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Decision Making, the P3, and the Locus Coeruleus–Norepinephrine System

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Psychologists and neuroscientists have had a long-standing interest in the P3, a prominent component of the event-related brain potential. This review aims to integrate knowledge regarding the neural basis of the P3 and to elucidate its functional role in information processing. The authors review evidence suggesting that the P3 reflects phasic activity of the neuromodulatory locus coeruleus–norepinephrine (LC-NE) system. They discuss the P3 literature in the light of empirical findings and a recent theory regarding the information-processing function of the LC-NE phasic response. The theoretical framework emerging from this research synthesis suggests that the P3 reflects the response of the LC-NE system to the outcome of internal decision-making processes and the consequent effects of noradrenergic potentiation of information processing.

Keywords: Decision making, P300, norepinephrine, source

Scalp-recorded event-related potentials (ERPs) have been of major importance for the study of cognitive processes and the way these processes are implemented in the brain. The P3 (or P300), first reported in 1965 (Desmedt, Debecker, & Manil, 1965; Sutton, Braren, Zubin, & John, 1965), has perhaps been the single most studied component of the ERP, probably in part because this potential is so prominently present in many sensory-evoked waveforms. Since 1965, major progress has been made in delineating the antecedent conditions for the P3. In addition, many different hypotheses have been proposed regarding the functional significance of the P3. However, although most of these hypotheses have in common that they link the P3 process to the features of stimulus processing, a precise, mechanistic account is still lacking. Researchers have also recognized the importance of determining the neural basis of the P3, which may pose critical constraints on functional theories. As articulated by Pritchard (1981) in a classic P3 literature review in *Psychological Bulletin,*

> At any rate, future research would have to demonstrate that any functional role proposed for P300 could be manipulated by manipulating the neuronal populations generating P300. At this time a clear understanding of the neural generators of P300 is lacking. (Pritchard, 1981, p. 533)

Today, more than 20 years later, many pieces of the P3 generator puzzle are known. However, important conceptual gaps remain in the understanding of precisely how the P3 relates to information processing, and there have not been any recent systematic attempts to integrate the body of findings into a coherent theoretical framework.

The current review aims to integrate existing knowledge regarding the neural basis of the P3 and to elucidate the functional role in information processing of the process underlying the P3. In particular, we present an overview of the evidence suggesting that (a) the P3 reflects the response of the neuromodulatory locus coeruleus–norepinephrine (LC-NE) system to the outcome of stimulus evaluation and decision making (by decision making, we refer to processes responsible for determining the presence or identity of task-relevant stimuli and mapping these onto appropriate responses, processes that typically occur within hundreds of milliseconds—cf. Gold & Shadlen, 2001; Ratcliff, 1978) and (b) the observed properties of the P3 reflect an important information-processing function of the LC-NE system, which is to potentiate the response to motivationally significant events. These functions are consistent with previous empirical and theoretical work on the LC-NE system. To our knowledge, the LC-P3 hypothesis of the P3 was first proposed by Pineda, Foote, and Neville (1989; see also Desmedt & Debecker, 1979, for an early hypothesis about the role of neuromodulation in P3 generation). Although this group has reported substantial evidence for the involvement of the LC-NE system in P3 generation (e.g., Pineda et al., 1989; Pineda & Westerfield, 1993; Swick, Pineda, & Foote, 1994; cf. Pineda, 1995), this line of research has not been systematically pursued by others. During this period, the development of the interdisciplinary field of cognitive neuroscience has resulted in an increased interest in the role of neuromodulatory mechanisms in cognitive function on the one hand and cognition and electrophysiological brain activity on the other hand (e.g., Braver & Cohen, 2000; Holroyd &

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Coles, 2002; Li, 2003; Montague, Dayan, & Sejnowski, 1996; Nieuwenhuis et al., 2002; Robbins, 1997; Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999; Yeung, Botvinick, & Cohen, 2004). This, together with new insights into the role of locus coeruleus (LC) dynamics in attention and decision making (cf. Aston-Jones, Rajkowski, & Cohen, 2000; Clayton, Rajkowski, Cohen, & Aston-Jones, 2004; Usher et al., 1999), has encouraged us to further consider and elaborate the LC-P3 hypothesis.

The review is organized as follows. We start by characterizing the phenomenology of the P3 and by providing a summary of the antecedent conditions for the P3. Although it is beyond the scope of the present article to present an in-depth analysis of this work (see Donchin & Coles, 1988; Picton, 1992; Pritchard, 1981), we review key findings that bear on the cognitive functions with which the P3 is thought to be associated, focusing in particular on simple decision-making tasks to which our theory of LC is relevant. Following this, we present an overview of research that has attempted to identify the neural structures involved in P3 generation. Next, we turn our attention to the LC-NE system. Following an introduction of the basic properties of this system, we review the evidence for the involvement of this system in P3 generation. We then discuss empirical work and a recently proposed theory of the information-processing function of the LC-NE system in simple decision-making tasks, suggesting a crucial role for this system in facilitating the behavioral response associated with the outcome of decision making. Finally, to evaluate the implications of this theory for an understanding of the functional significance of the P3, we focus on work that has investigated the relation between the P3 and task performance. In the Discussion, we outline how the LC-P3 hypothesis that emerges from this review relates to previous theories of the P3. Implications for understanding empirical phenomena such as the attentional blink and clinical disorders such as attention-deficit/hyperactivity disorder (ADHD) are also discussed.

P3: Basic Properties and Antecedent Conditions

The P3 is a broad, positive, large-amplitude potential with a typical peak latency between 300 and 400 ms following presentation of stimuli in any sensory modality (Sutton et al., 1965). The component is typically measured in the ERP waveform, which is the result of an averaging process, but can usually also be identified and measured in single-trial waveforms, particularly if these are low-pass filtered. Although the scalp distribution of the classic P3 generally has a maximum over central-parietal midline electrodes, there appear to be small differences in topography across different sensory modalities and experimental paradigms (reviewed in Johnson, 1993). Finally, as is elaborated below, intracranial recordings have identified multiple cortical and subcortical regions that exhibit synchronous P3-like activity.

An important factor affecting the amplitude of the P3 is the *subjective probability* of the eliciting stimulus (for a detailed discussion, see Donchin & Coles, 1988). The most common paradigm for studying the P3 is the *oddball task,* in which low-frequency target stimuli (*oddballs*) are embedded in a train of nontarget stimuli (*standards*). The subject is required either to actively respond to each target stimulus or to passively attend to the stimulus sequence (the latter is often used in animal studies). Duncan-Johnson and Donchin (1977) found that P3 amplitude is inversely related to the probability of the rare event in an oddball sequence. Further research found that this probability effect depends on the probability of the general class of which the stimulus is perceived to be a member rather than on the probability of the individual stimulus (Courchesne, Hillyard, & Courchesne, 1977; Johnson & Donchin, 1980). Furthermore, as first reported by K. C. Squires, Wickens, Squires, and Donchin (1976), P3 amplitude is not dependent just on the global probability of stimulus events but also on local probabilities; that is, it is influenced by expectations elicited by the recent stimulus-sequence history. For instance, the P3 to an oddball target stimulus is larger when the target stimulus is preceded by a series of nontarget stimuli than when it is preceded by a series of other targets. Finally, the effects of local and global target probability on the P3 may be mediated, at least in part, by differences in target-to-target interval (Croft, Gonsalvez, Gabriel, & Barry, 2003; Gonsalvez & Polich, 2002).

P3 amplitude is also highly sensitive to the *motivational significance* of the eliciting stimulus.[1] The motivational significance of a stimulus can vary depending on the specific task context in which it occurs. For instance, when equated for frequency of occurrence, target stimuli (i.e., stimuli requiring a response) typically elicit higher P3 amplitudes than nontarget stimuli (e.g., Duncan-Johnson & Donchin, 1977). Some stimuli can also be inherently more motivationally significant than others. For example, emotionally valent stimuli, whether experienced as positive or negative, are associated with larger P3s than emotionally neutral stimuli (Johnston, Miller, & Burleson, 1986; Keil et al., 2002). A specific example of emotionally valent stimuli is feedback stimuli indicating monetary gains or losses. Several researchers have found that the P3 is sensitive to the absolute magnitude of the feedback outcome regardless of whether it concerns a gain or a loss of money (Johnston, 1979; Sutton, Tueting, Hammer, & Hakerem, 1978; Yeung & Sanfey, 2004). Painful stimuli also elicit a slow P3-like potential that is sensitive to the frequency of occurrence (Zaslansky, Sprecher, Tenke, Hemli, & Yarnitsky, 1996).

The effects of subjective probability and motivational significance on P3 amplitude are modulated by a third variable, the amount of attention paid to the stimulus (cf. Johnson, 1993). It has been consistently found that, provided that interstimulus intervals are moderately short, only attended stimuli elicit a reliable P3 component. The same stimuli that would under normal circumstances elicit a robust P3 do not elicit a P3 when they are deliberately ignored or when subjects' attention is occupied by another, secondary task (Donchin & Cohen, 1967; Duncan-Johnson & Donchin, 1977; Hillyard, Hink, Schwent, & Picton, 1973). However, dual-task studies have shown that the P3 to a primary task stimulus is affected most if the secondary task poses increasing perceptual demands (Wickens, Kramer, Vanasse, & Donchin, 1983; cf. Kok, 2001). In contrast, P3 amplitude is relatively unaffected by the motor demands of the secondary task (Israel, Chesney, Wickens, & Donchin, 1980). Indeed, the experimental variables known to affect P3 amplitude have generally been classified as influencing perceptual or attentional processes. P3 am-

[1] By motivationally significant stimuli, we mean stimuli that are either relevant to the current task or that have the potential to be associated with some form of utility (positive or negative).

plitude has been shown to be relatively insensitive to variables related to response generation (e.g., Kok, 1978; McCarthy & Donchin, 1981) and to physical properties of the stimulus, although one exception is tone intensity, which is positively correlated with P3 amplitude (e.g., Covington & Polich, 1996; Roth, Dorato, & Kopell, 1984). Indeed, if an initially unattended stimulus has sufficient intensity to capture attention and intrude into consciousness, a P3 may be observed (Putnam & Roth, 1990; Ritter, Vaughan, & Costa, 1968).

Novel and highly deviant or salient task-irrelevant stimuli constitute a specific class of motivationally significant, attention-capturing stimuli. When these stimuli are embedded in a standard oddball sequence of target and nontarget stimuli (a *novelty oddball task*), their presentation elicits a P3 component, usually labeled *P3a* (or *novelty-P3,* in the case of novel stimuli), that is somewhat different from the typical P3 (or *P3b*) associated with familiar but infrequent task-relevant stimuli (Courchesne, Hillyard, & Galambos, 1975; N. K. Squires, Squires, & Hillyard, 1975; Yamaguchi & Knight, 1991b; for review, see Friedman, Cycowicz, & Gaeta, 2001). The P3a does not exhibit the typical parietocentral scalp distribution but instead has a prominent frontocentral distribution. Also, the P3a peaks 60–80 ms earlier than the P3b, and if a stimulus is sufficiently obtrusive, the P3a can be elicited even if subjects are not actively engaged in the task. In any case, P3a amplitude to task-irrelevant stimuli rapidly habituates as the novelty of such stimuli decreases with repeated presentations (Courchesne et al., 1975; Yamaguchi & Knight, 1991b). Finally, although the P3a is specifically pronounced for task-irrelevant attention-capturing stimuli, Spencer and colleagues have demonstrated that a small P3a can also be elicited by rare target stimuli in the oddball task (e.g., Spencer, Dien, & Donchin, 2001).

