Investigating the role of the noradrenergic system in human cognition

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Abstract

Animal research and computational modeling have indicated an important role for the noradrenergic system in the regulation of attention and behavior. According to a recent theory, the noradrenergic system is critical for the optimization of behavioral performance—by facilitating responses to motivationally significant stimuli and regulating the tradeoff between exploitative and exploratory behaviors (Aston-Jones & Cohen, 2005). However, until recently, crucial empirical tests of this theory in human subjects have been lacking. This is not so surprising since the study of neuromodulation in humans poses considerable methodological challenges. In this chapter we will discuss recent progress made in the development and validation of non-invasive measures and methods for investigating noradrenergic function in humans. This methodological progress has opened up new opportunities for testing predictions and further development of theories of noradrenergic function.

1. Introduction

As their name suggests, neuromodulators such as dopamine, acetylcholine and norepinephrine (NE) modify the effects of neurotransmitters—the molecules that enable communication between neurons. Neuromodulatory systems are involved in almost every mental function, including attention, learning and emotion (Robbins, 1997), and they are disturbed in many neurological and psychiatric disorders, such as attention-deficit/hyperactivity disorder (ADHD), post-traumatic stress disorder, and schizophrenia.

For a long time researchers have associated neuromodulators with basic, nonspecific functions such as signalling reward (dopamine) and regulating arousal (NE). But recent research has shown that neuromodulators have more specific functions in learning and decision making. This progress is especially apparent in cognitive neuroscience, in which neurophysiological data from animal studies have been used to develop highly sophisticated theories about the role of neuromodulatory systems in human cognition (Frank & Claus, 2006; Holroyd & Coles, 2002; Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999). This chapter focuses specifically on the role of the noradrenergic system in optimizing task performance, with a strong emphasis on the question how we can investigate the function of this system in human subjects.

The locus coeruleus (LC) is the brainstem neuromodulatory nucleus responsible for most of the NE released in the brain. It has widespread projections throughout the neocortex. The LC-mediated noradrenergic innervation increases the responsivity of efferent target neurons (Berridge & Waterhouse, 2003), which can be modeled as a change in the gain (steepness) of the neurons' activation function (Servan-Schreiber, Printz, & Cohen, 1990). Although cell recordings in non-human primates have yielded a wealth of information regarding the dynamics of the noradrenergic system, to date there has been very little empirical research on the activation dynamics and function of this system in humans. This is not so surprising since the study of the noradrenergic system in humans poses considerable methodological challenges. First, the LC is a very small nucleus and lies deep within the brainstem, necessitating the use of refined non-invasive imaging techniques to record its activity. And second, it is not possible to directly measure the neurophysiological effects of NE in the human brain. The study of these effects requires the development of indirect measures, or the measurement of changes in behavior and brain activity brought

about by pharmacological manipulations of the noradrenergic system. Nevertheless, if we want to achieve a thorough understanding of the functions of the human noradrenergic system, we need to confront these challenges.

In this chapter we will discuss recent progress made in the development and validation of non-invasive measures and methods for investigating noradrenergic function in humans. The discussed methods include functional imaging, scalp electrophysiology, the application of computational models of the monkey noradrenergic system to the study of human attention phenomena, pupillometry, and psychopharmacology. As we will show, this methodological progress has opened up new opportunities for testing predictions and further development of theories of noradrenergic function.

2. The function of phasic LC responses

When an animal is actively engaged in performing a task, LC neurons exhibit a rapid, phasic increase in discharge rate to task-relevant and otherwise motivationally salient stimuli. For example, such *LC phasic responses* are observed for target stimuli in a simple target-detection task in which monkeys are required to respond to rare target stimuli presented at random intervals embedded in a train of distractor stimuli. Provided that the animal is engaged in the task, these target stimuli cause a phasic increase in LC firing rate that peaks approximately 100-150 ms post-target and approximately 200 ms prior to the response (Figure 1; e.g., Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994; Clayton, Rajkowski, Cohen, & Aston-Jones, 2004) . Importantly, the LC does not exhibit this type of phasic response to distractor stimuli, nor is the phasic response associated with any other task-related events once training is complete (reward delivery, fixation point, response movements, etc.). However, similar phasic responses are elicited by unexpected, intense, threatening, or otherwise salient stimuli that demand effective processing and action (Aston-Jones, Rajkowski, & Cohen, 1999).

The ensuing release of NE in cortical areas temporarily increases the responsivity of these areas to their afferent input (Berridge & Waterhouse, 2003), selectively potentiating any activity present concurrent with LC activation. It has been shown that when applied in a temporally strategic manner (e.g., when driven by the identification and evaluation of motivationally relevant stimuli), increases in

responsivity produce an increase in the signal-to-noise ratio of subsequent processing and a concomitant improvement in the efficiency and reliability of behavioral responses (Servan-Schreiber et al., 1990). Accordingly, it has been found that LC phasic activation reliably precedes and is temporally linked to behavioral responses to task-relevant stimuli (Bouret & Sara, 2004; Clayton et al., 2004). In addition, studies have reported a direct relation between the strength of LC activity and response accuracy in choice-reaction time tasks (Rajkowski, Majczynski, Clayton, & Aston-Jones, 2004). Together, these findings suggest that phasic noradrenergic signals play an important role in optimizing responses to motivationally significant stimuli (for an elaborate discussion of this topic, see Aston-Jones & Cohen, 2005).

