

## Review

## Neurocognitive Aging and the Hippocampus across Species

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**There is extensive evidence that aging is associated with impairments in episodic memory. Many of these changes have been ascribed to neurobiological alterations to the hippocampal network and its input pathways. A cross-species consensus is beginning to emerge suggesting that subtle synaptic and functional changes within this network may underlie the majority of age-related memory impairments. In this review we survey convergent data from animal and human studies that have contributed significantly to our understanding of the brain–behavior relationships in this network, particularly in the aging brain. We utilize a cognitive as well as a neurobiological perspective and synthesize data across approaches and species to reach a more detailed understanding of age-related alterations in hippocampal memory function.**

## Memory and the Aging Hippocampus

Episodic memory, or memory for ‘events’, is thought to be particularly vulnerable to the effects of advancing age [1]. Neurobiological evidence suggests that alterations in the medial temporal lobes are implicated in these cognitive deficits. Recent advances in the field have substantially enhanced our understanding of the mechanisms involved in age-related memory decline. In this review we synthesize recent behavioral and neurobiological observations in the aging hippocampal memory system across species.

## Memory Impairments with Aging: A Cognitive Perspective

A cognitive perspective allows us to understand age-associated memory decline, which is one of the most frequently reported age-related cognitive complaints. It also allows us to dissociate normal from pathological aging. Evaluating cognitive alterations in older animals and humans also significantly informs the search for neurobiological alterations that underlie these alterations. Using this perspective, we can gain a deeper appreciation for brain–behavior relationships in the context of the aging brain. This is crucial for developing sensitive measures to detect subtle changes in cognition and for developing appropriately targeted therapeutic interventions that engage specific neurobiological mechanisms.

## Impaired Spatial Memory and Navigation

Spatial memory (i.e., memory for spatial configurations and ability to navigate in an environment) is a key component of episodic memory that has been generally shown to decline with age across species [2–5]. Two possible strategies can be used to navigate within an environment: ‘place’ learning (learning the spatial location – largely dependent on the hippocampus) and ‘response’ learning (learning the response such as ‘turn left’ – largely dependent on the striatum) [6]. Older rats [7] and older monkeys [8] are more likely to use a response strategy and rely less on spatial ‘place’ information compared to young animals. A recent longitudinal study found that chimpanzees experience decline in spatial memory over time [9]. Older humans appear to predominantly use a striatal response strategy [10,11], and the extent to which a place strategy continues to be used is correlated with hippocampal volume [12]. Spatial navigation training is

## Trends

The role of neurogenesis in the dentate gyrus in the context of neurocognitive aging has been recently revisited, given data suggesting that neurogenesis continues into older adulthood.

The lateral entorhinal and perirhinal cortices represent early sites of vulnerability in aging and age-related decline. Designing tasks and approaches to examine these extrahippocampal pathways is crucial.

Hyperexcitability in the hippocampal network is a key pathological state in the aging brain that confers risk for Alzheimer’s disease (AD), potentially linking AD and subclinical epilepsy.

Epigenetic imaging (e.g., HDAC PET) is an emerging technology that will allow more detailed examinations of epigenetic changes related to memory decline in the aging human brain.

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also associated with preservation of hippocampal volume in older adults [13]. A recent study showed that age-related impairments in spatial navigation were most evident in new environments and not in well-learned environments, although the ability of older adults to vividly remember the details of the well-known environment was still impaired [14].

Despite the overall findings that spatial memory and navigation are impaired with age, there is significant individual variability. For example, Gallagher and colleagues have consistently reported that some aged rats perform on par with young rats (aged-unimpaired, AU) and some show spatial learning and memory deficits (aged-impaired, AI) (reviewed in [15]). The same is true in diversity outbred (DO) mice, which are designed to model the genetic diversity present in human [16]. Overall, data across species strongly suggest that spatial learning, memory, navigation, and the use of spatial strategies are impaired in aging, but these effects are highly variable within the aging population. This variability may be due to differences in cognitive reserve [17] or normal aging versus early cognitive decline due to Alzheimer's disease (AD) [18].

#### Impaired Recollection and Spared Familiarity

It has been proposed that recognition memory involves two distinct processes: recollection (recalling specific details of an experience such as where and when it occurred) and familiarity (having a sense of experience but lacking any specific details) [19,20]. A recent meta-analysis of 25 studies [21] using remember/know (RK), receiver operating characteristic (ROC), and process dissociation (PD) procedures revealed consistent recollection impairments in older adults, with relative sparing of familiarity. The ROC procedure has also been adapted to examine constructs analogous to recollection and familiarity in the rodent. For example, [22] used common household odors as stimuli and varied the payoff ratio for correct responses so as to manipulate criterion, or bias for old and new responses. ROC curves were generated and showed that young rats use both recollection and familiarity, while aged rats exhibit a selective loss of recollection and relative sparing of familiarity, similar to the effects of hippocampal damage and similar to effects previously reported in humans. Furthermore, recollection but not familiarity was correlated with spatial memory performance.

