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Review

Neurocognitive Aging and the Hippocampus across Species

Stephanie L. Leal[1,2] and Michael A. Yassa[2,*]

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.

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.

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

[1]Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD, USA
[2]Department of Neurobiology and Behavior, Institute for Memory Impairments and Neurological Disorders, and Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA, USA

*Correspondence: myassa@uci.edu (M.A. Yassa).

 http://dx.doi.org/10.1016/j.tins.2015.10.003

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 nonmatching 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