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Noradrenergic dysregulation in the locus coeruleus: Implications for neuropsychiatric disease pathophysiology- A systematic review

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ABSTRACT

The locus coeruleus [LC] is a dense cluster of noradrenergic neurons located in the dorsal pons of the brainstem and serves as the brain's principal source of noradrenaline (NA). This neuromodulatory system plays a central role in regulating arousal, attention, stress response, sleep-wake cycles, and emotional behavior. The LC's extensive efferent projections render it highly sensitive to both external environmental stressors and intrinsic factors, including age-related neuronal loss, which can compromise cognitive function, emotional regulation, and psychiatric stability. Emerging evidence implicates dysfunction in LC-noradrenergic signaling as a shared pathophysiological mechanism underlying multiple neuropsychiatric disorders, including major depressive disorder, schizophrenia, autism spectrum disorder, obsessive-compulsive disorder, and post-traumatic stress disorder. This review integrates current clinical, neuroanatomical, and functional studies to highlight how aberrant LC-noradrenergic dynamics contribute to key features of these psychiatric disorders, such as impaired cognitive control, emotional dysregulation, altered sensory processing, and maladaptive stress responses. We also highlight the critical interplay between LC dysfunction and disrupted sleep-wake architecture owing to the importance of the LC in sleep-wake regulation. Disruptions in LC activity profoundly affect both rapid eye movement (REM) and non-REM sleep, which in turn exacerbate psychiatric symptoms, including insomnia, hypervigilance, and affective instability. By synthesizing findings from rodent models, human neuroimaging studies, and post-mortem analyses, we reveal distinct patterns of LC pathology in this narrative review, ranging from hypoactivity and dendritic atrophy to hyperresponsivity and excessive NA release that are associated with symptoms of psychiatric disorders. Finally, we review recent advances in neuromodulatory strategies targeting LC-noradrenergic pathways, including pharmacotherapies (e.g., α2-adrenergic agonists, NA reuptake inhibitors), chemogenetics, and non-invasive brain stimulation techniques. These emerging therapies offer promising avenues for restoring LC-mediated network homeostasis and improving clinical outcomes in treatment-resistant psychiatric populations. In summary, this review positions LC as a convergent hub of vulnerability and a compelling therapeutic target in neuropsychiatric disease. Elucidating the mechanisms of LC-NA dysfunction holds potential not only for refining disease models but also for advancing precision medicine approaches for complex psychiatric disorders.

1. Introduction

The locus coeruleus is a small cluster of catecholaminergic neurons in the dorsolateral pons region of the brainstem that synthesize and release the noradrenaline (NA) neurotransmitter, which is the most important neuromodulatory factor in the central nervous system (CNS). The LC plays an essential role in the modulation of several behavioral and physiological processes, such as attention and arousal behaviors (Aston-Jones et al., 1999), central chemosensory function regulating cardiorespiration (Cui et al., 2011; Gargaglioni et al., 2010; Oliveira et al., 2017), and pathophysiology of several neurological diseases like stress, anxiety, schizophrenia, depression, as well as neurodegeneration

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(O. Borodovitsyna et al., 2018; Chalermpalanupap et al., 2013; Seki et al., 2018; Weiss et al., 1994). In addition, the LC has been implicated in modulating and regulating several higher-order cognitive functions of the brain, including diverse types of learning paradigms as well as acquisition and consolidation of spatial, contextual, and cued-fear conditioned memory systems (Glennon et al., 2018; Ogren et al., 1980; Soya et al., 2013; Swift et al., 2018; Wagatsuma et al., 2018; Weiss et al., 1994). Therefore, major cognitive functions are at risk due to pathological insults to the LC that are essential hallmarks of several neuropsychiatric and neurodegenerative diseases. Recent reports suggest that LC neurons are highly susceptible to atrophy during aging and the progression of various psychiatric diseases such as depression, anxiety, schizophrenia, and post-traumatic stress disorder (PTSD), among others (L. S. Morris, J. G. McCall, et al., 2020; Suttkus et al., 2021; Zhang et al., 2019). The changes in noradrenergic neurotransmission dynamics play a central role in the development and progression of several psychiatric illnesses, including heightened LC activity in anxiety and PTSD disorders and decreased activity in other neuropsychiatric disorders like depression and suicide.

Studies have suggested that in the progression of several neuropsychiatric diseases like depression, schizophrenia, and anxiety, LC's neural transmission dynamics as well as morphological integrity are significantly altered (Chaudhury et al., 2015; Liang Gong et al., 2021; Mäki-Marttunen et al., 2020; Suttkus et al., 2021). LC controls stress and anxiety-related processes by neuromodulation of higher-order limbic systems, including amygdala and hippocampus as well as through the corticotropin-releasing factor (CRF) receptors present on LC neurons (Curtis et al., 1995; Domin and Śmiałowska, 2024; Liang Gong et al., 2021; McCall et al., 2017). Furthermore, LC also modulates the reinforcement and reward-based positive emotions associated with the use of drugs and psychostimulants (Hall et al., 2024; Volkow et al., 2019). Therefore, LC is a prime target for drugs of abuse, and single-unit recording studies have shown that noradrenergic receptor-mediated signaling across the brain plays an important role in the early stages of addiction, including opioid, nicotine, and cocaine addictions (Hall et al., 2024). Further, chronic stress elevates the reactivity of the LC to future stressors, which causes anxiety behaviors, and these responses are largely mediated by LC projections to the basolateral amygdala (BSL), a main brain center for generating fear-related responses (M. Grueschow et al., 2021; Laurel S. Morris et al., 2020; Naegeli et al., 2018). Stress or fear enhanced the expression of tyrosine hydroxylase (TH) enzyme mRNA as well as cfos (an indicator of neuronal activity), pointing to the fact that stress activates LC neurons (R. A. McDevitt et al., 2009). Therefore, dysregulation of the LC-NA system is intricately involved in many stress-related psychiatric disorders like PTSD and anxiety. Recent reports suggest that the overactivity of the LC-NA system mediates the signs of PTSD, including hyper-responsiveness and heightened arousal to an unexpected life-threatening environmental stimulus (Naegeli et al., 2018). Hyperarousal is one of the underlying factors for anxiety-related behaviors, and LC has been implicated in hyperarousal mediated by CRF signaling that activates LC, causing arousal, as LC is an established brain area responsible for arousal and alertness (McCall et al., 2024; Ross and Van Bockstaele, 2020) (Naegeli et al., 2018).

Recent advances in cutting-edge technologies for imaging and finding early biomarkers for various psychiatric diseases, LC stands out as an important target for deep-brain stimulation and pharmacological interventions to mitigate psychiatric disease symptoms. Altered neural networks in the LC have been implicated in depressive like behaviors such as major mood disorders (MDD) and lack of interest in daily activities, as well as in autism patients (Duman et al., 2019). Recent discovery that LC co-releases dopamine with NA attracted many psychiatric-neurologists to investigate LC signaling and receptor-based dynamics in drug addiction and depressive behaviors (McNamara and Dupret, 2017; Tsetsenis et al., 2022). The role of LC in psychiatric disorders is not only because of the sudden onset of these pathologies that dysregulate the LC-NA system, but also age-mediated degeneration of LC cells that plays an important role in accelerating psychiatric anomalies such as depression, anxiety, and mood disorders. Neurodegeneration in the LC has been shown to increase the risk of depression and MDD as the supply of noradrenaline to the dopaminergic neurons is deemed to be essential for their functionality (Guinea-Izquierdo et al., 2021). Studies on human subjects concluded that late-life-associated MDD shows changes in LC neurotransmission dynamics, especially during cognitive processing, suggesting that LC dysfunctions contribute to the depression and cognitive decline associated with MDD in the elderly (Del Cerro et al., 2020; Maturana-Quijada et al., 2024). Furthermore, LC-NA dysfunctions have been linked with hallucinations and delusions, as well as a lack of attention observed in schizophrenic patients (Köhler et al., 2019; Pelegrino et al., 2023). Studies have also linked the LC activity with pupil dilation and its correlation with cognitively demanding tasks. In schizophrenia, reports show that patients display decreased task-evoked pupil dilation during attention-requiring tasks, suggesting LC dysfunction in the pathophysiology (Pelegrino et al., 2023). Post-mortem analysis of a schizophrenic patient's brain shows some typical abnormalities in the LC-NA system, including a higher accumulation of neuromelanin pigments and an increase in cell volume in these pigmented noradrenergic cells (Lohr and Jeste, 1988; Marner et al., 2005). Taken together, these studies highlight the need to focus on LC dysfunctions in neuropsychiatric disorders, and this updated review will summarize the recent findings that focus on LC-NA impairments in mental health, along with possible therapeutic targets based on the LC-NA neurotransmission dynamics to mitigate these disorders. This review, unlike previous systematic reviews, will also highlight the pharmacological importance of these LC-NA dysregulations in mitigating the disease burden by drug design based on these novel findings. Lastly, as the LC is one of the most important sleep-wake regulatory nuclei and sleep serves as a gateway for memory consolidation, we will also highlight the LC-NA dysfunctions concerning sleep disturbances and consequent effects on cognition.

