Locus coeruleus-norepinephrine: basic functions and insights into Parkinson's disease

Bilal Abdul Bari1,*, Varun Chokshi1,*, Katharina Schmidt2,*,

1 The Solomon H. Snyder Department of Neuroscience, Brain Science Institute, Kavli Neuroscience Discovery Institute, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
2 Department of Physiology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Funding: This work was supported by the National Institutes of Health grant F30MH110084 (to BAB).

Abstract

The locus coeruleus is a pontine nucleus that produces much of the brain's norepinephrine. Despite its small size, the locus coeruleus is critical for a myriad of functions and is involved in many neurodegenerative and neuropsychiatric disorders. In this review, we discuss the physiology and anatomy of the locus coeruleus system and focus on norepinephrine's role in synaptic plasticity. We highlight Parkinson's disease as a disorder with motor and neuropsychiatric symptoms that may be understood as aberrations in the normal functions of locus coeruleus.

Key Words: catecholamines; copper; neurodegenerative diseases; neuromodulation; neuronal circuits; neuropsychiatric symptoms; noradrenaline; synaptic plasticity

Introduction

The locus coeruleus (LC) is a norepinephrine-producing nucleus found in the dorsal pons of most vertebrates. The LC was first described in the late 1700s by Félix Vicq d'Azyr (Tubbs et al., 2011) although sources frequently credit Johann Christian Reil (Reil and Meckel, 1809). Contemporary interest in the LC began with anatomical work by Fumio Sano and Glenn Russel, who independently concluded that the LC is a distinct nucleus with similar - though not identical - appearance across species (Maeda, 2000). Like other neuromodulatory structures, the LC contains an exceedingly small number of cells, yet projects to much of the brain. The human LC is estimated to contain approximately 30,000 neurons that provide norepinephrine to a substantial fraction of the brain's 100 billion neurons (Mouton et al., 1994). The LC is therefore anatomically poised to modulate a wide range of functions, including homeostasis, sensory processing, motor behavior, and cognition. This review aims to summarize the basic physiology of the LC-norepinephrine system, its function in normal behavior, and its associated neural pathways. We then use this foundation to gain insight into pathophysiology, with an emphasis on Parkinson's disease (PD). PD is a long-term neurodegenerative disease with both motor and neuropsychiatric symptoms (Rommelfanger and Weinshenker, 2017). PD is traditionally thought to be a disorder of the midbrain dopamine system, since it manifests with substantial dopaminergic neuron loss and is treated with L-DOPA administration, a dopamine precursor. In this review, we augment this perspective by highlighting recent work that emphasizes the contributions of norepinephrine dysfunction to pathogenesis.

We searched PubMed and Google Scholar using the keywords 'locus coeruleus' and 'norepinephrine' for basic science references and added 'Parkinson's disease' for disease-specific references. We focused mainly on articles published between 2010 and 2019. We included older, seminal references when they were relevant to the scope of this review.

Basic Physiology

Seminal studies of LC physiology developed the idea that the system is a crucial node in arousal or attention. This key hypothesis has continued to shape the design and interpretation of modern experiments (Carter et al., 2010; Lovett-Barron et al., 2017). One of the first systematic studies to employ single-unit recordings in awake animals - rats and squirrel monkeys - found that LC neurons homogeneously increase stimulus-evoked firing in response to salient auditory, visual, and touch stimuli (Foote et al., 1980). This was an important finding, as previous studies in anesthetized animals found that only noxious stimuli could elicit robust increases in firing, which led to hypotheses that the system was primarily concerned with fear or nociception. It was also discovered that LC exhibit lower spontaneous firing during sleep, further...
cementing its role in arousal (Aston-Jones and Bloom, 1981).