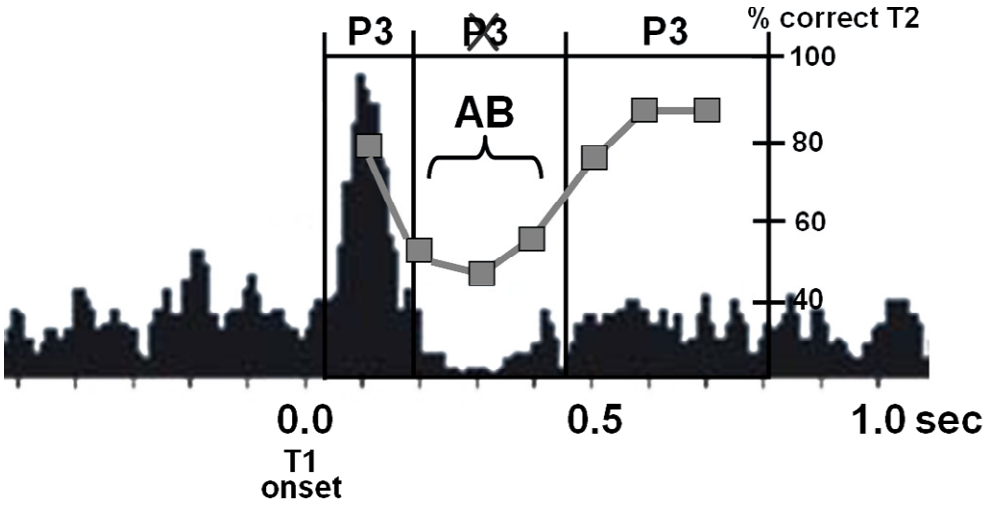

Figure 1. Peristimulus time histogram of activity from a typical monkey locus coeruleus (LC) neuron during target trials in a target-detection task. Following the target (T1) LC activity exhibits a sharp phasic response, followed by a refractory period, followed by a return back to baseline. The plotted curve indicates typical results in a human attentional-blink (AB) experiment: accuracy for a second target (T2) is critically dependent on the time interval between the two targets. If T2 is presented 200-450 ms following T1, T2 accuracy is dramatically impaired and T2 does not elicit a second P3. Note the similarity in the timing of the LC refractory period, the attentional blink, and P3 occurrence.

3. Functional imaging of the LC

Functional magnetic resonance imaging (fMRI) would be a suitable and highly convenient method for measuring phasic LC signals in human subjects. But unfortunately, imaging of the LC with fMRI is far from straightforward, due to the LC's small size (~ 1 cm in length in humans) and its location deep down in the brainstem. Previous fMRI studies of the noradrenergic system have therefore either focused on LC

projection areas (e.g., Strange & Dolan, 2007) or have been forced to note that their conclusions regarding activation in the LC region must remain tentative (e.g., Raizada & Poldrack, 2008; Sterpenich et al., 2006).

A relatively simple methodological requirement for LC imaging concerns immobilizing the subject's head to prevent motion of the LC from one voxel to the next, and investigating the data from individual subjects rather than the grand-average to prevent spatial "smearing". An alternative solution for the averaging problem is the use of a brainstem normalization algorithm to improve overlap of the brainstem across subjects for group analysis (Napadow, Dhond, Kennedy, Hui, & Makris, 2006). Another requirement is the use of high-resolution scan sequences designed to image small brain structures. This is needed to minimize the effects of partial volume averaging. A final challenge concerns the fact that the LC lies immediately adjacent to the fourth ventricle, resulting in movement artifacts caused by pulsatile flow of the cerebrospinal fluid. To remedy this problem one can use 'cardiac gating' (Guimaraes et al., 1998). This means that the heart beat is used as a trigger for the fMRI image acquisition, so that each slice image is always acquired during the same moment of a heart beat cycle. This maximizes the chance that the same brain tissue falls into a particular voxel every time it is measured.

A recent study has demonstrated that the above-described set of methods allows the effective measurement of blood oxygen-level dependent (BOLD) signals in dopaminergic midbrain nuclei (D'Ardenne, McClure, Nystrom, & Cohen, 2008). The authors suggest that, using these methods, it should also be possible to investigate other neuromodulatory nuclei such as the LC. Our group is currently making significant progress in this direction, but until this work begins to bear fruit, we will consider alternative approaches for localizing the LC. One such approach is the triangulation method (Komisaruk et al., 2002): The LC is closely surrounded by multiple nuclei with elementary sensory or motor functions (e.g, swallowing, detecting subtle facial stimulation). These regions can be functionally mapped with fMRI in a short period, thus generating for each individual a functional reference map for localizing the approximate location of the LC. Another approach is to use a noradrenergic drug agent and examine with fMRI whether the main effect of drug versus placebo activates a voxel cluster consistent with the estimated location of the LC. This voxel cluster can then be used as a region-of-interest for

investigating task effects on LC activity (Minzenberg, Watrous, Yoon, Ursu, & Carter, 2008). Finally, neurochemists have recently developed a noradrenergic tracer (for use in humans), a radioactive molecule that has high affinity for the NE transporter and that can be imaged with positron emision tomography (Takano et al., 2008). This is likely to be an effective method for localizing the LC, which has a high density of NE transporters. Similar tracers have been successfully used in imaging other neuromodulatory systems in humans (e.g., dopamine; Cools, Stefanova, Barker, Robbins, & Owen, 2002).

4. The P3 component of the event-related potential

While relatively direct measurement of LC phasic activity using fMRI has not yet been realized, it seems possible to obtain non-invasive measures of the distant, post-synaptic effects of such phasic activity. In particular, it has recently been proposed that the modulatory effect of phasic NE release in the neocortex can be measured in human subjects by recording the the P3(00) component of the scalp-recorded event-related potential (Nieuwenhuis, Aston-Jones, & Cohen, 2005).

