The involvement of the Locus Coeruleus (LC)– noradrenaline (NA) system in sleep regulation and its association with Alzheimer's disease.

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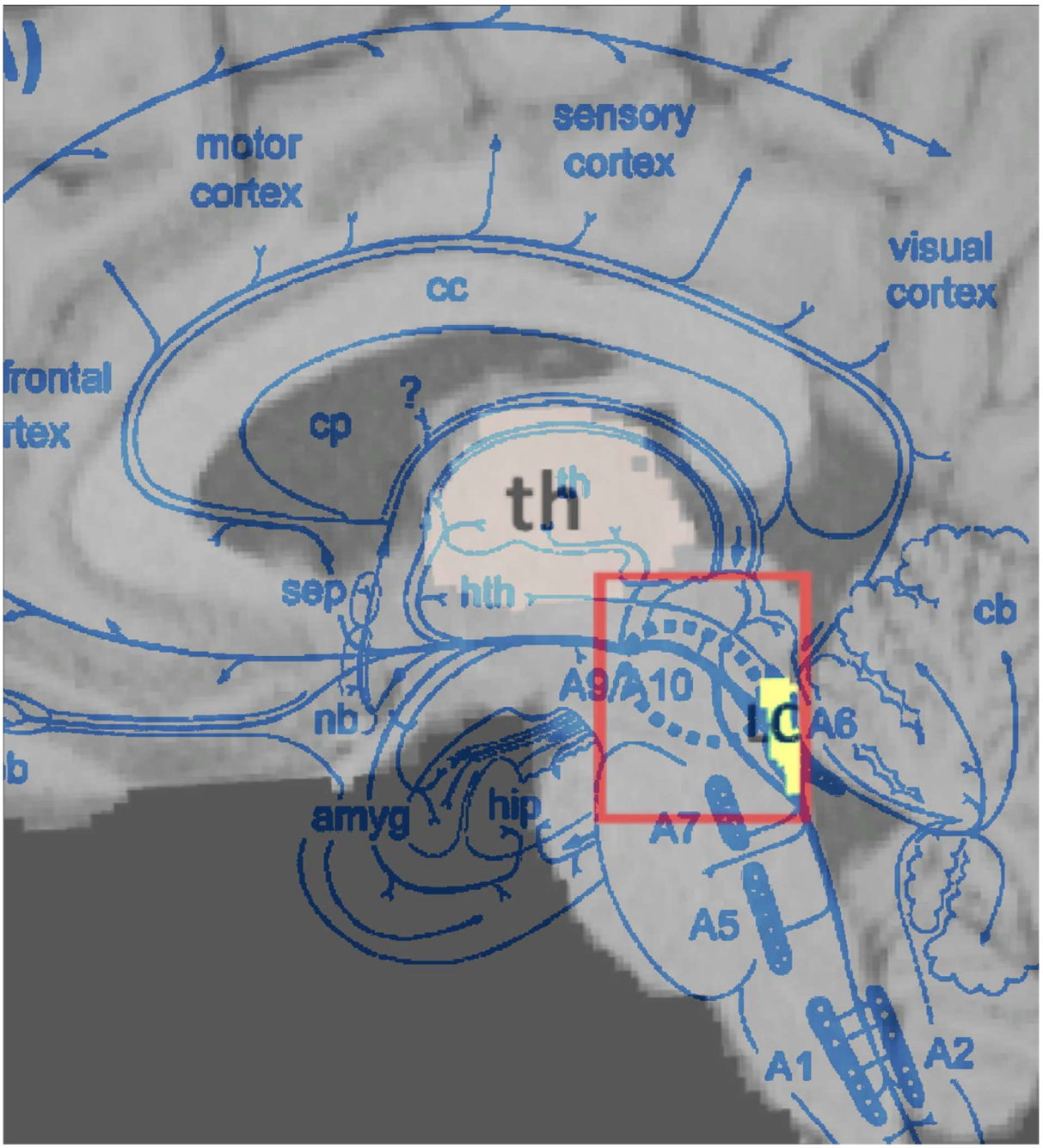

Figure 1. Anatomical diagram showing the location of LC, neuronal projections, and relevant brain structures, superimposed on the MRI scan of the sagittal section of the brain. **[**Adapted from Sun et al. (2020)]

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Abstract

Reported Locus Coeruleus (LC) cell death in Alzheimer's disease (AD) is extensive. However, the connection between LC-NA and AD was largely overlooked in the research. The LC, being the first structure in the brain to express AD associated neuropathology, is sensitive to neurodegenerative processes, suggesting a significant role in early AD development. Disturbances in the LC-NA system, along with sleep impairment, can trigger a cascade of neuroinflammatory processes, leading to chronic low-grade inflammation, blood brain barrier (BBB) disruption, and eventual AD pathogenesis. This is further worsened by the impairment in the glymphatic system - a key pathway for the removal of neurotoxic waste like β-amyloid during sleep - due to sleep-wake dysregulation. Generally, sleep disturbances are often exacerbated by LC-NA dysregulation, and are associated with elevated Aβ or tau levels, thereby intensifying AD pathogenesis.

This review discusses potential therapeutic interventions targeting the LC-NA system, including the enhancement of REM/NREM sleep and drugs like AChE inhibitors and orexin antagonists. Notably, the use of PDE4 inhibitors presents a promising strategy to address both AD and sleep pathologies. Ultimately, investigating the intricate interplay between the LC-NA system, sleep disruption, and neuroinflammatory processes is imperative to deepen the understanding of AD.

1. Introduction

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder generally characterized by a decline in global cognition and progressive memory deterioration [1]. AD has been the leading cause of dementia, and is emerging as one of the most deadly and severe neuropathologies of current age, with the estimated occurrence of worldwide dementia to triple by 2050 [2–4]. AD progresses in stages from mild cognitive impairments (MCI) to advanced dementia, which can take years to develop [5]. Nonetheless, a pre-clinical AD, which is a stage described by the presence of early pathological changes in the brain without noticeable cognitive impairments, is detectable by positron emission tomography (PET) about 15 years prior to the development of cognitive symptoms of AD [5]. It is therefore imperative to identify predictors of AD in the early stages in order to prevent irreversible structural and functional brain damage.

Pathologically, the main features of AD are the accumulation of β-amyloid (Aβ) plaques and tau neurofibrillary tangles (NFTs) in neocortical and subcortical regions of the brain [6]. Derived from amyloid precursor protein (APP) via proteolytic cleavage, Aβ contributes to aggregation of Aβ plaque, with variants such as $A\beta_{1-42}$ and $A\beta_{1-43}$, exhibiting higher tendencies of aggregation compared to $A\beta_{1-43}$ [7,8]. Even under healthy ongoing processes, Aβ is continuously produced, with some Aβ deposition observed even in cognitively normal individuals [9,10]. However, over time Aβ protein sheets accumulate to form Aβ plaques [11], which are detectable in pre-clinical AD stage through imaging and cerebrospinal fluid (CSF) analysis [12]. Said Aβ plaque formation has been associated with synaptic dysfunction, neuronal loss, cognitive impairment, and tau aggregation into intracellular NFTs [13,14].

