

# Locus coeruleus in memory formation and Alzheimer's disease

Tony James<sup>1</sup> | Bartosz Kula<sup>2</sup> | Seowon Choi<sup>2,3</sup> | Shahzad S. Khan<sup>4</sup>  |  
Lane K. Bekar<sup>5</sup> | Nathan A. Smith<sup>1,2</sup>  

<sup>1</sup>George Washington University School of Medicine and Health Sciences, Washington, DC, USA

<sup>2</sup>Center for Neuroscience, Children's National Research Institute, Children's National Hospital, Washington, DC, USA

<sup>3</sup>Thomas Jefferson High School for Science and Technology, Alexandria, VA, USA

<sup>4</sup>Department of Biochemistry, Stanford University, Stanford, CA, USA

<sup>5</sup>Department of Anatomy, Physiology and Pharmacology, University of Saskatchewan, Saskatoon, Canada

## Correspondence

Nathan Anthony Smith, Center for Neuroscience Research, Children's National Hospital, 111 Michigan Ave, NW, Washington, DC 20010, USA.  
Email: nasmith2@cnmc.org

## Funding information

Army Research Office, Grant/Award Number: W91NF2010189; National Science Foundation, Grant/Award Number: 1926781; National Institute of Neurological Disorders and Stroke, Grant/Award Number: K01NS110981

## Abstract

Catecholamine neurons of the locus coeruleus (LC) in the dorsal pontine tegmentum innervate the entire neuroaxis, with signaling actions implicated in the regulation of attention, arousal, sleep–wake cycle, learning, memory, anxiety, pain, mood, and brain metabolism. The co-release of norepinephrine (NE) and dopamine (DA) from LC terminals in the hippocampus plays a role in all stages of hippocampal-memory processing. This catecholaminergic regulation modulates the encoding, consolidation, retrieval, and reversal of hippocampus-based memory. LC neurons in awake animals have two distinct firing modes: tonic firing (explorative) and phasic firing (exploitative). These two firing modes exert different modulatory effects on post-synaptic dendritic spines. In the hippocampus, the firing modes regulate long-term potentiation (LTP) and long-term depression, which differentially regulate the mRNA expression and transcription of plasticity-related proteins (PRPs). These proteins aid in structural alterations of dendritic spines, that is, structural long-term potentiation (sLTP), via expansion and structural long-term depression (sLTD) via contraction of post-synaptic dendritic spines. Given the LC's role in all phases of memory processing, the degeneration of 50% of the LC neuron population occurring in Alzheimer's disease (AD) is a clinically relevant aspect of disease pathology. The loss of catecholaminergic regulation contributes to dysfunction in memory processes along with impaired functions associated with attention and task completion. The multifaceted role of the LC in memory and general task performance and the close correlation of LC degeneration with neurodegenerative disease progression together implicate it as a target for new clinical assessment tools.

## KEYWORDS

Alzheimer's disease, dopamine, locus coeruleus, memory, norepinephrine

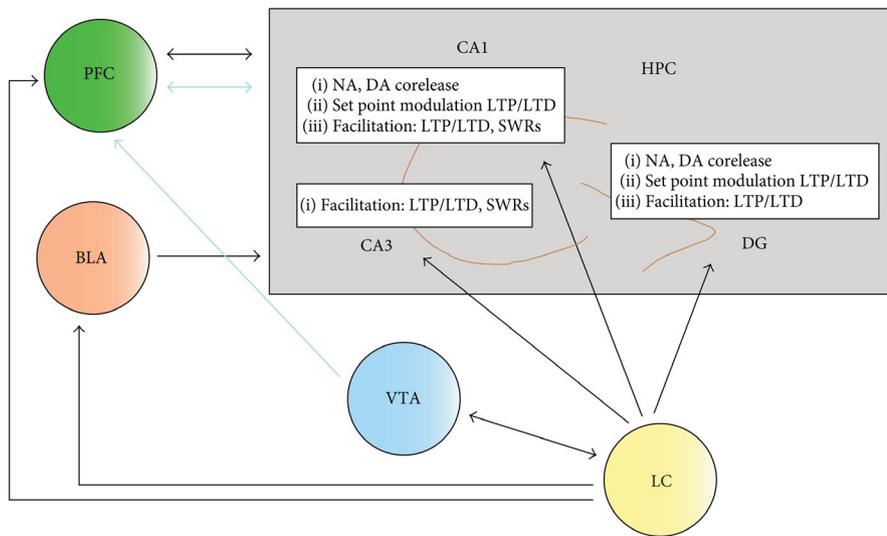
## 1 | INTRODUCTION

The locus coeruleus (LC) was described in the 18th century by Félix Vicq d'Azyr as a blue spot located in the

dorsal-rostral pons of freshly dissected brain. It contains densely packed medium-sized neurons that innervate the entire brain with unmyelinated projections. The LC provides relatively dense innervations to the thalamus and amygdala,

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. *European Journal of Neuroscience* published by Federation of European Neuroscience Societies and John Wiley & Sons Ltd



**FIGURE 1** The postulated network involving the LC in memory formation. Modified from (Hansen, 2017)

and relatively sparse innervations of the neocortex, hippocampus, cerebellum, and spinal cord (Levitt & Moore, 1978). However, the LC is the primary source of norepinephrine (NE) innervations in the brain (Aston-Jones & Cohen, 2005) and is now understood to provide a mixed NE and dopaminergic (DA) innervation in the hippocampus (Duszkiewicz et al., 2019; Kempadoo et al., 2016; Smith & Greene, 2012; Takeuchi et al., 2016). The LC has diverse functions defined by its wide range of neuroanatomic targets, being implicated in aspects of attention, arousal, the sleep–wake cycle, learning, memory, anxiety, pain, mood, and brain energy metabolism (Aston-Jones & Cohen, 2005; Benarroch, 2009; Llorca-Torrallba et al., 2016; Morita et al., 2019; Redmond & Huang, 1979; Sara, 2015; Sara & Bouret, 2012; Takahashi et al., 2010; Uematsu et al., 2015). For this review, we shall focus on the LC-NE/DA modulation of memory, entailing the encoding, consolidation, retrieval, and reversal of hippocampus-based memory. This modulation is obtained by the co-release of NE and DA from the LC along with the classical mesencephalic dopaminergic innervation from the ventral tegmental area (VTA).

NE release in the brain activates signaling at  $\alpha_1$ -,  $\alpha_2$ -,  $\beta_1$ , and  $\beta_2$ -adrenoceptors. These receptors are heterogeneously expressed in the brain and are associated with several cell populations. While cortical astrocytes express all four adrenoceptor types, cortical microglia only express  $\alpha_2$ - and  $\beta_2$ -adrenoceptors, and cortical neurons express  $\alpha_1$ ,  $\alpha_2$ , and  $\beta_1$ - adrenoceptors (Gyoneva & Traynelis, 2013; Hertz et al., 2010; Liu et al., 2019; O'Donnell et al., 2012; Salgado et al., 2011). These receptor subtypes are thought to be differentially activated by different firing patterns of the LC neurons, such that  $\beta$ -adrenoceptors respond to the interplay between tonic and phasic firing, thus adding a dimension of complexity to the post-synaptic responses (Aston-Jones & Cohen, 2005). The tonic and phasic firing patterns of LC neurons contribute to memory formation by inducing

long-term potentiation (LTP) and long-term depression, which is a fundamental dichotomous role of the LC in the regulation of learning and memory formation (Hansen & Manahan-Vaughan, 2015; Lemon et al., 2009; Nakahata & Yasuda, 2018). This noradrenergic modulation in specific forms of hippocampal memory processing is complemented by DA signaling at dopamine  $D_{1/5}$  receptors (Hansen, 2017; Lemon & Manahan-Vaughan, 2012).

Due to the LC's important role in all phases of memory formation and retrieval, the progressive degeneration of LC neurons and innervations in Alzheimer's disease (AD) may be clinically relevant. The relationship of LC cell number to MCI and AD progression was initially highlighted by Wilson et al. in 2013. They showed that diminished LC neuronal density had an independent association with the progression of cognitive decline rates (Wilson et al., 2013). Recent post-mortem analyses show a ~30% loss of LC neurons in patients with mild/severe amnesic cognitive impairment (aMCI) compared to cognitively intact individuals, which is followed by an additional ~25% neuronal loss upon conversion to AD (Kelly et al., 2017). Thus, there is a substantial and progressive degeneration of LC neurons in AD, which is likely to impair catecholamine signaling in the hippocampus and possibly alter the surviving LC neurons' tonic/phasic patterns. A better understanding of the consequences of reduced LC-NE/DA input to the hippocampus may inform new therapeutic strategies in AD (Kelly et al., 2017).

