# Investigation of Age-Related Cognitive Decline Using Mice as a Model System: Behavioral Correlates

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**Objective:** *With recent advances in molecular genetics, mouse models have been generated for a number of disease states. Recently, the authors and others have begun to examine normal age-related cognitive decline using mice as a model system. In this article, and the companion article that follows, the authors present data intended to better parameterize the aging phenotype in mice and examine the possible underlying neuronal mechanisms with special emphasis on age-related changes in calcium homeostasis.* **Methods:** *Young (4–6-month-old) and aged (22–24-month-old) C57BL/6 mice were analyzed in terms of their spatial learning abilities in the hidden platform version of the Morris water maze and the delay win-shift version of the Olton radial arm maze.* **Results:** *Although aged mice exhibited cognitive impairments in both behavioral tasks used, the extent of impairment differed between the two tasks, which might prove to be advantageous under certain experimental settings.* **Conclusions:** *Like in other areas of biomedical research, mice have become an invaluable research tool in the investigation of learning and memory. It is expected that similar benefits can be realized by developing mouse models for age-related cognitive decline.* (Am J Geriatr Psychiatry 2006; 14:1004–1011)

**Key Words:** Mice, learning and memory, aging, cognition, behavior

Learning and memory impairments, independent of overt pathology such as Alzheimer disease, are considered to be a normal component of aging. It is estimated that approximately 40% of people over the age of 65 experience some sort of age-related cognitive impairment.[1] The exact nature of the underling neuronal changes that give rise to these age-related deficits remains unknown; however, there is mounting evidence that one brain region—the hippocampus—seems to be particularly sensitive to aging and is thought to be responsible, at least in part, for the age-related cognitive decline that occurs during normal aging (for a recent review[2]). This idea gains support from behavioral experiments demonstrating that aged humans,[3] rats,[4] and mice[5] perform poorly in tasks that require spatial learning strategies, a

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function ascribed to the hippocampus, further suggesting age-related impairments in hippocampal function.

At the neuronal level, there are a number of age-related changes that could account for the impairments in hippocampal-dependent learning and memory. These include, but are by no means limited to, structural changes such as atrophy and demyelination, changes in transmitter release or receptor compliment, mitochondrial dysfunction, and oxidative stress (for a review[6]). In addition, as described in the accompanying article,[7] there is mounting evidence that a number of age-related changes in neuronal function may be the result of deregulation of cytosolic free calcium homeostasis (for recent reviews[8,9]).

An important first step in identifying therapeutic targets for the amelioration of age-related cognitive decline is the development of an animal model that possesses the behavioral and neurophysiological attributes of this disease state. Recently, we and others have begun to use mice to study age-related changes in learning and memory as well as neuronal function.[10] Although much of the current literature has used rats in the investigation of cognition and aging, mice offer several advantages over rats. Mice are smaller than rats thereby reducing the housing costs. In addition, mice have relatively short lifespans often reaching active senescence by 18–20 months[11] and therefore are less costly to age. Perhaps most importantly, with recent advances in molecular genetics, mice have been derived with a large number of single gene mutations that affect the cellular substrates of learning and memory.[12,13] With this in mind, we have begun to carry out experiments designed to better parameterize age-related changes in hippocampal learning and memory tasks, and in the companion article, we investigate the putative neuronal substrates of these changes.

## METHODS

### Mice

All mice (C57BL/6Nia) used in the behavioral experiments presented here were obtained from the National Institutes on Aging colony at Harlan Sprague Dawley (Indianapolis, IN). Young animals were 4–6 months of age at the start of the experiments and aged animals were 22–24 months of age. All experiments were conducted with the approval of the University of California, Los Angeles Animal Research Committee of the Chancellor's Office of Protection of Research Subjects under continuous supervision of the campus veterinarian.

### Morris Water Maze

The pool was 1.2 m in diameter and made of polypropylene white plastic. Water temperature was maintained at $28 \pm 1$°C and made opaque with nontoxic white paint (Jazz Liquid Tempera; Van Aken International, Rancho Cucamonga, CA) to hide the escape platform. The Plexiglas platform was 10 cm in diameter. The water surface was 15 cm from the rim of the pool, and the inner wall was kept carefully wiped to eliminate any local cues. The rim of the pool was approximately 1.2 m from the nearest visual cue. The walls of the room were painted white, and each wall had a single salient cluster of cues (i.e., black poster). The room had adjustable indirect illumination. A camera was fixed to the ceiling of the room 1.5 m from the water surface. The camera was connected to a digital tracking device and the tracking information was processed by a desktop PC computer with the HVS Image 2020 water maze software (HVS Image Ltd., Twickenham, Middlesex, U.K).