More generally, visual recognition memory in aged monkeys tested using the delayed non-matching to sample (DNMS) tasks reveals impairment in object recognition (although there is individual variability in the aging population) [23]. However, little work has been done to determine whether aging alters recollection versus familiarity processes in non-human primates. Recent studies using visual recognition memory tasks in rhesus monkeys suggest that performance is supported by recollection- and familiarity-like processes [24,25]. This opens up the possibility of using tasks highly analogous to those used in humans to study these memory processes in aged non-human primates. While these distinctions are used widely in the literature, there is much debate as to what brain regions are involved in these processes, whether recollection is a continuous or threshold process, or whether the distinction between recollection and familiarity is even necessary [26].

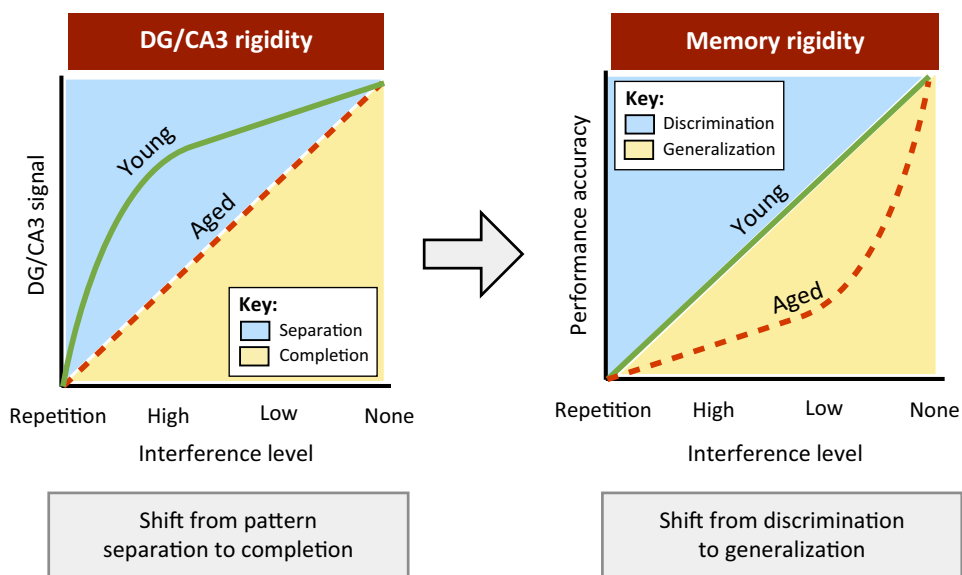
#### Increased Susceptibility to Interference with Aging

Disambiguating similar experiences and overcoming interference is a crucial feature of episodic memory [27]. Tasks designed to test this process parametrically vary the level of interference across learning stimuli and test the ability of subjects to mnemonically discriminate stimuli at a later time. Several human studies have evaluated this 'mnemonic discrimination', across several domains in young and aged subjects, largely motivated by rodent studies (reviewed in [28]). For example, in object mnemonic discrimination tasks, participants are shown pictures of everyday objects with some new, some repeated, and some similar but not identical 'lures'. Participants are asked to remember whether items were previously shown (i.e., targets), not shown before (i.e., foils), or are similar but not identical to previously shown items (i.e., lures). These studies

have shown reductions in discrimination in the object [29–32], spatial [33–35], temporal [36,37], and affective/valence [38] domains. Interestingly, there is some evidence to suggest that the magnitude of spatial discrimination deficits noted is not as large as for object discrimination [30].

Similar studies have shown object novelty discrimination deficits in aged rats [39,40] and monkeys [40]. Age-related impairments in spatial discrimination have also been noted in rats [41] and non-human primates [42]. Very little work has been done in aged rodents and non-human primates to determine whether aging alters temporal or affective discrimination processes. However, tasks such as that used by Gilbert and colleagues [43] and a novel inhibitory avoidance discrimination task [44] may be helpful as models. New versatile touchscreen designs may allow assessment of mnemonic discrimination across many domains [45].

