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# Social housing protects against age-related working memory decline independently of physical enrichment in rats

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ABSTRACT

Longitudinal human studies suggest that as we age, sociality provides protective benefits against cognitive decline. However, little is known about the underlying neural mechanisms. Rodent studies, which are ideal for studying cognition, fail to examine the independent effects of social housing while controlling for physical enrichment in all groups. In this study, rats were socially housed or nonsocially housed throughout their lifespan and tested in the radial arm maze to measure working memory (WM) and reference memory longitudinally at 3 ages. In old age, exclusively, socially housed rats made significantly less WM errors than nonsocially housed rats, while reference memory errors did not differ between groups at any age. Anxiety, as assessed behaviorally and physiologically, could not account for the observed differences in WM. These data provide the first evidence that social enrichment alone can prevent age-related WM deficits in spite of the effects of practice seen in longitudinal designs. Importantly, our model will facilitate future investigations into the mechanisms underlying the neuroprotective benefits of sociability in old age.

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## 1. Introduction

As human life expectancy rises, it is more important than ever to understand how normal aging affects cognition and how environmental factors impact these age-related cognitive changes. It is well established that cognitive functions, such as memory, deteriorate in normal aging (Harada et al., 2013; Kirova et al., 2015; Murman, 2015) and that environmental factors such as education, exercise, and diet can attenuate this decline (Barnes, 2015; Mora, 2013; Patel, 2012; Valls-Pedret et al., 2015; Vemuri et al., 2014). These effects have been replicated extensively in animal models, often using working memory (WM) and reference memory (RM) as measures of cognitive health (Albeck et al., 2006; Algeri, S. et al., 1991; Andres-Lacueva et al., 2005; Bennett et al., 2006; Frick and Benoit, 2010; Frick and Fernandez, 2003; Frick et al., 2003; Harati et al., 2011; Harburger et al., 2007a,b; Leal-Galicia et al., 2008; Markowska and Savonenko, 2002; Pitsikas and Algeri, 1992; Pitsikas et al., 1991). Throughout this literature, social engagement has emerged as one of the lifestyle factors that affect how cognition is altered with age. However, although the effects of acute social isolation have been studied extensively (An et al., 2017; Grigoryan et al., 2010; Huang et al., 2011; Leser and Wagner, 2015; Okudan and Belviranli, 2017; Pisu et al., 2011; Quan et al., 2010; Shao et al., 2015; Wongwitdecha and Marsden, 1996a,b; Yusufishaq and Rosenkranz, 2013), the independent effects of social housing in the presence of other forms of enrichment is largely understudied.

Extensive human evidence shows that sociability in old age has positive effects on cognition (Berkman, 2000; Cohen and Janicki-Deverts, 2009; Huxhold et al., 2014; Krause, 2007; Menec, 2003; Rowe and Kahn, 1997). Several longitudinal human studies, for instance, use baseline cognitive measurements in midlife (50–60s) and compare them to observations 2–20 years later (Barnes et al., 2004; Holtzman et al., 2004; Kats et al., 2016; Zuelsdorff et al., 2017). Overall, they find that having greater social resources correlates with cognitive benefits in midlife to older age when controlling for multiple factors such as race, socioeconomic status, baseline cognitive ability, physical activity, and medical conditions. These studies are invaluable clinically but are limited by confounding variables such as culture, upbringing, and other experiences, and by lack of data at younger ages. In addition, these epidemiological studies do not provide a model for investigating the neural underpinnings of memory decline.

Rodents, like humans, exhibit age-related memory decline in several domains including spatial learning, RM, and WM (Barnes,

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[1] VLT conceived and designed experiments, oversaw data analysis, wrote and edited manuscript; TBW collected and analyzed data, and edited manuscript; VRHM analyzed data and wrote manuscript. Nonstandard abbreviations: socially housed (SH), nonsocially housed (NSH), goal box (GB).

