Arousal, exploration and the locus coeruleus-norepinephrine system

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Citation

Jepma, M. (2011, May 12). *Arousal, exploration and the locus coeruleus-norepinephrine system*. Retrieved from https://hdl.handle.net/1887/17635

Chapter 1

General introduction

Part of this chapter is based on: Nieuwenhuis, S., & Jepma, M. (2010). Investigating the role of the noradrenergic system in human cognition. In T. Robbins, M. Delgado, & E. Phelps (Eds.), *Decision making. Attention & Performance, Vol. XXIII*. Oxford: Oxford University Press.

The locus coeruleus-norepinephrine system

As their name suggests, neuromodulators such as dopamine, acetylcholine and norepinephrine 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. This thesis focuses specifically on the role of the noradrenergic system in human cognition and brain function.

The locus coeruleus (LC) is the brainstem neuromodulatory nucleus responsible for most of the norepinephrine (NE) released in the brain. The LC has widespread projections throughout the neocortex, thalamus, midbrain, cerebellum and spinal cord (Aston-Jones, Foote, & Bloom, 1984; Berridge & Waterhouse, 2003). 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. For example, 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.

The adaptive gain theory of LC-NE function

For a long time researchers have associated the LC-NE system with basic, nonspecific functions such as regulating arousal and the sleep-wake cycle (Aston-Jones et al., 1984; Jouvet, 1969). But recent research has shown that neuromodulators have more specific functions in the control of behavior (e.g., Aston-Jones & Cohen, 2005; Sara, 2009). According to an influential recent theory, the adaptive gain theory (Aston-Jones & Cohen, 2005), the LC-NE system has a critical role in the optimization of behavioral performance—by facilitating responses to motivationally significant stimuli and regulating the tradeoff between exploitative and exploratory behaviors. The adaptive gain theory is largely based on neurophysiological observations in behaving animals, which will be described in the following sections.

The function of the phasic LC response

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 (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). 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.

Phasic versus tonic LC firing mode and corresponding control states

Besides the phasic increases in activity following motivationally significant stimuli, there are also 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 1). 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 1): 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 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 and 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.

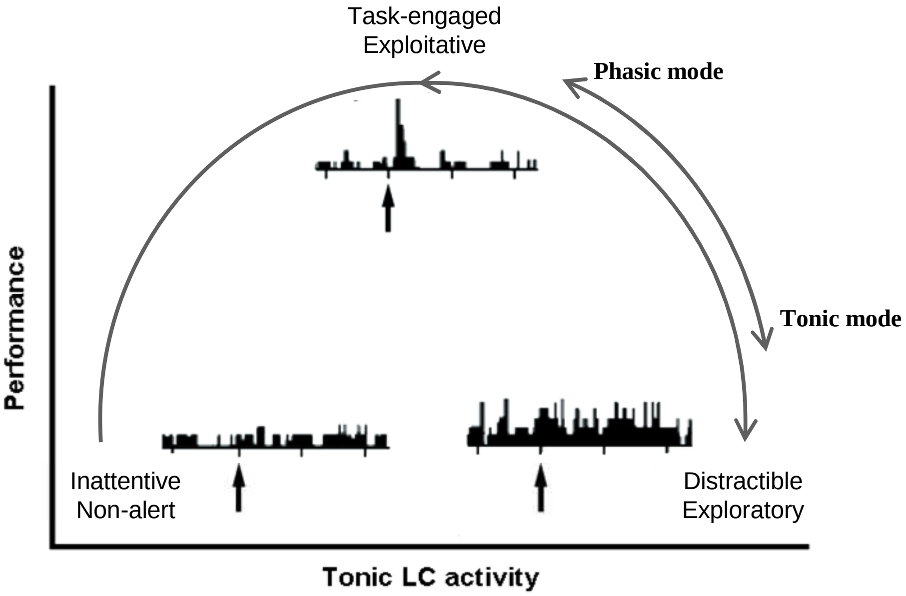

Figure 1. Inverted-U relationship between tonic LC activity and performance in tasks that require focused attention. Moderate LC tonic activity is associated with optimal performance and prominent phasic LC activation following task-relevant stimuli (phasic LC mode). High levels of tonic LC activity 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. 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.

Most of the evidence for the hypothesized link between utility, LC firing mode and exploitative vs. exploratory behavior comes from animal studies, but even that evidence is sparse. Importantly, crucial empirical tests of the theory in humans have been lacking. To fill this gap, we have used noninvasive methods to test the main assumptions of the adaptive gain theory in human participants (Chapters 2 and 3).

