Neural Plasticity

New Insights into the Role of the Locus Coeruleus-Noradrenergic System in Memory and Perception Dysfunction

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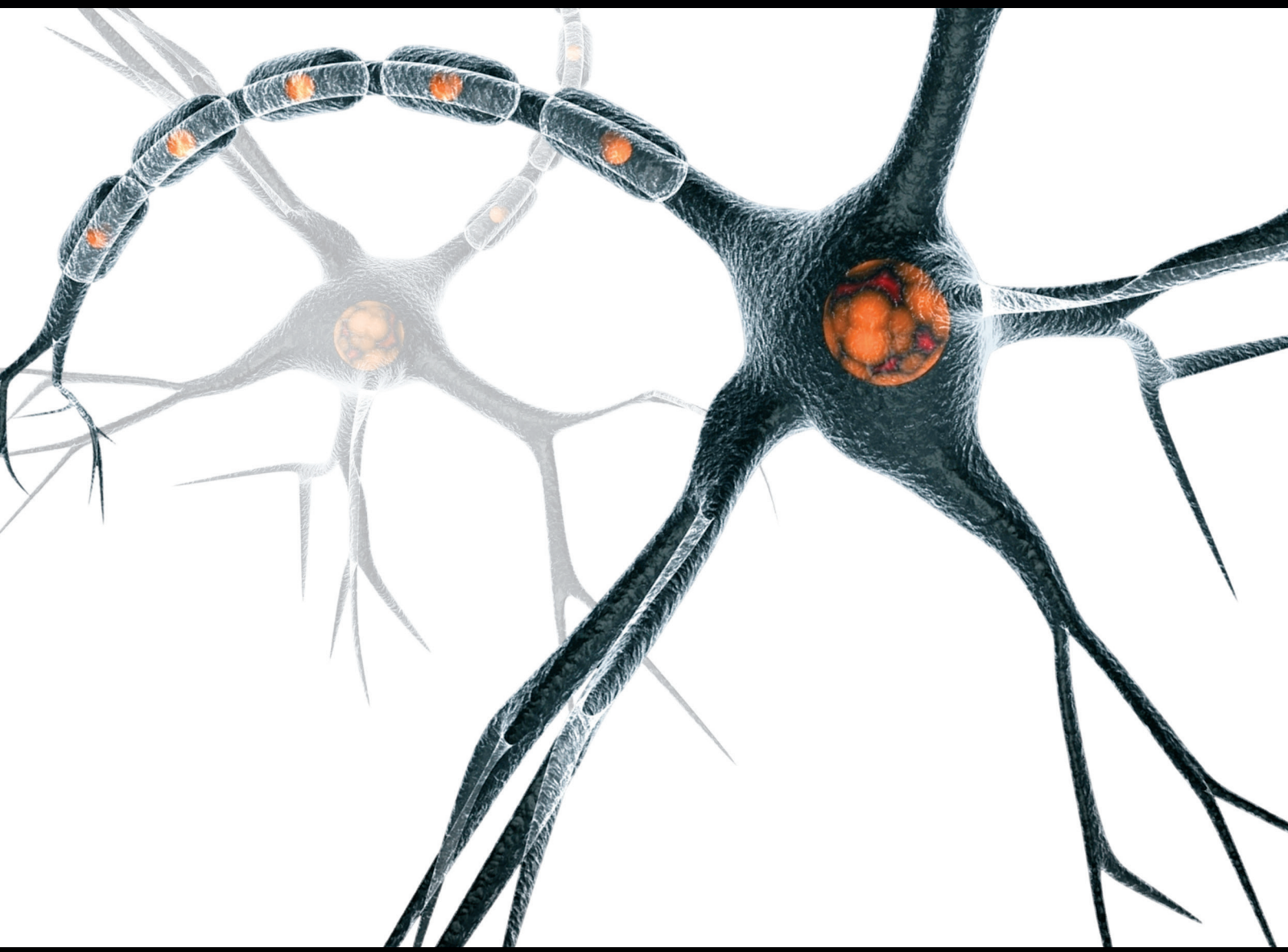

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Contents

New Insights into the Role of the Locus Coeruleus-Noradrenergic System in Memory and Perception Dysfunction
O. Eschenko, P. B. Mello-Carpes, and N. Hansen
Volume 2017, Article ID 4624171, 3 pages

Locus Coeruleus and Dopamine-Dependent Memory Consolidation
Miwako Yamasaki and Tomonori Takeuchi
Volume 2017, Article ID 8602690, 15 pages

Down but Not Out: The Consequences of Pretangle Tau in the Locus Coeruleus
Termpanit Chalermpalanupap, David Weinshenker, and Jacki M. Rorabaugh
Volume 2017, Article ID 7829507, 9 pages

Genesis and Maintenance of Attentional Biases: The Role of the Locus Coeruleus-Noradrenaline System
Mana R. Ehlers and Rebecca M. Todd
Volume 2017, Article ID 6817349, 15 pages

The Longevity of Hippocampus-Dependent Memory Is Orchestrated by the Locus Coeruleus-Noradrenergic System
Niels Hansen
Volume 2017, Article ID 2727602, 9 pages

Could LC-NE-Dependent Adjustment of Neural Gain Drive Functional Brain Network Reorganization?
Carole Guedj, David Meunier, Martine Meunier, and Fadila Hadj-Bouziane
Volume 2017, Article ID 4328015, 12 pages

Noradrenergic Modulation of Cognition in Health and Disease
Olga Borodovitsyna, Matthew Flamini, and Daniel Chandler
Volume 2017, Article ID 6031478, 14 pages

Hindawi
Neural Plasticity
Volume 2017, Article ID 4624171, 3 pages
https://doi.org/10.1155/2017/4624171

Editorial

New Insights into the Role of the Locus Coeruleus-Noradrenergic System in Memory and Perception Dysfunction

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From an evolutionary perspective, perception and memory are fundamental capacities of living beings providing adaptive behavior that is necessary for survival in ever-changing environment. Conscious and unconscious perception is generated by the interaction between many brain regions following the transduction of sensory stimuli. Sensory processing leads to cortical integration of the sensory impressions that are eventually converted to memory representations; the efficiency of sensory integration and memory retrieval underlies adaptive behavior. Everyday activities as simple as, for example, drinking water could be differentially perceived depending on an individual's emotional and arousal state. The contextual, environmental, and emotional importance of the perceived stimuli determines if the subjective experiences are subsequently remembered.

The locus coeruleus (LC) is the small nucleus in the dorsal pons comprising the main source of noradrenaline (NA) in the forebrain via its diffuse projections [1]. The LC's noradrenergic neurons are activated to aversive, rewarding, or other salient stimuli, as well as during transition from sleep to wakefulness [2–4]. Following LC activation, NA is simultaneously released from the LC terminals in the multiple brain regions [1, 5] and facilitates both local and long-range network processing as well as the experience-triggered synaptic plasticity [6–8].

In general, cognitive flexibility and adaptive behavior greatly benefit from the fact that sensory experiences, once generated by a sensory-driven network, are consequently stored within a memory supporting network with the hippocampal formation as a key element. Moreover, sensory representations are integrated with the contextual and emotional information and the retrieval of these stored associations facilitates behavioral response selection. Both the perception and the memory of events are modulated by activation of adrenoreceptors. The LC contributes to the manifold of mechanisms underlying perception and experience-induced plasticity by NA-dependent regulation of the neuronal excitability or alteration of the signal to noise ratio [6, 7, 9].

In this synopsis of the special issue, we initially focus on the role of LC for declarative memory that comprises memory about events (episodic memory) or facts (semantic memory) and mainly relies on the hippocampal formation [10]. In vivo and in vitro studies showed that a high-frequency microstimulation of the LC facilitates cellular processes related to memory formation such as synaptic long-term depression and/or potentiation in the hippocampus [11, 12]. Besides, the activation of the LC-NA system is known to facilitate memory retrieval [13] and seems to be involved in memory persistence [14].

We thus asked the following.

(1) How is the LC involved in the hippocampus-dependent memory at the synaptic and microcircuit level? N. Hansen has chronologically reviewed the latest literature addressing the role of NA modulation for different stages of information processing such as encoding, consolidation, retrieval, and reconsolidation. He focuses on studies that support the role of LC in promoting hippocampal long-term plasticity

and memory storage. Furthermore, he elucidates the critical nodes, such as the amygdala and prefrontal cortex, within a large-scale memory supporting network, whose activity in turn is modulated by NA. Finally, he proposes that the persistency of declarative memory is primed by the LC activity. M. Yamasaki and T. Takeuchi explain in their article how LC activity influences synaptic processes underlying memory consolidation in the hippocampus. They provide electrophysiological, immunohistochemical, and optogenetic evidence for the dopamine D1/5 receptor's involvement in the persistence of hippocampal synaptic plasticity and in the behavioral expression of memory. Furthermore, they discuss the role of the LC-dopamine system in mediating the environmental novelty signal and novelty-associated memory augmentation.

(2) Is the LC-NA system also involved at the macrocircuit level? Does NA mediate the optimization of cognition and behavior ensuring cognitive and behavioral flexibility or enhanced memories? To answer this question, C. Guedj et al. investigated cortical gamma oscillations and tested the hypothesis that the coherence in gamma rhythm drives the reorganization of brain networks. According to the theory of Aston-Jones [15], NA release increases the neural gain. C. Guedj et al. suggested that the neural gain is modified by local NA release leading to the amplitude increase of gamma oscillations. This, yet hypothetic, mechanism may enhance neuronal communication and thus optimize functioning of the long-range brain networks. However, this hypothesis and proposed mechanism of the LC-mediated regulation of the brain network dynamics await the direct experimental evidence from electrophysiological studies.

(3) How does the LC contribute to associative learning? This fundamental question addresses another type of memory: the implicit memory that involves associative and nonassociative learning. The cerebellum and the amygdala are critical for associative learning. M. R. Ehlers and R. M. Todd pursued the attention-related activity of LC and proposed that the LC-NA system is important for generating selective attention through associative learning in order to prioritize relevant environmental information. Specifically, they address a difference in NA availability among ADRA2b polymorphisms and make a link to psychopathology by discussing possible determinants for the development of attentional biases. They report how the LC-NA system influences aversive and appetitive conditioning in the course of associative learning and relate their findings to psychiatric disorders such as anxiety, depression, and addiction.

(4) In the next section, we attempt to integrate the knowledge about the LC involvement in memory mechanisms at the synaptic, microcircuit, and network level in the context of human psychiatric disorders associated with memory and perception dysfunction. O. Borodovitsyna et al. reviewed the role of the LC-NA system in the pathophysiology of neurological disorders such as Parkinson's disease, neuropsychiatric disorders such as Alzheimer's disease, and psychiatric disorders such as attention deficit and hyperactive disorder and schizophrenia. They provide an elaborate overview on relating the functional changes in the LC-NA system with the cognitive symptoms associated with these disorders. Understanding the role of LC in cognitive dysfunction might lead to novel approaches restoring the LC function that might in turn help in developing better treatment for these patients. The article by T. Chalermpalanupap et al. pointed out the potential role of hyperphosphorylated tau protein in the LC as a sign of neurodegeneration and progression of Alzheimer's disease. Reviewing data obtained using different animal models, they question if the hyperphosphorylated tau protein accumulates in LC neurons, impairs the LC function, and also spreads throughout the brain from the NA release sites when the LC is phasically firing; answering these questions could generate new treatment strategies.

Taken together, in this special issue, we provide strong and diverse evidence for the crucial involvement of the LC-NA system in perception, memory, and behavior. Finally, the role of LC in pathophysiology of human brain disorders associated with memory and perception dysfunction is delineated, and potential starting points for treatment strategies are highlighted.

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P. B. Mello-Carpes
N. Hansen

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Review Article

Locus Coeruleus and Dopamine-Dependent Memory Consolidation

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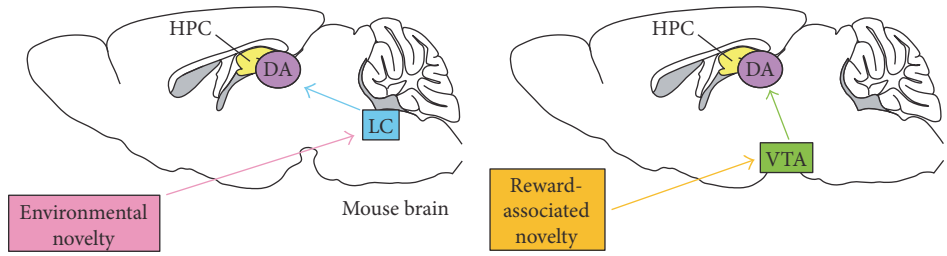
Most everyday memories including many episodic-like memories that we may form automatically in the hippocampus (HPC) are forgotten, while some of them are retained for a long time by a memory stabilization process, called initial memory consolidation. Specifically, the retention of everyday memory is enhanced, in humans and animals, when something novel happens shortly before or after the time of encoding. Converging evidence has indicated that dopamine (DA) signaling via D_1/D_5 receptors in HPC is required for persistence of synaptic plasticity and memory, thereby playing an important role in the novelty-associated memory enhancement. In this review paper, we aim to provide an overview of the key findings related to D_1/D_5 receptor-dependent persistence of synaptic plasticity and memory in HPC, especially focusing on the emerging evidence for a role of the locus coeruleus (LC) in DA-dependent memory consolidation. We then refer to candidate brain areas and circuits that might be responsible for detection and transmission of the environmental novelty signal and molecular and anatomical evidence for the LC-DA system. We also discuss molecular mechanisms that might mediate the environmental novelty-associated memory enhancement, including plasticity-related proteins that are involved in initial memory consolidation processes in HPC.

1. Introduction

Many people have vivid memories of the first dinner date with their partner, including details like the name of the restaurant and the food they had. In contrast, it is very difficult to remember what you had for dinner a few weeks ago. Most everyday memories, including episodic-like memories that we may form automatically in the hippocampus (HPC) [1–3], are forgotten, whereas some of them are retained for a long time by a memory stabilization process (initial memory consolidation). Initial selective retention occurs when something novel or salient happens shortly before or after the time of memory encoding, as in "flashbulb memory" [4, 5]. Unexpected novel events create a "halo" of enhanced memory, triggering an initial memory consolidation which extends not only forwards but also backwards in time, boosting retention of trivial memories that would normally be forgotten. Thus, initial consolidation serves as the "gate" to long-term memory, so that only a subset of information is retained for long enough to be subject to stabilization in the neocortex via a complementary process of "systems memory consolidation" [6, 7].

Animal studies of novelty-associated enhancement of memory persistence have enabled analysis of possible mechanisms [8–13] and established that novelty-triggered initial memory consolidation is sensitive to blockade of dopamine (DA) D_1/D_5 receptors and protein synthesis inhibitors in HPC. Pharmacological studies of hippocampal synaptic plasticity have supported the notion that D_1/D_5 receptors act as a gating mechanism for long-term persistence of plastic changes [14, 15]. However, the literature remains unclear and often contradictory regarding the neuronal source of DA in HPC. An influential hypothesis called the "HPC-VTA (ventral tegmental area) loop" model, proposed over a decade ago [16], postulates that tyrosine hydroxylase- (TH^+-)



(a) LC-HPC system (b) VTA-HPC system

Figure 1: Two distinct novelty systems. There are two types of novelty: "environmental novelty" (e.g., new environment with objects never seen before) and "reward-associated novelty" (e.g., new reward in an unexpected location). They are associated with release of dopamine (DA) in the hippocampus (HPC) but might be processed by different systems with different time windows. (a) The locus coeruleus- (LC-) HPC system mediates environmental novelty which modulates the retention of memory with a broad time window (~1 hr). (b) The ventral tegmental area- (VTA-) HPC system might mediate reward-associated novelty which modulates the memory with a narrow time window.

expressing neurons of VTA project to the hippocampal formation [17, 18] and release DA under circumstances of novelty or surprise [16, 19]. Nevertheless, VTA-TH$^+$ axons are sparse in HPC [17, 18], raising a possibility that other sources of DA, including dense TH$^+$ axons from the locus coeruleus (LC), might play a significant role [20, 21].

To seek the neuronal source of hippocampal DA that mediates the beneficial effect of novelty on memory persistence, we combined an optogenetic approach with an everyday memory task in mice. Surprisingly, we found that LC-TH$^+$ neurons, originally defined by their canonical noradrenaline (NA) signaling, mediate postencoding novelty-associated enhancement of memory retention in a manner consistent with possible corelease of DA along with NA in HPC [22] (Figure 1(a)). Our results are complemented by the subsequent direct detection of DA corelease from LC axons in HPC [23]. In this review paper, we discuss the following issues with focus on the LC-DA system: (i) a role of hippocampal D_1/D_5 receptors in the novelty-induced memory enhancement, (ii) two distinct novelty systems (VTA-HPC and LC-HPC systems) of dopamine-releasing (DAergic) memory modulation, (iii) brain areas that might convey environmental novelty signal to HPC, (iv) molecular and anatomical basis for D_1/D_5 receptor-mediated signaling in HPC, and (v) proteins that might mediated the environmental novelty-associated memory enhancement in HPC.

2. Novelty-Induced Memory Enhancement Depends on D_1/D_5 Receptors in HPC

Activity-dependent hippocampal synaptic plasticity (long-term potentiation (LTP) and long-term depression (LTD)) may underpin the neural mechanisms of hippocampus-dependent learning and memory [3, 13, 24, 25]. Frey and colleagues [26] established the separate existence of early- and late-forms of LTP (E-LTP and L-LTP, resp.) in the hippocampal CA1 region, the latter being defined as protein synthesis dependent. Their work also provided the first experimental evidence suggesting that neuromodulators, especially DA, play a significant role in the transition from E-LTP to L-LTP at CA3–CA1 synapses [27]. DA effects are essentially heterosynaptic rather than homosynaptic (i.e., activity of DAergic inputs affect the strength of other synapses). Hippocampal D_1/D_5 receptors play a specific role in control of temporal persistence of LTP at CA3–CA1 synapses ex vivo [12, 14, 15, 28–30]. In awake animals, D_1/D_5 receptor activation is crucial for persistence of LTP in CA1, confirming the results ex vivo [10, 28]. Pharmacological manipulations of hippocampal D_1/D_5 receptors also indicate that DA is required for the persistence of memories including aversive contextual [31–34], spatial [35, 36], object recognition [33] and paired associate [37] learning. Interestingly, Karunakaran and colleagues showed that learning-induced plasticity of hippocampal parvalbumin neurons was specifically required for long-term memory consolidation through D_1/D_5 receptors [38]. Although hippocampal D_1/D_5 receptors may play a disproportionate role in the persistence of hippocampal memory, it has also been implicated in facilitating the induction of E-LTP (reviewed in [21]) and, thereby, the entry of information into earlier memory [39].

Since available pharmacological agonists and antagonists of dopamine D_1-like receptors do not discriminate D_1 and D_5 receptors [40], numerous gene knockout studies were conducted in order to elucidate the precise function of D_1 and D_5 receptors in roles of hippocampal synaptic plasticity and memory [41–47] (reviewed in [21]). Yet, differentiating the function of hippocampal D_1 and D_5 receptors may seem like a daunting task, because there is a caveat in global knockout studies in that they lack regional selectivity. To overcome this issue, Sarinana and colleagues developed knockout mice lacking either D_1 or D_5 receptors selectively in granule cells of the dentate gyrus (DG) [48]. They demonstrated that DG-D_1 receptor deletion, but not DG-D_5 receptor deletion, impairs persistence of memory in contextual fear conditioning, highlighting the role of DG-D_1 receptors in gating persistence of hippocampus-dependent memory (but also see [28]). It should be noted, however, that D_5 receptor mRNA is also expressed strongly in the CA3 and CA1 [48] and LTP at CA3–CA1 synapses ex vivo and spatial memory are impaired in D_5 receptor global knockout mice [47]. Thus, it is also possible that hippocampal D_5 receptor outside DG could have an important role in the persistence of hippocampus-dependent memory.

There are many lines of evidence suggesting that the persistence of memory is determined largely by neural activity

that occurs at the time of memory encoding. However, the synaptic tagging and capture (STC) hypothesis of protein synthesis-dependent LTP, developed by Frey and Morris [49–51], offers the intriguing but distinct perspective that the persistence of memory is also dependent on independent neural activity afferent to the same pool of neurons mediating synaptic plasticity that occurs before or after memory traces are encoded. According to this hypothesis, the local setting of "synaptic tags" at activated glutamatergic synapses during memory encoding can be dissociated from synthesis and distribution of plasticity-related proteins (PRPs) that is induced by surrounding events (e.g., unexpected novel events). PRPs are then captured by synaptic tags in order to stabilize synaptic changes—a process that is critical for initial memory consolidation.

Indeed, *in vivo* electrophysiological experiments showed that exploration of a novel environment results in facilitation of persistence of synaptic plasticity in the CA1 area [52]. This novelty-associated facilitation of persistence of synaptic plasticity in CA1 was prevented by a D_1/D_5 receptor antagonist [10]. Also, considering that exploration of a novel environment leads to upregulation of immediate early genes (IEGs) such as *Arc*/*Arg3.1* and *Homer1a*/*Vesl-1S* [8, 53], the STC hypothesis predicts that unrelated novelty exploration before or after memory encoding should enhance the persistence of a recently encoded memory [3]. This prediction was first confirmed using a hippocampus-dependent inhibitory avoidance task in rats [11]. Our group has developed an "everyday" memory task for rats and mice whose use has revealed that (i) unrelated novel experiences can facilitate the persistence of spatial memory and (ii) this novelty-induced enhancement of memory persistence was prevented by the intrahippocampal injection of a D_1/D_5 receptor antagonist (but not by a β-adrenoceptor receptor antagonist), or by blockade of hippocampal protein synthesis [12, 13, 22]. Complementary results have been obtained using different learning tasks including inhibitory avoidance, taste memory, object recognition, and contextual fear conditioning [54–58]. Interestingly, Moncada and colleagues showed that novelty-induced memory persistence is also sensitive for hippocampal β-adrenoceptor blockade in inhibitory avoidance test [56], in line with *in vivo* electrophysiological results that there are a D_1/D_5 receptor-independent mechanism of STC hypothesis [59]. Recently, Nomoto and colleagues elegantly showed that a D_1/D_5 receptor-dependent mechanism shared hippocampal neural ensemble for a weak object recognition memory and unrelated novelty is necessary for novelty-induced enhancement of memory persistence [60].

3. Two Distinct Novelty Systems of Dopaminergic Memory Modulation in HPC

The prevailing "HPC-VTA loop" model of DAergic consolidation [16] postulates that novelty-associated enhancement of hippocampus-dependent memory is mediated by a subiculum-accumbens-pallidum-VTA-HPC pathway, an idea supported by animal and human studies [32, 61–63]. If this hypothesis holds, then it follows that HPC would receive an innervation from VTA-TH^+ neurons, environmental novelty would activate VTA-TH^+ neurons, and activation of VTA-TH^+ neurons should be necessary and sufficient for novelty-induced enhancement of memory persistence. However, TH^+ axons from VTA mainly target to the ventral HPC [17, 18, 23, 64, 65] and TH^+ neurons represent only 10% of hippocampus-projecting neurons in VTA [17], resulting in a sparse projection in the dorsal HPC [22, 23]. Optetrode recordings revealed that VTA-TH^+ neurons were slightly activated by environmental novelty [22, 66]. Postencoding optogenetic activation of VTA-TH^+ neurons was without a significant effect on memory persistence. Moreover, pharmacological blockade of VTA-TH^+ neurons during environmental novelty had no effect on novelty-associated memory enhancement [22]. Importantly, the impact of "environmental novelty" may differ qualitatively from that of "reward-associated novelty." Reward expectancy is a critical component of the execution of learned actions until they become habitual [67]. Longstanding data point that the substantia nigra (SN)/VTA system thought to play important role for processing unexpected reward [68–70]. Such reward signals are primarily coded by DA, which modulates the synaptic connections in the striatum within a narrow time window [71]. Considering that memory retention is also enhanced by reward magnitude [12, 22, 72], we now hypothesize that VTA-HPC system might mediate reward-associated novelty which modulates the retention of memory with a narrow time window (Figure 1(b)). Keeping with this hypothesis, there was a narrow time window for impact of pharmacological VTA inactivation on both synaptic plasticity *in vivo* and memory in the passive avoidance task [73]. Optogenetic activation of hippocampus-projecting VTA-TH^+ axons can bidirectionally modulate CA3–CA1 synaptic responses ex vivo [74], and optogenetic activation of VTA-TH^+ axons in HPC at the time of learning enhances spatial memory after 1 hr [66]. Interestingly, VTA activation associated with visual novelty did not correlate with memory enhancement in humans [75]. In contrast, recent study in humans have demonstrated that postlearning SN/VTA-hippocampal interactions contribute to preferential retention of episodic memory that are learned in high-reward contexts [76].

Considering that DA acts not only as a neurotransmitter in its own right but also as the precursor for NA, TH^+ axons originating from the LC (A6, in rat nomenclature) [77] are another potential source of DA in HPC. The LC has long been implicated in novelty, attention, arousal, and cognition [78–83], and its firing is tied to distinct changes in neocortical activation during sleep [84]. The LC receives prominent direct inputs from many cortical and subcortical areas and sends extensive projections throughout the brain and spinal cord with the exception of the basal ganglia and SN, all of which are dense with axonal projections or cell bodies of DAergic SN/VTA neurons [85, 86]. Dense innervation of all hippocampal areas by LC axons has been demonstrated by prior anatomical studies (Figure 2(a)) [87–93]. Recently, cell type-specific tract tracing experiments have confirmed these observations and further established that TH^+ axons from LC far outnumber those from VTA (Figure 2(b)) [22, 23]. The LC has two different types of firing patterns: constant "tonic" activity (1–3 Hz) and intermittent "phasic"

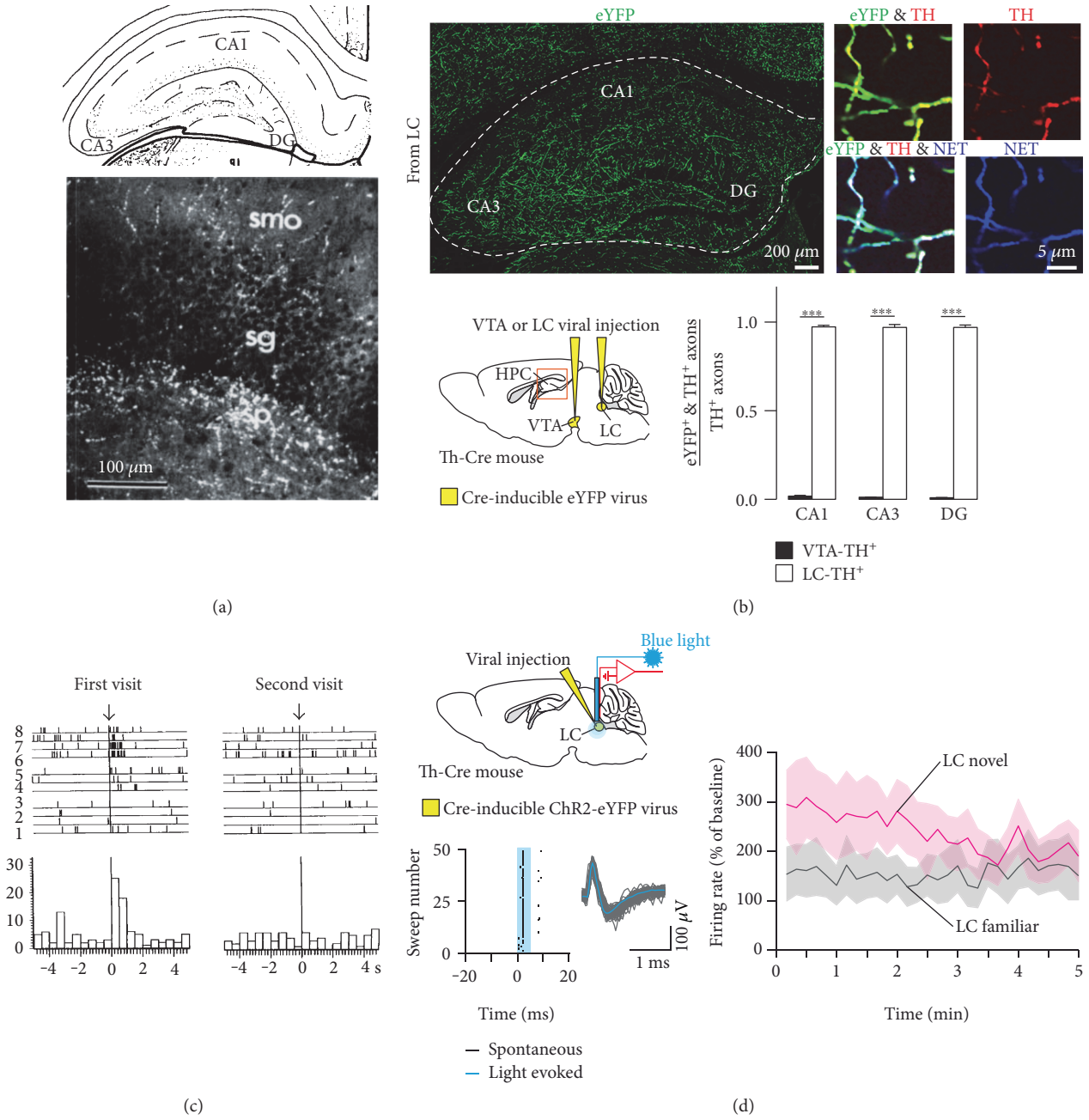


FIGURE 2: Hippocampal projections from LC neurons and increased LC neuron activity by environmental novelty. (a) Immunofluorescence of DβH in HPC. (a) is reproduced from [88]. (b) TH^+ axons in the dorsal HPC originate from LC-TH^+ neurons. Quantification shows stronger TH^+ projections from LC than from VTA in CA1, CA3, and DG. $^{***}p < 0.001$, paired t-test. (b) is reproduced from [22]. (c) Response to novelty and its habituation in LC neurons. (c) is reproduced from [96]. (d) LC-TH^+ neurons show strong response to environmental novelty that habituates over 5 min. (d) is reproduced from [22].

impulse activity (8–10 Hz) [78], that have been correlated to different behavioural states [94]. The LC neurons are activated in response to environmental novelty that habituates over time (Figures 2(c) and 2(d)) [22, 95, 96].