## 2 | LOCUS COERULEUS-NOREPINEPHRINE/DOPAMINE RELEASE IN MEMORY FORMATION

To perform its functions in memory formation and retrieval, the LC innervates three primary sites in the brain, all of which are in functional association with the hippocampus: the

basolateral amygdala (BLA), ventral tegmental area (VTA), and the prefrontal cortex (PFC) (Figure 1). The hippocampus is a complex structure composed of three major subfields CA1, CA2, and CA3, as well as the dentate gyrus, subicular complex, and perforant path innervation from the entorhinal cortex (Schultz & Engelhardt, 2014). For the present purposes, we consider the CA1, CA3, dentate gyrus, and entorhinal cortex as the main hippocampal elements involved in memory formation. The hippocampus of the rat is also functionally divided between the dorsal hippocampus, which is associated with memory retrieval, and the ventral hippocampus, which is related to context learning (Eichenbaum, 2017; Hansen, 2017).

The involvement of the BLA and hippocampus in anxiety and fear has been extensively studied over the past 30 years (Shin & Liberzon, 2010; Tovote et al., 2015). Lesions in either BLA or hippocampus inhibit the formation of fearful memories during conditioning, which can be mimicked by an infusion of glutamate antagonists into the hippocampus (McHugh et al., 2004). The opposite effect, enhancement of fear response, is observed upon infusion of glutamate receptor agonists into the hippocampus or electrical stimulation of BLA. The use of monosynaptic retrograde tracers proved that BLA input to the hippocampus is direct and specifically targets ventral CA1 (vCA1) (Felix-Ortiz et al., 2013; Yang & Wang, 2017) with the preponderance of inputs originating from the posterior rather than the anterior BLA (Yang & Wang, 2017; Yang et al., 2016).

A considerable body of evidence suggests that noradrenergic, dopaminergic, and cholinergic systems in BLA are important modulators of memory consolidation. Intra-BLA infusions of noradrenergic, dopaminergic, or cholinergic agonists enhance memory retention when applied post-training and are critical in the modulation of memory retention induced by other neurotransmitters (Garrido Zinn et al., 2016; Hatfield & McGaugh, 1999; Introini-Collison et al., 1996; LaLumiere et al., 2003, 2004; McGaugh, 2004; Mello-Carpes & Izquierdo, 2013; Power et al., 2003). In turn, infusion of noradrenergic or cholinergic antagonists abolishes the memory enhancement induced by DA, glucocorticoids, or opioids (Garrido Zinn et al., 2016; Introini-Collison et al., 1996; McGaugh et al., 1988; Mello-Carpes & Izquierdo, 2013; Power et al., 2000; Quirarte et al., 1997; Roozendaal et al., 1999). Notably, the interaction between the BLA and the hippocampus is also associated with social recognition memory, which is significantly impaired in AD (Figure 1). Recent studies show that disturbance of the BLA-hippocampus network in either direction leads to impairment in social recognition via disruption of dopamine D<sub>1/5</sub> receptors and/or  $\beta$ -adrenoceptors in the CA1 region of the hippocampus and BLA (Garrido Zinn et al., 2016). The BLA contributes to modulating the communication between the hippocampus and PFC, thus possibly contributing to

memory-storage mechanisms. In the context of fear conditioning, signaling from the BLA to the nearby central nucleus of the amygdala ultimately communicates with the nucleus accumbens in supporting memory consolidation and retrieval (Lim et al., 2017).

Direct input from the LC is one of the primary sources of NE in BLA (Chen & Sara, 2007; McCall et al., 2015, 2017). Conditioning stimuli and direct stimulation of LC or stimulation of LC fiber terminals innervating the BLA trigger similar fear responses in rodents and result in increased BLA neuron firing (McCall et al., 2015, 2017). Moreover, an increase in anxiety and avoidance is also apparent when  $\beta$ -adrenoceptors/rhodopsin chimeras are utilized to increase firing in BLA neurons by mimicking  $\beta$ -adrenoceptor-activation (Siuda et al., 2015). In addition, infusion of  $\beta$ -adrenoceptor antagonists into the BLA during/shortly after conditioning or stimulation inhibits fear response, whereas an infusion of  $\alpha$ -adrenoceptor antagonists seems to have an opposite effect (Garrido Zinn et al., 2016; Mello-Carpes & Izquierdo, 2013; Roozendaal et al., 1999; Siuda et al., 2015).

Interestingly, LC neurons not only modulate the activity of BLA but also receive reciprocal input from the central amygdala (CeA), which in turn receives input from BLA, suggesting a feedback pathway between BLA and LC (McCall et al., 2017). During stress responses, CeA modulates the tonic activity of LC-NE neurons. Photostimulation of CeA increases tonic activity in LC, leading to increased behavioral avoidance in rodents, to an extent scaling with the tonic activity in LC. On the other hand, the inhibition of LC-NE neuron tonic activity decreases anxiety. Interestingly, the CeA descending innervation to LC seems to originate specifically from corticotropin-releasing hormone (CRH+) neurons (McCall et al., 2017).

Previous studies found DA to be involved in the consolidation of episodic memories, synaptic plasticity, and spatial learning (Huang & Kandel, 1995; Kentros et al., 2004; Muzzio et al., 2009; da Silva et al., 2012; Xing et al., 2010). For many years, the VTA was believed to be the major source of DA input in the hippocampus (Bethus et al., 2010; Lisman & Grace, 2005). However, over the past decade, this view has been challenged by the discovery that the contributions of VTA DA inputs vary greatly between hippocampal regions. While the ventral hippocampus receives an abundance of VTA projections, the dorsal hippocampus is innervated sparsely, and only ~10% of the projections are dopaminergic (Gasbarri et al., 1994, 1997). This low VTA DA input cannot be solely responsible for the robust effect of DA in the dorsal hippocampus, suggesting the involvement of DA inputs arising from different sources. Given that DA is the immediate precursor of NE synthesis and that DA at hippocampal synapses is removed via the plasma membrane NE transporter (Borgkvist et al., 2012; Guiard et al., 2008; Moron et al., 2002), there is reason to suppose that there is

co-release of NE/DA from LC terminals. Indeed, electrical and/or pharmacological activation of LC increases DA levels in the hippocampus and enhances synaptic transmission (Devoto & Flore, 2006; Lemon & Manahan-Vaughan, 2012). In addition, the selective knockout of tyrosine hydroxylase (the rate-limiting enzyme in the DA/NE synthesis pathway) in LC, but not in VTA neurons, inhibits the enhancement in synaptic transmission (Smith & Greene, 2012). However, these findings do not reject the involvement of VTA in hippocampal memory formation. Although the VTA indeed projects dopaminergic input to the hippocampus's CA2 region, the VTA itself is not the primary source of DA input for hippocampal areas involved in memory formation such as the dentate gyrus (Duszkiewicz et al., 2019; Takeuchi et al., 2016).

Recent studies suggest that co-released NE/DA is involved in memory formation by controlling the transcription and translation of plasticity-related proteins (PRPs), which are key factors in spine formation. Sustained LTP/LTD in post-synaptic spines encourages memory formation through the development of synaptic tags, which are hypothetical markers of the structural changes underlying learning (Frey & Morris, 1997, 1998). Synaptic tag formation is thought to be initiated by short-term potentiation at the post-synaptic spine, which generates a molecular marker acting as an anchor on the spine to attract somatic gene products enabling storage and consolidation of memories (Rogerson et al., 2014). While the midbrain DA innervation from the VTA might contribute to tag formation, retrograde tracing studies implicate the catecholaminergic inputs from the LC as being more distinctly responsible (Takeuchi et al., 2016). The authors of that study concluded that the LC signaling amplifies LTP through the co-release of DA acting on  $D_{1/5}$  receptors to enhance hippocampal memory formation and spatial learning (Kempadoo et al., 2016; Takeuchi et al., 2016). This model would suggest that the co-release of NE and DA from LC terminals in the dorsal hippocampus enhances memory consolidation by amplifying LTP to promote spatial memory formation. The convergent VTA-derived DA signaling would then play a supportive role in this mechanism. In contrast, the LC-derived catecholamine signaling regulates the LTP/LTD interplay leading to PRP synthesis and spine formation to consolidate hippocampal-episodic memory and spatial memory (Hansen, 2017; Kempadoo et al., 2016; Nakahata & Yasuda, 2018; Takeuchi et al., 2016).

The PFC is another critical element in the hippocampal network that encodes and retrieves memory. Projections from the PFC modulate hippocampal activity via the entorhinal cortex in the medial temporal lobe. Current theory holds that the rodent PFC receives contextual information relevant to learning from the ventral hippocampus and controls memory retrieval via projections back to the dorsal hippocampus (Eichenbaum, 2017). In this model, the combined LC and

VTA catecholamine projections to the PFC aid in modulating memory formation by consolidating reciprocal communication between the PFC and the hippocampus. Application of a  $D_{1/5}$  receptor antagonist in the dorsal hippocampus or medial PFC resulted in impairments of object recognition memory (De Bundel et al., 2013). According to the scenario, both brain regions must participate in successful memory retrieval, which is facilitated by the theoretical co-release of NE and DA and their concerted targeting of  $D_{1/5}$  receptors in the PFC and the hippocampus (Hansen, 2017; Hansen & Manahan-Vaughan, 2014; Smith & Greene, 2012).

