The locus coeruleus: where cognitive and emotional processing meet the eye

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Abstract

The pupil offers a window into how arousal shapes the way we think, learn, and behave. Yet arousal is a complex and multifaceted construct, leaving many open questions about the relationship between pupil size and different neurocognitive processes. Exciting new research has linked pupil measures to activity in the locus coeruleus (LC), the brain's primary supplier of norepinephrine (NE), creating new opportunities to study a neuromodulatory system that long seemed inaccessible in human research. In this chapter, we review evidence showing that pupillometry reveals the role of the locus coeruleus-norepinephrine (LC-NE) system in energizing attention and amplifying mental selectivity. We also synthesize computational and neurobiological models of how the LC-NE system implements neural gain, a process by which processing salient information is enhanced and processing lower priority information is suppressed. In the latter half of the chapter, we turn to a classic dual-curve model of arousal-performance interactions to explain what (quality of information processing), when (level of arousal), and where (locus of priority signal) LC activity influences information processing in the brain. We conclude by summarizing how pupillometry can be used to test the influence of LC activation on key parameters of attention and arousal.

Overview

In recent years, pupillometry has experienced a resurgence in popularity as a technique for studying arousal and its complex effects on cognition. Arousal is often characterized as a combination of psychological and physiological responses to external stimulation (e.g., a danger signal) or internal mental processes (e.g., solving a math problem). It also relates to patterns of autonomic activity and wakefulness, both local and large-scale brain network dynamics, and a wide array of behavioral outcomes. Thanks in large part to pupillometry, it is now understood that fluctuations in arousal states help to supply the energy required to meet processing demands (capacity), tune attention to task-relevant information (selectivity), and determine which sources of information are preferentially processed and remembered (quality). In this chapter, we dissect the meaning of "pupil as an index of arousal" with respect to different aspects of information processing in the mind and brain. We also focus on the critical role of one of the brain's core arousal systems, the **locus coeruleus-norepinephrine (LC-NE) system**, in regulating these complex processes.

To begin, we review findings converging on the idea that non-luminance-mediated changes in pupil size are regulated by arousal and mental processes. We introduce **classic models of arousal-cognition interactions** and present evidence showing that pupil-linked arousal signals index what we perceive, attend to, and remember. We then synthesize cross-species research establishing a strong link between the LC-NE system and attentional control of the pupil.

In the second part of the chapter, we shift our discussion to how the LC-NE system influences **mental and neural selectivity** by implementing **neural gain**, a computational process by which strong patterns of brain activity are amplified and weaker patterns of brain activity are suppressed. We begin by describing influential computational and neurophysiological models of LC-arousal interactions, including adaptive gain theory. In this discussion, we explain how these frameworks capture the important contributions of distinct LC processing modes to task performance.

Extending this work, we describe a neurobiological account of how LC-NE system activation implements neural gain through its influence on local patterns of brain activity. We then interpret this new model through the lens of classic theories of arousal-performance interactions to explain how the priority of different inputs - and patterns of activity in the regions and functional networks that support those representations - may shift according to the overall level of arousal.

Moving from there, we discuss how the LC-NE system serves to energize adaptive behaviors, including regulating action selection, action execution, and effort. We explore how fluctuations in arousal and LC activity enable organisms to meet task demands by influencing **attentional capacity**, or the availability of mental resources. We trace a common theme that the LC helps mobilize resources at the mental, physical, and physiological levels. Additionally, we examine how adaptive adjustments in global arousal levels and sustained LC activity may also determine **attentional intensity**, or the amount of mental resources that are specifically devoted to processing task-relevant information.

At the end of this chapter, we propose a unifying framework of LC-NE system function to reconcile predictions from multiple models of arousal and attention. We conclude by summarizing different pupil measures and what they reveal about the LC's strong influence over the selectivity, capacity, and quality of information processing in the brain.

1. Foundational links between arousal, cognition, and the pupillary response

Arousal is at the core of our mental and physical lives. In addition to promoting general wakefulness, the ebb and flow of arousal states enable organisms to adapt to their constantly changing environments. Early theoretical work endeavored to capture these effects by formulating models of arousal and attention. These theories offered elegant solutions to some challenging problems in cognitive psychology, including the issue of how arousal tunes the allocation policy, or selectivity, of attention. They also laid a strong foundation for future neurocomputational models that formalized the effects of arousal on our ability to sustain and direct limited mental resources to process important information. To begin, we briefly summarize some of these key theories and how they have promoted a deeper understanding of arousal-cognition interactions.

1.1 Relationships between arousal and task performance

As it pertains to cognition, arousal is thought to be a domain-general construct that regulates the recruitment and allocation of attentional resources. One influential framework, the Capacity Model of attention, characterizes these effects of arousal in terms of its dual influences on attentional capacity and the allocation policy of attention (Kahneman, 1973). Attentional capacity can be conceptualized as the energy that is available for *any* information processing. A low arousal level, characterized by drowsiness or listlessness, is associated with a diminished

attentional capacity. As a result, less energy is available for information processing. Increasing the level of arousal promotes wakefulness and increases the available attentional capacity for cognitive processing. Thus, the first part of the Capacity Model of attention captures how arousal might regulate the amount of mental resources that are available at any given moment. The second part of the Capacity Model proposes that arousal exerts control over the allocation of this pool of resources. An increase in arousal narrows the breadth of attention, restricting the amount of cognitive processes that receive these valuable resources.

One of the litmus tests for the Capacity Model and other cognitive theories is how well they can explain the relationship between arousal and behavioral performance. In a classic experiment, researchers examined how mice performed on a luminance discrimination task as a function of the intensity an electric shock administered for incorrect responses (Yerkes & Dodson, 1908). The results showed the shape of the relationship between performance and arousal (i.e., shock intensity) depended on the difficulty of the task condition. When the task was simple (i.e., discriminating between dark versus bright luminance), the arousal-performance curve increased monotonically. By contrast, when the task was difficult (i.e., discriminating between dark versus gray), the arousal's relationship with performance followed an "inverted-U" function, whereby performance peaked for intermediate levels of shock. This famous characterization of the arousal-performance relationship has since been replicated in other animal and human research across many different paradigms (Broadhurst, 1957).

Despite its massive influence on the fields of cognitive psychology and neuroscience, the classic arousal-performance relationship is often misrepresented (Diamond et al., 2007). Many researchers mistakenly ascribe the "inverted-U" function to all behavioral tasks, despite the presence of an additional monotonic pattern. In actuality, different tasks appear to follow different arousal-performance curves, with the shape of these functions being largely determined by the difficulty and nature of the task (Yerkes & Dodson, 1908). While the arousal-performance curve for "difficult" tasks can be appropriately described by an "inverted-U" function, which has been received the most attention in cognitive psychology research. However, this preoccupation with the inverted-U function has also led researchers to neglect the presence of the "easy" curve, which is characterized as a linear relationship between arousal and task performance. That is, for tasks that engage habitual or emotional responses that are more reflexive and require little cognitive effort, arousal will continue to benefit rather than impair performance as it increases. This distinction between easy and hard tasks has critical

implications for how we interpret the role of arousal in influencing different brain and behavioral outcomes.

1.2 The cue utilization hypothesis and the rigidity-lability paradox

Why do some arousal-performance curves follow the “inverted-U” function? And why do different tasks produce different arousal-performance curves? One of the early attempts to address these questions is the cue utilization hypothesis (Easterbrook, 1959), which elegantly explains how the relationship between the level of arousal and performance is modulated by task or response demands. According to this seminal hypothesis, at a low level of arousal, attention is broadly allocated among a large pool of cues, or cognitive processes, that may be task-relevant or task-irrelevant. This low arousal state is frequently described as a state of inattentiveness, in which performance on any task is generally poor.

As arousal increases to moderate levels, however, the focus of attention also narrows and filters out task-irrelevant cues while preserving task-relevant cues. By promoting attentional focus on task-relevant information processing, moderate levels of arousal facilitate a state of task engagement, in which task performance is generally optimized. As arousal levels increase passed this task-optimal zone, the focus of attention may become too narrow to support some task-relevant cues, thus impairing task performance. In other words, the task-optimal level of arousal (i.e., the “peak” of the “inverted-U” function) is achieved when the focus of attention is large enough to encompass all task-relevant cues but also small enough to exclude all task-irrelevant cues (Easterbrook, 1959).

A corollary to this explanation is that the task-optimal level of arousal depends on the number of cues demanded by the task. Because difficult tasks demand more cue utilization, the narrowing of attention filters out task-relevant cues at lower levels of arousal, resulting in an earlier “inverted-U” peak. In contrast, tasks that demand less cue utilization are impaired by the narrowing of attention at higher levels of arousal. This difference in cue utilization demands between difficult and easy tasks helps account for the existence of dual arousal-performance curves: for more difficult tasks, the task-optimal peak occurs at moderate levels of arousal; for easier tasks, performance peaks at higher levels of arousal until it eventually plateaus (Diamond et al., 2007).

Based on the findings of the time, the cue utilization hypothesis provided a compelling, high-level account of the arousal-performance relationship by describing how arousal influences cue

utilization. However, while the key assumption that increasing arousal narrows the focus of attention was well supported by many studies (Bahrick et al., 1952; Broadbent, 1971; Bursill, 1958; Callaway & Dembo, 1958; Hockey, 1970), other studies had linked high levels of arousal to increased distractibility (Korchin, 1964; Woodhead, 1964). Thus, arousal appears to have the paradoxical effect of simultaneously narrowing attentional focus while also increasing attentional distractibility. Simply put, arousal makes attention more rigid yet more labile (Callaway & Stone, 1960; Kahneman, 1973; Wachtel, 1967).

Wachtel (1967) addressed this rigidity-lability paradox by dissociating two independent properties of attentional selectivity: its breadth and its stability. Using the metaphor of attention as a beam of light (Hernández-Peón, 1964), the breadth refers to the width of the flashlight beam while the stability refers to the amount of scanning across a field. Thus, in line with the cue utilization hypothesis, increasing arousal narrows the width of the flashlight beam, such that fewer cues are illuminated by the beam of light (**Figure 1**). However, high arousal also reduces the stability of the flashlight beam, leading to more movement and scanning across the array of cues (**Figure 1C**). By narrowing the attentional beam and inducing more scanning, high levels of arousal simultaneously increase the likelihood of task cues being dropped and non-task cues being captured by the attention. This conceptual description of arousal's dual effects on the rigidity and lability of attentional selectivity is an important foundation through which later researchers tested and developed neurocomputational models.

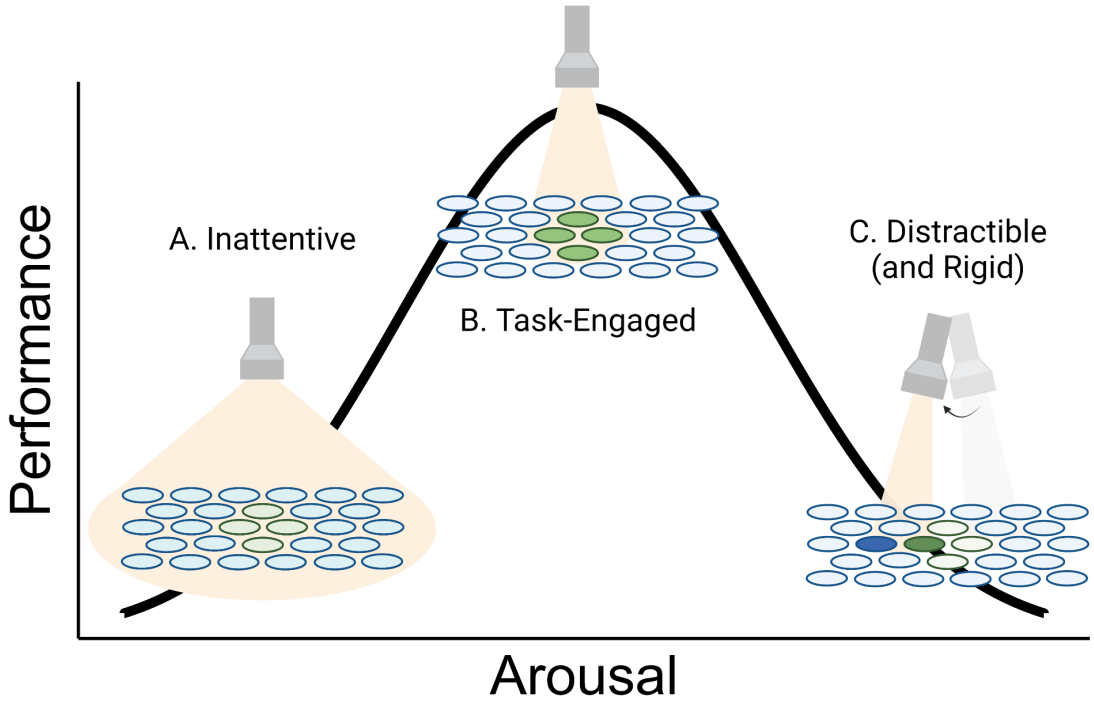

Figure 1. The attentional flashlight and the "inverted-U" arousal-performance curve. Task performance varies as a function of overall levels of global arousal, with the attentional beam narrowing with increasing arousal. (A) At low levels of arousal, the beam is diffuse and attentional capacity is low, capturing a wide range of sensory inputs, or cues (circles). (B) At moderate levels of arousal, the attentional beam focuses on the set of task cues and enhances their processing (dark green circles), corresponding to an optimal, task-engaged state and optimal performance. (C) At high levels of arousal, the attentional beam remains narrow while scanning more often across the field of task cues (circles). This results in simultaneously more rigid and labile attentional processes that encourages the selection of task-irrelevant cues, or distractors (blue circles). One consequence of this relationship between arousal and the "attentional flashlight" is its effect on task performance is that it follows an "inverted-U" function for cognitively demanding tasks. Image created with BioRender.com.

1.3 The pupil as a window into arousal-cognition interactions

The influential models we have discussed so far drew important links between background levels of arousal and fluctuations in attentional states. They also provided a framework for understanding how transient, or phasic, arousal responses signal mental workloads and the amount of information devoted to processing a behaviorally relevant event. While these ideas provided testable hypotheses about arousal-attention interactions, they still required a tool or biomarker that could help quantify cognitive and arousal effects in the laboratory. For this endeavor, researchers turned to pupillometry, a non-invasive technique that measures physiological and mental activity through changes in pupil diameter. Pupil size is an easily

measurable physiological variable that has frequently been used to quantify both tonic and phasic arousal. Beginning in the 1960s, this inspired researchers to use pupillometry to study how arousal modulates attention and mental operations during a wide range of cognitive and affective processes, including effort, affect, salience, novelty, and surprise. Here, we showcase just a few of the key findings regarding the functional significance of pupil responses to behavior.

One influential program of research examined how pupillary response track information processing load, or mental effort, during a demanding cognitive task (Beatty & Lucero-Wagoner, 2000; Simpson & Hale, 1969; van der Wel & van Steenbergen, 2018). For example, Hess & Polt (1964) observed greater pupillary responses when subjects were performing difficult arithmetic problems (e.g., complex multiplication) compared to simple addition problems. A few years later, Kahneman & Beatty (1966) demonstrated that pupil size tracks working memory load in a digit span task, suggesting that a larger pupil reflects the amount of information being juggled in mind and/or the complexity of cognitive operations needed to maintain task performance. Pupil size increased as digits were sequentially presented and encoded into working memory, and the magnitude of this pupillary response was greater for longer digit spans (Kahneman & Beatty, 1966). A subsequent study using a pitch discrimination task demonstrated that trials in which tones were more difficult to discriminate elicited greater pupil dilations (Kahneman et al., 1967). Taken together, these findings indicated that demanded greater mental effort elicit larger task-evoked pupillary responses.

According to some theories of arousal, an increased demand for task-related information processing, or mental effort, is thought to be supplied by an increase in arousal (Kahneman, 1973). Models of arousal and attention suggest that the continuous monitoring and evaluation of task demands adjust mental effort, leading to an appropriate adjustment in arousal and the capacity and selectivity of attention (Aston-Jones & Cohen, 2005; Kahneman, 1973). Thus, the pupillary response may reflect fluctuations in arousal that support the information processing load demanded by the current task (Beatty & Lucero-Wagoner, 2000; Bradshaw, 1967; Pribram & McGuinness, 1975; Zénon, 2019). Indeed, a large body of work demonstrates that pupil dilations are elicited by an increase in cognitive control, a topic we discuss in more detail in Section 5.3.

Another extensive program of research focuses on pupillary responses that are evoked in a bottom-up, rather than goal-directed, manner. The idea that pupillary responses reflect affect in

emotional stimuli was first explored by Hess & Polt (1960). Although they reported differential pupillary responses to emotional stimuli of different valences (i.e., pupil constriction to negative stimuli and dilation to positive stimuli), numerous subsequent studies have disputed this result (Bradley et al., 2008; Partala & Surakka, 2003). Using images with validated arousal and valence ratings, Bradley et al. (2008) demonstrated that the pupil dilates to arousing stimuli, irrespective of their valence. Such studies have converged on the notion that the magnitude of the pupil dilation to an emotional stimulus varies as a function of arousal, irrespective of valence (see also Zekveld et al., 2018). In light of its close link to autonomic arousal responses, pupil dilation has also become a popular measure of fear conditioning (de Voogd et al., 2016; Reinhard & Lachnit, 2002).

Exogenous elicitors of arousal do not need to be inherently emotional. The pupillary response has also been shown to signal both contextual and absolute novelty. Importantly, these two forms of novelty differ in that contextual novelty refers to stimuli that are unexpectedly encountered within a certain context, while absolute novelty refers to stimuli that were never encountered before (Kafkas & Montaldi, 2018). One of the most robust demonstrations of a link between the pupil and contextual novelty is the oddball task. This commonly used paradigm manipulates novelty through the infrequent presentation of an oddball stimulus, which stands out from its surrounding stimuli by virtue of its semantic, perceptual, or emotional features. Many studies using the oddball detection paradigm across different sensory modalities have demonstrated that the pupil dilates more to oddball stimuli than to standard stimuli, or information that is presented more frequently (Gilzenrat et al., 2010; Murphy et al., 2011, 2014). This novel versus standard effect is also observed when the contextually novel stimuli does not require an overt button response, although the effect is slightly diminished (Krebs et al., 2018; Mather et al., 2020). Moreover, the dynamics of the pupillary fluctuations during the task covaried with brainstem arousal regions, such as the locus coeruleus, thought to mediate the arousal response (Murphy et al., 2014). Together, these findings suggest that the contextual novelty is associated with an arousal response that can be tracked with pupillometry.

It is worth pointing out that the other form of novelty, absolute novelty, yields different pupillary effects. When shown new stimuli versus familiar stimuli, participants exhibited either more pupil constriction or diminished pupil dilation (Kafkas & Montaldi, 2014; Naber et al., 2013; Võ et al., 2007). The contrasting effects of absolute versus contextual novelty may suggest that contextual novelty is more closely tied to activation of noradrenergic pathways (Mather et al., 2020; Murphy et al., 2014) while absolute novelty is more closely associated with activation of

cholinergic pathways in the brain (Duszkiewicz et al., 2019; Kafkas & Montaldi, 2018). It is also noteworthy that pupil constriction effects observed in old/new recognition paradigms are in response to “common” absolute novelty (e.g., first time seeing *this* apple) rather than “distinct” absolute novelty (e.g., first time seeing *any* apple; Duszkiewicz et al., 2019). Whether or not pupil dilations to these different types of novelty reflect the same underlying process remains an open question, given that distinct absolute novelty is very challenging to study in humans.

Pupil dilations also track with surprise, which is a function of a mismatch between one’s expectations about an outcome of an event and what actually occurs (Ekman & Davidson, 1994). When individuals have higher confidence in their incorrect expectations, they encounter a greater degree of surprise. In other words, surprise is a prediction error of certainty that signals the presence of unexpected information and elicits an increase in arousal. Several studies have demonstrated the link between surprise and arousal by showing that the pupillary response to feedback is modulated by surprise (Braem et al., 2015; de Gee et al., 2014; Nassar et al., 2012). Moreover, in an experiment that dissociated reward and uncertainty prediction errors, Preuschoff (2011) demonstrated that the pupil dilation response varied as a function of uncertainty prediction error, but not reward prediction error. While it is well known that the dopaminergic system signals reward prediction errors, the pupillary findings suggest that the noradrenergic arousal system may signal the uncertainty-related prediction error (Preuschoff, 2011).

