



Rethinking early Alzheimer's disease: An impaired internal model updating disorder?

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ABSTRACT

Although sporadic Alzheimer's disease (AD) has long been conceptualized primarily within a molecular framework centered on amyloid- β and hyperphosphorylated tau pathology, this perspective does not fully explain the early vulnerability of specific brain networks or the emergence of non-cognitive symptoms, even decades before memory decline. The present review directly addresses this question by proposing an integrative, systems-level, translational framework that links age-related sensory dysfunction—most notably olfactory impairment—to the failure of predictive sensorimotor internal models and to early network instability. Persistent prediction-error mismatch could impose sustained compensatory demands on key neuromodulatory and adaptive control hubs involved in internal model updating, particularly the locus coeruleus and the cerebellum. Their widespread connectivity and pivotal function in modulating plasticity and network interactions may render them particularly vulnerable to chronic hyperactivity. Over time, this compensatory state may contribute to maladaptive plasticity, neuroinflammation, and conditions that facilitate the progressive accumulation and propagation of AD hallmarks across interconnected networks, including the medial temporal, sleep-regulatory, autonomic, and affective circuits. This perspective offers a hypothesis-driven, mechanistic, systems-level framework for the early emergence of non-cognitive AD manifestations, including olfactory dysfunction, sleep disturbances, autonomic dysregulation, and affective symptoms. Accordingly, these features may provide promising avenues for improving early risk stratification and identifying individuals in preclinical disease stages. Importantly, interventions targeting sensory processing, neuromodulatory balance, and sleep regulation may represent potential early disease-modifying strategies.

1. Background

Imagine this scenario. A large data analysis firm employs thousands of workers who have been diligently working for years in a highly monitored environment designed to optimize efficiency and minimize errors. Massive, powerful mainframes perform astonishingly complex computations at a constant pace—day after day, without pause or vacation. To sustain this relentless rhythm, the company has installed high-capacity cooling systems that operate at full capacity to keep server room temperatures low enough to prevent overheating, which could jeopardize operations. Each day, a specialized supplier delivers tanks filled with refrigerant, which are promptly installed. By evening, when the tanks are empty, they are set aside in a designated area for daily removal. This very complex production machine critically depends on keeping the mainframes running efficiently and properly cooled. Now

imagine that one day the data input system malfunctions. The problem may stem from a slowdown or a decline in the quality of incoming information—perhaps due to sensor failure or a degradation of the connections between the data sources and the processing centers. As a result, the servers must work harder: not only must they process lower-quality data, but they also must rely more heavily on previously stored information to compensate for missing inputs, performing complex calculations to predict or model those inputs. Replacing the acquisition system is not an option. The company has invested substantial capital in its construction, and removing any of its components could compromise the entire operation. Consequently, as performance demands increase, server room temperatures rise sharply, and the existing supply of coolant tanks is no longer sufficient. The supplier increases deliveries, and at first, this appears to resolve the issue. However, the vicious cycle triggered by the loss of input data quickly becomes clear: the servers, now

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forced to operate under constant overload, begin to wear out more rapidly. The company must order increasingly larger amounts of refrigerant, driving costs to unsustainable levels and causing the supplier to neglect other clients. Environmental regulations governing the disposal of these materials make their removal increasingly complex, and there are insufficient transporters available each night. As a result, the empty tanks start to accumulate. Initially, there are only a few, barely noticeable, but as the crisis worsens, they accumulate beyond the designated zones—spilling into the employee parking lot and even blocking access routes, thereby restricting movement in and out of the facility. This situation significantly reduces employees' quality of life, prompting them to express frustration to management. Unable to address the root cause, the executives decide to act on two fronts. First, they hire specialized contractors to remove the tanks—an operation that's highly polluting and, in some respects, dangerous—performed by unscrupulous mercenary crews who damage fences and infrastructure while maneuvering heavy machinery through spaces not designed for such vehicles. These breaches allow small animals to enter the premises, gnawing on cables that transmit information and worsening the problem. At the same time, the company deploys security teams that initially restore order among the increasingly unhappy staff. Over time, however, intoxicated by their authority, these guards start to mistreat the workers, further damaging morale and well-being. Many employees eventually quit—including the maintenance technicians responsible for the mainframes—disheartened by the impossibility of solving the problems. As maintenance ceases, the mainframes' performance deteriorates until one day a server shuts down. This marks the beginning of the end: soon after, the remaining machines follow, each collapsing under the load previously shared by the others. Finally, the lights go out in a once-thriving facility—now empty of workers, filled with tanks and debris, the remnants of well-meaning but misguided efforts. The company's board of directors criticizes the managers, blaming them for failing to dispose of the tanks properly or for hiring reckless security forces. However, the real issue was never the tanks or the guards. The origin of the catastrophe lay in the failure of the data-acquisition system, which overloaded the mainframes and set in motion an irreversible path toward their functional collapse. Although this story is fictional, it may closely resemble the landscape of Alzheimer's disease (AD). The following sections will explain the reasons behind this parallel.

2. AD pathophysiology: need for a different perspective?

AD is the most common primary neurodegenerative dementia worldwide (Frisoni et al., 2025b). Despite decades of research to elucidate its pathophysiology, AD pathogenesis remains only partially understood (Rajah Kumaran et al., 2023). For many years, the amyloid cascade hypothesis has been—and remains—the most influential and widely endorsed conceptual framework, proposing that the core neuropathological features of AD develop through a defined, deterministic, cause-effect sequence: the formation of amyloid- β (A β) oligomers leads to early synaptic dysfunction, followed by extracellular A β plaque deposition, which in turn disrupts neuronal physiology and promotes tau hyperphosphorylation, aggregation, and intracellular accumulation (namely neurofibrillary tangles, NFTs), ultimately resulting in neurodegeneration and clinical symptoms (Hampel et al., 2021). Although experimental and clinical evidence have supported this model, it has also been the subject of considerable criticism, and there remains no consensus on the precise cascade of events that leads to the characteristic clinical manifestations of AD, which are typically amnesic in the earliest stages (Kasper P. Kepp et al., 2023). Importantly, this model suggests that A β is the earliest molecular driver, a finding that remains controversial (Selkoe and Hardy, 2016). A crucial unresolved question concerns the triggers that initiate this pathological cascade. With the exception of familial forms of AD—associated with genetic variants that alter the balance between production and clearance of neurotoxic proteins and whose pathophysiological mechanisms are

relatively well characterized—the vast majority of sporadic cases (i.e., >95 % of AD patients) remain largely unexplained (Andrews et al., 2023; Bisceglia et al., 2022; Braak and Del Tredici, 2015). It is generally assumed that sporadic AD arises from a complex interplay between genetic and epigenetic vulnerability and environmental exposures; however, establishing direct causal links has proven difficult (Migliore and Coppedè, 2022). For example, although untreated arterial hypertension is widely regarded as a significant risk factor, only a subset of hypertensive individuals develop AD (Abdulrahman et al., 2022; Daugherty, 2021; Lennon et al., 2024). What consistently emerges across epidemiological studies is that advancing age is the strongest risk factor for the disease, with incidence doubling every six years (Frisoni et al., 2025b; Hong et al., 2024), raising a fundamental question: why does aging itself confer such marked vulnerability to AD? In other words, what changes during aging that may constitute a necessary and/or sufficient condition for triggering the AD cascade?

Notably, the central nervous system (CNS) is organized to promote survival by operating as a predictive system that optimizes sensorimotor interactions with the environment (Friston et al., 2016; Pezzulo et al., 2021b). Within this framework, memory plays a pivotal role. It is not merely passive storage but a dynamic, flexible process that enables internal simulation, the recombination of past information, and the prediction of future states, thereby supporting adaptive, anticipatory behavior rather than purely reactive responses (Benedek et al., 2023; Buzsáki et al., 2022; Simons et al., 2022). To perform these complex computations, the CNS critically depends on the proper functioning of systems that convey information from the external world (i.e., sensory pathways), those that close the loop through action (i.e., effector systems), and the networks that integrate these signals (Franklin and Wolpert, 2011; J. S. Li et al., 2023; Roth et al., 2014). Therefore, the well-known age-related deterioration of sensory systems compromises the efficiency of predictive processing and sensorimotor integration—processes that are particularly relevant to memory (Abbas et al., 2024; Billig et al., 2020; Hsu et al., 2021; Humes et al., 2013; Wolpe et al., 2016). Notably, impairment of short-term and episodic memory is the most prototypical clinical feature of early AD, suggesting that failures in these predictive and integrative mechanisms may be tightly linked to disease pathophysiology (Frisoni et al., 2025b; Nellesen et al., 2015).

In this context, increasing attention has been directed toward several early alterations that consistently precede the onset of overt cognitive symptoms and the classical neuropathological hallmarks, yet are often underappreciated in models of AD pathogenesis. Specifically, these include olfactory dysfunction, early degeneration of the locus coeruleus (LC), cerebellar alterations, and sleep disturbances (Y. Chen et al., 2022; Murphy, 2019; Yang et al., 2024; Y. Zhang et al., 2022). A hypothetical explanation of how these factors interact and converge during the earliest phases of AD pathophysiology will be discussed in the following sections.

3. Sensory systems, particularly the olfactory system, are early, vulnerable targets of aging

Olfaction is a chemical sense that distinguishes itself among the sensory modalities. Indeed, odor stimuli can induce immediate changes in affective state and arousal levels and also trigger almost instantaneous retrieval of the emotional dimensions and personal experiences associated with a given stimulus (Cai et al., 2025; Glachet and El Haj, 2021; Kadohisa, 2013; Masaoka et al., 2021). Moreover, the forgetting rate for olfactory stimuli is lower than that for other sensory modalities (Cornell Kärnekull et al., 2015; Larsson and Willander, 2009). In brief, olfactory function depends on millions of ciliated sensory neurons within a specialized neuroepithelium in the posterior portion of the nasal cavity. Each neuron projects a single axon to the olfactory bulb (OB), the first central processing station for incoming olfactory information (Brunert et al., 2023; Courtiol and Wilson, 2016; Firestein, 2001; Giessel and

Datta, 2014). From the OB, via the olfactory tract and the olfactory tubercle, information reaches the olfactory cortex, which comprises the anterior olfactory nucleus and the piriform, transentorhinal, and periamygdaloid cortices and maintains direct connections with the mediodorsal nucleus of the thalamus. From these regions, third-order neurons project to numerous targets, including the orbitofrontal cortex, the subiculum, the thalamus and hypothalamus, the basal ganglia, and several brainstem nuclei. This organization—hierarchical and sequential, yet notably lacking a necessary thalamic relay for direct cortical access—may help explain the long-term retention of olfactory memories and their strong emotional valence, given the tight anatomical and functional coupling among the amygdala, hippocampus, and transentorhinal cortex (Kehl et al., 2024; Li and Wilson, 2024; Savic et al., 2000; White, 2009).

Notably, olfaction is one of the systems in which neurogenesis continues relatively robustly into adulthood (Durante et al., 2020; Naffaa, 2025). During the first decades of life, the olfactory epithelium has a high neurogenic potential, enabling it to maintain function through the regeneration of senescent cells (Brann and Firestein, 2014; Durante et al., 2020). With aging, this potential declines markedly, leading to morphological and functional alterations, particularly when combined with other risk factors (Chen et al., 2019, 2017; Child et al., 2018; Fitzek et al., 2022; Kondo et al., 2020; Ueha et al., 2016). Importantly, age-related olfactory alterations are not solely due to the straightforward loss of these stem cells but are instead linked to dysfunction, as evidenced by an altered transcriptional profile (Oliva et al., 2022). Thus, by midlife—and even more so in older age—presbyosmia (i.e., age-related loss of smell), hyposmia, or even anosmia, defined as a primary, late-onset loss of the sense of smell, are common (Boesveldt et al., 2017; Murphy et al., 2002). Notably, anosmia is the most prevalent sensory impairment in the general population, and the upward trend is expected to continue following the COVID-19 pandemic (Desiato et al., 2021; Han et al., 2020). This is even more relevant given that, beyond the suggested association with olfactory dysfunction, SARS-CoV-2 infection has also been linked to an elevated risk of cognitive decline (Di Giorgio et al., 2022; Zhao et al., 2023).

Due to its remarkable plasticity, i.e., the CNS's capacity to adapt its structure and function to internal or external demands or damage, the olfactory system responds to sensory loss through structural and functional reorganization of key network nodes, including the piriform cortex and the sniffing-induced network (Gazerani, 2025; Iravani et al., 2021; Kollndorfer et al., 2015; Reichert et al., 2018). Hypothetically, these adaptive changes might play a pivotal role in triggering the downstream neuropathological cascade, together with other predisposing factors. Indeed, sensory deficits are common features of normal aging, but they may also serve as early biomarkers of incipient neurodegenerative processes (Hong et al., 2024; Murphy, 2019). In particular, olfactory dysfunction often precedes the onset of measurable cognitive deficits by many years, and similar early alterations have been reported in other sensory modalities, which are likewise vulnerable to age-related degenerative and pathological changes (Hong et al., 2024; Lad et al., 2024; Murphy, 2019; Schubert et al., 2017; Jing Wu et al., 2025). Nevertheless, olfaction warrants special attention because key regions of the olfactory system exhibit neuropathological hallmarks of AD at very early disease stages, before overt cognitive symptoms become detectable (Braak and Braak, 1997; Hyman et al., 1991; McLaren and Kawaja, 2024; Murphy, 2019; Ohm and Braak, 1987). Moreover, one of the earliest brain regions to show AD-related pathology, possibly the first, is the LC, a brainstem nucleus that is the main source of noradrenergic innervation to the entire CNS and is densely interconnected with the OB and the anterior piriform cortex (Y. Chen et al., 2022; Geng et al., 2025; Guérin et al., 2008; Meyer et al., 2025). Crucially, degeneration of the LC may result from early dysfunction in the olfactory system and related networks, possibly reflecting increased compensatory demands on this neuromodulatory hub (discussed below) (Diez et al., 2024; Jacobs et al., 2021a; Poe et al., 2020; Prokopiou et al., 2023; Sun et al., 2020;

Ubeda-Bañon et al., 2020; Van Egroo et al., 2023). Interestingly, olfactory epithelium organoids derived from basal stem cells of genetically modified animal models exhibit abnormal aggregation and accumulation of AD pathological hallmarks, which increase with disease progression (M. Liu et al., 2024). Thus, beyond the possible prion-like diffusion of neurotoxicity from the LC, the olfactory epithelium may also be among the earliest sites of the AD pathological process, potentially independent of contributions from other regions, although the evidence remains preliminary (Chalermphanupap et al., 2017).

Regardless of the underlying mechanism, odor identification is markedly impaired in about 85 % of patients with AD and in individuals with mild cognitive impairment (MCI), and it may even predict progression to MCI (Guo et al., 2023; Igeta et al., 2024; Rahayel et al., 2012; Roalf et al., 2017; Yaffe et al., 2017). Notably, MCI patients with more pronounced olfactory deficits are more likely to belong to the amnesic subtype, which carries the highest risk of conversion to AD (Roberts et al., 2016; Tabert et al., 2005; Yaffe et al., 2017). Hence, greater olfactory impairment is associated with a higher probability of progression to AD, representing not merely an epiphenomenon of aging but also a clinically meaningful marker of AD-related neuropathology. Crucially, even individuals with subjective cognitive decline (SCD)—a condition characterized by self-reported cognitive complaints in the absence of objective neuropsychological impairment, and, particularly when memory is affected, considered a potential earliest stage along the AD continuum—exhibit olfactory dysfunction (Cedres and Olofsson, 2024; Jobin et al., 2021; Laukka et al., 2023a; Munro et al., 2023). This further supports the possibility of a close association between olfactory impairment and AD-related pathology, extending this link to an even earlier, preclinical stage. Olfactory measures appear to outperform visual and auditory sensory deficits in predicting AD progression (Fischer et al., 2016; Liu et al., 2025; Murphy, 2019). This specificity likely reflects the distinctive organization of the olfactory network, which consistently overlaps with brain regions selectively vulnerable in AD (Daulatzai, 2015; Vasavada et al., 2015). Compared with healthy controls, patients with AD—and some already at the MCI stage—show altered functional activity in the insula, amygdala, primary olfactory cortex, piriform cortex, and entorhinal cortex (Kareken et al., 2004; Vasavada et al., 2015; Wang et al., 2010; S. Yang et al., 2025). Early alterations in medial temporal lobe structures, particularly in the entorhinal region, may disrupt hippocampal connectivity, thereby impairing the transfer and consolidation of information critical for long-term memory formation (Adams et al., 2022; Berron et al., 2021, 2020; Granger et al., 2023; Tran et al., 2022). In fact, the hippocampus supports the formation of flexible associations among entities that co-occur in space and time, thereby facilitating not only their encoding but also their retrieval through the coordination of cortical regions that store information about specific aspects of the events (Simons et al., 2022). Indeed, impaired communication among regions vital for memory may result in impairments characteristic of the AD spectrum. This is especially evident in the advanced stages, but is likely also present during the prodromal phases, as existing information is no longer updated with new or external data (Weiler et al., 2016). Even if only hypothetically, this mechanism may provide a plausible link between very early olfactory deficits, sometimes detectable even in asymptomatic stages, and the subsequent development of cognitive impairment, particularly memory dysfunction.

A key question is why these regions appear altered even at pre-symptomatic stages, given that the primary damage initially affects olfactory system structures. Reasonably, these areas may exhibit compensatory increases in activity in response to early dysfunction of the olfactory system (B. Chen et al., 2022; Mormino et al., 2012; X. Zhang et al., 2024; Zhu et al., 2025). Such hyperactivity, detectable from the prodromal phase, may reflect not only an attempt to integrate sensory information effectively despite qualitatively and quantitatively degraded inputs but also an increased reliance on interactions with other network nodes that encode previously established associations. In fact,

the system may increasingly rely on stored representations that were accurately learned in the past to maintain appropriate interactions with the environment (Hampstead et al., 2016; Jonin et al., 2022; Liang et al., 2020; Požar et al., 2024). Importantly, this interpretation aligns with the pattern of memory impairment typically observed in patients with early AD, who often exhibit a temporal gradient, with relatively preserved remote memories and disproportionately impaired recent memories (De Simone et al., 2020; Langlois et al., 2016; Leyhe et al., 2009; Müller et al., 2016). Consistently, even in the context of normal aging, there is a tendency to shift from robust episodic recollection to a more semantic, integrated mode of information retrieval (Levine et al., 2002). However, this process is markedly accelerated during the initial stages of AD (Weiler et al., 2016). Within this framework, newly formed associations may fail to guide environmental interactions adequately, and, consequently, may not be sufficiently reinforced or consolidated (Fulton et al., 2024; Yan et al., 2022). Regardless of its precise functional meaning, enhanced neural activity in these temporal lobe regions is associated with increased A β production (Bero et al., 2011; Jagust and Mormino, 2011; Mormino et al., 2012). Crucially, A β deposition begins in the temporal lobe, specifically in olfactory network structures, supporting this possible interpretation (Thal et al., 2000; Wu et al., 2013). While A β plays a physiological role in synaptic function within a tightly regulated range, excessive levels—potentially driven by sustained overactivation—may contribute to the synaptopathy that characterizes the earliest stages of AD (Cai et al., 2023; Sehar et al., 2022). Therefore, AD neuropathology may not originate from primary damage to the cortical areas classically associated with the disease, but rather from secondary dysfunction of these regions resulting from altered activity within sensory systems, particularly the olfactory system (and the LC) (Daulatzai, 2015; Yan et al., 2022; S. Yang et al., 2025). Compensatory increases in activity within these olfactory-related brain regions may elevate local A β levels, thereby creating a permissive environment for the spread of phosphorylated tau (pTau), which then exerts deleterious effects on cognitive function (Prokopiou et al., 2023). Accordingly, the density of NFTs in the OB—which is reduced in volume in patients with SCD, MCI, and AD—closely correlates with tau pathology in the entorhinal cortex, thereby supporting this exploratory pathophysiological link (B. Chen et al., 2022; Christen-Zaech et al., 2003; Thomann et al., 2009b, 2009a).

Thus, although the evidence is not yet definitive, this pattern may represent a crucial yet often overlooked component of early AD pathophysiology. This oversight may be partly attributable to the lack of routine clinical tests to assess olfactory function, and to patients' frequent unawareness of olfactory deficits (Liao et al., 2024). Similarly—albeit potentially less tightly coupled because of differences in the underlying neural networks—age-related visual and hearing deficits are characterized by compensatory hyperactivation of sensory and higher-order cortical areas, particularly frontal regions associated with increased cognitive load (Alain et al., 2022). Finally, aging is often accompanied by social isolation, which may further limit external feedback on the accuracy of sensorimotor associations (Bellucci et al., 2025). This lack of corrective feedback, particularly when sensory inputs are degraded, may exacerbate reliance on maladaptive predictive mechanisms (Wnuk et al., 2025; Wolpe et al., 2016; J. Zhang et al., 2022). This complex interplay among sensory decline, compensatory neural hyperactivity, and reduced environmental feedback might constitute a fundamental substrate for early alterations in older adults who subsequently develop AD.

