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Hallmarks of healthy cognitive aging: inter-individual differences in aging trajectories

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Abstract

Cognitive aging is a highly heterogeneous process, with some individuals preserving stable cognitive performance across the lifespan while others exhibiting pronounced decline. This marked interindividual variability indicates that chronological age alone is a poor predictor of cognitive health. Rather than reflecting uniform degeneration, cognitive aging emerges from divergent biological trajectories spanning molecular, cellular, and network levels.

In this review, we synthesize emerging biological hallmarks of healthy cognitive aging, emphasizing studies that characterize longitudinal cognitive trajectories in humans or distinguish aged individuals who retain learning capacity from those who do not. We focus on the medial temporal lobe, a region critical for episodic memory and spatial navigation, and examine how variability in its integrity contributes to distinct cognitive outcomes.

Across species, convergent evidence suggests that cognitive decline is more closely linked to alterations in network regulation and synaptic plasticity than to overt neuronal loss. We identify key mechanisms shaping individual trajectories, including large-scale network organization, excitation–inhibition balance, neuromodulatory tone, glial and vascular regulation, adult hippocampal neurogenesis, and cellular homeostasis. These processes operate within an interconnected system in which disruptions in core regulatory mechanisms can propagate across levels of organization.

Together, this synthesis supports a system-level framework in which cognitive resilience depends on the preservation of coordinated network dynamics. We advocate for longitudinal, multidimensional approaches to identify early shifts in regulatory balance and inform strategies to maintain cognitive function across the lifespan.

Keywords.

Cognitive Aging; inter-individual differences; medial temporal lobe; Episodic Memory;spatial memory; Hallmarks

GLOSSARY BOX

NORMATIVE AGING – results from complex aging processes in the absence of disease.

COGNITIVE AGING – changes in an individual's cognitive abilities over time, affecting domains such as perception, memory, attention, processing speed, executive function, and language. Neurodegenerative diseases can accelerate or exacerbate cognitive aging.

SUCCESSFUL AGING – a late-life aging trajectory characterized by preservation of cognitive functions.

VULNERABILITY – increased susceptibility to steeper functional decline to a reference population. Cognitive vulnerability may or may not manifest as a higher risk of neurodegenerative disease.

BRAIN MAINTENANCE – individual differences in the manifestation of age-related brain changes and pathology that allow some individuals to exhibit little or no cognitive decline with age.

MEMORY CONSOLIDATION – the process by which temporary, newly acquired information is gradually stabilized in the brain and transformed into more permanent, lasting memories. Through this process, short-term memories are converted into long-term memories, making them more resistant to interference and decay over time.

PATTERN SEPARATION – the process by which the brain encodes similar but distinct experiences or stimuli as separate and unique representations. It helps preserve the integrity of similar memories stored in overlapping neuronal populations, allowing accurate recall of specific information and preventing interference.

PATTERN COMPLETION the process by which the brain retrieves memories based on incomplete cues. When we encounter a familiar partial stimulus, pattern completion helps the brain to reconstruct and retrieve the associated information, context, or memory trace.

HIGHER COGNITIVE HEALTH (HCH) – individuals with a stable or less declining trajectory compared to those with a more pronounced negative trajectory. In cross-sectional studies, individuals with higher cognitive health show better performance than those with lower cognitive health, typically defined using performance-based stratification (e.g., median split) or relative to normative data.

LOWER COGNITIVE HEALTH (LCH) – individuals with a more pronounced negative trajectory. In cross-sectional studies, individuals with lower cognitive health show lower performance than individuals with higher cognitive health.

CORE REGULATORY MECHANISMS – mechanisms that establish and maintain the operating regime of neural systems.

ANCILLARY MECHANISMS – mechanisms that depend on the integrity of core regulators and influence outcomes by shaping robustness, flexibility, or vulnerability.

I . INTRODUCTION

A. Cognitive aging is not uniform

Global population aging is rapidly increasing the prevalence of age-associated cognitive decline, threatening independence, quality of life, and healthcare sustainability[1]. While cognitive changes are common in later life, the biological hallmarks that distinguish normative aging from those leading to Alzheimer's disease remain insufficiently defined. This gap limits early detection and preventive intervention. A systematic investigation of these hallmarks is essential to identify modifiable targets that promote healthy cognitive aging.

Cognitive aging is a gradual and highly heterogeneous process in which the brain's capacity to process, integrate, and use information changes over time. Unlike the rapid and relatively stereotyped decline observed in neurodegenerative diseases, age-related cognitive change unfolds slowly and varies substantially across individuals: some maintain high levels of cognitive function well into late-life, whereas others experience pronounced decline[2,3]. This inter-individual variability underscores that cognitive aging is not an inevitable consequence of chronological age, but instead reflects the interaction of biological, environmental, and experiential factors. Accordingly, cognitive health can be conceptualized as a continuum ranging from preserved to vulnerable functioning, analogous to physical health. Elucidating the biological determinants that shape these trajectories is therefore critical for understanding healthy cognitive aging and designing personalized interventions.

Both cross-sectional and longitudinal approaches have contributed important insights into cognitive aging. Cross-sectional studies are valuable for identifying broad age-related differences and generating mechanistic hypotheses. However, longitudinal studies are uniquely informative, as they directly track within-individual change over time, enabling the estimation of cognitive trajectories, the identification of factors associated with preserved function, and the detection of adaptive brain reorganization. Throughout this review, we emphasize longitudinal evidence as the most powerful framework for uncovering the neurobiological mechanisms that support cognitive resilience, while integrating cross-sectional findings to provide complementary mechanistic context.

B. Literature selection methodology

We adopted a structured, iterative approach to article selection. For the rodent literature, we began with a seminal review in the field[2] and systematically traced both its cited references and the subsequent references within those studies. To reduce potential bias arising from cross-citation among closely allied laboratories, we also used the "similar papers" function in PubMed to identify relevant articles beyond the original citation network. For the human literature, we relied on an expert consensus approach. Papers proposed by members of the author group were incorporated into the corpus and additional articles were identified through citation chaining, that is, by examining the reference lists of key papers, until no new themes or references emerged (conceptual saturation). Finally, we also consulted systematic reviews and meta-analyses to identify broader trends and synthesize established findings.

C. How to measure cognitive health?

We take a broad and descriptive approach to the topic of cognitive health. This is necessary due to the substantial discrepancies in definitions within domains and between human and animal studies. In human longitudinal research, cognitive health is often defined by comparing individuals with stable or minimally declining cognitive trajectories to those with more pronounced negative change (Figure 1). Comparable distinctions can be applied to animal studies, even though longitudinal research in animals remains scarce. In cross-sectional designs, cognitive health is frequently inferred from relative performance differences, such as median splits, normative comparisons, or percentile-based thresholds. An important limitation of cross-sectional definitions is that they provide little insight into whether differences in cognitive health stem from varying rates of cognitive change or reflect pre-existing differences in cognitive performance from early adulthood. Furthermore, a median-split, does not in itself indicate whether individuals below the median are cognitively unhealthy, as it may simply capture normal variation around the average.

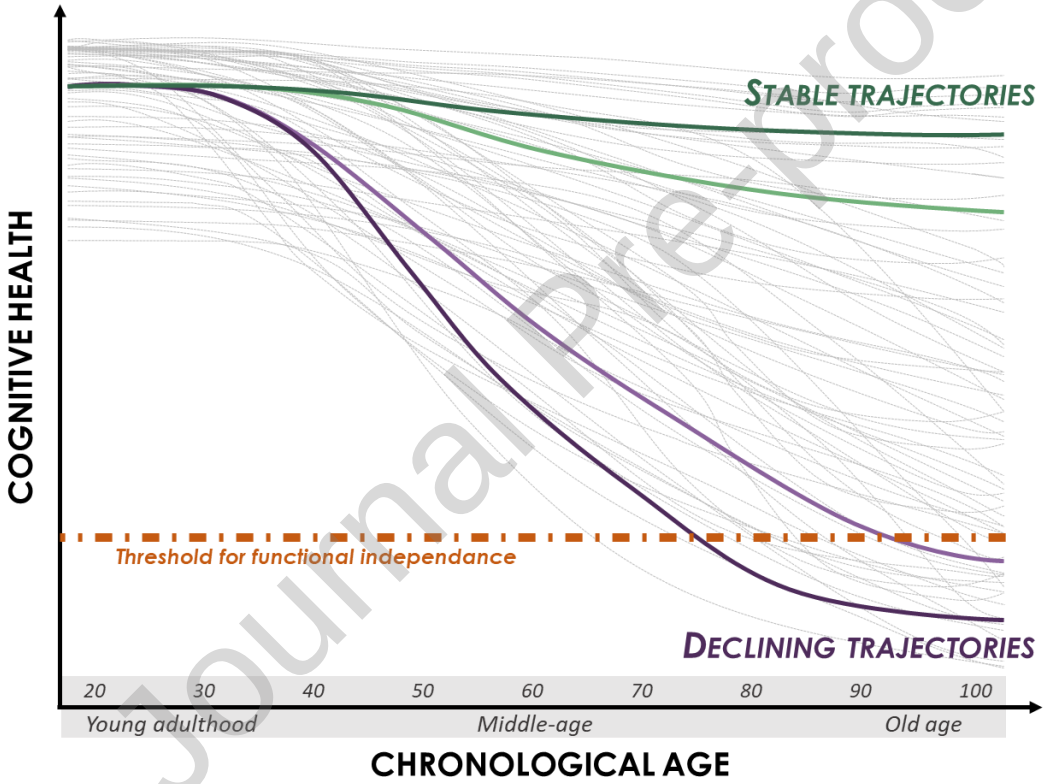

Figure 1: Theoretical illustration of inter-individual variability in cognitive aging trajectories.
Each grey line represents one individual hypothetical cognitive health trajectory. Established and emerging mechanisms that determine whether a given individual experiences more stable (in green) vs. declining (in purple) trajectories are the focus of this review. The orange line marks the threshold for functional independence; once an individual's cognitive health drops below this level, autonomous daily living is compromised.

In this review, we focus on episodic memory and spatial navigation as core behavioral phenotypes of cognitive aging in both humans and rodents. These functions show early sensitivity to aging, yet can remain relatively preserved in some older adults[3–4], making them particularly informative for distinguishing healthy from vulnerable cognitive trajectories. Both functions rely heavily on medial temporal lobe (MTL) circuits, whose cellular, synaptic, and network-level organization have been extensively characterized across species. Moreover, the computational operations underlying episodic memory and navigation, such as relational binding, sequence encoding, and map-based

inference, are redeployed across multiple cognitive domains. Thus, insights gained from these functions provide a window into more general principles of cognitive aging.

D. How to define a hallmark of cognitive health?

Human aging is accompanied by a progressive increase in the risk of cognitive dysfunction that is widely attributed to the time-dependent accumulation of molecular and cellular defects that disrupt key biological pathways, ultimately giving rise to aging-associated phenotypes and disease. In landmark studies characterizing aging, López-Otín and colleagues[4,5] conceptualized these processes as twelve interconnected "hallmarks of aging": genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, impaired macroautophagy, chronic inflammation, and dysbiosis.

While each hallmark has been extensively studied as an independent driver of aging, far less is known about how these pathways interact and jointly influence individual aging trajectories. Given the multifactorial nature of aging phenotypes, a comprehensive understanding of both individual pathways and their crosstalk is essential for the rational development of interventions targeting aging and age-related diseases.

Dissecting these reciprocal relationships will be critical for designing therapeutic strategies that target multiple hallmarks simultaneously, thereby mitigating age-related functional decline and promoting healthy aging. Moreover, recent work has revealed pronounced heterogeneity in aging across organs and systems, leading to the identification of tissue and organ-specific aging clocks[6] that predict chronic disease risk and mortality[7]. These findings suggest that the relevance and temporal dynamics of individual hallmarks may vary substantially across biological contexts. Initial studies in mice have begun to define organ-specific temporal signatures of aging hallmarks[8]. Such insights will be essential for the development of personalized, temporally informed interventions targeting specific organs or systems[9].

