as indicated. Note that phasic activation following target stimuli only occur during the lower tonic activity (epochs A and C), and are absent during elevated tonic activity (epoch B). Epochs A and C correspond to the phasic mode in our terminology, to capture the lower tonic rate and phasic activation following task stimuli, whereas epoch B corresponds to the tonic LC mode to capture the higher tonic rate of activity with no phasic activations.

from one task and finding another goal-behavior that is adaptive in an altered context or motivational state.

Neural network models of LC-NE function

The data described above pose important questions about LC activity and its relationship to behavioral performance: Which physiological mechanisms underlie the phasic and tonic modes of LC activity and transitions between them, and how do these mechanisms interact with cortical mechanisms responsible for task performance to produce the patterns of behavior associated with each mode of LC function? Computational modeling has recently begun to address these questions. In an initial effort, Usher et al. (1999) constructed a model composed of two components: 1) a detailed, population-level model of LC; and 2) a more abstract connectionist network that was the simplest network capable of simulating performance in the signal-detection task. This model revealed that alterations in electrotonic coupling among LC neurons can produce the two modes of LC activity. The model also revealed how the corresponding alterations in gain of cortical units receiving LC inputs can either facilitate task performance (phasic mode) or produce more distractible, less task-focused responding (tonic mode). (See Usher et al., 1999; Aston-Jones et al., 2000; Aston-Jones and Cohen, 2005, for more details and discussion of this model.)

Simple mathematical model can be used to describe decision processes and analyze them for optimality. To consider how LC may play a role in optimization of task performance, we must characterize the mechanisms that underlie task performance. We can think of these as being composed of a set of decision processes that may involve perception, memory, evaluation, or action. Cognitive and neuroscientific studies have made considerable progress in identifying mechanisms associated with the simplest decision processes involved in 2AFC tasks (e.g., Hanes and Schall, 1996; Shadlen and Newsome, 1996, 2001; Schall and Thompson, 1999; Gold and Shadlen, 2000). The dynamics of both neural activity and behavioral performance observed in such tasks have been described accurately by a simple mathematical model, often referred to as the drift diffusion model (DDM). This, in turn, provides a useful framework for defining and evaluating the optimization of performance.

Page limitations prohibit an extensive discussion of the DDM. In brief, this framework describes decision processes in terms of simple accumulators that integrate signals favoring each of the two choices and respond when the difference between these signals exceeds a threshold value. The DDM offers a mathematically precise characterization of the dynamics and outcome of decision making in such tasks (Laming, 1968; Ratcliff, 1978; Smith and Ratcliff, 2004).

The DDM is appealing in the present context because it provides a framework within which we can formally define optimal performance. The DDM itself is, in fact, the optimal process for 2AFC decision making (i.e., it is the most accurate for a given speed of decision making, and the fastest for a given level of accuracy; Wald [1947]). Furthermore, because the DDM provides a good description of simple, single-layered neural networks that implement 2AFC decision processing, we can infer that such single-layered networks can approximate optimal performance in 2AFC decision processing. We know, however, that real neural architectures in fact involve many layers (e.g., Reddi, 2001; Schall, 2003) presumably because different tasks require decision processes that integrate information of different types, at varying levels of analysis, and from a variety of sources.

The inefficiency of multilayered integration can be ameliorated if, at the time a unit in the task-relevant decision layer crosses a threshold, a signal is issued ensuring that this information rapidly and directly influences the behavioral response. The LC phasic signal accomplishes precisely this effect. The LC phasic response is triggered when sufficient activity accumulates in one of the units in the decision layer of the behavioral network. The resulting LC phasic response increases the gain of all units in the

behavioral network, which drives units toward binary responding, in effect eliminating further integration in any subsequent layers. Because this occurs at a time when the relevant decision unit has just crossed threshold and is therefore highly active, all units "downstream" will assume states that are heavily determined by this particular input.