Pharmacological inhibition of LC prevents the beneficial effect of environmental novelty on memory persistence [22]. Critically, postencoding optogenetic activation of LC-TH^+ neurons mimics this environmental novelty effect (Figure 3(d)). Surprisingly, this LC-TH^+ neuron photoactivation-driven memory enhancement is sensitive to hippocampal D_1/D_5 receptor blockade and resistant to β-adrenoceptor blockade (Figure 3(d)). In line with these results, electrical activation of LC results in persistent synaptic plasticity at CA3–CA1 synapses *in vivo*, which is prevented by D_1/D_5 receptor antagonist (Figure 3(b)) [52]. Furthermore, selective optogenetic activation of hippocampus-projecting LC-TH^+ axons mediates a D_1/D_5 receptor-sensitive and β-adrenoceptor-resistant enhancement of synaptic transmission and LTP at CA3–CA1 synapses ex vivo [22], consistent with the idea that LC-TH^+ might release DA in HPC [20, 97]. Our results are

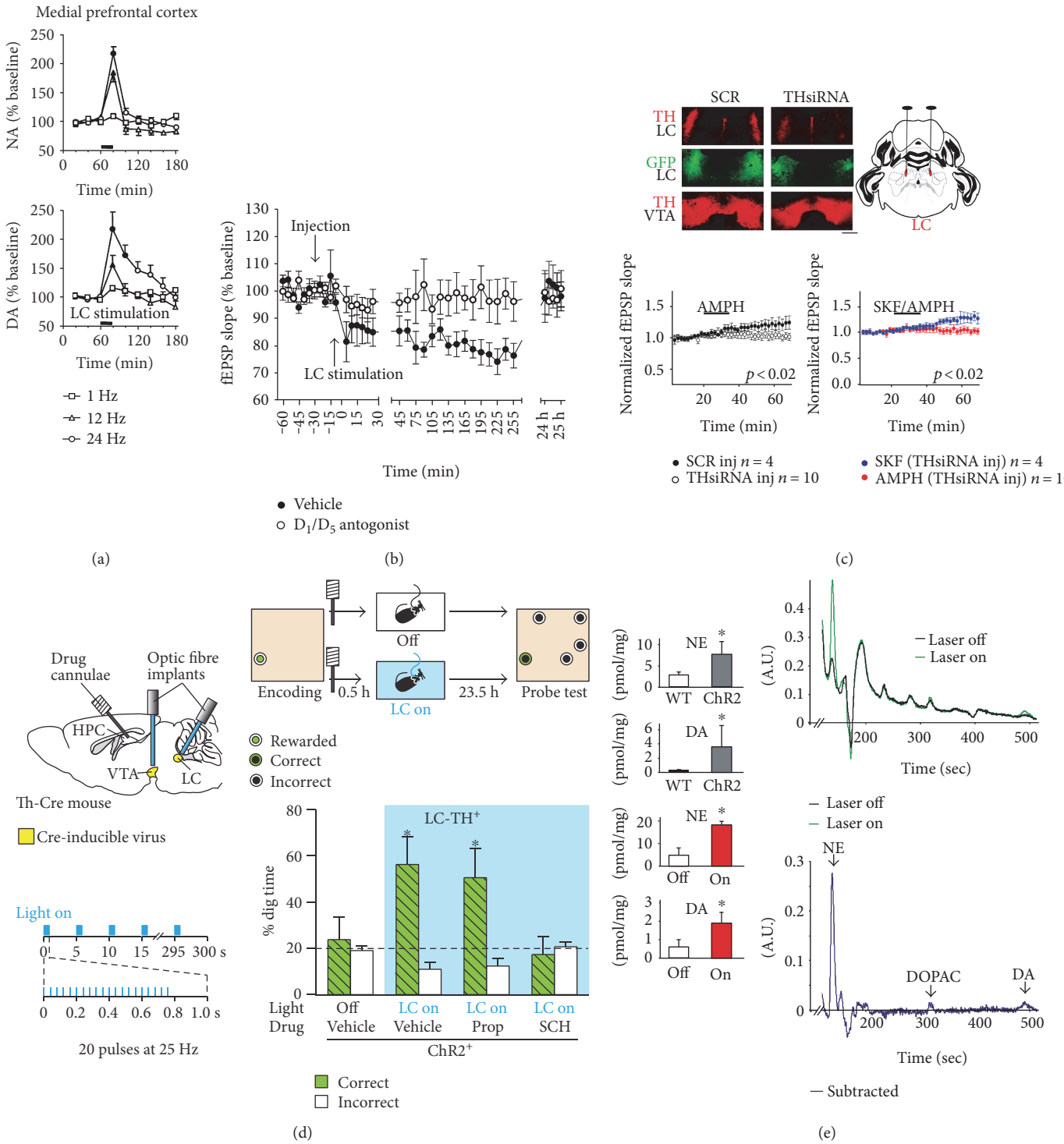


Figure 3: Noncanonical release of DA from LC-TH$^+$ axons in HPC. (a) LC electorical stimulation-induced increase of NA (top) and DA (bottom) in the medial prefrontal cortex. (a) is reproduced from [106]. (b) LC electorical stimulation-mediated D_1/D_5 receptor-sensitive facilitation of CA3–CA1 LTD *in vivo*. (b) is reproduced from [52]. (c) TH knockdown in LC prevents D_1/D_5 receptor-mediated enhancement of excitatory transmission in HPC. (c) is reproduced from [20]. (d) Optogenetic activation of LC-TH$^+$ neurons enhances persistence of memory in a manner consistent with release of DA in HPC $^*p < 0.05$ versus chance, t-test. (d) is reproduced from [22]. (e) Optogenetic activation of LC-TH$^+$ axons in HPC produces an increase in DA release in the dorsal HPC. $^*p < 0.05$, t-test. (e) is reproduced from [23].

complemented by the subsequent direct detection of DA corelease along with NA from LC-TH$^+$ axons in HPC (Figure 3(e)) [23]. Taken together, these observations collectively indicate that LC-HPC system is activated by environmental novelty and mediates postencoding memory enhancement via the noncanonical release of DA in HPC (Figure 1(a)).

In contrast, a recent study showed that electrical activation of LC can mimic the beneficial effect of environmental novelty on memory persistence of the inhibitory avoidance and spatial object recognition tasks in rats in a hippocampal β-adrenoceptor-sensitive manner [61]. Further studies will be required to access how the DAergic and noradrenergic systems interact mechanistically in processing environmental novelty in HPC.

It is not yet clear, however, how the environmental novelty signal reaches the LC-TH$^+$ neurons. Computational models [98] have proposed that novelty is computed in the hippocampal CA1 through a process that compares the "predictions" that arrive from CA3 via the Schaffer collaterals with the "reality" that arrives directly from the neocortex via the perforant path. According to this view, CA1 acts as a "comparator" that detects mismatches between predictions from CA3 and actual sensory input from the neocortex [16]. Based on this model, one possibility is that novelty detection occurs in HPC, which then activates LC-TH$^+$ neurons that project back to HPC. There has been, however, little direct empirical evidence to support the CA1 comparator model so far. In addition, a recent study [86] found no direct projections from HPC to LC-TH$^+$ neurons. Therefore, it is likely that the environmental novelty signal reaches LC-TH$^+$ neurons from HPC via a relay (e.g., the medial prefrontal cortex [99]). Second possibility is that LC-HPC projection is part of a parallel circuit independent of the HPC-VTA loop. There are many areas of the brain that will respond stronger to novel stimuli. Among them, the superior colliculus shows strong response to novel visual stimuli [100] as well as novel multisensory information [101]. Neurons in the superior colliculus habituate their novelty response over time in a similar way to the environmental novelty-associated response in LC neurons. It is also noted that the superior colliculus constitutes a large fraction of direct synaptic input to LC-TH$^+$ neurons [86].

4. Molecular and Anatomical Basis for D_1/D_5 Receptor-Mediated Signaling in HPC

In catecholamine synthesis pathway, TH is the rate-limiting enzyme under basal conditions. However, when DβH (dopamine-β-hydroxylase), the enzyme that converts DA to NA in synaptic vesicles of LC-TH$^+$ terminals, becomes saturated and rate limiting [102, 103], not all of the DA in the vesicle is converted to NA, and the probability of corelease of DA and NA would increase. In support of this hypothesis, it has been demonstrated that chemical and electrical stimulation of LC neurons elicits release of both DA and NA in the medial prefrontal cortex (Figure 3(a)) [97, 104–106] and HPC [107, 108]. Smith and Greene were the first to provide direct electrophysiological evidence for this idea (Figure 3(c)) [20]. More recent optogenetic studies have further provided physiological and biochemical evidence for noncanonical release of DA from LC-TH$^+$ axons in HPC (Figures 3(d) and 3(e)) [22, 23]. Taken together, it is thus plausible that LC-TH$^+$ axons are the source of DA in the dorsal HPC.

In DA signaling, dopamine transporter- (DAT-) mediated reuptake plays a key role in limiting DA diffusion and defining DA transients [109]. Similar to the sparse expression in the medial prefrontal cortex [110, 111], however, DAT expression is extremely low in HPC [112–114]. Instead, norepinephrine transporter (NET), which also has an affinity for DA [97, 115, 116], is abundantly expressed on the plasma membrane of LC-TH$^+$ axons in HPC. As is the case for the medial prefrontal cortex [117], heterologous reuptake by NET contributes to the clearance of DA in HPC [118, 119]. Although the difference between the kinetics and efficacy of DA reuptake by DAT and NET remains elusive, the major DA clearance system in HPC is similar to the medial prefrontal cortex, where slow and sustained pattern of DA release is observed during a large variety of cognitive and motivational functions [120].

Now that it has been established that LC-TH$^+$ axons are likely to be an essential constituent of DA signaling in the dorsal HPC, it is imperative to further explore their distribution patterns and as well as their connectivity with hippocampal principal neurons and various types of interneurons. As consistently demonstrated in prior studies by DβH immunohistochemistry as well as autoradiography [88, 89, 91, 93], there are some regional and laminar differences in innervation density of LC axons. To summarize simply, LC innervation covers the entire HPC, and it is especially high in DG. Laminar distribution pattern is also different depending on subregions. In the subiculum and CA1, the density of LC axons is clearly higher in the stratum lacunosum moleculare. In CA3, the highest density is found in the stratum lucidum, where mossy fibers of DG granule cells make synapses on pyramidal neurons. In DG, it is the highest in the polymorph layer in the hilus and the lowest in the granule cell layer (but see [23]). It should be also noted that the density of LC axon is moderately high in the molecular layer. Thus, the differential distribution pattern within each region suggests that the cellular targets of LC-TH$^+$ axons might differ depending on the subregions. Furthermore, considering that different subregions exercise distinct functions in information processing within HPC [121], it would be noteworthy that the densest regional LC-TH$^+$ innervations in HPC are those of the DG and subiculum, which correspond to its main cortical input and output stations, respectively [122, 123].

Of further consideration is whether specialized DA release sites exist on LC-TH$^+$ axons, and if so, how these DA release sites are distributed in HPC, especially in relation to localisation of D_1 and D_5 receptors. In this regard, we are still at the very beginning of the path to get the whole picture. For example, the synaptic profile of TH$^+$ axons in HPC is still a controversial issue. Previous immunoelectron microscopic analyses have shown that TH$^+$ axons often make direct contact with pyramidal neurons and γ-aminobutyric acid-releasing (GABAergic) interneurons [90, 124, 125]. Even at such contact sites, however, the great majority of them do not form synapse-like specializations, including uniform cleft width between the apposed membranes and thickening of the apposed membranes [90, 125, 126]. By contrast, a small fraction of them seem to make symmetrical synapses with soma and dendritic shaft of GABAergic interneurons [90]. In recent years, however, it has become clear that morphologically defined "DA synapse," which is formed between TH$^+$

terminals and dendritic elements that exhibit ultrastructural features of symmetrical synapses, is not likely to be the site of DA transmission. Specifically, D_1 receptors are almost exclusively located at the extrasynaptic membrane [127, 128] and not localized to DA synapses [129]. Thus, future studies are required to determine the release site of DA in LC-TH$^+$ axons and their spatial relationship with D_1 and D_5 receptors in HPC.

Our current knowledge regarding the expression pattern of D_1 and D_5 receptors in HPC is still limited and inconclusive [48, 130–138]. Distribution of D_1/D_5 receptors in HPC was first demonstrated by binding studies using radiolabelled ligands. Although the signal intensity in HPC is much lower than in "DA-rich regions" such as the striatum, low to moderate levels of binding to D_1/D_5 receptors are observed in the molecular layer of DG [130, 139–142]. In situ hybridization studies have further uncovered differential expression patterns of D_1 receptor mRNA in the ventral and dorsal HPC. D_1 receptor mRNA is expressed in dispersed cells in CA3/CA1 and DG in the ventral HPC, while it is mainly expressed in DG granule cells in the dorsal HPC [48, 130, 142]. These observations are further supported by a recent study on transgenic mice expressing eGFP (enhanced green fluorescent protein) under control of the D_1 receptor promotor, which shows that it is mainly expressed in DG granule cells and a subset of GABAergic interneurons in the hilus and CA1/CA3 [137, 138]. In spite of this clear expression pattern, subcellular distribution of D_1 receptor remains elusive, mainly because D_1 receptor protein expression in HPC is quite low compared with the striatum. In situ hybridization studies have consistently shown that D_5 receptor mRNA is dominantly expressed in HPC [48, 131–133]. At the cellular level, there is a consensus that D_5 receptor is expressed in pyramidal neurons in CA1/CA3 and granule cells in DG [48, 131–134]. However, further analyses are needed in order to determine its subcellular localization and expression in GABAergic interneurons.

It is now widely accepted that DA receptors can form both homomers and heteromers with several other classes of receptors, including other G protein-coupled receptors (GPCRs) and ionotropic receptors [143, 144]. D_1 receptor directly couples with the GluN1 and GluN2A subunits of the *N*-methyl-D-aspartate (NMDA) receptor and modulates the NMDA receptor currents [145, 146]. Recently, Kern and colleagues showed that D_1 receptor and ghrelin receptor form heteromers in a complex with Gαq and initiate a noncanonical cAMP-independent signaling pathway that regulate DA-dependent hippocampal synaptic plasticity and memory [147]. Similarly, D_5 receptor directly couples to the γ2 subunit of the GABA subtype-A receptor, modulating the inhibitory current [148].

5. Plasticity-Related Proteins and Novelty-Associated Memory Enhancement in HPC

Optogenetic activation of hippocampus-projecting LC-TH$^+$ axons at the time of learning enhances a D_1/D_5 receptor-sensitive 24 hr memory in a spatial object recognition task [23]. However, from the perspective of the STC hypothesis [49, 51], our behavioural protocol [22], in which there is a 30 min delay between encoding and exposure to environmental novelty, can dissociate the encoding phase from the consolidation processes. It could allow us to exclude the possibility of DAergic modulation of memory encoding via, for example, changes in attention [23, 149] and alterations in CREB- (cyclic adenosine monophosphate response element-binding protein-) mediated changes in neuronal excitability [150]. Our proposed mechanism for postencoding environmental novelty-associated memory enhancement is as follows: hippocampal D_1/D_5 receptor activation induced by environmental novelty triggers nuclear gene transcription and nuclear/dendritic synthesis and distribution of PRPs that are captured by "synaptic tags" in order to stabilize synaptic changes within hippocampal excitatory neurons [51].

Pharmacological activation of D_1/D_5 receptors enhances Zif268/Egr-1/Krox-24 and Arc expression in DG *in vivo* [151]. D_1/D_5 receptor activation also stimulates local protein synthesis in the dendrites of hippocampal neuron *in vitro* [152, 153]. On the other hand, LTP-induced expression of Zif268 and Arc in CA1 is significantly reduced in global D_1 receptor knockout mice [44, 46]. It has been established that exploration of a novel environment causes upregulation of several IEGs in HPC [8, 154–156]. However, important questions remain open regarding the specific role of particular PRPs in novelty-induced enhancement of memory persistence. Although several proteins, including Homer1a, Arc, BDNF (brain-derived neurotrophic factor), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor, actin and PKMζ (protein kinase Mζ), have been suggested as possible key mediators of persistence of long-lasting synaptic plasticity and memory [157], they only provide partial explanations of the phenomenon. For example, synaptic activity-induced *Homer1a* and *Arc* gene products are targeted to active or inactive synapses, respectively, *in vitro* [158, 159], but their roles in environmental novelty-induced memory persistence remain largely unexplored.

The local setting of synaptic tags and the capture of PRPs by tagged synapses might have occurred in activated dendritic spines at glutamatergic synapses in HPC. The capture of PRPs by tagged synapses, critical for initial memory consolidation, results in an increase of both the strength of the synaptic transmission ("functional plasticity") and volume of dendritic spines ("structural plasticity") [51]. Functional and structural plasticity is thought to involve the insertion of AMPA receptors at the postsynaptic membrane [160] and the remodelling of actin cytoskeleton [161, 162], respectively. Thus, we predict the features of PRPs to be as follows: PRPs are (i) enriched in dendritic spines and (ii) involved in the regulation of AMPA receptor trafficking and/or remodelling of actin cytoskeleton. It has been reported that 1755 gene products are enriched in postsynaptic dendritic spines (SynaptomeDB, http://metamoodics.org/SynaptomeDB/index.php [163]).

One possible experiment for identifying key PRPs critical for environmental novelty-induced memory boost would be translational profiling acquired under different behavioural and physiological conditions (Figure 4). The intellectual background to this approach is STC hypothesis [49, 51]

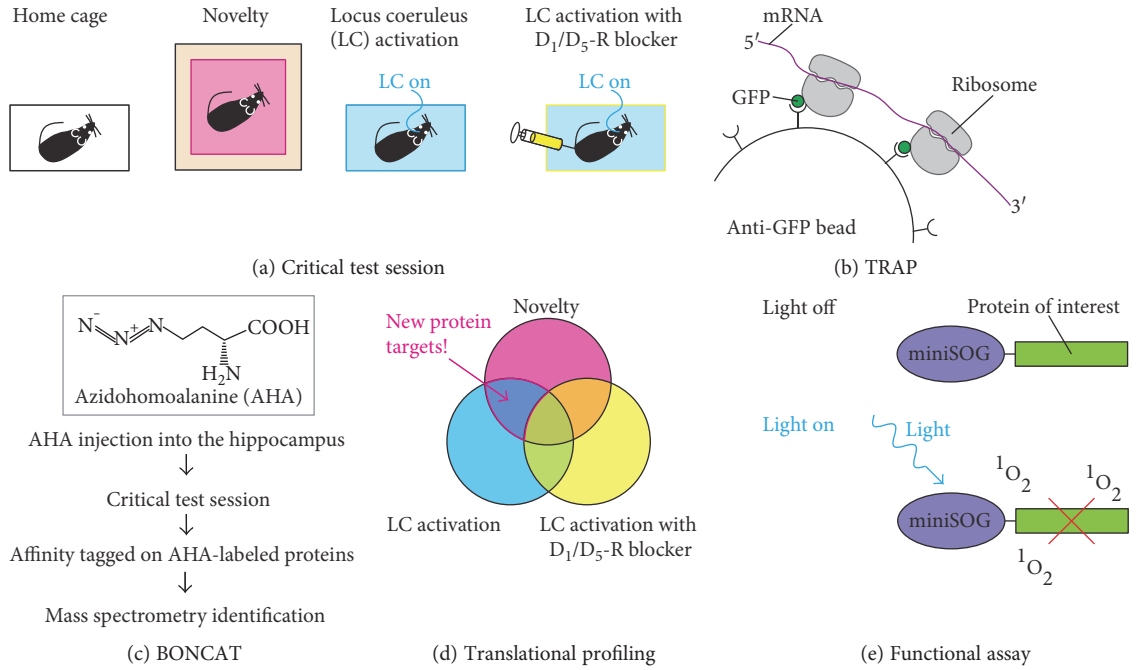


Figure 4: Identification of key PRPs (plasticity-related proteins) by using optogenetics and translational profiling. (a) The critical test session would include (i) a behavioural condition that enhances memory (novelty), (ii) optogenetic activation of LC neurons (LC on), and (iii) LC activation with D_1/D_5 receptor blocker (LC on with D_1/D_5-R blocker) that might block the relevant synthesis of PRPs mediated by DAergic signaling in key target neurons. These conditions are compared to a home cage condition. (b) The TRAP technology, involving cell type-specific expression of green fluorescent protein- (GFP-) tagged ribosomal protein and GFP immunoprecipitation, enables the selective isolation of "translated mRNAs" in genetically defined neurons. (c) BONCAT (bioorthogonal noncanonical amino acid tagging) technology, involving labelling of newly synthesized proteins by AHA (azidohomoalanine), which can be later tagged for isolation and identification by mass spectrometry. (d) Candidate PRPs would be identified through the Venn diagram overlap of experimental conditions. (e) Optogenetic inhibition of a candidate PRP using "miniSOG," a genetically encoded singlet oxygen generator [168]. After light illumination, singlet oxygen ($^1O_2$) is generated by miniSOG leading to the inactivation of fusion protein of interest.

whereby the mechanisms mediating memory encoding (tag-setting) and consolidation (sequestration of PRPs) are independent events. Previous results [164] support this dissociation between tag-setting (calcium/calmodulin-dependent protein kinase (CaMK) II signaling pathway) and the availability of PRPs (CaMKIV signaling pathway). The critical test session after which tissue is taken would include novelty exploration and optogenetic activation of LC-TH^+ neurons that can enhance memory retention (Figure 4(a)) [22]. In addition, it would include photoactivation of LC-TH^+ neurons with systemic injection of D_1/D_5 receptor antagonist that might block the relevant synthesis of PRPs mediated by DAergic signaling in hippocampal neurons. These conditions would be compared to a baseline home cage condition. Recently developed techniques "TRAP" (translating ribosome affinity purification) (Figure 4(b)) [165] and "BONCAT" (bioorthogonal noncanonical amino acid tagging) (Figure 4(c)) [153] allow us to selectively isolate translated mRNAs and newly synthesized proteins during the critical test session, respectively. Translational profiles acquired under different behavioural and physiological conditions would be then compared (Figure 4(d)). Specifically, comparisons among a subset of genes translated in these different conditions can be used to zero-in on candidate PRPs.

If candidate PRPs would be identified, the next logical step is to assess whether the candidate PRPs are preferentially targeted to activated spines using two-photon glutamate uncaging with time-lapse imaging [166]. Subsequently, it is imperative to characterise the function of the candidate PRPs that are induced by environmental novelty in novelty-associated enhancement of memory persistence. Methods to optically control the activity of specific proteins [167], when available, would allow us to disable the function of the candidate PRPs by illumination with light during initial memory consolidation in a spatially and temporally precise manner (Figure 4(e)). These sets of experiments would identify key PRPs that mediate novelty-associated enhancement of memory persistence within excitatory neurons in HPC. Among the brain disorders, the breakdown of memory (associated with stress, aging, and age-associated disorders) causes great concern. Identification of proteins that enhance retention of everyday memory will have the potential to reveal new drug targets for treatment or restoration of lost memory function. These proteins will also constitute good candidates for "biomarkers" for impairments such as forgetfulness and age-associated memory decline.

6. Conclusions

Most everyday memories may form automatically in HPC. The key role of this memory system is to filter our unnecessary information but keep the important memories by a

mechanism that involves novelty-associated DA release in HPC. Recent optogenetic studies have revealed that projections from noradrenergic LC-TH$^+$ neurons to HPC can drive the postencoding environmental novelty-associated enhancement of memory retention through noncanonical release of DA in HPC. These studies also raise an intriguing possibility that the impact of environmental novelty may differ qualitatively from that of reward-associated novelty and projections from VTA-TH$^+$ neurons to HPC might mediate reward-associated novelty which modulates the memory retention with a narrow time window. Initial consolidation triggered by two distinct dopaminergic novelty systems could help make encoded memory traces last long enough for the effective function of the more extended process of system consolidation by which hippocampus-dependent memories guide the eventual stabilization of neocortical memory networks.

Conflicts of Interest

No competing interests exist.

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Review Article

Down but Not Out: The Consequences of Pretangle Tau in the Locus Coeruleus

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Degeneration of locus coeruleus (LC) is an underappreciated hallmark of Alzheimer's disease (AD). The LC is the main source of norepinephrine (NE) in the forebrain, and its degeneration is highly correlated with cognitive impairment and amyloid-beta (Aβ) and tangle pathology. Hyperphosphorylated tau in the LC is among the first detectable AD-like neuropathology in the brain, and while the LC/NE system impacts multiple aspects of AD (e.g., cognition, neuropathology, and neuroinflammation), the functional consequences of hyperphosphorylated tau accrual on LC neurons are not known. Recent evidence suggests that LC neurons accumulate aberrant tau species for decades before frank LC cell body degeneration occurs in AD, suggesting that a therapeutic window exists. In this review, we combine the literature on how pathogenic tau affects forebrain neurons with the known properties and degeneration patterns of LC neurons to synthesize hypotheses on hyperphosphorylated tau-induced dysfunction of LC neurons and the prion-like spread of pretangle tau from the LC to the forebrain. We also propose novel experiments using both *in vitro* and *in vivo* models to address the many questions surrounding the impact of hyperphosphorylated tau on LC neurons in AD and its role in disease progression.

1. Introduction

Alzheimer's disease (AD) is an insidious and debilitating illness affecting approximately 46.8 million people worldwide [1], representing a significant social and economic burden. AD has proven difficult to study and treat due to the combination of a long prodromal phase and the heterogeneous nature of clinical symptoms and pathology. Despite intensive research examining the pathologic hallmarks of AD, amyloid-β (Aβ) plaques and tau neurofibrillary tangles (NFT), no disease modifying therapies have emerged [2]. Clinical trials targeting mid- to late-stage AD have failed, potentially due to the irreversible neuronal damage and loss that has already occurred by the time of diagnosis. As a result, research efforts have shifted towards earlier AD detection and treatment.

