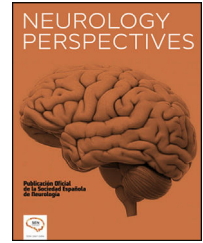




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ORIGINAL ARTICLE

Locus coeruleus: Clinical aspects of its involvement in Parkinson's disease



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KEYWORDS

Locus coeruleus;
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Abstract The Locus coeruleus (LC) is a brainstem structure that plays a critical role in neurological functions and is very frequently affected in such neurodegenerative diseases as Parkinson's disease (PD) and Alzheimer's disease. In the case of PD, it is affected early in the disease course, impairing such functions as sustained attention, conditioned learning, memory consolidation, pain regulation, mood, sleep cycles, and pupil dilation in response to stimuli such as stress or fear. Developing a study protocol tailored to all these functions is important in order to assess its dysfunction, especially in patients at early stages or at risk of developing one of these diseases. In the near future, neuroimaging or biochemical biomarker studies are expected to enable a better understanding of its functioning and allow for the early detection of functional abnormalities.

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PALABRAS CLAVE

Locus coeruleus;
Enfermedad de Parkinson;
Fallo autonómico;
Deterioro cognitivo;
Noradrenalina

Locus coeruleus: aspectos clínicos de su implicación en la enfermedad de Parkinson

Resumen El Locus coeruleus (LC) es una estructura tronco-encefálica crítica en funciones neurológicas que se afecta muy frecuentemente en enfermedades neurodegenerativas como la enfermedad de Parkinson (EP) y la enfermedad de Alzheimer. En el caso de la EP su afectación es precoz y afecta a funciones como la atención sostenida, el aprendizaje condicionado, la consolidación de la memoria, la regulación del dolor, el estado de ánimo, los ciclos del sueño o la midriasis como respuesta a estímulos como el estrés o el miedo. Elaborar un protocolo de estudio

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adaptado a todas estas funciones es importante de cara a valorar su disfunción, especialmente en pacientes en fases precoces o a riesgo de presentar una de estas enfermedades. Es de esperar que en un futuro próximo el estudio de biomarcadores de neuroimagen o bioquímicos permitan entender mejor su funcionamiento y detectar precozmente anomalías de su función.
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Introduction

The locus coeruleus (LC) is a small nucleus of approximately 20,000–30,000 predominantly noradrenergic (NA) neurons. Despite its small size, it is connected to multiple regions of the central nervous system (CNS), including the forebrain, cerebellum, spinal cord, hypothalamus, and basal ganglia.^{1,2} It measures approximately 10–15 mm long and 2–3 mm wide and is located in the dorsal region of the pons (Fig. 1). The LC is made up of 2 types of NA neurons, which are distributed heterogeneously across the nucleus: large, multipolar neurons containing neuromelanin; and smaller, fusiform cells with extensive dendritic branching, which lack this pigment.³ The LC receives inputs from multiple SNC structures, including the prefrontal cortex, amygdala, preoptic area, paraventricular nucleus of the hypothalamus, reticular formation, and cerebellum.^{1,4} Connections have been described with over 100 anatomical areas (Fig. 2).^{4,5} The central part of the nucleus, populated with NA neurons, is surrounded by another layer predominantly made up of GABAergic neurons, which regulate the function of the NA neurons.⁶

1. Functions of the locus coeruleus in humans

The LC is involved in such functions as attention, level of arousal, capacity for learning, regulation of sleep cycles, and mood. Pioneering studies have shown that NA neurons of the LC

present a relatively narrow range of discharges, with patterns varying according to its activity in different situations. For instance, these neurons are practically silent during rapid eye movement (REM) sleep, whereas they present low-amplitude tonic activation during normal arousal and a pattern of intermittent tonic firing during focused attention, which becomes continuous under stress.^{2,7} During non-REM sleep, LC activity is intermittent, with phasic firing coinciding with the microarousals characteristic of this sleep phase. Furthermore, NA neurons of the LC regulate sleep–wake rhythms and activity modulated by light exposure. Prolonged deprivation of these light stimuli induces a loss of NA fibres, reducing the amplitude of the sleep–wake rhythm.⁸ The LC receives considerable inputs from the brainstem, and especially the gigantocellular reticular nucleus, and responds to tactile, olfactory, visual, and vestibular stimuli; this underscores its role in the interaction of cognitive and emotional responses in situations of stress.⁹ Prolonged, repeated activation of the LC leads to maladaptive responses; this malfunctioning is the basis of the pathological stress response in several neuropsychiatric diseases.¹⁰

