Abstract

Research on the biology of aging seeks to enhance understanding of basic mechanisms and thus support improvements in outcomes throughout the lifespan, including longevity itself, susceptibility to disease, and life-long adaptive capacities. The focus of this review is the use of rats as an animal model of cognitive change during aging, and specifically lessons learned from aging rats in behavioral studies of cognitive processes mediated by specialized neural circuitry. An advantage of this approach is the ability to compare brain aging across species where functional homology exists for specific neural systems; in this article we focus on behavioral assessments that target the functions of the medial temporal lobe and prefrontal cortex. We also take a critical look at studies using calorie restriction (CR) as a well-defined experimental approach to manipulating biological aging. We conclude that the effects of CR on cognitive aging in rats are less well established than commonly assumed, with much less supportive evidence relative to its benefits on longevity and susceptibility to disease, and that more research in this area is necessary.

Key Words: aging; hippocampus; memory impairment; mindspan; neurocognition; orbitofrontal cortex; rat strain; spatial; water maze

Introduction: Lifespan, Healthspan, and Mindspan

A basic tenet in the biology of aging is that the passage of time is an inadequate framework for understanding the life history of an organism or a species. According to this view, remarkable variations in lifespan reflect fundamental differences in the biology of aging across species. Likewise, the biology of aging, rather than the mere passage of time, could be key for understanding individual differences within a species, where chronological age alone is a poor predictor of the length of a life. From a lifespan perspective, then, biology, and specifically genetics, not only controls early development and maturation but also may drive characteristic changes late in life that represent the biological process of aging. Biological endowment could include factors that contribute to senescence as well as those that confer resistance to such processes.

At the same time, inherited endowment interacts with life experiences and environmental exposures in shaping the biology of aging and can accelerate or delay the course of aging; the impact of calorie restriction is an experimentally well-controlled example (Kemnitz 2011, in this issue). Understanding the intersections of gene-environment interactions has become both a great challenge and an enormous opportunity in the field of aging research.

Biological scientists have discovered genetic, pharmaceutical, and environmental treatments that increase the lifespan of laboratory research animals (Kenyon 2010). In this effort, another significant challenge is to disentangle underlying aging processes from morbidities that become increasingly prevalent at older ages. Because growing old is associated with a sharply increased risk for certain diseases, an objective has been to focus on the organism late in life apart from pathological conditions for which aging may be permissive and apart from the cumulative effects of adverse health history and chronic illness. At least this is what (we think) is meant by the term “healthy aging”—that the condition of the individual is representative of underlying aging processes and that aging itself is not a disease.

Although lifespan has been a commonly used index in the field of aging research, “healthspan” is increasingly used to denote the period of life during which the organism is generally healthy and free of serious disease (Sprott 2011, in this issue). The relationship between lifespan and healthspan is complex and not fully explored. Treatments such as calorie restriction can increase lifespan and concomitantly reduce age-related disease (but see Gardner 2005). By contrast, increasing lifespan without prolonging healthspan would have enormous adverse consequences in practice, requiring an ever-growing fraction of society’s resources to treat and care for the disabled elderly. Optimal aging, then, would depend on conditions that both promote long life and compress morbidity to achieve greater healthspan.

We focus in this review on the related topic of “mindspan,” the maintenance of mental abilities over the lifespan. Disorders that impair mental capacities late in life are among the most feared consequences of aging. Dementia, with
Alzheimer’s disease (AD) accounting for the vast majority of cases, exacts a staggering toll on individuals, families, and society (e.g., Fillit and Hill 2005). Because the greatest risk factor for AD is aging itself, research on brain aging may improve understanding of the biological conditions for this devastating late-life disease and eventually offer entry points for compression of this morbidity.

Mindspan has a special place in aging research for other reasons as well. Even in the course of normal aging, independent living hinges on an individual’s ability to adapt successfully. For example, adapting to changes in physical mobility may require problem solving, flexible adjustments, and new routines. Such abilities to adapt can be compromised when cognitive function fails. So mindspan makes a disproportionate contribution to the quality of life for the older individual.