Updating expectations based on feedback is an important component of learning and decision-making. Surprise serves as a strong signal that increases arousal in response to unexpected information. This modulates the capacity and selectivity for the processing of surprising information, which can rapidly facilitate learning and benefit future decision-making (de Gee et al., 2020). It can also facilitate evidence accumulation in dynamic environments and may bias perceptual decision-making based on priors (Krishnamurthy et al., 2017) or motivational effects (Leong et al., 2021).

Similarly, context shifts, such as changes in one’s thoughts, feelings, or surroundings, signal the presence of new information and are important for updating one’s internal model of the world. Pupil dilations are thought to track context shifts that are both internal (e.g., when switching between cognitive tasks) and external (e.g., when encountering a change in the environment). For example, research in both monkeys and rodents show that the pupil dilates when environmental contingencies change (Rajkowski et al., 1994; Sara, 2009; Sara & Segal, 1991).

Similar results have been obtained in human pupillometry research. Namely, transitions from highly regular and structured auditory sequences to new variable, irregular, or regular sequences elicit robust pupil dilations, suggesting the pupil tracks the statistics of the environment (Zhao et al., 2019).

Shifts from contextual stability to instability, or change, also have consequences for how we encode temporally extended sequences of information. In one pupillometry study, Clewett et al., (2020) manipulated the context during item sequence learning by presenting auditory tones in either the left or right ear during a block of images. The event boundary, or the shift in context from the auditory tone presented in the left ear to the right ear, reliably elicited a pupil dilation. Distinct temporal characteristics of this boundary-evoked pupil dilation were also related to temporal memory measures of episodic memory formation. This finding suggests that fluctuations in pupil size signal arousal processes that construct event representations in long-term memory.

In a similar vein, shifts in internal belief states, such as a violation of expected statistical regularity, may also produce an increase in arousal and pupil dilation. In a predictive inference task, subjects were asked to guess numbers that were randomly sampled from a Gaussian distribution of either high or low variance about an unknown mean (Nassar et al., 2012). After a series of trials, participants develop an internal belief state about this unknown mean. When the underlying mean switches, participants experience a violation of their internal belief states, which is followed by a period of elevated pupil size. The increased pupil size may reflect an increase in arousal after the change point, which may be adaptive in situations where a rapid updating of internal belief states is required. Critically, because no perceptual change occurs when the underlying mean switches, this study supports the idea that an increase in arousal occurs for general contextual changes, whether they are internal (e.g., internal expectations) or external (e.g., a change in environments).

The highly selective effects of arousal on memory are indexed by pupil dilations. For example, when viewing a series of overlapping image pairs, threat-induced arousal amplified the memory benefit for the prioritized image at the cost of the non-prioritized image, revealing the influence of arousal on the selectivity of information processing (Clewett et al., 2018). Pupil dilations were associated with greater memory selectivity and greater activity in arousal regions of the brain, connecting the behavioral effects with physiological markers of arousal. Interestingly, pupil dilation can also serve as a predictor of successful retrieval of emotionally arousing memories.

Larger pupil dilations during encoding relate to greater activity in arousal-related brain regions, such as the LC, during retrieval (Sterpenich et al., 2006). Thus, pupil dilation appears to be an indicator of the selective benefit of emotional arousal during both encoding and retrieval. As emotional stimuli tend to be better remembered than neutral stimuli, these findings also align with broader literature linking larger stimulus-evoked pupil dilations to stronger encoding processes (Goldinger & Papesh, 2012; Papesh et al., 2012).

Finally, studies have used pupillometry to study how arousal influences the waxing and waning of attention across time. Attentional states shape cognitive processing and are an important variable for explaining variability in behavioral performance and task engagement over time. In using pupil diameter to infer tonic levels of arousal, researchers identified ranges of baseline pupil diameter corresponding to an “exploitative” state (more task engagement) and an “explorative” state (less task engagement; Gilzenrat et al., 2010; Jepma & Nieuwenhuis, 2011; Van Den Brink et al., 2016). The “exploitative” state is not only characterized by improved task performance, but it also facilitates larger phasic task-evoked pupil dilations. The neural mechanisms connecting baseline, or non-stimulus-related, changes in pupil diameter to these attentional states will be a primary focus in later sections.

In summary, a large body of work has used pupillometry to study how arousal modulates information processing across multiple cognitive domains. While the pupil can reflect state changes in attention and arousal due to top-down factors like mental effort or fatigue, it can also reflect phasic increases in arousal elicited by salient events in the environment, including shifts in environmental contingencies or biological imperatives. Different pupil dynamics can thereby characterize and quantify the varied influences of arousal processes on mental selectivity and capacity, as predicted by earlier theoretical frameworks.

1.4 Challenges of understanding arousal: multiple pathways, multiple effects

Pupil changes are highly sensitive to changes in arousal and relate to key parameters of attention. But what neurophysiological mechanisms support these complex relationships? Is arousal merely a readout of different cognitive processes? Or does it reveal causal relationships between specific brain systems and information processing?

While researchers have uncovered much of the neurocircuitry that regulates pupil size, the functional significance of these pathways to cognitive processes is less clear. Part of the reason for this under specification is that central arousal systems are very complex and comprised of

multiple brainstem neuromodulatory pathways, including the noradrenergic, cholinergic, serotonergic, dopaminergic, and reticular activating systems (Jones, 2003; Larsen & Waters, 2018). Although some of these neuromodulatory pathways may have redundant functions (e.g., promoting wakefulness), they likely exert different effects on their ascending brain targets. Arousal is also very multi-faceted, and contains affective, autonomic, and wakeful components (Satpute et al., 2019). Further, the literature is riddled with perplexing findings like directional fractionation, a term referring to the low correlations between pupil size and other autonomic markers of arousal, such as heart rate (Lacey & Lacey, 2007).

Although it is worth noting the complex, multidimensional nature of the arousal systems (Thayer, 1978), a clear consensus is beginning to emerge that one neuromodulatory system is a key mediator of cognitive control over the pupil: the locus coeruleus-norepinephrine (LC-NE) system. Indirect evidence of this relationship comes from work showing that pupil dilations are sensitive to the same mental processes and salient events that engage the LC-NE system. In fact, many of the studies outlined in the previous section report corroborating evidence of LC activity occurring alongside task-related pupil changes (Larsen & Waters, 2018). Pharmacological data indicates that drugs that modulate activity in the LC-NE system elicit changes in pupil size. Perhaps most convincingly, there is now direct evidence from neuroanatomical tracings as well as optogenetic stimulation and electrode recording work in animals demonstrating a causal link between LC activity and the pupil. Throughout the rest of this chapter, we focus on what this relationship reveals about the essential and multifaceted roles of LC activity in mediating arousal's effects on attention, neural processing, and behavior (Aston-Jones & Cohen, 2005; Berridge & Waterhouse, 2003).

2. The LC-NE arousal system and pupillometry

2.1 Functional neuroanatomy of the LC-NE system

The locus coeruleus (LC) is a small brainstem nucleus bilaterally positioned on the rostral aspect of the pons and serves as the primary supplier of norepinephrine (NE) to most of the brain (Berridge & Waterhouse, 2003). As a key hub region of ascending arousal systems, the LC plays an important role in regulating global arousal states, including overall levels of wakefulness and alertness (Carter et al., 2010). Remarkably, despite its small size – approximately 30,000-50,000 neurons in the human brain – the LC also has far-reaching and robust effects on attention and memory processes (**Figure 2**). Much cross-species work

demonstrates that dynamic patterns of LC-NE system activation regulate executive function, working memory, and behavioral flexibility (Poe et al., 2020; Sara, 2009). Activation of the LC also helps direct mental resources processes where they are most needed, either by facilitating focused attention or reorienting attention towards unexpected or salient stimuli (Corbetta et al., 2008; Sara, 2009). LC activity furthermore facilitates the encoding and consolidation of emotionally salient and novel information, ensuring that organisms can store and recall memories of motivationally relevant experiences (Mather et al., 2015; McGaugh, 2000; Poe et al., 2020; Sara, 2009). Such enhancements may be accomplished through the regulation of synaptic plasticity, including through modulatory effects on amygdala and hippocampal circuitry (Bergado et al., 2011; Berridge & Waterhouse, 2003; Hansen, 2017; Harley, 1987; Mather et al., 2015; Tully & Bolshakov, 2010).

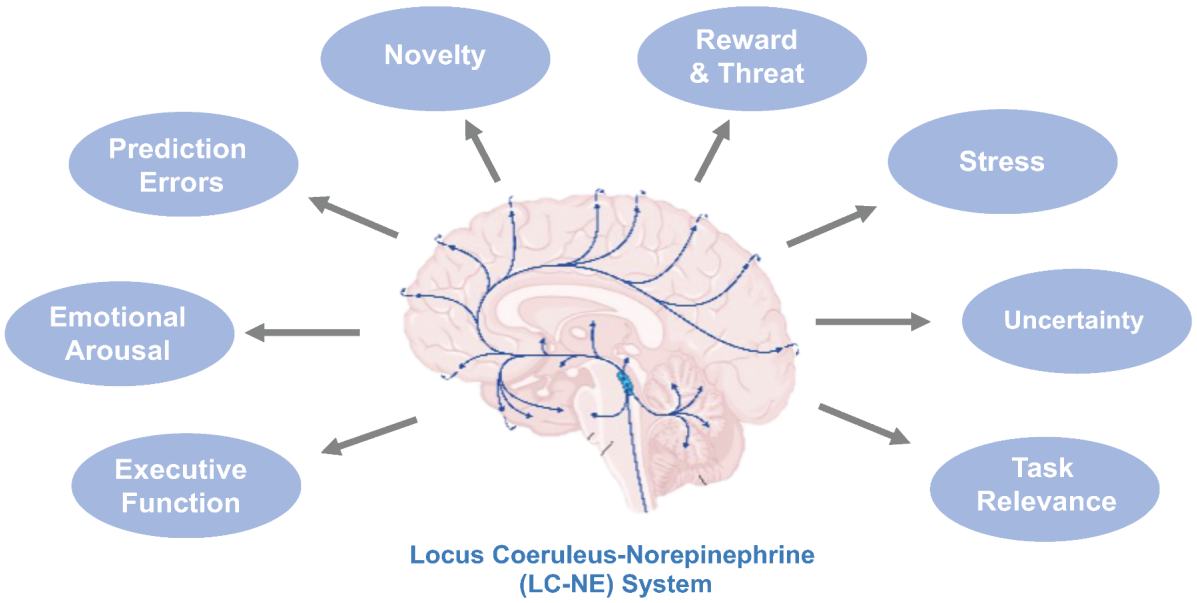

Figure 2. The locus coeruleus-norepinephrine (LC-NE) system supports a wide variety of cognitive and emotional processes. The LC-NE system sends dense efferent projections across most of the brain, enabling it to modulate local brain activity patterns. Its wide reach also enables it to shape functional dynamics of large-scale brain networks under arousal. Image created with BioRender.com.

The LC sends dense efferent projections to most regions of the brain, enabling it to regulate both local patterns of brain activity as well as brain-wide communication between different functional networks (Berridge & Waterhouse, 2003; Poe et al., 2020). Under arousal, NE is diffusely released at its cortical and subcortical targets, where it engages various adrenoreceptors that have distinct functional properties, spatial distributions, and binding

affinities for NE (Berridge & Waterhouse, 2003). Broadly, this includes alpha1-adrenoreceptors, alpha2-adrenoreceptors, and beta-adrenoreceptors. While a full description of these receptors is beyond the scope of this chapter, it is important to note that different receptors exert different effects on neural excitation and synaptic plasticity. Thus, different spatiotemporal patterns of adrenoreceptor activation elicit distinct effects on brain activity under arousal, including supporting increases in neural gain.

In addition to functional differences in adrenoreceptors, the LC can influence arousal and cognitive processing through changes in its own firing rate. LC neurons fire in two distinct modes: (1) phasic, or transient, activity that typically involves firing rates of ~8-10 Hz (Aston-Jones & Bloom, 1981), and (2) tonic, or background, activity that typically involves firing rates ~1-6 Hz. Phasic LC responses are characterized by strong burst of activity that occur in response to salient inputs, such as novel, unexpected, goal-relevant, or rewarding stimuli (Aston-Jones & Bloom, 1981; Bouret & Sara, 2005; Foote et al., 1980; Sara & Bouret, 2012). Research also shows that these transient LC responses are closely aligned with the appearance of target stimuli (Aston-Jones et al., 1994), consistent with the idea that LC activation acts as a temporal filter for processing task-relevant information (see also Nieuwenhuis et al., 2005). Phasic LC responses facilitate the encoding of salient information and promote optimal task performance, particularly on tasks that require focused attention and the detection of target information (Aston-Jones et al., 1997; Clayton et al., 2004; Sara, 2009). Even in the absence of an external stimulus, pairing optogenetic stimulation of LC phasic activity with low intensity sensory stimulation can enhance the salience and encoding of those sensory representations (Vazey et al., 2018). This modulatory pattern mimics LC effects that are typically observed in response to intense or salient environmental stimuli.

By contrast to stimulus-linked bursts in LC activity, tonic LC activity is typically characterized by sustained – often described as “background” - levels of LC activation (Berridge & Waterhouse, 2003). Neurophysiological findings in monkeys indicate that spontaneous LC activity fluctuates over the course of a behavioral test session (Aston-Jones et al., 1996), which also seems to have important consequences for how attention and decision processes vary from trial to trial. High tonic levels of LC output are also closely tied to states of wakefulness and global arousal, such as during acute stress. Together, these different modes of LC activity are critical for regulating dynamic switching between different forms of learning and decision-making strategies (Aston-Jones & Cohen, 2005).

In many ways, the LC is blind to what is happening in the world. So, what determines how fast LC neurons will fire? Adaptive adjustments in LC firing are largely accomplished via top-down influences from higher-cortical regions, including the prefrontal cortex (Aston-Jones and Cohen, 2005), that signal and promote the prioritization of different stimuli. Once activated, the LC can reinforce those task-relevant or salience-related signals by modulating neural activity across the rest of the brain, including in sensory cortical regions representing those inputs. Along with the lateral prefrontal cortex (LPFC), the OFC and ACC send dense projections to the LC (Arnsten & Goldman-Rakic, 1984; Jodo et al., 1998). At the subcortical level, the LC also receives dense afferents from the amygdala (Price & Amaral, 1981), which is known to activate the LC during emotionally arousing or stressful experiences (Valentino & Van Bockstaele, 2008). We suggest that the dominant locus of top-down inputs to the LC is largely determined by the current level of arousal, biasing which forms of priority will guide behavior and neural processing at a given moment. We will explore these arousal-dependent effects of LC modulation in more detail in Section 4.3.

Traditionally, the LC is characterized as a uniform cluster of neurons, each with widely diffuse projections to the neocortex. This anatomy implies that the LC controls a homogenous and global release of NE, which is consistent with the state-level modulatory effects of arousal (Sara & Bouret, 2012; Usher et al., 1999). However, a closer look at subpopulations of LC neurons reveals a more modular organization, with evidence of specialization and specificity in its inputs (Uematsu et al., 2017), outputs (Chandler et al., 2013; Chandler & Waterhouse, 2012), molecular composition (Chandler et al., 2014), and neuronal firing patterns (Schwarz & Luo, 2015; Totah et al., 2018). Recent work suggests that this structural modularity also supports the functional modularity of the LC-NE system. For example, specific ensembles of LC neurons projecting to the amygdala have been linked to aversive learning, whereas a separate ensemble of LC neurons projecting to the medial prefrontal cortex have been linked to extinction learning (Uematsu et al., 2017). In mice, distinct spatiotemporal signatures of LC phasic responses are also associated with distinct aspects of learned behaviors during a go/no-go task (Breton-Provencher et al., 2022).

Considering these findings, many researchers now view the LC as a flexible system that can support both global states of arousal as well as more fine-tuned responses to salient information (Bouret & Sara, 2005; Foote & Berridge, 2019; Munn et al., 2021; Poe et al., 2020; Shine, van den Brink, et al., 2018; Wainstein et al., 2022). Thus, the LC-NE system may promote the selective processing of important information via a spatial specificity that enables a targeted

release of NE *where* those representations are activate as well as a temporal specificity that enables release of NE *when* those salient events occur.

2.2 Neuroanatomical evidence linking pupil dynamics to the LC-NE system

The autonomic circuitry underlying the pupillary light and dark reflexes has been relatively well established (Loewenfeld & Lowenstein, 1993). However, only recently has research begun to uncover the mechanisms that drive cognitive activity-related changes in the pupillary response. Researchers now recognize that both the cholinergic and noradrenergic pathways, key neuromodulatory systems underlying arousal, play a role in driving pupillary fluctuations that track arousal (Reimer et al., 2016). Yet from a birds-eye view, the bulk of the literature points to an especially strong link between the LC-NE system and the pupil. We review these key findings below.

Early direct evidence of the LC's involvement in pupillary fluctuations came from resting state recordings of the pupil and LC neurons in monkeys (Rajkowski, 1993). At rest, the pupillary fluctuations covaried with tonic LC fluctuations, such that periods of elevated LC activity corresponded to larger pupil diameters. Later studies using microelectrode stimulation of LC neurons demonstrated a direct link between LC activation and a phasic pupil response (Joshi et al., 2016; Liu et al., 2017; Reimer et al., 2016; **Figure 3**). These microstimulation studies further solidified the involvement of the LC in the circuitry underlying arousal-mediated pupillary response. Notably, these studies also implicated other structures, such as the intermediate layer of the superior colliculus (Joshi et al., 2016) and the basal forebrain (Reimer et al., 2016). suggesting that the noradrenergic system may influence the pupil via multiple pathways and that the cholinergic pathway also has a role in the control of the pupillary circuitry. However, compared to other structures, microstimulation of LC neurons produces especially robust and consistent results in terms of the magnitude and latency of the resulting pupil dilation (Joshi et al., 2016).

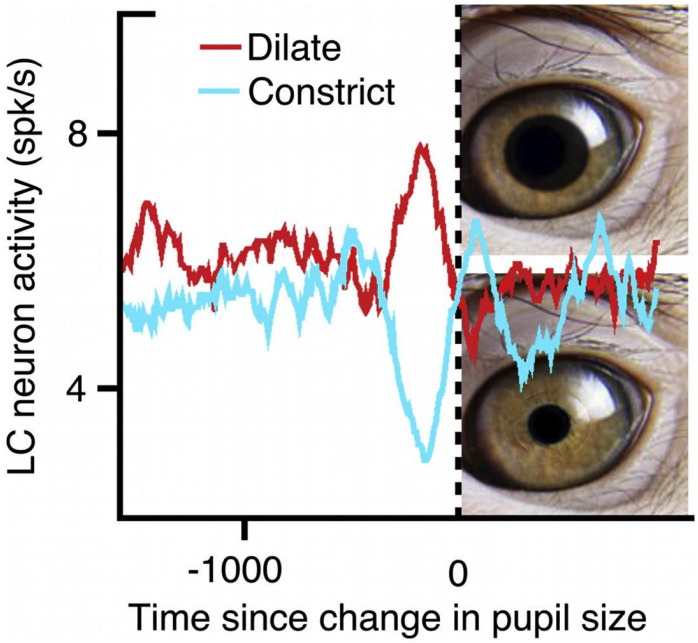

Figure 3. Temporal fluctuations in pupil size tracks LC neuron activity. In simultaneous electrode recordings of monkey LC neurons and pupil diameter, a spike in LC activity precedes pupil dilation, whereas a dip in LC activity precedes pupil constriction. Figure obtained from Costa & Rudebeck (2016).

While the LC acts on both the parasympathetic and sympathetic limbs of the pupil circuitry, there may be differences in the laterality of these effects (Liu et al., 2017). In rats, unilateral LC stimulation resulted in a lateralized dilation of both pupils, meaning that the ipsilateral pupil dilated more than the contralateral pupil. When surgically removing cells from the cervical spinal cord that are part of the sympathetic pupillary circuitry, the lateralization disappeared, suggesting that the LC's influence on the sympathetic limb is solely ipsilateral while its influence on the parasympathetic limb is bilateral.

Another technique that has produced evidence of LC's involvement in the regulation of pupil size is vagus nerve stimulation (VNS). The vagus nerve projects to the nucleus of the tractus solitarius, which in turn has projections to the LC among other target regions. Although not as direct as LC microstimulation experiments, VNS is an intriguing technique for indirectly probing the LC via projections from the nucleus tractus solitarius (Jodoin et al., 2015). Moreover, it has some potential for use in human studies, as VNS is an FDA-approved treatment for epilepsy and depression in humans and it has a related non-invasive procedure called transcutaneous vagal nerve stimulation (tVNS).