One area of interest in early AD involves the locus coeruleus (LC), the major brainstem noradrenergic nucleus that innervates and supplies norepinephrine (NE) to the forebrain [3]. In search of the earliest detectable AD-like neuropathology, Braak and colleagues surveyed postmortem brains from over 2000 individuals throughout the lifespan for Aβ and aberrant forms of tau and found evidence that hyperphosphorylated tau began accumulating in the LC of individuals around 40 years of age [4]. Notably, pretangle tau in the LC was *always* detected in brains containing Aβ plaques but was also found on its own in brains from younger individuals in the absence of all other AD-related pathologies. Based on these results, Braak amended his canonical staging of AD to include the LC as the first brain region to show tau pathology [4, 5]. These studies had several limitations and were initially questioned. For example, because postmortem analysis was employed, it is impossible to know whether the individuals with hyperphosphorylated tau in the LC would have eventually developed AD. Furthermore, Braak examined early forms of hyperphosphorylated tau, and initial studies failed to find more advanced forms of hyperphosphorylated tau or NFTs reminiscent of AD pathology in the forebrain [6]. However, recent studies have confirmed a variety of pretangle tau species and NTFs in the LC that increase with AD

severity [7, 8]. Finally, hyperphosphorylated tau staining in early AD has been reported in the dorsal raphe nucleus (DRN), which together with the LC forms part of the isodendritic core (IC) that appears particularly vulnerable to neurodegeneration [8, 9]. Thus, while the exact origin of aberrant tau in AD is still under debate, it is clear that hyperphosphorylated tau in the LC is among the first detectable signs of AD-like neuropathology in the brain. The detrimental role of hyperphosphorylated tau (both due to loss of normal function as well as gain of toxicity) has been heavily investigated, but mainly in the context of cortical neuron populations (reviewed in [10, 11]). Although LC neurons die in later stage disease (see below), it is not known whether pretangle tau pathology precipitates their degeneration.

The LC is a small nucleus (~22,000–55,000 and 1500 neurons per hemisphere in humans and rodents, resp.) in the brainstem and the main source of NE for the forebrain [3]. Despite the size of the nucleus, LC neurons innervate most of the brain, excluding the basal ganglia [12–15]. For the purposes of this review, we will highlight key findings relevant to AD but direct the reader to several excellent sources for a comprehensive description of LC neuroanatomy [3, 16, 17]. LC neurons send collateralized projections throughout the brain from topographically distinct regions along the rostral/caudal and dorsal/ventral axes [15], which exhibit projection-specific geometry and vulnerability in AD. In early AD, pretangle tau accumulation is the greatest in the middle third of the LC, which densely innervates the hippocampus and cortex [8, 15, 18]. As AD progresses, cell loss is concentrated to the rostral and middle sections of the LC, leaving the caudal potion, which primarily targets the cerebellum, spinal cord, and other brainstem nuclei, relatively spared [15, 19]. The cause of this apparent selective regional vulnerability is unknown but could be the result of excitotoxic glutamatergic inputs from the cortex, which are concentrated in the middle of the LC [3]. In addition, the dorsal portion of the LC projects heavily to AD-associated regions such as the entorhinal cortex (EC), hippocampus, and frontal cortex, while the ventral portion innervates the spinal cord, potentially indicating specialized function [15, 18]. Indeed, recent work has shown that LC neurons have unique cellular properties based on their projection targets [20]. Combined, these results suggest that distinct populations of LC neurons may be especially vulnerable to degeneration based on projection targets and cellular properties.

Canonical roles for the LC have been described for attention, stress responses, and arousal; these studies have been extensively reviewed and will not be covered in detail here [16, 17, 21]). Degeneration of the LC is a ubiquitous feature of AD [19, 22–24], occurring in mid- to late- stage disease (~Braak III-IV)[19, 25]. Moreover, loss of LC neurons better predicts onset and severity of AD symptoms and Aβ/NFT pathology than cell loss in any other brain region implicated in AD, including the hippocampus, EC, and nucleus basalis of Meynert [26]. NE has anti-inflammatory properties, primarily mediated via β-adrenergic receptors (ARs) on glial cells, and directly enhances Aβ clearance via microglia activation [27]. Besides NE, LC neurons also produce and release brain-derived neurotropic factor (BDNF), a potent trophic peptide that enhances synaptic plasticity and Aβ clearance while reducing tau phosphorylation [28]. BDNF is particularly important for maintaining LC innervation in forebrain in old, but not young, rats and LC-derived BDNF may represent a resilience factor for age-dependent cell loss in AD [29]. Thus, it is not surprising that chemical or genetic elimination of LC neurons enhances cognitive deficits, cortical inflammation, and Aβ deposition in amyloid-based mouse models of AD [30–36]. Although LC lesioning studies have not been reported in transgenic tau models, LC lesions in APP transgenic mice increase forebrain hyperphosphorylated tau levels, suggesting that LC degeneration may impact tau pathology [37]. While losing LC neurons may be a turning point in AD progression, it appears that pretangle tau accumulates in LC neurons decades prior to their demise [4, 19, 25]. Since hyperphosphorylated tau is known to disrupt cellular function, this begs the question of whether aberrant tau accumulation is altering LC neuron function in mild cognitive impairment (MCI), a prodromal form of AD, and early AD. This review focuses on the potential impact of hyperphosphorylated tau accrual on LC neurons and suggests experimental approaches to probe the functional relationship between hyperphosphorylated tau and the LC in AD progression.

2. Role of Hyperphosphorylated Tau on LC Morphology and Function

Pretangle tau emerges in the LC in individuals around 40 years old, yet degeneration of LC neurons is not apparent until mid-stage AD, suggesting that LC neurons could be harboring pathogenic tau species throughout the decades-long prodromal stage of AD. Given that hyperphosphorylated tau in cortical neurons disrupts a wide variety of functions, it seems likely that it is also corrupting LC function, perhaps early in AD.

Since LC degeneration was first described in AD, it was also noted that surviving LC neurons are morphologically ragged, with "swollen and misshapen" somas, reduced arborization, and thick, shortened neurites [38]. Alterations in LC innervation have been reported in the hippocampus and cortex of AD patients. Morphologic changes in LC fibers along with decreased LC fiber density [38, 39], tissue NE levels [40], and compensatory increases in ARs [41] indicate noradrenergic dysfunction and potential retraction of LC innervation from these regions in AD. Whether hyperphosphorylated tau accumulation contributes to this dysfunction is not known. One study found increases in hippocampal α2AR levels, a compensatory sign of low NE transmission, in Braak I, a stage when tau pathology begins to appear in the EC [7]. In the forebrain, hyperphosphorylation of tau leads to its dissociation from microtubules and causes disassembly, impairing axonal stability, axonal transport, and neurotransmission [42, 43]. Likewise, LC neurons from MCI and AD patients, which have increased expression of the 3R:4R tau isoforms and decreased expression of a variety of axonal and synaptic structure proteins, a pattern consistent with structural instability [25]. Notably, mRNA expression of *map1b* and *synaptopodin*, which are negatively

correlated with global cognition scores across AD development, suggest a link between instability and cognitive decline [25]. A recent study found that LC neurons containing hyperphosphorylated tau have fewer synaptic inputs than neighboring LC neurons without pathogenic tau, indicating that hyperphosphorylated tau may contribute to synapse retraction [7]. Moreover, inflammatory markers are upregulated in LC neurons across Braak stages I–IV, suggesting that hyperphosphorylated tau may also produce local inflammation [7]. While it is not yet clear what causes LC dysfunction and degeneration, the cross-sectional studies allude to the potential role of aberrant tau.

LC dysfunction and degeneration have been identified in a variety of neurodegenerative diseases including AD, Parkinson's disease, chronic traumatic encephalopathy, and multiple sclerosis that impact the aforementioned IC [44–47]. The IC is a conserved set of nuclei, containing the LC, DRN, substantia nigra, and basal nucleus of Mynert that share many cellular and anatomic features and are similarly affected in AD [9]. Dysfunction in the IC, especially the LC and DRN, has been postulated to contribute to disruptions in mood and sleep that precede memory loss in AD [9]. New stereological experiments have detected pretangle tau in the DRN as well as the LC in early AD (Braak 0) [19]. In addition, nuclei in the IC release neuromodulators via volume transmission rather than specialized synaptic contacts. Due to this mode of signaling, disruptions in these neuromodulators are likely to have a broad impact on wide populations of neurons and glia compared to synaptic transmission. The neurons in the IC share fundamental properties including long, unmyelinated projections that create high bioenergetic demand and may make these neurons particularly sensitive to a variety of insults [3, 48, 49]. Similar to substantia nigra neurons, LC cells have tonic firing patterns due to calcium influx from L-type calcium channels [50], and one study found that tonic activity and L-type calcium channels increase mitochondrial stress in LC neurons, leading to cellular dysfunction over time [50]. Similarly, cognitive performance in amnestic MCI and AD patients is negatively correlated with disruption of mitochondrial and cellular stress proteins in LC neurons, suggesting that early cellular stress in LC neurons may be contributing to AD progression [25]. Furthermore, the LC is a critical mediator of the physiologic stress response, and chronic stress increases tau hyperphosphorylation in the LC of mice [51]. Taken together, LC neurons appear to be susceptible to both cellular and physiologic stressors.

The LC is also anatomically susceptible due to its position near the fourth ventricle and significant vascularization by blood vessels devoid of the blood brain barrier (BBB) [52]. Thus, LC neurons are likely exposed to high levels of toxins, pathogens, and peripheral immune cells lurking in the cerebrospinal fluid and blood [44, 49]. In fact, heavy metals, presumably from the blood, can be detected in the LC, although metal-containing neurons seem to be distinct from those that contain hyperphosphorylated tau, suggesting some regional/cell type specificity for pathology in the LC [52]. Furthermore, chemically lesioning the LC disrupts the BBB; dysfunction/degeneration of the LC may impact neuroinflammation throughout the brain and contribute to the leaky BBB observed in AD patients [31, 53].

Neuroinflammation, which is profoundly influenced by the LC/NE system, is a hallmark of AD (reviewed here [27, 54]). A proinflammatory environment in the forebrain is an early phenotype of many mouse AD and tauopathy models, yet few have examined whether inflammation occurs in the LC. Recent evidence indicates the increasing presence of microglia and expression of interleukin 6 in the LC across the Braak stages in humans [7]. Similarly, rats expressing wild-type human tau have increased expression of inflammatory cytokines and reductions of the NE biosynthetic enzyme, tyrosine hydroxylase, in the LC, and hippocampus [55]. Chronic infusion of lipopolysaccharide into the 4th ventricle resulted in exposure- and age-dependent increases in microglia and concurrent declines in LC neuron density [56]. Combined, these data suggest that hyperphosphorylated tau and inflammation may reduce LC neuron health, especially with age. Due to the interconnected nature of inflammation, tau pathology and LC/NE signaling, careful examination of the interplay between these factors is warranted.

While hyperphosphorylated tau is likely disrupting LC function, whether hyperphosphorylated tau is itself toxic or rather confers sensitivity to secondary insults (i.e., a "two-hit" model), it is still unresolved [10, 11]. Postmortem evidence suggests that if pretangle tau toxicity exists in the LC, it is not swift and takes years or even decades to result in neuron loss [4, 19]. Given the timing, the two-hit model seems an attractive hypothesis because the LC seems anatomically destined to experience chronic toxicant exposure from the blood and CSF [49]. One possibility is that LC neurons may be somewhat resilient to stressors early in life but succumb to them overtime. If this is correct, identifying factors contributing to resilience and extend them could delay onset or progression of a variety of neurodegenerative diseases. Yet, no mechanistic studies assessing the effect of pretangle tau on LC neuron survival have been published, and additional research is necessary to answer these questions. In sum, the structure of LC neurons in combination with their metabolic demands and anatomic position confers both increased exposure and sensitivity to cellular stressors. In light of these characteristics, it is perhaps not surprising that LC neuron dysfunction and degeneration are implicated in a variety of neurodegenerative diseases in addition to AD. Further study of LC neurons is necessary to understand their cellular vulnerability and resilience, especially in the context of hyperphosphorylated tau.

3. *In Vitro* Model Systems to Examine the Consequences of Hyperphosphorylated Tau in LC Neurons

The techniques available to examine LC neuron function *in vitro* with cell-type specificity are limited due to the small size of this nucleus that requires fine dissection and low tissue yields for traditional approaches. While hyperphosphorylated tau disrupts normal cellular function and leads to

abnormal morphology and neurotransmission in hippocampus neurons *in vitro* and in transgenic mice [10, 57, 58], little attention has been paid to the LC. One approach could be the use of immortalized catecholaminergic cell lines and primary LC cell cultures expressing various forms of wild-type and pathogenic tau to examine the impact on LC neuron morphology and neurotransmission via microscopy and biochemical methods already validated for forebrain neurons. Dissection for primary cultures could be aided by the use of TH-GFP mice and rats, which creates fluorescent catecholamine neurons and has been employed to facilitate making dopamine neuron cultures [59]. Furthermore, these cultures could be used to examine the sensitivity of LC neurons to a variety of stressors (toxins, immune stress, tau fibrils, etc.). By utilizing TH-GFP rodents to visualize living LC neurons, these results could also be translated to slices to assess real-time imaging of immune infiltration and tau engulfment, as well as electrophysiological recordings to examine the effect of hyperphosphorylated tau on neuron activity. The ability to visualize and selectively manipulate signaling cascades makes these *in vitro* and *ex vivo* systems extremely powerful and well equipped to examine how hyperphosphorylated tau affects LC neuron health in the context of AD-related pathology and stressors in the LC microenvironment. *In vitro* systems are also ideal for high-throughput screening of small molecules that modulate hyperphosphorylated tau accrual and degeneration in the LC.

4. Tau Seeding and Spread from the LC

In AD, tau pathology is first detected in the LC, then appears in the interconnected brain regions in a temporarily and spatially distinct manner [4]. Some of the densest LC projections can be found in the EC and dentate gyrus of the hippocampus, the next brain regions affected in Braak I and II, respectively, before eventually reaching other parts of the forebrain (e.g., cerebral cortex) [3, 5]. This pattern mirrors the clinical symptoms, beginning with early changes in a variety of non-cognitive areas like sleep and affect, attributed to alterations in the IC, followed by subtle memory impairment, and the steady decline across higher function cognitive domains [9, 60]. This distribution has driven the hypothesis that pathogenic tau can spread transsynaptically *in vivo* via "templated protein corruption" or "seeding" [61]. Indeed, injections of mouse mutant tau aggregates [62, 63], human AD brain lysate [64, 65], recombinant tau [66], or tau-expressing virus [42] into the forebrain of mice induces tau pathology near the injection site as well as in the interconnected brain regions, indicating spread. Furthermore, the spread of early tau pathology has been observed in mice that express aggregate-prone tau only in the EC, an area affected in Braak I [43, 67]. While the precise mechanism of how intercellular tau protein propagates remains unclear, proposed mechanisms include extracellular release and reuptake, possibly in conjunction with neuronal activity or firing [58]. Notably, neuronal activity hastens the spread of tau pathology from the EC to the DG, and Aβ pathology from the hippocampus to the forebrain, suggesting that dampening neuronal activity may retard pathogenic protein spread in AD [68, 69].

There is much debate on whether the pretangle tau in the LC indicates that the LC truly initiates AD tau pathology. While studies show the presence of pretangle tau in the LC in young individuals, there is no way to determine whether these individuals would have eventually developed AD. Other factors (repeated concussions, stress, and heavy drug use) also increase hyperphosphorylated tau in the LC [46, 51, 55, 70] and could trigger the appearance of aberrant tau. The only attempt to examine the spread of tau pathology from the LC experimentally delivered puzzling results. Transgenic mice expressing aggregate-prone human tau that were given intra-LC injection of preformed tau fibrils showed pretangle tau spread to many areas of the brain, but oddly spared the expected AD-associated targets, the EC, and hippocampus [71]. Because the results did not recapitulate the stereotyped pattern of tau pathology in early AD (LC-EC-hippocampus), the authors suggested that pathogenic tau does not spread from the LC in human disease; this interpretation may be premature, and study limitations should be considered. For instance, although fibril injections are a widely used model of prion-like protein spread, attention should be given to the source of tau and brain region. First, various tau species are differentially taken up and transported in neurons depending on their size, isoform, and modifications [72–74]. Thus, it is plausible that the conformation/species of the synthetic tau fibrils injected into the LC were preferentially targeted to the brain regions other than the EC/hippocampus. Moreover, the PS19 mice and fibrils used in this study express a P301S mutant tau, which has different seeding capacity than tau aggregates in AD [75]. Second, because catecholaminergic and glutamatergic neurons have very different cellular properties, the mechanisms underlying tau internalization and spread may also differ. Furthermore, LC neurons are not homogeneous, and it is possible that differences in electrophysiological properties may favor internalization and spread to the forebrain but not the EC or hippocampus [20]. One potential solution to these limitations is to develop a model that selectively expresses wild-type human tau in the LC and therefore has a wider compliment of tau species, does not rely on tau internalization, and may more representative of tau spread from this region in humans. Whether the LC represents the initial site of pathology or reflects a nonspecific response to brain insults is still under debate [6]. Additional studies, using a variety of seeding models, are necessary to resolve this question.

Regardless of the model system used, the field could benefit from more investigations focused on the age-dependent emergence of tau pathology across brain regions. For example, while Braak staging is the gold standard from a clinical standpoint, it is rarely applicable in animal models because tau transgenes are typically driven by ubiquitous promoters that express tau in all neurons simultaneously. As the AD field pivots to early disease detection and treatment, examination of early pathology, especially within the LC, of animal models may present new models for understanding early disease mechanisms and potential therapies.

5. *In Vivo* Models of Tau Spread

The majority of tau propagation experiments have been performed in mice. Compared to humans, mice express fewer tau isoforms, and those that are expressed are resistant to hyperphosphorylation and aggregation [76]. Because it is very difficult to coax endogenous mouse tau to form aberrant species, tau seeding studies have generally been done in transgenic mice that ubiquitously express mutant tau [57]. While this provides a receptive template for tau propagation, mutant tau has different properties than wild-type tau, and the relevance of this model to AD is unclear [72–74]. In fact, unphosphorylated, rather than hyperphosphorylated or aggregated, tau was found to be the agent of spread in rats with virally expressed wild-type human tau in the hippocampus [42]. In addition, obvious confounds exist when using ubiquitous expression of tau to study spread between brain regions. Rats present a potential solution to these issues. Rats express the same 6 isoforms of tau as humans, albeit in a different 3R : 4R ratio (1 : 9 in rats and 1 : 1 in adult humans) [76]. Nevertheless, rats reproduce some aspects of tauopathies that mice do not [76–78]. Notably, conversion of wild-type human tau into pretangle tau occurs in SHR72 rats expressing the 4R human tau isoform, but not mice harboring a similar transgene [78, 79]. In addition, tau pathology propagates from the hippocampus in rats injected with SHR72 rat homogenate [78] or viral-mediated expression of human tau [42]. The power of using rats for tau research is perhaps best characterized by the TgF344-AD rat, which harbors the same mutant amyloid precursor protein and presenilin 1 transgene used to make the APP/PS1 mice [77, 80]. This transgenic rat is, to our knowledge, the only animal model that manifests *endogenous* tau pathology, while its APP/PS1 mouse counterpart does not [76, 77]. While in the past, mice were an economically and technically favorable species for genetic models, additional consideration should be given to rat models, especially given recent advances in gene editing technology. Where appropriate, rat-based models may be able to recapitulate missing pieces of the tau puzzle, including conversion of wild-type human tau to pathogenic species, the generation of endogenous tauopathy in response to amyloid and the propagation of tau in the absence of widespread mutant tau expression.

While tau spread in the hippocampus and cortex has been examined under a variety of conditions [42, 62–66], only the aforementioned single study using fibril injections has been examined in regards to seeding from the LC [71]. Exclusive anatomic targeting of tau fibrils to the LC is technically very challenging due to the small size of this nucleus (1500 neurons in a rodent), and there is no way to ensure noradrenergic neuron specificity. By contrast, genetic strategies have been successful in targeting LC neurons to produce effector and reporter proteins with cell-type specificity through promoter-driven expression using NE synthesis enzymes (TH, DBH) [81–83], LC transcription factors (Phox2b) [84, 85], and LC specification genes (Ear2 and DBH/En1) [36, 86, 87]. Recent work has shown selective and robust viral-mediated expression using Phox2b-dependent promoters [84, 85], Cre-dependent expression in TH-Cre mice [81, 88], or microinjections of virus containing a constitutive promoter [89]. This viral-mediated approach has several advantages for answering LC-based questions in a wide variety of existing AD models. By using intra-LC infusion of virus and an LC-specific promoter, one can achieve expression of desired proteins exclusively in LC neurons without the time and cost of traditional transgenic methods that often produce expression in other noradrenergic cell populations [84]. This approach is especially well suited for the investigation of tau seeding from the LC, where a variety of tau mutants could be expressed in the LC of a mouse or rat and examined for spread over time. This technique would allow for a high degree of anatomic specificity as well as a continuous, cell-autonomous source of tau unachievable by tau fibril infusion. Moreover, this approach is compatible with the latest brain clearing techniques (CLARITY, 3DISCO, and SeeDB) that would allow for more thorough investigation of tau spread [90–92].

6. Modulation of Tau Spread by LC Activity

Hippocampal hyperexcitability occurs in humans with MCI and rodent models of tauopathies and AD [93–97]. In mice, AD-associated hyperexcitability is reversed by tau deletion, suggesting that tau is the causative agent [95, 96, 98]. Synaptic activity facilitates tau transfer *in vitro*, and chemogenetic activation of EC neurons enhances tau spread *in vivo* [68, 95, 98]. These results are consistent with a feed-forward mechanism in which pretangle tau accrual promotes hyperexcitability, in turn facilitating its release and spread. Similar to its effects on hippocampal neurons, hyperphosphorylated tau may enhance LC neuron firing and facilitating tau spread from this nucleus. If true, this would imply that LC hyperactivity may facilitate AD progression, which at face value would be contrary to clinical evidence indicating that LC *degeneration* worsens AD. These results would not necessarily be mutually exclusive and may be dependent on disease stage. For example, enhanced LC activity early in AD, prior to cell loss or substantial drops in NE neurotransmission, may be harmful due to the enhanced spread of tau. By contrast, driving LC activity later in AD progression when the LC is degenerating, NE levels are low, and tau pathology is already abundant in the forebrain which may alleviate cognitive symptoms and retard furthering disease progression. Indeed, restoring NE levels with L-DOPS, a synthetic NE precursor, reduces Aβ pathology and/or improves memory in 5xFAD and APP/PS1 mice [31, 32]. Likewise, DREADD-induced LC activity restored behavioral performance in a mouse model of Down syndrome, which shares many APP-related pathologies [85]. Additional research examining potential tau-mediated LC hyperactivity, as well as activity-dependent tau spread from these neurons, is necessary to determine this relationship.

Whether hyperactivity in LC neurons contributes to AD pathogenesis is further complicated by the firing patterns of LC neurons. Similar to other catecholamine neurons, LC cells fire in two distinct modes: low tonic (sustained 0.1–5.0 Hz) and high phasic (10–20 Hz bursts) [21]. LC function follows the Yerkes-Dodson curve, with low tonic firing being

associated with inattentive behavior, while high tonic firing leads to distractibility and is aversive in mice [21, 81]. Tonic activity is important for behavioral flexibility, while phasic activity is required for attention and optimal task performance [21]. Thus, if pretangle tau were causing LC "hyperactivity," alterations in tonic or phasic firing could produce opposing effects on valence and cognition. It is also possible that the enhancement of tau spread is specific to a particular firing pattern. For example, neuropeptides produced by LC neurons such as galanin are thought to be preferentially released during phasic bursting [99–101]; this may also be true for tau. Activity-dependent tau spread has only been examined in excitatory neurons, which show very little tonic activity, and thus it is difficult to hypothesize whether tau transmission occurs selectively in either firing state. However, enhanced tau propagation is observed following either DREADD-induced tonic firing or optogenetic-induced burst firing, suggesting no firing state preference for tau transmission [68]. Whether this holds true for LC neurons will need to be investigated.

Whether hyperphosphorylated tau directly causes LC hyperactivity could be examined by electrophysiology in *ex vivo* slice preparations or *in vivo* recordings, and therapies that modulate LC excitability could be developed. If hyperactivity is enhancing tau spread, then reducing LC activity should retard propagation. This could be achieved using optogenetics, chemogenetics, or pharmacological agents. For example, the NE transporter inhibitor atomoxetine suppresses tonic LC activity while leaving phasic bursting largely intact, which could have the advantage of inhibiting tau spread while preserving cognition [102]. In future studies, it will be important to examine and manipulate LC firing to gain further understanding of early disease states and potentially elucidate novel avenues for AD treatment.

7. Conclusion

The exact role of hyperphosphorylated tau in the LC in the context of AD is shrouded in mystery. However, the ever-mounting clinical data suggests that at the very least, the LC contributes to disease progression and may be the site of its earliest manifestations. It is in our best interest to explore a variety of circuits and neuromodulators impacted in AD and not just the canonical brain regions and signaling cascades. The LC system represents an especially attractive candidate, since these neurons project to and modulate key nuclei affected in AD, and NE has powerful influences on cognition and behavior. In addition, it is somewhat remarkable that LC neurons appear to be able to tolerate aberrant tau species for many years before succumbing to frank degeneration, indicating that a large therapeutic window of opportunity exists when LC neurons are dysfunctional but not dead. We propose that future research focuses on two questions: (1) what is the impact of hyperphosphorylated tau on LC function and (2) can/does LC-derived tau seed forebrain pathology. The answers to these questions will inform the development of LC-based therapies for the prevention and/or treatment of AD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Genesis and Maintenance of Attentional Biases: The Role of the Locus Coeruleus-Noradrenaline System

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Emotionally arousing events are typically better remembered than mundane ones, in part because emotionally relevant aspects of our environment are prioritized in attention. Such biased attentional tuning is itself the result of associative processes through which we learn affective and motivational relevance of cues. We propose that the locus coeruleus-noradrenaline (LC-NA) system plays an important role in the genesis of attentional biases through associative learning processes as well as their maintenance. We further propose that individual differences in and disruptions of the LC-NA system underlie the development of maladaptive biases linked to psychopathology. We provide support for the proposed role of the LC-NA system by first reviewing work on attentional biases in development and its link to psychopathology in relation to alterations and individual differences in NA availability. We focus on pharmacological manipulations to demonstrate the effect of a disrupted system as well as the *ADRA2b* polymorphism as a tool to investigate naturally occurring differences in NA availability. We next review associative learning processes that—modulated by the LC-NA system—result in such implicit attentional biases. Further, we demonstrate how NA may influence aversive and appetitive conditioning linked to anxiety disorders as well as addiction and depression.

1. Introduction

Emotional salience enhances both attention and memory. For example, we typically remember emotionally arousing events better than mundane ones, reliving the birth of a child or a teenage humiliation with a high degree of vividness decades later [1–3]. We remember these events better in part because we pay heightened attention to emotionally relevant aspects of our environment that signal potential punishment and reward [4, 5]. In turn, such patterns of heightened attention are themselves the result of emotional learning processes that tune our perceptual systems to prioritize such affectively and motivationally relevant cues (e.g., [6–8]). Visual selective attention, or *attentional prioritization*, is the process by which we tune ourselves to the world so that, of the millions of bits per second transmitted by the retina [9], the information that is most important, or salient to us, reaches awareness and guides action. *Affect-biased attentional prioritization* [10], or selective prioritization of what is emotionally or motivationally relevant, can be highly adaptive, as emotional arousal signals events that are important to attend and remember in the interest of survival. Yet at the extreme ends of the spectrum, affect-biased attentional prioritization of specific categories of stimulus, which are often unconscious and automatic, is symptomatic of psychopathology. For example, implicit biases toward stimuli associated with threat characterize anxiety disorders [11], and biases to attend trauma-related cues characterize posttraumatic stress disorder (PTSD) [12]. According to popular models of PTSD, such trauma-related biases are themselves the result of Pavlovian associative learning processes [13]. Moreover, altered biases in attention to reward-related cues are linked to both depression [14, 15] and addictive behaviours [16–18]. In addiction as well, biases to addictive cues are

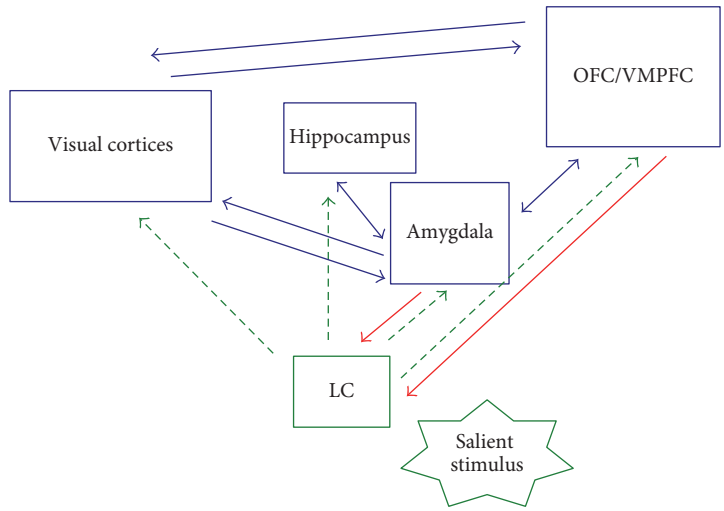


Figure 1: Key pathways emphasized by the biased attention by norepinephrine (BANE) model: green dashed lines indicate noradrenaline (NA) pathways. Red lines indicate projections to the locus coeruleus (LC). Thicker lines indicate direct modulation of visual cortex activity in affect-biased attention. NA activity is implicated in both stimulus-encoding and selective attention [27]. A salient stimulus activates locus coeruleus (LC) neurons, which project widely to cortical and subcortical regions. Adapted with permission from "Neural and genetic processes underlying affective enhancement of visual perception and memory" by Markovic et al. [4]. Copyright 2014 by Elsevier.

thought to result from learning associations between the cue predicting reward and the actual reward [16]. It should be noted that affectively biased attentional prioritization is only one of several forms of *attentional bias* studied in relation to psychopathology. Indeed, whereas attentional prioritization measures preexisting filters that inform what we will see of the world before we ever encounter it, many clinical studies have focused on another form of attentional bias: difficulty with *attentional disengagement* from salient stimuli once they have already been observed [19]. In this paper, we will focus on the role of the locus coeruleus (LC) and noradrenaline (NA) system in the less-explored domain of attentional prioritization, as well as the ways in which emotional learning processes can give rise to specific habits of attentional tuning. Evidence directly linking the LC-NA system to maladaptive patterns of emotional learning associated with attentional biases in psychopathology is sparser. With that caveat, we will review convergent evidence for hypotheses about the role of NA in posttraumatic stress disorder, depression, and addiction and highlight future research directions to establish more direct links.