To summarize, within this hypothetical interpretative framework, damage to the olfactory system would drive both the accumulation of “compensatory” A β in medial temporal cortical regions and increased LC activity (discussed in Section 4). The latter, in turn, begins to accumulate pTau, which—via a prion-like mechanism—might spread to the OB and to closely connected temporal regions, from which it may further propagate throughout the olfactory network (Braak et al., 2011; Thal et al., 2002). This feedback loop may explain the close interrelationship

observed between modifications in these functionally distinct yet interconnected and physiologically cooperative systems. Although olfactory dysfunction may be one of the earliest triggers of neurodegeneration, it is nevertheless essential to consider the next step, which is hypothesized to be the secondary degeneration of the LC, that could account for further characteristic elements of the early stages of AD.

4. The LC: a trade union between sensory impairments and cognitive decline

The LC is a small nucleus located in the posterior rostral pons adjacent to the fourth ventricle's lateral floor. Despite its small number of neurons, it is the core hub of the central noradrenergic system and receives extensive projections from numerous cortical and subcortical regions, to which it, in turn, sends widespread, divergent, but precisely segregated efferent projections (Groves et al., 2025). Indeed, the LC integrates information from neuroendocrine nuclei, the autonomic nervous system, and cognitive-affective regions and is critically involved in regulating many functions, including memory formation, attention, the sleep-wake cycle, immune and autonomic regulation, and the “fight or flight” response (Duszkiewicz et al., 2019; Hansen, 2017; Krohn et al., 2023; Lecas, 2004; Osorio-Forero et al., 2022; Reyes, 2025; Ross and Van Bockstaele, 2021; Titulaer et al., 2021). Furthermore, although often overlooked, it has significant connections with cortical motor regions, olivocerebellar circuits, and descending projections to the spinal cord (Poe et al., 2020). Here, its role in sensory information processing is particularly relevant. LC activation can alter the responses of individual cells, local circuits, and neural networks to both exogenous and endogenous stimuli (Berridge and Waterhouse, 2003; Waterhouse and Navarra, 2019). Consistently, it modulates the thresholds and properties of receptive fields across sensory modalities, particularly in the olfactory domain (Bouret and Sara, 2002; Escanilla et al., 2010; Poe et al., 2020). Indeed, the OB is densely innervated by the LC, and the release of noradrenaline (NE) here is essential for increasing the signal-to-noise ratio, modulating odor thresholds, and supporting olfactory learning through short- and long-term forms of synaptic plasticity (de Almeida et al., 2015; Linster et al., 2011; Manella et al., 2013; Sara, 2009). Specifically, noradrenergic projections target different cellular types in the OB, including both the glomerular and deeper layers, and the distributions of noradrenergic receptor subtypes are layer-specific (Cleland, 2010; de Almeida et al., 2015; Li et al., 2015; Linster et al., 2011; Tan et al., 2010). Moreover, by suppressing the spontaneous activity of mitral cells, NE increases the number and amplitude of odor-evoked responses (Escanilla et al., 2010; Manella et al., 2017). In addition, the LC may modulate external tufted cells, which in turn activate local inhibitory neurons that reduce olfactory nerve input (Ennis et al., 2001; Zhou et al., 2016). Therefore, the essential role of the LC in modulating the olfactory network from its earliest regions is well established.

Notably, the LC is also crucial in the transition from memory to behavior, integrating memory, sensory inputs, and system states to adapt to environmental interactions and bodily states during memory retrieval (Duan et al., 2025). Moreover, it facilitates the generalization of learned associations through interactions with the hippocampus and the amygdala (Duan et al., 2025). In particular, the LC plays a critical role in mediating responses to violations of predictions about upcoming interactions with the environment (Jordan, 2024). Recent Bayesian formulations of LC activity indicate that it encodes errors in predicted sensations and actions, suggesting that it increases firing when internal models of these relationships are inaccurate, causing predictions to diverge significantly from expectations (Jordan, 2024; Sales et al., 2019; Yu and Dayan, 2005). Such predictions are derived from memory, specifically from sensorimotor relationships encoded through past organism–environment interactions (Bar, 2009; Butz et al., 2025). Here, interactions between the LC and the hippocampus are likely essential for regulating episodic memories driven by so-called prediction errors, i.e.,

the mismatch between what is predicted from the system's current state and memories of similar prior interactions and the outcome actually obtained (Spampinato and Celnik, 2021). This interaction is bidirectional, as hippocampal (top-down) modulation conveys information relevant to computing prediction error to the LC—likely via cortical regions such as the prefrontal cortex and the anterior cingulate cortex—which, in turn, generates signals that determine whether, at the hippocampal level, new memories will be formed or existing ones will be updated (bottom-up) (Barron et al., 2020; Groves et al., 2025; Palacios-Filardo and Mellor, 2019; Sinclair et al., 2021). Both of these cortical regions are key to mediating responses to novel or salient stimuli and to exerting cognitive control over hippocampal processing (Bouret and Sara, 2004; Craigmyle, 2013; Tomassini et al., 2022). Interestingly, the LC is involved in multiple types of prediction errors and in more general novelty signals arising from environmental interactions (Breton-Provencher et al., 2022; Jordan and Keller, 2023; Niv and Schoenbaum, 2008; Schultz, 2017). Such errors indicate the need to update—or create—memories and therefore require reactivating memory traces from long-term storage, bringing them into a state of heightened plasticity that allows their modification (Bayer et al., 2025; Sinclair et al., 2021; Sinclair and Barense, 2019). The neuromodulators released by the LC, primarily NE and, to a lesser extent, dopamine, appear crucial for driving these increases in plasticity (Kempadoo et al., 2016; Schwarz and Luo, 2015). This system enables continuous updating of the organism's best internal models of environmental interactions (Grella and Donaldson, 2024; Harley, 2004; Maurer and Nadel, 2021). The hippocampus is essential for determining the spatiotemporal sequence of activation of neuronal ensembles distributed across multiple neocortical sites (Groves et al., 2025). When the discrepancy between predicted and actual outcomes is large, LC input enables reconfiguring the previous sequence, preserving only those neuronal ensembles that still reflect the organism's interaction with the world and replacing those that no longer provide an accurate representation of the organism's engagement with its environment (Bouret and Sara, 2004). Specifically, whereas the hippocampal CA3 subfield encodes predictions, the CA1 region encodes what is actually experienced (Groves et al., 2025; Lisman and Grace, 2005). The greater the mismatch between these two signals, the stronger the activation of the LC—and, to a lesser extent, of the dopaminergic ventral tegmental area—which project to both regions to support single-trial acquisition of a new contextual memory in CA3 and the encoding of new information and/or the reinforcement of pre-existing memories in CA1 (Kempadoo et al., 2016; Lisman and Grace, 2005; Wagatsuma et al., 2018). Thus, prediction errors generated in the hippocampus and adjacent cortical areas elicit responses in the LC, which, in turn, enable plastic changes in the very regions from which the prediction errors originated (Groves et al., 2025). Indeed, NE-dopamine co-release has been reported in both the hippocampus and cortical areas (Devoto et al., 2020, 2005; Kempadoo et al., 2016).

Notably, the LC also encodes variables related to arousal and sleep–wake regulation (Grueschow et al., 2020; Van Egroo et al., 2022). Low tonic LC activity (slow discharge rates, ~0.1–8 Hz) is observed during transitions from wakefulness to sleep or during behaviors characterized by increased parasympathetic tone, whereas higher tonic levels are associated with wakefulness and, when particularly elevated, with stress (Bouret and Sara, 2004; Devilbiss and Waterhouse, 2011; McCall et al., 2015). By contrast, phasic LC activity (i.e., brief bursts of firing at ~10–20 Hz, often followed by periods of relative quiescence) is particularly associated with novelty encoding (Devilbiss and Waterhouse, 2011; Groves et al., 2025). Notably, LC is almost silent during rapid eye movement (REM) sleep, whereas increased activity may precede unprovoked nocturnal arousals (Aston-Jones and Cohen, 2005; Foote et al., 1980). Moreover, during non-REM (NREM) sleep, it is critically involved in modulating sleep spindles (discussed in Section 6) and, thus, in memory consolidation (Kjaerby et al., 2022; Osorio-Forero et al., 2022). Importantly, hippocampal sharp-wave ripples, typically

observed during NREM sleep, play a fundamental role, in coordination with the LC and cingulate and prefrontal cortical regions, in enabling an “offline” comparison of prior knowledge with actual experience, thereby optimizing memory representations (Groves et al., 2025; Momennejad et al., 2018; Robinson et al., 2026).

Therefore, the LC is essential to preserving cognitive functioning. Indeed, its degeneration is not considered a component of the physiological aging process (Theofilas et al., 2017). Even in healthy older adults, higher neuronal density in the LC is associated with a slower decline in cognitive performance (Wilson et al., 2013). Interestingly, an inverted-U-shaped relationship is observed between magnetic resonance imaging (MRI)-assessed LC signal and age, with the fifth decade serving as a tipping point (Beardmore et al., 2021; K. Y. Liu et al., 2017). LC connectivity also correlates with subjective states of arousal and anxiety, possibly due to its association with the amygdala (Liebe et al., 2022; McCall et al., 2017). Importantly, mood and anxiety-spectrum disturbances often emerge around midlife, and several studies suggest that these affective symptoms predict subsequent cognitive decline (Chan et al., 2026; Frank et al., 2026; John et al., 2019; Krohn et al., 2023). Such affective alterations may hypothetically appear when catecholamine synthesis in the LC begins to decline, that is, when its functional reserve is exhausted, and the initially effective compensatory mechanisms lose their efficacy (Mir et al., 2025; Parent et al., 2022). If this possible sequence of events is correct, age-related olfactory dysfunction may initially increase compensatory activity in the LC, which, over time, leads to functional exhaustion and triggers subsequent stages of neurodegeneration. As the damage progresses, the alterations are not only functional but also macrostructural. Indeed, significant loss of LC volume has been documented in AD and other neurodegenerative disorders (Betts et al., 2019a; Jacobs et al., 2021a; Madelung et al., 2022). Consistently, LC neuronal loss is a hallmark of early AD pathophysiology and correlates with disease severity and duration, supporting its causal role in disease progression (Betts et al., 2019a, 2019b; Cassidy et al., 2022; Olivieri et al., 2019; Zarow et al., 2003). A loss of approximately 30 % of LC neurons marks the transition from the absence of cognitive symptoms to mild impairment, whereas a further 25 % loss is associated with progression to the moderate stage of AD (Kelly et al., 2017; Matchett et al., 2021). Therefore, although this interpretation remains necessarily speculative at present and represents only one of several possible explanatory frameworks, the evidence discussed here suggests that such mechanisms may contribute to a plausible trajectory of AD alterations. While further studies are required to substantiate this hypothesis, the present findings support the view that these processes merit consideration as potential contributors to early disease dynamics.

Importantly, in line with this view, tau can begin accumulating decades before clinical onset, even in the absence of cortical A β deposits (Braak and Del Tredici, 2011, 2012a). Consistently, A β and tau initially deposit in distinct brain regions: tau in the brainstem (and later in the entorhinal cortex), and A β in the neocortex. However, once present, tau can promote A β pathology (Ehrenberg et al., 2017; Theofilas et al., 2017). Nevertheless, because of the prolonged persistence of tau in surviving LC neurons, a “two-hit” hypothesis has been proposed, indicating that, in addition to abnormal tau, a secondary trigger is required to induce LC neuron death (Theofilas et al., 2017). This vulnerability may depend, at least in part, on metabolites specific to the noradrenergic system, which can interact with tau and A β (Kang et al., 2022; Lancini et al., 2023). When LC activity increases, cerebrospinal fluid (CSF) levels of these metabolites also rise, thereby accelerating the accumulation of AD hallmarks (Krohn et al., 2023). In fact, increased NE levels have been observed from the earliest stages of AD (Palmer et al., 1987). Furthermore, in LC, a small neuronal population must meet the needs of the entire CNS (Poe et al., 2020). In addition, the axons of the LC are only partially myelinated and therefore energetically inefficient (Lushchak et al., 2021; Paker et al., 2026). This imposes high metabolic demands even under physiological conditions, thereby increasing oxidative stress due to sustained mitochondrial workload (Evans et al., 2022). Although

LC neurons containing tau aggregates can survive for prolonged periods, their ability to secrete NE is nonetheless impaired (Braak and Del Tredici, 2012a). These neurons also exhibit alterations in transcriptional profiles that may reflect compensatory neuroprotective responses but, depending on the stage of disease progression and additional sources of injury, may instead accelerate neurodegeneration (Weinshenker, 2018). The relationship, however, is even more complex. NE can also inhibit A β aggregation by destabilizing protofibrils, suggesting that, at physiological concentrations, it may exert protective effects, whereas elevated levels may accelerate the neuropathological cascade that begins with tau accumulation (Kang et al., 2022; Lancini et al., 2023; Zou et al., 2019). Similarly, NE has a U-shaped effect on neuronal targets: facilitation is initially modest, increases at higher concentrations, and then declines rapidly at excessive levels (Devlbiss et al., 2006). Therefore, the compensatory increase in LC activity, initially useful for counteracting peripheral alterations, could itself contribute to worsening deficits over time, thereby degrading signal processing (Devlbiss and Waterhouse, 2000). Consistently, an increase in LC activity may serve as an early compensatory strategy with protective effects, whereas in later phases it has been associated with detrimental effects (Jacobs et al., 2021a; Koops et al., 2025; Prokopiou et al., 2022; Weinshenker, 2018). Tau itself can increase neuronal excitability, thereby exacerbating the hyperactivity initially associated with compensatory LC responses (Crimins et al., 2012; Rudy et al., 2015; Weinshenker, 2018). Moreover, at least in part, these effects may be driven by disease-related changes in the energy demands of LC neurons, given the tight coupling between neurotransmission regulation and glucose metabolism (Dienel, 2019). Increased glucose availability in the LC, as expected with a significant increase in its activity, may further intensify this cycle of hyperexcitability, given that extracellular glucose promotes the formation of A β oligomers (Dienel, 2019; Kedia et al., 2017; Pierre et al., 2003). Interestingly, increased LC activity has been associated with elevated CSF levels of pTau181, the pTau isoform most extensively characterized in AD (Jack Jr. et al., 2024; Koops et al., 2025). However, given the early onset of these alterations, additional biomarkers may be more sensitive, even at the SCD stage (Gonzalez-Ortiz et al., 2024; Palmqvist et al., 2025; Warmenhoven et al., 2025). Such biomarkers could facilitate detection through minimally invasive approaches, including blood-based assays (Antonioni et al., 2023b, 2025e, 2025g). To summarize, sustained and excessive increases in activity—reflecting the need to compensate for damage that cannot be effectively resolved—may ultimately harm LC targets that rely on its compensatory support, leading to functional exhaustion of the LC and widespread consequences for the entire CNS.

Importantly, a lower novelty-related LC activity (i.e., the phasic firing pattern) has been observed in AD and is associated with tau diffusion in the temporal cortex and the onset of memory decline, particularly in the context of increased A β levels, supporting that functional exhaustion of LC compensation marks the transition to symptomatic stages (Ghosh et al., 2021; Prokopiou et al., 2023; Wagatsuma et al., 2018). Accordingly, phasic patterns of LC activity appear to exert a neuroprotective effect, mitigating tau-related impairments in olfactory and spatial learning compared with tonic firing modes (Omoluabi et al., 2021). Indeed, phasic stimulation preserves LC fiber density, in contrast to the marked fiber loss observed with tonic or absent stimulation—an alteration consistently linked to tau spread (Kelly et al., 2017; Rorabaugh et al., 2017). Specifically, from the LC, pre-tangle pTau pathology (i.e., a precursor of NFTs prone to aggregation, also observed at Braak stage 0) can propagate to interconnected cortical regions as the disease progresses (Harley et al., 2021; Poe et al., 2020; Stratmann et al., 2016). From the medial temporal lobe, tau pathology may spread to neocortical areas, particularly in the presence of A β , suggesting a facilitating (rather than causative) role for A β in the diffusion of misfolded tau within the brain (van der Kant et al., 2020). Thus, an age-related tauopathy may be a necessary condition for A β to catalyze tau propagation (Spire-Jones et al., 2017). This could also explain why even

people with autosomal dominant AD, in which A β overproduction is significant, develop symptoms only after 30–60 years (Frisoni et al., 2022). Moreover, individuals with A β but no tau pathology are relatively common, whereas those with tau pathology without A β are extremely rare (Jack et al., 2019). Therefore, A β accumulation may, at least in part, reflect a compensatory response to various forms of synaptic damage, whereas tau pathology appears more specifically associated with the early stages of the neuropathological cascade (Arnsten et al., 2021; Elman et al., 2014; Herz, 2025; Huang, 2024). Accordingly, overt memory impairments typically emerge at more advanced Braak stages (III–IV), when tau tangles reach the hippocampus, medial temporal cortex, insula, and association cortices (Harley et al., 2021; Theriault et al., 2022). Consistent with this trajectory of pathological spread, LC integrity correlates negatively with tau burden not only in temporal regions but also in the parietal and frontal cortices (Jacobs et al., 2021a). Moreover, tau pathology within the LC predicts more rapid memory decline, particularly in the presence of elevated A β levels, whereas preserved catecholamine synthesis in the LC predicts a lower temporal tau burden, confirming the pivotal role of LC breakdown in disease progression (Ciampa et al., 2022; Jacobs et al., 2021a). The reasons temporal regions are particularly vulnerable, despite the LC's widespread projections, remain a matter of debate. This selective vulnerability has been attributed to the specificity of LC projections and to the regional distribution and density of NE receptors, which are particularly abundant and diverse in temporal regions (O'Callaghan, 2025; Schwarz et al., 2015). Although currently speculative, it is also possible that functional changes within these regions, resulting from primary olfactory dysfunction, render them particularly susceptible to tau dissemination and accumulation, as suggested by increased A β levels.

Why only some individuals, despite similar early pre-tangle tau accumulation, progress to overt tau pathology within the LC may depend, among other factors, on genetic susceptibility. Apolipoprotein E (ApoE), especially the ϵ 4 allele—the strongest genetic risk factor for sporadic AD—appears to be critical (Frisoni et al., 2022; Martens et al., 2022). Specifically, increased LC activity leads to the production of a toxic metabolite of NE metabolism, 3,4-dihydroxyphenylglycolaldehyde, which promotes tau aggregation and propagation (Burke et al., 1998; Weinshenker, 2018). However, this neurotoxic effect is observed primarily in ApoE4 carriers, whereas the ϵ 3 allele appears to mitigate this process (Kang et al., 2021). This may partly explain why the prevalence of ϵ 4 allele carriers is notably high among individuals with MCI and AD and why it is associated with a more than 10-year reduction in age at onset (Belloy et al., 2019; Mattsson et al., 2018). Interestingly, the impact of ApoE4 on the risk of AD is greatest between ages 55 and 70, after which it tends to decline (Saddiki et al., 2020). Reasonably, this may be the age range in which sensory alterations, particularly olfactory ones, most strongly interact with the comorbidity burden, which increases with age (Murphy, 2019; Nelis et al., 2019). Subsequently, hypothetically, due to effective compensation or other forms of reserves, its impact is less decisive (Frisoni et al., 2022; Groot et al., 2018; Mitoma et al., 2020). Furthermore, ApoE is implicated in multiple AD pathophysiological processes, including inflammation, A β clearance, blood-brain barrier (BBB) permeability, and cholesterol metabolism (Davis et al., 2020; Jeong et al., 2019; Montagne et al., 2020; Reale et al., 2012; Thal et al., 2007). Moreover, other factors may also play a relevant role, such as hormonal factors, given their critical role in sleep regulation and hippocampal function, and their association with an increased risk of AD among female carriers of ApoE4 (Altmann et al., 2014; Fisher et al., 2018; Galea et al., 2013; Harrington et al., 2022; Haufe et al., 2022). This supports a complex, multifactorial pathophysiology in which age-related mechanisms, environmental factors, and genetic vulnerability interact to shape disease progression, as is often the case in neurodegenerative disorders (Antonioni et al., 2023a; Frisoni et al., 2022; Kasper P. Kepp et al., 2023; Rahman et al., 2020).