Across behavioral studies in animals and humans, convergent evidence suggests that aging is associated with decreased capacity for distinguishing among experiences that share common contextual elements. We suggest that these information-processing deficits underlie many of the episodic memory problems reported in older age, as well as explain the types of memory errors often made by older adults (e.g., false recognition). In general, these deficits can be characterized as ‘memory rigidity’ where there is an age-related requirement for higher levels of dissimilarity across experiences for discrimination to be successful. Data are consistent with a conceptual model in which the relationship between interference and performance is largely linear in young adults and more exponential in older adults (Figure 1, right). Table 1 summarizes the cognitive changes observed in aging discussed above.



Trends in Neurosciences

**Figure 1. Schematic Representation of Cross-Species Computational Changes Occurring in the Aging Hippocampus and Cognitive Consequences.** Neurobiological (left) and cognitive (right) alterations are described as a function of interference level (x axis), which is quantified on a continuum from exact repetitions (left) to novel experiences (right). Given this framework, changes occurring in the dentate gyrus (DG)/CA3 region of the hippocampus can be characterized as a form of representational rigidity. Across species, DG/CA3 coding properties are consistent with pattern separation in young subjects, and reduced pattern separation (a bias towards pattern completion) in older subjects. The consequence of these neurocomputational alterations manifests as an impairment in discrimination performance on tasks designed to assess hippocampal pattern separation. In other words, older subjects tend to overgeneralize at the expense of discrimination. This appears in the absence of global memory deficits in conditions where there is minimal interference such as exact repetitions or brand-new items.

Table 1. Summary of Age-Related Alterations In Episodic Memory

Feature	Major Finding	Refs
Spatial memory	Impaired memory for spatial locations and impaired spatial navigation ability	[2–18]
Recollection	Impaired recollection and relatively spared familiarity	[19–25]
Interference/discrimination	Impaired ability to discriminate highly similar experiences across object, spatial, temporal, and affective domains	[27–42]

Memory Impairments with Aging: A Neurobiological Perspective

The medial temporal lobe (MTL) (Figure 2) has a well-established role in memory processing [46,47] and is particularly vulnerable to the effects of advancing age. We discuss these effects in detail below.

Reduced Perforant Path Input to the Hippocampal Dentate Gyrus (DG) and CA3

In aged rats, the DG receives approximately one-third fewer synaptic connections from entorhinal cortex (EC) layer II than in young rats [48,49]. The amount of synaptic reduction of the perforant path correlates with the degree of spatial memory impairment in aged rats [49]. Electrophysiological studies have shown that stimulating the perforant path generates less excitation in the DG in aged rats compared to young rats [50]. In aged humans, ultrahigh-resolution diffusion imaging,

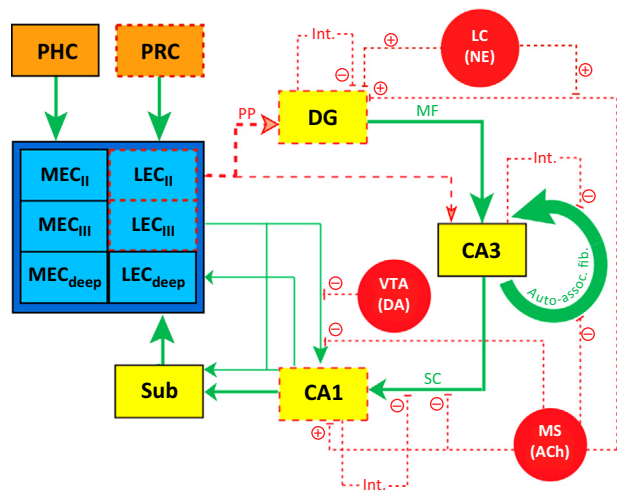


Figure 2. Simplified Schematic of the Hippocampal Network and Summary of Neurobiological Changes Occurring in the Context of Age-Related Memory Impairment. The most upstream age-related vulnerability in this network is hypothesized to occur at the level of the perirhinal cortex (PRC), as well as in the lateral entorhinal cortex (LEC), in particular the superficial layers. Downstream, perforant path (PP) input from the EC to the dentate gyrus (DG) and CA3 is blunted with age, while the mossy fiber (MF) and Schaffer collateral (SC) projections appear largely intact. The DG exhibits loss of neurogenesis as well as aberrant ensemble dynamics, while the CA3 appears to be hyperexcitable, thus reinforcing the auto-associative recurrent collateral network (Auto-Assoc. Fib.) of the region. Inhibitory interneuron (Int.) projections to all hippocampal subregions are also degraded with age, perhaps contributing to the shifted excitation/inhibition balance in the hippocampus. Modulatory cholinergic (ACh) input from the medial septum (MS) and diagonal band of Broca (not shown) is diminished. Similarly, dopaminergic (DA) projections from the ventral tegmental area (VTA) as well as noradrenergic (NE) projections from the locus coeruleus (LC) are also diminished with age. Synaptic plasticity as well as place-cell firing alterations in the CA1 region also occur with age. Overall, the network exhibits several neurobiological changes that shift the computational bias from learning new information towards emphasizing previously learned information. Lines and boxes in broken red lines are hypothesized to exhibit some age-related deficits. Green lines and black bordered boxes suggest that there are insufficient data in the literature to make informed conclusions regarding age-related impairment. Figure partly adapted from [12]. Abbreviations: MEC, medial entorhinal cortex; PHC, parahippocampal cortex; Sub, subiculum.