Well-controlled behavioral experiments added to this view and began to paint a more nuanced picture. In macaques trained to respond to an oddball visual stimulus, target stimuli were found to drive robust phasic firing while non-target stimuli elicited no changes (Rajkowski et al., 1994). The phasic response scales with the expected value of the stimulus (Bouret and Richmond, 2015) and the effort required to produce the action (Varazzani et al., 2015). Further analyses revealed that this phasic response is better aligned to the action than the stimulus (Aston-Jones and Cohen, 2005; Bouret and Richmond, 2015). LC responses do not always precede overt motor behavior, as behavioral tasks designed to separate stimuli from actions have found phasic responses to both (Kalwani et al., 2014), and similar spontaneous movements (i.e., not in response to a cue) do not elicit changes in firing. Altogether, these findings have lent evidence to the hypothesis that LC is necessary to promote arousal or mobilize effort (Sara and Bouret, 2012; Varazzani et al., 2015; Xiang et al., 2019). However, one intriguing study trained monkeys to perform a countermarching saccade task and found that - although LC responds to go cues and to saccades - it does not respond when saccades are appropriately cancelled (Kalwani et al., 2014). Although the full implications of this finding have yet to be thoroughly understood, it challenges the most straightforward interpretation of the arousal/effort hypotheses, since inhibiting a planned saccade is an effortful and demanding action.

LC responds vigorously to novel stimuli. However, if the stimuli are not behaviorally relevant, the response decays rapidly. Activity reappears during reversal learning or extinction (Sara and Segal, 1991), and after reversal, the LC response to stimuli can be expressed before behavioral expression of reversal (Aston-Jones et al., 1997). Additionally, LC neurons are sensitive to changes in task states in monkeys performing a decision-making task (Jahn et al., 2019). These studies lent evidence to the idea that LC is important for learning new behavioral contingencies.

The LC is now appreciated to have at least two modes of firing, with consequences for behavioral performance: a background tonic mode, and a short-timescale phasic mode (Varazzani et al., 2015). The first hints of a relationship between LC and behavioral performance came from primate studies which found that low tonic activity is correlated with task disengagement and drowsiness. Elevated tonic/low phasic firing is also correlated with task disengagement, although monkeys are distractible in this regime (Varazzani et al., 2015). A sweet spot in the middle, with low tonic activity and high phasic activity, is related to good task engagement. These modes of firing elicit different release profiles of norepinephrine and distinct modulation of downstream circuits (McBurney-Lin et al., 2019).

Role in Learning and Memory

Manipulation of the LC-norepinephrine system has profound consequences for cognitive behavior. Lesion studies have reported gross deficits in learning, with LC-ablated animals taking much longer to learn to run down a runway for food reward (Anlezark et al., 1973). This was likely not due to gross motivation deficits, as control and lesioned animals had similar body weights and exploratory behavior in an open field. Vicarious trial-and-error, an index of learning, is disrupted with target-specific pharmacological manipulation of norepinephrine (Amemiya et al., 2016). LC-norepinephrine manipulation affects distinct phases of memory processing, depending on task conditions and details of manipulation (Khakpour-Taleghani et al., 2009). Other studies have pointed to a more nuanced role in learning when task contingencies change. Recent optogenetic manipulation experiments have argued that disparate effects on learning may be a consequence of projection-target specificity and downstream computations (Uematsu et al., 2017).

Unified Accounts of Locus Coeruleus Function

One of the earliest general theories of LC hypothesized that norepinephrine release from LC facilitates learning associations between stimuli and outcomes (Kety, 1970). This theory has received support over the years, but the exact role of LC with learning is nuanced and remains to be fully explored. Modern theories of LC function have taken into account numerous findings since Kety’s hypothesis was formulated. One theory holds that LC encodes for unexpected uncertainty - that is, when the world changes in an unpredictable manner (Dayan and Yu, 2006). The functional effect is to influence inference and mediate changes in synaptic plasticity to allow for rapid learning. This theory has received support from human pupillometry studies (Nassar et al., 2012). Another similar theory, the adaptive-gain hypothesis, argues for an inverted-U relationship between tonic LC activity and behavioral performance (Varazzani et al., 2015). Low and high tonic LC are associated with task disengagement, with high tonic LC favoring distractibility and exploratory behavior. When tonic LC is in between these extremes, task engagement is high. The function of these LC patterns is to optimize reward/utility, which is hypothesized to be under the control of prefrontal value circuitry. The adaptive-gain hypothesis has likewise received support from human pupillometry studies (Gilzenrat et al., 2010; Jepma and Nieuwenhuis, 2011). Another similar account holds that LC signals higher-order prediction errors to enable fast-timescale behavioral change (Sales et al., 2019). Finally, since the effects of LC manipulation are occasionally specific to extinction learning, we propose that LC is involved in the generation of latent states (Gershman et al., 2017). This theory predicts that during extinction learning (after a cue has been associated with an outcome), the brain does not degrade the original memory but rather associates the extinction memory with a new latent state. The original cue-outcome memory remains in the brain, largely unaffected. If LC is over- or underactive, the brain may create too many or too few latent states. Dysfunction of the LC-norepinephrine system may
therefore result in cognitive deficits, particularly in learning, memory, and decision making.