As previously noted, the LC is essential for mediating hippocampal

synaptic plasticity through the coordinated release of NE and dopamine (Poe et al., 2020). Indeed, beyond its well-known involvement in long-term potentiation (LTP), it also plays a key role in long-term depression (LTD), habituation, and synaptic depotentiation (Grella et al., 2019; Hagen et al., 2016; James et al., 2021; Poe et al., 2010). Importantly, LTP and LTD, which are specific increases or decreases in synaptic strength or efficacy, respectively, are considered foundational to learning mechanisms across the CNS, particularly in the hippocampus (Gazerani, 2025; Hayashi, 2022). Crucially, evidence from non-invasive brain stimulation (NIBS) techniques has shown that alterations in synaptic plasticity, particularly LTP, are among the most consistent neurophysiological biomarkers of AD neuropathology, detectable as early as the MCI stage and capable of predicting conversion to overt dementia (Di Lorenzo et al., 2020, 2016; Koch et al., 2016, 2014, 2012;

Motta et al., 2018). Thus, LC dysfunction, together with alterations in the olfactory network, may constitute a key neurobiological correlate of these plasticity deficits and have compelling therapeutic implications, as discussed in subsequent sections. Fig. 1 provides a schematic overview of the organization of the olfactory network and its relationship to the LC and the hippocampus.

Notably, the LC interacts extensively with the cerebellum, another possible key node in early AD pathophysiology (see Section 5) (Arleo et al., 2024; Yang et al., 2024). Similarly, the LC is tightly interconnected with the nucleus basalis of Meynert in the basal forebrain, another critical element in this context (España and Berridge, 2006; Hampel et al., 2018). Importantly, shifts between phasic and tonic firing modes of the LC modulate electroencephalography (EEG) alpha-band activity (8–12 Hz) via thalamic gating mechanisms that are crucial for cortical

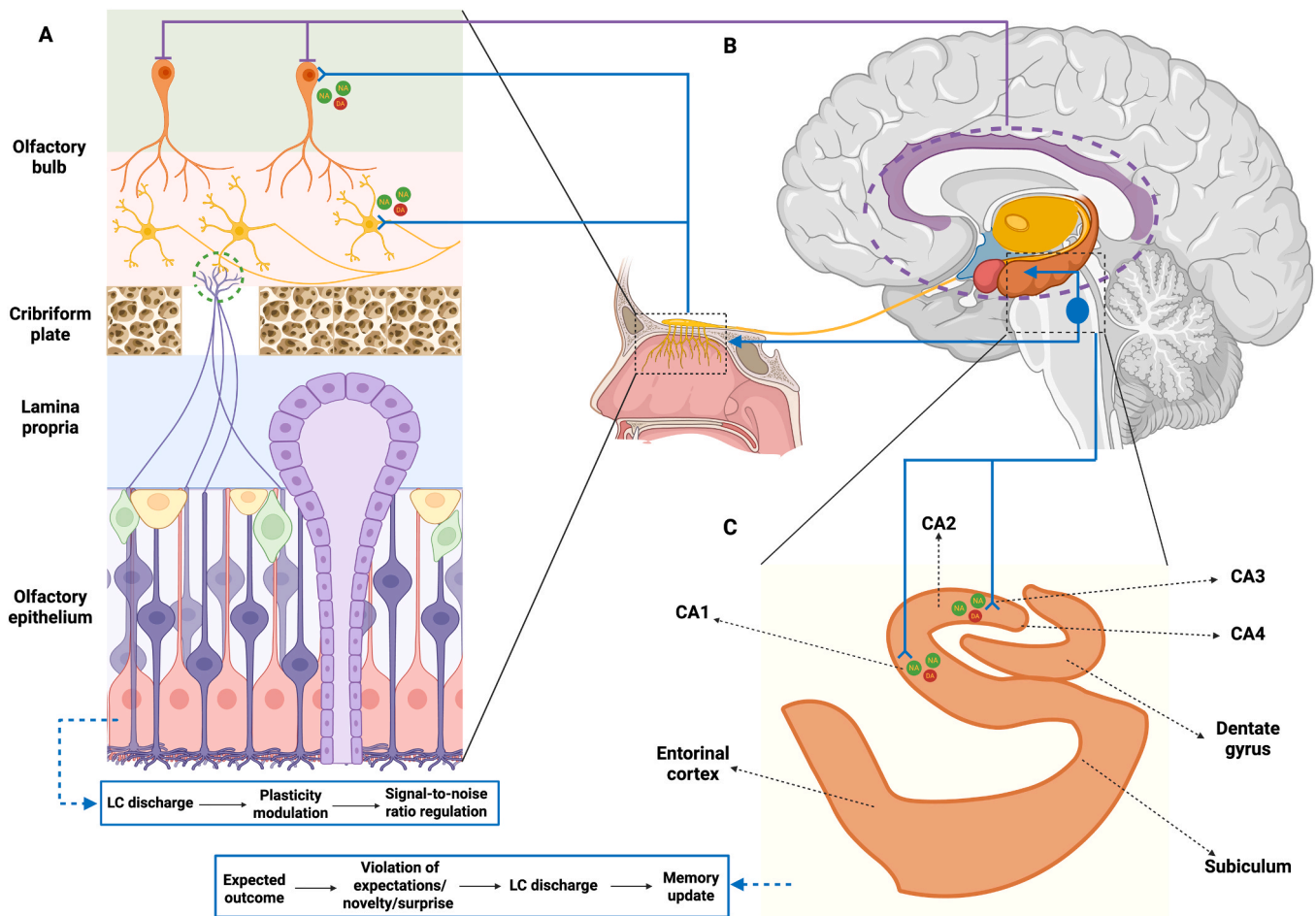


Fig. 1. Olfactory–LC–hippocampal circuitry supporting prediction-error signaling and plasticity. Panel A shows a schematic representation of the olfactory pathway (Brunert et al., 2023; Courtiol and Wilson, 2016; Firestein, 2001; Giessel and Datta, 2014). A specialized neurosensory epithelium (dark purple cells), with protruding cilia that bear odorant receptors, is interspersed with supporting sustentacular cells (light orange cells), basal stem cells (light green and yellow cells), and Bowman's mucus-secreting glands (cavity surrounded by light purple cells). Each olfactory sensory neuron projects to the OB. Mitral and tufted cells (yellow cells) synapse with the olfactory nerve, forming the olfactory glomeruli (green dotted circle). Axonless granule neurons (orange cells) form reciprocal dendrodendritic synapses that provide feedback and lateral inhibition. Both mitral/tufted cells and granule cells receive innervation from the LC (blue lines), with the release of dopamine (small red circles) and, above all, NE (small green circles), which mediate neuroplastic effects (Cleland, 2010; de Almeida et al., 2015; Ennis et al., 2001; Escanilla et al., 2010; Li et al., 2015; Linster et al., 2011; Manella et al., 2017; Tan et al., 2010; Zhou et al., 2016). Top-down modulation from cortical areas of the olfactory network (purple lines) modulates granule cell activity in response to prior expectations or contextual information (Adams et al., 2019; Boyd et al., 2012; Mazo et al., 2016). Panel B highlights the relationships between the olfactory system and the LC. Information from the OB reaches the olfactory cortex via the olfactory tract and the olfactory tubercle (yellow line) and, from there, a complex ensemble of brain areas involved in odor information processing (purple-dotted circle) (Courtiol and Wilson, 2015; Strauch et al., 2022; Zhou et al., 2019). The LC projections (blue lines) broadly innervate cortical and subcortical targets (Liebe et al., 2022; Poe et al., 2020). It modulates the OB (central dotted square) and the hippocampal regions (right dotted square). Panel C provides a schematic view of the medial temporal lobe, illustrating LC noradrenergic and dopaminergic modulation of hippocampal subfields, particularly CA3, which processes contextual memory, and CA1, which encodes new information and/or reinforces pre-existing memories (Kempadoo et al., 2016; Lisman and Grace, 2005; Wagatsuma et al., 2018). Overall, LC-mediated neuromodulation may coordinate plasticity, memory updating, and adaptive behavior across olfactory, hippocampal, and distributed cortical networks via sensory-driven prediction errors. Created with Biorender.com.

inhibition, desynchronization, and selective attention (Fang et al., 2025; Jensen and Mazaheri, 2010; McCormick, 1989). These processes are essential for efficient sensory processing, and enhanced functional connectivity between the LC and the nucleus basalis of Meynert supports rapid, flexible, global shifts in cortical connectivity states in response to contextual demands (Dahl et al., 2020; Mather et al., 2016; Mather and Harley, 2016; Taylor et al., 2022; Wainstein et al., 2022). Accordingly, alterations in alpha-band oscillations have been proposed as potential early biomarkers across the AD continuum, detectable at the SCD and MCI stages (Babiloni et al., 2023; Carpi et al., 2026; López-Sanz et al., 2016; Perez et al., 2024; Polverino et al., 2022). Given that cortical neuropathology is minimal or nearly absent during these preclinical phases, these EEG alterations may be driven, at least in part, by increased LC activity and subsequent tau accumulation, which, in turn, disrupts the circuits responsible for generating and regulating these rhythms (Jacobs et al., 2021a; Matchett et al., 2021). Thus, quantitative EEG or transcranial magnetic stimulation (TMS)-EEG techniques, both during wakefulness and sleep, could be useful tools for the early identification of AD neuropathology (Antonioni et al., 2025b; Bernardi et al., 2025; Fischer et al., 2023).

Beyond its role in neuromodulation, the LC regulates neuro-inflammatory processes, neurovascular coupling (i.e., the dynamic matching of cerebral blood flow to neuronal metabolic demands), and BBB integrity by modulating tight junctions (Bekar et al., 2012; Erdő et al., 2017; Giorgi et al., 2020; Iadecola, 2017; Kalinin et al., 2006; Luissint et al., 2012; Thomsen et al., 2017). Their disruption alters brain perfusion and facilitates the infiltration of peripheral pro-inflammatory factors into the CNS, creating a cytokine-rich environment—already amplified by physiological aging—that further exacerbates ongoing neurodegenerative processes and worsens cognitive performance (Giorgi et al., 2020; Huang et al., 2021; Knox et al., 2022; X. Li et al., 2023). In addition, microglial dysfunction associated with these changes, likely acting synergistically with altered catecholaminergic signaling from the LC, further impairs synaptic plasticity (Bettcher and Kramer, 2014; Ciampa et al., 2022; Gao et al., 2023; Hansen, 2017; Hussain et al., 2021; Yamasaki and Takeuchi, 2017). Altogether, these alterations—already detectable in presymptomatic stages and markedly pronounced at clinical onset—suggest that LC dysfunction may induce pathological changes not only within the CNS but also at the CNS–periphery interface, which might be crucial for explaining the progressive amplification of damage as neuropathology advances (Biagioni et al., 2024; Blau et al., 2012; Fernández-Matarrubia et al., 2025; Ghanbarian et al., 2025; Heneka et al., 2015; Jacobs et al., 2021c; Mir et al., 2025; Parbo et al., 2017). Indeed, the LC exhibits dense interactions with the capillary bed and lies immediately adjacent to the CSF in the fourth ventricle, making it highly susceptible to environmental toxins (Galgani et al., 2025b; Giorgi et al., 2020; Nikolenko et al., 2024; Pamphlett, 2014). Moreover, LC degeneration is associated with cerebral microangiopathy, regardless of cortical AD pathology, and may therefore represent a substrate for vascular injury (Freeze et al., 2023).

Finally, given its pivotal role in modulating sleep-related processes (discussed in Section 6), early degeneration of the LC may also provide a mechanistic explanation for the frequent and often severe sleep disturbances observed in AD (Ferini-Strambi et al., 2024; Ju et al., 2014; Krohn et al., 2023; Slutsky, 2024). These disturbances emerge during the preclinical stage and progressively worsen over time, ultimately leading to a profound disruption of the sleep–wake cycle (i.e., the so-called sundowning phenomenon), in which patients tend to sleep during the day and wander at night (Ehrenberg et al., 2018; Toccaceli Blasi et al., 2023; Van Egroo et al., 2022, 2019; Warfield et al., 2023). This behavioral dysregulation often necessitates the use of high doses of antipsychotic medications, which carry substantial risk profiles, and frequently culminates in institutionalization (Canevelli et al., 2016). Moreover, disruption of sleep architecture results in a marked reduction in slow-wave sleep (SWS) because sleep becomes highly fragmented (Himali et al., 2023; Lim et al., 2013). SWS is the phase most strongly

associated with the clearance of neurotoxic metabolites accumulated during wakefulness, mediated by sleep-dependent expansion of perivascular spaces and activation of the glymphatic system. Consequently, impaired SWS exacerbates the accumulation and propagation of both tau and A β , thereby reinforcing the vicious cycle described above—particularly in older patients with sleep disturbances due to common comorbidities and polypharmacotherapy (Barthélemy et al., 2020; Beschorner and Nedergaard, 2024; Dagum et al., 2026; Himali et al., 2023; Nedergaard and Goldman, 2020; Rollo et al., 2026a; Tekieh et al., 2022). Indeed, even a single night of disrupted sleep increases CSF levels of neurotoxic proteins, highlighting how rapidly damage can accrue when this mechanism persists and worsens over time (Ju et al., 2017; Shen et al., 2023). At this stage, it may also be important to consider a third element—closely linked to olfactory dysfunction and LC alterations—that could plausibly contribute to the early pathophysiological processes of AD, namely cerebellar involvement. While the precise relevance and temporal dynamics of cerebellar alterations in AD remain incompletely understood, accumulating evidence suggests that this region may play a more active role in early network dysfunction than traditionally assumed.

5. The cerebellum: another cue of the early breakdown of the sensorimotor prediction system

The cerebellum is a structure of the posterior cranial fossa that contains more than half of all neurons in the entire CNS. Although traditionally considered exclusively involved in motor coordination, it also contributes to a wide range of sensory, cognitive, and emotional functions owing to its extensive connections with numerous cortical and subcortical regions (Schmahmann, 2019). Indeed, although originally used as a reference region, it is now recognized to exhibit specific structural and functional alterations, in some cases even before the MCI stage (Antonioni et al., 2025h; Y. Chen et al., 2023b; Hoxha et al., 2018; Guangdong Liu et al., 2024b; Yang et al., 2024). Thus, the cerebellum appears pivotal in the complex early pathophysiology underlying the prodromal clinical features of the disease.

First, the cerebellum is a key structure for generating feedforward internal models of sensorimotor relationships with the external environment (Caligiore et al., 2017). It receives extensive input from both cortical and subcortical regions, conveying information about the system's current state and motor commands to peripheral effectors (Antonioni et al., 2024c). This allows the cerebellum to compare predicted sensory outcomes from existing internal models with actual sensory feedback and, in the event of a mismatch, generate prediction-error signals that can be used to correct subsequent interactions with the environment or update the internal models. Through its connections with the basal ganglia and the hippocampus, it can not only access models derived from prior experiences but also contribute to modifying pre-existing neuronal ensembles that encode them (Antonioni et al., 2024c; Bostan and Strick, 2018; Caligiore et al., 2017; Rondi-Reig et al., 2022). Importantly, the complex interactions among the cellular elements of cerebellar circuitry enable the expression of multiple forms of short- and long-term synaptic plasticity, widely regarded as the neurobiological substrates of learning and, consequently, of the updating of internal models (D'Angelo, 2018a; Gao et al., 2012). Indeed, granule cells (GrC) receive input from a network of interconnected regions via mossy fibers (MF) and, in turn, give rise to parallel fibers (PF) that synapse onto both Purkinje cells (PC)—the sole output neurons of the cerebellar cortex, which exert inhibitory control over the deep cerebellar nuclei (DCN) from which efferent projections to other CNS stations originate—and onto inhibitory interneurons (D'Angelo and Casali, 2012). This highly organized circuitry allows sensorimotor relationships to be updated in response to coincident incoming stimuli and to error signals conveyed by climbing fibers (CF) arising from the inferior olive (IO) (D'Angelo, 2018a; D'Angelo and De Zeeuw, 2009). Indeed, each CF projects to a single PC, modulating the

PC's interactions with PF and signaling discrepancies between predicted and actual outcomes (Coemans et al., 2004). In addition, this architecture supports multiple forms of feedback and feedforward regulation, thereby greatly increasing the cerebellum's computational complexity and flexibility in information processing (De Zeeuw and I, 2021; Gao et al., 2012). Importantly, the cerebellum expresses a wide range of intrinsic rhythms and oscillations that provide a temporal scaffold for synchronizing information-processing operations not only locally but also across interconnected cortical networks (De Zeeuw et al., 2008). Thus, the cerebellum is a central hub within the distributed network that updates sensorimotor relationships with the external environment.

Here, the interactions between the LC and the cerebellum are particularly consistent with a role in adaptive updating. Indeed, in the context of predictive processing, prediction errors can trigger corrective plasticity in the internal model that generates predictions (Keller and Mrosovsky, 2018). This process is likely mediated by a gating mechanism that increases neuroplasticity in response to prediction errors (Hovsepian et al., 2023; McDougle et al., 2019). As noted,

neuromodulatory systems are crucial for conveying signals that modulate this gating process (Choi et al., 2005; He et al., 2015). Consistently, the LC modulates plasticity gain, thereby regulating the extent to which local prediction errors shape internal models (Jordan and Keller, 2023). Thus, the LC serves as a central controller of the learning rate, accelerating model updates in contexts of novelty, uncertainty, or rapid environmental change. Moreover, it is critically involved in context-dependent motor correction, in which the cerebellum is also pivotal (Spampinato and Celnik, 2021; Witts et al., 2023). Notably, noradrenergic projections from the LC (likely overlapping with pathways conveying signals of surprise and novelty to the hippocampus) pass through the superior and middle cerebellar peduncles and modulate synaptic plasticity, neuronal excitability, and responsiveness to sensory and motor inputs, both at the level of the cerebellar cortex—particularly in PC—and within the DCN (Caestecker et al., 2025; Ma et al., 2023; Paker et al., 2026; Poe et al., 2020; Saitow et al., 2025; Steindler, 1981; Waterhouse et al., 2022; Waterhouse and Navarra, 2019). Consistently, connections between the LC and the cerebellum, at both the cortical and

