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Olfactory Memory:

A Bridge between Humans and Animals in Models of Cognitive Aging

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Abstract

Odor-recognition memory in rodents may provide a valuable model of cognitive aging. In a recent study we used signal detection analyses to distinguish odor recognition based on recollection versus that based on familiarity. Aged rats were selectively impaired in recollection, with relative sparing of familiarity, and the deficits in recollection were correlated with spatial memory impairments. These results complement electro-physiological findings indicating age-associated deficits in the ability of hippocampal neurons to differentiate contextual information, and this information-processing impairment may underlie the common age-associated decline in olfactory and spatial memory.

Keywords

aging; olfaction; hippocampus; recollection; familiarity; spatial memory; receiver operating characteristic

Cognitive aging involves the loss of higher-order intellectual capacities, which is associated with deterioration of brain function. In humans, cognitive aging most prominently involves memory impairment, and in particular a decline in episodic recall—the ability to bring to mind specific recent experiences.¹ The disproportionate loss of episodic memory is similar to what one might expect of a mild form of damage to the medial temporal lobe area,^{2–5} inspiring the development of animal models of cognitive aging based on studies of functions of medial temporal lobe structures and, in particular, of the hippocampus. These studies have indeed shown that aged rats are impaired on tests of hippocampal function and that this cognitive impairment can be related to deterioration of neurobiological markers of function within the hippocampus.^{6,7}

While these studies have shown important correspondences between humans and animals, the validity of the animal model is somewhat limited by distinctions in the types of memory in which age-associated impairment is observed. Specifically, whereas in humans, cognitive aging is marked by a selective deficit in recollection, in rodents cognitive aging is observed as a deficit in spatial, but not nonspatial, memory. Clearly the validity of the rodent model can be assessed and potentially improved by an examination of the relationship between age-related deficits in spatial memory and in recollection. However, such a comparison requires a method for examining recollection in animals, which is a challenging task.

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Conflicts of Interest

The authors declare no conflicts of interest.

Studying Recollection in Aged Rats

Recent studies have offered an approach to assessing episodic recollection in animals. This approach is based on a method that was developed for measuring recollection in humans and has also been applied in assessments of episodic recollection in cognitive aging. The method involves signal-detection analyses that distinguish two processes that support our ability to recognize recently experienced stimuli: recollection of the prior experience with studied items and a sense of familiarity for the stimuli in the absence of recollection of the study experiences.^{8,9} In these experiments, subjects initially study a list of stimuli, then recognition memory is assessed by asking subjects to distinguish test presentations of the studied (old) stimuli from additional (new) stimuli. In addition, signal-detection analysis requires testing across a range of biases that vary the criteria for classifying test stimuli as “old” or “new.” Based on these data, a receiver operating characteristic (ROC) function is generated from the probability of hits (that is, correct identifications of old items) versus that of false alarms (i.e., incorrect identifications of new items as old) across the range of bias levels (see Fig. 1A).

The ROC function typically exhibits two major features that have been differentially associated with recollection and familiarity. First, the ROC curve is asymmetrical such that the hit rate is elevated toward the y-intercept, and a recollection index based on this feature has been associated with high-confidence recollection.^{8,9} Second, the shape of the ROC function is typically curvilinear, and a familiarity index based on the degree of curvature reflects the strength of familiarity,⁸ but also see Ref.¹⁰. Damage to the hippocampus has been associated with loss of the recollective component of the ROC function, reflected in a decrease in the y-intercept, and sparing of the familiarity component, reflected in a normal degree of curvature.^{4,8,9} Furthermore, of particular relevance to cognitive aging, signal detection analyses on aged humans also reveal a pattern of impaired recollection and spared familiarity,^{11,12} and the deficit in recollection has been associated with decreased hippocampal activation.¹¹

In contrast to these studies on episodic recollection, animal models of cognitive aging using rats have focused on spatial memory deficits that suggest a deterioration of hippocampal function.^{7,13} These studies examine learning and memory in animals performing the Morris water maze task and have described age-associated memory impairments highlighted by an impairment when performance requires the use of spatial cues, in contrast with intact memory when performance is guided by non-spatial stimuli.^{14,15} The selective spatial impairment is correlated with decreased hippocampal synaptic densities, weakened synaptic plasticity, decreased cholinergic modulation, and alterations in the spatial firing patterns of hippocampal neurons.^{7,13} While the studies on humans and on animals both suggest age-associated compromise of hippocampal function, the extent to which the impairment in spatial memory in rodents is related to the deficit in episodic recollection in humans is unknown.