2. LC-NA system dysregulation as a neurobiological substrate of psychiatric disorders

Globally, the disease burden associated with mental health anomalies constitutes a significant socioeconomic hurdle and poses a great challenge to scientists owing to the complexity of brain disorders (Marcus Grueschow et al., 2021; Twenge et al., 2010). As the two schools of thought in neuroscience behind brain functioning, "modularity theory and holism hypothesis", scientists have started exploring different brain areas and connections between them, as the complexity and diversity of symptoms observed in psychiatric disorders emerge to be associated with multiple cognitive aspects not controlled by one brain region but by several distinct neural networks distributed across the central nervous system. Among other brain regions that are essential for brain physiology and optimal cognition, the LC is notable as it supplies 60–70 % of noradrenaline (NA) to the central nervous system, and NA, being an essential neurotransmitter for optimal brain functions, can have deleterious effects when its levels are altered (Guinea-Izquierdo et al., 2021; Haenisch et al., 2009). LC is involved in a plethora of neurological disorders, both congenital as well as acquired ones; hence, any pathophysiological aberration to the LC-NA system leads to the initiation or acceleration of many CNS disorders, accompanied by symptoms ranging from stress, anxiety, to panic attacks, attention deficits, and depression. Integrity of the LC-NA system is not only altered at physiological levels, but morphological attributes of this nucleus, like loss of cells, morphological changes in cytoarchitecture, and increased microglial activation, also contribute to the development of neuropsychiatric diseases. Therefore, deciphering the role of LC in the modulation of such pathophysiological processes would provide useful future insights regarding treatment strategies. Further, LC-NA integrity is prone to various challenges and toxins due to the peculiar anatomical location of LC near the 4th ventricle that often flushes this neuropil with

waste products and harmful metal ions, and due to this, LC is the first nucleus that is affected in neuropsychiatric disorders (L'Heureux et al., 1986; Mather and Harley, 2016). Since NA has widely distributed adrenergic receptors throughout the CNS, and they are mostly excitatory in their action (α1 and β receptors are excitatory, whereas α2 receptors are inhibitory), imbalances in the LC-NA system predispose the CNS to several other pathologies culminating in various neuropsychiatric diseases. We will now highlight the recent findings regarding the involvement of the LC-NA system in the following psychiatric disorders (Fig. 1).

2.1. LC-NA system: A potential modulator of post-traumatic stress disorder and anxiety

Post-traumatic stress disorder (PTSD) is a neuropsychological condition in which the persistence of extreme fear despite the absence or cessation of a fearful stimulus results in continuous and vivid recall of life-threatening and traumatic events, causing behavioral and psychological abnormalities (Runnels et al., 2009). Stress activates a plethora of CNS pathways that synergistically elevate arousal and attention, and exposure to repeated stressors ultimately leads to anxiety and other related pathologies. Under normal conditions, several brainstem areas are recruited for orientation and alertness during a stressor or threat for survival and safety; however, their exaggerated response even in the absence of a real threat is associated with abnormal behaviors in anxiety disorders such as PTSD (Berridge and Waterhouse, 2003; Bouras et al., 2023; Marcus Grueschow et al., 2021; Ulrich-Lai and Herman, 2009). An essential role of LC-NA dysregulation in the development and pathophysiology of PTSD has been again reassured by clinical as well as basic neuroscience research studies that suggest hyperactivation of the LC-NA

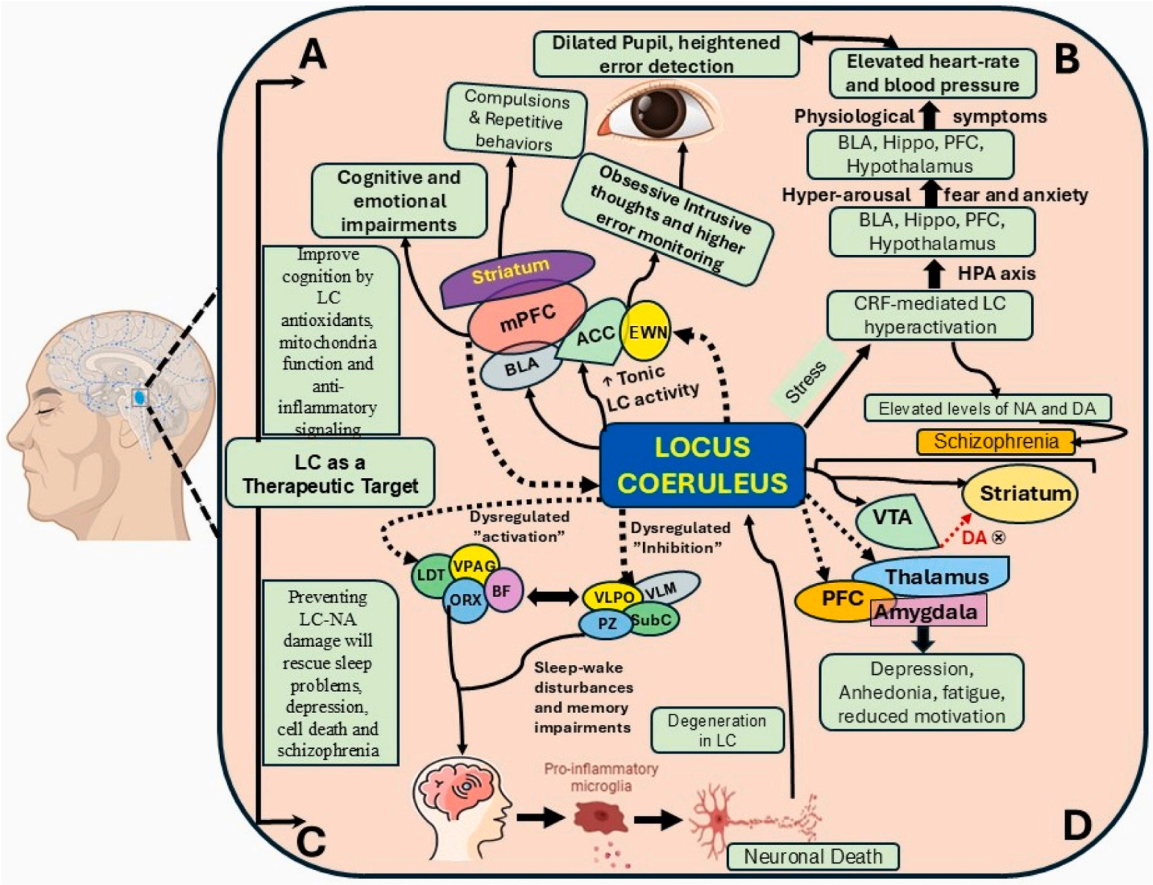


Fig. 1. A schematic model showing the involvement of the LC-NA system in various neuropsychiatric disorders and as a potential therapeutic target for their mitigation. The figure has been casually divided into four quadrants, A-D, and each quadrant has been specified for major and related pathologies that are caused by LC-NA dysfunction. **A-**Role of LC-NA dysregulation profoundly affects cognition and emotional optimization that are associated with and are common pathologies found in several broad spectrum of psychiatric illnesses, such as depression, anxiety, PTSD, and obsessive-compulsive disorders. Input and output from the LC-NA system to higher-order brain centers, including mPFC, ACC, and BLA, are impaired in psychiatric disorders. **B**-Overactivation of the LC-NA system due to stressors activating corticotropin-releasing factor-dependent signaling in the HPA axis, resulting in fight-or-flight responses amidst panic attacks with an elevated blood pressure and heart rate. Hyperactivation of the HPA also leads to pupil dilation and heightened error detection associated with fearful behaviors. **C**- The LC-NA system is an integral part of sleep-wake regulatory networks, inhibiting sleep-promoting VLPO, VLM, and PZ, whereas providing neuromodulatory activation to orexinergic, histaminergic, and BF neurons promoting arousal. Dysregulation of this two-arm modulatory input causes sleep-wake disruption that subsequently leads to cognitive impairments and cardiovascular dysfunctions in psychiatric patients. Sleep disturbances also raise the level of pro-inflammatory cytokines, exacerbating microglial activation that together cause neuronal degeneration and mood changes, as well as worsening of existing mental issues. **D**- LC-NA system plays an important role in the development and progression of depression and schizophrenic symptoms as it provides and receives inputs from dopaminergic nuclei, higher cognitive brain areas like the PFC and hippocampus, as well as emotional centers such as the amygdala. The LC to VTA input is vital for optimal activation of dopaminergic neurons, and the impairment of this deprives the striatum of dopamine, a common reason behind MDD. The LC-NA system and its associated receptor repertoire act as a potential target to mitigate the symptoms of various psychiatric disorders. (**Abbreviations**: LC-locus coeruleus, PFC-prefrontal cortex, VTA-ventral tegmentum area, BLA-basolateral amygdala, Hippo-hippocampus, medial PFC, ACC-anterior cingulate cortex, EWN-Edinger-Westphal nucleus, NA-noradrenaline, HPA-hypothalamic-pituitary-adrenal axis, VLPO-ventrolateral preoptic nucleus, BF-basal forebrain, VPAG-ventral periaqueductal gray nucleus, ORX-orexin, PZ-trapezoid body, VLM-ventrolateral medulla, Sub-coeruleus nucleus, DA-dopamine, and CRF-corticotropin-releasing factor).

system in anxiety and PTSD behaviors. As the LC-NA system is a crucial neuromodulator of arousal and vigilance, studies have reported that alterations to this system, especially its hyperactivation, are responsible for many of the symptoms of anxiety disorders (Bouras et al., 2023). Several studies have suggested that LC is robustly activated by stressor stimuli, and many behavioral and cognitive impairments associated with stress involve LC and other noradrenergic cell groups (Olga Borodovitsyna et al., 2018; Ross A. McDevitt et al., 2009). Reports suggest that during stress and anxiety states, the LC neuronal activity is significantly upregulated (Fig. 1), resulting in the discharge of large amounts of NA into higher-order brain regions, especially the prefrontal cortex and amygdala, which are the main players essential for PTSD related behaviors (Atzori et al., 2016; O. Borodovitsyna et al., 2018; Laurel S. Morris et al., 2020).