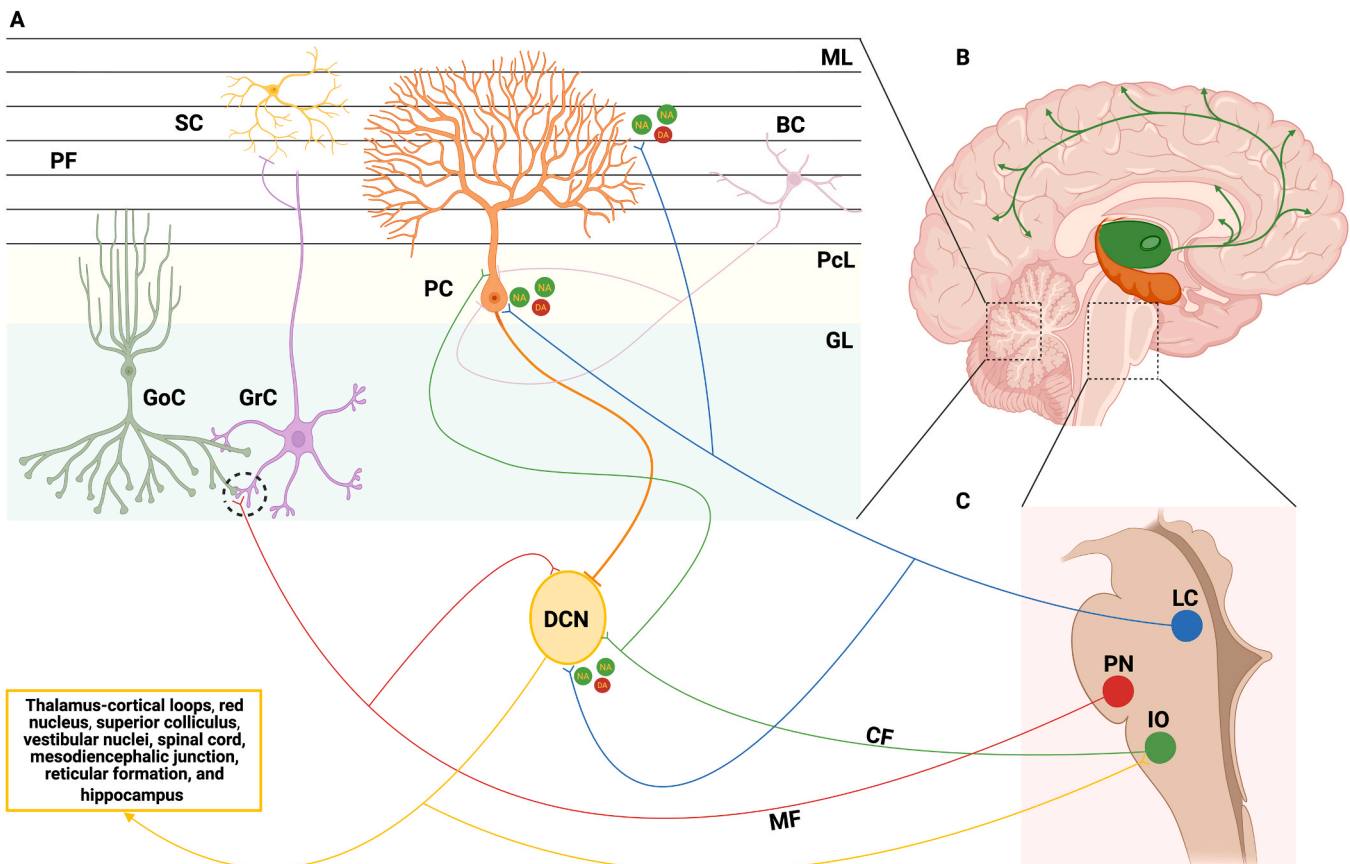


Fig. 2. Cerebellar circuitry and its interaction with the LC in predictive processing and adaptive plasticity. Panel A shows the cerebellar microcircuitry (D'Angelo, 2018; D'Angelo and Casali, 2012; Habas, 2023; Rondi-Reig et al., 2022). In the granule cell layer (GL), GrC, which receive input via MF, give rise to PF that synapse onto PC and onto inhibitory interneurons, including stellate cells (SC) and basket cells (BC), which mediate feedforward inhibition on the PC. The cell bodies of PC lie in the layer that bears their name (PcL), whereas their dendritic arbors develop in the molecular layer (ML). The PC integrate this contextual information with error signals conveyed by CF from the IO. Through their inhibitory projections to the DCN, PC regulate cerebellar output to a wide range of targets. In the GL, Golgi cells (GoC) are inhibitory interneurons that filter MF inputs and regulate GrC excitation (D'Angelo et al., 2013; Y. Tang et al., 2021). The dotted circle in the GL identifies a cerebellar glomerulus, i.e., the synapse between an MF, a GrC, and a GoC, representing the primary input organization of the cerebellar circuitry. This architecture supports multiple forms of synaptic plasticity (Gao et al., 2012). Panel B illustrates large-scale cerebello-thalamic-cortical loops (Habas, 2023; Rondi-Reig et al., 2022). Panel C shows brainstem nuclei, namely the LC, pontine nuclei (PN), and IO. Noradrenergic (small green circles) and, to a lesser extent, dopaminergic (small red circles) projections from the LC reach the cerebellar cortex, particularly PC, and synapse on PC and PF, as well as on the DCN—via the superior and middle cerebellar peduncles—modulating neuronal excitability and synaptic plasticity at multiple scales. In the predictive-processing framework, the LC integrates global prediction-error signals and encodes a context-dependent measure of surprise, thereby serving as a controller of the learning rate (Caestecker et al., 2025; Carey and Regehr, 2009; Carlson et al., 2021; Ma et al., 2023; Ohmae and Medina, 2015; Paker et al., 2026; Poe et al., 2020; Saitow et al., 2025; Stanley et al., 2023; Steindler, 1981; Waterhouse et al., 2022; Waterhouse and Navarra, 2019; Zang and De Schutter, 2019). Thus, through coordinated interactions with cerebellar circuits (and the hippocampus), LC-mediated neuromodulation gates plasticity during novelty, uncertainty, or rapid environmental change, thereby supporting efficient motor correction, cognitive adaptation, and continuous updating of internal models. Created with BioRender.com.

DCN levels, have been shown to enhance PC activity (Dietrichs, 1988; Moises et al., 1981; Szabadi, 2013). Specifically, NE appears to modulate associative synaptic plasticity between PC and CF (Carey and Regehr, 2009; Ohmae and Medina, 2015; Zang and De Schutter, 2019). Moreover, LC innervation is essential for regulating DCN activity, particularly in the context of cognitive behaviour (Carlson et al., 2021). Similarly, a specific LTP effect between PF and PC, mediated by NE release, is critical for aversive learning, shaping cognitive and motor fear responses via DCN targets in the brainstem (Stanley et al., 2023). Therefore, the coordinated interactions among the LC and the cerebellum (together with the hippocampus) appear well-suited to support the continuous updating of the brain's best available models of the world. Fig. 2 shows a schematic of the cerebellar circuitry and its connections with the LC.

As mentioned, the involvement of the cerebellum in AD pathophysiology is now supported by extensive research (Jacobs et al., 2018). It is widely recognized that alterations in large-scale brain networks can precede the onset of overt clinical symptoms by decades (Ereira et al., 2024; Planche et al., 2022; van Niftrick et al., 2022). Beyond cerebellar functional changes that may arise secondary to olfactory dysfunction (discussed below), the cerebellum may be directly involved through the spread of AD-related neuropathology originating in the LC. Indeed, the LC and the cerebellum are tightly interconnected and jointly support sensorimotor and mnemonic functions (Canton-Josh et al., 2022; Poe et al., 2020; Sara, 2009; Stanley et al., 2023; Zeidler et al., 2020). The LC regulates neurotransmitter balance in the cerebellum, so reductions in noradrenergic input at this level can impair learning-related plasticity (Cartford et al., 2004; Hirano et al., 2023; Poe et al., 2020; Stanley et al., 2023). Given that LC–cerebellar connections remain relatively preserved despite ongoing neuropathological progression, there is a close correspondence between the severity of neuropathological damage in brainstem nuclei (including the LC) and in the cerebellum (Irmeler et al., 2012; Mann et al., 1990; Marcyniuk et al., 1986; Rüb et al., 2016, 2001). Thus, tau pathology may spread via prion-like mechanisms from the LC to the cerebellum along these specific pathways (Gilvesy et al., 2022; Iba et al., 2015). Reasonably, this process may be further exacerbated by cerebellar functional alterations driven by the need to compensate for peripheral sensory deficits, which require more frequent integration of inputs that deviate from established internal models and, consequently, greater reliance on previously encoded memories to interact effectively with the environment (Mohan and Vanneste, 2017; Roth et al., 2013). Such demands entail increased interactions with the hippocampus, which, as discussed, is directly affected by olfactory system pathology (Dintica et al., 2019; Kubota et al., 2020; Rondi-Reig et al., 2022; Sato et al., 2024; Zeidler et al., 2020). This scenario may thus give rise to a vicious cycle of damage that progressively worsens alterations across all examined regions, particularly in the presence of functional exhaustion of the LC (Geng et al., 2025; Lu et al., 2019; Manella et al., 2017; Meyer et al., 2025; Rey et al., 2012).

In addition to tau pathology, likely as a consequence of excessive compensatory functional load, the cerebellum also exhibits substantial accumulation of A β (Arleo et al., 2024; Jacobs et al., 2018; Lopez et al., 2024). Cerebellar amyloid deposits have been reported in patients with sporadic AD, particularly in the GL and Pcl (Cheron et al., 2022; Jacobs et al., 2018; Lomoio et al., 2012; Lopez et al., 2024). Notably, the burden of these deposits is inversely correlated with age at disease onset (Cole et al., 1993, 1989). Therefore, at least within this speculative framework, the cerebellum may serve as a structural and functional compensatory reserve. The saturation of this reserve—if one considers, as in the hippocampus, that amyloid burden is a proxy for functional exhaustion and the onset of synaptopathy—may mark the transition to clinical symptom emergence (Bie et al., 2018; Mitoma et al., 2021, 2020; Munoz-Musat et al., 2025; Parodi et al., 2010). Indeed, neurotoxic A β oligomers, in addition to classical plaques, have been detected in the cerebellum (Hoxha et al., 2018; Tomic et al., 2009). Moreover, macroscopic alterations in cerebellar gray matter have also been reported, with characteristic spatial patterns (Gellersen et al., 2017; Samstag

et al., 2025; Toniolo et al., 2023; Zhang et al., 2026). In the early stages (even in SCD and MCI), involvement predominates in the posterior lobes and the vermis—regions most strongly connected, respectively, with fronto-parietal-temporal cognitive networks and with brainstem structures—whereas the anterior lobe, primarily implicated in sensorimotor functions, is involved later and in a less regionally specific manner as neuropathology progresses, consistent with clinical observations at symptom onset and during disease progression (Jacobs et al., 2018; Toniolo et al., 2023; Van Rossem et al., 2025; Zhang et al., 2026).

Importantly, white matter abnormalities have also been observed, even at the MCI stage, following a similar posterior-to-anterior gradient, further reinforcing the notion that connectivity plays a critical role in AD progression (Ahmed et al., 2014; Li et al., 2013; Mascalchi et al., 2014; Olazarán et al., 2013; Teipel et al., 2010; Toniolo et al., 2020). Indeed, the regions most affected early on appear to be those most strongly functionally coupled to the default mode network (DMN)—a set of brain regions active during restful wakefulness and during internally oriented cognition, including mind-wandering, mental time travel, and the simulation of future events (Menon, 2023). Additionally, the olfactory network is tightly connected to brain regions within the DMN (Gottfried, 2010; Olofsson et al., 2012; Zelano et al., 2011). Given the DMN's crucial role in integrating memory and semantic representations to form a coherent “internal narrative,” and the importance of olfactory memories in this context, the functional relevance of the interaction between the DMN and the olfactory network seems consistent (Kemmerer, 2025; Menon, 2023; Zhou et al., 2021). Accordingly, the DMN modulates olfactory network activity and related behavioral responses, and this activity is dynamic and responsive (Karunanayaka et al., 2017). Moreover, the hippocampus is a crucial node in both the olfactory network and the DMN, and their interplay is essential for accurate information encoding (Barnett et al., 2021; Ezama et al., 2021; Kobayashi and Amaral, 2007; Miller et al., 2008; Wahlheim et al., 2022; Yeshurun et al., 2009). In these processes, the cerebellum, through its interactions with the hippocampus and other key hubs, such as the precuneus and the cingulate cortex, which are critical for integrative and motivational functions, may play an important modulatory role (Kawabata et al., 2022; Kucyi et al., 2015; Menon, 2023; Sanz-Morales and Melero, 2024). Notably, the DMN is among the networks most consistently and early affected in AD, and its disruption correlates with clinical severity, particularly in episodic memory (Babiloni et al., 2023; Buckner et al., 2005; Chhatwal et al., 2018; Ozdemir et al., 2025; Wang et al., 2024). Consistently, functional MRI (fMRI) studies have demonstrated that alterations in posterior cerebellar regions are present at the MCI stage and extend to anterior regions with the onset of clinically overt AD, at which point abnormalities become less focal and more widespread (Bai et al., 2011; Bernard et al., 2025; Lin et al., 2024; F. Tang et al., 2021). This pattern may reflect the progressive spread of neuropathology and/or functional exhaustion of neighboring regions recruited to compensate for initially affected areas. Consistent with a compensatory role for cerebellar activity, greater cerebellar activation has been associated with better performance during information encoding, including in longitudinal studies of AD (Fliessbach et al., 2007; H. Li et al., 2023; McLaren et al., 2012; Olivito et al., 2020). It is also possible, however, that such hyperactivation reflects amyloid-related hyperexcitability, which may initially be compensatory but ultimately becomes neurotoxic (Giorgio et al., 2024; Zott et al., 2019). These findings suggest that the cerebellum may be an early target of AD, and symptoms may partly result from disrupted cerebellar computations that coordinate with cerebral networks via distributed loops. Breakdown of these loops causes functional disturbances that align with AD's network topography and a posterior-to-anterior cerebellar damage gradient.

Here, it is hypothesized that the primum movens of this cascade lies in early damage to the olfactory function, driven by the complex interplay among the olfactory system, the LC, and the cerebellum. Is there evidence linking olfactory and cerebellar function? At first glance, the olfactory system and the cerebellum appear to be anatomically and

functionally distant and to share little, if anything, beyond indirect interactions mediated by the DMN (Jung et al., 2022; Pisano et al., 2021; Waymel et al., 2020). However, olfaction involves not only the passive perception of odors but also the active transport of sensory information that gives rise to coordinated oscillations across an extended network of olfactory regions—namely, sniffing—which can induce such network dynamics even in the absence of odor stimulation (Granget et al., 2025). Thus, given its central role in generating internal models, the cerebellum may be crucial for linking a motor act to its expected sensory consequence (in this case, olfactory input) (Baumann et al., 2015; Schmahmann et al., 2019). Indeed, it adjusts timing to manage odorant intake by regulating sniffing strategies (Esclassan et al., 2012; Lefèvre et al., 2016; Reisert et al., 2020). Consistently, the cerebellum monitors and evaluates prediction errors between expected and actual olfactory outcomes from respiratory sampling (Simonyan et al., 2007; Sobel et al., 1998b). These findings support the cerebellum's role in synchronizing the timing of temporally salient events, particularly in conjunction with other components of the timing network (Antonioni et al., 2025d; Koch et al., 2009). Because the cerebellum also modulates attentional aspects of behavior, partly through its interactions with frontal networks, it is not possible to entirely exclude cerebellar involvement in the regulation of these mechanisms, even in olfactory tasks (Antonioni et al., 2024c; Picazio et al., 2016; Schmahmann et al., 2019). However, evidence suggests that its function is more specifically olfactory. Accordingly, cerebellar activation is elicited by odors alone (Albrecht et al., 2010; Iannilli et al., 2013; Small et al., 1997; Sobel et al., 1998a; Wabnegger and Schienle, 2019; Yousem et al., 1997; Zhang et al., 2021). In particular, this activation is observed not only during basic processes such as odor detection but also during more cognitively demanding tasks, including odor recognition memory and discrimination of odor quality or intensity (Bensafi et al., 2008; Savic, 2001; Small et al., 1997; Yousem et al., 1997). Moreover, cerebellar activation is crucial for olfactory memory in the absence of prefrontal activity, further emphasizing its specificity and its involvement in networks that support the processing of self-referential thoughts and memory retrieval, such as the DMN (Menon, 2023; Qureshy et al., 2000). Furthermore, olfactory deficits may stem from changes in cerebellar circuitry, particularly between PF and PC, or between PC and CF (Deiss and Baudoin, 1997). Accordingly, unilateral cerebellar lesions impair olfactory identification in the absence of cognitive complaints (Mainland et al., 2005). Similarly, patients with complete or partial loss of the sense of smell exhibit gray matter alterations in several brain regions, including the cerebellum, possibly due to compensatory plasticity in response to altered input (Abolmaali et al., 2008; Bitter et al., 2010a, 2010b; Peng et al., 2013). Further support for this view comes from olfactory impairments observed in patients with lesions of the ventrolateral thalamus, a region not directly connected to primary olfactory areas but a principal target of cerebellar output (Spampinato et al., 2023). In fact, patients with cerebellar lesions or damage to this thalamic region showed that the ventrolateral thalamus is involved in olfaction to a degree comparable to that of the cerebellum in odor-detection thresholds (Zobel et al., 2010).

A seminal fMRI study showed that certain cerebellar areas are not merely related to sniffing per se but specifically to odor recognition and are located in the posterolateral regions, particularly lobule VI and Crus I and II (Schmahmann, 2023; Sobel et al., 1998a). In contrast, anterior cerebellar regions are specifically activated by sniffing. This aligns with the cerebellum's division into anterior lobes for sensorimotor functions and posterolateral lobes for cognitive-affective roles (Schmahmann, 2023). Aging is associated with regionally specific alterations in activity within these cerebellar territories, suggesting that age-related changes in the olfactory system may be accompanied by functional alterations in cerebellar regions dedicated to olfactory processing (Ferdon and Murphy, 2003). Importantly, these age-related alterations are specific to the olfactory network and are not merely attributable to alterations in the trigeminal system (Fitzek et al., 2022; Laska, 2001; Sabiniewicz et al., 2023). These same cerebellar regions show increased

activation during cued-recall tasks in patients with AD who exhibit episodic memory deficits (Bäckman et al., 1999; Bernard et al., 2025). This is particularly relevant, given that approximately 85–90 % of patients with AD consistently exhibit olfactory alterations (Murphy, 2019). In addition, altered activation of the anterior cingulate cortex has been highlighted in older adults during odor-stimulus presentation, another region that is strictly interconnected with the posterior-lateral cerebellar areas (Cerf-Ducastel and Murphy, 2004; Habas, 2023; Schmahmann, 2019; Yousem et al., 1999). Similarly, neurodegenerative disorders characterized by prominent, progressive cerebellar damage often exhibit marked alterations in olfactory performance, even if sometimes to a lesser extent than in patients with AD, Parkinson's disease (PD), and schizophrenia, which are, indeed, characterized by specific cerebellar alterations (Abele et al., 2003; Connelly et al., 2003; Jacobs et al., 2018; Kang et al., 2024; T. Li et al., 2023). Taken together, these findings suggest that age-related changes in the olfactory system may induce—at least in the early stages—compensatory functional changes across a broad network of areas, not only within medial temporal structures but also in cerebellar regions and, subsequently, in interconnected nodes (such as the anterior cingulate cortex). Reasonably, a key factor underlying these distributed alterations is dysfunction of the LC, which could account for concurrent changes across multiple nodes of this complex, highly interconnected network (Caestecker et al., 2025; Groves et al., 2025; Poe et al., 2020).

In later disease phases, but still in the early stages of AD pathophysiology, the cerebellum also exhibits pronounced neuro-inflammatory alterations, including increases of up to 91 % in microglial cell density and changes in astrocytic subtypes and their immunoreactivity (Alvarez et al., 2015; Krbot et al., 2018; Singh-Bains et al., 2019; Yang et al., 2024). Notably, these alterations are particularly prominent near amyloid plaques, suggesting that the inflammatory response may initially limit the spread of damage, as plaques may act as reservoirs that sequester toxic oligomers up to a threshold (Bigi et al., 2022; Gaunt et al., 2023; Heneka et al., 2015; Kuwabara et al., 2014; Tsering et al., 2025). Beyond this threshold, however, a chronic inflammatory state is triggered, becoming deleterious and, in turn, promoting further worsening and propagation of the pathology (Heneka et al., 2025). This is particularly relevant in AD, where disease-related inflammation amplifies the pro-inflammatory milieu associated with aging, commonly referred to as “inflammaging” (Franceschi et al., 2017; Giunta et al., 2008). Finally, contributing to this process, again in an age-dependent manner, is the increase in oxidative stress, associated with functional exhaustion of endogenous scavenging systems and impaired mitochondrial biogenesis (Abadin et al., 2024; Butterfield and Boyd-Kimball, 2019; Calvo-Rodriguez et al., 2024; Ionescu-Tucker and Cotman, 2021).

It is worth noting that the cerebellum, alongside the LC, is also involved in regulating sleep. Thus, disturbances in sleep patterns, which are of key importance in this context, will be described in the next section.

6. A further target of early AD-related neuropathological changes: sleep

Sleep is a universal biological phenomenon. Although it remains only partially understood, it is now widely accepted to play fundamental roles in psychophysical well-being, including the regulation of immune, autonomic, and brain metabolic processes, as well as in learning and memory consolidation (Franken and Dijk, 2024; Irwin, 2015; Jaggard et al., 2021; Sulaman et al., 2023). The human macrostructure of sleep consists of a cyclic alternation of NREM and REM sleep, typically organized into 4–5 cycles per night. NREM sleep is further subdivided into stages based on EEG rhythms and the presence of characteristic graphoelements—such as K-complexes and sleep spindles—which together define the microstructure of sleep (Baranwal et al., 2023; Parrino et al., 2025; Sulaman et al., 2023). Although long underestimated, sleep is now recognized as a key factor in the

pathophysiology of several neurodegenerative conditions, including AD (Ferini-Strambi, 2024; Peter-Derex et al., 2015). Indeed, patients with AD, even in the pre-symptomatic stages, experience sleep alterations, including sleep fragmentation, with increases in “light” sleep and decreases in REM sleep, SWS, and sleep spindles, often preceding the onset of overt cognitive symptoms by many years (Bender et al., 2026; Galbiati et al., 2018; Kegyess-Brassai et al., 2025; Lucey et al., 2021; Wang and Holtzman, 2020; Winer et al., 2021; Zhang et al., 2019; Y. Zhang et al., 2022). Here, it is hypothesized that such early alterations may, at least in part, depend on dysfunction of the LC and the cerebellum, because both structures play critical roles in the proper modulation of sleep architecture. These disturbances may, in turn, fuel a vicious cycle that exacerbates the accumulation of neurotoxic byproducts and neuroinflammation, which are likely key drivers of subsequent disease progression.

