Influence of Calorie Restriction on Measures of Age-Related Cognitive Decline: Role of Increased Physical Activity

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Controversy exists as to whether lifelong 40% calorie restriction (CR) enhances, has no effect on, or disrupts cognitive function during aging. Here, we report the effects of CR versus ad-lib feeding on cognitive function in male Brown Norway × Fisher344 rats across a range of ages (8–38 months), using two tasks that are differentially sensitive to age-related cognitive decline: object recognition and Morris water maze (MWM). All ages performed equally in object recognition, whereas, as a group, CR rats were impaired. In contrast, there was an age-related impairment in the MWM that was attenuated by CR as measured by time in proximity with and latency to reach the platform. Distance to the platform, a more sensitive measure, was not affected by CR. Finally, CR resulted in an overall increase in physical activity, one of several behavioral confounders to consider in the interpretation of cognitive outcomes in both tasks.

Key Words: Morris water maze—Object recognition—Animal models of aging—Calorie restriction.

LIFELONG calorie restriction (CR) is the only nongenetic intervention that consistently increases life span in mammals including mice, rats, and most likely nonhuman primates (1–3). Indeed, since McCay and colleagues (2) published their initial findings more than 70 years ago, numerous animal studies have shown that CR reduces oxidative damage (4) and lowers inflammation (5), while improving metabolic functioning and energy utilization (6). More recently, attention has focused on the impact of CR on health over the life span, also referred to as “health span” (7–10). This body of work suggests that CR slows the progression of many age-related diseases and/or protects against their development (11).

In the context of brain aging, data suggest that CR is protective against neurotoxicity and neurodegenerative diseases, although controversy exists as to whether CR enhances, has no effect on, or disrupts actual cognitive function during aging. One such procedure that has been widely used to assess learning and memory in aged rodents is the spatial discrimination version of the Morris water maze (MWM). The typical procedure involves placing the rat in a pool, which contains a platform hidden beneath the surface of the water in a fixed location. Over many trials, the rat must learn to make use of distal cues in the environment to triangulate the platform’s location so that it may escape the pool. Several studies have documented the effects of lifelong 40% CR using this procedure, and the results are quite contradictory. In one case, the same investigator has shown that lifelong CR simultaneously improves and confers no benefit to cognitive performance in 24-month-old Brown Norway × Fisher344 (F344×BN) and F344 rats, respectively (12,13).

Several factors may underlie these differential findings. For example, it is well known that rodents placed on a caloric restrictive diet across the life span demonstrate a sparing of function in various motor performance tests and an increase in overall physical activity (14–17). This increase in physical activity may provide the appearance of an improvement in cognitive function in those types of behavioral procedures such as the MWM, which require the animal to locomote through its environment to demonstrate learning and memory performance. Furthermore, few studies have investigated the benefit of CR for cognitive function with very advanced age. Broadening this analysis is significant in the context of longevity experiments that use manipulations like CR because it is presently unclear how far the health-span effects of CR (eg, enhanced performance in memory tasks) might extend into the life span. Thus, it is critical to determine whether enhanced longevity is associated with increases or limitations of cognitive capacity.

Therefore, in the present article, we analyze the appropriateness for using the MWM to study the effects of CR on declining cognitive performance across a range of ages, which extend into later phases of the life span of the F344×BN rat. The F344×BN rat is particularly suitable for these experiments given the lower incidence of age-related pathologies observed in this strain compared with others, therefore minimizing the contribution of these conditions to cognitive outcomes. We also explore the hypothesis that CR-related changes in physical activity may confound interpretation of data collected using the MWM and other cognitive tasks, such as the object recognition.
CR, COGNITION, AND PHYSICAL ACTIVITY