From these findings, it is evident that the BLA, VTA, and PFC together play crucial roles in supporting the LC-NE/DA-mediated processing and memory retrieval in the hippocampus (Figure 1). Co-release of the catecholamines in the CA1 and DG helps regulate set-point modulation of the LTP/LTD balance, a phenomenon known as metaplasticity. In this process, the co-release of NE and DA adjusts the threshold of activation to induce LTP or LTD, thus favoring one or the other plastic change on the post-synaptic target (Hansen, 2017; Maity et al., 2016; Nakahata & Yasuda, 2018). This initial priming allows for sustained or suppressed LTP or LTD in the post-synaptic target by increasing the trafficking of PRP expression and the initiation, consolidation, and retrieval of various forms of hippocampal memory. This catecholamine co-release also facilitates the establishment of a balance between LTP/LTD in all three hippocampal areas mentioned above: the CA1, CA3, and DG. In addition to effects on the LTP/LTD balance, NE release in the hippocampus facilitates sharp waves and ripples (SWR) in CA1 and CA3, which are oscillatory patterns first described in EEG recordings made during immobility and sleep. These SWRs are thought to aid in hippocampal memory consolidation (Ul Haq et al., 2016). Decreases in SWR in the CA3 region are associated with sleep or immobility, whereas increases in the CA1 and CA3 regions are associated with improved memory consolidation (Buzsaki, 2015; Ul Haq et al., 2016). Also, recent studies have highlighted the role of SWR on the CA3-DG circuit. In this model, SWR in the CA3 is responsible for encoding, storage, and retrieval of memory, whereas the DG aids in pattern separation of input from the entorhinal cortex (Hansen, 2017; Nakahata & Yasuda, 2018; Senzai, 2019).

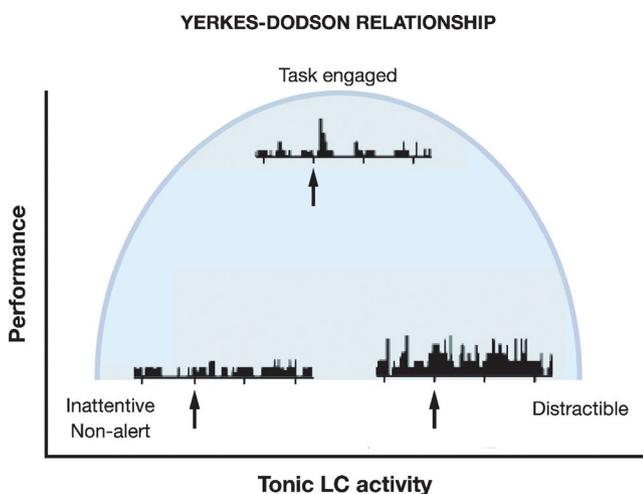
### 3 | PHASIC AND TONIC ACTIVITY OF LC NEURONS IN MEMORY FORMATION

Electrophysiological studies of the firing patterns of LC neurons have revealed two distinct modes of activity, which are designated as tonic and phasic firing. The physiological significance of these two modes of firing has been described primarily in the behavioral context of optimization in performance, attention, and arousal in decision making (Aston-Jones

& Cohen, 2005). It is of great importance to understand how these aspects of behavior are modulated as a function of LC neuron firing patterns. Notably, these two activity states of the LC are not mutually exclusive in achieving a given task. Rather, a functional balance between states is best described in the Yerkes-Dodson relationship model (Figure 2), wherein tonic activity has two major outcomes: high tonic firing leading to distractibility (explorative) behavior in rats, or low or absent tonic firing in association with inattentive non-alert activities such as sleep (Aston-Jones & Bloom, 1981; Aston-Jones et al., 1999; Berridge & Waterhouse, 2003). In this model, the phasic firing of LC-NE neurons is associated with alertness and behavioral arousal leading to task engagement. Yet, the phasic firing pattern does not predominate upon successful task completion (Figure 2). This suggests that there is a balance between the median tonic firing rate and spike frequency in phasic firing, which contributes to the successful completion of the present behavioral task. Such a task may be termed an exploratory behavior where the subject exploits a heightened state of attention along with activated learning and memory to complete a task successfully. In this model, the intervals of higher phasic activity help to filter out distracting stimuli and thus maintain enhanced task performance, whereas the intervals of lower tonic activity support alternative behavioral approaches to achieving the objective (Rajkowski et al., 2004). Alternating between these two LC neuronal activity states facilitates disengagement from task-specific processes. This means that the behavior associated with the interplay of tonic and phasic firing contributes to decision-making processes and is responsible for mapping task-relevant stimuli to an appropriate response, which primarily involves goal-directed motor activity (Aston-Jones &

Cohen, 2005). The selection and execution of motor activity also serve to provide information regarding the relevant internal process, since the selection of the appropriate response is heavily dictated by memory retrieval. This model of LC function was developed further by assigning a refined definition of the optimization of task performance, wherein a set of decision processes involving perception, memory, evaluation, and finally, the action is outlined (Gold & Shadlen, 2000; Hanes & Schall, 1996; Schall & Thompson, 1999; Shadlen & Newsome, 2001). Although memory is a multi-factorial process, the Yerkes-Dodson model provides a framework to infer potential deficits in memory retrieval by noting unexpected motor activity outcomes (Figure 2.).

This conceptual model is embodied in the adaptive gain theory, which intrinsically ties together two forms of memory since the theory is predicated upon the storage of information in long-term memory and its subsequent retrieval. In studies aiming to understand this aspect of LC activity, rats were trained for several weeks on a set of associated tasks. After attaining the criterion, the rats were treated just before testing for memory retention with the  $\alpha_2$ -adrenoceptor antagonist idazoxan, which increased firing and enhanced signaling at post-synaptic receptors of LC neurons due to autoreceptor blockade (Sara & Devauges, 1989). The idazoxan treatment led to fewer errors in task performance compared to untreated mice. The authors concluded that enhanced LC phasic activity facilitated the outcome of memory-driven decision processing. That conclusion is supported by other studies showing that manipulation of LC-NE function impacts working memory, such that treatment with  $\alpha_2$ -adrenoceptor agonists like clonidine or guanfacine facilitated working memory performance in aged monkeys (Avery et al., 2000; Mao et al., 1999; Rama et al., 1996; Ramos et al., 2006). However, since these molecular interactions are harder to quantify, there remains a need to disentangle the interactions between phasic and tonic LC-signaling in memory formation and retrieval. In the studies cited above, the  $\alpha_2$ -adrenoceptor was the only pharmacological target, but other classes of adrenoceptors in the hippocampus may also mediate effects of LC activity on formation, consolidation, and retrieval of memories (Gao et al., 2016; O'Dell et al., 2015). Further studies targeting the excitatory  $\alpha_1$ - or  $\beta$ -adrenoceptors might elucidate the role of NE in memory formation, as might studies investigating interactions with dopamine  $D_{1/5}$  receptors in memory formation and retrieval (Hansen, 2017).



Aston-Jones, G and Cohen, JD. 2005  
Annu. Rev. Neurosci. 28:403–50

**FIGURE 2** The role of phasic and tonic LC activity in task performance and potential for enhanced memory formation and retrieval. Modified from (Aston-Jones & Cohen, 2005)

## 4 | LTD AND LTP REGULATION IN NEURONAL SYNAPTIC SPINES

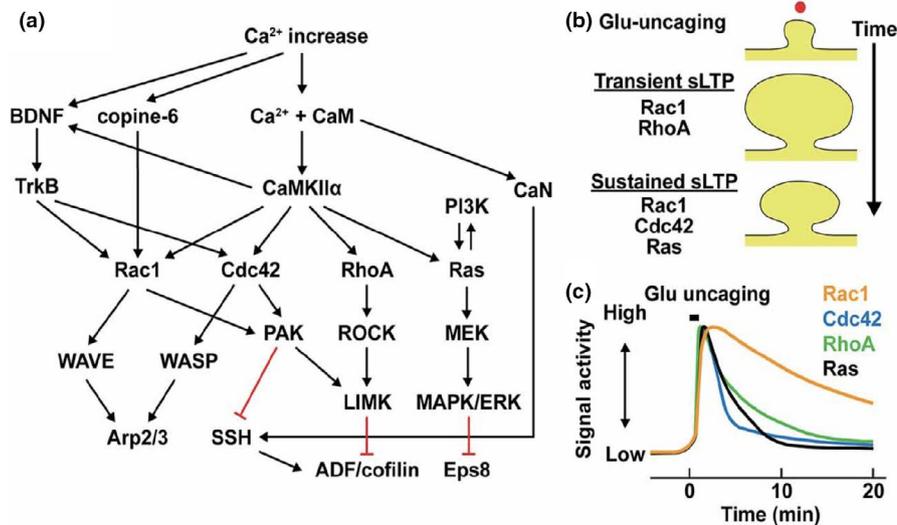
The firing of LC neurons plays a key role in long-term synaptic plasticity by not only enhancing LTP in rodents but also by facilitating LTD as a cellular mechanism of memory