Before the water maze, the mice were handled for two minutes each day for 10 days. Every training trial began with the animal on the platform for 30 seconds. The mouse was then placed into the water facing the wall of the pool and allowed to search for the platform. The trial ended either when an animal climbed onto the platform or when a maximum of 60 seconds had elapsed. At the end of each trial, the mouse was allowed to rest on the platform for 30 seconds. In a block of trials, the starting position was varied pseudorandomly among six start positions. The platform location remained in the same pool position for a particular mouse for the duration of training, but groups of animals were trained with different platform positions to avoid quadrant biases. Animals were given six trials per day (in blocks of two trials, one-minute intertrial intervals and one-hour interblock intervals) for five days. In between training blocks, animals were returned to their home cage to rest. The time to reach the platform (escape latency), along with swim speed, path length, and so

on, was acquired and analyzed online by the tracking software. A probe trial was administered on day 5, one hour after the last training trial. During the probe tests, the platform was removed from the pool. Animals were started in a position opposite the location of the training platform position and allowed to swim for 60 seconds. For analysis, both the amount of time each mouse spent searching in each pool quadrant and the number of times the mouse crossed the former platform location were measured.

As a control for motivation, swimming ability, and sensory perception required to perform in the spatial version of the water maze, on the day after water maze testing, the mice were run in the visible-platform version of the water maze. They were given six trials in blocks of two trials with one-minute intertrial intervals and a one-hour interblock interval. In this version, a distinct local cue (a black and white stopper top) was fixed to the center of the hidden platform by a stainless steel rod (10 cm tall). Both the position of the marked platform and the start position of the mice were pseudorandomly varied from trial to trial. The start position of the mice and the position of the platform were offset by 45° in the pool so that the mice never started right behind the platform.

### Delay Win-Shift

The apparatus consisted of an eight-arm radial maze for mice purchased from Med Associates (Georgia, VT) and significantly modified. The base of the center octagonal hub and arms were made from white PVC. The center hub included eight clear Plexiglas doors that were operated remotely by the experimenter seated in an adjacent room. The first half of each arm (30 cm) was walled on either side by clear plexiglas with the remaining distance of the arm open except for a small (0.5 cm tall) aluminum rail (we have settled on this configuration after finding that in pilot experiments, mice do not readily enter a completely open arm, and completely enclosing the arms appeared to lack a sufficient response cost). A small ceramic food cup was fixed to the end of each arm. The maze was bolted to a small circular platform and elevated from the floor. Distal cues (posters, cage racks and shelving, and so on) were fixed and remained constant throughout the experiment.

Hippocampal memory was assessed using a win-shift paradigm adapted from Packard.[14] The experiment consisted of a week of pretraining followed by 15 days of training. During the pretraining phase, animals were food-deprived to 85%–90% of their prefood-deprived body weight. During this period, animals were shaped to eat eight reward pellets (20-mg chow pellets) per day from food cups identical to those on the maze. During the first 12 days, training consisted of one session per day with each session being composed of two phases. During the first phase (trial A), four of eight arms were baited. The animal was placed in the center hub, and the doors to these four arms were opened while the remaining four doors were kept closed. The animal was allowed to enter the arms and retrieve the reward pellets until all the pellets were consumed or five minutes had elapsed, at which time the animal was removed from the maze and placed in a holding cage for two minutes during which time the maze was thoroughly cleaned with 70% ethyl alcohol. In the second phase (trial B), the alternate four arms were baited. The animal was returned to the center of the maze and all eight doors were opened. The trial ended when the animal had eaten all four of the reward pellets or five minutes had elapsed. The baiting pattern of the maze was pseudorandom and was different from session to session, as was the order in which the animals are run. During the remaining three days of training (days 13–15), the sessions were identical to the first 12 with the exception that the intertrial delay was expanded to 60 minutes.