which measures microstructural features of white matter, demonstrated age-related degradation in perforant path integrity, which correlated with memory deficits in older adults [51,52].

#### Reduced Pattern Separation in the DG/CA3 Network

The hippocampus is thought to be involved in two key computations: pattern separation and pattern completion. Pattern separation is the process of reducing interference among similar inputs by using non-overlapping representations, and is thought to rely on hippocampal DG and its strong mossy fiber connection to the CA3. Pattern completion is the process by which representations can be retrieved when given partial or degraded input and is ascribed to hippocampal CA3, where the recurrent collaterals of the region may act as an auto-associative network [27,28]. These computations are thought to underlie mnemonic discrimination and give rise to our rich episodic memories.

Age-related changes in the DG/CA3 network are thought to strengthen the CA3 auto-associative network at the cost of processing new information, thus biasing the hippocampal network away from pattern separation and towards pattern completion (model reviewed in [53]). This manifests as 'rigidity' in spatial representations in CA3 neurons while navigating similar environments (i.e., a failure to remap). Notably, these age-related spatial coding deficits were only found in aged-impaired rats. This model was recently extended to older humans using high-resolution (1.5 mm isotropic) functional magnetic resonance imaging (fMRI) capable of resolving hippocampal subfields. During an object mnemonic discrimination task (described earlier), older adults were found to exhibit 'representational rigidity' in the DG/CA3 region (Figure 1, left), where they required more dissimilarity for successful pattern separation (novelty response to lures) [52]. This was associated with impaired memory performance in older adults as well as their perforant path integrity, providing strong cross-species support for the model proposed in [53].

In contrast to these results, a recent study using Zif268/Egr1 (early growth response 1) as a marker of cellular activity showed that the DG in older animals was more likely to recruit distinct granule cell populations during two visits to highly similar or even the same environments. However, if two highly-distinct environments are visited, this age-related change is no longer apparent [54]. While one potential interpretation of these results is an increase in pattern separation in the DG, which would be consistent with the known decline in inhibitory control in the region, a potential alternative is that the stability of DG representations is compromised with age. The authors show that this change in DG activity correlates with decline in the ability of aged animals to disambiguate similar contexts in a sequential spatial recognition task, suggesting that this change, whether an increase in sparsity or a form of representational instability, is dysfunctional.

#### Excitation/Inhibition Balance in the Aging Hippocampus

Wilson and colleagues [55] demonstrated that place cells in the aged rodent CA3 region exhibit abnormally elevated firing rates. Recently, intracranial recordings in freely moving animals and extracellular recordings in hippocampal slices both revealed frequent spikes in the CA3 of aged mice, while these spikes occurred only occasionally in the CA3 of young mice. Spontaneous field potentials with large amplitudes originating from CA3 were also frequently observed in hippocampal slices of aged mice, but rarely in slices from young adults [56]. In AI rats, a reduction in gene expression underlying synaptic inhibition was reported and this predicted spatial learning deficits [57]. Consistent with rodent studies, fMRI studies in humans have also demonstrated similar evidence of hyperactivity in the DG/CA3 network [58], the extent of which predicted memory performance impairments.

While it is likely that several factors contribute to age-related changes in hippocampal excitation/inhibition balance, it is clear that the loss of inhibitory tone plays an important role. Numbers of

glutamate decarboxylase 67 (GAD67)- and somatostatin (SOM)-positive interneurons decline with age across multiple fields of the hippocampus, however, alterations specifically in AI rats were observed exclusively in the hilar region of the DG [59]. The total number of NeuN (neuronal nuclei/RBFOX3)-immunoreactive hilar neurons was unaffected, suggesting the observed decline likely reflects a loss of target protein rather than neuronal death. Stereological quantification of SOM-immunoreactive neurons in the DG hilus of DO mice showed that high-performing young and aged-unimpaired DO mice had similar numbers of SOM-positive interneurons, and AI DO mice had significantly fewer such neurons [16].