NFTs are comprised of highly phosphorylated tau proteins [6]. Tau is a microtubule-associated protein (MAP) primarily found in neuronal axons [15], and it plays vital role in supporting microtubule integrity, alongside being involved in synaptic structure and function [16–18]. Under pathological conditions, tau proteins become hyperphosphorylated, causing dissociation from microtubules, ultimately leading to NFT formation [19,20]. Accumulation of NFTs and tau phosphorylation, as shown by correlational PET scans, are closely linked with impairment in neuronal function in AD [6]. These neuropathological hallmarks primarily manifest in the entorhinal cortex and hippocampus, these being regions critical for cognitive function [21].

AD can be classified genetically into two forms: familial and sporadic [22]. Familial form is linked with the specific genetic markers, namely the APP, presenilin (PSEN) 1, and PSEN 2 genes [23]. In particular, the processing of APP is enhanced by PSEN 1 and 2, leading to the formation of toxic forms of Aβ [24]. The identified mutations in abovementioned genes were shown to contribute to altered Aβ production in familial AD, which can lead to Aβ accumulation and the subsequent accumulation of NFTs [25]. Therefore, these findings support the amyloid cascade hypothesis, underlining the importance amyloid pathology and its associated neurotoxic effects in AD [13,25].

Although the mechanisms of Aβ accumulation and NFT formation in AD provide an insight in understanding the pathology, the existing hypotheses underlying AD development are inconclusive, with precise pathogenic processes remaining unclear. However, sleep disturbance has been a focal subject of the AD pathology for a substantial time and can potentially provide a deeper understanding of AD pathogenesis [26,27].

Categorically, Aβ plaques and NFTs are typically observed in the brain regions such as the locus coeruleus, hypothalamus, and the cortical layers, these being critical for modulation of the sleep wake cycle [28]. In longitudinal meta-analysis studies it has been established that sleep irregularities predict the development of AD-linked dementia [17]. Changes of sleep parameters provided by polysomnography (PSG) studies observed in preclinical AD supports the hypothesis of a bidirectional relation between sleep and AD [29,30]. Remarkably, most of the nuclei responsible for the sleep-wake regulation are affected by the AD neuropathology before the onset of cognitive impairments [31]. Locus coeruleus (LC)-noradrenaline (NA) system is a major part of the crucial sleep-wake circuitry [32], which can provide a novel understanding of the relational link between AD and sleep.

Therefore, this review aims to provide a comprehensive overview of LC-NA system and its significance for AD in the context of sleep-wake regulation. It will attempt to find and relate LC-NA activity to the processes behind Aβ clearance in order establish the link between LC-NA system and AD pathogenesis. Ultimately, the objective of this review is to synthesize current research and explore the role of neuroinflammation and immunity, as well as to strive towards a better understanding of the complex mechanisms underlying AD.

2. Locus coeruleus (LC)-noradrenaline (NA) system: neuroanatomy and function

2.1. LC structure and anatomy

Locus coeruleus, also known as 'blue spot' due to the presence of neuromelanin granules within its structure, is a nucleus comprised of a dense cluster of neurons which serves as the main source of NA for the central nervous system (CNS) [33,34]. LC is located bilaterally in the brainstem right beneath the cerebellum, specifically in the rostral pontine tegmentum. It extends from the level of the inferior colliculus to the motor nucleus of the trigeminal nerve [33,34]. By having extensive networks of ramified axons that diffuse globally in the neuroaxis, LC mediates the release of NA into hippocampus,

amygdala, thalamus, and neocortex [35]. The release of NA to the CNS by LC is carried out by the efferent projections, which are distinguished into two ascending fibre systems – dorsal noradrenergic bundle and the rostral limb of the dorsal periventricular pathway [34].

There is strong evidence from the recent studies supporting the idea that the LC projections are organized in a modular design [35–37]. This implies that the LC channels are separated, potentially allowing for distinct pathways of NA action [38]. Furthermore, the LC allows for the release of NA in a selective fashion, specific to different regions it projects to, thus allowing for different effects in corresponding target areas [35,38].

In contrast, integration of LC efferent input, which concerns the afferents of LC, is less well known [33]. However, there have been light and electron microscopy immunocytochemical studies on the neuronal processes of LC extending outside the nucleus proper, or the LC 'core' [39]. It was thus indicated that the dendrites of LC neurons extend into two pericoerulear zones (peri-LC) where they receive extensive non-noradrenergic input, for example GABAergic [39]. This shows that peri-LC dendrites serve as important centres for integration of signals in the LC. Additionally, GABAergic neurons of peri-LC were found to play a local regulatory role of LC-NA cell activity [40,41]. Subsequent findings unveiled that the LC core receives signals from medullary nuclei, regions of brainstem and forebrain. Inputs that innervate peri-LC GABAergic neurons were found to be partially distinct from those that directly target the LC-NA neurons [35,41,42]. This emphasizes the structural complexity that LC anatomy possesses, highlighted by the signalling not only limited to NA, but also the involvement of GABA in the peri-LC.

Consequently, varied sources of inputs can elicit distinct effects on the output of LC-NA neurons, both through direct and indirect pathways, by selectively targeting either the LC core or the peri-LC [43]. In the end, further investigation on the structural connectivity of the afferent neurons with LC core and peri-LC networks is needed for an improved understanding of the functional component of LC. A better examination into the LC structure and anatomy would deepen the insight into the LC-NA's relationship with the sleep-cycle, the associated sleep pathology, and the emergence of AD.