2. Role of the locus coeruleus in cognition

Projections from the LC to the prefrontal cortex modulate such functions as attention and executive function,¹¹ mediated by G protein–coupled receptors (alpha and beta adrenergic receptors). Tonic activation is involved in modulating sustained



Figure 1 Macroscopic image of the pons. The bilateral dorsal region displays 2 punctiform areas; these correspond to the locus coeruleus and are visible due to the structures' neuromelanin content.

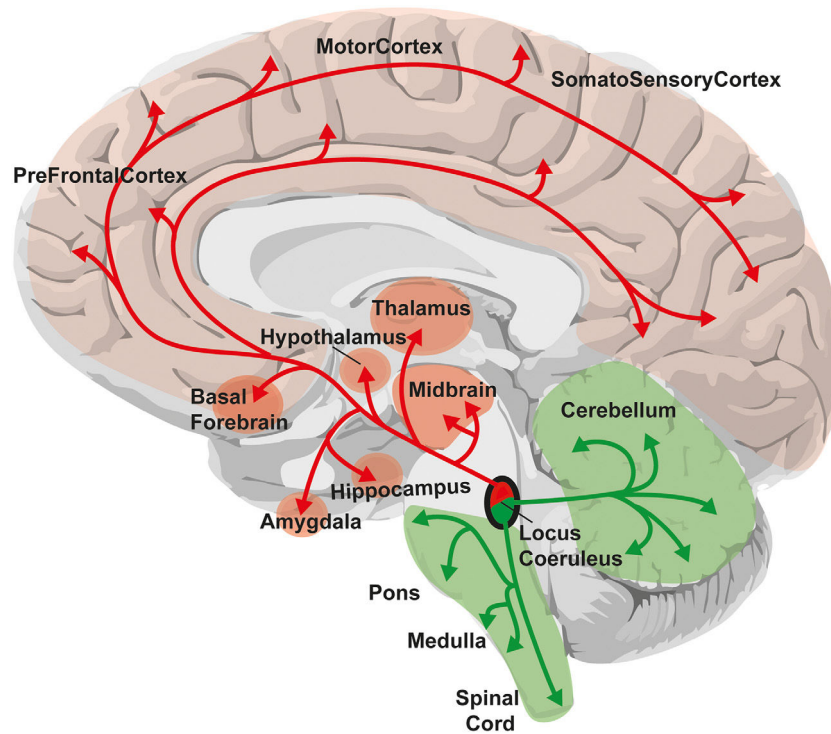


Figure 2 Anatomical drawing showing the main connections of the dorsal (red) and caudal (green) regions of the locus coeruleus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

attention, whereas phasic activation facilitates specific behaviours. The prefrontal cortex projects to the cingulate cortex and modulates stochastic or unpredictable behaviour. LC-NA afferents act on the forebrain, modulating emotional processing, whereas when they act on the medial prefrontal cortex, they improve mental flexibility. Projections to the basolateral amygdala facilitate fear-conditioned learning, consolidate emotional learning, and can cause anxiety in the event of overactivation (Fig. 2).^{1,12} The initial response to stress is due to the liberation of corticotropin-releasing factor from various nuclei in the brain; among these, some hypothalamic nuclei and the central nucleus of the amygdala are connected to the LC, which would participate later in the response to stress.¹⁰

The relationship between the level of LC-NA activity and wakefulness explains a considerable part of the role of the nucleus in learning during consciousness. It has been shown both in humans and in animals that LC activity is related to fluctuations in pupil size and to the level of attention and wakefulness.¹³ In these animal models, increased activation was observed in the case of conditioned learning (reward and punishment).¹⁴ LC-NA activation is fundamental to focused learning. The LC has projections to the hippocampus, strengthening the memory process. Increased activity in LC axonal projections in the hippocampus is reported during the process of passive learning.¹⁴ Activation increases in response to novel stimuli, and training and learning lead to decreased LC activity.