Emerging findings demonstrate that VNS treatment influences tonic LC-NE system activity. In rats, long-term VNS treatment resulted in elevated tonic LC firing rates (Dorr & Debonnel, 2006) and increase in extracellular NE concentrations in the prefrontal cortex and hippocampus (Manta et al., 2012). In humans undergoing VNS therapy for major depression and epilepsy, average pupil diameter was larger during periods when chronic VNS was turned on compared to when it was turned off (Jodoin et al., 2015). Additionally, some rodent studies have demonstrated that a phasic delivery of VNS evokes a pupil dilation that co-occurs with increases in other noradrenergic biomarkers (Collins et al., 2021; Mridha et al., 2021). Thus, VNS appears to exert both tonic and phasic influences on pupil size via the LC-NE system.

However, evidence linking the more indirect tVNS with LC-NE activation has thus far been mixed. In two studies comparing the effects of tVNS to sham stimulation, there were no effects of tVNS on baseline pupil diameter or task-evoked pupil change during an auditory oddball task (Keute et al., 2019) and an attentional blink task (Burger et al., 2020). The discrepancy between tVNS and VNS research may be due to differences in the stimulation strength of the vagus nerve (Mridha et al., 2021). Indeed, in systematically manipulating the intensity of the tVNS and the luminance of the environment, Capone et al., (2021) demonstrated that tonic tVNS induces an increase in the ipsilateral pupil diameter only under certain stimulation intensity (2 mA) and under low luminance conditions. Using a similar stimulation intensity (2.2 mA), Sharon et al., (2021) demonstrated that phasic tVNS pulses also induced pupil dilations. More work should be done to identify the optimal parameters for tVNS stimulation to induce changes in various LC-NE biomarkers.

Pharmacological studies have also provided some evidence that the LC-NE system is linked to the pupillary fluctuations. Studies using clonidine (alpha-2 agonist) and yohimbine (alpha-2 antagonist) directly inhibit or stimulate LC neurons by targeting alpha-2 adrenoceptors on LC neurons (for review, see Szabadi, 2018). Clonidine is thought to preferentially bind to the alpha-2 autoreceptors on LC neurons (Berridge & Waterhouse, 2003).For example, clonidine has been shown to induce pupil constriction (Hou et al., 2005; Phillips et al., 2000), while yohimbine has been shown to induce pupil dilation(Phillips et al., 2000). Moreover, the administration of modafinil, a wakefulness-promoting drug that indirectly increases LC activity, has been found to increase pupil size along with other autonomic and behavioral markers of LC-NE activity (Hou et al., 2005).

Although it certainly appears that the LC plays a role in the arousal-mediated pupillary response, a complete view of the connections between the LC and the pupil circuitry is still being formulated. The circuitry responsible for the pupillary light and dark reflexes consists of a sympathetic limb, which dilates the pupil via its excitatory influence on the iris dilator muscles, and a parasympathetic limb, which constricts the pupil via its excitatory influence on the iris constrictor muscles (Loewenfeld & Lowenstein, 1993). Given the relatively delayed latency between LC microstimulation and the onset of pupil dilation (~500ms; Joshi et al., 2016), researchers speculate that the LC has indirect connections to the pupil circuitry.

It is now thought that the LC modulates pupil size via multiple indirect pathways that either inhibit the parasympathetic limb or excite the sympathetic limb. One potential parasympathetic pathway is through the LC's inhibitory influences on the Edinger-Westphal nucleus, which is a key node in the parasympathetic limb of the pupillary reflex circuitry (Joshi & Gold, 2020; Szabadi, 2018). A second possible mechanism involves the LC sending excitatory signals to the sympathetic (dilation) limb via the intermediolateral cell column of the spinal cord (Joshi & Gold, 2020; Liu et al., 2017). Based on the finding that lesions to the parasympathetic or sympathetic pathways reduced normal patterns of LC-mediated pupil dilations (Liu et al., 2017), it is likely that both limbs of the pupil circuitry are involved in a coordinated effort to modulate pupil diameter.

In summary, accumulated evidence implicates the LC-NE system in supporting the arousal-mediated pupillary response. In addition to more causal manipulations of LC activity, functional magnetic resonance imaging (fMRI) methods have been used to examine the LC-pupil link. In a seminal fMRI study in humans, it was revealed that pupil dynamics covary with BOLD signal in a brainstem region consistent with the LC region when subjects rested or performed an oddball task (**Figure 4**; Murphy et al., 2014). This finding has since sparked a flurry of interest in using combinations of neuroimaging, pharmacology, and pupillometry to study the relationship between the pupil, cognition, and LC neuromodulation in humans. Wherever relevant, we highlight this important work throughout the rest of this chapter.

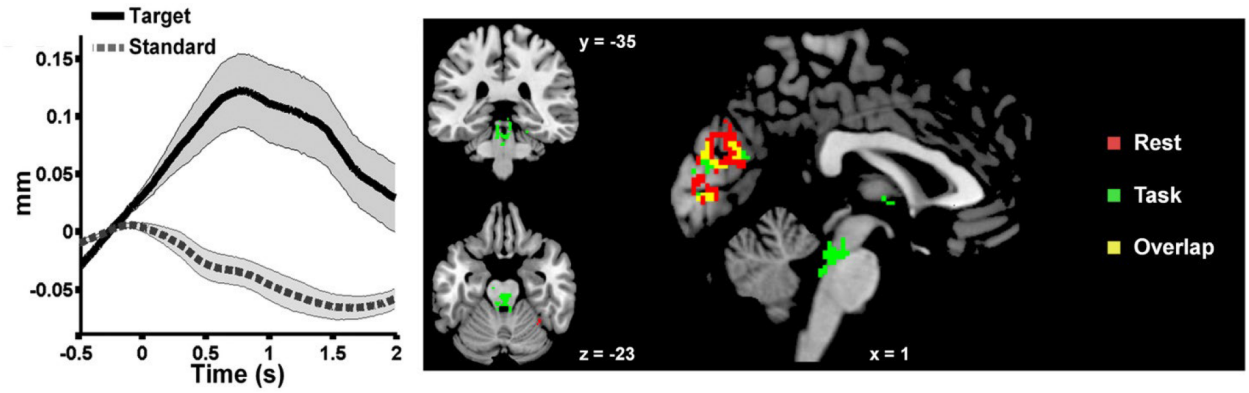

Figure 4. Pupil dynamics covary with BOLD signal in a brainstem region that overlaps with the known location of the locus coeruleus. (Left) Contextually novel oddball targets induce a strong pupil dilation compared to standard, or more frequent, stimuli. (Right) In non-spatially smoothed functional images, pupil diameter covaries with BOLD signal in a region of the brainstem that overlaps with the LC during an oddball detection task (green mask). This functional activation in the LC is not observed while participants rest (red mask). Figure adapted from (Murphy et al., 2014)

3. LC-NE system modulates neural gain and the breadth of attention

3.1 Arousal adaptively amplifies attentional selectivity

The rigidity of attention, which describes how arousal narrows attentional focus (Easterbrook, 1959), is a useful characterization of one aspect of arousal's influence on mental selectivity. Specifically, arousal is often described as an *amplifier* of selectivity, in which behaviorally relevant processes receive more mental resources at the cost of processing irrelevant information (Mather & Sutherland, 2011). In many contexts, this arousal mechanism adaptively tunes processing in favor of high priority information, such as goal-relevant, novel, emotional, or perceptually salient stimuli to facilitate a winner-takes-more and loser-takes-less effect in perception and memory (Lee et al., 2014a,b; Mather & Sutherland, 2011; Sakaki et al., 2014; Sutherland & Mather, 2012).

Researchers have proposed a neurocomputational model based on neural gain to explain how arousal facilitates some (high-priority) processes while simultaneously suppressing other (low-priority) processes. Neural gain is a parameter of a neuron's responsivity function, which describes the relationship between the strength of input signals received by the neuron and the strength of the output signals sent by the neuron (**Figure 5, the "S-shaped" functions**). An increase in neural gain increases the steepness of the responsivity function, meaning that the activity of a neuron receiving high excitatory inputs is further enhanced while the activity of a

neuron receiving low excitatory inputs is suppressed. Arousal may therefore modulate neural gain, with current levels of brain activity determining whether neuronal processing and accompanying mental representations are further enhanced or further suppressed (Aston-Jones & Cohen, 2005; Eldar et al., 2016).

It is now widely accepted that the LC-NE system helps regulate neural gain. The important role of LC activity in shaping neural selectivity first stemmed from evidence that NE enhances signal-to-noise processing in the brain (Hasselmo et al., 1997; Hirata et al., 2006; Waterhouse et al., 1980; Waterhouse & Navarra, 2019). The release NE modifies the responsiveness of neurons, effectively sharpening the sensory receptive field to facilitate neuronal activity involved in signal processing while suppressing neuronal activity related to background noise (Manunta & Edeline, 2004). These physiological effects have also been formalized in several computational neural-network models of LC function (Servan-Schreiber et al., 1990; Usher et al., 1999).Together, these physiological findings inspired the idea that NE promotes neural gain.

While an indiscriminate increase in neural gain may address the rigidity of arousal-attention interactions, it cannot fully explain why attention is also labile under high arousal. To address this issue, one influential theory highlighted the distinct computation and physiological functions of different modes of LC output. We review this model and its important predictions in the next section.

3.2 Adaptive Gain Theory: a model of how distinct LC processing modes influence behavior

How might the LC regulation of signal-to-noise processing in the brain influence mental selectivity or decision-making processes? According to Adaptive Gain Theory, the selective enhancement of task-relevant processes depends on the temporal specificity of stimulus-linked phasic LC activity (Aston-Jones & Cohen, 2005). Task cues, such as the appearance of a sensory target or goal relevant stimulus, elicit phasic bursts of LC firing, resulting in a momentary increase in neural gain for those active task representations. By contrast, task-irrelevant processes are relatively less active during this period and are suppressed with this phasic increase in arousal and phasic LC activation.

The magnitude of the task-evoked, phasic LC response is constrained by tonic, or background, levels of LC activity. Tonic LC activity fluctuates alongside changes in behavioral states, ranging from a low arousal state of drowsiness to a high arousal state of stress. Under low levels of

tonic LC activity, task cues elicit low phasic LC responses, corresponding with the impaired task performance seen during a low arousal, inattentive state. With intermediate levels of tonic LC activity, task-related phasic LC responses reach a peak magnitude, corresponding with optimal task performance seen during peak task engagement. Under high levels of tonic LC activity, phasic LC responses again diminish, corresponding with worse task performance and increased distractibility.

In addition to environmental influences like external stressors, arousal states and the related tonic LC activity may also be influenced by changes in utility over the course of performing the task. Dynamic transitions between the two modes of LC activity appear to be driven by cost-benefit evaluations carried out in higher cortical regions, such as the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC; Aston-Jones & Cohen, 2005). The dACC is a key region for supporting the metacognitive function of evaluating task utility. It also helps up-regulate tonic LC activity as task utility diminishes. Such arousal-related adjustments in behavioral modes correspond with shifts in neural gain processes throughout the brain.

Notably, this relationship between the tonic LC activity and phasic LC activity resembles the inverted-U “difficult” curve that describes arousal-performance relationship. As tonic LC activity is thought to reflect an individual’s arousal state, this tonic-phasic LC relationship can be used to explain the arousal-task performance relationship. Generally, performance is poor during periods of low arousal and low tonic LC activity, which is characterized by diminished task-related phasic LC responses. In this low arousal state, individuals may be inattentive and prone to off-task or exploratory mind wandering because a lack of phasic neural gain prevents the selective facilitation of task-relevant processes (Mittner et al., 2016).

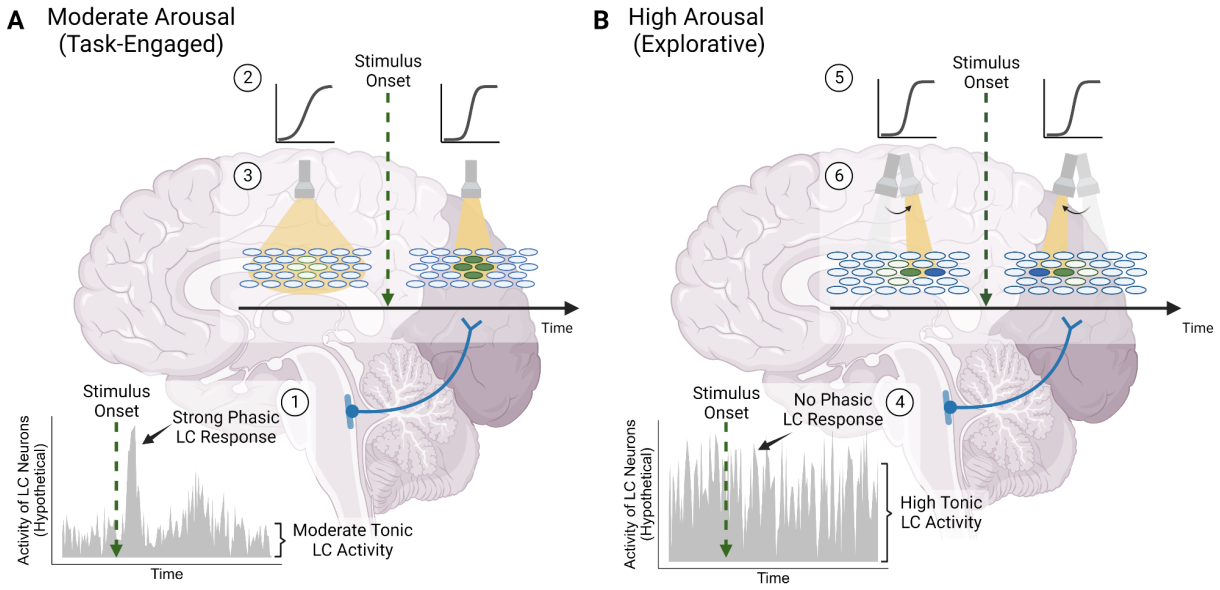

Figure 5. LC-NE system activity, neural gain, and attentional selectivity in response to the onset of a task-relevant stimulus. (A) Under moderate arousal and tonic LC activity, (1) the onset of a task-relevant stimulus triggers a strong phasic LC response. (2) This LC response results in an increase in neural gain that (3) facilitates attentional selectivity for the set of task-relevant cues (green circles). (B) Under high arousal and high tonic LC activity, (4) the onset of a task-relevant stimulus fails to trigger a strong phasic LC response. (5) However, neural gain remains persistently high, even during periods when there is no task-relevant information processing. (6) This results in a rigid and labile attentional beam, such that attentional selectivity for the set of task-relevant cues is impaired. Instead, attention becomes "distracted" and becomes grabbed by task-irrelevant cues. Note: the trajectory of the blue NE neuron is schematic; it would not pass over the cerebellum. Image created with BioRender.com.

Under an intermediate arousal state with moderate tonic LC activity, relatively strong phasic LC responses boost task-relevant processing. By enabling the phasic increase in neural gain in response to task cues, moderate tonic LC activity provides the optimal conditions for goal relevant behavior, target detection, and the exploitation of known rewards (Aston-Jones et al., 1997; Aston-Jones & Cohen, 2005; Rajkowski et al., 2004). While not directly linked to the LC, this also accords with other work showing an inverted-U relationship between pupil-linked arousal and sensory cortical activity. In this study in mice, intermediate levels of arousal were associated with reduced cortical noise and optimal performance in a tone-in-noise detection task. These effects were also accompanied by enhanced activity in sensory-evoked thalamic and cortical responses, consistent with an increase in neural gain (McGinley et al., 2015). Given the strong LC-pupil link, it is plausible that the LC helps drive these gain effects under arousal.

At high levels of tonic LC activity, task performance is impaired due to sustained and high levels of neural gain reducing the ability of task cues to elicit a phasic LC response. As a result, these

high-arousal states are more likely to induce noisier decision-making and attentional disengagement during goal-directed tasks (e.g., Aston-Jones & Cohen, 2005). Indeed, empirical studies show that behavioral variability and exploratory behaviors increase under arousal. For example, DREADD (Designer Receptors Exclusively Activated by Designer Drugs) induced LC tonic activity in rodents leads to greater decision noise in a path foraging task, leading to disengagement from patch exploitation (Kane et al., 2017). Activating LC-NE system inputs to the ACC has also been shown to increase decision noise (i.e., stochastic choices) and consequently greater behavioral variability in rodents (Tervo et al., 2014). In monkeys performing a pitch discrimination task, increased distractibility coincided with periods of elevated baseline pupil diameter, an indirect index of tonic LC activity (Rajkowski, 1993). Similar effects have been shown in human studies, whereby larger baseline pupil diameters track task utility in a foraging-like task (Gilzenrat et al., 2010) and decisions to explore unknown rewards (Jepma & Nieuwenhuis, 2011). Additionally, larger pupil diameters correlate with periods of high belief (Nassar et al., 2012) and periods of decision uncertainty that predict subsequent shifts in serial choices (Urai et al., 2017). Together, these studies are consistent with prior computational models positing a relationship between tonic LC activity and inverted-U arousal-performance function (Aston-Jones & Cohen, 2005). They also highlight the tight regulation of dACC function by LC activation (e.g., Aston-Jones & Cohen, 2005; Joshi et al., 2016; Joshi & Gold, 2022), with high levels of activation predicting more exploratory behavior, larger pupil diameters, and persistently high neural gain.

As previously mentioned, arousal's general effect of increasing neural gain manifests as increased "attentional rigidity", or a narrower focus of attention on strong, high priority inputs (Mather et al., 2015). But if increasing neural gain narrows the focus of our attention, why do we become more distractible under very high levels of arousal? One solution to this puzzle is provided by Adaptive Gain Theory, which accounts for the "attentional lability" side of the rigidity-lability paradox by characterizing high levels of arousal as a state of persistently high neural gain (Aston-Jones & Cohen, 2005). This persistently high state of neural gain indiscriminately tunes the responsiveness of neurons, even when task-relevant cues are absent (e.g., during an interstimulus interval). Persistently high neural gain thereby facilitates information processing for *any* cue, resulting in more exploratory decisions and behavioral variability. These effects are akin to the metaphor of a "labile" beam of attention that frequently switches its focus among competing task-irrelevant processes (**see Figure 5b**; Gilzenrat et al., 2010).

Importantly, an elevated state of tonic LC activity diminishes the phasic LC response to task-relevant cues, preventing a discrete and temporally specific increase in neural gain. Consequently, attention not only becomes more sensitive to bottom-up and distracting cues, but also less sensitive to the onset of goal-relevant information. The seemingly paradoxical nature of attention as being both rigid and labile under high arousal can thereby be attributed to the constraints placed on phasic LC firing by elevated levels of tonic LC activity.

3.3 Arousal and informational gain in the brain: The Glutamate Amplifies Noradrenergic Effects (GANE) model

In the previous section, we reviewed computational models of how fluctuations in LC activity adaptively influence the gain of information processing. Here, we will discuss a recent neurobiological model of how the LC-NE system implements this process of gain in the brain. The highly influential AGT model makes strong predictions about the role of different modes of LC activity in mediating the relationship between arousal and behavioral flexibility (Aston-Jones & Cohen, 2005). For many years, however, it was unclear how the all-or-none firing pattern of the LC could elicit opposite neural and behavioral outcomes for competing sensory inputs. That is, if task-relevant inputs are constantly competing with distracting stimuli for a foothold in awareness, how would the LC ‘know’ which inputs to enhance and which inputs to suppress?

To address this longstanding question, the Glutamate Amplifies Noradrenergic Effects (GANE) model posits that arousal-induced phasic activation of the LC biases sensory processing and memory formation to favor high-priority representations at the expense of processing low-priority representations (Mather et al., 2015). According to GANE, the effects of NE release on neural excitation differ as a function of local levels of brain activity that are regulated by glutamate, the brain’s primary excitatory neurotransmitter. At the core of this model is the idea that glutamate provides the neural substrate of priority signals in the brain, with priority being determined by the goal-relevance, perceptual salience, novelty, or emotional significance of a stimulus (**Figure 6**). By modulating NE levels locally, high glutamate levels are self-regulating: they recruit additional NE to strengthen their corresponding representations even further. As a result, winning mental representations “win more” under arousal, while losing representations take even less.