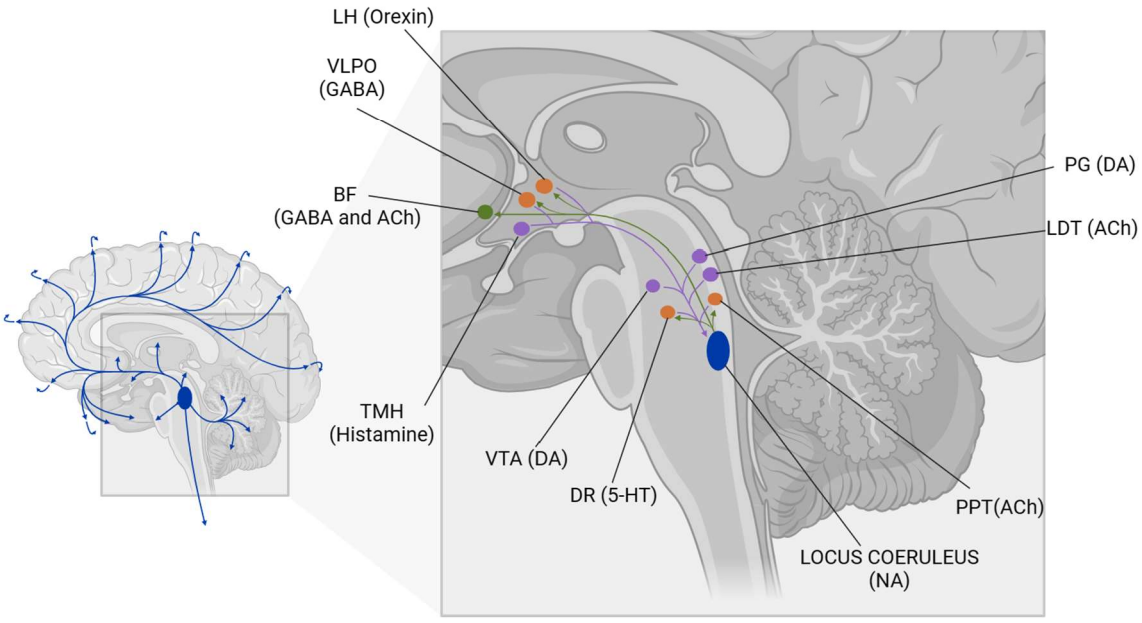

Figure 2. Efferent and afferent anatomy of locus coeruleus (LC). Noradrenergic projections of LC in the brain which cover hypothalamus, amygdala, thalamus, and neocortex. (left). Interconnectivity of LC with other sleep-wake centers in the brain (right). 5-HT – serotonin; Ach – acetylcholine; BF – basal forebrain; DA – dopamine; DR – dorsal raphe; LC – locus coeruleus; LDT – laterodorsal tegmentum; LH – lateral hypothalamus; NE – norepinephrine; PG – periaqueductal grey matter; PPT – pediponculopontine tegmentum; TMN – tuberomammaliary nucleus; VLPO – ventrolateral preoptic area; VTA – ventral tegmental area. [Adapted from Van Egroo et al. (2022)]

2.2. Noradrenaline as a neurotransmitter and its role in the central nervous system

The release of NA within a specific neural pathway relies upon the presence and characteristics of α and β-adrenergic receptors on pre- and postsynaptic terminals [33]. The nine receptor subtypes identified, α1A, α1B, α1D, α2A, α2B, α2C, β1, β2, and β3, exhibit unique distribution patterns, levels of sensitivity to NA, and modes of actions within the networks in which they are interwoven [33]. Both distinct and overlapping effects on cell signalling can be observed, in which α1 and β serve an excitatory function, and α2 inhibitory [33]. Overall, LC-NA is primarily involved in neuromodulation of core

behavioural states, involving the control of wakefulness/arousal, and state-dependent cognitive processes [44,45]. Ultimately, recent electrophysiological and lesion studies have highlighted the role of LC in waking, orienting reflex, cognitive flexibility, sensory gating, goal-directed activity, analgesia, pain and stress responses, fear conditioning, and fear extinction learning [36]. This illustrates the multitude of cognitive processes that LC-NA mediates, many of which are heavily involved in sleep cycle or affected by AD.

NA as a neurotransmitter has a wide array of effects that translate into alterations in the response properties of sensory neurons of various sensory systems. Particularly, NA influences the receptive-field properties of visual cortical neurons [46,47], odour detection and discrimination thresholds in the olfactory bulb [48], frequency tuning plasticity in the auditory cortex [49], auditory perception [50], and performance in visually guided tasks [51]. Notably, the modulatory effects of LC-NA activation follow an inverted–U function, with optimal effects occurring at intermediate NA concentrations – a relationship described as the Yerkes-Dodson law [52,53]. The action of NA is different depending on the receptor subtype. That is, α1 receptors are utilized for strengthening of sensory neuronal responses at moderate concentrations, whereas α2 receptors are used for degrading signal processing at higher concentrations, as demonstrated by in vitro studies [54]. For instance, through the activation of α-adrenoreceptors NA enhances the response of the dorsal lateral geniculate nucleus upon receiving visual stimuli [55]. Furthermore, NA contributes to cortical plasticity by selectively modifying the frequency tuning curves of auditory cortex neurons when paired with specific tone frequencies [49]. These changes are observed in thalamic and cortical sensory regions, and include changes in the magnitude [49,52,55–58] and timing of stimulus evoked discharges [59,60]. Therefore, wakefulness and enhanced neuronal responsiveness is regulated by cholinergic and noradrenergic systems, which inhibit thalamocortical rhythms by modulating specialized potassium currents in thalamic and cortical neurons, thereby promoting an excitatory state necessary for cognitive processes [57]. In such way, NA is a central neurotransmitter not only necessary for activation and maintenance of cognitive states, but is also a critical component of sleep physiology. Therefore, mechanism of action of NA can shed light on the neurodegenerative processes, such as AD.

LC-NA system, being part of the reticular formation, is comprised of the ascending and descending pathways [61]. The ascending pathways is heavily involved in the arousal and sleep regulation, and therefore will be the focal subject in this review. Anatomically, the ascending arousal system consists of the pedunculopontine (PPT), laterodorsal tegmental (LDT) nuclei, the raphe nucleus, and the ventral tegmental area (VTA). These nuclei release acetylcholine (ACh), serotonin (5-HT), and dopamine (DA), respectively. By working in conjunction with wakefulness-promoting systems of the basal forebrain (ACh), the histamine-orexin axis in hypothalamus, and the fast action neurotransmitters (glutamate and GABA), the sedative and sleep-promoting effects of GABAergic and galaninergic neurons in preoptic area, melanin concentrating hormone (MCH) of the hypothalamus, and the GABAergic neurons in the parafacial zone is thus counteracted, leading to homeostatic regulation of sleep-wake cycle [32]. The coordinated balancing of these neuronal systems is required for the healthy brain function and dysregulation of such can be descriptive of a neurodegeneration process.

2.3. Function of the LC-NA system in sleep-wake regulation

As shown by neuronal retrograde tracing studies [62], LC-NA neurons are indeed modular, which was additionally supported by the viral-genetic tracing [35]. Thus, the corresponding target areas of LC-NA efferent action in the sleep-wake circuitry are cholinergic and GABAergic neurons of the basal forebrain, GABAergic neurons of the ventrolateral preoptic area (VLPO) in the anterior hypothalamus, orexinergic neurons of the lateral hypothalamus, serotonergic neurons of the dorsal raphe, and cholinergic neurons of the PPT nucleus [31,32,63]. These neuronal circuits play a critical role in sleep-wake regulation.