Methods

Animals

Two experiments were conducted using separate sets of male F344xBN rats obtained from the National Institute on Aging (NIA) rodent colony at ages which precede (young: 8 months and middle age: 12–15 months), coincide with (old: 25–27 months), and beyond which (very old: 35–38 months) deficits in functional status are observed in this strain. We make use of this strain as a model of “normal” aging insofar as this strain lives longer than either the Wistar or the F344 in the absence of disease-specific anomalies such as kidney disease and hypertension (20). Thus, this cross strain allows for the dissociation of the overt contribution of disease versus aging to cognitive decline. The first set of rats was originally used for studies to investigate the relationship between biologic markers of skeletal muscle fitness (reported in a separate manuscript) and physical function. This set included all age groups (8–10 rats per group) and, following grip strength assessment, was tested in the object recognition procedure described later. The second set was specifically ordered and used to investigate the relationship between cognition (MWM) and brain fitness (also reported in a separate manuscript). This set included all age groups (8–12 rats per group) with the exception of the 8-month-old rats (young). At NIA, all rats were fed ad libitum (AL; NIH-31 diet) until 14 weeks of age. The CR regimen was initiated by incremental caloric reduction of 10% per week over 4 weeks, reaching full 40% CR by Week 17. The vitamin-fortified NIH-31 diet fed to CR rats provided 60% over 4 weeks, reaching full 40% CR by Week 17. The CR regimen was initiated by incremental caloric reduction of 10% per week until 14 weeks of age. The CR regimen was ordered and used to investigate the relationship between cognition (MWM) and brain fitness (also reported in a separate manuscript) and physical function. This set included all age groups (8–10 rats per group) and, following grip strength assessment, was tested in the object recognition procedure described later. The second set was specifically ordered and used to investigate the relationship between cognition (MWM) and brain fitness (also reported in a separate manuscript). This set included all age groups (8–12 rats per group) with the exception of the 8-month-old rats (young). At NIA, all rats were fed ad libitum (AL; NIH-31 diet) until 14 weeks of age. The CR regimen was initiated by incremental caloric reduction of 10% per week over 4 weeks, reaching full 40% CR by Week 17. The vitamin-fortified NIH-31 diet fed to CR rats provided 60% of the calories and 100% of the vitamins consumed by AL rats. After arriving at our facilities, rats were housed in a specific pathogen-free facility throughout the experiments and were fed this same diet 1 hour prior to the onset of the dark cycle in an attempt to synchronize circadian rhythms to that of AL rats (21–24). These housing facilities are accredited by the American Association for Accreditation of Laboratory Animal Care. Rats were maintained on a 12-hour light and 12-hour dark cycle with water available AL. Rats were assessed on a weekly basis for signs of overt health problems using a standardized form. Measures included checking for sudden decline in body weight, redness around the eyes and nostrils, ruffled coat, open sores on tail, and hunched posture. Rats were also palpated during these assessments to monitor for symptoms of disease and gross tumors.

Cognitive Function

Object recognition.—Apparatus.—Test objects were presented in a square arena (1 × 1 m) with walls 0.46 m high. The arena was an opaque Nalgene tub. The test objects were made of plastic and metal and were too heavy to be displaced by the rats. The objects varied in size, the largest being approximately 15 × 15 × 14 cm and the smallest being approximately 7 × 7 × 12 cm. The rats’ behavior in the arena was monitored by an overhead video camera and later scored by two observers and tested for interrater reliability.

Procedure.—Rats were given one habituation session in which they were allowed to explore the arena, free of objects, for 5 minutes. Testing began the following day. Two test sessions (sample and testing) were given spaced approximately 24 hour apart. In the sample phase, two similar objects were placed in two adjacent corners of the arena approximately 10 cm from the edges. The rat was then placed in the arena, facing away from the objects, and was allowed to explore the arena and objects for 5 minutes. During the testing phase, one of the objects from the “sample” phase was replaced, in a random fashion, with a novel object. As in the sample phase, the rat was then placed in the arena, facing away from the objects, and was allowed to explore the arena and objects for 5 minutes. The basic measurement is the time the rat spent exploring each object. Exploration of an object is defined as directing the nose less than 2 cm to the object and actively exploring it. Turning around or sitting on the object was not considered exploration. A memory index was calculated based on the difference between sample and testing phases. This was defined as ratio of time spent exploring the two objects divided by total time spent exploring both objects during ((Object 1–Object 2)/ [Object 1 + Object 2]). This was used to control for any difference in level of exploration over the various phases of the experiment.

Morris water maze.—Apparatus.—Rats were tested in a black tank, 167 cm in diameter, positioned in a well-lit room containing (when appropriate) an assortment of 2- and 3-dimensional cues. The tank was filled with water (27°C ± 2°C) to a depth of 60 cm and made opaque by the addition of non-toxic, white powder tempera (nonegg based; Palmer Paint Products, Troy, MI) in order to obscure a hidden escape platform. Swimming rats were recorded using an automated tracking system (Ethovision, Noldus, The Netherlands). The tracking system received images from a camera mounted 3 m above the surface of the water and stored the acquired data in a computer connected to the camera.