In a later section, we show that the antecedent conditions for the P3 are similar to those for LC phasic activity. Also, we argue that these antecedent conditions are consistent with a theory of LC-NE function that proposes that LC phasic activity is driven by the outcome of stimulus-driven decision-making processes and that this effect may be mediated by concurrent evaluation of the motivational significance of the eliciting event.

P3 Generators

There appears to be a consensus that the P3 has multiple neural generators, although there is no general agreement regarding the identity of these generators. Many candidate structures have been proposed on the basis of intracranial recordings in patients and scalp recordings from neurosurgical patients or patients with brain damage. Investigations have also employed direct neuronal recordings in nonhuman species as a means of localizing the P3. This approach has been motivated by the finding of P3-like activity in animals such as monkeys, cats, and rats under conditions that are similar to those in human studies (Arthur & Starr, 1984; Jodo, Takeuchi, & Kayama, 1995; O'Connor & Starr, 1985). Below, we summarize the main findings (for extensive reviews, see Frodl-Bauch, Bottlender, & Hegerl, 1999; Hansenne, 2000; Soltani & Knight, 2000). Most of these P3 studies have used the standard or novelty oddball paradigm.

Intracranial recording studies have revealed large P3-like potentials in medial temporal lobe structures (including hippocampus and amygdala) in humans (Halgren et al., 1980; McCarthy, Wood, Williamson, & Spencer, 1989; Smith et al., 1990), monkeys (Paller, McCarthy, Roessler, Allison, & Wood, 1992), and cats (Kaga, Harrison, Butcher, Woolf, & Buchwald, 1992). Similar P3-like potentials have been observed in the thalamus of humans (Yingling & Hosobuchi, 1984) and of cats (Katayama, Tsukiyama, & Tsubokawa, 1985). Potentials in medial temporal lobe structures showed steep amplitude gradients and polarity inversions (i.e., indicating a local source) and comparable latency to the surface-recorded P3, suggesting a generator in these structures. However, several studies have failed to find significant reductions in P3 amplitude following unilateral temporal lobectomy (Johnson, 1988; Stapleton, Halgren, & Moreno, 1987) or following bilateral lesions of the hippocampus (Polich & Squire, 1993), suggesting that hippocampal P3 activity does not contribute significantly to the scalp-recorded P3. A more fundamental argument against P3 generators in medial temporal or subcortical structures is based on biophysical considerations suggesting that the possible contribution of these structures to the scalp-recorded electroencephalogram (EEG) is much too small to account for large-amplitude potentials like the P3 (Birbaumer, Elbert, Canavan, & Rockstroh, 1990; Lutzenberger, Elbert, & Rockstroh, 1987).

Whereas scalp-recorded parietal P3b activity elicited by task-relevant stimuli is typically spared following hippocampal lesions, such lesions have been reported to result in substantial, bilateral reductions of the frontocentral P3a elicited by novel stimuli (Knight, 1996; Knight & Scabini, 1998). Although, as discussed above, the hippocampus is unlikely to be a direct generator of P3 activity, these results have been taken as evidence for the importance of interactions between hippocampus and prefrontal cortex in detecting novel stimuli (cf. Soltani & Knight, 2000). According to this view, hippocampal lesions reduce the activity in prefrontal regions implicated in P3a generation (cf. Knight, 1984).

Lutzenberger et al. (1987) have argued that large-amplitude potentials like the P3 must have widespread, synchronous, and primarily cortical sources. Consistent with this view, intracranial P3-like activity has been recorded from multiple cortical areas (reviewed in Soltani & Knight, 2000). Although these areas are distributed throughout the neocortex, two main clusters have been identified: One cluster includes the temporal-parietal junction (TPJ; consisting of the supramarginal gyrus and caudal parts of the superior temporal gyrus) and adjacent areas (Halgren et al., 1995; Kiss, Dashieff, & Lordeon, 1989; Smith et al., 1990). This region is thought to be involved in perceptual processing, as is illustrated by the fact that TPJ lesions frequently result in visual hemineglect, a failure to notice and orient to salient stimuli in the contralesional visual space (e.g., Payne, Lomber, Geeraerts, van der Gucht, & Vandenbussche, 1996; Rafal, 1994). Studies involving human patients have found that lesions of the TPJ region produce marked reductions of the P3 associated with infrequent, task-relevant stimuli and novel stimuli (Knight, Scabini, Woods, & Clayworth, 1989; Verleger, Heide, Butt, & Kömpf, 1994; Yamaguchi & Knight, 1991a, 1992). The second major cluster identified by intracranial recordings is in lateral prefrontal cortex (Baudena, Halgren, Heit, & Clarke, 1995). This is also consistent with lesion studies, which have found that lesions affecting lateral prefrontal cortex substantially reduce the amplitude of the P3a to novel stimuli—the P3b, however, remains largely unaffected by such lesions (Knight, 1984; McCarthy & Wood, 1987; Yamaguchi & Knight, 1991a).

Several functional imaging studies using the oddball paradigm have aimed to validate the above findings from lesion studies and intracranial recordings. Analogous to ERP research, the methodological approach of these imaging studies involves a comparison of the hemodynamic response to oddball targets versus standard distractors. Although a variety of areas have been reported, the areas of activity most consistently associated with target processing have been in the prefrontal cortex, TPJ region, and thalamus (e.g., Downar, Crawley, Mikulis, & Davis, 2002; Kiehl, Laurens, Duty, Forster, & Liddle, 2001; Marois, Leung, & Gore, 2000; McCarthy, Luby, Gore, & Goldman-Rakic, 1997; Menon, Ford, Lim, Glover, & Pfefferbaum, 1997). However, because of the low temporal resolution of current functional imaging techniques, these activations may also reflect neural activity related to processes, such as response execution, that have not been implicated in P3 generation. To our knowledge, only one imaging study has employed a parametric design, allowing a more sensitive estimate of the brain areas involved in P3 generation. Horovitz, Skudlarski, and Gore (2002) examined the effect on the functional magnetic resonance signal of systematic variations in oddball target frequency, a manipulation known to affect P3 amplitude. Brain regions that, like the P3, increased activation with decreases in target frequency were the supramarginal gyri, right medial frontal gyrus, thalamus, and insula, supporting a role for these structures in P3 generation. Other regions, such as the cingulate cortex, were activated more by targets than by nontargets, but their signal changes did not vary with target frequency.

To summarize, convergent evidence suggests that P3-like activity can be recorded in several, widely separated brain areas. These include some medial temporal and subcortical structures (e.g., the hippocampal formation, amygdala, and thalamus), but these structures are unlikely to contribute directly to the scalp-recorded P3. In contrast, two broad regions of the neocortex can be distinguished that seem to be critical for the observation of the P3 at the scalp: One region, surrounding the TPJ, seems to be critical for the generation of both the P3a and the P3b. Another region, in the lateral prefrontal cortex, is critically involved mainly in the generation of the P3a to novel stimuli. Taken together, this evidence suggests the possibility of multiple, relatively independent sources that exhibit P3-like activity, some of which is volume-conducted to the scalp and some of which is not. However, as has been argued by Pineda et al. (1989), the notion of independent sources is unlikely to account for the uniform latency of P3 activity across the spatially distributed sites discussed above. Instead, a more plausible hypothesis is that the P3 activity reflects the influence of a broadly distributed neural system that synchronously impacts several brain areas. As is argued below, the LC-NE system exhibits the anatomical, physiological, and functional properties necessary to subserve such a role.

Basic Properties of the LC-NE System

The LC is a nucleus in the pontine region of the brain stem that consists of cells containing norepinephrine (NE), which provide the primary source of noradrenergic innervation in the forebrain.[2] The LC projects throughout the cerebral cortex, thalamus, midbrain, cerebellum, and spinal cord (Aston-Jones, Foote, & Bloom, 1984; Berridge & Waterhouse, 2003) and is the sole source of NE input to the hippocampus and neocortex. Although the LC projects widely throughout the cortex, it exhibits substantial regional and laminar specificity in its efferent projections.

A common view of the LC-NE system is that it is important for the regulation of sensory signal transmission. Electrophysiological studies have shown that iontophoretic application of NE on single neurons leads to an enhancement of evoked responses relative to spontaneous activity (reviewed in Berridge & Waterhouse, 2003). Occasionally, this results in responses to otherwise subthreshold synaptic inputs. In some studies, NE was found to suppress spontaneous activity to a greater extent than activity evoked by afferent stimulation (Foote, Freedman, & Oliver, 1975; Segal & Bloom, 1976), whereas, in other studies, NE was found to augment evoked activity with minimal or no effect on the rate of spontaneous activity (Waterhouse & Woodward, 1980). In these latter studies, NE-induced enhancement of evoked activity was observed both for excitatory (e.g., glutamatergic) and inhibitory (e.g., GABAergic) synaptic transmission. In general, findings regarding the neurophysiological effects of NE support the view that it acts to increase the gain or responsivity of neurons to afferent input in projection regions of the LC-NE system (Figure 1; Servan-Schreiber, Printz, & Cohen, 1990). The consequences of this physiological mechanism for higher level information processing is discussed in a later section, below.

Direct physiological recordings have identified two components of activity within the LC itself: The first involves its spontaneous (baseline) rate of discharge, referred to as *tonic activity*; the second involves brief, rapid increases in firing rate, referred to as *phasic activity.* LC tonic activity varies typically between 0 and 5 Hz and can be divided roughly into four ranges that appear closely related to the level of arousal of the animal (and are closely aligned with the familiar Yerkes-Dodson inverted-U-shaped curve for arousal). The LC exhibits low basal activity during sleep and is essentially quiescent during paradoxical or REM sleep (Aston-Jones & Bloom, 1981a; Hobson, McCarley, & Wyzinski, 1975). LC tonic activity rises slightly but remains relatively low ($<$2 Hz) during periods of drowsiness, of quiet waking, and when the animal is engaged in endogenously driven, vegetative activity when vigilance is low (e.g., Aston-Jones & Bloom, 1981a, 1981b; Rajkowski, Kubiak, & Aston-Jones, 1994). Tonic levels are moderately increased (2–3 Hz) during engagement in exogenously driven tasks and are associated with accurate task performance. However, further increases in tonic activity ($>$3 Hz) are typically associated with distractibility and erratic performance (e.g., significantly increased numbers of false alarms in a target-detection task; Aston-Jones et al., 2000; Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994; Usher et al., 1999).

In addition to fluctuations in LC tonic activity, LC neurons can exhibit phasic responses (i.e., brief, high levels of discharge at about 20 Hz) to highly salient unconditioned environmental stimuli, as well as to task-relevant stimuli in many modalities (Aston-Jones & Bloom, 1981b; Aston-Jones, Rajkowski, et al., 1994; Foote, Aston-Jones, & Bloom, 1980). According to the LC-P3 hypothesis, the P3 is an electrophysiological correlate of the LC phasic response. Such phasic activity typically occurs with a short

[2] The name locus coeruleus means blue spot, which refers to the dark blue color of LC neurons in fresh human tissue resulting from the pigment melanin contained in these cells.