Moreover, the brain is a special case in biology: more genes are expressed there than in all the other body organs combined. So, for the study of late-life biology, the brain presents a complex system with great heterogeneity among its components and networks. Many questions remain, for example, about the special vulnerability or resistance of different types of neurons in the brain and why some neural networks are more prone to failure than others, as appears to be the case in neurocognitive aging.

Finally, the brain’s interface with the environment and experience is uniquely designed to register life history. The property of neural plasticity is powerfully engaged by the brain’s core function of processing information. More than any other system in the body, the brain can reveal much about the influences of environment and experience on late-life outcomes. All of this rich complexity presents a formidable challenge for the scientific study of mindspan.

Animal Models and Neurocognitive Aging: Why Rats?

There are inherent advantages and disadvantages with all animal models and, as for all studies involving animals, it is important to consider the problem under study in choosing models for aging research. Short lifespans (e.g., those of Caenorhabditis elegans and Drosophila melanogaster) are a favorable feature for studies of aging in a relatively limited time frame. Nonhuman primates, by contrast, take decades to grow old. In this discussion we are interested in the basis for cognitive change at older ages using models that can give insight into the experience of aged humans, and thus consider this objective to explain why rats have been the most commonly used model for such research.

Diverse models are used in neuroscience research to study both highly specialized (species-specific) adaptations and neurobiological mechanisms that are more conserved across species. For example, certain molecular and cellular mechanisms of neural plasticity have proven more general than might have been anticipated, spanning from invertebrates to mammalian brains (Kandel 2001). At the level of neural systems analysis, however, studies that are behaviorally relevant to humans have most successfully exploited the use of mammalian models, including rodents. Indeed, remarkable homology exists in the neural systems for a number of complex behavioral functions—conditioned fear comes to mind as an example that translates well across mammalian species with respect to brain circuitry and the conditions that govern learning (LeDoux 2000). For studies of aging that focus on specialized neural systems for cognition, rodents offer models with shorter lifespans than primates but with significant homologies in the organization and function of brain systems of interest.

There is broad consensus that structures of the medial temporal lobe (MTL) are critically involved in memory loss in aged animals from rodents to primates (Rapp 2009); in the following sections, we describe the applicability of rodents for modeling mammalian memory systems in ways that translate successfully to humans. In addition to memory decline, aging is marked by changes in cognitive functions that are ascribed to the prefrontal cortex (PFC). The study of age-related alterations in PFC, focusing on core behavioral functions of specific prefrontal circuitry, is becoming increasingly feasible in rodent models.

Although much research in the cognitive neuroscience of aging has employed rats, mice are more widely used now than in the past. For instance, mice have led the way to new knowledge through the tools of gene targeting, and there is increasing interest in using them to model both normal cognitive processes and disorders of cognition. But the increased use of mice also comes with a challenge: a huge corpus of knowledge about the brain—from connectional neuroanatomy to the encoding in ensembles of neurons—exists for rats without comparably detailed studies in mice. Moreover, experimental psychologists and behavioral neuroscientists have long worked with rats in a rich and deep tradition of research, grounded in behavioral theory and built around carefully controlled paradigms that are less well characterized in mice. In particular, research in rats—far more so than in other rodent species—has yielded the knowledge in cognitive and behavioral neuroscience that underpins the study of aging, and has in recent decades greatly enhanced understanding of the effects of aging on the mind.

Inbred, Hybrid, and Outbred Models

The National Institute on Aging (NIA) supports rodent resources for aging research through a program initiated in 1974 (Sprott 1991). The NIA resource has provided Fischer 344 (F344) rats since inception, possibly accounting for the relatively greater use of this model in aging research even today. Sprague-Dawley rats were initially provided by the NIA but dropped out of favor (Sprott 1991). Three options for aging rats, all genetically defined, are now available under the NIA program: the F344, Brown-Norway (BN), and F1 hybrid of F344 x BN strains.

