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Noradrenergic neuromodulation in ageing and disease

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ABSTRACT

The locus coeruleus (LC) is a small brainstem structure located in the lower pons and is the main source of noradrenaline (NA) in the brain. Via its phasic and tonic firing, it modulates cognition and autonomic functions and is involved in the brain's immune response. The extent of degeneration to the LC in healthy ageing remains unclear, however, noradrenergic dysfunction may contribute to the pathogenesis of Alzheimer's (AD) and Parkinson's disease (PD). Despite their differences in progression at later disease stages, the early involvement of the LC may lead to comparable behavioural symptoms such as preclinical sleep problems and neuropsychiatric symptoms as a result of AD and PD pathology. In this review, we draw attention to the mechanisms that underlie LC degeneration in ageing, AD and PD. We aim to motivate future research to investigate how early degeneration of the noradrenergic system may play a pivotal role in the pathogenesis of AD and PD which may also be relevant to other neurodegenerative diseases.

1. Introduction

The locus coeruleus (LC), Latin for 'blue spot', is a brainstem nucleus first described in 1786 by Félix Vicq-d'Azyr (Vicq-d'Azyr, 1786). Despite its small size, the LC projects to and receives input from widespread brain regions (Liebe et al., 2022; Szabadi, 2013) and is thus involved in numerous functions related to cognition such as memory formation (Amaral and Foss, 1975; Gibbs et al., 2010; Hansen, 2017; Kety, 1972; Zornetzer and Gold, 1976), attention, sensory processing (Bouret and Sara, 2002; Lecas, 2004), novelty (Vankov et al., 1995; Yamasaki and Takeuchi, 2017) and emotional memory (Hämmerer et al., 2018). It is involved in autonomic functions such as blood pressure (Sved and Felsten, 1987), immune function (Lehnert et al., 1998; Rassnick et al., 1994) and the sleep-wake cycle (for a review see Osorio-Forero et al., 2022). Furthermore, it is involved in the fight or flight response by modulating heart rate, blood pressure, salivation and pupil dilation (Ross and Van Bockstaele, 2021; Samuels and Szabadi, 2008). Alterations to the noradrenergic system occur as a result of degeneration, that therefore may impair these functions. Indeed, in humans, the LC has recently become increasingly relevant in healthy aging because several cognitive functions supported by the noradrenergic system, such as verbal intelligence (Clewett et al., 2016), response inhibition (Liu et al., 2020; Tomassini et al., 2022), memory (Calarco et al., 2022; Dahl et al., 2019; Langley et al., 2022; Liu et al., 2020), emotional memory (Hämmerer et al., 2018; Sterpenich et al., 2006), attention and processing speed (Calarco et al., 2022) decline in older age (Harada et al., 2013).

In addition to ageing, degeneration and dysfunction of the LC noradrenergic system (LC-NA) also occurs during the first stages of Alzheimer's (AD) and Parkinson's (PD) disease and may contribute to the

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spread of pathology (see Section 4.). There is significant loss in LC volume and MRI contrast in both AD and PD (Betts et al., 2019a; Jacobs et al., 2021a; Madelung et al., 2022; Theofilas et al., 2017; Zarow et al., 2003). The LC-NA system is mainly linked to AD pathology through its metabolites, whose levels increased and interact with tau and amyloid-beta (Aß) pathology: a recent review and meta-analysis found elevated cerebrospinal fluid (CSF) MHPG levels in AD compared to healthy controls, while noradrenaline (NA) levels were unchanged (Lancini et al., 2023). Moreover, as the noradrenergic metabolite 3, 4-Dihydroxyphenyl Glycolaldehyde (DOPEGAL) interacts with tau, NA has been suggested to indirectly accelerate the progression of AD disease (Kang et al., 2022). In PD, the LC also shows structural degeneration early in the disease, which might be linked to non-motor symptoms that occur prior to substantia nigra (SN) degeneration such as anxiety (Lapiz et al., 2001), depression (Remy et al., 2005) and REM sleep disturbances (Ehrminger et al., 2016; García-Lorenzo et al., 2013).

Finally, given the link between LC integrity and symptoms of neurodegenerative diseases and ageing, the LC presents as a natural target for therapeutic interventions to ameliorate those symptoms. And indeed, different therapeutic interventions, that increase noradrenergic levels, have successfully been used to improve cognition in individuals with PD and in individuals with mild cognitive impairment (MCI) and AD.

In this review, we summarise the involvement of the LC-NA system in healthy aging and in neurodegenerative disease. The aim of this review is to summarise the latest research findings and encourage further research on the involvement of the noradrenergic system in both healthy aging and in the aetiology of AD and PD.

2. The noradrenergic system

The LC is the main source of NA in the brain. The LC's azure look stems from high levels of neuromelanin (NM), a byproduct of NA synthesis and NA metabolism that binds metal ions (Zucca et al., 2006) Due to its exposed location next to the 4th ventricle, the LC is more vulnerable to inflammatory molecules and toxins (for a review see Evans et al., 2022; Matchett et al., 2021). Moreover, LC axons are partially myelinated therefore less cost-efficient, resulting in higher energy consumption, which in turn leads to higher levels of highly reactive oxygen species (ROS) (Lushchak et al., 2021). Thus, the LC is more vulnerable to the effects of ROS (for a review see Evans et al., 2022).

The LC receives afferent connections from the neocortex (Cedarbaum and Aghajanian, 1978; Luppi et al., 1995), prefrontal cortex (PFC) (Arnsten and Goldman-Rakic, 1984; Sesack et al., 1989), amygdala (Cedarbaum and Aghajanian, 1978; Charney et al., 1998), and ventral tegmental area (VTA) (Deutch et al., 1986) among other structures.

Efferent projections have been grouped into three major noradrenergic pathways: **1)** the **cortical (or ascendant) pathway** (Szabadi, 2013), which includes projections to the ventral tegmental area (VTA) (Alvarado et al., 2023; Mejias-Aponte, 2016), SN (Mejias-Aponte, 2016; Rommelfanger and Weinshenker, 2007), amygdala (McCall et al., 2017; Uematsu et al., 2017), hippocampus (Haring and Davis, 1985; Jones and Moore, 1977; Takeuchi et al., 2016), hypothalamus (Giorgi et al., 2021; Schwarz and Luo, 2015), thalamus (Beas et al., 2018; Rodenkirch et al., 2019), basal forebrain (España and Berridge, 2006), PFC and sensory cortices (McBurney-Lin et al., 2019; Schwarz and Luo, 2015; Szabadi, 2013), **2)** the **spinal pathway (or descendent)** which includes brainstem nuclei such as the nervus vagi (Nosaka et al., 1982), sympathetic premotor nuclei (Head et al., 1998; Tavares et al., 1996) and the oculomotor nucleus (Carpenter et al., 1992) as well as various spinal nuclei via **3) cerebellar pathways** (Fu et al., 2011), where it connects to both cerebellar cortex and nuclei (Dietrichs, 1988) and potentiates Purkinje cell spiking (Moises et al., 1981), for a comprehensive review on LC connections see Szabadi and colleagues (Szabadi, 2013).

Via the cortical pathways, the LC-NA system has been shown to be involved in various cognitive processes such as memory (Clewett et al., 2016; Takeuchi et al., 2016), attention (Dahl et al., 2019; Unsworth and Robison, 2017) and sleep (Van Egroo et al., 2022). Via these projections, the LC plays a crucial role in modulating the dopaminergic system. Notably, noradrenergic terminals in cortical regions and the hippocampus have been found to co-release dopamine (DA), indicating a functional overlap (Devoto et al., 2020, 2008, 2005; Kempadoo et al., 2016; Pozzi et al., 1994; Smith and Greene, 2012; Takeuchi et al., 2016). Moreover, the LC projects to the ventral tegmental area (VTA), a key hub of the dopaminergic pathway, and modulates dopamine release in the nucleus accumbens (nACC) and prefrontal cortex (PFC) (Sara, 2009). Additionally, the LC has direct projections to the PFC, which, in turn, sends inhibitory relay signals to the VTA. Reciprocal connections exist between the VTA, PFC, and LC, forming a complex network that allows for bidirectional modulation (Sara, 2009). NA modulation is also implicated in psychiatric disorders such as PTSD (Debiec and LeDoux, 2006), depression (Brunello et al., 2002; Kobayashi et al., 2022; Remy et al., 2005), ADHD (del Campo et al., 2011), schizophrenia (Meisenzahl et al., 2007; Toda and Abi-Dargham, 2007), and substance use disorders (Downs and McElligott, 2022), where alterations in noradrenaline-dopamine signalling play a role.

The descendent pathways have been linked to sympathetic functions such as blood pressure (Anselmo-Franci et al., 1999) and muscle tonus (Kiyashchenko et al., 2001) while the LC cerebellar pathways remain understudied up to date.