Several models propose that NREM sleep primarily downregulates synapses potentiated during wakefulness via LTP, encoding information of limited relevance, whereas REM sleep supports the integration of salient information into relevant cortical networks (Sterpenich et al., 2014; Tononi and Cirelli, 2014, 2006). Importantly, the LC plays a pivotal role in NREM sleep, particularly in the generation of sleep spindles. Indeed, its stimulation reduces spindle occurrence and, consequently, sleep-dependent memory consolidation, whereas LC inhibition increases spindle density by specifically modulating thalamic activity (Aston-Jones and Bloom, 1981; Hayat et al., 2020; Novitskaya et al., 2016; Osorio-Forero et al., 2021; Swift et al., 2018). In addition, the LC exhibits learning-dependent increases in activity that are phase-locked to slow oscillations (Eschenko et al., 2012; Eschenko and Sara, 2008). During NREM sleep, timely LC discharges are essential for promoting plasticity and memory consolidation during replay of neuronal ensembles activated during wake experiences (Sara, 2015). Conversely, REM sleep serves as a protected simulation environment in which alternative scenarios can be explored, thereby optimizing sensorimotor models for subsequent interactions with the environment during wakefulness (Alyssa et al., 2025). Consistently, this is the unique stage during which the CNS is not exposed to NE release, thereby allowing upregulation of NE receptors and maximizing their potential to induce LTP in subsequent wakefulness (Amar and Mallick, 2015; Siegel and Rogawski, 1988). Crucially, LC activity is physiologically silent during REM sleep, which is fundamental to memory integration, and abnormal LC activity during sleep may compromise these processes (Kjaerby et al., 2022). Accordingly, dreaming (particularly the kind of dreams associated with REM sleep) could arise from internal models that run unconstrained by sensory input, leading to plasticity processes that generalize these models (Aru et al., 2020). Similarly, dreaming may be associated with memory consolidation (Wamsley, 2014). Thus, low NE levels during REM sleep may not only promote dreaming and its effects on memory consolidation but also facilitate other forms of cortical plasticity (Aru et al., 2020; Kjaerby et al., 2022). Therefore, alterations in LC activity associated with olfactory dysfunction could disrupt sleep patterns and impair memory performance.

Notably, REM sleep is also essential for regulating emotionally salient memories (Mendoza-Alvarez et al., 2025). Re-experiencing events in the absence of autonomic activation mediated by NE release appears crucial for preserving relevant components of memory while attenuating associated hyperarousal, likely through functional disengagement from the amygdala (Cabrerá et al., 2024; van der Helm et al., 2011). Thus, REM sleep is essential for the adaptive storage of emotionally meaningful memories and for simulating future scenarios in a way that allows them to be experienced with reduced distress. Accordingly, REM sleep dysregulation may represent an additional correlate of early anxiety- and mood-spectrum disturbances observed in the disease course, as excessive noradrenergic tone during wakefulness may persist into the night, thereby preventing effective emotional recalibration (Pesonen et al., 2024). Reasonably, alterations in the LC, particularly hyperactivation in the context of early olfactory

dysfunction, may significantly disrupt the sleep profile. Indeed, even during physiological aging, significant modifications occur in the macro- and microstructure of sleep, including increased fragmentation; as a result, lighter sleep stages increase at the expense of SWS and REM sleep (Mander et al., 2017). Consistent with the high levels of NE that persist during sleep, numerous nighttime awakenings (i.e., sleep fragmentation) are common during the prodromal stages of AD (Leng et al., 2019; Musiek et al., 2015; Van Egroo et al., 2024). Importantly, both reduced structural integrity of the LC system (i.e., the end of effective compensatory hyperactivity) and greater daytime dysfunction due to sleep disturbances independently predict an increased likelihood of conversion to MCI (Elman et al., 2021).

Interestingly, the cerebellum exhibits sleep-related activity patterns that differ from those typically observed in the cerebral cortex. These activities can influence sleep architecture at both macro- and micro-structural levels (Canto et al., 2017). In fact, the sleep-wake cycle both modulates and is tightly influenced by a reverberating circuit involving the cerebellum-thalamus-neocortical loops (Andre and Arrighi, 2003; De Zeeuw et al., 2008). Consistently, the same cerebellar regions that are most active during wakefulness while performing specific tasks also show greater activation during REM sleep, plausibly reflecting the importance of their interaction with cortico-subcortical networks in consolidating and integrating wakefulness-acquired information (Cousins et al., 2016; Fischer et al., 2002; Maquet et al., 2000). The cerebellum contributes to sleep regulation, and, conversely, sleep disturbances can lead to cerebellar dysfunction, including reductions in cerebellar volume (Li et al., 2021; Liu et al., 2023; Song and Zhu, 2021; Torres-Herraez et al., 2022; Xu et al., 2022, 2021). Importantly, these alterations also affect the microstructure. In particular, age-related reductions in sleep spindle duration—an expression of thalamocortical dialogue, in which cerebellar modulation of thalamic activity is likely critically involved—have been associated with decreased cerebellar gray matter and impairments in motor memory consolidation (Fogel et al., 2017; Xu et al., 2021).

Notably, sleep also plays a fundamental role in regulating autonomic functions, contributing critically—through modulation of the sympathetic-parasympathetic balance—to the control of blood pressure and heart rate (Ikeda and Shinohara, 2026; Zoccoli and Amici, 2020). Accordingly, disturbances of sleep architecture are associated with dysregulation of these mechanisms, thereby preventing the physiological nocturnal dipping of blood pressure and heart rate that normally occurs during NREM sleep (Nisbet et al., 2014; Silvani, 2008; Tobaldini et al., 2013). This, in turn, leads to elevated blood pressure that persists into wakefulness and is a major contributor to arterial hypertension in the general population (Javaheri et al., 2024; Kancierska et al., 2023; Parati et al., 2025). Indeed, sleep disruption is associated with marked sympathetic activation and increased hypothalamic-pituitary-adrenal axis activity, resulting in elevated adrenaline levels that sustain elevated blood pressure over a prolonged period and may lead to chronic, even drug-resistant hypertension (Gangwisch, 2014; Guyon et al., 2014; Makarem et al., 2021; Seravalle et al., 2018). Importantly, LC modulation plays a vital role during sleep in regulating blood pressure and heart rate, likely through its connections to the ambiguous nucleus and the parasympathetic nucleus of the vagus nerve (Osorio-Forero et al., 2025, 2022; Samuels and Szabadi, 2008). Thus, autonomic function dysregulation during sleep in AD is not solely due to sleep disturbances but also reflects changes in other key brain regions modulated by the LC (Krohn et al., 2023; Nikolenko et al., 2024; Samuels and Szabadi, 2008; Zoccoli and Amici, 2020). Consistently, the cerebellum also regulates autonomic functions, and it is therefore plausible that cerebellar damage not only disrupts sleep per se (thereby impairing visceral regulation) but also directly compromises cerebellar modulation of autonomic control (Harper et al., 2000; Kim and Lee, 2016; Nisimaru, 2004; Romano et al., 2020; Urbini et al., 2023; Zhu et al., 2006). This modulation likely occurs through both cerebellar influence on interconnected brain regions and direct connections between the

cerebellar cortex and nuclei and the hypothalamus, a key hub for autonomic regulation (Golanov and Reis, 1995; Zhu et al., 2006). Once again, the relationship appears bidirectional: autonomic dysfunction can damage the cerebellum, and cerebellar dysfunction can, in turn, exacerbate autonomic dysregulation, thereby perpetuating the vicious cycle discussed (Baker and Kimpinski, 2020; Bodranghien et al., 2016). Consistently, elevations in blood pressure are common during the prodromal phases of AD (Lennon et al., 2019; Walker et al., 2019). Thus, although hypertension has traditionally been regarded as a risk factor for disease development—given its potential to disrupt BBB integrity and impair neurovascular coupling—the evidence suggests that, at least in some cases, midlife arterial hypertension may also be a clinical manifestation of an underlying neuropathological process that is already present and actively progressing (Barisano et al., 2022; Katsi et al., 2020; Shinohara, 2025).

Notably, the olfactory system is highly plastic, and its cellular elements undergo odor-experience-dependent changes (Barnes and Wilson, 2014; Moreno et al., 2009; Yokoyama et al., 2011). Indeed, through plasticity mechanisms, experience-induced alterations may influence the sensitivity and acuity of the olfactory system and associate odor quality with contextual meaning or hedonic value (Barnes and Wilson, 2014). Therefore, functional plasticity is essential for preserving proper olfactory function (Cheetham et al., 2016; Gillmeister et al., 2025; Sailor et al., 2016; Wilson et al., 2004; Wu et al., 2020). Consistently, activity recorded during sleep in the OB and the piriform cortex is highly neuroplastic, and there are close correlations between SWS duration and odor-fear memory performance (Barnes et al., 2011; Wilson, 2010). Furthermore, during SWS, enhanced interactions have been observed between key olfactory network structures and cortical regions, suggesting that sleep is critical for preserving olfaction (Onisawa et al., 2017). In addition, sharp-wave ripples have been observed in the piriform cortex and resemble those in the hippocampus, whose role in memory consolidation is well established (Buzsáki, 2015; Joo and Frank, 2018; Narikiyo et al., 2014). Whereas other large-scale brain networks are characterized by thalamically orchestrated synchronization across distributed cortical areas, thereby giving rise to the slow oscillations typical of SWS, the olfactory system lacks such thalamic gating (Crunelli et al., 2018; Schreiner et al., 2022; Shine et al., 2023). In this context, sharp-wave ripples may be the functional equivalent within the olfactory network, supporting coordinated activity and information processing in the absence of thalamic modulation (Manabe et al., 2011). Given the role of sleep in regulating synaptic plasticity and enhancing sensory acuity following perceptual learning, alterations in sleep architecture may lead to dysfunction of the olfactory system (Alain et al., 2015; Reimann et al., 2025; Trecca et al., 2024; Yamaguchi, 2017). Consistently, olfactory impairments have also been reported in non-neurodegenerative sleep disorders, such as obstructive sleep apnea syndrome (OSAS) (Iannella et al., 2021; Karakurt et al., 2020). In the case of AD, longitudinal clinical data from the preclinical stages suggest that primary olfactory dysfunction may trigger downstream effects on the LC and the cerebellum, followed shortly thereafter by effects on nocturnal sleep profiles (Fortier-Lebel et al., 2025; Huang et al., 2025; Lucey et al., 2021; Roberts et al., 2016; Wang et al., 2021). Moreover, functional connectivity between the piriform cortex and the amygdala, hippocampus, and neocortical areas is significantly enhanced during NREM sleep (particularly SWS), suggesting that replay within these circuits is essential for assigning meaning and hedonic value to learned associations (Wilson et al., 2011; Wilson and Yan, 2010). However, this state-dependent change in piriform cortex activity is highly dependent on neurotransmitter signaling during sleep, particularly acetylcholine, whose dysregulation in AD is well known (de Almeida et al., 2013; Hampel et al., 2018). This underscores the bidirectional relationship between sleep and olfactory function and suggests that, in patients with AD and comorbid conditions such as OSAS, whose prevalence increases with age, pathological processes may be further exacerbated (Cavallès et al., 2024; Rollo et al., 2026a). Therefore, sleep is also critically

impaired from the early stages of the disease, likely due to the interplay among the crucial pathophysiological elements discussed here.

7. Bridging predictive processing and AD pathophysiology: focus on molecular mechanisms

While the previous sections examined in detail the consequences of age-related sensory changes on predictive coding, with particular attention to the implications from a network perspective, this section explores the molecular evidence linking errors in predictive coding to the proposed pathophysiological cascade. Indeed, a mechanistically grounded interpretation of this framework can be articulated by linking predictive coding dynamics to key processes in AD pathophysiology, thereby further supporting this integrative view. As previously described, in predictive coding architectures, persistent sensory uncertainty or degraded afferent precision requires sustained prediction-error signaling and, thus, compensatory gain modulation by the LC–noradrenergic system (Jordan, 2024; Jordan and Keller, 2023). This increased activity of the LC leads to enhanced NE release, whose downstream metabolites appear to facilitate tau protofibril phosphorylation, particularly in APOE4 carriers—but not in carriers of the APOE3 or APOE2 isoforms, which are, indeed, relatively protective against AD onset (Kang et al., 2021; Silva et al., 2019; Weinshenker, 2018). Tau aggregates are thought to begin accumulating as early as the first decades of life (Braak and Del Tredici, 2012b, 2011); however, only upon aberrant hyperphosphorylation do these assemblies become prone to pathological aggregation and dissemination, ultimately forming the characteristic neurofibrillary pathology of AD (Rawat et al., 2022). Importantly, the LC is one of the earliest, possibly the very first, sites of pTau accumulation (Hary et al., 2025). From the LC, pTau may subsequently propagate to anatomically interconnected regions, potentially through prion-like trans-synaptic spreading mechanisms (Clavaguera et al., 2017; Mudher et al., 2017).

Amyloid pathology appears to facilitate this propagation process, a point of particular relevance within the present framework (van der Kant et al., 2020). Indeed, neuroplastic and predictive coding alterations induced by degraded sensory inputs are unlikely to remain confined to primary sensory systems. Rather, they progressively extend to broader brain networks, especially those linked to sensory modalities characterized by early signal degradation, most prominently the olfactory system (B. Chen et al., 2022; Mormino et al., 2012; X. Zhang et al., 2024; Zhu et al., 2025). These networks may undergo sustained compensatory increases in activity to optimize the processing of impoverished sensory information and enhance interactions with distributed cortical hubs that store previously acquired, more reliable internal representations (Hampstead et al., 2016; Jonin et al., 2022; Liang et al., 2020; Požar et al., 2024). Such compensatory recruitment may transiently support perceptual inference by integrating degraded incoming signals with preserved memory-based priors. However, chronic hyperactivity and persistent prediction-error signaling within these interconnected circuits may simultaneously increase metabolic stress, neuromodulatory burden, and vulnerability to tau and amyloid-related pathological processes, thereby contributing to the progressive network spread of Alzheimer-type neurodegeneration (Hein et al., 2025; J. Zhang et al., 2024). Crucially, chronic elevation of neuronal firing and synaptic activity within these compensatory networks is highly biologically relevant, as both A β release and tau secretion are strongly activity-dependent processes. Experimental studies have shown that increased synaptic activity enhances amyloidogenic processing of the amyloid precursor protein (APP) and promotes extracellular A β release at active synapses (Buckner et al., 2005; Cirrito et al., 2005; Kamenetz et al., 2003; Schroeder and Koo, 2005). Likewise, neuronal hyperexcitability facilitates tau phosphorylation and propagation, possibly through activation of kinases and stress-related signaling cascades (Nishida et al., 2024; Shimojo et al., 2020; Su et al., 2024; Targa Dias Anastacio et al., 2022; X. Wu et al., 2025).

Conversely, tau can directly enhance neuronal excitability, which may further exacerbate hyperactivity associated with compensatory responses (Crimins et al., 2012; Rudy et al., 2015; Weinshenker, 2018). Therefore, chronic prediction-error processing may create a state of sustained excitatory and metabolic pressure that progressively shifts adaptive plasticity toward maladaptive proteostatic overload (Migeot et al., 2022; Peters et al., 2017).

Importantly, the LC is positioned to mediate this transition. As mentioned, early compensatory hyperactivity of LC neurons increases NE release, thereby enhancing neural gain, optimizing signal-to-noise

ratios, and stabilizing internal models under conditions of uncertain sensory input (McBurney-Lin et al., 2019; Theriault et al., 2025). However, prolonged noradrenergic activation has several downstream consequences that may directly favor molecular pathology. First, sustained adrenergic signaling increases oxidative stress and mitochondrial burden in highly active neurons, thereby facilitating tau hyperphosphorylation through redox-sensitive kinase pathways (Corbi et al., 2013; Manukyan et al., 2023; Sanchez-Padilla et al., 2014; X. Wu et al., 2025). Second, NE metabolism itself generates reactive metabolites that have been proposed to promote tau misfolding and pre-tangle

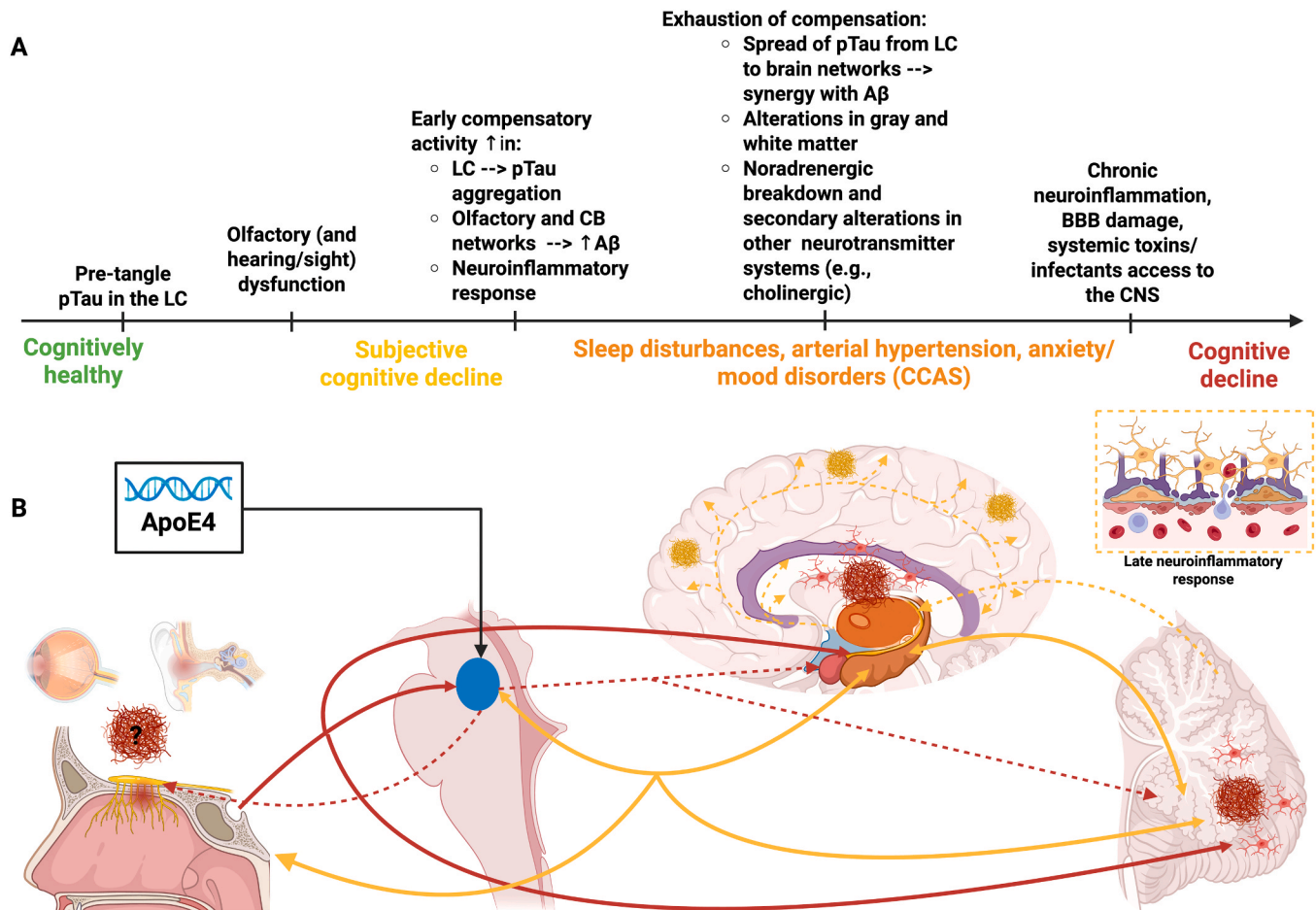


Fig. 3. A sensory-driven, LC-centered model of AD progression from early compensation to cognitive decline. Panel A presents a timeline of the pathophysiological cascade. The earliest stage features pre-tangle pTau accumulation in the LC of healthy young individuals (Harley et al., 2021; Poe et al., 2020; Stratmann et al., 2016). Age-related sensory dysfunction acts as an upstream trigger, altering predictive brain networks (Groves et al., 2025; Murphy, 2019). This induces early functional compensation, marked by increased LC activity, pTau aggregation, engagement of olfactory and cerebellar networks, and a protective neuroinflammatory response (Cuello, 2017; Jacobs et al., 2021a; Koops et al., 2025; Palmer et al., 1987; Prokopiou et al., 2022; Weinshenker, 2018). Reasonably, this stage corresponds to SCD (Fortier-Lebel et al., 2025; Wang et al., 2021). As compensatory mechanisms become strained, secondary alterations emerge, including sleep disturbances, arterial hypertension, anxiety, and mood disorders (which, in some cases, align with cerebellar cognitive-affective syndrome, CCAS) (Alvaro et al., 2013; J. Chen et al., 2023; Huang et al., 2025; Schmähmann, 2023). Exhaustion of compensatory mechanisms leads to the spread of pTau from the LC to distributed brain networks, synergistic interactions with A β , noradrenergic breakdown, and dysfunction of other neurotransmitter systems (Ahmed et al., 2014, p. 201; Gellersen et al., 2017; Hampel et al., 2018; Harley et al., 2021; Krohn et al., 2023; Poe et al., 2020; Samstag et al., 2025; Stratmann et al., 2016; Toniolo et al., 2023, 2020; Zhang et al., 2026). Finally, chronic neuroinflammation and BBB disruption accompany overt cognitive decline (Cuello, 2017; Eimer et al., 2025; Heneka et al., 2025; Knox et al., 2022). Panel B shows the network-level interactions underlying these processes. Solid red arrows indicate early functional compensatory pathways between the peripheral olfactory system and the LC, the cortical olfactory network, and the cerebellum, whereas solid yellow arrows represent secondary compensatory routes (B. Chen et al., 2022; Mitoma et al., 2020; Mormino et al., 2012; X. Zhang et al., 2024; Zhu et al., 2025). Dashed red arrows indicate primary pTau propagation from the LC, while dashed yellow arrows indicate secondary dissemination from downstream sites (Braak et al., 2011; Mudher et al., 2017; Thal et al., 2002). Red amyloid plaques indicate early A β accumulation within regions engaged in functional compensation (speculatively in the olfactory epithelium), which are frequently surrounded by red microglia, i.e., an early, protective inflammatory response (Armsten et al., 2021; Cuello, 2017; Fan et al., 2017; Herz, 2025; Huang, 2024; M. Liu et al., 2024). Yellow plaques represent secondary A β accumulation associated with the spread of neuropathology (Iadanza et al., 2018; Thal et al., 2002, 2000). The dashed yellow inset highlights late-stage chronic neuroinflammation (Barisano et al., 2022; Fan et al., 2017; Heneka et al., 2025). Microglial-driven maladaptive plasticity accelerates network failure (Peña-Ortega, 2025; G. Yang et al., 2025). ApoE4 facilitates pre-tangle pTau aggregation (Frisoni et al., 2022; Martens et al., 2022). Overall, the figure presents a unified framework spanning the long preclinical phase to the later emergence of cognitive symptoms, emphasizing the bidirectional, network-level nature of these alterations. Created with BioRender.com.

aggregation (Kang et al., 2021; Silva et al., 2019; Weinshenker, 2018). Third, chronic hyperactivity increases local energy demand while impairing synaptic proteostasis, thereby reducing the efficiency of autophagic and lysosomal degradation systems required for the clearance of misfolded neurotoxic species (Jiang and Bhaskar, 2020; Malik et al., 2019; Martínez et al., 2023; Morrone et al., 2023; Orr and Oddo, 2013; L. Yang et al., 2025).