Studies on several army veterans who suffered war-associated PTSD symptoms showed alterations in their LC-NA system, as suggested by the post-mortem analysis of their brain tissues, which revealed that their LC had a substantially lower cell count than the control subjects (H. S. Bracha et al., 2005; McCall et al., 2024). In addition to lower cell count in the LC of war veterans, this particular study has also found that their remaining LC surviving neurons had upregulated NA-biosynthetic machinery, like elevated gene expression, especially for tyrosine hydroxylase (TH), post-synaptic adrenergic receptors, and dopamine beta hydroxylase (DBH) genes (H. Stefan Bracha et al., 2005; H. S. Bracha et al., 2005). In PTSD, the behavioral as well as autonomic hyperactivity might be due to an over-reactive alert/alarm system where attention and motor movements controlled by the lateral pre-motor cortex and superior cerebellar cortex are specifically modulated by a hyper-responsive LC-NA system (Naegeli et al., 2018). Furthermore, recent studies have suggested that the LC-NA system is responsible for regulating pupil size in tune with the height of arousal response, and fear/anxiety hyperdilates the pupil size as a defense mechanism that is evolutionarily conserved (Swift et al., 2018). Other studies using functional magnetic resonance imaging (fMRI) revealed that PTSD patients when exposed to white noise, displayed a heightened number of eye blinks and elevated heart rate with dilated pupils than those of healthy subjects mediated by hyperactivity of the LC region and the areas connected with the LC and also involved with alertness and heightened motor responses (Naegeli et al., 2018). Other observed changes in the LC-NA system concerning PTSD include elevated sensitivity of α-2 adrenergic receptors along with exaggerated responses in arousal, as well as memory memory-strengthening role of NA in case of aversive/negative memory-related events that are resistant to the extinction process (L. S. Morris, J. G. McCall, et al., 2020; Southwick et al., 1999). Additionally, positron emission tomography (PET) and radioligand ($11\ ^{C}$)-methyl-reboxetine binding assay for the availability of norepinephrine transporter (NET) in the LC has suggested that in PTSD, there is a significant reduction in NET availability in the LC that alters NA neurotransmission dynamics (Logan et al., 2007; Pietrzak et al., 2013). These findings imply that potential therapeutic or psychotherapy therapies that target the LC-NA system's hyper-responsiveness are worthwhile research avenues in treating PTSD and related disorders.

The locus coeruleus does not function in isolation as a threat-detection center within the central nervous system; rather, the amygdala, a key structure within the limbic system, assumes predominant responsibility for threat assessment and the initiation of defensive responses (Fig. 1). Notably, the locus coeruleus exhibits substantial efferent projections to the amygdala, exerting modulatory influence on amygdala output during threat stimuli processing through dual neurotransmitter mechanisms: the action of corticotropin-releasing factor (CRF) and noradrenergic signaling, both facilitated by the high density of corresponding receptors within amygdala nuclei. (McCall et al., 2017; Runnels et al., 2009; Soya et al., 2013). Optogenetic activation of LC projections within the basolateral amygdala (BLA) enhanced the release of NA into the BLA, causing its activation and consequently stimulating anxiety-oriented behavioral changes, and these effects are mediated by β-adrenergic receptors (McCall et al., 2017). Other reports also support the hypothesis that the activation of BLA by epinephrine agonists specific for β-adrenergic receptors induces acute social anxiety in animal models (Sears et al., 2013; Siuda et al., 2016). It has been shown that chronic stress in rodents causes a significant amplitude of LC-NA activity against subsequent stressors, which is often associated with the progression of pathophysiological attributes of anxiety-like behaviors as well as PTSD (Laurel S. Morris et al., 2020).

Pharmacological investigations have revealed that CRF, acting on LC-amygdala pathways, plays an essential role in LC-activation-mediated stress-oriented behaviors. Studies have found that when external CRF was injected into the LC, it could not induce behavioral depression when assessed in a swim test, but its infusion significantly enhanced anxiety levels in rodents (Weiss et al., 1994). Interestingly, when pharmacological inhibition of LC was carried out, it led to an increase in anxious behavior, in contrast to activation of LC, which decreased anxiety-associated behaviors (Weiss et al., 1994). Additionally, LC has a well-established role to play in emotional and sleep-wake physiology, and it has been suggested that patients with psychiatric disorders, specifically depression and anxiety, display chronic insomnia disorder with strongly correlated pathological insults to the LC-NA system being the major contributing factors (Liang Gong et al., 2021). Noradrenergic LC-NA is intricately implicated in chemosensory-mediated CO_2-dependent panic attack responses in anxious and depressive behaviors by modulation of limbic brain areas, such as the amygdala (Johnson et al., 2011; Wemmie, 2011; Winter et al., 2017). Moreover, the LC-NA system is a significant facilitator of stress-based anxiety and a possible target of treatment for problems of depression and anxiety caused by stress (McCall et al., 2015). Utilizing in vivo chemogenetic and optogenetic manipulations, it was shown that LC neuronal inhibition during the time of stress results in lower chances of developing subsequent anxiety-type behaviors, whereas higher LC activity during stress promotes anxiety-like behaviors through inputs from corticotropin-releasing hormone-positive (CRH^{+ve}) amygdala neurons to LC neurons (McCall et al., 2015). Again, this study has found that after 30-minute restraint-induced stress in wild-type mice, significant stress-mediated anxious behavior with a concomitant increase in cfos expression in the LC was observed, suggesting anxiety-induced LC activation (McCall et al., 2015, 2017). These studies provide compelling evidence that the LC-NA system is intricately involved in PTSD and anxiety-related disorders directly or through neuromodulation of limbic and higher-order brain areas, which process the behavioral outcomes of these psychiatric disorders.

2.2. Dysfunction in the LC-NA system contributes to the pathophysiology of depression

As per the 2023 report of the WHO, around 4 % of the global population and 6 % of adults over 60 years of age suffer from depression and associated symptoms. About 280 million people worldwide experience the symptoms of major depressive disorder (MDD), and it is observed that it is more prevalent in women. Therefore, MDD places a significant socioeconomic and health burden on mankind throughout the world (Konig et al., 2019; Konnopka and König, 2020). WHO defines depression as "a common illness characterized by a persistent sadness and a loss of interest in activities that one normally enjoys, accompanied by an inability to carry out daily activities, for at least two consecutive weeks ". Additionally, it may impair hunger and sleep, as well as cause patients to feel a lack of energy and be unable to concentrate. Complex relationships involving societal, behavioral, and biological variables are among the causes of depression. Childhood hardship, loss, and job uncertainty are all factors that can contribute to and/or hasten the onset of depression. Depression symptoms are thought to be caused by alterations in neurochemical and structural parameters of the meso-corticolimbic brain circuits, which control mood and behavior through brain regions including the prefrontal cortex (PFC), hippocampus,

amygdala, and nucleus accumbens (Duman et al., 2016). The neural circuitry involved in depression encompasses several brain regions that are directly modulated by the LC-NA system (Gao et al., 2025; Zhang et al., 2018).

Numerous disruptions in noradrenergic, serotonergic, and dopaminergic signaling and their related metabolic activities are the major causative factors in the pathophysiology of depression (Jesulola et al., 2018). Studies have suggested that acute and persistent stress is the major physiological factor contributing to the development of depression (Bonanno et al., 2011; Marcus Grueschow et al., 2021). Interestingly, such stressful stimuli make the LC-NA system hyper-reactive, and the heightened responses of this system under chronic and acute stress have made the LC-NA system a prime target for antidepressant medications (Marcus Grueschow et al., 2021; West et al., 2009). Many studies have reported that acute as well as chronic stress and anxious stimuli in animal models strongly activate the LC-NA system, as evidenced by the higher cfos expression in tyrosine hydroxylase-positive cells of the LC area (Marcus Grueschow et al., 2021; Laurel S. Morris et al., 2020; Naegeli et al., 2018; Weiss et al., 1994). The neurotransmitter of the LC, norepinephrine, plays an essential role in several executive functions, modulating intelligence, cognition, as well as motivation, which are of primary importance in shaping social relationships. It has been found that social dysfunctions, such as social defeat or social seclusion, are important attributes found in depressed people (Moret and Briley, 2011). Several studies have provided evidence that in depression-suffering patients and animal models, there is an alteration in the concentration of norepinephrine and its metabolites in the CSF as well as in the blood, suggesting the role of noradrenergic signaling in the development or progression of the disorder (Jesulola et al., 2018; Roy et al., 1988; Seki et al., 2018).

Previously, it was suggested that most of the antidepressant drugs decreased the activity of the LC-NA system, whereas it was found that non-antidepressant drugs, taken as a control, did not alter the activity of LC (Grant and Weiss, 2001; West et al., 2009). However, it was also reported that not all of the antidepressant drugs would reduce the LC activity; rather, some of the drugs, such as “mirtazapine,” have increased the LC neuronal activity, suggesting a drug-dependent effect on the LC-NA system (Grant and Weiss, 2001). Moreover, LC-NA hyper-responsiveness to stress does not usually act individually; rather, its projections to the limbic areas, especially the amygdala, play a great role in stress and anxiety (Fig. 1) associated with depression pathology (Marcus Grueschow et al., 2021). Additionally, several differences have been observed in the LC-NA system when post-mortem brain samples of depressed patients were analyzed and compared to those of healthy controls (Moret and Briley, 2011; Stahl, 2000). Furthermore, transgenic mice engineered for enhancement in the LC-NA system displayed a significantly lowered risk for stress-mediated depression-like behaviors, suggesting a potent role for LC-NA to play in these pathways (Moret and Briley, 2011; Stahl, 2000). Effective anti-depressant drugs selectively increase NA levels, and it has been observed that when these drugs were stopped by depressed patients, causing the NA levels to dwindle, these patients showed relapse of depression, indicating the importance of optimal NA levels in the CNS (Moret and Briley, 2011). Interestingly, genetic studies on human subjects have demonstrated a link between behavioral characteristics and vulnerability to depression and changes in the norepinephrine transporter gene (NET) that affect neurotransmitter release in the CNS (Lin and Madras, 2006). Studies have further provided evidence in this regard by knocking out the NET gene in mice and found that these animals were resistant to stress-induced depressive-behavioral alterations (Haenisch et al., 2009). Further, genetic polymorphism of NET-T182C, a NET gene, has been associated with an elevated risk of depression (Ono et al., 2004). Together, these studies suggest that LC-NA modulation plays an essential role in the development and progression of depression as well as associated psychobiological pathologies (Fig. 1). Future studies will unravel the vital and life-improving pharmacokinetic significance of LC-NA as a target in treating depression and associated behavioral defects in depressed patients.