The P3 is a prominent, positive large-amplitude potential with a broad, midline scalp distribution, and a typical peak latency between 300 and 400 ms following presentation of stimuli in any sensory modality (for a review see Polich, 2007). First reported in 1965 (Sutton, Braren, Zubin, & John, 1965), the P3 has undoubtedly been the single most studied component of the event-related potential. Yet, until recently, psychologists and neuroscientists have failed to come up with a precise, mechanistic account that elucidates the functional role in information processing of the process underlying the P3, as well as its neural basis. Strong evidence for subcortical involvement in P3 generation has come from a study showing largely intact P3 components to unilaterally presented visual stimuli in the unstimulated hemisphere of a split-brain patient (Kutas, Hillyard, Volpe, & Gazzaniga, 1990). Given that in split-brain patients interhemispheric transfer of information is not possible at the cortical level, this finding indicates that critical input and/or output signals of the P3 process must have passed through one of the intact subcortical commissures. The hypothesis that the P3 reflects the LC-mediated phasic enhancement of neural responsivity in the cortex is supported by a wealth of data from intracranial recordings, lesion

studies, psychopharmacology, functional imaging, and other methods, as summarized below (for an extensive review see Nieuwenhuis, Aston-Jones et al., 2005).

First, the antecedent conditions for the P3 are similar to those reported for the LC phasic response. In general, P3 amplitude 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. Important factors affecting the amplitude of the P3 are the subjective probability of the eliciting stimulus, its task-relevance, and its salience (e.g., intensity, novelty). Like the LC phasic response, the P3 is also enlarged for stimuli with intrinsic significance such as emotionally valent stimuli, whether experienced as positive or negative.

Second, the distribution and timing of intracranial and scalp-recorded P3 activity are consistent with the anatomical and physiological properties of the noradrenergic system. For example, functional imaging studies, inctracranial recordings, and lesion studies have indicated that brain areas showing or contributing to P3 activity are scattered across the brain (Soltani & Knight, 2000), consistent with the widespread projections from the LC to cortical and subcortical areas. In addition, the pattern of P3 generators shows a spatial specificity that mirrors the projection density of the LC. Furthermore, P3 onset latency in simple two-alternative forced choice tasks is consistent with the latency of LC phasic activity (~150-200 ms), if one takes into account the relatively slow conduction velocity of LC fibers. Additionally, the relatively early timing of P3 activity in frontal and subcortical areas (e.g., thalamus; Klostermann et al., 2006) is consistent with the trajectory of LC fibers, which first reach these areas and only then veer backwards to innervate posterior cortical areas.

Third, several studies have reported direct evidence for an LC generator of the P3. These include psychopharmacological studies, which have shown that P3 amplitude is modulated in a systematic fashion by noradrenergic agents such as clonidine (Swick, Pineda, & Foote, 1994), and entirely abolished following drug-induced NE depletion (Glover, Ghilardi, Bodis-Wollner, & Onofrj, 1988). Also, a recent study has found that individual differences in the noradrenergic gene that affects the activity of the alpha-2a receptor are a key determinant of P3 amplitude (Liu et al., 2009). In addition, lesion studies have demonstrated a selective effect on P3 amplitude of LC lesions (Pineda, Foote, & Neville, 1989). Finally, larger and faster P3s are associated with more accurate and faster behavioral responses, a pattern that

mirrors the relation between LC phasic activity and task performance, and that is consistent with the functional role ascribed to the noradrenergic system.

In the past, some authors have argued that the P3 peaks too late to influence behavioral responses, thereby challenging the LC-P3 theory. However, several counter-arguments are worth noting. First, even if the peak of the P3 sometimes occurs after the registration of the response, the *onset* of the P3 generally occurs before the response. Second, the potentiating influence of the noradrenergic system on behavioral responding is likely to be modest in typical laboratory tasks, which use simple stimuli and discrete button-press responses. These tasks are performed so quickly that the noradrenergic modulation of the relevant cortical areas (as reflected in the P3) may sometimes occur too late to facilitate the response. It is plausible that the facilitatory influence of the noradrenergic system is more prominent in real-life situations, which are characterized by multimodal, crowded sensory environments and a range of potential, often time-consuming response options. Finally, the LC-P3 theory does not claim that the P3 process is *necessary* for responding; of course, subjects can decide to respond before their perceptual system has fully analyzed the stimulus. The hypothesis claims that *if* the P3 occurs before the response, then the response will be facilitated and more efficient.

The LC-P3 theory offers a theoretical framework that allows the separate research literatures on the noradrenergic system and P3 each to inspire new predictions and research within the other domain. Because empirical knowledge about P3 function in humans by far exceeds that of the LC, it may prove fruitful for our understanding of LC function to identify and test cross-domain predictions inspired by the P3 literature.

5. Projections to the LC and the link with the orienting response

An important question is how the LC−this tiny brainstem nucleus−knows whether a stimulus is motivationally significant. To date, the best available answer is that some of the most prominent descending cortical projections to the LC come from two frontal brain structures that are thought to play a critical role in evaluating costs and rewards: the anterior cingulate cortex and the orbitofrontal cortex (Figure 2; Arnsten & Goldman-Rakic, 1984; Aston-Jones & Cohen, 2005; Lee, Kim, & Waterhouse, 2005).