2. Attentional Biases

2.1. Attentional Biases in Development. Attentional biases appear early in development and specific biases predict later emergence of a range of maladaptive outcomes. A body of recent research has focused on the etiology of maladaptive attentional biases in childhood and adolescence and has suggested a causal role for such biases in the development of anxiety disorders [20]. Research by Perez-Edgar and colleagues has examined the role of attentional bias in moderating the link between temperament and psychopathology over development. Their research points to attentional biases observed early in development as a key mechanism linking temperamental inhibition—a temperament style associated with shyness, which involves higher levels of fearful responses to novel environmental stimulation measurable at birth—to later social withdrawal and anxiety. For example, behavioural inhibition in toddlers has predicted later social withdrawal in children who showed an attentional bias to threat at 5 years old [21], and attention bias to threat in adolescence has predicted adolescent social withdrawal [22]. Such developmental patterns also extend to biases towards reward. Temperamental exuberance is linked to both externalizing problems and attentional bias to reward in children [23]. Convergent evidence suggests a link between attention bias in development and vulnerability to substance abuse. In adolescence, externalizing problems are strongly associated with substance abuse problems [24], and in adulthood, a history of addiction has been linked to generalized enhancement of attentional bias for reward [17]. To date, development of individual differences in attentional bias associated with anxiety and depression has been primarily linked to individual differences in serotonergic function and variation in the 5HTTLPR region of the serotonin transporter gene—albeit only in some populations and in certain contexts [25, 26]. Yet, not only have findings been equivocal, but most of these studies have focused on biases operationalized as difficulties in disengaging attention [19]. We propose that NA plays a crucial role in implicit attentional prioritization, rather than effortful disengagement of attention. Specifically, we suggest that it may play a role in both the genesis and maintenance of such selective attentional biases as they are tuned by life experience.

2.2. The Role of NA in Biasing Attentional Prioritization. Although the role of NA in guidance of attention to salient aspects of the environment has been thoroughly reviewed elsewhere ([4, 27–29]), we recapitulate some key points here. The LC-NA system has been found to play a key role in modulation of visual attention to salient aspects of the

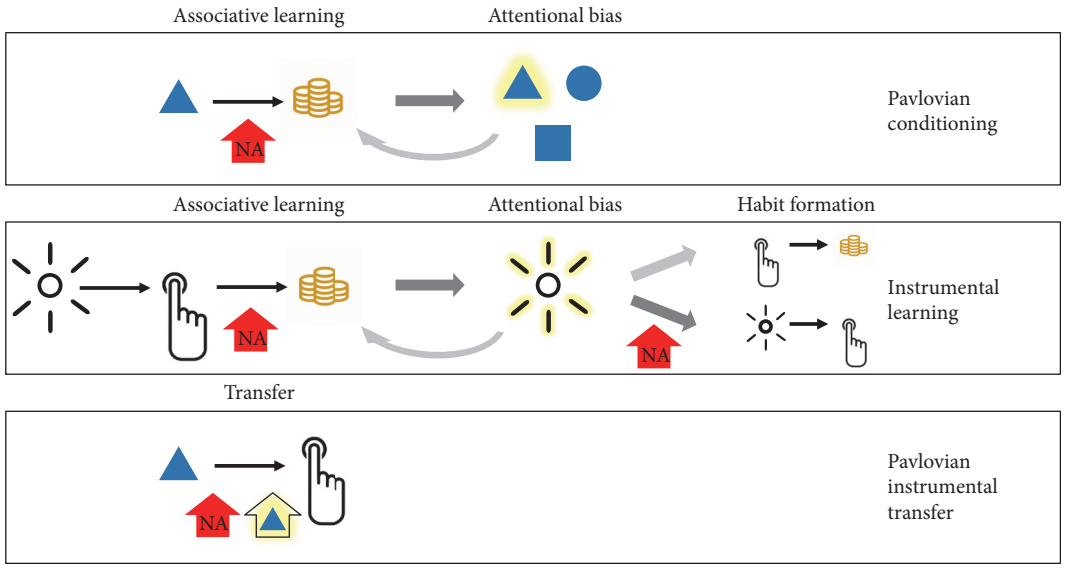
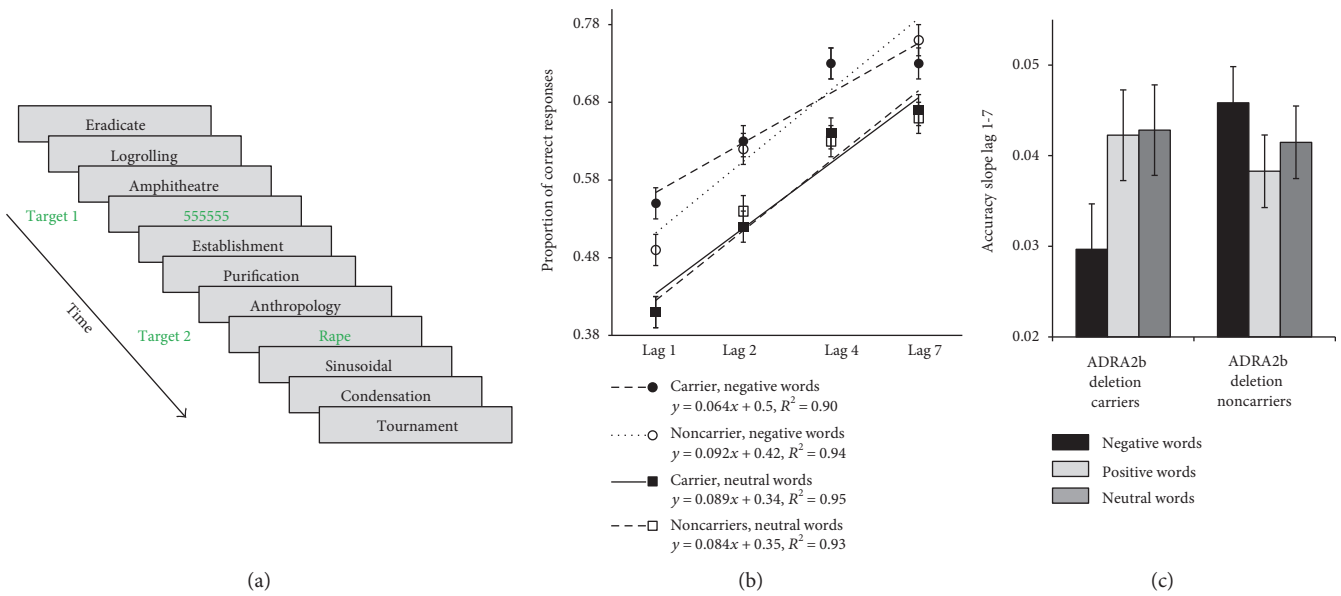


Figure 2: Overview over how (appetitive) noradrenaline (NA) modulated associative learning may give rise to attentional biases. In a simple Pavlovian conditioning paradigm, NA may influence associative learning processes leading to attentional bias for conditioned stimuli (CS) (for both appetitive and aversive unconditioned stimuli). In instrumental learning, initial learning of action-outcome relation is affected by NA giving rise to attentional biases for action-triggering stimuli. In a second step, attentional biases and noradrenergic processes may bias behaviour towards the habitual by strengthening stimulus-response over action-outcome relations. Finally, Pavlovian CS can influence instrumental responding, a process that may be influenced by both NA and attentional biases to the CS. Enhanced associative learning can manifest in excessive attentional biases characteristic of psychopathology.

world (for review, see [4]) (Figure 1). NA neurons in the LC are phasically activated by salient environmental events, including visually salient, novel, task-relevant, or emotionally salient stimuli [30–32], resulting in release of NA. Such phasic LC activity has been associated with selective attention to relevant stimuli [33]. Current theoretical models suggest that phasic NA specifically plays a role in modulating neural gain associated with biased competition processes, reducing the threshold of sensory neurons to cues that are *relevant* either due to explicit task-related demands, visual salience, or motivational/affective salience acquired through life experience [4, 29, 34], while raising the threshold for neurons processing irrelevant ones. Phasic NA activity is thus thought to increase discrimination between relevant and irrelevant environmental information [35], improving the signal-to-noise ratio for relevant stimuli [36]. In their recent GANE model, Mather and colleagues have further emphasized interactions between glutamate and NA processes in creating hotspots that modulate effects of arousal on learning and memory [29]. Yet, LC-NA activity is also important for sensor-gating processes by which silent neurons become responsive to relevant stimuli, with additional neurons recruited in a process that does not necessarily require suppression of surrounding neurons [27, 37]. Importantly, LC-NA activity plays a role in establishing biases for particular categories of stimulus via associative learning (Figure 2). LC neurons can initially fire in response to direct reward and punishment and subsequently fire to any stimuli associated with the salient event [27]. Studies in rodents suggest that, in development, when noradrenergic alpha2b receptors mature, emotional learning is strongly reduced [38]. Moreover, modulation of long-term changes in synaptic strength and gene transcription allows the NA system to guide behaviour based on stimulus salience within a given context [39].

Our own research has contributed to a body of evidence indicating that biologically conferred differences between individuals, including genetic variations influencing NA activity, are associated with affect-biased attention to either emotionally arousing stimuli in general or positively or negatively valenced stimuli in particular [40–44]. In humans, genotyping for a common (~50%) deletion variant of the *ADRA2b* gene, which codes for alpha2b NA receptors and is thought to be associated with higher levels of intercellular NA [45, 46], provides a tractable window into the role of naturally occurring differences in NA availability on human cognitive endophenotypes. Building on previous research establishing a role for *ADRA2b* in emotional enhancement of memory, we used genotyping to examine the role of NA in affectively biased attentional prioritization, which might partly account for emotional enhancement of memory effects. As enhanced encoding of emotionally salient stimuli has been found to predict both subsequent recall and recognition memory (e.g., [47]), we hypothesized that carrying the deletion variant would be associated with a priori attentional tuning to emotional stimuli, resulting in higher likelihood of encoding emotionally salient stimuli. One method of measuring attentional prioritization is with an attentional blink paradigm (Figure 3). In this experiment, in every trial, an observer is faced with a rapid stream of stimuli and from it has to report two targets. When the second target (T2) appears within 500 ms of the first, observers are typically unable to report it [48]. This is called the *attentional blink*, because it is as if the mind blinks while neurocognitive resources are still tied up in encoding the first target (T1).



(a) (b) (c)

Figure 3: (a) Sample trial in attentional-blink (AB) task. Two targets were presented among several distractors: target 2 was a positive, negative, or neutral word. It was presented after target 1 after zero (Lag 1), one (Lag 2), three (Lag 4), or six (Lag 7) distractors. At the end of each trial, participants had to report both targets. (b) Proportion of correct responses for *ADRA2b* deletion carriers and noncarriers as a function of the lag between the two targets and emotion category. (c) The slope for accuracy from Lag 1 to Lag 7 as a function of group and emotion category. Adapted from "Genes for emotion-enhanced remembering are linked to enhanced perceiving" by Todd et al. [41]. Copyright 2013 by Sage Publications.

Yet, when T2 is emotionally salient, the attentional blink is somewhat reduced, in a robust finding we refer to as *emotional sparing*. Following on the work of Di Lollo and colleagues [49], we have proposed that emotional sparing reflects implicit attentional tuning that facilitates awareness of emotionally relevant stimuli. Crucially, we have found that, whereas both carriers and noncarriers of the *ADRA2b* deletion variant show emotional sparing for both positive and negative stimuli, deletion carriers show an even greater sparing effect for negative stimuli, indicating a role for naturally occurring NA differences in biases in attentional prioritization [41] (Figure 3). Thus, putatively higher levels of NA availability were associated with attentional prioritization of affectively salient stimuli, such that they were more likely to be perceived, relative to neutral stimuli, in the first place. In an additional study, we showed participants positively and negatively arousing as well as low arousal scenes and measured recognition memory for the images in a surprise memory task one week later. Here, we found that enhanced subjective ratings of stimulus arousal during encoding were linked to enhanced memory one week later in deletion carriers only. Thus, putative differences in NA availability were associated with a stronger pattern of emotional enhancement of memory. These findings were consistent with nonhuman animal findings indicating that higher NA availability at encoding interacts with NA-mediated consolidation processes to produce enhanced memory for emotional events (for review, see [50]). Our own biased attention by norepinephrine (BANE) model emphasizes the role of the LC-NA system in brain circuits that mediate guidance of visual attention to emotionally salient stimuli, focusing on modulation of visual cortex by brain systems centered on the amygdala, ventromedial prefrontal cortex (VMPFC), and LC [4] (Figure 1). In a functional magnetic resonance imaging (fMRI) study, we found that *ADRA2b* deletion carriers subjectively perceive emotionally salient stimuli to be more perceptually vivid (higher signal-to-noise ratio) relative to neutral stimuli than noncarriers [40] (Figure 4). This effect of emotionally enhanced vividness (EEV) is associated with amygdala modulation of the visual cortex [47]. Consistent with the nodes of brain networks emphasized by the BANE model, this effect of putatively greater NA availability on EEV was associated with enhanced activity in hubs of the BANE network, particularly VMPFC (Figure 3). The prevalence of the *ADRA2b* deletion variant makes it a tractable tool for examining naturally occurring NA variation-related activity of alpha2b receptors in humans. However, other receptor subtypes also play an important role in modulating NA's effects on cognition. A substantial amount of animal research has demonstrated the importance of high affinity alpha2 and lower affinity alpha1 receptors for optimal functioning of the prefrontal cortex (PFC). More specifically, it has been shown that moderate levels of NA promote PFC functions such as working memory and top-down attention mechanisms as well as decision-making and emotion regulation (for review, see [51, 52]). Thus, it is likely noradrenergic activity at that these receptors also play a role in biased attention and learning.

2.3. Attentional Bias as Product of Emotional Learning. As mentioned above, implicit biases in attentional prioritization not only influence what we encode and remember but they are also themselves the product of learning and memory (Figure 2). Our research has found that in "real life," the

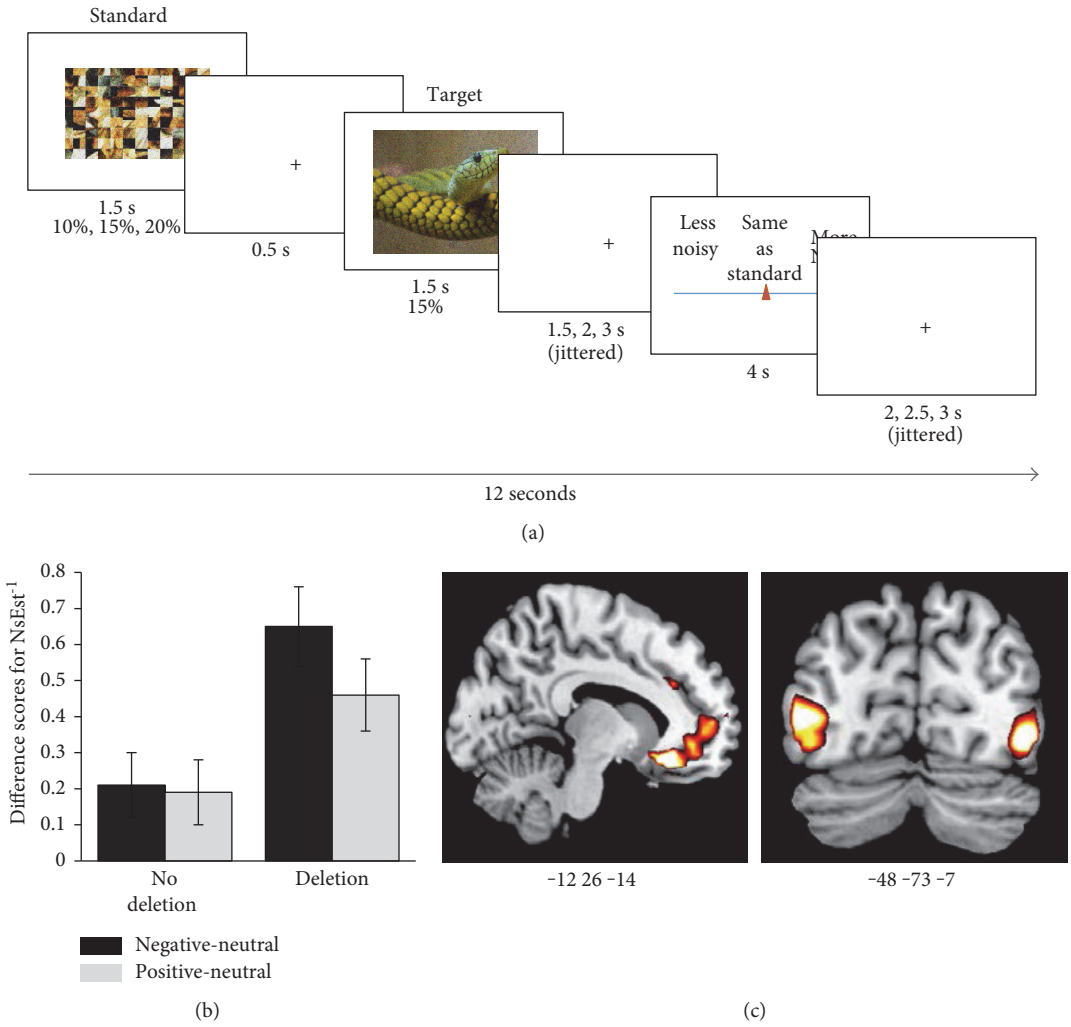


Figure 4: (a) Noise Estimation task to determine emotionally enhanced vividness (EEV). A standard (scrambled image) was overlaid with varying levels of noise. The standard was followed by the target overlaid with 15% noise. Participants were asked to indicate whether the target had more or less noise relative to the standard. (b) Difference scores for ratings of inverse noise estimation ($NsEst^{-1}$), a measure of perceptual vividness for negative and positive > neutral stimuli in noncarriers and carriers of the *ADRA2b* deletion variant. Deletion carriers show greater EEV than noncarriers. (c) Statistical maps showing parametric modulation by EEV in the ventromedial prefrontal cortex for *ADRA2b* carriers > noncarriers and in the lateral occipital complex showing modulation by EEV across both groups. Adapted with permission from "Neurogenetic variations in norepinephrine availability enhance perceptual vividness" by Todd et al. [40]. Copyright 2015 by the Society for Neuroscience.

categories of stimulus for which attentional selection is biased are strongly shaped by traumatic experiences. Through these experiences, neutral stimuli are linked to high emotional arousal through associative learning processes [12, 53]. Moreover, the degree of this bias predicts PTSD diagnosis and is highly correlated with anxiety symptoms. Such examples of high-arousal associative learning experiences mirror effects found in controlled laboratory experiments using fear conditioning and complement a wide literature linking fear conditioning to anxiety disorders [54–57]. On the other end of the valence spectrum, attentional biases for substance-related stimuli, or cues, which predict craving in addiction can also be created through classical conditioning processes [58, 59]. Thus, considerable evidence suggests that attentional biases towards specific categories of salient stimuli develop through associative learning processes, and they do so at time scales that can range from minutes to decades. Moreover, evidence in humans and nonhuman animals suggests that NA also plays a role in such associative learning processes, potentially contributing to the biases that predict psychopathology (Figure 2).

3. Associative Learning in Humans and Nonhuman Animals

Associative learning is used as an umbrella term to refer to different types of learning that are characterized by the development of conscious or unconscious associations between a certain cue or action and the occurrence of a specific stimulus. For example, in an aversive *classical conditioning* paradigm, an animal learns to associate an initially neutral stimulus (CS+) with an aversive stimulus or event (US) that

elicits an innate response [60]. After learning, the presentation of the CS+ alone leads to the aversive response. In *operant conditioning* or *reinforcement learning*, an animal learns that performing a certain action (e.g., pressing a lever) is followed by a specific outcome (e.g., delivery of food reward). Similar paradigms have been developed to study associative learning in humans. In the following paragraphs, we will review research on aversive and appetitive conditioning in both human and nonhuman animals, focusing on the role of NA and its relation to psychopathology.

3.1. Aversive Conditioning. The study of aversive conditioning in nonhuman animals has a long history of employing mild electric shocks as US and tones or lights as typical CS + stimuli. Robust conditioning can be achieved after only a few continuous pairings of the CS with the US. Aversive conditioning in humans can employ a wide range of possible CS and US [61], and the extent of associative learning can be assessed by skin conductance response (SCR), eye blink reflex, and subjective stimulus ratings [1]. Aversive associations can also be learned quickly through instrumental or operant conditioning, in which subjects learn that a certain action will be followed by an aversive event. Studies of aversive conditioning have become essential for understanding the emergence of fear and fear-related disorders [62] and are important in identifying individual differences underlying susceptibility to anxiety disorders [63].

3.1.1. Neurocircuitry Underlying Aversive Conditioning. The brain circuitry underlying aversive conditioning is also quite well mapped. Research in nonhuman animals as well as lesion and neuroimaging studies in humans has identified the amygdala, the hippocampus, and the ventromedial prefrontal cortex as key nodes in brain systems underlying aversive conditioning. The amygdala plays a role in integration of information about CS and US and controlling fear responses via projections to autonomic and endocrine control systems in the brainstem [62]. Lesions of the amygdala are associated with impairments in both cue and context conditioning. In contrast, targeted lesions of the hippocampus lead to impaired context conditioning but not simple cue conditioning [64], indicating a dissociation between the roles of these two structures. The VMPFC is not only involved in extinction of learned fear by suppression of amygdala activity through interneurons [65, 66] but has also been shown to modulate fear-related activity in the amygdala and play an essential role in modulating fear expression [67]. Critically, this set of brain regions receives dense noradrenergic projections from the LC [68, 69].

3.1.2. The Role of NA in Aversive Conditioning—Relation to Psychopathology. Alterations in this circuit mediated by the LC-NA system are thought to underlie maladaptive patterns of fear learning expressed as fear and anxiety disorders such as PTSD [70, 71]. Fear learning is of course highly adaptive and critical for animals' well-being and survival. In situations of potential or actual threat or danger, rapid fear and defense mechanisms—including the release of NA and stress hormones—are activated [72, 73]. However, fear and stress responses are adaptive only when the timing and level of their activation are appropriate to the situation. A dysregulation of fear response or defensive behaviour can develop into a fear or anxiety disorder [74]. For example, posttraumatic stress disorder (PTSD) is an anxiety disorder characterized in part by attentional biases to mild stressors or cues related to the traumatic event that gave rise to the disorder as well as intrusive memories of the traumatic event [12, 75]. Pavlovian fear conditioning has been widely used as an animal model for PTSD contributing to the current understanding of the disorder [13]. Animal models of fear conditioning and human studies with PTSD patients and healthy controls provide evidence for a critical role of NA in this example of disordered fear learning. For example, patients with PTSD show greater baseline cerebral spinal fluid (CSF) NA concentrations [76] as well as elevated CSF NA levels after exposure to trauma-related material [77]. Much research on NA and PTSD has focused primarily on symptoms of the disorder or the fear response. For example, human studies found that the administration of the alpha2-adrenergic antagonist yohimbine (resulting in enhanced NA release) led to increased anxiety in patients with PTSD but not in control subjects [78]. Similarly, human PTSD symptoms have been alleviated by blocking NA activity: "beta blockers," which reduce activity of beta-adrenergic receptors, have been demonstrated to be effective to reduce symptoms of anxiety in PTSD [79]. Convergent findings have demonstrated that pharmacological activation of inhibitory autoreceptors or blockade of postsynaptic alpha-1 adrenoceptors normalized exaggerated startle responses to contextual reminders of stress in a rodent model of PTSD [80]. Similarly, more recent human research has demonstrated that application of alpha1-adrenergic antagonists has been further shown to reduce psychological distress to trauma-related cues [81], and noradrenergic antidepressants have been demonstrated to be more successful than serotonergic antidepressants especially in patients with comorbid alcohol dependence [82]. Moreover, carriers of the *ADRA2b* deletion variant showed greater susceptibility to intrusive traumatic memory than noncarriers, suggesting a role for these receptors in the intrusive memory component of PTSD [45].

While one long-prevalent idea has been that PTSD results from disturbances in memory consolidation [83]—a process that has been shown to be highly modulated by NA [84]—recent intensification of interest in memory reconsolidation [85] has sparked new research in the field of PTSD and NA. Memory reconsolidation describes the process by which reactivation of a memory makes it modifiable. The potential to harness reconsolidation processes to manipulate traumatic memory is promising for the treatment of PTSD given its common resistance to extinction. Critically, it has been shown that beta-adrenergic stimulation of the amygdala after retrieval can enhance memory reconsolidation of fear memories, which makes them resistant to extinction, suggesting that noradrenergic activity during retrieval is likely to contribute to the formation of fear memories [86]. In turn, blockage of reconsolidation by alpha2-adrenergic agonist clonidine (resulting in reduced NA levels) has been shown to disrupt fear-related memories [87]. Thus, there is

substantial convergent evidence linking PTSD, as an example of a disorder thought to be the result of disrupted fear learning, to altered noradrenergic transmission in fear learning and possible memory modulation. We speculate that NA-modulated alterations in fear learning observed in patients with PTSD may give rise to robust attentional biases for trauma-related cues observed in patients [12], demonstrating that specific affectively biased attentional sets develop as a result of individual differences in associative learning. Future research should test this hypothesis directly. While assessing NA activity in vivo in humans has been highly challenging to date (the LC is too small and variable between individuals to be reliably located with MRI [88]), pupil dilation is being found to be a relatively reliable index of LC activity [89–91], and imaging of neuromelanin has been recently employed as a measure of individual differences in LC structure [92, 93].

3.2. Appetitive Conditioning. Appetitive conditioning is an associative learning process by which initially neutral stimuli or events become associated with a reward and hence gain motivational salience (Figure 2). In appetitive classical conditioning, the presentation of a cue (CS+) becomes passively associated with a reward (US). Reward learning is more often studied in the form of appetitive operant conditioning or reinforcement learning. Here, a reward is obtained after the animal performs a certain action, which is hence reinforced [94]. Operant conditioning is thought to be driven by two distinct processes. Investigating the temporal dynamics of these processes is critical for the understanding of psychopathology related to reinforcement learning such as the development of addictive behaviours [95]. Early in the learning process, animal behaviour is predominantly goal directed; the animal performs the action leading to a reward (e.g., drug taking), the action-outcome association is developed [96]. Later behaviour becomes much more habitual or even compulsive, that is, that no longer the reinforcing property of the reward (e.g., the drug) leads to action completion but the action is performed irrespective of the actual outcome and even despite negative consequences [97]. Critically, this shift in behaviour has been shown to be promoted by glucocorticoid and NA release as part of the stress response [98, 99] (Figure 2). Neuroimaging data suggest that NA and glucocorticoid action disrupt the neural basis for goal-directed behaviour [100]. The authors report that under influence of these stress hormones, the OFC became insensitive to changes in outcome value while brain regions related to habit behaviors (e.g., dorsal striatum) were unaffected allowing those behaviours to take over under acute stress.