Procedure.—Cue discrimination.—Rats were first habituated to the pool by allotting 30 seconds free swim and four trials to climb onto a platform from four different directions. Then rats were given three blocks of five trials of cue training for a total of 15 trials. A white flag was attached...
to the platform and the platform was extended 1 cm above the water level. No intentional cues other than the platform and flag were available to the rat during this phase. Latency and path length to escape to the escape platform were measured. If the animal failed to find the visible platform three out of the last five trials, it was excluded from further study in spatial discrimination (see later).

Spatial discrimination.—For spatial discrimination, the escape platform was hidden approximately 1.5 cm beneath the water level and placed in an area of the pool different from the location used for “cue discrimination” training. The platform remained in the same location relative to the distal cues in the room. Training consisted of six blocks of three trials. Intertrial intervals were approximately 10 minutes. On each trial, the rat was placed in the pool from one of four equally spaced start locations (N, S, E, and W) and was given 60 seconds to escape during each trial; if they did not escape within the allotted time, they were gently guided to the platform where they remained for 10 seconds. Start locations were randomized across each rat and trial. The water was stirred between trials to eliminate the use of odor trails as cues. Between each trial and following performance in the swim task, rats were towel dried and returned to their home cages. Ambient heat from ceramic heat lamps was used in the behavioral space to facilitate drying and warming under supervision by lab personnel. Latency to escape (seconds to reach the platform), swimming speed (velocity; centimeters per distance traveled), distance (centimeters traversed in maze), and proximity (% time within 40 cm of the platform) were measured.

Probe trials.—After the fifth block of training, rats received a probe trial where the platform was removed from the pool and the animal was allowed to swim for 60 seconds. A discrimination or “immediate” memory index was computed using the following formula: \[ \frac{t(G) - t(O)}{t(G) + t(O)} \], where \( t(G) \) and \( t(O) \) represent the time in the goal and opposite quadrant, respectively. Time spent in the goal quadrant and proximity was also assessed. Rats were subsequently given the “reminder” sixth block of training following this immediate probe trial, which was not included in assessing learning. The following day, the platform was again removed for a free-swim probe trial to measure 24-hour retention of the task and the memory index, quadrant time, and proximity were recalculated. We have previously used a similar strategy of training and probe trials to examine learning and memory during aging in mice and rats (25–29).

Activity and Strength

Locomotor activity.—A gross measure of locomotor activity was assessed by placing rats in the same apparatus as described in the object location task without any objects present. The same tracking system as described in the MWM experiment was used to assess overall movement in the arena over a 5-minute period of time.

Grip strength.—Forelimb grip strength was determined using an automated grip strength meter (Columbus Instruments, Columbus, OH). The experimenter grasped the rat by the base of the tail and the scruff of the neck and suspended it above a grip ring. After about 3 seconds, the animal was gently lowered toward the grip ring and allowed to grasp the ring with its forepaws. The experimenter quickly lowered the animal’s body to a horizontal position and tugged the animal’s tail until its grasp of the ring was broken, again supporting the body by grasping the scruff of the neck. The mean force in grams was determined with a computerized electronic pull strain gauge that was fitted directly to the grasping ring and was divided by body weight. Average measurements from three successful trials were taken as the final outcome. Successful trials were defined as those in which the animal grasped the ring with both forepaws and pulled the ring without jerking. Failure to exhibit three successful trials resulted in an average of those trials that were successful.

Statistical Analyses

Two-way analyses of variance (ANOVAs) were used to establish main effects (eg, Diet × Age and with blocks for spatial discrimination in the MWM) and interactions. Follow-up Student–Newman–Keuls post hoc comparisons were then employed to determine specific differences. For the grip strength and the object recognition tasks, the set of rats used included young, middle age, old, and very old groups. For the MWM experiments, a second set was used including middle age, old, and very old rats (see description of each cohort in the Animals section).