Interestingly, predictive coding failure may also impair glymphatic and neuroimmune clearance mechanisms. Consistently, LC activity exerts major regulatory control over sleep architecture and arousal state, both of which critically influence glymphatic flux and interstitial clearance of soluble A β and tau (Falgàs et al., 2026; Nedergaard and Goldman, 2020; van Hattem et al., 2025). During early compensatory phases, persistent LC activation and elevated arousal likely reduce SWS efficiency, thereby diminishing glymphatic clearance and favoring extracellular accumulation of toxic proteins (Ross and Van Bockstaele, 2021; Swift et al., 2018). This mechanism provides a biologically plausible link between early sleep disturbances, chronic prediction-error signaling, and progressive pathological aggregate deposition. Simultaneously, prolonged neuronal hyperactivity activates microglia within overloaded networks (Abiega et al., 2016; Dissing-Olesen et al., 2014). Initially, this response may be protective, supporting synaptic remodeling and protein clearance; however, chronic activation progressively shifts glial cells toward maladaptive inflammatory phenotypes marked by impaired phagocytosis, excessive synaptic pruning, cytokine release, and BBB destabilization (Heneka et al., 2025, 2015). Such changes further compromise clearance efficiency and promote A β accumulation and the spread of pTau pathology across structurally and functionally connected networks (Laurent et al., 2018; Roemer-Cassiano et al., 2025; Webers et al., 2020).

From this perspective, predictive coding dysfunction is not merely a computational abstraction but may reflect a biologically grounded process linking chronic compensatory neural activity to progressive failures across proteostasis, neuromodulatory regulation, sleep-dependent clearance, and neuroimmune homeostasis. The model therefore predicts that brain regions subjected to sustained prediction-error burden and compensatory hyperactivity should preferentially show early A β accumulation, tau hyperphosphorylation, altered glial states, and subsequent network degeneration—a pattern often consistent with current observations in preclinical AD.

8. An integrative overview of early AD pathophysiology and its clinical implications

Fig. 3 provides an overview of the pathophysiological process discussed here.

Although AD has traditionally been conceptualized as arising from the sequential accumulation of A β and pTau, in cases not driven by known genetic mutations, the mechanisms that trigger these processes remain largely unclear (Kasper P Kepp et al., 2023). First, a weak correlation has been reported between cerebral amyloid burden and cognitive dysfunction, even years later, despite substantial hippocampal deposition (Cohen et al., 2019; Dubois et al., 2018; Neve and Robakis, 1998; Schmitz et al., 2004; Sturchio et al., 2022, 2021). Thus, the originally postulated direct cause-and-effect relationship appears at least incomplete, particularly when considering the multitude of additional risk factors that may facilitate disease onset and modulate its trajectory (Frisoni et al., 2022; Haass and Selkoe, 2022; Kasper P. Kepp et al., 2023). Moreover, while newer disease-modifying therapies have shown promising results—especially in carefully selected patients—early monoclonal antibodies were able to remove a large proportion of cerebral amyloid deposits without meaningfully altering the trajectories of cognitive decline. Indeed, several clinical trials have failed, even when treatment was initiated at the MCI stage (Ayton and Bush, 2021; Castellani and Perry, 2012; Chhabra et al., 2024; Doody et al., 2014; Fox et al., 2025; Imbimbo et al., 2021; Karran and De

Strooper, 2022; Nicoll et al., 2019; van Dyck et al., 2025). In genetic animal models of disease—often characterized by rapid, extensive development of AD neuropathological features within short timeframes, without additional risk factors, and sometimes dependent solely on A β or tau, thus significantly differing from human AD—these monoclonal antibodies appear to reverse cognitive impairments (Games et al., 1995; Herrup, 2015; Hsiao et al., 1996; Padmanabhan and Götz, 2023; Puzzo et al., 2015; Singhaarachchi et al., 2025). Hence, in controlled experimental settings where dysfunction can be directly attributed to the accumulation of neurotoxic products, removing amyloid leads to cognitive improvement; however, this does not always hold true in humans. Therefore, although A β and pTau are undoubtedly central to AD pathophysiology, they may not constitute the primary initiating event in the disorder, at least in isolation (Kasper P Kepp et al., 2023). Importantly, at physiological nanomolar concentrations, monomeric A β exerts neurotrophic effects and may contribute to proper synaptic transmission, BBB integrity, regulation of ion channel dynamics, and antimicrobial defense (Brothers et al., 2018; Kamenetz et al., 2003; Kumar et al., 2016; Lee et al., 2007; Yu et al., 2006). Consequently, indiscriminate removal of amyloid may have significant implications for CNS health, and it remains uncertain to what extent A β clearance alone can yield enduring therapeutic benefits. Targeting amyloid plaques, which may be deposits that impede the spread of oligomers, could exacerbate the toxic effects of A β fibrillar products (Tolar et al., 2021). Instead, the ideal target may be the A β oligomers themselves, to prevent synaptic damage caused by their accumulation and to restore the monomeric forms that are important for physiological function (Fantini et al., 2020; Kepp, 2016). However, because A β oligomers are in equilibrium with both monomeric and aggregated species, the lack of clinical efficacy of previous treatments, despite the removal of A β monomers or plaques, raises concerns (Panza et al., 2019). Moreover, even drugs specifically designed to target A β oligomers failed to provide significant clinical benefits (Arndt et al., 2018; Heidebrink and Paulson, 2024). If amyloid accumulation indeed reflects, at least in the earliest stages, a compensatory response of the regions in which it arises, it follows that the timing of therapeutic intervention is likely to be a critical determinant of treatment efficacy. Specifically, interventions should be administered within a window that does not undermine these early compensatory mechanisms yet is sufficiently timely to prevent the synaptic damage associated with the accumulation of toxic oligomeric species. When the risks associated with these treatments are considered, it becomes evident that their use requires careful evaluation, particularly in the absence of a comprehensive understanding of the disease (Avgerinos et al., 2021). Finally, significant A β deposition is a common finding even in cognitively healthy older adults, further raising concern about this hypothetical sequence of events (Bennett et al., 2006; Filip et al., 2025; Jagust, 2016; Morris et al., 2010).

Against this background, the aim of the present work was not to challenge the amyloid cascade hypothesis, which provided crucial insights into the complex biology of AD. Instead, it is important to emphasize that this theory appears incomplete because it does not fully account for factors that may be essential to understand AD pathophysiology, particularly given that the traditional focus on hippocampal A β accumulation may not invariably reflect the true starting point. Here, it is hypothesized that the accumulation of AD neuropathological hallmarks—primarily tau, as supported by its much stronger correlation with clinical progression than A β —may be triggered by sensory deficits, particularly olfactory impairment, which is almost invariably present with aging (Murphy, 2019; Musiek and Holtzman, 2015). This, in turn, may promote the accumulation and spread of neurotoxic species in critical regions of the CNS, foremost the LC, which initially undergoes compensatory changes in activity but becomes increasingly vulnerable to neurodegeneration over time (Krohn et al., 2023). In rapid succession, this process may reasonably induce dysfunction in cerebellar circuits and medial temporal lobe networks, both of which may be affected not only by neuropathology propagated from the LC but also by functional

disturbances secondary to olfactory system dysfunction, with which they are tightly interconnected. These processes might give rise to sleep complaints, blood pressure alterations, and mood disturbances that precede, by a substantial margin, the cognitive impairments classically associated with AD, which typically emerge only at later stages, likely when compensatory mechanisms have been exhausted, pTau has spread widely, and neural damage has become extensive. Neuroinflammatory changes secondary to these alterations may initially serve a compensatory role but later become sources of additional injury, synergizing with LC dysfunction to promote BBB disruption. This, in turn, exposes the CNS to peripheral toxic and infectious agents, further amplifying the vicious cycle of damage (Sweeney et al., 2018). Consistently, both A β and pTau exhibit antimicrobial activity, suggesting that both A β plaques and NFTs may also represent an orchestrated innate immune defense response to microbial infection in the CNS, at least in some cases and at some stages of the disease course, when the BBB is significantly damaged, or the neuroinflammatory environment is permissive to direct neuronal infection (Eimer et al., 2025; Heneka et al., 2025; Knox et al., 2022; Sian-Hulsmann and Riederer, 2024; Vojtechova et al., 2022). Interestingly, two peaks of microglial activation have been observed during the longitudinal progression of AD: an early peak with a protective role and a second, pro-inflammatory peak (Cuello, 2017; Fan et al., 2017). Glial cells also exhibit plasticity mechanisms that interact with neuronal mechanisms to shape adaptation to diverse stimuli (Dzyubenko and Hermann, 2023). In chronic inflammation, microglia may induce various forms of maladaptive plasticity, particularly when LC damage is present (Peña-Ortega, 2025; Schramm and Waisman, 2022; G. Yang et al., 2025; Zhao et al., 2024). Therefore, anti-inflammatory agents targeting microglia may be most effective in the later stages of the disease, whereas in the early stages, they may be detrimental without a pathophysiologically informed modulation strategy (Topalis et al., 2026; Villarejo-Galende et al., 2020).

Collectively, these observations suggest that the olfactory system, the cerebellum, and sleep—both directly and through LC-mediated mechanisms—might be key players in the earliest stages of AD. Thus, even if this is merely speculation for the moment, several important implications follow. First, olfactory impairment, even if often overlooked in current clinical practice, may be among the most noninvasive, cost-effective, and sensitive tools for early screening and identification of individuals who are candidates for disease-modifying therapies, particularly when combined with subtle cognitive deficits (especially SCD) and early biomarkers, and potentially even in isolation, before other markers of more advanced damage emerge (Jobin et al., 2025; Dongming Liu et al., 2024; Liu et al., 2025; Shrestha et al., 2025). Moreover, this framework opens the possibility of targeting olfactory dysfunction through broader, mechanism-informed interventions to reduce maladaptive network stress and restore physiological predictive processing. From this perspective, olfactory impairment may not only serve as a clinical biomarker of early AD but also be a modifiable source of chronic compensatory neural activity within olfactory–limbic–LC circuits. Accordingly, interventions aimed at preserving or restoring sensory fidelity could theoretically reduce aberrant network hyperactivity and downstream neuromodulatory stress. Consistently, recent work has demonstrated that olfactory training can improve not only olfactory function but also cognition and promote structural and functional changes (Vance et al., 2023). Although speculative, this could be useful in this context, as realigning the LC's activity toward patterns more akin to physiological ones could justify a reduction in harmful hyperactivity, as discussed in the previous sections. Furthermore, given that age-related degeneration of other sensory modalities (primarily hearing and sight) likely synergizes with the onset and progression of the neuropathological cascade described, interventions that improve these modalities, both from a peripheral perspective and through promising strategies that modulate the brain network, could be equally useful in the early stages of the disease to slow its progression (Chadha et al., 2023; Lin, 2024; Martorell et al., 2019; Monteiro et al., 2022; Sprinzel

and Riechelmann, 2010; Thamizhmani et al., 2024; US Preventive Services Task Force, 2022). Thus, in addition to structured olfactory training paradigms, future strategies could include multimodal sensory-enrichment programs that integrate olfactory, auditory, visuo-spatial, and somatosensory stimulation to reinforce adaptive cross-network interactions and support efficient updating of sensory predictions (Gkintoni et al., 2025; Mathias and von Kriegstein, 2023). Such interventions may be particularly relevant during the preclinical or prodromal stages, when large-scale network integrity remains partially preserved (Guo et al., 2016a). Experimental evidence from environmental enrichment paradigms further suggests that sustained sensory and cognitive stimulation may modulate synaptic plasticity, neuro-inflammatory and neurotrophic pathways, and stress-related neuromodulatory systems, including LC-dependent noradrenergic transmission (Dinse and Tegenthoff, 2015; Mather and Harley, 2016; Q. Zhang et al., 2025). Although these approaches remain largely underexplored in AD, they align with the evidence presented in the present work (Yang et al., 2021). Additional olfactory-targeted strategies may also warrant investigation. For example, interventions aimed at improving nasal airflow and the quality of olfactory input—such as treating chronic rhinosinusitis, reducing environmental pollutants, or managing sinonasal inflammatory conditions—could theoretically mitigate persistent sensory degradation and the compensatory hyperactivation hypothesized in this framework (Ajmani et al., 2016; Dan Liu et al., 2024a; Wei et al., 2025). Furthermore, strengthening public health strategies for smoking prevention and cessation may be highly relevant. Indeed, beyond its well-established multisystem detrimental effects on human health, chronic tobacco exposure profoundly impairs olfactory function in a dose-dependent manner, contributing to sensory degradation and altered olfactory processing (Glennon et al., 2019; Maritz and Mutemwa, 2012; Wälchli et al., 2025). Importantly, olfactory loss associated with smoking may be reversible, which is fundamental from a preventive perspective (Ajmani et al., 2017). Finally, although still highly speculative, interventions aimed at preserving or enhancing olfactory neurogenic capacity during aging may also deserve consideration. Adult neurogenesis, particularly within olfactory-related and hippocampal circuits, has been implicated in sensory adaptation, memory processing, and network plasticity (Malvaut and Saghatelian, 2016; Sakelaris and Riecke, 2025; Surget and Belzung, 2022). Strategies capable of sustaining these regenerative and plastic processes throughout aging could theoretically improve the adaptive updating of internal models, maintain network flexibility, and increase resilience to the pathological cascades described in this framework (Kim et al., 2025; Lledo and Saghatelian, 2005). However, the translational relevance of these approaches in humans remains hypothetical and will require substantial experimental validation.

Conversely, clinically applicable treatment strategies could be developed much more quickly using non-invasive neuromodulation techniques. Indeed, the cerebellum may be a critical target not only for early disease detection but also, perhaps more importantly, for therapeutic intervention. Given the cerebellar involvement in a wide range of cognitive, sensory, and affective functions and the selective early involvement of posterolateral cerebellar regions along the AD continuum, clinical assessment should extend beyond the exclusion of overt motor coordination abnormalities (Antonioni et al., 2024c; Bernard et al., 2025; Y. Chen et al., 2023b; Schmahmann, 2019). Instead, sensitive tools specifically designed to detect subtle and insidious deficits at the earliest stages are required. Indeed, identifying patients—particularly those with olfactory impairment—who exhibit features consistent with the so-called cerebellar cognitive affective syndrome (CCAS) may serve as an additional criterion for selecting individuals who could benefit from early intervention (Hirsch et al., 2025; Hoche et al., 2018). Furthermore, the cerebellum may serve as a central node in the early pathophysiology from multiple perspectives. Indeed, it may be involved in the genesis of cholinergic dysfunction. This is not surprising, given that the basal forebrain cholinergic

system—particularly the nucleus basalis of Meynert—represents a cholinergic relay station that modulates activity across the entire neocortex, effectively constituting a telencephalic extension of the ascending reticular activating system, of which the LC is a key component (Edlow et al., 2012; Miyawaki et al., 2023). Consistently, orexinergic neurons of the lateral hypothalamus, which are instrumental in sustaining wakefulness, send dense projections to the LC (Hagan et al., 1999; Soya et al., 2017). Degeneration of the olivo-ponto-cerebellar system is associated with morphological alterations in the Meynert nucleus, suggesting that the cerebello-cortical loop, at least indirectly, modulates these basal forebrain structures, while it is also a major target of cholinergic modulation (He et al., 2023; Tagliavini and Pilleri, 1985; Turner et al., 2011). In AD, the nucleus basalis of Meynert exhibits significant neuronal loss (Hanna Al-Shaikh et al., 2020). This loss leads to central cholinergic deficits and related cognitive dysfunction and underlies the neurobiological basis for primary symptomatic treatments in AD, such as cholinesterase inhibitors (Giacobini et al., 2022; 2018). This is particularly relevant not only because acetylcholine plays a well-established role in memory and sleep-wake regulation, but also because it serves as a key neurobiological substrate of sensorimotor integration—one of the functions most markedly altered, from a neurophysiological standpoint, in AD (Allard and Hussain Shuler, 2023; Ananth et al., 2023; Fore et al., 2020; Liu et al., 2018; Ozen Irmak and de Lecea, 2014; Platt and Riedel, 2011; Yang et al., 2022). Moreover, altered sensorimotor integration is a common feature of olfactory dysfunction, cerebellar alterations, and sleep disturbances, further strengthening this pathophysiological link (Cross et al., 2021; Irvani et al., 2021; Stone et al., 2019; Tamburin et al., 2003; Xu et al., 2026; Yan et al., 2022). Crucially, patients with AD exhibit specific impairments in anticipatory behaviors—processes that depend on the integrity of internal models generated and continuously updated by the cerebellum, together with the noradrenergic and cholinergic circuitries (de Nobile et al., 2025; Fore et al., 2020; Iosif et al., 2026; Prestori et al., 2013).

In AD, various neuromodulation approaches have recently shown promise, both in the short and long term, with a safe profile, particularly when targeting a crucial node of the DMN, such as the precuneus (Antonioni et al., 2025c; Koch et al., 2022, 2024, 2025; Mencarelli et al., 2024). Therefore, the cerebellum may be a valuable target, particularly in early disease stages, such as SCD and MCI (Manto et al., 2022). Indeed, TMS-EEG studies have shown that cerebellar repetitive TMS (rTMS) protocols, which induce long-lasting neuroplastic changes, can significantly modulate cerebellar-cortical connections, thereby influencing inhibitory interneuron activity and the intrinsic EEG oscillations of interconnected areas (Casula et al., 2016; Koch et al., 2008). Given that alterations in excitation/inhibition balance are central to AD pathophysiology, cerebellar NIBS protocols, which primarily act on GABAergic circuits in interconnected brain regions via the thalamus, could normalize this imbalance, leading to significant clinical improvements, as already shown in other pathological contexts (Antonioni et al., 2024c; Baroni et al., 2024; Burns et al., 2026; Fortel et al., 2023; Koch et al., 2019; Maestú et al., 2021; Martino Cinnera et al., 2025; Taub et al., 2013). Moreover, dysfunction of the cholinergic, dopaminergic, and noradrenergic systems, which are key players in sleep regulation, neurodegeneration, and neuroinflammation, is fundamental to AD pathophysiology (Craig et al., 2011; Koch et al., 2014; Martorana and Koch, 2014; Motta et al., 2023; Oh et al., 2019b). Since rTMS may modulate these circuits, the therapeutic potential of these protocols extends to this dimension of AD pathophysiology as well (Sharbafshaaer et al., 2024). Notably, cholinergic circuit dysfunction manifests as an alteration in a distinctive neurophysiological biomarker—namely, short-latency afferent inhibition (SAI)—a hallmark of AD (Koch and Spampinato, 2022). Cerebellar rTMS has been shown to modulate SAI exclusively in patients with AD, not in healthy subjects (Di Lorenzo et al., 2013). This further supports the hypothesis that the cerebellum may be involved in AD pathophysiology and that its modulation could

target neurobiological mechanisms underlying the disease. Interestingly, beyond cerebellar stimulation, promising experimental neuromodulatory approaches, including vagus nerve stimulation and other brainstem-targeting paradigms, have been hypothesized to modulate LC firing patterns and noradrenergic signaling, potentially reducing maladaptive hyperactivation while preserving network flexibility and sleep architecture (Hulsey et al., 2017; Seminc et al., 2024). This could hold promise for fine-tuning LC activity, preventing a shift toward chronic hyperactivity associated with functional exhaustion while still ensuring compensatory function, ideally in combination with other interventions (such as those discussed above) that, at least in theory, can counteract the underlying pathophysiology. Although the potential of neuromodulatory treatments in clinical neurorehabilitation is extremely promising, significant gaps remain, particularly in real-world clinical practice (Poumajaf et al., 2026). Consequently, attention should also be directed towards more established strategies that are already widely applicable, even beyond highly specialized centers.