Signalling between LC and the projecting areas occur via NA. NA synthesis starts with the amino acid tyrosine, which is converted into dihydroxyphenylalanine (DOPA) and then into DA by the enzymes tyrosine hydroxylase (TH), and DOPA decarboxylase. After its synthesis, DA is transported into noradrenergic neurons, which contain the enzyme dopamine β-hydroxylase (DBH), that converts DA to NA (Molinoff and Axelrod, 1971). The synthesised NA is then stored in presynaptic vesicles and released into the synaptic cleft where it binds to the G-coupled adrenergic receptors (Ars) type β, α1, and α2 with respectively intermediate, higher, and lowest affinity (Molinoff, 1984). The effect of NA depends on the type of receptors expressed on the postsynaptic neurons. Binding to α1 or β adrenergic receptors produces stimulatory effects while binding to α2 adrenergic receptors produces inhibitory effects on cell signalling (Schwarz and Luo, 2015; Szabadi, 2013).

After exerting its modulatory effect, NA is removed from the synaptic cleft by either reuptake via NA transporters or by degradation by the enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) and aldehyde reductase (AR) into several metabolites.

NA is metabolised into normetanephrine (NMN) and 3-methoxy 4 hydroxyphenylglycol aldehyde (MOPEGAL) by COMT and MAO, or into DOPEGAL, 3,4-dihydroxyphenylglycol (DHPG) and subsequently 3-Methoxy-4-hydroxyphenylglycol (MHPG) by MAO, AR and COMT. MHPG, considered as the major metabolite of NA in the brain (Schanberg et al., 1968), is further converted to MOPEGAL via alcohol dehydrogenase (ADH), and into vanillylmandelic acid through aldehyde dehydrogenase (Eisenhofer et al., 2004; Kamal and Lappin, 2022; Molinoff and Axelrod, 1971).

2.1. LC firing modalities

The LC has two firing modes: tonic (persistent) and phasic (short bursts). Animal studies suggest that electric LC stimulation in rats leads to higher NA release when the neurons are stimulated by *phasic* rather than tonic stimulation (e.g., Florin-Lechner et al., 1996). By shifting the balance between these two firing modes (Berridge and Waterhouse, 2003), the LC modulates arousal levels (Aston-Jones and Cohen, 2005; Chen and Sara, 2007, see Section 2) and supports memory encoding (Klukowski and Harley, 1994; Mather et al., 2016; Sara, 2015, 2009, see Section 2). Thalamic alpha wave strength, which has been linked to cortical inhibition and desynchronization as well as selective attention (Jensen and Mazaheri, 2010), have also been linked to shifts between phasic and tonic firing (McCormick, 1989).

Thus, the LC might facilitate information processing overall (Rodenkirch et al., 2019) and in particular the processing of high-priority stimuli over less-prioritised stimuli (Mather et al., 2016). Although differences in LC firing have not yet been systematically analysed in healthy aging and disease, a disturbance, such as increased noradrenergic levels during the early stages of AD (Palmer et al., 1987) and a decline in LC connectivity in healthy aging (Langley et al., 2022), may impair the ability of the LC to modulate downstream targets and functions such as corticothalamic waves and vice versa: As reviewed by Chalermpalanupp and colleagues (Chalermpalanupap et al., 2017), results from a tau pathology rat mouse model suggested that increasing noradrenergic levels later in the disease might alleviate tau-mediated pathology.

2.2. Role in neuroinflammation and neurovascular system

The locus coeruleus-noradrenergic (LC-NA) system plays a major role in modulating neuroinflammation (Evans et al., 2022) and the neurovascular system (Giorgi et al., 2020).

NA released by LC neurons play a role in the inflammatory responses through adrenergic receptors (Feinstein et al., 2002) as it can regulate the expression of proinflammatory cytokines (Flierl et al., 2009; Li et al., 2015), but it can also increase the peripheral inflammatory response (Grisanti et al., 2010; Kavelaars et al., 1997; Spengler et al., 1990). NA also regulates the activity of T cells and microglia (Kahn et al., 1985; O'Neill and Harkin, 2018; Tanaka et al., 2002).

LC-lesioned animal models show neuronal damage, increased microglia and inflammatory response (Bharani et al., 2017; Song et al., 2019a, 2019b) and the anti-inflammatory effects of LC-NA system play also a role in neurodegenerative diseases: direct stimulation of the LC-NA system via vagus nerve stimulation (VNS) reduced both inflammatory activation and a-synuclein accumulation in LC-lesioned rats (Farrand et al., 2017) and In the presence of amyloid pathology, lower NA levels in the LC target areas might impair the microglia in those areas, therefore precluding amyloid to be cleared or surrounded by it (Heneka et al., 2010). Therefore, NA can be an endogenous anti-inflammatory agent (Feinstein et al., 2002) and a loss in LC neurons and consequent alterations of NA signalling could further exacerbate the inflammatory component of AD (Kelly et al., 2019) and PD (Qin et al., 2007). This modulation helps maintain a balanced immune environment in the brain. Moreover, it influences the cerebral blood flow (CBF) via the modulation of the neurovascular unit (NVU), a group of cells that are involved in the mechanism of coupling between energy demand and cerebral blood flow (Iadecola, 2017): in the neurovascular system, LC-NA induces vasoconstriction, resulting in a global reduction of cerebral blood flow (CBF) and redistribution of blood primarily to activated brain regions (Bekar et al., 2012).

Furthermore, the LC-NA plays a significant role in maintaining the homeostasis of the blood-brain barrier (BBB) (Erdő et al., 2017) as it controls the expression of tight junctions (TJs) (Kalinin et al., 2006) and consequently the permeability of the BBB to water and solutes (Thomsen et al., 2017).

3. Cognitive functions

Recently, several reviews on noradrenergic involvement in cognitive function have been published, most notably a review by Gina Poe and colleagues providing a comprehensive overview of LC embryonal development, anatomy and function (Poe et al., 2020). Here we provide a brief overview of recent reviews on LC function and cognition The LC is tightly linked to sleep architecture: Decreases in LC activity (Foote et al., 1980) and noradrenergic levels (Kalen et al., 1989) are linked to the transition from wakefulness to sleep where the LC is virtually silent during REM sleep (Foote et al., 1980). Similarly, increases in LC activity precede unprovoked rousing from sleep (Aston-Jones and Bloom, 1981). Increasing noradrenergic levels pharmacologically shortens REM sleep and prolongs wakefulness across species (De Sarro et al., 1987; Spiegel and DeVos, 1980). Interestingly, LC activity during NREM sleep has also been linked to memory consolidation and sleep spindle activity (Kjaerby et al., 2022; Osorio-Forero et al., 2021). Several afferents to and efferents from sleep promiting regions enable this tight involvement in sleep (Lew et al., 2021; Samuels and Szabadi, 2008; Saper and Fuller, 2017). For comprehensive reviews on the topic see Van Egroo et al. (2022) and Osorio-Forero et al. (2021).

Through its links to the entire neocortex (Szabadi, 2013), the LC has been tightly linked to arousal and attention. As described by the GANE model, the LC is capable of increasing the neuronal activity required for the processing of currently prioritized stimuli while suppressing neuronal activity of other brain regions (Mather et al., 2016). The complex activity of the LC acts to coordinate adaptive neural dynamics as recently reviewed by (Wainstein et al., 2022). Another theory on the LC's involvement in attentional modulation proposes that the LC modulates the magnitude of the cortical alpha wave, which is a measure for disengagement, through a thalamic gating mechanism. This allows for optimal sensory processing (Dahl et al., 2022). Although it has been shown in vitro that the LC is capable of inactivating about 90% of rat midbrain cholinergic neurons (Williams and Reiner, 1993), which also are essential to maintaining attention (Knudsen, 2011), the behavioural consequence of such inactivation is currently unknown. In humans, higher connectivity between the LC and nucleus basalis of Meinert has been linked to more dynamic global shifts in cortical functional connectivity states (Taylor et al., 2022). For a concise review on the noradrenergic-cholinergic interaction see Slater et al. (2022).

Through its dopaminergic (Kempadoo et al., 2016; Takeuchi et al., 2016) and noradrenergic (Guo and Li, 2007; O'Malley et al., 1998) connections to the hippocampus, the LC is shown to be crucial for memory consolidation (Duszkiewicz et al., 2019; Pintus et al., 2018; Takeuchi et al., 2016; Titulaer et al., 2021) and for novelty (Takeuchi et al., 2016). It has been hypothesized that while the LC is important for the processing and consolidation of intense, first-time novel experiences, the VTA is involved in semantic novelty of objects of a known category (Duszkiewicz et al., 2019). It has also suggested that the dopaminergic and noradrenergic system are important for rule-shifting during cognitive tasks (Pajkossy et al., 2018). For a comprehensive overview over noradrenergic projections see Szabadi (2013).

4. Noradrenergic dysfunction in healthy ageing

From an early age on, the LC accumulates tau (Harley et al., 2021) Mounting evidence has shown that high LC "integrity" correlates well with cognitive performance in older age (Bachman et al., 2021; Dahl et al., 2020; Parent et al., 2022), which is not surprising giving its vast cortical connections (Szabadi, 2013), its crucial role in cognition (Poe et al., 2020), and it its protective role against neuroinflammation (Giorgi et al., 2020; McNamee et al., 2010).

4.1. Age-related differences in functional and structural LC connectivity

The functional and structural connectivity of the NA system in aging

and AD has recently gained more interest as a means for understanding the role of the LC-NA system in aging and age-related cognitive decline.