storage (Matsuzaki et al., 2004; Zhou et al., 2004). In a necessarily simplistic model, LTP mediates enhanced memory formation and consolidation by provoking an initial structural LTP (sLTP) to initiate the formation of PRPs (Figure 3). However, a sustained LTP activates spine formation via glutamate uncaging, leading to changes in mRNA transcription and protein translation in the post-synaptic spine and ultimately regulating the expansion and stabilization phase of spine development (Harvey et al., 2008; Nakahata & Yasuda, 2018). Cellular and molecular studies indicate that sustained LTP increases intercellular calcium release, leading to the activation of down-stream calcium response elements (Figure 3). Chief among these is the  $Ca^{2+}$ /calmodulin-dependent protein kinase II (CaMKII $\alpha$ ), which is a serine/threonine-specific protein kinase responsible for activating several critical factors in spine enlargement that proceed to a contraction of the spine size known as stabilization (Chang et al., 2017; Lee et al., 2009; Nakahata & Yasuda, 2018). In this  $Ca^{2+}$ -signaling cascade, Rac1, Cdc42, RhoA, and Ras are all key regulators between the two phases of spine enlargement and stabilization that follow the initial LTP (Figure 3). While Rac1 and RhoA are crucial during the initial expansion phase, Rac1, Cdc42, and Ras play major roles in stabilizing mRNA and proteins associated with the stabilization phase (Figure 3). Further studies show that the cellular localization of CaMKII $\alpha$  during the initial transient sLTP influences the outcome of a subsequent bout of sustained sLTP (Bosch et al., 2014; Hedrick et al., 2016; Murakoshi et al., 2011).

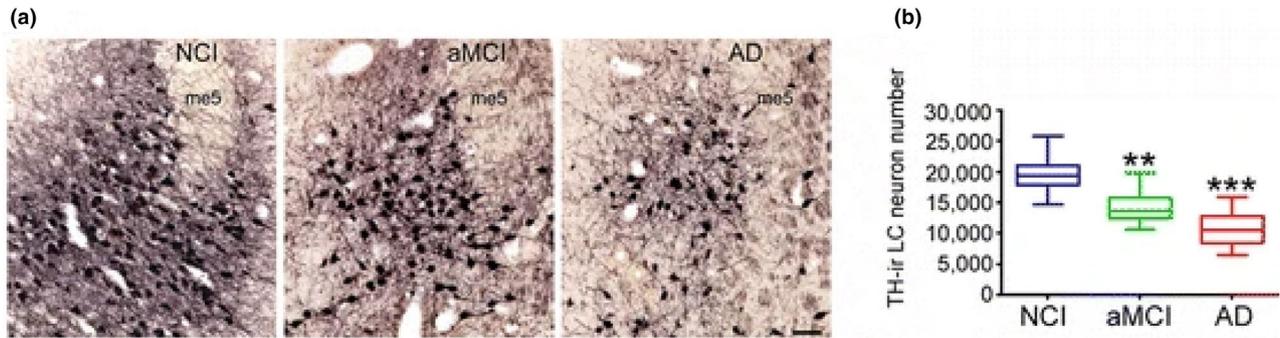
### 5 | THE LOSS OF LC ACTIVITY IN THE DEVELOPMENT OF ALZHEIMER'S DISEASE

One of the major features of AD pathology is the progressive degeneration of LC neurons (Figure 4). The prevalence of

neurofibrillary tangles, which are composed of the microtubule-associated protein tau, is the best pathological marker of AD progression in the brain. While endogenous tau proteins are generally localized to neuronal axons, during the earliest stages of AD, hyper-phosphorylated tau is detected in somata and dendrites prior to neurofibrillary tangle formation and neuronal loss. Indeed, a comprehensive histological study of over 2,300 brains aged 1 to 100 years revealed the temporary dynamic of AD-associated pathological changes in tau proteins (Braak et al., 2011). A primary objective of that study was to identify the earliest changes in aberrant phosphorylation of tau at serines 202 and 205 using the AT8 antibody. The findings identified LC neurons as the cell population showing the earliest appearance of immunoreactivity for AT8, preceding the onset in classically tau-positive regions such as the entorhinal cortex (Braak et al., 2011). Importantly, that study and the preponderance of experimental evidence from other sources have shown that tau pathology spreads throughout the brain via a "prion-like" mechanism. The cross-sectional data suggest that local seeding of tau aggregates leads to transfer into neighboring brain regions, where the pathological tau species function as a template for tau aggregation in previously healthy neurons. To determine the relationship of tau phosphorylation to the prion hypothesis, a follow-up study was performed to investigate tau seeding capacity in the LC (Kaufman et al., 2018). In that study, tau seeding was followed by tauopathy in the trans-entorhinal and entorhinal cortices, whereas seeding capacity was not detected within the LC until later AD stages. Hence, additional work that includes the use of a broader array of phospho-tau antibodies, as well as phospho-null and phospho-mimetic tau molecules, could help to disentangle tau phosphorylation in the LC from tau seeding capacity. In one *post-mortem* study, a group of ( $n = 10$ ) amnesic mild cognitive impairment (aMCI) patients had a 30% loss of LC-NE neurons compared to age-matched normal controls (NCIs), and a further 25% reduction was



**FIGURE 3** Role of Rac1, Cdc42, RhoA, and Ras in LTP and LTD spine formation. Modified from (Nakahata & Yasuda, 2018)



**FIGURE 4** Tyrosine hydroxylase (TH) immunohistochemistry shows a 55% loss in LC noradrenergic neurons in contrast to individuals dying without cognitive impairment (NCI) amnesic mild cognitive impairment (aMCI) and Alzheimer's Disease (AD) by TH- immunohistochemistry. Modified from (Kelly et al., 2017)

seen in the group dying with AD (Kelly et al., 2017). Thus, the end stage of AD involved a ~55% loss of LC neurons compared to age-matched controls (Figure 4). Further analysis showed that cognitive test scores in the subgroups with no cognitive impairment (NCI) and those with aMCI showed a significant correlation ( $r \sim 0.5$ ) with LC neuron counts *post-mortem*. Among the various clinical scores, the global cognitive score (GCS), episodic memory, working memory, and visuospatial ability all had significant correlations with LC counts ( $p < .05$ ). Notably, there were no significant correlations with the mini-mental state exam score, semantic memory, and perceptual speed in the other clinical examinations. Analysis of mRNA transcripts in the three sets of post-mortem samples showed reduced expression of genes involved in mitochondrial respiration and redox homeostasis. The authors also observed increases in neuritic plaques density and dysregulation of structural plasticity with disease progression in the LC of post-mortem AD tissue samples with increasing disease progression (Kelly et al., 2017).

Rodent research supports the functional significance of the LC to the onset of tau pathology, and AD-like behavioral deficits were also recently revealed in rodent models involving the LC. In one study, TgF344 rats (containing the Swedish mutations in the Amyloid Precursor Protein and  $\Delta$  exon 9 mutations in presenilin 1) displayed tau pathology in the LC prior to the development of hyper-phosphorylated tau in the entorhinal cortex or hippocampus (Rorabaugh et al., 2017). In the same study, spatial learning was impaired in TgF344 rats, and LC activation using DREADDs was sufficient to restore reversal learning. In another study, the role of tau in cognitive changes was probed by transducing into the LC of TH-Cre rats, a pseudo-phosphorylated form of the human tau gene (Ghosh et al., 2019). These genetically modified rats were tested for their ability to discriminate odors. As expected, injection of tau specifically into rats aged 14–16-month resulted in deficits in odor discrimination some 5–6 months later, thus mimicking the anosmia of

AD. Altogether, these recent rodent studies support the early observations made by Braak and colleagues and highlight the importance of early pathology in the LC to AD disease progression.

In addition to the loss of normal neurological signaling and function, accumulating evidence describes the immunological impact of the loss of NE in the CNS. Thus, recent data have demonstrated that NE degeneration causes a retraction of microglia processes in their resting and activated states via impaired signaling at  $\alpha_2$ - and  $\beta_2$ -adrenoceptors (Gyoneva & Traynelis, 2013; Liu et al., 2019). The degenerative loss of this neurotransmitter in the CNS leads to microglial dysfunction and increased neuroinflammation. In murine models, it has been demonstrated that NE is responsible for suppressing proinflammatory transcription, cytokine, and chemokine production in microglia (Heneka et al., 2010). That study also showed that the decreased brain NE concentration leads to reduced motility of microglia to sites of amyloid plaques and impaired onset of active phagocytosis, even extending to effects on synaptic pruning. In addition, one study on the activation of microglia by lipopolysaccharide showed NOS2 induced death of rat cortical neurons in culture (Madrigal et al., 2005). This apoptosis was caused by the overproduction of IL-1 and IL-1b, which are key proinflammatory cytokines. In the same study, the application of NE reduced cytokine production, initiating a rescue of the cortical neurons (Madrigal et al., 2005). Interestingly, concomitant alterations in GFAP + and Iba1 + glial cells were observed in the LC of 16-month-old TgF344 AD model rats, and infusion of human pseudo-phospho-tau into the LC resulted in the accumulation of human tau into cortical neurons and microglia (Ghosh et al., 2019; Rorabaugh et al., 2017). Concurring with these experimental results, human post-mortem samples suggest that ongoing and progressive neuroinflammation occurs during AD disease, and the extent of this neuroinflammation is a crucial factor in increased mortality (Hoogendijk et al., 1995; Sarlus & Heneka, 2017).

