Noradrenaline Regulation of Brain-Body Communication

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Abstract

Norepinephrine (NE) and its methylated form, epinephrine (Epi), are catecholamines that serve as both neurotransmitters and hormones, regulating a wide array of physiological functions. In the central nervous system (CNS), NE acts as a neurotransmitter, primarily released by the locus coeruleus (LC), to regulate vigilance states and optimize behavioral performance. It is also the primary neurotransmitter of the peripheral, sympathetic nervous system, responsible for tonic and reflexive changes to cardiovascular tone. Conversely, Epi operates primarily as a hormone released by the adrenal medulla, to regulate metabolic homeostasis and orchestrate the body's response to acute stress. While there is no evidence for direct connections between the central and peripheral adrenergic systems, various feedforward and feedback circuits enable them to collaborate and synchronize brain-body responses to stimuli. A notable example of this interaction is evident in the body's response to stress, where multiple adrenergic systems work in concert to elicit a fight-or-flight response to perceived danger. Reciprocal communication between the LC, other adrenergic systems in the brain, and the NE-driven sympathetic nervous system induces a state of heightened arousal, enhances the processing of sensory stimuli, and facilitates adaptive behavioral responses to stressors.

In this chapter, we will explore adrenergic systems in the brain and body and share evidence for multiple channels of communication between them. We will trace the anatomical connections and physiological characteristics of NE-producing neurons in the brain and the peripheral nervous system. We will also describe adrenergic systems in the body, projections of the sympathetic postganglionic neurons, the vasal ganglia of the cranial nerve, and release of NE and Epi by the adrenal medulla into the bloodstream. Importantly, this chapter will elucidate the circuits and pathways of communication between NE in the central and peripheral nervous systems that regulate and synchronize cognitive processes and physiological responses. Finally, we will explore various neurological disorders, including chronic pain and

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Alzheimer's disease (AD), that show evidence for deficits in adrenergic systems and disruption of the communication between the brain and body.

Keywords

Norepinephrine · Locus Coeruleus · Sympathetic ganglia · Arousal · Fight-or-flight response

Abbreviations

Ach	Acetyl choline
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
ARAS	Ascending reticular activating system
ATP	Adenosine triphosphate
CeA	Central amygdala
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
CRH	Corticotropin releasing hormone
DRG	Dorsal root ganglia
DSP4	N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride
EEG	Electroencephalogram
Epi	Epinephrine
GANE	Glutamate amplifies noradrenergic effects
GPCRs	G-protein coupled receptors
HPA	Hypothalamic-pituitary-adrenal axis
LC	Locus Coeruleus
LMTRS	Low threshold mechanoreceptors
LTP	Long-term potentiation
MERFISH	Multiplexed error-robust fluorescence in situ hybridization
NAc	Nucleus accumbens
NE	Norepinephrine
NGF	Nerve growth factor
NPY	Neuropeptide Y
NREM	Non-rapid eye movement
NTS	Nucleus tractus solitarius
PAG	Periaqueductal gray
PKA	Protein kinase A
PTSD	Post-traumatic stress disorder
PVN	Paraventricular nucleus of the hypothalamus
REM	Rapid eye movement
RPE	Reward prediction error
SAM	Sympathetic-adrenomedullary axis
TH	Tyrosine hydroxylase

Norepinephrine (NE, also known as noradrenaline) and epinephrine (Epi, also known as adrenaline) are monoamine neurotransmitters and hormones that are widely distributed in the brain and body. NE is widely released in the central nervous system (CNS), while epinephrine (Epi) is present in relatively low amounts in the mammalian brain. Outside the brain, NE is one of the primary neurotransmitters of the autonomic nervous system and also functions as a hormone released by the adrenal medulla. On the other hand, Epi functions primarily as a hormone, mainly secreted by the adrenal gland and by a small number of neurons in the medulla oblongata. NE and Epi are synthesized in the body from dietary amino acids through a series of enzymatic reactions and are the targets of numerous clinically significant drugs that modify the noradrenergic system (Fernstrom and Fernstrom 2007). Together, these molecules play a vital role in the maintenance of homeostasis through the autonomic nervous system, the modulation of memory through adaptive gain of neuronal circuits, and the regulation of behavior through changes in sensorimotor processing.

2.1 Noradrenaline in the Brain

NE-producing neurons in the CNS form a relatively small group of cells primarily residing in portions of the medulla oblongata, pontine, and dorsal vagal complex. Early studies of monoaminergic distribution and histochemical staining identified 7 groups of cells (named A1 - > A7) based on their location and projection patterns (Felten and Sladek 1983),

with the A6 group or the Locus Coeruleus (LC) being the most widely studied. The LC is the largest of these nuclei, comprising almost 50% of NE neurons in the brain. Though small in number, noradrenergic neurons project widely throughout the brain and spinal cord, innervating almost every brain region and regulating multiple aspects of sensory processing, learning, and motor control. Groups of NE neurons in the ventral and dorsal tegmentum of the medulla oblongata and the pons (A1, A2, A3, A7) form the ventral ascending noradrenergic pathway while the LC forms the primary dorsal ascending pathway. Ascending NE fibers arising from the A1, A2, A5, and A7 nuclei project to the midbrain reticular formation, the entire hypothalamus, and parts of the limbic cortex. Descending fibers from these nuclei terminate in the ventral and intermediate nuclear columns of the spinal cord (Felten and Sladek 1983; Guyenet 1991).

The A1 group of neurons, located in the caudal ventrolateral medulla of the brainstem, is thought to be primarily involved in the regulation of cardiovascular control, including maintenance of blood pressure. A large fraction of A1 cells co-express neuropeptide Y (NPY) and a smaller fraction express galanin (Guyenet 1991; Everitt et al. 1984). Tracing studies indicate that the A1 nucleus projects to various regions in the hypothalamus, the median preoptic area, the bed nucleus of stria terminalis, and the nucleus tractus solitarius (NTS) (Guyenet 1991). The A2 group of cells lies within the hindbrain dorsal vagal complex and supports its role in vagal sensory-motor reflex flow. Extensive reciprocal connections to the majority of the NTS, various hypothalamic nuclei, and various limbic and cortical forebrain regions make the A2 nucleus an important crossroad of visceral motor outflow and interoceptive feedback to the brain (Rinaman 2011). Projections from the A2 cell group are thought to relay gastric and cardiovascular (i.e., visceral) signals to regions such as the amygdala and nucleus accumbens (NAc), modulating their activity and shaping learning of emotional stimuli (Rinaman 2011; Kerfoot et al. 2008). The A5 and A7 nuclei form 2 clusters of noradrenergic cells in the pontine tegmentum. While the vast majority of A5 neurons innervate the intermediolateral cell column of the spinal cord, tracing studies also demonstrate projections to the central amygdala, hypothalamus, periaqueductal gray (PAG), and NTS (Byrum and Guyenet 1987). Chemogenetic activation of A5 neurons drives sympathetic nerve activity to increase blood pressure (Souza et al. 2022a), suggesting a role for these cells in the modulation of blood flow. On the other hand, A7 neurons relay antinociceptive signals from the ventral PAG to the dorsal horn of the spinal cord (Bajic et al. 2001; Clark and Proudfit 1991).

While the various noradrenergic nuclei display territorial specialization in their downstream projections, they all play a part in both relaying visceral information to the brain and modulating bodily functions through the regulation of autonomic and endocrine functions. However, direct modulation of complex behavior is mediated almost exclusively by the LC (or the A6 group), which is the sole noradrenergic nucleus innervating the cerebral cortex.

2.1.1 The Locus Coeruleus and Its Connections in the Brain

The majority of NE-producing neurons are located in the LC, or "blue spot":a small nucleus located deep in the brainstem that supplies far-reaching noradrenergic innervations to the brain (Poe et al. 2020). Despite its small number of neurons, ~3000 neurons in the rodent brain (Sara 2009) and ~50,000 in the human brain (Sharma et al. 2010), the LC sends out dense projections to most cortical and subcortical areas (Schwarz and Luo 2015) (illustrated in Fig. 2.1). Importantly, the LC is the only source of NE for the hippocampus and neocortex, areas essential for higher cognitive and emotional processes (Poe et al. 2020; Aston-Jones and Cohen 2005; Breton-Provencher et al. 2021). Similarly, LC neurons are thought to receive excitatory inputs from a diverse set of brain regions including most brainstem nuclei and forebrain areas (Schwarz and Luo 2015; Breton-Provencher et al. 2021). Additionally, the dense core of NE-producing neurons that make up the LC receives several

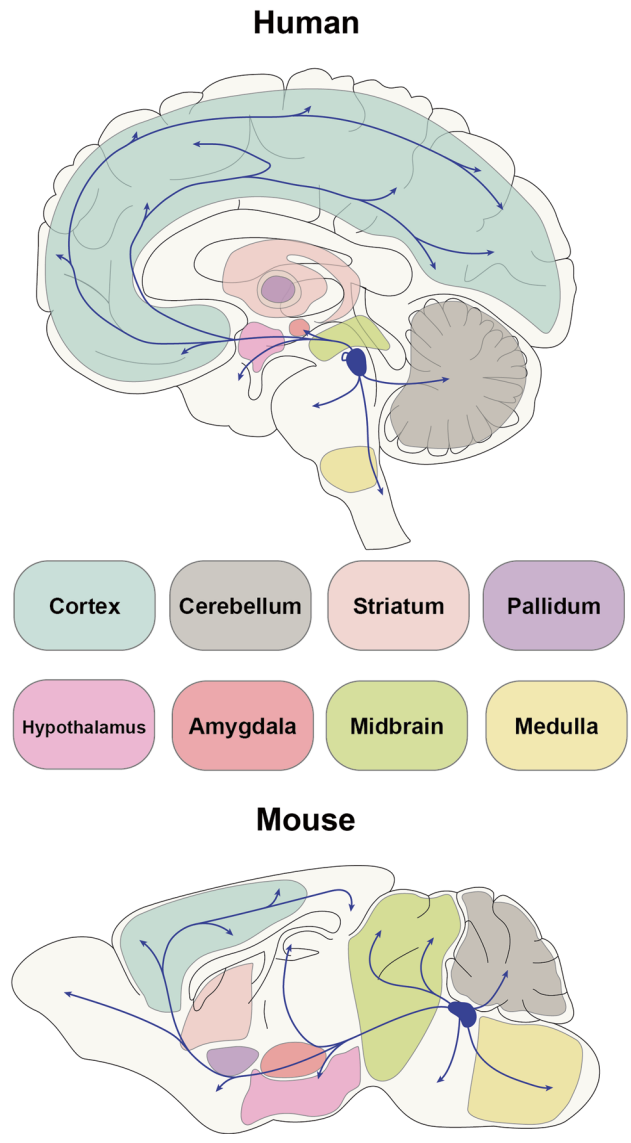

Fig. 2.1 NE connections in the brain. Projections of the Locus Coeruleus, the brain's primary noradrenergic nucleus, in the human *(top)* and mouse *(bottom)* brain. (Adapted with permission from (Breton-Provencher et al. 2021))

local (Breton-Provencher and Sur 2019; Jones 1991a) and long-range (Ennis and Aston-Jones 1989; Dimitrov et al. 2013) GABAergic connections as well as inputs from cholinergic and neuropeptide-S expressing neurons (Jones 1991a; Xu et al. 2004). The wide range of convergent inputs to LC-NE neurons suggests their recruitment in the detection of salient sensory stimuli as well as in the regulation of goal-directed behaviors. For example, the LC receives afferent projections from the gigantocellular reticular nucleus in the brainstem—which responds to tactile, visual, auditory, vestibular, and olfactory stimuli (Martin et al. 2010)—resulting in LC activation following salient sensory stimulation. On the other hand, projections from the central amygdala recruit LC-NE neurons to the body's stress response (Bouret et al. 2003; Curtis et al. 2002; Van Bockstaele et al. 1998), while LC inputs from distinct subregions of the medial prefrontal cortex suggest a role for LC-NE in the modulation of learning and memory (Sara and Hervé-Minvielle 1995; Jodo and Aston-Jones 1997; Jodo et al. 1998).

Historically, the LC was considered to be a homogenous nucleus, with no distinct organization of inputs along its rostro-caudal axis and a uniform release of NE into the forebrain, cerebellum, brainstem, and spinal cord (Aston-Jones and Waterhouse 2016). This suggests that the LC integrates information from and broadcasts signals to many brain regions, consistent with its key function in modulating global brain states. In an important study, Schwarz et al. (2015) used the TRIO (tracing the relationship between input and output) method to virally trace the input and output relationships of LC neurons. They reported that LC neurons have a largely indiscriminate input-output relationship, with LC neurons that project to diverse brain regions also receiving similar densities of inputs from the same regions. Despite this highly integrative architecture of LC-NE connectivity, they also found some heterogeneity of LC sub-circuits. LC-NE neurons that project to the medulla received disproportionately fewer inputs from the central amygdala than those projecting to other areas. This implies that medulla-projecting LC neurons are preferentially immune to stress-related activation by the amygdala, creating a modularity of networks within the LC circuit. Since then, multiple studies have shown spatial heterogeneity of LC-NE projections, with anatomical evidence for target-specific distributions of LC axons. MAPseq (Multiplexed Analysis of Projections by Sequencing) analysis using axon-specific RNA barcodes to distinguish between the projections of specific neurons revealed that individual LC neurons have preferred cortical targets (Kebschull et al. 2016). Multiple studies have demonstrated differential roles of LC projections to different hippocampal sub-regions (CA1, CA3, and dentate gyrus) in mediating various aspects of learning and memory (Wagatsuma et al. 2018; Chowdhury et al. 2022). Subpopulations of LC-NE neurons projecting to the medial prefrontal cortex, an area involved in cognition and executive function, and the motor cortex that mediates goal-directed movement, show discrete anatomical, biochemical, and electrophysiological properties (Breton-Provencher et al. 2022; Chandler et al. 2014). These distinct projection patterns allow LC-NE neurons to modulate the activity of different brain regions in a task-dependent manner. For example, specific NE release in the motor cortex facilitates the execution of movement, while a salient reinforcement signal is more broadly distributed among cortical regions to improve subsequent performance (Breton-Provencher et al. 2022). Similarly, LC neurons projecting to the amygdala facilitate aversive learning, while an independent population projecting to the medial prefrontal cortex extinguishes those aversive responses to enable flexible behaviors (Uematsu et al. 2017). Such modular organization of LC neurons, along with variations in NE receptor densities and subtypes across different brain regions, allow LC-NE neurons to modulate distinct brain regions in a flexible, task-specific manner.