Liebe and colleagues (Liebe et al., 2022) investigated both the structural and functional connectivity of the LC using 7 T MRI and found that brain areas with higher structural connection to the LC also showed increased resting state functional connectivity to the LC. These include the thalamus, ventral diencephalon, basal ganglia, motor cortex, cerebellum, amygdala, nucleus accumbens, and temporal brain areas including the EC, presubiculum, and hippocampus (Liebe et al., 2022). However, this link diminishes with age. Interestingly, connectivity also was linked to subjective anxiety and alertness (Liebe et al., 2022).

High-resolution diffusion tensor imaging-based tractography (DTI) showed that compared to younger adults, older adults showed reduced integrity of the central tegmental tract (CTT), which branches into the thalamus and rostral LC (Langley et al., 2022). Reduced integrity of the CTT also correlated with verbal memory delayed recall scores, measured by Rey- Auditory Verbal Learning Test (RAVLT). Porat and colleagues (Porat et al., 2022) also found decreased FA in the ascending noradrenergic bundle in older adults compared to younger adults (Porat et al., 2022). It should be emphasised that both studies found an increase in LC FA in older compared with younger adults (Langley et al., 2022; Porat et al., 2022). These results suggest that the integrity of the LC and its projections measured using DTI, are independently affected by ageing.

Cross-sectional differences in high-resolution resting state functional connectivity (rfMRI) in a cohort of 19–74 years of age followed a nonlinear correlation between left LC and most areas of frontal, temporal, parietal regions and the nucleus basalis of Meyner (MBN) (Jacobs et al., 2018): they showed an increase in connectivity until 25 years of age followed by a continuous decrease until 60 years of age and a subsequent increase at old ages (Jacobs et al., 2018). In contrast to this, Song and colleagues (Song et al., 2021) showed an inverted U-shape functional connectivity between the LC and visual, sensory and auditory cortices and a U-shape correlation to frontal areas. The differences may be explicable by a 10x larger sample size used in the Song study.

Moreover, it was shown that cross-sectionally, older adults showed stronger functional connectivity between LC and visual processing regions (Lee et al., 2020). Additionally, cross-sectionally, in older adults, there is a decrease in LC-frontoparietal functional connectivity (Lee et al., 2018) and a decrease in functional connectivity between the LC and areas linked to the salience network (Lee et al., 2020) while the functional activity between the salience and the frontoparietal network increases (Lee et al., 2020). However, no differences in LC-parahippocampal functional connectivity were found (Lee et al., 2018). These results suggest that in older adults attentional selectivity, which relies on frontoparietal regions is reduced, while stimuli perception is intact.

It remains to be determined whether these differences underlie differences in LC MRI signal, driven in part by age-related differences in LC NM (Keren et al., 2015), and not accounting for additional physiological measures, such as the extent of tau pathology or differential imaging techniques and parameters across studies (Liu et al., 2017).

4.2. The role of tau and amyloid on LC function

Tau is a small soluble protein with a flexible structure that helps with microtubule stabilisation (Avila et al., 2016). Accumulation of misfolded tau tangles, one hallmark feature of AD pathology, may occur in the LC already at an early stage in life.

As reviewed by Harley and colleagues (Harley et al., 2021), even at adolescence, most brains have pre-tangles, a precursor to tau tangles, in the LC, that might spread to other regions such as the transentorhinal (TEC) and/or entorhinal cortices (EC) (Harley et al., 2021). These AT8-positive, misfolded pre-tangle tau seeds spreading from the LC might be the origin of tau pathology in AD (Braak et al., 2011; Stratmann et al., 2016).

This has also been shown in animals, where tau pathology in AD mice models spread from LC to the forebrain and other regions affected by tau pathology early in human AD thus potentially recapitulating tau human pathology spread (Kang et al., 2019). However, another group has theorised that tau pathology originates in the EC and then spreads to the LC (Kaufman et al., 2018).

Memory symptoms typically appear when tau tangles reach the hippocampus, temporal insular and association cortex at Braak stage III-IV in AD (Therriault et al., 2022), which corresponds to tau spread at very old age in healthy ageing.

Aß plaques are the other hallmark feature of AD. At nanomolar concentration, Aß might regulate cellular activation (Turner et al., 2003). However, when accumulated, Aß plaques hinder normal cell functioning and cause hyperactivity (for review see Hector and Brouillette, 2021). In the absence of Aβ, episodic-memory performance is best explained by tau burden in the areas defined by Braak staging as I-III, the TER/EC, suggesting a link between tau and cognitive decline (Maass et al., 2018).

In a group composed of healthy older adults, patients with MCI and AD patients, Jacobs and colleagues (Jacobs et al., 2021a) showed a negative correlation between LC positron emission tomography (PET) signal intensity, a measure of LC integrity and tau deposition in the EC as well as the medial and lateral temporal regions and medial parietal-frontal regions. For healthy participants, this correlation remained only in the EC. In a subset with elevated Aβ levels, LC integrity was associated with greater tau pathology outside the temporal lobe, extra medial-temporal lobe, lateral temporal and medial-lateral parietal and frontal regions. The autopsy data confirmed these results as LC tau tangle density correlated with Braak stages and in the context of elevated Aβ burden, also with steeper retrospective memory decline, supporting the role of LC in tau pathology progression (Jacobs et al., 2021a).

In the context of Aβ burden, Ciampa and colleagues (Ciampa et al., 2022) showed that higher LC catecholamine synthesis capacity, measured with PET in older adults, was related to lower tau in the temporal lobe.

Moreover, adjusting for Aß status, catecholamine synthesis in the LC but not in the raphe, midbrain, and striatum, was associated with lower rates of tau accumulation over time and with better-than-expected memory performance adjusting for individual's tau burden (Ciampa et al., 2022).

Low LC catecholamine synthesis is also related to vulnerability to affective dysregulation, measured as high neuroticism and depression, and tau PET burden in the amygdala (Parent et al., 2022). Interestingly, low conscientiousness and high neuroticism are indirectly related to increased tau burden in the amygdala, via their association with low LC catecholamine synthesis capacity (Parent et al., 2022). Therefore LC vulnerability could be involved in affective dysregulation and neuroticism.

These results are strong indicators for the LC and the brainstem as among the regions of earliest tau accumulation, if not the earliest, showing a prevalent involvement of tau in LC dysregulation.

4.3. LC integrity is linked to cognitive performance in older age

As explained in Section 1, the LC contains high levels of NM, which permits the visualisation of the LC using NM-sensitive MRI (for a review see Betts et al., 2019b). Normalised NM-sensitive MRI contrast values inside the LC have become a popular method to assess the "integrity" of the LC in vivo (Betts et al., 2019b). It has been shown that LC MRI contrast (consistent with an increase in neuromelanin) increases up until about 60 years of age and then decreases thereafter (Liu et al., 2019; Zecca et al., 2004). Several studies have also now shown, LC MRI contrast is related to cognitive function. In older participants, a positive association has been found between LC MRI contrast and episodic memory performance (Dahl et al., 2022; Hämmerer et al., 2018), as well as a delayed memory score (RAVLT) (Dahl et al., 2019). Overall LC

integrity has been linked to a cognition score composed by education, occupational attainment and verbal IQ, which was particularly pronounced in the rostral subsection, and reading intelligence score (Clewett et al., 2016). In particular, the rostral subsection has also been linked to delayed memory performance (Dahl et al., 2019) and response inhibition (Tomassini et al., 2022) as well as attention, delayed memory performance and processing speed (Calarco et al., 2022). In addition, LC integrity has also been associated with cortical thickness (Bachman et al., 2021).

In older age, significant variability in LC integrity has been observed (Betts et al., 2019a) and age-related differences in LC have not been consistently observed in cognitively intact older adults in the range of 60–80 (Betts et al., 2019b, 2017; Giorgi et al., 2021).

It remains to be determined whether these differences in the MRI signal of the LCs are due in part to age-related differences in LC neuromelanin (Keren et al., 2015; Zucca et al., 2006), although additional physiological measures such as the extent of tau pathology or different imaging techniques and parameters are not considered in the various studies (Liu et al., 2017).

4.4. The effect on neuroinflammation and neurovascular system

Ageing and age-related disorders are characterized by elevated pro-inflammatory markers (Franceschi et al., 2000), which contribute to the progression of neuropathology. Systemic inflammation further exacerbates this process by triggering the activation of microglia, which infiltrate the brain through the blood-brain barrier (Bettcher and Kramer, 2014; Heneka et al., 2015; Perry, 2010; Perry et al., 2007). The presence of pro-inflammatory cytokines in older adults has been associated with cognitive impairment, highlighting the detrimental effects of inflammation on brain function (Cunningham et al., 2009; Cunningham and Hennessy, 2015; Franceschi and Campisi, 2014; Holmes, 2013; Qin et al., 2007; Simen et al., 2011).

Moreover, the degeneration of noradrenergic neurons in the LC and the natural process compromise the integrity of the blood-brain barrier (BBB) (Kalinin et al., 2006; Luissint et al., 2012). This compromised BBB amplifies the effects of systemic inflammation, allowing inflammatory substances to infiltrate the brain more easily. In aged rats with LC-NA lesions, the inflammatory response is intensified, and there are notable alterations in brain-derived neurotrophic factor (BDNF) levels, showing the role of the LC/NA system in modulating neuroinflammation (Bharani et al., 2017).