An arm entry was scored when the animal reached the final 25% of the arm where the food cup was located. The decision to use this criterion was based on previous experiments[15,16] in which we found that C57BL/6 mice made numerous entries onto the initial segment of the arm without going out onto the arm. This observation was independent of age or genotype. In addition, this measure ensured that we only counted animals that actually visited the food cup, which we considered to be the more conservative measure.

### Statistical Analysis

Two-way analysis of variance (ANOVA) (age and training as factors) with repeated measures was used to analyze the acquisition data from the water maze experiments. Between-group comparisons for the remainder of the water maze data were made using a one-way ANOVA. Selective search strategy in the

water maze was assessed using a single-group t-test with a hypothesized mean of 25%. Data acquired during the delay win-shift experiments was analyzed using a nonparametric Mann-Whitney U (corrected for ties) in Figure 1A. Multiple group comparisons in Figure 1B were made using a Kruskal-Wallis test (corrected for ties) followed by a post hoc comparison using Dunn's test, which corrects for multiple comparison. All comparisons are the result of two-tailed analysis. All data in the figures are presented as means ± standard error of the mean (SEM) and mean ± standard deviation (SD) of the means are detailed in the text for each measure.

## RESULTS

### Morris Water Maze

Spatial learning in the Morris water maze is hippocampus-dependent,[17,18] and performance in this task is sensitive to aging.[19,20] To determine the extent and distribution of age-related impairment in mice, we tested young (N = 13) and aged (N = 13) C57BL/6Nia mice in both the spatial (hidden platform) and cued (visible platform) versions of the Morris water maze (Figure 1). Mice were trained using six trials a day (60-second trials in blocks of two, with a one-minute intertrial interval and a one-hour interblock interval) for 5 days. After the last trial, on day 5, a probe trial was conducted in which the platform was removed and the amount of time the animals spent in each of the four4 quadrants was recorded. On the following day, a visible platform test was given in which animals received six more training trials (as before) with the exception that the platform was clearly marked.

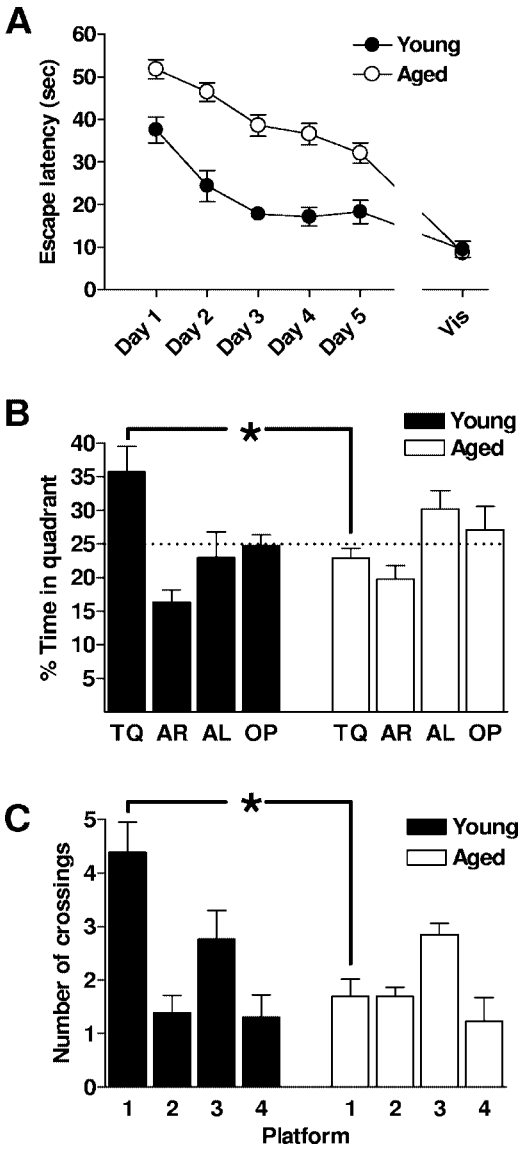
During the training phase (Figure 1A), young animals exhibited a steady decrease in mean escape latency from 37.5 ± 11.0 on day 1 to 18.3 ± 9.7 (mean ± SD). Similarly, escape latencies in the aged animals decreased from 51.8 ± 7.8 on day 1 to 32.1 ± 8.7 (mean ± SD). Statistical analysis using a two-way ANOVA revealed a significant effect of training on both groups (effect of training: $F_{4,96} = 21.5$, $p < 0.0001$). However, there was a significant difference in the escape latencies of the aged animals compared with the young animals (effect of age: $F_{1,24} = 97.6$, $p < 0.0001$). This difference was not the result of a sensory motor deficit, because the escape latencies during the visible platform portion of the experiment were indistinguishable between young (9.47 ± 6.8; mean ± SD) and aged (8.5 ± 3.2; mean ± SD) animals ($F_{1,24} = 0.24$, $p = 0.6307$) (Figure 1A).