Other recent theories on the role of the LC-NE system in cognition

Since the publication of the adaptive gain theory, researchers have proposed several new accounts of the role of the LC-NE system in cognitive function. Yu and Dayan (2005), for example, proposed that tonic NE activity signals *unexpected uncertainty* arising from unanticipated changes in the nature of a task or behavioral context. According to Yu and Dayan, this elevated tonic NE activity in turn promotes bottom-up relative to top-down processing which facilitates learning about the external environment. As a complementary extension of this idea, Dayan and Yu (2006) proposed that phasic increases in LC/NE activity encode unexpected uncertainty arising from unexpected events or state changes *within* a task, and serve to interrupt ongoing cognitive processing associated with the default task state. In a similar vein, Bouret and Sara (2005) conceptualized the phasic LC response as a “network reset” signal that allows rapid stimulus-induced cognitive shifts and behavioral adaptation by facilitating the reorganization of target neural networks.

Whereas the adaptive gain theory mainly focuses on the regulation of attention and performance, these other accounts address the role of the LC-NE system in learning-related processes, and hence can be seen as complementary to the adaptive gain theory. The functions of the LC-NE system proposed by these accounts are broadly consistent with the adaptive gain theory. The adaptive gain theory’s assumption that the LC tonic mode promotes an exploratory control state, for example, implicitly suggests that this will facilitate learning about the external environment, consistent with Yu and Dayan’s (2005) account.

The role of the LC-NE system in neuropsychiatric disorders

Given the important role of the LC-NE system in cognition and behavior (e.g., Sara, 2009), it is not surprising that dysfunctions of this system have been associated with several neuropsychiatric disorders (e.g., Siever & Davis, 1985). Aston-Jones, Iba, Clayton, Rajkowski, and Cohen (2007) have proposed that dysregulation of the tonic and phasic components of LC activity may give rise to a variety of psychiatric conditions. For example, they hypothesized that a “hypertonic” LC mode may underlie some symptoms of attention-deficit/hyperactivity disorder (ADHD), post-traumatic stress disorder, and manic-depressive disorder. These disorders are associated with concentration problems, sleeplessness and impulsivity—symptoms that resemble the distractible behaviors of monkeys in the tonic LC mode. Conversely, a chronically “hypotonic” LC mode may give rise to the limited emotionality and flat affect that are common symptoms in depressed patients. The idea that LC dysfunction is implicated in depression is supported by findings of LC cell loss and depleted NE levels in the brains of suicide victims (e.g., Arango, Underwood, & Mann, 1996; Ordway, Schenk, Stockmeier, May, & Klimek, 2003). In addition, Aston-Jones et al. (2007) speculated that a “hyperphasic” LC mode may be responsible for the extremely focused attentive state and impaired ability to shift attention to new stimuli that are observed in autistic patients (Mann & Walker, 2003). It is important to note that these ideas are still very speculative. Thus, although there is substantial evidence that the noradrenergic system is involved in various neuropsychiatric conditions, the exact etiology underlying the relationship between LC/NE dysfunction and neuropsychiatric disorders remains to be determined.

Chapter 4 of this thesis focuses on a very special case of noradrenergic dysfunction: dopamine-β-hydroxylase (DβH) deficiency. DβH deficiency is a rare genetic disorder characterized by a complete lack of NE in both the peripheral and central nervous system. Thus, patients with DβH deficiency may be seen as having a selective and complete lesion of the noradrenergic system. Informal clinical observations suggest that DβH-deficient patients do not have obvious cognitive impairments, which is remarkable given the important role of the LC-NE system in normal cognitive function and in neuropsychiatric disorders. This suggests that DβH-deficient patients may have subtle neurocognitive deficits that have remained unnoticed in informal observations. We tested five DβH-deficient patients and a healthy control group on a comprehensive neurocognitive test battery to provide a systematic evaluation of neurocognitive function in DβH deficiency (Chapter 4).