LC tonic mode produces adaptive adjustments of gain that optimize performance across tasks (exploration vs. exploitation)

In considering optimal performance thus far, our focus has been on performance within a single task, in which the LC phasic response produces adaptive adjustments in gain that serve to optimize performance of that task. In contrast, the LC tonic mode produces a persistent increase in gain (i.e., responsivity of widespread LC target neurons) that renders the system more sensitive to task-irrelevant stimuli. With respect to the current task, this is clearly disadvantageous. However, this tonic increase in gain may be adaptive by facilitating a change in behavior if either the current task is no longer remunerative or if more valuable opportunities for reward or new behavioral imperatives have appeared. From this perspective, optimization involves not only determining how to best perform the current task, but also considering its utility against alternative courses of action and pursuing these if they are more valuable.

For example, what happens when a previously identified source of reward becomes unavailable or less valuable as the agent becomes sated (e.g., the defining structure of the lattice changes)? Under such conditions the optimal strategy is to resume exploring the environment, sampling different behaviors until new sources of reward are discovered. This is exactly the role played by increases in tonic LC activity and attenuation of the phasic LC response in the adaptive gain theory: Increased baseline release of NE increases the gain of units in the network indiscriminately, making them more responsive to any stimulus. The broad efferent network of LC projections is well suited for this role because it applies the tonic gain increase across global targets and circuits, thereby allowing a broad scan of possible new reward sources.

UTILITY ASSESSMENT IN FRONTAL CORTEX REGULATES LC MODE

This theory suggests a critical question: What determines when LC should transition between phasic and tonic modes? That is, how does LC know when current task utility exceeds or has fallen below an acceptable value? If LC is to respond in a truly adaptive fashion, then it must have access to information about rewards and costs. A growing body of evidence suggests that two frontal structures, the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), play critical roles in evaluating rewards and costs, respectively. Furthermore, recent studies—motivated by our theory of LC—reveal that the most prominent descending cortical projections to LC come from these two frontal structures.

OFC plays a role in the evaluation of reward. The OFC receives input from all modalities of high-order sensory cortices, in particular areas processing information with strong appetitive significance, such as taste and olfaction, as well as primary limbic structures such as the ventral striatum and amygdala (Rolls et al., 1990; Carmichael et al., 1994; Baylis et al., 1995; Carmichael and Price, 1995a,b; Ongur and Price, 2000). Neurons in monkey OFC are activated by rewarding stimuli in various modalities but not by stimulus identification alone nor by response preparation (Roesch and Olson, 2004; Rolls, 2004). These, and a host of other studies in monkeys (Rolls et al., 1989; Critchley and Rolls, 1996; Tremblay and Schultz, 1999; Schultz et al., 2000; Sugrue et al., 2004) and humans (Thut et al., 1997; Breiter et al., 1997, 2001; Knutson, 2000; McClure SM, 2004; Small, 2001; O'Doherty, 2002), provide strong evidence that OFC plays an important role in the evaluation of reward.

ACC plays a role in the evaluation of cost. Like OFC, ACC receives convergent inputs from a broad range of neocortical and subcortical structures (Mesulam, 1981; Devinsky, 1995). Neurophysiological studies in the monkey as well as human electrophysiological and neuroimaging studies have consistently demonstrated that ACC is responsive to negatively valenced information such as pain, errors in performance, negative feedback, monetary loss, and even social exclusion (Falkenstein, 1991; Gehring, 1993; Miltner, 1997; Eisenberger, 2003; Holroyd, 2003, 2004a,b; Ito et al., 2003; Yeung et al., 2005). In addition to explicitly negative information, ACC responds robustly and reliably to task difficulty and conflicts in processing (e.g., Barch, 1997; Carter et al., 1998; Botvinick et al., 1999; Duncan and Owen, 2000; Botvinick, 2001, 2004; Ullsperger, 2001). Thus, converging evidence suggests that ACC is responsive to a variety of negatively valenced signals—from pain to internal states that predict degraded performance—all of which may serve as indices of performance-related cost.