2.1.2 Theories of the Role of LC-NE in Brain Function

Although NE is primarily recognized for its role in regulating arousal, it also plays a pivotal role in modulating learning and memory. NE profoundly shapes how the brain processes, adapts to, and integrates new information. Several theories propose distinct mechanisms by which LC-NE activity influences cognitive flexibility, decision-making, and behavioral adaptation, underscoring its critical involvement in learning-related processes (Poe et al. 2020; Breton-Provencher et al. 2021). One such theory is the *Network Reset Theory*, proposed by Bouret and Sara, which posits that the LC becomes highly active in response to surprising outcomes or contextual shifts that demand behavioral change (Bouret and Sara 2005). This manifests as a phasic activation of LC-NE, which precedes changes in neuronal activity across other cortical regions within single trials. Phasic LC activation triggers a widespread release of NE, particularly in the cortex, effectively "resetting" cortical networks. By disrupting ongoing activity patterns, this resetting mechanism primes the brain to adapt more flexibly to new contexts. Such an adaptive process is especially apparent in behavioral tasks

where stimulus-reinforcement contingencies change abruptly. In these situations, NE serves as a catalyst for behavioral shifts, enabling the brain to disengage from existing routines or predictions and prioritize the processing of novel stimuli. Such a mechanism is crucial in learning environments that require rapid adjustment to new circumstances, allowing for greater behavioral flexibility. This theory also aligns with the broader concept of NE as a modulator of attention, facilitating the brain's ability to focus resources on the most relevant and salient stimuli while suppressing distractions from familiar, less pertinent information. This theory is complemented by the work of Yu and Dayan (2005), who suggest that NE globally signals "unexpected uncertainty" in the external environment (Yu and Dayan 2005). In their model, NE release is triggered when there is a mismatch between expected and actual outcomes. This release enhances bottom-up information processing and updates the brain's internal predictions, or "priors," to optimize future responses. Unlike the Network Reset Theory, which emphasizes rapid, trial-specific NE activation, their model describes a slower timescale of NE release that unfolds across multiple trials. Both theories highlight the critical role of outcome predictability and reliability in triggering the LC-NE response.

Another prominent theory for explaining the role of NE in learning and behavior is the *Adaptive Gain Theory*, developed by Aston-Jones and Cohen (2005). This theory proposes that NE's influence on cognitive performance and behavioral flexibility can be understood through two distinct modes of activity in the LC: phasic and tonic. In the phasic mode, the LC exhibits brief, rapid bursts of NE release in response to task-relevant stimuli, particularly in contexts where an elevated level of attention is required. Phasic NE release sharpens focus on important stimuli, enhancing sensory processing and facilitating task performance. This allows the brain to exploit known information and optimize behavior for efficient learning and execution in a goal-directed behavior. In contrast, the tonic mode is characterized by a sustained increase in baseline NE release that is not associated with specific task demands. This mode is linked to increased distractibility and reduced task performance. Unlike phasic NE activity, the tonic mode allows the brain to disengage from current tasks and promotes exploration of new contingencies in novel or uncertain environments. In this way, tonic NE activity is essential for enabling behavioral flexibility when the exploitation of existing strategies is no longer effective.

These two modes of NE activity are well illustrated by the contrasting behavioral performance observed in animals performing simple decision-making tasks (Aston-Jones et al. 1994). For instance, in a signal detection task where an animal is trained to associate one stimulus with a behavioral response to receive a reward, and to avoid responding to another stimulus to prevent a punishment, measurements of NE release can be linked to specific behaviors. Phasic NE activity is predominantly observed during periods of strong behavioral performance, particularly when the animal responds to reward-predicting stimuli or adjusts behavior after a reversal in stimulus-reward contingencies. On the other hand, tonic NE activity is associated with poor behavioral performance, during which the animal's ability to discriminate between stimuli and its response threshold to those stimuli decreases. The balance between phasic and tonic LC-NE activity is thought to mediate a key trade-off between exploitation and exploration. In situations that demand focus and precise action, phasic bursts of NE facilitate exploitation by enhancing attention and suppressing distractions. Conversely, during periods of uncertainty or low task engagement, increased tonic NE levels enable the brain to shift toward exploration and consider alternative strategies. This dynamic switch between modes allows the LC-NE system to regulate learning and decision-making in a flexible, context-dependent manner.

The *GANE (glutamate amplifies noradrenergic effects)* model, also called the glutamate amplification of learning model, offers a more mechanistic view of NE's role in learning. This model, proposed by Mather and colleagues, suggests that NE's influence on learning is not uniform across brain regions but is highly specific to

areas where strong excitatory activity already exists (Poe et al. 2020; Mather et al. 2016). This model posits that when neurons release elevated levels of glutamate in response to a stimulus, nearby NE varicosities and astrocytes sense this increase and signal for the release of NE from the LC. This local NE release, in turn, amplifies the effects of glutamate, creating a feedback loop that enhances neural activity in circuits engaged in processing the most relevant or salient information. As a result, the combination of glutamate and NE potentiates the neural representation of important stimuli, prioritizing learning and memory formation in these regions.

The GANE model introduces a layer of specificity to the role of NE in learning by emphasizing how NE selectively amplifies activity in highly activated circuits rather than uniformly affecting the entire brain. This stands in contrast to earlier models that focus primarily on widespread NE release during states of heightened arousal. According to the GANE model, NE's action is more targeted and input-specific, affecting regions like the hippocampus, amygdala, and prefrontal cortex—areas heavily involved in spatial learning, emotional memory, and decision-making. In these regions, the NE-glutamate interaction promotes long-term potentiation (LTP), strengthening synaptic connections and enhancing the consolidation of memories. Moreover, the GANE model helps explain how NE can both enhance and suppress neural activity depending on the context. When glutamate levels are high, NE amplifies the excitatory signals, boosting attention and learning for the most critical stimuli. Conversely, in areas with lower glutamate activity, NE can suppress activity, helping to filter out irrelevant information and focus cognitive resources on more important tasks. This dual role of NE in enhancing relevant inputs while dampening distractions allows for highly efficient processing of information, optimizing learning in complex environments where multiple stimuli compete for attention. Additionally, unlike previous theories, the GANE model highlights the importance of secondary messengers like glutamate and astrocytes. It introduces an astrocyte-mediated mechanism of NE release, which modulates the effects of LC-NE on learning and behavior. This astrocyte involvement provides a more elaborate understanding of how NE modulates neural activity, making the GANE model particularly significant in explaining the localized and dynamic nature of NE's influence on learning and memory.

Recent findings have expanded our understanding of how NE contributes to learning and memory, further refining existing theories like the Network Reset and Adaptive Gain models. For instance, Brenton-Provencher et al. demonstrated that phasic LC-NE activity is closely tied to behavioral performance in reinforcement learning tasks, particularly during surprising outcomes (Breton-Provencher et al. 2022). Their findings suggest that LC-NE activity not only signals unexpected events but also encodes a reward prediction error (RPE), influencing subsequent behavioral adjustments. This dynamic role of NE in updating predictions based on surprising outcomes highlights its critical function in learning, suggesting that NE activity supports the optimization of behavior by refining internal models of the environment. Such insights underscore the importance of NE in shaping cognitive flexibility and learning through mechanisms that integrate prediction, uncertainty, and behavioral feedback.

2.2 NE and Epinephrine in the Body

A major source of NE in the body is the adrenal glands. The adrenal glands are small, pyramidal-shaped organs that sit on top of each kidney. The names noradrenaline and epinephrine are derived from this anatomical location, with "ad" meaning "near," epi meaning "upon," and "nephros" meaning "kidneys." The adrenal gland has an outer cortex and an inner medulla consisting of chromaffin cells. Cholinergic preganglionic neurons in the spinal cord project onto chromaffin cells on the adrenal medulla and activate nicotinic receptors on these cells. The chromaffin cells synthesize NE and store it

in chromaffin granules where it can be released into the bloodstream or converted to Epi by phenylethanolamine-N-methyl transferase. This release of NE and Epi into the bloodstream can influence various tissues and organs that express adrenergic receptors including the heart, blood vessels, and skin (Axelrod 1962; Wurtman and Axelrod 1966).

In addition to the adrenal gland mediated release of NE and EPI into the bloodstream, NE also plays a significant role in transmission of information throughout the body via the autonomic nervous system. The autonomic nervous system consists of the sympathetic and parasympathetic nervous system. While the primary neurotransmitter of the parasympathetic system is acetylcholine (ACh), it works in concert with the sympathetic nervous system and other adrenergic systems to coordinate various interactions between the brain and body. Additionally, NE is a major driver of the sympathetic nervous system where postganglionic neurons in the spinal cord send out adrenergic projections to most major organs in the body (Boron and Boulpaep 2009).

2.2.1 The Sympathetic Nervous System

The sympathetic nervous system begins with neurons in the spinal cord (sympathetic preganglionic neurons) projecting to ganglia in the peripheral nervous system (sympathetic postganglionic/chromaffin cells). Postganglionic sympathetic neurons receive synapses from preganglionic neurons residing in the lateral horn (intermediolateral column, IML) of the spinal cord which send their axons out through the ventral roots. Sympathetic postganglionic neurons all share a common progenitor in the dorsal neural tube and thus have conserved roles (Wehrwein et al. 2016). The axons of these postganglionic neurons project extensively throughout the body and have dense-core vesicles that contain NE. These post-ganglionic neurons produce most of the NE used in the sympathetic nervous system. The abundance of NE-filled vesicles along each axon allows for many en passant synapses which can modulate the impact of affected cells (Smolen 1988). The following section details the effects of NE release from different postganglionic sympathetic neurons on various tissues (also illustrated in Fig. 2.2).

2.2.2 Sympathetic Postganglionic Chain Ganglia

The foremost ganglia within the chain of ganglia are the superior cervical ganglia, which projects many tissues in the head and face including the pupils, conjunctiva, salivary, and lacrimal glands. In smooth muscles that regulate the iris, NE can elicit a contraction without triggering an action potential. When NE is released in the salivary gland, salivation increases. The superior cervical ganglia also travel alongside the internal carotid and vertebral arteries as they enter the skull and branche in tandem with the brain's vasculature. NE release can induce contraction or dilation of vascular smooth muscle cells depending on the expression of distinct types of adrenergic receptors. In arteries and veins, a burst of action potentials in sympathetic ganglia releases NE along with NPY or adenosine triphosphate (ATP), resulting in a vasoconstrictor response. After an injury, blood vessels reinnervated by sympathetic neurons exhibit heightened vasoconstriction and appear more reactivatable (Boron and Boulpaep 2009; Klimaschewski et al. 1996).

Located inferior to the cervical ganglia are the middle cervical ganglion, stellate ganglion, and thoracic postganglionic sympathetic chain. These three ganglionic chains provide sympathetic innervation to the majority of tissues in the upper limbs and torso including sweat glands, hair follicles, lungs, skeletal muscle as well as cardiac tissues. In the sweat glands of the mouse paw, NE facilitates the development of the sweat response. Interestingly, in rodents, sympathetic neurons that innervate sweat glands switch from using NE to ACh during late postnatal development (Tafari

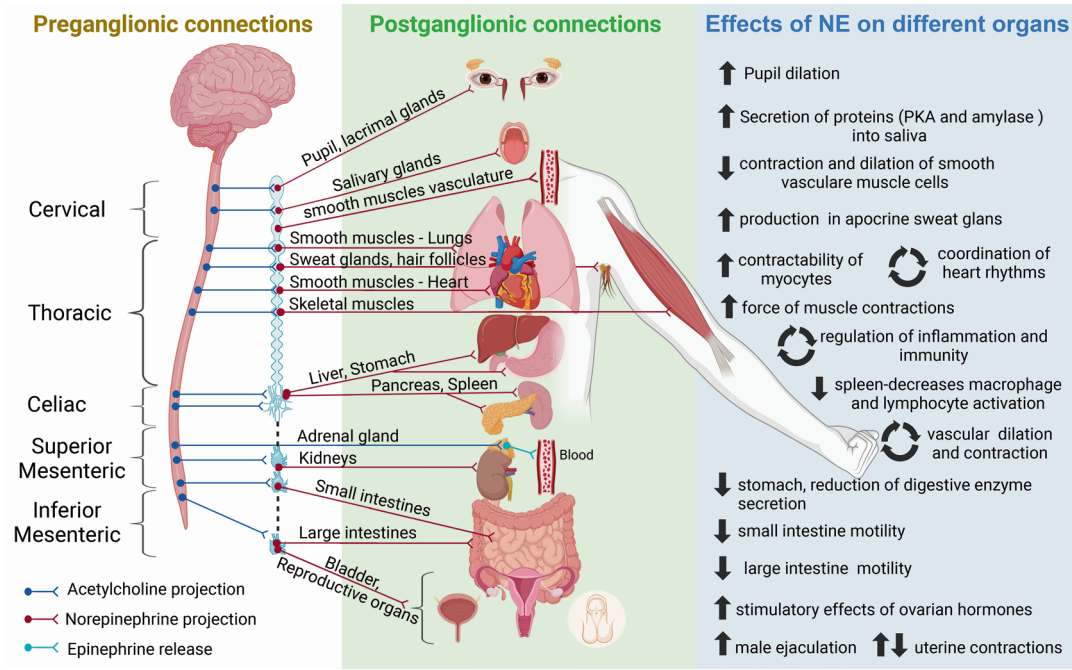

Fig. 2.2 NE connections in the body. Projections of the sympathetic nervous system to various organs in the body and the effect of NE release on their function. Preganglionic neurons in the spinal cord send cholinergic projections to postganglionic neurons *(left)*. These then innervate various organs throughout the body, releasing NE *(middle)* and modulating their function *(right)*

et al. 1997). In hair follicles, the arrector pili muscle anchors the sympathetic innervation from the chain ganglia. These sympathetic nerves form synapse-like connections with hair follicle stem cells, which communicate with NE and affect skin conditions, hair follicle immune system, hair pigmentation loss, and hair growth (Zhang et al. 2021). In lung tissue, NE stimulation relaxes airways and reduces constriction. Skeletal muscles receive sympathetic input from the chain ganglia which may influence the function of the neuromuscular junction, metabolism, and regeneration of muscle fibers. The effects of NE on muscle cells depend significantly on the organ system the muscle is a part of. In some tissues, adrenergic stimulation increases and in others it decreases activity. Experimentally, infusing muscles with NE results in repeated contractions measured as a tetanus or a single long twitch that lasts 10 times longer than non-NE mediated muscle contractions (Boron and Boulpaep 2009).