In addition, the afferents of LC-NA integrate non-noradrenergic inputs from orexinergic, GABAergic, histaminergic, dopaminergic, serotonergic, and cholinergic neurons [31,32,63]. This represents an array of various signals that are processed in the LC. Prominently, the presence of GABAergic neurons in the peri-LC [41] has been shown to play an inhibiting role in local regulation of tonic and phasic activity of LC-NA in sleep. Tonic activity refers to a baseline level of neuronal firing and is generally associated with non-rapid eye movement (NREM) sleep due to lower neuronal activity. Whereas phasic activity refers to bursts of neuronal firing occurring in a rhythmic manner, which is commonly associated with rapid eye movement (REM) sleep due to increased neuronal activity [64]

LC activity is timed to release NA during NREM sleep memory processing, coinciding with the peaks of slow oscillations, which contributes to the synaptic potentiation and safeguarding of neural circuits [65]. Conversely, synaptic downscaling is represented by LC-NA silence prior to NREM spindles and REM memory processing [66–68]. Hence, disruption of LC-NA activity during these sleep stages can indeed impair memory consolidation [69,70], which is a common denominator of AD. In conditions such as PTSD, insomnia, opioid withdrawal and pre-clinical AD, an overactive LC is observed, which is contributory to emotional and hippocampal memory deficits [71,72], while the decline of LC-NA activity in late-stage AD could impair NA delivery to the forebrain synapses, leading to dementia [73]. Therefore, the modular organization of LC-NA make it an important information integration centre essential for modulation of sleep and wakefulness. These functions are adversely impacted by AD symptomatology.

3. Role of sleep in LC-NA system and Alzheimer’s disease

3.1. Overview of sleep architecture

Sleep is a complex electrophysiological process necessary for homeostasis maintenance. Understanding sleep architecture, the structure and pattern of sleep cycles, is crucial when exploring neurodegenerative conditions, such as AD. Electrophysiology (EEG) recordings distinguish between distinct patterns of brain activity. For instance, REM sleep is associated with Beta (15-40 Hz) and Theta (4-7 Hz) waves. Beta waves are linked with wakefulness as can be described by the increased activity in the limbic system and visual cortex. Meanwhile, Theta waves are linked with active dreaming experience. Also called paradoxical sleep, REM sleep is hence canonically essential for memory consolidation [74].

On the other hand, NREM stages can be further distinguished into stages: NREM 1, 2, and 3. NREM 1 is marked by Theta waves, NREM 2 by sleep spindles (12-15 Hz) and K-complexes (slow waves), and NREM 3 by Delta waves (0.5-4 Hz). In EEG recordings of the initial stages of NREM, a decreased activity in the frontal and parietal lobes is observed. This is followed by decreased activity of cortical regions in NREM 2 stage, culminating in NREM 3, the deepest stage of sleep also known as slow-wave sleep (SWS), characterized by minimal brain activity.

Wakefulness, arguably constituting a part of sleep cycle, is represented by Alpha (8-13 Hz) waves in the EEG readings [75]. This state is progressively downregulated, especially during transition from phasic to tonic cognitive states [64]. The structure and phases of sleep are important because sleep irregularities accompany AD even at pre-clinical stage, as well as being a predisposing factor of AD development [76–78]. Therefore, sleep architecture can serve as a useful descriptive component of AD and should thus be assessed.

3.2. How disrupted sleep affects LC-NA and AD

Polysomnography (PSG), combining EEG, electromyography (EMG) and electrooculography (EOG) signals simultaneously, offers an objective evaluation of sleep metrics [79]. PSG is a tool capable of providing a valuable insight of the sleep architecture and the physiological changes associated with AD. For example, a disruption in SWS activity, quantified by the change in Delta frequency, has been linked with significantly increased Aβ levels, thus underpinning NREM SWS involvement in Aβ clearance [80]. Therefore, disturbance of SWS can possibly be an early biomarker for AD, as it can be identified even at MCI stage [81].

Moreover, the neurodegeneration due to disturbed REM sleep can be explained by the dysregulation of the orexinergic system, which is positively associated with tau protein levels in AD [82]. Likewise, tau deposition is evident in cholinergic neurons, making cholinergic system another quantifier of early AD pathology [83]. Even though not being an explicit part of LC-NA architecture, orexinergic and cholinergic neurons are indirectly linked to it via the afferent anatomy, with their inputs serving an important role in sleep modulation associated with LC activity.

Additionally, sleep spindles of NREM 2, being a product of complex communication between thalamic, limbic, and cortical regions, were shown to be altered in PSG studies [84]. Compromised structure and function of these brain regions, make sleep spindles an additional biomarker for AD detection [85].

In vivo microdialysis in mice demonstrated a direct association of sleep deprivation with elevated NA levels in the prefrontal cortex following prolonged period of wakefulness, with LC-NA neurons efferent to medial prefrontal cortex particularly affected neuronal stress [86]. An altered activity of catecholamine function of LC-NA can therefore lead to detrimental effects on cognitive function, due to imbalance in NA transmission.

At the same time, photoactivation of orexinergic neurons, afferents of LC, via dual optogenetic technique, has been shown to interfere with the sleep-wake transitions [87]. This suggests that disruption of the afferent signalling in LC can lead to disturbed sleeping patterns explained by the LC-NA's crucial involvement in modulation of endogenously and sensory triggered transitions between sleep and wakefulness [88]. Although it is important to note that REM sleep duration or probability of NREM to REM sleep transition remained unchanged upon either optogenetic stimulation or inhibition [89], implying that these are likely to be mediated by another regulatory component of sleep. Hence, LC's precise role must thus be distinguished and isolated.

The conglomerative findings on the involvement of LC-NA system in sleep macro- and microstructure emphasize the role that LC-NA fulfils in keeping the balance between synaptic potentiation during NREM and depotentiation during REM sleep [90]. Overall worsening of stability and synchronization of the LC-NA system can interrupt the normal rhythmicity of LC-NA neuronal firing, which can result in irregular NA release, descriptive of modulatory impairments of sleep and wakefulness.

Hence, LC-NA is an important integration centre involved in sleep regulation, mainly through noradrenergic release and coordinated action of adrenergic receptors. Its proper functioning in sleep spindle generation, alongside normal NREM Delta and REM sleep Theta oscillations, is imperative for normal memory processing [69]. Therefore, it is suggestive of a bidirectional relation between abnormal LC activity and memory impairments associated with AD [69].