RESULTS

Grip Strength

The mean grip strength achieved, adjusted to individual body weight, was analyzed using a two-way ANOVA with diet and age as between-subjects factors. Body weight data for all groups are summarized in Table 1. There was a main effect of diet and age (both \( p < .001 \)) such that CR rats outperformed AL rats and younger rats outperformed older rats (young > middle age = old > very old; all \( p < .005 \); Figure 1). This was in agreement with previous reports from our laboratory (30).

Object Recognition

Habituation.—During habituation, time spent moving in the arena was used as a gross indicator of activity level and
assessed using a two-way ANOVA with diet and age as between-subject factors. There was an overall effect of age \((p = .003)\) and diet \((p < .001)\) on activity level, with the CR rats demonstrating overall increases relative to the AL group. Post hoc analyses revealed that the young group differed from all other groups (all \(p\) values <.05) with the exception of the middle age groups which itself did not differ from the old and very old groups (all \(p\) values >.05; Figure 2).

Object exploration.—During the sample and test phases, analyses were performed using a two-way ANOVA with diet and age as between-subject factors on the total time spent exploring both objects and the discrimination ratio. There was a main effect of diet \((p < .001)\) and age \((p = .011)\) on total time spent exploring objects during the sample phase and a main effect of diet \((p = .003)\) on the total time spent exploring objects during the test phase (Figure 3). Post hoc analyses revealed that during the sample and test phases, CR rats spent significantly more time exploring both objects relative to the AL rats \((p < .05)\). However, during the sample phase, only the young and middle age groups spent more time exploring objects relative to the old group (all \(p\) values <.05; with no differences observed with the very old group (all \(p\) values >.05).

Discrimination ratio. —There was a main effect of diet \((p = .047)\) on memory as measured by the discrimination ratio during the testing phase (Figure 4). Overall, AL rats focused more on the novel object relative to the CR rats indicating that, in this task, CR does not improve memory. However, this procedure may not be optimal for examining memory in CR rats due to differences in overall increases in activity levels across all ages with this intervention as described later.

Morris Water Maze

Cue discrimination.—For the cue test, a criterion was established such that any animal that did not find the platform (three out of the last five trials) was eliminated from further statistical analysis. Four AL very old and five CR very old failed to reach this criterion, revealing no effect of diet on sensory deficits observed in the very oldest rats.

<table>
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<th>Table 1. Body Weights (g) ± SEM for Grip Strength</th>
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Note: AL = ad libitum; CR = calorie restriction.
*Main effect of diet: AL > CR; all \(p\) values <.001.
†Effect of age within diet: different from old; all \(p\) values <.01.
‡Effect of age within diet: different from young; all \(p\) values <.01.
measure as all rats maintained the same swimming speed throughout the duration of the experiment (all p values > .05). Because there was no interaction of age and diet with blocks of training, all data were subsequently collapsed across all five blocks of training and analyzed using a two-factor ANOVA with diet and age as between-subject factors. However, all data are presented across blocks, broken down by age and diet effects shown (Figure 5).

For the latency and velocity measures, there were main effects of age and diet (all p values < .05), which most likely reflected differences in activity levels while performing in this task (Figure 5). With regard to diet effects, CR rats demonstrated a decrease in latency (p = .046) to find the platform, which was mediated by an increase in swim speed (p = .003) relative to the AL group. A similar pattern was observed across ages in that the middle age group demonstrated a shorter latency to reach the platform and increased swim speed relative to the old and very old groups (all p values < .05). However, for distance, there was simply a main effect of age (p = .0005). In this case, there was no difference between the middle age and very old groups (p ≤ .05) although old rats demonstrated increased distances relative to both groups (p < .05). We interpret this to show that middle age rats swam faster and reached the platform sooner, while covering shorter distances. However, rats in the old groups swam slower, demonstrated increased latencies and distances to the platform. Very old rats covered less distance, at reduced velocities, and therefore, reached the platform at an increased latency. Therefore, increases in activity and/or improved motor function most likely contribute to the age differences and positive effects observed and dietary manipulation.

In contrast, when proximity to the platform was analyzed as a measure of learning performance, there was a main effect of diet (p = .039) in the absence of a main effect of age (p > .05; Figure 5).