2.3. Unveiling the locus coeruleus' role in schizophrenia: a noradrenergic perspective

Schizophrenia is a widely known neurological disorder that is characterized by distortions in the perception of reality, logical reasoning, language, and emotions, as well as distortion of self and behavior. Schizophrenia is a chronic and severe cognitive disorder affecting 20–25 million people globally. Patients suffering from this disorder are characterized by observing hallucinations, including hearing and seeing unreal and life-threatening things, as well as experiencing delusions. Many neurobiologists hypothesize that the phenomenology of schizophrenia, especially the cognitive impairments, could be explained by a defective interaction of genetic susceptibility with stress-mediated LC-NA modulation (Mäki-Marttunen et al., 2020). A situation already included in the "disconnection hypothesis" in the onset of schizophrenia, dysregulations in the LC-NA system may lead to significant errors in sensory-prediction tasks that trigger the difficulty in decreasing incoming stimuli because of the prior predictions, and eventually, the inability to place the sensory experience in a context (Friston et al., 2016). Interest in the LC-NA system in schizophrenia and associated disorders was mainly accelerated after Wise and Stein found that post-mortem schizophrenic human patients had reduced activity of the LC-NA enzyme called dopamine beta-hydroxylase (DBH) (Wise and Stein, 1973). Further, as described LC-NA system is vital for cognition as well as motivation-oriented behaviors, and pathological aberrations in this system account for cognitive and motivational impairments in schizophrenia (Mäki-Marttunen et al., 2020). These data suggested that the weakening of the LC-NA system is associated with schizophrenia as well as the malfunctioning of reward pathways associated with the disorder.

While disrupted dopaminergic and glutamatergic signaling are widely recognized as central to the pathophysiology of schizophrenia (Fig. 1), growing evidence highlights the LC-NA system as a significant contributing factor (Borodovitsyna et al., 2017; Yamamoto and Hornykiewicz, 2004). It has been suggested that the LC-NA system plays an essential role in neural network activations required for executive control, such as processing of working memory, and interestingly, hallucinatory as well as inattentive symptoms in schizophrenic patients are linked with disrupted functions in LC-NA associated with impairments in working memory (Suttkus et al., 2021). Several reports suggested that schizophrenic patients often have excessive levels of noradrenaline in limbic brain areas as well as in their cerebrospinal fluid, suggesting the involvement of the LC-NA system in schizophrenic disorder (Farley et al., 1978; Lake et al., 1980). Additional studies also found that schizophrenic patients had elevated levels of NA as well as other catecholamine metabolites in their plasma as well as cerebrospinal fluid (CSF), indicating aberration in the tone of LC-NA in these patients (Bondy et al., 1984; Kemali et al., 1982). Consecutive studies have confirmed that hyperactivity of the LC-NA system is associated with positive symptoms of schizophrenia, whereas reduced activity of the LC-NA system was associated with negative symptoms of the disease, as NA-α2 receptor agonists have had a positive impact on cognitive symptoms often disrupted in schizophrenia (Fitzgerald, 2014). Future pharmacotherapeutic interventions targeting the LC-NA and the corresponding adrenergic receptors might pinpoint novel and specific targets to treat cognitive impairments associated with schizophrenia (Ghanemi and Hu, 2015; Maletic et al., 2017). These studies targeting the LC-NA receptor system, when analyzed at cellular and synaptic levels and associated ion channels, will elaborate our understanding of the NA-mediated effects on mood and cognition in schizophrenic patients.

Additionally, noradrenergic cells in the LC heavily innervate several forebrain areas associated with attention as well as perception, including the prefrontal cortex. This makes LC an important target for

treating symptoms associated with schizophrenia or reducing the aggressiveness of these symptoms at least (Mäki-Marttunen et al., 2020; Suttkus et al., 2021). Previous reports suggest that antipsychotic drugs systematically administered in schizophrenic animal models had increased LC neuronal activities compared with sham control subjects (Nilsson et al., 2005). Moreover, studies have revealed that LC neurons not only secrete NA but they co-release dopamine along with NA, modulating the dopaminergic system, which is of utmost importance in schizophrenic symptoms (Kempadoo et al., 2016; Seki et al., 2018). Interestingly, the biosynthetic pathways of dopamine, serotonin, and noradrenaline share several enzymatic and metabolic steps, highlighting a common monoaminergic framework whose dysfunction is strongly implicated in the symptoms of psychiatric disorders such as depression, mood dysregulation, and schizophrenia. Additionally, reports suggest that dopaminergic malfunction in the prefrontal cortex is playing an important role in cognitive decline among schizophrenic patients (Aoyama et al., 2014), suggesting that LC-PFC interlinking could be pivotal to the pathophysiology of schizophrenia. Moreover, having established the role of dopamine in schizophrenia, it is worth mentioning that studies have found that lesioning of the LC-NA system induced morphological as well as metabolic changes in mesocortical dopaminergic neurons because NA is essential for the optimal functioning of dopaminergic cells in the CNS(Jovanovic et al., 2022; Tassin, 1992). Additionally, these LC-NA-dependent changes in dopaminergic neurons in the prefrontal cortex have been shown to play an important role in the pathogenesis of schizophrenia (Tassin, 1992). It was experimentally shown that dopaminergic afferents as well as LC-NA afferents reciprocally regulate sensitivity and control of dopamine and beta-adrenergic receptors in the cortex, respectively(Tassin, 1992). Additionally, lesions of the LC-NA system have been shown to cause microglial-recruitment-mediated dopaminergic neuronal degeneration in the midbrain, which accelerated the development of schizophrenic symptoms (Jovanovic et al., 2022). These results suggest that the LC-NA system interacts with and modulates the dopaminergic system in the midbrain, as well as regulates the activity of the prefrontal cortex. Insults to this LC-NA system play a crucial role in the pathogenesis of schizophrenia. Future research may unravel the vital targets in the LC-NA system to be manipulated through pharmacological interventions to treat various symptoms of schizophrenia disease, especially cognitive as well as self-awareness impairments.

2.4. The locus coeruleus in autism spectrum disorders: neurobiological insights into arousal and attention dysregulation

Autism spectrum disorders (ASD) are transmissible developmental disorders described by disability in social interaction, communication, recurring and stereotyped patterns in behaviors, and attentional functioning (Faras et al., 2010). Leo Kanner, an American psychiatrist, in 1943 applied the term “early-infantile autism” to designate the children who displayed impairments in social interactions (Kolvin, 1971). In addition to this, ASD patients also exhibit diminished visual engagement with environmental stimuli (Bast et al., 2018). There is reduced phase-altering and orienting to external stimuli, thus causing aberrant attentional functions. Phase alerting is defined as a response to contextual information, which is reflected by the response to stimuli if preceded by cues (Faras et al., 2010). The facilitated response to a spatial stimulus after a predictive cue is defined as orienting (Fan et al., 2002). The unusual attentional behavior (alerting and orienting) in children with ASD has been associated with the altered activity of the LC-NA system (Bast et al., 2018). The LC-NA is a well-known neuromodulatory system that modulates attention, orientation, and neurocognitive behaviors, which are compromised in ASD(Bast et al., 2018). Also, the LC receives direct synaptic inputs from deep cerebellar nuclei and cerebellar Purkinje cells, regulating the LC activity, and it has been suggested in post-mortem reports of ASD patients that 75 % of reported cases had impairments in Purkinje cellular physiology as well as a reduced number of these cells in such patients (Hampson and Blatt, 2015; Schwarz et al., 2015). The noradrenaline release in the cerebral cortex, hippocampus, and cerebellum is produced and transported by LC projections to these areas of higher-order brain function (Berridge and Waterhouse, 2003). The complex and selective patterns of LC innervation within and across different forebrain structures gain access to different neural networks (Berridge and Waterhouse, 2003; Laurel S. Morris et al., 2020). For example, the preferential noradrenergic innervation of some parts of the visual system provides vital spatial-visual analysis. It has been seen that visuomotor responses and other visual sensory domains are impaired in autism (Berridge and Waterhouse, 2003; Hampson and Blatt, 2015; Schwarz et al., 2015). These networks are influenced by distinct intracellular signaling cascades that allow the exhibition of the dynamic range of neuronal responses, which are essential for efficient and flexible behavioral adaptations (Berridge and Waterhouse, 2003). In children with ASD, altered attentional function via atypical LC–NA activity is regarded as a developmental mechanism leading to poor social attention as well as social interaction and communication deficits (Mehler and Purpura, 2009). The indicators of atypical LC-NE activity are increased tonic pupil dilation and altered pupil reactivity, mostly observed in ASD children (Faras et al., 2010). It may develop by altered signaling, which eliminates important and anticipated rewards during phasic alerting and decreases activation of the ventral frontoparietal attention system, thus decreasing orientation to stimuli and increasing tonic activity with reduced phasic reactivity to exogenous stimuli.