Additionally, microglial dysfunction, combined with the compromised BBB (Hussain et al., 2021) and reduced tissue perfusion in aging, plays a significant role in impairing synaptic plasticity (Erdő et al., 2017), that is an important mechanism for memory formation which becomes impaired in aging and neurodegenerative diseases (Blau et al., 2012).

5. The noradrenergic system and neurodegenerative diseases

5.1. Alzheimer's disease

AD is a neurodegenerative disease which constitutes the vast majority of the cases of dementia in the older population (Evans et al., 2022) with a prevalence in Europe of around 1%, an incidence that is expected to triple by 2050 (Prince et al., 2015). AD can be considered a proteinopathy as it is defined by the presence of amyloid plaques (Braak and Braak, 1991) and tau aggregates called neurofibrillary tangles (NFTs) (Goedert, 1993).

NA plays a complex role in the pathogenesis and progression of AD, encompassing both protective and contributory effects. NA exerts its protective effect by destabilising Aβ protofibril, impeding their assembly into insoluble plaques (Zou et al., 2019). Moreover, it might have a protective effect against oxidative stress caused by amyloid, by stimulating CAMP production through b-adrenergic receptors, resulting in the activation of the nerve growth factor (NGF) or brain-derived neurotrophic factor (BDNF) (Counts and Mufson, 2010) and regulates inflammation through microglia modulation (Mori et al., 2002; Sugama and Kakinuma, 2021).

However, it might also be implicated in the further progression of AD pathology as compensatory mechanism for LC neuronal loss during aging and AD, like changes in the receptors and increased excitability of remaining NA neurons might be implicated in the aetiology or further progression of Aß pathology.

NA signalling is implicated in amyloid toxic effects through α2-adrenergic receptors. Amyloid activated the glycogen synthase kinase (GSK), enzyme responsible for tau phosphorylation, by binding on an allosteric site of α2-adrenergic receptor, therefore redirecting NA signalling. The activation of GSK can be facilitated by concurrent binding of amyloid on the allosteric site and NA on the main site of the receptor. In fact, when this happens, amyloid can exert its effect at a concentration as low as 1% of what is typically required for amyloid to exert the effect alone.

The increase of NA turnover and thus the production of the toxic NA metabolite 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL) (Weinshenker, 2018), might play an important role in tau LC-derived toxicity (Burke et al., 1999). DOPEGAL is the product of NA metabolism by the enzyme monoamine oxidase A (MAO-A) (see Section 1. for an overview on NA biosynthesis). It can be considered toxic as, in contrast to NE, it promotes tau aggregation and propagation (Kang et al., 2022, 2019) and induces tau-mediated neuronal cell apoptosis (Burke et al., 1998). Mice lacking DBH, the protein that converts dopamine to NA, and therefore the ability to produce NA, showed reduced tau pathology. Models in which the asparagine endopeptidase (AEP), which is necessary for tau cleavage, was knocked out, showed attenuated LC neuronal degeneration in the presence of DOPEGAL (Kang et al., 2020). A further link between AD and tau, mediated by DOPEGAL has been shown in mice and AD brain tissue. Apoe4 allele induced DOPEGAL tau-mediated toxicity, while Apoe3 prevents it by binding tau and blocking the cleavage into misfolded tau (Kang et al., 2021). Tau neurotoxicity has also been shown to lead to hippocampal atrophy and cognitive deficits (Kang et al., 2021). Together these studies show that NA, but specifically its metabolite DOPEGAL, have a toxic neuronal effect, which is mediated by tau (for a review Kang et al., 2020). DOPEGAL is then processed to MHPG, the major NA metabolites in the brain (Burke et al., 1999), which has been also associated with compensatory mechanisms of LC surviving neurons and AD progression (Hoogendijk et al., 1995; Nakamura and Sakaguchi, 1990). Higher NA turnover (MHPG:NA ratio) inversely correlated with LC neuronal cells (Hoogendijk et al., 1995). Higher CSF levels of MHPG were also associated with greater tau and amyloid concentration (Riphagen et al., 2021) in the CSF and with lower cortical thickness in mild stages of AD (van Hooren et al., 2021). Finally, the presence of MHPG facilitates tau spreading in AD mice model (Koppel et al., 2019) suggesting a parallel with the DOPEGAL action of neuronal apoptosis and pathology enhancement in the presence of tau pathology.

In the presence of amyloid pathology, lower NA levels in the LC target areas might impair the microglia in those areas, therefore precluding amyloid to be cleared or surrounded by it (Heneka et al., 2010). Therefore, NA can be an endogenous anti-inflammatory agent (Feinstein et al., 2002) and a loss in LC neurons and consequent alterations of NA signalling could further exacerbate the inflammatory component of AD pathology (Kelly et al., 2019).

5.2. The LC-NA system in the context of AD

The loss of LC neurons in AD occurs at early stages (Betts et al., 2019a, 2019b; Braak and Braak, 1991), is most pronounced in the rostral and middle LC portion (Beardmore et al., 2021; Betts et al., 2019a; Theofilas et al., 2017; Tomlinson et al., 1981) and appears to correlate with disease duration (Zarow et al., 2003) and disease severity (Cassidy et al., 2022; Olivieri et al., 2019). In fact, a post-mortem analysis showed

a decrease in LC volume by circa 8% for every Braak stage (Theofilas et al., 2017). Reduced LC volume during AD is also supported by in vivo studies showing reduced LC MRI contrast in AD compared to healthy controls (Betts et al., 2019a; Cassidy et al., 2022; Li et al., 2022; Olivieri et al., 2019).

Animal studies suggest that the NA system might interact with Aβ pathology. Catecholamines, including NA showed a dose-dependent inhibitory effect on the aggregation of amyloid fibrils potentially by destabilising amyloid protofibrils in vitro (Huong et al., 2010). In rats, the LC might protect against amyloid pathology as lesioning of the LC led to an increase in amyloid and inflammation compared to non-lesioned controls (Kelly et al., 2019). Conversely, decreased NA levels might impair amyloid clearance thus further propagating amyloid accumulation (Dobarro et al., 2013; Ni et al., 2006).

As LC integrity and NA production are affected in AD, these results support the idea that the loss of LC/NA-mediated protection in AD may enhance the risk of amyloid aggregation in the brain, as the anti-amyloid aggregatory and inflammatory effect of NA might be impaired due to its reduced levels.

The NA system might also link tau and amyloid pathology in AD: Wang and colleagues demonstrated in vitro and in an AD mouse model that amyloid binds hyperactive alpha 2 receptors on an allosteric site activating a tau phosphorylation cascade (Wang, 2020).

Tau pathology is related to LC integrity and functioning: lower LC neuron count is associated with higher plasma tau levels (Murray et al., 2022) and LC integrity is shown to be decreased in tau-positive participants (Cassidy et al., 2022) and inversely correlated to tau in the EC in healthy participants (Jacobs et al., 2021a). As tau induces neuronal hyperexcitability (Crimins et al., 2012; Rudy et al., 2015), this might also be hypothesised to be the case for LC neurons (Weinshenker, 2018), facilitating the spread of tau through its axonal pathways, as tau is capable of trans-synaptic propagation (Kang et al., 2022, 2019). However, Liu and colleagues (Liu et al., 2021) did not observe an increase in LC hyperactivity in AD compared to healthy controls with respect to fluorodeoxyglucose (FDG) PET, a tracer used to image metabolic activity (Liu et al., 2021).

Increased activity of the remaining LC neurons has also been suggested by studies reporting increased NA levels in AD, hypothesising this increased activation as the cause of increased NA production and therefore NA levels (Raskind, 1984; Raskind et al., 1997, 1999), however, this has not been seen consistently in the literature. In fact, a recent meta-analysis focusing on NA and MHPG data in AD found a trend towards lower levels of NA in CSF markers and significantly increased MHPG CSF markers in participants with AD dementia compared to healthy controls (Lancini et al., 2023).

The discrepancies between studies on NA levels in participants with AD may have several causes, such as the use of different diagnosis criteria, methods of severity calculation, as well as small sample sizes that may limit statistical power. Furthermore, although the meta-analysis did not detect any differences between studies caused by confounding variables, inter- and intra-laboratory differences may have played a role: differences in sample storage, handling and equipment could have influenced the results, despite the use of similar or identical protocols.

As discussed by Lancini and colleagues (Lancini et al., 2023), in the presence of amyloid and tau, NA metabolite MHPG seems to be a more sensitive measure of AD symptoms characterisation, therefore altered metabolism, more than production might play a substantial role in AD.