The heart receives intricate innervations by noradrenergic fibers from the sympathetic system and cholinergic nerve fibers from the parasympathetic system. The balance between these opposing innervations allows for normal heart rhythms as sympathetic neurons accelerate, while parasympathetic postganglionic neurons slow the heart rate. To do this, the sinoatrial node is densely innervated by both NE and ACh fibers to modulate the pacemaker cell's depolarization rate. In the atrioventricular node, NE stimulation increases conduction velocity to decrease the delay of electrical impulse to allow for proper filling of the ventricles. The bundle of His and the ventricular muscle mostly receive NE fibers. NE binding to β1 receptors on the ventricular myocytes increases extracellular calcium influx and results in enhancing the contractile force of the muscles. Furthermore, NE plays a crucial role in coordinating the contractile forces of each muscle in the heart, which is essential for adapting to

changes in heart rate during exercise. Unlike skeletal muscle, cardiac muscle cannot rely on frequency or multiple fiber summation to regulate contraction strength, as each cardiac muscle cell must contract only once per heartbeat, coordinated with neighboring cells. Instead, NE binds to β adrenergic receptors, stimulating the production of cAMP, which activates protein kinase A (PKA). PKA then phosphorylates L-type Ca^{2+} channels, enhancing the passive influx of Ca^{2+} and subsequently increasing contractile force (Boron and Boulpaep 2009).

2.2.3 Celiac Ganglia

The two celiac ganglia are the largest ganglia in the autonomic nervous system. They sit on celiac trucks of the abdominal aorta. The celiac ganglia are innervated by spinal cord neurons from the lower thoracic and upper lumbar spinal levels (T12-L1) and innervate the upper abdominal cavities including much of the upper digestive and accessory structures including the stomach, gallbladder, pancreases, and liver. In the enteric system, including the stomach and upper gastrointestinal tract, NE release inhibits digestion. NE release into the liver regulates the production and release of glucose while relaxing smooth muscles in the gallbladder and pancreas. Overall, NE stimulation results in the inhibition of biliary and pancreatic digestive function. The celiac ganglia are also connected to several other sympathetic ganglia, including the thoracic-aorticorenal ganglia, which innervate the kidneys, the lumbar superior mesenteric ganglia which innervate the small intestines, and the inferior mesenteric ganglia/prevertebral ganglia which innervate the colon, anal sphincter, urinary bladder, and genitalia. NE in the colon slows down digestion and induces contractions of smooth muscles in the anal sphincter, urinary bladder, and induces ejaculation (Gutman and Weil-Malherbe 1967; Kimura et al. 2009).

2.3 Brain-Body Connections Through the Adrenergic System

The synthesis and release of NE and Epi by various nuclei in the central and peripheral nervous systems underscore their crucial role in transmitting signals throughout the brain and body. In addition, the release of NE and Epi into the blood, primarily by the adrenal glands, leads to widespread adrenergic signaling across organ systems. This extensive signaling network of adrenergic molecules makes them ideal candidates to integrate information processing between the brain and body. This adrenergic network is vital to the execution of a wide range of physiological and behavioral functions, most notably the fight-or-flight response to threats. In the following section, we describe the anatomical connections between the brain and body driven by adrenergic signaling and explore physiological processes that are coordinated through these connections.

2.3.1 Anatomical Adrenergic Connections Between the Brain and Body

NE influences the autonomic and peripheral nervous system which has direct connections to and from the brain. The sympathetic nervous system originates with neurons in the spinal cord (sympathetic preganglionic) that project to ganglia in the peripheral (sympathetic postganglionic/ chromaffin cells) nervous system. This effectively connects the brain to the body via two synapses, one predominantly using ACh and the other NE. Various NE sympathetic postganglionic contributions to several major functions are already outlined above. Another channel of communication between the central and peripheral nervous system is through the vagal nerve. The vagal nerve is one of the longest nerves in the body and

is named for its "wandering" projections. The vagal nerve contains both motor and sensory neurons. While the cholinergic motor neurons are housed in the dorsal motor nucleus of the medulla oblongata in the brainstem, the sensory neurons reside distally through the jugular foramen in the jugular and nodose ganglia outside of the skull. This nerve then "wanders" and projects to most of the organs in the abdominal cavity, including the heart, lungs, liver, and gastrointestinal tract (Paintal 1973; Berthoud and Neuhuber 2000; Prescott and Liberles 2022). Thus, the vagal nerve is a direct conduit between the periphery and the brain, transmitting signals related to various bodily functions (Zhao et al. 2022), including heart rate (Coleridge and Coleridge 1994; Zeng et al. 2018), digestion (Powley et al. 2019), and immune response (Jin et al. 2024; Bin et al. 2023). Direct stimulation of the vagal nerve activates the NTS neurons, which project to the LC (Ter Horst et al. 1991) and induces NE release in the brain (Groves et al. 2005; Hulsey et al. 2017). Additionally, peripheral NE signaling, which influences arousal and stress responses, can interact with the vagus nerve to relay information about the body's physiological state. This information helps the brain integrate these signals, facilitating appropriate behavioral and physiological responses.

2.3.2 Influences on Major Sensory Systems

The LC-NE system plays a crucial role in shaping sensory perception across all modalities. Primary sensory neurons, located in the dorsal root ganglia and the cranial nerve V, can receive NE and Epi signals directly through the bloodstream. These pseudo unipolar neurons express adrenergic receptors in various levels and can be organized into functionally meaningful populations such as proprioceptors, cool sensing neurons, peptidergic Aβ rapidly adapting Aβ-RA-LTMRS (low threshold mechanoreceptors) (Le Pichon and Chesler 2014), and Aδ-LTMRs. These neurons innervate the majority of the periphery. NE can modulate the activity of neurons in various sensory pathways resulting in enhancing signal processing, filtering out noise, and optimizing perceptions for appropriate behavioral outcomes. These effects on sensory processing are dependent on factors such as arousal, attentional state, and specific task demands. The following is a brief summary of how NE affects each of the sensory modalities (Waterhouse and Navarra 2019).

Olfaction NE plays a critical role in the modality of olfaction as evidenced by the many NE inputs from the LC to the olfactory bulb and accessory olfactory bulb. For instance, about 30% of the LC neurons in rats project to the olfactory bulb, most of which project to the subglomerular layers, specifically the internal plexiform layer and the granule cell layer (Shipley et al. 1985). The projection to this area is nearly ten times greater than to any other part of the cerebral cortex (Basbaum 2008). Additionally, the MERFISH (multiplexed error-robust fluorescence in situ hybridization) spatial transcriptomic data from the Allen Brain Atlas shows the highest expression of α1 adrenergic receptors in the olfactory bulb of the mouse (Yao et al. 2023; Kunst et al. 2023; Zeng et al. 2023) (also see Box 2.1 and Fig. 2.2). This strong connection between the LC and the olfactory bulb aligns with theories that suggest a crucial role of LC neurons in enhanced sensory vigilance and regulation of growth and adaptability of neural connections. Previous studies have shown that presentation of olfactory cues in behaving animals elicits high LC activity and subsequent release of NE in the olfactory bulb. Such an olfactory bulb-specific NE increase was not seen after exposing the animal to a loud noise or an electrical stimulation of its forepaw. This NE increase to odorant stimuli persisted even when sympathetic cervical ganglionectomy was performed (Chase and Kopin 1968; Aston-Jones and Bloom 1981). The formation of olfactory memories to pheromones (Brennan et al. 1990) and the regulation of pregnancy and maternal behaviors (Kaba and Keverne 1988) require intact NE terminals in the olfactory bulb. Increases of NE turnover in the bulb are also seen in the immediate 4 hours after mating,

but not to re-exposures to the same pheromones. This allows new males to block the impregnation by males who have previously copulated with the same female. Lesioning the olfactory bulb in the females blocks memory formation. NE inputs to the olfactory system have also been shown to influence the formation of cross modal associations. For example, in neonatal rats, NE release as a result of pleasant gentle tactile stimulation leads to a preference for an associatively paired odorant (Kaba et al. 1989). On the other hand, evidence for a specific role of NE in olfaction at the cellular and network level is somewhat inconsistent. In one study, stimulating the LC before performing paired pulse stimulations of the lateral olfactory tract resulted in immediate depression of the synapses. Two minutes later, paired pulse inhibition was significantly potentiated (Okutani et al. 1998). Others found that LC stimulation resulted in depression of granule cell field potentials (Perez et al. 1987). Iontophoretic injections of NE inhibit mitral cells in cats (McLennan 1971) and rabbits (Salmoiraghi et al. 1964), but activates mitral cells in turtle olfactory bulbs (Kaba et al. 1989; Jahr and Nicoll 1982).

Box 2.1: Adrenergic Receptors in the Brain and Body

The experimental infusion of NE in the brain commonly elicits inconsistent and mixed responses from postsynaptic neurons. One simple reason for this could be due to the diversity of adrenergic receptors that bind NE and the different intracellular signals they elicit. Adrenergic receptors are grouped into three subtypes which preferentially couple with a major subfamily of G-protein coupled receptors or GPCRS (Gs, Gq/11, and Gi). α1-adrenergic receptors (α1A, α1B, and α1D) preferentially couple with the Gq subfamily, α2-adrenergic receptors (α2A, α2B, and α2C) preferentially couple with Gi, and β-adrenergic receptors (β1, β2, and β3) preferentially couple with Gs (Motiejunaite et al. 2021). Recent advancements in single cell sequencing have provided a comprehensive view of adrenergic receptor expression levels in different tissues. The following section highlights the findings from several single cell sequencing datasets in the mouse central and peripheral nervous systems.

Figure 2.3 demonstrates the extensive distribution of adrenergic receptors *in the brain*, where both neuronal and non-neuronal cells across various brain regions express a diverse array of receptors (Yao et al. 2023; Zeng et al. 2023). Of the α1-adrenergic receptors, α1A is the most broadly and strongly expressed receptor in the brain and can be found in both neurons and astrocytes. It is most prominently expressed in GABAergic neurons of the cortical caudal ganglionic eminence and the olfactory bulb. α1B is highly expressed in GABAergic cerebral cortex caudal ganglionic eminence neurons, glutamatergic thalamic neurons, intratelencephalic-extratelencephalic neurons, near-projecting corticothalamic layer 6b neuron as well as ependymal astrocytes and oligodendrocytes. α1D receptors have the lowest overall expression of adrenergic receptors with sparse expression levels in glutamatergic dentate gyrus and intra telencephalic-extra telencephalic neurons. Of the α2-adrenergic receptors, α2A is the most broadly expressed. These receptors are most prevalent in ependymal astrocytes, vasculature, GABAergic neurons in cerebral nuclei lateral ganglionic eminence, and glutamatergic neurons in near-projecting corticothalamic layer 6b. α2B receptors have fairly low overall expression: they are expressed in glutamatergic thalamic neurons. The α2C receptors are mainly expressed in glutamatergic neurons of the cerebral nuclei lateral ganglionic eminence and dentate gyrus. Of the β-adrenergic receptors, β1 receptors are broadly expressed across cell types. They have the highest expression in glutamatergic intra telencephalic–extra telencephalic neurons, glutamatergic thalamic neurons, glutamatergic medial habenula–lateral habenula neurons, glutamatergic dentate gyrus immature neurons, ependymal astrocytes, as well as immune cells. β2 and β3 receptors have exceptionally low expression levels in the brain. β2 receptors are seen in immune, vascular, and GABAergic cerebellum cells while