OFC and ACC send strong convergent projections to LC

The theory of LC-NE function outlined above predicts that LC should receive information about task-related utility from high-level structures. Little in the way of prefrontal cortex (PFC) projections have been reported to LC in prior rat studies, but there has been little such examination in primates, where the PFC is more highly developed than in rodent. Therefore, we undertook anatomic studies in monkey to determine the extent to which LC receives top-down cortical projections in primate. These studies revealed a consistent and striking pattern of cortical projections in the primate LC, the preponderance of which come from OFC and ACC (Rajkowski et al., 2000; Aston-Jones et al., 2002; Zhu et al., 2004; Aston-Jones and Cohen, 2005).

As illustrated in Figures 5 and 6, focal injections of retrograde tracer into the monkey LC revealed a large number of labeled neurons in OFC and ACC (Rajkowski et al., 2000; Aston-Jones et al., 2002; Zhu et al., 2004; Iba et al., in prep.). These retrograde results have been confirmed by injection of anterograde tracers into OFC or ACC, which yielded prominent fiber and terminal labeling in the monkey LC nucleus and peri-LC dendritic area (Fig. 5) (Zhu et al., 2004; Iba et al., in prep.). Importantly, these OFC and ACC projections appear to be the major cortical inputs to LC; relatively few neurons in other cortical areas were retrogradely labeled from LC injections. Interest-