Importantly, neural gain is predominantly thought to occur during strong phasic LC responses to salient inputs, because phasic LC responses yield greater volume release of NE than tonic activation. In this way, transient LC responses are time-locked to external demands, ensuring

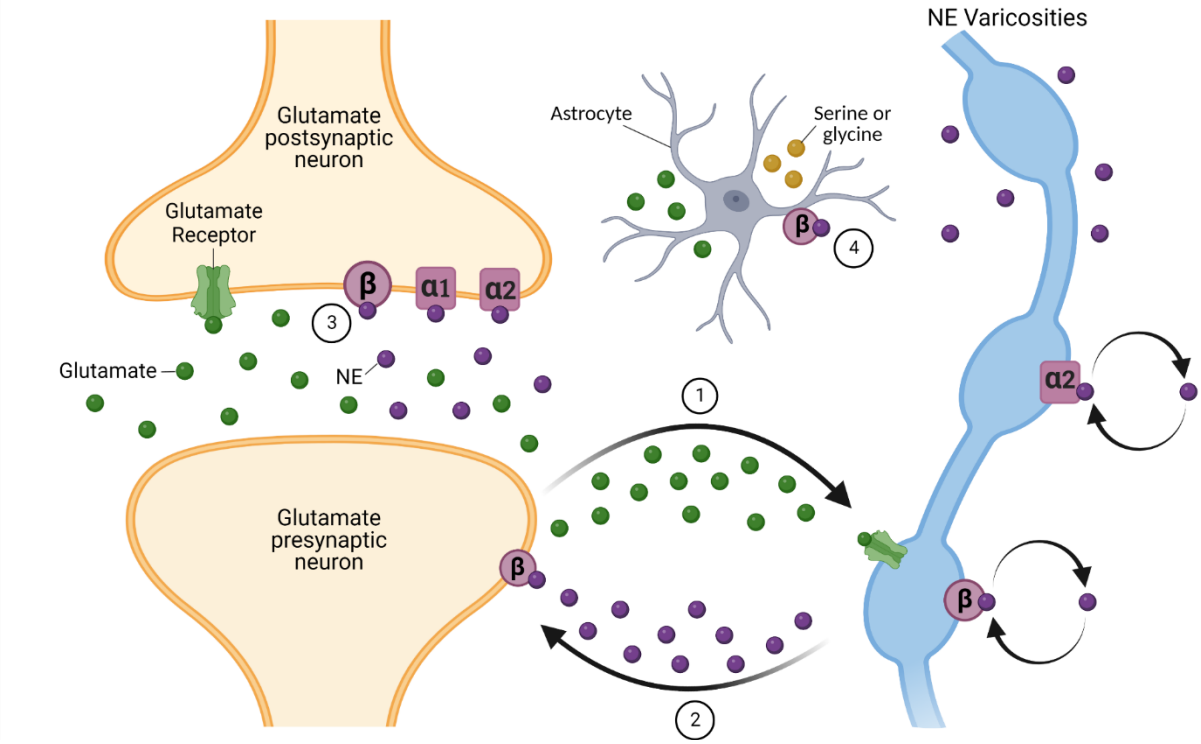

Figure 6. Glutamate amplifies noradrenergic effects (GANE) model of how LC activation implements neural gain. According to GANE, a surge in LC activity under arousal will lead to the diffuse release of NE from varicosities at target brain sites (large blue shape on right). High levels of glutamate signal the priority, or salience, of a stimulus, such that higher concentrations of glutamate correspond with strong sensory inputs or active mental representations. (1) If local glutamate levels are high enough, they will spill over into extracellular space and bind to their corresponding receptors along NE axons. This binding stimulates even greater release of NE from nearby varicosities, thereby up-regulating local NE concentrations in these highly active areas. (2) In turn, elevated NE levels will bind to presynaptic glutamate axon terminals and trigger even greater release of glutamate in those synaptic pathways. (3) In these synaptic pathways transmitting strong, high-priority information, NE levels will also be sufficiently elevated to gain access to beta-adrenergic receptors on the postsynaptic glutamate neuron. Although NE engages all receptor subtypes, the beneficial effects of beta-adrenoreceptors will prevail. Namely, binding to these specific adrenoreceptors enhances the throughput of strong signals and enhances synaptic plasticity, which supports stronger memory consolidation. (4) Elevated NE will also engage beta-adrenoreceptors on nearby astrocytes, which support the excitability of nearby neurons. Together, these self-regulating positive feedback loops, or “NE hotspots” up-regulate the excitation of already highly active synaptic pathways. As a result, phasic LC activation increases neural gain and amplifies perceptual and memory selectivity. For additional details, see Mather et al. (2015). Figure created by Ziyuan Chen with BioRender.com.

that behaviorally relevant stimuli receive the boost they may need to garner valuable mental resources.

Arousal-related increases in neural gain rely on two concentration-dependent functions of NE: the ability to further weaken low priority inputs and the ability to further strengthen high priority inputs. While LC activity is typically associated with states of intense mental activation or stress (Berridge & Waterhouse, 2003; Sara, 2009), its predominant function is to suppress most patterns of brain activity. In brain regions processing task-irrelevant or noisy information, NE's widespread release inhibits weak patterns of neural activity by engaging inhibitory alpha2-adrenoreceptors. Because alpha2-adrenoreceptors have a higher affinity for NE than other adreno-receptor subtypes, they will be engaged first and inhibit most patterns of brain activity under low-to-moderate levels of arousal. This widespread inhibition in turn creates ideal neurochemical conditions for enhancing signal-to-noise processing.

In contrast to regions processing irrelevant information, NE has the opposite modulatory effect on areas with strong activity. In these brain regions representing high priority representations, levels of local glutamate are high enough to spillover from synapses and bind to nearby NE varicosities, large swellings along the length of LC fibers that release NE into extracellular space. This additional local release of NE is thought to generate NE levels that are high enough to engage low-affinity beta-adrenergic receptors in neural pathways transmitting salient information. Beta-adrenoreceptors have potentiating rather than inhibitory effects on neural activity, thereby ensuring that high priority representations gain privileged access to limited mental and metabolic resources (Mather et al., 2015).

The processing benefits of beta-adrenoreceptor engagement are manifold. First, engaging beta-adrenoreceptors enhances neuronal excitability even further by stimulating even greater local release of glutamate (**Figure 6**). This in turn creates a positive glutamate-NE feedback loop, or "NE hotspot", that up-regulates strong mental representations even further (Mather et al., 2015). Highly salient mental representations are therefore self-selecting in that they can recruit phasic LC responses to up-regulate their own level of activity.

Second, the engagement of beta-adrenoreceptors has been shown to enhance long-term potentiation and synaptic plasticity. Thus, beyond initial perceptual and attentional processing, beta-adrenoreceptors may selectively enhance encoding and consolidation of high priority inputs (Salgado et al., 2012). Meanwhile, the inhibitory effects of alpha2-adrenoreceptor activation prevails in regions with lower activity, and this may reduce synaptic plasticity and prevent long-term memory consolidation (Salgado et al., 2012).

Third, engaging beta-adrenoreceptors recruits metabolic resources, including glucose and oxygen, to active brain regions. This helps ensure that active neurons receive the resources needed to continue to process high priority information (Bekar et al., 2012). Interestingly, this ability of NE to direct energetic resources to meet sensory or tasks demands may help account for the effects of arousal on regulating levels of mental energy and attentional capacity (as reviewed in detail in Section 5.4). The GANE model expands upon this link by suggesting that mental and physical energy will be focused onto select regions processing high priority information. Thus, the gain of prioritized representations and/or task-relevant motor responses in the brain is supported by synergistic interactions between LC activity and both attentional and physiological resource allocation.

Finally, the local up-regulation of neuronal activity at NE hotspots has larger ramifications for global communication patterns across the brain. Activation of beta-adrenoreceptors modulates alpha, gamma, theta oscillations both locally and across brain regions (Mather et al., 2015). Engaging these receptors may also preferentially route prioritized information through large-scale frontoparietal (Corbetta et al., 2008; T.-H. Lee et al., 2018; Robbins & Arnsten, 2009) and salience brain networks that coordinate attentional selectivity and responses to behaviorally relevant information (Hermans, Henckens, et al., 2014; T.-H. Lee et al., 2018). Additionally, direct connections between the LC and prefrontal cortex, thalamus, and amygdala may enable activity in these regions to up-regulate their own priority signals. This in turn would fuel NE hotspots both locally as well as in their posterior sensory and parietal cortical targets (e.g., amygdala projections to early visual cortex or parietal cortex; (Markovic et al., 2014).

In summary, the GANE model proposes that local interactions between neuronal excitation and NE release regulate a delicate balance between local neuronal excitation and inhibition across the brain. Phasic LC activity occurs in response to behaviorally relevant inputs and tips the scale of excitation in favor of these representations to increase their priority. Glutamate levels play the lead role in signaling the importance of incoming stimuli and determine whether a mental representation will be further enhanced or further suppressed under such transient increases in arousal. Throughout the brain, phasic LC activity implements neural gain by promoting a few hotspots of neuronal excitation amidst a backdrop of neuronal suppression. Ultimately, this stratification of brain activity under arousal ensures that strong, high-priority stimuli win the competition for limited mental resources when it matters most.

3.5 Empirical support for the GANE model

In humans, combining neuroimaging methods with pupillometry has provided initial support for the GANE model. In one fMRI study, participants were motivated to encode a background scene while ignoring a transparent overlaid object (**Figure 7**). Scenes thereby acquired high priority through their goal relevance. Physiological arousal, as indexed by cue-evoked pupil dilation, was induced on half the trials by threatening to deduct money if participants forgot the target scene during a subsequent recognition memory test. Threat of punishment enhanced memory for high-priority scenes and impaired memory for low-priority objects. Enhanced scene memory was also correlated with greater threat-evoked pupil dilations as well as increased activity in the parahippocampal place area (PPA), a region specialized to respond to the high priority scene information (Clewett et al., 2018). Thus, a surge in arousal up-regulated local activation of the high priority mental representation. Critically, weighting brain activity by the magnitude of these pupil dilations revealed a link between LC activation and threat-enhanced memory for prioritized scenes.

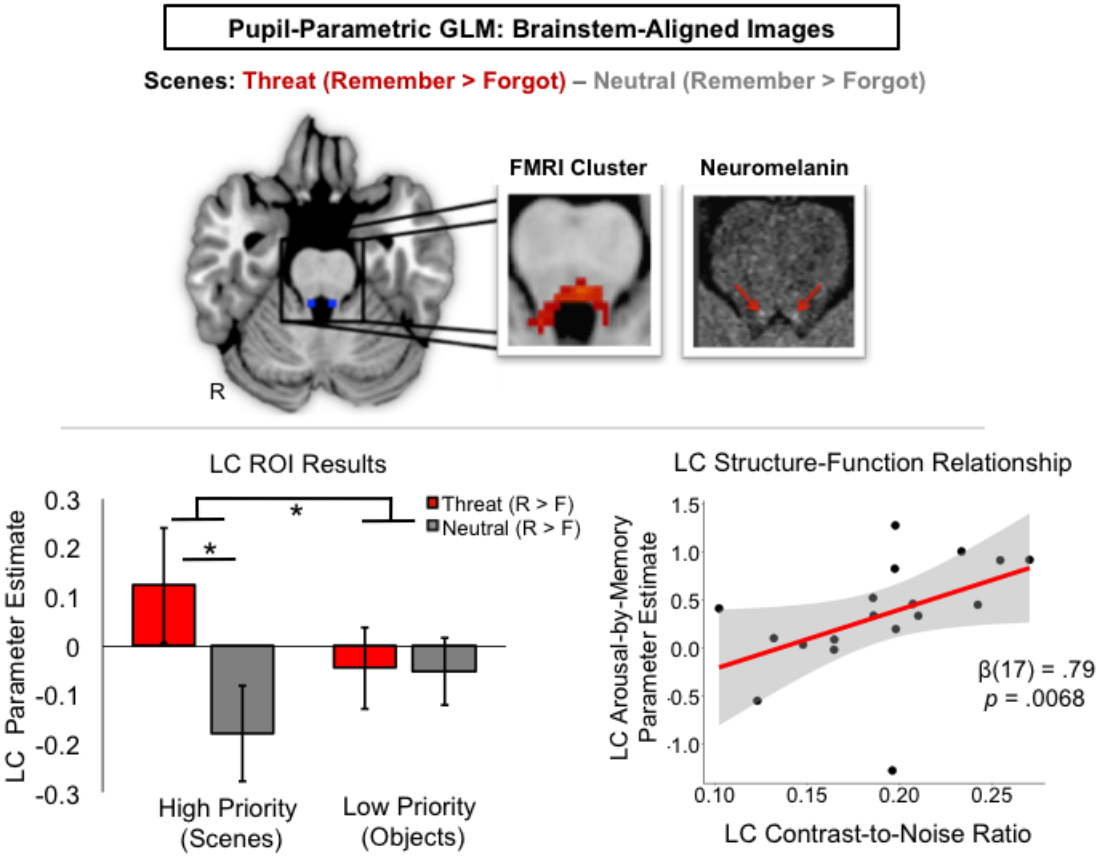

Figure 7. Neuroimaging evidence that threat-evoked pupil dilations modulate LC-enhanced encoding of high priority information. In this pupil-parametric fMRI analysis, participant's whole-brain statistical parametric maps were weighted according to the magnitude of pupil dilation when people were motivated to encode a goal-relevant scene and ignore a

distracting object image. Qualitative comparisons revealed substantial overlap between a cluster of activation that overlapped with the known location of the LC (red) and a standard LC mask from the literature (blue dots). The functional cluster from fMRI also overlapped with an area consistent with one participant's neuromelanin-sensitive weighted image, a structural scan that reveals LC neurons (bright dots; top panel). A region-of-interest analysis using each participant's own neuromelanin-defined LC showed the direction of this memory effect, with pupil-weighted arousal enhancing LC activation during threat trials but not neutral cue trials (bottom left). The degree to which participants engaged the LC during threat-related scene encoding was also correlated with his/her LC neuromelanin contrast-to-noise ratio (CNR), a putative biomarker of LC structural integrity (bottom right). *$p < .05$; R = scene remember; F = scene forgot. Figure taken from Clewett et al. (2018).

Building on these findings, a separate fMRI study showed that phasic pupil dilations to threatening cues were correlated with activation of a frontoparietal network that coordinates attentional selectivity and is highly sensitive to NE release (Lee et al., 2018; Robertson, 2014). This discrete increase in arousal also corresponded with greater functional connectivity between the LC and the PPA in young adults. In addition, Lee et al. (2018) performed computational modeling to instantiate GANE using biologically plausible parameters of NE, glutamate, and GABA concentrations in the brain. As expected, the results of these simulations mirrored priority-dependent activation patterns observed in PPA. Together, these neuroimaging studies demonstrate LC-related amplification of local priority signals in the brain, an effect that can be indexed by task-relevant increases in pupil dilation.

4. Relationship between tonic LC activity and classic arousal-performance curves: how arousal states shift the locus of priority signals in the brain

A key strength of the GANE model is that it provides considerable flexibility about the types of priority that can be amplified under arousal (see Mather & Sutherland, 2011). In so doing, this model encompasses a wide range of behavioral findings that emotional arousal can enhance cognitive selectivity in a wide range of contexts and for diverse inputs. It is noteworthy that in its current form, GANE posits that *phasic* LC activation amplifies neural gain and promotes the processing of prioritized information, irrespective of whether priority is determined by an input's emotional significance, perceptual salience, novelty, or goal relevance. All these factors are known to activate the LC (Mather et al., 2015; Sara, 2009), making this region well equipped to momentarily boost processing of important mental representations *when* they are active. But this temporal specificity depends on strong phasic LC signals that are permitted under intermediate levels of tonic LC activity (Aston-Jones & Cohen, 2005).

An important challenge for the GANE model is addressing how norepinephrine can enhance neural gain at both intermediate and high levels of arousal. As we reviewed earlier, not all tasks or types of learning are impaired by this high tonic LC state, as suggested by the monotonic arousal-performance curve (Diamond et al., 2007; Yerkes & Dodson, 1908). This suggests that rather than impairing all stimulus-evoked responses, high arousal may instead lead to qualitative shift in the type of information processing that benefits from increased neural gain.

It is important to stress that while GANE predicts that hotspots will emerge locally in sensory cortices processing high priority information (e.g., a visual input), the priority signal itself often arises from top-down inputs from other regions, such as the LPFC (e.g., Lee et al., 2018). Thus, NE hotspots not only arise in regions representing high priority sensory information but also in the brain regions that evaluate and modulate stimulus priority in the first place. We propose that viewing the GANE model through the “easy” (monotonic) and “difficult” (inverted-U) curves of the arousal-performance function may explain shifts in the neural locus of priority signals under arousal (**Figure 8**). Our proposal builds on earlier work proposing that these two curves map onto the activation states of separate but interacting brain systems that are differentially sensitive to NE concentration and, in most cases, support different types of priority: the LPFC and the amygdala (Diamond et al., 2007).

4.1 The curvilinear component of the arousal-performance curves: modulation by prefrontal cortex and frontoparietal networks

For tasks involving goal-directed behavior, arousal and LC activity modulate cognitive processing according to an inverted-U function (Diamond et al., 2007). Specifically, intermediate levels of arousal seem to represent a “sweetspot” wherein neural gain benefits processing of many types of prioritized information, especially those that demand focused attention (**Figure 8**). One of the key targets of LC neuromodulation is the prefrontal cortex (PFC), which plays an essential role in supporting a wide range of executive functions, including working memory, inhibitory control, conflict monitoring, and decision making (Funahashi & Andreau, 2013; Fuster, 1989; Petrides, 2005; Robbins, 2000; Robbins & Arnsten, 2009). Additionally, the PFC coordinates priority via top-down inputs to posterior sensory cortical regions by tagging and amplifying goal-relevant processing while suppressing task-irrelevant processing (Gazzaley et al., 2005; Lee et al., 2018).

Converging evidence from humans and animals indicate that the LPFC is highly sensitive to the release of different catecholamines, including NE and DA (Arnsten, 2007; Robbins & Arnsten, 2009). Like the curvilinear component of arousal-performance relationship, these neuromodulatory systems also regulate LPFC-mediated cognitive processes according to an inverted-U function (Arnsten, 2007; Arnsten & Li, 2005; Robbins & Arnsten, 2009). Too little NE leads to drowsiness, whereas too much NE induced by stress leads to impaired PFC function. Noradrenergic modulation of broader frontoparietal network function also plays an important role in optimizing selective attention under moderate arousal, including reorienting attention to salient inputs (Bouret & Sara, 2005; Corbetta et al., 2008), enhancing goal-relevant attention (Lee et al., 2018; Mather et al., 2020; Murphy et al., 2014), regulating cognitive effort and focus (Grueschow et al., 2020; Minzenberg et al., 2008; Raizada & Poldrack, 2008), and exploiting known sources of reward (Aston-Jones & Cohen, 2005).

Neuroimaging research in humans also supports the idea that task-related pupil dilations provide a window into LC-PFC interactions under moderate levels of arousal. Such modulation isn't limited to local LPFC effects but rather extends to patterns of functional connectivity both within and between large-scale functional networks. For example, in one human fMRI study, isometric handgrip was shown to lower tonic states of arousal several minutes later, creating ideal conditions for phasic LC activation to emerge. Indeed, oddball-evoked pupil dilations were correlated with faster target detection processes, which were facilitated by activation of a right frontoparietal attention (Mather et al., 2020). In a similar finding, phasic LC activation was shown to be tightly coupled with oddball-evoked pupil dilations and frontoparietal network activation (Murphy et al., 2014). Pupil responses to goal-relevant targets might thereby provide a useful window into phasic LC activation and its modulation of LPFC- and executive-network mediated cognitive processes.

Recent fMRI work in humans has combined pupillometry and graph measures to examine how phasic LC activation influences the dynamic configuration of frontoparietal networks. These studies reveal that pupil dilation is correlated with graph measures of network integration and neural gain, with these patterns being most pronounced in frontoparietal networks that are engaged during target processing (Shine, et al., 2018a,b). Pharmacological manipulations lend additional support to the idea that the frontoparietal network is highly sensitive to phasic LC activation. Administration of atomoxetine, a NE transporter blocker that increases free levels of NE in the brain, promotes a neurochemical brain state that enables phasic LC responses to prevail (Shine, van den Brink, et al., 2018). Under atomoxetine administration, measures of

neural gain and frontoparietal network integration are increased (Shine, van den Brink, et al., 2018). Likewise, administration of modafinil, another NE transporter blocker drug that inhibits NE transporters and the reuptake of NE from synapses, induces a low-tonic/high-phasic mode of LC activity that leads to enhanced task-evoked LC activity during a mentally demanding task (Minzenberg et al., 2008). Such increases in the LC phasic mode also corresponded with increased LC-PFC functional connectivity and better task performance (Minzenberg et al., 2008).