Higher CSF levels of MHPG, are associated with higher levels of p-tau (Jacobs et al., 2021b; Riphagen et al., 2021) and higher amyloid-β 42 under high levels of inflammation in CSF (Riphagen et al., 2021) and lower cortical thickness in mild stages of AD (van Hooren et al., 2021) in humans. Additionally, a structural equation model (SEM) analysis showed a strong link between neuropsychiatric symptoms and MHPG and p-tau, suggesting that noradrenergic dysfunction is coupled to AD pathology and clinical symptoms (Jacobs et al., 2021b). Also, the increase in the noradrenergic metabolite DOPEGAL has been shown to promote tau aggregation and propagation in mice models (Kang et al., 2022, 2019) and to induce tau-mediated neuronal cell apoptosis in AD postmortem human brain tissue (Burke et al., 1999, 1998, 1997).

5.3. LC neurodegeneration and AD symptoms

In line with accumulating evidence of NA being intricately linked with AD pathology, links between an LC-NA system and cognitive and clinical symptoms of AD dementia are increasingly reported. General cognition as measured by the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) and memory performance has been shown to be positively correlated to LC integrity (Li et al., 2022) and CSF noradrenergic levels (Elrod et al., 1997). Also, CSF MHPG is correlated to memory deficits in participants with Subjective cognitive decline (SCD), MCI and AD (Jacobs et al., 2021b).

LC neuronal loss results in the dysregulation of circadian rhythms early in the disease process (Van Egroo et al., 2019) and in fact sleep impairment is another symptom that occurs early in AD and can also precede cognitive symptoms (Ehrenberg et al., 2018; for a review see Van Egroo et al., 2022). Critically, as studies in animal models showed an intact sleep architecture is required to clear neurotoxic waste products from the brain, such as Aß (Xie et al., 2013), and that sleep loss affected tau (Barthélemy et al., 2020), sleep disruption might accelerate the propagation of AD pathology starting a vicious cycle (Tekieh et al., 2022).

5.4. The effect on neuroinflammation and neurovascular system

In AD, degeneration to the LC-NA may lead to the breakdown of the blood-brain barrier (BBB) and microglia activation, impairing amyloid clearance, exacerbating amyloid accumulation, promoting neuroinflammation, and causing neuronal death. Decreased levels of NA disrupt the regulation of pro-inflammatory cytokines, leading to further LC cell loss creating a negative feedback loop (I et al., 2014).

In-vivo, neuroinflammation can be assessed with PET tracers that bind mitochondrial translocator protein (TSPO), that is overexpressed in cells with activated microglia (Werry et al., 2019). In AD participants, TSPO tracer binding was found to be increased (Hamelin et al., 2016; Kreisl et al., 2016), indicating inflammation and microglial activation (Werry et al., 2019) and to be correlated with amyloid pathology (Fan et al., 2015) and severity of disease (Kreisl et al., 2013). Controls and MCI did not show elevated TSPO showing that inflammation occurs after the conversion to MCI into AD (Kreisl et al., 2013). This finding suggests that elevated TSPO expression may reflect a more pronounced LC-NA dysregulation and could therefore serve as possible marker of disease progression in longitudinal studies, despite to this date no study correlated TSPO measure with LC markers (Giorgi et al., 2020). In line with the PET study from Fan and colleagues (Fan et al., 2015), postmortem studies have also demonstrated the presence of activated microglia surrounding amyloid plaques in AD brains (Taipa et al., 2018).

NA also plays a crucial role in clearing Aβ by microglia and suppressing Aβ-induced cytokine production, where a reduction in NA levels may contribute to insufficient suppression of pro-inflammatory mediators, contributing to AD progression (Heneka et al., 2010; Kalinin et al., 2007; Kong et al., 2010). Experiments in mice have demonstrated that NA β-adrenergic stimulation protects cortical and LC cells from Aβ-induced cell loss (Evans et al., 2020). Moreover, Both 5xFAD mice (Kalinin et al., 2012) and P301S tau mice (Chalermpalanupap et al., 2018) show microglial and astrocyte activation in the LC compared to wild-type mice. In mice, NA maintains the clearance of Aβ via microglia and suppresses Aβ-induced cytokine production as β-adrenergic stimulation by NA protects cortical and LC cells from Aβ-induced cell loss (Evans et al., 2020). These studies collectively suggest that a reduction in NA levels may contribute to the progression of AD and Aβ accumulation, making NA a potential target for

pharmacological treatment.

5.5. Parkinson's disease

PD - similar to AD - is one of the most common neurodegenerative diseases worldwide, with an incidence rate for women and men of respectively 37.55 and 61.21 per 100,000 person-years (Hirsch et al., 2016). The main hallmark of the disease is a significant reduction of dopaminergic cells in the substantia nigra pars compacta (SNpc) and the presence of α-synuclein aggregates, called Lewy Bodies (Dickson et al., 2008). Recently, the role of NA in the development and progression of idiopathic PD has drawn increased attention (Espay et al., 2014; Paredes-Rodriguez et al., 2020).

Cellular accumulation of misfolded alpha-synuclein is one of the hallmark features of PD (Atik et al., 2016). Spectroscopic and calorimetric experiments suggest that NA stabilizes alpha-synuclein in intermediate states into stable, cytotoxic species (Singh and Bhat, 2019) thus possibly contributing to the generation of alpha-synuclein. Some theories propose that alpha-synuclein misfolds in the gut and then spreads to the brain (Berg et al., 2021; Braak et al., 2003; Engelender and Isacson, 2017). A recent mouse model paper suggests a protective noradrenergic mechanism against this spread: acute chemogenic NA-depletion in PD Mouse models was linked to enteric inflammation and increased enteric alpha-synuclein levels 2 weeks later and Substantia Nigra neuronal degeneration as well as constipation and motor deficits 3–5 months later (Song et al., 2023). It has been suggested that already in healthy elderly, higher LC neuronal density might be protective against deleterious effects of brainstem Lewy body numbers on cognition (Wilson et al., 2013). Another PD mouse model suggests that the noradrenergic system might also be protective against dopaminergic neuronal depletion despite increasing alpha-synuclein aggregation and microgliosis (Jovanovic et al., 2022).

In humans, the LC might be beneficial against PD pathology even before symptom onset: already in healthy subjects, higher LC neuronal density diminishes the association between brainstem Lewy body numbers (Wilson et al., 2013).

5.6. The LC-NA system in the context of PD

Comparative studies of subcortical nuclei found a high loss of LC neurons in idiopathic PD, which is greater than the neuronal loss observed in the nucleus basalis of Meynert and SNpc (Huynh et al., 2021; Zarow et al., 2003). LC volume is found to be reduced (Hwang et al., 2022), together with NA and MHPG CSF levels (Lancini et al., 2023), and NM-sensitive MRI indicates subregion-specific degeneration of the caudal and middle sub-portion of the LC (Doppler et al., 2021; Madelung et al., 2022; Ye et al., 2022). Other studies showed an overall decrease in LC MRI contrast (Schwarz et al., 2017; Wang et al., 2018). A meta-analysis on white matter degeneration in PD found no change (Wei et al., 2021; Zhang and Burock, 2020) or even improved white matter integrity (Taylor et al., 2018) in LC tracts compared to healthy volunteers suggesting they may be unaffected in PD.

Several hypotheses such as the Braak model, and recently also the brain-gut hypothesis (Borghammer and Van Den Berge, 2019; Horsager et al., 2020) integrate the LC into early- to mid-stages of PD. However, due to the heterogeneity of the disease (Farrow et al., 2022), a parsimonious model describing the whole breadth of variability is still lacking.

As recently reviewed by Lancini and colleagues (Lancini et al., 2023), NA transporter density, measured with PET NA transporter (NET) tracer, is decreased in PD suggesting a functional decline to the noradrenergic system including LC terminals (Doppler et al., 2021) besides structural degeneration. Additionally, LC- specific α-synuclein expressing mouse models showed degeneration of noradrenergic neurons (Henrich et al., 2018), changes in the abundance and integrity of the immune system (Butkovich et al., 2018; Henrich et al., 2018) and Parkinsonian symptoms (Henrich et al., 2018).

Hyperactivation of remaining noradrenergic neurons in LC occurs in rats after lesioning the nigrostriatal pathway (Wang et al., 2009), an effect that was also in line with in vitro results and in a mouse model of PD (Matschke et al., 2022). Interestingly, in mice stimulation of the noradrenergic system protects against neuronal depletion but does not prevent alpha-synuclein aggregation and immune system degeneration, suggesting an immune system-independent mechanism (Jovanovic et al., 2022). However, early LC degeneration is also linked to non-motor symptoms such as anxiety and depression, that are typical in early stages of the disease (Bremner et al., 1996; Remy et al., 2005). In LC-lesioned animal models of PD, neuronal damage leads to increased microglia and greater inflammatory response to alpha-synuclein (Bharani et al., 2017; Song et al., 2019b). Conversely, indirect stimulation of the LC-NA system via invasive vagus nerve stimulation (iVNS) in rats, led to reduced inflammation as well as a-synuclein accumulation and increased locomotion in LC-lesioned rats (Farrand et al., 2020, 2017). Considering the role that chronic inflammation plays in the pathogenesis and further progression of PD (Qin et al., 2007), these results indicate that LC-NA system dysregulation may be involved in this process. To our knowledge, in humans, there have been no correlations between noradrenergic levels in PD and inflammation markers, which would be an important step for future studies.