3. Anatomical functions and the locus coeruleus

Whereas the parasympathetic nervous system response is rapid and homogeneous due to the fast entry and reabsorption of acetylcholine in cholinergic synapses, the

sympathetic nervous response is slower and more complex. One example of this is the different activation pathways of the sympathetic nervous system in response to different stimuli, such as physical exercise, stress, and fear. The sympathetic response to both stimuli causes the tachycardia and increased arterial blood pressure inherent to NA activation of the sympathetic nervous system, and the increased sweating caused by cholinergic activation. However, mydriasis is less pronounced during physical exercise and more striking in fright or fear reactions. This difference in NA sympathetic response may be explained by the variable modulation of the LC and its connections with such structures as the amygdala, limbic system, or hypothalamus. The LC functions as a centre containing sympathetic neurons with projections to preganglionic neurons of the intermediolateral column of the spinal cord and subsequently to the radial muscles of the iris, triggering mydriasis. Inhibitory parasympathetic neurons project to preganglionic neurons of the Edinger-Westphal nucleus of the midbrain, subsequently innervating the iris sphincter muscle, causing miosis. LC-NA neurons receive inputs from the hypothalamic suprachiasmatic nucleus, orexin-producing neurons in the lateral-posterior hypothalamus, and other brainstem structures. However, parasympathetic neurons receive information from the amygdala, from the network involved in the sleep-wake cycle, and from nociceptive collaterals from the spinothalamic tract.^{15,16}

In the case of PD, various studies reporting post-mortem and MRI findings have been unable to demonstrate a relationship between LC degeneration and the presence of neurogenic orthostatic hypotension (NOH), a frequent finding in advanced stages of the disease.^{17,18} However,

other studies have demonstrated predominantly caudal regional involvement in patients with PD and NOH and/or apathy.¹⁹ We may conclude that the LC is involved in all those NA sympathetic activities (alertness, concentration, mydriasis, etc) linked to preparation for such diverse situations as hunting, in animals, and sitting examinations, in students, to name 2 very different examples. Lack of activation of this pathway leads to increased apathy, depression, and fatigue, as is seen in many patients with PD (Table 1).

4. Locus coeruleus activity in behaviour

Two main theories have been proposed to explain the role of the LC in sensory-motor behaviour. The adaptive gain theory²⁰ seeks to explain the tonic and phasic phases of the LC-NA system. Phasic activity prevails during optimal behavioural functioning, in which transient increases in activity facilitate task-related decision processes.²⁰ On the other hand, tonic activity predominates during periods of poor performance in an activity. In this manner, through adaptive gain, LC-NA activity optimises the reward between exploration (seeking new options) and exploitation (focusing on an existing solution) by alternating between phasic and tonic activity, respectively.

The network reset theory^{21,22} explains the LC-NA system's capacity to coordinate and reorganise brain states in response to different stimuli or critical situations. This process involves a "reset" or adjustment in neural processing and levels of alertness to facilitate rapid changes in attention, perception, and action in response to specific situations or unexpected events.^{21,22} These activation contexts lead NA neurons of the LC to induce generalised cortical activation, resetting the network in the cerebral cortex. This mechanism would enable, for example, shifting attention from a previous stimulus to new stimuli, to which attention and learning are directed. Similarly, it has been suggested that a sudden increase in LC-NA phasic activity indicates "uncertainty," provoking a reset in the network's activity to enable an update.²² By signalling the need to update previous activities, LC-NA would suppress top-down influences driven by information favouring sensory signals to enable learning and optimisation of behavioural responses to

novel stimuli. The LC-NA also interacts with the ventral tegmental area, regulating mesocorticolimbic pathway activity (dopaminergic activity) to reinforce behaviours conditioned by reward.²³