During the probe trial (Figure 1B), young animals spent on average significantly more time (35.8 ± 13.3; mean ± SD) in the quadrant in which the platform was previously located (training quadrant [TQ]) than would be expected by chance ($t_{12} = 2.93$, $p = 0.0125$ compared with 25%). On the other hand, in aged animals, the average percent time spent in the TQ (22.9 ± 5.5; mean ± SD) was essentially at chance ($t = -1.38$, $p = 0.1934$ compared with 25%). Furthermore, the amount of time aged animals spent in the TQ was significantly less than that of young animals ($F_{1,24} = 10.5$, $p = 0.0035$). In fact, only one aged animal in 13 spent over 30% of the probe trial in the TQ. Similar results were obtained for the average number of times the animals crossed the place where the platform was located during training (Figure 1C). Aged animals made significantly fewer platform crossings (1.7 ± 1.2 mean ± SD) when compared with young animals (4.4 ± 2.1 mean ± SD; $F_{1,24} = 16.7$, $p = 0.0004$). These results demonstrate that spatial learning in the water maze is impaired in aged C57BL/6 and are consistent with previously published reports.[21–24]

### Radial Arm Maze

The radial maze as first pioneered by Olton[25] exploits rodents' innate foraging behavior. The eight-arm radial maze was originally configured such that food-deprived animals were released from the center hub and allowed to freely traverse the maze until all the rewards were recovered from each of the eight arms that radiated from the center hub. In this version of the task (commonly referred to as the win-shift version), successful foraging is accomplished when animals enter each of the arms only once; a repeat entry to a previously visited arm is considered an error. Animals with hippocampal damage perform poorly in the win-shift paradigm.[26–28] The win-shift paradigm has also been extended to examine the effect of imposing a delay between choices, which forces the animals to forage prospectively using information acquired before the delay to predict the correct arms on the subsequent trial.[29–31] We have examined the performance of young (N = 9) and aged (N = 9) C57BL/6Nia mice in a version of

**FIGURE 1. Aged C57BL/6 Mice Are Impaired in the Spatial Version of the Morris Water Maze**




(A) Average time to reach the escape platform (escape latency) in seconds is plotted for each of the training days (day 1–5) as well as for the visible platform trail, when the platform was clearly marked. (B) Results from probe trial on the day after training. Aged animals (N = 13) spent significantly less time in the quadrant of the pool where the platform was located during training (training quadrant [TQ]) when compared with young animals (N = 13). The dashed line (25%) represents random or "chance" performance. AR: adjacent right; AL: adjacent left; OP: opposite. (C) Similar results were obtained when platform crossings were examined during the probe trial. Aged mice were much less likely to cross the location where the platform was located during training (platform 1 corresponds to the platform in the TQ). Data are represented here as the mean ± standard error of mean. *p <0.05; one-way analysis of variance; see text for standard deviations and detailed statistics.