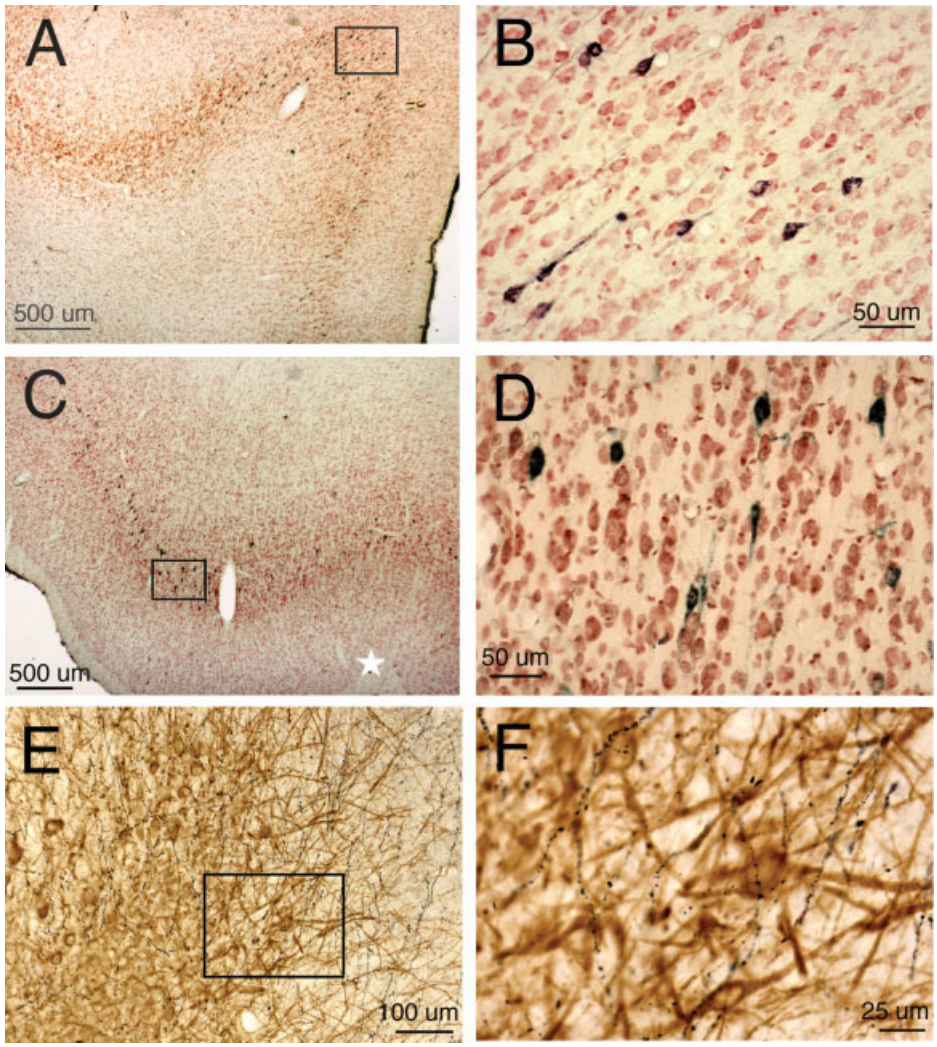

Fig. 5. Projections to the LC from the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC) in monkey. **A:** Low-power photomicrograph of a frontal section through the ACC showing retrogradely labeled neurons in area 24b/c. Area shown is just ventral to the cingulate sulcus. **B:** High-power photomicrograph showing retrogradely labeled neurons in the ACC (corresponding to rectangle in A). Note labeled cells located in deep layer V/superficial layer VI. **C:** Low-power photomicrograph of a frontal section through the OFC showing retrogradely labeled neurons in area 12. Lateral orbital sulcus is at star. **D:** High-power photomicrograph showing retrogradely labeled neurons in the OFC (corresponding to rectangle in C). Note cells located in deep layer V/superficial layer VI. Neutral red counterstain used for sections in panels A–D: Medial is at right, dorsal is at top. **E,F:** Low- (E) and high-power (F) photomicrographs of a frontal section through the LC and peri-LC showing fibers and terminals labeled from an injection of the anterograde tracer biotinylated dextran amine in the ipsilateral OFC (area 12) of an African green monkey. Noradrenergic neurons and processes are stained brown with an antibody against tyrosine hydroxylase. Note close juxtaposition of OFC fibers and terminals with noradrenergic somata and dendrites. Lateral is at right, dorsal is at top. Scale bars = 50 μm in A,B,D; 500 μm in C; 100 μm in E; 25 μm in F.

ingly, the bulk of OFC inputs to LC appear to originate in the caudolateral OFC, the same area that receives strong direct olfactory and taste primary reinforcer inputs (as noted above). Numerous retrogradely labeled neurons also extend caudally from the OFC into the anterior insular cortex. ACC neurons that innervate LC are located in both dorsal and ventral ACC subdivisions (including areas 24, 25, and 32) and densely populate layer 5/6 throughout the rostral ACC. These results indicate that OFC and ACC provide prominent direct input to LC in monkey and that these projections are the major cortical influences on LC neurons. These studies also indicate that OFC and ACC inputs to LC in the monkey are stronger than those in the rat, where prefrontal fibers terminate nearly exclusively in the peri-LC dendritic zone and do not appreciably enter the LC nucleus proper (described above). Nonetheless, the prefrontal cortex influences LC activity in rat, either by innervation of distal dendrites or by indirect synaptic circuitry, as indicated by physiological responses of LC neurons to prefrontal stimulation (Sara and Herve-Minvielle, 1995; Jodo and Aston-Jones, 1997; Jodo et al., 1998).

OFC and ACC may regulate LC function

The evidence reviewed above indicates that OFC and ACC each play an important role in assessing utility and that both of these structures project directly to LC. These findings suggest that these frontal areas could influence LC function on the basis of assessments of utility, consistent with the adaptive gain theory of LC function. There are two ways in which this could occur: OFC and ACC could drive LC phasic activity directly, and they could modulate LC mode of function.

OFC and ACC may drive LC phasic activation. If LC phasic responses are driven by the outcome of decision processes, an important question is: What cortical regions convey this information to LC? The obvious candidates are regions that house the neural accumulators associated with the decision processes, which have typically been localized to cortical sensorimotor integration areas (e.g., to lateral intraparietal cortex and frontal eye fields for visual tasks requiring an oculomotor response). However, these areas do not provide substantial direct projections to LC. Alternatively, it is possible that the outcome of decision