Together, these imaging studies support the idea that moderate levels of global arousal – whether they are induced by drugs, acute exercise, or general wakefulness – promote brain states that are highly conducive to phasic LC activity. With LPFC function intact at intermediate levels of arousal and alertness, attentional resources are appropriately deployed to enhance task engagement and performance.

4.2 Monotonic component of the arousal-performance curves: modulation by the amygdala and salience network

In contrast to the inverted-U relationship between the LC-NE system, LPFC, and frontoparietal network connectivity, the linear arousal-performance function that is theorized to reflect simple and sometimes reflexive behaviors as well as enhanced encoding of highly emotional memories may be more closely tied to amygdala activation (Diamond et al., 2007; **Figure 8**). The amygdala plays a central role in facilitating attention and memory for emotionally arousing stimuli (Cahill et al., 1994, 1995, 1996; LaBar & Cabeza, 2006). Much of these amygdala-mediated enhancements are driven by inputs from the noradrenergic system (Cahill et al., 1995, 1995; Strange & Dolan, 2004). For instance, pharmacological administration of reboxetine enhances amygdala-mediated emotional memory enhancements and biases attention selectively towards emotional information (Markovic et al., 2014).

Importantly, much of these amygdala-mediated memory enhancements are mediated by beta-adrenoreceptors, suggesting the presence of local NE hotspots under emotional arousal. For example, beta-adrenoreceptor blockers reduce amygdala activity and reduce emotional memory enhancements (Strange & Dolan, 2004). Drugs that suppress amygdala activity can also disrupt the consolidation of emotionally arousing experiences (Ferry et al., 1999; Roozendaal et al., 2008).

The preferential enhancement of emotional representation is thought to occur in part through NE biasing the amygdala to modulate plasticity or processing in targets elsewhere in the brain, including the hippocampus and sensory cortex (McGaugh et al., 2002). This finding is further corroborated by fMRI evidence in humans showing that amygdala strengthens memories of highly emotional scene images by modulating activity in the regions that process scene information and the hippocampus (Fastenrath et al., 2014).

From a neurophysiological perspective, we anticipate that intermediate arousal states should benefit processing of emotional stimuli. For example, manipulating sustained arousal levels via simple exercise can modulate emotional memory enhancements. In one pupillometry study, isometric handgrip led to overall increases in pupil diameter, indexing an elevated tonic state of arousal. Importantly, this heightened arousal state was also related to a gain in memory selectivity for negative over positive and neutral information, whereby negative emotional memories were further enhanced following handgrip compared to images encoded following a no-handgrip control condition (Nielsen et al., 2015).

Genetic studies of the alpha-2B-adrenoreceptor (ADRA2B) allele deletion variant also offer indirect evidence supporting a link between enhanced emotional memory selectivity under tonically (or trait) elevated levels of NE. While the exact mechanism is unclear, it is thought that NE levels are high in these individuals. ADRA2B deletion carriers show increased availability of NE that may amplify negative emotion-related memory enhancements (Rasch et al., 2009). Individuals with this genetic deletion variant also show greater attention towards (Todd et al., 2013) and memory for emotionally arousing information (de Quervain et al., 2007).

Genotyping evidence lends additional support to the idea that noradrenergic activation of the amygdala enhances the preferential processing of emotionally arousing information against a backdrop of tonically elevated NE. But whether this ostensible gain relates to the mid-point or far-right of the monotonic arousal-performance function is somewhat unclear. Fortunately, the linearity of the amygdala-centric arousal-performance function helps circumvent this ambiguity about the tonic level of LC activation and NE in emotional arousal manipulations. Regardless of an individual's overall level of arousal, the presentation of emotional stimuli will typically enhance neural gain and selectivity for those stimuli in perception and memory.

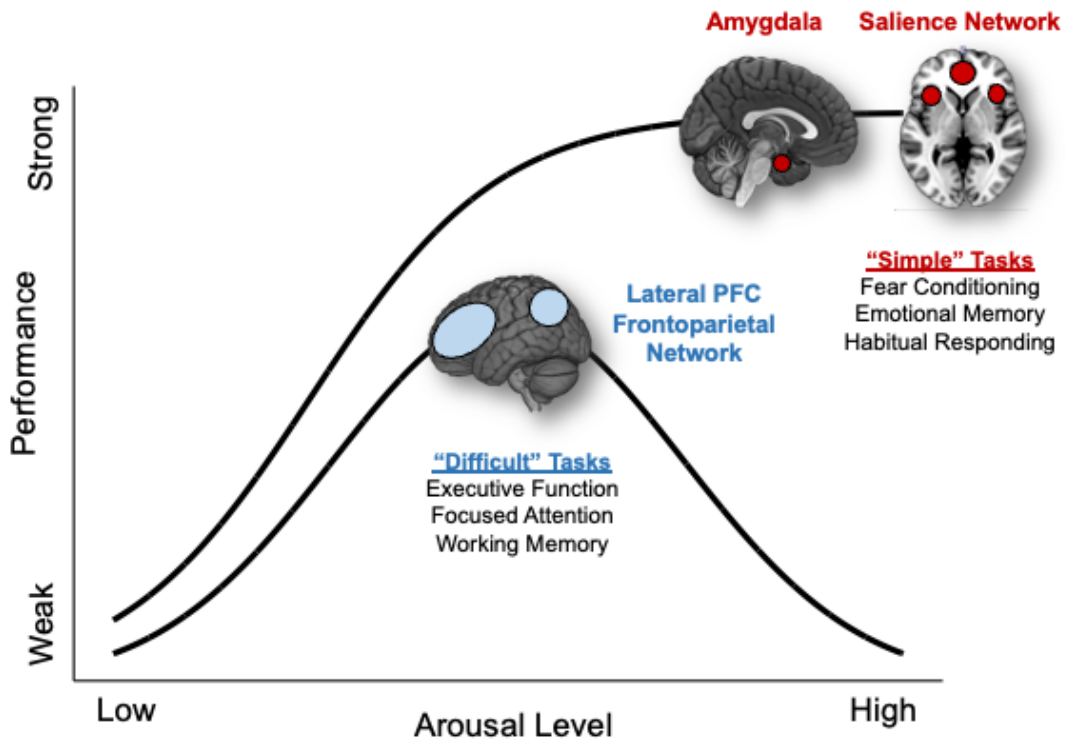

Figure 8. Mapping different brain regions and functional networks to the classic arousal-performance curves. Tonic, or background, arousal levels may dictate whether performance and learning processes will be biased towards networks that support difficult mental operations, such as the frontoparietal network (blue dots), or towards regions and networks that support more simple tasks, such as the amygdala and salience network (red dots). Cognitive processes required for difficult tasks, such as focused attention and working memory, are optimal at intermediate levels of arousal when prefrontal cortical function is intact. Different forms of priority supported by these regions, including top-down attention, will benefit from a surge in phasic LC activity and, as a result, an increase in phasic neural gain. However, these executive processes are impaired when arousal is too high due to impairments in prefrontal cortex function. On the other hand, amygdala and salience network activation gradually increase with arousal and peak under stress (far right of arousal axis). Under these high-arousal conditions, amygdala and salience network activation enhance attention and memory for bottom-up, emotional, or habit-related information via LC-mediated increases in persistently high states of neural gain. Figure adapted from Diamond et al. (2007).

4.3 The far right of the arousal-performance curves: effects of stress and very high tonic arousal on LC and brain activity

Existing empirical findings dovetail with multiple models of LC-NE function and the curvilinear model of the arousal-performance relationship: at intermediate levels of tonic, or background, arousal, phasic LC activation enhances cognitive selectivity for bottom-up, top-down, or emotional priority. In this way, multiple brain regions that regulate the selective processing of

important information, including the amygdala and LPFC, are poised to amplify neural gain and modulate the strength of NE hotspots both locally and at their target brain sites.

But what happens at extreme levels of arousal, such as stress? Are all sources of priority equally competitive or do some informational inputs gain an advantage in the competition for limited mental resources? Emerging findings suggest that not all sources of priority have equal stakes in the competition for mental resources and behavior control when arousal is very high. To be able to explain the full range of arousal and NE's effects on neural gain, then, the GANE model must also be able to address how elevated arousal states amplify attentional and memory selectivity in the absence of strong phasic LC responses. Of particular importance to applications of pupillometry to psychology research, GANE must also be able to reconcile how different pupil measures, including stimulus-evoked dilation and overall pupil diameter, can simultaneously account for context-dependent biases in learning and memory.

Why might this shift in stimulus priority occur under stress? One key answer might lie in how stress influences the function of different brain regions. Stress elicits robust impairments in LPFC executive functions, including working memory and goal-directed attention (Arnsten, 2009). By contrast, amygdala function generally remains intact at intermediate and high levels of arousal, with stress potentiating many amygdala processes (Roozendaal et al., 2009).Functional connectivity between the LC and amygdala also increases following acute psychological stress (van Marle et al., 2010). The degree to which the LPFC is impaired by a highly emotional or stressful event might thereby enable researchers to predict whether the arousal-performance curve will be linear or curvilinear (Diamond et al., 2007). Simply put, the relationship between arousal and prioritization can be distinguished by whether or not the task recruits LPFC activity (Diamond et al., 2007). Flexible regulation of higher-order executive functions peak at intermediate levels of arousal/tonic LC activity but are significantly impaired under high states of arousal or stress (i.e., the far right of the inverted-U). Because the amygdala is potentiated by stress, its priority signals will likely prevail under these high-arousal conditions, leading to different behavioral and learning outcomes (**Figure 8**).

Presently, little work has examined relationships between LC activity, pupil diameter (as opposed to dilation), and behavior under stress. Across many stress studies, the pupil is often used to verify the successful induction of stress rather than used as a trial-level measure to predict task performance or memory. In some studies, acute stress has been shown to blunt pupil dilation responses during the encoding of different neutral and negative pictures

(Henckens et al., 2009; Qin et al., 2012), consistent with the idea that phasic LC responses diminish under conditions of high tonic activity. While attenuation of pupil dilation wasn't associated with encoding performance under stress, it is possible that pre-stimulus baseline measures of pupil diameter would provide a more accurate measure of stress-related memory enhancements. It is also noteworthy that other work demonstrates that fMRI indices of neural gain, such as representational precision in occipitotemporal cortex, are reduced when cortisol levels are elevated, as would occur under stress (Warren et al., 2016). This gain reduction, however, was not linked to differences in a simple image categorization task, so it is unclear how these changes in neural gain relate to behavior.

At the core of the GANE model is the idea that selective and local activation of low affinity beta-adrenoreceptors facilitate glutamatergic activity and synaptic plasticity in regions representing a high priority stimulus. While such task- or stimulus-evoked neural gain is proposed to occur under conditions of phasic LC activity, it is important to acknowledge that stress elicits increases in tonic levels of LC activity (Mana & Grace, 1997). Under stress, the release of corticotropin-releasing factor CRF also increases the tonic firing rate of LC neurons, leading to elevated levels of NE being released across both cortical and subcortical brain regions (Valentino et al., 1998). Such increases in LC output can generate high enough NE concentrations to engage beta-adrenoreceptors and, by extension, trigger NE hotspots (Mather et al., 2015).

Because the NE hotspots triggered by persistently high neural gain are not time-locked to the processing of task-relevant stimuli, *any* active mental process may be amplified by the increased neural gain, possibly manifesting as distractibility observed under high arousal states. Although this persistently high neural gain leads to task-irrelevant processing, evidence suggests that performance on "easy" tasks benefit, or at least do not suffer, from high arousal states (Yerkes & Dodson, 1908). Here, we argue that stress, or a state of extremely high arousal, induces a qualitative shift in attention and mental resource allocation towards specific sources of priority; namely, motivational significance driven by emotional salience or more automatic and habitual behaviors.

Supporting this idea, attention tends to be biased towards processing emotional stimuli under stress, which occurs in part due to activation of the amygdala and the salience network (Hermans et al., 2014; Hermans et al., 2011). Intriguingly, one study showed that inducing acute stress prior to studying emotional word lists leads to a subsequent emotional memory enhancement in ADRA2B deletion variant carriers, a group of individuals thought to have

tonically elevated levels of NE (Zoladz et al., 2014). Thus, high tonic levels of arousal and NE concentration may lead to selective memory enhancements for emotional material. From the perspective that the amygdala drives emotional memory enhancements, this may provide indirect evidence of greater emotional selectivity under stress and very high NE levels.

Additionally, human neuroimaging evidence shows that acute stress inductions lead to enhanced sensory cortical processing in response to emotional faces compared to neutral faces (van Marle et al., 2009). At the behavioral level, stress is associated with heightened attentional vigilance (van Marle et al., 2010), especially towards the source of threat (Rued et al., 2019). Furthermore, viewing negative pictures under stress relates to an increase in an EEG component that relates to increased elaborative processing (Weymar et al., 2012). Administration of propranolol, a beta-adrenoreceptor blocker, has also been shown to prevent stress-induced activation of large-scale salience brain network that supports hypervigilant attentional states and coordinates behavioral responses to threat (Hermans et al., 2011).

Interestingly, the behavioral and neural effects of stress are also mimicked by chemogenetic activation of the LC in mice (Zerbi et al., 2019). This elegant study combined chemogenetics with resting-state fMRI to show that strong global activation of the LC led to a drastic shift in brain-wide functional connectivity, with the strongest modulation occurring in amygdala and salience networks. Strong, global activation of the LC was accompanied by a large increase in overall pupil diameter, consistent with the idea that these effects were driven by a large increase in tonic LC activation that would typically be observed under stress (Zerbi et al., 2019).

4.4 Stress-induced release of cortisol may fuel NE hotspots and persistently high neural gain

One important open question is whether NE hotspots still emerge under conditions of high tonic LC activation, especially in the presence of other stress hormones that modulate activity in attentional and memory regions across the brain. Two defining features of the stress response are the release of cortisol, or glucocorticoids, across the brain as well as the activation of the sympathetic nervous system and LC (Joëls & Baram, 2009; McEwen, 2007). While glucocorticoids impair PFC function (Arnsten, 2009), they may actually fuel the emergence of NE hotspots in other select brain regions. Both beta-adrenoreceptor activation (Ferry et al., 1997) and the administration of glucocorticoids (Reznikov et al., 2007) have also been shown to

enhance glutamate release in the amygdala, providing the necessary fuel to generate an NE hotspot.

The co-release of NE and cortisol under emotional arousal or stress also plays an important role in promoting the formation of declarative memories. Pharmacological manipulations that elevate both NE and cortisol levels elicit a negative response bias towards fearful faces in the amygdala (Kukolja et al., 2008). This finding lends additional support to the idea that stress and LC activation will enhance neural gain processes mediated by the amygdala through a combination of cortisol and beta-adrenoreceptor activation. Up-regulation of NE hotspots in the amygdala would then serve to further strengthen the throughput of emotionally salient information through both sensory and hippocampal networks (Markovic et al., 2014; Tully & Bolshakov, 2010).

Extending this idea, acute stress is known to activate hippocampal-amygdala pathways that prioritize the encoding and storage of emotional information (Kukolja et al., 2011). Such enhancements occur alongside stress-induced impairments in PFC function (e.g., van Stegeren et al., 2010), with elevated levels of cortisol and NE in the PFC impairing goal-directed attentional processes (Schwabe et al., 2012). As a result, behavioral control tends to shift towards more habitual behaviors and prefrontal cortical regions become more insensitive to reward devaluation (Schwabe et al., 2012). This behavioral shift may be mediated, at least in part, by beta-adrenoreceptors (Schwabe et al., 2011). In sum, stress may shift the locus of priority signals in the brain from the prefrontal cortex to the amygdala. By activating beta-adrenoreceptors in a region that is responsive to threatening or emotional stimuli and is not compromised by cortisol release, NE hotspots can still emerge to promote some level of selectivity under stress.

4.5 High arousal amplifies hard-wired or habitual learning preferences via brain-wide LC effects

While not driven by stress, per se, recent neuroimaging work also aligns with the idea that elevated arousal states promote persistent neural gain. Unlike research focused specifically on one brain network or activity in one brain region, this influential study examined arousal-related changes in brain-wide network topography using a combination of graph metrics and pupillometry. Participants performed a reward learning task in which they had to determine whether rewards were associated with the categorical nature or perceptual features of a stream of images. Pupillometry was used to track fluctuations in arousal across the task and to examine

how stimulus-driven changes in arousal were related to the functional integration of different brain networks. Importantly, this study also used average pre-stimulus pupil diameter, a measure of tonic LC activity, as opposed to task-evoked pupil dilations to index neural gain (Eldar et al., 2013). The results revealed that larger pre-stimulus pupil diameters were associated with greater neural gain across the brain but not overall task performance.

At first blush, these results seem to run counter to the idea that high tonic LC activation should impair perceptual and memory selectivity. A closer examination of the data, however, reveals that these global increases in pupil diameter and neural gain corresponded with better performance when trials were aligned with the participants' intrinsic learning preferences, namely whether participants prefer to learn from the conceptual or perceptual features of target information. Like other high-arousal behaviors, such as habitual responding, these behavioral, neural, and pupil patterns align well with the linear "easy" component of the arousal-performance relationship. At high tonic levels of arousal, as indexed by higher pre-stimulus pupil diameters, learning and neural gain were preferentially biased towards more hard-wired, habit-related information and away from top-down attention/control.

Interestingly, these graph measures of neural gain were indexed by local patterns of functional integration amidst more global increases in network segregation. On the surface, this brain network topology appears to be qualitatively different from the functional network connectivity patterns observed during phasic gain states (Shine et al., 2018a). In those lines of work, brain-wide networks become more functionally integrated with each other to support focused attention, which was also related to task-evoked pupil dilations and drug-induced brain states conducive to phasic LC responses (i.e., under atomoxetine administration; Shine et al., 2018b). It is possible that large pupil diameters may be a better metric of persistent gain states in the brain and bear their own signature of network integration and segregation patterns. On the other hand, phasic, stimulus-evoked pupil dilations during cognitive tasks may serve as a better metric of phasic LC activity and neural gain – that is, neural processes focused on representations of goal-relevant stimuli. In these instances, task-relevant gain would optimize task performance via LC modulation of more functionally integrated and cooperative brain states.

Network neuroscience studies have helped to reveal the effects of arousal on large-scale network dynamics and their relation to cognitive processing (Shine, 2019; Shine et al., 2018a; Shine et al., 2016). They also support the critical role of the LC-NE system in regulating global

arousal states and different types of neural gain, which may be indexed by pupil measures collected at different timepoints; namely, whether arousal is measured during pre-stimulus baseline periods or in response to task-relevant stimuli. Further, converging evidence in this field points to diverse effects of the tonic and phasic modes of LC processing on information processing via the reorganization of dynamic brain networks (Wainstein et al., 2022). While additional work is needed to understand how these network dynamics relate to different behaviors, the application of graph theory measures to study the function of the LC-NE system is an exciting direction for future research.

4.6 Summary: LC activation patterns shape the quality of information processing in the brain

Much research has focused on how task-evoked phasic LC activation can implement neural gain for a wide range of prioritized information. Yet other work suggests that high tonic levels of LC activity may facilitate a qualitatively different form of neural gain, leading to different behavioral outcomes. The key differences between these phasic and tonic neural gain states may depend on the temporal specificity of LC activation, background levels of arousal, and the differential sensitivity of brain regions to the local and concentration-dependent effects of NE on different adrenoreceptors.

Here, we suggest that the “easy” and “difficult” curves of the arousal-performance relationship may help explain some of these qualitative shifts in information processing. These two arousal-performance curves are thought to map onto two separate but interacting brain systems that show different sensitivity to elevated states of arousal and NE release. On the one hand, the lateral PFC and its broader cortical networks support complex executive functions, including goal-directed behavior and top-down attention. On the other hand, the amygdala supports the processing of “easy” cue-based or highly emotional information (Diamond et al., 2007). Consistent with the GANE model, both the amygdala and LPFC are activated by phasic LC activity and behaviorally relevant stimuli. As shown in **Figure 8,** this may explain why stronger phasic LC activation at an intermediate level of tonic arousal can enhance neural gain irrespective of the type of priority. Namely, top-down inputs from multiple brain regions can regulate processing of *task relevant* and *temporally specific* inputs, reflecting the mid-point of both the monotonic and curvilinear features of arousal-performance relationship.

As tonic arousal continues to increase, however, neural gain may become decoupled from task demands as individuals begin to explore new behaviors or mind wander. Accordingly, increases in global arousal may promote the reconfiguration of large-scale functional networks to promote high persistent neural gain for distracting information and, in cases like stress, emotional or habit-related information. This pattern accords with the far-right portion of the inverted-U component of the arousal-performance curve, where performance on complex cognitive tasks becomes noisier and attention becomes less focused on the task at hand.