For each measure, separate two-way ANOVAs with diet and age as factors were run for the immediate and 24-hour recall probe trials (Figure 6). There was no effect of diet, in any measure, at either time point (all p values > .05). However, in all three measures, and at both time points, there was an overall main effect of age (all p values < .05). In the immediate test, middle age rats outperformed both old and very old groups (all p values < .05, respectively) and old rats performed better than very old rats (all p values < .05). During the 24-hour recall test, there was also a main effect of age,
although in this case, the middle age rats outperformed the old and very old groups (all p values <.05). These data suggest that across these age ranges, acquisition of a spatial search strategy or long-term recall is impaired on this task and CR confers no benefit.

**Discussion**

Here, we report the effects of lifelong CR on cognitive function in male F344×BN rats across a wide range of ages, including very advanced age (38 months of age). Performance was assessed using two tasks that are sensitive to detecting age-related cognitive decline: object recognition and MWM spatial discrimination. In accordance with the literature, we demonstrate a dissociation across tasks such that all ages performed equally in object recognition, whereas there was progressive age-related impairment on the memory component of the spatial discrimination procedure. In addition, we demonstrate that CR may improve selected parameters of learning (proximity and latency to reach the platform) in the spatial discrimination version of the MWM, although not affecting others such as distance, which is a more sensitive measure in that it is not confounded by performance (swimming speed) in this task. CR also failed to affect memory on this task (as measured in the probe trials) and perhaps actually impaired memory in the object recognition task. Several parameters may explain these effects and are discussed in detail later.

Consistent with our findings, there are published reports suggesting that performance in the object recognition task is not disrupted with age in rodents. For example, two separate research groups (31,32) have compared 6- and 22- to 24-month-old male rats across two different strains: F344 and Wistar rats. Similar procedures were employed in each study such that following a habituation phase, rats were exposed to five salient objects in the testing arena. On subsequent trials, rats experienced both modification of the spatial location and novelty of those objects. Results were consistent across both studies such that older rats, when exposed to a “novel” object, spent the same amount of time exploring that object as did the young rats. However, when confronted with the spatial displacement of a familiar object, old rats explored all objects less, whereas young rats increased exploration of that displaced object.

To our knowledge, there is only one other study currently published in the literature using F344×BN rats in the object recognition procedure (19), and, in contrast to our findings, these investigators report an age-related decline (between 4- and 32-month-old rats). Procedurally, the task is run in exactly the same way with the exception of a 10-hour retention test (24 hours in the current study) and exploration times in the sample and test phases of only 3 minutes compared with 5 minutes in our study. Future studies need to parametrically vary retention test and time allowed for exploring objects across a wider range of ages in order to more fully characterize object recognition memory in the F344×BN rat.
There are no data in the literature regarding the effects of CR on object recognition performance in any strain of rat. In our study, CR rats actually performed more poorly across all ages relative to their AL-fed controls. This was most likely explained by the CR group’s overall increase in physical activity as measured during the habituation phase and by the increased time spent exploring both objects during both the sample and the test phases relative to the AL group. Therefore, rats never habituated to the testing environment and were most likely in a heightened motivational state due to their fasted status.

This motivational status most likely played a similar role with regard to performance of the learning component of the MWM spatial discrimination task. As has been previously reported by us and others (13,25,27,33–38), we observed a progressive age-related increase in latency to reach the platform, which was reversed with CR. The reduced latency to reach the platform in both aged and CR rats may best be explained by the overall increase in swim speed in CR rats. Interestingly, when using proximity as a measure, which is influenced less by swimming speed, age effects were mitigated and CR rats actually performed better than rats in the AL group. The spatial discrimination procedures also allow for the evaluation of acquisition of a spatial search strategy and memory or the ability to retain learned information over time. During the probe trial, we observed a decrease in the memory index, quadrant time, and proximity across age at both the immediate and the 24-hour time points, that was unaffected by CR.

There are a handful of studies that examine the effects of CR on cognitive performance using the MWM in aged rats, with differing results. For example, Markowska and
consideration of these influences is critical to the study of chronic, lifelong food deprivation versus short-term food deprivation on learning and cognition. However, two studies in mice and rats have shown that nutritional supplementation with glucose just prior to cognitive testing facilitates learning (39,40). For example in rats, Yanai and colleagues (41) demonstrated impaired cognition in rats receiving CR on performance in the MWM which was reversed with administration of an intraperitoneal glucose injection 30 minutes prior to testing where no other detrimental effects are observed. Still, whether this is an effect of acute glucose administration on learning and memory or whether this is akin to “satiation” in the context of lifelong CR is still an empirical question. In addition, neither of these studies investigated whether an equalization of physical activity contributed to these effects. Therefore, consideration of these influences is critical to the study of learning and memory with regard to lifelong CR and aging.