In the brain, this framework may help explain the striking inter-individual variability in cognitive aging and guide strategies to enhance resilience and preserve cognitive function into late life. We propose operational criteria for defining **hallmarks of healthy cognitive aging**: (Figure 2).

1. **Trajectory relevance**: They should shape the trajectory of specific cognitive abilities, thereby contributing to identifiable behavioral phenotypes.
2. **Circuit specificity:** They should occur in brain regions and circuits that support well-defined cognitive processes – here, with an emphasis on episodic memory or spatial navigation.
3. **Association with cognitive change:** Their magnitude should ideally be quantitatively associated with rates of cognitive change as measured longitudinally, or with variation in cross-sectional memory levels.

In summary, by integrating evidence from human and animal studies, accounting for inter-individual differences in memory abilities, and by emphasizing longitudinal and mechanistic approaches, this review aims to delineate the biological hallmarks that support preserved cognitive function in aging.

II. BEHAVIORAL PHENOTYPES OF HEALTHY COGNITIVE AGING, EPISODIC MEMORY AND SPATIAL NAVIGATION

We focus on episodic memory and spatial navigation, two complementary cognitive functions[10] that exhibit early vulnerability to aging yet remain remarkably preserved in a subset of older adults. We concentrate on these domains for several reasons. First, both critically depend on brain structures in the MTL, whose constituent cell types, synaptic mechanisms, and network dynamics have been mapped in detail across rodents, non-human primates, and humans, thereby enabling age-related alterations to be linked to defined neural computations. Second, the computational operations that allow the same circuit to encode past episodes and current location, including sequence binding, relational mapping, and path integration, are not domain-specific but are redeployed across cognitive systems; insights from these functions therefore inform broader abilities such as semantic memory, prospective cognition, and model-based decision making. Finally, several aging principles identified in the hippocampal–entorhinal system, including reduced representational specificity, decreased within-network segregation, and excitation–inhibition imbalance, have also been reported in other circuits such as primary sensory and motor cortices[11,12]. Thus, episodic memory and navigation provide a mechanistically grounded and cross-species tractable framework for capturing general principles of cortical aging while offering the added advantage of early sensitivity.

A. How does aging affect episodic memory?

Not all long-term memories are equally affected by aging. In contrast to non-declarative (implicit) memory, which is relatively preserved across the lifespan[13], declarative memory, defined as the conscious recollection of facts and events, is particularly sensitive to the aging process. Episodic memory, a sub-domain of declarative memory[14], refers to the ability to encode, store and consciously re-experience events anchored to specific places and moments in time. Episodic memory shows gradual age-related decline starting around the age of 60[15], although the magnitude and trajectory of decline vary substantially across individuals and are influenced by genetic and lifestyle factors[16]. Age-related alterations particularly affect free recalland the flexible use of learned information, as well as the ability to mentally travel back and forth in time to remember episodes and plan future actions[17,18]. Beyond the temporal dimension, episodic memory is inherently relational, enabling the formation of distinct representations that share overlapping elements, a process known as pattern separation, and the retrieval of complete memory traces from partial cues, known as pattern completion. Given that both processes are particularly vulnerable to aging[3,19]. Consequently, neural mechanisms supporting associative recall and pattern completion are likely to become compromised with advancing age. Although the precise relationship between pattern separation and pattern completion remains debated, cognitive aging has been associated with a bias away from pattern separation toward pattern completion, particularly in humans[3,19].

B. How does aging affect spatial navigation?

The progressive decline in navigational abilities has been well-documented in both humans and rodents with advancing age. Meta-analytic evidence suggests that older

adults are less able to form allocentric, map-like representations and instead default to egocentric, route-based strategies[20]. Aging impairs the formation and flexible use of spatial relational maps, particularly in tasks requiring the integration of multiple locations and paths into a coherent representation, the maintenance of goal locations, and the strategic selection of navigational strategies[21]. However, spatial navigation is a complex cognitive function, and age-related deficits can emerge at various stages, ranging from interpreting sensory spatial information, integrating and consolidating distinct spatial memories, and ultimately executing effective navigational behavior[22].

While some reports of navigational decline in humans may be influenced by specific experimental paradigms, such as desktop-based virtual reality, that may introduce cohort effects[23], navigational impairments have also been demonstrated in ecologically valid tasks involving active movement. For example, in a path integration task requiring participants to track their position while walking along short, circuitous paths, older adults exhibited increased positional uncertainty[24]. Similarly, in a real-world analogue of the Morris Water Maze, older participants showed specific impairment in allocentric navigation[25].

Comparable performance deficits have been reported in aged mice and have been linked to compromised vestibular input[26]. Converging evidence across species firther demonstrates that aging is often characterized by (i) a shift away from allocentric, MTL-dependent navigation strategies[27,28], and (ii) a reduced ability to flexibly switch between egocentric and allocentric strategies[29]. Importantly, these impairments are also evident in real-word navigation tasks[25], including a reduced ability of older adults to use shortcuts[30]. Together, these deficits, which extend beyond general impairments in learning and memory, suggest that age-related navigational decline arises from both impaired spatial coding and more generalized learning and memory deficits, that also affect non-spatial behaviors.

In summary, cognitive aging is a highly heterogeneous process, with individuals experiencing varying degrees of decline in episodic and spatial memory abilities. n the following section, we examine the neural substrates that underlie these inter-individual differences. Given the central role of the MTL, particularly the hippocampus, in learning and memory, this circuit will serve as the primary focus of the remainder of this review.

III . HALLMARKS OF HEALTHY COGNITIVE AGING

In this section, we review the hallmarks of healthy cognitive aging. Within this framework, age-related cognitive outcomes emerge from the interaction between upstream control systems and downstream modulatory mechanisms, as well as peripheral and systemic factors that shape cognitive trajectories.

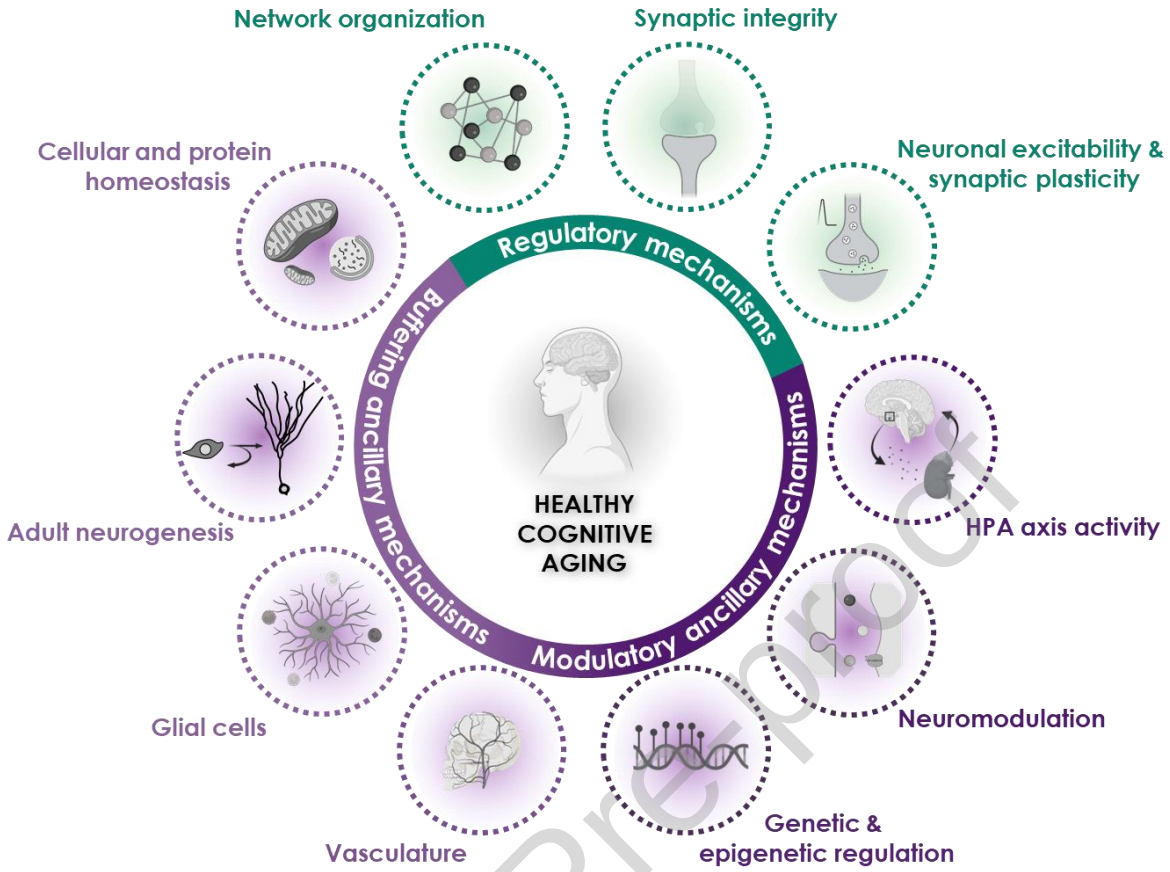

Figure 2: Hallmarks of healthy cognitive aging. Cognitive aging emerges from interactions between three functional classes of mechanisms operating across multiple scales. **Core regulatory systems**, including excitation–inhibition balance, synaptic plasticity rules, and large-scale network organization, which together establish the operating regime and stability of brain function. **Modulatory ancillary mechanisms**, such as neuromodulation, hormonal regulation, genetic and epigenetic regulation, and vascular function, adjust the gain, timing, and context of neural processing without redefining core rules. **Buffering ancillary mechanisms**, including cellular and protein homeostasis, adult neurogenesis, glia, and vasculature, mitigate the functional impact of age-related perturbations by absorbing stress and preserving performance. Importantly, several mechanisms, such as adult neurogenesis, glial function, and vascular regulation, can assume dual roles during aging depending on demand and pathological burden, providing flexibility but also points of vulnerability. Upstream life-course factors (e.g., stress, nutrition, exercice environmental exposures) bias these interactions early, shaping individual aging trajectories.

A. Network organization

Encoding and retrieving episodic memories can be understood within neural-level models of spatial memory and imagery such as the model proposed by Bicanski & Burgess[31]**.** We adopt this framework here because (i) a substantial body of behavioral and neurophysiological evidence supports its key predictions, and (ii) its explicit description of coordinate transformations enables direct comparison across rodents, non-human primates and humans. In this model, stimuli first registered in egocentric coordinates within early sensory and posterior parietal cortices are recast via the retrosplenial cortex into allocentric representations in medial temporal structures; the hippocampal place-cell map then serves as a viewpoint-independent record that can be re-anchored to the current perspective to guide action. Head-direction and boundary signals from the subiculum, the metric provided by grid cells in the entorhinal cortex (EC), and flexible ego/allocentric coding in the retrosplenial cortex support this

exchange, while cingulate, premotor and striatal circuits support the translation of spatial goals into context-appropriate movements.