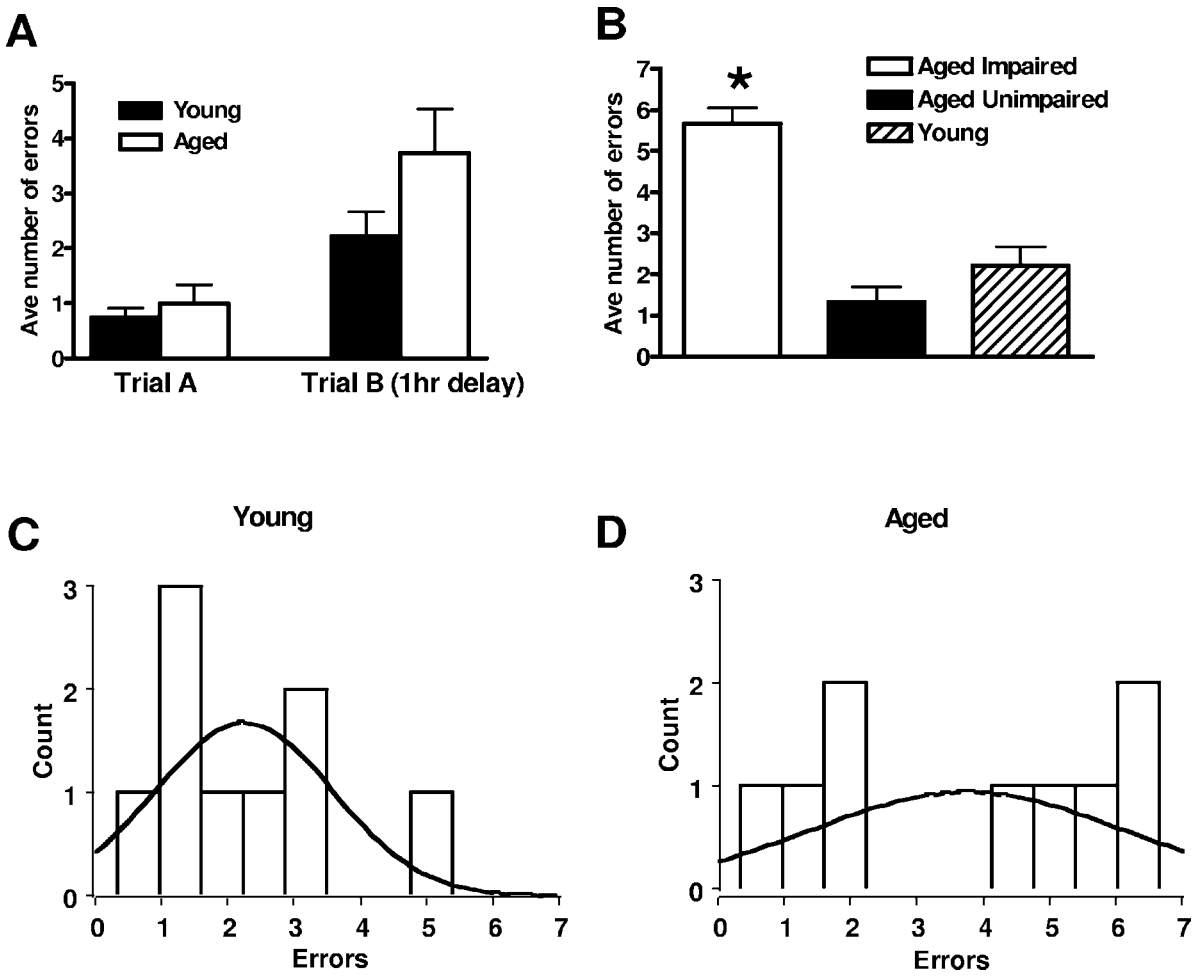
the radial maze (known as delayed win-shift) adapted from Packard[14,32] with slight modification.

Mice were given 12 days of win-shift training and testing on an eight-arm radial maze. Each day consisted of two phases. In the training phase (trial A), four randomly selected arms were baited and open. Mice were given five minutes to retrieve all reward pellets. An error was defined as a reentry into a previously baited arm. After retrieval of the pellets, the mouse was placed in a holding cage, and after a two-minute delay, the mouse was returned for the testing phase (trial B) in which all eight arms were now open, and only the four previously unbaited arms were now baited. An error was defined as a reentry into a previously baited arm either between- or within-phase. After 12 days with a two-minute interphase delay, the number of errors made by aged mice (1.0 ± 1.0; mean ± SD) and young mice (1.3 ± 1.5; mean ± SD) was not significant (U Prime = 42.5; tied p = 0.8589; Mann-Whitney U). Mice were then tested for an additional 3 days with a 60-minute interphase delay.

As shown in Figure 2A, aged animals as a group appear not to be impaired on the long-delay (60-minute) shift phase (3.7 ± 2.4; mean ± SD) compared with young mice (2.2 ± 1.4; mean ± SD) (U Prime = 54.0; tied p = 0.7217; Mann-Whitney U). However, when segregated into aged-impaired (>4 errors) and aged-unimpaired (<4 errors), (Figure 2C, D) based on individual performances,[33] there was a significant difference among age-unimpaired (1.3 ± 0.7; mean ± SD), age-impaired (5.7 ± 0.8; mean ± SD), and young (2.2 ± 1.4; mean ± SD) mice (df = 2, H = 10.0 p = 0.0069; Kruskal-Wallis test) with the aged-impaired making significantly more errors than either the young or age-unimpaired groups (p <0.0001 for both comparisons; Dunn's test).