3.2.1. Neurocircuits Underlying Appetitive Conditioning. Converging evidence from human and nonhuman studies suggests that the amygdala plays a key role in appetitive conditioning. The amygdala has been shown to be critical for outcome evaluation and cost estimation [101, 102] as well as for the development of CS-US associations and attentional modulation in reward processing [103–105]. Due to its rich connections with the OFC and striatum, the BLA is also important for integration and relay of information allowing for flexible, goal-directed behaviour [95, 101, 103]. The OFC in turn receives information from the amygdala and is central for reward evaluation and outcome expectancies [106]. Besides the OFC, the anterior cingulate cortex (ACC) has been shown to be an essential node of circuitry required for normal contingency learning [107] as well as for the discrimination of multiple conditioned stimuli [108]. The striatum has been suggested to play a general role in the processing of stimulus salience [109] and is also of major importance for the formation of habits [110] and hence for psychopathology associated with appetitive learning. The central role of dopaminergic action in the ventral striatum with projections to the prefrontal cortex and amygdala is well established and has been extensively reviewed elsewhere [111–113]. However, this set of brain regions also receives dense noradrenergic projections from the LC [68, 69] and displays a high density of alpha2-adrenergic receptors [114]. As mentioned above, due to its small size and considerable variability in location, LC activation has been challenging to measure with common neuroimaging methods such as fMRI [115]. However, from animal research, it has long been known that the LC displays conditioned responses after only a few learning instances for both aversive as well as appetitive reinforcers [116] as further discussed in the next section.

3.2.2. The Role of NA in Appetitive Learning—Relation to Psychopathology. Increasing evidence suggests that the LC-NA system not only is important for aversive conditioning but also plays a role in reward processing related to addiction. Decades of research have established that dopamine (DA) is essential for the reinforcing effects of various rewards such as drugs [117–119]. A selective role of DA in reward learning has been shown to be that of a mediator of incentive salience that is the motivational properties that a stimulus develops through conditioning [112, 118]. In other words, DA has been shown to be essential for the "wanting" of a reward, but not for the associated pleasure, or "liking," or for the associative learning process. Furthermore, DA has been shown to be a key for the coding of reward prediction errors, operationalized as the difference between anticipated and actual reward [120]. In contrast, the contribution of NA has been relatively neglected [121] despite its abundance throughout the brain and its central role in arousal, attention as well as cognitive flexibility and adaptation [27, 35]. However, recent investigations have linked activation of the noradrenergic system to motivation. NA has been shown to be important for morphine-associated conditioned place preference (CPP) [122] as well as its rewarding effects [123]: decreasing noradrenergic activity (by stimulating alpha2-adrenergic autoreceptors) inhibits the development of CPP, while enhancing NA availability (by receptor inhibition) facilitates conditioning for actual reward learning processes. Previous research has further demonstrated that if NA transmission in the mPFC is blocked, DA release in the nucleus accumbens in response to morphine or amphetamine is abolished, suggesting that prefrontal NA has a central role in the rewarding effects of some drugs [124, 125]. The authors speculate that this effect can be explained by blocking NA effects on the striatum via three distinct routes: NA activates (1)

excitatory projections to the ventral tegmental area, (2) glutamatergic projections to the nucleus accumbens, and (3) GABAergic neurons controlling DA neurons through double inhibition. Thus, in this instance, NA may work as a control instance-mediating reward-associated dopaminergic activity. Future research has to be conducted to provide evidence for this hypothesized role. A series of single-cell recording studies conducted in monkeys by Bouret and Richmond further supports the involvement of the LC-NA system in reward learning. Single-cell recordings from LC neurons during a task with both Pavlovian and operant components revealed that LC neurons are activated during conditioned responses and their response is modulated by goal-directed processes [126]. Directly comparing activity of noradrenergic LC and dopaminergic substantia nigra pars compacta neurons suggests that these neurotransmitters play slightly different roles, with DA responding to rewarded actions—possibly related to value—while NA neurons fire in response to unrewarded action, potentially suggesting it signals the cost associated with an action [127]. More recent research further suggests that the LC plays a role in reward processing by integrating motivationally relevant information such as cue information and reward size [128]. The authors extend their interpretation of the results to conclude that the LC is necessary to trigger actions requiring a high amount of energy because the incentive salience is low. This idea is supported by their findings showing that noradrenergic neurons increase their firing rate with increased effort in an effort-based decision-making task [91]. That is, LC activation is necessary to produce behavioural energy in such a task after a cost-benefit analysis, while dopaminergic activity codes information about the costs and benefits involved. Empirical evidence further suggests that the LC might be related to environmental uncertainty. In an fMRI study, phasic pupil diameter as a proxy for LC activity correlated with uncertainty during learning in a predictive-inference task [129]. In contrast, another study revealed a negative response to unexpected uncertainty in the LC while human participants performed a decision-making task [130]. The authors speculated that theses conflicting results could be explained by the characteristics of phasic LC mode. Phasic firing has been associated with enhanced task engagement [35] and involves both a decreased baseline firing rate as well as increased phasic responding to task-relevant stimuli [130]. Thus, while the results of the first study fall in line with the predicted association of phasic firing rate and task performance, the results of the second study suggest that the signal observed under conditions of high uncertainty reflect baseline activity [130]. As summarized in a recent theoretical paper, this empirical evidence supports the idea that the LC-NA system may work as an uncertainty signal-driving behaviour to adapt to environmental changes [131]. Extrapolating from these findings, we propose that the activation of the LC-NA in situations of uncertainty with respect to reward expectations facilitates attentional biases for reward-related cues (Figure 2). Such biases in turn allow for more efficient and eventually habitual tracking [59] of cue-outcome relations. Failures of reward evaluations may give rise to the excessive attentional biases for reward-related cues that have been found to characterize addiction [59].

Putative neuronal mechanisms underlying the role of LC-NA in attentional mechanisms related to reward have been further elucidated in a recent study suggesting a major role of the LC-NA system in modulating neural gain [34]. Under some circumstances, increased gain, which is associated with greater NA availability, narrows attention to those categories of stimulus that individuals are already predisposed to attend to and strengthens only the strongest neural connections. As a result, behaviour can become more rigid, flexibility can be impaired, and habitual behaviours are favored [34]. This model is in line with an existing theory relating the LC-NA system to neural gain [35] as well as with empirical evidence showing that pupil diameter as an index of LC activity predicts exploration versus exploitation between individuals as well as across trials [132]. The model has important implications for reward learning as it can explain the described shift from goal-directed to habitual behaviour. Such a shift observed upon simultaneous noradrenergic and glucocorticoid action [100, 133] and is prevented when noradrenergic activity is blocked [134]. That is, under conditions of high gain or high NA levels, behaviour shifts from flexible, goal-directed behaviour to more rigid, habitual control of behaviour. It is no longer the rewarding outcome driving ones' behaviour but simple stimulus-response mechanisms that have been established [133]. It also proposes neural mechanisms underlying the development on habitual or automatic attentional biases from reward learning [59]. Future studies employing convergent techniques to manipulate and measure NA activity in humans, such as pupil dilation [89], stress induction, pharmacological challenges, and genotyping, will be necessary to further investigate the role of NA in appetitive conditioning and its relevance for psychopathology.

A prevailing view in the addiction literature is to characterize addiction as a disorder of appetitive learning [97]: On the one hand, drugs act as reinforcers, such that the rewarding effect of the drug leads to enhanced drug taking. On the other hand, environmental stimuli that become associated with the drug effects can acquire incentive salience through Pavlovian conditioning [95]. An important component of addiction is an imbalance of goal-directed and habitual behaviours. In the beginning, drug taking or substance use is a goal-directed process guided by the reinforcing properties or the "liking" of the drug. However, over time behaviour can shift towards the habitual. That is, "wanting" or craving for the substance develops irrespective of the rewarding outcome and often despite accompanying negative consequences—a process shown to be dependent on dopaminergic action [117]. Thus, instead of relying on action-outcome relations, addicts show a high degree of stimulus-response instrumental responding. Support for this idea can be found in both human and nonhuman animal research (for review, see [97]). These findings raise the question of what determines whether behaviour shifts from goal directed to habitual and what may make some people more prone to experience the shift. We propose that the LC-NA system contributes to this shift and that individual differences in NA availability may underlie differences in vulnerability to addictive habits (Figure 2). As described earlier, in some contexts, high NA levels have been associated with more rigid, less

flexible behaviour [34]. Thus, either transient elevation of NA levels (e.g., by acute stress) or altered NA availability based on genotype (e.g., *ADRA2b* polymorphism) may explain greater predisposition to maladaptive habit formation observed in some individuals. In fact, both human and nonhuman studies have revealed that chronic or acute stress can bias behaviour towards the habitual [98, 135, 136] adding to the literature showing that acute stress—and resultant NA and corticosteroid action—elevates drug self-administration and promotes relapse [137, 138]. Pavlovian learning has also been shown to be a factor in drug addiction since environmental and drug-related cues can promote craving, drug taking, and relapse [97]. As described earlier, associative learning can largely modulate attentional biases—for example, to drug-related cues—which in turn guide or control our behaviour. Biases to those reward-related cues, which become habitual based on learned associations [59], can in turn inform instrumental behaviour through Pavlovian-instrumental transfer (PIT), in which an initially neutral cue that becomes associated with the drug may elicit instrumental or habit behaviour such as drug taking (Figure 2). Critically, PIT has likewise been demonstrated to be promoted by acute stress [139] and thus is likely influenced by NA-related processes. Yet, whereas empirical evidence points towards an involvement of the LC-NA system in normal reward learning, evidence for a role of the LC-NA system in addiction is sparse [140].

While addiction is characterized by attentional biases associated with increased approach motivation, the opposite picture is present in patients with major depressive disorder (MDD). Anhedonia—the inability to experience pleasure—is a cardinal symptom of depression [141, 142]. Importantly, anhedonia is characterized by reduced attentional biases to reward [143]. This again is thought to be due to altered patterns of associative learning observed in depression [144–146]. A number of studies have suggested that patients with depression display a deficit in approach motivation are less responsive to rewards and show reduced activation in reward circuitry (for review, see [147]). A recent study employed a computational meta-analysis to formalize the relation between anhedonia and reinforcement learning and to answer the question of whether MDD patients simply show reduced reward sensitivity or whether the ability to learn from a reward signal is impaired [148]. The results suggested that the actual learning rate—that is, the speed with which the action-outcome association is established—is not affected in patients with depression. However, patients show overall reduced effort and willingness when working for the same reward as controls, suggesting that their reward sensitivity is reduced. Besides its direct relevance for the psychopathology of anhedonia, these findings also suggest that reward-related learning has at least two distinct contributions: learning rate and reward sensitivity [148]. This distinction is critical for our understanding of how associative learning informs attentional biases. Consistent with the proposed link between attentional biases and associative learning processes, patients with anhedonia display altered reward learning as well as reduced attentional biases [149, 150]. This suggests that altered learning processes indeed give rise to differences in attentional prioritization related to psychopathology. In line with the above proposed role of NA in reward learning, there is additional evidence that acute stress, as a natural stimulator for NA and glucocorticoid release, affects reward sensitivity [151–153]. It is critical to point out that based on current research, noradrenergic processes are not easily distinguishable from the involvement of the dopaminergic and serotonergic system. The goal of this review is to propose the LC-NA system as an additional factor contributing to the pathological alterations observed.

In summary, a large body of literature suggests that NA-mediated alterations and individual differences in the appetitive associative learning system give rise to specific patterns of biased attention. Attentional biases can both be strengthened (e.g., addiction) and weakened (e.g., depression) through reward learning and can develop into deeply habitual patterns of orienting to the world that underlie the etiology and maintenance of psychopathology.

4. Conclusion

In summary, we have argued that NA plays an important role in the genesis and maintenance of biased attention patterns that are established via associative learning processes. Here, we first reviewed evidence for the emergence of attentional biases linked to psychopathology in development and the role of putative individual differences in NA availability in such biases. We next reviewed associative learning processes that can give rise to such biases, as well as evidence suggesting a role for NA in specific patterns of fear learning linked to PTSD and appetitive learning linked to both addiction and depression. Based on convergent evidence, we propose that attentional biases play a key role in creating and maintaining prioritization of relevant cues as well as the transfer of reward learning to habitual behaviours associated with addiction. We hypothesize that after attentional biases for reward-related cues are formed through associative learning processes, they are themselves used to inform and prompt behaviours. More specifically, they may facilitate the formation of habitual behaviours by redirecting attention from the outcome to the cue. This is a possible mechanism that could explain why habitual behaviours are performed even if the outcome changes towards the negative. In addition, such biases themselves form deeply habitual patterns of orienting to the world, which can play an important role in etiology and maintenance of psychopathology.

5. Future Directions

A number of outstanding questions remain. First and foremost, little is known about the role of NA in appetitive learning in humans. While previous research in humans demonstrated a role of stress in habit formation and Pavlovian-instrumental transfer, it remains to be investigated whether initial reward learning is affected by NA availability. Future research can examine this by manipulating NA availability, for example, through acute stress induction or by using the *ADRA2b* genotype as a source of naturally occurring differences in NA availability. It will be important to

delineate how both operant and Pavlovian conditioning are affected by these manipulations and whether it is actual learning rate or reward sensitivity that is affected. Future research should aim to disentangle these two components of reward learning. If stress is used as a means to activate the LC-NA system, the intensity and type of stressor need to be considered [154]. Effects of stress are most likely to be observed when the stressor acts on those brain regions that are involved in task completion [154, 155]. The effects of varying stress levels are best represented in the well-established inverted U curve of arousal, which indicates that performance is best at intermediate stress or arousal levels while both low and high stress levels have a relative negative impact [156, 157]. Thus, the level of arousal, as well as the source of stress, will play a crucial role in both the general effects of NA on learning as well as their translation into attentional biases.

Moreover, the proposed link between associative learning and attentional biases needs to be tested directly in humans. That is, once the role of NA in associative learning is fully established, one should examine whether newly learned associations result in attentional biases for cue- or outcome-related stimuli.

In addition, the directionality of the proposed link needs to be investigated further. While converging evidence suggests that associative learning processes form attentional biases, attentional biases are likely to influence later instances of emotional learning. It is unclear whether activity of the LC-NA would further reinforce existing biases by influencing subsequent learning processes or whether one of main roles of this neurotransmitter system is to facilitate learning processes that give rise to attentional biases. It is likely that the process can be mediated at both ends; however, this problem needs to be investigated in more detail.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Review Article

The Longevity of Hippocampus-Dependent Memory Is Orchestrated by the Locus Coeruleus-Noradrenergic System

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The locus coeruleus is connected to the dorsal hippocampus via strong fiber projections. It becomes activated after arousal and novelty, whereupon noradrenaline is released in the hippocampus. Noradrenaline from the locus coeruleus is involved in modulating the encoding, consolidation, retrieval, and reversal of hippocampus-based memory. Memory storage can be modified by the activation of the locus coeruleus and subsequent facilitation of hippocampal long-term plasticity in the forms of long-term depression and long-term potentiation. Recent evidence indicates that noradrenaline and dopamine are coreleased in the hippocampus from locus coeruleus terminals, thus fostering neuromodulation of long-term synaptic plasticity and memory. Noradrenaline is an inductor of epigenetic modifications regulating transcriptional control of synaptic long-term plasticity to gate the endurance of memory storage. In conclusion, locus coeruleus activation primes the persistence of hippocampus-based long-term memory.

1. Introduction

The locus coeruleus (LC) resides in the brainstem's dorsal pons, is the main origin of noradrenaline (NA) in the central nervous system, and is linked to the hippocampus [1], thus being essential for hippocampus-based declarative memory formation [2]. Nevertheless, LC projections are ubiquitous in the brain, targeting other brain structures involved in memory formation such as the amygdala [3] and the prefrontal cortex [4]. However, its projection specificity encompasses unique roles in memory processes [5]. The LC-NA system regulating memory function must be considered as an orchestra composed of different neural circuits that are functionally linked to the hippocampus, such as the amygdala [6] or prefrontal cortex [2] receiving projections from the LC [3, 4] thus making them subject to NA modulation. The orchestra's function is guaranteed by each neuronal circuit's activity.

2. Noradrenaline Release after Locus Coeruleus Activation

The LC is activated after novelty [7] and arousal [8]. NA is released within the LC after its activation [9, 10]. In addition, electrical activation of the LC leads to NA release in the rodent dentate gyrus [11], an important input structure in the hippocampus (Figure 1). A model of LC function proposed by Atzori et al. [12] related the NA concentration in different brain activation states regulating sleep and wakefulness with the activation of α1-, α2-, and β-adrenoreceptors. β-adrenoreceptors are believed to be activated by interplay between tonic and phasic firing of LC neurons [12] in the hippocampus that is innervated by LC projections [13] and richly endowed with β-adrenoreceptors [14, 15].

The noradrenergic system's importance and modulatory role in forming memories was postulated by Kety in the 1970s [16, 17]. A decade later, this hypothesis was confirmed

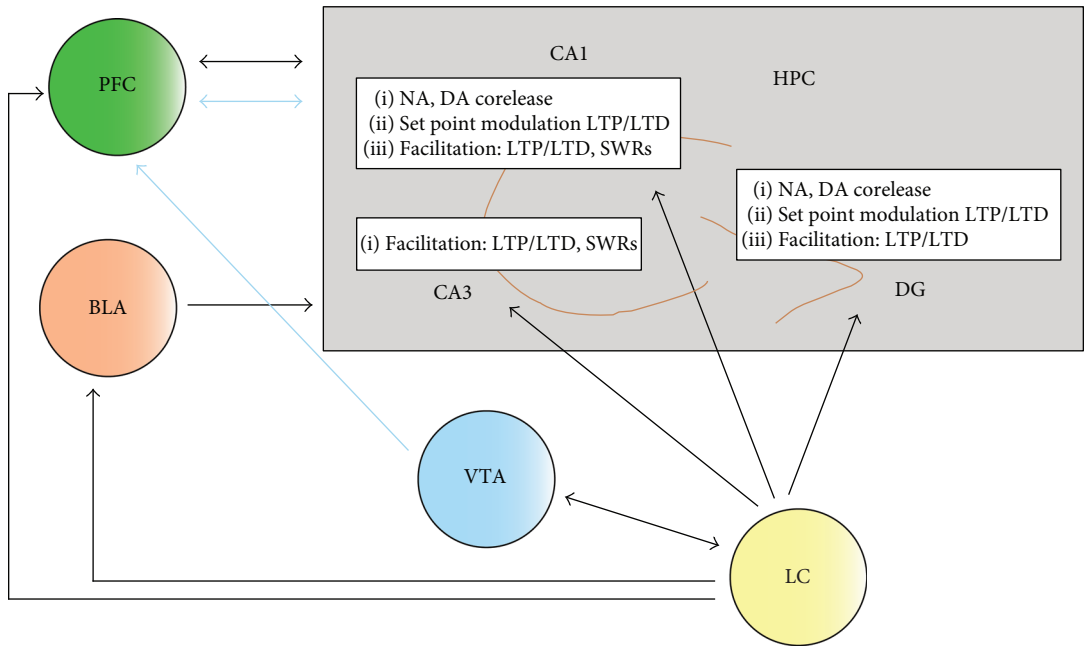

Figure 1: Priming of hippocampus-based memory via locus coeruleus activation. The ventral tegmental area (VTA) and LC are interlinked by fiber projections [35]. After locus coeruleus (LC) activation, noradrenaline (NA) and dopamine (DA) are released in the dentate gyrus of the hippocampus from LC terminals [11, 13]. The LC projects also to the CA1 and CA3 region of the hippocampus [82]. The main mechanisms involved in how memory is primed by NA and DA are indicated in boxes at specific hippocampal subregions [25–28, 33, 63, 72]. Moreover, two other brain structures such as the basolateral amygdala (BLA) and the prefrontal cortex (PFC) receive projections from the LC [3, 4] and participate in noradrenergic and dopaminergic modulation of hippocampus-based memory [6, 49, 61]. BLA = basolateral amygdala, DG = dentate gyrus, HPC = hippocampus, LC = locus coeruleus, LTP = long-term potentiation, LTD = long-term depression, PFC = prefrontal cortex, SWRs = sharp wave ripples, VTA = ventral tegmental area.

by experimental data in the rodent hippocampus. Harley's group was the first to demonstrate that applying NA can enhance the spike activity of the field potential in the dentate gyrus elicited by stimulating the perforant pathway [18] which is a major input pathway to the hippocampus connecting the entorhinal cortex with the dentate gyrus. Furthermore, NA depletion in the dentate gyrus promotes long-term potentiation (LTP) [19]. These findings suggest NA's major role in hippocampal LTP and memory, as LTP is considered a cellular mechanism of learning and memory [20].

3. Memory Encoding and Consolidation Are Promoted by Locus Coeruleus Activation

Early experiments in rats in the 1970s revealed that bilateral LC lesions can impair hippocampus-based spatial memory encoding assessed by the T-maze task [21] (see Table 1 for examples of memory modulation via LC activation). Memory consolidation is a key step toward building robust long-term memories. In the same decade, another group demonstrated by electrolytic LC lesions in mice that the LC is essential to this step in consolidating memory within a critical time period [22]. Experiments in rats two decades later revealed that the LC is involved in spatial and nonspatial learning processes [23], demonstrating that unilateral LC lesions lead to slightly, and bilateral LC lesions to strongly affected nonspatial and spatial memory functions [23]. Memory consolidation is further influenced by the occurrence of sharp wave ripples. These are patterns of cortical oscillations that circulate and transfer information as hippocampal representations between the entorhinal cortex and hippocampus to other brain circuits in order to enable memory consolidation. Mostly, sharp wave ripples arise from the hippocampus' CA3 subregion and originate during sleep or immobility [24]. In vitro experiments in the rat indicated that β-adrenoreceptor agonism can facilitate sharp wave ripples and LTP [25], supporting the NA's role in modulating sharp wave ripples as well as synaptic plasticity and thereby hippocampal representations to consolidate memory (Figure 1).

4. Long-Term Synaptic Plasticity Is Modulated by Locus Coeruleus Activation

Nowadays, however, there is evidence that LC activation does not just enhance LTP in rodents [26]—it also facilitates long-term depression (LTD) [27, 28] as another putative mechanism of cellular memory storage [29] (Figure 1). High-frequency electrical stimulation of the LC combined with test pulse stimulation of input pathways to hippocampal subfields such as the (1) perforant path and (2) the Schaffer collaterals resulted in LTD in the dentate gyrus or CA1 region of rats [27, 28]. The modulation of LTP and/or LTD via LC activation highlights the LC's crucial role in selecting important information for further long-term storage. Electrophysiological and behavioral animal data

Table 1: Modulation of hippocampus-dependent memory via locus coeruleus activation.

Memory stages	Method of LC activation/suppression	Effect on memory	Reference
Encoding	Bilateral LC lesions	Impaired spatial memory in T-maze	[21]
	Electrical LC stimulation with 100 Hz	Improved acquisition of food-reinforced task	[57]
	Bilateral/unilateral LC lesions	Unilateral mildly, bilateral severely impaired memory assessed by Greek cross version of water maze	[23]
	LC clonidine injection	Deficits in attention, radial maze: no effect on working memory	[83]
	Electrical LC stimulation with 100 Hz	Promoted encoding of spatial memory via ß-adrenoreceptor activation	[27]
	LC lidocaine injection	Impaired acquisition of reference and working memory	[84]
	DSP 4 treatment in APP/PS1 mice	Exacerbation of short-term olfactory memory deficits	[85]
	Immunotoxic ablation of LC neurons	Water maze task: working memory deficits	[86]
	Photostimulation of LC axons	Spatial object recognition memory enhancement, D1/5 receptor dependent	[41]
Consolidation	Electrolytic LC lesions	Memory consolidation is achieved	[22]
	LC lidocaine injection	Affected memory retention in an inhibitory avoidance task after training impaired memory consolidation	[87]
	LC muscimol microinfusion	Impaired object recognition memory consolidation	[88]
	Electrical LC stimulation with 100 Hz	Caused reference memory deficit	[89]
	Electrical LC stimulation with 20 Hz	No effect on spatial learning	[89]
	Photostimulation of LC TH+ neurons	Novelty associated memory enhancement, D1/5 receptor dependent	[40]
Retrieval	Electrical LC stimulation	Facilitated memory retrieval	[50]
	Idazoxan treatment	α2 receptor antagonism enhance memory retrieval	[51]
	Electrical LC stimulation	Reduced forgetting via activation of ß-adrenoreceptors	[52]
	LC agmatine infusion	Facilitated memory retrieval, yohimbine facilitated, whereas clonidine attenuated the effects of agmatine within the LC	[90]
Extinction	Electrical LC stimulation with 100 Hz	Improved extinction of food-reinforced task	[57]

APP/PS1: amyloid precursor protein/presenilin 1; D1/5: dopamine D1/5 receptors: Hz: hertz; LC: locus coeruleus; min: minutes; SP4: N-(2-chloroethyl)-N-ethyl-bromo-benzylamine; LC: locus coeruleus; TH+: thyrosine hydroxylase positive.

indicate that LTD's supposed role in forgetting is overly simplistic. LTD also serves to encode fine spatial details in an environment as demonstrated in an in vivo study in rats showing facilitated LTD after exploring objects in new locations, whereas exploration of the novel environment without objects impaired LTD [30]. In contrast, LTP is facilitated in rats if they explore an empty holeboard as an indicator for global space [30]. Considering LTD's aforementioned roles such as encoding fine spatial details [30, 31] and of LTP—the encoding of the global environment [30, 32]—the LC's modulatory function seems to contribute to both aspects of spatial memory and relies largely on activation of ß-adrenoreceptors [27].

However, both ß-adrenoreceptors [27] and dopamine D1/5 receptors [33] are key mediators for LC-induced LTD in rodents. D 1/5 receptor agonism during novel environmental exploration promotes LTD in the CA1 region over 24 hours, whereas LC-induced LTD is blocked by a dopamine D1/5 receptor antagonism in the rat [33]. These animal study findings led to the conclusion that dopamine D1/5 receptor agonism is capable of priming late LTD depending on protein synthesis [34]. This in turn suggests that dopamine D1/5 receptors play a role in persistent memory storage. The same facilitated late LTD phenomenon was observed in the rat in perforant path-dentate gyrus synapses when a ß-adrenoreceptor agonist was applied prior to electrical LC activation [28]. Thus, LTD can be facilitated by both the application of a D1/5 receptor and ß-adrenoreceptor agonist prior to the LC activation, meaning that NA acting on ß-adrenoreceptors, in addition to dopamine (DA) activating D1/5 receptors are important for long-term memory storage. Moreover, the enhancement of spatial memory episode is critically dependent on the ß-adrenoreceptors after LC activation, as demonstrated in an episodic-like memory task [27].

5. Memory Consolidation Depends on the Corelease of Noradrenaline and Dopamine via Locus Coeruleus Terminals in the Hippocampus

The LC is reciprocally interlinked with the ventral tegmental area (VTA) [35] (Figure 1). Furthermore, other immunohistochemical studies support the direct connection from the VTA to the LC [36, 37]. The interaction of these brainstem structures is highly relevant for the modulation of synaptic long-term plasticity and memory, as DA deriving from

the VTA might be released from LC terminals in the hippocampus [13] modulating synaptic plasticity and memory via D1/5 receptor activation [38] (Figure 1). Recent evidence indicates that the LC and VTA control the synthesis of plasticity-related proteins (PRPs) for a synaptic tag [39] to promote the storage and consolidation of a memory at the site where the synaptic tag was initiated. Viral-tracing experiments revealed prominent LC and very few VTA fibers projecting into the dorsal part of hippocampus in rodents [40]. Further retrograde tracing techniques exhibited cells with retrograde labels only in the LC, not in the VTA, indicating that the LC and not the VTA sends functionally relevant projections to the hippocampus. Optogenetic and electrophysiological animal studies confirmed the LC's function in amplifying LTP via a dopamine D1/D5 receptor and not ß-adrenoreceptor-dependent mechanism [40]. Further immunohistochemical studies proved DA's release from the LC into the dorsal hippocampus. In addition, optogenetic activation of noradrenergic LC neurons in rodents led to an enhancement of spatial memory that was dependent on D1/5 receptors, but not ß-adrenoreceptors [41]. These findings seem to imply that memory consolidation is enhanced by the corelease of NA and DA in the dorsal hippocampus [40, 41] through the LC to hippocampus pathway (Figure 1). DA's role in memory encoding is not yet fully understood, but there is recent evidence that it might help encode memory by diminishing stimuli perception that interferes with memory formation [42] and by making stimuli salient for subsequent memory encoding [38].

