The Locus Coeruleus and Adaptive Gain Theory: A Review

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Writer's Comment: *I have always been interested in the mind and, I think, much like any professional scientist who studies the brain, I am fascinated by what consciousness is. However, in the neuroscience community, the questions that can be asked are limited by the available tools. As such, my research this past year used pupil diameter measurements as a proxy for arousal state, with our goal being to explain a behavioral phenomenon on the context of its neurobiological correlates. I registered for UWP 104E with the intention of writing about the research that I was participating in, and it was fortunate that my first venture into scientific writing occurred in a classroom setting. Professor Demory provided me with an amazing resource and was able to help guide me through each of our assignments such that I left the class with the feeling that I had grown as both a writer and as a scientist.*

Instructor's Comment: *One of the great pleasures in teaching UWP 104E (Writing in the Sciences) is the opportunity to learn about cutting edge research that my students are participating in right here at UC Davis. My role is to show students how to structure scientific papers, how to organize and present scientific information to various kinds of audiences, how to write effective sentences, and how to edit and review each other's work. The students' role is to bring in what they're learning in their upper division science classes, their internships, their laboratory experience. In this particular case, Zack was doing research in Joy Geng's laboratory at the Center for Mind and Brain, and he was able to draw on that research for all his papers in my class. This research, which combines cognitive psychology and neuroscience and studies how and why people attend to specific stimuli, "is crucial [to quote one of Zack's earlier papers] to our understanding of how we perceive the world around us." It has implications for psychology, biology, medicine, even economics, as it can help to explain how people respond to such things as advertising. In this review article, Zack has produced a thorough, sophisticated, and authoritative synthesis of recent research that helps to illuminate the fascinating work currently being done by cognitive neuroscientists.*

—*Pamela Demory, University Writing Program*

Introduction

The locus coeruleus (LC) is a small portion of the pons containing pigmented nuclei; hence its Latin name, translated as "blue spot." Noradrenergic LC neurons have projections to both cortical and sub-cortical areas. Within the locus coeruleus – norepinephrine (LC-NE) system, NE functions as a neurotransmitter. However, unlike other common neurobiological molecules, such as glutamate and GABA (the primary excitatory and inhibitory neurotransmitters in the brain, respectively), NE signaling adjusts the likelihood of post-synaptic cell activity. This general mechanism, which increases the activity of excitatory post-synaptic neurons and also further inhibits the firing of inhibitory post-synaptic neurons, is referred to as gain modulation (Servan-Schreiber, Printz, & Cohen, 1990).

In light of such properties, researchers have suggested that the main function of the LC-NE system is to monitor and effect changes in arousal state (Berridge & Waterhouse, 2003). For example, using rats as subjects, Aston-Jones and Bloom (1981) demonstrated that, in response to attention-capturing and goal-oriented stimuli, LC neurons exhibited small bursts of activity. This information led some researchers to speculate that the LC-NE network helps orient and maintain attention to desirable environmental stimuli, functioning as the neurobiological equivalent of the adrenal gland (Aston-Jones & Cohen, 2005). However, in subsequent studies, behavioral data from both animal and human subjects prompted these same researchers to redefine their theories of how the LC-NE system mediates changes in arousal state. As a general phenomenon, arousal state is a vital determinant of sleep, wakefulness, anxiety, and motivation (Aston-Jones & Cohen, 2005). Research on the LC-NE system, as well as related brain areas, may ultimately help scientists further understand attentional, stress, and emotional and affective disorders (Aston-Jones, Rajkowski, & Cohen, 19990, as well as help elucidate how our brains process information from our surroundings to optimize response. This review will first detail the contemporary theory proposed to explain the present body of data as well as its behavioral manifestations. Next, behavioral and anatomical data will be presented, from both past and current research, which corroborate this mechanism. The review will conclude with a summary of the existing state of the field as well as opportunities for future study.

Adaptive Gain Theory

Over the past few decades, researchers have identified two firing modes of LC neurons: phasic and tonic. The phasic mode denotes a high frequency of bursts occurring over a short time interval; this corresponds to task-related decision-making as well as focused and precise behavior directed toward contextually-relevant rewarding stimuli. In contrast, the tonic mode is characterized by an overall increase in LC neuronal firing in the absence of phasic events; it is associated with labile attention and global distractibility (Aston-Jones & Cohen, 2005). Overall, the activity of LC-NE neurons follows the classic Yerkes-Dodson curve of arousal state (Yerkes & Dodson, 1908). In the context of the LC-NE system, tonic LC activity is measured against task performance; like the Yerkes-Dodson curve, the overall relationship between the two resembles an inverted "U." At low levels of tonic activity, drowsiness and low arousal inhibit focus. However, high levels of tonic activity can likewise promote task disengagement due to greater distractibility. The best observed performance occurs during intermediate levels of tonic LC activity, which also coincide with an increase in LC phasic activity (Aston-Jones et al., 1999). Thus, moderate levels of LC activity are most conducive to phasic LC neuron firing and, therefore, maximum cognitive arousal.