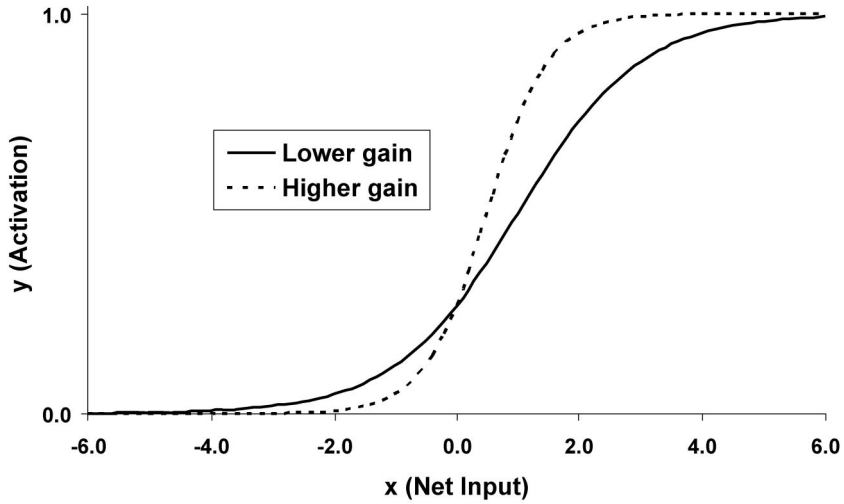

Figure 1. Model of neural responsivity or gain (Servan-Schreiber, Printz, & Cohen, 1990). The response of a typical neuron can be described by its activation function, a function relating the neuron's net afferent input *x* to its probability of firing or activation *y*. Activation functions are typically modeled as monotonously increasing sigmoid functions, such as the logistics in this figure. The unit's activation at zero net input corresponds to a neuron's baseline firing rate. Positive net inputs correspond to excitatory stimuli; negative net inputs correspond to inhibitory stimuli. In line with the response functions of actual neurons, the function is asymmetric around a net input of 0. Following Servan-Schreiber et al. (1990), we assume that norepinephrine increases the gain of individual locus coeruleus target neurons. Increasing gain drives up a unit's response to a positive input and drives down its response to a negative input (compare the dotted and the solid lines).

latency following the eliciting stimulus (~100–150 ms in monkeys, 15–70 ms in rats), characteristically occurs uniformly among LC cells, and does not exhibit topographic specificity with regard to the nature of the eliciting event (i.e., it appears to reflect a stereotypic, LC-wide response to the eliciting event). LC phasic activity typically precedes the behavioral response to the eliciting stimulus and is more tightly locked to the timing of the behavioral response than to the stimulus onset (Bouret & Sara, 2004; Clayton et al., 2004; Rajkowski, Majczynski, & Aston-Jones, 2004). As we discuss below, this suggests that the LC may be responding to internal processing of the stimulus (e.g., categorization) rather than the sensory event itself and that it has a direct influence on the timing of the behavioral response. Consistent with this hypothesis and with the proposed relationship of LC phasic responses to the P3, phasic responses are observed primarily when the animal appears to be engaged by a task (and LC tonic activity is in the moderate range). Periods of drowsiness, sleep, or distracted behavior (accompanied by high levels of LC tonic activity) are associated with an absence of LC phasic responses (Aston-Jones & Bloom, 1981a, 1981b; Rajkowski et al., 1994). Note that when tonic activity is either low or high, LC phasic responses are small or absent, thus so should be the P3. This relationship is considered in the Discussion, below.

Finally, it is important to note that LC phasic responses are often followed by a period of relative quiescence (~200–500 ms following the stimulus). It has been proposed that this prolonged attenuation of noradrenergic activity following a phasic discharge is caused by inhibitory noradrenergic autoreceptors or potassium channels in LC neurons that, when activated, suppress cell firing activity (Aghajanian, Cedarbaum, & Wang, 1977; Andrade & Aghajanian, 1984; Egan, Henderson, North, & Williams, 1983; Williams, North, Shefner, Nishi, & Egan, 1984; cf. Nieuwenhuis, Gilzenrat, Holmes, & Cohen, in press). Below, we relate this functional refractoriness of the LC following motivationally significant stimuli to a well-characterized attentional phenomenon: the attentional blink. Here, however, we turn our attention to a review of the antecedent conditions for an LC phasic response, which are important for relating this response to attentional phenomena and the P3.

LC-NE Phasic Response: Antecedent Conditions

The antecedent conditions for the LC phasic response are similar to those reported for the P3. In general, LC phasic activity is more closely related to the overall motivational significance and/or arousing nature of a given stimulus than to the affective valence of the stimulus (cf. Berridge & Waterhouse, 2003).

A number of monkey studies have investigated LC activity in a visual oddball task, similar to that used in human P3 research (Aston-Jones, Rajkowski, & Kubiak, 1997; Aston-Jones, Rajkowski, et al., 1994; Rajkowski et al., 1994; Swick, Pineda, Schacher, & Foote, 1994). In these studies, monkeys were required to foveate a series of conditioned stimuli. These consisted of infrequent target stimuli (e.g., a vertical bar) and frequent nontarget stimuli (e.g., a horizontal bar). LC neurons were phasically activated selectively by presentation of the target stimuli and only weakly or not at all by presentation of nontarget stimuli. No LC response was elicited by the fixation spot occurring at the start of each trial, reward presentation, lever-release response, or eye movements. Moreover, recordings during reversal learning training indicated that this selective response to targets was independent of the physical characteristics of the stimuli. Indeed, the only sensory attribute

known to affect the LC response is tone intensity (Grant, Aston-Jones, & Redmond, 1988). Furthermore, following reversal, the LC began to respond to the new target before this was observed of the overt behavioral response. Thus, LC phasic activation in the oddball task has been specifically observed following infrequent target stimuli that have motivational significance and has shown a sensitivity to these variables that was at least as great as (and sometimes greater than) overt responding.

In the oddball studies discussed above, an LC phasic response was observed to stimuli that were both task relevant (i.e., requiring a response to elicit a reward) and infrequent, two factors known to influence P3 amplitude. A similar influence has been reported for the amplitude of the LC phasic response. For instance, it has been found that the LC response to target stimuli is larger when target probability is 10% than when it is 50% (Alexinsky, Aston-Jones, Rajkowski, & Revay, 1990). Also, the LC response is smaller to the second of two consecutive target stimuli in an oddball sequence (Aston-Jones, Rajkowski, et al., 1994), suggesting that the sensitivity of the LC to global probability may in part be mediated by sensitivity to local probability, as seems to be the case for the P3. Finally, the LC response occurs for targets but is small or absent for nontargets when both are equally frequent (Alexinsky et al., 1990; Aston-Jones et al., 1997).

In general, the LC is highly sensitive to the motivational significance of environmental stimuli. Novel stimuli typically elicit an LC phasic response (Sara & Segal, 1991; Vankov, Herve-Minvielle, & Sara, 1995). Like the P3a, this response habituates quickly with repeated presentations if the stimulus is motivationally insignificant (Aston-Jones & Bloom, 1981b). Furthermore, like the P3, LC neurons display sensitivity to both appetitive and aversive stimuli (e.g., Foote et al., 1980; Rasmussen, Morilak, & Jacobs, 1986), such as preferred food or threatening stimuli. Painful sensory stimulation also evokes a significant LC response (Hirata & Aston-Jones, 1994; Segal, 1979).

To summarize, the LC phasic response is driven by the meaning and frequency of attended environmental stimuli while being relatively insensitive to their physical attributes. In addition, an LC response occurs to unattended stimuli that are salient by virtue of novelty or intensity. These antecedent conditions bear remarkable similarity to the antecedent conditions reported for the P3. This parallel between the P3 and the LC response received more direct support from an oddball study in which monkey LC neurons and behavioral discrimination data were recorded along with electrophysiological scalp potentials (Aston-Jones, Chiang, & Alexinsky, 1991). LC activity and electrophysiological scalp potentials recorded from frontal and parietal electrodes at latencies of 200–300 ms poststimulation were selectively augmented by target stimuli. Furthermore, during reversal training, LC activity and scalp potentials altered their selectivity following a similar time course that closely paralleled changes in behavioral discrimination performance.

Role of the LC-NE Phasic Response in P3 Generation

According to the LC-P3 hypothesis, phasic activity of the LC and the resulting release of NE at axon terminals is critical in generating the P3. In this section, we review the neurophysiological evidence for this claim.

LC-NE System: Projection Areas, Timing, and Relation to Spontaneous EEG Activity

As noted above, the LC has a highly divergent efferent projection system (cf. Aston-Jones et al., 1984; Foote, Bloom, & Aston-Jones, 1983). Although the number of detailed studies is limited (Levitt, Rakic, & Goldman-Rakic, 1984; Morrison & Foote, 1986), the available evidence also suggests a high degree of regional specificity of NE innervation that is broadly consistent with the regional specificity of P3 activity. First, within the primate neocortex, NE innervation seems to be particularly high in inferior parietal cortex and somatosensory cortex and is least dense in visual cortical areas, especially in primary visual cortex. Second, there is a substantial innervation throughout the frontal pole (see also Foote & Morrison, 1987). Third, within the temporal lobe, there is greater innervation of the superior temporal gyrus (in the TPJ region) than of the inferior temporal gyrus. Furthermore, in neocortex, NE fibers preferentially innervate Layer V, which contains large, radially oriented pyramidal cells of the kind presumed to be involved in generating scalp EEG activity (Levitt et al., 1984). Moreover, the latency of the LC phasic response (~150–200 ms poststimulus) and the slow conduction velocity of NE fibers and time course of NE physiological effects (~150 ms postdischarge) suggest that the time course of LC impact on cortical processing is on the order of magnitude of the typical P3 latency (Aston-Jones, Segal, & Bloom, 1980; Berridge & Waterhouse, 2003; Foote et al., 1983; cf. Pineda, 1995). It is interesting to note that the latency difference between the frontal P3a and the more posterior P3b might be explained by the anatomy of noradrenergic fibers, which—unlike most other cortical afferents—first innervate the frontal cortex and then continue caudally to innervate more posterior areas of cortex (Morrison, Foote, O'Connor, & Bloom, 1982; Morrison, Molliver, & Grzanna, 1979). Thus, it is plausible that the regional specificity of NE innervation and its timing may explain the modal scalp distribution and latency of the P3.

Dense NE innervation has also been reported for the thalamus (in particular, the primate pulvinar nucleus and the reticular nucleus), amygdala, and hippocampus (Morrison & Foote, 1986; see also Foote et al., 1983), three structures that exhibit intracranial P3 activity. It is important to note that NE release in these spatially separated sites is almost simultaneous (cf. Berridge & Waterhouse, 2003), consistent with the relative uniformity of timing of P3 activity across sites. In contrast, the basal ganglia are nearly devoid of noradrenergic input (Berridge & Waterhouse, 2003). The corresponding results from intracranial recording studies are mixed: Although several studies have measured P3-like potentials in basal ganglia structures (e.g., Kropotov & Ponomarev, 1991; Velasco, Velasco, Velasco, Almanza, & Olvera, 1986), only one has found steep amplitude gradients and polarity inversions of these potentials (Rektor et al., 2003), signs of the presence of local generators (Vaughan, Weinberg, Lehmann, & Okada, 1986). Furthermore, lesion studies in humans (Frisch, Kotz, Von Cramon, & Friederici, 2003) and rabbits (Wang et al., 1997) have reported no effects of basal ganglia lesions on the scalp-recorded P3. Although it would seem that the basal ganglia lie too deep to contribute substantially to the surface-recorded P3 (see the section P3 Generators, above), in one study these lesions completely abolished the P600, a scalp potential with similar morphology to the P3 (Frisch et al., 2003).