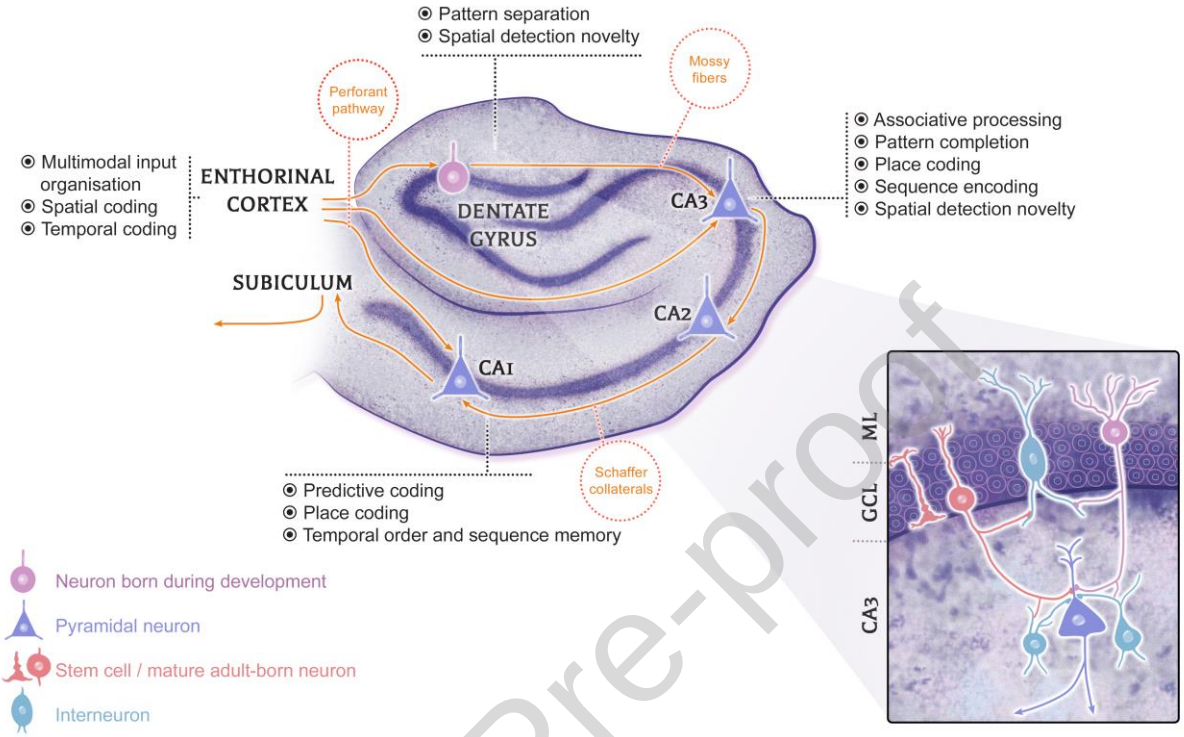

Figure 3: Anatomical organization and functions of the hippocampal formation and the tri-synaptic circuit. CA: Cornu Ammonis. GCL: granule cell layer. ML: molecular layer.

Within the hippocampus, the trisynaptic pathway (dentate gyrus (DG) and Cornu Ammonis (CA3, CA2 and CA1))[32] plays a key role in various aspects of declarative and spatial memory. The DG and CA subfields process distinct spatial and non-spatial information supporting various cognitive processes[33–40]. Specifically, the DG and CA3 are involved in encoding and retrieving episodic memories, primarily through pattern separation and pattern completion mechanisms[41–44] (Figure 3). These processes are orchestrated over similar time-scales in the hippocampus, particularly during memory-based decision-making[45]. The reactivation of past experiences during new learning promotes the formation of distinct representations of overlapping memories in the DG/CA2-3, while simultaneously enabling the relational integration of these representations in the CA1 subfield[46]. Memory content reactivated in the subiculum predicts successful performance in tasks that rely on inferring indirect relationships among events, thereby indexing the relational nature of the cognitive map[46].

The ability to extract regularities across experiences depends on the ability to detect patterns, but also deviations from these patterns. The CA1 subfield plays a key role in this balance by detecting novelty and mismatches between expected and actual experiences, which is crucial for updating memories and learning new information[47–50]. Network modelling has proposed that encoding individual episodes and extracting regularities across experiences involve two partially dissociable systems: the EC-DG-CA3 pathway, and the direct projection from the EC to CA1, respectively[51,52].

1 Brain networks in humans

In humans, age-related deficits in episodic and spatial memory have frequently been associated with changes in task-related patterns of fMRI hippocampal activity[53–57]. The importance of task-related functional MRI in this context was recently emphasized[58], but we will also consider evidence from task-free resting-state fMRI studies and from structural MRI studies. For example, longitudinal analyses from the Vallecas Project show that Superagers (octogenarians whose episodic-memory scores match adults 20-30 years younger) exhibit both larger baseline grey-matter volumes in core medial-temporal regions (bilateral hippocampus and EC) and a markedly slower five-year atrophy rate in the same structures than age-matched controls[59]. In the same cohort *Superagers* also showed overall preservation of the white matter microstructure (especially anterior tracts), suggesting preserved structural brain connectivity. Nevertheless, fMRI studies in Superagers have revealed inconsistent findings regarding network profiles[60].

A second commonly reported finding in aging research is functional dedifferentiation, or reduced neural selectivity, which has been observed both in MTL regions[61–63] and in early sensory cortices[11]. Functional dedifferentiation refers to the loss of neural specialization, such that neuronal populations respond more broadly during cognitive tasks, including episodic memory processing. While this phenomenon is often interpreted as a compensatory mechanism counteracting declining efficiency in regions such as the hippocampus, it may negatively impact episodic memory in various ways. Broader activation patterns can increase source memory errors, promote intrusion of irrelevant information, and disrupt temporal order representations. In normatively aging humans, deficits in pattern separation abilities have been associated with increased activity of the CA3/DG ensemble and reduced activity of the CA1 and the anterolateral part of the EC[64–67]. Consistent with this view, human fMRI studies measuring amyloid beta and tau accumulation have identified and confirmed the hyperactivity of the CA3/DG ensemble associated with early tau accumulation[68–70]. In addition, robust evidence of age-related neural dedifferentiation for scenes vs. objects in the parahippocampal place area was linked to changes in recognition memory performance[61]. Moreover, longitudinal evidence suggests that less functional dedifferentiation in aging could help preserve episodic memory performance. For instance, older adults with better-maintained default mode network (DMN) connectivity over time exhibit slower episodic memory decline[71]. Together, these findings suggest that maintenance of neural specificity at both regional and network levels is critical for sustaining episodic memory in aging.

Connectivity studies have also revealed the importance of hippocampal-cortical circuits. Disruption of the structural connectivity and integrity of limbic system tracts (the fornix, the uncinate fasciculus and the cingulum tract) that connect the MTL regions to distributed cortical regions of an extended mnemonic circuit, including the so-called Default Mode Network (DMN; posterior cingulate, medial parietal and prefrontal cortices, medial/lateral temporal lobe) have been detected in aged subjects[72–75]. In addition, changes in the MTL functional connectivity with different parts of the DMN were shown to be closely associated with memory performance[71,76–78]. However, resting-state fMRI studies have also reported age-related increases in functional connectivity in other brain regions, potentially blurring the segregation properties of the intrinsic connectome. Both this loss of integration and segregation within intrinsic networks may be associated with the dedifferentiation observed in task-related fMRI[79].

The importance of network integrity for preserved cognitive function has also been demonstrated in the context of spatial navigation. fMRI studies have shown that older adults with superior path integration abilities show entorhinal signals comparable to younger adults. Specifically, in a study that combined fMRI and real-space navigation[80], a subgroup of older adults exhibited preserved path integration performance and a magnitude of grid cell-like codes in EC that was similar to younger adults. Furthermore, changes in connectivity within and between MTL structures appear to modulate navigational performance in old age, in particular during complex tasks requiring subjects to form cognitive maps. For example, increased informational connectivity between area CA1 and parahippocampal, entorhinal and perirhinal cortices has been associated with less distinct spatial memory encoding in older adults[81], and a reduction of local inhibitory circuits within the hippocampus may further impair the precision of spatial maps[82].

In contrast to the gradually accumulating cross-sectional evidence, longitudinal studies that track the development of navigational computations are scarce. One notable exception is the work by Korthauer and colleagues[73] who tested older adults twice over a period of eight years. While performance in a virtual Morris Water Maze did not change significantly, the authors observed cross-sectional associations between task performance and the integrity of the bilateral uncinate fasciculus.

Together, these findings demonstrate that preserved neural computations within MTL structures, as well as connectivity with other key components of episodic memory and the navigation circuit, are important contributors to preserved cognitive health in old age.
These findings are summarized in Table 1.

2. Brain networks in rodents

One seminal study used autoradiographic [^{14}C]-2-deoxy-D-glucose (2DG) to demonstrate that spatial memory deficits in animals, evaluated using the Morris water maze, were associated with reduced glucose consumption in restricted limbic regions, including the DG, CA1, CA3, and prefrontal cortex[83]. This finding suggests that maintenance of metabolic activity within the hippocampal network may support cognitive health.

Using fMRI in rodents, better spatial memory performance has been linked to preserved resting-state functional connectivity of the retrosplenial/posterior cingulate cortex (RSC/PCC), analogous to the DMN in humans[84]. Additionally, higher functional connectivity within left CA3 and CA1 regions has been associated with higher cognitive health (HCH)[85]. However, HCH rats exhibited a distinct network signature compared to young rats, suggesting adaptive network remodeling[84].

Hippocampal place cells fire in specific spatial locations, forming a neural representation of space. This cognitive map supports efficient navigation by enabling orientation, landmark recognition, and route planning. As an animal moves, place cells activate sequentially, encoding spatial trajectories critical for navigation. In aged rats, many CA1 place cells exhibit delayed firing in familiar environments, and the degree of firing variability, also referred to as overdispersion, predicts individual performance in delayed-match-to-sample (DMTS) memory tasks[86]. Memory for locations is further reinforced through replay of neural activity sequences recorded during active exploration. These replay events occur remotely in time and space relative to the original experience and are crucial for learning and memory[87,88]. While robust in young animals, replay is notably absent in the CA1 of rats with lower cognitive health (LCH)[89].

Furthermore, *in vivo* recordings of place fields have demonstrated that CA3 and CA1 neurons in aged LCH rats display inflexible place fields and elevated firing rates, contributing to spatial memory deficits[90,91].

Studies using immediate-early gene (IEG) expression, a group of genes rapidly and transiently activated in response to various stimuli[92], have revealed network disruptions in LCH rats, with the relative exception of the DG[93,94]. These disruptions include heightened excitability of the RSC/PCC, cortical regions, and CA3, alongside reduced CA1 activity[95–99]. Increased CA3 excitability in LCH animals has also been associated with elevated activity in the lateral entorhinal cortex (LEC), suggesting a mechanistic link between hyperactivity in these regions and further underscoring the importance of maintaining network integrity[98]. *These findings are summarized in Table 2.*

Preservation of large-scale network integrity emerges as a central determinant of cognitive trajectory. HCH individuals maintain coordinated hippocampal–cortical communication and balanced integration across distributed networks. In LCH individuals, progressive imbalance in network dynamics favors instability and reduced computational precision, biasing memory systems toward vulnerability.

B. Neuronal and synaptic integrity

A striking feature of normative cognitive aging is that large-scale neuronal loss is largely absent in parahippocampal and hippocampal networks[100–103]. Instead, vulnerability emerges at the level of synaptic architecture and microcircuit organization. Across entorhinal–hippocampal circuits, cognitive decline is associated not with wholesale degeneration, but with subtle yet functionally meaningful alterations in presynaptic connectivity, postsynaptic structure, and receptor composition.

In the entorhinal cortex (EC), alterations appear regionally selective. In the lateral EC (LEC), but not the medial EC (MEC), LCH animals exhibit reduced synaptophysin levels and a reduced number of reelin-expressing neurons[104], consistent with compromised presynaptic integrity and altered input to downstream hippocampal structures. This early disruption at the cortical interface may bias hippocampal computations before overt structural degeneration becomes apparent.