Synaptic Plasticity Mechanisms of Noradrenergic Signaling

The role of LC in learning, memory, and behavioral flexibility has stimulated interest in noradrenaline's mechanism of action. Synaptic plasticity mechanisms are particularly well-suited to re-adapt neural circuitry to process new sensory inputs and task contingencies to produce desired actions. Initial work from Bear and Singer (1986) demonstrated that synergy of both adrenergic and cholinergic neurotransmission is required for experience-dependent plasticity in the primary visual cortex. Later studies showed that norepinephrine has independent effects on plasticity throughout the brain including visual cortex (van den Pol et al., 2002; Huang et al., 2013), frontal cortex (Lim et al., 2010), primary auditory cortex (Martins and Froemke, 2015), hippocampus (Takeuchi et al., 2016) and amygdala (Johansen et al., 2014). In mice, chemogenetic stimulation of LC induces rapid increases in brain-wide functional connectivity in regions involved in salience processing (Zerbi et al., 2019). Importantly, these findings appear to translate to the human brain, as fMRI studies have shown changes in brain-wide connectivity with increased catecholamine concentration (van den Brink et al., 2016).

Noradrenergic signaling can produce both synaptic weakening as well strengthening. This is, in part, due to heterogeneity of downstream receptors. Norepinephrine can have an excitatory effect on its target neurons through α1 (Gq-coupled) and β (Gq-coupled) adrenergic receptors and inhibitory effects through α2 (Gi-coupled) adrenergic receptors (McBurney-Lin et al., 2019). An interesting theory suggests that, given the same history of synaptic activity, a synapse can be primed for either potentiation or depression depending on the G-coupled receptor activated by neuromodulators (van den Pol et al., 2002). This bidirectional plasticity has been shown in visual cortex (Seo et al., 2007; Huang et al., 2013; He et al., 2015) and could be the answer for rapid modulation of synaptic connectivity by neuromodulators. Further, He et al. (2015) suggested particular neuromodulators can prime synapses for a specific polarity of plasticity. Norepinephrine dependent regulation of the AMPA receptor population could allow for widespread plasticity through the cerebral cortex (Hu et al., 2007). At a circuit level, the ability of norepinephrine to differentially regulate inhibitory cells (through α1 receptors) and excitatory cells (through α2 and β receptors), as observed in the basal forebrain and cortex, could produce a change in excitatory/inhibitory drive onto their downstream targets. This would trigger plasticity mechanisms in target neurons in order to maintain excitatory/inhibitory balance (McBurney-Lin et al., 2019).

Afferent Pathways of the Locus Coeruleus

The myriad of LC functions can be explained, in part, by its functional connectivity. Modern studies have exploited the specificity of viral transgenic tools to label the LC afferent population and revealed that LC receives inputs from a remarkably diverse number of regions (Schwarz et al., 2015; Uematsu et al., 2017). Almost all areas of the neocortex project to the LC (Schwarz et al., 2015), with strong glutamatergic projections from the prefrontal cortex (Jodo and Aston-Jones, 1997) and corticotropin-releasing factor projections from the amygdala (Szabadi, 2013). Sleep-promoting GABAergic neurons in ventralateral preoptic nucleus, a region of the hypothalamus, inhibit LC during slow wave sleep (Szymusiak and McGinty, 2008) and orexinergic neurons in lateral hypothalamus/perifornical area send strong excitation to LC to promote wakefulness (Szabadi, 2013). LC neurons also receive excitatory input from dopaminergic neurons in the ventral tegmental area. Because infusion of dopamine into LC inhibits sleep (Crochet and Sakai, 2003), this pathway is thought to be part of the wakefulness promoting pathway. Given the important role of the midbrain dopamine system in motivated behavior, this pathway may also be critical for LC's function in reward-based learning. Other reviews provide detailed information regarding further important input pathways (Szabadi, 2013; Schwarz and Luo, 2015).