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1979; Barnes et al., 1980; Beatty et al., 1985; Bierley et al., 1986; Bizon et al., 2009; Caprioli et al., 1991; Chrobak et al., 1995; Dellu et al., 1997; Frick et al., 1995; Gallagher et al., 1993; Kadar et al., 1990; Lindner et al., 1992; Rapp et al., 1987; Rowe et al., 1998; Wyss et al., 2000) and have been instrumental in translational fields of learning and memory. It is also well established that environmental enrichment (EE) both prevents and rescues these age-related impairments (Bennett et al., 2006; Frick and Benoit, 2010; Frick et al., 2003; Frick and Fernandez, 2003; Harati et al., 2011; Harburger et al., 2007a,b; Leal-Galicia et al., 2008; Mora, 2013; Patel, 2012). However, because EE typically includes both physical and social components, the degree to which social housing alone contributes to these effects is unknown (Frick et al., 2003; Frick and Fernandez, 2003; Harburger et al., 2007a). Although it is clear that rats, like humans, display complex social structures (Barnett, 1975; Wang et al., 2014) and are ideal for studying sociality in old age, the effects of social housing alone on age-related cognitive decline have yet to been explored. To our knowledge, no other study has investigated the independent effects of social housing on age-related decline while controlling for other types of enrichment, thus teasing apart the social and physical components of EE.

Another consideration for the present study is that most of the work on age-related cognitive decline has been done using cross-sectional designs. Although valuable and robust, these studies may not be directly relevant to the human experience. In human aging populations, cognitive functions decline even on tasks for which individuals may have lifetime experience. In rodent cross-sectional studies, however, aged rats are compared to young controls on a task that they are both experiencing for the first time. This is more akin to presenting an entirely new task to an elderly person rather than observing how their performance on particular tasks declines over time. Because there is evidence that age-related cognitive decline is less pronounced when subjects have had previous experience (Algeri et al., 1991; Dellu et al., 1997; Matzel et al., 2011), a longitudinal study provides enhanced sensitivity and power when assessing age-related decline (Caprioli et al., 1991; Dellu et al., 1997). In addition, a repeated measures design allows for a more in-depth study of the higher individual variability in aging populations (Fischer et al., 1992; Frick et al., 1995; Gallagher and Burwell, 1989; Rapp and Amaral, 1992). Thus, a longitudinal approach provides a valuable model for human cognitive decline because it takes experience and lifelong individual variability into account.

Two types of memory systems that suffer considerably in normal aging are WM and RM, with WM being one of the first memory systems to be compromised (Dudchenko, 2004; Frick et al., 1995). WM is a limited capacity system that holds short-term information in support of an individual task, whereas RM holds long-term memories acquired with repeated exposure to a certain task. These age-related impairments, particularly in WM, are disruptive to overall quality of life because they can appear as early as middle age and are observed in both spatial and nonspatial domains (Bizon et al., 2009; Bopp and Verhaeghen, 2005; Frick et al., 1995; Kadar et al., 1990; Lester et al., 2017; Lindner et al., 1992; Pitsikas and Algeri, 1992; Wang et al., 2011; Wyss et al., 2000). Identifying how specific lifestyle factors impact WM is imperative, especially considering that WM disruptions may be predictive of disease-related decline (Summers and Saunders, 2012) and are thought to be a mechanism for decline in higher order cognition (Bopp and Verhaeghen, 2005; Salthouse, 1994; Salthouse et al., 1991). Although WM and RM are known to decline with age, the extent to which sociality alone prevents this decline is unknown.

In this study, we assessed the effects of long-term, sustained social housing on WM and RM using the radial arm maze (RAM). Because there is evidence that anxiety levels are correlated with cognitive decline (Lupien et al., 2009; McEwen and Sapolsky, 1995) and that isolation causes anxiety (Ago et al., 2014; Fone and Porkess, 2008), we also explored anxiety measures in the open field test (OFT) and in the elevated zero maze (EZM). Rats were socially housed (SH) in a large group colony and compared to nonsocially housed (NSH) rats at 3 time points in their lifetime; late adulthood (10 months), middle age (16 months), and old age (23 months). Physical enrichment, including housing in a large multilevel cage, extensive handling, and access to self-directed exercise, was provided for both groups. We hypothesized that performance on the RAM would improve in middle age due to experience and then decline in old age for NSH rats but not for SH rats. Although many studies have explored aging and cognition in rats, to our knowledge, we present the first longitudinal assessment of housing rats socially versus nonsocially in WM and RM tasks.