Cellular Basis of P3: Role of the LC-NE System

If the LC-NE system is the source of the P3, then it should be possible to relate the cellular effects of NE release to the generation of the scalp-recorded electrical potential. As stated by Frodl-Bauch et al. (1999),

> It is now widely accepted that ERPs [such as the P3] result from intracortical currents induced by excitatory and inhibitory postsynaptic potentials (EPSPs, IPSPs), which are triggered by the release of neurotransmitters. Therefore, ERPs reflect postsynaptic effects of neurotransmitters like glutamate and GABA and indirect modulating effects from neuromodulators like acetylcholine, noradrenaline, dopamine or serotonin. (Frodl-Bauch et al., 1999, p. 87)

However, beyond this general statement, there has been little agreement to date as to the cellular basis for the P3 (cf. Otto, 1978). The LC-P3 hypothesis suggests some specific mechanisms, that may allow progress to be made in this direction.

Both excitatory and inhibitory effects of NE are found in the cortex, typically associated with alpha1 and alpha2 receptor activation, respectively. However, the modulatory effects of NE may be of greatest relevance to the P3. As described above, NE is often found to enhance the synaptic responses of cortical neurons to their other inputs, in effect increasing the gain of cortical neuronal activity. This modulatory effect of NE is typically associated with beta adrenoceptor activation (Berridge & Waterhouse, 2003). One possible cellular mechanism for P3 generation involves this modulatory action of NE, which might serve to amplify signal conduction (and thereby an enhanced scalp potential) as follows.

We speculate that activation of cortical pyramidal neurons by novel or task-relevant stimuli generates a current sink in the soma region (corresponding to depolarization in the active zone leading to impulse activity) and a current source in the apical dendrites near the cortical surface and location of recording electrodes. This current source would appear as a positive deflection in an ERP recording. The modulatory effect of NE may substantially increase the probability of an input generating postsynaptic responses in cortical neurons, especially those due to afferent impulse activity. In fact, this type of modulation has been reported in previous studies (Waterhouse et al., 1988). Thus, stimuli that activate the LC and cause release of NE in the cortex might generate larger cortical responses that would be reflected in larger magnitude current sources in apical dendrites and, therefore, larger P3 potentials. This effect would be especially pronounced in cortical areas that receive particularly dense NE inputs, such as the TPJ, and should correspond temporally to the time of NE release in cortical target areas following a stimulus (~200 ms in monkeys). The duration of the P3 may exceed that of direct NE action somewhat because of the slow speed of electrotonic conduction of current from the active zone at the soma through the apical dendrites of cortical pyramidal neurons. Alternatively, NE may produce a prolonged depolarization of cortical neurons that would increase their responsiveness to other inputs, as has been reported for dopamine (Gorelova, Seamans, & Yang, 2002) and for NE in spinal neurons (see Heckman, Lee, & Brownstone, 2003, for review). This depolarization (associated with the P3 potential) may outlast the increased responsivity of pyramidal neurons to extrinsic inputs due to recruitment of inhibitory interneurons or other unknown mechanisms.

Relation to Spontaneous EEG Activity

If NE release impacts scalp-recorded potentials by means of the cellular mechanisms described above, then one would expect LC tonic activity to also have an impact on scalp-recorded EEG. Indeed, there is substantial evidence for a tight link between LC activity and characteristics of the spontaneous EEG that is also consistent with the aforementioned relation between tonic LC activity and behavioral state. Early studies indicated that, in general, LC neurons exhibit gradual changes in firing rate in anticipation of changes in the power spectrum and the degree of synchronization of the EEG, two important determinants of arousal state (Aston-Jones & Bloom, 1981a; Hobson et al., 1975). However, despite the consistency of these observations, they were correlational in nature and thus did not provide evidence for a causal relationship between LC function and EEG activity. More recently, such evidence has come from studies involving direct stimulation (Berridge & Foote, 1991) or suppression (Berridge, Page, Valentino, & Foote, 1993; see also Swick, Pineda, & Foote, 1994) of tonic LC activity. These studies have confirmed that changes in LC activity are closely associated with profound changes in the power spectrum of cortical EEG. Furthermore, they have shown that unilateral activation of the LC elicits robust bilateral arousal of cortical EEG, whereas bilateral inactivation of the LC is required to decrease cortical arousal. These findings indicate that LC activity plays a causal role in cortical arousal and that activity in one LC is sufficient to produce or maintain electrical signs of cortical arousal. To what extent this influence is directly mediated by NE acting in the thalamocortical circuits or is produced by other neurotransmitter systems that project to thalamocortical neurons (e.g., Cape & Jones, 1998) is currently unclear.

Evidence From Psychopharmacological Studies

Several animal studies have examined the effect of pharmacological manipulations of LC activity on the P3 to evaluate the involvement of the LC-NE system in P3 generation. Many of these studies have used the antihypertensive drug clonidine, a noradrenergic autoreceptor agonist, which at low doses decreases LC firing and attenuates the release of NE from axon terminals (Svensson, Bunney, & Aghajanian, 1975; see Coull, 1994). Swick, Pineda, and Foote (1994) found that clonidine decreased the area of the auditory oddball P3 recorded from squirrel monkeys. This result could not be readily explained in terms of reduced arousal—a potential side effect of clonidine—because behavioral performance and early ERP components were not affected by clonidine. The same dose of clonidine did not affect the amplitude or area of the monkey P3 in another study (Pineda & Swick, 1992), which used a passive visual oddball task. These findings seem to suggest that the visual and auditory P3s are differentially susceptible to noradrenergic influences. It is interesting to note, however, that it appears to be the modality of the context provided by the frequent standard stimuli, rather than the modality of the infrequent P3-evoking targets, that modulates the effect of clonidine. Pineda and Westerfield (1993) used a repetitive tone as standard stimulus and a different-pitched tone and yellow rectangle as auditory and visual oddballs, both of which elicited large P3-like potentials in the placebo condition. Administration of clonidine reduced the

magnitude of both the visual and auditory P3s at parietal recording sites. In contrast, in a similar experiment, Pineda, Westerfield, Kronenberg, and Kubrin (1997) found no drug effects on monkey P3 amplitudes elicited by visual and auditory oddball stimuli embedded in a visual context. In addition to these effects of clonidine, it has been reported that administration of guanfacine, another NE agonist, increased auditory P3 amplitude in one of two macaque monkeys tested (O'Neill et al., 2000). Preliminary evidence for the critical involvement of the TPJ in P3 generation comes from studies by Pineda and colleagues showing that microinjections of noradrenergic antagonists and agonists in the TPJ result in reductions of P3 amplitude in monkeys (Pineda, Hsieh, Komesu, & Holloman, 1995; Pineda, Shafer, & Belmonte, 1993).

Other suggestive evidence for the importance of NE in P3 generation was reported by Glover, Ghilardi, Bodis-Wollner, and Onofrj (1988). These researchers investigated event-related scalp potentials in monkeys before and after administration of MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a drug that depletes dopamine and NE and induces a parkinsonian syndrome. MPTP administration led to a significant decrease of the amplitudes of early evoked potentials elicited by auditory oddball stimuli. After about 40 days, these potentials progressively returned to pretreatment amplitude in the monkeys (2 out of 5) that partially recovered from the behavioral consequences of MPTP. The effect on the P3, however, was even more striking: The robust P3 potentials recorded before drug administration were completely abolished for more than a month in all animals post-MPTP. After 50–60 days, the P3 spontaneously reemerged but only in the two monkeys that recovered behaviorally. Although these results could in principle be attributed to the depletion of dopamine instead of NE, administration of a dopamine precursor, although somewhat effective in reversing the effects of MPTP on behavior and early evoked potentials, did not restore the absent P3-like potentials. As is discussed below, other evidence is also incompatible with a significant role for dopamine in P3 generation.

Human studies have yielded similar results for pharmacological manipulations. Joseph and Sitaram (1989) found that administration of clonidine resulted in a decrease in human auditory P3 amplitude, which was most marked in the occipital and left temporoparietal regions. Duncan and Kaye (1987) also reported that clonidine decreased auditory P3 amplitude. Lovelace, Duncan, and Kaye (1996) gave participants several doses of clonidine or a placebo in separate testing sessions. The highest dose increased reaction time and decreased performance accuracy in an auditory oddball task while decreasing the amplitude of the auditory P3. In contrast, no significant effects were observed in a similar task with visual stimuli, again suggesting a modality asymmetry in the effects of clonidine. However, Halliday et al. (1994) found a clear reduction of P3 amplitude in participants performing a visual discrimination task following clonidine, indicating that the modality differences are not robust. Although the effects of clonidine on P3 amplitude have been mostly consistent across studies, the results regarding the effects on P3 latencies have been more mixed, with some studies reporting a decreased latency (Duncan & Kaye, 1987; Joseph & Sitaram, 1989) and others reporting an increased latency (Halliday et al., 1994; see also Swick, Pineda, & Foote, 1994). Finally, consistent with the microinjection studies discussed above, a recent neuroimaging study has found that clonidine attenuates activity in the human TPJ (Coull, Nobre, & Frith, 2001).

Evidence From Lesion Studies

A few studies have investigated the effects of lesions to the LC-NE system on the P3. Pineda et al. (1989) examined the ERPs of squirrel monkeys in a passive auditory oddball paradigm and demonstrated that LC lesions significantly reduced the area of P3-like potentials while leaving several early ERP components intact. The effect of stimulus probability on P3 amplitude that was present in prelesion measurements was also substantially disrupted by the lesions. In addition, the results showed a statistically significant positive correlation between the extent of LC damage, as determined by histological reconstructions, and the percentage decrease in P3 area. Ehlers and Chaplin (1992) investigated intracranial oddball P3 activity from the hippocampus, thalamus, frontal cortex, and LC in rats before and after neurochemical lesions to the ascending dorsal noradrenergic bundle. Prior to the lesions, the rats exhibited marked probability-sensitive P3 potentials in the hippocampus, but not in the thalamus, frontal cortex, and LC. The lesions led to a dramatic reduction in hippocampal NE, without altering levels of dopamine and serotonin, along with reduced hippocampal P3s. Similar reductions were not evident for early hippocampal ERP components. Indeed, lesions led to increased early ERP components at cortical leads.

Finally, one study has analyzed P3 changes in three human patients who survived stroke damage in the pontomesencephalic junction (Fukaya, Katayama, & Kurihara, 1999). In each patient, the LC region was destroyed, as indicated by MRI. All three patients were in a comatose or vegetative state and showed no recognizable responses indicative of cognitive processing. It is important to note that this in itself is not predictive of whether or not a P3 will be observed because some comatose patients have been reported to elicit P3 potentials in a passive oddball paradigm (cf. Reuter & Linke, 1989). None of the stroke patients showed a P3 to visual or auditory oddball stimuli or to mild somatosensory shocks, with the exception of one patient who showed a reliable P3 only to visual stimuli. Nevertheless, these results should be interpreted with caution because the lesions were not confined to the LC region and potentially included important sensory pathways (measurements to control for this possibility were only partially reported, if at all). Indeed, the patient with the intact visual P3 had a more focal lesion than the other two patients. Then again, this patient was investigated 8 years after the stroke onset, perhaps allowing for the possibility that the observed P3 activity was due to the gradual emergence of compensatory changes in the LC-NE system (see Berridge & Waterhouse, 2003, for a discussion of plasticity of the LC-NE system).

Involvement of Other Neurochemical Systems

The pharmacological and lesion studies reviewed above provide substantial evidence for a crucial role of the LC-NE system in P3 generation, with some indications that the strength of this relationship is contingent on stimulus modality. Some of these studies have also highlighted the TPJ as a specific site of noradrenergic effects, consistent with the important role of this region in P3 generation. However, other neurochemical systems almost certainly influence the P3 as well (including glutamatergic and cholinergic systems; for reviews, see Frodl-Bauch et al., 1999; Hansenne, 2000). There is considerable overlap between the projection

sites of some of these systems, and their interactions are complex and not yet well understood, making it hard to identify the specific influence of each system. Nevertheless, doing so and distinguishing the effects of the different neurotransmitter systems are important goals for many reasons (not the least of which is the hope of providing a rational approach to pharmacological intervention in pathology).