Strong evidence has been provided that supports the hypothesis that several processes causing developmental aberrations in the LC-NA system are associated with the development of ASD. For instance, genetic polymorphism of the β2-adrenergic receptor gene ADRB2, especially the variant that overstimulates the receptor owing to increased activity, leads to impairments in brain development and susceptibility to ASD in dizygotic twins (Cheslack-Postava et al., 2007; Connors et al., 2005). Further, the LC-NA system plays an essential role in abnormal emotional behaviors in ASD patients, which is predominantly developmental as well as physiological in nature. An interesting study has shown that inhibiting LC-NA signaling in mouse models during the early and critical developmental period of postnatal day 10–21 significantly alters adult emotional behaviors as well as stress-induced LC activity, often associated with ASD (Meng et al., 2018). Additionally, the LC-NA system has a profound role in the neuromodulation of mesocortical dopaminergic neurotransmission, and both the signaling pathways have been implicated in the pathology of ASD (Huang et al., 2021; Koevoet et al., 2022). Moreover, the LC-NA system is known to regulate attention flexibility, and dysregulations of attention and social interaction are the prominent features of ASD pathology (Aston-Jones et al., 1999; Bast et al., 2018; Berridge and Waterhouse, 2003; Koevoet et al., 2022). ASD children and their parents also display significantly reduced activity of the enzyme dopamine β-hydroxylase (DBH) (an essential enzyme in the biosynthetic pathway of dopamine and noradrenaline), as well as increased concentrations of noradrenaline in the serum of these patients (Lake et al., 1977). Recent research suggests that monoamine neurotransmitters such as NA and dopamine play a significant role in the development and progression of ASD. Notably, the majority of both conventional and next-generation antipsychotic agents approved for use in ASD modulate dopaminergic and serotonergic neurotransmission. Additionally, acute psychopharmacological studies using propranolol have demonstrated that transient noradrenergic inhibition may facilitate improvements in social communication and linguistic processing in individuals with ASD (Bast et al., 2018; London, 2018; Zamzow et al., 2017, 2016). Additionally, the use of β-adrenergic receptor blockers in managing ASD emotional as well as behavioral deficits has been reported to be effective in various case studies (Ratey et al., 1987; Sagar-Ouriaghli et al., 2018). Studies with resting-state fMRI have suggested that in ASD adolescent subjects, LC-NA and dopaminergic systems displayed a significantly reduced connectivity with brain areas involved in visual and motion

perception tasks, such as the postcentral gyrus, angular gyrus, as well as the middle temporal gyrus of visual area (Huang et al., 2021). Moreover, half of the reported cases of ASD display an increased pupil diameter, which in turn is due to the higher activity of the LC-NA system (Arora et al., 2021; Joshi and Gold, 2020). Based on these observations, pharmacological inhibition of LC-NA signaling, especially by β-adrenergic receptor antagonists such as propranolol, has been shown to improve many behavioral deficits associated with ASD (Beversdorf, 2020). These studies suggest that the LC-NA system and its neuromodulatory impacts on dopaminergic neurotransmission are intricately involved in the pathogenesis of ASD and present themselves as a novel target to treat the disorder in the future.

Several studies conducted on human subjects have shown that LC-NA activity dysfunction contributes to the etiology of ASD. A recent study conducted on children with ASD reported that attentional abnormalities associated with the disorder are mainly due to a faulty LC-NA regulation as indexed by pupillometric parameters (Zhao et al., 2022). This study concluded that children with ASD had aberrant arousal response, typically linked with dysfunctional LC_NA, to social cues along with mismatched dilation in non-social conditions, causing hyper-arousal to irrelevant stimuli. Further, Kim et al. conducted a resting eye-tracking task to measure tonic pupil diameter as well as a three-stimulus oddball paradigm to assess phasic responsiveness in LC-NA using pupil dilation response and event-related potentials in 27 children with ASD. The study showed that children with ASD displayed increased tonic and decreased phasic activities of the LC-NA system compared to the control group (Kim et al., 2022). Similarly, Nico et al., studied 139 ASD subjects with pupillometry and stimulus-evoked pupillary response and concluded that in ASD individuals, a positive association exists between baseline pupil size and stimulus-evoked pupillary response, showing a significant elevation and then a sharp decline in baseline pupil size (Bast et al., 2025). Another 12-week randomized, double-blind, and placebo-controlled trial tested the effects of 200 mg milnacipran (NE-reuptake inhibitor) on ASD subjects in the age range of 18–50 to observe if stimulating the LC activity could mitigate the behavioral symptoms associated with the disease. Interestingly, milnacipran improved the core symptoms of ASD, measured using scales such as Conners Adults ADHD Rating Scale-Observer Version (CAARS-O), Aberrant Behavior Checklist (ABC), and Clinical Global Impressions Improvement Scale (CGI-I), respectively (Noone et al., 2014). Further, a resting-state functional connectivity study on boys with ASD, aged 7–15 years, using functional magnetic resonance imaging, showed that their LC-NA system displayed a reduced connectivity with the postcentral gyrus area, which is essential in processing and interpreting sensory inputs such as touch, pain, and temperature (Huang et al., 2021). A recent study conducted on 24 school-going autistic children with an equal number of healthy children with age and IQ-matched, showed that autistic children had larger resting pupil size, a marker of LC-NA activation, and performed a faster search in a visual search paradigm task (Keehn et al., 2023).

2.5. *The noradrenergic substrate of intrusive thoughts and compulsions: LC-NA dysfunction in OCD*

Obsessive-compulsive disorder (OCD) is a mental illness characterized by the display of repetitive behaviors that are usually exacerbated by stress or anxiety. The obsessive behaviors are time-wasting as well as cause anxiety, distress, and impairments in socio-occupational interactions, as well as performances (Brock and Hany, 2020). Obsessions are known as intrusive thoughts that generate excessive distress, which the person tries hard to neutralize by consciously diverting their thought process as well as by indulging in rituals (Fenske and Petersen, 2015). The most prevalent obsessions are the urges to have everything "exactly right" as well as anxieties of infection, hostility, and injury. Washing and cleansing, inspecting, looking for validation, repeating, organizing, and arranging are some of the compensating compulsions for these obsessions(Krebs and Heyman, 2015). OCD usually surfaces in adolescence and is highly under-reported as well as an untreated mental disorder; therefore, early diagnosis as well as pharmacological intervention is vital (Brock and Hany, 2020). The WHO identifies OCD as one of the top ten and most debilitating disorders by monetary loss and a decreased quality of life, since it may impede a person's social growth and development, affecting the daily routine of life (Veale and Roberts, 2014).

Although the neuronal circuitry, as well as neurotransmission imbalance that underlie obsessional behaviors, are not well understood, increasing evidence from neurobiological as well as neuroimaging experiments suggests that the anterior cingulate cortex (ACC), an area at the cortical and limbic interface, plays a role in the pathophysiology of OCD (Fig. 1) and its associated symptoms (Alarcón et al., 1994; McGovern and Sheth, 2017; Micallef and Blin, 2001). Since the LC-NA system has a profound role in stress and anxiety-related behaviors, it has been hypothesized that the LC-NA system might be playing an active role in stress-induced OCD behaviors by modulating ACC (Fig. 1). A recent study reported that LC-NA signaling in ACC is significantly involved in stress-mediated repetitive behaviors in OCD animal models (Lustberg et al., 2020). These authors showed that dopamine beta-hydroxylase-knockout mice ($dbh^{-/-}$), deficient in NA, lacked marble burying and nestlet shredding, two behavioral models of OCD in rodents, compared to the control mice, and pharmacological rescue with external NA administration restored these behaviors in these NA-deficient mice (Lustberg et al., 2020).

Various compelling pieces of evidence support the view that the LC-NA system and its associated pathologies, including sensitivity of adrenergic receptors, play a vital role in the pathophysiology of OCD. For instance, it has been observed that increased concentration of noradrenaline metabolites in the plasma of OCD patients, polymorphism of the gene coding for the NA-metabolizing enzyme known as COMT, as well as changes in neuroendocrine responses against adrenergic drugs, all seem to be part of the pathophysiology of OCD (Brambilla et al., 1997; Karayiorgou et al., 1999; Pooley et al., 2007; Siever et al., 1983). Furthermore, it has been shown that intravenous administration of a single dose of α2-adrenergic receptor agonist clonidine (2 μg/kg) in 18 OCD patients and 10 normal subjects resulted in a significant decrease in obsessions as well as compulsions in those 18 subjects, while a placebo did not cause any change in these behaviors (Hollander et al., 1991). However, another study involving the administration of α2-adrenergic receptor antagonist yohimbine in 12 OCD patients not previously on drugs did not find any difference in OCD-related behaviors when compared to the normal healthy subjects, except for a rise in cortisol levels in OCD patients, suggesting that different receptors of the LC-NA system could regulate the OCD symptoms differently (Rasmussen et al., 1987). Taken together, these studies suggest that the LC-NA system, specifically its adrenergic receptors as well as important projections of LC to the brain areas involved in perception, decision making, and cognition, such as the prefrontal cortex, amygdala, and ACC, all regulate the pathophysiological symptoms in OCD. Further research, including the investigations regarding genetic differences in adrenergic receptor responsiveness as well as innovative drug designing targeting LC-NA components, will provide essential inputs to manage OCD related behavioral deficits, providing these patients with relief.

Dysfunction of the locus coeruleus (L. S. Morris, A. Tan, et al.) and central noradrenergic (NE) signaling has been posited as an important factor in OCD, especially via systems associated with arousal, action monitoring, and stress-induced repeated behaviors (Adams et al., 2018). The data in humans is inconsistent, but emerging neuroimaging and neuromelanin MRI studies indicate LC changes in OCD, especially the stress component, while restricted pharmacological trials examining noradrenergic drugs provide ambiguous outcomes. Targeted searches performed across PubMed/PMC and preprint servers for terms including "locus coeruleus", "noradrenergic", "norepinephrine", "obsessive--compulsive disorder", "OCD", and "animal model"," human subjects" (searches conducted 1970–2025) and after the exclusion of reviews,

unpublished data and editorials, only around 90 studies were included (Fig. 2) that actually investigated the role of LC-NA in all the discussed psychiatric diseases in this manuscript. One among them, a recent study, tested the hypothesis that OCD, which is characterized by stress and repetitive behaviors, in some patients has been mitigated by the neurosurgical ablation of the anterior cingulate cortex (ACC) that receives NA projections from the LC (Brennan et al., 2013; Chang et al., 2023). The authors used NA-deficient (Dbh -/-) mice and NA-competent (Dbh +/-) controls in marble burying and nestle shredding tasks. The study found that pharmacological restoration of NA synthesis in Dbh $^{-/-}$ mice significantly rescued nestle shredding behavior, whereas both tasks were suppressed in control mice by anti-adrenergic drugs (Brennan et al., 2013).