## 6 | DISCUSSION

The LC-NE/DA innervation is involved in all stages of hippocampal-based memory formation, consolidation, and retrieval, and the LC degeneration in AD is an early marker and key factor in the disease progression and cognitive symptoms. The involvement of LC degeneration may have implications for new therapeutic interventions. LC pathology is a prominent finding in the post-mortem analysis of AD patients (Adolfsson et al., 1979; Feinstein et al., 2016; Gannon et al., 2015; Szot et al., 2009). Indeed, some LC degeneration is present at the early stages of the disease, which could be a contributing factor to cognitive impairments (Gannon et al., 2015; Gannon & Wang, 2019; Grudzien et al., 2007; Ross et al., 2019). There have emerged clear associations between LC-NE neuron loss and the antemortem clinical manifestations of neurological impairments in AD patients, thus suggesting LC degeneration as a biomarker for disease progression. Indeed, PET studies with the noradrenaline transporter ligand (S,S)-[<sup>18</sup>F] FMeNER-D2 show a distinct decrease in binding density in LC and in the thalamus, which is the densest terminal region (Gulyas et al., 2010). Since AD manifests with multiple symptoms that are not always easily distinguishable from those of other forms of dementia, improving the accuracy of early diagnosis would enable appropriate patient care. Neuropsychiatric or cognitive testing informed by an understanding of the contribution of LC NE/DA in hippocampal memory processes could help to pinpoint defects in the LC. Currently, clinical testing for suspicion of AD assesses multiple aspects of memory, retention, mood, motor function, and cognitive dysfunction. However, we note the seeming relationship between impaired NE-signaling and behavioral aspects of attention deficit hyperactivity disorder (ADHD), which may overlap with cognitive changes in AD. This implies that cognitive testing drawn from the ADHD literature may facilitate early AD diagnosis. In other domains, the individual extent of NE loss may contribute to specific behavioral aspects of AD (Herrmann et al., 2004). Consideration of the noradrenergic component of aspects of the clinical and pathophysiological picture of AD could prove to be crucial in designing future interventions, which are more likely to be efficacious with efficacy when implemented early in disease progression.

### ACKNOWLEDGMENTS

We thank Professor Paul Cumming of Bern University for comments, edits, and critical discussion for this manuscript. This work was supported by the National Institutes of Health Grant K01NS110981, the National Science Foundation NSF1926781, and the Department of Defense ARO W91NF2010189 to N.A.S.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest with respect to this review article.

### AUTHOR CONTRIBUTIONS

All authors contributed to the writing of this manuscript and have reviewed the final version.

### PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ejn.15045>.

### DATA AVAILABILITY STATEMENT

There are no original data associated with this manuscript.

### ORCID

Shahzad S. Khan  <https://orcid.org/0000-0003-3962-0226>  
Nathan A. Smith  <https://orcid.org/0000-0002-9254-5360>

### TWITTER

Nathan A. Smith  @Smithlab2018

### REFERENCES

- Adolfsson, R., Gottfries, C. G., Roos, B. E., & Winblad, B. (1979). Changes in the brain catecholamines in patients with dementia of Alzheimer type. *British Journal of Psychiatry*, *135*, 216–223. <https://doi.org/10.1192/bjp.135.3.216>
- Aston-Jones, G., & Bloom, F. E. (1981). Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *Journal of Neuroscience*, *1*, 876–886. <https://doi.org/10.1523/JNEUROSCI.01-08-00876.1981>
- Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience*, *28*, 403–450. <https://doi.org/10.1146/annurev.neuro.28.061604.135709>
- Aston-Jones, G., Rajkowski, J., & Cohen, J. (1999). Role of locus coeruleus in attention and behavioral flexibility. *Biological Psychiatry*, *46*, 1309–1320. [https://doi.org/10.1016/S0006-3223\(99\)00140-7](https://doi.org/10.1016/S0006-3223(99)00140-7)
- Avery, R. A., Franowicz, J. S., Studholme, C., van Dyck, C. H., & Arnsten, A. F. (2000). The alpha-2A-adrenoceptor agonist, guanfacine, increases regional cerebral blood flow in dorsolateral prefrontal cortex of monkeys performing a spatial working memory task. *Neuropsychopharmacology*, *23*, 240–249. [https://doi.org/10.1016/S0893-133X\(00\)00111-1](https://doi.org/10.1016/S0893-133X(00)00111-1)
- Benarroch, E. E. (2009). The locus ceruleus norepinephrine system: Functional organization and potential clinical significance. *Neurology*, *73*, 1699–1704. <https://doi.org/10.1212/WNL.0b013e3181c2937c>
- Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Research. Brain Research Reviews*, *42*, 33–84. [https://doi.org/10.1016/S0165-0173\(03\)00143-7](https://doi.org/10.1016/S0165-0173(03)00143-7)
- Bethus, I., Tse, D., & Morris, R. G. (2010). Dopamine and memory: Modulation of the persistence of memory for novel hippocampal NMDA receptor-dependent paired associates. *The Journal of*