Across species, the data suggest that CA3 hyperactivity is an index of network dysfunction and disinhibition, and is not evidence of adaptive compensation. This elevation in activity can be targeted with inhibitory pharmacological manipulations that reduce excitation (levetiracetam, LEV; or valproic acid, VPA) or enhance inhibition (neuropeptide Y, NPY) [60], reversing memory deficits in treated animals. When treated, hilar SOM expression was fully restored in AI rats [59] and AI DO mice, suggesting that this is a pharmacologically modifiable target [16]. It is important to note that neural hyperactivity in and of itself is not necessarily evidence of dysfunction, and there are other instances where it might be adaptive [61].

A clinical trial using LEV was recently conducted in individuals with amnesic mild cognitive impairment, a prodrome of AD mainly characterized by memory loss [62]. A low dose of LEV successfully reduced DG/CA3 hyperactivity and reversed deficits on the object mnemonic discrimination task [62,63]. Hippocampal hyperexcitability in aging and age-related disorders appears to be a generally reversible condition in both animals and humans [16,62–64], which has translational potential for age-related memory loss and AD.

#### Reduced Modulatory Input to the Aging Hippocampus

Modulatory inputs to the hippocampus generally decline with age. These events could contribute to the imbalance of excitation and inhibition leading to hippocampal dysregulation. Although the traditional view of modulatory loss with aging has implicated neuronal cell loss, more recent data suggest that these changes are more likely to be the result of dendritic and synaptic loss as well as of axonal degeneration and decreases in trophic support [65].

#### Acetylcholine (ACh)

The cholinergic hypothesis of aging dates back to a seminal study in which young human subjects who were given scopolamine, a cholinergic antagonist, showed memory impairments that were very similar to the memory impairments reported in aged individuals [66]. The basal forebrain cholinergic system provides cholinergic projections to the hippocampus that are thought to degrade with aging [65]. This degradation appears to be specific to animals with memory deficits because AU rats have intact cholinergic signaling mechanisms [67–69]. Reduced ACh-mediated modulation may contribute to the bias of CA3 pattern completion [53]. Activation of the medial septum with the cholinergic agonist carbachol reverses place-cell coding deficits in CA1 in aged rats [70]. More recently, the acetylcholine mimic physostigmine was used to successfully reverse decreases in hippocampal theta power in aged rats during novel maze exploration [71]. Overall, these results suggest that cholinergic modulation plays a crucial role in the computational balance in the hippocampus and provide evidence for a cholinergic mechanism for age-related memory impairment. Without normal ACh modulation of the hippocampus, pattern separation and completion computations may be altered, leading to dysfunction in discrimination abilities with age.

#### Dopamine (DA)

Several studies have reported an age-dependent degeneration of substantia nigra/ventral tegmental area DA neurons in aging [72,73], which may affect the ability of the hippocampus



to consolidate memories [74]. Reductions in the level of dopamine in the aging hippocampus in rats and humans have been frequently reported and are surveyed in [75]. Studies conducted in healthy older adults suggest that pharmacological enhancements of DA activity enhance scene recollection [74], memory specificity [75], and object-place learning [76]. Thus, it appears that reversing age-dependent declines in DA modulation has benefits for memory performance in older rats and humans. Overall, this suggests that there are alterations in DA input to the hippocampus, which may result in changes in memory performance by altering synaptic plasticity mechanisms. The impact of DA modulation on the computational balance in hippocampal subfields has not been examined in detail in the context of discrimination and generalization and should be targeted in future studies, perhaps by including reward/punishment in interference designs.

#### *Norepinephrine (NE)*

A reduction of NE input to the hippocampus [77] as well as changes in peripheral epinephrine levels [78] have been reported in animal models of aging. The extent of NE depletion in dorsal hippocampus is associated with the extent of memory deficits in aged animals [79]. NE depletion is also associated with impaired long-term potentiation (LTP) in the CA1 of aged rodents during fear conditioning, a deficit that was attenuated by treating the animals with NE [80]. Thus, NE depletion appears to contribute to age-related memory loss, and replenishment approaches may be beneficial in reversing the deficits. Interestingly, the DG is the target of NE modulation directly and indirectly via the basolateral amygdala [81]. The DG also receives strong modulation via direct NE projections from the locus coeruleus (LC) to the DG, and glutamatergic projections from the basolateral amygdala (BLA), which is innervated by noradrenergic projections from the LC [82]. A recent experiment in humans [83] found a significant effect of NE modulation (measured via salivary  $\alpha$ -amylase, sAA) on mnemonic discrimination behavior, whereby higher levels of sAA were associated with better performance. This suggests that NE may facilitate hippocampal pattern separation and potentially provides a mechanism for memory deficits stemming from NE loss with age.