Importantly, the cerebellum is also a pivotal region in the mirror neuron system (MNS), i.e., a network of neurons active during both the execution of an action and the observation of the same or a logically related action (Errante et al., 2023; Errante and Fogassi, 2020). Importantly, the MNS is altered in AD (Farina et al., 2020). Although the MNS's functions appear to be preserved with physiological aging, they are altered in MCI and, most notably, in patients with AD (Farina et al., 2017). Notably, the EEG mu rhythm, widely regarded as a neurophysiological biomarker of sensorimotor integration associated with MNS activity, is typically disrupted in this patient population (Fox et al., 2016, p. 201; Moretti et al., 2011). Therefore, even in the context of AD, MNS could play an important role in diagnosis, prognosis, and treatment response, as suggested in other patient populations (Antonioni et al., 2024a, 2024c; Ciullo et al., 2026; Milani et al., 2025). Beyond damage to cortical regions—which, as noted above, may be more closely associated with later pathological stages—it is reasonable that early cerebellar dysfunction may also account for these findings (Antonioni et al., 2024c; Yang et al., 2024). Additionally, because the cerebellum is connected to cortical inhibitory interneurons with mirror properties, alterations in these interneurons may also contribute to these abnormalities, particularly given that parvalbumin-positive interneurons are key targets of AD neuropathology (Antonioni et al., 2024c; Smeralda et al., 2024). Finally, as the cerebellum modulates brain networks by influencing the thalamus, thalamic dysfunction may also underlie the EEG alterations associated with MNS functioning (as well as, in part, alpha-band alterations discussed in the previous sections) (Biesbroek et al., 2024; Habas et al., 2019). Overall, the cerebellum plays a fundamental role, directly or indirectly, in accounting for these converging lines of evidence, as already suggested in other (though in some pathophysiological respects similar) neurodegenerative disorders, such as frontotemporal dementia (FTD) (Antonioni et al., 2023c, 2025f, 2025h; Manto et al., 2022). Therefore, early identification of individuals with AD neuropathology could enable the timely implementation of both pharmacological and non-pharmacological therapeutic strategies. These may include NIBS—especially targeting the cerebellum—and interventions based on MNS function to improve sensorimotor integration.

Finally, sleep disturbances—particularly those linked to anxiety- or mood-related symptoms, especially if new or worsening around midlife, and in patients with recently developed, treatment-resistant hypertension—may serve as an additional indicator for the earliest stages of disease (Alvaro et al., 2013; J. Chen et al., 2023; Makarem et al., 2021; Palta et al., 2021; Santisteban et al., 2023; Ungvari et al., 2025; Jinhuan Zhang et al., 2025). Beyond their diagnostic relevance, they are essential from a therapeutic perspective. Indeed, sleep-focused interventions may have even broader translational potential because sleep directly influences several mechanisms implicated in AD pathophysiology, including glymphatic clearance, synaptic homeostasis, neuroimmune regulation, metabolic stress, and tau propagation

(Proserpio et al., 2018). Thus, normalizing sleep patterns through sleep hygiene, circadian rhythm alignment, management of comorbid conditions (e.g., OSAS, systemic illnesses), and careful use of sleep-modulating medications may counteract key pathophysiological mechanisms, thereby substantially slowing disease progression and widening the therapeutic window for effective interventions (Aktan Süzgün et al., 2025; Javed et al., 2023; Lacerda et al., 2024; Van Egroo et al., 2019; Xia and Hu, 2025). In particular, treating insomnia, which is very common in this patient population, with safe, evidence-based approaches such as cognitive behavioral therapy for insomnia (CBT-I) may be relevant not only for slowing disease-related pathological processes but also for improving quality of life and mood, and reducing the pharmacological burden (Ferini-Strambi et al., 2020; Latella et al., 2025). Consistently, by improving sleep continuity and restoring a more physiological sleep architecture, CBT-I could theoretically mitigate several mechanisms implicated in AD pathophysiology, including chronic hyperarousal, impaired glymphatic clearance, and neuro-inflammatory activation (Mander et al., 2016). Similarly, early treatment of sleep breathing disorders with continuous positive airway pressure (CPAP) or other targeted interventions—such as mandibular advancement devices or positional therapies—may be especially important for reducing sleep fragmentation and intermittent hypoxic burden (Blackman et al., 2021; Ciavarella et al., 2025; Rollo et al., 2024). These factors are increasingly recognized as potential contributors to AD-related neurodegeneration, which can synergize with neuropathological hallmarks through oxidative stress, vascular dysfunction, neuroinflammation, and altered neuronal excitability (J. Zhang et al., 2025; W. Zhang et al., 2025). Consequently, prompt identification and management of sleep disorders may represent a clinically actionable strategy not only for symptomatic improvement, but also for potentially attenuating the progression of neuropathological processes associated with AD. Moreover, chronobiological interventions aimed at stabilizing circadian rhythmicity may represent an important complementary strategy. Timed bright-light exposure, circadian reinforcement protocols, sleep–wake schedule regularization, and interventions targeting social and behavioral zeitgebers may help preserve physiological oscillatory dynamics and reduce chronic LC activation associated with sleep fragmentation and nocturnal arousal instability (Ferini-Strambi et al., 2020; Landry and Liu-Ambrose, 2014). Emerging evidence also supports the potential relevance of strategies to enhance SWS. For instance, acoustic closed-loop stimulation and NIBS techniques synchronized with slow oscillations may improve glymphatic function and reduce activity-dependent accumulation of toxic protein species (Krone et al., 2025; Ngo et al., 2013). Similarly, pharmacological approaches targeting orexin signaling are attracting increasing interest, given orexin's central role in arousal regulation and neuronal activity (Hung and Yamanaka, 2023). Consistently, recent preclinical findings suggest that dual orexin receptor antagonists (DORAs) may not only improve insomnia symptoms but also restore the sleep–wake cycle and sleep continuity, thereby enhancing glymphatic clearance and reducing A β accumulation (Ragsdale et al., 2025). Moreover, DORAs could reduce tau-mediated neurodegeneration and pTau levels in a mouse model of tauopathy, possibly exerting a neuroprotective effect (Parhizkar et al., 2025). Although these findings will require confirmation in dedicated clinical populations, they suggest that treating sleep disturbances with these pharmacological agents could be particularly valuable in AD patients, not only to improve sleep quality but also to potentially counteract disease-related pathophysiological mechanisms at the earliest stages (Carpi et al., 2024). This possibility is especially relevant in light of recent studies demonstrating the efficacy and safety of DORAs in older adults, supporting the view that these compounds may represent a clinically feasible strategy to exert meaningful effects on disease-related neurobiology while maintaining a favorable safety profile (Rollo et al., 2026b).

However, it is essential to emphasize that these therapeutic perspectives should currently be considered hypothesis-generating rather

than disease-modifying strategies with established efficacy. Consequently, future translational studies will require longitudinal, biomarker-driven designs that integrate neurophysiological, sleep-architecture, and sensory testing to determine whether interventions targeting these systems can meaningfully alter disease trajectories rather than merely improve symptoms or quality of life. Importantly, the neurophysiological insights gained over recent decades into how internal models of sensorimotor relationships function could prove highly useful in demonstrating the validity of the theoretical framework discussed here. The concept of “impaired internal model updating” refers to a progressive failure of the brain’s predictive-processing architecture to efficiently revise internal representations of the environment in response to changing sensory inputs and prediction errors (Friston et al., 2017; Qela et al., 2025). Within predictive coding frameworks, the brain continuously generates hierarchical models that anticipate incoming sensory information, while neuromodulatory systems—particularly the LC-NE system—regulate the precision and salience of prediction-error signals that are required for adaptive model updating (Friston, 2008; Jordan, 2024; Pezzulo et al., 2021b). In the proposed model of early AD, age-related sensory degradation (especially olfactory dysfunction) chronically increases uncertainty and mismatch between expected and incoming signals, thereby persistently engaging LC-dependent compensatory mechanisms (Jordan, 2024; Jordan and Keller, 2023). Initially, this state may enhance arousal, attentional gain, and network flexibility; however, sustained overactivation is likely to produce maladaptive consequences. In this framework, “impaired internal model updating” denotes a transition from adaptive, compensatory prediction-error processing to a rigid, energetically inefficient state in which neural systems can no longer appropriately recalibrate priors, contextual expectations, and behavioral responses (Keller and Sterzer, 2024). Empirically, this hypothesis is testable at multiple levels. For instance, a specific EEG biomarker associated with predictive coding and the neural representation of a stimulus, namely the mismatch negativity, is already consistently altered at the MCI stage (Lindín et al., 2013; Mowszowski et al., 2012). Similarly, MCI patients are characterized by alterations in the P300, an event-related potential that, particularly in its late components, has been linked to the cognitive processes required to update internal models in response to prediction errors, and to the ability to detect such errors (Papaliagkas et al., 2008; Qela et al., 2025; Tsolaki et al., 2017). Crucially, these metrics show characteristic alterations in both AD patients and those with MCI, even when assessed with olfactory stimuli, suggesting their potential as useful metrics for characterizing the neurophysiological correlates of changes in internal models from the earliest stages of age-related sensory decline (Fatima and Nabi, 2025; Morgan and Murphy, 2002; Tripanpitak et al., 2026). Moreover, interestingly, pupillometry-based indices of LC activity could provide noninvasive, albeit indirect, measures of dysfunctional model updating and NE dysregulation in the AD continuum (Junjie Wu et al., 2025). In addition, fluid biomarkers related to LC activity—particularly those reflecting NE metabolism—along with markers of neuroinflammation that reflect adaptive responses in early disease stages and more chronic, maladaptive inflammatory states during neuropathological progression, and disease-specific indices of pathological processes such as pTau, could provide valuable tools not only for obtaining a static snapshot of disease stage from a pathophysiological perspective but, more importantly, for capturing longitudinal trajectories of disease progression (Antonioni et al., 2023b, 2025e, 2025g; Galgani et al., 2025a; Heneka et al., 2025; Riphagen et al., 2021; van Hooren et al., 2021). As neuroimaging has proved essential in many areas of research into neurodegenerative diseases, it is likely to play a key role in this context by deepening the brain regions involved in the processes under investigation (Risacher and Apostolova, 2023). For example, functional neuroimaging studies examining altered coupling between the LC, the olfactory network, and the cerebellum, or between cerebellar circuits and large-scale networks involved in internal model updating and predictive processing, may provide particularly relevant

mechanistic insights, even if further research is needed to confirm this possibility across the AD spectrum (Huang et al., 2026; Kakei et al., 2026; Khatun et al., 2026; Kim et al., 2026; Liebe et al., 2020). Furthermore, advanced neuroimaging approaches that characterize LC metabolic activity or functional integrity could help identify biological correlates of disrupted predictive coding mechanisms (Aghakhanyan et al., 2023; Ciampa et al., 2022; Weinshenker, 2018). These biomarkers could serve as objective correlates of alterations in sensorimotor predictive coding, as they may reflect the complex dynamics of LC and internal-model updating in brain regions, including the hippocampus and the cerebellum (Antonioni et al., 2024c; Jordan, 2024; Kim et al., 2026; Weinshenker, 2018). Although most currently available evidence remains preliminary and is still largely used to distinguish patients from healthy controls in overt disease stages, these approaches may hold considerable promise for the early identification of individuals with ongoing neuropathological processes during the preclinical phases. Importantly, if the present model is validated, these biomarkers could eventually serve not only diagnostic purposes but also as surrogate endpoints for monitoring the biological effects of interventions, such as those discussed above, aimed at improving or normalizing internal model updating mechanisms. Indeed, if these strategies effectively reduce the compensatory burden on LC-dependent networks, they could theoretically normalize neuroimaging activity patterns, decrease the excessive production of potentially neurotoxic NE metabolites, shift neuroinflammatory responses toward more adaptive, less chronically maladaptive phenotypes, and potentially facilitate the reduction or stabilization of the neuropathological hallmarks of AD. Such applications would not only help test and refine the speculative framework proposed here but, more importantly, could substantially advance understanding of the complex pathophysiology underlying AD. This deeper mechanistic insight will likely be essential to the future development of biologically informed, personalized therapeutic strategies implemented at the earliest stages of disease. Collectively, these approaches would hopefully enable the proposed framework to move from a theoretical construct to a falsifiable, multimodal model of preclinical AD progression.

9. Different interpretations and future perspectives

Importantly, several key components of the present framework—including olfactory dysfunction, sleep disturbances, affective symptoms, autonomic dysregulation, LC involvement, and cerebellar alterations—are not unique to AD, but are instead transdiagnostic features shared across neurodegenerative and neuropsychiatric conditions, including PD, dementia with Lewy bodies, vascular cognitive impairment, traumatic brain injury, depression, and even normal aging (Bain et al., 2026; Chen and Nakagawa, 2023; Hilz et al., 2020; Guangdong Liu et al., 2024b; S.-Y. Liu et al., 2017; Marin et al., 2023; Mather, 2025; Murphy, 2019; Nakagawa and Yamada, 2023; Purkayastha et al., 2019; van der Flier et al., 2018; Van Egroo et al., 2022). Indeed, although the focus has been on the role of LC degeneration in AD, it is now known that this finding is common across various neurodegenerative conditions (Betts et al., 2019b; Mir et al., 2025). However, in AD, this finding may not merely be an epiphenomenon associated with the spread of neurodegeneration but rather a cardinal mechanism of the process from its early stages. Indeed, the consequences of tau accumulation in the LC are disease-specific in AD, and marked neuronal loss in the LC has emerged as a distinctive AD phenotype (Oh et al., 2019a). Consistently, even in so-called “atypical” AD phenotypes characterized by early clinical manifestations distinct from the prototypical short-term memory impairment, pTau accumulation is invariably present in the LC from the earliest disease stages, potentially reflecting underlying olfactory dysfunction in these patients (Bateman et al., 2012; Y. Chen et al., 2022; Dunlop et al., 2025; Graff-Radford et al., 2021; Olivieri et al., 2019). In contrast, amyloid deposition, which influences the subsequent spread of pTau, initially predominates within selectively

vulnerable cortical networks that differ from those affected in prototypical AD and are often shaped by distinct genetic backgrounds (Constantinides et al., 2019; Cuyvers and Sleegers, 2016; Henry and Gorno-Tempini, 2010; Ossenkoppele et al., 2022; Schott et al., 2016). Interestingly, among LC neurons, there is a division between those that project to the primary motor cortex and those that send axons to the prefrontal regions (Aston-Jones and Waterhouse, 2016). These neurons differ in excitability thresholds and protein expression, highlighting that functional subdivision can also occur at the level of individual LC neurons. Moreover, the dorsal regions of the LC primarily project to the hippocampus, whereas the ventral regions project to the cerebellum, putamen, and caudate nucleus (Mason and Fibiger, 1979; Nikolenko et al., 2024). Furthermore, neurons at the posterior pole project to the thalamus, whereas those at the anterior pole project to the hypothalamus. In contrast, LC neurons that project to the olfactory network and the amygdala are often more widely distributed (Mason and Fibiger, 1979). Therefore, it seems reasonable that, at least during the early stages, a selective topography of neuropathological damage critically shapes the subsequent clinical trajectory. Within this hypothetical framework, cerebellar dysfunction observed in AD may primarily stem from olfactory impairment rather than from direct LC damage. Indeed, AD-related neuropathology initially affects the rostral and intermediate portions of the LC, consistent with the proposed pathophysiological progression (Beardmore et al., 2021; Betts et al., 2019a; Dahl et al., 2022; Krohn et al., 2023; Matchett et al., 2021; Theofilas et al., 2017). Accordingly, cerebellar dysfunction secondary to LC degeneration may emerge at later stages when neuropathology extends to the caudal LC.

In contrast, in PD, the temporal sequence may be reversed. Consistent with the hypothesis of a peripheral—most likely enteric—origin of pathological α -synuclein aggregation, neuropathological changes may initially involve the caudal LC, thereby possibly leading to a lesion topography pattern opposite to that observed in AD (Borghammer et al., 2021; Kim et al., 2019; Takahashi et al., 2025). Moreover, because neurons connected to the olfactory network are more widely distributed across the LC, a more extensive spread of α -synuclein within the LC may be required to mediate the emergence of olfactory dysfunction, either by disrupting NE-dependent regulation of synaptic plasticity in the OB and piriform cortex or by prion-like propagation of α -synuclein pathology to these regions (Biagioni et al., 2024; Chandler et al., 2019; Geng et al., 2025; Henrich et al., 2018; Steiner et al., 2018). This distinction aligns with the contrasting clinical presentations of the two disorders, namely an early motor phenotype in PD and a predominantly cognitive onset in AD (Frisoni et al., 2022, 2025b; Sveinbjornsdottir, 2016). In this context, olfactory impairment may play a less causal pathophysiological role in PD, as the rostral LC—thought to survive longer—may continue to support hippocampal integration more effectively and for longer than in AD (Krohn et al., 2023; Mason and Fibiger, 1979; Nikolenko et al., 2024). Thus, even if only hypothetically, in PD, an olfactory deficit could be an epiphenomenon linked to a breakdown of the LC (and therefore to the loss of its modulatory action at both the olfactory stations and the interconnected medial temporal regions), caused by ascending neuropathological damage rather than being the initial trigger, as in AD. Consistently, REM sleep behavior disorder (RBD), a well-established prodromal marker of PD, is associated with a later clinical onset than in individuals without RBD (Högl et al., 2018; Iranzo et al., 2016). RBD reflects dysfunction of brainstem regions caudal to the LC, including the sublaterodorsal nucleus and the pedunculopontine tegmental nucleus. Beyond supporting a topographically driven model of disease progression, RBD may represent a compensatory response to early neuropathological damage, thereby delaying overt clinical manifestation—analogous to what is hypothesized to occur in AD, where increased noradrenergic tone and its effects on olfactory and hippocampal networks may initially sustain function despite ongoing pathology (Antonioni et al., 2024b). Moreover, in PD, a significant reduction in NE release in the cerebellum has been observed, consistent with known LC alterations in this patient population, which lead to

significant changes in motor coordination, gait, autonomic regulation, and cognitive-motivational function (Hirano et al., 2023; Wu and Hallett, 2013). Consistently, LC degeneration exceeds that of the Meynert nucleus in AD and the substantia nigra in PD, suggesting a crucial role in both diseases (Zarow et al., 2003). This supports a common pathophysiological process underlying both conditions while preserving specific features, at least across time points, owing to the distinct topography of damage progression. Therefore, despite the common finding of an olfactory deficit preceding the clinical onset, the role of olfaction may be profoundly different between the two conditions. Indeed, it could represent an extremely early marker for intervention in AD, but not necessarily in PD, where, according to the proposed model, a possible equivalent could be constipation and, subsequently, RBD, as neuropathological damage is likely to originate primarily from the periphery, particularly the gut (Borghammer et al., 2021; Doty, 2017; Kalia and Lang, 2015; Marin et al., 2018; Takahashi et al., 2025). However, these relationships are complicated by the fact that, in the general population, olfactory deficits and constipation have multiple causes beyond primary neurodegeneration (Barberio et al., 2021; Murphy et al., 2002). Despite this, the potential of these time windows preceding clinical onset may be fundamental and should be appropriately exploited within a sound anamnestic and clinical approach to increase confidence in the underlying cause.