Efferent Pathways of the Locus Coeruleus

Since individual LC neurons have little molecular and morphological diversity (compared to neuromodulators like the dorsal raphe serotonergic system), the diverse nature of LC function may be explained by projection profiles of neuronal subsets (Seo and Bruchas, 2017). The classical view holds that LC broadly and nonspecifically modulates neuronal function throughout the brain via volumetric transmission. However, these findings were mostly inferred from experiments using non-specific labeling techniques. This view has been recently challenged with the development of molecular labeling techniques. There is evidence for some modularity, but there is extensive collateralization of many output pathways (Schwarz and Luo, 2015; Kebchull et al., 2016). Overall, there are at least three major efferent pathways originating from LC (Figure 1): 1) ascending pathway projections to the cortex, 2) cerebellar pathway and 3) descending pathway projections to the spinal cord (Szabadi, 2013). The ascending pathway is mostly involved in arousal, behavioral flexibility, and brain state mediation. The descending pathway is thought to control lower-level motor actions. The cerebellar pathway is remarkably understudied and a distinct function is unclear. However, the cerebellar cortex has robust expression of noradrenergic receptors and disruption of this signaling impairs motor function. We intentionally limit the scope of this review but other references provide more details (Szabadi, 2013; Schwarz et al., 2015). We will focus on the ascending and descending pathways.

Ascending pathway

The ascending pathway is made up of projections to the limbic system, midbrain, thalamus, basal forebrain and all of the neocortex (Figure 1). This pathway is thought to be involved
in behavioral flexibility, cognitive control, wakefulness, formation and retrieval of episodic and emotional memories, modulation of pain, response to stress, cardiovascular regulation, nociception, pupillary light reflex, and some sympathetic and parasympathetic functions.

The neocortex and basal forebrain are heavily innervated by LC (Szabadi, 2013; Schwarz and Luo, 2015; McBurney-Lin et al., 2019). Expression of excitatory noradrenergic receptors (α1 and β) on excitatory neurons and inhibitory receptors (α2) on GABAergic neurons allows LC to exert excitatory influence on these areas (Szabadi, 2013; Schwarz and Luo, 2015), which would prime LC to modulate cortical arousal and cognition.

LC extensively projects to the thalamus, primarily to excitatory neurons expressing the excitatory α1 receptor (Szabadi, 2013). Through the thalamus, LC affects sensory processing, wakefulness, stress detection and pain modulation (Szabadi, 2013; Beas et al., 2018; Rodenkirch et al., 2019). Outside of the thalamus, LC has bidirectional connectivity with the hypothalamus; this circuitry is part of sleep-wake circuitry through ventrolateral preoptic area and lateral hypothalamic/perifornical areas, stress response through the paraventricular nucleus, and neuroendocrine functions through the arcuate nucleus (Szabadi, 2013; Schwarz and Luo, 2015). In the midbrain, dopaminergic neurons in the ventral tegmental area and substantia nigra receive noradrenergic innervation from LC (as well as other brainstem adrenergic regions) (Rommelfanger and Weinshenker, 2007; Mejias-Aponte, 2016). This particular pathway highlights the fact that neuromodulators influence each other, suggesting a need to understand their combinatorial functions, so we may better understand physiology and pathophysiology.

The role of LC in learning and memory is thought to depend in part on the amygdala and hippocampus. The amygdala, known to mediate fear and anxiety responses (Sah, 2017), contains all major noradrenergic receptors; these have been implicated in formation and retrieval of emotional memories (Szabadi, 2013; Uematsu et al., 2017). LC is the exclusive source of noradrenaline in the hippocampus and, like the amygdala, all major adrenoreceptors have been reported (Szabadi, 2013). The LC-hippocampus pathway is critical for the formation, consolidation and retrieval of memories (Sara and Devaughes, 1988; Takeuchi et al., 2016). Recent studies have revealed a special case for LC neurotransmission. Dopamine, a precursor of norepinephrine, is released from LC terminals in the dorsal hippocampus to support the formation of novelty-based memory (Kempadoo et al., 2016; Takeuchi et al., 2016; Wagatsuma et al., 2018).