#### *Reduced Adult Neurogenesis in the Aging DG*

Although neurogenesis continues throughout life, its rate is thought to decline with increasing age [84–86]. It has been proposed that the age-related decline in neurogenesis may underlie memory deficits and could contribute to pathological conditions such as AD [87–89]. The exact role of adult neurogenesis in modulating learning and memory mechanisms is not well understood. It has been suggested that neurogenesis may play an important role in pattern separation. When DG neurogenesis was knocked down by focal X-irradiation, deficits were seen in a touchscreen task that relies on fine discrimination [90]. Several studies have also demonstrated that enhancement of neurogenesis via exercise [91] as well as genetically enhancing the survivability of newborn granule cells [92] improved discrimination performance, which is thought to rely on pattern-separation mechanisms. While neurogenesis may contribute to DG function, neurogenesis alone is not sufficient to preserve function during normal aging [93], and is not correlated with the extent of age-related memory impairments [94].

More recently, nuclear-bomb-test-derived  $^{14}\text{C}$  in genomic DNA was used to assess neurogenesis rates throughout the lifespan and found that rates are comparable in middle-aged humans and mice, with only a modest decline during aging [95]. Assessing the role of declining neurogenesis in age-related memory impairment requires the development of sensitive techniques that are capable of assessing the state of newborn granule cells *in vivo*. Despite some modest success using spectroscopic techniques [96], new tools need to be developed to dynamically assess and track neurogenesis in humans *in vivo*, such that the contributions of neurogenesis to memory and cognition in humans can be evaluated and to

determine how this could impact therapeutic interventions aimed to reverse age-related cognitive decline.

#### Reduced Brain-Derived Neurotrophic Factor (BDNF) in the Aging Hippocampus

Aging has been associated with a reduced capacity to induce and respond to growth factors [97], which are necessary for development, survival, and plasticity of neurons. BDNF is one of the many trophic factors altered in aging (see [98] for more comprehensive review). Decreases in hippocampal BDNF have been hypothesized to contribute to memory impairment in aging [99], perhaps by reducing LTP [100], a deficit that appears to be reversible via exogenous administration of BDNF [100]. BDNF depletion also appears to be linked to synapse loss [101]. In humans, cerebrospinal fluid (CSF) BDNF levels are reduced in older adults and are associated with poorer memory performance [102]. Enhancing neurotrophic support has thus shown some promising effects in reversing age-related memory impairments by increasing BDNF levels either directly or indirectly (e.g., via physical exercise). This mechanism may be a potential avenue for therapeutic intervention to slow down or reverse age-related cognitive decline.

#### Synaptic Plasticity Alterations in the Aging Hippocampus

Age-related deficits in plasticity correlate with memory impairments in aged animals [4]. Aged rats have deficits in both LTP induction and maintenance and an increased probability of both long-term depression (LTD) and LTP reversal [50,103]. DNA microarray analysis comparing young, middle-aged, and old rodents found that LTP-specific gene expression is altered in aging and suggests that dysregulation of synaptic protein synthesis contributes to the age-dependent reduction in LTP persistence [104].

Aged rats appear to be more susceptible to LTD and depotentiation than adult rats [105]. Recently it was found that, unlike CA1 synapses, LTP in CA3 is minimally affected by age. Both *N*-methyl-D-aspartate (NMDA)-dependent and metabotropic glutamate receptor (mGluR)-dependent LTD are substantially reduced in aged rodents with memory impairment. However, AU rats had intact mGluR LTD [106], which suggests that pharmacological manipulations targeting mGluR LTD may be helpful in compensating for age-related memory effects. The threshold for LTP induction is increased in aged rats, potentially making it more difficult for aged rats to encode a memory, while the threshold for LTD induction is decreased, potentially making it easier for aged rats to erase a memory [103,107]. Overall, these changes suggest that plasticity is altered in the aging hippocampus in such a way that biases it away from learning new information.

#### Changes in Functional Transcriptomes

Several lines of evidence implicate the immediate early gene (IEG) *Arc* (activity-regulated cytoskeleton-associated protein) in the sustained modification of neuronal networks [108,109]. Relative to young rats, the DG in aged rats had fewer granule cells that transcribe *Arc* 8 h after spatial exploration. This decrease was correlated with impaired spatial memory [110]. A recent study found that experience-dependent *Arc* mRNA expression in the hippocampus fails selectively among aged rats with spatial memory deficits. This group also had increased basal *Arc* protein levels in the CA1 field [111]. Another study also utilizing *Arc* mRNA imaging showed that distal CA1 neurons exhibit more remapping with environmental change than proximal CA1 in adult animals, whereas aged rats showed no differences in remapping across the CA1 axis [112]. This effect may be secondary to impairments in the lateral entorhinal cortex (LEC) input to distal CA1. We discuss these changes in LEC later in the review. Overall, the failure of IEG-based remapping suggests that there is failure in learning and encoding new environments, which is consistent with the behavioral deficits reported in aged animals.



