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Teaching old rats new tricks: Age-related impairments in olfactory reversal learning

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Abstract

Recent work suggests that normal aging may be associated with decline in different brain systems. In the present study, young and aged Long-Evans rats were tested in a spatial version of the Morris water maze dependent on medial temporal lobe function and also on an odor discrimination reversal task previously used to investigate orbitofrontal function. Aged rats acquired the odor discrimination problems normally but were impaired in acquiring subsequent reversals of the problems. A subset of the aged rats also exhibited impaired spatial learning in the water maze. There was no correlation between reversal performance and spatial learning in the aged rats, indicating that the reversal learning impairment was not related to decline in medial temporal lobe function. Instead the performance of the aged rats on the odor discrimination task resembled that of young rats with neurotoxic lesions of orbitofrontal cortex. These data indicate that rats show independent decline of different brain systems during normal aging and suggest orbitofrontal cortex as one prefrontal area where changes may be localized for further study.

Keywords: Aging; Rats; Discrimination; Reversal; Orbitofrontal; Olfactory

1. Introduction

The development of a rat model for the effects of aging on hippocampus and the medial temporal lobe system has provided considerable information relevant to understanding cognitive decline in normal aging. This approach has assessed medial temporal lobe function using a standardized spatial version of the Morris water maze in which performance is sensitive to hippocampal lesions in young rats. Repeated experiments have demonstrated that a proportion of aged Long-Evans rats perform poorly in this task relative to controls, exhibiting prolonged and non-spatial search strategies when required to remember the location of a submerged platform relative to distal cues placed around the perimeter of the pool [15]. By providing a standardized index of function, such testing has allowed rigorous examination of the underlying neural substrate to determine the etiology of the age-related decline in medial temporal lobe function [14,17]. Contrary to expectations, these studies indicate that functional decline is not the result of neuronal loss [35,37] but rather is associated with a complex set of alterations including changes in synaptic connectivity and function, gene expression and signal transduction [1,6,7,18, 29,48]. These findings are correlated with deficits in spatial cognition and accompanied by changes in encoding and neural representations in the hippocampus [49,50].

At the same time, additional models are needed to capture the effects of aging on other aspects of cognitive function in humans. For example, normal aging in humans can be associated with poor judgment, perseveration and impulsivity, impaired recall of source information and information for temporal order [8,36,44]. These symptoms of age-related cognitive decline closely resemble, at least in mild form, those found in younger individuals with prefrontal lesions [24,25,32,38,45]. Altered prefrontal function is also evident in functional imaging studies that show age-related declines and changes in blood flow and activation patterns during the performance of certain "prefrontal" tasks [20]. Notably, such prefrontal symptoms often occur in the absence of the declarative memory deficits associated with medial temporal lobe impairment and appear to reflect a differential and somewhat independent decline with aging. For example, when aged subjects were formally evaluated on a battery of neuropsychological tests, impaired perfor-

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mance was accounted for by independent factors related to the assessment of prefrontal or medial temporal lobe function by different groups of tests [19]. Like medial temporal lobe deficits, deficits linked to prefrontal dysfunction appear to occur against a background of preserved neuron number in these areas [30], ruling out this simple explanation for the cognitive decline. As a result, an understanding of the role of prefrontal cortex in the pathology of normal aging is likely to depend heavily on the development of adequate animal models. Such animal models would allow researchers to carefully examine the structural, molecular, and neurophysiological markers associated with the age-related decline as has been done in medial temporal lobe structures.

Although previous work to develop a prefrontal model of normal aging in rats has focused on medial wall, the orbitofrontal region (OFC) within prefrontal cortex may provide a model in rats that closely parallels a homologous region in the primate brain. Neuroanatomical connectivity and key functions determined by lesion and electrophysiological recording studies are remarkably similar between rats and primates [31,33,43]. Importantly this region is less closely related to medial temporal lobe structures than medial wall in the rat, and its role in spatial tasks appears to be limited [11]. Thus age-related deficits that involve OFC would be less prone to contributions from effects of aging on medial temporal lobe structures.

One function that appears to be particularly sensitive to OFC damage is the ability to use information regarding the current incentive value of cues to guide goal-directed or adaptive behavior. Early reports noted that primates with damage to prefrontal cortex [13,23], and OFC in particular [21,26], exhibited impulsive or disinhibited behavior. These symptoms typically result when otherwise appropriate responses are made in inappropriate circumstances and are particularly evident in controlled settings involving extinction or devaluation testing and in rapid reversal learning. For example, both humans [38] and non-human primates [27] with lesions in the orbitofrontal area are able to learn simple discrimination problems normally but exhibit impaired acquisition of those same discrimination problems if the response contingencies associated with the items are subsequently reversed, such that the previously positive item becomes negative and vice versa. Rather than altering their responses to reflect the new contingencies, lesioned subjects continue to perseverate in the old pattern of responding. Although such deficits may be found after damage elsewhere in the brain, reversal learning appears to be particularly sensitive to OFC damage. Recently we have found that rats show a similar deficit on olfactory discriminations and reversals after OFC lesions; rats learn the initial discriminations normally but are impaired in subsequent reversal training [34].

In the present study, we have used this olfactory reversal paradigm to test for cognitive deficits in aged rats. Young and aged rats were characterized on a series of odor discriminations followed by several new problems with reversals after each problem was acquired. The same rats were also tested in the spatial version of the Morris water maze to provide an index of medial temporal lobe function. As discussed above, previous studies have shown that a subpopulation of aged Long-Evans rats is impaired in this task, exhibiting spatial learning scores significantly outside the range of young rats, and this impairment has been related to changes in structure and function in medial temporal lobe structures. In the current study, performance of aged rats in this task was compared to performance in the odor discrimination reversal task.

2. Methods

2.1. Subjects

The subjects consisted of 9 young and 22 aged pathogen-free Long-Evans male rats. Aged rats were obtained as retired breeders at 8–9 months of age from Charles River Laboratories, Wilmington, MA. Young rats were obtained from the same company at the start of the experiment. Young rats were 4 months old at the start of odor discrimination training and 5 months old at the start of water maze testing. Aged rats were 21–22 months old at the start of odor discrimination training and 22–23 months old at the start of water maze testing. Rats were housed individually on a 24-h light/dark cycle with ad libitum access to food and water except during odor discrimination training. During odor discrimination training, the rats continued to have ad libitum access to food but were only allowed access to water for 30–60 min at the end of the day after the training sessions were completed. The health of all subjects during this phase was monitored to ensure adequate hydration. All testing was performed during the light phase of the cycle. During the course of the study, five aged rats died, and data from these rats were excluded from the study. Viral screening and necropsies performed on the remaining 17 aged rats indicated that they were healthy at the end of the study.

2.2. Odor discrimination testing

Odor discrimination testing procedures were similar to those employed by us previously. These procedures were adapted from those developed for olfactory studies by other labs [11,12,46].

2.2.1. Apparatus

Odor discrimination training was conducted using a set of 4 identical operant chambers similar to that described elsewhere [40]. Each operant chamber was constructed of aluminum and measured approximately 18" on each side but with sloping walls narrowing to an area of 12" × 12" at the bottom. An exhaust fan was located on the upper back wall of the operant chamber, and the front wall was hinged to open outward and provide access to the interior of the