Within the dentate gyrus (DG), overall numbers of axodendritic (primarily inhibitory) and axospinous (primarily excitatory) synapses in the middle molecular layer do not differ according to cognitive status[105], underscoring that synapse number alone does not explain cognitive variability. However, qualitative synaptic features do differ: perforated axospinous synapses, characterized by discontinuous postsynaptic densities and often associated with enhanced synaptic efficacy, are more abundant in HCH animals than in LCH animals. Together with reduced synaptophysin immunoreactivity in LCH animals[106], these findings suggest that cognitive vulnerability reflects diminished synaptic complexity and strength rather than simple synapse loss.

In CA3, LCH animals show reduced synaptophysin levels in lacunosum-moleculare[106], accompanied by altered AMPA receptor expression: decreased receptor levels in perforated synapses of the stratum lucidum and increased expression in the stratum radiatum relative to young and HCH animals[107]. This redistribution of receptor composition likely reflects compensatory, but potentially destabilizing, adjustments within recurrent excitatory networks.

By contrast, CA1 exhibits relative preservation of synaptophysin levels and CA3–CA1 synapse density[106–108]. Yet even in the absence of overt synaptic loss,

postsynaptic densities are smaller in LCH animals[109], indicating reduced synaptic efficacy.

Cognitive aging is not defined by gross neuronal loss but by qualitative changes in synaptic organization. In HCH individuals, preserved synaptic architecture sustains circuit precision and stable information transfer. In LCH individuals, subtle microcircuit remodeling reflects degradation processes that weaken network fidelity despite preserved anatomy.

C. Neuronal excitability and synaptic plasticity

The synaptic alterations described above are closely linked to changes in intrinsic neuronal excitability, excitation/inhibition (E/I) balance, and the regulation of synaptic transmission and plasticity across entorhinal–hippocampal circuits.

1. Neuronal excitability

In LCH animals, intrinsic excitability is reduced in EC neurons. During trace eyeblink conditioning, a task requiring sustained firing, these neurons fail to maintain persistent spiking[110]. This deficit is attributed to enhanced post-burst afterhyperpolarizations (AHPs), which dampen excitability and constrain synaptic plasticity. Increased AHPs in the EC further limit effective communication with the DG[111] and are associated with reduced EC–DG plasticity in aged animals[112]. These findings underscore the importance of preserving EC–DG transmission to maintain DG excitability and cognitive function during aging.

In contrast, the absence of synaptic loss in CA1 suggests that memory impairments arise from functional rather than structural alterations. Both fast and slow post-burst AHPs are increased in LCH animals[113], consistent with impaired CA3-CA1 communication[114–118]. Accordingly, Schaffer collateral stimulation in LCH animals evokes reduced field excitatory post-synaptic potentials (fEPSP) in CA1[119]. This may reflect weaker drive from the DG onto CA3 pyramidal neurons, and increased recurrent excitation within CA3[107].

Although unitary CA3–CA1 EPSP amplitudes remain unchanged with age[120], many synapses may be functionally silent in LCH animals, possibly representing a homeostatic response to CA3 hyperexcitability[107]. Supporting this view, aged animals exhibit NMDA receptor overactivation following glutamate or glycine stimulation despite an overall reduction in receptor density[121,122].

Together, these findings suggest that aging-related cognitive vulnerability reflects a redistribution of excitability across subregions: reduced drive at cortical inputs and CA1 output stages, coupled with excessive or poorly regulated activity within CA3 recurrent circuits.

2. Excitation-inhibition balance

Preserved cognition appears to depend on adaptive inhibitory control mechanisms in HCH animals. In the hilus, levels of GAD67 and somatostatin (SOM) are reduced in LCH but elevated in HCH rats[123,124] consistent with enhanced GABAergic signaling supporting healthy cognition[125,126]. Similarly, increased tonic inhibition in CA1 of HCH rats correlates with enhanced GABAergic transmission and preserved memory performance[127].

Conversely, LCH animals exhibit evidence of reduced feedforward inhibition following LEC stimulation, potentially reflecting diminished parvalbumin interneuron

recruitment, SOM loss, or generalized reductions in interneuron excitability[128]. Pharmacological antagonism of GABA receptors impairs memory even in high-performing aged rats[129], reinforcing the view that healthy cognitive aging depends on a tightly regulated excitation/inhibition balance.

3. Regulation of synaptic plasticity

Presynaptic alterations across hippocampal circuits are likely to disrupt activity-dependent synaptic plasticity underlying learning and memory. In aging, long-term potentiation (LTP) is reduced at Schaffer collateral–CA1[130,131] but relatively preserved in CA3[132], whereas long-term depression (LTD) is decreased across subregions[131–133]. Aging is also associated with a polarity shift in plasticity induction: weak low-frequency stimulation elicits LTP rather than LTD, driven by enhanced NMDA receptor activation and Ca^{2+} influx at CA1 synapses[119] (see also[133]). This LTD-to-LTP shift correlates with poorer performance in a Y-maze task[119], implicating dysregulated NMDA-dependent Ca^{2+} signaling in cognitive decline.

Overall, cognitive health in aging depends on the preservation of excitatory synaptic efficacy alongside effective inhibitory control within hippocampal networks. In LCH animals, excitatory inputs are reduced, inefficient, and structurally altered, resulting in impaired synaptic plasticity. Disrupted excitatory transmission combined with deficient inhibitory regulation likely contributes to the loss of network integrity. Thus, maintaining intrinsic excitability, balanced ecxcitation/inhbition signaling, and adaptive synaptic plasticity emerges as a key hallmark of successful cognitive aging.

D. Hypothalamic-pituitary-adrenal (HPA) axis

Beyond intrinsic circuit properties, systemic endocrine regulation critically modulates hippocampal network stability. The stress hormone cortisol, or corticosterone in rodents, has long been considered as a key molecular driver for resilience and vulnerability to stress-related disorders. The chronic actions of glucocorticoids (GCs) have been hypothesized to promote brain aging, based on observations that plasma corticosterone levels in aging rats positively correlate with biomarkers of hippocampal aging[134]. This glucocorticoid cascade hypothesis proposes that cumulative exposure, even to physiologically normal GC concentrations, may gradually contribute to brain aging, whereas prolonged elevation of GCs, as observed during chronic stress, could further accelerate this process[135,136].

The hippocampus plays a central role in the negative feedback regulation of the Hypothalamic–Pituitary–Adrenal (HPA) axis. Age-related hippocampal dysfunction may therefore impair inhibitory feedback control, resulting in sustained elevations of circulating corticosterone and increased adrenal activity. This creates a potential feed-forward loop in which hippocampal vulnerability and HPA dysregulation mutually reinforce one another. Marked inter-individual differences exist in HPA axis activity. In rodent models, GC-mediated signaling in the hippocampus is significantly altered in LCH rats[137–142]. Interestingly, the age-related alterations in HPA axis precedes the emergence of memory deficits, supporting the idea that stress axis dysregulation may represent an early driver of cognitive vulnerability rather than a mere consequence of decline[140]. Comparable patterns have been reported in humans during normative aging[143,144]. However, the relationship between glucocorticoids and cognitive trajectories is complex. The impact of GC exposure likely depends on the cell-specific balance between mineralocorticoid receptors and glucocorticoid receptors, as well as

on the individual's genetic background, lifetime stress history, and cellular context[145,146]. Nevertheless, the role of the HPA axis and exposure to GCs appear to impact memory abilities with age, and therefore represent one of the hallmarks for cognitive health.

Overall, converging evidence suggests that regulation of the HPA axis and lifetime exposure to glucocorticoids constitute critical determinants of cognitive aging. Dysregulated stress signaling emerges as a biological hallmark that may shift individuals toward vulnerable cognitive trajectories, whereas preserved feedback control and receptor balance may support resilience across aging.

E. Neuromodulation

Neuromodulation in cognitive aging converges on cholinergic, noradrenergic, dopaminergic, and purinergic systems. However, relatively few human cross-sectional studies (and especially longitudinal ones) have examined changes in neuromodulation during cognitive challenge. As a conclusion, firm conclusions about how neurotransmitter alterations drive cognitive aging require further investigation of neurochemical dynamics during active task performance[58].

Cholinergic transmission plays a central role in synchronizing network oscillations and modulating plasticity, learning, and memory. The basal forebrain cholinergic system, comprising the medial septum, diagonal band of Broca, and nucleus basalis of Meynert, provides major projections to the cortex and hippocampus[147]. Aging is associated with moderate degeneration in this circuit, cholinergic hypofunction, and progressive memory decline[147]. Reductions in cortical cholinergic markers, including ChAT, muscarinic and nicotinic receptor binding, and acetylcholine levels, correlate with dementia severity, and anticholinergic drugs impair memory in healthy individuals, supporting the cholinergic hypothesis[148]. Degeneration of the basal forebrain and entorhinal cortex in prodromal individuals suggests that cholinergic dysfunction may precede overt memory impairment[149]. In rodents, spatial deficits correlate with progressive alteration of sept-hippocampal cholinergic neurons[149–153], and cholinergic grafts can rescue age-related impairments[154–156]. However, septo-hippocampal deafferentation in young animals does not consistently impair memory[157,158], suggesting that acetylcholine may not be strictly essential but that cholinergic changes increase vulnerability to cognitive decline.

Noradrenergic transmission from the locus ceruleus provides the primary adrenergic input to the forebrain[159] and regulates attention, arousal, stress adaptation, and neuroimmune function[160]. The locus ceruleus is among the earliest sites of tau and α-synuclein pathology in Alzheimer's disease, with dysfunction emerging years before marked neuronal loss[159], implicating it in age-related cognitive disorders. Nonetheless, the degree of locus ceruleus degeneration in healthy aging and its cognitive significance remain uncertain[161]. Animal studies report correlations between memory performance and locus ceruleus neuron number[162], as well as hippocampal noradrenaline concentration[153].

Dopaminergic transmission has long been implicated in cognitive aging[163]. Molecular imaging studies in healthy older adults show associations between episodic memory performance and hippocampal dopamine D2 receptor availability[164], with

longitudinal declines in D2 levels observed over 10- years[165]. In navigational tasks, L-DOPA enhances hippocampal directional signals in older adults[166]. In rodents, an increase in dopaminergic turnover (3,4-dihydroxyphenylacetic acid/dopamine ratio; DOPAC/DA) has been reported in the dorsal hippocampus of HCL[153] indicating that preservation of dopamine signaling may therefore support healthy cognitive aging.

Purinergic modulation, particularly via adenosine signaling, fine-tunes synaptic communication and neuron–glia interactions[167]. Under basal conditions, adenosine primarily activates A_1 receptors to inhibit glutamatergic transmission in the hippocampus[168], while A_{2A} receptors modulate A_1 receptor actions[169]. Aging alters hippocampal A_{2A} receptor expression and signaling, increasing receptor density and G-protein coupling[119,170–174] and enhancing glutamatergic release[171]. This shift promotes mGluR5-dependent NMDA receptor overactivation, increased Ca^{2+} influx[119], and LTD alterations linked to age-related cognitive impairment, effects that can be reversed by A_{2A} receptor blockade. Polymorphisms of the A_{2A} receptors encoding gene *ADORA2A* are associated with episodic memory performance and hippocampal volume[175]. Together, purinergic modulation represents a key contributor to cognitive health in aging.

Across cholinergic, noradrenergic, dopaminergic, and purinergic systems, cognitive aging appears to reflect a reconfiguration of neuromodulatory balance rather than failure of a single transmitter system. HCH individuals preserve modulation sufficient to sustain coordinated plasticity and selective information routing. In LCH individuals, altered neuromodulatory balance reflects degradation processes that lower the threshold for network-level disorganization.