DA and NA seem to modulate memory formation in complementary fashion. The conditions resulting in a NA and DA release differ substantially. LC neurons are activated after novelty [7], arousal [8], and aversive or reward-related stimuli as well [43, 44]. However, VTA neurons also respond to novelty, arousal, and aversive or reward-related stimuli [45–48]. Which of these conditions leads preferentially to the activation of the LC or VTA neurons remains an open question. The different release conditions of NA and DA may indicate that the two occupy different facets in memory function. A study in rats revealed such different NA and DA effects on memory with several opposite effects. Both the antagonism of dopamine D1/5 receptors and the agonism of ß-adrenoreceptors in the hippocampus impaired social recognition memory in rats [49].

6. Impact of the Amygdala on the Noradrenergic and Dopaminergic Modulation of Hippocampus-Dependent Memory

Social recognition memory depends on the interaction between the hippocampus and basolateral amydala [49]. Coinfusion of a dopamine D1/5 receptor antagonist in combination with a ß-adrenoreceptor agonist in the CA1 region and a dopamine D1/5 receptor agonist together with a ß-adrenoreceptor antagonist in the basolateral amygdala impede social recognition memory [49]. These findings indicate that social recognition memory is controlled by both dopamine D1/5 receptors and ß-adrenoreceptors in the CA1 region of the hippocampus and basolateral amygdala. The latter is involved not only in social recognition but also in hippocampus-based and prefrontal cortex-dependent memory [6] as proven indirectly by a recent in vivo study in rats showing that the basolateral amygdala can regulate hippocampal-prefrontal cortex LTP via alpha$_2$- and ß-adrenoceptors [6] as a possible memory-storage mechanism. These animal data may lead me to presume that there is an NA-dependent neuronal pathway between the amygdala, hippocampus, and prefrontal cortex starting with LC projections to the basolateral amygdala [3] (Figure 1). In addition, these experimental data might suggest that the basolateral amygdala is critically involved in the noradrenergic and dopaminergic modulation of hippocampus-dependent memory.

7. Memory Retrieval and Reversal Are Triggered by Locus Coeruleus Activation

Memories are both stored and more rapidly retrieved in conjunction with LC activation [50]. The facilitation of memory retrieval by NA was confirmed in two further experimental studies [51, 52]. The increase in NA in one of those studies resulted from the blockade of α2-adrenoreceptors [51]. This is likely related to the increased firing rate of LC neurons with consecutive NA release in the hippocampus due to an antagonism of the α2-adrenoreceptor's inhibitory receptor properties [53] (Table 1). In the other study, LC stimulation caused a facilitated memory retrieval that was blocked by pretreatment with a ß-adrenoreceptor antagonist [52] (Table 1). In conclusion, the promoted memory retrieval in both studies was probably mediated by activating ß-adrenoreceptors.

Memory formation is a dynamic process at each memory stage. Memories are often labile and can be destabilized if they are not reconsolidated after retrieval. Reconsolidation is a memory phase that is required for the persistence of a memory trace [54]. Sara proposed that dynamic memory stages such as consolidation or reconsolidation are modulated by the LC-NA system [55]. Other studies indicated that the LC-NA system also has an impact on memory reversal [56] and extinction [57] (Table 1). The NA-dependent modulation of memory stages might be influenced by interactions between NA and other neurotransmitters, for example, with glutamate that is important for synaptic excitation and long-term synaptic plasticity. It interacts locally with NA released from the LC to augment important neuronal representations and to choose among them for long-term memory storage (as recently hypothesized in the "Glutamate Amplifies Noradrenergic effects" (GANE) theory [58]).

8. Locus Coeruleus Modulation of Prefrontal Cortex Activity Controls Hippocampus-Based Memory

Recent evidence suggests that the prefrontal cortex is almost as important as the hippocampus for encoding memory and memory retrieval [2]. Eichenbaum proposed a circuit model of prefrontal-hippocampal interactions to support memory

formation [2]. In his model, the prefrontal cortex receives contextual information via the ventral hippocampus and controls memory retrieval by projections from the prefrontal cortex to the dorsal hippocampus [2]. The LC [1] and VTA [59] are known to project to the prefrontal cortex. Memory retrieval suppression is induced through the prefrontal cortex's modulation of hippocampal activity [60] suggesting that the prefrontal cortex can modulate hippocampus-dependent memory. There is recent evidence that application of a dopamine D 1/5 receptor antagonist in the dorsal hippocampus or medial prefrontal cortex impairs object recognition memory, whereas dopamine D1/5 receptor agonism facilitates objection recognition memory in rats [61]. Moreover, the NA transporter inhibitor reboxetine also facilitates object recognition memory in these rodents [61]. This facilitated that object recognition memory can be reversed by the antagonism of D1/5 receptors in the prefrontal cortex [61]. These findings highlight the key role of the LC-induced release of NA and LC- and VTA-induced release of DA in the prefrontal cortex in modulating memory that result from interplay between the hippocampus and prefrontal cortex (Figure 1).

9. Memory Priming by Locus Coeruleus Activation

NA is known to induce epigenetic modifications (for instance DNA methylation, histone acethylation, and/or phosphorylation) that regulate the transcription for synaptic long-term plasticity in the murine CA1 region in vitro [62]. NA might shape the activation matrix of synapses and further response of synapses to new incoming stimuli, that is, in the murine CA1 region in vitro [63], a concept termed metaplasticity [64, 65]. Metaplasticity is a neurophysiologic phenomenon that serves to enable robust memories by selecting and filtering information via changes in synaptic plasticity. Moreover, it might result from experience-dependent changes in synaptic plasticity driven by epigenetic modifications of transcriptional genes, that is, DNA methylation [66]. Moreover, both LC activation and interaction with other drugs such as atypical antipsychotics such as clozapine and olanzapine or nicotine may promote hippocampal metaplasticity [67]. This concept of NA-induced metaplasticity might shift or reset the sliding threshold for hippocampal synaptic plasticity. By shifting the set point, the response to new incoming stimuli changes, potentially inducing modifications in synaptic long-term plasticity. On the cellular level, this set point is decisive for the resultant type of plasticity such as LTD or LTP. The set point can be considered as an adjustable threshold for inducing LTD or LTP that favors LTP or LTD. The latter are known to regulate spatial memory formation in complementary fashion [30, 31] with their unique roles in spatial memory as depicted above. It is thus tempting to postulate a shifting set point for hippocampal memory storage by LC activation and consecutive NA release in the hippocampus analogous to that for the bidirectional synaptic plasticity exemplified in the visual system [68, 69]. As derived from animal studies, this set point modulation by LC activation is believed to occur in the hippocampal CA1 region and dentate gyrus, but is not limited to those shown in Figure 1. A set point adjustment is likely in these hippocampal subfields, as the LC's activation facilitates LTD in these regions (to test pulses that per se do not evoke changes in basal synaptic transmission) [27]. However, how exactly the amount and duration of NA and/or DA release after LC activation alters the set point for memory storage remains an open question. Here, the timing of LC activation seems to be decisive [26]. For example, activating the LC before the high-frequency stimulation (HFS) of perforant path input fibers to the dentate gyrus inhibited short-term potentiation, whereas the same LC activation after applying HFS depotentiated LTP in rats [26]. These findings lead me to presume that the timing of LC activation is crucial for the persistence of a memory trace. Whether LC reactivation reoccurs minutes after a novel or salient stimulus that per se activates the LC immediately after novel stimuli begin [70] appears to be highly relevant for the encoding of those novel or salient stimuli into long-term memory. Identifying these temporal activation characteristics could prove to be a key step in discovering how NA gates memory priming. My assumption is that the amount of NA release at each time due to LC activation is what regulates the set point for memory modulation. I base this assumption on experiments showing that hippocampal LTD and LTP in the dentate gyrus is dependent on the β-adrenoreceptor agonist concentration in the rat. Lower concentrations of β-adrenoreceptor agonist elicit LTD, whereas higher concentrations of the β-adrenoreceptor agonist cause LTP [71], suggesting that a higher hippocampal NA concentration (resulting from a phasic or high tonic LC activation and a lower hippocampal NA concentration after a low tonic LC activation) might shift the set point for LTD/LTP induction.

Another intriguing candidate for a set point modulation triggered by LC activation is cortical oscillations. We know for one that LC activation is followed by an increase in theta power parallel to the LTP in rodents [72]. On the other hand, no LTP was observed when gamma frequencies are ameliorated after LC activation [72]. LC-facilitated CA1 LTD in rats is accompanied by the transient suppression of theta frequencies [27], which suggests that a theta frequency increase or suppression after LC activation might be responsible for directing synaptic plasticity (LTP or LTD) and forming subsequent memories. Although the precise mechanisms of set point modulation remain unclear, there are several factors that argue for the presumption that the LC primes hippocampal memory.

10. Concluding Remarks and Implications

Considered together, the LC-NA system comprises an essential function in modulating the stages and persistence of hippocampus-dependent memory. In several human disease states involving LC impairment, LC neurons are lost, such as in Alzheimer's disease [73] and in posttraumatic stress disorder, NA's availability is reduced [74]. In temporal lobe epilepsy, hippocampal neurons are often lost due to hippocampal sclerosis with consecutive suspected altered noradrenergic function based on LC projections to the hippocampus.

LC dysfunction thus contributes to the underlying pathophysiology of these diseases, knowledge that could help us identify factors that protect the LC from degeneration and to identify patients in an early state of Alzheimer's disease [73]. In a recent study, patients with amnestic mild cognitive impairment exhibited a 30% loss of neuronal cells in the LC [75]. Those patients may have a prodromal stage of Alzheimer's disease. In patients clinically diagnosed with Alzheimer's, LC neuronal loss was further enhanced, as detected in the patients with amnestic mild cognitive impairment [75], suggesting a progressive loss of neurons in the LC characteristic of the neurodegenerative process and believed to correlate with cognitive dysfunction. LC neurodegeneration's molecular pathology was analyzed in tissue samples from deceased patients with amnestic mild cognitive impairment, revealing reductions in messenger ribonucleic acids in synaptic structural plasticity [75] believed to be important for memory storage [76], highlighting the important role that the loss of noradrenergic LC cells plays in the development of cognitive dysfunction in Alzheimer's disease. There is ongoing debate as to which drugs might be theoretically preferable for patients with Alzheimer's disease: adrenergic drug blockage or adrenergic drug stimulation [77]. The debate is based on experimental data in Alzheimer animal models. Adrenergic drug blockage has been observed to alleviate cognitive deficits and the neuropathological changes in Alzheimer's disease such as amyloid beta and tau pathology [78]. On the other hand, adrenergic receptor activation might promote neurogenesis [79] and reduce neuroinflammation and amyloid beta and tau pathology [80].

In another disease affected by LC dysfunction, namely, posttraumatic stress disorder, the reduced availability of noradrenaline transporter is the basic idea behind developing NA reuptake blockers that cause anxiolytic effects in anxious arousal states [74]. Moreover, in an animal model of focal hippocampal epilepsy, electrical LC stimulation via activation of ß-adrenoreceptors reduced hippocampal epileptic activity [81].

It is therefore important that we understand LC pathophysiology in these disease states so as to design drugs to help restore LC dysfunction.

To sum up, I propose that the cellular plasticity mechanisms induced by LC activation listed below are among the mechanisms that regulate the persistence of long-term memory (Figure 1):

(a) Facilitation of synaptic hippocampal LTD and/or LTP via the corelease of NA and DA in the hippocampus [26–28, 33]. In particular, the noradrenergic and dopaminergic modulation of late LTD facilitated by electrical LC activation is of major relevance in the formation of long-term memory (Figure 1).

(b) Facilitation of hippocampal sharp waves ripples via ß-adrenoreceptors after NA release in the hippocampus (Figure 1). This mechanism was proven in an in vitro study in the rodent [25]. This study implies an improvement in memory consolidation via increased hippocampal sharp wave ripples.

(c) NA-induced epigenetic modifications of transcriptional control of synaptic hippocampal long-term plasticity. This proposed mechanism was demonstrated in an in vitro study in the CA1 region [63].

(d) NA-elicited shifts of the set point for LTP and/or LTD (Figure 1) causing hippocampal metaplasticity. This is a hypothetical mechanism demonstrated indirectly in experiments. NA is shown on the one hand to facilitate LTD and thus to lower the threshold for inducing LTD in hippocampal synapses. On the other hand, the LTP threshold is modulated via NA as LTP and is depotentiated when LC activation follows immediately after LTP induction [26]. It is thus reasonable to assume that an LC-induced NA release shifts the thresholds inducing hippocampal long-term plasticity. However, the exact molecular mechanism by which NA sets the threshold of synaptic long-term plasticity remains unclear. On the network level, potential mechanism candidates for the threshold shifting of LTP or LTD are an NA-facilitated increase or suppression in theta frequencies [27, 72]. It is conceivable that the set point modulation is also induced by DA released from LC terminals.

Taken together, these mechanisms based on the reviewed literature lead me to assume that the LC-NA system's pivotal role is to prime the longevity of hippocampal long-term memory.

Conflicts of Interest

The author declares that no conflicting interests exist.

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Review Article

Could LC-NE-Dependent Adjustment of Neural Gain Drive Functional Brain Network Reorganization?

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The locus coeruleus-norepinephrine (LC-NE) system is thought to act at synaptic, cellular, microcircuit, and network levels to facilitate cognitive functions through at least two different processes, not mutually exclusive. Accordingly, as a reset signal, the LC-NE system could trigger brain network reorganizations in response to salient information in the environment and/or adjust the neural gain within its target regions to optimize behavioral responses. Here, we provide evidence of the co-occurrence of these two mechanisms at the whole-brain level, in resting-state conditions following a pharmacological stimulation of the LC-NE system. We propose that these two mechanisms are interdependent such that the LC-NE-dependent adjustment of the neural gain inferred from the clustering coefficient could drive functional brain network reorganizations through coherence in the gamma rhythm. Via the temporal dynamic of gamma-range band-limited power, the release of NE could adjust the neural gain, promoting interactions only within the neuronal populations whose amplitude envelopes are correlated, thus making it possible to reorganize neuronal ensembles, functional networks, and ultimately, behavioral responses. Thus, our proposal offers a unified framework integrating the putative influence of the LC-NE system on both local- and long-range adjustments of brain dynamics underlying behavioral flexibility.

1. Introduction

The locus coeruleus-norepinephrine (LC-NE) system is involved in a wide range of cognitive functions including perception, working memory, attention, emotional processes and learning, and memory [1–5]. While its widely distributed projections [6–10] and its involvement in the sleep-wake cycle [11–13] have long confined this neuromodulator to a role in arousal and vigilance [14–17], it is now considered as a system with a more complex role in cognitive functions. The specific topography of the norepinephrine receptors and transporters in the brain represents a key element of this complexity [18]. The impact of norepinephrine signaling on brain activity is the result of a fine balance between excitatory and inhibitory actions via these various receptor types onto the target regions depending on the context [19, 20].

Phasic responses of the LC neurons are triggered by behaviorally relevant stimuli [21–23], novel or salient stimuli [24], and stressors [25, 26] and vary with the level of vigilance [1, 27, 28]. More recent evidence from electrophysiological recordings also suggests an influence of the LC-NE system beyond sensory processing [29] to facilitate behavioral adaptation or flexibility. Based on these properties, several theoretical models have suggested that the LC-NE system orchestrates the transition between different behavioral/cortical states to adjust to the current context [30–35]. For the purpose of this review, we will focus on two influential models suggesting that the LC-NE system facilitates behavioral adaptation by two different, not mutually exclusive, processes: (1) a "reset signal" allowing large-scale brain network reconfiguration to adapt and respond appropriately to the environment [33, 36] and (2) a modulation of neural gain in its target regions that increases the signal-to-noise ratio and tune neural network dynamics to optimize behavioral responses [32, 37, 38]. We will describe these two models and present our recent findings together with new data on

NE-dependent modulations of both global and local brain functional connectivity dynamics. In light of these findings, we then propose a NE-dependent mechanism of action at the whole-brain level unifying these two theoretical models. Specifically, we propose that the LC-NE system modulates neural gain locally that in turn drives large-scale brain network reorganizations. We also discuss the functional significance of these local-to-global modulations in brain dynamics driven by the LC-NE system on neural signaling and behavioral flexibility.

2. The LC-NE System and Functional Brain Network Reorganization

Bouret and Sara [33] interpreted the NE action from the simplified models of "central pattern generator circuits" of the crustaceans, which have been widely used to explore neuromodulatory mechanisms. These simplified circuits highlighted the capacity of neuromodulators to reorganize or reconfigure neural networks [20, 39]. Bouret and Sara [33] thus suggested that the LC phasic activity plays the role of a "reset signal", facilitating behavioral transitions. They described an intratask state in which attention is directed toward "expected" and task-relevant stimuli and where behavioral transitions allow the initiation of motor responses required for the current task. For example, in rats performing an odor discrimination task, flashing lights indicating the start of each trial induced an orientating response of the animal toward the port delivering the odor and systematically triggered a phasic LC discharge [40]. Alternatively, the extratask state is described as a state more sensitive to behavioral transitions and attentional reorienting. Bouret and Sara [33] suggest that the reset signal can interrupt ongoing activity in existing functional networks (see also [41]), in order to trigger brain network reorganizations and thus promote the establishment of a new behavior (Figure 1(a)). According to this model, the impact of the LC-NE system would depend on the context and could therefore promote changes within and between any given functional networks in line with the numerous NE-dependent effects observed at the behavioral level.

In line with this hypothesis, Coull et al. [42] demonstrated in a positron emission tomography study conducted in human subjects that during an attentional discrimination task, the administration of clonidine, an α_2 norepinephrine agonist, modulated the efficiency of the connections between the frontal and parietal areas and between the parietal cortex and the thalamus compared to the placebo condition. Another recent functional magnetic resonance imaging (fMRI) study in humans also highlighted a NE-dependent modulation of functional connectivity in the presence of aversive stimuli [43]. Subjects were exposed to aversive stimuli activating and increasing functional connectivity within the salience network, a network including the amygdala, the anterior insula, and the anterior cingulate cortex, and involved in attentional reorientation in response to emotional stimuli [44, 45]. They reported that the administration of a β-norepinephrine antagonist reduces the activation and functional connectivity within the salience network in response to aversive stimuli. These studies therefore demonstrate NE-dependent modulation of the functional connectivity within large-scale brain networks.

We recently brought the first empirical evidence that enhancing NE transmission using atomoxetine (ATX), an agent that increases extracellular levels of NE by occupying the presynaptic NE-reuptake transporters [46–48], induces functional brain network reorganizations at rest [49] (Figure 1(b)). In particular, we showed that boosting NE transmission led to (1) a switch in the functional coupling in the brainstem network, which includes the LC nucleus and the frontoparietal attention network, (2) decreased functional connectivity between sensory-motor and associative networks, and (3) decreased correlations within sensory-motor networks. The brainstem network including the LC nucleus, which was negatively correlated with the frontoparietal attention network in the placebo condition, became positively correlated with the latter after ATX administration. Together with the findings of Coull et al. [42] described above, the changes in functional connectivity within and between the frontoparietal attention network and the brainstem nuclei could represent a central feature of the NE action on attentional processes to adjust to the surrounding context [36, 50]. In addition, the decrease in functional connectivity strength between resting-state networks (RSNs) and within sensory-motor networks might reflect a reduction of noise correlation, another feature that could favor stimulus selection [51, 52]. This finding echoes with the electrophysiological studies showing that NE improves perceptual processes within sensory cortices by decreasing the spontaneous neuronal discharges on the one hand and by increasing the evoked responses to the relevant stimuli on the other hand [53–55]. To conclude, according to Bouret and Sara [33], the "reset signal" triggered by the LC phasic discharge would guide the behavior toward the most relevant stimulus of the environment at a given moment. The ability of the LC-NE system to promote behavioral transitions would be achieved through large-scale, behavior-specific reconfigurations of brain networks, depending on the context, thus permitting the expression of a multitude of brain states. Our recent findings provide the first empirical evidence of such NE-dependent large-scale brain network reorganization at rest [49]. Future studies using a whole-brain approach could provide evidence of context-specific brain network reorganizations driven by the LC-NE system.

3. The LC-NE System and Neural Gain Adjustment

Another theory suggests a modulation of the neural gain driven by the LC-NE system [32]. Simply explained, neural gain modulations have been suggested to affect neural communication. When neural gain increases, excited neurons become even more active and inhibited neurons become even less active, thus increasing the contrast of the activity pattern in a neuronal circuit [56]. It was suggested that rapid changes in neuronal responsiveness and interactions induced by gain adjustment may trigger dynamic modulations of functional connectivity [57–59]. The model put

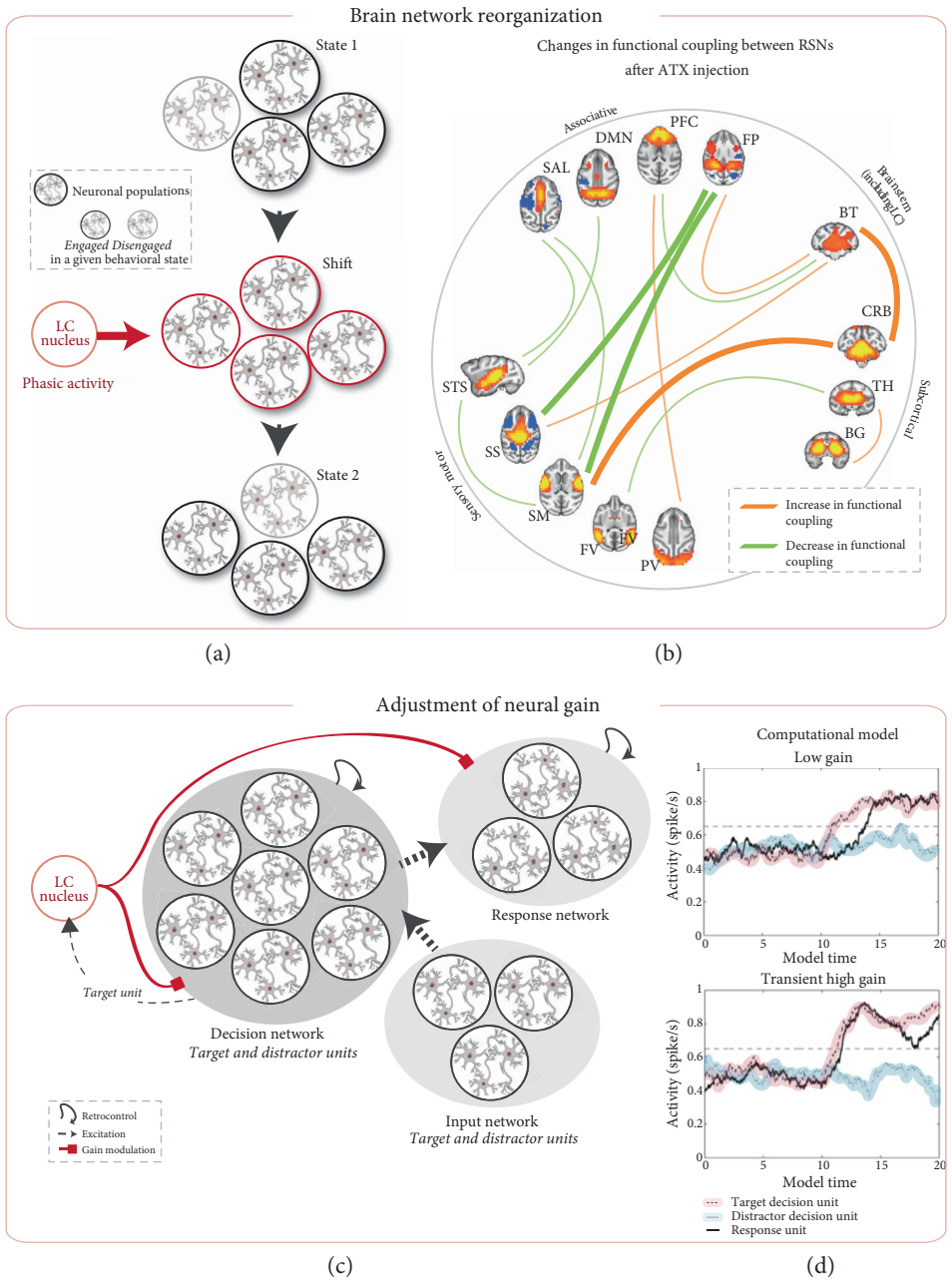


Figure 1: LC-NE system theoretical models ((a) and (b)) brain network reorganizations adapted from Bouret and Sara [33]. (a) A behavioral state is associated with a given functional network with a specific spatiotemporal pattern of neuronal activity. When a stimulus induces a behavioral shift, the LC activation immediately preceding this change modulates the underlying interactions between the neuronal populations via its simultaneous action on several of its target structures, promoting changes within and between functional networks (state 1 → state 2). (b) Overview of the functional coupling changes between 13 resting-state networks (RSNs) following ATX injection (from Guedj et al. [49]). Line thicknesses reflect the correlation strength of the ATX-induced changes. ATX injection modulated the functional coupling of the subcortical network including the LC and decreased the functional coupling between associative and sensory-motor networks. The frontoparietal network, negatively correlated with the brainstem network including the LC region in the saline condition, switched to a positive correlation under ATX ((c) and (d)) adjustment of neural gain. (c) Architecture of the computational model described by Usher et al. [38]. The LC inputs regulate the gain via a multiplier effect on the decision and the response networks. (d) Simulated time courses of activity for the response and decision model units under various neural gain levels (low and high gain). A transient increase of the neural gain induced by a LC phasic response improves the processing of the target stimulus, resulting in faster and sharper increase in response unit activity. Adapted from Usher et al. [38] and Gilzenrat et al. [60]. Circles represent a defined neuronal population. The red circle represents the population of LC neurons. ATX = atomoxetine, BG = basal ganglia, BT = brainstem, CRB = cerebellum, DMN = default-mode network, FP = frontoparietal, FV = foveal visual, PFC = prefrontal cortex, PV = peripheral visual, SAL = salience, SM = somatomotor, SS = somatosensory, STS = superior temporal sulcus, and TH = thalamus.

forward by Aston-Jones and Cohen (*The Adaptive Gain Theory*, [32]) proposed a key role of the norepinephrine system in optimizing behavioral performance, which would involve (1) a regulation of the balance between exploitation and exploration behaviors and (2) an improvement of neural responses to relevant stimuli. Considering the capacity of the LC-NE system to guide transitions between behavioral states in line with Bouret and Sara's proposal, the authors suggest a role in behavioral adjustment, which implies taking part in a fundamental trade-off in their expression: the exploitation of well-known sources of reward against the exploration of the environment looking for other opportunities of higher or more stable value.

In the *Adaptive Gain Theory* largely based on electrophysiological observations in behaving animals, Aston-Jones and Cohen distinguished two distinct modes of activity of the LC neurons: phasic and tonic [1]. In the phasic mode, phasic bursts of LC neurons (i.e., stimulus evoked) are observed in close relationship with goal-directed behaviors. It was proposed that the LC phasic mode would act as an attentional filter for irrelevant stimuli, promoting task-related behaviors. This filter is temporally restricted (to task-related events), but spatially extended given the wide projections of LC neurons [32]. In the tonic mode, spontaneous activity is high while phasic bursts are rare or absent, and behavior is more disorganized. This mode is thought to facilitate shifts of attention and the exploration of alternative opportunities. The LC activity modes would therefore adjust the balance between these two fundamental states: exploitation versus exploration to optimize behavior in a changing environment. According to the *Adaptive Gain Theory* view, the adjustment between exploitation and exploration is associated with a NE-dependent modulation of the neural gain in target areas. Such changes of the neural gain arise in a strategic and time-limited manner and improve locally the signal-to-noise ratio [37, 38, 60, 61] (Figure 1(d)). Usher et al. [38] explored the impact of such changes in neural gain on behavioral performance during an attentional discrimination task. In this task, behavioral responses were modeled in a simplified network in which two alternative representations of the stimulus (target or distractor) compete. The noise in sensory processing related to the perceptual overlap between targets and distractors induces a competition between the neural representations of the two alternatives. In this circuit, LC units received afferent inputs from the decision unit and sent projections back to both decision and response units (Figure 1(c)). In tonic mode, the gain level remained constantly high, inducing a strong competition between neural pools encoding the target (the real "signal") and the distractor (considered as a "noise"). This condition led to greater variability in reaction times and greater difficulty in discriminating target stimuli. Conversely, in phasic mode, the gain level remained generally low, which leads to a greater resistance to noise. In this state, the presence of a target stimulus elicits a transient phasic discharge that translates into a brief increase of the gain across the network. This transient increase improved the processing efficiency during a specific time window, thus facilitating performance, that is, target discrimination (Figure 1(d)).