- Neuroscience: The Official Journal of the Society for Neuroscience*, 30, 1610–1618.
- Borgkvist, A., Malmlof, T., Feltmann, K., Lindskog, M., & Schilström, B. (2012). Dopamine in the hippocampus is cleared by the norepinephrine transporter. *International Journal of Neuropsychopharmacology*, 15, 531–540.
- Bosch, M., Castro, J., Saneyoshi, T., Matsuno, H., Sur, M., & Hayashi, Y. (2014). Structural and molecular remodeling of dendritic spine substructures during long-term potentiation. *Neuron*, 82, 444–459. <https://doi.org/10.1016/j.neuron.2014.03.021>
- Braak, H., Thal, D. R., Ghebremedhin, E., & Del Tredici, K. (2011). Stages of the pathologic process in Alzheimer disease: Age categories from 1 to 100 years. *Journal of Neuropathology and Experimental Neurology*, 70, 960–969. <https://doi.org/10.1097/NEN.0b013e318232a379>
- Buzsáki, G. (2015). Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus*, 25, 1073–1188. <https://doi.org/10.1002/hipo.22488>
- Chang, J. Y., Parra-Bueno, P., Laviv, T., Szatmari, E. M., Lee, S. R., & Yasuda, R. (2017). CaMKII autophosphorylation is necessary for optimal integration of Ca(2+) signals during LTP induction, but not maintenance. *Neuron*, 94(800–808), e804. <https://doi.org/10.1016/j.neuron.2017.04.041>
- Chen, F. J., & Sara, S. J. (2007). Locus coeruleus activation by foot shock or electrical stimulation inhibits amygdala neurons. *Neuroscience*, 144, 472–481. <https://doi.org/10.1016/j.neuroscience.2006.09.037>
- da Silva, W. C., Kohler, C. C., Radiske, A., & Cammarota, M. (2012). D1/D5 dopamine receptors modulate spatial memory formation. *Neurobiology of Learning and Memory*, 97, 271–275. <https://doi.org/10.1016/j.nlm.2012.01.005>
- De Bundel, D., Femenia, T., DuPont, C. M., Konradsson-Geuken, A., Feltmann, K., Schilström, B., & Lindskog, M. (2013). Hippocampal and prefrontal dopamine D1/5 receptor involvement in the memory-enhancing effect of reboxetine. *International Journal of Neuropsychopharmacology*, 16, 2041–2051. <https://doi.org/10.1017/S1461145713000370>
- Devoto, P., & Flore, G. (2006). On the origin of cortical dopamine: Is it a co-transmitter in noradrenergic neurons? *Current Neuropharmacology*, 4, 115–125.
- Duszkiewicz, A. J., McNamara, C. G., Takeuchi, T., & Genzel, L. (2019). Novelty and dopaminergic modulation of memory persistence: A tale of two systems. *Trends in Neurosciences*, 42, 102–114. <https://doi.org/10.1016/j.tins.2018.10.002>
- Eichenbaum, H. (2017). Memory: Organization and control. *Annual Review of Psychology*, 68, 19–45. <https://doi.org/10.1146/annurev-psych-010416-044131>
- Feinstein, D. L., Kalinin, S., & Braun, D. (2016). Causes, consequences, and cures for neuroinflammation mediated via the locus coeruleus: Noradrenergic signaling system. *Journal of Neurochemistry*, 139(Suppl 2), 154–178. <https://doi.org/10.1111/jnc.13447>
- Felix-Ortiz, A. C., Beyeler, A., Seo, C., Leppla, C. A., Wildes, C. P., & Tye, K. M. (2013). BLA to vHPC inputs modulate anxiety-related behaviors. *Neuron*, 79, 658–664. <https://doi.org/10.1016/j.neuron.2013.06.016>
- Frey, U., & Morris, R. G. (1997). Synaptic tagging and long-term potentiation. *Nature*, 385, 533–536. <https://doi.org/10.1038/385533a0>
- Frey, U., & Morris, R. G. (1998). Synaptic tagging: Implications for late maintenance of hippocampal long-term potentiation. *Trends in Neurosciences*, 21, 181–188. [https://doi.org/10.1016/S0166-2236\(97\)01189-2](https://doi.org/10.1016/S0166-2236(97)01189-2)
- Gannon, M., Che, P., Chen, Y., Jiao, K., Roberson, E. D., & Wang, Q. (2015). Noradrenergic dysfunction in Alzheimer's disease. *Front Neurosci*, 9, 220. <https://doi.org/10.3389/fnins.2015.00220>
- Gannon, M., & Wang, Q. (2019). Complex noradrenergic dysfunction in Alzheimer's disease: Low norepinephrine input is not always to blame. *Brain Research*, 1702, 12–16. <https://doi.org/10.1016/j.brainres.2018.01.001>
- Gao, V., Suzuki, A., Magistretti, P. J., Lengacher, S., Pollonini, G., Steinman, M. Q., & Alberini, C. M. (2016). Astrocytic beta2-adrenergic receptors mediate hippocampal long-term memory consolidation. *Proceedings of the National Academy of Sciences of the United States of America*, 113, 8526–8531.
- Garrido Zinn, C., Clairis, N., Silva Cavalcante, L. E., Furini, C. R., de Carvalho Myskiw, J., & Izquierdo, I. (2016). Major neurotransmitter systems in dorsal hippocampus and basolateral amygdala control social recognition memory. *Proceedings of the National Academy of Sciences of the United States of America*, 113, E4914–4919. <https://doi.org/10.1073/pnas.1609883113>
- Gasbarri, A., Sulli, A., & Packard, M. G. (1997). The dopaminergic mesencephalic projections to the hippocampal formation in the rat. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 21, 1–22. [https://doi.org/10.1016/S0278-5846\(96\)00157-1](https://doi.org/10.1016/S0278-5846(96)00157-1)
- Gasbarri, A., Verney, C., Innocenzi, R., Campana, E., & Pacitti, C. (1994). Mesolimbic dopaminergic neurons innervating the hippocampal formation in the rat: A combined retrograde tracing and immunohistochemical study. *Brain Research*, 668, 71–79. [https://doi.org/10.1016/0006-8993\(94\)90512-6](https://doi.org/10.1016/0006-8993(94)90512-6)
- Ghosh, A., Torralville, S. E., Mukherjee, B., Walling, S. G., Martin, G. M., Harley, C. W., & Yuan, Q. (2019). An experimental model of Braak's pretangle proposal for the origin of Alzheimer's disease: The role of locus coeruleus in early symptom development. *Alzheimer's Research & Therapy*, 11, 59. <https://doi.org/10.1186/s13195-019-0511-2>
- Gold, J. I., & Shadlen, M. N. (2000). Representation of a perceptual decision in developing oculomotor commands. *Nature*, 404, 390–394. <https://doi.org/10.1038/35006062>
- Grudzien, A., Shaw, P., Weintraub, S., Bigio, E., Mash, D. C., & Mesulam, M. M. (2007). Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. *Neurobiology of Aging*, 28, 327–335. <https://doi.org/10.1016/j.neurobiolaging.2006.02.007>
- Guiard, B. P., El Mansari, M., & Blier, P. (2008). Cross-talk between dopaminergic and noradrenergic systems in the rat ventral tegmental area, locus ceruleus, and dorsal hippocampus. *Molecular Pharmacology*, 74, 1463–1475. <https://doi.org/10.1124/mol.108.048033>
- Gulyas, B., Brockschneider, D., Nag, S., Pavlova, E., Kasa, P., Beliczai, Z., Legradi, A., Gulya, K., Thiele, A., Dyrks, T., & Halldin, C. (2010). The norepinephrine transporter (NET) radioligand (S, S)-[18F]FMeNER-D2 shows significant decreases in NET density in the human brain in Alzheimer's disease: A post-mortem autoradiographic study. *Neurochemistry International*, 56, 789–798. <https://doi.org/10.1016/j.neuint.2010.03.001>
- Gyoneva, S., & Traynelis, S. F. (2013). Norepinephrine modulates the motility of resting and activated microglia via different adrenergic receptors. *Journal of Biological Chemistry*, 288, 15291–15302. <https://doi.org/10.1074/jbc.M113.458901>

- Hanes, D. P., & Schall, J. D. (1996). Neural control of voluntary movement initiation. *Science*, 274, 427–430. <https://doi.org/10.1126/science.274.5286.427>
- Hansen, N. (2017). The longevity of hippocampus-dependent memory is orchestrated by the locus coeruleus-noradrenergic system. *Neural Plasticity*, 2017, 2727602. <https://doi.org/10.1155/2017/2727602>
- Hansen, N., & Manahan-Vaughan, D. (2014). Dopamine D1/D5 receptors mediate informational saliency that promotes persistent hippocampal long-term plasticity. *Cerebral Cortex*, 24, 845–858. <https://doi.org/10.1093/cercor/bhs362>
- Hansen, N., & Manahan-Vaughan, D. (2015). Hippocampal long-term potentiation that is elicited by perforant path stimulation or that occurs in conjunction with spatial learning is tightly controlled by beta-adrenoreceptors and the locus coeruleus. *Hippocampus*, 25, 1285–1298. <https://doi.org/10.1002/hipo.22436>
- Harvey, C. D., Yasuda, R., Zhong, H., & Svoboda, K. (2008). The spread of Ras activity triggered by activation of a single dendritic spine. *Science*, 321, 136–140. <https://doi.org/10.1126/science.1159675>
- Hatfield, T., & McGaugh, J. L. (1999). Norepinephrine infused into the basolateral amygdala post-training enhances retention in a spatial water maze task. *Neurobiology of Learning and Memory*, 71, 232–239. <https://doi.org/10.1006/nlme.1998.3875>
- Hedrick, N. G., Harward, S. C., Hall, C. E., Murakoshi, H., McNamara, J. O., & Yasuda, R. (2016). Rho GTPase complementation underlies BDNF-dependent homo- and heterosynaptic plasticity. *Nature*, 538, 104–108. <https://doi.org/10.1038/nature19784>
- Heneka, M. T., Nadrigny, F., Regen, T., Martinez-Hernandez, A., Dumitrescu-Ozimek, L., Terwel, D., Jardenhazy-Kurutz, D., Walter, J., Kirchhoff, F., Hanisch, U. K., & Kummer, M. P. (2010). Locus coeruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 6058–6063. <https://doi.org/10.1073/pnas.0909586107>
- Herrmann, N., Lanctot, K. L., Eryavec, G., & Khan, L. R. (2004). Noradrenergic activity is associated with response to pindolol in aggressive Alzheimer's disease patients. *Journal of Psychopharmacology*, 18, 215–220. <https://doi.org/10.1177/0269881104042625>
- Hertz, L., Lovatt, D., Goldman, S. A., & Nedergaard, M. (2010). Adrenoceptors in brain: Cellular gene expression and effects on astrocytic metabolism and [Ca(2+)]<sub>i</sub>. *Neurochemistry International*, 57, 411–420. <https://doi.org/10.1016/j.neuint.2010.03.019>
- Hoogendijk, W. J., Pool, C. W., Troost, D., van Zwieten, E., & Swaab, D. F. (1995). Image analyser-assisted morphometry of the locus coeruleus in Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. *Brain*, 118(Pt 1), 131–143. <https://doi.org/10.1093/brain/118.1.131>
- Huang, Y. Y., & Kandel, E. R. (1995). D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, 92, 2446–2450. <https://doi.org/10.1073/pnas.92.7.2446>
- Introini-Collison, I. B., Dalmaz, C., & McGaugh, J. L. (1996). Amygdala beta-noradrenergic influences on memory storage involve cholinergic activation. *Neurobiology of Learning and Memory*, 65, 57–64.
- Kaufman, S. K., Del Tredici, K., Thomas, T. L., Braak, H., & Diamond, M. I. (2018). Tau seeding activity begins in the transentorhinal/entorhinal regions and anticipates phospho-tau pathology in Alzheimer's disease and PART. *Acta Neuropathologica*, 136, 57–67. <https://doi.org/10.1007/s00401-018-1855-6>
- Kelly, S. C., He, B., Perez, S. E., Ginsberg, S. D., Mufson, E. J., & Counts, S. E. (2017). Locus coeruleus cellular and molecular pathology during the progression of Alzheimer's disease. *Acta Neuropathologica Communications*, 5, 8. <https://doi.org/10.1186/s40478-017-0411-2>
- Kempadoo, K. A., Mosharov, E. V., Choi, S. J., Sulzer, D., & Kandel, E. R. (2016). Dopamine release from the locus coeruleus to the dorsal hippocampus promotes spatial learning and memory. *Proceedings of the National Academy of Sciences*, 113, 14835–14840. <https://doi.org/10.1073/pnas.1616515114>
- Kentros, C. G., Agnihotri, N. T., Streater, S., Hawkins, R. D., & Kandel, E. R. (2004). Increased attention to spatial context increases both place field stability and spatial memory. *Neuron*, 42, 283–295. [https://doi.org/10.1016/S0896-6273\(04\)00192-8](https://doi.org/10.1016/S0896-6273(04)00192-8)
- LaLumiere, R. T., Buen, T. V., & McGaugh, J. L. (2003). Post-training intra-basolateral amygdala infusions of norepinephrine enhance consolidation of memory for contextual fear conditioning. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 23, 6754–6758. <https://doi.org/10.1523/JNEUROSCI.23-17-06754.2003>
- Lalumiere, R. T., Nguyen, L. T., & McGaugh, J. L. (2004). Post-training intrabasolateral amygdala infusions of dopamine modulate consolidation of inhibitory avoidance memory: Involvement of noradrenergic and cholinergic systems. *European Journal of Neuroscience*, 20, 2804–2810. <https://doi.org/10.1111/j.1460-9568.2004.03744.x>
- Lee, S. J., Escobedo-Lozoya, Y., Szatmari, E. M., & Yasuda, R. (2009). Activation of CaMKII in single dendritic spines during long-term potentiation. *Nature*, 458, 299–304. <https://doi.org/10.1038/nature07842>
- Lemon, N., Aydin-Abidin, S., Funke, K., & Manahan-Vaughan, D. (2009). Locus coeruleus activation facilitates memory encoding and induces hippocampal LTD that depends on beta-adrenergic receptor activation. *Cerebral Cortex*, 19, 2827–2837.
- Lemon, N., & Manahan-Vaughan, D. (2012). Dopamine D1/D5 receptors contribute to de novo hippocampal LTD mediated by novel spatial exploration or locus coeruleus activity. *Cerebral Cortex*, 22, 2131–2138. <https://doi.org/10.1093/cercor/bhr297>
- Levitt, P., & Moore, R. Y. (1978). Noradrenergic neuron innervation of the neocortex in the rat. *Brain Research*, 139, 219–231. [https://doi.org/10.1016/0006-8993\(78\)90925-3](https://doi.org/10.1016/0006-8993(78)90925-3)
- Lim, E. P., Dawe, G. S., & Jay, T. M. (2017). Activation of beta- and alpha-2-adrenoceptors in the basolateral amygdala has opposing effects on hippocampal-prefrontal long-term potentiation. *Neurobiology of Learning and Memory*, 137, 163–170. <https://doi.org/10.1016/j.nlm.2016.11.020>
- Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: Controlling the entry of information into long-term memory. *Neuron*, 46, 703–713. <https://doi.org/10.1016/j.neuron.2005.05.002>
- Liu, Y. U., Ying, Y., Li, Y., Eyo, U. B., Chen, T., Zheng, J., Umpierre, A. D., Zhu, J., Bosco, D. B., Dong, H., & Wu, L. J. (2019). Neuronal network activity controls microglial process surveillance in awake mice via norepinephrine signaling. *Nature Neuroscience*, 22, 1771–1781. <https://doi.org/10.1038/s41593-019-0511-3>
- Llorca-Torralba, M., Borges, G., Neto, F., Mico, J. A., & Berrocoso, E. (2016). Noradrenergic Locus Coeruleus pathways in pain modulation. *Neuroscience*, 338, 93–113. <https://doi.org/10.1016/j.neuroscience.2016.05.057>