5. Role of the locus coeruleus in pain modulation

The LC receives noxious sensory glutamatergic stimulation via the nucleus paragigantocellularis.²⁴ It also has connections in both directions with the principal trigeminal nucleus and the spinal trigeminal nucleus. The LC would represent a fundamental node in descending inhibitory NA signals towards the spinal cord; this descending regulation also involves the magnocellular nucleus and the periaqueductal grey matter. Functional MRI studies report increased activation in the lateral region of the pons in association with hyperactivity of the LC and parabrachial nucleus in situations triggered by thermal nociception.²⁵ Acute pain triggers a response in the LC, causing spinal analgesia; furthermore, through its connections with such other structures as the amygdala, cingulate cortex, and hippocampus, it causes aversion, increased vigilance, and modification of sensory thresholds via ascending pathways.²⁶ However, this protective activity against acute pain is not successful for chronic pain, causing central facilitation, anxiety, increased aversive memory, and behavioural alterations through effects on bulbar nuclei, the prefrontal cortex, and the amygdala.²⁶ These changes may contribute to the development and maintenance of chronic pain, due to alteration of the balance between inhibition and facilitation in the CNS through interaction in both ascending nociceptive pathways and descending inhibitory pathways.⁵⁸⁻⁶⁰

The LC is also involved in the modulation of affective and emotional aspects. Dysregulation of the LC-NA system may influence emotional responses to pain, such as anxiety and depression, which often present as comorbidities of chronic pain conditions. This emotional component may further exacerbate the general experience of pain, contributing to the chronification of symptoms.

From an anatomical perspective, the LC interacts with 2 ascending nociceptive pathways.²⁷ The lateral pathway ascends from laminae IV-V of the dorsal horn, decussating and ascending to the sensory cortex. The LC has a global

Table 1 Identification of the noradrenergic subtype of PD. The candidate biomarkers may assist in identifying the noradrenergic subtype of Parkinson's disease, including clinical, neuroimaging, and mental/physical test findings.

Lesion topography	Clinical symptoms	Paraclinical tests
Central involvement Locus coeruleus A6, bulbar noradrenergic cell groups A4 and A5, nucleus of the solitary tract A2, noradrenergic cell group A1.	Depression, attention deficit, mental fatigue, impaired capacity for learning, circadian sleep rhythm alterations, RBD, chronic pain, and pupillary disorders.	MRI with sequences sensitive to neuromelanin ¹¹ C-MeNER PET CSF norepinephrine and dihydroxyphenyl glycol levels, Neuropsychological tests, Binocular pupillometry
Peripheral involvement Sympathetic ganglia, postganglionic sympathetic terminals, intermediolateral columns, afferent baroreflex failure	NOH, postural orthostatic tachycardia syndrome, riser pattern on blood pressure monitoring, intestinal rhythm alterations, baroreflex failure, vesicoureteral reflux	Cardiac MIBG SPECT Plasma norepinephrine in decubitus and standing positions Plasma dihydroxyphenyl glycol QST CHEPS Urodynamic study

¹¹C-MeNER: (S,S)-¹¹C-2-(α -(2-methoxyphenoxy)benzyl)morpholine; CHEPS: contact heat-evoked potential stimulator; CSF: cerebrospinal fluid; MIBG: meta-iodobenzylguanidine; NOH; neurogenic orthostatic hypotension; RBD: REM sleep behaviour disorder; QST: quantitative sensory testing.

influence on the final perception of pain, as it inhibits spontaneous activity of the involved areas of the sensory cortex (50%–80% in the entire cortex) and increases the firing rate in others (10%–40% in deeper layers). The medial nociceptive pathway processes signals from unmyelinated fibres (C fibres) and ascends from lamina I via the spinothalamic tract towards the rostral, dorsal, and insular cortex, and processes diffuse, less localised pain.