Curiosity and exploration

As described above, the adaptive gain theory proposes that the LC-mediated trade-off between exploitative and exploratory behaviors is driven by assessments of task-related utility. However, there are also many examples of exploratory behaviors that are not directly related to task utility but seem to be driven by the innate desire to learn or experience something that is unknown. This drive to know or experience new things is typically referred to as curiosity. In many circumstances, both animals and humans have a natural tendency to explore novel, unexpected or uncertainty-inducing stimuli (Berlyne, 1960; Daffner, Mesulam, Scinto, Cohen, Kennedy, et al.,1998; Ennaceur & Delacour, 1988; Hughes, 2007; Wittmann, Daw, Seymour, & Dolan, 2008), which suggests that the exploration of curiosity-inducing stimuli is intrinsically rewarding. In the reinforcement-learning literature, the bias towards the exploration of novel or uncertain options is captured by the concept of an "exploration bonus" that is assigned to novel or uncertain stimuli to increase their expected value and promote their exploration (e.g., Kakade & Dayan, 2002; Sutton & Barto, 1998).

Pharmacological studies in rats have suggested that curiosity-related exploratory behavior is mediated by the LC-NE system (Devauges & Sara, 1990; Sara, Dyon-Laurent & Hervé, 1995; Mansour, Babstock, Penney, Martin, McLean, et al., 2003). These studies found that drug-induced enhancements of phasic LC/NE activity resulted in increased exploration of novel and unexpected objects (i.e. specific exploration), but did not increase general exploratory activity (Devauges & Sara, 1990; Mansour et al., 2003). In contrast, pharmacological and environmental manipulations that enhance tonic LC/NE activity have been found to result in increased spontaneous sampling of random environmental stimuli, and in wider-ranging and more varied movement patterns (i.e. diversive exploration; Flicker & Geyer, 1982; Mansour et al., 2003). These findings are consistent with the assumptions of the adaptive gain theory that the phasic and tonic modes of LC activity promote, respectively, focused and divided attention.

The distinction between specific and diversive exploration resembles the distinction that has been proposed between specific and diversive curiosity, referring to the desire for a particular piece of information versus the more general stimulation-seeking motive that is closely related to boredom (Berlyne, 1960). A second, orthogonal, distinction has been made between perceptual curiosity, which is evoked by novel, strange or ambiguous perceptual stimuli, and epistemic curiosity, which refers to the desire for intellectual knowledge which applies mainly to humans (Berlyne, 1954).

In the 1960’s and 70’s, curiosity was a topic of intense investigation among experimental psychologists, resulting in an extensive theoretical framework for understanding curiosity and related behaviors. According to a classic psychological theory, curiosity evoked by ambiguous or conflict-inducing stimuli produces increased levels of arousal and is experienced as an aversive state, due to lack of information (e.g., Berlyne, 1966). The theory further proposes that termination of this condition, through access to relevant information, is rewarding and promotes learning. Although curiosity is one of the most basic biological drives in both animals and humans, and has been identified as one of the key motives for learning and discovery, the topic has been largely neglected in cognitive neuroscience; hence the neural mechanisms underlying curiosity are still poorly understood. Chapter 5 of this thesis describes a study in which we investigated the neural correlates of human perceptual curiosity.

Arousal, accessory stimuli and temporal uncertainty

Most of the topics discussed in this thesis are closely linked to arousal, a fundamental property of behavior. The concept of arousal is strongly related to attention, anxiety, stress and motivation, but has proven difficult to define. The LC-NE system is often associated with arousal, based on classical findings that tonic LC activity covaries with stages of the sleep-wake cycle (e.g., Aston-Jones & Bloom, 1981a; Hobson, McCarley, & Wyzinski, 1975) and that LC neurons exhibit strong phasic responses to salient and arousing stimuli (e.g., Aston-Jones & Bloom, 1981b; Grant, Aston-Jones, & Redmond, 1988). In addition, the inverted-U relationship between tonic LC activity and performance (Figure 1) resembles the Yerkes-Dodson relationship between arousal and performance, one of the most important components of arousal theory (Duffy, 1957; Yerkes & Dodson, 1908). Recent studies have corroborated the notion that the LC-NE system plays a crucial role in the regulation of arousal (e.g., Gompf, Mathai, Fuller, Wood, Pedersen, et al., 2010; Carter, Yizhar, Chikahisa, Nguyen, Adamantidis, et al., 2010).