There is some evidence that the P3 is affected by pharmacological manipulation of glutamate, the most prevalent excitatory neurotransmitter system, and GABA, the most prevalent inhibitory neurotransmitter system (cf. Frodl-Bauch et al., 1999). As discussed above, it is well known that the presence of NE increases the effects of these neurotransmitters on neurons in the cortex and elsewhere. Indeed, the interaction between NE and other active substances may result in regional specificity of an otherwise global modulatory effect of synaptically released NE (for an example with NE and the neuropeptide VIP, see Magistretti & Morrison, 1988).

There is also strong evidence for the influence of the cholinergic system on P3 generation. For instance, it has repeatedly been shown that the anticholinergic drug scopalamine decreases the amplitude and increases the latency of the P3 in humans (e.g., Hammond, Meador, Aung-Din, & Wilder, 1987; Meador et al., 1987). Furthermore, lesions to the nucleus basalis of Meynert, the primary source of neocortical acetylcholine, result in a significant amplitude reduction of the P3 in rabbits (Wang et al., 1997). At the same time, other studies have complicated this picture. For example, one study examined the effect of radiofrequency lesions to the medial septal area on the scalp-recorded P3 in cats (Harrison, Buchwald, Kaga, Woolf, & Butcher, 1988). The medial septal area is a major, largely cholinergic source of input to the hippocampus, and destruction of this area led to a marked acetylcholine depletion in hippocampus and cingulate and enthorinal cortex. This was associated with a transient enhancement followed by the disappearance of scalp-recorded P3 activity. Postmortem histology indicated that there was no acetylcholine depletion in neocortical areas (including those implicated in P3 generation), raising questions about how the P3 disappearance was related to the effects of the lesions on the cholinergic system. It is interesting to note that the general region of the medial septal area receives a relatively dense noradrenergic innervation and is thought to serve a critical role in the modulation of forebrain EEG activity (cf. Berridge & Waterhouse, 2003). Thus, it is possible that this area serves as a way station, mediating the effects of NE release on the cortex. At the same time, it is important to note that many ascending LC fibers projecting to the cortex traverse this region, raising the alternative possibility that lesions to this area affected the P3 by disrupting direct projections from the LC to the cortex (i.e., the fibers of passage problem). Harrison et al. (1988) showed that two control animals, with lesions just anterior of the medial septal area, showed intact postoperative P3s. Unfortunately, the authors did not measure NE depletion in the experimental and control animals. Together, these findings and the well-documented role of the cholinergic system in the regulation of attention (e.g., Robbins, 2002) indicate that future research needs to explore the distinct contributions of NE and acetylcholine as well as interactions between these systems in P3 generation (e.g., Cape & Jones, 1998; cf. Wang et al., 1997).

Human pharmacological studies have yielded conflicting results regarding the effect of dopamine and serotonin on the P3 (Hansenne, 2000). Many of the studies that found an effect of dopaminergic or serotonergic receptor agents on the P3 were carried out with psychiatric patients in the absence of a control group, complicating the interpretation of the results. Critical evidence against an important role of the dopamine system and serotonin system in P3 generation was reported by Ehlers, Wall, and Chaplin (1991). These authors investigated the effects in rats of neurochemical lesions of the ventral tegmental area, a major source of dopaminergic projections to the forebrain. These lesions were found to produce a 30–46% reduction in dopamine but did not significantly alter intracranially recorded P3-like potentials (see also Ehlers & Chaplin, 1992). Likewise, pharmacologically induced depletions (50%) of serotonin in a second group of rats led to significant reductions in early negative evoked potentials but left late positive potentials unaffected. Thus, among neuromodulatory systems, the prevailing evidence suggests that whereas the LC-NE and possibly the cholinergic systems play a critical role in P3 generation, the dopamine and serotonin systems do not.

The LC-NE System and Behavior

Evidence for the role of NE in behavioral performance comes from two separate lines of research: (a) lesion and pharmacological studies that have examined the effect of disturbances of the LC-NE system on discrimination performance and distractibility and (b) electrophysiological research in nonhuman species that has correlated activity of the LC-NE system with indices of task performance.

Response Accuracy

Robbins and colleagues (Carli, Robbins, Evenden, & Everitt, 1983; Cole & Robbins, 1992) investigated the effects of destruction of the dorsal noradrenergic ascending bundle on performance of rats in a variant of the continuous performance task, requiring sustained monitoring for visual target stimuli that could occur in five different locations. Animals showed impaired target-discrimination performance (more false alarms and missed targets) and prolonged reaction times but only when bursts of loud white noise were interpolated just prior to the presentation of each stimulus or when the interstimulus interval was made unpredictable. Other studies have reported that NE-depleted rats are significantly more distracted by irrelevant stimuli during discrimination learning (Oke & Adams, 1978; Roberts, Price, & Fibiger, 1976). Furthermore, Clark, Geffen, and Geffen (1987, 1989) have shown that administration of clonidine (presumably reducing LC-NE activity) affects human target-detection performance under focused and divided attention conditions in a dichotic listening task and reduces the costs of invalid spatial cues in a covert spatial attention task. All of these findings are consistent with the suggestion that reducing LC-NE activity impairs task-focused performance.

In human participants performing a continuous performance task, clonidine has also been found to impair the sensitivity of target-detection performance while leaving response criterion unaffected (Coull, Middleton, Robbins, & Sahakian, 1995). In addition, the drug atipamezole, which increases NE release in the brain, improved signal-detection performance of rats when tested under

data-limited conditions (Sirvio et al., 1993). Finally, Selden and colleagues showed that lesions of ascending LC fibers produced deficits in responding to explicit cues but enhancements in contextual conditioning in both (cold) water maze (Selden, Cole, Everitt, & Robbins, 1990) and conditioned suppression tests (Selden, Robbins, & Everitt, 1990), consistent with a role of the LC system in focusing of attention.

The above findings suggest that experimenter-induced manipulations of LC-NE function have a large impact on performance in attention-demanding tasks, particularly under high-demand conditions. Corroborating these findings, several studies have found that natural variations of LC activity in the monkey show striking correlations with changes in performance (e.g., Aston-Jones et al., 2000; Aston-Jones, Rajkowski, et al., 1994; Usher et al., 1999). As noted earlier, it was found that variations in tonic LC activity were closely associated with changes in performance on the oddball task. Specifically, periods of good performance (high signal-detection accuracy) were associated with moderate levels of LC tonic activity, and consistent LC phasic responses to target stimuli. In contrast, periods of higher tonic LC activity and the absence of LC phasic responses were associated with poor performance, characterized by hyperactive behavior, greater distractibility (indexed by failures to fixate prior to stimulus delivery), increased false-alarm rates, and a slowing and widening of the reaction time distribution. Furthermore, irrespective of tonic discharge rate, LC phasic responses were preferentially observed for hits compared with false alarms (Aston-Jones, Rajkowski, et al., 1994; Rajkowski et al., 2004). Thus, it appears that modest tonic activity and LC phasic responses are closely associated with accurate signal discrimination in monkeys performing the oddball task.

Additional evidence suggests that the LC activity plays a causal role in oddball task performance (Ivanova, Rajkowski, Silakov, Watanabe, & Aston-Jones, 1997). In a monkey exhibiting elevated tonic discharge rates and poor oddball task performance (associated with a high degree of distractibility and task-unrelated motor activity), microinfusion of clonidine into the LC suppressed tonic LC activity, enhanced phasic responses, and significantly improved task performance. Conversely, in monkeys performing the task well, activation of LC neurons by local microinjection of the cholinergic agonist pilocarpine disrupted task performance, presumably by increasing LC tonic activity into the range in which phasic responses are diminished.

Reaction Time

The work discussed above has focused primarily on behavioral accuracy and its correlation with the magnitude of LC phasic responses. In contrast, two recent primate studies have examined in detail the relationship between reaction time and the timing of LC phasic responses in two-alternative forced-choice tasks (Clayton et al., 2004; Rajkowski et al., 2004). These studies found that LC phasic responses consistently preceded behavioral responses by ~200–250 ms. Furthermore, the latencies of LC and behavioral responses showed a strong covariation as a function of differing levels of stimulus discrimination difficulty (see also Aston-Jones et al., 1997). These findings were confirmed by examining response-locked histograms of LC activity, which revealed a much tighter distribution of LC responses than stimulus-locked histograms. Thus, the latency of the LC phasic response varied with reaction time not only across conditions differing in task difficulty but also on a trial-to-trial basis, indicating a close temporal relationship between LC and behavioral responses (see also Bouret & Sara, 2004).

A Theory of the Role of the LC-NE System in Information Processing

If the LC-NE system is responsible for the P3, then one should be able to exploit knowledge about the information-processing function of this system to better understand the functional significance of the P3. The findings discussed above concerning the relationship of LC activity to task performance and the effects of NE at the neural level have recently led to the development of a theory concerning the role of the LC-NE system in cognitive function (Aston-Jones et al., 2000; Cohen, Aston-Jones, & Gilzenrat, 2004; Usher et al., 1999). According to this theory, LC tonic and phasic responses play complementary roles in regulating the state of cognitive processing. Together, these are hypothesized to regulate the balance between exploratory versus specific, goal-directed (e.g., task-focused) behavior (Usher et al., 1999). Specifically, when LC tonic activity is high and phasic responses are absent, the sustained, widespread, and indiscriminant increase of neuronal responsivity to inputs (associated with ongoing NE release) allows the system to respond to a broad class of events, as required during exploratory behavior. In contrast, moderate levels of LC tonic activity that are associated with LC phasic responses to target stimuli ensure that, in this mode, enhanced signal processing and behavioral responses are restricted to task-relevant stimuli. That is, with lower levels of NE release at baseline, the system is overall less responsive to external events. However, target events elicit an LC phasic response, which produces a transient increase in NE release and therefore an adventitiously timed increase in responsivity, which facilitates the response to the target. Thus, in the phasic mode, the LC functions as an attentional filter that selects for the occurrence (i.e., timing) of task-relevant stimuli, much as cortical attentional systems filter the content of a stimulus. The existence of such a temporal filter is consistent with several recent psychophysical studies (e.g., Coull & Nobre, 1998). At the same time, by increasing the gain of cortical representations, the LC phasic response can also enhance the effects of cortical selection by content (e.g., the top-down modulation by prefrontal cortex). Together, these effects allow the LC phasic response to selectively facilitate responses to task-relevant stimuli when they occur. In the next section, we use the insights offered by this theory to leverage an understanding of the relationship between the P3 and task performance. First, however, it is important to briefly review how the theory relates the LC phasic response to information-processing and, in particular, decision-making processes.

An impressive convergence of theory and data from mathematics, psychology, and neuroscience has begun to suggest that decision-making processes (at least under conditions of two-alternative forced choice) can be simply but accurately characterized as a random walk (Laming, 1968; Stone, 1960) or its contin-

uous equivalent, a drift-diffusion process (Ratcliff, 1978).[3] Mathematically, this is the optimal decision-making process—by that, we mean the process that provides the quickest response for a fixed level of accuracy or, conversely, generates the highest accuracy (and therefore, presumably, reward) for a fixed time interval (e.g., Wald, 1947). Psychologically, it appears to accurately characterize reaction time latency distributions and error rates in a number of two-alternative forced-choice tasks (e.g., Ratcliff, 1978; Ratcliff, Van Zandt, & McKoon, 1999) and can be used to predict parameters of the decision-making process (e.g., speed–accuracy trade-off; Bogacz et al., 2004). Neuroscientifically, it explains the dynamics of neuronal activity and the relationship of this activity with decision-making behavior (Hanes & Schall, 1996; Ratcliff, Cherian, & Segraves, 2003; Roitman & Shadlen, 2002). The specifics of this theory are beyond the scope of this article (for a review and detailed discussion, see Bogacz et al., 2004). However, what is relevant here is that the drift-diffusion process is most simply and most faithfully implemented by a single-layer neural network that computes the difference in evidence favoring the two alternatives (Bogacz et al., 2004; Usher & McClelland, 2001).