### Changes in Epigenetic Signatures

Memory impairment in aged mice is associated with blunted behavioral regulation of hippocampal histone acetylation. An increase in histone deacetylase (HDAC) activity with age may silence normal gene expression, leading to impairments in the formation of memory. The administration of HDAC inhibitors, which are known to elevate histone acetylation and facilitate learning in rodents when administered into the hippocampus [113,114], mimics the effect of environmental enrichment [115] and is associated with recovery of cognitive function in a mouse model for AD-like neurodegeneration [115]. Systemic injections of the HDAC inhibitor sodium butyrate ameliorate age-associated deficits in object recognition memory in rats when the injection is given immediately, but not 6 h after training [116]. The results indicate that HDAC inhibitors may be able to ameliorate aging-related memory impairments by influencing the early consolidation phase of memory formation. It is possible that HDAC inhibitors remove age-related transcriptional repression, thereby allowing memories to be consolidated. Understanding the role that histone acetylation plays in neurocognitive aging of the hippocampus is complex but has garnered recent interest in the field. With the advent of molecular approaches to examining these epigenetic changes across species, discovery in this area will likely have a substantial impact on understanding age-related memory loss and bridge to translational approaches to intervention.

### Beyond the Hippocampus: Age-Related Changes in the Medial Temporal Lobe

The hippocampus receives sensory input via LEC and medial entorhinal (MEC) cortices, which in turn receive input from the perirhinal (PRC) and parahippocampal (PHC)/postrhinal (POR) cortices respectively. The LEC/PRC pathway is thought to support object/nonspatial information, while the MEC/PHC pathway is thought to support spatial information [117]. Data from studies of rats and humans suggest a selective vulnerability of the LEC/PRC pathway to age-related decline. For example, PRC alterations have been observed in rodent studies [108,118–120]. PRC Arc protein is reduced in aged rats relative to young after exploring new objects in a familiar environment or exploring the same objects but in a different environment [108]. Firing rates in aged PRC are also reduced during object exploration [121]. These neurobiological changes are hypothesized to underlie object discrimination deficits reported in aged rats [40]. This is also supported by a recent study using fMRI in humans showing reduced engagement of bilateral anterior PRC in older adults during complex object discrimination [122]. The LEC exhibits an age-related reduction in reelin expression, and an increase in phosphorylated tau (p-tau), both of which are specific to aged rats with memory impairment [123]. The LEC/PRC region is the first site of neurodegenerative loss in AD [124] and may in fact be a site where tau pathology begins and subsequently spreads to other sites in the brain [125]. Whether the p-tau changes observed in the aged outbred rats (that do not develop AD) are a precursor that is necessary but perhaps not sufficient for subsequent neurofibrillary tangle pathology and neurodegeneration, which are defining feature of AD in humans, is still unclear but is potentially an interesting avenue of exploration because targeting p-tau with interventional approaches may have benefits for both age-related memory loss and AD.

The question of ‘aging’ versus ‘disease’ is one that has been subject to much debate recently, and although we cannot discuss the issue in detail in this review, we have focused on particular features of neuropathology in the aging hippocampal memory system which may set up a core vulnerabilities that in some circumstances (e.g., in humans), can interact with other factors to lead to subsequent neurodegenerative changes. We point the reader, however, to another recent review that treats these issues in much more detail [18].

Recent evidence has also shown that newborn granule cells in the DG are selectively innervated by LEC [126] which, as suggested above, is selectively vulnerable to aging and AD. This may

Table 2. Summary of Age-Related Neurobiological Alterations to the Hippocampus

Feature	Major Finding	Refs
Pattern separation	Reduced pattern separation and rigidity in spatial/mnemonic representation	[52,53]
Perforant path input	Reduced input from EC to hippocampus	[48–52]
Excitation/inhibition balance	Hyperactivity in CA3, loss of inhibition on CA3	[16,59–64]
Modulatory input	Reduced cholinergic, dopaminergic, and norepinephrine inputs into the hippocampus	[65–83]
Adult neurogenesis	Reduced DG neurogenesis	[86–98]
Neurotrophic support	Reduced growth factors, such as BDNF	[97–102]
Synaptic plasticity	Increased threshold for LTP; decreased threshold for LTD	[4,50,103–107]
Functional transcriptomes	Arc expression reduced	[108–112]
Epigenetic modifications	Decreased histone acetylation	[113–116]
Input regional integrity	PRC and LEC dysfunction	[40,113,117–126]

have implications for learning mechanisms because the predominant view is that the LEC selectively provides external sensory input to the hippocampus, with the PHC and MEC providing internally generated self-motion for path integration [127]. The relationship between LEC and DG neurogenesis has yet to be explored in detail in the context of aging, but will likely be a very important direction of future research.