Under extremely high arousal and global NE release, LPFC function becomes impaired and amygdala-centric processing will likely prevail. This should result in a qualitative shift in information processing towards emotional sources of priority. Beta-adrenoreceptors are more readily engaged under stress when global levels of NE are elevated, creating optimal conditions for NE hotspots to emerge in the amygdala and nodes of the salience network when emotional stimuli are encountered. The concomitant release of the stress hormone cortisol is also likely to fuel NE hotspots by amplifying glutamatergic signaling in the amygdala. Noradrenergic modulation of persistent neural gain and NE hotspots is thereby likely to obey the linear component of the arousal-performance function.

By interpreting the GANE model and large-scale network dynamics through the lens of the original account of the arousal-performance relationship (Yerkes & Dodson, 1908), we hope this section has illuminated how background or global arousal states could determine the nature of local and global patterns of brain activity. This would in turn lead to biases in the types of information that will be prioritized by top-down regions of the brain and whose processing will benefit from a corresponding increase in neural gain.

5. LC-NE system regulation of attentional capacity and effortful behavior

Classic neurocognitive models of arousal dissociate separate aspects of attention. As we've reviewed throughout this chapter, phasic arousal and LC activity play lead roles in facilitating adaptive gain and amplifying selectivity in attention and memory. Background arousal levels may also bias information processing towards processing bottom-up or top-down information and privilege different brain systems to win the competition for behavioral control. In the following section, we will review evidence suggesting that in addition to influencing the selectivity and quality of information processing in the brain, tonic arousal and LC activity also regulate another key parameter of attention: capacity. We discuss findings showing that tonic LC-NE activity sets the overall attentional state, and thereby determines if working memory

performance and other executive functions, such as cognitive flexibility, will function efficiently (Chamberlain & Robbins, 2013; Coull et al., 2004; Minzenberg et al., 2008). In addition, we examine how LC activity helps supply organisms with the mental and physiological energy needed to respond to and encode behaviorally relevant events.

5.1 Evaluation of task utility and task performance modulates tonic LC-NE activity

Attention is costly - we must “pay” attention to information we wish to process. This quantitative component of attention, the resources we invest into performing a specific task, is often described as “attentional intensity” (Robison & Unsworth, 2017). But limitations on the availability of mental resources challenge an organism’s ability to regulate and sustain attenton and energy levels sufficient to meet different task demands. As discussed in previous sections, cognitive demands can be met by modulating attentional selectivity, or the allocation of the limited cognitive resources towards task-relevant processes. In this section, we focus on a second means of meeting task demands - how arousal also modulates attentional capacity to increase the available pool of cognitive resources.

Situations that require intense focus or difficult choices are often accompanied by an increase in arousal, which is likened to the concept of recruiting mental effort (Kahneman, 1973; Shenhav et al., 2017). As reviewed throughout this chapter, the pupil serves as an especially powerful tool for measuring and evaluating the amount of effort needed to perform a difficult task (Just et al., 2003; Kahneman & Beatty, 1966; Laeng et al., 2012; van der Wel & van Steenbergen, 2018). Insofar as LC activity is directly linked to fluctuations in pupil size, the LC-NE system might therefore be essential for adjusting attentional intensity to match task demands via its modulation of both attentional capacity and selectivity (Unsworth & Miller, 2021; Unsworth & Robison, 2017b).

The LC-NE system is well suited to regulate attentional capacity, given its dense connections to brain networks that support both bottom-up and goal-driven attention, including the salience and frontoparietal networks (Corbetta et al., 2008; Hermans et al., 2011; T.-H. Lee et al., 2018; Mather et al., 2020; Unsworth & Robison, 2017a). Neuroenergetic models of attention and arousal propose that attentional capacity is constrained by background arousal states (Kahneman, 1973), which are set by levels of tonic LC activity (Aston-Jones & Cohen, 2005). This leads to the question of how tonic arousal and LC-NE activation levels are adjusted. Earlier models posit that an evaluation center assesses task demands and utility, and drives adjustments in arousal levels to support task-related information processing (Kahneman, 1973).

Extending this idea, Adaptive Gain Theory proposes that multiple evaluation centers in the brain, consisting of the dACC and OFC, integrates inputs about performance feedback and reward to adaptively adjust tonic levels of LC-NE system activity (Aston-Jones & Cohen, 2005). As cost-benefit evaluations fluctuate during cognitive or decision-making tasks, the dACC and OFC may regulate tonic LC activity to bias arousal processes towards either task-engaged behavior or more exploratory behavior. Thus, Adaptive Gain Theory hypothesizes that the dACC and OFC coordinate changes in tonic LC-NE activity in response to fluctuating task utility and task demands.

An emerging body of evidence supports the existence of rich anatomical and functional connections between the LC-NE system and the anterior cingulate cortex. For instance, direct microstimulation of the ACC elicits a pupil dilation, albeit weaker and more delayed compared to the stimulation of the LC (Joshi et al., 2016). This shared physiological function and bidirectional connections between the two structures (Koga et al., 2020) suggest that the ACC and the LC form one part of the arousal network. Researchers have also found that this LC-anterior cingulate cortex network is involved in resolving task conflict, which refers to the maintenance of goal-directed behavior in the presence of distracting stimuli (Ebitz & Platt, 2015). This study found increased neuronal activity in the dorsal anterior cingulate cortex signaled the presentation of distracting stimuli, especially when performing a goal-directed task. Moreover, this activation of the dACC predicted a change in baseline pupil diameter, indexing an increase in tonic LC-NE activity. Thus, the anterior cingulate cortex's role in maintaining goal-directed behavior in the face of distractors may be mediated by an increase in tonic LC activity.

In addition to signaling the presence of distractors that conflict with goal-directed behavior, the anterior cingulate cortex (ACC) has been implicated in signaling reward and plays a role in monitoring task utility (Bush et al., 2002; Kennerley et al., 2006). Recent work has linked this utility-monitoring function to changes in tonic LC levels (de Gee et al., 2022). In this study, periods of high task utility corresponded with periods of task-optimal tonic LC activity, as determined when pre-stimulus pupil diameters were stabilized at an intermediate level. This finding suggests that motivation is an important input into the evaluation centers that regulate tonic LC activity, and that this process may mediate motivation-driven improvements in task performance. These findings align with the idea that the ACC monitors bottom-up (e.g., distractors) and top-down (e.g., reward) inputs and modulates tonic LC-NE arousal levels, thereby adaptively adjusting attentional intensity to match the situation.

5.2 Setting the global arousal state: LC interactions with the salience network

Through its dense efferent projections, the LC is essential for regulating global arousal states and for promoting the functional integration or segregation of large-scale brain networks. There appears to be an especially strong relationship between pupil measures and fluctuations in activity within the salience network, a collection of brain regions primarily anchored in dACC and anterior insula (DiNuzzo et al., 2019; Joshi et al., 2016; Joshi & Gold, 2022; Seeley et al., 2007; Zerbi et al., 2019). For example, the change rate of pupil diameter (i.e., first-order temporal derivative of pupil size) is positively correlated with salience network activity both while individuals rest in an MRI scanner (Schneider et al., 2016), detect salient oddball stimuli (Murphy et al., 2014), must sustain attention (DiNuzzo et al., 2019), or perform a mentally demanding working memory task (Fietz et al., 2021). During fear learning, stimulus-evoked pupil dilations have also been shown to track with salience network activation on a trial-by-trial basis (Leuchs et al., 2017). Salience network responses, including responses localized to both the anterior insula and dACC, also correspond with behavioral errors during continuous attention tasks (Kucyi & Parvizi, 2020) and Stroop interference tasks (Critchley et al., 2005).

Pupil-linked responses in the salience network appear to relate to multiple forms of priority. These relationships also seem to respect the monotonic arousal-performance curve, as pupil dilations are linearly correlated with the magnitude of salience network activation (Mäki-Marttunen, 2021). Interestingly, one neuroimaging experiment showed an inverted-U relationship between pupil dilation and accuracy on two cognitively demanding tasks (Mäki-Marttunen, 2021). Additionally, Maki-Marttunen (2021) demonstrated that pupil dilations were positively correlated with functional integration within the salience network.

Because both resting (non-task-related) and task-related pupil dilations correspond with increases in salience network activity or connectivity, we believe that salience network activation likely represents the capacity of attention. Indeed, human neuroimaging work shows that salience network activation is associated with tonic alertness rather than selective attention (Sadaghiani & D'Esposito, 2014). This was theorized to index an effortful process of maintaining mental resources to meet current processing needs (Sadaghiani & D'Esposito, 2014). Within-network functional integration of the salience network is also linearly correlated with other measures of sympathetic nervous system activation, such as heart rate (Young et al., 2017), consistent with its role in representing tonic arousal levels. Together these findings suggest that salience network engagement does not reflect the content or priority of information processing

at a given moment. Instead, its activity reflects the number of domain-general resources that can be recruited through other regions or networks that signal priority, such as the fronto-parietal network (Menon & Uddin, 2010).

As described earlier, monotonically increasing levels of arousal (and therefore salience network activity) may correspond with a qualitative shift in information processing and patterns of inter-network functional connectivity. Namely, at very high levels of arousal, the salience network might prioritize emotional information via stronger functional integration of the amygdala (Hermans et al., 2011). Cohesion between executive control and the salience network has also been shown to be maximal at intermediate levels of arousal, suggesting that phasic LC activity enhances coordinated activity between brain networks that support alertness and task-focused attention (Bouret & Sara, 2005). However, when arousal levels were especially high, this pattern of executive and salience inter-network communication diminished.

Broadly, our view is also consistent with the role of the dACC in detecting errors and signaling the need for additional resources, effort, and behavioral adjustments. Following detection of these salient events, descending inputs from the dACC adjust LC tonic activity accordingly to meet these demands (Aston-Jones & Cohen, 2005; Sara, 2015). Increased functional coupling between the LC and other nodes of the salience network, namely the anterior insula, has also been observed following negative or uncertain action outcomes (Clewett et al., 2013). Finally, the close link between the salience network and tonic arousal dovetails with evidence that insula and dACC activation drive exploration (e.g., Blanchard & Gershman, 2018) and hypervigilance (Hermans et al., 2011), two behaviors that are strongly associated with very high levels of tonic arousal and LC activation.

5.3 Pupil-linked LC activity is related to task difficulty and effort

The principle that arousal supplies the energy, or capacity, for cognitive processes is a common thread that runs through many neuroenergetic models of arousal and attention (Kahneman, 1973). Recent research has now begun to explore the possibility that the LC implements this process in the brain by mobilizing attentional resources when an increase in mental effort is required (Killeen et al., 2013). Remarkably, this function appears to be domain-general and consistent across species, as the LC is reliably engaged by a wide variety of perceptual discrimination and decision-making tasks. For example, evidence in humans (Raizada & Poldrack, 2008) and rodents (Doucette et al., 2007; McBurney-Lin et al., 2019) shows that the LC-NE system activation increases during challenging sensory discriminations. In addition to

facilitating perceptual decisions, the LC is recruited to support higher-order cognitive processes, including response conflict resolution (Grueschow et al., 2020) and cognitive control (Köhler et al., 2016). Pupil dilations during a mentally demanding multiple object tracking task correlate with activity in a brainstem region consistent with the location of the LC (Alnaes et al., 2014). This pupil-linked LC effect is also modulated by cognitive load, suggesting that arousal-related activation of the LC may track attentional resource allocation. Functional connectivity between the LC and prefrontal cortical has been shown to occur during successful conflict resolution on an emotional Stroop task (Grueschow et al., 2020). Conflict trials on this task were also associated with increased pupil dilation, an autonomic arousal effect that is reliably observed across many Stroop experiments (Brown et al., 1999; Hershman & Henik, 2019; Laeng et al.,

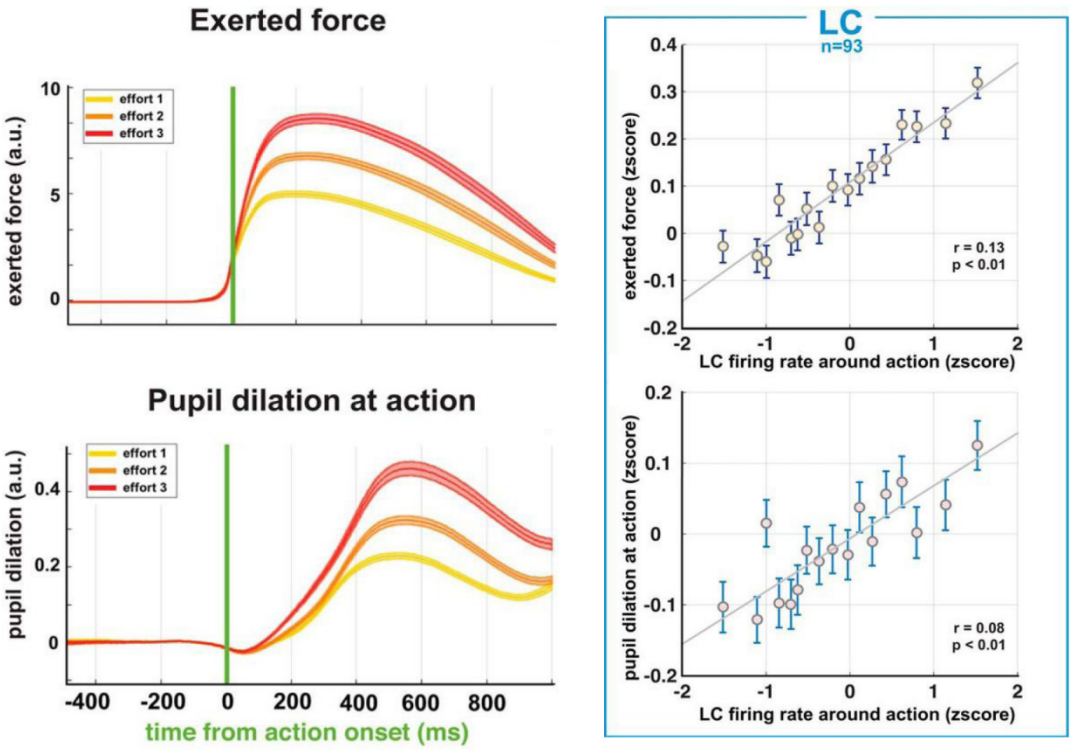

Figure 9. Expected effort tracks with pupil dilation and LC firing rate. (Top left) In a lever press task, monkeys exerted the most force when the largest amount of effort was expected (effort 3). (Bottom left) Pupil dilation was greatest for trials in which monkeys expected to spend the largest amount of effort. (Right) LC firing rate had a positive, linear relationship with both exerted force and pupil dilation. Together, these findings suggest a link between the pupil-linked LC-NE system and the recruitment of effort to meet expected task demands. Figure adapted from Varazzani et al. (2015).

2011).

The LC may also be involved in coordinating the supply of *physical* energy needed to fuel goal-driven actions. Indeed, spikes in LC activity have been reported across different species during motivated behavior. Electrode recordings in monkeys reveal that LC firing is related to the amount of physical effort that is necessary to receive a juice reward (Varazzani et al., 2015; **Figure 9**). Researchers also found that LC activity not only spiked during presentation of the reward cue, but also scaled with the amount of force that was necessary for lever pressing to acquire that reward. Importantly, phasic LC activity during the lever press was also correlated with the magnitude of pupil dilation, supporting the idea that transient pupil responses serve as an index of LC activity and effort.

Work in rodents also corroborates this link between phasic LC activity and successful task execution. Using a sophisticated combination of optogenetics, electrode recordings, and tracing techniques in rodents, Breton-Provencher et al., (2022) showed that phasic LC activity spikes in the period preceding a lever-press during a Go/No-Go task. Interestingly, they also observed specificity in the LC projections involved in this behavior. Namely, pre-movement NE release primarily occurred in target motor regions and not in task-irrelevant cortical regions (Breton-Provencher et al., 2022). These results suggest that there may be specificity in LC modulation during cognitive tasks, such that LC activity selectively enhances processing in task-relevant regions and drives task-relevant actions that emerge from decisions to act (see also, Clayton et al., 2004; Pavlenko & Kulichenko, 2003). Likewise, phasic LC activity tracks effort production as well as difficulty in monkeys performing discounting tasks (Bornert & Bouret, 2021). Specifically, LC activation during action initiation not only scales with the level of force production, but also with behavioral response times related to this decision period.

In addition to driving motivated behavior, LC-mediated task execution also appears to influence subsequent memories for those experiences. Neuroimaging evidence in humans shows that phasic LC activation facilitates task responses in ways that boost episodic encoding (Yebra et al., 2019). Using a combination of pupillometry and fMRI, researchers showed that LC activation selectively occurred during successful encoding of images paired with “Go” responses. This memory boost for action-related stimuli also corresponded with greater pupil dilation, reinforcing the link between phasic LC activation and action-evoked pupil responses.

5.4 LC activation coordinates the supply of metabolic resources

Task-related responses in the LC may be essential for facilitating cognitive control, especially under high task demands and when stimuli or behaviors conflict. But does the LC also supply

the physiological resources needed to meet these cognitive demands? Intriguingly, the answer appears to be yes. Empirical evidence supporting this view comes from a study examining the relationship between LC activity and neurovascular coupling, whereby LC-NE activation redistributed blood flow towards highly active brain regions (i.e., sensory regions being stimulated; Bekar et al., 2012). Interestingly, patterns of LC modulation also exhibited a gain-like effect in blood delivery, with vasoconstriction occurring more globally across less active brain regions and vasodilation occurring more locally in stimulated sensory regions. Thus, LC activity helps couple blood distribution changes with local demands for oxygen, which is a critical component of the oxidative metabolic pathways that generate energy in neurons.

In addition to modulating neurovascular dynamics, the LC also regulates the brain's utilization of glucose, the metabolic equivalent of fuel for neuronal activity (for review, see Mergenthaler et al., 2013). Studies have found that NE interactions with astrocytes trigger glycogenolysis, the process of breaking down glycogen stores into glucose (Dienel & Cruz, 2016; Magistretti et al., 1981; Sorg & Magistretti, 1991). NE-astrocytic interactions also induce glycolysis, the initial phase of glucose metabolism that yields the intermediate by-product pyruvate (Magistretti & Allaman, 2018). In astrocytes, this pyruvate is often converted to lactate, even under aerobic conditions (Magistretti & Allaman, 2018). Both pyruvate and lactate are then transported to neurons, where they serve as fuel for the final metabolic step that produces the bulk of the energy used in neurons.

Recent studies implicate the LC-NE arousal system in the engagement of these metabolic pathways. In mice, various arousal manipulations induced global cortical activation that corresponded to an increased production of lactate. Importantly, this increased lactate production corresponded with physiological markers of LC activity, including pupil dilation (Zuend et al., 2020). Intriguingly, NE-driven production of lactate not only fuels neuronal activity (Coggan et al., 2018), but may also serve as a signaling molecule that enhances the formation of spatial memory (Newman et al., 2011). Thus, NE is thought to play a critical role in modulating energy availability for neuronal use by triggering glucose metabolic pathways in astrocytes (Berridge & Waterhouse, 2003). Because the local production of intermediate by-products lactate and pyruvate relies on beta-adrenoreceptor activation (Vaishnavi et al., 2010), it is tempting to speculate that local NE hotspots drive this selective allocation of energetic resources to enhance neural gain and mental selectivity (e.g., Mather et al., 2015).

5.5 Summary: LC activation supports attentional capacity and goal-directed actions

In summary, noradrenergic system regulation of central blood flow, glucose utilization, and astrocytic activity provides a plausible biological substrate for linking LC activity to both physical and mental energy, or effort. Importantly, this mobilization of resources also exhibits spatiotemporal specificity. Through targeted projections across the brain, the LC may help amplify processing of task-relevant information under arousal by ensuring task-relevant brain regions receive the biological resources they need to sustain and mount appropriate responses to various challenges in the environment. Importantly, fluctuations in tonic LC activation also set attentional states, leading to both intra- and inter-subject variations in attentional control over time.

Tonic arousal and LC activation track with the functional dynamics of the salience network, a collection of brain regions that facilitate adaptive task switching, reorganize other functional networks, and promote appraisals of motivational significance. Increases in pupil size correlate with activity in central nodes of the salience network, with the dACC dynamically regulating LC output to modulate adaptive gain and enhance behavioral utility. We suspect that reciprocal LC interactions with the salience network reflect the amount of effort that is needed to implement goal-directed actions and meet homeostatic demands under stress. In this way, the salience functional network is well positioned to modulate tonic arousal and attentional capacity via its interactions with the LC and other large-scale functional networks.