A growing body of work implicates the anterior cingulate cortex in action monitoring and reinforcement-guided decision making (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Rushworth, Behrens, Rudebeck, & Walton, 2007). Activation of the anterior cingulate may provide a neural signal that greater control is required to successfully meet internal goals or external demands (Botvinick, Cohen, & Carter, 2004). As we have discussed, the LC is in a unique position neurophysiologically to provide such an augmentation in control by globally affecting system responsivity. There is also strong evidence that the orbitofrontal cortex plays an important role in reinforcement-guided decision making. For example, neurons in orbitofrontal cortex respond to the reward value of stimuli in varying modalities, and the magnitude of the neural response reflects the relative reward value of the corresponding stimuli (Rolls, 2004). Recent studies that have compared the distinctive contributions of the anterior cingulate and orbitofrontal cortex suggest that the former represents action-reward contingencies whereas the latter represents stimulus-reward contingencies (Rushworth et al., 2007). Taken together, these findings suggest that the anterior cingulate and orbitofrontal cortex may jointly provide the LC with ongoing evaluations of task utility (see section 7; Aston-Jones & Cohen, 2005).

In addition to these direct projections from frontal structures, many other cortical and limbic structures, including the amygdala and hypothalamus have indirect connections with the LC. Interestingly, most of these cortical and limbic signals are relayed by the rostral part of the ventrolateral medulla, the area that provides the largest input to the LC (Figure 2; Aston-Jones, Ennis, Pieribone, Nickell, & Shipley, 1986). Importantly, this same area of the medulla is also a key region for the regulation of the symphathetic branch of the autonomic nervous system. Neurons in this area are involved in controlling sympathetic activation of the pupil, sweat glands, the heart, and other autonomic organs. Indeed, LC firing rate and sympathetic nervous system activity have a strong temporal correlation (cf. Aston-Jones, Rajkowski, Kubiak, Valentino, & Shipley, 1996). Anatomical considerations suggest that this correlation reflects parallel downstream influences of a common afferent source in the medulla.

There is also ample evidence for a tight link between the psychophysiological manifestations of noradrenergic and sympathetic nervous system activity: the P3 and the *orienting response*, a collection of

autonomic nervous system reflexes that includes pupillary dilation, a drop in skin resistance, and a momentary change in heart rate (Sokolov, 1963). In the 1970s, psychophysiologists were intrigued by the idea that the P3 might reflect a neural correlate of the orienting response. Like the P3, the orienting response is elicited by novel, intense, and otherwise motivationally significant stimuli. Moreover, both the P3 and the orienting response are well known to rapidly habituate to initially novel, task-irrelevant stimuli. In the 1980s, empirical and theoretical comparisons between the P3 and orienting response reached an impasse, in part because a neurobiological basis for these comparisons was lacking (Donchin et al., 1984). Our recent analysis suggests that the close link between these two phenomena reflects the co-activation of the noradrenergic and sympathetic systems by a common afferent pathway (Nieuwenhuis, de Geus, & Aston-Jones, submitted).

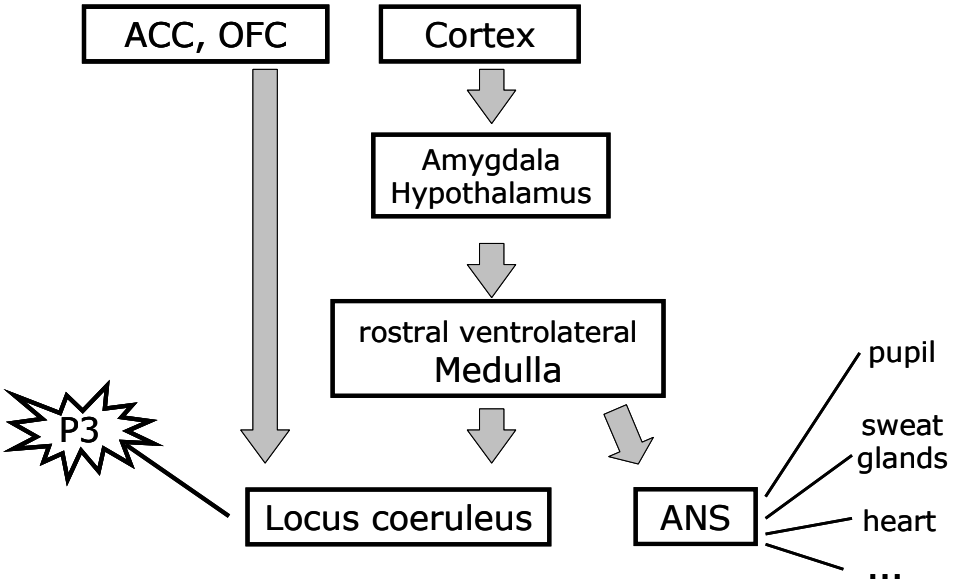

Figure 2: Schematic outline of descending projections to the locus coeruleus and autonomic nervous system (ANS). Although there is substantial evidence that autonomic (mainly cardiovascular) responses have a direct influence on LC activity (Berntson, Sarter, & Cacioppo, 1998), this anatomical route is too slow to explain the rapid, phasic LC responses to motivationally significant stimuli. ACC = anterior cingulate cortex; OFC = orbitofrontal cortex.