- Madrigal, J. L., Feinstein, D. L., & Dello Russo, C. (2005). Norepinephrine protects cortical neurons against microglial-induced cell death. *Journal of Neuroscience Research*, *81*, 390–396. <https://doi.org/10.1002/jnr.20481>
- Maity, S., Jarome, T. J., Blair, J., Lubin, F. D., & Nguyen, P. V. (2016). Noradrenaline goes nuclear: Epigenetic modifications during long-lasting synaptic potentiation triggered by activation of beta-adrenergic receptors. *Journal of Physiology*, *594*, 863–881.
- Mao, Z. M., Arnsten, A. F., & Li, B. M. (1999). Local infusion of an alpha-1 adrenergic agonist into the prefrontal cortex impairs spatial working memory performance in monkeys. *Biological Psychiatry*, *46*, 1259–1265.
- Matsuzaki, M., Honkura, N., Ellis-Davies, G. C., & Kasai, H. (2004). Structural basis of long-term potentiation in single dendritic spines. *Nature*, *429*, 761–766. <https://doi.org/10.1038/nature02617>
- McCall, J. G., Al-Hasani, R., Siuda, E. R., Hong, D. Y., Norris, A. J., Ford, C. P., & Bruchas, M. R. (2015). CRH engagement of the locus coeruleus noradrenergic system mediates stress-induced anxiety. *Neuron*, *87*, 605–620. <https://doi.org/10.1016/j.neuron.2015.07.002>
- McCall, J. G., Siuda, E. R., Bhatti, D. L., Lawson, L. A., McElligott, Z. A., Stuber, G. D., & Bruchas, M. R. (2017). Locus coeruleus to basolateral amygdala noradrenergic projections promote anxiety-like behavior. *Elife*, *6*, 1–14. <https://doi.org/10.7554/eLife.18247>
- McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience*, *27*, 1–28. <https://doi.org/10.1146/annurev.neuro.27.070203.144157>
- McGaugh, J. L., Introini-Collison, I. B., & Nagahara, A. H. (1988). Memory-enhancing effects of post-training naloxone: Involvement of beta-noradrenergic influences in the amygdaloid complex. *Brain Research*, *446*, 37–49.
- McHugh, S. B., Deacon, R. M., Rawlins, J. N., & Bannerman, D. M. (2004). Amygdala and ventral hippocampus contribute differentially to mechanisms of fear and anxiety. *Behavioral Neuroscience*, *118*, 63–78. <https://doi.org/10.1037/0735-7044.118.1.63>
- Mello-Carpes, P. B., & Izquierdo, I. (2013). The Nucleus of the Solitary Tract → Nucleus Paragigantocellularis → Locus Coeruleus → CA1 region of dorsal hippocampus pathway is important for consolidation of object recognition memory. *Neurobiology of Learning and Memory*, *100*, 56–63.
- Morita, M., Ikeshima-Kataoka, H., Kreft, M., Vardjan, N., Zorec, R., & Noda, M. (2019). Metabolic plasticity of astrocytes and aging of the brain. *International Journal of Molecular Sciences*, *20*(4), 941.
- Moron, J. A., Brockington, A., Wise, R. A., Rocha, B. A., & Hope, B. T. (2002). Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: Evidence from knock-out mouse lines. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *22*, 389–395. <https://doi.org/10.1523/JNEUROSCI.22-02-00389.2002>
- Murakoshi, H., Wang, H., & Yasuda, R. (2011). Local, persistent activation of Rho GTPases during plasticity of single dendritic spines. *Nature*, *472*, 100–104. <https://doi.org/10.1038/nature09823>
- Muzzio, I. A., Levita, L., Kulkarni, J., Monaco, J., Kentros, C., Stead, M., Abbott, L. F., & Kandel, E. R. (2009). Attention enhances the retrieval and stability of visuospatial and olfactory representations in the dorsal hippocampus. *PLoS Biology*, *7*, e1000140. <https://doi.org/10.1371/journal.pbio.1000140>
- Nakahata, Y., & Yasuda, R. (2018). Plasticity of spine structure: Local signaling, translation and cytoskeletal reorganization. *Frontiers in Synaptic Neuroscience*, *10*, 29. <https://doi.org/10.3389/fnsyn.2018.00029>
- O'Dell, T. J., Connor, S. A., Guglietta, R., & Nguyen, P. V. (2015). beta-Adrenergic receptor signaling and modulation of long-term potentiation in the mammalian hippocampus. *Learning & Memory*, *22*, 461–471.
- O'Donnell, J., Zeppenfeld, D., McConnell, E., Pena, S., & Nedergaard, M. (2012). Norepinephrine: A neuromodulator that boosts the function of multiple cell types to optimize CNS performance. *Neurochemical Research*, *37*, 2496–2512. <https://doi.org/10.1007/s11064-012-0818-x>
- Power, A. E., McIntyre, C. K., Litmanovich, A., & McGaugh, J. L. (2003). Cholinergic modulation of memory in the basolateral amygdala involves activation of both m1 and m2 receptors. *Behavioural Pharmacology*, *14*, 207–213. <https://doi.org/10.1097/00008877-200305000-00004>
- Power, A. E., Roozendaal, B., & McGaugh, J. L. (2000). Glucocorticoid enhancement of memory consolidation in the rat is blocked by muscarinic receptor antagonism in the basolateral amygdala. *European Journal of Neuroscience*, *12*, 3481–3487. <https://doi.org/10.1046/j.1460-9568.2000.00224.x>
- Quirarte, G. L., Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America*, *94*, 14048–14053. <https://doi.org/10.1073/pnas.94.25.14048>
- Rajkowski, J., Majczynski, H., Clayton, E., & Aston-Jones, G. (2004). Activation of monkey locus coeruleus neurons varies with difficulty and performance in a target detection task. *Journal of Neurophysiology*, *92*, 361–371. <https://doi.org/10.1152/jn.00673.2003>
- Rama, P., Linnankoski, I., Tanila, H., Pertovaara, A., & Carlson, S. (1996). Medetomidine, atipamezole, and guanfacine in delayed response performance of aged monkeys. *Pharmacology, Biochemistry and Behavior*, *55*, 415–422. [https://doi.org/10.1016/S0091-3057\(96\)00111-6](https://doi.org/10.1016/S0091-3057(96)00111-6)
- Ramos, B. P., Stark, D., Verduzco, L., van Dyck, C. H., & Arnsten, A. F. (2006). Alpha2A-adrenoceptor stimulation improves prefrontal cortical regulation of behavior through inhibition of cAMP signaling in aging animals. *Learning & Memory*, *13*, 770–776. <https://doi.org/10.1101/lm.298006>
- Redmond, D. E. Jr, & Huang, Y. H. (1979). Current concepts. II. New evidence for a locus coeruleus-norepinephrine connection with anxiety. *Life Sciences*, *25*, 2149–2162. [https://doi.org/10.1016/0024-3205\(79\)90087-0](https://doi.org/10.1016/0024-3205(79)90087-0)
- Rogerson, T., Cai, D. J., Frank, A., Sano, Y., Shobe, J., Lopez-Aranda, M. F., & Silva, A. J. (2014). Synaptic tagging during memory allocation. *Nature Reviews Neuroscience*, *15*, 157–169. <https://doi.org/10.1038/nrn3667>
- Roozendaal, B., Nguyen, B. T., Power, A. E., & McGaugh, J. L. (1999). Basolateral amygdala noradrenergic influence enables enhancement of memory consolidation induced by hippocampal glucocorticoid receptor activation. *Proceedings of the National Academy of Sciences of the United States of America*, *96*, 11642–11647. <https://doi.org/10.1073/pnas.96.20.11642>
- Rorabaugh, J. M., Chalermpananupap, T., Botz-Zapp, C. A., Fu, V. M., Lembeck, N. A., Cohen, R. M., & Weinschenker, D. (2017). Chemogenetic locus coeruleus activation restores reversal learning in a rat model of Alzheimer's disease. *Brain*, *140*, 3023–3038. <https://doi.org/10.1093/brain/awx232>