## 2. Materials and methods

### 2.1. Subjects and housing

Twenty male Long-Evans rats (*Rattus norvegicus*) arrived from Charles River Laboratories on postnatal day (PND) 21, and it was reported that all animals came from separate litters. On arrival, rats were randomly assigned to one of 2 groups: 10 rats were SH in one cage, and 10 were NSH in individual cages. One SH rat died of natural causes (PND 264), leaving 9 rats in the SH group. Housing for both groups consisted of large, wire-mesh metal cages (Ferret Nation, Amazon) and incorporated physical components of EE such as platforms, running wheels, tunnels, and chew toys. SH rats had constant access to all 8 other cage mates in one large cage (36 × 24 ×63 in.), whereas NSH were housed in individual cages (17 × 12.75× 24 in.). Subjects had access to water *ad libitum*, and rat chow (LabDiet, St. Louis, MO) was provided daily. Chow rations of 90% free-feeding weight were administered following testing each day. Rats in both housing groups were extensively handled throughout their lifetime. At the time of testing, subjects were not experimentally naïve because they were part of a larger study and participated in unrelated behavioral experiments, including memory and spatial navigation tasks. All procedures described in the present study were approved by the Institutional Animal Care and Use Committee of Providence College.

### 2.2. Behavioral tasks

#### 2.2.1. Radial arm maze

The RAM apparatus consists of 8 arms radiating outward from a central platform (Noldus Technologies, Sturbridge, MA; parts from Med Associates, Fairfax, VA). Each arm is surrounded by 3 Plexiglas walls that confine subjects during testing and facilitate video tracking. Eight automated pellet dispensers were connected to troughs at the end of each arm where pellets (45 mg) could be given. Automated guillotine doors separated each arm from the central platform. All automated programming and video tracking was completed using Ethovision software (Noldus Technologies, Sturbridge, MA).

Within each age point, subjects received 15 daily sessions. Testing occurred in late adulthood (adult), middle age (middle), and old age (aged) on PND 308-325, PND 475-493, and PND 699-717, respectively. For all 3 ages, the same 4 arms were always baited (arms 1, 3, 5, 8), and 4 were never baited (2, 4, 6, 7); baited and nonbaited arms are always referred to as correct and incorrect locations, respectively. At the start of each session, subjects were placed in the enclosed central platform for 10 seconds, after which, all doors opened simultaneously. Once the subject made a choice (i.e., traveled halfway down an arm and whole body was out of the central platform), the doors leading to the other 7 arms were closed.

A trial was complete when the subject returned to the central platform; all doors were closed for a 10-second intertrial interval, and then all doors were opened once again. Within sessions, subjects were rewarded only on the first entry to a correct, baited location and never during revisits to a correct location or any visit to incorrect locations. Sessions were considered complete after the subject chose all 4 correct arms, entered 16 total arms, or 5 minutes elapsed, whichever occurred first. The apparatus was cleaned with 70% isopropyl alcohol between subjects.

Before testing at all age points, rats were habituated to the maze to eliminate potential differences in baseline exploratory behavior between SH and NSH rats (Fig. S2). Subjects were provided with several extra-maze cues: they included incidental features of the testing room including a table, computer, door, and so forth, as well as added cues of shapes drawn on large whiteboards that surrounded 2 opposite sides of the maze. Guillotine doors were removed from the apparatus, and rats were free to explore all arms for 5 minutes. In adulthood, habituation was conducted for 5 days before the start of testing; four sessions with no rewards and one session with a food reward at the end of each of the 8 arms. In middle and old age, rats were habituated with no reward for one session and with reward for one session. Arm entries were manually recorded by the experimenter, and t-tests were used to ensure that total arm entries were equal between groups on the last day of habituation.

#### 2.2.2. Open field test

Within each age point, rats received one session of the OFT. Testing occurred in adulthood, middle age, and old aged rats on PND 339, 560, and 766, respectively. Testing occurred inside a square, open-topped wooden box (81 × 81 × 51 cm) sealed with black waterproof paint. Rats were individually tested on one session during which they were allowed to freely explore the arena for 5 minutes. To initiate a trial, subjects were placed along a wall of the apparatus and never forced into the center area by experimenters. In this task, elevated thigmotaxis (i.e., spending more time near the walled areas) and longer latencies to enter the center of the arena indicate increased anxiety.

#### 2.2.3. Elevated zero maze

Within each age point, rats received one session of the EZM. Testing occurred in adulthood, middle aged, and aged rats on PND 174, 464, and 689, respectively. The EZM (122 cm diameter, 51 cm height off ground) was divided into 4 sections; 2 walled and 2 open. Rats were tested on one session in which they could freely explore the open and walled sections of the maze for 5 minutes. In this task, longer times spent in closed areas and longer latencies to enter the open areas indicate increased anxiety.