The present model therefore emphasizes not merely the presence of these clinical or biological alterations but their integration into a predictive-processing and compensation-based cascade centered on chronic sensory uncertainty, sustained LC engagement, maladaptive network plasticity, and synergistic interactions among tau pathology, A β accumulation, and neuroinflammation. At the same time, the framework is compatible with the increasingly recognized concept of mixed and overlapping pathologies in late-life neurodegeneration. In particular, sporadic AD frequently coexists with vascular lesions, α -synuclein pathology, TDP-43 pathology, or systemic inflammatory processes, all of which may modulate compensatory capacity and accelerate network failure (Attems and Jellinger, 2014; Baiardi et al., 2024; Bayraktaroglu et al., 2025; Frisoni et al., 2022; James et al., 2016). Accordingly, the model should not be interpreted as exclusively AD-specific but rather as a mechanistic framework that may be particularly relevant to sporadic AD while retaining broader transdiagnostic applicability across neurodegenerative conditions characterized by chronic impairment of predictive regulation and progressive failure of adaptive network compensation. Importantly, although age-related sensory dysfunction and the consequent compensatory alterations in predictive coding may plausibly accelerate neuropathological progression across multiple neurodegenerative disorders, the evidence discussed here suggest that, especially in the presence of permissive risk factors—most notably the *ApoE4* genotype, although additional genetic and environmental modulators are likely involved—these mechanisms may serve as a very early pathogenic trigger, or at least a relevant upstream contributor, in sporadic AD (Frisoni et al., 2022; Kang et al., 2021). By contrast, in other neurodegenerative conditions, these same processes may exert a more secondary or modulatory role within disease progression. For instance, in synucleinopathies such as PD, the characteristic caudo-rostral propagation patterns suggest partially distinct initiating mechanisms, whereas in disorders such as FTD, the strong genetic and immune-mediated background may reduce the relative causal weight of sensory-driven predictive dysregulation (Benussi et al., 2019; Borghammer et al., 2021; Borroni et al., 2017; Bright et al., 2019; Kim et al., 2019; Takahashi et al., 2025). Therefore, the transdiagnostic relevance of this framework likely lies less in a uniform etiological role and more in the possibility that similar maladaptive network responses may interact with disease-specific vulnerabilities and propagation pathways, ultimately contributing to neurodegeneration through partially shared yet hierarchically distinct mechanisms. In contrast, in genetic AD cases, the picture is more controversial, given that the abnormal overproduction of A β from a relatively early age could lead to widespread synaptic

alterations that are not necessarily aligned with the causal sequence of age-related events discussed here (Lanoiselée et al., 2017; Nan et al., 2025; Tavalin, 2024). Therefore, the possibility of generalizing this model to genetic cases requires further study, particularly to better understand the longitudinal trajectories of neuropathological damage accumulation and the pathophysiology of cognitive impairment in this specific category of AD patients.

Although this work focused on olfactory dysfunction, it cannot be excluded that analogous considerations—albeit, as hypothesized, less directly implicated pathophysiologically—may also apply to other sensory modalities. Consistently, in animal models of AD, alterations in visuomotor integration are frequently observed from the early stages (Liebscher et al., 2016). Several core mechanisms of sensorimotor integration, including LTP-like plasticity and the modulatory roles of NE and acetylcholine, are broadly disrupted in AD, suggesting that deficits arise in a transmodal manner (Benussi et al., 2021, 2017; Di Lorenzo et al., 2020; Hampel et al., 2019; Krohn et al., 2023). Moreover, hearing loss has been identified as a key and potentially modifiable risk factor for dementia (Lin, 2024; Livingston et al., 2020). Reasonably, this reflects not only the essential function of this sensory modality—which, like olfaction, is subject to age-related physiological decline known as presbycusis—in forming internal models, but also differences in clinical awareness and management (Beckmann et al., 2020; Campos et al., 2018; Froese and González-Grandón, 2020; Gates and Mills, 2005; Schulte et al., 2020). Indeed, auditory deficits are less likely to be overlooked or underdiagnosed, in part because of their critical impact on daily life, and effective treatments are widely known and accessible (Lin, 2024; Pacala and Yueh, 2012; Wilson et al., 2017; Yueh et al., 2003). In contrast, olfactory decline is often perceived as less relevant and is commonly underassessed in both clinical practice and by patients, even in cases of severe deficits (Cao et al., 2022; Toro et al., 2023; Whitcroft and Hummel, 2019). These considerations, together with the particularly strong links between the olfactory network and key early drivers of AD pathophysiology, suggest that olfactory impairment may play an even more prominent role. Hopefully, the arguments presented will raise awareness of the importance of systematically evaluating olfactory function in elderly patients, not least because identifying and treating potentially reversible causes of olfactory dysfunction may hypothetically help counteract or slow the cascade of events outlined above (Dan et al., 2021; Dongming Liu et al., 2024; Liu et al., 2025; Tian et al., 2023). Indeed, if the pathophysiological sequence proposed here is correct, distinct sensory deficits are hypothesized to emerge after olfactory impairments, or, if they occur concurrently, to play a less decisive role because of their weaker interaction with the principal early drivers of AD pathophysiology. Future studies will be essential to confirm whether the temporal ordering of events follows the sequence outlined here and, if so, to determine how early interventions might modify the natural history of the disease from its earliest stages. Although speculative, the comparatively less direct involvement of sensory modalities other than olfaction in mediating the deficits described here may also depend on the thalamus's presence within their processing pathways. Indeed, the thalamus does not merely serve as a passive relay station for afferent information en route to the cortex; rather, it is a critical modulatory hub that actively shapes sensory processing by dynamically segregating, integrating, and coordinating distributed cortical networks in a context-dependent manner (Rikhye et al., 2018; Shine, 2021; Shine et al., 2023). Notably, a substantial proportion of thalamic inputs do not arise from the periphery but instead originate from cortical regions to which the thalamus projects. These cortico-thalamic loops exert top-down control over thalamic processing and, crucially in the present context, enable the thalamus to play a role in comparing incoming sensory signals with prior expectations (Guo et al., 2020; Miller-Hansen and Sherman, 2022; Sampathkumar et al., 2021; Sherman, 2016). As such, the thalamus may, at least transiently, enable compensatory or vicarious processing of deficits affecting sensory modalities such as vision and audition (Guillamón-Vivancos et al.,

2025; Paricio-Montesinos and Gründemann, 2025; Whitt et al., 2022, p. 20). This compensatory mechanism, however, may be unavailable to olfaction, further underscoring the functional significance of olfactory deficits.

It is also essential to note that the relationship among AD neuropathology, olfactory dysfunction, and sleep disturbances remains controversial with respect to both causality and temporal progression. For example, a recent study showed that long sleep duration may represent a risk factor for AD (Xiang et al., 2024). Moreover, although the vast majority of AD patients have impaired olfactory function, a significant 10–15 % retain normal olfactory function, even in the overt stages of the disease (Murphy, 2019). It is therefore plausible that, beyond acting either as potential triggers of the neuropathological cascade (in the case of olfactory dysfunction) or as early manifestations of ongoing neurodegenerative processes (in the case of sleep disturbances), as proposed within the present conceptual framework, these alterations may also contribute dynamically and interactively to disease pathophysiology. Their impact is likely modulated by disease stage, network vulnerability, and genetic background, which may interact with additional risk factors in a complex, bidirectional manner throughout the disease course. However, several longitudinal studies have consistently shown that olfactory impairment is a strong predictor of dementia development from very early stages (Adams et al., 2018; Laukka et al., 2023b; Oltra et al., 2026). Furthermore, crucially, a different Mendelian randomization analysis has shown that AD may causally influence sleep patterns, whereas no evidence emerged of a causal role for disturbed sleep patterns in AD (Huang et al., 2020). In other words, the results highlight that altered sleep may be an early manifestation of AD neuropathology rather than an independent causal factor in the disease. This could suggest that AD neuropathology alters sleep patterns, which, in turn, could exacerbate and facilitate the progression of ongoing neuropathological accumulation. Indeed, sleep fragmentation and impaired SWS can promote tau and A β accumulation through altered glymphatic clearance, neuronal hyperactivity, and neuroinflammatory mechanisms, while the accumulation of tau and amyloid pathology within hypothalamic, brainstem, and cortical sleep-regulatory circuits further exacerbates sleep disruption (Heneka et al., 2025; Nedergaard and Goldman, 2020; Slutsky, 2024; Wang and Holtzman, 2020). Considering its crucial role in sleep regulation, it is reasonable to propose that changes in the LC—resulting from the discussed age-related olfactory alterations, as a compensatory mechanism, and from its being the main site of pTau accumulation—are key contributors to these sleep disturbances, at least in some cases (Van Egroo et al., 2022). However, based on current evidence, these non-cognitive symptoms could be better conceptualized as early network-level modifiers and amplifiers that interact recursively with evolving neuropathology, and further studies are needed to establish their causal or epiphenomenal role at a specific time point.

Importantly, although the primary damage initially affects the sensory domain, it is equally true that sensory stimuli must be embodied to acquire meaning for the CNS, particularly in the context of aging and AD (Buzsáki and Watson, 2012; Dzwiza-Ohlsen and Kempermann, 2023; Friston et al., 2016). This principle may help explain why sniffing modulates activity within the olfactory network even in the absence of odorants and why analogous mechanisms may operate across other sensory domains (Granget et al., 2025). Moreover, it may partially substantiate the well-documented benefits of physical exercise, particularly moderate aerobic activity (Behrad et al., 2024; Chen and Nakagawa, 2023; Müller et al., 2018; Silva et al., 2024; Tari et al., 2025). Beyond reducing exposure to risk factors, such as obesity, and by promoting the release of neurotrophic factors, physical activity may contribute to the embedding of sensory information within coherent internal models (Buzsáki, 2026; Fischer, 2016; Khalil, 2024; Nithianantharajah and Hannan, 2009). It strengthens the functional coupling between sensory inputs and motor outputs, reinforces sensorimotor representations, and enhances the updating and stability of internal models. Indeed, increased motor engagement enriches experiential

input and cognitive demand, thereby enhancing learning (Antonioni et al., 2025a, 2024c; Dzwiza-Ohlsen and Kempermann, 2023). As predictive abilities improve, individuals become better able to anticipate future events and adjust more effectively to environmental challenges, including the outcomes of their own actions and those of others.

Another relevant ongoing debate concerns the extent and timing of cerebellar involvement in AD. Previous neuropathological studies have reported relatively limited classical AD pathology in the cerebellar cortex compared with the neocortex and limbic regions (Hirano and Zimmerman, 1962; McElroy et al., 2024). It is important to consider that, until relatively recent years, the cerebellum was largely regarded as a “silent bystander” in the context of neurodegenerative diseases (Schmahmann, 2016). Consequently, it was frequently used as a reference region to normalize pathological alterations in other brain areas—considered more directly relevant to disease pathophysiology—or was even excluded altogether from analytical templates and network-based investigations (Arleo et al., 2024; Lyoo et al., 2015; Tissot et al., 2023; Vemuri et al., 2017). In this light, many historically negative or inconclusive findings regarding cerebellar involvement should be interpreted with caution, as they may partly reflect methodological and conceptual limitations rather than a true absence of cerebellar contribution to disease processes. Importantly, as previously discussed, growing evidence supports structural, functional, and neuropathological alterations in cerebellar circuits, often beginning in the prodromal stage (Y. Chen et al., 2023a; Guo et al., 2016; Jacobs et al., 2018). A recent longitudinal study has confirmed that cerebellar degeneration is not confined to advanced stages but emerges early and interacts dynamically with cortical networks (Um et al., 2026). Furthermore, structural covariance research has shown that disruptions in LC–cerebellar connectivity appear early in AD, further reinforcing the conceptual framework outlined here (Tang et al., 2023). However, although it now seems well established that this structure is affected by neuropathological damage as the disease progresses, the extent to which the cerebellum is involved in the earliest stages of AD remains poorly understood. In fact, some of the factors that contribute to the cerebellum’s selective vulnerability in the context of AD are also associated with normal aging (McElroy et al., 2024). Consistently, recent research indicates that alterations characteristic of physiological aging in the cerebellum partially overlap with those observed in AD, thereby complicating the interpretation of their role in disease progression (Gellersen et al., 2021). This makes it difficult, at present, to establish a primary role for the cerebellum in the early pathophysiology of AD, rather than secondary involvement arising from changes that primarily affect other brain regions, because cerebellar alterations may be secondary, compensatory, or network-mediated rather than primary drivers of disease progression. Notably, the present model is also broadly compatible with this second possibility. Specifically, it does not require the cerebellum to represent an initial locus of irreversible neurodegeneration; instead, it proposes that cerebellar engagement emerges early as part of a distributed compensatory network recruited in response to sensory uncertainty, predictive-processing imbalance, and increased demands on LC-mediated neuromodulatory systems. Under this interpretation, early cerebellar hyperconnectivity or functional reorganization may initially reflect adaptive compensation rather than overt pathology, whereas later cerebellar dysfunction may arise secondarily through transneuronal spread, diaschisis-like processes, chronic neuroinflammation, or progressive network disintegration. Given that evidence of cerebellar involvement in the early stages of AD remains limited, further studies will be essential to clarify the cerebellum’s role in the early pathophysiology of AD and to determine the extent to which its alterations are relevant to the progression described here.

Finally, and importantly, this view aligns with recent evidence suggesting that, from an evolutionary perspective, memory is not only—or even primarily—designed to support recollection but also to enable prediction (Vecchi and Gatti, 2020). Indeed, memory allows fragments

of past experience to be flexibly recombined into dynamic configurations that support internal simulation and anticipatory behavior (Barron et al., 2020; Pezzulo et al., 2021a). Within this framework, the interplay among the hippocampus—critical for encoding and defining the spatiotemporal organization of neuronal ensembles underlying episodic representations—the LC, which dynamically modulates the coupling between memory and ongoing experience through NE and dopamine, and the cerebellum, which plays a pivotal role in generating and updating internal models based on prediction errors, appears essential, particularly in the context of sleep, as this work aimed to underscore (Groves et al., 2025; Krohn et al., 2023; Spampinato and Celnik, 2021).

10. Conclusions

Starting with the simple metaphor of a highly efficient company whose mainframes show declining performance due to disruptions in the input system, this work discussed possible converging evidence that dysfunction first arises within the olfactory system and then, in rapid succession or perhaps in parallel, involves the LC, the cerebellum, sleep regulation, and medial temporal lobe networks. At this point, the reader will have appreciated that the “company” represents the CNS; the mainframes correspond to hubs that compute our interactions with the external world in terms of prediction errors—here, primarily the LC and the cerebellum. The input systems, as in real life, are our sensory modalities (chiefly olfaction, though not exclusively), whereas the “cooling system” metaphorically captures the mechanisms that enable plasticity and learning, such as A β synthesis and the release of NE and dopamine, which are replenished overnight to ensure readiness for the following day. The specialized waste-removal company encompasses sleep in general—through its LC-silencing effects—and, more specifically, the glymphatic system, with regard to the clearance of neurotoxic by-products (here symbolized by the coolant tanks). The “mercenaries” hired for disposal partially overlap with the “security forces,” namely, neuroinflammatory processes that are initially recruited to sustain compensation and contain sites of toxic accumulation, but that later act to ultimately exacerbate neural damage. Notably, these processes also include intracellular degradation mechanisms, involving dedicated pathways that attempt to dismantle accumulated neurotoxic products at the cost of further damaging the “mainframes” themselves (a topic beyond the scope of the present work) (Bhushan et al., 2025; Fleming et al., 2022; Nixon, 2024). Subsequently, the infrastructural damage mirrors BBB dysfunction, which permits the entry of “animals”—here representing systemic toxins and infectious agents—thereby further amplifying the pathological cascade. Ultimately, the collapse of the “mainframes” leads workers to leave—or, in biological terms, neurons to die—thereby causing the company's failure, that is, the onset of cognitive decline. Although this story is only a hypothesis about one possible course of events leading to the neuropathological hallmarks of AD, the findings reviewed may provide important insights into the pathophysiology of sporadic AD and critically inform how individuals might be identified—and potentially treated—at the earliest stages, well before the onset of MCI. Such an approach could maximize the efficacy of emerging disease-modifying therapies while likely providing substantially improved safety, given that, with aging, neuropathological processes and comorbidities increase the risk profile (Dolphin et al., 2024; Fox et al., 2025; Frisoni et al., 2025a; Jellinger and Attems, 2015).

In summary, the framework proposed here integrates several previously disconnected observations into a unified mechanistic account of the prolonged preclinical phase of AD, centered on the interplay among sensory dysfunction, LC–noradrenergic compensation, progressive proteinopathy, cerebellar and medial temporal lobe involvement, and neuroinflammatory remodeling. Several components of this model are strongly supported by existing evidence. These include the very early accumulation of pretangle tau within the LC in cognitively intact individuals (Braak and Del Tredici, 2012b, 2011), the essential involvement of the olfactory system in the sensorimotor predictive coding

network (Lyons and Gottfried, 2025; Pierchajlo et al., 2024; Zelano et al., 2011), the early olfactory dysfunction in AD pathophysiology (Adams et al., 2018; Laukka et al., 2023b; Murphy, 2019; Oltra et al., 2026), the vulnerability of the LC to metabolic stress and tau-related degeneration (Kang et al., 2021; Matchett et al., 2021; Weinshenker, 2018), and the close relationship between the LC and sensorimotor predictive coding (Groves et al., 2025; Jordan, 2024). Likewise, substantial evidence supports the existence of an initially adaptive neuro-inflammatory response that may transiently preserve tissue homeostasis before transitioning to chronic, maladaptive activation (Cuello, 2017; Fan et al., 2017; Heneka et al., 2025). Building on these established findings, the present model proposes a more speculative hypothesis that age-related sensory degradation is an upstream, systems-level stressor that chronically increases predictive-processing demands across distributed networks, thereby driving sustained LC-dependent compensatory activity. According to this interpretation, prolonged noradrenergic compensation initially preserves cognitive performance but also creates conditions that favor pTau aggregation, A β accumulation, sleep dysregulation, and progressive network instability (Weinshenker, 2018). The cerebellum is further hypothesized to actively participate in these early compensatory adaptations, rather than merely serving as a passive site of secondary pathology (Chaudhari et al., 2021; Guo et al., 2016a; Mitoma et al., 2020). In this framework, SCD may reflect the clinical correlate of a still-compensated but increasingly metabolically strained network state. As compensation progressively fails, tau pathology spreads through anatomically and functionally connected systems, likely via prion-like mechanisms, while chronic neuroinflammation, BBB dysfunction, and neurotransmitter-system breakdown amplify large-scale network disintegration and overt cognitive decline (Heneka et al., 2025; Mudher et al., 2017; J. Zhang et al., 2024). Importantly, several key aspects of this model remain unresolved and require direct experimental validation in clinical populations. These include whether sensory dysfunction is truly causal rather than epiphenomenal, the precise mechanisms linking NE metabolism to tau aggregation and dissemination, the extent to which cerebellar compensatory recruitment modifies disease trajectory, and, most importantly, whether early modulation of LC activity, sensory input, or sleep can alter long-term progression. Consequently, the model should be regarded not as a definitive pathogenic sequence but as an integrative, testable systems-neuroscience framework that yields experimentally falsifiable predictions and may help reconcile the long temporal gap between the earliest molecular alterations and the delayed emergence of classic cognitive symptoms in AD. Hopefully, this review will stimulate further research along this trajectory, generating additional evidence to support the proposed sequence of events and ultimately bringing the scientific community closer to identifying a truly curative intervention for a condition that affects millions of individuals worldwide and represents an ever-growing global public health challenge.

List of abbreviations

A β : amyloid- β
 AD: Alzheimer's disease
 ApoE: apolipoprotein E
 APP: amyloid precursor protein
 BBB: blood-brain barrier
 BC: basket cells
 CBT-I: cognitive behavioral therapy for insomnia
 CCAS: cerebellar cognitive-affective syndrome
 CF: climbing fibers
 CNS: central nervous system
 CPAP: continuous positive airway pressure
 CSF: cerebrospinal fluid
 DCN: deep cerebellar nuclei
 DMN: default mode network
 DORAs: dual orexin receptor antagonists

EEG: electroencephalography
 fMRI: functional MRI
 FTD: frontotemporal dementia
 GABA: gamma-aminobutyric acid
 GL: granule cell layer
 GoC: Golgi cells
 GrC: granule cells
 IO: inferior olive
 LC: locus coeruleus
 LTD: long-term depression
 LTP: long-term potentiation
 MCI: mild cognitive impairment
 MF: mossy fibers
 ML: molecular layer
 MNS: mirror neuron system
 MRI: magnetic resonance imaging
 NE: noradrenaline
 NFTs: neurofibrillary tangles
 NIBS: non-invasive brain stimulation
 NREM: non-rapid eye movement
 OB: olfactory bulb
 OSAS: obstructive sleep apnea syndrome
 PC: Purkinje cells
 PCL: Purkinje cell layer
 PD: Parkinson's disease
 PN: pontine nuclei
 pTau: hyperphosphorylated tau
 RBD: REM sleep behavior disorder
 REM: rapid eye movement
 rTMS: repetitive TMS
 SAI: short-latency afferent inhibition
 SC: stellate cells
 SCD: subjective cognitive decline
 SWS: slow-wave sleep
 TMS: transcranial magnetic stimulation

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The author conceived the review, conducted the literature search, and drafted the manuscript.

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