5.7. LC degeneration correlates with PD symptoms

NM-sensitive MRI correlates with a number of different PD symptoms. Rostral LC integrity has been linked to motor symptoms ipsilaterally (Ye et al., 2022) and lower LC contrast has also been linked to self-evaluation of motor accuracy (Hezemans et al., 2022). Several memory tests such as MoCA and Berlin model of intelligence structure (BIS) scores (Ye et al., 2022), as well as short-term verbal and numerical memory performance (Prasuhn et al., 2021), have been shown to be associated with higher LC MRI contrast. LC integrity in PD is also related to cognition: scores on episodic and short-term memory as well as lexical fluency (Prasuhn et al., 2021), response inhibition (Ye et al., 2021) and trail-making test (TMT) results (Li et al., 2019) all correlate with LC integrity. Additionally, left caudal and whole LC integrity have been linked to orthostatic blood pressure (Madelung et al., 2022) and sleep disruption (Doppler et al., 2021): sleep cyclic alternative patterns (CAP) are diminished in PD and the rate of CAP was shown to be correlated with noradrenergic PET binding only in patients but not in healthy control participants while the duration of CAP subphases is altered in PD patients as well. Finally, increased NA transporter binding and decreased DA transporter binding in PD were linked to increased anxiety (Carey et al., 2021).

5.8. The effect on neuroinflammation and neurovascular system

In PD, LC-NA degeneration contributes to increased neuroinflammation through reactive microglia and oxidative stress (Giorgi et al., 2020). Animal studies have demonstrated that lesioning of the LC leads to heightened activation of microglial cells (af Bjerkén et al., 2019) and inflammation in SN dopaminergic cells and when combined with systemic inflammation, LC degeneration exacerbates degeneration in the nigrostriatal pathway, hippocampus, and motor cortex in PD models (Bharani et al., 2017; Herrera et al., 2000; Song et al., 2019b, 2019a).

The presence of inflammation in dopaminergic areas in PD has been shown in vivo, as PET studies using tracers of microglia-activation showed increased binding in basal ganglia, substantia nigra, and fronto-temporal cortex in individuals with PD (Edison et al., 2013; Gerhard et al., 2006; Iannaccone et al., 2013) and individuals diagnosed with PD and dementia (PDD) displayed a significantly more extensive microglia activation pattern compared to individuals with PD (Edison et al., 2013). This result provides further evidence for the involvement of neuroinflammatory responses in exacerbating the disease despite to this

date no study correlated this measure with LC markers (Giorgi et al., 2020).

In PD rat models, indirect stimulation of LC-NA activity through vagus nerve stimulation has shown potential in reducing neuroinflammation and protecting dopaminergic cells (Farrand et al., 2020), whilst administration of NA in dopaminergic neurons reduces the production of ROS and rate of neurodegeneration (Butkovich et al., 2018).

Animal studies using models of PD have provided further support for the role of LC degeneration in neuroinflammation and oxidative stress (see Giorgi et al., 2020 for a review). The reverse influence of inflammation has also been investigated: lipopolysaccharide-induced inflammation in DSP-4-induced LC lesion mice exacerbated degeneration to the nigrostriatal pathway, hippocampus, and motor cortex and increased microglial activation (Bharani et al., 2017; Song et al., 2019a, 2019b).

6. Methods to investigate the LC-NA system

The currently most established methods to investigate the structure and function of the LC-NA system include structural and functional magnetic resonance (sMRI and fMRI), PET, electroencephalography (EEG) (for a review see Nieuwenhuis et al., 2011, 2005), and pupillometry (for a review see Viglione et al., 2023).

Sasaki and colleagues demonstrated the possibility of measuring LC cell density using a neuromelanin-sensitive MRI protocol (Sasaki et al., 2006). In that study, brain images from healthy people and people with PD were acquired with a T1-weighted Turbo Spin Echo (TSE) protocol, a neuromelanin-sensitive sequence. In healthy adults, the contrast intensity in the LC resulted in high signal intensity in areas that were consistent with the anatomical location of the two NM-rich regions LC and SN. The anatomical precision of this technique has been further confirmed in postmortem tissue demonstrating colocalization between MRI signal and NM-containing neurons (Cassidy et al., 2019; Keren et al., 2015). Different neuromelanin-sensitive MRI sequences have since then been used as a non-invasive 'integrity' measure for simultaneous assessment of the LC (for a review see Betts et al., 2019b; Galgani et al., 2020; Liu et al., 2017; Sulzer et al., 2018) and SN (for a review see Sulzer et al., 2018). However, to date, the mechanisms underlying MRI contrast in the LC remain unclear (see Betts et al., 2019b for a comprehensive review). LC tracts have been studied in vivo (Liebe et al., 2022) using magnetic resonance tractography (Jbabdi and Johansen-Berg, 2011), a method that investigates brain white matter tracts and through which biologically accurate measures of fibre connectivity can be obtained (Smith et al., 2015). DTI can be significantly affected by several factors, namely low-resolution MRI, crossing-fibres, noise, and distortions. These influences introduce complexities and potential limitations, as they may impede the accurate delineation of the LC. Furthermore, in the context of neurodegenerative disorders such as AD and PD, the challenges associated with DTI LC measures become more pronounced, due to the potential reduction in LC's structural integrity, which adds an additional layer of complexity to the assessment process (Zhang et al., 2020; Zhang and Burock, 2020).

Changes in brain activation during tasks are approximated using functional fMRI, a sequence that measures the changes in blood-oxygen levels in the brain that occur in response to neuronal activity (Buxton et al., 2004). These images are registered on structural MRI images to allow a correct identification of the area that was active during the task, which is especially important in the case of LC activity (Turker et al., 2021). However, investigating LC activity with fMRI presents challenges due to its size, location, and inter-individual variability.

The LC shows significant inter-individual variability, particularly in the context of aging (Liu et al., 2019), making it challenging to establish a consistent region of interest (ROI) across individuals (Turker et al., 2021). Moreover, limited resolution of standard MRI techniques can lead to partial volume effects, where LC voxels contain non-LC tissue (Cassidy et al., 2022). The proximity of the LC to large sources of physiological noise, such as the CSF and the 4th ventricle, means that spatial smoothing during preprocessing may introduce additional physiological noise (Turker et al., 2021). Taken together, variations in voxel size and smoothing kernel across studies contribute to between-study variability, as evident from the heterogeneity of these measures between studies (Liu et al., 2017). Recently, Yi and colleagues proposed an optimised spatial transformation pipeline for the LC, along with a method to quantify the precision of spatial transformations, that could be of help to increase future comparability across studies (Yi et al., 2023). Finally, the BOLD signal of the LC can be influenced by physiological noise, potentially attenuating the fMRI response (Liu et al., 2017).

PET imaging uses radiotracers that specifically bind to sites and molecules of interest, thus allowing for an assessment of their spatial distribution in the brain. Of particular interest for the LC-NA system is the MeNER tracer (Schou et al., 2003), that was successfully used to quantify NA transporters levels in healthy and PD (García-Lorenzo et al., 2013; Sommerauer et al., 2018). Both AD and PD are multisystemic diseases, therefore it is informative to also use PET tracers that allow visualisation of brain pathology, neuroinflammation, cholinergic and monoamine neurotransmitter systems, synaptic density as well as metabolism (for a review on AD see Bao et al., 2021; Gutiérrez et al., 2022, for a review on PD see Prange et al., 2022). PET tau measures of LC are currently not feasible as PET tau tracer binds to neuromelanin rather than specifically binding to tau protein leading (off-target binding) (Jacobs et al., 2021a; Lee et al., 2018; Marquié et al., 2015).

The firing activity of the LC-NA system can be detected during wake using EEG, as the event-related wave P3b, the parietal subcomponent of the P3 reflects phasic activity of the LC-NA system (Nieuwenhuis et al., 2005; Polich, 2007). LC-NA modulation of sleep (Van Egroo et al., 2022) can be assessed by concurrent polysomnography and PET Mener in aging and disease, as sleep instability measured as cyclic alternating pattern (CAP) had been shown to correlate with NA transporter density in brainstem in PD (Doppler et al., 2021).

Pupillometry is also used as an indirect measure for LC activation (Joshi et al., 2016; Szabadi, 2013) as the fluctuations in the firing rate of LC neurons closely parallel changes in pupil diameter (Aston-Jones and Cohen, 2005; Gilzenrat et al., 2010; Joshi et al., 2016).

Levels of NA and its metabolites in blood (Katunina et al., 2023; Teunissen et al., 2022) and CSF (David and Malhotra, 2022; Lotankar et al., 2017) have also been used and are under constant development. Despite being the closest measure to the central nervous system (CNS), CSF biomarkers still require specific protocols and a deeper understanding of their dynamics in order to be considered reliable measurements of central NA (Lancini et al., 2023).