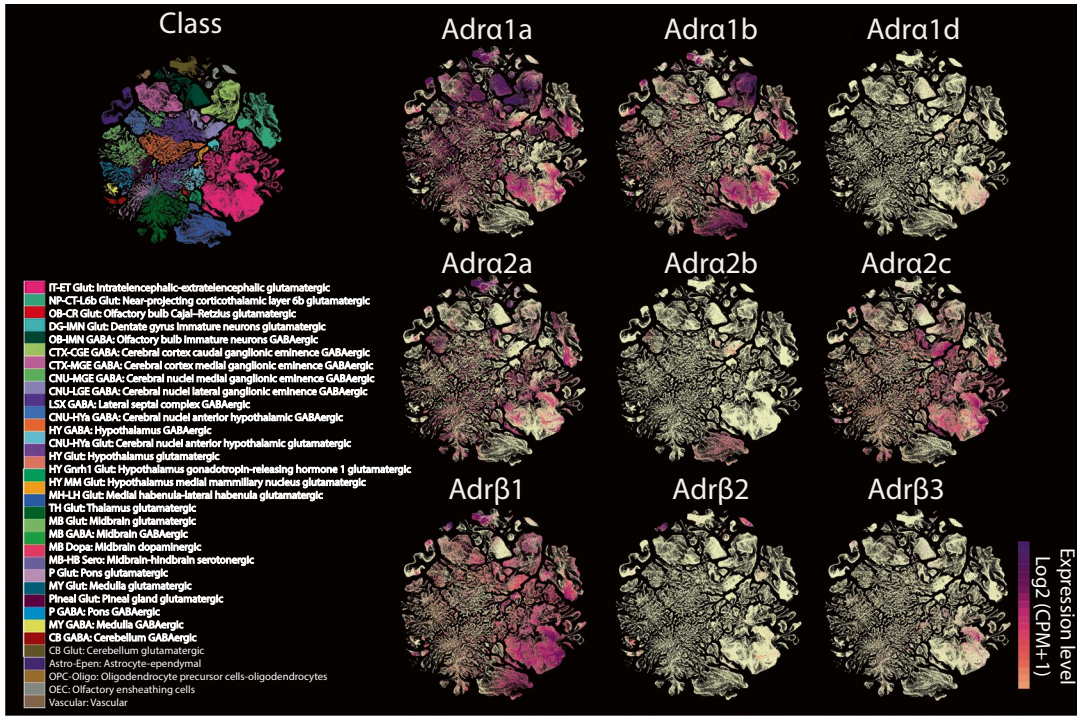

Fig. 2.3 Adrenergic receptors in the brain. Uniform Manifold Approximation and Projection (UMAP) representation of transcriptomic cell types of the whole mouse brain with cell classes differentiated by color *(left)*. Adrenergic receptor subtype expression profiles overlaid onto UMPAP colored in magenta *(right)*. (This figure was generated from the whole brain 10x scRNAseq dataset of the Allen Brain Cell Atlas (Yao et al. 2023; Zeng et al. 2023). https://portal.brain-map.org/atlases-and-data/bkp/abc-atlas)

β3 receptors are expressed by glutamatergic cerebral nuclei anterior hypothalamic and midbrain dopaminergic neurons.

In the periphery, sequencing studies reveal that adrenergic receptors are expressed on different cell types within the dorsal root ganglia (Sharma et al. 2020). These expression patterns allude to functionally specific roles NE could have in different somatosensory modalities. α1B receptors are expressed in proprioceptors, Aβ-RA-LTMRS (low threshold mechanoreceptors), and Aδ- LTMRs, while α1A and α1D have low to no overall expression in any sensory neurons. α2A receptors are expressed in calcitonin gene-related peptide (CGRP)-eta, CGRP-epsilon, and in early developmental somatostatin neurons. α2B receptors are selectively expressed in just proprioceptors. α2C receptors are broadly expressed in Aβ-RA-LTMRS, Aδ-LTMRs, proprioceptors, Aβ-field LTMRS, CGRP-eta, CGRP-zeta, CGRP-epsilon peptidergic nociceptors, and Trpm8 cooling neurons. β1receptors are present at exceptionally low levels throughout primary sensory neurons but are expressed in c-LTMRS, Aδ- LTMRs, and proprioceptors (Sharma et al. 2020). *In vagal neurons* of the jugular and nodose ganglia, neurons predominantly express α2-adrenergic receptors. α2A receptors are highly expressed in several classes of nodose ganglia (NG10, NG8) as well as in a population of jugular neurons (JG4). α2C receptors are expressed by nearly every class of jugular and nodose neurons with the highest expression seen in NG6, JG4, and NG1 (Kupari et al. 2019). *In the heart*, NE activates β-adrenergic receptors on cardiac pacemaker neurons, leading to tachycardia, and also stimulates β receptors on cardiac myocytes, increasing cardiac contractility.

Additionally, NE can induce vasoconstriction by activating α1 and α2 adrenergic receptors in the blood vessels (Myagmar et al. 2017).

The diversity and specific expression in different tissues of adrenergic receptors make them an exciting target for clinical interventions. For example, smooth muscles in the prostate predominantly express α1A-receptors; therefore, α1A-adrenergic antagonists could be used therapeutically to treat prostatic hypertrophy. β3-adrenergic receptors are found uniquely in brown adipose tissue and the gallbladder and could be targeted for obesity treatments. In the heart, β-1 and α-1B receptors are present in all myocytes. α1A is present in 60%, and β-2 and β-3 are detected in only 5% of myocytes (Myagmar et al. 2017). An α2-receptor agonist, dexmedetomidine, is routinely used in operating rooms to manage pain and sedation (Brown et al. 2018).

Somatosensation NE can affect the somatosensory system at multiple levels of the ascending somatosensory pathway beginning with sensory neurons in the periphery (trigeminal ganglia/cranial nerve 5 and dorsal root ganglia) and centrally in the spinal cord, brainstem, thalamus, and somatosensory cortex. Since LC neurons project so widely across the somatosensory pathway, they can have bidirectional effects on somatosensation. For example, in the spinal cord, they can both enhance and suppress pain signals depending on the receptors the tissues express. Furthermore, there is evidence that NE centrally can improve tactile discrimination. Iontophoretic NE application in the rat somatosensory cortex enhances excitatory and inhibitory transmission without directly altering neuron firing (Waterhouse et al. 1990a). Differential patterns of LC activation can differentially facilitate somatosensory signals from whisker-stimulation (Waterhouse et al. 1990a; Devilbiss et al. 2006; Devilbiss and Waterhouse 2004). Specifically, stimulating LC potentiates the responses of layer 5 barrel cortex neurons to whisker deflection and sharpens their receptive field. These support that idea that NE establishes a sensory processing state that selectively influences neuronal responsiveness to afferent signals during different phases of whisker movement.

Vision NE can affect the visual system at levels of the thalamic lateral geniculate nucleus and the visual cortex. Iontophoretic application of NE into the lateral geniculate nucleus enhanced neuronal responses to afferent optic stimulation, an effect abolished when all NE stores are pharmacologically depleted (Rogawski and Aghajanian 1980). Additionally, in vivo and in vitro experiments demonstrated that the effects of NE in the visual system relied on adrα1 receptors, which mediated the conversion of lateral geniculate neuron activity from burst firing to single spike firing and improves signal transmission (Holdefer and Jacobs 1994; McCormick et al. 1991). The switch from a state of rhythmic oscillation and low excitability to a state of increased excitability and responsiveness supports the role of NE in facilitating changes from the drowsiness seen in slow-wave sleep to periods of waking and attentiveness. NE also influences neuronal activity in the visual cortex. Specifically, NE enhances the signal-to-noise ratio for visual inputs, particularly through α2 receptor-mediated pathways (Kolta and Reader 1989). NE's influence increases the precision of visual processing, such as direction selectivity and velocity tuning, by modulating responses to threshold-level stimuli (Waterhouse et al. 1990a). Additionally, NE reuptake inhibitors, like atomoxetine, were found to improve cortical excitability and response accuracy in visuomotor tasks, emphasizing NE's impact on attention and sensory-motor integration within cortical circuits (Grefkes et al. 2010).

Auditory In the auditory system, noradrenergic effects are bidirectional and follow an inverted-U response profile. While minimal LC activity and low NE levels provide limited modulation, increasing LC discharge and NE release optimally enhance neuronal responses to synaptic input. However, this facilitation diminishes as LC activity and NE levels rise further, ultimately hindering neuronal responsiveness. Experimental

local administration of NE improved the selectivity of auditory cortical neurons for pure-tone frequencies (Manunta and Edeline 1997) but did not boost signal-to-noise ratios or activate subthreshold synapses (Edeline et al. 2011). These varied responses to NE are likely the result of differences in receptor expression. Slice experiments demonstrate that NE modulates GABAergic signaling differently through receptor-specific actions. NE increases GABA release by acting on α2 and β receptors, enhancing inhibitory presynaptic input, while α1 receptor activation suppresses postsynaptic GABA responses, amplifying responses to excitatory stimuli (Salgado et al. 2012). This dual action is thought to enhance sensory focus on relevant auditory signals. Recent research further demonstrated that NE enhances behavioral auditory discrimination and perceptual salience in long-term tuning of auditory cortex responses to specific tones (Martins and Froemke 2015).

2.3.3 Noradrenergic Modulation of Arousal

Recent advances in neuroscience have uncovered numerous physiological functions influenced by the interplay of central and peripheral catecholamines. One such function is the control of arousal. While the concept of arousal has an intuitive appeal, a formal, unified characterization of the term remains elusive, with researchers instead describing various aspects of arousal such as an awakening from sleep or sedation, or a heightened sense of emotional reactivity and alertness. For the purposes of this chapter, we define general arousal as a continuum of increased sensitivity to environmental stimuli (Berridge 2008). The body is in a heightened state of relative responsiveness, preparing for action through the activation of various neurological (e.g., cortical and sympathetic neural activation) and bodily systems. The physiological signs of arousal are varied, encompassing elevated heart rate, blood pressure, respiration rate, muscle tension, perspiration, and metabolic rate. The importance of precise control over arousal levels is undeniable. Dampened arousal can lead to drowsiness, sleep, and even unconsciousness (Aston-Jones and Cohen 2005). On the other hand, heightened arousal, triggered by a salient event or emotionally strong memories can facilitate attention, motivation, and learning while driving behavioral responses, but can also lead to distractibility and anxiety (Aston-Jones and Cohen 2005; Breton-Provencher et al. 2021; Sara and Bouret 2012). In 1908, Yerkes and Dodson described a nonlinear relationship between arousal and behavioral performance (Yerkes and Dodson 1908). Their study examined how task difficulty and stress affect performance in a discrimination task. Since then, numerous studies across various animal models have investigated this connection, culminating in the "Yerkes-Dodson Law," which describes an inverted U-shaped relationship between arousal and behavioral performance (Aston-Jones and Cohen 2005; Breton-Provencher et al. 2021). Cognitive tasks requiring attention are optimally performed at intermediate arousal levels, with performance declining significantly if arousal is too high or too low.

Arousal involves components across the central, sympathetic, and peripheral nervous systems, as well as the circulatory, respiratory, and visceral motor systems. Various brain regions, parts of the autonomic nervous system, and the endocrine system work collectively to modulate the levels of brain-body arousal. In the brain, neural regulation of arousal involves activation of multiple systems across the brain, including alterations in hippocampal theta oscillations (dos Santos Lima et al. 2019; Jarosiewicz and Skaggs 2004), thalamic bursting (Bastos et al. 2021; Murata and Colonnese 2018; Miller et al. 1989; McCormick and Bal 1997), and cortical activation (Tauber et al. 2024; Eisen et al. 2024; Ährlund-Richter et al. 2024). In the late 1940s, the pivotal work of Moruzzi and Magoun first identified the role of the brainstem reticular formation in mediating arousal states (Moruzzi and Magoun 1949). Activation of these regions resulted in a shift in cortical activity from a high-voltage slow-wave electroencephalogram (EEG)

signal to a low-voltage, fast activity pattern. As clinicians, Moruzzi and Magoun noted that this shift in cortical activity is similar to that seen during an arousal response to natural stimuli and is abolished during anesthesia. The brain regions involved in mediating this arousal response collectively came to be known as the ascending reticular activating system (ARAS). The central noradrenergic system, driven by the LC, is one of the major components of ARAS in the brain. In 1988, Adams and Foote developed a combined recording-infusion probe that uses electrophysiological recordings to enable precise placement of pharmacological agents in the vicinity of LC neurons (Adams and Foote 1988), enabling selective and verifiable activation of the LC. Using this technique, Berridge and Foote showed that LC activation reliably induced a shift in frontal cortical EEG activity from low-frequency, high-amplitude to high-frequency, low-amplitude, along with induction of an intense hippocampal theta rhythm (Adams and Foote 1988). Such shifts in forebrain activity, reflected in altered EEG signals, have long been established as a signature of changes in arousal states (Bonnet and Arand 2001; Makeig and Inlow 1993). Since then, numerous studies have demonstrated a causal relationship between LC-NE and arousal states. LC-NE neurons are silent during rapid eye movement or REM sleep, exhibit low activity levels during non-REM (NREM) sleep, and are most active during wakefulness and periods of high vigilance (Osorio-Forero et al. 2021; Liang et al. 2021; Swift et al. 2018; Eschenko et al. 2012; Hayat et al. 2020). Importantly, changes in LC neuronal activity precede transitions in arousal state (Aston-Jones and Cohen 2005; Breton-Provencher and Sur 2019; Foote et al. 1980), thereby implying that they play a causal role in driving these transitions (Berridge and Waterhouse 2003). Moreover, the relationship between LC-NE activation and optimal behavioral performance follows the typical Yerkes-Dodson inverted-U curve, consistent with the view that the LC mediates arousal (Aston-Jones and Cohen 2005; Breton-Provencher et al. 2021; Sara and Bouret 2012).