6. The attentional blink as a marker of LC dynamics

Above, we have discussed that task-relevant stimuli in choice reaction-time tasks typically elicit a large P3 and that this may reflect the large LC phasic response to such stimuli. Nieuwenhuis and colleagues explored

the question what happens if we present a second task-relevant stimulus soon after the LC response to the first (Nieuwenhuis, Gilzenrat, Holmes, & Cohen, 2005). This question was inspired by the observation that the LC phasic response to task-relevant stimuli is typically followed by a brief period during which the LC is essentially inactive and unperturbable (due to local auto-inhibition; Aston-Jones et al., 1994). This socalled refractory period starts between 200-250 ms after the eliciting stimulus, and usually lasts until about 400-450 ms post-stimulus (Figure 1). Importantly, human ERP experiments have shown that that if a second target stimulus is presented during roughly this interval, the target elicits no P3, consistent with the notion that the LC is refractory (Figure 1; Vogel, Luck, & Shapiro, 1998; Woods, Hillyard, Courchesne, & Galambos, 1980). In contrast, if the second target is presented a little later (> 500 ms), when LC baseline activity is back up to normal, the target elicits a normal-sized P3.

Nieuwenhuis, Gilzenrat et al. (2005) noted that the LC refractory period also coincides with the timing of a psychophysical phenomenon, the *attentional blink*: the transient impairment in perceiving the second of two targets presented in close temporal proximity in a rapid stream of distractors (Figure 1; Shapiro, Arnell, & Raymond, 1997). This observation led to the hypothesis that the attentional blink may be mediated by the momentary unavailability of noradrenergic potentiation during the refractory period associated with the first target. Because of the unavailability of NE, subsequent target stimuli that are presented during the refractory period do not receive the benefit of LC-mediated facilitation and, therefore, suffer a deficit in processing. To test this hypothesis, Nieuwenhuis and colleagues extended an existing computational model of monkey LC dynamics and its impact on target-detection performance (Gilzenrat, Holmes, Rajkowski, Aston-Jones, & Cohen, 2002). Computer simulations indicated that the model, when presented with an attentional-blink task, produced a pattern of deficit in its target-detection performance that was very similar to that associated with the attentional blink observed in empirical studies.

Aside from its occurrence and timing, the LC model explains various other properties of the attentional blink. For example, if the second target follows the first without intervening distractors, performance for the second target is often (partially) spared ('lag-1 sparing'; Shapiro et al., 1997). The LC model reproduces this phenomenon because the residuum of NE release associated with the first target

benefits processing of the second target, allowing it to escape the disrupting effect of LC refractoriness. Another property of the attentional blink concerns the role of the distractor immediately following the first target (i.e., the T1+1 distractor). Many early studies have found that the attentional blink occurs only if the T1+1 distractor is presented, not if it is omitted, and therefore most models explain the attentional blink as the result of a process triggered by the presentation of the T1+1 distractor (Shapiro et al., 1997). In contrast, the core mechanism in the LC model produces an attentional blink regardless of the presence of the T1+1 distractor, because the occurrence of a LC phasic response is independent of this distractor item. Although this was initially regarded as a limitation of the LC model, recent empirical work has demonstrated that, provided that the probe task for second-target accuracy is sensitive enough, a substantial attentional blink can be observed even when the two targets are separated by a blank screen (Nieuwenstein, Potter, & Theeuwes, 2009).

Although fundamentally different from the LC model, two recent computational models of the attentional blink incorporate a crucial architectural component that produces target-evoked, transient, nonspecific attentional responses that facilitate the conscious identification of briefly presented, masked targets (the' blaster' in Bowman & Wyble, 2007; the 'boost' function in Olivers & Meeter, 2008). The proponents of these models have explicitly recognized the similarity between the properties of these attentional mechanisms and properties of the LC (Bowman, Wyble, Chennu, & Craston, 2007; Olivers, 2007), indicating a striking correspondence between computational and neurophysiological models of the attentional blink.

Finally, a couple of studies have provided indirect support for the involvement of the noradrenergic system in the attentional blink. First, functional imaging studies have suggested that target processing in the attentional blink task is mediated by a widespread cortical network including parietal cortex, anterior cingulate cortex, and lateral frontal cortex, which are some of the cortical areas with the densest noradrenergic innervation (cf. Nieuwenhuis, Gilzenrat et al., 2005). Second, split-brain patients show a typical attentional blink even when the two targets are presented to two different hemispheres (Giesbrecht & Kingstone, 2004), suggesting a subcortical basis for the attentional blink. And third, a psychopharmacological study has found that changes in noradrenergic tone modulate the attentional blink

(De Martino, Strange, & Dolan, 2008). This study found that beta-adrenergic blockade with propranolol impaired attentional-blink performance, whereas NE reuptake inhibition with reboxetine improved attentional-blink performance, at least for emotional target stimuli. However, another study found no reliable effect of the alpha-2 receptor agonist clonidine on the attentional blink (Nieuwenhuis, van Nieuwpoort, Veltman, & Drent, 2007). This is remarkable because the LC refractory period, proposed to be responsible for the attentional blink, is possibly caused by the activation of alpha-2 inhibitory autoreceptors in the LC (Aghajanian, Cedarbaum, & Wang, 1977). It is unclear whether this discrepancy between model and data is due to insufficient sensitivity of the empirical study (e.g., dose too low; use of a between-subject design; see Nieuwenhuis et al., 2007, for an extensive discussion) or presents a falsification of the LC model of the attentional blink.