In general these neurobiological alterations contribute to a condition in the aging hippocampus that alters its computational balance such that there is neural rigidity, leading to an age-related requirement for higher levels of dissimilarity across experiences for pattern separation to be successful. The data are consistent with a conceptual model in which the relationship between interference and performance is largely logarithmic in young adults and more linear in older adults (Figure 1, left). The neurobiological changes in the hippocampus observed in aging, discussed above, are summarized in Table 2.

### Concluding Remarks: A Cross-Species Synthesis

Despite differences in procedures and approaches across studies in both animals and humans, a cross-species consensus begins to emerge with respect to the mechanisms for episodic memory deficits associated with the aging hippocampus. First, cortical input to the hippocampal system is compromised with age. In particular, the LEC/PRC pathway to the hippocampus (which is associated with nonspatial information) appears to be a site of early vulnerability. This degrades the quality of input to the hippocampus, a dysfunction, which is made more significant due to the synaptic degradation in the perforant path input from the superficial layers of the EC to the DG and CA3. The ability of the DG/CA3 network to maintain appropriate excitation/inhibition balance and learn new information is compromised due to the loss of this crucial input, as well as other structural functional alterations (decreased neurogenesis, decreased modulatory input, decreased inhibition and hyperexcitability), which substantially reduce its capacity for pattern separation. As a result of these neural changes, memory loss manifests as a shift from mnemonic discrimination of similar experiences to generalization. These age-related deficits and their underlying neural bases provide a mechanistic explanation for many of the previously reported episodic memory changes with age, such as loss of contextual memory and recollection. While these findings have significantly informed our understanding of the neurocognitive condition of the aging hippocampus, much remains to be learned. For example, considerably less is known about how other vulnerabilities in the aging hippocampus, such as reduced BDNF, increased histone acetylation and transcriptional repression, as well as lowered IEG activity, may contribute

### Outstanding Questions

Numerous behavioral tasks assessing mnemonic discrimination and its underlying pattern-separation process have been developed in young rodents [43,44,128] and monkeys [24,25], but have yet to be applied to aged animals. These paradigms, which are sensitive to subtle memory changes in aging, will be useful in understanding the impact of neurobiological changes on memory.

Many studies have investigated alterations in modulatory systems regulating hippocampal function, with recent studies showing promising therapeutic results by reversing these alterations in aged animals and humans [74,76,80], but more work needs to be done to fully elucidate the impact that altering the balance of these modulators can have on memory impairments in aging.

In addition to having several subfields, each with its own distinct connectivity and function, the hippocampus is subject to additional heterogeneity. For example, input and output connectivity varies according to the longitudinal axis (dorsal and ventral [129]) of the hippocampus as well as the transverse axis (proximal and distal [130]). Similarly, the entorhinal cortex, in addition to its distinct layered structure, can be divided into lateral and medial EC [125], each thought to subserve different functions. More work is needed to parse the effect of aging on these subdivisions because discovering selective vulnerabilities in the hippocampal network may aid in developing therapeutic approaches to slow down age-related memory decline.

While a host of cognitive tasks have been used to examine the integrity of the hippocampus in humans, developing more-sensitive tasks to assess individual differences in memory functioning, and selecting tasks within a larger parametric space to investigate variability in aging, will allow us to tease apart age-related changes that occur in normal aging versus pathological aging [18].

Despite some early attempts [96], currently there is no widely accepted method to assess neurogenesis in humans *in vivo*. Assessing the role that declining neurogenesis might play in age-related memory impairment requires the development of sensitive techniques that are capable of

to the shift in hippocampal computational balance. We suggest that developing cross-species approaches to examining these changes is crucial to move forward. These approaches must include technical innovations, allowing us to better understand the neurobiological alterations in the hippocampal network, as well as conceptual innovations in developing cognitive paradigms that provide analogous insight into cross-species behavior.

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assessing the state of newborn granule cells *in vivo*.

Examining alterations in epigenetic mechanisms in aging is still in the early stages. Establishing the means to assess HDAC activity in the aging hippocampus in humans is crucial to progress and has yet to be accomplished, although recent advances in developing novel PET tracers for HDAC imaging [131] may hold promise for this endeavor.

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