6. The locus coeruleus and Parkinson's disease

PD is the second most frequent neurodegenerative disease after Alzheimer's disease. Its prevalence has doubled in the last 25 years, and it is the fastest-growing neurodegenerative disease.²⁸ The loss of striatal dopaminergic projections causes the majority of motor symptoms of the disease. Although the LC is affected before the substantia nigra in the majority of patients,^{29,30} there is evidence of a subtype of PD with a greater NA deficiency, both in the LC and in peripheral synaptic terminals.^{31–33} In addition to such vegetative symptoms as NOH or bladder dysfunction, this deficiency is associated with motor symptoms, sleep disorders, pain, and psychiatric and cognitive symptoms.^{33,34} With respect to motor symptoms, the postural instability and gait difficulty phenotype are associated with much greater loss of NA neurons than other phenotypes, such as those with predominant tremor.³⁵ Currently, the pharmacological treatment of these symptoms is based on selective inhibition of norepinephrine reuptake, blocking the presynaptic alpha 2 adrenergic receptor, and the use of a norepinephrine prodrug, the artificial amino acid L-threo-3,4-dihydroxyphenylserine.

In the CNS, norepinephrine participates actively in neuromodulatory circuits and in aspects of sensory-motor processing. Most norepinephrine is located in the NA neurons of area A6 (locus coeruleus) (Figs. 1 and 2). In the early stages, the NA endophenotype of PD may be mistaken for multiple system atrophy. Levels of norepinephrine and its metabolites in the cerebrospinal fluid (CSF), cardiac MIBG (iodine meta-iodobenzylguanidine) SPECT, screening for dysautonomic signs, and skin biopsies to detect alpha-synuclein may assist in differential diagnosis.^{34,36–38} Patients with PD present a loss of 60%–70% of NA neurons in the LC³³; on the other hand, physiological ageing is associated with loss of NA neurons in the caudal part of the nucleus, whereas the loss of these neurons in Alzheimer's disease is asymmetrical, with greater involvement in the rostral area (Fig. 2).³⁹ Specific MRI sequences (T1-weighted spin echo and magnetisation transfer ratio MRI) can be used to view neuromelanin-loaded neurons of the LC.^{40,41} Recent studies have suggested that the main source of contrast on MRI neuromelanin sequences is the large amount of intracellular water inside NA and dopaminergic neurons.⁴¹ The role of neuromelanin MRI as a quantifiable biomarker of different psychiatric and neurodegenerative diseases is currently unclear.⁴¹ Recent research has associated NA loss in the LC and other CNS structures with the presence of REM sleep behaviour disorders (RBD), which are associated with NOH and cognitive problems. Furthermore, a correlation is reported between the presence of RBD and the loss of peripheral NA neurons, as measured with cardiac MIBG SPECT.⁴² This is explained by the role of norepinephrine in

modulating REM sleep through efferent connections between the LC and the subcoeruleus and the lateral pontine tegmentum.³¹ With regard to plasma norepinephrine, elevated levels are reported in early stages, with a gradual reduction as the disease progresses, particularly in patients with peripheral autonomic failure. However, a metabolite of norepinephrine, dihydroxyphenyl glycol, presents reduced levels in the CSF from the initial stages.^{33,43} The change in plasma norepinephrine upon standing, as well as the response of serum growth hormone levels to injection of apomorphine or clonidine, may represent diagnostic biomarkers to differentiate between patients with Parkinson's disease and peripheral autonomic failure, and patients with multiple system atrophy with predominantly central autonomic failure (Table 1).³⁶

7. Proposed study for the functional assessment of the locus coeruleus (Table 2)

It is difficult to isolate the specific functions of the LC-NA system from those of other structures affected in PD, such as the substantia nigra, other brainstem nuclei, the limbic system, and even postganglionic structures of the sympathetic nervous system, to name a few examples. According to the Braak staging system, the LC is affected early in the disease course, before the substantia nigra.^{29,44} Within this model, there will be exceptions to this progression from the brainstem towards the cerebral cortex, with some authors distinguishing between a form in which the disease initially affects peripheral structures, particularly in the autonomous nervous system (body-first form), and another in which it begins in the brain (brain-first form). Early involvement of the LC is associated with RBD and would fit within the body-first category, with early involvement visible on cardiac MIBG scintigraphy.⁴⁵ In conclusion, we may study patients with idiopathic forms of RBD or pure autonomic failure preceding the development of PD or Lewy body dementia, in order to study LC-NA involvement in isolation.