Projections from LC to the brainstem are thought to be critical for parasympathetic and sympathetic functions (Szabadi, 2013).

**Descending pathway**

The coeruleo-spinal pathway is formed by widespread projects from dorsal and caudal LC neurons to the spinal cord, with some collateralization in the brainstem (Figure 1). The targets are sensory neurons in the dorsal horn, motor neurons in the ventral horn and preganglionic neurons in intermediolateral nuclei (Szabadi, 2013). LC norepinephrine largely inhibits sensory neurons in the dorsal horn, as these cells express inhibitory α1 receptors. One primary function is pain desensitization, as activation of this receptor subtype provides analgesia/hyperalgesia. The net effect of norepinephrine in the ventral horn is excitation, due to expression of α1 receptors. This is consistent with the finding that LC activity is low during REM sleep, since muscle tone is lost (Szabadi, 2013; Sara, 2017).

**Locus Coeruleus Dysfunction in Parkinson’s Disease – Motor and Neuropsychiatric Symptoms**

Given LC’s role in a number of basic functions, one may expect that dysfunction should similarly lead to a wide
range of symptoms. Indeed, significant neuronal loss in LC is associated with neurodegenerative disorders, such as PD and Alzheimer’s disease (German et al., 1992; Hoogendijk et al., 1995; Marien et al., 2004), as well as psychiatric diseases such as depression (Oruday and Klimek, 2001). In order to link the basic findings of LC function with disease, we will specifically focus on PD, a disorder with both motor and psychiatric symptoms (Gold and Chrousos, 2002; Marien et al., 2004). Although the literature lacks clear mechanistic explanations, we attempt to link symptoms of PD with LC dysfunction and highlight plausible mechanistic links.

PD is primarily thought to be a disease of dopaminergic cell loss in the substantia nigra. However, recent evidence has pointed to LC norepinephrine as a critical component of this disease (Rommelfanger and Weisshenker, 2007). In PD, LC cell loss occurs throughout the nucleus and extends into the peri-LC subcoeruleus region. The remaining neurons exhibit significant shrinkage and have an altered phenotype (Hoogendijk et al., 1995). In animal models of this disease, noradrenergic signaling from LC provides protection from dopaminergic cell loss in the substantia nigra (Srinivasan and Schmidt, 2003; Marien et al., 2004). One study confirmed dopaminergic cell death in the substantia nigra of PD patients and observed dramatic cell loss in the LC (Zarow et al., 2003). Furthermore, in a mouse model of PD (mutation of the PARK2 gene), there is cell loss from the LC while the nigrostriatal system is unaffected (Von Coelln et al., 2004). LC’s projections to motor cortices and the spinal cord could provide crucial insight for understanding wide-ranging symptoms in PD.

Neuropsychiatric Symptoms in Parkinson’s Disease

LC is associated with early non-motor symptoms of PD such as depression (Remy et al., 2005) and anxiety (Rahman et al., 2009; McColl et al., 2015; Zhu et al., 2017). A useful biomarker for neurodegeneration in PD is neuromelanin – a byproduct of dopamine and norepinephrine synthesis - which can be accessed through MRI. Neuromelanin is decreased in both the substantia nigra and LC of PD patients and LC neuron loss is exaggerated in patients with depressive symptoms (Wang et al., 2018). One link between LC and depression is the observation that stressful episodes can potentiate depressive symptoms. This is possibly due to interactions between the stress-induced corticotropin-releasing hormone system and LC (Gold and Chrousos, 2002; Gold et al., 2015), as corticotropin-releasing factor (potentially released from the amygdala (Reyes et al., 2008) is increased in the LC of patients with depression (Bissette et al., 2003). The link between stress and depression is strengthened by the observation that in post-traumatic stress disorder, 50% of patients develop depression (Pitman et al., 2012). In addition, patients with melancholic depression suffer from hyperarousal, anxiety, and sleep disturbances and have elevated norepinephrine levels in the plasma and cerebrospinal fluid (Wong et al., 2000). The treatment of depression frequently requires targeting the LC-norepinephrine system with serotonin-norepinephrine reuptake inhibitors and norepinephrine reuptake inhibitors (Zhou, 2004).