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1Abbreviations used in this article: CR, calorie restriction; MTL, medial temporal lobe; OFC, orbitofrontal cortex; PFC, prefrontal cortex
Interestingly, initial behavioral models for cognitive functions in aged rats frequently used the outbred Long-Evans strain (Barnes 1979; Barnes et al. 1980; Meaney et al. 1988; Rapp et al. 1987). While the NIA hybrid (F344 x BN) could provide a viable alternative to Long-Evans rats (based on life- and healthspan), programs built on the outbred model have continued (Gallagher et al. 1993; Rowe et al. 1998; Wilson et al. 2006). The use of different inbred and outbred rats in aging research is fortuitous, as comparisons across these strains indicate whether generality exists for findings in models that differ in genetic/biological background.

In addition to a ready supply of aged rats for investigators, the establishment of the NIA rodent resources set new standards for health and husbandry by introducing and advocating for careful practices in the use of barrier breeding and housing facilities in aging research. Even the early studies of health and pathologies for different rat strains from the NIA program continue to be of value.

Pathologies and disabilities in aged rats are particularly important to identify in studies intended to target cognitive change; behavioral performance can be compromised by conditions that have no bearing on cognitive processes. Our resource of outbred Long-Evans rats early on established exclusion criteria based on clinical tests and necropsies to facilitate our focus on healthy aging. Based on experience with testing at different ages, we reduced the age at which we assess “aged” rats from 29 to 24 months old, at which point cognitive change has substantially occurred in the study population and remains relatively stable, while the incidence of pathologies is low enough that few exclusions are necessary.

### Case Studies: Memory and the Medial Temporal Lobe

Evidence from rodents, monkeys, and humans indicates that normal memory for the facts and events of life critically requires the function of a set of interconnected structures in the MTL, including the hippocampus and surrounding parahippocampal regions. Although neurobiological differences exist across species, the organizational and functional principles governing the memory system are sufficiently similar to bridge from laboratory rats to humans. Using rat models, aging research has built on this understanding to study memory across the lifespan.

In an early stream of studies (1980s-1990s), rats at older ages were compared to young adults in tests of spatial cognition to assess hippocampus-dependent learning and memory. On the heels of O’Keefe and Nadel’s (1978) *Hippocampus as a Cognitive Map*, Barnes (1979) described the behavioral effects of aging in a spatial task and concurrently studied synaptic plasticity (in vivo long-term potentiation) in Long-Evans rats, comparing mature adult (10- to 16-month-old) and aged (28- to 34-month-old) subjects. In addition to age-dependent behavioral impairment, behavioral performance was correlated with the ability to modify synaptic efficacy at the input to the hippocampus (perforant path synapses in the dentate gyrus). Barnes and colleagues (1980) also used an analytical approach to define the basis of age-related behavioral impairment in spatial learning and memory. They trained aged (26-month-old) and young adult (9-month-old) Long-Evans rats on a T maze (also called a 3-arm maze) task designed to allow for the use of any one of several memory strategies. When given such options, young and aged rats performed on a par. In probe tests for the strategy used, however, young rats predominantly employed a “place” strategy (remembering the spatial location of the goal) more than the aged rats, while the latter relied on a response strategy (remembering a fixed motor sequence to the goal) more often than their younger counterparts.

The insight that aging disproportionately affects hippocampus-dependent spatial memory has since received broad support across a range of spatial tasks (e.g., circular platform, eight-arm radial maze, Morris water maze). This profile of aging, albeit with variable onset consistent with strain differences in lifespan (e.g., impairment emerging initially by the age of 12 months in F344 [Bizon et al. 2009] but only after 18 months in Long-Evans rats [Bizon and Gallagher 2003; Gallagher, unpublished data]), applies similarly to inbred, hybrid, and outbred strains and is evident in both male and female aged rats (Fischer et al. 1991; Meaney et al. 1991).