Even though LC has been associated with OCD symptoms associated with attentional and arousal dysfunctions, owing to the atypical anatomical location of LC and its small size, human evidence of links between LC function and OCD has been restricted by limitations in discerning LC with current neuroimaging techniques. A recent human study employed a computational LC localization and segmentation algorithm in conjunction with ultra-high field 7-Tesla and $0.4 \times 0.4 \times 0.5$ mm quantitative MR imaging to define the LC in 29 human individuals, including those with and without anxiety or stress-related disorders (L. S. Morris, A. Tan, et al., 2020). Their data suggested that subjects with anxiety or stress-related disorders had an expanded LC than controls, which was associated with suboptimal attention and inhibitory control, with higher anxious arousal (L. S. Morris, A. Tan, et al., 2020). Additionally, the difficulty in evaluating LC limits direct human LC imaging in OCD; however, neuromelanin-sensitive MRI techniques have recently made it possible to probe the LC in vivo in disorders related to stress and anxiety, revealing altered LC signal or volume in pathological anxiety states, which are theoretically relevant to OCD given shared hyperarousal features. These neuroimaging methods show promise for subtyping arousal-related phenotypes across disorders (McCall et al., 2024). Compared to other diseases, there is a lack of postmortem studies regarding the role of LC-NA in OCD. However, systematic reviews point to a lack of high-powered histopathology investigations that specifically investigate the LC-NA system in OCD brains (Lochner et al., 2024). Even though there are limited studies on the subject, there is some compelling evidence for a dysfunctional LC-NA system and adrenergic receptor sensitivity in subjects with compulsive disorders. Higher plasma levels of NA metabolites, altered neuroendocrine responses to LC-NA antagonists as well as genetic polymorphisms in the NA-metabolizing enzyme COMT, have been reported in OCD subjects (Brambilla et al., 1997; Dhiman et al., 2025). Future studies with advanced LC-NA imaging, probing with different biomarkers of OCD, are needed to establish a strong connection between LC-NA dysfunctions in OCD progression.

3. A dysfunctional LC-NA system: A hidden driver of cognitive impairments behind neuropsychiatric disorders

It is important to mention that the LC-NA system is intricately involved in the acquisition, processing, consolidation, and recall of various types of memories, whether implicit or explicit. Since we have highlighted how LC-NA dysfunction contributes to various neuropsychological disorders, it is not surprising that cognitive impairments accompany all of these disorders. Interestingly, LC has a well-established role in the modulation of cognition as well as its essentiality for general brain physiology, which is broadly acknowledged. Noradrenaline released by the LC is one of the important neuromodulators regulating mood, attention, perception, as well as other cognitive abilities, including the acquisition and recall of learned information (Susan J. Sara, 2009; Soya et al., 2013; Swift et al., 2018; Wagatsuma et al., 2018). As stated above, many neurodegenerative diseases affecting neuromodulatory systems, including that of LC-NA, result in diverse types of cognitive impairments along with physiological impediments. Various studies, including pharmacological stimulation and lesions in rodents and monkeys as well as humans, substantiated the role played by LC in modulating cognitive functions through the amygdala, hippocampus, and frontal cortical brain areas (Fig. 1), as LC projects to these areas

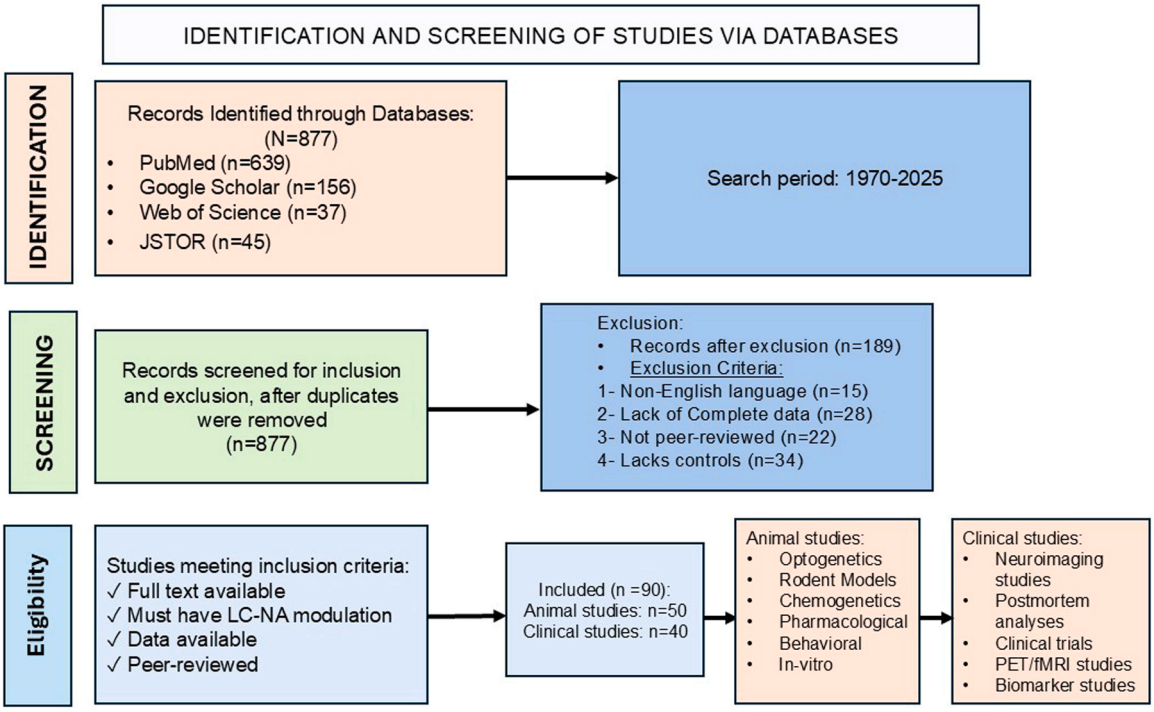


Fig. 2. PRISMA diagram depicting the type of databases searched and the inclusion and exclusion criteria for the search results. This diagram represents the core studies, both animal and clinical ones, that are cited and discussed in the manuscript, in addition to the narrative flow of hypotheses and ideas derived from various systematic reviews and narrative reviews.

profusely (S. J. Sara, 2009; Swift et al., 2018; Wagatsuma et al., 2018). Various behavioral paradigms designed to assess and quantify learning, memory, and attention in rodents as well as in primates suggest that LC-NA lesions significantly impaired cognition, including visuospatial attention and reference memories (Mair et al., 2005; Wagatsuma et al., 2018). Studies have shown that the optimal concentration of noradrenaline neurotransmitters in the prefrontal cortex is of utmost importance for optimal performance in working memory and attention-based tasks (Hämmerer et al., 2018; Suttkus et al., 2021). Reports suggest that reducing presynaptic NA release by injecting α2-noradrenergic receptor agonists like clonidine in the LC impairs performance, whereas a higher concentration of clonidine at post-synaptic sites enhances performance in non-human primates because optimal levels of NA in the prefrontal cortex are necessary for cognitive task performance efficiency(Arnsten and Goldman-Rakic, 1985; Ramos and Arnsten, 2007). These results together indicate that LC physiology is essential for optimal cognitive potential in animals, including humans, and pathophysiological insults to this brainstem nucleus debilitate cognition at a global level by affecting other higher-order brain areas.

LC-NA transmission dynamics exerts a widespread influence via phasic and tonic firing modes, which regulate network gain, signal-to-noise ratios, and cortical state transitions. Therefore, it is pertinent that pathological insults to the LC-NA system are bound to affect cognitive abilities in various ways. Age-related decline in surviving cells in the LC, along with morphological changes associated with these pathologies, has been shown to induce a decline in cognitive and other behavioral outcomes, including episodic memories, especially those linked with negative events like fear and anxiety (Hämmerer et al., 2018; Krohn et al., 2023). Moreover, reports suggest that in aged animal models, the reduced release of extracellular noradrenaline caused a decline in the formation of negative emotional memories, which can be rescued by administering noradrenaline or inhibiting its reuptake by norepinephrine reuptake inhibitor (NET) drugs (Luo et al., 2015). A noradrenergic reuptake inhibitor and a widely used antidepressant, desipramine, has been shown to improve mood and rescue age-related memory deficits by modulating the LC-NA system, which again firmly establishes an essential role played by the LC in cognitive disabilities due to neurodegenerative diseases affecting the LC-NA system (Luo et al., 2015). Future studies regarding the role of LC in cognitive decline in healthy aging versus diseased cohorts by measuring LC integrity at morphological as well as physiological parameters would provide greater insights, as LC shows pathological indications at the earliest stages of brain pathologies (Betts et al., 2019; Grudzien et al., 2007; Mather and Harley, 2016). Research has shown that education, as well as engaging in mentally challenging activities, produces late-life "cognitive reserve" in humans, and coincidentally, activation of the LC-NA system contributes to such processes immensely (Adolfsson et al., 1979; Mather and Harley, 2016). These studies suggest that the LC-NA system plays an essential role in cognitive abilities, and pathological insults to the system deteriorate cognition in aged and diseased individuals. Moreover, additional investigations are required to come up with advanced drug-designing methodologies targeting the LC-NA system for the rescue of cognitive decline during the progression of neurodegenerative and other neurological disorders. Further, refinements in biomedical high-resolution neuroimaging, such as neuromelanin-sensitive MRI to map LC integrity and its correlation with cognitive phenotypes in psychiatric populations, are much needed.