F. Genetic and epigenetic regulation

Beyond circuit-level alterations, emerging evidence indicates that genetic and epigenetic regulation plays a central role in determining whether aging trajectories remain cognitively stable or progress toward decline. Rather than reflecting fixed vulnerability, cognitive aging appears to depend on the capacity of transcriptional and chromatin-regulatory programs to dynamically adapt to experience and physiological stress. Comparative studies in humans and animal models increasingly reveal molecular signatures that distinguish HCH individuals from their LCH counterparts, offering insight into mechanisms that support lifelong memory preservation.

Transcriptomic profiling of the dentate gyrus (DG) and CA3 in aged rodents demonstrates that learning impairments correlate with coordinated changes in gene expression. Reduced performance in spatial discrimination tasks is associated with lower expression of transthyretin, a gene implicated in cognitive maintenance[176,177]. More broadly, LCH animals exhibit decreased expression of genes involved in synaptic transmission and adult neurogenesis[178–180], suggesting reduced molecular support for plasticity and circuit renewal. At the same time, transcriptional changes are regionally specific. In CA3, genes related to synaptic plasticity and excitatory neurotransmission are upregulated in LCH animals relative to HCH animals[178], consistent with the CA3 hyperactivity described earlier. In CA1, impaired cognition is associated with altered expression of synaptic genes and genes regulating Ca^{2+} regulation[179], aligning with physiological evidence of disrupted excitability and plasticity thresholds. Importantly, successful cognitive aging is not characterized by globally elevated gene expression. Nearly half of the genes repressed under basal conditions in HCH animals are among

those induced during learning[125]. This suggests that cognitive resilience may depend less on sustained activation and more on a distinctive and adaptive genetic expression regulation.

Epigenetic mechanisms provide a molecular substrate through which environmental signals and neural activity shape transcriptional programs over time. Chromatin modifications can either promote transcription, such as histone acetylation and phosphorylation, or repress it, through DNA methylation, histone methylation, SUMOylation, deacetylation, deamination, and proline isomerization[181]. Although their roles in age-related cognitive decline are only beginning to be elucidated[182], accumulating evidence suggests that epigenetic regulation contributes critically to cognitive divergence during aging. Several epigenetic signatures associated with superior memory performance in young adults and HCH rodents are absent in LCH animals[183].

Recent multiomic single-nucleus analyses of the human hippocampus further support this view. Chromatin accessibility profiles segregate according to cognitive trajectory across multiple cell types, including neural stem cells, immature neurons, astrocytes, and CA1 pyramidal neurons. Individuals with preserved cognitive aging exhibit regulatory signatures enriched in synaptic plasticity and glutamatergic signaling pathways, whereas individuals with declining trajectories display early alterations in plasticity-related gene networks[184]. These findings indicate that epigenetic regulation is not globally diminished with age, but differentially organized across individuals in a manner that aligns with brain networks alterations in cognitive aging discussed earlier.

In the context of histone acetylation, basal levels of histone deacetylase (HDAC) proteins do not differ substantially by cognitive status. However, following learning, HCH animals exhibit reduced HDAC protein levels in the DG and CA1 (though not in CA3) an adaptive response absent in LCH animals[183]. This suggests that successful learning in aged brains may involve context-dependent remodeling of acetylation-regulating machinery. Notably, total histone acetylation levels (both at baseline and after training) do not significantly differ between HCH and LCH animals[183], and enhancement of hippocampal acetylation fails to rescue memory deficits in LCH animals[185]. These findings indicate that global increases in acetylation are insufficient to restore cognitive function. Instead, the timing, localization, and gene specificity of chromatin remodeling may be more critical than overall levels of modification. The functional significance of the adaptive HDAC response observed in HCH animals therefore remains to be fully clarified.

DNA methylation patterns further illustrate the complexity of epigenetic regulation in aging. The aged hippocampus exhibits global hypomethylation[186], alongside aberrant methylation changes in activity-dependent genes such as the IEG *Arc* within CA1 and DG[187]. These alterations may contribute to the dysregulated neural activity described in earlier sections. Reduced methylation has been linked to decreased expression of the DNA methyltransferase Dnmt3a2, an enzyme essential for activity-dependent methylation. Restoration of Dnmt3a2 levels in CA1 rescues memory performance in contextual fear and novel object recognition task[188], demonstrating a causal relationship between methylation capacity and cognitive function. However, the relationship between methylation and cognition is not unidirectional. Hypomethylation of genes encoding several transcription factors has been associated with higher learning abilities[186], indicating that both hypo- and hypermethylation can be adaptive depending on genomic context. Thus, successful cognitive aging does not appear to depend on global shifts toward either increased or decreased methylation or

acetylation. Rather, it likely requires finely tuned, locus-specific epigenetic regulation that preserves responsiveness while preventing transcriptional noise.

Taken together, genetic and epigenetic hallmarks of cognitive health converge on a central principle: resilience during aging depends on molecular flexibility. HCH individuals maintain the capacity to dynamically regulate gene expression in response to experience, whereas LCH individuals exhibit dysregulated baseline activity, maladaptive transcriptional shifts, and impaired chromatin responsiveness. Accordingly, maintenance of learning ability may rely on coordinated interactions between transcriptional control and epigenetic modulation, enabling hippocampal circuits to adapt to age-related stressors without drifting into hyperactivity, rigidity, or instability. Genetic and epigenetic regulation thus represent critical upstream determinants of circuit stability and plasticity in the aging brain.

G. Vasculature

Neurovasculature aging is one of the key factors in brain aging and significantly influences the risk of neurodegenerative diseases. Structural alterations, coupled with the metabolic and homeostatic disruptions induced by aging, profoundly affect all the essential functions of the neurovasculome[189,190]. Human studies have highlighted alterations of the small cerebral vasculature, particularly in the cortex and hippocampus. Age-related arteriolar smooth muscle cell turnover, its phenotypic alterations, and associated thickening and stiffening of vascular walls, and microvascular density loss are well-established[191,192]. In addition, aging promotes persistent endothelial, pericyte and resident immune cell activation, with subsequent cellular senescence and blood-brain barrier leaks. This can lead to neurovascular uncoupling and disturbed microvascular hemodynamics, with subsequent defective removal of brain proteins and metabolite waste[193–195].

The hippocampus is particularly susceptible to age-related small vessel alterations, as highlighted by leaks of the blood-brain barrier in cognitively normal elderly individuals in the CA1, CA3 and DG. These vascular alterations were related to pericyte injury, the number of impaired cognitive domains[196] and predicted cognitive decline[197,198]. Vascular risk, particularly mid-life arterial hypertension, promotes premature and pronounced aging of the small cerebral vasculature, a condition known as cerebral small vessel disease (CSVD)[199].

Adequate hippocampal perfusion, ensured by adequate blood supply through sufficient vessel density, has been associated with preserved grey matter volume and better cognitive performance in both CSVD and aging. This suggests that maintaining appropriate hippocampal perfusion could act as a protective factor against the progressive deterioration of the small cerebral vasculature[200–202]. Furthermore, the vascular component of the BOLD signal is the largest contributor to resting-state variability and can be used to account for the neurovascular contribution to the changes in the BOLD signal observed with aging. This highlights the importance of considering vascular health when interpreting resting-state functional neuroimaging in aging populations.

Vascular aging represents an active determinant of cognitive trajectory rather than a passive background process. The integrity of perfusion, neurovascular coupling, and barrier function constrains the metabolic and homeostatic stability of hippocampal circuits. In HCH individuals, preserved vascular function supports the energetic

demands of plasticity and maintains network stability. In LCH individuals, vascular compromise reflects degradation processes that reduce metabolic support and lower the threshold for circuit-level dysregulation.

H. Glial cells

While much of the research on cognitive aging has focused on neuronal circuits, glial cells are increasingly recognized as critical regulators of brain resilience and vulnerability. Although data on interindividual variability in astrocytes, microglia, and oligodendrocytes remain comparatively limited, emerging evidence suggests that age-related differences in glial function may significantly influence synaptic plasticity, learning, and memory[203–205]. Rather than passive support cells, glia actively shape the microenvironment in which neuronal computations unfold and may therefore represent key modulators of cognitive trajectories.

Astrocytes, the most abundant glial cells in the central nervous system, play a pivotal role in neuronal function and synaptic plasticity. Through their perisynaptic processes, they form the tripartite synapse by closely associating with pre- and postsynaptic neuronal elements, while also interacting with other astrocytes, endothelial cells at the neurovascular interface, and oligodendrocytes to maintain white matter integrity[206,207]. Early studies suggested that astrocyte numbers increase with age. However, subsequent work indicates that astrocyte density does not change[208,209] and is largely independent of memory performance in aged rats. In addition age-related increase in markers of reactive gliosis (in all hippocampal subfields) occur independently of the cognitive status[209]. In contrast, other findings reveal that aged male mice impaired in working memory display increased astrocytic arborization and elevated markers of reactive gliosis within CA1[210]. Beyond morphology and gene expression, relatively little is known about how aging alters the homeostatic and metabolic functions of astrocytes. Given their central role in glutamate clearance, energy metabolism, and modulation of synaptic transmission, even subtle impairments in astrocytic regulation could amplify excitotoxic stress, disrupt excitation–inhibition balance, and compromise plasticity. Clarifying how astrocytic functional states differ between HCH and LCH individuals remains an important gap in the field.

Microglia, the resident immune cells of the brain, continuously survey the neural environment and contribute to synaptic remodeling, phagocytosis, cytokine signaling, and neurinflammatory regulation[210,]. Their activation state is highly dynamic and can influence not only neuronal viability but also oligodendrocyte function and myelin maintenance. In aged rodents, significant alterations in microglial number and cytokine signaling have been reported in the CA1 region of LCH rodents[210,211]. At the systems level, large-scale proteomic analyses of human brain donors longitudinally assessed for cognitive performance demonstrate that cognitive stability is associated with reduced expression of inflammation-related proteins in the prefrontal cortex[212]. These findings support a link between preserved cognition and restrained neuroinflammatory tone. However, neuroinflammation (MHC II pathway-associated gene expression, and microglial activation) alone does not uniformly predict cognitive decline in rodents [179,209]. Microglial activation can support plasticity and debris clearance under certain conditions while exacerbating synaptic dysfunction under others. Thus, as with neuronal excitability and epigenetic regulation, cognitive outcomes likely depend on the regulation and timing of microglial responses rather than on simple increases or decreases in inflammatory markers.

Oligodendrocytes, crucial for lifelong myelin remodeling, also exhibit age-related functional changes that could contribute to cognitive variability. These cells are most densely concentrated in white matter regions, where myelination demands are highest. Aging adversely affects white matter integrity through a cascade of structural, molecular, and cellular alterations[207]. In LCH rats, elevated expression of myelin-associated inhibitors, such as MAG, Nogo-A, and OMgp, as well as their receptor NgR1, suggests dysregulation of myelinogenic pathways[213,214]. Such changes may restrict structural remodeling and limit the capacity for adaptive synaptic reorganization, thereby contributing to cognitive decline. Because network synchronization depends critically on conduction timing, even modest alterations in myelin integrity may disrupt large-scale connectivity and memory processes.

Astrocytes, microglia, and oligodendrocytes collectively shape the cellular environment that sustains synaptic plasticity, metabolic support, inflammatory balance, and network synchronization. Although interindividual data remain limited and controversial, evidence do not support that differences in glial regulation contribute meaningfully to divergence in cognitive trajectories.

I. Adult hippocampal neurogenesis

The existence of ongoing neurogenesis in the adult mammalian DG is now widely recognized[215]. Adult hippocampal neurogenesis (AHN) encompasses multiple stages, including activation, proliferation, and fate specification of neural stem cells (NSCs), followed by migration of their neuronal progeny, differentiation into dentate granule cells, and eventual integration into the granule cell layer. Once incorporated into hippocampal circuits, these adult-born neurons actively contribute to memory processing and cognitive function[215,216].