Recently, a theory was proposed to explain this relationship in the context of behavioral optimization. In their 2005 review article, Aston-Jones and Cohen proposed adaptive gain theory (AGT), which unites the available data from behavioral and electrophysiological studies of the LC-NE system. AGT contains specific postulations for what each mode of LC activity constitutes. In their proposal, they suggest that phasic mode corresponds to exploitative behavior, during which the subject attends to task-relevant stimuli and ignores unrelated environmental cues. Conversely, they state that tonic mode decreases event-related attention and causes eventual disengagement so that other sources of potential reward in the surrounding environment can be explored. AGT is also thought to mediate the shift between these two states in response to the perceived value of the present task. Specifically, AGT supports the notion that the LC-NE system optimizes performance by providing continuous evaluations of the value associated with a certain activity. This idea is supported by the discovery that the orbitofrontal cortex and anterior cingulate cortex, two frontal lobe areas involved with value judgment, strongly innervate the LC (Rajkowski, Lu, Zhu, Cohen, & Aston-

Jones, 2000). Noradrenergic gain modulation underscores both modes of activity, and AGT predicts that LC firing patterns dictate the effect that such adjustments have on such brain areas, which are specifically involved in assessing whether a particular task is worth exploiting further or discarding in favor of alternate forms of prospective reward.

Behavioral Data

Pupil Size as an Indicator of LC Mode

A known indicator of goal-directed performance is pupil size. In the mid-twentieth century, pupillometry was a popular method of measuring phenomena such as effort during problem solving (Hess & Polt, 1964) and the degree of difficulty of a pitch-discrimination task (Kahneman & Beatty, 1967). Dormant for a long time, pupillometry as an experimental method has resurfaced in the last few decades, particularly in investigations of the locus coeruleus (LC), the sole neural source of norepinephrine (NE). A study in which monkeys performed an oddball task (in which animals respond to displays of rare targets and refrain from responding to the more frequent distracter cues) found that average pupil sizes were larger during periods of tonic LC firing and smaller during phasic LC activity (Rajkowski, Kubiak, & Aston-Jones, 1993). This correlation between pupil diameter and LC mode paved the way for future studies to further examine the relationship.

Numerous studies using monkeys as subjects (Aston-Jones, Rajkowski, & Kubiak, 1997; Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994; Rajkowski et al., 1993) demonstrated an increase in goal-oriented performance during phasic LC activity, as well as greater distractibility during tonic activity. For example, using surgically implanted electrodes, the Aston-Jones group (1994) found that the magnitude of LC response was diminished in monkeys during extended periods of an oddball task during epochs of poor task performance. In the same experiment, phasic firing from the population of LC neurons under scrutiny occurred with a short latency period to task-related stimuli. These and other findings led researchers to consider whether such relationships could be exhibited in human subjects as well. However, since direct neuronal recordings are too invasive, pupil measures became more popular in studies collecting data from human subjects.

These subsequent studies using people as participants did in fact demonstrate similar relationships to those observed in the pupillometry data of monkeys. A study using the drugs clonidine and yohimbine, both of which target adrenergic receptors, demonstrated that patients receiving clonidine exhibited luminance-dependent pupillary dilations (consistent with phasic LC activity), whereas patients receiving yohimbine exhibited larger pupil sizes in higher illumination compared to placebo (consistent with tonic LC activity) (Phillips, Szabadi, & Bradshaw, 2000). In the context of AGT, phasic LC firing was found to correlate with task-related stimuli (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010), consistent with the predictions made by Aston-Jones and Cohen (2005). These results suggested that the mechanism by which LC-NE activity modulates pupillary activity in monkeys is similar to how it functions in humans.