Control of arousal states is thought to arise through two basic aspects of LC function. First, extensive projections from the LC to various sensory regions of the cerebral cortex and thalamus enhance the accumulation of salient sensory information. Second, its numerous connections to other brain regions such as the prefrontal cortex, amygdala, and hippocampus, modulate the processing of external stimuli to drive behavioral responses. In addition, projections to other arousal centers in the brain serve to amplify LC control over vigilance states. The LC is also thought to promote wakefulness via activation of α and β1 receptors in the general regions of the medial septal area and the medial preoptic area (Berridge 2008). In the somatosensory cortex, phasic LC activation or local NE infusions inhibit spontaneous activity (Waterhouse and Navarra 2019; Waterhouse et al. 1988) and reduce response latency and jitter (Lecas et al. 2004), while facilitating cortical representation of sensory stimuli (Vazey et al. 2018). Safaai and colleagues demonstrated a coupling between phasic LC activity and cortical fluctuations that can enhance cortical responses to weaker stimuli (Safaai et al. 2015). Similar effects of LC-NE activation have been observed in the auditory (Kiissp and Vater 1989; Manunta and Edeline 1999), visual (Waterhouse et al. 1990b; McLean and Waterhouse 1994) and olfactory (Hasselmo et al. 1997; Ciombor et al. 1999) cortices. Thus, LC control of arousal states could stem from a heightened mode of sensory processing. Similarly, NE modulation over critical regions involved in learning and memory as well as motor function demonstrates its role in facilitating behavioral execution (see reviews by (Aston-Jones and Cohen 2005; Breton-Provencher et al. 2021)). LC activity in the hippocampus modulates the encoding and integration (Chowdhury et al. 2022) of spatial memories, while reinforcement signals to the PFC improve performance accuracy in subsequent trials (Breton-Provencher et al. 2022). Noradrenergic signals also enhance the responsiveness of motoneurons in the spinal cord (Fung and Barnes 1987; Witts et al. 2023) as well as pyramidal neurons in the motor cortex

(Fung and Barnes 1987; Dymecki et al. 2022), thereby driving the initiation or execution of motor responses (Breton-Provencher et al. 2021; Breton-Provencher et al. 2022). Thus, the LC appears to improve the detection and processing of salient sensory stimuli leading to a switch in vigilance states to facilitate an optimal behavioral response.

In addition to the LC, other noradrenergic cell groups in the brain contribute to certain aspects of arousal. For example, A2 cells in the nucleus of the solitary tract receive sensory feedback from the cardiovascular, respiratory, and alimentary systems via inputs from the vagal nerve, the area postrema, and direct visceral afferents of the solitary tract (Kalia and Sullivan 1982; Appleyard et al. 2007; Cunningham et al. 1994). Consequently, these cells respond to a broad array of interoceptive signals. Medullary A2 neurons are thought to engage arousal circuits by relaying gastric and cardiovascular signals to the amygdala and neurons in the shell of the NAc (Kerfoot et al. 2008; Kirouac And and Ciriello 1997; Mehendale et al. 2004). Moreover, A2 cells have been shown to innervate LC-NA neurons, providing a direct feedback link between visceral signals and the central arousal circuit in the brain (Van Bockstaele et al. 1999).

Noradrenergic activation in the brain via either the LC or the adrenal medulla results in well-defined patterns of autonomic activation. The LC sends direct connections to both the sympathetic and parasympathetic nervous system through its descending projections in the brainstem and spinal cord. In general, NE release by LC neurons increases sympathetic activity via the activation of α_1-adrenoceptors on preganglionic sympathetic neurons (Lewis and Coote 1990) and reduces parasympathetic activity via the activation of α_2-adrenoceptors on preganglionic parasympathetic neurons (Yaci et al. 2002; Unnerstall et al. 1984; Smith et al. 1995). In turn, sympathetic nerves carry NE signals to smooth muscles of the heart and sweat glands, constricting local blood vessels to induce a moderate increase in heart rate and blood pressure (Boron and Boulpaep 2009). Barosensitive C1 adrenergic cells in the rostral ventrolateral medulla respond to these changes in blood pressure and help to tightly control heart rate and blood pressure during periods of high arousal (Lipski et al. 1995). A key aspect of the central adrenergic system's involvement in arousal regulation is demonstrated through its control of pupillary activity. In addition to changes in blood flow and respiration, fluctuations in pupil size have been intricately linked to levels of sedation and alertness and have been demonstrated as a reliable index of arousal (Hou et al. 2006; Bradley et al. 2008). Numerous studies have shown that fluctuations in pupil size track both LC activity (Breton-Provencher and Sur 2019; Reimer et al. 2016) and cortical state (Reimer et al. 2014). Descending projections from the LC to noradrenergic neurons of the intermediolateral column in the spinal cord activate sympathetic control of pupil size, activating iris sphincter muscles and dilating the pupil. In parallel, LC inhibition of cholinergic preganglionic motoneurons in the Edinger-Westphal nucleus inhibits parasympathetic drive and relaxes the sphincter muscles to permit dilation (Larsen and Waters 2018). Thus, the consequences of LC activation are observable as an increase in pupil diameter (Breton-Provencher and Sur 2019; Reimer et al. 2016), increases in heart rate and blood pressure (Lightman et al. 1984; Ward and Gunn 1976), suppression of the baroreflex response (Hwang et al. 1998), and a reduction in salivation (Samuels and Szabadi 2008).

2.3.4 Fight-or-Flight and Stress Response

A particularly important circumstance of precise control over arousal levels is demonstrated by the execution of the body's stress response. In 1915, Canon first coined the term "fight-or-flight" to describe the body's stress response which compiled various visceral changes occurring as a consequence of nociceptive events, hunger, cold, exercise, and strong emotions (Cannon 1915). The stress response is an acute physiological reac-

tion to a real or perceived threat. Cognitive evaluation of sensory inputs and internal states elicits widespread bodily responses aimed at adaptation or escape from the stressful stimuli. The brain shifts to a state of hyperarousal and heightened attention, accompanied by surges of adrenaline and cortisol in the blood. This in turn increases heart rate and muscle tension, while dilating the pupils to enhance vision, increase sensory processing, and promote adaptive physiological reactions. The stress response to physical or psychological stressors involves the activation of two different networks or "axes" of cascading signals between various regions of the brain and body—sympathetic-adrenomedullary axis (SAM) and the hypothalamic-pituitary-adrenal axis (HPA). The diverse visceral and peripheral connections of adrenergic and noradrenergic neurons described in previous sections allow them to respond to a range of psychological, physical, and metabolic stressors. Multiple lines of evidence indicate that noradrenergic neurons in the brain are activated by both physical and psychological stressors. Studies of immediate early-gene expression following aversive electric shocks show activation of brainstem adrenergic and noradrenergic nuclei (Pezzone et al. 1993).

The SAM Axis The SAM axis triggers a quick, transient response to stress, thereby heightening arousal and vigilance. This allows for a rapid assessment of threats and formulation of strategic responses to tackle them. Perception of acute threats or stressors leads to the activation of the LC and other adrenergic and noradrenergic nuclei in the brainstem (Pezzone et al. 1993; Valentino and Van Bockstaele 2008). The LC is thought to receive information about stressful stimuli through multiple convergent pathways. In addition, components of the limbic circuits, mainly the prefrontal cortex, amygdala, and hippocampus are each activated by psychological stressors (McEwen et al. 2015; Roozendaal et al. 2009; Janak and Tye 2015). The interconnections between these regions and the LC create a feedback loop that regulates the stress response. The NTS in the brainstem serves as an important interface between visceral sensory signals and the brain, relaying information about physical perturbations such as pain, blood loss, inflammation, or respiratory distress (Ulrich-Lai and Herman 2009). For example, noradrenergic A2 neurons in the NTS are consistently activated by stimulation of afferent fibers of the solitary tract (Appleyard et al. 2007). Adrenergic C1 neurons in the rostral ventrolateral medulla drive an increase in sympathetic nerve activity to maintain blood pressure following hemorrhagic shock (Souza et al. 2022b). A2 neurons in the NTS trigger sympathetic responses following acute restraint stress, raising heart rate and corticosterone levels (Bundzikova-Osacka et al. 2015). NTS neurons also respond to interoceptive inputs from the gut and airways (Ran et al. 2022). Projections from the NTS relay information about these stressors to other regions of the brain, including the paraventricular nucleus (PVN) of the hypothalamus (Bailey et al. 2006) and the central amygdala (CeA) (He et al. 2022), triggering the stress response. The SAM response to these various stressors is mediated primarily by catecholamines, primarily Epi and NE from the adrenal medulla and NE from sympathetic nerves. Descending projections from the PVN, LC, and adrenal medulla through the spinal cord transmit stressor responses from the brain to various effector tissues. One such instance involves post-ganglionic activation of the chromaffin cells in the adrenal medulla, which promptly releases substantial amounts of both Epi and NE into the bloodstream. Epi and NE from the autonomic nerves and in the blood bind to adrenergic receptors in smooth muscles and various organs. Preganglionic neurons also activate the sympathetic response, elevating blood pressure, cardiac output, and metabolic activity, thereby preparing the body to either "fight" or "flee" from the perceived threat (Godoy et al. 2018). In addition, circulating Epi activates peripheral β-adrenergic receptors on vagal afferents (Roozendaal et al. 2009), sending stress signals back to the NTS and the brain, thus amplifying the stress response.

The HPA Axis The hypothalamus-pituitary-adrenal (HPA) axis recruits the endocrine system and hormonal messengers to deliver an amplified and more prolonged response to stress. Neurosecretory cells within the PVN secrete corticotropin releasing hormone (CRH, previously called corticotropin-releasing factor or CRF) into the hypophyseal portal system. CRH then stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH) into the bloodstream, stimulating the synthesis and release of glucocorticoids from the adrenal glands into the blood (cortisol in humans, corticosterone in rats and mice) (Herman et al. 1997). Glucocorticoids then bind to mineralocorticoid and glucocorticoid receptors in various stress-responsive regions of the brain to induce a behavioral response to the stressful stimulus (McEwen et al. 2015; Roozendaal et al. 2009). Furthermore, brain circuits that are responsible for regulating the stress response intersect with those involved in learning and memory, such as the LC, amygdala, hippocampus, and prefrontal cortex, thus providing a means to tailor the fight-or-flight response based on past experience and predicted outcomes (McEwen et al. 2015; Roozendaal et al. 2009; Janak and Tye 2015; McEwen 1999). While glucocorticoids are thought to be the main drivers of the HPA axis, several studies have demonstrated the influence and participation of central and peripheral catecholamines in the modulation of this stress response. For example, inhibition of postganglionic sympathetic nerves attenuated corticosterone release following chronic restraint stress (Lowrance et al. 2016). The LC and various adrenergic nuclei in the NTS express glucocorticoid receptors which allow them to be activated by the HPA response. Additionally, the amygdala, hippocampus, and medial prefrontal cortex all respond to emotionally significant stimuli, subsequently activating the PVN, LC, and other catecholaminergic cells in the ventrolateral medulla and NTS (Godoy et al. 2018; Myers 2017). Moreover, glucocorticoid receptors co-localize with adrenoreceptors, facilitating an interaction between the SAM and HPA axes (Godoy et al. 2018). The LC-NE network is also a major target of CRH. CRH immunoreactive fibers have been shown to innervate both the inner nucleus of the LC and the pericoerulear zones (Valentino et al. 1992), and are thought to boost tonic LC activity and induce anxiety-like behaviors (Curtis et al. 2012; Curtis et al. 1997; McCall et al. 2015). Interestingly, the release of CRH within the LC is regulated by glucocorticoids, (Valentino and Van Bockstaele 2008), allowing the HPA axis control over shifts in arousal and thereby modulating behavioral flexibility (Snyder et al. 2012). Thus, a hierarchical organization relays stress-related information from limbic structures to sympathetic and parasympathetic effectors, which is necessary to translate emotional stimuli into physiological responses.

The consequence of Epi release from the adrenal medulla is thought to be a largely acute and short-lived response, initiated by events in the SAM axis. However, prolonged stress and circulating glucocorticoids, released by the adrenal gland during signaling via the HPA axis, in turn controls Epi levels in the bloodstream. Numerous studies have demonstrated that PNMT activity, and hence Epi synthesis, is affected by glucocorticoids and the stress response (Wurtman and Axelrod 1966; Ross et al. 1990). It has long since been recognized that prolonged exposure to highly emotional or traumatic stressors contributes to the development of mood and anxiety disorders, including post-traumatic stress disorder (PTSD) and major depressive disorder (Roozendaal et al. 2009). A prolonged period of elevated adrenergic and noradrenergic signaling contributes to the development of these disorders. For instance, repeated stress-induced elevation of Epi induces sustained vasoconstriction and elevated blood pressure, increasing the risk for stress-induced hypertension (Ulrich-Lai and Herman 2009). *Chapter 11 of this book further details the diverse responses of the brain and body to various stressors and the maladaptation of these responses due to chronic stress.*

2.4 Disrupted Adrenergic Modulation in Disease

2.4.1 Pain

Central NE and Pain The integration of neural circuits that modulate the perception of pain includes LC-NE neurons that project axons into the spinal cord. In general, NE in the motoneurons of the spinal ventral horn facilitates nociceptive spinal reflex responses, while NE in the spinal dorsal sensory horn suppresses these nociceptive reflex responses. Increased rates of NE turnover in the dorsal spinal cord have been observed in rat models of arthritis pain, indicating that pain activates descending noradrenergic systems (Weil-Fugazza et al. 1986). The stimulation of these dorsal descending axons that release NE can exert an antinociceptive effect (Proudfit 1988; Jones 1991b). Experiments in animals and clinical studies in humans have shown that central administration of NE, or of synthetic alpha adrenergic receptor agonists into the spinal cord, produces an anti-nociceptive effect (Pertovaara 2007). Conversely, administration of α2-adrenoceptor antagonists or knocking out α2-adrenoreceptors reverses these analgesic effects and increases nociceptive responses. Selective depletion of spinal NE by intrathecal injections of DSP4 (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride) attenuates morphine-induced analgesia (Zhong et al. 1985). These experiments clearly demonstrate how important NE fibers are in descending spinal modulation.

Sympathetic Nervous System and Pain The sympathetic arm of the autonomic nervous system is critically involved in the generation of pain. In addition to its conventional role of transmitting signals from the CNS to peripheral target cells such as smooth muscle cells and secretory cells, the peripheral sympathetic noradrenergic neurons have several direct and indirect roles associated with protection of bodily tissues via pain.