A recent human study explored the relationship between neural gain at the whole-brain scale using fMRI and behavioral performance in a learning task [62]. In order to infer the neural gain variations dependent on the norepinephrine system, the authors measured the pupillary diameter. Using a network simulation, they provided mechanistic insights into the link between neural gain, brain-wide neural interactions and topology, and behavioral responses. They explored two brain properties that reflect the functional topology of the brain: the functional connectivity strength (the mean of absolute correlation score between various brain regions) and the clustering coefficient (reflecting the rate of node agglomeration in a network). They observed that a high gain (inferred from a large basal pupillary diameter) was associated with increased functional connectivity strengths and stronger clustering coefficients and vice versa. These results fit with the *Adaptive Gain Theory* and related computational models [37, 38, 60, 61], suggesting that an increase of the neural gain facilitates neural communication.

To summarize, according to the *Adaptive Gain Theory*, cognitive flexibility seems to be associated with variations of the basal (tonic) activity of the LC neurons that would permit a fine regulation of the neuronal activity across the brain via the variety of norepinephrine receptors and their particular topography. This regulation likely involves the interplay between several brain regions such as regions of the frontal cortex [32, 35], together with parietal regions and sensory-motor networks.

4. Co-Occurrence of Neural Gain Adjustment and Functional Brain Network Reorganization Induced by a NE Challenge?

In the previous sections, we reviewed theoretical and empirical evidence in favor of a role of the LC-NE system in dynamically modulating both short- and long-range neural dynamics that could permit cortical state adjustment to the changing environment [30, 31]. The next question we ask is how these two mechanisms, namely the large-brain network reorganization and the neural gain adjustment, could interact to facilitate behavioral flexibility. To answer this question, we first attempted to provide evidence of the co-occurrence of these mechanisms at the whole-brain level within the same subject and under the same condition. Providing the evidence of the co-occurrence of a whole-brain network reconfiguration with an adjustment of the neural gain would help better characterize the effect of this neuromodulator. As described above, a recent computational work suggested that an increase in baseline pupil diameter, interpreted as an increase in neural gain induced by a LC-NE activation, was associated with clustered neural interactions [56, 62, 63]. We directly tested this hypothesis by investigating, under a NE challenge, RSN topology in the same dataset as that in Guedj et al. [49] that demonstrated a NE-dependent large-scale brain network reorganization. Here, we used graph theory properties to infer the state of neural gain [62]. Specifically, we

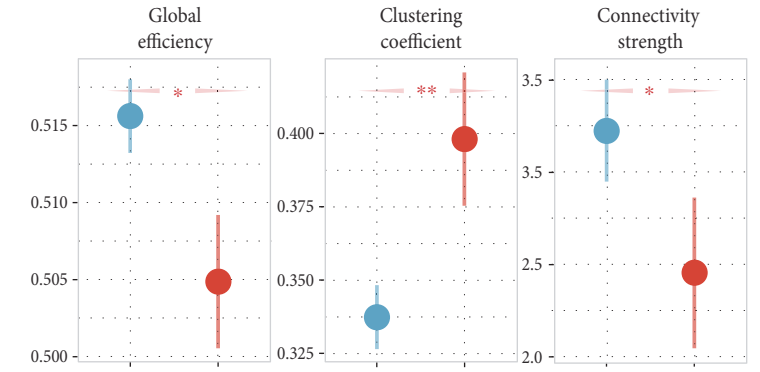
characterized the effect of ATX on the quality of information spread (global efficiency and clustering coefficient) and the strength of functional connectivity, at the whole-brain level and within specific RSNs (see Supplementary Material available online at https://doi.org/10.1155/2017/4328015 for the details on the methods).

Briefly, three monkeys participated in the study, as described in Guedj et al. [49]. Resting-state fMRI scans ($2 \times 2 \times 3$ mm; TR = 2 s; 400 TRs) were acquired under two conditions: ATX (0.5 mg/kg), an inhibitor of NE reuptake, or saline (control condition) injections were administered intramuscularly one hour before the scanning session. Spontaneous slowly fluctuating brain activity (0.01–0.1 Hz) was extracted. Matrices with 471 defined gray matter areas served to construct functional connectivity graphs—one graph per monkey and per run. An area corresponded to a volume of $4 \times 4 \times 6\,\text{mm}^3$ (eight voxels) to minimize artifactual correlations between neighboring voxels [64] while retaining a relative fine-grained approximation of the neural gain. Normalized correlations (Fisher r-to-z transformation) between the regional mean time series of each pair of areas were then computed, and a threshold based on the absolute values of their correlation coefficient was applied to retain only the 10% of the highest correlation scores. This density was selected as it was the smallest density that maximizes the number of connected nodes [65] (see Figure S1) while minimizing the number of spurious edges in each area [66]. For each graph, we estimated different metrics: the global efficiency, the clustering coefficient, and the connectivity strength. These metrics were computed for the whole brain and for each of the thirteen "real" networks previously identified with the independent component analysis (ICA) approach [49] (see Supplementary Material for a more detailed description on these metrics). The global efficiency reflects the level of global integration within a network and corresponds to the averaged inverse shortest path length between all pairs of nodes in the network. The clustering coefficient informs us about the "local efficiency" as it reflects the number of connections that exists between the nearest neighbors of a node as a proportion of the maximum number of possible connections [67]. It can be regarded as a measure of information spread in the immediate neighborhood of each node as described above in Eldar et al. [62]. The connectivity strength is defined as the mean of the correlation coefficient between each node and all the other nodes within the network. We then examined the effect of ATX on these three metrics using a linear mixed model, including the pharmacological condition as fixed factor and the subject as random intercept. For the graph properties computed within each ICA-identified network, we also included the "ICA-identified network" type as a fixed factor.

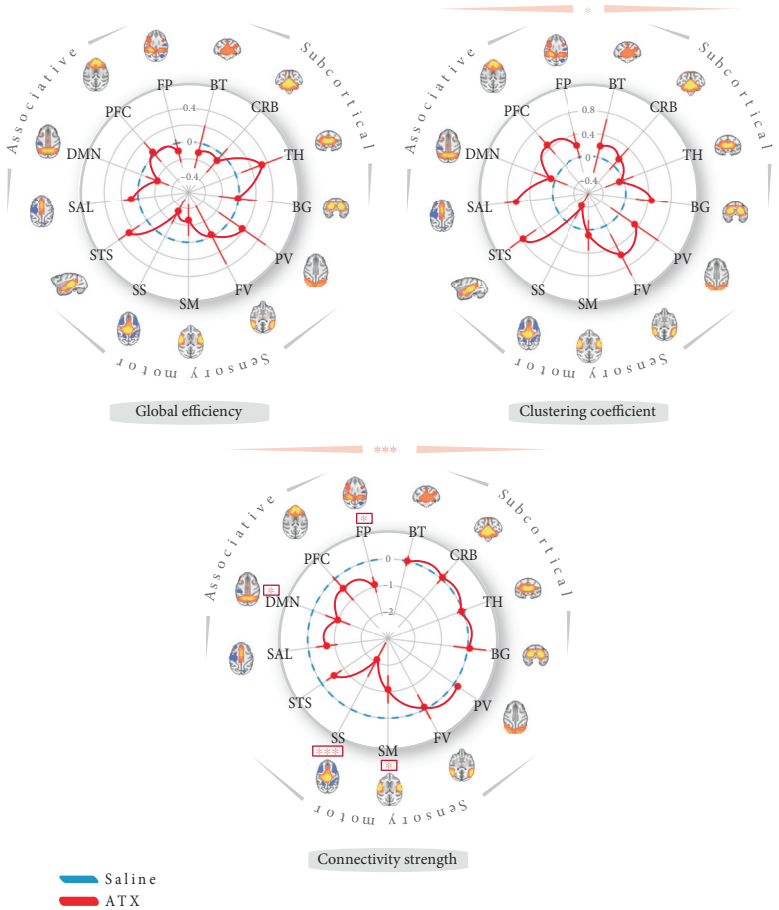
We found that boosting NE transmission altered the global brain topology, shifting its functional architecture toward a stronger local efficiency (Figure 2(a)), by significantly reducing the global efficiency, while increasing the clustering coefficient. Enhanced local efficiency following ATX injection was also found within specific RSNs previously characterized as independent networks (i.e., ICA-identified networks, see [49], Figure 2(b)). We also observed a decrease in connectivity strength at the whole-brain level and within sensory-motor and associative brain networks (Figures 2(a) and 2(b)) following ATX injection in accordance with our previous results [49]. As postulated by Eldar et al. (2013), the increase in the clustering coefficient could reflect an increase in neural gain. In other words, and together with our previous findings [49], we suggest that boosting NE transmission triggers large-scale brain network reorganizations, enhances the local neuronal communication at the whole-brain level, and adjusts functional connectivity within sensory-motor and associative brain networks. Importantly, this finding corroborates the idea that the LC-NE system plays a key role in shaping cortical states via its highly distributed projections throughout virtually all the brains [55, 56, 63, 68]. While our results are consistent with those of Eldar et al. [62], they contrast with a recent study that has also investigated the effect of ATX on the whole brain at rest [69]. Similar to our study, Van Den Brink et al. [69] compared the brain topology of healthy human subjects at rest using fMRI before and after the administration of a dose of ATX, in a similar range as that administered to our animals. They found that ATX led to a decrease of the clustering coefficient measured on region-level graphs using an atlas-based brain parcellation (90 regions). One possibility is that the discrepancy between the two studies is due to the difference in the definition of the graphical nodes. The clustering coefficient might indeed vary as a function of spatial scale [64]. In Van Den Brink et al.'s study, they used an atlas-based brain parcellation (90 regions) while in our study, we used a finer-grained spatial resolution (471 regions). Furthermore, all graph properties are calculated on a matrix where a threshold is traditionally applied to obtain a sparse network, therefore considering only the strongest brain connections. It is therefore also possible that this discrepancy simply reflects differences in graph densities. Future works should further investigate spatial effects of NE administration on functional connectivity depending on graph density and the choice of parcellation scale.

5. Correlations in Band-Limited Amplitude Envelope of the Gamma Rhythm: A Key Role in the NE-Dependent Local-to-Global Neuronal Dynamics?

Thus far, we found that on the one hand, boosting NE transmission led to large-scale brain network reorganizations, and on the other hand, it increased the local efficiency that could reflect an improvement of the neural gain. In the next sections, based on the assumption that the modulation of neural gain could represent the mechanism underlying the flexibility of neural networks [57–59], we propose that the two mechanisms are interdependent such that the increase of neural gain inferred from the clustering coefficient could induce large-scale brain network reorganizations, facilitating a wide range of cognitive processes (Figure 3). The demonstration of the co-occurrence of these two mechanisms following the stimulation of the LC-NE system is an important first step toward this assumption.



(a) Global properties



(b) ICA-identified network properties

Figure 2: ATX effect on network architecture—(a) global graph properties. Global efficiency, clustering coefficient, and connectivity strength, under saline (blue) and ATX (red) pharmacological conditions. (b) ICA-identified network properties. The three spider plots represent the global efficiency, the clustering coefficient, and the connectivity strength computed for each ICA-identified resting-state networks (see Guedj et al. [49]). Importantly, these scores were expressed as a difference between the ATX condition and the saline control condition. Blue lines represent no difference between the two pharmacological conditions (difference equals to 0). Red stars indicate statistical differences between saline and ATX conditions: stars above the spider plots indicate a main effect of the pharmacological condition while stars above the networks indicated an interaction between the pharmacological condition and the ICA-identified network type (∗∗∗ = p value < 0.0001; ∗∗ = p value < 0.001; ∗ = p value < 0.05). Throughout this figure, the results are plotted as mean ± SEM. ATX = atomoxetine, BG = basal ganglia, BT = brainstem, CRB = cerebellum, DMN = default-mode network, FP = frontoparietal, FV = foveal visual, ICA = independent component analysis, PFC = prefrontal cortex, PV = peripheral visual, SAL = salience, SM = somatomotor, SS = somatosensory, STS = superior temporal sulcus, and TH = thalamus.

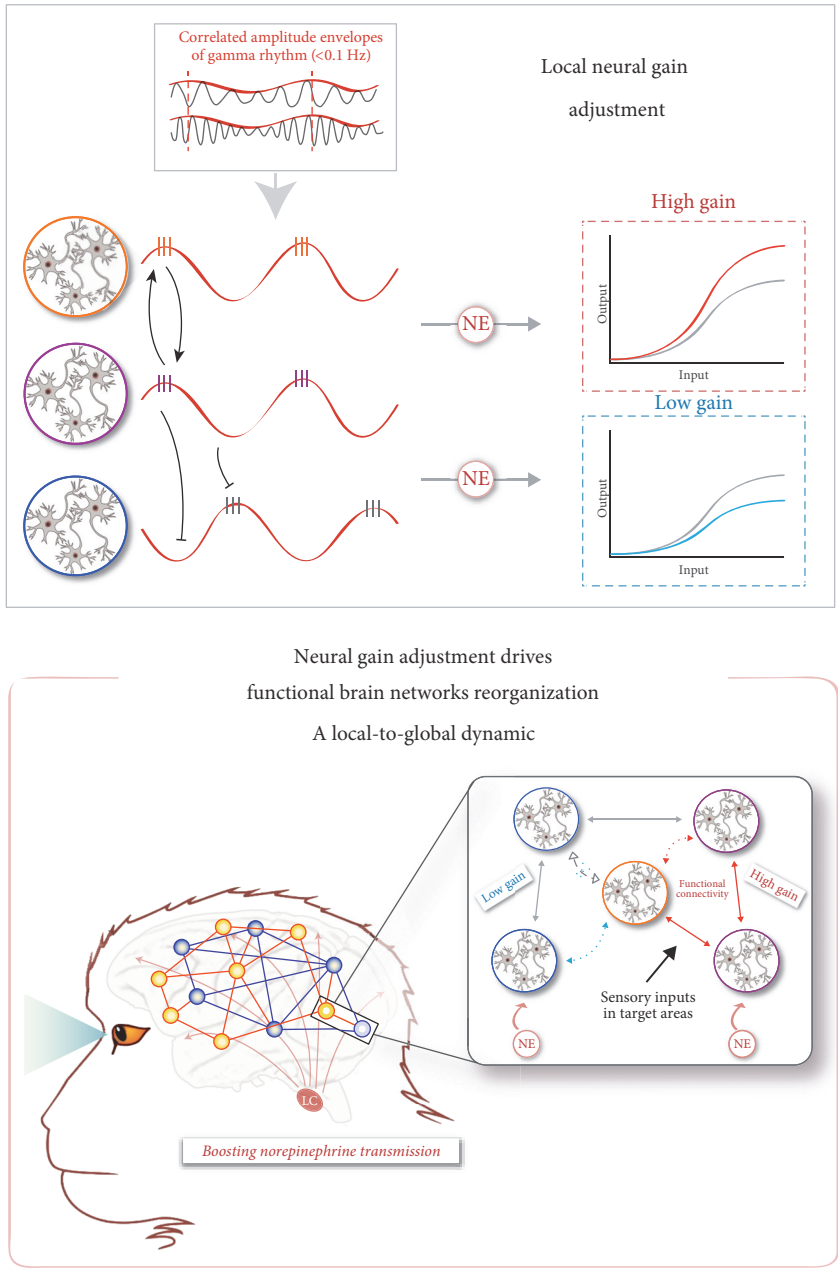


Figure 3: Mechanism proposed for the NE-dependent local-to-global neuronal dynamics—top panel—relationship between the amplitude envelope correlations in gamma rhythm and NE-dependent local neural gain adjustments. The orange and purple neuronal populations, whose amplitude envelopes cofluctuate, allow the increase in neural gain induced by the norepinephrine system activation to be effective and to spread (upper-right inset, red trace), whereas the purple and blue neuronal populations that exhibited a distinct temporal dynamic do not allow the increase in neural gain to be expressed locally, and this results in a decrease in neural gain (bottom-right inset, blue trace)—bottom panel—boosting norepinephrine transmission is thought to induce an increase in neural gain. The insert illustrates an example of the effect of neural gain adjustment on interactions between different neuronal populations. The five groups of neurons are anatomically interconnected. Sensory input signals influence the activity of target regions (purple and orange groups of neurons). Norepinephrine transmission also modulates the activity of groups of target neurons (violet and blue groups of neurons), increasing or decreasing the neural gain, respectively. The amplification of gain in the neuronal violet group then induces an increase in the functional connectivity between violet and orange groups (red arrows). Similarly, the reduction in neural gain in the blue neuronal group induces a decrease in functional connectivity between blue and orange groups (blue arrow and cross). Thus, under the influence of this local modulation of neural gain, neural networks reconfigure, creating a new organization of functional networks at the whole-brain scale.

It also provides a unified framework of the LC-NE theories [32, 33] and underlines a central feature of this system on the dynamics of the brain functional connectivity.

5.1. Spontaneous Brain Activity and Gamma Rhythm. It has been suggested that slow fluctuations in brain activity might be under brainstem control and may be related to behavioral

variations [63, 70–72]. Here, we further suggest that a LC-NE-dependent adjustment of the neural gain could drive functional brain network reorganizations through coherence in the gamma rhythm (>30 Hz). Although the correspondence between the hemodynamic response measured using fMRI and the neuronal dynamic measured locally using electrophysiological recordings is far from clear, there exists some evidence suggesting correspondence between correlations in fMRI signals (i.e., functional connectivity) and correlations between the amplitude envelopes of band-limited cortical activity at distant points in the brain [70, 73, 74]. The correlations between the amplitude envelopes of band-limited cortical activity are a measure of the comodulation of the amplitude envelopes of oscillations in two areas, often spatially remote [75]. The covariations between the amplitude envelopes are very slow, within a similar range as those observed in resting-state fMRI fluctuations, with a frequency below 0.1 Hz [76]. At rest, electrophysiological studies in both humans and animals revealed that the amplitude envelopes in the gamma rhythm exhibit spatial coherence between functionally related areas [72, 74, 77, 78]. As RSNs, these fluctuations display consistent interhemispheric correlations and spatial specificities [74]. In particular, Schölvinck et al. [72] recently provided evidence of a more consistent relationship between spontaneous fMRI signals and gamma-range band-limited power by recording from multiple cortical areas in the awake monkey during "resting-state" fMRI scans using implanted electrode arrays. They also reported correlations, though less consistent, between spontaneous fMRI signals and the band-limited power derived from other frequency bands, which may suggest frequency division multiplexing [79], that would serve to convey information through separate frequency bands.

5.2. Could Neural Gain Adjustment Drive Functional Brain Network Reorganization? Fries [57] proposed that the presence or absence of correlations in gamma-range band-limited power serves as a mechanism for the local neural gain adjustment within and between neuronal populations. Thus, a local increase in neural gain could influence more distal neuronal populations whose amplitude envelopes cofluctuate, whereas such impact would be less effective in neuronal populations whose amplitude envelopes fluctuate with a distinct temporal dynamic (Figure 3(a)). Interestingly, a recent optogenetic manipulation modulating the level of gamma rhythmic inputs suggests that gamma oscillations enhance signal transmission by increasing neural gain [80]. The gamma rhythm is mainly governed by inhibitory interneurons that generate synchronized activity by imposing rhythmic inhibition onto the entire local network. As a consequence, pyramidal cell responses can only occur during periods of fading inhibition [81]. These "windows of opportunity" play a critical role in shaping neuronal network dynamics [58]. A study demonstrated, in awake cats and monkeys, that short- and long-range neural interactions depend on the phase relation of pairs of recording sites in the visual cortex, such that effective connectivity is maximal for the phase relation at which the two sites typically synchronize [82]. The ubiquity of this oscillatory activity could facilitate a fine modulation of the neuronal responsiveness at the whole-brain scale via a balance between high- and low-gain levels to shape neuronal activity depending on the context [82–85]. Accordingly, as shown in Figure 3(b), we propose that the interplay between high- and low-neural gains driven by the amplitude correlations, associated with the spread of gamma-band synchronization, could fine tune the functional connectivity between the brain areas, therefore inducing the large-scale brain network reorganizations that we reported at rest under a NE challenge [49].

Apart from the relationship that might exist between the local adjustment of neural gain and the correlations in gamma-range band-limited power, Voloh and Womelsdorf [86] proposed a role for the "phase resetting" of oscillatory activities in the coordination of large-scale brain network. Phase resetting refers to the realignment of ongoing oscillatory activities in relation to a given event, and it is thought to facilitate the transmission of a combination of multiple signals through a common neural substrate over large anatomical distances [79]. Such a phenomenon has been demonstrated between the anterior cingulate cortex and the lateral prefrontal cortex of monkeys in a task involving covert stimulus selection [87]. As suggested by Voloh and Womelsdorf [86], these mechanisms might participate in reorganizing oscillatory activity across the brain depending on the context [86]. These mechanisms could also be under the influence of neuromodulators. In some way, this phase resetting could be related to the "reset signal" driven by the LC-NE system as proposed by Bouret and Sara [33].

In sum, the co-occurrence of NE-dependent changes in local and global neuronal resting-state dynamics suggests a functional relationship between these two mechanisms. Via the temporal dynamic of gamma-range band-limited power, the release of NE could adjust the neural gain, promoting interactions only within the neuronal populations whose amplitude envelopes are correlated, thus making it possible to reorganize neuronal ensembles, functional networks, and ultimately, behavioral responses. The co-occurrence of both the local and global changes in functional connectivity patterns that we described above following a NE challenge at rest fits with this hypothesis. They also leave open questions about how these mechanisms are recruited during goal-directed behavior and how they adjust in different task contexts. As reviewed above, depending on its activity (i.e., tonic and phasic modes), the LC has been associated with different levels of behavioral flexibility. Its properties also allow this system to act at multiple time scales [1, 32], thus inducing behavioral transitions between tasks or within a given task in response to relevant stimuli [33, 41, 88]. Accordingly, a modulation of the tonic LC activity could adjust the neural gain, inducing the reconfiguration of functional networks toward a brain state adapted to the current context (extratask transition), while phasic LC firing could fine tune an established functional circuit in order to modulate its activity within a shorter timescale in response to a relevant stimulus in the environment (intratask transition). It is likely that depending on the task context, the LC-NE system shapes these local-to-global neuronal dynamics at the whole-brain level and this local-to-global adjustment

could involve different oscillatory bands and involve the interaction with other neuromodulators [89].

6. Conclusions: Functional Implications of the Role of Gamma Rhythm in the NE-Dependent Brain Mechanisms

While the impact of the LC-NE system on cognitive processes is far from clear, we proposed here a unified framework integrating the putative influence of the LC-NE system on both local- and long-range adjustments of brain dynamics. Local NE-dependent adjustment of the neural gain toward a more structured and effective neuronal communication could drive long-range reorganization of functional brain networks via the gamma rhythm amplitude envelopes. The NE-dependent flexibility in the RSN functional topology and interactions that we have highlighted could be governed by the dynamics of gamma rhythm oscillations which has often been proposed as a mechanism for assembling neurons into synchronous networks capable of conducting information throughout target regions [57, 74, 82]. To the best of our knowledge, NE-evoked modulation of gamma rhythm has not yet been demonstrated in the behaving state. However, we believe that there exists converging evidence making our framework plausible. On the one hand, NE-dependent modulation of oscillatory activity has been shown in different frequency bands. For instance, Bari and Aston-Jones [90] demonstrated modulation of the LC neurons firing rate and sensory-evoked LFPs, spike-field and EEG-field coherences in cortical regions of the rat following ATX injection. Brown et al. [91] demonstrated that the stimulation of the LC affected different rhythms in the hippocampus (θ rhythm and β and γ frequencies, and see also [92–94]). On the other hand, changes in oscillatory activity across different frequency bands have been repeatedly linked to changes in goal-directed behavior (e.g., [95–97]). In particular, gamma oscillations have been observed in a variety of processes, from sensory perception [98] to selective attention [99, 100], maintenance of working memory [81, 101, 102]. In the attentional domain, gamma-band synchronization among neurons is enhanced in the primate brain during tasks involving the selection of a target stimulus among distractors [97, 99, 103] and can mediate long-range communication across distant brain areas [97]. And finally, as reviewed by Başar and Güntekin [104], abnormalities in the oscillatory dynamics have been described in a variety of disorders including the attention deficit hyperactivity disorder that appears more closely linked to dysfunctions of the catecholaminergic system. Here, by assembling these evidences, we further suggest that neuromodulation might help fine tune the oscillatory dynamics. We believe that our integrated framework on the role of the LC-NE system on local- and long-range adjustments of brain dynamics posits a new interesting hypothesis that could be directly tested using multisite electrophysiological recordings combined with pharmacological manipulations.

Conflicts of Interest

The authors declare no competing financial interests.

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Review Article

Noradrenergic Modulation of Cognition in Health and Disease

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Norepinephrine released by the locus coeruleus modulates cellular processes and synaptic transmission in the central nervous system through its actions at a number of pre- and postsynaptic receptors. This transmitter system facilitates sensory signal detection and promotes waking and arousal, processes which are necessary for navigating a complex and dynamic sensory environment. In addition to its effects on sensory processing and waking behavior, norepinephrine is now recognized as a contributor to various aspects of cognition, including attention, behavioral flexibility, working memory, and long-term mnemonic processes. Two areas of dense noradrenergic innervation, the prefrontal cortex and the hippocampus, are particularly important with regard to these functions. Due to its role in mediating normal cognitive function, it is reasonable to expect that noradrenergic transmission becomes dysfunctional in a number of neuropsychiatric and neurodegenerative diseases characterized by cognitive deficits. In this review, we summarize the unique role that norepinephrine plays in prefrontal cortical and hippocampal function and how its interaction with its various receptors contribute to cognitive behaviors. We further assess the changes that occur in the noradrenergic system in Alzheimer's disease, Parkinson's disease, attention-deficit/hyperactivity disorder, and schizophrenia and how these changes contribute to cognitive decline in these pathologies.

1. Introduction

The monoamine transmitter norepinephrine (NE) is synthesized and released by several small brainstem nuclei, and it has important modulatory roles in a number of forebrain functions. While classically thought to be primarily involved in sensory signal detection [1, 2] and general arousal and alertness in the waking state [3–5], more recent evidence suggests that NE plays important roles in behavior and cognition, such as attention [6–10], behavioral flexibility [11–14], and learning and memory [15–20]. Although disruption of these cognitive functions is not diagnostic of one specific disease state, it is symptomatic in a host of neuropsychiatric and neurodegenerative disorders [21–27]. Importantly, there is strong evidence linking dysfunction of the noradrenergic system to many such conditions, including depression [28, 29], anxiety [30, 31], attention-deficit hyperactivity disorder (ADHD) [32–36], schizophrenia [37–39], autism [40], Parkinson's disease [29, 41, 42], and Alzheimer's disease [27, 43, 44]. NE in the prefrontal cortex (PFC) and hippocampus is particularly important in the maintenance of multiple discrete behavioral and cognitive functions in both health and disease [7, 8, 15, 19, 20, 45–48]. It has been demonstrated that manipulations of the NE system in hippocampal and prefrontal regions are capable of selectively altering discrete aspects of behavior. For example, NE within the medial PFC is required for extradimensional shifting, a higher order measure of behavioral flexibility, but not for other measures of behavioral flexibility that are dependent upon the integrity of other neural substrates [7, 8].

NE is also required for hippocampal memory consolidation and retrieval [16, 17, 48]. Because NE has been identified as a potent modulator of various measures of prefrontal [45, 46, 49–55] and hippocampal function [15, 17, 47, 48], it is highly important to understand how the locus coeruleus (LC) and forebrain noradrenergic signaling adapt in various disease states. For example, early sensory deficits that occur in Alzheimer's and Parkinson's diseases that precede major cognitive decline and motor deficits might be related to deficits in noradrenergic signaling [43, 44, 56] due to its facilitatory role in sensory signal discrimination [1, 51, 57–59]. Indeed, LC neurons are known to degenerate in both of these

conditions [27, 29, 42, 56], potentially limiting forebrain noradrenergic facilitation of sensory perception. In this review, we will summarize the role and actions of NE in PFC and hippocampus and how it contributes to behavior and cognition. Furthermore, we will consider how both the LC proper and forebrain noradrenergic transmission are known to change in some disease states characterized by disordered cognition and how behavioral deficits in a multitude of neuropsychiatric and neurodegenerative diseases might allude to dysfunction of the noradrenergic system (Table 1). Recognition of the noradrenergic system as a major contributor to normal cognition and that its dysfunction can precipitate cognitive impairment represents an important step forward in identifying causes of and potential therapies for a number of pathological states.