Other disorders like chronic neuropathic pain can induce depression associated with noradrenergic impairment (Alba-Delgado et al., 2013). In pain-related anxiety, corticotropin-releasing hormone induces activation of extracellular signal-regulated kinase 1/2 signaling to upregulate LC function (Borges et al., 2015). Stress is known to increase the firing of LC neurons (Bingel et al., 2011), which, in turn, induces arousal and can precipitate anxiety and aversion (McColl et al., 2015).

Patients with PD commonly suffer from sleep disturbances, a non-motor symptom thought to be related to LC pathology (Braak et al., 2003; Abbott et al., 2005). As previously mentioned, the LC norepinephrine system is part of the sleep-wake cycle through projections to wake-promoting regions (Szabadi, 2013; Schwarz, 2015). Almost all PD patients suffer from sleep disturbances with individual variability, which include disordered breathing, vivid dreaming and excessive daytime sleepiness (Chaudhuri et al., 2006; Verban et al., 2008). The LC system is known to be involved in chemoreception to maintain normal breathing, a function that is disrupted in PD (Oliveira et al., 2017). PD patients also suffer from cognitive impairment, even in the early stages of the disease (Weintraub et al., 2015). We suggest that these impairments may be understood as disruptions in LC’s computational functions (adaptive gain, unexpected uncertainty, generation of latent states).

Motor Symptoms in Parkinson’s Disease

Motor symptoms of PD arise in humans when ~80% of dopamine neurons are lost in the substantia nigra (Rommelfanger and Weisshenker, 2007). Interestingly, this may not be sufficient to generate motor symptoms. Pharmacological application of MPTP, a drug that selectively destroys dopamine cells, causes significant dopamine loss in the nigrostriatal system yet does not generally result in profound motor symptoms. When MPTP is combined with pharmacological ablation of the LC, the classic motor symptoms of PD emerge (Marien et al., 1993; Rommelfanger and Weisshenker, 2007). Mice that lack the norepinephrine transporter gene are partially protected from MPTP toxicity, suggesting that extracellular norepinephrine may be protective against dopamine cell death (Rommelfanger et al., 2004). Interestingly, ascending LC projections to the forebrain are not the only contributors to PD, as dysfunction of the descending cerulospinal tract may also play a key role in rigidity (Paulus and Jellinger, 1991).

Typical motor symptoms of PD become apparent when α-synucleinopathy can be detected and substantia nigra deterioration occurs (Braak et al., 2003). α-Synuclein, a presynaptic protein thought to regulate neurotransmission, is overexpressed in PD and believed to contribute to dysregulation of homeostasis, cell death, and may contribute to disease propagation (Stefanis, 2012). Interestingly, α-synuclein plaques are not only involved in compartmentalization of dopamine in the substantia nigra, but also alter the storage
of norepinephrine in the dentate gyrus (Yavich et al., 2006). It has been suggested that α-synucleinopathy might interfere with an antioxidant role for norepinephrine. Both extracellular dopamine and norepinephrine can prevent free radical formation and act to protect neurons against oxidative stress (Troadee et al., 2002; Traver et al., 2005). This protective role could explain why norepinephrine transporter knockout protects against MPTP toxicity. The antioxidant role of cathecolamines is further supported by the localization of dopamine β-hydroxylase, the enzyme that catalyzes the hydroxylation of dopamine to norepinephrine, to the mitochondrial membranes of LC neurons (Issidorides et al., 2004).

**Copper-Rich Food for Thought**

Copper is an essential cofactor for dopamine β-hydroxylase (Schmidt et al., 2018). Under normal conditions, copper levels are enriched in the LC (Schmidt et al., 2019) and are higher than in the substantia nigra (Zecca et al., 2004). In particular, copper is thought to play a protective role in these brain regions, and copper dysregulation could contribute to neuronal cell death. One hypothesis is that the protective effect of copper could be due to the anti-oxidative role of superoxide dismutase 1, a copper-dependent enzyme (Genoud et al., 2017; Trist et al., 2017). The malfunction of superoxide dismutase 1 in the substantia nigra of PD patients may contribute to dopaminergic cell loss (Trist et al., 2019). Consistent with this idea, there is a decrease in copper levels and expression of copper transporter Ctr1 in both the substantia nigra and LC of PD patients (Davies et al., 2014; Genoud et al., 2017).