- Ross, J. A., Reyes, B. A. S., & Van Bockstaele, E. J. (2019). Amyloid beta peptides, locus coeruleus-norepinephrine system and dense core vesicles. *Brain Research, 1702*, 46–53. <https://doi.org/10.1016/j.brainres.2018.03.009>
- Salgado, H., Garcia-Oscos, F., Patel, A., Martinolich, L., Nichols, J. A., Dinh, L., Roychowdhury, S., Tseng, K. Y., & Atzori, M. (2011). Layer-specific noradrenergic modulation of inhibition in cortical layer II/III. *Cerebral Cortex, 21*, 212–221. <https://doi.org/10.1093/cercor/bhq081>
- Sara, S. J. (2015). Locus Coeruleus in time with the making of memories. *Current Opinion in Neurobiology, 35*, 87–94. <https://doi.org/10.1016/j.conb.2015.07.004>
- Sara, S. J., & Bouret, S. (2012). Orienting and reorienting: The locus coeruleus mediates cognition through arousal. *Neuron, 76*, 130–141. <https://doi.org/10.1016/j.neuron.2012.09.011>
- Sara, S. J., & Devauges, V. (1989). Idazoxan, an alpha-2 antagonist, facilitates memory retrieval in the rat. *Behavioral and Neural Biology, 51*, 401–411.
- Sarlus, H., & Heneka, M. T. (2017). Microglia in Alzheimer's disease. *Journal of Clinical Investigation, 127*, 3240–3249. <https://doi.org/10.1172/JCI90606>
- Schall, J. D., & Thompson, K. G. (1999). Neural selection and control of visually guided eye movements. *Annual Review of Neuroscience, 22*, 241–259. <https://doi.org/10.1146/annurev.neuro.22.1.241>
- Schultz, C., & Engelhardt, M. (2014). Anatomy of the hippocampal formation. *Front Neurol Neurosci, 34*, 6–17.
- Senzai, Y. (2019). Function of local circuits in the hippocampal dentate gyrus-CA3 system. *Neuroscience Research, 140*, 43–52. <https://doi.org/10.1016/j.neures.2018.11.003>
- Shadlen, M. N., & Newsome, W. T. (2001). Neural basis of a perceptual decision in the parietal cortex (area LIP) of the rhesus monkey. *Journal of Neurophysiology, 86*, 1916–1936. <https://doi.org/10.1152/jn.2001.86.4.1916>
- Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology, 35*, 169–191. <https://doi.org/10.1038/npp.2009.83>
- Siuda, E. R., McCall, J. G., Al-Hasani, R., Shin, G., Il Park, S., Schmidt, M. J., Anderson, S. L., Planer, W. J., Rogers, J. A., & Bruchas, M. R. (2015). Optodynamic simulation of beta-adrenergic receptor signaling. *Nature Communications, 6*, 8480.
- Smith, C. C., & Greene, R. W. (2012). CNS dopamine transmission mediated by noradrenergic innervation. *Journal of Neuroscience, 32*, 6072–6080. <https://doi.org/10.1523/JNEUROSCI.6486-11.2012>
- Szot, P., Van Dam, D., White, S. S., Franklin, A., Staufienbiel, M., & De Deyn, P. P. (2009). Age-dependent changes in noradrenergic locus coeruleus system in wild-type and APP23 transgenic mice. *Neuroscience Letters, 463*, 93–97. <https://doi.org/10.1016/j.neulet.2009.07.055>
- Takahashi, K., Kayama, Y., Lin, J. S., & Sakai, K. (2010). Locus coeruleus neuronal activity during the sleep-waking cycle in mice. *Neuroscience, 169*, 1115–1126. <https://doi.org/10.1016/j.neuroscience.2010.06.009>
- Takeuchi, T., Duszkiewicz, A. J., Sonneborn, A., Spooner, P. A., Yamasaki, M., Watanabe, M., Smith, C. C., Fernandez, G., Deisseroth, K., Greene, R. W., & Morris, R. G. (2016). Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature, 537*, 357–362. <https://doi.org/10.1038/nature19325>
- Tovote, P., Fadok, J. P., & Luthi, A. (2015). Neuronal circuits for fear and anxiety. *Nature Reviews Neuroscience, 16*, 317–331. <https://doi.org/10.1038/nrn3945>
- Uematsu, A., Tan, B. Z., & Johansen, J. P. (2015). Projection specificity in heterogeneous locus coeruleus cell populations: Implications for learning and memory. *Learn Mem, 22*, 444–451. <https://doi.org/10.1101/lm.037283.114>
- Ul Haq, R., Anderson, M., Liotta, A., Shafiq, M., Sherkheli, M. A., & Heinemann, U. (2016). Pretreatment with beta-adrenergic receptor agonists facilitates induction of LTP and sharp wave ripple complexes in rodent hippocampus. *Hippocampus, 26*, 1486–1492.
- Wilson, R. S., Nag, S., Boyle, P. A., Hizek, L. P., Yu, L., Buchman, A. S., Schneider, J. A., & Bennett, D. A. (2013). Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. *Neurology, 80*, 1202–1208. <https://doi.org/10.1212/WNL.0b013e3182897103>
- Xing, B., Kong, H., Meng, X., Wei, S. G., Xu, M., & Li, S. B. (2010). Dopamine D1 but not D3 receptor is critical for spatial learning and related signaling in the hippocampus. *Neuroscience, 169*, 1511–1519. <https://doi.org/10.1016/j.neuroscience.2010.06.034>
- Yang, Y., & Wang, J. Z. (2017). From structure to behavior in basolateral amygdala-hippocampus circuits. *Frontiers in Neural Circuits, 11*, 86. <https://doi.org/10.3389/fncir.2017.00086>
- Yang, Y., Wang, Z. H., Jin, S., Gao, D., Liu, N., Chen, S. P., Zhang, S., Liu, Q., Liu, E., Wang, X., Liang, X., Wei, P., Li, X., Li, Y., Yue, C., Li, H. L., Wang, Y. L., Wang, Q., Ke, D., ... Wang, J. Z. (2016). Opposite monosynaptic scaling of BLP-vCA1 inputs governs hopefulness- and helplessness-modulated spatial learning and memory. *Nature Communications, 7*, 11935. <https://doi.org/10.1038/ncomms11935>
- Zhou, Q., Homma, K. J., & Poo, M. M. (2004). Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. *Neuron, 44*, 749–757. <https://doi.org/10.1016/j.neuron.2004.11.011>

**How to cite this article:** James T, Kula B, Choi S, Khan SS, Bekar LK, Anthony Smith N. Locus coeruleus in memory formation and Alzheimer's disease. *Eur J Neurosci.* 2021;54:6948–6959. <https://doi.org/10.1111/ejn.15045>