2. Role of Norepinephrine in Prefrontal Cortical and Hippocampal Function and Behavior

Norepinephrine was originally thought to play a principal role in promoting waking due to the correlation between LC discharge rate and an animal's behavioral state [60–62] and the fact that artificial activation of LC promotes a forebrain EEG associated with waking in both the cortex and hippocampus [3–5]. A somewhat more specialized view for the role of NE came to light when it was shown that NE and LC activation can modulate the response properties of sensory neurons following stimulation in a dose-dependent manner [1, 2, 57]. Therefore, in addition to promoting waking, NE at particular levels might facilitate detection of sensory stimuli by priming sensory neurons. For example, LC stimulation and drugs that promote noradrenergic transmission have both been shown to increase responsiveness to visual stimulation in primary sensory neurons in the lateral geniculate nucleus [9, 10, 63, 64]. Through these combined actions, NE may have procognitive effects simply by rendering animals more alert and more sensitive to salient sensory stimuli in their environments. This is important because a major component of cognition is attention: the ability to ignore irrelevant sensory stimuli and focus on those that are behaviorally relevant. It is known that LC is activated by salient sensory stimuli that predict reward and that these responses are plastic such that they shift to new reward predictive stimuli when previously useful stimuli lose their predictive value [14, 49, 65–67].

These observations suggest that LC maintains an active role in regulating sustained and flexible attention that is more complex than simply increasing sensory neuronal responsiveness to nonspecific stimuli. Thus, if all sensory neurons became more sensitive to stimulation through the actions of NE when LC was activated by the reward predictive stimulus, it would be difficult for an animal to attend the relevant stimulus and ignore the irrelevant stimuli. Therefore, there is likely a degree of filtering or selection, either by LC or its terminal fields, that allows LC to respond preferentially to the relevant stimulus. A likely sight for this selection is in PFC neurons, which likewise show preferential responsiveness to task-relevant stimuli [46, 49]. Interestingly, the psychostimulant methylphenidate, a NE/dopamine reuptake inhibitor, simultaneously improves cognitive functions such as attention and working memory as well as prefrontal neuronal responsiveness [68]. It also preferentially increases NE concentration in PFC compared to other LC terminal fields [68–70]. These findings suggest a unique relationship between NE in PFC and cognition. Indeed, lesion studies have shown that denervation of NE fibers, but not cholinergic fibers, in medial PFC impairs extradimensional shifting, which can be rescued by administration of the selective NE reuptake inhibitor atomoxetine [7, 8].

Attention is not the only cognitive process modulated by NE in PFC circuits. It is also known that working memory is highly dependent upon noradrenergic transmission in the PFC. Specifically, delay-related firing, an electrophysiological correlate of working memory in prefrontal neurons, occurs in response to a behaviorally relevant stimulus and persists in its absence until reward can be retrieved. This type of activation of prefrontal neurons is potentiated by activation of the α_{2A} receptor and diminished by its antagonists, which improve and impair working memory, respectively [71]. Interestingly, NE has a high affinity for the α_{2A} receptor and is therefore engaged during low to moderate levels of NE and LC activation. When prefrontal NE concentration increases due to elevated LC discharge, as might occur during stress, the lower affinity α_1 receptor becomes engaged, inhibiting prefrontal cortical function and working memory.

A potential mechanism for this is through α_1 receptor-mediated long-term depression (LTD) in PFC synapses [72], which has been associated with improvement in measures of behavioral flexibility [73]. It has been proposed that this switch allows lower order sensorimotor cortical areas to guide behavior with little modulation by prefrontal operations [45, 50]. Inhibition of PFC and cognitive functions such as working memory and sustained attention might be beneficial to animals under certain circumstances, such as during stress for promoting behavioral flexibility. In this way, attentional reserves can be dissociated from specific stimuli and reallocated to others in the environment that facilitates escape from the stressor under guidance by more posterior cortical areas or to identify novel behavioral contingencies.

Disinhibition of PFC is known to impair behavioral flexibility [74], a major cognitive function which is disrupted in schizophrenic patients [75]. Research has shown that α_1 receptor-dependent LTD is impaired in an animal model of schizophrenia [76], which could potentially account for some of the perseverative behaviors seen in this patient population. Therefore, it seems that "optimal" cognition is context-dependent and may be heavily modulated by NE. Furthermore, in some circumstances, enhancement of working memory and sustained attention might be beneficial and behavioral flexibility maladaptive, while in other circumstances, the opposite would be true. The switch between these two behavioral modes appears to be at least partially dependent on differential engagement of α_1 and α_{2A} receptors. This notion is supported by evidence that suggests transmission at these receptors might be impaired in diseases characterized by cognitive deficits such as schizophrenia and ADHD [46].

Despite the important role that NE has in PFC function, particularly at the α_{2A} and α_1 receptors, activation of the β

Table 1: Clinical and preclinical anatomical and functional changes in NE/LC system and related cognitive symptoms of Alzheimer's disease, Parkinson's disease, ADHD, and schizophrenia.

	Alzheimer's disease	Parkinson's disease	ADHD	Schizophrenia
Functional/anatomical changes in NE/LC system	(i) Decreased LC volume and cell numbers with a rostrocaudal gradient [27, 44, 99] (ii) Tau protein assembles in LC into neurofibrillary tangles starting in early adulthood [95, 96] (iii) Decreased CNS levels of NE [92, 93, 102–105] (iv) Impaired hippocampal neurogenesis [101] (v) Impaired synaptic plasticity [104, 105]	(i) General destruction of LC without pattern topography [27, 44, 99] (ii) α-synuclein accumulation in LC [120] (iii) Loss of protective effect of α_2AR on NE/DA system [122, 123]	(i) Imbalances in DA/NE monoamine systems [132] (ii) PI3Kγ deficiency [130, 131] (iii) Impairment of NE transmission in PFC [71, 135, 137, 138] (iv) Improvement in behavioral symptoms by modulators of NE transmission [8, 10, 134, 135] (v) Dysregulation of signaling at the α_{2A} receptor [71, 135, 137]	(i) Orbitofrontal cortex in DISC1+/+ mice contain shorter tyrosine hydroxylase (TH) positive fibers compared to wild-type mice [165, 166] (ii) Impaired α_1 receptor-dependent LTD [76] (iii) Decreased binding of adrenergic probe to β_1AR [166, 173]
NE-related behavioral changes	(i) Early sensory deficits: impaired olfactory discrimination [56, 124] (ii) Behavioral perseveration modulated by innervation of medial PFC [5, 7, 8, 53, 125, 126] (iii) Memory decline [18, 85, 104, 105, 124, 127]		(i) Deficits in working memory, sustained attention, hyperactivity, impulsivity, behavioral flexibility [44, 134]	(i) Positive symptoms associated with high NE state [142, 153–155, 169, 170] (ii) Impaired spatial working memory [158–161, 170]

receptor in PFC produces minimal effects on behavior and circuit operations [34]. Activation of the β receptor in the hippocampus, however, plays a major role in hippocampal-dependent cognitive function. Specifically, activation of the β receptor is necessary for both contextual and spatial memory consolidation and retrieval [15–17, 47, 48], as well as contextual fear memory [77]. Interestingly, however, it has been shown that mice genetically lacking NE display normal fear memory [78], suggesting that in its absence, other transmitter systems might play a compensatory role to restore it. Research suggests that the activation of the β receptor increases neuronal excitability in the dentate gyrus, CA1, and CA3 [79–81] and facilitates learning by promoting both long-term depression and long-term potentiation in hippocampal synapses [18–20]. Which type of plasticity occurs seems to depend upon the degree of activation of the β receptor [82].

Less evidence exists for a role for α-adrenergic receptors in hippocampal function. However, the α_1 receptor may play an opposing role in hippocampal synaptic plasticity and memory formation and recall. Local application of the α_1 receptor antagonist prazosin into the dentate gyrus has been shown to increase the rate of learning of active avoidance. Conversely, this behavior was acquired more slowly when the α_1 agonist phenylephrine was administered [83]. This may be explained in part by the observation that α_1 receptor activation increases action potential generation in inhibitory CA1 interneurons, leading to inhibition of pyramidal cells [84]. Moreover, prazosin has been shown to limit memory deficits in a mouse model of Alzheimer's disease [85], further supporting the notion that activation of the α_1 adrenergic receptor (AR) is detrimental to hippocampal-dependent mnemonic processes. Interestingly, LC degenerates in Alzheimer's disease [27, 29, 44], which due to the well-established role of the β receptor in memory consolidation and recall as well as the particularly dense noradrenergic innervation of the hippocampus [18], likely contributes to some of the cognitive deficits displayed by this patient population. Importantly, manipulations that promote noradrenergic transmission are known to facilitate memory consolidation in normal aging patients as well as those showing mild cognitive impairment [86], suggesting that this transmitter system represents a viable target for the treatment of disease characterized by memory deficits. The strong evidence for the contribution of the LC/NE system to cognition in general through its actions at various receptor subtypes in PFC and hippocampus suggests that it represents a broad target for the treatment of the symptoms of various neurodegenerative, neuropsychiatric, and neurodevelopmental disease states, outlined below (Table 1).

3. Role of LC/NE System in Neuropathologies

3.1. Alzheimer's Disease. More than 35 million people worldwide live with dementia (5.5 million in the United States), and the number is set to almost double every 20 years. Moreover, the rate of undetected dementia is about 61.7% [87]. Alzheimer's disease (AD) is the most common form of dementia. Its pathogenesis includes amyloid plaque formation [88] and accumulation of tau protein [89] with subsequent oxidative and inflammatory brain damage [90, 91]. LC is a major contributor to AD progression: both preclinical studies of animal models of AD and clinical studies on postmortem human brain tissue [92] report decreased LC volume and numbers of tyrosine hydroxylase-positive LC cells. One proposed mechanism for forebrain NE loss in AD is a decrease in somatostatin receptor-2 (SSTR2) in LC neurons [93]. Significant somatostatin and SSTR-2 reduction has been described in normal aged brains across species and in human AD brains. Accordingly, a preclinical study of SSTR-2 knockout mice has revealed degeneration of noradrenergic axons with swollen varicosities and cluster-like structures [94], likely the result of accumulation of intra-axonal material due to impaired axonal transport [93].

A more prevalent hypothesis for LC degeneration and NE loss in AD is that accumulation of neurofibrillary tangles, comprised of abnormally phosphorylated tau protein, contributes to LC cell death and degeneration. Normal tau is a soluble protein which promotes assembly of tubulin, stabilizes microtubules, and facilitates axonal transport [89]. Hyperphosphorylated tau self-assembles into cytotoxic insoluble paired helical filament structures, contributing to cell death and impaired axonal transport [90]. According to Braak's classification of AD, LC plays a critically important role in pathogenesis of AD by undergoing accumulation of tau protein earlier than in other brain regions, which then serves as a primary source of the protein to the brain [95], causing neuronal degeneration and negatively impacting cognitive function. Animal models also demonstrate the accumulation and spreading of tau in LC. Stereotaxic injection of a bacterial vector carrying the human tau isoform into rodent LC leads to ipsilateral as well as contralateral accumulation of tau protein in the LC beginning the second week after injection, with frontal cortex becoming tau-positive in three months. Interestingly, maximum tau accumulation was observed from one to three months with decreases after six months due to loss of LC neurons [96]. This study did not find evidence of tau accumulation in hippocampal regions even six months after injection [96], despite the described accumulation of tau in human brains with AD [97]. This may suggest that LC cells innervating frontal cortex are distinct from those innervating hippocampus and uniquely susceptible to tau toxicity. This hypothesis is supported by prior observations from our laboratory showing an anatomically and functionally distinct projection from LC to frontal cortex [98].

Furthermore, evidence suggests that LC degeneration in AD affects mostly rostral cortically-projecting neurons and spares the caudal region [99], bolstering the argument for some degree of heterogeneity in LC susceptibility to AD pathogenesis. Identification of unique factors or markers that are expressed by LC neurons that are susceptible to AD pathogenesis may be informative of ways to limit or prevent LC degeneration experimentally, as well as for preventative/therapeutic purposes. If loss of LC cells that innervate frontal cortical regions contributes to the impaired cognition and dementia seen in AD, then limiting their damage

might help to prevent the development of these symptoms. Notably, NE has been shown to be neuroprotective by reducing oxidative stress [100]. Thus, the early loss of NE that would follow LC degeneration might exacerbate later cognitive decline by failing to limit frontal cortical cell death.

Despite the lack of evidence for hippocampal tau in the aforementioned study, it is important to note that a body of data exists which suggests the necessity of proper hippocampal NE for normal cognition. Specifically, immunotoxic ablation of LC in young rats results in reduced proliferation of progenitor cells in hippocampal dentate gyrus [101]. Furthermore, systemic administration of the neurotoxin DSP-4, which selectively destroys noradrenergic neurons, dramatically depletes hippocampal NE [42, 102, 103]. Hippocampal tau accumulation and noradrenergic axonal degeneration in human AD patients could contribute to hippocampal dysfunction and cognitive decline, due to the role of NE in long-term potentiation and synaptic plasticity [18]. Impairment of hippocampal NE transmission due to accumulation of hyperphosphorylated tau and axonal degeneration could manifest as impairments in hippocampally dependent cognition and memory. In support of this hypothesis, it has been shown that genetic overexpression of amyloid precursor protein and presenilin-1, or genetic deletion of Ear2, which promotes LC development [104, 105], both modestly impair hippocampal long-term potentiation and spatial memory. These two genetic modifications together, however, act synergistically to further impair these functions [104]. Collectively, these data confirm a permissive role for LC-derived NE in hippocampal neurogenesis and function.

In addition to its role as a source of tau to the brain, LC cell death might further exacerbate AD progression by limiting forebrain concentrations of NE. Preclinical investigations of the role of LC in AD pathogenesis suggest a neuroprotective and anti-inflammatory role for NE [106]. In vitro, NE increases IkBα [107], an inhibitor of proinflammatory transcription factor NF-kB. Inflammation is an important component in AD pathogenesis and promotes microglial activation [108], complement cascade, and inflammatory cytokine release [109] with nitric oxide activation. Animal studies have shown anti-inflammatory effects of pretreatment with a β-adrenergic receptor agonist [109] and α_2 receptor antagonist [110] on inflammation development in neurons after injection of β amyloid into LC-ablated animals. It is important to note that some discrepancies exist between preclinical animal studies and clinical human studies: LC in animal AD models tends to be involved in late stages of pathology, compared to its degeneration in early disease progression in humans. Therefore, the development of better AD animal models with primary effects on the noradrenergic system occurring early in pathogenesis will be an important factor in better understanding the sequence of pathologic processes that occur in the human AD brain.

3.2. Parkinson's Disease. The second most common cause of dementia are pathologies accompanied by Lewy body formation, including Parkinson's disease (PD) [111] and dementia with Lewy bodies. Considering the similar underlying pathophysiology, the effects of these diseases on LC will be considered together. The prevalence of PD is 200–300/100,000 [112], and even though motor symptoms are the primary concern, dementia occurs in as many as 80% of cases [113]. Despite weaker evidence for dysfunction of the noradrenergic system than the dopaminergic system in PD, it is critically important to consider the role of this transmitter system for a complete understanding and better management of cognitive impairment and emotional symptoms in PD patients that often accompany the more characteristic motor deficits seen in these diseases. The hallmarks of PD are degeneration of dopaminergic substantia nigra neurons and accumulation of α-synuclein in the form of Lewy bodies [114]. α-synuclein is a protein abundant in presynaptic terminals. It has been proposed that α-synuclein induces polymerization of purified tubulin into microtubules [115] and assists in vesicle fusion with presynaptic terminals and vesicle recycling [116]. Mutations in the α-synuclein gene could cause it to polymerize into filaments, which, with time, leads to nerve degeneration [117]. Indeed, postmortem studies of PD brains have described a loss noradrenergic neurons in LC and subcoeruleus in general, without topological preferences in contrast to LC degeneration in AD [99]. Furthermore, LC neuronal degeneration is accompanied by loss of overall structure, swollen cells with accumulated Lewy bodies, and short and thin dendrites [118, 119]. These neuronal changes collectively lead to overall decreased concentration of NE through the brain impacting LC terminal fields such as PFC and hippocampus thereby detrimentally affecting cognition.

According to Braak staging [120], LC accumulates α-synuclein and degenerates prior to substantia nigra, which exacerbates degeneration of the nigrostriatal pathway due to loss of neuroprotective and trophic influences of NE [100]. The neuroprotective action of NE is evidenced by the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; a potent neurotoxin which destroys dopaminergic neurons) model of PD: compared to controls, mice with increased concentrations of NE in the central nervous system are less susceptible to neurotoxic effect of MPTP [121]. Another study in monkeys revealed differences between animals with and without LC lesions after MPTP. Animals with LC damage had persistent Parkinsonian motor signs by nine weeks, and postmortem histology demonstrated severe neuronal loss in substantia nigra (SN) as well as profoundly decreased dopamine content, while animal without LC destruction mostly recovered by six to nine weeks after early PD symptoms, and showed only moderate loss of SN neurons [122]. These observations further confirm the protective role of NE on the nigrostriatal pathway. What is more, the protective effect of NE seems to occur through α_{2A} receptors: when blocked by the specific antagonist yohimbine, MPTP toxicity in the SN is exacerbated [123].

There is also substantial evidence that LC degeneration contributes directly to the cognitive and emotional disturbances experienced by PD patients that precede dopaminergic motor deficits. Simple sensory discrimination is impaired in PD patients early in disease progression [56, 124], as well as various aspects of behavioral flexibility [125, 126] which have been shown in animal studies to be dependent upon

intact noradrenergic signaling in PFC [7, 8, 53]. Evidence for a neurochemically complex etiology of cognitive impairment seen in PD comes from observations that treatment with dopamine agonists alone can ameliorate some, but not all behavioral deficits seen in this patient population. Behaviors which are not improved by dopaminergic agonists include attentional set shifting, task switching abstract rules, pattern and spatial recognition memory, associative learning, and verbal memory [127]. Given the importance of NE in modulating these cognitive functions [55], and extradimensional set shifting in particular, the LC/NE system represents a viable target for treatment options for sensory and cognitive deficits that accompany the more canonical motor deficits seen in PD. Mild cognitive decline or other behavioral markers for noradrenergic dysfunction that present prior to PD motor symptoms such as impaired sensory discrimination [56] might therefore be used as surrogate markers for early PD development, allowing for early intervention and preventative strategies to improve health outcomes within this disease population.

3.3. Attention-Deficit/Hyperactivity Disorder. Attention-deficit/hyperactivity disorder (ADHD) is a clinically heterogeneous and multifactorial disorder characterized by prevailing symptoms of poor attention, impaired working memory, and hyperactivity and/or impulsivity [44]. Worldwide prevalence is about 5.29% among children with higher levels in North America and Europe [128] and 3.4% among adults globally [129]. While ADHD presents with little evidence for neuroanatomical changes, and diagnostic criteria are limited to behavioral signs, there are animal models in which pathogenesis is explained by a lack of phosphoinositide 3-kinase PI3Kγ [130]. This enzyme has been shown to play an important role in NMDA synaptic plasticity [131]. Knockout of PI3Kγ in animals lead to increased levels of cAMP and subsequent stimulation of the transcription factor CREB, which regulates the ratio of NA to DA in PFC and striatum [132]. Impairment of the NE/DA ratio could lead to dysregulation of synaptic plasticity, which in turn promotes behavioral flexibility [133]. The pathogenesis of ADHD is connected to imbalances in dopaminergic and noradrenergic monoamine systems, which are therefore widely used as effective targets for its treatment [134].

Another proposed mechanism for ADHD is impaired NE transporter (NET) function. Drugs that inhibit NET such as methylphenidate and atomoxetine have been shown to improve sensory signal processing and behavioral outcomes in animals performing signal detection, flexible attention, and sustained attention tasks [8–10, 135]. However, it has been shown that availability and distribution of NET is not changed in ADHD patients according to a PET scan study [136], suggesting a potentially complex etiological origin for disease symptoms. Regardless, behavioral and pharmacological evidence still suggests that noradrenergic transmission is an effective therapeutic target for the treatment of ADHD symptoms and impaired working memory specifically at the presynaptic α_{2A} receptor. Administration of the α_{2A} agonists clonidine and guanfacine both improve behavioral and electrophysiological indices of working memory through inhibition of cAMP and strengthening of the functional connectivity of PFC networks [71, 135, 137], measures which are impaired by receptor antagonists such as yohimbine [71, 135, 138].

Dysfunctional noradrenergic transmission within the PFC seems to be implicated in the hyperactivity and attention impairment seen in ADHD. Motor hyperactivity can be induced in nonhuman primates through local administration of the α_{2A} antagonist yohimbine [138], providing further evidence for a specific role of prefrontal NE in modulating aberrant behavior in ADHD. Additional evidence for this hypothesis comes from observations that selective ablation of prefrontal noradrenergic fibers promotes perseveration and behavioral rigidity [7, 8], hallmarks of ADHD which are alleviated by inhibitors of NE reuptake [8]. Collectively, these observations lend support to the hypothesis that prefrontal NE is at least targetable for the treatment, if not directly related to the development of ADHD-like behavioral symptoms.

3.4. Schizophrenia. Schizophrenia (SCZ) is a debilitating mental illness which affects roughly 0.5% of the population and is considered to be one of the top ten causes of disability by the World Health Organization [139]. The illness is most effectively treated with antipsychotic drugs [140]; however, the variation of efficacy and side effects between patients for any one drug is substantial [141] and highlights our poor understanding of the disease. SCZ is characterized by positive symptoms such as delusion, hallucinations, and disordered thought and by negative symptoms such as blunted affect, inattention, and abulia [142]. While a major prevailing hypothesis is that altered dopaminergic and/or glutamatergic signaling contribute to SCZ development and etiology [143], there is evidence that the LC-NE system also plays a role in its major symptoms [144]. Specifically, on the basis of pharmacological, biochemical, and psychophysiological evidence, it has been proposed that both positive and negative symptoms may be the result of dysregulation of NE. NE has been found to be elevated in both the blood plasma [145] and cerebrospinal fluid of patients with SCZ, especially those with positive symptoms such as paranoia [145–147]. Postmortem studies have also reported increased markers for NE in the brains of schizophrenic patients [148–150]. Moreover, symptoms are often comorbid with insomnia [151], which is associated with the LC-NE system due to its role in promoting wakefulness [152].

In general, drugs that decrease, either directly or indirectly, noradrenergic transmission in the brain, such as α-methyldopa [153], clonidine [154], and propranolol, [155] tend to ameliorate positive symptoms. α-methyldopa, which interferes with the synthesis of both norepinephrine and dopamine, in conjunction with chlorpromazine, a D2 dopamine receptor antagonist, has been shown to be effective at treating schizophrenic behaviors as measured by the Inpatient Multidimensional Psychiatric Scale (IMPS) and the Brief Psychiatric Rating Scale (BPRS) [153]. Clonidine, in patients with predominantly positive symptoms according to the New Haven SCZ Index, has proven effective to improve symptoms with equal efficacy as a standard

dopaminergic antagonist neuroleptic, while simultaneously alleviating tardive dyskinesia [154]. It has also been shown to increase executive function in patients [156] and restore NE lesion-induced cognitive impairment in the frontal cortex in nonhuman primates [157]. Furthermore, propranolol improves scores on a modified BPRS similarly to chlorpromazine [155]. Conversely, drugs that tend to increase NE concentration, such as methylphenidate [158], cocaine [159], yohimbine [160], and desipramine [161], tend to worsen positive symptoms. Specifically, methylphenidate, a catecholamine reuptake inhibitor, triggered or exacerbated psychotic symptoms in SCZ patients who were in the active phase of their disease [158]. Cocaine, another catecholamine reuptake inhibitor, induced paranoia as reported by cocaine-dependent patients [159], and yohimbine, an α_{2A} adrenergic antagonist, caused dysphoria after administration that was not seen in healthy subjects [160]. After 4 weeks of receiving desipramine, a norepinephrine reuptake inhibitor, patients performed more poorly on the BPRS hallucinatory behavior item [161].

Atypical antipsychotics have varying effects on the NE system. Clozapine and olanzapine, dopamine antagonists, have been shown to increase firing rates [162, 163] and Fos expression in the LC [164]. This observation, coupled with the clozapine's high affinity for the β receptor ($K_i > 5000$), indicates that it may promote strong actions on noradrenergic signaling in the brain. Additionally, the NET inhibitor reboxetine has been shown to selectively increase prefrontal levels of DA, which might contribute to some DA abnormalities in SCZ [163]. Further evidence for the role of interactions between dopaminergic and noradrenergic transmission in PFC comes from the observation that risperidone, an antagonist of dopamine and serotonin receptors, improves working memory function, an effect which is blocked by propranolol [164]. This suggests that risperidone may improve cognitive function by indirectly modulating noradrenergic signaling. Collectively, these findings show that while a constellation of transmitter actions contribute to cognitive function and dysfunction, modulation of the noradrenergic system in particular seems to promote myriad positive and negative therapeutic outcomes in the schizophrenic patient population.

Unlike the general consensus for degeneration of noradrenergic cell bodies and axons in AD and PD, anatomical evidence for an altered LC-NE system in SCZ is conflicting. Orbitofrontal cortices of a transgenic mouse model for SCZ that expresses a mutant version of a gene that predicts susceptibility in human SCZ patients (DISC1) were shown to contain shorter tyrosine hydroxylase (TH) positive fibers compared to wild-type mice [165, 166]. It is important to note, however, that these studies did not differentiate between NE and DA positive tyrosine hydroxylase profiles, so further investigation is necessary to determine the contribution of each of these transmitter systems to anatomical and behavioral changes seen in this animal model. However, DISC1 mutants display deficits in spatial working memory [167], which has also been linked to dysregulation of the NE system [168]. Human studies of schizophrenic brains have yielded mixed results about anatomical and morphological changes that occur in the noradrenergic system. One postmortem study reported that LC cells from schizophrenic brains are 50% larger than in control brains [169], while a similar study conducted in the same year concluded that there is no such change of the LC in SCZ [170]. Lastly a postmortem study showed that iodoclonidine, a derivative of clonidine, bound more weakly to β receptors in the hippocampus in the brains of SCZ patients [171], suggesting altered noradrenergic signaling in these patients, but not necessarily structural changes to the LC/NE system. At present, there is no consensus regarding the abnormalities of the LC in SCZ patients. Because of the diversity of symptoms and drug efficacies among patients, it is likely that LC-NE aberrations may differ between patients.

Despite lacking evidence for anatomical changes in LC of SCZ patients and animal models, there is behavioral evidence for dysfunction of the noradrenergic system. A surrogate marker widely used for SCZ-like symptoms clinically and preclinically is prepulse inhibition (PPI). This is a phenomenon in which a weak nonstartling acoustic stimulus is presented prior to a stronger more salient stimulus, and the presentation of the former inhibits the behavioral reaction to the latter. Disruption of this behavior such that the reaction to the second pulse is not diminished by the presence of the first is a phenotypic marker of SCZ in both the clinical patient population as well as in animal models for SCZ such as DISC1 mutant mice [172–174]. PPI in mice has been shown to be restored by atomoxetine [175], a selective norepinephrine reuptake inhibitor, suggesting that lowered NE levels may be a contributor to decreased PPI. Conversely, pharmacological stimulation of LC with a number of drugs causes a deficit in PPI, which is reversed by administration of clonidine [176]. Collectively, while there is less evidence for anatomical changes that occur in the LC in SCZ patients, there are clear clinical and preclinical data that suggest at least functional alterations in the LC/NE system take place in this disease.

4. Conclusions

The LC, with its broad axonal arborization, and NE as a major modulatory monoamine in the CNS orchestrate the full range of their effects on cognitive processes through interactions with α_1, α_2, and β receptors which have varying affinities for NE and topographical localization in the CNS and promote distinct cellular and network effects through the brain [16, 71, 72, 85, 177–179]. While classically viewed as a mediator of waking and modulator of sensory signal detection, strong evidence now exists arguing for an important role of this transmitter system in cognition in both health and disease. It has been proposed that the LC/NE system contributes to cognition through its role in promoting wakefulness and improving sensory signal detection that are necessary for navigating through and learning in a complex dynamic world [12, 13]. There is also clear evidence for a trophic and neuroprotective role for NE throughout the brain that limits neurodegenerative processes in cognitive and motor circuits and promotes hippocampal neurogenesis necessary for mnemonic processes [100, 101, 106, 120]. A greater appreciation for the precise way in which NE promotes cognition in the normal brain is crucial to developing

a better understanding of how noradrenergic transmission goes awry in diverse neuropathologies such as AD, PD, ADHD, and SCZ (Table 1). This includes anatomical and neuroplastic changes within the LC and its efferent network as well as alterations in adrenergic receptor levels and distributions throughout the brain, particularly in PFC and hippocampus. Such new information will lead to new approaches to restore normal LC function and improve cognition and quality of life for millions of afflicted individuals through better treatment strategies for these patient populations.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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