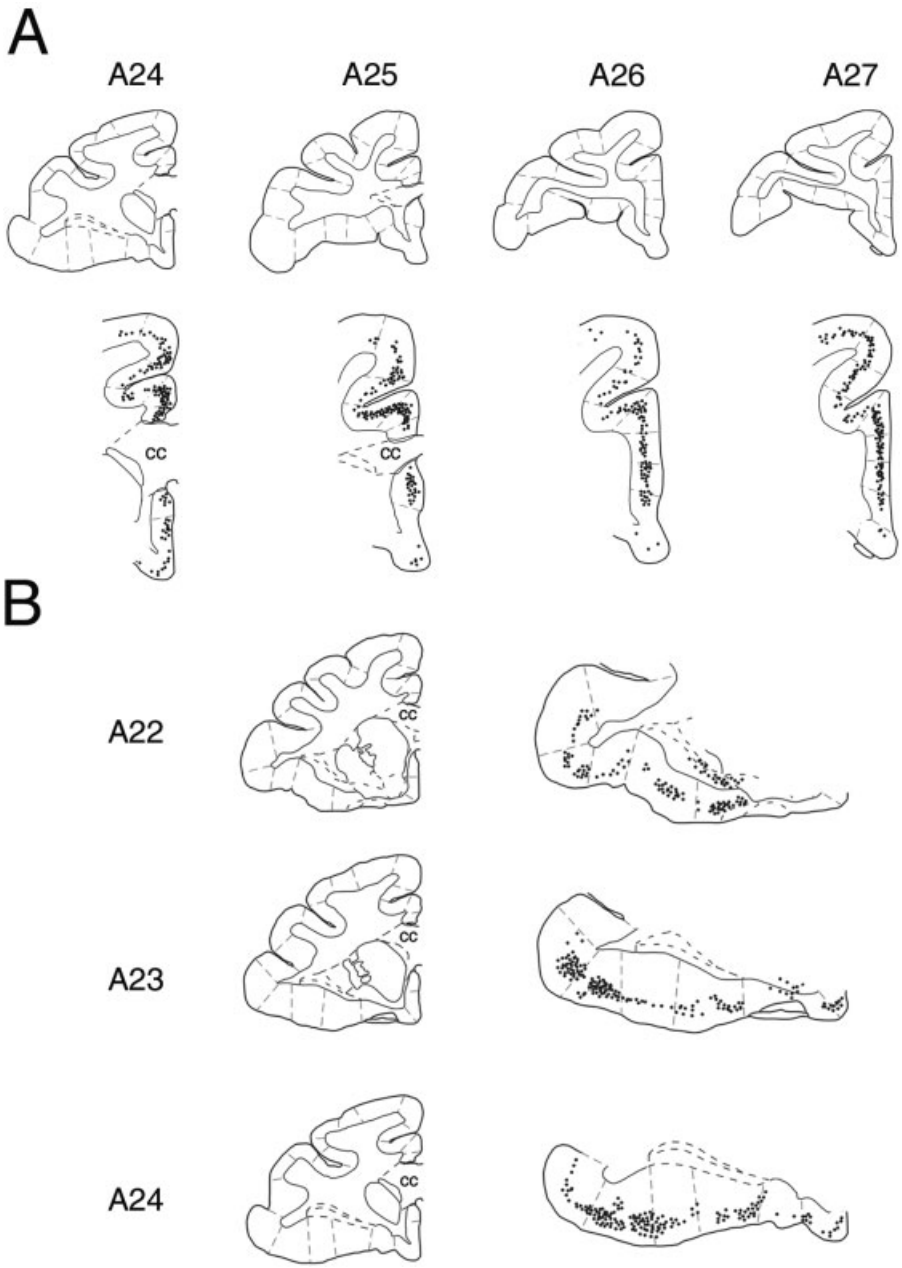

Fig. 6. Plots of retrogradely labeled neurons in ACC and OFC after injections of CTb into monkey LC. **A:** ACC neurons labeled from the monkey LC. Lower sections are high-power views containing plotted cells; upper sections are low-power views to give orientation. **B:** OFC neurons labeled from the monkey LC. Sections at right are high-power views containing plotted cells; sections at left are low-power views to give orientation. For both panels, A22–A27 refer to distances in mm from the interaural line. Plots were composed on atlas sections from Paxinos et al. (2000).

processes is relayed to LC indirectly via OFC, ACC, or both, which receive inputs from a wide array of sensorimotor areas (Morecraft et al., 1992; Carmichael and Price, 1995b; Baylis et al., 1995). Such relays may weight decision-related signals by motivational significance—that is, perceived utility of the current task. This is consistent with the fact that LC phasic responses are limited to goal-related events (e.g., target but not distractor stimuli in a signal-detection task), with an amplitude modulated by the motivational significance of the stimulus (e.g., the reward associated with appropriate performance) (Aston-Jones et al., 1994; Rajkowski et al., 2004). Thus, OFC and ACC may relay the outcome of task-related decision processes, modulated by their assessed utility, driving the LC phasic response. Studies are presently under way to test this hypothesis more directly.