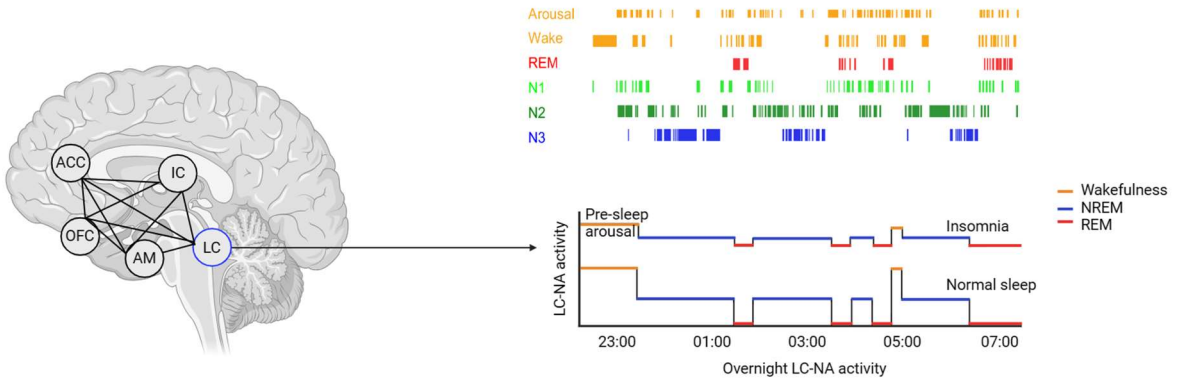

Figure 4. LC-NA activity and sleep. LC-NA tonic firing rate is highest during wakefulness, lower during NREM and is completely silent during REM phase of sleep. Insufficient LC-NA silencing can become a cause of insomnia. Timing of NA release is important for a balanced potentiation and depotentiation of synapses, therefore REM sleep becomes disrupted if LC remains active and NA is released. Resulting absence of REM sleep without NA present interferes with synaptic plasticity in limbic areas of the brain such as claustrum and anterior cingulate cortex. These areas have been found to have genes associated with insomnia, which highlights the implications of LC function and its connected networks in sleep homeostasis. ACC - anterior cingulate cortex; AM - amygdala; IC - insular cortex; LC – locus coeruleus; OFC – orbito-frontal cortex. [Adapted from Van Egroo et al. (2022) and Van Someren (2021)]

4. Neurodegenerative changes in the Locus Coeruleus associated with Alzheimer's disease

Certain changes in the LC-NA system revealed by the recent MRI studies can be considered a part of normal ageing process, such as changes in neuromelanin, neuronal or dendritic shrinkage, and including reduced NA-mediated plasticity in LC terminals and hippocampus [73,91,92]. Yet LC remains a highly vulnerable spot of neurodegeneration. Since chances of developing AD increase with progressing age, pathological ageing is considered one of the risk factors for AD pathogenesis, with LC being the first structure in the brain where tau hyperphosphorylation can be observed [93,94]. Substantial loss of neurons in LC due to AD pathology implies a possible causal link between LC damage and AD [95].

Furthermore, ^{18}fluorodeoxyglucose PET used to measure regional brain metabolism through glucose consumption had confirmed a significant difference in neuronal activity between REM and NREM sleep [96,97]. A higher metabolic rate in REM can be explained by the continuous firing pattern of the cortical neurons, which explains Beta and Theta power in EEG recordings [98]. This is contrasted by SWS of NREM stage, during which LC is generally inactive, described by the neuronal silence [99]. A disrupted REM sleep pattern is noted when LC is insufficiently inactive, which underlines the importance of properly regulated noradrenergic neuron firing [90]. Additionally, Aβ was observed to be released into interstitial fluid (ISF) during the periods of elevated activity in neurons, those associated with REM or waking state, which led to notion that a higher synaptic activity leads to elevated Aβ levels in the ISF [100]. Thus, it can be hypothesized that LC-NA disfunction, leading to abnormal NA production and increased neuronal firing, could potentially result in unusually high synaptic activity which may disrupt REM or NREM sleep, possibly contributing to Aβ accumulation in AD. Vice versa, it should be appreciated that LC damage can be an emerging property of AD, reiterating an idea of reciprocal causation between the two elements.

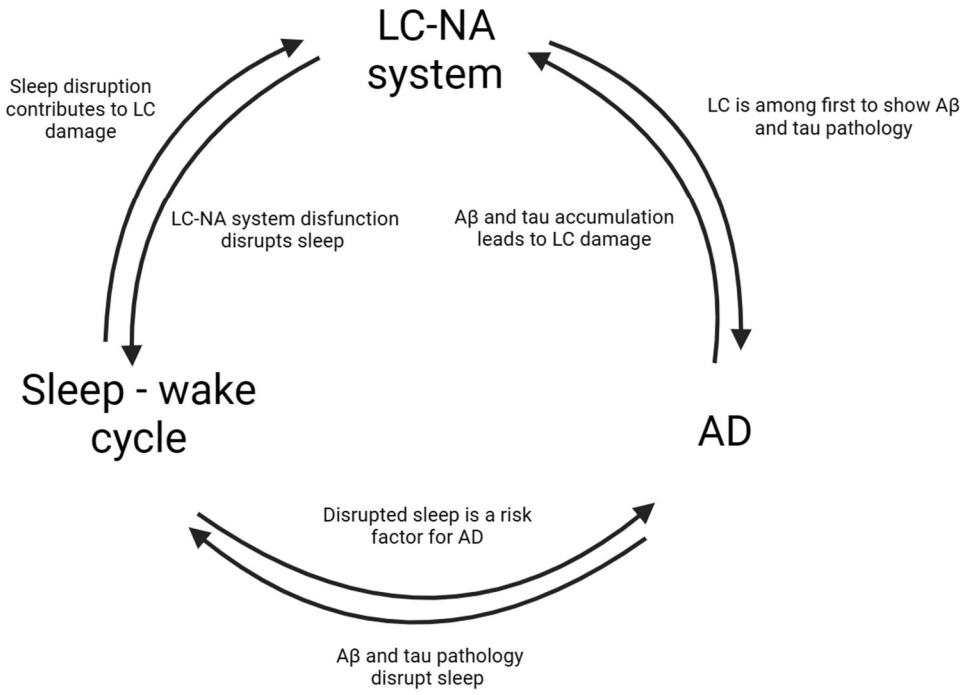

Figure 3. Vicious cycle between LC-NA system, sleep-wake cycle, and AD. A schematic diagram showing the causal relationship between LC, sleep, and AD representing an emerging framework. [Adapted from Van Egroo et al. (2022)]

5. Interplay between Aβ pathology, neuroinflammation, and the LC-NA system

5.1. Impact of AD associated pathology on LC-NA system.

Experimental LC lesions in animal models further support the role of LC in the early AD development [93]. LC-NA circuit damage, collectively quantified by NFT's presence, death of noradrenergic neurons, and Aβ aggregation, exceeds even that of nucleus basalis, which is the primary source of cholinergic input and is among first structures to show signs of NFT accumulation in AD [101]. Post-mortem studies displayed the presence of tau in its pre-NFT form at the very early preclinical stage of AD [102–104], underlining the vulnerability and sensitivity of LC-NA to neurodegenerative processes.

NA as the neurotransmitter itself acts as a possible risk factor for the AD related LC damage [93]. After synaptic release, NA is taken up into the cytoplasm by the NA transporter where the cytoplasmic form of NA can be converted into chemically reactive and toxic metabolites [93]. For example, a product of monoamine oxidase (MAO) cleavage can be a cause of neurotoxicity as a result of damage to proteins, lipids, and nucleotides [93]. Overly active LC with dysregulated NA production can thus precede a higher NA turnover and 3,4-Dihydroxyphenylglycolaldehyde, a neurotoxic metabolite, production, constraining a cellular stress [93].