7. The locus coeruleus as a therapeutic target

7.1. Drug interventions targeting the noradrenergic system

Numerous noradrenergic drugs have been tested to improve cognition in neurodegenerative diseases:

Methylphenidate is a noradrenergic and dopaminergic reuptake inhibitor that is mainly used to treat Attention deficit hyperactivity disorder (ADHD). In a randomised trial, methylphenidate improved apathy but not neuropsychiatric symptoms in participants with AD, compared to placebo (Mintzer et al., 2021) while in participants with MCI, it improved global cognitive scores and memory after 3 days of daily intake (Press et al., 2021). In PD mouse models, methylphenidate improved sleep and daily functioning (Oakes et al., 2021). A recent review showed that methylphenidate improved cognition in a wide variety of conditions associated with elderly: it improved depressive symptoms, accelerated post-stroke recovery and improved outcome measures after stroke (Swartzwelder and Galanos, 2016).

Atomoxetine, a presynaptic NET inhibitor also used in ADHD treatment, did not improve cognition in a 5-week trial with participants with

MCI but was associated with an increase in noradrenergic plasma and CSF levels and a reduction in CSF tau and pTau 181 (Levey et al., 2022). It is also associated with altered protein levels of pathophysiology related to synaptic and metabolism, glial immunity and inflammation-related proteins as well as an increase in the Brain-Derived Neurotrophic Factor (BDNF) (Levey et al., 2022). Finally, atomoxetine as a treatment for MCI has been shown to be associated with an increase in fMRI functional connectivity between the insula and the hippocampus (Levey et al., 2022). In PD, atomoxetine plasma concentration correlated with fluency in an animal category and letter fluency test (Borchert et al., 2019) and improved inhibition in a stop-signal task (Borchert et al., 2019; O'Callaghan et al., 2021).

Clonidine, an alpha-2 receptor agonist commonly used against hypertonia, has been shown in PD to improve movement initiation in a stop signal task and to modulate the activity of the dorsomedial prefrontal and anterior cingulate cortices, which are linked to the inhibitory network (Criaud et al., 2022).

A meta-analysis of 19 randomised controlled trials that performed interventions in AD patients using noradrenergic drugs found a positive effect on the MMSE and apathy but no improvement on attention (David et al., 2022).

As noradrenergic drugs have shown beneficial effects in improving LC-related affected functions in both healthy participants and participants with diseases, they are a promising tool for potential early or even later-stage intervention.

7.2. Targeting the noradrenergic system via the vagus nerve

Transcutaneous vagus nerve stimulation (taVNS) offers the possibility of electrical non-invasive stimulation of the cymba conchae of the external ear, which has nerve fibre connections to the vagus nerve (Peuker and Filler, 2002) and is thought to stimulate the LC-NE system via the nucleus tractus solitarius (NTS) (Butt et al., 2020; Ruffoli et al., 2011). IVNS has already been shown to increase the firing rate of LC neurons (Hulsey et al., 2017) to stimulus-specific cortical plasticity in the motor cortex (Hulsey et al., 2019) and to a reduction in inflammatory markers (for a review see Ludwig et al., 2021). Additionally, iVNS led to an increase in NA release in brain regions pathologically affected early in AD and PD, such as the hippocampus, basolateral amygdala and cortical target areas (Hassert et al., 2004; Hulsey et al., 2019; Manta et al., 2013). This is consistent with the results of electrical tonic stimulation of the LC, which resulted in higher NA release and increased activation of the PFC (Florin-Lechner et al., 1996).

As taVNS is less invasive than iVNS, it is a more promising therapy avenue: results combining taVNS and fMRI have demonstrated the efficacy of taVNS to effectively increase activity in the NTS and LC as well as in LC-NE projection areas such as the amygdala and hippocampus (Sclocco et al., 2019; Yakunina et al., 2017). Meanwhile, taVNS is also being investigated as a potential therapy to improve cognition in early AD (for a review see Vargas-Caballero et al., 2022) as well as motor and nonmotor symptoms in PD (Cakmak et al., 2017; Zaehle and Krauel, 2021). Further taVNS studies should take into account interindividual differences in the integrity of the stimulated LC-NE system to accurately validate the benefit of taVNS for an individual (Ludwig et al., 2021).

7.3. Targeting the noradrenergic system via environmental enrichment

Environmental enrichment is the concept of providing a cognitively or physically stimulating and challenging environment for humans and animals, which improves cognition and overall brain health: it has been shown that mice in an enriched environment display increased cortical thickness in sensory areas (Engineer et al., 2004) and perform better in cognitive tasks (Yuan et al., 2012). The number of years of education (Lövdén et al., 2020), a large social circle (Smith et al., 2018) and a cognitively demanding occupation (Stebbins et al., 2022), all considered to be an enriched environment, be beneficial for cognitive performance potentially from early childhood onwards (Schoentgen et al., 2020).

The LC seems to be an important link between environmental enrichment and cognitive reserve: in mice, exposure to different odours caused neuronal growth in murine olfactory bulbs (Veyrac et al., 2009). However, this was blocked by the administration of ß-antagonists during the environmental enrichment period (Veyrac et al., 2009). As moderate LC activity is crucial for attention (Aston-Jones and Cohen, 2005) and as LC activation also has been linked to anti-inflammatory function (McNamee et al., 2010) and BDNF secretion (Ivy et al., 2003), frequent LC activation would conceptually be beneficial for overall brain health (for reviews on the importance of NA in healthy aging see Mather, 2021; Mather and Harley, 2016). Results of the effect of cognitive training on delaying dementia have been conflicting (Sharp and Gatz, 2011; Wilson et al., 2013) and more research is required in that field.

An increasing number of studies have investigating whether physical exercise can be beneficial in aging and neurodegeneration.

In humans, it has been shown across age groups that exercise training across a variety of tasks such as strength training (Ağgön et al., 2020), very light exercise (Kuwamizu et al., 2022), cycling and heavy running (Strobel et al., 1997) can increase blood plasma noradrenergic levels (Ağgön et al., 2020; Strobel et al., 1997) and dilate pupil size, that is a proxy of LC activity (Kuwamizu et al., 2022). The increase in noradrenergic levels during physical exercise correlates with better cognitive performance: during light cycling for 1 min, the increased level of the noradrenergic metabolite MHPG of healthy young males from the rest to exercise condition correlates with their faster response time in a mildly mentally challenging 4-choice reaction time task (McMorris et al., 2008). However, this effect could have also been explained by differences in exercise intensity (McMorris, 2003).

Recently, it has been shown in animal studies that exercise and cognitive training through environmental enrichment can also increase levels of NA (Naka et al., 2002) improve cognition (Bindra et al., 2021) and may in part be mediated by ß-adrenergic receptors (Ebrahimi et al., 2010). In Male Wistar rat model, it was shown that a pharmacological decrease in hippocampal noradrenergic levels with timolol, β-adrenergic receptor antagonist, decreased long-term object recognition memory persistence while intrahippocampal NE injection had the opposite effect (da Silva de Vargas et al., 2017). The same group furthermore showed that in this rat model, object recognition memory consolidation was accompanied by an increase in NE and BDNF (Mello-Carpes et al., 2016). They furthermore showed that the increase in BDNF was eliminated if the increase in NE was eliminated suggesting a causal relationship between both increases. Additionally, In Male Sprague-Dawley rats, the beneficial effects of exercise on cognition were shown to be partially dependent on NA as giving the noradrenergic blocker propranolol immediately after training abolished the increase in hippocampal BDNF mRNA levels (Ivy et al., 2003).

Physical activity decreases the risk for dementia, although the type of exercise and optimal frequency is still to be defined (for a review see Iso-Markku et al., 2022; López-Ortiz et al., 2023). In mice, the beneficial effect of environmental enrichment on protection against AD has been linked to the activation of ß-adrenergic receptors (Li et al., 2013).

8. Future outlook

It has been shown that LC degeneration is strongly linked to age and pathology-related cognitive and physical decline, and may even precede it. This might be expressed by a decline in LC-related functions such as decreased muscle tonus, decreased working memory, sleeping problems and hypertension.

As in healthy older adults, direct links between LC activity and task performance are lacking, future human studies in both healthy young and older adults should link differences in CSF NA levels or LC fMRI activity tasks to differences in task performance to have a more direct link between LC and other outcome measures such as task performance.

More emphasis should be put on LC tract integrity as it might drive

the link between LC integrity and cognition. However, this is more challenging methodologically: the LC is a small structure, DTI requires more advanced systems than structural MRI and LC white matter tracts can be difficult to differentiate from surrounding tracts. Additionally, LC tractography is not as well established as LC integrity measurements. Therefore, future research is needed to first establish standardised methods for measuring LC tract integrity and to improve the accuracy and reliability of this outcome measure.

The hypothesis that degeneration of the LC might accelerate the progression of AD dementia, which in turn might further impair the LC, is often complicated by the heterogeneity of data in cross-sectional designs. However, longitudinal studies such as the DELCODE study (Jessen et al., 2018), which collect structural measures and CSF data from the same participants every year, or the longitudinal Harvard Aging Brain Study (HABS) (Dagley et al., 2017), will allow matching changes in individual differences in LC integrity with individual changes in task performance. Also studies that include longitudinal cognitive measures and post-mortem data like the Religious Orders Study (ROS) and Aging Project (MAP) (Bennett et al., 2018), allow to compare measures obtained in vivo.

The LC-NA system can be targeted through exercise, pharmacologically and potentially via the vagus nerve in humans and has shown promise as a target for healthy aging, AD and PD. However, large-scale trials are lacking. Also, to maximise the effect, a combination of these methods should be attempted.