### The Morris Water Maze

Because the Morris water maze has been used extensively in aging research with rat models, it deserves some special comment. The first publication on the use of this task in a study of hippocampal function appeared almost 30 years ago (Morris et al. 1982). In the typical “hidden platform” version of the task, rats are trained to find a camouflaged escape platform positioned just below the water surface in a swimming pool. The location of the platform remains constant from trial to trial but the rat’s starting point differs. Because there are no local cues that mark the position of the platform, the rat’s ability to locate it efficiently depends on the animal’s use of a configuration of extramaze cues surrounding the pool. Young adult rats learn to swim directly to the platform within relatively few training trials from any of a number of start locations at the perimeter of the pool.

Although optimal performance in the hidden platform version of the task requires that rats learn the location of the platform, this is not the only learning strategy that can yield improved performance, especially on training trials. Probe trials, when the platform is removed and the search strategy more directly assessed, provide the best analytical assessment of a hippocampal basis for behavioral performance (e.g., compare data in Figures 1 and 3 of Morris et al. 1982). Probe trial analysis is similarly needed to assess the behavioral strategy and cognitive basis for age differences in the water maze and has shown aging effects broadly across rat models such as F344 (Clark et al. 1992; Frick et al. 1995;
Often, animals that are characterized for hippocampus-dependent cognition in the water maze are also tested in a control “cue” learning task. In the same pool as for the hidden platform assessment, the cue task assesses performance with a visible platform; a lack of age difference in performance suggests a cognitive impairment apart from differences in sensorimotor and motivational factors. However, when aged rats are less proficient than young in the cue task, any number of confounding factors could be at play; for example, poor visual acuity could prevent the use of a visible platform to guide performance (and similarly affect use of more distal cues in the hidden platform task). In populations where cue learning differences have been most often reported (e.g., in Sprague-Dawley rats: Spencer et al. 1995; in F344 rats: Clark et al. 1992), loss of visual function is likely to play a role due to greater retinal degeneration in aged albino strains; for instance, Spencer and colleagues (1995) found that all but one (26/27) aged Sprague-Dawley rats that failed in water maze learning had severe retinal degeneration. In order to exclude nonspecific contributions to spatial memory performance, some studies (e.g., Tombaugh et al. 2005) have used cue training to exclude aged rats with such impairment. Aged Long-Evans and F1 F344 × BN hybrid rats, on the other hand, exhibit proficient cue task performance across a spectrum of deficits in hippocampal place learning (Gallagher et al. 1993; Markowska and Savonenko 2002).

In general, behavioral studies of aging that are conducted in a specific neural system framework are more attentive to potential confounds. For example, by limiting analysis of neurophysiology in the hippocampus in behaviorally characterized F344 rats that had intact cue learning, Tombaugh and colleagues (2005) were able to isolate differences in a neurophysiological change at hippocampal CA1 synapses that correlated with behavioral status. If aged rats had been included with peripheral limiting conditions (e.g., blindness), such results might have been obscured. As in all behavioral research targeting a particular cognitive domain, adequate screening for confounding factors is essential.

Nonspatial Tests

Behavioral studies on aging have recently extended the examination of learning and memory functions that depend on the MTL in rodents and in humans to nonspatial domains. A two-process model of recognition memory has shown that, similar to clinical cases of MTL damage, aged humans have a disproportionate loss of recollection with relative sparing of the ability to make recognition judgments based on familiarity (Anderson et al. 2008). Behavioral testing procedures to isolate recollection and familiarity components of recognition performance have been developed for rats, using nonspatial odor cues, and have shown that aged rats with deficits in spatial memory resemble young rats with hippocampal damage: recollection is impaired but familiarity remains intact (Robitsek et al. 2008; Sauvage et al. 2008). Other odor learning tasks have shown effects of aging in rats that have no deficits in odor detection. For example, LaSarge and colleagues (2007) found that the performance of aged F344 rats in water maze spatial learning was consistent with their ability to discriminate among novel odors: rats with impaired water maze performance were similarly impaired in the nonspatial odor learning task, whereas aged cohorts with preserved cognitive function did equally well in both spatial and nonspatial assessments. The presence and severity of hippocampus-dependent spatial memory also correlates with flavor memory in aged Long-Evans rats (Gallagher and Burwell 1989; Rowe et al. 1998). These findings not only extend the effects of aging to a broader spectrum of memory assessments but also implicate age-related dysfunction of the MTL system, as seen in humans with memory loss.