A final caveat concerns the nutritional status of the rats at the time of testing. More specifically, it is unclear whether the effects observed using the MWM are dependent on the acute or long-term effects of CR and the timing of feeding (during the light cycle) and how this status contributes to increased physical activity. For example, there is clear evidence in both rats and mice that the AL-feeding cycle acrophase occurs in the middle of the dark cycle (21–24). Therefore, on the one hand, both CR and AL rats could potentially be in a relatively equally short-term fasted state during behavioral tests. On the other hand, it is also the case that CR-maintained rodents fed during the light phase exhibit patterns of motor activity, body temperature, and metabolic energy expenditure that are independent of the light cycle and instead dependent on the feeding time. The result is a full or partial phase shift in motor activity from that of AL-fed rats (21–24). In particular, CR rats exhibit an anticipatory increase in physical activity, temperature, and metabolism before feeding time. In the context of the current studies, we eliminated this confound by feeding our CR rats just prior to the onset of the dark cycle, and our results are very similar to those obtained by Markowska and Savonenko (13) using phase-shifted F344xBN rats.

In light of these findings, there has still never been a study that examines the dissociation between the effects of chronic, lifelong food deprivation versus short-term food deprivation on learning and cognition. However, two studies in mice and rats have shown that nutritional supplementation with glucose just prior to cognitive testing facilitates learning (39,40). For example in rats, Yanai and colleagues (41) demonstrated impaired cognition in rats receiving CR on performance in the MWM which was reversed with administration of an intraperitoneal glucose injection 30 minutes prior to testing where no other detrimental effects are observed. Still, whether this is an effect of acute glucose administration on learning and memory or whether this is akin to “satiation” in the context of lifelong CR is still an empirical question. In addition, neither of these studies investigated whether an equalization of physical activity contributed to these effects. Therefore, consideration of these influences is critical to the study of learning and memory with regard to lifelong CR and aging.

An additional finding of this study is that CR delays declining physical function in advanced aging (38-month-old rats) even in the absence of a ubiquitous effect on cognitive function. This was reflected in the increase in grip strength and overall increase in a time-limited assessment of movement in all CR groups. Notably, there was a decline in strength and movement across ages regardless of diet. Somewhat controversial is the correction of grip strength performance to whole body weight when there are such large differences between AL- and CR-fed rats not only in overall weight but also in terms of body composition (fat vs lean components). In our experiment, we did not directly measure total fat and lean compartments, so that a correction of grip strength based on muscle mass was not possible, although CR rats surely have a reduced lean mass relative to AL-fed rats based on previous studies. However, several studies in humans suggest that declining strength with age is not merely a result of a reduction in lean skeletal muscle mass but may be better predicted by fat mass and/or fat to lean ratio (42–44). Therefore, we use whole body weight as our correction factor. Future studies will include the use of imaging technologies (such as time domain nuclear magnetic resonance) to further investigate the combined and individual contribution of these compartments to performance.

We and others (30,45,46) have previously demonstrated that across a more narrow range of ages, physical function is increased with lifelong CR. This is consistent with our current findings but we further extend this into very advanced aging. What is particularly interesting is that this may be accounted for by the fact that across all ages, again there was an increase in physical activity and/or function in the CR groups. Interestingly, Minor and colleagues (47) have demonstrated a similar dissociation using mice as participants. Therefore, CR may differentially affect the measurement of physical ability and cognitive function as each is currently and conventionally tested, due to increases in physical activity. In addition, these studies demonstrate that although the field focuses on the importance of “biologic mechanisms” that contribute to CR effects on a variety of functional outcomes, “behavioral mechanisms” play just as likely a role in determining health effects outcomes and may have potentially greater clinical application. Finally, we hope this study raises awareness to the complications of studying learning and memory in the context of CR with regard to the genetic, motivational, and nutritional status of rats used as participants and expands the age range across which the effects of lifelong CR are studied and understood.

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