While human studies have provided evidence supporting the persistence of AHN across adulthood and aging[217,218], important questions regarding its functional relevance in older adults remain unresolved. Recent work indicates that when inter-individual variability is taken into account, HCH individuals exhibit distinct neurogenic profiles, characterized by higher numbers of immature neurons compared to LCH individuals[184]. These findings suggest that the biological significance of AHN in human aging may not be captured by average proliferation rates alone, but rather emerges when variability in cognitive trajectories is considered, reinforcing the importance of addressing inter-individual differences when defining hallmarks of cognitive aging.

In rodents, several lines of evidence indicate that AHN represents a key mechanism underlying inter-individual differences in cognitive aging. First, levels of AHN measured one month after learning predict spatial memory performance in aged rats in the water maze. Specifically, the numbers of proliferating cells, surviving cells, and newly generated neurons were significantly higher in HCH compared to LCH[102]. Second, age-related memory deficits result not only from numerical alterations in the pool of adult-born neurons, but also from changes in the dynamic homeostatic regulation of AHN in response to learning[219]. Third, dentate granule cells born in young adult and middle-aged rats are more actively recruited by spatial learning in HCH animals than LCH animals[94]. These findings suggest that vulnerability to cognitive aging is associated with an alteration of the integration of these neurons over time and their impaired functional recruitment during a cognitive task. Consistent with this interpretation, neurons generated in young adult rats maintained stable glutamatergic connectivity and preserved mitochondrial homeostasis in HCH animals. In contrast, in

LCH individuals, these neurons exhibited pronounced deficits in both synaptic connectivity and mitochondrial function[220]. Strikingly, an individual's cognitive aging trajectory could be predicted as early as 8 months of age, a stage at which impairments in adult-born neuron integration were already detectable. Importantly, direct optogenetic stimulation of these adult-born neurons was sufficient to enhance memory retrieval abilities in LCH animals back to similar levels observed in HCH animals[220].

Adult hippocampal neurogenesis represents a dynamic contributor to interindividual variability in cognitive aging in rodents. In HCH individuals, adult-born neurons not only survive but remain metabolically stable, synaptically integrated, and functionally recruitable, supporting circuit flexibility and memory precision. In LCH individuals, impaired long-term integration and reduced functional engagement of these neurons reflect degradation processes that weaken dentate network stability and narrow the adaptive range of hippocampal circuits. Although the functional relevance of adult neurogenesis in humans continue to be debated, emerging evidence suggests that differences in immature neuron populations across cognitive trajectories may hold biological significance. Clarifying how variability in AHN relates to preserved versus declining cognition in humans will therefore be essential for determining its translational relevance in cognitive aging.

J. Cellular and protein homeostasis

1 . Cellular homeostasis

Maintenance of cellular homeostasis is a fundamental determinant of brain aging and cognitive health. Because the brain exhibits exceptionally high metabolic demand compared to other organs, it is particularly vulnerable to mitochondrial dysfunction[221]. Mitochondria supply the energy required to sustain neuronal activity, while degradation systems maintain mitochondrial and cellular integrity, thereby enabling sustained metabolic performance. The tight interdependence between mitochondrial function and cellular quality control mechanisms is therefore essential for neuronal homeostasis. Disruption of this balance promotes cellular stress responses associated with aging, including the emergence of cellular senescence. Consistent with this view, increased markers of cellular senescence have been observed in the hippocampus of aged male mice impaired in spatial working memory[210]. However, another study failed to detect a correlation between spatial memory performance and senescence markers in the DG[220], suggesting that senescence may contribute to cognitive vulnerability in a context-dependent or region-specific manner.

Because neurons are post-mitotic and long-lived, they are especially susceptible to age-related declines in cellular degradation pathways, including the proteasome, endolysosomal system, and autophagy. Impairment of these systems promotes the accumulation of cellular damage, such as misfolded proteins and reactive oxygen species (ROS), leading to lipid peroxidation and protein oxidation[222–224]. Over time, damaged proteins and other intracellular debris aggregate to form lipofuscin, which progressively accumulates in the aging brain. In addition, altered redox homeostasis, associated with reduced activity of PRDX6, an enzyme critical for detoxifying oxidized phospholipids[225], and increased lipid peroxidation[226], has been observed in HCH animals, highlighting a growing role for lipidomics in understanding cognitive aging.

2 . Protein homeostasis

Within this broader framework of cellular homeostasis, maintenance of protein homeostasis, or proteostasis, plays a particularly important role in cognitive aging. Proteostasis encompasses the regulation of protein synthesis, folding, trafficking, and degradation, and its disruption represents a major vulnerability of aging neurons. One of the most prominent examples of age-related proteostatic failure in the brain is the abnormal accumulation of tau.

Tau, a microtubule-associated protein, plays a crucial role in neuronal outgrowth and axonal integrity by regulating the assembly, dynamic behavior and spatial organization of microtubules. During aging and in several age-related diseases, numerous human studies have identified that abnormal hyperphosphorylation of tau leads to its aggregation into neurofibrillary tangles, contributing to synaptic dysfunction and degeneration.

Although tau tangles are commonly found in the MTL of individuals over 65 years old, their abnormal spread into the neocortex appears to depend on the presence of Aβ plaques, a pathological feature is typically associated with mild cognitive impairment[227]. In contrast, so-called “Hidden” Aβ pathology is present in only approximately 30% of cognitively normal individuals aged around 80-year-old and weakly correlates with memory performance[228].

In vivo imaging studies using Positron Emission Tomography (PET) have consistently demonstrated the association between tau pathology in the MTL and episodic memory deficits and cognitive decline in elderly people[229–236], identifying tau pathology as a major contributor to cognitive aging. Strongest regional association between memory deficits in older adults and tau burden have been observed in the EC [233–235] where tau burden can account for approximately 20% of the observed memory variance[235]. There is also some evidence that Superaging is related to resistance against tau accumulation[228]. These data show that the early accumulation of tau in regions such as the EC is associated with memory deficits even in cognitively healthy individuals.

Recent advances in blood-based biomarkers, now allow non-invasive in vivo assessment of phosphorylated tau (p-tau) species and Aβ levels[237,238]. Studies in cognitively normal older adults have shown faster memory decline in individuals with higher plasma p-tau217 levels, closely mirroring findings from PET imaging[239]. Collectively, these data identify tau pathology as a prominent contributor to cognitive aging and support the necessity of incorporating tau biomarkers in future studies of cognitive aging

Notably, the early accumulation of tau and amyoid-peptides in aging is closely linked with neuronal network changes, including early hyperactivity in the hippocampus[240]. In this respect, early tau pathology has been also associated with functional dedifferentiation in older adults[68–70] (see also section on networks). There remains an ongoing debate about whether tau accumulation and functional dedifferentiation in MTL regions are part of normative aging or represent the earliest stage of pathological aging.

Animal studies provide complementary insights into age-related proteostatic failure. While standard laboratory mice and rats do not naturally develop amyloid plaques, though they can produce low levels of amyloid Aβ peptides[241], increased phosphorylated tau has been reported in the LEC of LCH rats[104]. In contrast, the Octodon degus, a South American rodent, and the gray mouse lemur, a non-human primate, naturally develop age-associated Aβ and tau pathology[238] linked to impairment in burrowing behaviour[242,243]. Similarly, in the gray mouse lemur

(Microcebus murinus), a non-human primate, extracellular Aβ burden has been associated with cognitive aging[244]. These two species represent unique natural models in the animal kingdom, offering valuable insights into both normal and pathological aspects of human brain aging.

Maintenance of cellular homeostasis, including mitochondrial function, redox balance, and efficient quality control systems, provides the foundation for neuronal stability in aging. In HCH individuals, preserved proteostatic regulation limits pathological protein accumulation and supports sustained synaptic and network integrity. In LCH individuals, progressive disruption of cellular and protein homeostasis, including increased vulnerability to tau dysregulation, reflects degradation processes that interact with excitability shifts and network instability to shape cognitive decline.

IV . Interconnectivity of Hallmarks of Successful Cognitive Aging

The evidence reviewed here indicates that cognitive aging does not arise from the linear accumulation of independent deficits, but from the dynamic interaction of multiple biological mechanisms that collectively shape brain network function. Rather than operating in isolation, the hallmarks of cognitive aging form an interconnected and hierarchically organized system. A limited set of ***core regulatory mechanisms***, including excitation–inhibition balance, synaptic plasticity, and large-scale network organization, exert upstream influence over ***ancillary mechanisms*** such as tau pathology, glial function, vascular integrity, neuromodulation, neurogenesis, and cellular homeostasis. These ancillary mechanisms act as ***amplifiers*** or ***buffers***, depending on the integrity of core regulatory systems.

Understanding how these hallmarks interact to shape individual cognitive trajectories remains a central challenge[245]. One illustrative example is the interplay between mitochondrial dysfunction and other aging mechanisms. As the primary source of ATP through oxidative phosphorylation, mitochondria are indispensable for sustaining neuronal activity in a highly energy-demanding organ such as the brain. The brain's high metabolic rate renders it particularly susceptible to oxidative damage, and mitochondrial dysfunction is a common feature of normal aging, brain injury, and neurodegenerative disorders[246,247]. Importantly, mitochondrial function is not autonomous but tightly regulated by systemic signals, including activity of the HPA axis. Glucocorticoids modulate mitochondrial activity both directly and indirectly through activation of the glucocorticoid receptor (GR). GRs are expressed in the cytosol and within mitochondria, where they influence mitochondrial gene expression through coordinated nuclear and mitochondrial signaling pathways[248–250]. Following ligand binding, activated GRs can translocate into mitochondria and bind to glucocorticoid-responsive elements within mitochondrial DNA, thereby regulating genes involved in oxidative phosphorylation and energy metabolism[248]. As HPA axis activity increases with age in LHC individuals, it is plausible that aging is associated with dysregulation of this mechanism, potentially leading to mitochondrial dysfunction.

Recent multiomic single-nucleus analyses of the human hippocampus further illustrate this hierarchical interdependence across hallmarks discussed here. Chromatin accessibility changes have been shown to segregate with cognitive trajectories in neural stem cells, immature neurons, astrocytes, and CA1 pyramidal neurons. Notably, individuals with preserved cognitive aging exhibit regulatory signatures consistent with maintained synaptic plasticity and glutamatergic signaling, whereas individuals with pathological trajectories show early alterations in plasticity-

related pathways[184]. These findings demonstrate that epigenetic regulation, neurogenesis, glial signaling, and excitatory synaptic integrity do not operate as independent hallmarks but are tightly coupled within a coordinated systems-level architecture. In this framework, core regulatory mechanisms such as synaptic plasticity and excitation–inhibition balance shape, and are shaped by, ancillary processes including neurogenesis and glial modulation, collectively determining resilience versus degradation of hippocampal networks.

Across the lifespan, the hallmarks of cognitive aging likely emerge through both parallel and sequential processes, evolving dynamically over the lifespan. Genetic instability and epigenetic alterations may arise early, followed by progressive mitochondrial inefficiency and increased reactive oxygen species production. Accumulation of oxidative damage, combined with declining proteostasis, promotes toxic protein aggregation, cellular senescence, neuroinflammation, and network dysfunction. These biological cascades are profoundly shaped by the exposome, including lifestyle, stress exposure, metabolic health, and environmental factors. Rather than representing independent endpoints, these hallmarks form a self-reinforcing network of interactions in which disruption in one domain can propagate across levels of organization, from molecular to cellular to systems neuroscience. Conversely, resilience in key regulatory nodes may stabilize the entire network and preserve cognitive function. This integrative framework suggests that successful cognitive aging depends not on the absence of individual hallmarks, but on the capacity of the system to maintain coordinated regulation across interconnected biological domains. Early, multidimensional anti-aging interventions targeting several hallmarks simultaneously may therefore offer the greatest potential to slow, mitigate, or prevent age-associated cognitive decline.