Behavioral assessments of aging conducted in a neural system framework have proven to be a powerful approach that ties cognitive decline to biological changes in aged brains. For capacities that depend on the MTL, studies in behaviorally characterized rats led to the realization that neuron loss was not a basis for cognitive decline. Unbiased stereology demonstrated similar numbers of neurons throughout the MTL system irrespective of age and cognitive status (Rapp and Gallagher 1996; Rapp et al. 2002). Rather than frank neurodegeneration, studies have isolated circuit-specific synaptic loss (Geinisman et al. 1986; Smith et al. 2000) and functional alterations at existing synaptic connections (e.g., Barnes et al. 1997; Nicholson et al. 2004; Tombaugh et al. 2005; Wilson et al. 2005). Those findings have enabled a better understanding of the network properties that become dysfunctional in the memory-impaired aged rat brain (Rosenzweig and Barnes 2003; Wilson et al. 2006).

The work just described illustrates the remarkable impact of studying individual and strain differences in aging outcomes. Long-Evans rats, which exhibit robust and reliable individual differences in cognitive aging, paved the way for identifying closely coupled features of aging in the hippocampal system that align with cognitive age apart from chronological age. Aged rats with spatial memory deficits exhibit striking changes in the hippocampal system that are not present in aged cohorts with preserved cognitive capacity (Nicholson et al. 2004; Smith et al. 2000). Researchers have also reported differences in behavioral status among genetically identical individuals in inbred strains and have used these differences to identify brain changes coupled to degree of cognitive decline (Bizon et al. 2009; Tombaugh et al. 2005). Perhaps this is not too surprising because isogenic individuals can exhibit different phenotypes (e.g., lifespan).

In addition to providing animal models that have relevance to cognitive change during aging in humans, all of
these models have greatly advanced knowledge of the biological basis of neurocognitive aging.

Case Study: Functions of the Prefrontal Cortex

Compared with the range and number of behavioral studies targeting the effects of aging on the MTL, the cognitive functions of PFC have been less extensively studied in aged rats. But recent advances in defining the behavioral functions of PFC systems in the rat are beginning to inform such research. One illustrative case is the role of the orbitofrontal cortex (OFC) in goal-directed behavior and decision making.

Orbitofrontal Cortex Functions

OFC neurons encode outcome expectations, information that can be used to guide actions. These encoding characteristics are present in both rat and monkey OFC, and parallel behavioral deficits occur across those species after OFC damage (Gallagher et al. 1999; Murray et al. 2007; Schoenbaum and Setlow 2001). Neuroimaging data support a similar function for OFC in humans (Gottfried et al. 2003). Thus, notwithstanding differences across species (e.g., in the classic cytoarchitectural criteria used to define prefrontal anatomy in the primate brain), functional homology with primate OFC has set the stage for rat models to further explore the effects of aging on OFC and the behavioral functions it supports (Preuss 1995; Schoenbaum and Setlow 2001).

But studies using paradigms that capture the function of OFC in aging are still relatively rare. In recent work with humans, Bechara and colleagues found impairments in some older adults on a gambling task that models the use of OFC in decision making; like patients with OFC damage, those elderly individuals were unable to adaptively guide their choices based on expected outcomes (Denburg et al. 2005).

The “normal” function of OFC is also credited with a widely observed phenomenon called delay discounting, in which actions can be biased in favor of more immediate rewards rather than deferred rewards even when larger benefits can be gained by waiting. In a recent study (Simon et al. 2010), aged F344 rats maximized outcomes compared to younger adults by an apparent attenuation of discounting.