7. Phasic versus tonic LC firing mode and corresponding control states

Above, we have discussed that phasic LC responses facilitate responding to the motivationally significant stimuli that tend to elicit these responses. Here we discuss the function of tonic (baseline) changes in LC activity (i.e., changes happening over the course of multiple seconds or minutes). Levels of LC tonic activity vary systematically in relation to measures of task performance (Figure 3). Aston-Jones and colleagues (1994) recorded LC activity in monkeys during performance of a target-detection task. Periods of intermediate tonic LC activity were accompanied by large LC phasic responses to target stimuli, and rapid and accurate responding. In contrast, periods of elevated tonic LC activity were consistently accompanied by relatively poor task performance, and distractible, restless behavior. Such phases were also consistently associated with a diminuition or absence of the target-evoked LC phasic responses observed during periods of good performance. These findings have led to the proposal that in the waking state there are two distinguishable modes of LC activity (Aston-Jones et al., 1999; Figure 3): In the *phasic mode*, bursts of LC activity are observed in association with the outcome of task-related decision processes, and are closely associated with goal-directed behavior. In the *tonic mode*, LC baseline activity is elevated but phasic bursts of activity are absent and behavior is more distractible.

According to the recently proposed adaptive gain theory (Aston-Jones & Cohen, 2005; Cohen, Aston-Jones, & Gilzenrat, 2004), the different modes of LC activity serve to regulate a fundamental tradeoff between two control states: exploitation versus exploration.The LC phasic mode promotes exploitative behavior by facilitating processing of task-relevant information (via the phasic response), while filtering out irrelevant stimuli (through low tonic responsivity). By increasing the phasic character of LC firing, the cognitive system is better able to engage in the task at hand, and maximize rewards harvested from this task. In contrast, the LC tonic mode promotes behavioral disengagement by producing a more enduring and less discriminative increase in responsivity. Although this degrades performance within the current task, it facilitates the disengagement of attention from this task, thus allowing potentially new and more rewarding behaviors to be emitted. Thus, the transition between the two LC modes can serve to optimize the trade-off between exploitation and exploration of opportunities for reward, and thereby maximizes overall utility.

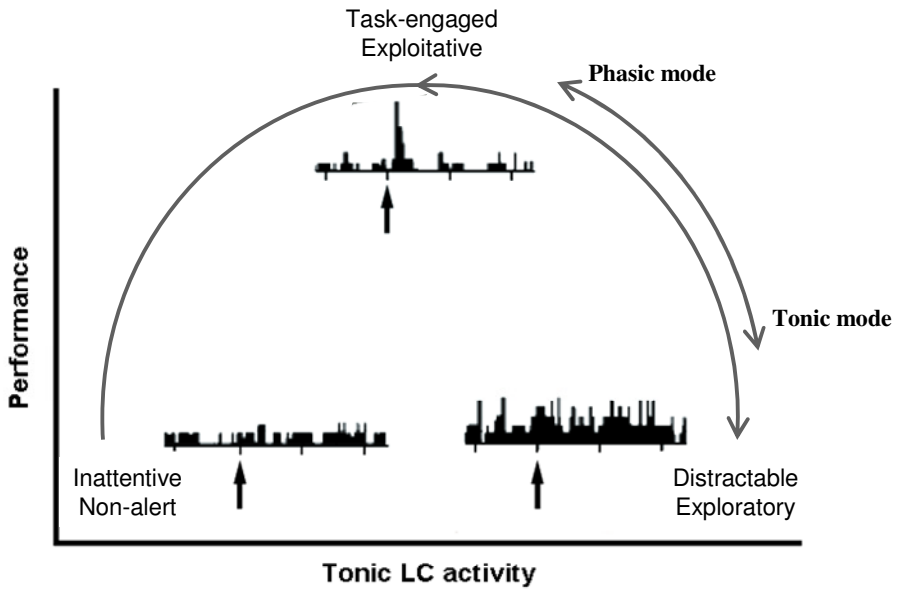

Figure 3: Inverted-U relationship between tonic LC activity and performance on tasks that require focused attention. Moderate LC tonic activity is associated with optimal performance and prominent phasic LC activation following task-relevant stimuli (phasic LC mode). High levels of tonic LC activity are associated with poor performance and the absence of phasic LC activity (tonic LC mode). According to Aston-Jones and Cohen (2005), shifts along the continuum between the phasic and tonic LC modes drive corresponding changes in the exploitation-exploration tradeoff. Figure adapted from Aston-Jones and Cohen (2005).

The adaptive gain theory further holds that the transition between phasic and tonic LC firing modes and the corresponding control states are driven by online assessments of utility by the frontal structures that provide a major input to the LC, the anterior cingulate and the orbitofrontal cortex (see section 5). According to the theory, the utility signals in these brain areas are integrated over different timescales and then used to regulate LC mode (Aston-Jones & Cohen, 2005). Brief lapses in performance, in the context of otherwise high utility, augment the LC phasic mode, resulting in improved task performance. In contrast, enduring decreases in utility drive transitions to the LC tonic mode, promoting disengagement from the current task and facilitating exploration of behavioral alternatives.

8. Pupillometry can reveal LC-mediated control state

Most of the evidence for the hypothesized link between low utility, tonic LC firing mode and a control state favoring exploratory behavior comes from animal studies, but even that evidence is sparse. Therefore, in order to generalize and further develop the adaptive gain theory (Aston-Jones & Cohen, 2005), it would be desirable to have at our disposal a non-invasive correlate measure of both tonic and phasic LC activity in humans. In recent work, Gilzenrat, Nieuwenhuis, Jepma, and Cohen (in press) have proposed that pupil diameter might provide such a measure.