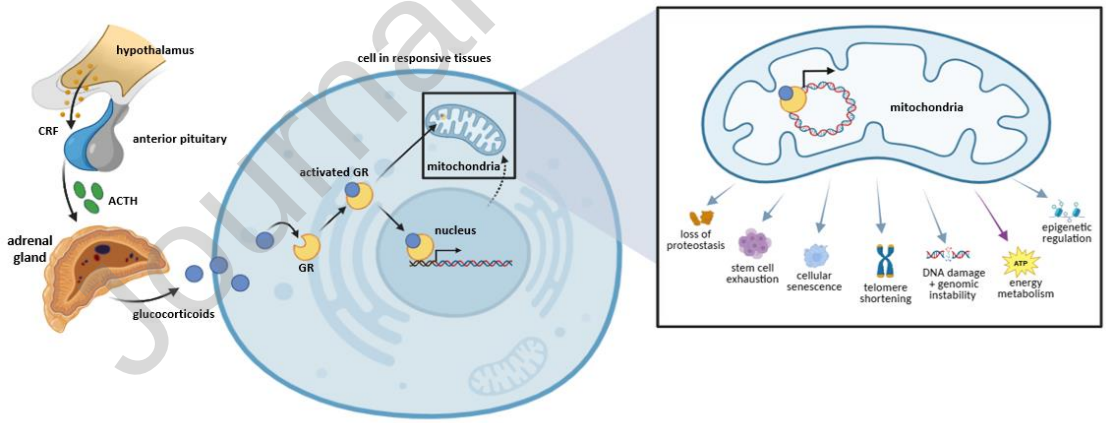

Figure 4: Interconnectivity of hallmarks of healthy cognitive aging.
HPA axis activity innitiating at the level of the hypothalamus, results in increased blood glucocorticoid levels. In glucocorticoid-resposive tissues, where cells expressing the glucocorticoid receptor are present, ligand-receptor binding leads to GR activation. The activated GR has direct effects (solid black arrows depicted within a schematic responsive cell) on the transcription of mitochondrial and nuclear genes[248–250]. The direct effect on nuclear genes may have indirect effects on mitochondrial genes (dashed arrow). Indeed, after transfer from the cytosol, activated GR accumulate in mitochondria and bind to mitochondrial DNA at sites similar to nuclear glucocorticoid resposive elements[251–254]. Most observations indicate that glucocorticoids regulate oxidative phosphorylation (OXPHOS) and mitochondrial energy metabolism, supporting the view that GR-mediated regulation of mitochondrial genes is crucial for energy metabolism, directly linking dysregulation of GR-mediated mitochondrial function to changes in energy metabolism as aging hallmark (purple arrow). However, despite a number of studies supporting the direct role of mitochondrial GR on the expression of mitochondrially encoded OXPHOS genes, mechanistic studies are limited[255]. Additionally, mitochondrial GR modulate apoptosis by interacting with or altering the distribution of Bcl2 family members[256]. Thereby GR-mediated regulation of mitochondrial genes could link HPA axis activity to the expression of some other aging hallmarks (blue arrows), such as genetic and epigenetic regulation, cellular senescence, mitochondria activity, deceased adult neurogenesis and protein aggregation.

V . LIMITATIONS, CONCLUSION, AND FUTURE DIRECTIONS

A . Limitations

Because our objective was to characterize naturally occurring interindividual variability in cognitive aging, we deliberately restricted the scope of this review to studies examining spontaneous differences that emerge during normative aging. We did not include the extensive literature based on genetic models designed to demonstrate the causal involvement of specific factors in age related memory decline, nor did we review pharmacological or interventional studies, including senolytics, exercise, dietary manipulation, or other treatments aimed at improving memory performance in aged subjects. This decision was guided by the following considerations.

Conceptual scope and coherence of natural aging processes. Our objective was to characterize naturally occurring interindividual variability in cognitive aging. Outbred rodents retain substantial genetic diversity, more closely resembling the heterogeneity observed in human populations. This variability is essential for understanding why some individuals maintain preserved memory across aging whereas others decline. Although genetic manipulations and targeted interventions are powerful tools for establishing causality, they often introduce artificial conditions that may not reflect the mechanisms underlying variability in typical aging. Including these studies would have shifted the emphasis of this review from variability in natural trajectories to experimental modulation of memory performance and substantially broadened its scope. To preserve conceptual coherence, we therefore focused on observational and correlational studies of naturally aging populations. We acknowledge that genetic and pharmacological approaches provide valuable complementary insights, but integrating those literatures would require a distinct analytical framework centered on causal manipulation rather than spontaneous variability.

Preservation of ecological validity. By focusing on spontaneous interindividual differences, we sought to capture the complexity and multifactorial nature of aging as it occurs outside experimentally induced models. This approach strengthens the translational relevance of the findings.

Avoiding mechanistic reductionism. Studies centered on single genes, pathways, or treatments are essential for mechanistic insight, yet they may oversimplify a process that is inherently multidimensional. Our framework instead emphasizes systems-level and integrative explanations of variability.

Terminology. Despite ongoing efforts to reach terminological consensus, the field continues to face conceptual ambiguity regarding terms such as “reserve,” “resilience,” and “succesfull” aging (see https://reserveandresilience.com/). To avoid reliance on terminology that remains inconsistently defined across studies, we adopted a mechanistic distinction between processes of degradation, which promote functional decline, and processes of preservation, which maintain cognitive performance. We therefore framed interindividual variability in terms of how these processes differ between individuals with LCH and those with HCH.

Much of the existing literature, however, focuses on performance differences without clearly distinguishing whether observed variations reflect increased degradation, enhanced preservation, or a combination of both. Individuals are frequently described as either “vulnerable” or “resilient,” implicitly suggesting mutually exclusive categories. Conceptually, this dichotomy may be overly simplistic. An individual could simultaneously exhibit heightened degradation processes and strong

preservation mechanisms. In this framework, vulnerability and resilience are not strict opposites, but reflect the dynamic balance between interacting biological processes that together shape cognitive trajectories.

Cross sectional versus longitudinal studies. Cross-sectional studies compare individuals of different ages and are valuable for identifying broad age-related differences. However, they cannot capture individual cognitive trajectories over time, are susceptible to cohort effects, and do not allow determination of the temporal or causal sequence through which neural and molecular alterations emerge. As a result, it often remains unclear whether specific neural or molecular "landmarks" precede and drive subsequent dysfunction or instead represent downstream consequences of earlier changes. Without repeated measurements within the same individuals, or carefully designed pseudo-longitudinal approaches, it is difficult to disentangle primary mechanisms from compensatory or secondary effects.

The complex interplay among hallmarks highlighted in this review underscores the urgent need for longitudinal studies that track cognitive trajectories over time to better understand these dynamics[257–259]. Initiatives of this kind has already begun, including longitudinal animal studies in the United States (https://www.nia.nih.gov/research/labs/about-irp/successful-trajectories-of-aging-reserve-and-resilience-in-rats) and across Europe focusing on human data (https://www.lifebrain.uio.no). Expanding and integrating such efforts will be essential for advancing a mechanistic understanding of healthy cognitive aging.

B . Conclusion

Cognitive aging is too often described as the gradual erosion of function driven by the accumulation of molecular damage. The evidence reviewed here supports a different interpretation. Marked interindividual variability in aging trajectories demonstrates that cognitive decline is neither inevitable nor uniform. Rather than reflecting simple degeneration, cognitive aging emerges from the dynamic regulation of interacting biological systems spanning molecular, cellular, circuit, and network levels.

Across species, a consistent principle becomes apparent. Chronological age alone is a poor predictor of cognitive outcome. Instead, the integrity of core regulatory processes, particularly excitation–inhibition balance, synaptic plasticity, and large-scale network organization, determines whether aging brains remain functionally stable or transition toward vulnerability. These core processes are embedded within a broader constellation of ancillary hallmarks, including neuromodulatory tone, glial regulation, neurovascular integrity, adult neurogenesis, proteostasis, mitochondrial function, and HPA axis signaling. Importantly, these hallmarks do not operate independently. They form an interconnected and hierarchically organized system in which perturbations in one domain propagate across others, while resilience within key regulatory nodes can stabilize the system as a whole.

Successful cognitive aging therefore does not require the complete absence of age-related biological alterations. Rather, it depends on the preservation of coordinated regulation across levels of organization. Aging brains can tolerate substantial molecular or structural change as long as network balance and adaptive plasticity are maintained. Conversely, even subtle disruptions in regulatory control may destabilize circuits and amplify downstream pathology. In this framework, cognitive trajectories are shaped less by isolated lesions than by the system's capacity to maintain dynamic equilibrium.

This perspective reframes cognitive aging from a model of linear decline to one of systems-level reconfiguration. It underscores the importance of identifying early shifts in regulatory balance rather than waiting for overt pathology to emerge. It also suggests that interventions targeting single pathways may be insufficient unless they restore coordination across interacting hallmarks. Strategies that stabilize core regulatory mechanisms, particularly those governing excitability, plasticity, and metabolic support, may offer greater leverage for preserving cognitive function.

Ultimately, advancing the field will require integrating molecular biology, systems neuroscience, longitudinal human cohorts, and refined animal models within a unified framework capable of capturing variability rather than averaging it away. By prioritizing inter-individual divergence over mean decline, cognitive aging research can move toward predictive models of individual trajectories and toward interventions aimed not merely at slowing deterioration, but at preserving functional stability across the lifespan.

BOX 1 – TAKE HOME MESSAGES

1. Cognitive aging is highly heterogeneous, and chronological age alone poorly predicts cognitive outcome.
2. In both humans and rodents, inter-individual differences in MTL-dependent memory emerge during aging.
3. Preservation of MTL network integrity is central to healthy cognitive aging.
4. Hippocampal subfields are differentially affected, reflecting region-specific vulnerability and network imbalance.
5. Increased hippocampal inhibition may represent a compensatory response to age-related circuit dysregulation.
6. Alterations in HPA axis regulation contribute to vulnerability in cognitively impaired individuals.
7. The contribution of glial and microglial activation, neuroinflammation and senescence to cognitive aging remains debated.

C . Future directions

Several key questions remain in the study of cognitive aging. First, to what extent does cognitive aging diverge from general somatic aging? Growing evidence indicates that brain aging is closely linked to the health of peripheral organs, and that different tissues age at varying rates with considerable individual variability. This emphasizes the importance of adopting holistic approaches in the study of cognitive aging[189,260–262]. Second, how do the multiple hallmarks of cognitive aging interact across the lifespan, and do specific constellations or temporal dynamics of these hallmarks drive vulnerability or resilience to cognitive decline? Third, can individual cognitive trajectory be predicted by early biomarkers reflecting these hallmarks prior to the onset of clinical impairments?

Addressing these questions requires a nuanced understanding of the interconnections among these hallmarks and their relative contributions to cognitive aging[263]. This endeavour is challenging but necessary for developing personalized strategies. Interventions targeting modifiable factors have emerged as promising strategies to support brain health in aging[264], however, future studies will need to establish a mechanistic understanding of how these factors influence specific hallmarks of cognitive aging. In preclinical models, progress toward this goal has been

more advanced[265,266], underscoring the critical need to translate these findings to humans. Achieving this will also require the refinement of animal models and the development of experimental parradigms that more closely capture the complexity and heterogeneity of human cognitive aging.

Moreover, research must broaden its scope beyond memory to include other cognitive domains, recognizing that cognitive aging is multifaceted. Additionally, the impact of early environmental factors on cognitive development and aging is crucial, as these factors may hold the key to more effective interventions[267].