Given the reciprocal relationship between degenerated LC and inflammation, more research should focus on the effects and combination of noradrenergic drugs with anti-inflammatory agents. This bidirectional interaction highlights the importance of targeting inflammation as a potential strategy to mitigate LC degeneration and subsequently delay the aging process.

A viable yet often overlooked target for ADis MHPG, which is closely related to tau, amyloid, inflammation, cortical thickness (Jacobs et al., 2021b; Riphagen et al., 2021; van Hooren et al., 2021) and, through its link with p-tau, to neuropsychiatric symptoms (Jacobs et al., 2021b).

9. Conclusion

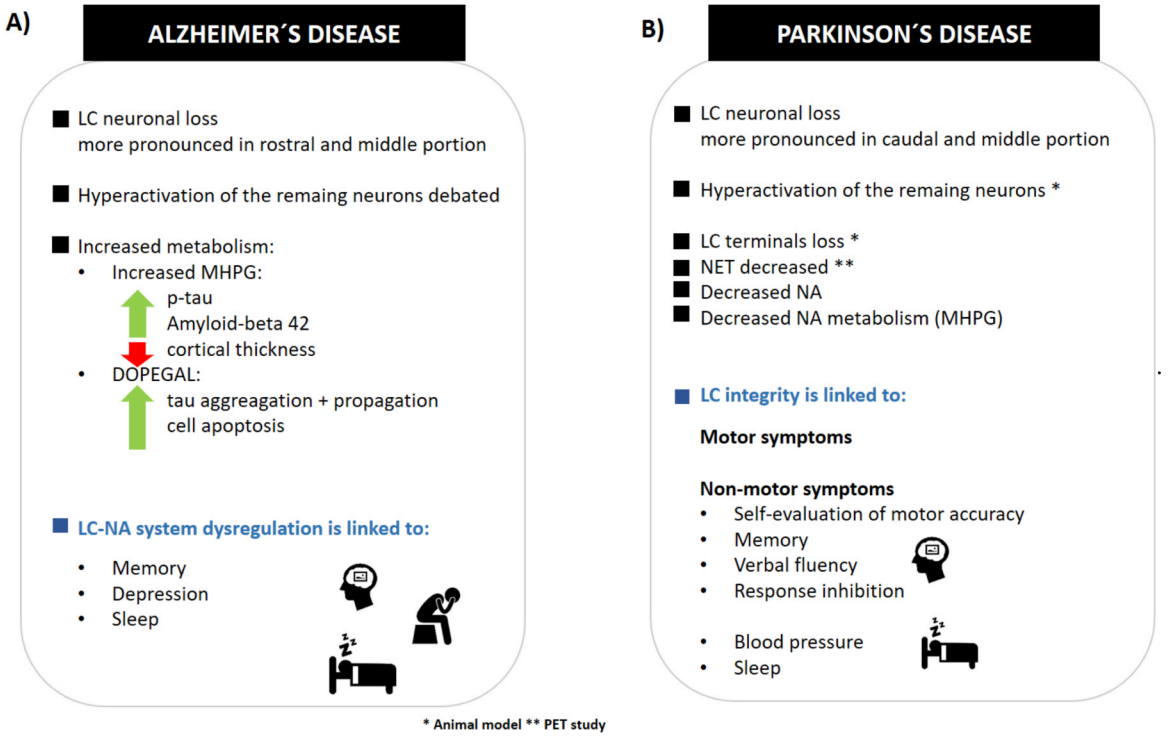
Recent developments in AD research have shown that the LC-NA system might be exacerbating pathology in a vicious cycle with NA metabolites promoting tau aggregation and tau promoting LC hyperactivity causing higher levels of NE metabolites. Additionally, a decreased protection from AD pathology due to decreased immune protection caused by LC degeneration might further exacerbate the disease (Box 1a). However, NA also seems to be protective against amyloid aggregation indicating a multifaceted LC involvement in AD.

In PD (Box 1b), the LC-NA system has been found to be involved in early-to-mid stages, as it is linked to early non-motor symptoms such as anxiety and depression, and its degeneration may accelerate PD progression.

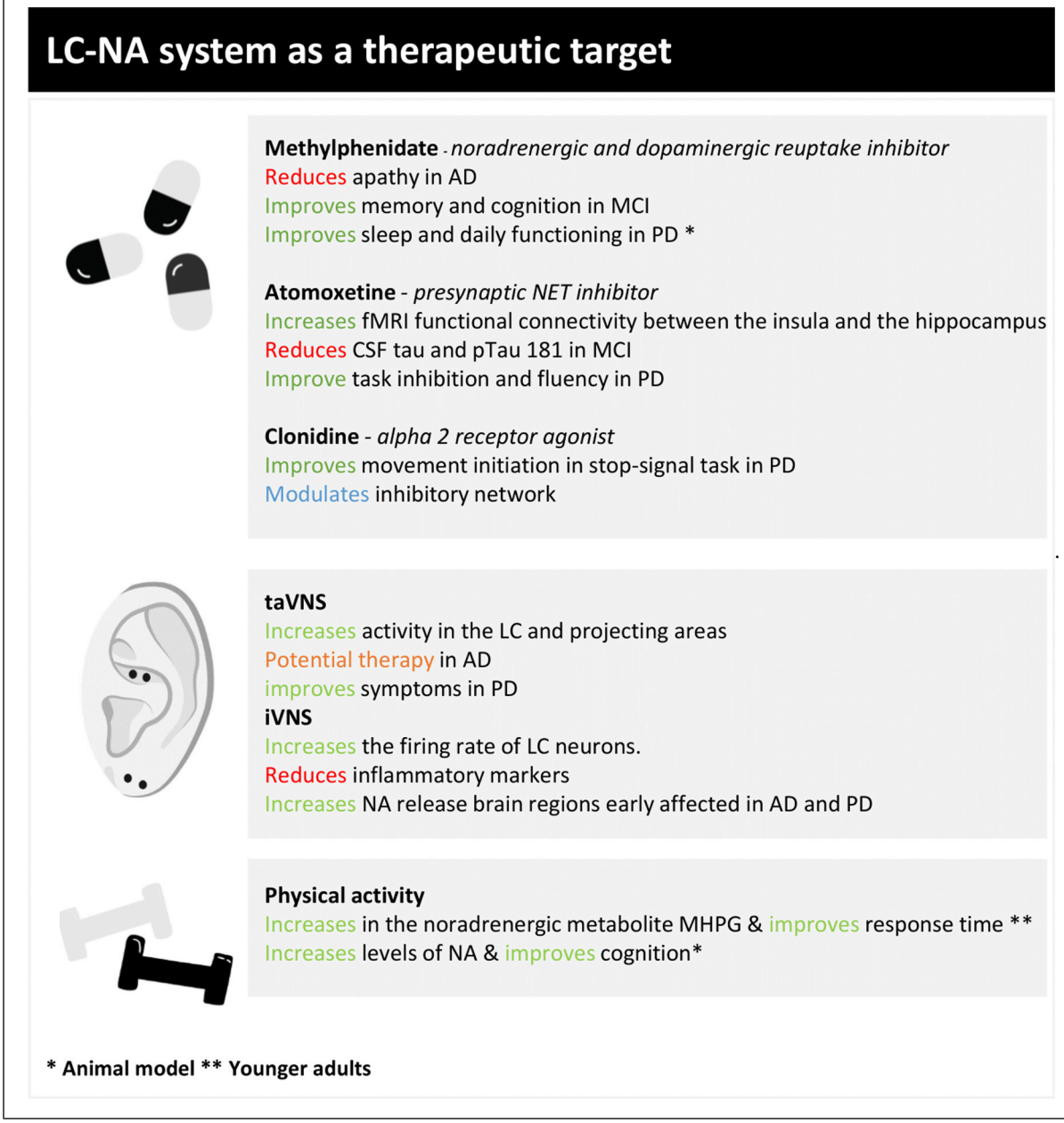
LC degeneration leads to neuroinflammation in aging and neurodegenerative through shared increased microglia mechanisms but also disease-specific mechanisms. In AD, LC degeneration contributes to increased microglial reactivity and disruption of the BBB), thereby accelerating the accumulation of Aß and tau proteins. On the other hand, in PD, LC degeneration primarily leads to increased microglial reactivity and oxidative damage. These mechanisms highlight the multifaceted role of LC degeneration in promoting neuroinflammation and the pathological processes associated with AD and PD.

Finally, multiple noradrenergic drugs, vagus nerve stimulation and physical exercise have all been shown to be promising therapeutic targets (Box 2) by potentially boosting noradrenergic function in aging and neurodegenerative disease thus alleviating some of their debilitating symptoms.

Box 1
Involvement of the LC-NA system in (A) AD and (B) PD.



Box 2
LC-NA as a therapeutic target.



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Competing interests

E.D has received payments for his role and works as consultant for Roche, Biogen, RoxHealth and expert testimony for UCL Consultancy, served at scientific advisory boards for EdoN Initiative and Ebsen Alzheimers Center (no payment) and Roche (personal financial support), and is a co-founder of the digital health start-up Neotiv.

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Data Availability

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

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