The role of OFC in guiding action also contributes to “flexibility.” Deficits in reversal learning, for example, are widely reported as a consequence of OFC damage and are seen in human aging. Although the ability to learn a simple discrimina-
prefrontal systems. While ID shifts (e.g., reversal learning) depend on OFC, ED shifts rely on the integrity of other functionally homologous regions of PFC in rats and primates (Birrell and Brown 2000; Dias et al. 1996).

Prefrontal Cortex Functions

The research just described suggests a degree of functional homology between primate dorsolateral PFC and rat medial frontal cortex, as both contribute to ED shift paradigms with susceptibility to age-related loss in that function. Studies of primates and rodents also reveal a corresponding function for these PFC regions in working memory, commonly defined as the ability to maintain (or bring to mind) information that is in current use. Tests of working memory in young adult rats are sensitive to the integrity of medial PFC: after damage to this area, impairments in these rats resemble those of aged rats (Ando and Ohashi 1991; Divac 1971; Kesner 2000). Neurobiological alterations in medial PFC also appear to result in age-related impairments (e.g., Mizoguchi et al. 2009; Ramos et al. 2003).

Based on the existing literature on memory and the MTL, it is difficult to assess whether generality across strains or impairment as a function of age within strain because relatively few studies have focused on the PFC in rodent models of aging. Given the prominence of prefrontal aging in the human population, however, it is likely that more research will focus on rodent models in the future.

A potentially important emerging concept is that aging occurs somewhat independently across the different neurocognitive systems we have reviewed. Reports have described individual differences in aged rats in tasks that are sensitive to PFC function, but those differences (in attentional set shifting, Barense et al. 2002; and in reversal learning, Schoenbaum et al. 2002) were not correlated with cognitive status of MTL function (assessed in both cases in the water maze). Neuropsychological research in humans has similarly suggested independence in the effects of aging on hippocampal and prefrontal systems (Glisky et al. 1995; Robbins et al. 1998). However, test-retest reliability of individual performance in PFC assessments in aged rats has not been examined or established, whereas such reliability has been repeatedly demonstrated in MTL assessments (Colombo et al. 1997; Robitsek et al. 2008). If a behavioral assessment (e.g., reversal learning) does not exhibit robust reliability for individual differences in a PFC domain, the absence of correlation with individual differences across behavioral domains is less interpretable.

Case Study: Calorie Restriction and Neurocognitive Outcomes

Calorie restriction (CR) is known to increase both lifespan and healthspan in a variety of species, including the most commonly studied rat strains (Masoro et al. 1991; Sprott 1997). However, the extent to which it attenuates neurocognitive decline in aged rats is unclear; the research is not extensive and provides equivocal evidence of benefit. This section presents the experimental challenges in conducting such research and a summary of some of the findings.

Behavioral studies on CR in aged rats face several broad challenges. First, the CR regimen itself makes it difficult to use commonly employed methods to motivate behavior in studies of cognitive function (i.e., food as a reward in hungry rats). How well is motivation equated in comparison groups with a long history of dietary difference? In addition to the question of whether rats are in a comparable state of deprivation (i.e., hunger), food itself may have different incentive value in the comparison groups. For motivating performance, thirst/water reward might avoid some of the issues surrounding the use of food. At least a comparable restriction regimen could be used for the comparison groups. It seems surprising then that, to the best of our knowledge, no such studies have been reported.

Investigators have described various approaches in studies using food. In tests of learning and memory, CR rats have been shifted to ad lib feeding prior to experiments (Beatty et al. 1987), or ad lib rats have been placed on different schedules of food deprivation while CR rats are maintained on their usual regimen (Stewart et al. 1989). Assessments of rats at different ages under such conditions show no substantial evidence for a benefit of CR in aged rats in spatial learning on the eight-arm radial maze (Stewart et al. 1989 using F344 rats; Bond et al. 1989 with Wistar rats; and Beatty et al. 1987 with Sprague-Dawley rats; but see Goodrick 1984 with Wistar rats in a 14-unit T maze task).