OFC and ACC may regulate LC mode. Our theory suggests that these frontal structures also influence LC function by driving transitions between phasic and tonic modes to regulate the balance between exploitation and exploration: When evaluations in OFC or ACC indicate the current task is providing adequate utility, they drive LC toward the phasic mode (by increasing electrotonic coupling, reducing baseline drive, or both), favoring exploitation of that task for associated rewards. However, when utility diminishes sufficiently over a prolonged duration, they drive it toward the tonic mode, favoring exploration. This process requires that

utility be evaluated over both short and longer time frames.

Compensatory adjustments following lapses in performance have repeatedly been observed (e.g., Rabbitt, 1966; Laming, 1968; Laming, 1979; Gratton, 1992; Botvinick et al., 1999; Jones, 2002). Furthermore, there is strong evidence that they are mediated by an evaluative function in frontal cortex, consistent with the mounting evidence discussed above that monitoring mechanisms within ACC detect lapses in performance and signal the need to augment top-down control for the current task (Botvinick, 2001). Signals from ACC to LC (indicating an adverse outcome), possibly complemented by signals from OFC to LC (indicating absence of an expected reward), may augment the LC phasic mode (by further increasing electronic coupling, reducing LC baseline drive, or both). This, in turn, would improve performance on subsequent trials by enhancing the LC phasic response and thereby augmenting the gain of units responsible for task execution. Increased phasic release of NE may also have direct enhancing effects on task-specific control representations in prefrontal cortex (PFC) (Arnsten et al., 1996; Cohen, 2004). This effect could further contribute to the compensatory increase in control following a transient decrease in performance and/or reward. One appeal of this hypothesis is that it provides a general mechanism by which the detection of momentary reductions in utility can augment task control without requiring the monitoring mechanism to have special knowledge about the nature of control required for every possible task. That is, a global signal (LC-mediated NE release) that adaptively adjusts gain throughout the processing system can interact with task-specific control mechanisms (e.g., in PFC) to produce requisite improvements in performance.

The foregoing account addresses circumstances in which overall task-related utility remains high, and momentary lapses in performance (and utility) can be rectified by enhancement of control. However, what happens if there is a persistent decline in utility? In such circumstances, augmenting control associated with the current task may no longer be advantageous, and the relationship between utility and task investment should reverse: Further decreases in utility should promote task disengagement rather than attempts to restore performance. That is, they should favor exploration over exploitation. The adaptive gain theory proposes that this is mediated by a transition to the LC tonic mode.

DISCUSSION

The adaptive gain theory suggests that the LC-NE system plays a more important and specific role in the control of performance than has traditionally been thought. This new theory is an important evolution of an LC theory that proposed roles for this system in vigilance and response initiation (Aston-Jones, 1985; Aston-Jones et al., 1991) by further specifying the mechanisms that might be involved in executing such functions. The presently proposed framework has a wide range of implications for understanding the neural mechanisms underlying both normal behavior and its impairment in clinical disorders associated with disturbances of decision making and control.

LC activity is plastic and may play a role in learning

A critical component of the adaptive gain theory is that the LC phasic response is driven by the outcome of task-relevant decision processes. This hypothesis implies that the LC phasic activation must be plastic in order to adapt to changes in task demands (e.g., the relevance of different decision processes). This implication is consistent with the physiological evidence. Most strikingly, reversal experiments demonstrate that LC phasic responses reliably track changes in the target stimulus. This plasticity must reflect the response characteristics of the systems that drive LC. This is consistent with the evidence, given our hypothesis that the LC phasic response is driven by frontal structures, including OFC and ACC. Rolls and colleagues (Thorpe et al., 1983; Rolls et al., 1996; see also Wallis and Miller, 2003) have shown that in behaving monkeys OFC responses change quickly to track changes in the motivational relevance of stimuli. These observations support the idea that both the selectivity and plasticity of the LC phasic response reflect afferent drive by frontal structures.