Ultimately, advancing our understanding of cognitive aging, and promoting healthy cognitive aging in particular, will require a multidisciplinary approach, integrating insights from biology, neuroscience, psychology, and social sciences, to comprehensively address the complexities of cognitive aging and design efficient targeted interventions.

BOX 2 – FUTURE DIRECTIONS AND OPEN QUESTIONS

1. There is a critical need for longitudinal and pseudo-longitudinal studies to more accurately delineate cognitive trajectories across the lifespan.
2. How can animal models be refined to better approximate the complexity of human cognitive aging?
3. Investigate whether the multiple cellular and systemic alterations observed in aging directly drive cognitive decline.
4. How do the hallmarks of cognitive aging interact across the lifespan?
5. Can early biomarkers predict individual cognitive trajectories before clinical impairment?
6. To what extent does cognitive aging diverge from general somatic aging?

Table 1 – Representative Human Studies Investigating Factors Underlying Individual Differences in Cognitive Task Performance

	Cortex	**Hippocampus**	**DG/CA3**
Structural connectivity			
Episodic Memory	Cingulate cortex: HCH>LCH[268]	HPC: HCH>LCH[269]	
Spatial Navigation	Uncinate fasciculus correlated with performance in a vWM[73]		
Grey matter morphometry			
Episodic Memory	HCH>LCH[270]	HCH>LCH[66]	HCH>LCH[65]
Pattern separation			
Functional/effective connectivity	PCC: Non Decliners > Decliners[76,77]		
Episodic Memory		Local inhibitory connectivity :	
Spatial navigation		Y>HCH>LCH[82]	
Functional activation			

Episodic Memory	Y=HCH>Average older[271]	Y=HCH>Average older[271]	Retrieval: HCH>LCH[66]
Spatial Navigation		Y<HCH>LCH[82]	
Pattern completion	alEC/area 35: HCH>LCH[68]	HCH>LCH[272]	HCH>LCH[272]
Pattern separation	alEC activity: HCH>LCH[68]	HCH<LCH[68]	DG-CA3/aIEC balance: HCH>LCH[67]
Functional dedifferentiation	PPA: HCH<LCH[62,63]		
Episodic Memory	PrC: HCH<LCH[62]		
	Posterior medial HCH>LCH[69]		
Dopamine		HCH>LCH[164,165]	
Episodic Memory			
BBB (DCE MRI, CSF sPDGFR**β**)		PHG, CA1, CA3, DG: HCH>LCH[196]	
Tau burden	EC: HCH<LCH[233,273]		
Episodic Memory	MTL: HCH<LCH[229]		
	ITG: HCH<LCH[233,230]		
	EC/ITG: Fast Decliner>Slow Decliner[231,232]		
	MeT: HCH<LCH (Amyloid$^-$)[234]		

Abbreviations: alEC: anterior-lateral entorhinal cortex; BBB: blood brain barrier ; CSF: cerebrospinal fluid; DCE: dynamic contrast-enhanced; DG: dentate gyrus; EC: entorhinal cortex; HCH= Higher cognitive health; HPC: hippocampus; ITG: inferior temporal gyrus; LCH=Lower cognitive health; MeT: Mesial temporal. PCC: posterior cingulate cortex; PHG: parahippocampal gyrus; PPA: parahippocampal place area; PrC: Perirhinal cortex; sPDGFRβ: soluble platelet-derived growth factor receptor-β pericyte marker; vWM: virtual water maze. Y=young.

Table 2 – Representative Animal Studies Examining Individual Differences in Cognitive Performance or Neuronal Function

	Cortical areas	**Dentate Gyrus**	**CA3**	**CA1**
Network Activity				
[^{14}C]-2-DG	PFC: HCH>LCH[83]	HCH>LCH[83]	HCH>LCH[83]	HCH>LCH[83]
fMRI	RSC/PCC:		**Resting-state functional connectivity (left side):** HCH>LCH[85]	**Resting-state functional connectivity** (left side): HCH>LCH[85]
	HCH>LCH			
Place cells			**Flexibility**: HCH>LCH[91]	**Flexibility**: HCH>LCH[91]
				Overdispersion: HCH>LCH[86]
				Replay : HCH>LCH[89]
Cellular activity (IEGs)	**Ctx Fear Cdt** (task-induced *arc*) LEC: HCH>LCH[96]		**Ctx Fear** (task-induced *arc*): HCH=LCH[96]	**Ctx Fear** (task-induced *arc*): HCH>LCH[96]
	T maze(*arc*) PFC: Y>HCH=LCH[93]	**T maze**(*arc*): =HCH=LCH[93]	**T maze** (*arc*): =HCH=LCH[93]	**T maze** (task-induced *arc*): Y= HCH>LCH[95]

	Object discrimination (*arc*) LEC: HCH<LCH[98]		**Object discrimination** (*arc*): Y=HCH<LCH[98]	
	WM (Lev-induced cFos): Y=HCH>LCH[97]	**WM** (Zif268): LCH=HCH[94]	**WM** (Lev-induced cFos): Y= HCH>LCH[97]	**WM** Lev-induced (cFos): Y= HCH>LCH[97]
Neuron number	EC: Y=HCH=LCH[101]	**GCL**: Y=HCH=LCH[100, 102,123]	Y=HCH=LCH[100]	Y=HCH=LCH[100]
		Hilus: Y=HCH=LCH[123]		
Synapse number		MML : Perforated synapses	**Perforated synapses**: Y= HCH>LCH[107]	**SR:** Y=HCH=LCH[107,108]
		Y= HCH>LCH[105]	**Nonperforated synapses**: Y=HCH=LCH[107]	**PSD area**: Y = HCH>LCH[109]
Synaptic markers	**Synaptophysin**[104]	**Synaptophysin**[106]	**Synaptophysin**[106]	**Synaptophysin**[106] :
	LEC: HCH>LCH	OML, MML, IML: Y=HCH>LCH	LM, SM:	LM, SR
	MEC:HCL=LCH		Y=HCH>LCH	Y=HCH=LCH
	Reelin[104]			
	LEC: Y=HCH>LCH			
	MEC: Y=HCH=LCH			
Neuronal excitabilty	**firing probability & AHP**: LEC III: HCH>LCH[110]	**mEPSC & mIPSC**: HCH>LCH[274]	**AMPAR** (perforated synapses): Y=LCH>HCH[107]	**Slow & Fast AHPs**:
			NMDAR: Y=LCH=HCH[107]	HCH<LCH[113]
				Learning-related AHP plasticity HCH>LCH[116]
				mEPSC & mIPSC: HCH=LCH[116]
				Tonic Inhibition: HCH=LCH[127]
				AMPAR & NMDAR:
				Y= HCH=LCH[107]
Synaptic transmission	LEC → GC : feed-forward inhibition HCH>LCH[128]		A/C3→CA3: Y=LCH=HCH[132]	fEPSP: HCH>LCH[167]
Synaptic plasticity			**NMDA-LTP**: HCH=LCH[132]	**LTP**: HCH>LCH[131]
			VGCC-LTP: HCH>LCH[132]	**NMDAR-LTP**: HCH>LCH[131]
			mGluR LTD : HCH>LCH[132]	**VGCC-LTP**: HCH>LCH[131]
			NMDA-LTD: HCH=LCH[132]	**LTD**: Y=HCH>LCH[133]
				STP&LTP: HCH>LCH[130]
				LTD-to-LTP: HCH>LCH[167]
Interneuron markers		**Gad67 GCL, ML**:	**Gad67 all fields**:	**Gad67**: Y= HCH=LCH[123]
		Y>HCH=LCH[123]	Y>HCH=LCH[123]	
		Gad67 Hilar:	**SOM**: Y>HCH=LCH[123]	***gad1***: Y<HCH[126]

		Y=HCH>LCH[123]	**Gad1 & GAD67 mRNA**:	
		SOM Hilar:	Y<HCH[126]	
		Y=HCH>LCH[123,124]		
		NPY Hilar: Y=HCH=LCH[123]		
		Gad1 mRNA: Y<HCH[126]		
Adult neurogenesis		**Rate of neurogenesis at old age**: HCH>LCH[102]		
		Activation adult-born neurons: HCH>LCH[94]		
		Integration adult-born neurons: HCH>LCH[220]		
Corticosteroid receptors				
GR	mPFC Y=HCH>LCH[141]	Y= HCH>LCH[142]	**Stratum pyramidale**	**Stratum pyramidale**
			Septal : Y=HCH=LCH[141]	Septal : Y=HCH=LCH[141]
			Temporal : Y=HCH>LCH[141]	Temporal : Y=HCH>LCH[141]
			Stratum granulosum	
			Septal : Y=HCH>LCH[141]	Y=HCH>LCH[142]
			Temporal : Y=HCH>LCH[141]	
MR			**Stratum pyramidale**	
			Septal : Y>HCH=LCH[141]	
			Temporal : Y=HCH=LCH[141]	
			Stratum granulosum	
			Septal : Y>= HCH=LCH[141]	
			Temporal : Y= HCH>LCH[141]	
Neuromodulation				
ACh content	PFC : HCH>LCH[152]	Y>HCH>LCH[152]		
Noradrenaline		HCH>LCH[153]		
DOPAC/DA		HCH>LCH[153]		
Adenosine $_{2A}$R		HCH<LCH[132]		
Glial cells				
Astrocytes		Y=HCH=LCH[208]	Y=HCH=LCH[208]	Y>HCH=LCH[208]
GFAP density		WB : Y>HCH=LCH[209]	WB :Y>HCH=LCH[209]	WB :>HCH=LCH[209]

Activation				HCH<LCH[210] Branch length: Y<HCH<LCH[210]	
Microglia					
Iba1 density		Y=HCH=LCH[209]	Y=HCH=LCH[209]	Y=HCH=LCH[209]	
Activation		Y<HCH=LCH[209]	Y<HCH=LCH[209]	Y<HCH=LCH[209]	
				Y=HCH<LCH[210]	
Oligodendrocytes **(myeline inhibition)**		Y=HCH<LCH[213,214]	Y=HCH<LCH[213,214]	Y=HCH<LCH[213,214]	
Cellular homeostasis					
Senescence					
		Y=HCH<LCH[210]			
		HCH=LCH[220]			
PRDX6, PL	**PL oxydation** : HCH<LCH[226]	**PRDX6**: Y= HCH>LCH[225]			
pTAU	LEC: HCH<LCH[104] MEC: HCH=LCH[104]				
Aβ deposits	Neocortex: HCH<LCH[244]	HCH<LCH[243,244]		HCH<LCH[243,244]	

Abbreviations: AHPs: afterhyperpolarization burst; Ctx Fear: contextual ear conditioning; DOPAC: 3,4-dihydroxyphenylacetic acid; Dopamine: DA; EC: entorhinal cortex; GC: granule cells; GCL: granule cells layer; GR: glucocorticoid receptor; HCH= Higher cognitive health (or age-unimpaired); IML: inner molecular layer; LCH=Lower cognitive health (or age-impaired); LEC: lateral entorhinal cortex; Lev: levetiracetam; LM: lacunosum-moleculare; MEC: medial entorhinal cortex; MML: medial molecular layer; MR: mineralocorticoid receptor; mPFC: medial prefrontal cortex; NPY: neuropeptide Y; OML: outer molecular layer; PL: Phospholipids; PFC: prefrontal cortex; RSC/PCC: retrosplenial/posterior cingulate cortex; SD: synaptic density; SOM: somatostatin; SR: stratum radiatum, WM: water maze. WB: western blot. Y=young.

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Declaration of interests

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Highlights

- Cognitive decline is highly heterogeneous, underscoring distinct aging trajectories
- Brain aging requires the establishment of new and specific biological hallmarks of aging
- Cognitive health in aging depends on preserved hippocampal circuit function
- Cognitive maintenance relies on both large-scale network integrity and cellular health