In follow-up analyses of the target-detection task data discussed in sections 2 and 7 (Aston-Jones et al., 1994), Rajkowski, Kubiak, and Aston-Jones (1993; see also Aston-Jones & Cohen, 2005) found that the monkey pupil diameter, which was recorded throughout the experiment, closely followed the LC tonic firing rate. Rajkowski and colleagues concluded that baseline pupil diameter varies with LC mode, such that the LC tonic mode is marked by a relatively large pupil diameter and the LC phasic mode is marked by a relatively small pupil diameter. Furthermore, a large number of studies with human subjects have shown that task processing is accompanied by rapid and large pupil dilations, consistent with the occurrence of an LC phasic response to task-relevant events (Kahneman, 1973). Typically, the size and duration of these dilations are positively correlated with task difficulty. Taken together, these previous human and animal studies show that task-related, effortful processing is associated with tonic constrictions (in the monkey) and phasic dilations (in the human) of the pupil. This tonic-phasic pupil

interaction mirrors the negative correlation between tonic and phasic LC activity, suggesting that pupillary responses track LC firing rate, reflecting both its tonic and phasic character. This hypothesis is consistent with the close link between LC activity and autonomic nervous system activity discussed in section 6.

Gilzenrat et al. (in press) conducted three experiments with young adults to investigate the value of pupil diameter as a marker of LC activity in humans. In Experiment 1 they examined the relationship between pupil diameter and task performance, using an auditory version of the target-detection task previously used in monkey LC studies. The results were consistent with the predictions of adaptive gain theory: trials with larger baseline pupil diameters were associated with poorer task performance, indicative of lapses of engagement mediated by spontaneous drift into LC tonic mode. Conversely, smaller baseline pupil diameters were associated with better performance, indicative of task engagement mediated by the LC phasic mode. In addition, larger baseline diameters were associated with smaller post-target dilations, and vice versa, consistent with the negative correlation between phasic and tonic LC activity.

In Experiment 2 the authors attempted to manipulate LC mode, and hence control state, by regulating the experienced processing conflict (~costs) and reward (which jointly determined task utility) across blocks of trials in a pitch-discrimination task (Kahneman & Beatty, 1967). The pupil exhibited smaller baseline diameters and larger dilations when both the amount of conflict and reward value were high, and likewise when both the amount of conflict and reward value were low. These results were predicted by the adaptive gain theory: Both conditions encouraged the LC phasic mode as both signaled a need for recruitment of control (either due to high conflict, or negative feedback) in circumstances in which the required additional effort appeared to pay off (either in the form of positive feedback, or through a reduction in conflict). Conversely, the block with high, protracted conflict and low reward was associated with larger baseline pupil diameters and smaller dilations. This block promotes the LC tonic mode and hence an adaptive breakdown in the recruitment of control, as conflict remains high and feedback remains negative despite effortful performance.

Finally, in Experiment 3 the authors focused on the effect of dynamic changes in task utility on pupil diameter, and at the relationship between pupil diameter and a measure of task disengagement, using a novel diminishing-utility task. Subjects performed a series of tone discriminations of progressively increasing difficulty with rewards for correct performance that increased in value with increasing task difficulty. Initially, the increases in reward value outpaced increases in difficulty (and associated increases in errors) so that subjects remained engaged in the task. However, after several trials, the increases in difficulty led to sufficient numbers of errors as to reduce reward rate even in the face of the increasing value of correct responses. At the beginning of every trial, subjects were allowed to press a reset button (an overt disengage behavior), which would start a new series of discriminations, beginning again with low difficulty and low reward value. Subjects behaved optimally on average, choosing to reset when the success (expected utility) of the discriminations began to decline. Early in each trial series there were large phasic pupil dilations for each discrimination. As would be predicted for LC phasic responses, these dilations declined in amplitude, and baseline (tonic) pupil diameter rose as the task became more difficult and expected utility began to decline. Baseline pupil diameter was greatest at the point at which subjects chose to abandon the current series, consistent with the hypothesis that this was mediated by an increase in LC tonic activity.

To summarize, in all three experiments the pupillometry and behavioral results showed a highly specific pattern that the adaptive gain theory would predict if pupil diameter indeed indexes LC activity: tonic and phasic pupil diameter (which were negatively correlated) were highly sensitive to dynamic changes in utility and highly predictive of task (dis)engagement. Thus, the confirmation of the theoretical predictions reaped a double reward: It served to validate the method, showing that pupillometry can reveal LC-mediated changes along the exploitation-exploration trade-off; and it helped validate the adaptive gain theory, since the predicted pupil dynamics were dictated by an assumption of close correspondence with observed LC firing patterns.

However, although the diminishing-utility task used in Experiment 3 allowed subjects to disengage from the task, a limitation of this experiment was that there were no opportunities to actually explore other options. We have recently addressed this issue in a pupillometry study using an n-armed bandit task (Sutton

& Barto, 1998). In this task subjects repeatedly chose one of four slot machines. The pay-offs of the four slots changed over time, such that the current pay-offs could only be learned through active sampling of the slots (i.e., exploration). Each choice made by the participants could be classified as exploitative or exploratory, by means of a model-based calculation of the expected value of the chosen slot relative to the other slots. The results confirmed our critical predictions that baseline pupil diameter was larger preceding exploratory versus exploitative choices, and that changes in baseline pupil diameter surrounding the transition between exploratory and exploitative control states were correlated with changes in task-related utility (Jepma & Nieuwenhuis, submitted).