We recently addressed this issue by employing a variant of the signal-detection analysis of recognition memory and by comparing spatial and recognition memory performance in young and aged rats.¹⁶ In these analyses, rats initially are presented with a list of 10 stimulus cups filled with clean playground sand, each scented with a different common food spice (e.g., oregano, cinnamon). The odors are selected randomly each day from a pool of 40, and the rat can obtain a food reward from each cup by digging in the sand. Then, following a 15-min memory delay, 20 stimuli, composed of the 10 old odors and 10 new odors (other stimuli from the pool) are sequentially presented in random order. On each test trial, the rat can dig in new test odors to obtain reward or, if the target stimulus is old, can refrain from digging and receive a reward elsewhere. Each day the reward amounts for correct responses to new and old items are selected from among five ratios to obtain different levels of bias toward new or old responses. The data are combined across 4 days of testing on each of the five bias levels to generate an ROC function.

Our previous work has shown that the ROC function of normal young rats has both asymmetrical and curvilinear components, similar to ROCs of humans, suggesting the use of both recollection-like and familiarity-like memory contributions to odor-recognition performance by rats.¹⁷ Furthermore, the ROC function of rats with hippocampal damage loses its asymmetry but remains curvilinear, indicating a selective loss of the contribution from recollection and sparing of familiarity. These findings suggest the hippocampus is critical to recollection in rats, whereas familiarity can be supported by other brain areas, similar to the findings in humans.⁸

Our analyses of aged rats first replicated the well-established finding that 2-year-old Long-Evans rats are impaired in the spatial version of the Morris water maze task¹⁵ and then compared the performance of individual animals in that task to their performance in the odor-recognition task. Our water maze task involves training rats to find an escape platform hidden below the water surface in a constant location within a tank filled with opaque water. On each trial, the rat begins from one of four different starting points; thus, it must learn to navigate to the same location defined by visual cues outside the maze rather than by swimming along a particular path. Performance was measured by a spatial memory index calculated as the average proximity of the rat to the target platform location on probe trials interspersed among training trials in which the escape platform was removed. By this measure, a low spatial memory index reflects memory for the platform location, whereas a high spatial memory index values reflects failure to learn.¹⁵ As found in previous studies, some aged rats were severely impaired in spatial memory, whereas others performed within the range of young control subjects; these rats are designated spatial impaired (SI) and spatial unimpaired (SU), respectively.¹⁶ The distinction between SI and SU groups, as well as a large range of raw scores from all aged and young rats, allowed us to relate variations in spatial-memory performance with performance on the odor-recognition task.

Overall recognition performance, measured as percent correct of all responses, was very modestly impaired in aged rats.¹⁶ Overall recognition performance was not significantly lower in aged than young rats ($F_{(1,27)} = 1.2$; $P = 0.3$), and there were no significant differences in overall recognition-memory performance between the groups of young, SU, and SI rats ($F_{(2,26)} = 1.08$; $P = 0.35$). However, when individual performance on the water maze was taken into consideration, there was a significant linear relationship between spatial memory index scores and overall recognition memory performance ($r^2 = 0.22$; $t_{(27)} = -2.78$; $P = 0.01$). The modest relationship between spatial memory index and overall recognition performance was due, in part, to the high variability of recognition scores by SI rats, leading us to compare high performing and low performing SI rats in subsequent analyses described below.

The results of ROC analyses on these data provided stronger evidence of impairment in recognition memory in aged rats and clarification about the source of variability in performance by SI rats. The ROC function of young control rats was asymmetrical and curvilinear, as observed in our previous study (Fig. 1A). By contrast, the ROC function of aged rats showed a decreased recollection index (lower y-intercept; $F_{(1,27)} = 4.7$, $P = 0.008$) with spared familiarity index (normal curvilinearity; $F_{(1,27)} = 0.65$, $P = 0.43$) (Fig. 1B,C). Thus, as found in humans, aged rats have a selective deficit in recollection with intact familiarity, and these findings are also similar to the pattern of performance in young rats with selective hippocampal damage.¹⁷ Furthermore, the recollection index correlated quite well with the spatial memory index ($r^2 = 0.43$; $t_{(27)} = -4.45$; $P = 0.0001$), indicating a close relationship between recollection-based odor recognition and spatial memory. By contrast, odor-recognition performance based on familiarity was not well correlated with spatial memory index ($r^2 = 0.0001$; $t_{(27)} = 0.08$; $P = 0.94$), suggesting distinct bases of spatial memory and odor familiarity.

Additional analyses compared the performance of the young group with SU and SI groups of aged rats (Fig. 1D–F). The ROC function of SU rats was asymmetric and curvilinear, such that SU rats did not differ from young rats in odor recollection ($t_{(16)} = 1.08$; $P = 0.33$). In sharp contrast, the ROC function of SI rats was fully symmetrical but was curvilinear. Thus, the recollection index of SI rats was substantially decreased compared with that of young rats ($t_{(19)} = 4.15$; $P = 0.0005$) and SU rats ($t_{(17)} = 2.87$; $P = 0.01$), and indeed was not significantly greater than zero ($t_{(10)} = 1.779$, $P = 0.11$), suggesting that recognition was supported solely by familiarity in rats that performed poorly in the spatial memory task. Neither aged group differed from young rats in the familiarity index ($F_{(2,26)} = 0.355$; $P = 0.23$). Thus the impairment in odor recognition is almost entirely limited to the group of aged rats that performed poorly in the water maze, and in that group recollection was virtually absent.