This requirement for single-layer computation, however, is in tension both with what is known about the brain and with its need to flexibly integrate information at multiple layers. That is, tasks may vary widely with regard to the level of information needed to determine a correct response. For example, one task may require that subjects discriminate targets from distractors based on a low-level perceptual feature, such as color, size, or orientation. Others may require a discrimination on much higher level features, such as semantic category (e.g., living vs. nonliving) or even more abstract properties (e.g., odd or even). Thus, it is not surprising that neural processing involves multilayered networks that are capable of integrating information and making discriminations at many levels of processing. Nevertheless, our theory maintains that for any given decision of a two-alternative forced-choice type, there is some single locus or layer that has the relevant information and that implements the diffusion process. Critically, the theory holds that all levels of processing beyond this layer are irrelevant to the decision and simply contribute noise and additional time to the response. This is where we believe the LC phasic response has its role.

First, we assume that the LC phasic response is driven by the outcome of the decision process. That is, the LC phasic response is driven by activity of units representing the winning alternative and is elicited as soon as this crosses the decision threshold. Second, we hypothesize, as discussed earlier, that the LC phasic response rapidly increases gain throughout the system (see Figure 1). This has the effect of driving responses in all layers of processing subsequent to the decision layer by the outcome of processing in the decision layer, functionally collapsing the multilayered system into a single layer once the decision has been made. Indeed, analyses have shown that adding an LC-like mechanism to a multilayered decision network allows it to approximate the (provably optimal) performance of a single-layer system (Brown, Gilzenrat, & Cohen, 2004).

This theory concerning the function of the LC phasic response is consistent with previous modeling work regarding the physiology and dynamics of LC activity (e.g., Gilzenrat, Holmes, Rajkowski, Aston-Jones, & Cohen, 2002; Usher et al., 1999), as well as empirical observations regarding the LC phasic response (e.g., Aston-Jones, Rajkowski, et al., 1994; Clayton et al., 2004). For example, the observation that the LC phasic response is driven by target stimuli and in fact acquires these more quickly than the behavioral response in reversal conditioning is consistent with the hypothesis that it is responsive to the earliest outcome of decision making in the brain. The theory also provides a natural account for the fact that LC phasic responses are more closely time-locked to response than sensory events (Bouret & Sara, 2004; Clayton et al., 2004). Variability in the duration of the decision process explains variability in the latency of the LC phasic response with respect to stimulus onset. In contrast, because the LC phasic response facilitates (accelerates) the behavioral response and because this is a stereotypic influence, the overt response is tightly time-locked to that of the LC. This is in fact what has been observed in both simulations and empirical data.

It is important to make one final comment concerning what our theory has to say about the events that drive the LC phasic response that is directly relevant to our consideration of the P3. So far, we have assumed that the LC phasic response is driven by a task-relevant decision process and serves to facilitate responding to the outcome of this process to optimize performance. This explains why the LC phasic response typically occurs to target stimuli (for which an action is required) and not to distractors (for which no action is required) or to false alarms (which are assumed to represent and have been successfully modeled as erroneous activation of representations in response layers past the decision process). However, as we have discussed above, the LC (and P3) also responds to highly salient environmental stimuli, even if these are task irrelevant. For example, a loud sound or an appetitively significant stimulus (e.g., the unexpected appearance of a strong reinforcer) can elicit an LC phasic response. The theory can accommodate this observation if we include one other assumption: Motivational significance is a relevant criterion for eliciting an LC phasic response.

Task-relevant stimuli can certainly be assumed to have motivational significance that has been acquired through training in the task. We need simply assume that other types of stimuli may be prewired to have motivational significance because they are inherently reinforcing (e.g., appetitive stimuli) or because of the evolutionary adaptive advantage of encoding them as such (e.g., intense or otherwise threatening stimuli). We assume that such stimuli have preferential access to decision-making processes (such as subcortical processing pathways; e.g., LeDoux, 1996) and that the outcome of these decision-making processes are assigned motivational significance in the same way as are task-relevant stimuli. The latter is consistent with the anatomic distribution of

[3] In two-alternative forced-choice tasks, a choice must be made between two responses based on limited information about which response alternative is correct. The diffusion model (which is a continuous version of the random walk model) assumes that the stimulus signal is associated with noise and that thus, at any point in time, there is uncertainty about which response alternative is correct. Therefore, the decision process integrates the difference in the information favoring each alternative over time. The average increase in evidence supporting the correct alternative per unit of time is called the *drift rate*. The model reaches a decision when the magnitude of the difference in information favoring each alternative reaches some critical value: the *threshold*.

afferent projections to the LC. For example, subcortical sources of afferent regulation of the LC and peri-LC area include the rostral ventrolateral medulla (Aston-Jones, Ennis, Pieribone, Nickell, & Shipley, 1986) and, possibly, the amygdala (Van Bockstaele, Chan, & Pickel, 1996), regions thought to be involved in the activation of the sympathetic nervous system, the control of eye movements, and emotional conditioning. Thus, at least on anatomic grounds, it is plausible that the influence of decision-making processes on the LC phasic response may be mediated by concurrent processing in subcortical structures that evaluate motivational significance. Thus, the preferential access assumption offers an explanation of why P3s can be elicited by motivationally significant events that are not immediately relevant to the task at hand.

The P3 and Behavior

According to the theory of LC function discussed above, the LC-NE system facilitates the responding to motivationally significant stimuli via a phasic postdecision release of NE. This mechanism provides an explanation of the observed correlation between activity of the LC-NE system and behavioral performance (discussed in the section The LC-NE System and Behavior, above). If the P3 reflects the impact of phasic NE release in neocortical areas, then, according to our theory of LC function, the P3 should also be closely associated with the speed and accuracy of responding. As is described in this section, the P3 literature is consistent with this hypothesis.

Response Accuracy

Previous research has established that there is a close relationship between P3 amplitude and the accuracy of signal detection: Stimuli that elicit a large P3 have a higher chance of being accurately discriminated. This relationship has led researchers to hypothesize that P3 amplitude reflects the degree of confidence felt by participants in their perceptual decisions (Hillyard, Squires, Bauer, & Lindsay, 1971). However, it should be kept in mind that the observations held in support of this relationship are correlational in nature. Therefore, if any direct causality underlies the correlation between the P3 and signal processing, this may well be in the reverse direction from that suggested by Hillyard et al. (1971). That is, the quality of signal processing may improve because the process indexed by the P3 has been activated to a greater extent. This is the direction of causality suggested by the LC-P3 hypothesis.

Systematic evidence for a link between P3 amplitude and the accuracy of signal processing comes from classical signal-detection experiments, in which participants have to decide on each trial whether or not a barely perceptible, sensory signal is present in continuous background noise. Typically, the signal is present on a random 50% of the trials, and the critical time interval is indicated by a perceptual marker in another sensory modality. This marker informs participants when to expect a possible signal and allows time-locking of the EEG signal for signal-absent trials. ERPs can then be computed separately for detected signals (hits), failures to detect signals (misses), incorrect reports of signal presence (false alarms), and correct reports of signal absence (correct rejections). The general findings have been a large P3 for hits, its amplitude varying with the degree of confidence with which the detection was made, and a small or absent P3 for misses (Cael, Nash, & Singer, 1974; Hillyard et al., 1971; Sutton, Ruchkin, Munson, Kietzman, & Hammer, 1982; Wilkinson & Seales, 1978). On signal-absent trials, the P3 is also generally small or absent, except for when the participant is extremely confident that a signal was present (K. C. Squires, Squires, & Hillyard, 1975).

Further evidence indicates that P3 magnitude increases monotonically as a function of d', an index of signal-detection sensitivity that is independent of participants' response bias. For instance, various signal-detection studies have reported a positive correlation of P3 amplitude on hit trials and d' across a range of signal intensities (e.g., Hillyard et al., 1971; Wilkinson & Seales, 1978). In another study, participants performed an automatic visual search (pop-out) task concurrently with a visual discrimination task (Hoffman, Houck, MacMillan, Simons, & Oatman, 1985). The relative importance of each task was systematically varied by instructions. ERPs revealed two consecutive P3 potentials, one associated with each task stimulus, that varied directly with the degree of attention paid to the corresponding task (cf. Wickens et al., 1983). It is important to note that, for both tasks, d' for accuracy of performance varied directly as a function of P3 amplitude across the various attention conditions.

P3 magnitude also varies with performance in signal-discrimination and recognition tasks. For example, in a study by Ritter and Vaughan (1969), participants had to discriminate between infrequent target stimuli and highly similar, frequent nontarget stimuli in a visual and an auditory condition. In both conditions, a P3 was observed only to detected targets and not to missed targets and nontarget stimuli. Parasuraman and colleagues (Parasuraman & Beatty, 1980; Parasuraman, Richer, & Beatty, 1982) examined signal detection and recognition within the same study. On half of the trials, participants were presented with a faint acoustic signal, at one of several frequencies, in the presence of noise. On the remaining trials, noise alone was presented. At the end of each trial, participants were to indicate, on a four-category confidence-rating scale, whether they had detected a signal and to press a key to indicate the frequency of the signal. The authors found that on signal-present trials, P3 amplitude varied directly with the degree of confidence that a signal had been presented and more so for correctly recognized signals than for incorrectly recognized signals. In addition, the P3 was significantly reduced for incorrect recognitions, especially if the recognition error was large (i.e., when two distant sound frequencies were confused by the participant). In line with this, it was found that P3 amplitude accurately predicted recognition performance on a trial-by-trial basis.

In sum, under the attention-demanding circumstances presented by signal-detection and recognition tasks, P3 amplitude varies directly with detection and recognition performance on signal-present trials. This is consistent with the LC-P3 hypothesis, according to which the P3 reflects a phasic increase in the response of neocortical neuronal assemblies to the detection (i.e., a threshold crossing in the decision process) of a motivationally salient event. Accordingly, the P3 is generally small or absent on signal-absent trials. This is consistent both with the LC-P3 hypothesis and with the findings reviewed earlier concerning the antecedent conditions for the P3 and the LC phasic response: In oddball tasks, these are largely restricted to trials on which a target is presented and detected.

Reaction Time

Another prediction following from the theory of LC function concerns the relationship between P3 latency and reaction time. In particular, given the close temporal relationship between LC latency and reaction time, P3 latency and reaction time should also covary as a function of (a) experimental factors known to affect the duration of the decision process and (b) incidental trial-to-trial fluctuations in processing speed.