Additionally, the LC-NA system displays pronounced vulnerability to age-related neuronal loss, with substantial evidence from several post-mortem and neuroimaging studies that demonstrated progressive LC cell degeneration highly correlated with cognitive decline in these respective subjects. As the LC-NA system and its projection systems to the hippocampus and amygdala are implicated in attention, sleep-wake regulation, cardiorespiratory regulation, and learning and memory (Kant and Jha, 2019; Mir and Jha, 2021a, 2021b, 2024; Mir et al., 2019; Mir et al., 2025), age-induced cellular loss in the LC significantly impairs cognitive abilities, attentional regulation, and arousal responses in the elderly. Various high-resolution neuromelanin-sensitive MRI studies in humans suggest that a decreased LC signal, especially in the rostral LC, predicts impaired memory performance and reduced learning in older adults, with "younger-like" rostral LC integrity associated with better memory outcomes (Dahl et al., 2019). Further, quantitative cell counts in the LC region from post-mortem samples from Alzheimer's and Parkinson's disease patients showed that the severe neuronal degeneration was found in the LC region than the nucleus basalis or substantia nigra (Zarow et al., 2003). In AD, neuronal loss was most severe and best correlated with the duration of illness, suggesting that LC neurons are vulnerable to age-related pathologies (Zarow et al., 2003). Age-mediated genetic alteration in the LC-NA system, as well as other brain areas, including epigenetic dynamics that decrease histone acetylation and increase DNA methylation on gene promoters, which are responsible for optimal learning and memory, have been targeted with histone deacetylase inhibitors to mitigate dementia (Evans et al., 2021; Mir et al., 2023; Mir and Rizvi, 2019). Moreover, early signs of neuronal degeneration found in LC by various biomarker and imaging studies could benefit the age-related demented population by starting early interventions (Kang et al., 2025; Meyer et al., 2025). Also, stereological quantification of pigmented LC cells shows progressive degeneration and cellular loss in normal aging and much greater depletion in Alzheimer's disease (Mouton et al., 1994). Additionally, human studies have suggested that a higher cellular density in the LC is associated with a slower cognitive decline with age compared to people with sparse LC-cell density, suggesting that the LC contributes to cognitive reserve in the elderly (Wilson et al., 2013). These studies together emphasize the significance of the LC-NA system in cognitive decline and relate non-invasive, in vivo measures of LC integrity to memory decline in the elderly.

4. Locus coeruleus and sleep homeostasis: A link between sleep disturbances and psychiatric health

In addition to playing an essential role in cardiovascular and cognitive functions, LC is also an integral and vital part of the ascending reticular activating system in the brainstem (Faras et al.) that regulates sleep-wake physiology and is responsible for promoting wakefulness when stimulated by electric or chemical stimuli (Aston-Jones et al., 1999; Kaitin et al., 1986; Swift et al., 2018). LC neurons have been marked as wake-active and REM-off neurons, as their activity induces vigilance and inhibition promotes REM sleep (Mir and Jha, 2021a, 2021b; Osorio-Forero et al., 2022). Interestingly, sleep abnormalities emerge as a distinctive characteristic feature in several neurodegenerative and neuropsychological diseases, and improving the quality of sleep in these patients might serve well to mitigate the disease symptoms (Abbott and Videnovic, 2016; Gottesman et al., 2024; Pillai and Leverenz, 2017). Additionally, currently reviewed literature suggests that sleep plays active roles in cellular rejuvenation, toxin clearance, thermal regulation, metabolic homeostasis, memory consolidation, chemosensory modulation of pH/CO_2, as well as brain development (Mir and Jha, 2021a; Mir et al., 2019; Shen et al., 2023; Xie et al., 2013). Recently, our data suggested that sleep also serves an important role in the maintenance of ionic homeostasis, which is a prerequisite for normal functioning of the central nervous system at cellular as well as cognitive aspects (Mir and Jha, 2021a, 2021b, 2024; Mir et al., 2019). Emerging studies have highlighted the bidirectional relationship between sleep and neurodegenerative diseases, including Alzheimer's and Parkinson's diseases (Fig. 1), in addition to modulating mood and cognition in several psychiatric disorders like depression and schizophrenia (Ibrahim et al., 2024; Shen et al., 2023). Reports suggest that sleep disturbances are predominant in aged individuals and patients with neurodegenerative and neuropsychological abnormalities; therefore, promoting and resetting sleep patterns in these patients helps them to a large extent.

Recent research has suggested that sleep enhancement by dual orexin receptor antagonists (DORAs) like suvorexant mitigates tau-phosphorylation as well as decreases Aβ-plaque accumulation in the brain tissue and improves cognition in AD subjects (Lucey et al., 2023; Zhou and Tang, 2022). Not only the neurodegenerative disorders, but improvements in total sleep time as well as quality of sleep result in significant improvements in the associated disease symptoms, often observed in several psychiatric disorders, including schizophrenia, PTSD, ASD, and anxiety (Ashton and Jagannath, 2020; Ben Simon et al., 2020; Chen et al., 2021; Ho et al., 2016; Maher et al., 2021). Therefore, sleep remains a vital pharmaceutical target to reduce the disease burden in these patients, and LC is one of the highly explored areas regarding sleep-wake regulation and thus could serve as a potential area for this intervention in disease mitigation. Reports suggest that sleep was disrupted when LC was electrically stimulated in a human subject, and sleep disruption is associated with degenerative and psychiatric diseases (Kaitin et al., 1986; Osorio-Forero et al., 2022). Several studies suggest that LC inhibition by several optogenetic and genome editing tools increases NREM sleep as well as the number of REM sleep bouts, thereby improving sleep, and this can be a great strategic method for enhancing sleep in various neurobiological pathologies, including neurodegenerative and psychiatric disorders (Carter et al., 2010; Mir et al., 2025; Osorio-Forero et al., 2022; Yamaguchi et al., 2018). It has been well established that insomniac people are at higher risk of developing neurodegenerative and neuropsychological diseases than normal healthy subjects (Mayer et al., 2021; Shamim et al., 2019). Furthermore, LC has been significantly implicated in the development and progression of insomnia as evidenced by the findings that in insomnia, there is a higher magnitude of changes in LC's functional connectivity to higher-order brain regions, causing a dysregulation in noradrenergic modulation that impairs the integrity of sleep regulation (Chen et al., 2023; L. Gong et al., 2021; Um et al., 2022). Therefore, it is worth to explore the interlink between sleep disruption and the likelihood of exacerbating neurodegenerative and neuropsychological disorders concerning LC-NA modulation as LC could be a potent pharmaceutical target to mitigate these brain disorders, and research in this direction could provide vital insights for the development of pharmacological drugs targeting LC-NA system for the improvement in disease manifestation.

5. Locus coeruleus as a potential target for therapeutic interventions to improve brain health

LC neurons are vulnerable because of their peculiar location near the 4th ventricle, their peacekeeping function, and owing to their higher metabolic demand to respond to a plethora of salient information during wakefulness (Evans et al., 2022). This higher metabolic demand during extended wakefulness, insomnia, and sleep disturbances leads to the accumulation of free radicals, causing oxidative stress that further damages LC neurons and other brain regions and interestingly oxidative stress, neuroinflammation and metabolic dysregulation of LC neurons and other brain regions are intricately involved in neurodegeneration as well as in psychiatric diseases (Deng and Yao, 2020; Freude et al., 2022; Mir et al., 2025; Wang et al., 2020). LC neuronal atrophy or its hyperactivation, as observed in neurodegenerative and psychological diseases like anxiety, PTSD, and stress, significantly alters the cellular morphology, function, and often causes failure of the LC-NA system to respond to excessive accumulation of neurotoxins such as hyperphosphorylated Tau and DOPEGAL, an LC-derived toxic metabolite produced under hyperactivation of the LC-NA system (Olga Borodovitsyna et al., 2018; Kang et al., 2020). It is pertinent that sleep disturbances and insomnia are prevalent in many brain disorders, including neurodegeneration could directly affect LC neuronal health as it has been shown that consistent LC activity, during sleep loss, causes mitochondrial stress in LC neurons that further gives rise to microglial activation and neuroinflammation (Heneka et al., 2010; Iannitelli and Weinshenker, 2023; Wang et al., 2020). As LC neurons consistently fire during wakefulness and are challenged with fatigue and oxidative stress, better sleep quality and sleep hygiene provide a bioenergetically replenishing and rejuvenating window for LC cells to recover and synthesize antioxidants, like activating sirtuin proteins, restore the GSH/GSR ratio (Zamore and Veasey, 2022). Further, stress management by different meditational and cognitive behavioral therapies could significantly reduce oxidative stress, neuroinflammation, and improve sleep, which protects the brain, including LC neuronal integrity for optimal cognitive function, mitigating symptoms in neurodegenerative and psychiatric diseases (Kaufmann et al., 2015; Patil et al., 2024; Rossman, 2019). Therefore, protecting LC neurons against oxidative stress and neuroinflammation could significantly mitigate the disease progression and delay the disease phenotype (Fig. 1). For instance, nitric oxide reacts with oxygen free radicals, generating significant oxidative stress that can be countered by nitric oxide synthase inhibitor "diphenyleneiodonium," and this inhibitor has been shown to protect LC neurons by mitigating mitochondrial oxidative stress in animal models of LC neurodegeneration (Evans et al., 2022; Wang et al., 2020). Interestingly, noradrenaline acts as an "antioxidant" in its capacity by inhibiting nitric oxide synthase by stimulating neurons to produce neuroprotective CX3CL1 that also decreases ROS generation in microglial cells, and antioxidant pathways and oxidative stress are main factors contributing to aging and neuropsychiatric disorders (Feinstein et al., 1993; Madrigal et al., 2007; Mir et al., 2025). Further, a high-fat diet and insulin dysregulation are both significant factors contributing to neurodegeneration in the LC-NA system via glycogen synthase kinase activation that finally culminates in cellular loss within LC, which can be alleviated by a ketogenic diet that counters ROS and neuroinflammation, indicating that dietary lifestyle is an essential way of mitigating LC degeneration (Figlewicz et al., 1993; Pinto et al., 2018; Sędzikowska and Szablewski, 2021). Therefore, nutritional diets rich in antioxidants with appropriate levels of proteins, fiber, less oil, and carbohydrates, as well as a good lifestyle such as timely food consumption, exercise, and enough sleep, will significantly prevent the onset of neurodegenerative and psychiatric diseases.