The assessment of spatial cognition in the water maze has been quite widely used in CR studies, but the findings for a benefit of CR are again not compelling. In one series of studies with the same set of protocols, the benefit of CR on spatial cognition was strain specific: CR treatment had no effect in either F344 (Markowska 1999) or BN rats (Markowska and Savonenko 2002), but improved performance in aged F1 F344 × BN rats (Markowska and Savonenko 2002). Because CR is not strain specific across these rat models with respect to effects on life- and healthspan, it is somewhat surprising that cognitive benefits are seen only in the F1 F344 × BN hybrid. Stewart and colleagues (1989) reported a small improvement in the water maze task in CR-treated aged F344 rats but only on training trial measures (see below).

Notwithstanding the positive results reported by Markowska and Savonenko (2002), other studies using the F1 hybrid rats have shown little or no CR-related protection that could be attributable to a benefit on hippocampus-dependent cognitive function (Carter et al. 2009; Fitting et al. 2008). The studies reported that aged CR rats exhibited somewhat improved performance on training trials but were not significantly better in measures of probe trial performance. Probe trials are important for assessing the cognitive basis of performance; young rats with hippocampal damage fail to show spatial bias on probes even though they show considerable improvement in training trial measures. A number of relatively inflexible cue-based strategies (such as swimming
a fixed distance from the wall) contribute to changes in such measures. So the evidence is not compelling to support a reliable effect of CR on cognition in the setting where it has been assessed most often.

The reliance on a relatively narrow range of cognitive assessments to study the effects of CR on neurocognitive aging should temper any conclusions about its efficacy. To the extent that impairments in age-related cognition extend across a range of assessments that cohere around MTL function, as reviewed in the section above on memory, one might expect that a benefit of CR would similarly be observed across a range of such tasks. Relatively little research has addressed this question but, at least in the case of F344 rats, that expectation is not met. In addition to the challenge of using appetitive tasks, performance factors could also play a role in other commonly used behavioral settings. Because poor thermoregulation can adversely affect water maze performance (Lindner and Gribkoff 1991), it is possible that body weight differences in CR aged rats could make those animals more subject to debilitation, offsetting other possible benefits. Alternatively, in a nondebilitating range of water temperatures, differences in lean body mass might factor into motivational differences, boosting performance in CR animals.

Evidence from rodent studies of neurocognitive aging points to independent processes across neural systems that serve different cognitive functions, but because most behavioral studies have focused on MTL function it is premature to conclude whether CR is of benefit as there have been few assessments of different cognitive functions. It is also critical to note that emerging evidence indicates that mediators of CR differ depending on the CR regimen (Greer and Brunet 2009). Thus effects of CR on neurocognitive aging could depend on the CR paradigm, which has received little systematic attention in behavioral studies.

In light of the resources dedicated to CR as a well-defined experimental treatment in the study of aging, and much emerging physiological data concerning its mediation, additional research on neurocognitive aging is certainly warranted.

**Conclusion**

Rats have been extensively used as a laboratory animal model of aging in behavioral studies of cognitive processes. Such research has relied on the widespread use of inbred F344 rats as well as other genetically defined (F1 hybrids) and outbred rat populations. Commonalities in age-related deficits tied to the function of the MTL, including the hippocampus, are observed across rat strains and resemble prominent features of neurocognitive aging in humans.

Far fewer studies using rats have focused on behavioral capacities that depend on PFC, although validated behavioral assessments that capture PFC functions in rats are emerging. Because PFC is strongly implicated in cognitive change in older populations, future research on PFC using rat models is likely. Somewhat surprisingly, we found little systematic evidence of cognitive benefit in studies of older rats maintained on CR. While changes in other endpoints such as lifespan and pathologies have demonstrated robust effects, the endpoints in studies of cognitive function present certain challenges that are often unaddressed in behavioral research comparing CR and ad lib–fed rats. We suggest that further research on CR and cognition is necessary to determine the benefit, or lack thereof, in aging rats.

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