The joint effect of experimental variables on P3 latency and reaction time has been the topic of numerous studies, which have been subjected to a rigorous meta-analysis by Verleger (1997). The results of this meta-analysis are broadly consistent with the LC-P3 hypothesis. Factors that increase the duration of the decision process by affecting the speed of evidence accumulation (or drift rate; e.g., stimulus degradation, reduced stimulus intensity, increased display size in visual conjunction search) have generally been found to increase P3 latency and reaction time by a similar amount. In contrast, factors that can be assumed to affect postdecisional processing (e.g., complexity of the response) slow down reaction time while leaving P3 latency essentially unchanged. A more complicated and divergent pattern of results is obtained for tasks that elicit conflicting response tendencies (e.g., the Simon, Stroop, and Eriksen flankers tasks) or that require the use of an untrained stimulus–response (S-R) mapping (e.g., spatial S-R compatibility tasks) with some of these tasks (Simon, Eriksen) showing relatively high sensitivity of P3 latency to changes in reaction time and others (Stroop, spatial compatibility) showing lower sensitivity. Although potentially important, there are two factors that complicate a straightforward interpretation of these results in terms of the LC-P3 hypothesis. First, at least for some of these tasks, there is currently no clear consensus regarding the relative degree to which various stages of information processing are affected by the critical task manipulations (see, e.g., Magen & Cohen, 2002). Second, our LC theory is based on neurophysiological and mathematical models of decision making that in turn are based almost exclusively on data from very simple two-alternative forced-choice tasks. At present, it is unclear to what extent the key principles in these models generalize to tasks involving conflicting sources of information. In such tasks, the dynamics of the decision processes may vary considerably from simpler ones (e.g., Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988) and may even involve more than one decision process (cf. Sato & Schall, 2003). At the moment, our theory does not address how these may drive the LC phasic response. At the very least, however, we do predict that the latency of LC and P3 responses should covary in such tasks.

P3 latency has also been shown to correlate with trial-to-trial variability in reaction times obtained in two-alternative forced-choice tasks. Ritter, Simson, and Vaughan (1972), using an auditory oddball task, found significant correlations (ranging between .50 and .79 for single participants) between single-trial P3 latency and reaction time. Furthermore, they showed that the frequency distribution of P3 latencies had a similar shape to the distribution of reaction times. Kutas, McCarthy, and Donchin (1977) found that when task instructions emphasized response accuracy over response speed in a visual oddball task, reaction times and single-trial P3 latencies were highly correlated, the response generally following the P3. In contrast, the correlation between P3 latency and reaction time was substantially reduced in a condition in which response speed was emphasized, a finding that we consider in the Discussion, below. The interaction among response accuracy, P3 latency, and reaction time is further illustrated by the observation that for trials with a given reaction time, accuracy is higher when P3 latency is short than when it is long (Coles, Gratton, Bashore, Eriksen, & Donchin, 1985). This observation seems consistent with the notion that the accuracy of responding benefits from a timely noradrenergic modulation, reflected in the P3.

Since the study of Kutas et al. (1977), few studies have examined the relationship between P3 latency and reaction time (e.g., Goodin, Aminoff, & Mantle, 1986; Makeig et al., 2004; Verleger, 2004), and these results have been mixed. Some studies have found a clear positive correlation between the two variables (e.g., Makeig et al., 2004; Pfefferbaum, Ford, Roth, & Kopell, 1980), with the P3 immediately following the response. Other studies, comparing average stimulus- and response-locked P3s, have noted that the P3 seems more or less equally time-locked to the stimulus as to the response. However, even if the P3 process is in principle time-locked to the response, this finding would be expected if the variability in reaction time is low. Unfortunately, these studies typically have failed to report the behavioral results necessary to evaluate this possibility.

The studies cited above have found that, at least in two-alternative forced-choice tasks, the P3 generally occurs around the time of the response. At first consideration, the relative timing of these two events may seem inconsistent with the LC-P3 hypothesis, which claims that the process underlying the P3 facilitates responding and so must occur before the response. However, this inconsistency may be due to conventions on how P3 latency is measured. Typically, this is defined with respect to the component peak, presumably because this aspect of the component is easiest to measure. Nevertheless, it may be arbitrary to measure the peak as opposed to some other feature of the P3, such as it its onset, which typically occurs well before the response (cf. Coles, Smid, Scheffers, & Otten, 1995). Insofar as the P3 reflects the influence of the LC phasic response in neocortical structures, onset may indeed be a more sensitive measure of the function of this system and its relationship to response facilitation (e.g., Clayton et al., 2004). Furthermore, as elaborated above, there may be a delay between the noradrenergic modulation assumed to facilitate responding and the onset of the electrophysiological signature of this modulation at the scalp. Thus, an evaluation of the LC-P3 hypothesis in the light of P3 peak latency data may be misleading if it does not take into account that the process of interest precedes the P3 peak by a relatively constant (but as yet not precisely known) time interval.

Discussion

According to the LC-P3 hypothesis, the P3 component of the scalp-recorded event-related brain potential reflects an NE-induced phasic enhancement of neural responsivity (gain) in neocortex. This enhancement is triggered by the outcome of a task-relevant decision process (e.g., stimulus categorization), which then facilitates responding based on the decision. This effect may be viewed as a time-locked heightening of selective attention, such that the probability is increased that the detection of incoming sensory signals is appropriately acted on via selective response facilitation (rather than sensory filtering). The literature review presented here is broadly consistent with

this hypothesis. The review indicates that (a) the timing and distribution of intracranial and scalp-recorded P3 activity are consistent with the anatomical and physiological properties of the LC-NE system; (b) P3 generation is dependent on normal functioning of the LC-NE system, as demonstrated by lesion and pharmacological studies; (c) the antecedent conditions for the P3 are highly similar to those for the LC phasic response—both are preferentially elicited by novelty, motivational significance (e.g., task relevance), and other salient stimulus characteristics that are potentially important for survival and goal-directed behavior; and (d) the functional role ascribed to the LC-NE system is consistent with the tight link between the P3 and the speed and accuracy of information processing. It is also likely that the LC-NE system interacts with other neurochemical systems in producing P3 activity. However, the influence of this interaction on cognition and the genesis of electrophysiological activity is not well understood. This provides a strong motivation for future neurophysiological research and computational modeling efforts that address interactions between neurochemical systems.

In elaborating the LC-P3 hypothesis, we have discussed a recently developed theory of the function of the LC-NE system that can accommodate key findings regarding the relationship between the P3 and task performance (Aston-Jones et al., 2000; Cohen et al., 2004; Usher et al., 1999). This is an important advance, especially because this theory is based on firm neuroscientific knowledge and is mechanistically explicit, thereby lending itself to empirical investigation. As elaborated above, the theory suggests that the neural system that generates the P3 is responsive to the outcome of simple decision-making processes: It is not responsible for the decision-making process itself, but instead, it acts to optimize information processing by modulating postdecision response processes. At the same time, in its present form, the theory leaves open important questions. For example, the theory assumes that only the outcome of motivationally significant decision processes drives the LC phasic response. However, what determines which processes are motivationally significant, and how do these come to influence the LC? One approach to answering these questions is to consider which brain structures project to the LC. Beyond inputs from multiple other brain stem nuclei (reviewed in Berridge & Waterhouse, 2003), the LC or peri-LC area receives afferent drive from a variety of sources including the prefrontal cortex (Arnsten & Goldman-Rakic, 1984; Jodo, Chiang, & Aston-Jones, 1998), anterior cingulate cortex (Rajkowski, Lu, Zhu, Cohen, & Aston-Jones, 2000), and orbitofrontal cortex (Aston-Jones et al., 2002). These structures are known to be important in decision making, in signaling novelty, and in representing task goals and affective value. It may be argued that they are, therefore, in an excellent position to evaluate the importance of information currently being processed and codetermine which information drives the LC phasic response. Furthermore, it appears that these relationships can be learned, as evidenced by the findings reviewed above that, in reversal conditioning, the LC acquires the new target before the motor system. However, what learning systems are engaged and how these operate are still unknown.

New Predictions and Theoretical Implications

The LC-P3 hypothesis offers a theoretical framework that allows the separate research literatures on the LC-NE system and P3 each to inspire new predictions and research within the other domain. Because empirical knowledge about the P3 exceeds that of the LC, cross-domain predictions regarding functional sensitivity mainly concern the LC. For example, a critical prediction for future research is that the size of the LC phasic response should display a similar sensitivity to previous trial type as has been observed for oddball P3 amplitude (cf. Swick, Pineda, Schacher, & Foote, 1994). Similarly, like the oddball P3, the LC phasic response should increase with increases in target-to-target interval (Croft et al., 2003). As a third example, it has repeatedly been found that the P3 can also be elicited by the absence of a stimulus when that absence delivers important information to the subject (e.g., Sutton, Tueting, Zubin, & John, 1967). Although it has been shown that rat LC cells show a vigorous LC response to the unexpected absence of a shock (Sara, Vankov, & Herve, 1994), it remains to be seen whether this result generalizes to other situations.

A fourth prediction concerns the close relationship between P3 latency and reaction time observed when accuracy of responding is stressed (Kutas et al., 1977). As noted, similar results have been reported for the onset of the LC phasic response and reaction times in primate studies in which reward is primarily linked to response accuracy; that is, LC phasic activation reliably precedes and is temporally linked to behavioral responses to attended stimuli (Bouret & Sara, 2004; Clayton et al., 2004; Rajkowski et al., 2004). It is interesting to note that a different pattern of results was found by Kutas et al. (1977) in a condition in which task instructions stressed speed over accuracy. In this condition, the correlation between reaction times and P3 latencies was low, and many responses occurred well before the P3. Not surprisingly, accuracy associated with these responses was relatively low, presumably because subjects responded prior to the complete evaluation of the stimulus allowed by the P3 process (cf. Holroyd, Yeung, Coles, & Cohen, 2005). This finding predicts that if monkeys are primarily rewarded for the speed (as opposed to accuracy) of their responses, this should substantially decrease the temporal contingency between LC phasic responses and reaction times. Finally, the LC-P3 hypothesis predicts that LC latency, like P3 latency, should not increase with RT as a function of factors that increase the complexity of the response.

Conversely, the LC literature may motivate new P3 research and shed new light on existing findings. For example, previous research has reported a strong correlation between pupil dilation and LC activity, suggesting that pupil dilation may be used as a noninvasive index of LC activity in research with human participants (Gilzenrat, Cohen, Rajkowski, & Aston-Jones, 2003; Rajkowski, Kubiak, & Aston-Jones, 1993). Although there is some evidence that P3 amplitude covaries with pupil dilation as a function of systematic changes in stimulus probability (Friedman, Hakerem, Sutton, & Fleiss, 1973), to our knowledge it has not been examined whether pupil dilation also correlates with more transient (i.e., trial-to-trial) fluctuations in P3 amplitude.

Another example concerns the relationship between P3 magnitude and arousal state. As noted earlier, LC phasic responses are primarily observed when LC tonic activity (and arousal) is at a moderate level and the subject is engaged in the task. From this, it follows that P3s should be smaller under conditions of low or excessive arousal. Accordingly, it is known that the P3, if present at all, is strongly reduced during sleep and in a presleep stage (Atienza, Cantero, & Escera, 2001). Furthermore, it has been argued that ADHD, charac-

terized by an overaroused state, may be due to abnormally high baseline levels of tonic LC activity (cf. Aston-Jones et al., 2000). This hypothesis is supported by the fact that both indirect and direct noradrenergic agonists are effective in the treatment of ADHD (for review, see Pliszka, 2001). If ADHD is associated with increased tonic LC activity, then ADHD patients should have reduced LC phasic responses and, according to the LC-P3 hypothesis, reduced P3 amplitudes. Indeed, ADHD is associated with robust reductions in P3 amplitude (for review, see Barry, Johnstone, & Clarke, 2003). As reviewed by Duncan (2003), similar arguments may apply to the finding of abnormal P3s in other psychopathologies involving dysfunctioning of the LC-NE system such as posttraumatic stress disorder (Aston-Jones, Valentino, Van Bockstaele, & Meyerson, 1994; McFarlane, Weber, & Clark, 1993). More generally, research on the P3 in psychiatric disorders such as schizophrenia (Jeon & Polich, 2003) and alcoholism (Polich, Pollock, & Bloom, 1994) may provide valuable information regarding possible noradrenergic dysfunction in these populations.