Morphologically, LC neurons display a constant and synchronous firing pattern. In case of stress response, for example to salient sensory stimuli, acute phasic bursting patterns superimposed on the tonic firing can be observed [105]. Such mechanism is energetically expensive, meaning that cells would rely heavily on mitochondrial phosphorylation, which can lead to accumulation of oxidative stress over time [93]. Additionally, since LC neuronal firing rhythmicity are maintained by Ca^{2+} channels, there is a further risk of mitochondrial toxicity due to excessive Ca^{2+} influx [93].

The location of LC below the fourth ventricle poses an additional risk for neuroinflammation [105]. LC neurons are located in close proximity to the ventricle, which allows for unrestricted flow of CSF [93]. In case of a compromised function of glymphatic system, CSF can become a source of neuroinflammation. This can be hypothetically connected to sleep impairment, as NREM stages are associated with the process of CSF flushing. LC is also heavily surrounded by brain capillaries, which in case of a compromised blood brain barrier (BBB) function, can lead to leakage of toxins and inflammatory molecules [106]. Lastly, LC axons are thought of as fragile since many are thin, long, branched, and unmyelinated, therefore making them sensitive to degradation [105].

5.2. Inflammatory processes and their influence on LC-NA system activity

Inflammation is of particular interest since it has been hypothesized that there is a direct relationship between the inflammatory responses and AD [107]. Disruption in circadian system, and as a result sleep, can be an a proinflammatory trigger inducive of such neuroinflammation [107]. Cytokines that are classically indicative of AD associated neuroinflammation, such as TNF-α, IL-1b, and IL-6, are involved in regulation of sleep [108]. Notably, the pro-inflammatory modulation by these cytokines is variable and potentially timing sensitive, as in there has been positive correlation shown of TNF- α and IL-6 involvement in sleep maintenance and SWS intensity in the evening [109].

The persistence of low-grade inflammation can be a risk factor for BBB disruption [107]. Thus, a negative impact on BBB permeability function possibly resulting from neurodegeneration [110], or chronic sleep disruption, [111] exacerbates neuroinflammation, which can be indicative of AD. In addition to impaired BBB permeability, sleep disruption affected vascular reactivity, decreased glucose transport, and induced microglia activation in animal models [112,113]. These cumulative findings further emphasize the pro-inflammatory state in AD pathology.

Moreover, pro-inflammatory cytokines have been linked to the increased levels of rod-shaped cofilin-actin bundles of filaments, or simply rods [114]. Cofilin serves the function of binding to actin filaments and promotes their disassembly, thereby controlling remodelling of actin filaments [114]. Under cellular stress, as observed in AD, cofilin becomes overactive leading to the formation of said rods. The connection between cofilin dysregulation and AD has been demonstrated in mice studies [115]. The formation of rods through cofilin sequestration disrupts actin dynamics, blocks neuronal transport, exacerbates mitochondrial potential loss, and ultimately contributes majorly to synaptic dysfunction[114,116,117]. Therefore, disruption of cofilin signalling due to sleep loss can potentially be linked to AD progression at the molecular level. The impact of sleep disruption on neuroinflammation, BBB integrity, and actin dynamics has direct implications on the LC-NA system's vulnerability to damage and dysfunction.

5.3. The glymphatic system: How sleep deprivation influences Aβ clearance and the role of astrocytes

In the brain, glymphatic system serves as a mechanism for clearance of toxic waste, such as Aβ, via CSF and ICF dynamics [118]. Evidence from human studies strongly suggests that CSF flow is related to amyloid pathology [118]. Moreover, it has been indicated that Aβ metabolism in blood and CSF of healthy adults is a part of circadian rhythm regulation [118]. Animal studies are in concordance with the notion that sleep-wake dysregulation may lead to dysfunction of glymphatic system, and clearance of toxic waste as a result [118]. Furthermore, the data underlines that sleep deprivation supresses glymphatic circulation of SCF-derived apolipoprotein E (ApoE) in the brain [118]. This poses a serious risk to BBB integrity, which is a crucial component of Aβ clearance.

It has been commonly reported that sleep deprivation or dysfunction leads to systemic inflammation and subsequent release of pro-inflammatory cytokines, which in turn alters BBB function [111,118]. Multiple studies have confirmed BBB's role in the Aβ transport and removal, which is regulated by ATP-binding cassette transporters and members of the low-density lipoprotein family in ApoE dependent and independent manner [119,120]. Apart from fulfilling a function in BBB integrity, ApoE interacts with astrocytes, contributing to Aβ elimination, hence a sleep disturbance might result in increased Aβ accumulation via feed-forward mechanism [118]. Astrocytes have been suggested to be involved in removal of toxic waste and metabolic support, especially during the SWS [118]. Interestingly, astrocytes have been indicated to be involved in sleep regulation through elucidated intraneuronal communication, and via modulating adenosine, a neurochemical involved in sleep regulation [121]. Hence, a sleep disturbance can affect astrocyte-ApoE dependent Aβ removal, which subsequently may result in increased Aβ accumulation via feed-forward mechanism [118].

In the hypothesis of glymphatic clearance, astrocytic aquaporin-4 (Aqp4) is required to remove toxic waste from the ICF [118]. The role of astrocytes in the glymphatic system, together with expression of Aqrp4 during sleep and in both stages (pre- and clinical), has already been evaluated [121,122]. Following research involving Aqp4-knockout mice affirmed these findings, revealing a reduction in $A\beta_{40}$ clearance which led to the deposition of Aβ in the cortex and hippocampus [123]. While there is no direct evidence showing the impact of sleep-wake cycles on Aqp4 expression, it has been noted that the clearance of exogenously introduced Aβ from the interstitial space substantially declines in awakened mice, and reverses during sleep [124]. Further evidence for sleep-wake state influencing the glymphatic system efficiency of Aβ clearance, rather than circadian rhythm, was provided [124]. Adrenergic signalling during waking state was shown to be responsible for increased resistance to the flow of interstitial fluid which in turn causes the decrease of interstitial space [124]. Combined, these findings suggest that the impairment in Aβ clearance seen in AD may primarily originate from astrocyte involvement in the glymphatic process during sleep. The efficiency of the glymphatic system in Aβ clearance is crucial to maintain LC-NA system integrity, as build-up of Aβ is one of the hallmarks of LC damage, which may lead to dysregulated NA release and disrupted sleep patterns.

6. Research methods and techniques for studying the LC-NA system and sleep in AD

Despite the interest, the LC-NA system has been under-investigated due to technical limitations. Recent advances in neuroscientific research tools gave a definite description and characterization of the 'blue spot'. The new observations of LC have been helping to affirm the significance of NA's involvement in the neurodegenerative disorders.