Among the proposed examinations, we may include those studying involvement of the autonomous nervous system, such as the tilt-table test, changes in heart rate and blood pressure in response to the Valsalva manoeuvre and deep breathing, peripheral blood levels of norepinephrine and its metabolites in decubitus and standing positions, and cardiac MIBG scintigraphy (Tables 1 and 2).^{46,47} Levels of the norepinephrine metabolite dihydroxyphenyl glycol may also be tested in the CSF.⁴⁸ These determinations may be a biomarker of LC degeneration, especially in premotor phases of PD.

The use of dynamic pupillometers to study pupillary function is particularly relevant.^{16,49} Pupillary function is clearly related to the level of attention, and with centres regulating the circadian rhythm of sleep, anxiety, and pain, as has been demonstrated in animal studies.¹⁵ Dynamic pupillometry measures pupil size and the speed of constriction or dilation in response to different stimuli such as light, drugs, or stress (Tables 1 and 2).

With regard to neuropsychiatric tests (Table 2), we should select those analysing specific LC functions, such as sustained attention, memory, and learning under stressful conditions. Among the first group of tests, we may note the Symbol Digit Modalities Test^{50,51}; the Salthouse Perceptual

Table 2 Functional areas to explore and functions impaired in locus coeruleus lesions.

Areas to explore	Specific tests	Degree of involvement
Haemodynamic autonomic functions	Tilt table Valsalva manoeuvre HRV with breathing	Decrease in HRV NOH
Pupillary function	Pupillometry	Decrease in pupillary response to light and emotional stimuli
Neuropsychological tests	Stroop test: measures attention Digit span: assesses verbal working memory Toulouse Pieron test Sustained vigilance tasks: evaluate the capacity for prolonged attention. RAVLT Hamilton Depression/Anxiety Rating Scales	Attention deficit Short-term memory alterations Depression and apathy
Sleep studies	Polysomnography Actigraphy	Loss of sleep stages Fragmentation Parasomnias such as RBD
Biomarkers of noradrenergic function	Blood and CSF norepinephrine levels CSF dihydroxyphenyl glycol level	Low in the event of central/peripheral noradrenergic involvement Reduced CSF dihydroxyphenyl glycol level

CSF: cerebrospinal fluid; HRV: heart rate variability; NOH: neurogenic orthostatic hypotension; RAVLT: Rey Auditory Verbal Learning Test; RBD: REM sleep behaviour disorder.

Comparison Test; the Stroop test,⁵² which evaluates sustained attention and inhibitory control; the Toulouse Pieron test⁵³; and the Conners Continuous Performance Test. To study the capacity for learning under conditions of stress or fear, memory tests with induced stress are recommended: participants learn a list of words, images, or a task under stressful conditions (for instance, time pressure, noise, or menacing images). The capacity for recall and recognition is measured. The Rey Auditory Verbal Learning Test, Hopkins Verbal Learning Test-Revised, and Brief Visuospatial Memory Test-Revised analyse immediate and delayed verbal and visual memory, and the capacity for learning over multiple tests.⁵⁴ Copying and recall of the Rey Complex Figure may also be used to evaluate patients' visual memory and perceptual organisation. The LC-NA system has an important role in depression^{55,56} and should be studied with depression scales. The Hamilton Depression Rating Scale is widely used in neurological disease, and especially such neurodegenerative diseases as PD.⁵⁷

Sleep studies may be performed using actigraphy, or with more complex polysomnography studies (Table 2). The LC presents significant activity during wakefulness, which decreases during non-REM sleep and is almost completely absent during REM sleep. Degeneration of the structure contributes to the sleep disorders observed in neurodegenerative diseases and in physiological ageing.⁵⁸ Not only does degeneration of the LC contribute to insomnia but also patients may present parasomnias, such as RBD. Patients with idiopathic RBD may display reduced neuromelanin uptake in specific brain MRI sequences.⁶⁰

Ethical considerations

This is not a clinical study, and no ethical considerations are applicable.

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Conflicts of interest

The authors have no conflicts of interest related to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neurop.2026.100220>.

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