We also compared the ROC functions of SI rats that had performed better with those that had performed worse in overall recognition (percent correct; Fig. 1G–I). These analyses showed that the two subgroups were severely and equivalently impaired in recollection. In contrast, the ROC function of the subgroup that was superior in overall recognition had a very strong curvature and its familiarity index was significantly greater than that of the subgroup with lower overall recognition performance ($t_{(9)} = 3.5$; $P = 0.007$) and that of young rats ($t_{(13)} = 3.06$; $P = 0.009$). Thus a subset of aged rats that are impaired in spatial memory compensate for their impairment through exaggerated use of familiarity as a strategy for odor recognition. This finding parallels the observation in humans that aging is associated with a stronger familiarity index and heightened activation of a cortical area neighboring the hippocampus.¹¹

Combining the findings from all of these analyses, the data show several parallels between cognitive aging in rodents and humans that strengthen the animal model. First, in both spatial and olfactory memory, aged rats show considerable variability in the severity of their spatial and olfactory memory impairments, similar to the pattern of findings on memory in aging humans.¹⁷ Second, the age-associated deficit in odor-recognition memory is isolated to an impairment in episodic recollection, also paralleling the findings on recognition memory in humans.^{11,12,17} Third, some aged rats compensate for their deficit in episodic recollection by over-employing intact familiarity as a basis for recognition, similar to the findings on humans¹¹ (see also Ref. 18). All of these findings support the hypothesis that cognitive aging has a common basis across species.

Neural Mechanisms Supporting Recollection

The present findings indicate a close association between the selective impairments in spatial memory and in odor recollection, suggesting a common underlying neurobiological basis. Here additional findings from animal models using spatial memory provide useful speculation on those mechanisms. This speculation comes from studies on hippocampal “place cells,” principal neurons in the hippocampus that fire reliably when a rat is in a particular location in a familiar environment.⁷ When young rats subsequently explore a novel environment, the patterns of spatial firing of individual hippocampal neurons typically change unpredictably, with some neurons ceasing to fire in the novel environment, others that did not fire in the familiar environment showing spatial firing patterns in the novel environment, and yet others changing the location associated with elevated firing rate. In a series of studies, we found that place cells of SI aged rats often fail to change when the animal is exposed to a novel environment and instead often show the same spatial firing pattern as they did in the familiar environment, and this rigidity of spatial representation predicts the spatial memory impairment in the water maze.⁷ This abnormality has been characterized as a failure in *pattern separation* of the contextual stimuli from the familiar and novel environments and a consequent tendency toward *pattern completion* of the representation of the familiar spatial context.

In the odor-recognition task, the relevant contextual stimuli associated with each odor include the preceding and following odors in the list each day, and the ability to remember the order of odors in a list depends on the hippocampus.¹⁹ In addition, we recently showed that the hippocampus encodes a list of odor stimuli by using a gradually changing temporal context signal.²⁰ It is likely that recollection of odors involves remembering these temporal-contextual features to distinguish odors on the current list from previous appearances of the same odors during earlier testing sessions. Thus, we suggest that a general age-associated deficit in pattern separation may underlie performance impairments in both the spatial and odor memory tasks. Specifically, in the odor-recognition task, a reduction in pattern separation could compromise the animal's ability to distinguish the temporal context of odors in the current list from that of prior appearances of the same odors in earlier lists. The result would be a catastrophic pattern of interference for the hippocampus and a consequent inability to recollect the experience of being presented with a specific odor in the current study list. This argument is speculative, but is consistent with the common observation of inappropriate intrusions of old memories associated with cognitive aging.²¹ The extension of the rodent model into aspects of odor-recognition memory allows for further examination of this and other hypotheses about the neurobiological bases of cognitive aging.

Acknowledgments

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Figure 1.

ROC functions and recollection and familiarity indices for odor-recognition performance in young and aged rats. Parameter estimates ($\pm$ SEM) of the contributions of recollection and familiarity calculated for each ROC function as described in Ref. ¹⁶. (A–C) Young versus all aged rats. (D–F) Aged rats analyzed separately for the group that was unimpaired in spatial memory (SU) and the group that was impaired in spatial memory (SI). (G–I) SI aged rats analyzed separately for the subgroup that had higher overall recognition scores (percentage correct) (SI-High) and the subgroup that had lower overall recognition scores (SI-Low). Reproduced from Reference ¹⁶.