While NE administration to healthy subjects does not alter mechanical sensitivity, it has several possible interactions under pathological conditions. Some of the most direct responses the sympathetic system has in reaction to noxious stimuli occur immediately after injury. When the sciatic nerve is injured by ligation or axotomy, sympathetic fibers sprout into the dorsal root ganglia (DRG), where the somata of the injured primary sensory neurons reside and wrap around these neurons with elaborate baskets of noradrenergic endings (McLachlan et al. 1993). Experimentally, nerve growth factor (NGF) can similarly induce sprouting of tyrosine hydroxylase (TH) immunoreactive fibers in the DRG (Chung et al. 1993; Jones et al. 1999). α2 adrenergic receptor expression is upregulated in both the DRG neurons and the NE axons. Some of these primary sensory DRG neurons, especially the nociceptive fibers and A-δ fibers, have been shown to depolarize directly from sympathetic NE stimulation (Birder and Perl 1999). Another direct role of NE is its role in the generation of sympathetic maintained pain after trauma. In many human clinical cases, stimulation of the sympathetic postganglionic neurons or increasing NE by intracutaneous injections can produce pain. Conversely, inhibition of these neurons via alpha-adrenergic blockers or pharmacological depletion of NE from vesicle stores with guanethidine can relieve pain (Jänig 2020).

Sympathetic neurons can also have indirect effects that contribute to pain after an injury. NE can activate the α adrenoreceptors on the blood vessels and result in vasoconstriction. NE can also activate β adrenoreceptors on macrophages and induce cytokine release. Experimental evidence has demonstrated that newly reinnervated blood vessels after lesions are hypersensitive to NE and exhibit enhanced vasoconstriction. Such NE-mediated effects can result in increasing the activity of afferent fibers, increasing inflammation, and generally modulating the experience of pain.

2.4.2 Aging and Alzheimer's Disease (AD)

Comprehensive studies on individuals aged 25 to 85 have revealed a gradual decline in noradrenaline levels across various brain regions as people

age, ultimately resulting in a loss of more than half of the initial cell density in the LC (Mann 1983). This decline is especially exacerbated in neurodegenerative disorders that accelerate neuronal deterioration such as Alzheimer's disease. The LC is one of the earliest regions to be affected by tau pathology and progressively deteriorates with the progression of AD and dementia (Jacobs et al. 2021; Braak et al. 2011; Braak and Del Tredici 2011). LC neurons progressively degenerate during the course of the disease and studies show a significant correlation between cell loss in the LC and the duration and progression of AD (German et al. 1992). Neurofibrillary changes in the LC have been detected in patients with mild cognitive impairment (Grudzien et al. 2007). Further, the number of neurofibrillary tangles correlates with the severity of dementia observed in AD patients (Bondareff et al. 1987). Experimental lesions of the LC in animal models of AD suggest a role for increased inflammation in the progression of AD. DSP4-induced degradation of LC projections significantly elevates glial inflammation as well as augmented deposits of amyloid plaques (Heneka et al. 2006). Recruitment of microglia to Aβ sites, as well as phagocytosis of plaques is disrupted with degradation of the LC. Conversely, restoring NE function rescues these impairments (Heneka et al. 2010). Together these studies suggest a key role for the noradrenergic system in the progression of AD. The early susceptibility of LC neurons to protein aggregates suggests that the noradrenergic system could be a promising target for early detection markers of AD.

2.5 Conclusion

Neural systems facilitating brain-body communication form intricate networks that integrate sensory and proprioceptive information with executive motor commands. As a pivotal chemical messenger with extensive networks across brain regions and diverse receptor expression in multiple organs within the body, we propose that NE plays a crucial role in linking neural control to physiological functions. Salient sensory and visceral stimuli alter LC-NE activity in the brain, prompting the LC to modulate the gain of sensory processing and motor output. Meanwhile, NE release through sympathetic nerves directly modulates the function of various organs, such as the heart, lungs, digestive tract, and muscles to organize coordinated responses to external stimuli. This dual role equips the noradrenergic system to facilitate processes that require integration of signals across the brain and body, such as the fight-or-flight response to stress. In addition, NE signaling in the brain influences the memory of salient events, thus allowing for flexibility in the control of physiological systems and adaptation of behavioral responses to stimuli. These diverse roles of NE offer promising prospects for a range of clinical applications, from the treatment of attention disorders and PTSD to the management of chronic pain and anesthesia.

References

Adams LM, Foote SL (1988) Effects of locally infused pharmacological agents on spontaneous and sensory-evoked activity of locus coeruleus neurons. Brain Res Bull 21(3):395–400

Ährlund-Richter S, Osako Y, Jenks KR, Odom E, Huang H, Arnold DB, Sur M (2024) Prefrontal Cortex subregions provide distinct visual and behavioral feedback modulation to the Primary Visual Cortex. bioRxiv 2024.08.06.606894

Appleyard SM, Marks D, Kobayashi K, Okano H, Low MJ, Andresen MC (2007) Visceral afferents directly activate catecholamine neurons in the solitary tract nucleus. J Neurosci 27(48):13292–13302

Aston-Jones G, Bloom FE (1981) Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. J Neurosci 1(8):887–900

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, Waterhouse B (2016) Locus coeruleus: from global projection system to adaptive regulation of behavior. Brain Res 1645:75–78

Aston-Jones G, Rajkowski J, Kubiak P, Alexinsky T (1994) Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. J Neurosci 14(7):4467–4480

Axelrod J (1962) Purification and properties of Phenylethanolamine-N-methyl transferase. J Biol Chem 237:1657–1660

Bailey TW, Hermes SM, Andresen MC, Aicher SA (2006) Cranial visceral afferent pathways through the nucleus of the solitary tract to caudal ventrolateral medulla or paraventricular hypothalamus: target-specific synaptic reliability and convergence patterns. J Neurosci 26(46):11893–11902

Bajic D, Van Bockstaele EJ, Proudfit HK (2001) Ultrastructural analysis of ventrolateral periaqueductal gray projections to the A7 catecholamine cell group. Neuroscience 104(1):181–197

Basbaum AI (ed) (2008) The senses: a comprehensive reference, vol 4, 1st edn. Elsevier, Amsterdam

Bastos AM, Donoghue JA, Brincat SL, Mahnke M, Yanar J, Correa J et al (2021) Neural effects of propofol-induced unconsciousness and its reversal using thalamic stimulation. elife 10:e60824

Berridge CW (2008) Noradrenergic modulation of arousal. Brain Res Rev 58(1):1–17

Berridge CW, Waterhouse BD (2003) The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Rev (Elsevier) 42:33–84

Berthoud HR, Neuhuber WL (2000) Functional and chemical anatomy of the afferent vagal system. Auton Neurosci 85(1–3):1–17

Bin NR, Prescott SL, Horio N, Wang Y, Chiu IM, Liberles SD (2023) An airway-to-brain sensory pathway mediates influenza-induced sickness. Nature 615(7953):660–667

Birder LA, Perl ER (1999) Expression of α2-adrenergic receptors in rat primary afferent neurones after peripheral nerve injury or inflammation. J Physiol 515(2):533–542

Bondareff W, Mountjoy CQ, Roth M, Rossor MN, Iversen LL, Reynolds GP, Hauser DL (1987) Neuronal degeneration in locus ceruleus and cortical correlates of Alzheimer disease. Alzheimer Dis Assoc Disord 1(4):256–262

Bonnet MH, Arand DL (2001) Impact of activity and arousal upon spectral EEG parameters. Physiol Behav 74(3):291–298

Boron WF, Boulpaep EL (2009) Medical physiology, 2nd edn. Saunders/Elsevier, Philadelphia

Bouret S, Sara SJ (2005) Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci 28(11):574–582

Bouret S, Duvel A, Onat S, Sara SJ (2003) Phasic activation of locus ceruleus neurons by the central nucleus of the amygdala. J Neurosci 23(8):3491–3497

Braak H, Del Tredici K (2011) The pathological process underlying Alzheimer's disease in individuals under thirty. Acta Neuropathol 121(2):171–181

Braak H, Thal DR, Ghebremedhin E, Del TK (2011) Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol 70(11):961–969

Bradley MM, Miccoli L, Escrig MA, Lang PJ (2008) The pupil as a measure of emotional arousal and autonomic activation. Psychophysiology 45(4):602–607

Brennan P, Kaba H, Keverne EB (1990) Olfactory recognition: a simple memory system. Science 250(4985):1223–1226

Breton-Provencher V, Sur M (2019) Active control of arousal by a locus coeruleus GABAergic circuit. Nat Neurosci 22(2):218–228

Breton-Provencher V, Drummond GT, Sur M (2021) Locus Coeruleus norepinephrine in learned behavior: anatomical modularity and spatiotemporal integration in targets. Front Neural Circuits 15:638007

Breton-Provencher V, Drummond GT, Feng J, Li Y, Sur M (2022) Spatiotemporal dynamics of noradrenaline during learned behavior. Nature 606(7915):732–738

Brown EN, Pavone KJ, Naranjo M (2018) Multimodal general anesthesia: theory and practice. Anesth Analg 127(5):1246–1258

Bundzikova-Osacka J, Ghosal S, Packard BA, Ulrich-Lai YM, Herman JP (2015) Role of nucleus of the solitary tract noradrenergic neurons in post-stress cardiovascular and hormonal control in male rats. Stress 18(2):221–232

Byrum CE, Guyenet PG (1987) Afferent and efferent connections of the A5 noradrenergic cell group in the rat. J Comp Neurol 261(4):529–542

Cannon WB (1915) Bodily changes in pain, hunger, fear and rage: an account of recent researches into the function of emotional excitement. D Appleton & Company, New York

Chandler DJ, Gao WJ, Waterhouse BD (2014) Heterogeneous organization of the locus coeruleus projections to prefrontal and motor cortices. Proc Natl Acad Sci USA 111(18):6816–6821

Chase T, Kopin I (1968) Stimulus-induced release of substances from Olfactory Bulb using the Push–Pull Cannula. Nature 217:466–467

Chowdhury A, Luchetti A, Fernandes G, Filho DA, Kastellakis G, Tzilivaki A, Ramirez EM, Tran MY, Poirazi P, Silva AJ (2022) A locus coeruleus-dorsal CA1 dopaminergic circuit modulates memory linking. Neuron 110(20):3374–3388.e8

Chung K, Kim HJ, Na HS, Park MJ, Chung JM (1993) Abnormalities of sympathetic innervation in the area of an injured peripheral nerve in a rat model of neuropathic pain. Neurosci Lett 162(1–2):85–88

Ciombor KJ, Ennis M, Shipley MT (1999) Norepinephrine increases rat mitral cell excitatory responses to weak olfactory nerve input via alpha-1 receptors in vitro. Neuroscience 90(2):595–606

Clark FM, Proudfit HK (1991) The projection of noradrenergic neurons in the A7 catecholamine cell group to the spinal cord in the rat demonstrated by anterograde tracing combined with immunocytochemistry. Brain Res 547(2):279–288

Coleridge HM, Coleridge JCG (1994) Pulmonary reflexes: neural mechanisms of pulmonary defense. Annu Rev Physiol 56(1):69–91

Cunningham ET, Miselis RR, Sawchenko PE (1994) The relationship of efferent projections from the area postrema to vagal motor and brain stem catecholamine-containing cell groups: an axonal transport and

immunohistochemical study in the rat. Neuroscience 58(3):635–648

Curtis AL, Lechner SM, Pavcovich LA, Valentino RJ (1997) Activation of the locus coeruleus noradrenergic system by intracoerulear microinfusion of corticotropin-releasing factor: effects on discharge rate, cortical norepinephrine levels and cortical electroencephalographic activity. J Pharmacol Exp Ther 281(1):163–172

Curtis AL, Bello NT, Connolly KR, Valentino RJ (2002) Corticotropin-releasing factor neurones of the central nucleus of the amygdala mediate locus coeruleus activation by cardiovascular stress. J Neuroendocrinol 14(8):667–682

Curtis AL, Leiser SC, Snyder K, Valentino RJ (2012) Predator stress engages corticotropin-releasing factor and opioid systems to alter the operating mode of locus coeruleus norepinephrine neurons. Neuropharmacology 62(4):1737–1745

Devilbiss DM, Waterhouse BD (2004) The effects of tonic locus ceruleus output on sensory-evoked responses of ventral posterior medial thalamic and barrel field cortical neurons in the awake rat. J Neurosci 24(48):10773–10785

Devilbiss DM, Page ME, Waterhouse BD (2006) Locus ceruleus regulates sensory encoding by neurons and networks in waking animals. J Neurosci 26(39):9860–9872

Dimitrov EL, Yanagawa Y, Usdin TB (2013) Forebrain GABAergic projections to locus coeruleus in mouse. J Comp Neurol 521(10):2373–2397

dos Santos Lima GZ, Lobao-Soares B, Corso G, Belchior H, Lopes SR, de Lima PT et al (2019) Hippocampal and cortical communication around micro-arousals in slow-wave sleep. Sci Rep 9(1):5876

Dymecki S, Bouret S, Wildner H, Waterhouse BD, Predale HK, Plummer NW et al (2022) Probing the structure and function of locus coeruleus projections to CNS motor centers. Front Neural Circuits 16:895481

Edeline JM, Manunta Y, Hennevin E (2011) Induction of selective plasticity in the frequency tuning of auditory cortex and auditory thalamus neurons by locus coeruleus stimulation. Hear Res 274(1–2):75–84

Eisen AJ, Kozachkov L, Bastos AM, Donoghue JA, Mahnke MK, Brincat SL et al (2024) Propofol anesthesia destabilizes neural dynamics across cortex. Neuron 112(16):2799–2813.e9

Ennis M, Aston-Jones G (1989) GABA-mediated inhibition of locus coeruleus from the dorsomedial rostral medulla. J Neurosci 9(8):2973–2981