Moreover, postmortem studies as well as refined imaging techniques in humans have established that LC's integrity has a direct correlation with a decline in cognitive efficiency observed in several brain disorders, including aging, neurodegeneration, and psychiatric diseases. Recent research suggests that LC is one of the regions that start to display neuronal disintegration and loss of fiber density at the earliest stages of disease progression, making it a vital area for image and fluid-based molecular biomarkers to diagnose several brain disorders at their earliest stages, possibly to provide a window of opportunity to start interventions (Betts et al., 2019; Chen et al., 2022). This early diagnosis by cutting-edge ultra-high field as well as magnetic resonance imaging techniques provides an important window for efficient early diagnosis, as well as treatment and mitigation of cognitive decline as well and helps in providing insights for the discovery of novel therapeutic targets based on LC-NA system exploitation (Van Egroo et al., 2023; Yi et al., 2023). In this direction, exploring the LC-NA neurotransmission pathways in the context of neurodegenerative and psychiatric diseases because noradrenaline provides neuroprotection by modulating synaptic plasticity, oxidative stress, as well as controlling neuroinflammation and bioenergetics in the brain (Briski et al., 2021; Mello et al., 2020; Singh et al., 2019). Studies have shown noradrenaline is as good an antioxidant in the brain as well-known antioxidants such as vitamin E, depicted from the findings that both reduce hydrogen peroxide generated ROS elevation in the synaptosomes (Álvarez-Diduk and Galano, 2015; Singh et al., 2019). Studies have also reported that scavenging ROS by noradrenaline is specific to its catecholamine ring as well as its unique pathways to sequestration of metallic ions that promote hydroxyl-group production through the Fenton reaction (Álvarez-Diduk and Galano, 2015). The therapeutic potential of targeting the LC-NA system is further supported by the findings of a study on four million Norwegians who

were prescribed a β-adrenergic agonist called "salbutamol". These subjects displayed a significant reduction in the risk for neurodegenerative Parkinson's disease, whereas the use of β-adrenergic antagonist propranolol heightened the risk for disease and exacerbated the disease-related symptoms (Mittal et al., 2017). Not only neurodegeneration but stimulation of pharmaceutical activation of β3-adrenergic receptors has also been suggested as a novel treatment strategy to mitigate depression, as associated anxiety in rodent models (Stemmelin et al., 2008). Therefore, it is pertinent that the LC-NA system is integral to brain health and optimization of its physiological function; hence, protection of the LC-NA system against endogenous and environmental insults will mitigate the disease progression. Future studies focusing on the preventive strategies to protect the LC-NA system, especially neurotransmitter regulation and cellular degeneration, as well as toxin accumulation in the LC, could shed more light on innovative ways to safeguard the LC and mitigate the age-associated as well as psychiatric behavioral symptoms observed in mental disorders. Lastly, enhancements in the NA signaling by unique beta-adrenergic agonists, as well as non-invasive modulation of LC activity by transcranial magnetic stimulation and or focused ultrasound, may offer help in activating LC, thereby improving cognitive impairments in various neuropsychiatric disorders. However, owing to the peculiar and deeper anatomical location of LC in the brain, future research must address methodological limitations to be able to target LC with precision and ease to harness the potential of LC-NA as a therapeutic target.

The LC-NA system constitutes a compelling therapeutic target for various mental health conditions, given its central role in regulating cardio-respiration, arousal, sleep-wake, attention, stress-reactivity, and cognition (Caestecker et al., 2025). Even though various pharmacological agents like noradrenaline reuptake inhibitors, α_2-adrenoceptor modulators, and β-adrenergic antagonists initially displayed promising results in restoring LC-NA system imbalances in depression, anxiety, and cognitive impairment (Breton-Provencher et al., 2021), alternative methods to modulate the LC-NA system are being developed. being explored as a potential target for transcranial magnetic stimulation (TMS) for mental health diseases. While presently, TMS applications target only the superficial cortex and near-surface brain areas, rapid advances in technology and neuroimaging are enabling researchers to innovate designs and find ways to modulate the deeper LC-NA system, which is involved in arousal, stress, and mood regulation, which lie at the core of psychiatric illnesses. Recently, human studies involving patients suffering from depression received accelerated high-frequency repetitive transcranial magnetic stimulation (aHF-rTMS), which was applied to the left dorsolateral prefrontal cortex (DLPFC), and on LC for mitigating drug-resistant major depression (Wu and Baeken, 2024). Authors reported that aHF-rTMS led to a significant reduction in LC functional connectivity, which improved the disease symptoms in these subjects. Whereas magnetic field penetration is a challenge to use these probing methods to study LC-NA modulation in humans owing to the depth of LC area, new alternative approaches like transcutaneous auricular vagus nerve stimulation (taVNS) and targeted ultrasound stimulation offer improved field of penetration and depth (Ludwig et al., 2021). A combination approach of targeted neuromodulation with pharmacologic modulation of the LC-NA system may therefore provide a novel and integrated therapeutic pathway for neuropsychiatric disorders.

6. Conclusions and future directions

The elucidation of brain circuitries that are an integral part of sleep-wake regulation and their functional impairments in brain diseases, especially in neurodegenerative and psychiatric disorders, is an area of intense research for disease management related to brain health. These studies highlighted in this updated review suggest that LC is one of the most important and early targets for a plethora of neurological diseases, including neurodegeneration and psychiatric pathophysiology, that are exacerbated as LC loses its integrity with disease progression. Interestingly, dysregulated LC neurotransmission might be an essential factor contributing to sleep-wake disruption often observed in these diseases. It has been difficult to establish whether sleep disturbances observed in neurodegenerative and psychiatric disorders are a causal factor for the disease progression or are simply a byproduct of these pathologies that might cause atrophy in sleep-wake regulating brain regions, including the LC. Because of LC-restricted synthesis of noradrenaline, where more than 60 % of total brain noradrenaline is synthesized, pathological insults to the LC nucleus deplete the higher-order brain areas of NA, an essential neurotransmitter, resulting in cognitive deficits, sleep-wake changes, as well as neurodegeneration (Jovanovic et al., 2022; Osorio-Forero et al., 2022; Zamzow et al., 2017). The LC-NA system is widely distributed throughout the brain, and pathological insults to this system prime the brain for various neurodegenerative and neuropsychological diseases. Recent developments in the cutting-edge technologies to dissect the brain function have drastically contributed to the understanding of brain functions contributed by deeper brain regions, such as the LC, which are often difficult to target with traditional methods of electrophysiology and do not yield solid proof results.

Therefore, we reviewed here recent studies that have utilized cutting-edge scientific tools such as designer receptors exclusively activated by designer drugs (DREADDs), optogenetics, fiber photometry as well as CRISPR (clustered regularly interspaced short palindromic repeats) to assess the role played by the LC-NA system in various neurological disorders and presented up-to-date findings relevant to this topic. I have also briefly described how the LC-NA system could serve as a potential therapeutic target to treat or mitigate the symptoms associated with neurodegenerative and psychiatric diseases. Depletion of the noradrenaline neurotransmitter in the brain regions that are essential for cognition, like the hippocampus, prefrontal cortex, and amygdala, jeopardizes the neuronal survival in these higher-order brain regions and causes significant neuronal atrophy and enhanced neuroinflammation, oxidative stress, and impaired phagocytosis in these areas, ultimately leading to cognitive deficits (Bondareff et al., 1981; Mercan and Heneka, 2022; Sampaio et al., 2020). Studies have shown that due to the less than optimal global levels of NA in LC pathologies, synaptic plasticity, synaptic pruning, neuronal survival, as well as firing properties of cortical and sub-cortical brain areas are severely affected (Bondareff et al., 1981; Mercan and Heneka, 2022; Sampaio et al., 2020). One of the plausible hypotheses for the reasons that LC is more prone to pathological insults is the anatomical localization of the nucleus close to the 4th ventricle (Bondareff et al., 1981; Pamphlett, 2014; Weinshenker, 2018). According to this hypothesis, cerebrospinal fluid carrying several metabolic waste products as well as toxins and fluxes the LC neurons more profoundly than other brain areas, as it lies at the edge of the ventricle (Bondareff et al., 1981). Post-mortem analysis of human subjects strongly supports the findings that LC in neurodegenerative diseases such as AD, PD, HD, and ALS display shrinkage along with morphometric alterations in addition to early cellular loss(Betts et al., 2019; Chen et al., 2022; Iannitelli and Weinshenker, 2023).

In other neuropsychological disorders such as schizophrenia, depression, and PTSD, the LC-NA system is significantly altered, especially in its default mode network, expression of genes coding for ion channels and receptors, and LC also displays hypo/hyperactivity, and the number of surviving cells is also affected by the disease pathology (Karolewicz et al., 2005; Krystal et al., 2018; Suttkus et al., 2021). Interestingly, in almost all the neurodegenerative as well as neuropsychological disorders, cognitive deficits are universal in these patients, and the two most important factors contributing to this are age and toxin-induced insults to the LC-NA system and deficits of NA into the higher order brain regions important for executive functions of the cognitive reservoir. Exploiting the functions as well as diverse efferent projections of the LC-NA, modulation of various biological processes, including sleep intervention, preventing cellular damage in the LC, as well as strategies to reduce age and metal-induced toxicity in the LC may

benefit the individuals who are more susceptible to neurodegeneration and psychiatric pathophysiology. More advanced techniques for probing the functions of LC-NA must be developed to investigate non-invasively the dynamics of LC-NA dysfunctions that are currently limited owing to the depth and typical anatomical location of the LC.

Taken together, this review provided updated findings and methodology designed to disseminate the role played by LC-NA in psychiatric disorders and how these neurobiological mechanisms could be targeted for treatment strategies. Further research is needed to develop sensitive and accessible neuroimaging techniques that can allow doctors to access the deep-lying LC in the brainstem. Moreover, we need to identify suitable peripheral or CSF biomarkers of LC-NA dysfunction, including various NA-based metabolites, neuroinflammatory markers that can diagnose the disorder at the earliest.

CRediT authorship contribution statement

Fayaz A. Mir (FAM) conceptualized the review, conducted the literature analysis, and wrote the manuscript, as well as edited and revised the manuscript for revised submission. S.K. Jha (SKJ) and Christa J Nehs (CJN) provided critical feedback and editorial suggestions during the revision process. All authors reviewed and approved the final version of the manuscript.

Declaration of Competing Interest

The author declares no competing financial or non-financial interests related to the content of this manuscript. There are no personal, professional, or institutional affiliations or relationships that could be perceived to influence the review's objectivity or interpretation.

Data availability

No data was used for the research described in the article.

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