6. A unifying model of the LC-NE system and arousal-attention interactions

For many years, researchers have sought to understand how arousal influences different parameters of attention and information processing. However, these psychological constructs are multifaceted and aren't always easily reconciled. Back in the 1970's, the Capacity Model of attention laid important groundwork for studying arousal-attention interactions by describing cognitive constructs like "capacity", "arousal", and "effort" (Kahneman, 1973). Since then, neurobiological and computational models have uncovered mechanisms that ground these ideas in the brain. Owing in large part to pupillometry research, it appears the LC-NE system may be a linchpin between different neuroenergetic and cognitive models of arousal and attention.

In this section, we recap many of the topics covered earlier in this chapter. We describe a unifying framework of LC-NE system that aims to account for different cognitive constructs, as outlined in **Figure 10.** Broadly, our framework expands upon the seminal Capacity Model

(Kahneman, 1973) by integrating theories and empirical work on the functional roles of phasic and tonic modes of LC activity in shaping neurocognitive processes (Aston-Jones & Cohen, 2005). We also highlight where tonic and phasic pupil biomarkers fit within the context of this expanded model of attention-arousal interactions.

6.1 Links between the LC-NE system and cognitive constructs of attention

The original Capacity model sparked discussions about arousal-attention interactions by distinguishing between state-specific (attentional capacity) and task-specific (later called attentional intensity) attentional resources (Kahneman, 1973). Attentional capacity, which has been likened to the idea of mental energy, represents the available pool of attentional resources that can be deployed for any cognitive process, whether task-relevant or not. Attentional capacity fluctuates with changes in arousal, which is in turn induced by environmental cues or from top-down cognitive and metacognitive factors. Of this attentional capacity, an allocation policy (here, referred to as “attentional selectivity”) determines attentional intensity by controlling how much attentional resources are devoted to task-relevant information processing **(Figure 10a)**. Presumably, the remaining attentional capacity that is unused by task-related processing is automatically allocated towards any task-irrelevant information processing, a core tenet within Perceptual Load Theory’s explanation of selectivity (Lavie & Tsal, 1994; **Figure 10b**).

An enduring feature of the Capacity Model is its proposal that arousal regulates both attentional capacity and attentional selectivity. Building on this foundation, leading neurocomputational, cognitive, and neurobiological models aim to capture how modulation of attention by different extrinsic (e.g., salience, surprise, and novelty) and intrinsic (e.g., mental effort and motivation) factors are mediated by arousal (Aston-Jones & Cohen, 2005; Kahneman, 1973; Richter et al., 2016; Unsworth & Miller, 2021; Unsworth & Robison, 2017a). As displayed at the center of **Figure 10**, the LC-NE system has been proposed as the mechanism that implements state arousal’s dual effects on attentional capacity and selectivity (Aston-Jones & Cohen, 2005). LC activity, and its release of NE, coordinates the delivery of oxygen and glucose from the bloodstream and induces astrocytic metabolic activity, thus regulating the supply of energy for local neuronal activity (Bekar et al., 2012; Zuend et al., 2020; **Figure 10c**). Therefore, an increase in tonic LC-NE activity sustains metabolic activity that fuels information processing,

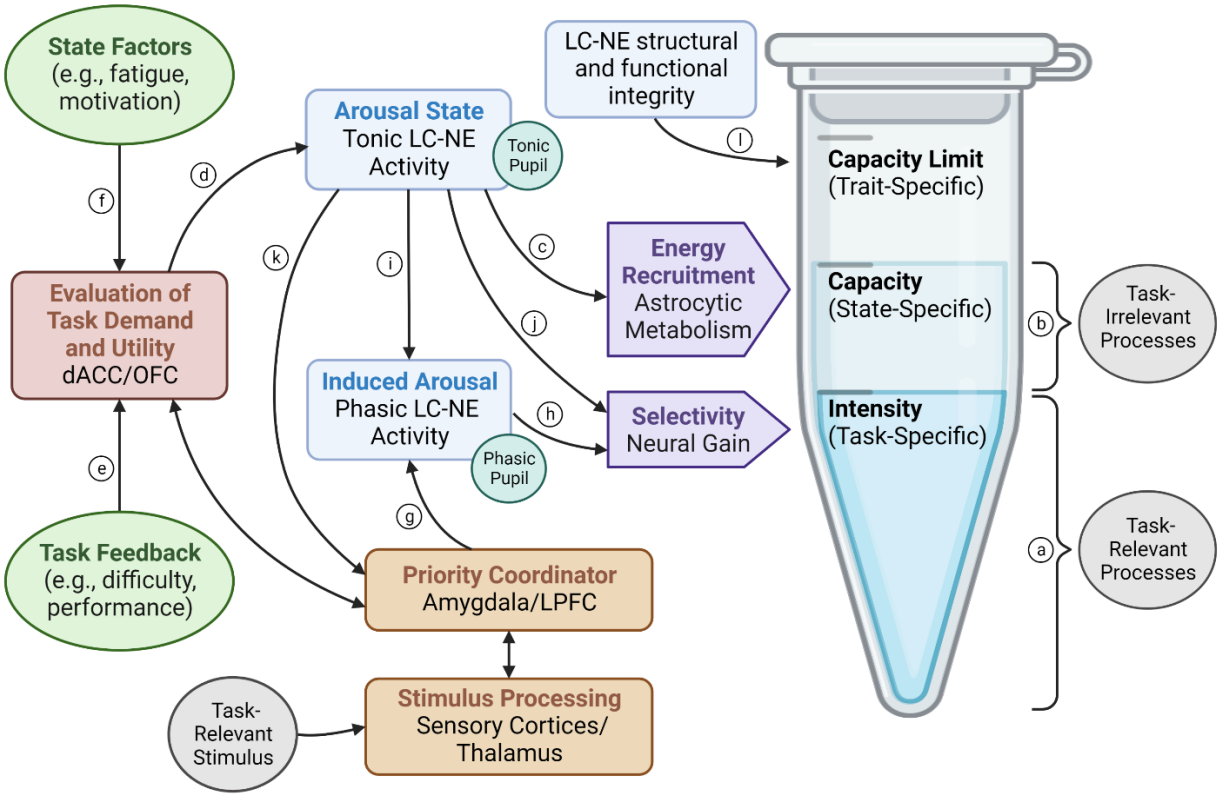

Figure 10. A unifying LC-NE system framework for integrating different models of arousal-attention interactions. This expanded model illustrates the underlying mechanisms that determine the attentional intensity (bottom layer of the vial with liquid), or the amount of attentional resources allocated to task-relevant processes. The LC-NE system influences state-dependent attentional capacity (middle layer of the vial) and intensity by mobilizing the delivery of energetic resources across the brain. The structural and functional integrity of the LC-NE system also place upper limits of the maximum number of mental resources that are ever available to process information (top mark of vial). To modulate the capacity, selectivity, and intensity of attention, distinct modes of LC activity interact with higher-order brain regions that evaluate stimulus salience and task utility. Further details corresponding to the numbered labels are described in the main text. Figure created with BioRender.com.

paralleling the hypothesized influence of state arousal on attentional capacity. What triggers this energizing function of the LC-NE system? The original Capacity Model posited that one important factor was mental effort, which reflected an individual's evaluation of task demands. When performing the task becomes more effortful, a metacognitive assessment of the situation triggers an increase in state arousal, leading to increased attentional capacity. From this idea, Adaptive Gain Theory proposed that the dACC and OFC evaluates task demands and task utility and drives an appropriate adjustment in tonic LC activity (Aston-Jones & Cohen, 2005; **Figure 10d**). These higher-order regions are important for monitoring task performance (**Figure**

10e) and integrating inputs from regions that also evaluate reward, cognitive conflict, and salience (**Figure 10f**). Thus, state factors that affect task utility, like fatigue and motivation, feed into these pathways to indirectly influence changes in attentional capacity and selectivity (Unsworth & Miller, 2021).

Through the neural gain framework, Adaptive Gain Theory explains how phasic LC-NE component, the substrate for "induced arousal", acts as a temporal filter for boosting the processing and prioritization of important information. As described in Section 3.2, the LC receives dense inputs from regions that evaluate the task relevance and the biological significance of stimuli, including the OFC, dACC, and amygdala. When salient events occur, activation of these brain regions recruit a phasic LC response (**Figure 10g**) to enhance neural gain in target regions throughout the brain (**Figure 10h**). Such neural gain may be implemented through complementary local and global processes, including the emergence of local NE hotspots (i.e., GANE model) within highly active regions. The phasic LC responses can also issue a brain-wide "reset" signal that promotes the reorganization of functional networks to prioritize behaviorally relevant information (Bouret & Sara, 2005). In general, phasic LC effects seem to target activity and functional connectivity within right-lateralized PFC regions and functional networks, including the ventral attention network (Corbetta et al., 2008; Sara, 2015). Together, these noradrenergic effects work in concert to focus whatever limited mental resources are available to process what matters most, when it matters most.

Earlier models of attention noted some perplexing findings about elevated state arousal's effects on selectivity; namely, the rigidity-lability paradox (Easterbrook, 1959; Wachtel, 1967). Adaptive Gain Theory offered a solution to this puzzle by describing how elevated tonic LC activity constrains phasic task-evoked LC activity (**Figure 10i**) while sustaining a state of high neural gain (**Figure 10j**; Aston-Jones & Cohen, 2005; Eldar et al., 2016). Together, these effects deny the temporal specificity of task-focused attention while enabling non-task cues to capture the enhancing effects of a persistently high neural gain. This account accords with the behavioral shift from task-exploitative at moderate arousal levels to explorative at high arousal levels (Aston-Jones & Cohen, 2005). Moreover, tonic LC activity boosts activity in amygdala-centric networks while also suppressing LPFC-centric functions (**Figure 10k**), shifting the balance of priority signaling – and by extension, behavioral control - from goal-directed to emotional or bottom-up information processing.

6.2 Aging as a model of LC changes and their relation to parameters of attention

Another important consideration is that there are upper limits on the quantity of mental resources within a given individual. While many models focus on how attentional capacity is state-dependent and fluctuates over time, it is intuitive that there is a ceiling to how many mental resources can ever be available. In theory, these biological constraints would manifest individual differences in cognitive abilities. Indeed, pupillometry studies show that baseline pupil diameters relate to trait-level differences in fluid intelligence and working memory capacity (Tsukahara et al., 2016; Tsukahara & Engle, 2021; Unsworth & Robison, 2020). Moreover, within-subjects measures of baseline pupil diameter are stable over very long periods of time, further supporting the idea that this may be an effective physiological marker of trait differences in attentional capacity and cognitive abilities (Robison et al., 2022; but see Tsukahara & Engle, 2021). Pupil diameter differences have also been reported across different disorders of attention, such as ADHD (Anderson & Colombo, 2009; Unsworth et al., 2019).

In recent years, there has been a surge of interest in examining how age-related shifts in LC-NE functional and structural integrity relate to cognitive decline and the neuropathology of Alzheimer's disease (AD; Betts et al., 2019; James et al., 2021; Mather & Harley, 2016). Seminal work on the etiology of AD demonstrated that tau pathology is observable in the LC even before the emergence of tau in the medial temporal lobe (MTL), a hallmark feature of the disease (Braak et al., 2011). Pupil dilation responses during digit span working memory tasks (Granholm et al., 2017) and salient auditory stimuli (Fletcher et al., 2015) are also blunted in individuals with AD, suggesting that LC phasic responses are compromised in age-related disorders. Diminished phasic LC responses may be exacerbated by age-related changes in the structure and/or function of higher-order brain regions, such as the LPFC, that signal priority and recruit transient LC activity (Moscovitch & Winocur, 1995). Additionally, altered LC interactions with the frontoparietal network could account for decrements in task-focused attentional processes and distractor inhibition, which are both characteristic of normal cognitive aging (Kennedy & Mather, 2019; Lee et al., 2018; Mather et al., 2020; Robertson, 2013).

Deficits in LC-NE structure and/or function may result in a reduced range in which the arousal-attention system can operate (Figure 10l). When demands on attentional resources exceed the overall supply, or trait attentional capacity, behavioral performance may fail. One compelling example of this is normal aging. Specifically, age-related issues with this supply-and-demand process help to account for lower working memory capacities in older adults (Schneider-Garces et al., 2010). While seemingly counterintuitive, age-related changes in the LC-NE system may relate to and/or be driven by a tonic increase rather than decrease in baseline arousal levels

(Mather et al., 2020). Elevated tonic arousal and LC activation appear to be a compensatory mechanism for decline in LC neurons (Mather et al., 2020). Heightened arousal also diminishes phasic LC discharges that are important for regulating neuroinflammation and clearing pathological markers of AD (Janitzky, 2020; Robertson, 2013).

If tonic LC activation increases, wouldn't this mean attentional capacity is also reduced from moment-to-moment? Turns out, this might not be the case: age-related increases in tonic LC activity might enhance *state*-dependent attentional capacity despite *trait* attentional capacity being lower. Models of arousal-attention interactions would suggest that beyond overall decrements in performance in older adults, elevated tonic LC activity would allow both task-relevant and task-irrelevant, or distracting, cues to consume whatever cognitive resources remain (Hasher & Zacks, 1988; Lavie & Tsal, 1994). Indeed, failures to inhibit distractions and maintain focused attention are some of the defining features of cognitive aging, and these failures appear to be exacerbated by stimulus-evoked increases in arousal (Lee et al., 2018).

To summarize, aging may be a good model of how trait levels of attentional capacity are set by neurobiological constraints. Trait levels of attentional capacity may decrease with age due to the degeneration of LC neurons (Clewett et al., 2016; Mather & Harley, 2016; Wilson et al., 2013). However, a disproportionate amount of these attentional resources may remain available due to a compensatory increase in tonic LC activity. The consequence of these resource increases is that older adults may become more distracted by task-relevant cues and exhibit more generalized increases in LC-mediated gain, especially under exogenous manipulations of arousal (e.g., Lee et al., 2018). Due to changes in higher-order brain regions like the LPFC with age, attentional intensity may also diminish along with a decrease in task-relevant phasic LC responses. There has been a rapid increase in the number of studies examining links between the LC and both pathological and healthy cognitive aging. We anticipate that this relationship will continue to be an area of intense interest in the coming years.

7. Methodological considerations for studying the LC-pupil link

Pupillometry is a highly effective technique for testing predictions about how the LC influences distinct aspects of neural processing and behavior, because tonic and phasic modes of LC activity can be linked to different pupil metrics. Here, we review how pupil measures reveal the influence of tonic and phasic patterns of LC activation on key parameters of arousal and attention. We also discuss how a careful consideration of the behavioral/arousal context may deepen our understanding of the link between pupil fluctuations and LC function.

With respect to the arousal and attention models described in this chapter, how can researchers benefit from acquiring pupillary measures of tonic and phasic modes of LC activity? Both tonic and phasic pupillary measures may capture latent attentional factors that explain trial-by-trial variability in behavioral performance. Tonic pupil measures index fluctuations in the background levels of LC-NE system activity throughout an experiment session (Rajkowski et al., 1994). This can provide researchers with insight into changes in the state of task-engagement, ranging from inattentive to engaged to distractible, and to relate task performance to fluctuations in attentional state. In contrast, phasic pupil measures are task-evoked, meaning that they are specifically tied

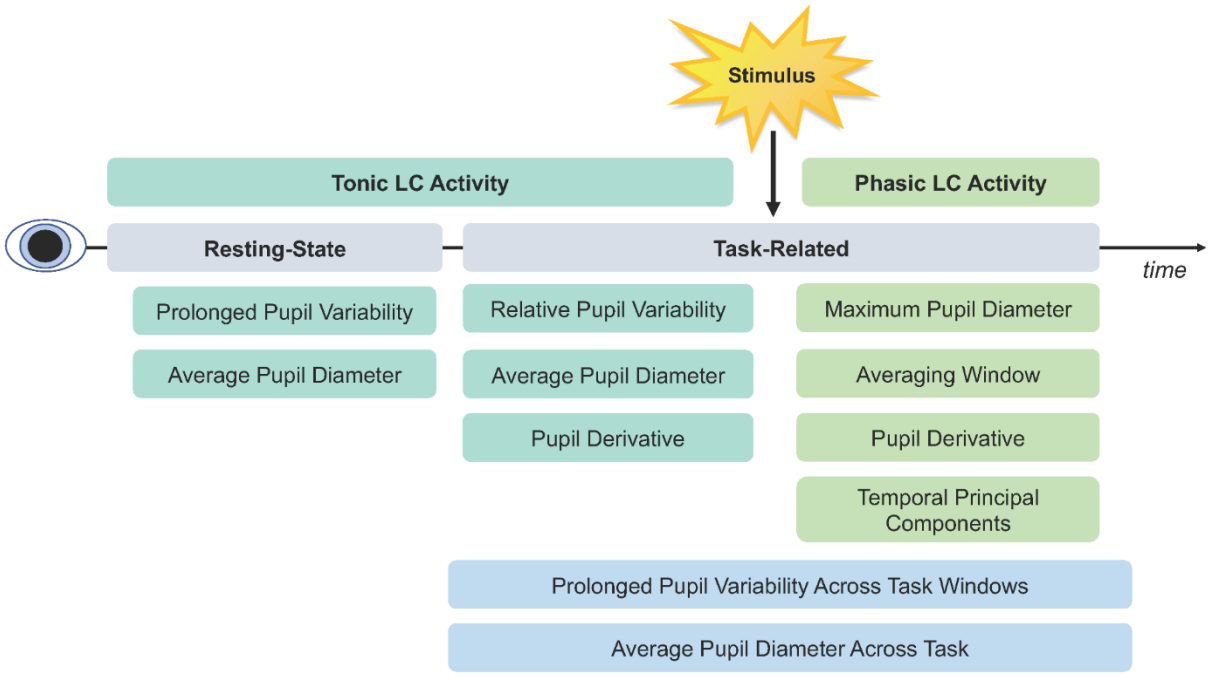

Figure 11. Pupillometry methods can be used to index phasic and tonic modes of LC activity. Different pupil measures can be used to infer tonic (turquoise colors) or phasic LC (green colors) activity depending on when the pupil is measured, how it is computed, and whether it is time-locked to the onset of a stimulus. These pupil measures can be acquired during a resting-state block or during different task periods (pre-stimulus baseline, post-stimulus, or across multiple trials). Most tonic LC estimates involve measuring pupil diameter, or size. On the other hand, task-evoked phasic LC and pupil dilation responses are linked to the onset of a stimulus; in some cases, these estimates involve normalizing an average pupil response by subtracting a pre-stimulus baseline estimate. In other cases, pupil dilation estimates are measured agnostically with respect to baseline (e.g., pupil derivative or temporal principal components). Pupil size and dynamics can also be measured across more prolonged periods of time by taking advantage of the high temporal resolution of pupillometry data. Measures of pupil diameter variability or average size across a task or at rest may index a mix of tonic and phasic LC activity that relate to state or trait level differences in cognitive flexibility and learning, respectively.

to the onset of a stimulus, a decision, or an action. Phasic measures may therefore capture the temporally specific component of attention related to the processing of a task-relevant event.

To reemphasize, a key distinction is that the tonic pupil aims to measure the attentional state in which certain task events occur, whereas phasic changes in pupil diameter aim to measure the attentional resources allocated towards a motivationally relevant stimulus. Thus, the tonic pupil is usually measured before an overt task event (e.g., during inter-trial intervals), reflecting the conditions that may predict behavioral responses to the ensuing task event. In contrast, the phasic pupil is often measured after a task event, reflecting the attentional or decision outcome related to that event.

How do we define tonic and phasic pupil measures? In general, researchers distinguish the two measures based on their temporal dynamics, with tonic measures capturing the lower frequency pupillary fluctuations and phasic measures reflecting the transient pupillary responses to a task event (Beatty, 1982). Many studies employ the intuitive approach of using a stimulus-evoked pupil dilation to index phasic activity and a pre-trial baseline pupil size to index tonic activity (Gilzenrat et al., 2010; Hong et al., 2014; Murphy et al., 2011). However, a quick survey of literature reveals many variations to this basic approach due to different theoretical and practical considerations (for a thorough overview of pupil methods, see Steinhauer et al., 2022). In the following sections, we review several approaches to measuring tonic and phasic LC-NE system activity from pupil data and discuss the validity and discrepancies surrounding these methods (**Figure 11)**.