The oddball paradigm has been shown to be a good measure of LC mode. In studies that include this task, an inverse relationship between the magnitude of phasic pupil dilations and pre-stimulus pupil size was found (Gilzenrat et al., 2010; Murphy, Robertson, Balsters, & O'Connell, 2011). In the context of AGT, larger phasic dilations are evoked by the task at hand (associated with exploitation and focus); conversely, larger overall baseline sizes reflect a more labile cognitive state in which the subject is not attentive to any task in particular (associated with exploration and distractibility). Accordingly, in such studies, large baseline pupil size was associated with higher error rates (Gilzenrat et al., 2010). In addition, large phasic dilations occurred as a result of correct responses to targets, while the dilations coinciding with distracter rejections were significantly smaller (Gilzenrat et al., 2010). The oddball paradigm was crucial to include in human experiments because the first pupillometry study performed by the Rajkowski group (1993) using monkeys as subjects employed this same task. By corroborating results from human subject experiments with monkey data, the researchers verified the inter-specific relationship between the two systems. These results provided a foundation upon which further investigations could be launched so as to more fully elucidate the proposed mechanism of LC-NE in humans.

Auditory discrimination tasks also evince similar correlations. In a second experiment by Gilzenrat et al. (2010), subjects compared a test tone to a reference tone, responding in each trial to whether the test tone was higher or lower in pitch than the reference tone. The experiment included impossible discrimination trials -- in which the test tone was the same frequency as the reference tone -- within four experimental blocks of thirty-six trials each. Subjects received trial-by-trial auditory feedback to their responses indicating whether they had responded correctly or in error. Two of the blocks contained six impossible-discrimination trials (low-conflict), while the other two contained twelve impossible-discrimination trials (high-conflict). One of the two blocks for each conflict category gave positive feedback on all impossible-discrimination trials, while the other block gave negative feedback on all impossible-discrimination trials. They found that positive feedback blocks did not affect baseline pupil size nor pupil dilations. However, in negative feedback blocks, baseline pupil diameter was higher in high-conflict blocks, while task-evoked dilations were smaller. These results support AGT in that low-conflict - negative feedback blocks contained lower baseline and higher dilation values consistent with LC phasic mode, reflecting the need for subjects to exert a greater level of task-related control. Similarly, high-conflict - positive feedback blocks also seem to reflect LC phasic mode because while difficulty increases, task-related reward is higher.

Visual discrimination is yet another means by which researchers can verify the purported effects of LC-NE system activity on pupil size. In a study assessing perceptual switching, or how a single object can be perceived two disparate ways, large and significant pupil dilations occurred when subjects notified researchers of changes in their assessments of an ambiguously-defined stimulus (Einhäuser, Stout, Koch, & Carter, 2008). These results likewise accord well with AGT because they reflect the ability of pupil size to indicate when subjective experience has shifted.

More complex studies assessing ongoing changes in task utility have also been performed that relate pupil size to the predictions of AGT. Some reports have suggested that subconscious assessments of task utility can be reflected in pupil size patterns. A third experiment performed by Gilzenrat et al. (2010) provided subjects with the opportunity to opt out of an auditory discrimination task when it became too difficult for them to distinguish between the reference and test pitches. Similarly, Jepma and Nieuwenhuis (2011) devised a paradigm in which reward probabilities for a four-armed bandit task, in which a subject is presented with four options on each trial and tries to choose the one with the highest possible reward, changed over time at arbitrary rates. Both designs demonstrated that within the context of each procedure, subjects performed close to optimally in terms of choosing the option with maximum expected value.

These results demonstrate fidelity with AGT, in that participants' baseline pupil sizes were lowest on trials immediately preceding exploitative choices (pertaining to expected value), while exploratory choices had significantly larger baseline pupil sizes (Gilzenrat et al., 2010; Jepma & Nieuwenhuis, 2011). Together, these experimental results suggest that pupil size as an indicator of LC activity accords well with AGT, and show that subconscious evaluations of reward probability are mediated by the LC-NE mechanism to optimize behavior for a given task.

The Relationship Between ERP and LC Activity

Event-related potentials (ERPs) are periods of recorded brain activity, measured via scalp electrodes. In cognitive neuroscience and psychological studies, they have been used to assess the electrical activity of neural processing in response to external stimuli. An ERP can be divided into various components, based on the direction of the potential (positive or negative) and the timing of the response elicited. The P3 component (also called P300 because it usually peaks 300 milliseconds after the event) is evoked in response to sensory perturbation (Sutton, Braren, Zubin, & John, 1965). The predictability of the presented stimulus has been shown to have an effect on P3 amplitude; specifically, amplitude was much larger when subjects were unable to predict the sensory modality of the next presented stimulus (Sutton et al., 1965).