Interestingly, in Wilson's disease, a classic disorder of copper accumulation caused by a mutation in the copper transporter ATP7B, patients often manifest with PD-like symptoms of tremor and gait impairment. These patients typically have abnormal serum catecholamine levels and suffer from similar neuropsychiatric symptoms as PD patients (Benhamla et al., 2007). A recent study suggested that the role of ATP7B is to sequester intracellular copper, which is required for secretion of dopamine β-hydroxylase, and thus provides regulation of intracellular and extracellular catecholamine (Schmidt et al., 2018). For these reasons, we speculate that aberrance in the copper-regulated catecholamine balance may contribute to symptoms in PD.

**Conclusion**

In summary, the LC-norepinephrine system is a pontine neuromodulatory nucleus with broad projections throughout the forebrain, cerebellum, and spinal cord. Classic studies have implicated LC in a myriad of functions such as arousal, behavioral flexibility, learning, memory, and wakefulness. LC neurons are remarkably homogeneous, especially when compared to other neuromodulatory structures. It is likely that functions of LC may be understood in terms of the relevant efferent pathways, target structures, and local receptor heterogeneity. Mechanistically, LC-norepinephrine has long been studied as a modulator of synaptic plasticity, allowing local circuits to dynamically adapt in the face of new inputs. The many functions of LC may help explain symptoms of PD, a neurodegenerative disease that is now understood to be a dysfunction of both the dopamine and norepinephrine system. LC-norepinephrine is neuroprotective in PD and its loss may contribute to both motor-related and non-motor-related symptoms. Thanks to modern research using cell-type-specific techniques, the circuit logic of LC is slowly becoming clear, with implications for understanding and treating disease.

**Acknowledgments:** We thank Jeremiah Y. Cohen and Hongdian Yang for comments on the manuscript.

**Author contributions:** All authors wrote the manuscript and approved the final manuscript.

**Financial support:** This work was supported by the National Institutes of Health grant F30MH110084 (to BAB).

**Copyright license agreement:** The Copyright License Agreement has been signed by all authors before publication.

**Plagiarism check:** Checked twice by iThenticate.

**Peer review:** Externally peer reviewed.

**Open access statement:** This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non-Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**Open peer reviewer:** Cristoforo Comi, University of Eastern Piedmont, Italy.

**References**

Abbott JD, Ross GW, White LR, Tanner CM, Masaki KH, Nelson JS, Curb JD, Petrovitch H (2005) Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology 65:1442-1446.

Alba-Delgado C, Llorca-Torralba M, Horrillo I, Ortega JE, Mico JA, Sanchez-Blazquez P, Meana J, Berrocoso E (2013) Chronic pain leads to concomitant noradrenergic impairment and mood disorders. Biol Psychiatry 73:54-62.

Ameniya S, Kubota N, Umemaya N, Nishijima T, Kita I (2016) Noradrenergic signaling in the medial prefrontal cortex and amygdala differentially regulates viscarious trial-and-error in a spatial decision-making task. Behav Brain Res 297:104-111.

Anlezark GM, Crow TJ, Greenway AP (1973) Impaired learning and decreased cortical norepinephrine after bilateral locus coeruleus lesions. Science 181:682-684.

Aston-Jones G, Bloom FE (1981) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci 1:878-886.

Aston-Jones G, Cohen JD (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 28:403-450.

Aston-Jones G, Rajkowski J, Kubiak P (1997) Conditioned responses of monkey locus coeruleus neurons anticipate acquisition of discriminative behavior in a vigilance task. Neuroscience 80:697-715.

Bear MF, Singer W (1986) Modulation of visual cortical plasticity by acetylcholine and noradrenaline. Nature 320:172-176.

Beas BS, Wright BJ, Skirzewski M, Leng Y, Hyun JH, Koita O, Ringelberg N, Kwon HB, Buonanno A, Penzo MA (2018) The locus coeruleus drives disinhibition in the midline thalamus via a dopaminergic mechanism. Nat Neurosci 21:965-973.