9. Pharmacological manipulations of LC-mediated control state

Pharmacological manipulations of the noradrenergic system provide a powerful means to study the functional role of this system in humans. The functional significance of the alpha-adrenergic and beta-adrenergic receptor systems are reviewed in detail elsewhere (Chamberlain, Müller, Blackwell, Robbins, & Sahakian, 2006; Coull, 1994). Here we focus on the selective NE reuptake inhibitors atomoxetine, reboxetine, and desipramine, because administration of these drugs (at a clinically relevant dose) increases synaptic concentrations of norepinephrine, thus mimicking the effects of elevated NE release that characterize the tonic LC mode. Atomoxetine is a common treatment for ADHD and reboxetine and desipramine are antidepressant drugs used in the treatment of clinical depression. Acute administration of NE reuptake inhibitors has opposing effects: In the LC it leads to a reduction of firing activity through the increased activation of inhibitory autoreceptors within the LC, while in the forebrain it results in increased extracellular NE levels due to the reuptake blockade. Importantly, the net effect of these two actions is still an increase in NE levels, and this effect is enhanced by chronic treatment (reviewed in Invernizzi & Garattini, 2004).

To date, no human or animal studies have directly investigated the effect of NE reuptake inhibitors on exploitative versus exploratory behaviors. However, there are several indications that these drugs promote behavioral disengagement and increase cognitive flexibility—other indications of the enduring and largely nonspecific increase in responsivity associated with the LC tonic mode. For example, acute and

chronic treatment with desipramine has been found to improve rats' attentional set-shifting, a measure of cognitive flexibility (Lapiz, Bondi, & Morilak, 2007). Furthermore, atomoxetine and desipramine have been reported to lead to improved reversal learning in discrimination tasks in which rats were trained to either reverse or retain a position-reward association learned in the previous session (Seu, Lang, Rivera, & Jentsch, 2009). In contrast, reboxetine did not improve performance during the retention phases, suggesting a specific improvement in cognitive flexibility, not in overall task performance. Interestingly, a similar facilitation in attentional set shifting and reversal learning has been obtained with the alpha-2 receptor antagonists idazoxan and guanfacine, which also activate the NE system but are less suitable for use in humans (Devauges & Sara, 1990; Steere & Arnsten, 1997). Another consistent finding is that atomoxetine improves human subjects' ability to stop an ongoing motor response when cued to do so (Chamberlain, Müller, Blackwell, Clark et al., 2006). Presumably the drug-related increase in cognitive flexibility facilitates disengaging from one task (responding) and switching to a new task (stopping the response). Remarkably, the same study found that atomoxetine did not improve reversal learning. Finally, reboxetine has been found to enhance social flexibility, as indicated by increased social engagement and cooperation and a reduction in self-focus in a stranger-dyadic social interaction paradigm (Tse & Bond, 2002).

We are currently conducting a study designed to provide a direct test of the effects of reboxetine on behavioral indices of task-(dis)engagement and the trade-off between exploration and exploitation (Jepma, Wagenmakers, te Beek, van Gerven, & Nieuwenhuis, in preparation). One group of subjects receives reboxetine (4 mg single dose), a second group receives citalopram (30 mg; positive control), a selective serotonin reuptake inhibitor with comparable alerting effects and pharmacokinetic properties as reboxetine, and a third group receives a placebo. Subjects perform two tasks described in section 8: the diminishing-utility task and the n-armed bandit task. For the diminishing-utility task our prediction is that subjects in the reboxetine group will reset (disengage) more often than subjects in the other two groups, because this type of behavior is indicative of the tonic LC mode. For the n-armed bandit task our prediction is that the reboxetine group will make more exploratory choices than the other two groups. Confirmation of these predictions will provide important support for the adaptive gain theory.

10. Concluding remarks

Much of the research reviewed in this chapter is exemplary for a research approach that has recently flourished: developing and validating measures and methods for studying a human neuromodulatory system (here: the noradrenergic system), and using these methodological advances to enhance our understanding of the role of this system in human cognition. In general, the work reviewed here is consistent with the adaptive gain theory, which posits a critical role for the noradrenergic system in the optimization of behavioral performance (Aston-Jones & Cohen, 2005). It seems probable that further research using the discussed methods will continue to unravel the function of this neuromodulatory system.

There are many similarities between the noradrenergic and dopaminergic systems. NE and dopamine are both neuromodulatory transmitters and have similar physiological effects on target systems (e.g., modulation of gain; Servan-Schreiber et al. 1990); like LC neurons, some midbrain dopamine neurons are responsive to both postitive and negative motivationally salient events (Matsumoto & Hikosaka, 2009); and like the noradrenergic system, the dopamine system has been implicated in the regulation of the exploration-exploitation tradeoff (sometimes referred to as the flexibility-stability tradeoff; Dreisbach et al., 2005; Frank, Doll, Oas-Terpstra, & Moreno, 2009). Despite these similarities, the relationships between these systems and how they interact has remained unclear. This is in part due to the fact that neuromodulatory systems are generally studied in isolation (but see Briand, Gritton, Howe, Young, & Sarter, 2007). A future challenge for empirical research will be to uncover how the noradrenergic and dopaminergic (and other modulatory) systems work in parallel to dictate cognitive function. An intriguing account of the interaction between dopamine and NE has been proposed by McClure, Gilzenrat, & Cohen (2005; Aston-Jones & Cohen, 2005). This proposal builds on the hypothesis that phasic activity of (valence-sensitive) dopamine neurons reflects reward prediction errors for reinforcement learning (Schultz, Dayan, & Montague, 1997). Dopamine-guided reinforcement learning requires an annealing procedure, favoring exploration during learning in new (or changing) environments and promoting exploitation when reliable sources of reward have been discovered. The adaptive gain theory proposes that the noradrenergic system serves this function, implementing an annealing mechanism that is adaptive to ongoing estimates of utility.

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