These results are consistent with the previous observation that individuals within the same cohorts of aged rodents exhibit variable rates of cognitive impairment.[34,35] It is interesting to note that in the delay win-shift task, we observed a segregation in performance with approximately half of the aged animals making more than three errors on trail B after the 60-minute delay (Figure 2D). This segregation into aged-impaired and aged-unimpaired groups has been demonstrated in rats and has been exploited to correlate age-related biomarkers with cognitive performance.[36]

**FIGURE 2. Aged C57BL/6 Mice Are Impaired in the Delay Win-Shift Version of the Olton Radial Arm Maze**




(A) Group data for the last three days on trial A and trial B after a one-hour delay. Average number of errors for young (N = 9) and aged mice (N = 9) was not significantly different on trial A. There was a statistically nonsignificant trend on trial B with the aged animals making on average more errors after the delay. (B) The same results from trial B in (A) are replotted separating aged learners and aged nonlearners. When separated this way, aged nonlearners made significantly more errors than young animals and aged learner groups ([C] and [D]). Histograms of data from trial B for young and aged mice with the number of errors plotted on the x-axis as a function of number of occurrences (count) on the y-axis. Data are represented as the mean ± standard error of mean in (A) and (B). *$p < 0.0001$ (Dunn's test) for comparisons between aged nonlearners and young or aged learner groups. See text for standard deviations and detailed statistics.

## DISCUSSION

There is an emerging consensus in the literature regarding spatial learning ability in aged mice. Most studies[21–24,39] but not all[40] find that aged mice are impaired in the spatial version of the Morris water maze. Data presented here are consistent with this general view. It is worth noting that in the experiments presented here, as well as in previous experiments from our laboratory,[10] we found severe impairments in the spatial version of the water maze in aged C57BL/6 mice. In the experiment reported here, only one of the 13 mice showed any evidence of spatial learning after 5 days of training. These results are in marked contrast to previous studies that report consistent and clear segregation of Long-Evans rats into aged-impaired and aged-unimpaired populations.[36,41] It is also important to note that this catastrophic learning impairment seen in C57BL/6 aged

mice is unlikely the result of sensory/motor impairments, because aged animals do as well as young mice when the platform location is clearly marked (Figure 1A).

The results from the water maze experiments are in contrast with the results obtained using the delay win-shift version of the radial arm maze. In the delay win-shift task, approximately half of the aged mice were significantly impaired when a one-hour delay was imposed with the remaining aged animals performing as well or better than the young mice. As was the case with the water maze, the age-related impairment does not appear to be a function of a nonspecific sensory or motor impairment, because all of the aged animals performed as well as young animals during the first phase (trial A) when the cognitive load was substantially lower. The fact that we did not observe this segregated distribution in the spatial version of the water maze may reflect the inherent difference in dry land and water maze performance in mice as has been previously suggested.[37,38]

Depending on the experimental goal, either task might be appropriate or advantageous. For example, studies designed to test whether a manipulation—either genetic or pharmacologic—ameliorates or reverse age-related cognitive decline, could use the Morris water maze as a measure of cognitive ability, given the large dynamic range that it affords in aged animals. On the other hand, if the experimental design is to rely on specific biomarkers that are to be correlated with age-related changes in cognition, the delay win-shift task would be more suitable given that it allows for comparisons of individuals within a given age group.

Finally, it is worth noting that the impairments that we have described are specific to age-related changes in neuronal function outside of specific pathologies such as Alzheimer disease; mice do not exhibit age-related neuropathologies such as formation of amyloid plaques of fibrillary tangles.[42] Therefore, in addition to the advantages already discussed, the development of transgenic mice that mimic changes known to occur during "normal" aging will likely become increasingly valuable as research tools and will also provide a framework from which future investigations will advance targeted therapies intended to ameliorate cognitive impairments in the elderly.

*This work was supported by NIH grants to AJS (R01 AG17499) and GGM (F32 AG5858). Additional support was provided by the Bank of America Giannini Foundation (GGM).*

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