PET has been an indispensable technique of visualizing Aβ and tau depositions. Comparative analyses of tracer accumulation in the brain regions allows to estimate the extent of Aβ and tau pathology, and longitudinal PET can provide an additional insight into AD progression. Empirical evidence supporting the amyloid cascade hypothesis, alongside Aβ and tau utilities as biomarkers for AD motivated an investigation into more rigorous neuroimaging agents [13]. However, the observed weak correlation between Aβ load and the severity of dementia, and the role of tau in neurodegeneration, implies an interdependency of Aβ and tau roles in AD, calling for improved radio tracing agents [125]. Moreover, the ability to quantitatively assess tau burden in the living brain would provide an immense perspective on tauopathies, analogous of the earlier breakthroughs in targeted Aβ probes [125]. The recent advances in radiotracers had emerged as instrumental in AD research, as it allows for a higher affinity towards Aβ or tau proteins in the brain [125], implying a more accurate and sensitive detection of AD biomarkers.

In studies involving mouse lesions or NA depletion, LC degeneration in AD has been linked to deteriorations in learning and memory associated with synaptic deficits [126–130]. In partially induced lesions in mice, increased LC firing and NA turnover was attained, outlining the role of LC-NA in sleep and AD [93].

Post-mortem AD studies have confirmed an elevated CSF NA turnover, implying both a failure in glymphatic system and a causative role of NA in AD origins [131–134]. Interestingly, human and animal post-mortem findings demonstrated that LC neurons can withstand tau burden for significantly long time before cell death [93]. Specifically, a transgenic mice overexpressing a mutant tau form with higher likeliness of hyperphosphorylation and accumulation (P301S), exhibited an AD tauopathy that damaged the forebrain, but not the LC by the time of mice's death at ~ 12 months [135,136]. The earliest presence of tau in LC before any other region of the brain has been reinforced by TgF344-AD transgenic mice, which overexpressed APP and PRES-1, with no cell death in LC after a year later noted [137]. This led to the 'two-hit' hypothesis, which speculates that a second trigger is needed, apart from tau, in order to initiate cell death in LC [138]. Although one animal study showcased rapid tau neurotoxicity, which utilized a direct injection of preformed NFTs into the LC [139]. Hence, in this case the mechanism behind cell death might differ from the endogenous tau formation [139].

An extension of a post-mortem study, which involved tyrosine hydroxylase immunohistochemistry and stereology of LC-NA neurons revealed a 30% neuronal loss in transition from no cognitive impairment (NCI) to amnestic mild cognitive impairment (aMCI), together with 25% neuronal loss in AD [140]. This was shown to significantly associate with poorer antemortem global cognitive function, and an increased post-mortem neuropathology [140]. Molecular mechanism behind LC neurodegeneration in aMCI was assessed by performing a microarray analysis, which demonstrates a reduction in some classes of function mRNA. Those are responsible for mitochondrial respiration, redox balance and AD related neuroplasticity, and specific levels of gene expression in these functional classes linked with cognitive neuropathology [140]. Notably, the increase in 3-repeated (3-R) to 4-repeated (4-R) isoforms of tau, combined 3R/4R tauopathy being focal in PET investigations, which is associated with the NFT formation and slower axonal transport, suggests LC neurons' susceptibility to oxidative stress and axonal degeneration happening prior to MCI [140].

Optogenetic or chemogenetic techniques of activating LC suggested a causative link in sleep dysregulation [89,141,142]. Considering the alterations in LC neurons firing pattern during phase of sleep and waking, and the sleep quality being a predictor of AD development, the evident changes in LC firing preceding sleep-wake transitions seem to emphasize the role of LC in sleep regulation and its potential contribution to the onset of AD. Indeed, inappropriate LC release of NA leading to sleep fragmentation during SWS or REM sleep highlights the complexity of LC-NA role in sleep and its significance in understanding AD.

However, an essential element considering LC hyperactivity is the possible development of compensatory mechanism in response to LC dysfunction [143]. For instance, one study showed an inverse correlation between high NA turnover and the numbers of surviving LC neurons in AD, while others reported an increased expression of tyrosine hydroxylase, a rate-limiting enzyme in NA biosynthesis, as well as axonal sprouting in hippocampus [134,144]. Furthermore, animal studies supported an observation of higher NA activity in relation to LC neurodegeneration [145,146].

Undoubtedly, new developments in the neuroscientific techniques shed more light on the 'blue spot' and its impact on sleep and AD. Although there is a substantial necessity for more investigations in the areas of transcriptomics, proteomics and epigenetics in order to locate the origins of AD within LC-NA circuitry, and to identify potential therapeutic targets.

7. Discussion

7.1.1. Sleep as a therapeutic target

Targeting sleep as a preventative strategy for AD can be useful since it is involved in Aβ clearance during NREM phase of sleep, and memory consolidation [74,124,147]. Considering that LC-NA activity is tightly linked with sleep regulation, enhancing NREM and/or REM sleep might be a viable strategy for the treatment and prevention of AD.

Sleep disruption has been demonstrated to be associated with elevated Aβ or tau levels [148–151]. In a group subjected to overnight sleep deprivation an increase in $A\beta_{1-38}$, $A\beta_{1-40}$, 1-42 CSF levels by 25-30% was reported, compared to the control [149]. Additionally, CSF tau has been demonstrated to increase by more than 50% during sleep deprivation [150].

Normal sleep function is associated with a 60% increase in interstitial space, leading to a higher rate in convective exchange of CSF in the glymphatic function [124]. Aβ clearance has been noted to be improved by SWS through glymphatic system, implying a hypothetical connection between the regulation of wakefulness through NA release, and sleep-dependent regulation of Aβ and tau levels [124]. Enhanced glymphatic function and clearance can improve Aβ and tau clearance, which can be possibly achieved by boosting astrocyte activation or the expression of Aqp4 channels.

The waking state is associated with a higher metabolic stress due to the increased oxygen and adenosine triphosphate (ATP) consumption [152]. Oxidative stress promotes Aβ accumulation, which in turn promotes oxidative stress further in a feedback loop fashion [153]. Hence, a disruption of the sleep-wake cycle, which can arise due to LC-NA dysregulation, can exacerbate Aβ pathogenesis, providing an additional supportive argument for the sleep improvement as a preventative strategy in AD.

A classical medication used in AD are acetylcholinesterase (AChE) inhibitors, which increase the amount of acetylcholine available – a neurotransmitter important in memory and learning – by inhibiting AChE and thus improving the cholinergic transmission [154]. Aside from improving or maintaining AD related dementia, AChE inhibitor donepezil has been shown to increase the duration of REM sleep [155,156].

Another possible therapeutic target can be orexin. Aβ levels have been reported to be associated with orexin, and in vivo microdialysis of mice had shown that orexin antagonist infusion decreased Aβ levels [26,157].

In an overly active LC-NA, damage can arise from glutamate excitotoxicity, which can be mediated by NMDA receptor blockage. For example, memantine, an NMDA receptor antagonist, can modulate NMDA receptor activity which may aid in alleviating AD symptoms and slow the disease progression [28].