The relationship between P3 and LC was first established in a study in which lesions made to the monkey LC affected the response magnitude of the P300 response (Pineda, Foote, & Neville, 1989). Psychopharmacological studies have shown that the NE agonist clonidine reduces LC firing and overall NE levels at synaptic connections (Coull, 1994). Clonidine had a similar effect on the P300 response when administered before an auditory oddball task using monkey subjects (Swick, Pineda, & Foote, 1994). These results can be explained within the context of AGT because NE functions to modulate the gain of cortical neurons, and several investigators have hypothesized that NE release by the LC increases the gain of surface-level neurons that correspond to the P3 response. This suggests that attenuation of the P3 component can be induced by an overall reduction in NE. Speculatively, increasing the responsivity of certain cortical areas corresponds to an overall increase in the magnitude of the P3 response (Nieuwenhuis, Aston-Jones, & Cohen, 2005).

The P3 component has also been correlated with pupillometry data to predict LC activity and mode. The sympathetic nervous system (SNS) is activated in response to external stress, and one of the ways it manifests itself is by causing the muscles surrounding the pupil to dilate (Nieuwenhuis, de Geus, & Aston-Jones, 2011). This is consistent with AGT, in that heightened arousal is associated with higher tonic LC activity, and should therefore be reflected by an overall increase in pupil size. The Murphy group (2011) found that P3 amplitude and pupil diameter exhibited a U-shaped relationship curve, such that the largest P3 values corresponded with intermediate pupil diameters, and both measures were correlated with optimal performance on an auditory oddball task. Also, large pupillary dilations were tightly correlated with increased P3 responses, showing that P3 may be implicated in responses to task utility (Murphy et al., 2011). These findings are supported by data that suggest that conditions immediately preceding P3 components are strikingly similar to those prior to LC phasic activity. Results show that, much like how P3 is sensitive to the predictability of stimuli, pupil size is also related to such probability measures (Qiyuan, Richer, Wagoner, & Beatty, 1985). While the evidence is limited, LC activity has demonstrated a repeated relationship with P3 magnitude, though indirectly through pupil response. Further studies examining these two behavioral indicators will be necessary to clarify the exact mechanism by which this occurs.

Conclusion

Recent studies have found a plethora of evidence supporting AGT, mainly from pupillometry data and ERP analysis. By using data from primates as the basis for future examinations, researchers have built upon the findings from those multi-faceted experiments to make predictions concerning similar tasks performed by humans. While manipulating neurons is not feasible when using humans as subjects, the literature supporting the correlations that were demonstrated in animals has provided enough evidence to implicate pupil size and P3 amplitude in LC activity.

A limitation of the link between pupil size and LC mode is that the underlying biological mechanism is currently unknown. Pupil size is therefore an indirect measure of LC activity, although the studies previously discussed, along with many others, have consistently demonstrated a link between the two in the context of AGT. Similarly, study of the P3 component in relation to LC activity and the pupil response has been sparse, but laboratories are now continually observing the link between the aforementioned behavioral indicators and are investigating the relationship further.

A related area of research, the distinction between expected and unexpected uncertainty, has implications for AGT. Expected uncertainty can be described as variation in a paradigm that does not change overall expectations. As an example, if a coin that has a 90% chance of showing heads was flipped hundreds of times, it would be expected that it land tails on a few trials. On the other hand, unexpected uncertainty reflects a dramatic shift in expectations. In the context of the previous example, this would occur if the coin began showing tails repeatedly over many trials, causing a revision of previous presumptions. These states of behavior are relevant to AGT because unexpected uncertainty is theorized to be tightly correlated with cortical NE levels (Yu & Dayan, 2005). In this case, tonic LC activity, known in AGT to correspond with exploration, would likewise correspond with unexpected uncertainty, in that a subject would be likely to seek out a new task due to radically altered expectations. Correlating high baseline pupil diameter with periods of unexpected uncertainty would undoubtedly aid in relating these two proposed behavioral states.

In summation, LC activity is vital to transitions between different arousal states of organisms. AGT has helped provide a framework upon which research on this small brain area can be structured. As mentioned previously, the implications of studying and understanding the underlying mechanisms of arousal are substantial. While all brain areas serve crucial purposes in the functionality of an organism, the LC-NE system innervates almost all of these important areas, making future investigations into what exactly these innervations mediate a crucial step in understanding the neural components of attention.

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