7.1 Measuring tonic LC activity using pupillometry

One of the main objectives of measuring pupil size is to index tonic LC-NE activity, which in turn is related to attentional and arousal states. This motivation stems from evidence that temporally prolonged fluctuations in LC firing rates correspond to low-frequency fluctuations in pupil size (Rajkowski, 1993). Fluctuations in the size of the pupil also track varying states of arousal, where low arousal states correspond to smaller baseline pupil size (Hou et al., 2005; Morad et al., 2000) and high arousal states correspond to larger baseline pupil size (Phillips et al., 2000).

A common approach to acquiring a tonic pupil measure is to calculate mean pupil size over a baseline, or non-stimulus-related, period. It is important to point out that the precise definition of this “tonic baseline” varies from study to study. For example, the baseline can refer to a “resting-state” period that is separate from the main task and usually lasts several minutes. This “resting-

state" baseline can be acquired before the task, after the task, or interspersed between blocks of the task. This approach defines a baseline that is completely separate from the main task, ensuring that this tonic pupil measure is uncontaminated by task-evoked pupillary changes. Researchers may use this form of tonic pupil to measure changes in attentional and/or arousal states before and after an intervention, such as following isometric handgrip (Nielsen et al., 2015), or if they want to relate attentional states to a block of task performance (Mather et al., 2020).

Other studies define a "tonic baseline" at the trial level during a cognitive task, enabling researchers to query changes in attention and task engagement from trial to trial. This approach often involves calculating the mean pupil size during a pre-trial baseline, usually during a preceding inter-trial interval lasting a few seconds (e.g., Eldar et al., 2013). This trial-level tonic pupil measure can then be related to trial-level task performance, which allows researchers to infer how different attentional and arousal states relate to task performance. For example, performance on sustained attention tasks were related to pre-trial tonic pupil size in an inverted-U relationship (Murphy et al., 2011; Van Den Brink et al., 2016). This inverted-U relationship was also observed between pre-trial tonic pupil size and the task-evoked P3 event-related potential, a measure of phasic LC-NE activity (Murphy et al., 2011). While a full discussion is beyond the scope of this chapter, pre-trial measures of pupil diameters have also been linked to different forms of mind wandering (Mittner et al., 2016; Unsworth & Robison, 2016) and attentional lapses (Madore et al., 2020). These results suggest that trial-by-trial tonic pupil measures are useful proxies for tonic LC-NE activity. They also align with the proposed relationship between tonic LC-NE system activity and an individual's current level of task engagement (Aston-Jones & Cohen, 2005).

While arousal modulations during sustained attention tasks span the full scale of the arousal-performance relationship, variations in arousal for most experiments cover only a segment of the full inverted-U curve (Joshi & Gold, 2020). Thus, for most cognitive tasks, the conventional approach of using a baseline to acquire tonic pupil measures forces researchers to assume the shape of the task's arousal-performance curve and the range of arousal that occurs during the task. To work around these assumptions, some researchers adopt less conventional measures of the tonic pupil. For instance, rather than inferring tonic LC activity per se, researchers instead use tonic pupil as a measure of task engagement (Gilzenrat et al., 2010; Jepma & Nieuwenhuis, 2011). This subtle reframing of the tonic pupil enables researchers to make behavioral predictions based on the level of task engagement, which relates to task performance in a

monotonic manner, rather than the level of tonic LC-NE activity, which relates to task performance as an “inverted-U” function.

Following this line of reasoning, researchers have proposed using a reverse inference approach to interpreting pupil effects on behavior – that is, using the magnitude of task-evoked pupil dilations to infer the state of task-engagement (Eldar et al., 2013, 2016; Hopstaken et al., 2015). In terms of Adaptive Gain Theory, a period of strong LC-NE phasic responses indicates that tonic LC activity is in a “phasic mode” that facilitates a state of task engagement. Therefore, a period characterized by larger pupil dilations is thought to reflect conditions that permit robust phasic LC-NE responses – that is, a state of greater task engagement. While this reverse inference approach facilitates interpretation of pupil-behavioral results, it also makes it challenging to draw interpretations regarding the tonic versus phasic dynamics of the LC-NE system (as both tonic and phasic measures would be derived from the same pupil dilation).

Rather than using the *task-evoked* pupil dilation to infer the state of task engagement, some researchers index the magnitude of task engagement using pupil size during a pre-stimulus baseline. For instance, Van Den Brink et al. (2016) used the temporal derivative of the pre-stimulus pupil timeseries as an indicator of task engagement. Baselines with larger temporal derivatives are driven by larger non-stimulus-evoked fluctuations in pupil dilations, perhaps reflecting a tonic LC-NE mode that is more permissive to larger phasic responses. In this sustained attention task, they found that baseline pupil size tracked with task performance according to an inverted-U relationship, in line with the expected relationship between tonic LC-NE activity (or arousal level) and task performance. However, they reported that the temporal derivative of baseline pupil tracked with task performance in a linear relationship, in line with the interpretation that a greater state of task engagement, irrespective of its place on the arousal-performance curve, promotes greater task performance.

Recent work suggests that a sudden increase in pre-stimulus baseline pupil size may index a state of persistently high and indiscriminate gain. A combination of pupillometry and computational modeling was used to examine how neural gain may influence cognitive control processes during a classic Stroop task (Tromp et al., 2022). In this study, researchers measured gain by taking the pre-trial pupil derivative (i.e., rate of change) as opposed to the stimulus conflict-evoked pupil dilation. Pupil analyses revealed that increased gain, or a larger increase in the pupil derivative, was related to faster responses but greater Stroop interference. One possible interpretation of these findings is that pre-trial gain amplifies any active input; that

is, a higher pupil state may reflect a persistent and indiscriminate increase in neural gain. This result also underscores that tonic arousal levels and neural gain can be regulated by many factors during cognitive tasks, some of which occur prior to the onset of a new stimulus.

Another “tonic” measure that has garnered interest is variability in pupil size either across a task or while participants rested. Even here, however, there are some discrepancies between how and when this variability is measured. For example, some studies measure pupil variability as deviations in pre-trial pupil size across all of the trials in a task (Madore et al., 2020; Unsworth & Robison, 2017a). In essence, this provides a “snapshot” of participants’ relative state of engagement prior to processing a relevant task stimulus. In most cases, greater variability reflects lapses in attention or greater mind wandering.

Other pupillometry work leverages the full temporal resolution of pupil sampling to examine how dynamic pupil fluctuations relate to behavior across a meaningful analysis window. This approach differs from examining pre-trial baselines in that it is agonistic to what drives pupil fluctuations across time. For example, it has been shown that moment-to-moment variability in

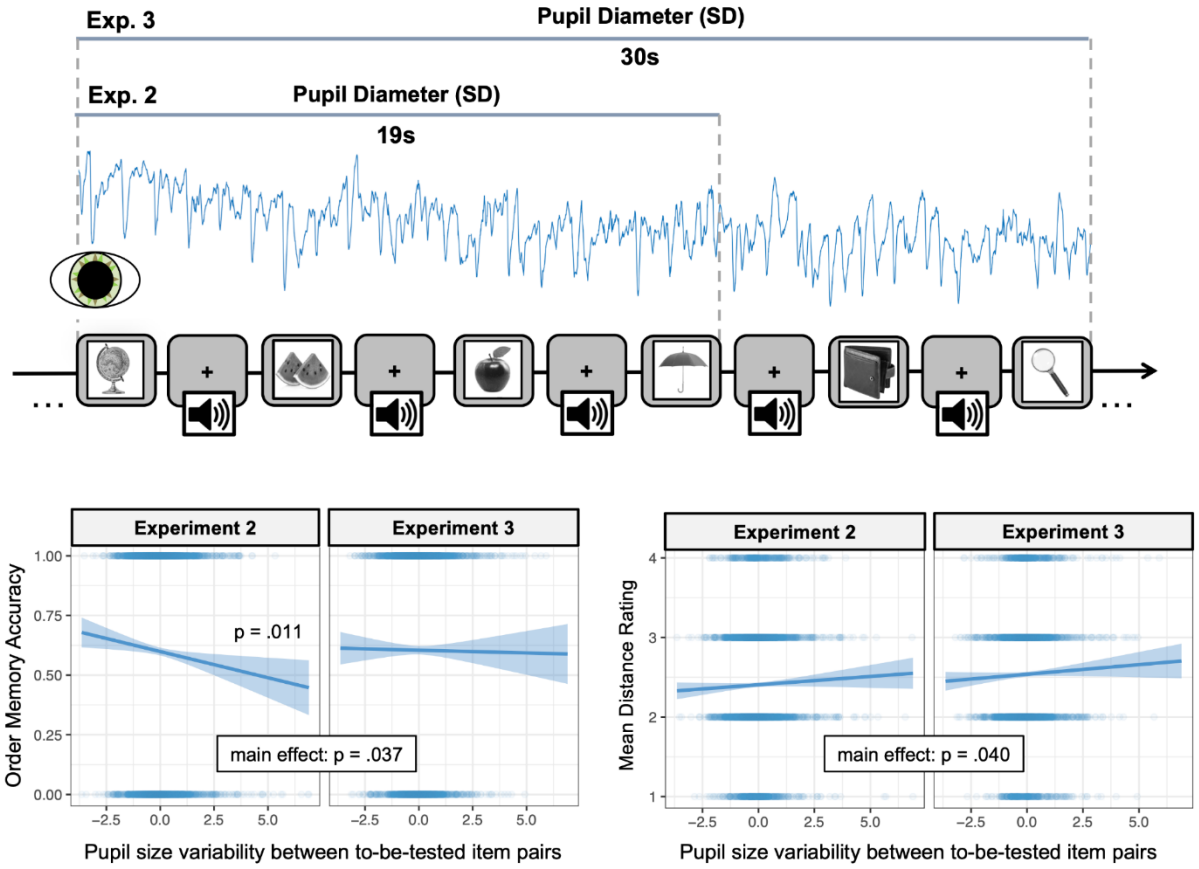

Figure 12. The temporal stability of pupil-linked arousal states facilitates temporal memory integration during sequence encoding. (Top Panel) To assess variability in pupil-linked arousal fluctuations across each sequence, the standard deviation (SD) of pupil diameter values was measured across continuous pupil samples between a pair of items that would later be tested for temporal order memory (bottom left; y-axis) and subjective temporal distance (bottom right; y-axis). This period was measured from the onset of the first image from a pair to the offset of the second image from that pair to capture the window during which inter-item associations were encoded and linked together. In Experiment 2, the temporal distance between item pairs was 19 seconds, and in Experiment 3, the temporal distance between item pairs was 30 seconds. (Left Bottom Panel) Mixed effect linear modeling revealed a significant relationship between temporal recency discrimination and pupil size variability, such that participants were better at remembering the order of item pairs if there had been less variable changes in pupil size between those items pairs at encoding. (Right Bottom Panel) Linear regression models revealed a significant relationship between temporal distance ratings and pupil size variability, such that participants were more likely to remember item pairs as having appeared closer together in time if there had been less variability in pupil diameter between those pairs at encoding. These results demonstrated that variability in pupil fluctuations can be meaningfully related to how information is processed and encoded over time. Figure taken from Clewett et al. (2020).

pupil size across a 20+ second window relates to temporal memory for pairs of items that spanned that exact window of time (Clewett et al., 2020; **Figure 12**). Specifically, during sequence encoding, continuous variability during the window of temporal encoding was related to worse temporal order memory and more expanded retrospective estimates of temporal distance between pairs of items spanning that window (Clewett et al., 2020). This finding suggests that temporally prolonged fluctuations in pupil size may reflect behaviorally relevant changes in arousal and attentional states that bind sequential representations in long-term memory. While more work is needed in this area of research, we believe it is likely that these pupil fluctuations relate to cognitive flexibility and the ability to adaptively engage the phasic mode of LC activity when necessary (i.e., to process a goal relevant stimulus). Using a similar approach, some studies measure resting-state (i.e., not explicitly related to a cognitive task) variability in pupil size as a trait measure of behavioral flexibility. For example, greater resting-state pupil variability has been linked to higher trait working memory capacity, as measured by the Letter-Number Sequencing (LNS) task (Aminihajibashi et al., 2019). The use of pupil variability to study tonic LC function is still a nascent area of research. However, we believe this approach holds great promise for understanding how we perceive and remember continuous experiences. It may also help reveal individual differences in people's ability to self-regulate their levels of arousal to meet shifting task demands, with implications for diagnosing different mental health disorders or assessing cognitive abilities.

7.2 Measuring phasic LC activity using pupillometry

One of the motivations for measuring the phasic LC response is to estimate the attentional intensity paid towards processing task-relevant stimuli. Researchers may use this estimate to explain differences in behavioral performance from trial-to-trial, between conditions, or between subjects. For example, a well-documented finding from auditory oddball experiments is that the pupil dilates more to tones that are presented infrequently (oddballs) compared to tones that are presented more frequently (the standard; Mather et al., 2020; Murphy et al., 2014). A basic interpretation of this finding is that the oddball tones draw more attentional intensity than standard tones. This dilation estimate can also be used to explain between-subjects variability in behavioral performance. Participants who exhibit greater oddball-evoked pupil dilations also detect oddballs more quickly, suggesting that individuals who paid more attention to salient stimuli tended to perform better on this task (Mather et al., 2020).

Phasic pupil measures can also be used to account for trial-by-trial fluctuations in behavioral performance and brain activity within an experimental condition. For example, researchers model the neuromodulation due to phasic LC-NE responses by weighting EEG and BOLD activity by the magnitude of trial-by-trial pupil dilations (Clewett et al., 2018; Murphy et al., 2011; Sterpenich et al., 2006). Using this approach in an fMRI study, we found that threat-induced arousal selectively enhanced successful encoding-related activity in sensory regions specialized to process goal-relevant information (Clewett et al., 2018).

Increasing evidence supports the notion that phasic pupil dilations can be used to index phasic LC-NE system activity. In animal models, studies have shown the spontaneous phasic LC firing and direct microelectrode stimulation of the LC reliably elicit a phasic pupil dilation (Joshi et al., 2016; Liu et al., 2017; Rajkowski et al., 1994; Varazzani et al., 2015). Similar findings using analogous stimulation techniques (e.g., tVNS) have been reported in humans (Capone et al., 2021).

In the context of an experiment with a single stimulus per trial interval, pupil dilation is conceptualized as a change in pupil diameter triggered by the onset of the stimulus. However, discrepancies in calculating pupil dilation may arise from how the pre-stimulus and post-stimulus windows are chosen. Sometimes, these windows are defined a priori based on the temporal dynamics of the task-evoked pupillary response and its return to baseline (Aminihajibashi et al., 2020; Mathôt et al., 2015). In practice, as temporal dynamics may be influenced by environmental factors that vary between experiment settings, researchers often opt for the

empirical approach of defining a pupil dilation window based on the observed elements of their pupil timeseries. For example, some researchers choose a window based on the peak pupillary response in a group-averaged timeseries (Clewett et al., 2018). A similar approach defines pupil dilation as the peak change in pupillary response from the pre-stimulus baseline. Although this approach gets around the issue that the temporal dynamics of the pupillary response are not the same across all trials, it still requires choosing a sensible duration for the moving window used to calculate the peak pupil diameter.

Oftentimes, the time-windows used for pupil dilation analyses are limited by different experimental constraints. For example, the duration of the inter-trial interval that may serve as a baseline or the duration of inter-stimulus intervals may not be long enough to capture the full timecourse of a stimulus-evoked pupillary response (e.g., rapid serial visual presentation designs). This latter issue is especially notable because while some studies define pupil dilation as the pupillary response evoked by a single stimulus, other studies define pupil dilation as the cumulative pupillary response evoked by a rapid succession of stimuli.

In some instances, pupil dilation is not defined as a discrete stimulus-evoked response. For example, in the classic digit span tasks, although the presentation of each digit leads to an increase in pupil size, it is common to define pupil dilation as the difference in pupil size during the delay period (i.e., after all digits have been played) minus the baseline period (e.g., Kahneman & Beatty, 1966; Piquado et al., 2010). But this definition of pupil dilation actually captures the influence of working memory maintenance processes during the delay period on pupil size and does not isolate the phasic pupil dilations elicited by each digit stimulus. Thus, the digit span pupil dilation arguably contains a mix of both phasic and tonic components of arousal.

Some researchers have adopted an alternative approach to inferring task-evoked phasic LC-NE system activity from pupillometry. These measures theoretically capture the critical component of the phasic pupillary response by looking at its temporal dynamics, such as its first derivative or slope (e.g., de Gee et al., 2020). There is empirical evidence that measures derived from the velocity of the pupil timeseries is a more specific index of the noradrenergic system than other neuromodulatory influences over the pupil, such as the basal cholinergic system (Reimer et al., 2016). Measuring pupil derivatives or slopes also holds several practical advantages over window-averaging techniques. Quantifying the slope of pupil change immediately after the onset of a stimulus avoids the issue of arbitrarily defining averaging windows to calculate a pupil

dilation score. It is also agnostic to the pre-stimulus baseline, and is proposed to be more robust to artifacts and more reliable for tasks with short inter-trial intervals (de Gee et al., 2020)

Another important challenge to studying the links between the LC, pupil, and behavior, is that the pupil is regulated by multiple brain regions and neuromodulatory pathways (Joshi & Gold, 2020). Fortunately, recent evidence shows that temporal principal component analyses (PCA) may be a useful way of dissociating the unique contributions of different autonomic and neuromodulatory pathways to pupil size. For example, pharmacological work shows that distinct characteristics of pupil dilations, or components, may be regulated by different autonomic pathways (Steinhauer & Hakerem, 1992). The degree of loading on these pupil components has also been associated with distinct cognitive and emotional processes, including sustained cognitive processing, conflict resolution, emotional responses, stimulus anticipation, motor responses, and salience detection (Clewett et al., 2020; Johansson et al., 2018; Steinhauer et al., 2004; Steinhauer & Hakerem, 1992; Verney et al., 2004; Wetzel et al., 2016; Widmann et al., 2018). For instance, oddball stimuli modulate an early-peaking (~800 ms) component under moderate light, but not under darker conditions when parasympathetic tone is low (Steinhauer et al., 2004; Widmann et al., 2018). This finding suggests that this early-peaking aspect of pupil dilation may specifically reflect parasympathetic inhibition of the pupil, which elicits dilation via relaxation of the sphincter muscle in the eye (Loewenfeld & Lowenstein, 1993).

Of relevance to this chapter, a separate pupil component that peaks around 1.5s post-stimulus has instead been linked to sympathetic activation (Steinhauer & Hakerem, 1992). Loading on this specific component relates to the onset of highly emotional stimuli (Widmann et al., 2018), consistent with the range of behaviorally relevant events known to activate the LC-NE system. Novel sounds also elicit a concomitant increase in loading on this component and the magnitude of the P3 event-related potential, another ostensible marker of LC activity (Nieuwenhuis et al., 2011; Widmann et al., 2018). The application of PCA to pupil data may be thereby serve as an effective method for pinpointing and quantifying the effects of LC neuromodulation on cognitive and emotional processing.

8. Closing Remarks

As a meaningful proxy for LC activity, the pupil offers a unique window into how arousal systems regulate what we perceive, feel, and remember. Novel combinations of advanced imaging techniques and pupillometry continue to lead to new revelations about the LC-NE system's role in modulating the capacity, selectivity, and quality of information processing in the

brain. Based on this compelling body of work, we propose that the LC-NE system is a throughline for integrating many influential models of arousal and attention.

Pupillometry promises to be an important technique for studying links between the LC-NE system and mental health. For example, the buildup of neurofibrillary tangles in LC neurons is an early feature of Alzheimer's disease, and presumably leads to functional deficits in the LC-NE system as well as its cortical and subcortical targets. Already, researchers are exploring if pupillometry can be used as a biomarker of LC-NE dysfunction in individuals with mild cognitive impairment and early Alzheimer's disease (Elman et al., 2017; Granholm et al., 2017; Kremen et al., 2019). Pupil-linked arousal signals have also been used to track different factors and conditions associated with altered noradrenergic signaling, including age (Morris et al., 1997; Piquado et al., 2010), stress (Kimble et al., 2010), depression (Siegle et al., 2001), PTSD (Mckinnon et al., 2020), and attention-deficit/hyperactivity disorder (Nobukawa et al., 2021; Wainstein et al., 2017). In time, pupillometry may help facilitate earlier diagnoses of these conditions and be used to assess the efficacy of various therapeutic interventions.

Through its broad neuromodulatory effects, LC activity is essential for amplifying attention, prioritizing task-appropriate decisions, and ensuring important experiences are encoded and stored as enduring memories. Pupillometry provides a powerful tool for uncovering these core functions of the LC-NE system, with an eye towards identifying new strategies for promoting healthy cognitive function and wellbeing.

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