Interactions between the LC-NE and dopamine systems are important for normal and disordered cognition

There are many similarities between the LC-NE and dopamine (DA) systems, but the relationships between these systems and how they interact have remained unclear. Recently, Montague et al. (1996) proposed a sophisticated theory of DA function that suggests that it implements the learning signal associated with a reinforcement learning mechanism. This theory affords a direct point of contact with the adaptive gain theory of LC-NE function.

Reinforcement learning requires an annealing procedure, favoring exploration during learning in new (or changing) environments and promoting exploitation when reliable sources of reward are discovered. The adaptive gain theory proposes that the LC-NE system serves this function, implementing an annealing mechanism that is adaptive to ongoing estimates of current utility. Thus, early in learning, when utility is low, LC remains in the tonic mode, favoring exploration. However, as sources of reward are discovered DA-dependent reinforcement learning strengthens behaviors that produce these rewards. This strengthening increases current utility, driving LC into the phasic mode, which further stabilizes and exploits the utility associated with DA-reinforced behaviors. This process continues until the current source of reward is either no longer valued or available. As utility declines, LC is driven back into the tonic mode, promoting exploration and learning of new behaviors. In this way the proposed functions of the LC-NE and DA systems may interact synergistically to implement an auto-annealing reinforcement learning mechanism that is adaptive both to the needs of the organism and changes in the environment. Although these theories of the LC-NE and DA systems are both early in their development, together they potentially offer a powerful new account of how these systems interact.

SUMMARY AND CONCLUSIONS

We have reviewed findings indicating that during the awake state the LC-NE system has two distinguishable modes of activity (phasic and tonic) and have described an adaptive gain theory of the LC-NE system that proposes specific functions for each of these modes. In the phasic mode a burst of LC activity, driven by the outcome of task-related decision processes, produces a widespread but temporally specific release of NE, increasing gain of cortical processing units and facilitating task-appropriate behavior. In this mode the event-locked nature of the LC phasic response acts as a temporal attentional filter, facilitating task-relevant processes relative to distracting events, thereby augmenting performance of the current task. The theory further proposes that computations regarding decision and utility in OFC and ACC drive these LC phasic responses.

We also propose that utility computations in the OFC and ACC produce the transitions between phasic and tonic modes in LC. Such transitions occur by the regulation of simple physiological variables within LC, such as electronic coupling, baseline drive, or both. High utility associated with performance of the current task favors the LC phasic mode. This mode is further augmented in response to momentary lapses in performance to maximally exploit the utility associated with the current task. However, persistent declines in utility drive a transition to the LC tonic mode. In the tonic mode a lasting increase in baseline NE release augments responsivity of target neurons to a broader class of events, while a concomitant attenuation of the LC phasic response degrades processing of events related to the current task. This indiscriminate release of NE promotes disengagement from the current behavioral routine while facilitating the sampling of others that may provide greater utility. These different LC modes serve to optimize the trade-off between exploitation of stable sources of reward and exploration of other, potentially more remunerative, opportunities in a changing environment.

Several decades of research have made it clear that disturbances of NE and DA are involved in most of the major psychiatric illnesses, including schizophrenia, depression, and anxiety disorders. Some disorders have been associated more closely with NE and others more closely with DA. However, until recently research has focused primarily on relatively simple hypotheses concerning static excesses or deficits of activity in these systems and has given virtually no consideration to interactions between them. The simplicity of these hypotheses has reflected a general lack of knowledge about the more complex dynamics that characterize the functioning of the NE and DA systems individually as well as their interaction. A more sophisticated understanding of these dynamics, and their relationship to cognition and behavior, promises to open up new avenues of inquiry. Realizing this potential, in turn, will afford greater understanding of how disruptions in the LC-NE and DA systems contribute to the complex patterns of behavior associated with psychiatric illness and how appropriate and effective interventions can be designed.

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