Eschenko O, Magri C, Panzeri S, Sara SJ (2012) Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. Cerebral Cortex [Internet] 22:426–435

Everitt BJ, Hökfelt T, Terenius L, Tatemoto K, Mutt V, Goldstein M (1984) Differential co-existence of neuropeptide Y (NPY)-like immunoreactivity with catecholamines in the central nervous system of the rat. Neuroscience 11(2):443462

Felten DL, Sladek JR (1983) Monoamine distribution in primate brain V. Monoaminergic nuclei: anatomy, pathways and local organization. Brain Res Bull 10(2):171–284

Fernstrom JD, Fernstrom MH (2007) Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain. J Nutr 137(6):1539S–1547S

Foote SL, Aston-Jones G, Bloom FE (1980) Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. Proc Natl Acad Sci USA 77(5):3033–3037

Fung SJ, Barnes CD (1987) Membrane excitability changes in hindlimb motoneurons induced by stimulation of the locus coeruleus in cats. Brain Res 402(2):230–242

German DC, Manaye KF, White CL 3rd, Woodward DJ, McIntire DD, Smith WK, Kalaria RN, Mann DM (1992) Disease-specific patterns of locus coeruleus cell loss. Ann Neurol 32(5):667–676

Godoy LD, Rossignoli MT, Delfino-Pereira P, Garcia-Cairasco N, de Lima Umeoka EH (2018) A comprehensive overview on stress neurobiology: basic concepts and clinical implications. Front Behav Neurosci (Frontiers Media S.A.) 12:127

Grefkes C, Wang LE, Eickhoff SB, Fink GR (2010) Noradrenergic modulation of cortical networks engaged in visuomotor processing. Cereb Cortex 20(4):783–797

Groves DA, Bowman EM, Brown VJ (2005) Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat. Neurosci Lett 379(3):174–179

Grudzien A, Shaw P, Weintraub S, Bigio E, Mash DC, Mesulam MM (2007) Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. Neurobiol Aging 28(3):327–335

Gutman Y, Weil-Malherbe H (1967) Subcellular distribution of norepinephrine in uteri of some species. Nature 214:108–109

Guyenet PG (1991) Central noradrenergic neurons: the autonomic connection. Prog Brain Res 88:365–380

Hasselmo ME, Linster C, Patil M, Ma D (1997) Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. J Neurophysiol 77(6):3326–3339

Hayat H, Regev N, Matosevich N, Sales A, Paredes-Rodriguez E, Krom AJ, Bergman L, Li Y, Lavigne M, Kremer EJ, Yizhar O, Pickering AE, Nir Y (2020) Locus coeruleus norepinephrine activity mediates sensory-evoked awakenings from sleep. Sci Adv 6(15):eaaz4232

He S, Huang X, Zheng J, Zhang Y, Ruan X (2022) An NTS-CeA projection modulates depression-like behaviors in a mouse model of chronic pain. Neurobiol Dis 174:105893

Heneka MT, Ramanathan M, Jacobs AH, Dumitrescu-Ozimek L, Bilkei-Gorzo A, Debeir T, Sastre M, Galldiks N, Zimmer A, Hoehn M, Heiss WD, Klockgether T, Staufenbiel M (2006) Locus ceru-

leus degeneration promotes Alzheimer pathogenesis in amyloid precursor protein 23 transgenic mice. J Neurosci 26(5):1343–1354

Heneka MT, Nadrigny F, Regen T, Martinez-Hernandez A, Dumitrescu-Ozimek L, Terwel D, Jardanhazi-Kurutz D, Walter J, Kirchhoff F, Hanisch UK, Kummer MP (2010) Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. Proc Natl Acad Sci USA 107(13):6058–6063

Herman JP, Cullinan WE, Herman JP, Cullinan WE (1997) Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci 20:78–84

Holdefer RN, Jacobs BL (1994) Phasic stimulation of the locus coeruleus: effects on activity in the lateral geniculate nucleus. Exp Brain Res 100(3):444–452

Hou RH, Scaife J, Freeman C, Langley RW, Szabadi E, Bradshaw CM (2006) Relationship between sedation and pupillary function: comparison of diazepam and diphenhydramine. Br J Clin Pharmacol 61(6):752–760

Hulsey DR, Riley JR, Loerwald KW, Rennaker RL, Kilgard MP, Hays SA (2017) Parametric characterization of neural activity in the locus coeruleus in response to vagus nerve stimulation. Exp Neurol 289:21–30

Hwang KR, Chan SHH, Chan JYH (1998) Noradrenergic neurotransmission at PVN in locus ceruleus-induced baroreflex suppression in rats. Am J Phys Heart Circ Phys 274(4):H1284–H1292

Jacobs HIL, Riphagen JM, Ramakers IHGB, Verhey FRJ (2021) Alzheimer's disease pathology: pathways between central norepinephrine activity, memory, and neuropsychiatric symptoms. Mol Psychiatry 26(3):897–906

Jahr CE, Nicoll RA (1982) Noradrenergic modulation of dendrodendritic inhibition in the olfactory bulb. Nature 297(5863):227–229

Janak PH, Tye KM (2015) From circuits to behaviour in the amygdala. Nature 517(7534):284–292

Jänig W (2020) Sympathetic nervous system and pain. In: The senses: a comprehensive reference: volume 1-7, Second Edition, vol 5, pp 349–378

Jarosiewicz B, Skaggs WE (2004) Level of arousal during the small irregular activity state in the rat hippocampal EEG. J Neurophysiol 91(6):2649–2657

Jin H, Li M, Jeong E, Castro-Martinez F, Zuker CS (2024) A body–brain circuit that regulates body inflammatory responses. Nature 630(8017):695–703

Jodo E, Aston-Jones G (1997) Activation of locus coeruleus by prefrontal cortex is mediated by excitatory amino acid inputs. Brain Res 768(1–2):327–332

Jodo E, Chiang C, Aston-Jones G (1998) Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. Neuroscience 83(1):63–79

Jones BE (1991a) Noradrenergic locus coeruleus neurons: their distant connections and their relationship to neighboring (including cholinergic and GABAergic) neurons of the central gray and reticular formation. In: Barnes CD, Pompeiano O (eds) Progress in brain research. Elsevier, pp 15–30

Jones SL (1991b) Descending noradrenergic influences on pain. Prog Brain Res 88(C):381–394

Jones MG, Munson JB, Thompson SWN (1999) A role for nerve growth factor in sympathetic sprouting in rat dorsal root ganglia. Pain 79(1):21–29

Kaba H, Keverne EB (1988) The effect of microinfusions of drugs into the accessory olfactory bulb on the olfactory block to pregnancy. Neuroscience 25(3):1007–1011

Kaba H, Rosser A, Keverne B (1989) Neural basis of olfactory memory in the context of pregnancy block. Neuroscience 32(3):657–662

Kalia M, Sullivan JM (1982) Brainstem projections of sensory and motor components of the vagus nerve in the rat. J Comp Neurol 211(3):248–264

Kebschull JM, Garcia da Silva P, Reid AP, Peikon ID, Albeanu DF, Zador AM (2016) High-throughput mapping of single-neuron projections by sequencing of barcoded RNA. Neuron 91(5):975–987

Kerfoot EC, Chattillion EA, Williams CL (2008) Functional interactions between the nucleus tractus solitarius (NTS) and nucleus accumbens shell in modulating memory for arousing experiences. Neurobiol Learn Mem 89(1):47–60

Kiissp M, Vater M (1989) Noradrenaline enhances temporal auditory contrast and neuronal timing precision in the cochlear nucleus of the mustached bat. J Neurosci 9(12):4169–4178

Kimura Y, Tadano T, Sakai K, Miyamoto A, Kisara K (2009) Changes of ejaculation due to suppression of noradrenaline biosynthesis by diethyldithiocarbamate. Andrologia 12(1):85–91

Kirouac And GJ, Ciriello J (1997) Medullary inputs to nucleus accumbens neurons. Am J Phys Regul Integr Comp Phys 6(273):R2080–R2088

Klimaschewski L, Kummer W, Heym C (1996) Localization, regulation and functions of neurotransmitters and neuromodulators in cervical sympathetic ganglia. Microsc Res Tech 35(1):44–68

Kolta A, Reader TA (1989) Modulatory effects of catecholamines on neurons of the rat visual cortex: single cell iontophoretic studies. Can J Physiol Pharmacol 67(6):615–623

Kunst M, McMillen D, Close J, Campos J, Hupp M, Martin N, et al (2023) Whole Mouse Brain Transcriptomic Cell Type Atlas – MERSCOPE v1. Available from: https://doi.org/10.35077/g.610

Kupari J, Häring M, Agirre E, Castelo-Branco G, Ernfors P (2019) An atlas of vagal sensory neurons and their molecular specialization. Cell Rep 27(8):2508–2523. e4

Larsen RS, Waters J (2018) Neuromodulatory correlates of pupil dilation. Front Neural Circuits (Frontiers Media S.A.) 12:21

Le Pichon CE, Chesler AT (2014) The functional and anatomical dissection of somatosensory subpopulations using mouse genetics. Front Neuroanat 8:21

Lecas JC, Et P, Curie M, Bernard S (2004) Locus coeruleus activation shortens synaptic drive while decreasing spike latency and jitter in sensorimotor cortex.

Implications for neuronal integration. European Journal of Neuroscience 19:2519–2530
Lewis DI, Coote JH (1990) Excitation and inhibition of rat sympathetic preganglionic neurones by catecholamines. Brain Res 530(2):229–234
Liang Y, Shi W, Xiang A, Hu D, Wang L, Zhang L (2021) The NAergic locus coeruleus-ventrolateral preoptic area neural circuit mediates rapid arousal from sleep. Curr Biol 31(17):3729–3742.e5
Lightman SL, Todd K, Everitt BJ (1984) Ascending noradrenergic projections from the brainstem: evidence for a major role in the regulation of blood pressure and vasopressin secretion*. Exp Brain Res 55:145–151
Lipski J, Kanjhan R, Kruszewska B, Smith M (1995) Barosensitive neurons in the rostral ventrolateral medulla of the rat in vivo: morphological properties and relationship to C1 adrenergic neurons. Neuroscience 69(2):601–618
Lowrance SA, Ionadi A, McKay E, Douglas X, Johnson JD (2016) Sympathetic nervous system contributes to enhanced corticosterone levels following chronic stress. Psychoneuroendocrinology 68:163–170
Makeig S, Inlow M (1993) Lapse in alertness: coherence of fluctuations in performance and EEG spectrum. Electroencephalogr Clin Neurophysiol 86(1):23–35
Mann DMA (1983) The locus coeruleus and its possible role in ageing and degenerative disease of the human central nervous system. Mech Ageing Dev 23(1):73–94
Manunta Y, Edeline J (1997) Effects of noradrenaline on frequency tuning of rat auditory cortex neurons. Eur J Neurosci 9(4):833–847
Manunta Y, Edeline JM (1999) Effects of noradrenaline on frequency tuning of auditory cortex neurons during wakefulness and slow-wave sleep. Eur J Neurosci 11:2134–2150
Martin EM, Pavlides C, Pfaff D (2010) Multimodal sensory responses of nucleus reticularis gigantocellularis and the responses' relation to cortical and motor activation. J Neurophysiol 103(5):2326–2338
Martins ARO, Froemke RC (2015) Coordinated forms of noradrenergic plasticity in the locus coeruleus and primary auditory cortex. Nat Neurosci 18(10):1483–1492
Mather M, Clewett D, Sakaki M, Harley CW (2016) Norepinephrine ignites local hotspots of neuronal excitation: how arousal amplifies selectivity in perception and memory. Behav Brain Sci 39:e200
McCall JG, Al-Hasani R, Siuda ER, Hong DY, Norris AJ, Ford CP et al (2015) CRH engagement of the locus coeruleus noradrenergic system mediates stress-induced anxiety. Neuron 87(3):605–620
McCormick DA, Bal T (1997) Sleep and arousal: thalamocortical mechanisms. Annu Rev Neurosci 20(1):185–215
McCormick DA, Pape HC, Williamson A (1991) Actions of norepinephrine in the cerebral cortex and thalamus: implications for function of the central noradrenergic system. Prog Brain Res 88(C):293–305
McEwen BS (1999) Stress and hippocampal plasticity. Annu Rev Neurosci 22(1):105–122
McEwen BS, Bowles NP, Gray JD, Hill MN, Hunter RG, Karatsoreos IN et al (2015) Mechanisms of stress in the brain. Nat Neurosci 18(10):1353–1363
McLachlan EM, Wilfid J, Marshall D, Martin M (1993) Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. Nature 363:543–546
McLean J, Waterhouse BD (1994) Noradrenergic modulation of cat area 17 neuronal responses to moving visual stimuli. Brain Res 667(1):83–97
McLennan H (1971) The pharmacology of inhibition of mitral cells in the olfactory bulb. Brain Res 29(2):177–184
Mehendale S, Xie JT, Aung HH, Guan XF, Yuan CS (2004) Nucleus accumbens receives gastric vagal inputs. Acta Pharmacol Sin 25(3):271–275
Miller JW, Hall CM, Holland KD, Ferrendelli JA (1989) Identification of a median thalamic system regulating seizures and arousal. Epilepsia 30(4):493–500
Moruzzi G, Magoun HW (1949) Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1(1–4):455–473
Motiejunaite J, Amar L, Vidal-Petiot E (2021) Adrenergic receptors and cardiovascular effects of catecholamines. Ann Endocrinol (Paris) 82(3–4):193–197
Murata Y, Colonnese MT (2018) Thalamus controls development and expression of arousal states in visual cortex. J Neurosci 38(41):8772–8786
Myagmar BE, Flynn JM, Cowley PM, Swigart PM, Montgomery MD, Thai K et al (2017) Adrenergic receptors in individual ventricular myocytes: the beta-1 and alpha-1B are in all cells, the alpha-1A is in a subpopulation, and the beta-2 and beta-3 are mostly absent. Circ Res 120(7):1103–1115
Myers B (2017) Corticolimbic regulation of cardiovascular responses to stress. Physiol Behav 172:49–59
Okutani F, Kaba H, Takahashi S, Seto K (1998) The biphasic effects of locus coeruleus noradrenergic activation on dendrodendritic inhibition in the rat olfactory bulb. Brain Res 783(2):272–279
Osorio-Forero A, Cardis R, Vantomme G, Guillaume-Gentil A, Katsioudi G, Devenoges C, Fernandez LMJ, Lüthi A (2021) Noradrenergic circuit control of non-REM sleep substates. Curr Biol 31(22):5009–5023.e7
Paintal AS (1973) Vagal sensory receptors and their reflex effects. Physiol Rev 53(1):159–227
Perez H, Hernandez A, Almli CR (1987) Locus coeruleus stimulation modulates olfactory bulb evoked potentials. Brain Res Bull 18(6):767–770
Pertovaara A (2007) Noradrenergic pathology and pain. In: Brain norepinephrine: neurobiology and therapeutics. Cambridge University Press, pp 385–407
Pezzone MA, Sen LW, Hoffman GE, Pezzone KM, Rabin BS (1993) Activation of brainstem catecholaminergic neurons by conditioned and unconditioned aversive stimuli as revealed by c-Fos immunoreactivity. Brain Res 608(2):310–318
Poe GR, Foote S, Eschenko O, Johansen JP, Bouret S, Aston-Jones G et al (2020) Locus coeruleus: a new look at the blue spot. Nat Rev Neurosci Nat Res 21:644–659