Obviously, the LC-NE system is not the only arousal-related system. It is generally accepted that arousal is a multifaceted construct which comprises a constellation of brain and somatic systems that subserve distinct but often overlapping functions (Neiss, 1988; Pribram & McGuinness, 1975; Robbins, 1997). One of these systems is the peripheral sympathetic nervous system. Motivationally significant stimuli or events typically elicit both a phasic LC response and a phasic response of the peripheral sympathetic nervous system that is often referred to as the *orienting response* (Lynn, 1966; Pavlov, 1927; Sokolov, 1963). The orienting response entails a collection of physiological changes, including a temporary dilation of the pupils, a rise in skin conductance, and a momentary change in heart rate, and is typically accompanied by a shift of attention toward the eliciting event. Anatomical considerations suggest that the parallel activation of the peripheral sympathetic nervous system and the LC-NE system following motivationally significant events reflects co-activation of these two systems by a common afferent source in the medulla (Aston-Jones, Ennis, Pieribone, Nickell, & Shipley, 1986; Nieuwenhuis, De Geus, & Aston-Jones, 2011). Nieuwenhuis et al. (2011) hypothesized that the co-activation of the LC-NE system and the peripheral sympathetic nervous system allows efficient mobilization for action in response to motivationally significant events: the LC-NE system facilitates the execution of cognitive decisions concerning proper behaviors in the face of urgent stimulus demand while, at the same time, the peripheral sympathetic nervous system facilitates physical execution of the chosen behaviors.

As described above, the orienting response and the phasic LC response are driven by motivationally significant task-relevant stimuli, but also by novel or intense task-irrelevant stimuli, such as unexpected loud sounds. The automatic orienting of attention towards salient task-irrelevant stimuli generally disrupts performance on the concomitant task (e.g., Parmentier, Elford, Escera, Andrés, & San Miguel, 2008; Schröger and Wolff, 1998). However, there are also instances where the occurrence of a task-irrelevant sound leads to faster responses to a simultaneously presented imperative stimulus in another modality (e.g., Bernstein, Clark, & Edelstein, 1969a,b; Hackley & Valle-Inclan, 1998, 1999; Valls-Solé, Solé, Valldeoriola, Muñoz, Gonzalez, et al., 1995). This phenomenon has been referred to as the *accessory-stimulus effect*, and is generally attributed to a temporary increase in arousal. Besides their effect on reaction times, accessory stimuli have been found to elicit an increase in response force (Miller, Franz, & Ulrich, 1999; Stahl & Rammsayer, 2005). Pharmacological manipulations in cats have shown that the availability of NE is critical for accessory-stimulus induced increases in motor activity, at least in the case of reflexive responses (Stafford & Jacobs, 1990). A possibility that remains to be explored is that an NE-mediated temporary increase in neuronal responsivity (or gain) also underlies the accessory-stimulus induced speeding of reaction times. It is interesting to note in this regard that changes in gain are closely related to, and under certain conditions can be equivalent to, changes in decision threshold (Servan-Schreiber, Printz, & Cohen, 1990). Thus, one possible mechanism underlying the speeding of responses by accessory stimuli is a temporary lowering of the decision threshold. Despite a substantial empirical database, there is no general agreement among researchers regarding the neurocognitive mechanisms underlying the facilitatory effect of accessory stimuli. Chapter 6 of this thesis describes two experiments that aimed to shed more light on the effects of accessory stimuli on different components of information processing.

The effects of task-irrelevant accessory stimuli on information processing are exogenously-driven (i.e. automatic). A possibly related endogenously-driven phenomenon is the speed-up of reaction times to an imperative stimulus when its timing is highly predictable. This phenomenon, referred to as the warning effect or temporal-preparation effect, is typically investigated by means of paradigms in which participants use temporal cues to anticipate the onset of an imperative stimulus. In contrast to the accessory-stimulus paradigm, the interval between the temporal cue and the imperative stimulus is long enough to enable deliberate preparation. Like the accessory-stimulus effect, temporal-preparation effects have been attributed to NE-mediated changes in alertness (Coull, Nobre, & Frith, 2001; Fernandez-Duque & Posner, 1997; Witte & Marrocco, 1997). Furthermore, it has been found that the firing rate of LC neurons increases during the interval between the temporal cue and the imperative stimulus (Yamamoto & Ozawa, 1989). This raises the possibility that the temporal-preparation effect and the accessory-stimulus effect may correspond to endogenous and exogenous instances of the same underlying process: whereas accessory stimuli, by virtue of their salience, may elicit an automatic NE-mediated increase in gain, temporal preparation may allow controlled gain modulations resulting in the optimization of system parameters at the expected onset of the imperative stimulus. Chapter 7 of this thesis describes two experiments in which we investigated temporal-preparation effects on information processing.