The LC-P3 hypothesis may also shed some light on differences in the scalp topography of the P3 under different experimental conditions. As discussed earlier, this hypothesis assumes that the neuromodulatory effect of NE is to enhance processing in target areas. That is, brain areas that are most engaged by a given task should show the greatest increases in activity. Thus, the effects of the LC-NE system, presumed to be reflected in the P3, should be greatest in areas specific to a given task. This may explain, for example, the difference in scalp topography between the P3a and P3b: The more anterior focus of the P3a may reflect the greater contribution of prefrontal structures to novelty processing (Knight, 1984), an effect that is enhanced by LC-NE engagement. A similar explanation may apply to changes in P3 scalp distribution that have been observed as a function of sensory modality and experimental paradigm (cf. Johnson, 1993; Pineda, 1995). Subcortical structures such as the LC might also serve to increase the functional integration or connection between active brain regions (cf. Picton, 1992). Tentative evidence for this view has been reported by Coull, Büchel, Friston, and Frith (1999). Using functional connectivity analysis, an application of structural equation modeling to human brain imaging data, these authors showed that administration of clonidine during performance of an attentional task modulated the strength of functional interactions between distant brain areas including frontal cortex, parietal cortex, thalamus, and LC. According to the LC-P3 hypothesis, these effects should be reflected in the P3, suggesting the interesting prediction that there should be increased coherence among areas showing the greatest P3. This could be tested using modern time-frequency analysis techniques (cf. Gross et al., 2004).

Relationship Among the P3, the LC-NE System, and the Attentional Blink

The LC-P3 hypothesis may have particularly interesting implications for an understanding of the attentional blink, a well-studied attentional phenomenon: When presented with a rapid serial visual presentation stream (at about 10 Hz) containing two target stimuli and multiple distractors, participants are typically impaired at the detection or identification of the second target when this follows correct detection or identification of the first target. This deficit, the attentional blink, lasts from about 200 to 500 ms following presentation of the first target, after which performance recovers (Raymond, Shapiro, & Arnell, 1992). It has been noted that the timing of the attentional blink coincides with a period of refractoriness in LC activity (due to activation of autoinhibition in the LC) that follows a phasic burst of LC activity (Usher et al., 1999). Thus, it has been hypothesized that the attentional blink may be mediated by the momentary unavailability of the LC phasic response (and attendant noradrenergic potentiation of information processing) following the LC response to the first target (Nieuwenhuis et al., in press). To test this hypothesis, simulations were run, using a computational model of LC activity and its impact on target-detection performance (Gilzenrat et al., 2002). The model accurately simulated the time course of the attentional blink, including *Lag 1 sparing,* the finding that processing of the second target is more or less spared if the second target immediately follows the first target without intervening distractors (i.e., at Lag 1; Raymond et al., 1992).

This hypothesis concerning the mechanisms that underlie the attentional blink also offers an account of the link between the attentional blink and the P3. Assuming that noradrenergic effects in neocortical target areas (i.e., an increase in neural responsivity) and the LC (autoinhibition) show a similar temporal profile (with the former shifted in time with respect to the latter because of the propagation delay to the neocortex), the hypothesized electrophysiological (P3) and behavioral (attentional blink) correlates of these physiological actions should show a similar duration and covary in size.[4] Indeed, this has been confirmed for the attentional blink and the P3 elicited by the first target in a rapid serial visual presentation stream (McArthur, Budd, & Michie, 1999). Consistent with the idea that the P3 and attentional blink follow a roughly similar time course, it has been reported that reaction times to probe stimuli delivered during the time course of the P3 were significantly slower if the previous stimulus was an infrequent stimulus compared with when it was frequent (Woodward, Brown, Marsh, & Dawson, 1991; see also Rockstroh, Müller, Cohen, & Elbert, 1992). Indeed, infrequent stimuli (which are associated with a larger P3) are followed by an increased attentional blink (Martens, Johnson, Elmallah, & London, 2003).

Furthermore, Vogel, Luck, and Shapiro (1998) found that the P3 associated with the second target is absent if this target is presented during the attentional blink, whereas other ERP components, including the N400 associated with meaning extraction, are intact. Rolke, Heil, Streb, and Hennighausen (2001) qualified this finding, reporting that the absence of a P3 to the second target is

[4] It is important not to confuse the refractoriness of the LC (during the 200–500 ms following a phasic response) with the noradrenergically mediated facilitation of processing that occurs following an LC phasic response. The potentiating effects of NE release are thought to endure for approximately 100–200 ms, producing a facilitation of information processing during that period. This explains the Lag 1 sparing effect observed in the attentional blink paradigm, in which a second target appearing immediately following the first is spared from the attentional blink deficit. According to the LC hypothesis of the attentional blink, this is because a second target that occurs soon enough after the first benefits from the residual effects of NE release produced by the LC phasic response to the first target. However, if the second target occurs outside this window (200–500 ms), then it fails to benefit from residual NE release but also fails to elicit an LC phasic response of its own, thus manifesting the attentional blink effect.

confined to misses; a normal P3 was observed for correctly reported targets (i.e., hits). According to the LC-P3 hypothesis, the absence of a P3 for missed targets is a direct consequence of the refractory period in LC activity during which noradrenergic potentiation is temporarily unavailable. Finally, the LC refractory period appears to be mirrored by a refractory period in P3 elicitation that has been reported by Woods, Hillyard, Courchesne, and Galambos (1980). In that study, participants were to count the number of auditory signals presented at short interstimulus intervals during a 1200-ms interval. For signals presented at 300 ms following the first signal (i.e., when the LC is still refractory), the P3 was greatly reduced in amplitude, whereas at interstimulus intervals larger than 300 ms (by which time the LC starts recovering from its refractory state), the P3 progressively returned to normal.

Comparison With Existing Theories

Early theories of the functional significance of the P3 have argued that the underlying process is dependent on some aspect of the outcome of stimulus processing and have associated the P3 with concepts such as the orienting response, the resolution of prior uncertainty about stimulus events, the cognitive evaluation of stimulus significance, reactive changes in state of arousal, and the confidence about perceptual decisions made (reviewed in Pritchard, 1981). These theories are broadly consistent with the LC-P3 hypothesis in that they all emphasize the role of the P3 process in responses to motivationally significant stimuli and relate this to the outcome of stimulus processing. However, the LC-P3 hypothesis allows us to be more precise about the mechanisms that may drive the P3. This is because it links the P3 to a specific neurophysiological mechanism, the LC-NE system. An existing computational theory about this system specifies its role in information processing and thereby provides a firm foundation for further theory development and testing of new predictions (Aston-Jones et al., 2000; Cohen et al., 2004; Usher et al., 1999). This also provides a framework for organizing and interpreting insights gained from earlier theories concerning the P3. In the remainder of this section, we compare and contrast the LC-P3 hypothesis with two alternative and highly influential hypotheses of the P3.

Context-updating hypothesis. The most influential theory of the P3 is the context-updating hypothesis put forward by Donchin and colleagues (Donchin, 1981; Donchin & Coles, 1988; see Verleger, 1988, for a critique). According to this theory, the P3 reflects the active consolidation or revision of a mental model of the environmental context of the observer. If stimuli deliver information that mismatches with part of the context model or are otherwise useful in maintaining or updating the memory representation of the environment, the model is updated, the amplitude of the P3 being proportional to the change in the model.

The context-updating hypothesis and the LC-P3 hypothesis have in common that they assume that the P3 process is preceded by some kind of evaluation of the significance of the stimulus. According to the context-updating hypothesis, the updating process indexed by the P3 is informed by a mismatch mechanism that is at play somewhere in the cognitive system, constantly comparing input with the model of the context. According to the LC-P3 hypothesis, stimulus evaluation is carried out by brain structures that project to the LC. As a result, the LC is selectively recruited by motivationally significant stimuli. Despite this commonality, the two hypotheses differ considerably regarding their interpretation of the P3 process. Studies reporting that P3 amplitude is predictive of subsequent memory recall of the eliciting stimulus have been held by Donchin and associates as strong support for the idea that the P3 indexes an updating of memory representations (cf. Donchin & Coles, 1988). Nevertheless, as has been noted by others (e.g., Mangels, Picton, & Craik, 2001), these findings are also consistent with an attentional role for the P3 process if one assumes that heightened attention improves the encoding and maintenance of information in memory. Thus, according to the LC-P3 hypothesis, the P3 may predict memory encoding and/or updating even though the P3 does not reflect the updating process itself. Indeed, although there is substantial evidence indicating that NE exerts a potent modulatory influence on working memory via its impact on receptors in prefrontal cortex, it has been proposed that this effect is mediated by noradrenergic modulation of sensitivity to distracting stimuli, whereas dopamine is primarily involved in the working memory function of prefrontal cortex (e.g., Arnsten, 1997; Braver & Cohen, 2000; Clark et al., 1987, 1989; Cohen & Servan-Schreiber, 1992).

Stimulus-evaluation hypothesis. This hypothesis arose from observations, discussed above, that P3 latency is sensitive to experimental variables known to affect stimulus-evaluation processes but is not sensitive to experimental variables affecting response selection processes. On the basis of these observations, it was suggested that P3 latency is an indication of the duration of stimulus-evaluation processes (Duncan-Johnson, 1981; Kutas et al., 1977; McCarthy & Donchin, 1981; see Verleger, 1997, for a critique). Although the stimulus-evaluation hypothesis does not specify the exact nature of the process manifested by the P3, its proposal has had a profound impact on the field of mental chronometry. The hypothesis, especially when considered from the perspective of a serial information-processing framework, suggested that researchers could use P3 latency to break down the reaction time into a portion associated with stimulus evaluation and a portion associated with response selection and execution.

The LC-P3 hypothesis and stimulus-evaluation hypothesis have comparable interpretations of the meaning of P3 latency. Both hypotheses suggest that P3 latency places an upper bound on the completion time of stimulus-evaluation processes. Both also acknowledge that the response can take place before the completion of stimulus-evaluation processes—as indicated by the observation of responses substantially preceding the P3—but that this occurs at the cost of accuracy. The LC-P3 hypothesis extends the stimulus-evaluation hypothesis in its interpretation of P3 latency by specifying more precisely the mechanisms involved in stimulus evaluation and their relation to the P3 process: This process, the LC phasic response, is driven by the outcome of a task-relevant decision process (e.g., deciding to what category a stimulus belongs). More specifically, it is elicited as soon as the diffusion process assumed to implement this decision process crosses an internal decision threshold. As noted earlier, the electrophysiological correlate of this process, the P3, is assumed to occur at a relatively fixed duration following the LC phasic response.

Conclusion

Through its modulatory actions on information processing, the LC-NE system potentiates responses to the outcome of internal decision processes that involve motivationally significant events, thereby guiding behavioral action in the service of task demands and other goals. The modulatory effects of the LC-NE system may be measurable at the scalp as the P3 component of the ERP. The literature reviewed here regarding the functional significance and neural basis of the P3 and the LC-NE system is largely consistent with this hypothesis. The LC-P3 hypothesis suggests promising avenues for future research: The P3 may provide a window into the functioning of the LC-NE system in humans, and knowledge of this system may be used in understanding the large body of literature regarding the P3. More generally, this article presents an illustration of how empirical knowledge of neurophysiological, electrophysiological, and cognitive phenomena may be integrated in developing theories that link brain activity to psychological function and behavior.

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