Powley TL, Jaffey DM, McAdams J, Baronowsky EA, Black D, Chesney L et al (2019) Vagal innervation of the stomach reassessed: brain−gut connectome uses smart terminals. Ann N Y Acad Sci 1454(1):14–30

Prescott SL, Liberles SD (2022) Internal senses of the vagus nerve. Neuron 110(4):579–599

Proudfit HK (1988) Chapter 27 Pharmacologic evidence for the modulation of nociception by noradrenergic neurons. Prog Brain Res 77(C):357–370

Ran C, Boettcher JC, Kaye JA, Gallori CE, Liberles SD (2022) A brainstem map for visceral sensations. Nature 609(7926):320–326

Reimer J, Froudarakis E, Cadwell CR, Yatsenko D, Denfield GH, Tolias AS (2014) Pupil fluctuations track fast switching of cortical states during quiet wakefulness. Neuron 84(2):355–362

Reimer J, McGinley MJ, Liu Y, Rodenkirch C, Wang Q, McCormick DA, Tolias AS (2016) Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. Nat Commun 7:13289

Rinaman L (2011) Hindbrain noradrenergic A2 neurons: diverse roles in autonomic, endocrine, cognitive, and behavioral functions. Am J Physiol Regul Integr Comp Physiol 300(2):R222–R235

Rogawski MA, Aghajanian GK (1980) Modulation of lateral geniculate neurone excitability by noradrenaline microiontophoresis or locus coeruleus stimulation. Nature 283

Roozendaal B, McEwen BS, Chattarji S (2009) Stress, memory and the amygdala. Nat Rev Neurosci 10:423–433

Ross ME, Evinger MJ, Hyman SE, Carroll JM, Mucke L, Comb M, Reis DJ, Joh TH, Goodman HM (1990) Identification of a functional glucocorticoid response element in the phenylethanolamine N-methyltransferase promoter using fusion genes introduced into chromaffin cells in primary culture. J Neurosci 10(2):520–530

Safaai H, Neves R, Eschenko O, Logothetis NK, Panzeri S (2015) Modeling the effect of locus coeruleus firing on cortical state dynamics and single-trial sensory processing. Proc Natl Acad Sci USA 112(41):12834–12839

Salgado H, Garcia-Oscos F, Martinolich L, Hall S, Restom R, Tseng KY et al (2012) Pre- and postsynaptic effects of norepinephrine on γ-aminobutyric acid-mediated synaptic transmission in layer 2/3 of the rat auditory cortex. Synapse 66(1):20–28

Salmoiraghi GC, Bloom FE, Costa E (1964) Adrenergic mechanisms in rabbit olfactory bulb. Am J Physiol-Legacy Content 207(6):1417–1424

Samuels ER, Szabadi E (2008) Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part II: physiological and pharmacological manipulations and pathological alterations of locus coeruleus activity in humans. Curr Neuropharmacol 6:254–285

Sara SJ (2009) The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci 10(3):211–223

Sara SJ, Bouret S (2012) Orienting and reorienting: the locus Coeruleus mediates cognition through arousal. Neuron 76(1):130–141

Sara SJ, Hervé-Minvielle A (1995) Inhibitory influence of frontal cortex on locus coeruleus neurons. Proc Natl Acad Sci USA 92(13):6032–6036

Schwarz LA, Luo L (2015) Organization of the locus coeruleus-norepinephrine system. Curr Biol (Cell Press) 25:R1051–R1056

Schwarz LA, Miyamichi K, Gao XJ, Beier KT, Weissbourd B, DeLoach KE, Ren J, Ibanes S, Malenka RC, Kremer EJ, Luo L (2015) Viral-genetic tracing of the input-output organization of a central noradrenaline circuit. Nature 524(7563):88–92

Sharma Y, Xu T, Graf WM, Fobbs A, Sherwood CC, Hof PR et al (2010) Comparative anatomy of the locus coeruleus in humans and nonhuman primates. J Comp Neurol 518(7):963–971

Sharma N, Flaherty K, Lezgiyeva K, Wagner DE, Klein AM, Ginty DD (2020) The emergence of transcriptional identity in somatosensory neurons. Nature 577(7790):392–398

Shipley MT, Halloran FJ, de la Torre J (1985) Surprisingly rich projection from locus coeruleus to the olfactory bulb in the rat. Brain Res 329(1–2):294–299

Smith MS, Schambra UB, Wilson KH, Page SO, Hulette C, Light AR et al (1995) α2-Adrenergic receptors in human spinal cord: specific localized expression of mRNA encoding α2-adrenergic receptor subtypes at four distinct levels. Mol Brain Res 34(1):109–117

Smolen AJ (1988) Morphology of synapses in the autonomic nervous system. J Electron Microsc Tech 10(2):187–204

Snyder K, Wang WW, Han R, McFadden K, Valentino RJ (2012) Corticotropin-releasing factor in the norepinephrine nucleus, locus coeruleus, facilitates behavioral flexibility. Neuropsychopharmacology 37(2):520–530

Souza GMPR, Stornetta DS, Vitali AJ, Wildner H, Zeilhofer HU, Campbell JN et al (2022a) Chemogenetic activation of noradrenergic A5 neurons increases blood pressure and visceral sympathetic activity in adult rats. Am J Physiol Regul Integr Comp Physiol 323(4):R512–R531

Souza GMPR, Stornetta RL, Stornetta DS, Guyenet PG, Abbott SBG (2022b) Adrenergic C1 neurons monitor arterial blood pressure and determine the sympathetic response to hemorrhage. Cell Rep 38(10)

Swift KM, Gross BA, Frazer MA, Bauer DS, Clark KJD, Vazey EM, Aston-Jones G, Li Y, Pickering AE, Sara SJ, Poe GR (2018) Abnormal locus coeruleus sleep activity alters sleep signatures of memory consolidation and impairs place cell stability and spatial memory. Curr Biol 28(22):3599–3609.e4

Tafari AT, Thomas SA, Palmiter RD (1997) Norepinephrine facilitates the development of the murine sweat response but is not essential. J Neurosci 17(11):4275–4281

Tauber JM, Brincat SL, Stephen EP, Donoghue JA, Kozachkov L, Brown EN et al (2024) Propofol-

mediated unconsciousness disrupts progression of sensory signals through the cortical hierarchy. J Cogn Neurosci 36(2):394–413
Ter Horst GJ, Toes GJ, van Willigen JD (1991) Locus coeruleus projections to the dorsal motor vagus nucleus in the rat. Neuroscience 45(1):153–160
Uematsu A, Tan BZ, Ycu EA, Cuevas JS, Koivumaa J, Junyent F et al (2017) Modular organization of the brainstem noradrenaline system coordinates opposing learning states. Nat Neurosci 20(2):1602
Ulrich-Lai YM, Herman JP (2009) Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 10:397–409
Unnerstall JR, Kopajtic TA, Kuhar MJ (1984) Distribution of α2 agonist binding sites in the rat and human central nervous system: analysis of some functional, anatomic correlates of the pharmacologic effects of clonidine and related adrenergic agents. Brain Res Rev 7(1):69–101
Valentino RJ, Van Bockstaele E (2008) Convergent regulation of locus coeruleus activity as an adaptive response to stress. Eur J Pharmacol 583(2–3):194–203
Valentino RJ, Page M, Van Bockstaele E, Aston-Jones G (1992) Corticotropin-releasing factor innervation of the locus coeruleus region: distribution of fibers and sources of input. Neuroscience 48(3):689–705
Van Bockstaele EJ, Colago EEO, Valentino RJ, Van Bockstaele E (1998) Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites: substrate for the co-ordination of emotional and cognitive limbs of the stress response. J Neuroendocrinol 10:743–757
Van Bockstaele EJ, Peoples J, Telegan P (1999) Efferent projections of the nucleus of the solitary tract to peri-locus coeruleus dendrites in rat brain: evidence for a monosynaptic pathway. J Comp Neurol 412(3):410–428
Vazey EM, Moorman DE, Aston-Jones G (2018) Phasic locus coeruleus activity regulates cortical encoding of salience information. Proc Natl Acad Sci USA 115(40):E9439–E9448
Wagatsuma A, Okuyama T, Sun C, Smith LM, Abe K, Tonegawa S (2018) Locus coeruleus input to hippocampal CA3 drives single-trial learning of a novel context. Proc Natl Acad Sci USA 115(2):E310–E316
Ward DG, Gunn CG (1976) Locus coeruleus complex: elicitation of a pressor response and a brain stem region necessary for its occurence. Brain Res 107(2):401–406
Waterhouse BD, Navarra RL (2019) The locus coeruleus-norepinephrine system and sensory signal processing: a historical review and current perspectives. Brain Res 1709:1–15
Waterhouse BD, Sessler FM, Jung-Tung C, Woodward DJ, Azizi SA, Moises HC (1988) New evidence for a gating action of norepinephrine in central neuronal circuits of mammalian brain. Brain Res Bull 21(3):425–432
Waterhouse BD, Ausim Azizi S, Burne RA, Woodward DJ (1990a) Modulation of rat cortical area 17 neuronal responses to moving visual stimuli during norepinephrine and serotonin microiontophoresis. Brain Res 514(2):276–292
Waterhouse BD, Ausim Azizi S, Burne RA, Woodward DJ (1990b) Modulation of rat cortical area 17 neuronal responses to moving visual stimuli during norepinephrine and serotonin micro iontophoresis. Brain Res 514(2):276–292
Wehrwein EA, Orer HS, Barman SM (2016) Overview of the anatomy, physiology, and pharmacology of the autonomic nervous system. Compr Physiol 6(3):1239–1278
Weil-Fugazza J, Godefroy F, Manceau V, Besson JM (1986) Increased norepinephrine and uric acid levels in the spinal cord of arthritic rats. Brain Res 374(1):190–194
Witts EC, Mathews MA, Murray AJ (2023) The locus coeruleus directs sensory-motor reflex amplitude across environmental contexts. Curr Biol 33(21):4679–4688.e3
Wurtman RJ, Axelrod J (1966) Control of enzymatic synthesis of adrenaline in the adrenal medulla by adrenal cortical steroids. J Biol Chem 241(10):2301–2305
Xu YL, Reinscheid RK, Huitron-Resendiz S, Clark SD, Wang Z, Lin SH et al (2004) Neuropeptide S: a neuropeptide promoting arousal and anxiolytic-like effects. Neuron 43(4):487–497
Yaci ED, Rampin O, Calas A, Jestin A, McKenna KE, Leclerc P et al (2002) α2a and α2c adrenoceptors on spinal neurons controlling penile erection. Neuroscience 114(4):945–960
Yao Z, van Velthoven CTJ, Kunst M, Zhang M, McMillen D, Lee C et al (2023) A high-resolution transcriptomic and spatial atlas of cell types in the whole mouse brain. Nature 624(7991):317–332
Yerkes RM, Dodson JD (1908) The relation of strength of stimulus to rapidity of habit-formation. J Comp Neurol Psychol 18:459–482
Yu AJ, Dayan P (2005) Uncertainty, neuromodulation, and attention. Neuron 46(4):681–692
Zeng H, Yao Z, van Velthoven C, Smith KA, Tasic B, Lee C, et al (2023) Whole Mouse Brain Transcriptomic Cell Type Atlas – 10x scRNAseq whole brain. [Dataset]. Available from https://assets.nemoarchive.org/dat-qg7n1b0
Zeng WZ, Marshall KL, Min S, Daou I, Chapleau MW, Abboud FM, Liberles SD, Patapoutian A (2018) PIEZOs mediate neuronal sensing of blood pressure and the baroreceptor reflex. Science 362(6413):464–467
Zhang J, Chen R, Wen L, Fan Z, Guo Y, Hu Z, Miao Y (2021) Recent progress in the understanding of the effect of sympathetic nerves on hair follicle growth. Front Cell Dev Biol 9:736738
Zhao Q, Yu CD, Wang R, Xu QJ, Dai Pra R, Zhang L et al (2022) A multidimensional coding architecture of the vagal interoceptive system. Nature 603(7903):878–884
Zhong F-X, Ji X-Q, Tsou K (1985) Intrathecal DSP4 selectively depletes spinal noradrenaline and attenuates morphine analgesia. Eur J Pharmacol 116(3):327–330