Benhamla T, Tiouriche YD, Abaoub-Germain A, Theodore F (2007) The neurotransmission of drug-induced tremor. Pharmacol Biochem Behav 87:1-4.

Benhamla T, Tirouche YD, Abaoub-Germain A, Theodore F (2007) The orexin-A receptor antagonist [125I]SCH 23390 selectively decreases orexin-A containing fibers in the substantia nigra of parkinsonian monkeys. J Neurochem 100:1242-1252.

Beringham N, McFadden K, Zhang X, Bhatnagar S, Reck S, Valentine R (2011) Early adolescence as a critical window during which social stress distinctively alters behavior and brain norepinephrine activity. Neuropsychopharmacology 36:896-909.

Bissette G, Klimmek V, Pan J, Stockmeier C, Oorday G (2003) Elevated concentrations of CRF in the locus coeruleus of depressed subjects. Neuropsychopharmacology 28:1328-1335.
Borges GP, Mico IA, Neto FL, Berrocoso E (2015) Corticotropin-releasing factor mediates pain-induced anxiety through the ERK1/2 signaling cascade in locus coeruleus neurons. Int J Neuropsychopharmacol doi: 10.1093/ijnp/pyv019.

Bouret S, Richmond BJ (2015) Sensitivity of locus coeruleus neurons to reward value for goal-directed actions. J Neurosci 35:4005-4014.

Braak H, Del Tredici K, Rub U, de Vo RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197-211.

Carter ME, Yizhar O, Chikahisa S, Nguyen H, Adamantidis A, Nishino S, Deisseroth K, de Lecea L (2010) Tuning arousal with optogenetic modulation of locus coeruleus neurons. Nat Neurosci 13:1526-1533.

Chaudhuri KR, Healy DG, Schapira AH (2006) Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 5:235-245.

Crochet S, Saki K (2003) Dopaminergic modulation of behavioral states in mesopontine tegmentum: a reverse microdialysis study in freely moving cats. Sleep 28:801-806.

Deisseroth K (2017) Ancestral circuits for the coordinated modulation of intrathalamic circuit dynamics. Nat Neurosci 22:120-133.

Dumont PR, Pakkenberg B, Gundersen HJ, Price DL (1994) Absolute number and size of pigmented locus coeruleus neurons in young and aged individuals. J Chem Neuroanat 7:185-190.

Kety SS (1970) The biogenic amines in the central nervous system: Their role in personality. Am J Psychiat 127:969-973.
Rommeldinger, K. (2007). Noradrenaline: The redheaded stepchild of Parkinson's disease. Biochem Pharmacol 74:177-190.

Rommeldinger, K., Weisshenker, D. & Miller, G. W. (2004). Reduced MPTP toxicity in noradrenaline transporter knockout mice. J Neurochem 91:1116-1124.

Sah P. (2017). Fear, anxiety, and the amygdala. Neuron 96:1-2.

Sales AC, Friston KJ, Jones MW, Pickering AE, Moran RJ (2017) Active inference model. PLoS Comput Biol 13:e1006267.

Samuelle A, Mangiagalli R, Armentero MT, Fancellu R, Bazzi E, Varetti M, Ferrigno A, Richelmi P, Nappi G, Blanfidi F (2005) Oxidative stress and pro-apoptotic conditions in a rodent model of Wilson's disease. Biochem Biophys Acta 1741:325-330.

Sara SJ (2017) Sleep to Remember. J Neurosci 37:457-463.

Sara SJ, Devauges V (1988) Priming stimulation of locus coeruleus facilitates memory retrieval in the rat. Brain Res 438:299-303.

Sara SJ, Segal M (1991) Plasticity of sensory responses of locus coeruleus neurons in the behaving rat: implications for cognition. Prog Brain Res 88:571-585.

Sara SJ, Bourou S (2012) Orienting and reorienting: the locus coeruleus mediates cognition through arousal. Neuron 76:130-141.

Schmidt K, Bari BA, Chokshi V, Schmidt K (2020) Locus coeruleus-norepinephrine: basic functions and insights into Parkinson's disease. Neural Regen Res 15(6):1006-1013. doi:10.4103/1673-5374.270297