Furthermore, evidence suggests that TNF-alpha signalling inhibition prior to amyloid plaque formation prevents glutamate excitotoxicity at a later AD stage in mouse model [158]. This indicates that administering TNF-alpha inhibitors in preclinical AD can be a means of prophylactics and prevention of later cognitive and synaptic deterioration [158].

7.1.2. LC-NA as a therapeutic target

In contrast, some novel therapeutic strategies aim to protect or enhance the LC-NA function, in order to normalize NMDA receptor activity, by modulating NA levels [33]. Certain selective NA reuptake inhibitors targeting NA synthesis, signalling or metabolism include atomoxetine [159], reboxetine [160], synthetic NA precursor L-3,4-dihydroxyphenylserine (L-DOPS) [161], and alpha2-adrenergic receptor agonist lofexidine [162]. NA reuptake inhibitors would prevent the reuptake of NA into pre-synaptic neurons, thus increasing NA concentration in the synapses and potentially improving cognition in AD.

Another argument for therapeutically raising CNS NA levels is provided by a 5xFAD transgenic mice study, in which LC damage was observed as evidenced by increased astrocyte activation, neuronal hypertrophy, reduced LC-enriched messenger RNA (mRNA) levels, and increased inflammation [163]. By increasing CNS NA levels treating 5xFAD mice with synthetic NA precursor L-DOPS, the learning in the Morris water maze test has improved [163]. It was concluded that L-DOPS reduced astrocyte activation, increased mRNA levels of neprilysin and insulin degrading enzyme, and of multiple neurotrophins, and increased brain-derived neurotrophic factor protein levels. Elevating NA levels, by the means of L-DOPS for example, can be a possible therapeutic strategy in improving AD pathology.

Drugs acting on LC co-transmitters can also have a therapeutic application [93]. Galanin is co-released with NA in several areas of the brain, and is known to inhibit the firing of LC neurons, and the release of NA accordingly [164]. In AD pathogenesis, the expression of galanin in LC is observed to be increased, which may be a compensatory protective response against excitotoxicity caused by LC overactivation [33]. Therefore, the galaninergic system can be subject for therapeutic approach for pre-clinical AD since galanin modulates LC activity and has neuroprotective properties [164]

More detailed understanding of LC's architecture allowed to consider novel minimally invasive procedures in modulating LC activity, such as neuronal circuits originating from the suprachiasmatic nucleus (SCN) that are relayed via the dorso-medial hypothalamus [43]. For example, retinal stimulation via chemogenetics, by exploiting SCN's strong innervation from specialized retinal ganglion cells, may be used to modulate LC for therapeutic benefit [165].

Similarly, transcutaneous vagus nerve stimulation has shown benefits in AD-related symptomatology, the effects of which are mediated through LC-NA activation [33]. Vagus nerve stimulation may also improve sleep quality in elderly by indirectly strengthening LC-NA function [166].

A better understanding of LC-NA system macro and microstructure, together with its efferent and afferent projections, co-transmitters, and survival factors, as well as its architectural modularity, will allow for a more accurate developments of therapeutic strategies against AD. An improvement in investigation techniques, with more longitudinal and cross-sectional studies of LC-NA can further provide a wider access to targets for intervention against the AD.

An enhanced synaptic and neuronal resilience against Aβ pathology was achieved with type 4 phosphodiesterase (PDE4) inhibitor, which is a class of drugs linked to both AD and sleep [167,168]. Although it is worth noting that the neuroprotective effect potentially arises outside of the direct Aβ pathway [169]. Additionally, recent studies reported the potential of PDE4 inhibitors to improve the clearance of aggregated tau [170]. Furthermore, elevated activity of PDE4 family leads to disruption in cAMP signalling cascade, which was identified as a major contributor to memory deterioration in sleep loss [171,172]. Thus, activation of cofilin is caused by dephosphorylation as a result of elevated PDE4A5 expression

in the hippocampus due to sleep loss, which can lead to include spine loss, lesser synaptic plasticity, and memory impairment [171–174]. The interplay between cofilin and PDE4 signalling, and cofilin's role in memory function, can make PDE4 inhibitors, such as rolipram, promising therapeutic interventions to tackle AD-related dementia alongside negative effects of sleep loss [147,172,173].

7.4. Future research directions and challenges in understanding the LC-NA system's role in AD-related sleep disruption

It has become clear that the role of glymphatic system in amyloid clearance and tau aggregation is heavily implicated in sleep and AD pathogenesis. However, additional animal studies relating glymphatic function with the LC-NA activity are needed in order to investigate pathways of LC-NA systems that are linked with sleep-wake dysregulation and AD in more detail.

It has been established that increased NA levels adversely affect glymphatic function by limiting the volume of the interstitial space, a more direct measure of LC-NA activity is required to further investigate the significance of NA concentrations and release [124]. Better understanding of the timing and synchronicity of NA action in LC-NA circuitry can provide insight in AD pathogenesis, sleep disorders and augment ongoing therapeutical approaches.

Moreover, optogenetic studies of LC-NA system in circadian regulation have not yet estimated its impact on glymphatic clearance, including long-term consequences. There is still an inconclusive consensus in favour of the glymphatic clearance system of the brain hypothesis, although the collected evidence thus far is supportive [175]. Therefore, there is a need for additional investigations dwelling into the study of the ordered processes during sleep, the functions behind each sleep sequence, and longitudinal studies assessing the physiological brain function, such as glymphatic clearance, at each precise stage.

Carrying out more longitudinal experiment designs concerning MCI and NCI AD individuals can contribute to a more precise understanding of the neuroprotective role of sleep-wake function [176] and LC-NA integrity [177]. Additionally, supplementing such longitudinal studies with parallel cross-sectional, transgenic mice models may allow for complementary, specific investigations on AD pathogenesis. For example, a PSG can be a powerful tool used in proposed longitudinal studies and yet, no PSG study has been done as of now to test the impact of LC-NA dysfunction on the sleep.

Interconnectivity of LC-NA system and its role as an effector of waking state through integration of orexinergic signalling [178], provide a strong argument for further investigations of separate LC-NA modalities in order to gain an independent insight on the function on each structural level of abstraction. Novel imaging approaches, organoid research and cross-sectional transgenic studies can provide such resolution, which can then assess the respective contributions of LC-NA networks to AD-related sleep dysregulation.

Lastly, it should be mentioned that while the causational relationship between sleep, LC-NA system and AD is heavily implicated, the serial causality remains speculative. While LC-NA disfunction can be potentially major risk factor for AD emergence with associated NA and sleep disruption, at the same time the AD progression itself may lead to the LC damage in the first place. Thus, further research should outline this distinction and future investigations would allow for better discerning of relationship between LC, AD and sleep.

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Afterword

Dedicated to all educators and researchers who cherish the flames of curiosity and scientific discovery,
And to the beauty of vast, deep as ocean, mind that always perseveres.