### 2.3. Corticosterone measurements

Corticosterone levels were analyzed at time of culling as a measure of overall stress. Trunk blood was collected and allowed to clot for 30 minutes at room temperature. The clot was removed by centrifugation and the supernatant stored at −80 °C. Serum was later thawed at room temperature, and corticosterone levels were measured by ELISA. Procedures were completed according to the commercial protocol provided by the Mouse/Rat Corticosterone ELISA Kit (ALPCO).

### 2.4. Data analysis

For the RAM, 3 measures were recorded: WM errors (i.e., within-session re-entries to a correct location), RM errors (i.e., any entry to an incorrect location), and total arm entries. For OFT, the arena was divided into a 4 × 4 grid, and time spent in the 4 center squares was recorded, as well as latency to enter the center. For EZM, time spent and latency to enter the open area were recorded. Repeated-measures analysis of variance tests were performed for each measure using housing group as the between-subject variable and age as the within-subject variable. Post hoc pairwise comparisons using the Bonferroni correction were used to follow up on significant effects of age. When appropriate, one-way ANOVAs were used to follow up on significant age-by-group interactions. In these cases, we compared SH to NSH within each of the 3 age points. All tests were considered statistically significant at $p < 0.05$.

## 3. Results

### 3.1. Cognition in the RAM

#### 3.1.1. Social housing protected against age-related WM decline

WM errors were assessed in SH versus NSH rats on the RAM at 3 time points; adulthood, middle age, and old age (Figs. 1 and 2A). An interaction of age-by-group ($F_{2,34} = 4.086$, $p = 0.026$), revealed that performance across ages depended on housing conditions. Post hoc one-way ANOVAs for each age showed that the SH group committed less WM errors than the NSH group in old age ($F_{1,17} = 6.696$, $p = 0.019$) but not in adulthood ($p = 0.598$) or middle age ($p = 0.311$). This indicates that housing conditions influenced performance in old age but not in adulthood or middle age. No main effect of group was observed overall ($p = 0.545$). An overall main effect of age ($F_{2,34} = 7.824$, $p = 0.002$), followed by post hoc pairwise comparisons, indicated that all rats made less WM errors in middle age compared to adulthood ($p = 0.007$), but then made more errors in old age compared to middle age ($p = 0.003$). WM errors in old age were equal to those in adulthood ($p = 1.00$). Taken together, these data indicate that when rats performed a familiar task in middle age, they made less WM errors compared to late adulthood regardless of housing conditions. In old age, however, rats housed nonsocially committed more WM errors compared to rats housed socially and compared to their own performance in middle age.

#### 3.1.2. Housing conditions did not affect RM at any age

RM errors in the RAM were also analyzed across the 3 ages (Fig. 2B). Similar to WM errors, RM errors for all rats decreased from adulthood to middle age and then increased from middle age to old age. This is evidenced by a main effect of age ($F_{2,34} = 39.911$, $p = 0.000$) and post hoc pairwise comparisons of adulthood versus middle age ($p = 0.000$) and middle age versus old age ($p = 0.000$). RM errors were significantly higher in old age than in adulthood ($p = 0.012$). Unlike WM, RM errors showed no group ($p = 0.368$) or age-by-group ($p = 0.893$) effects, indicating that performance was not influenced by housing conditions. These data indicate that RM for a familiar task improves in middle age but then declines in old age. Unlike WM, however, housing has no effect on RM performance at any age.

### 3.2. Housing conditions did not affect arm entries in RAM

Finally, total arm entries in the RAM were analyzed to ensure that exploratory behavior did not differ between the 2 housing groups (Fig. 2C). Indeed, no group ($p = 0.748$) or age-by-group effects ($p = 0.592$) were found in an overall repeated-measures analysis of variance test. A main effect of age ($F_{2,\ 34} = 37.247$, $p = 0.000$), followed by post hoc pairwise comparisons, showed that total arm entries for all rats decreased from adulthood to middle age ($p = 0.000$) and then increased from middle age to old age ($p = 0.000$). Arm entries were also significantly higher in old age compared to adulthood ($p = 0.019$). Thus, like WM and RM errors,

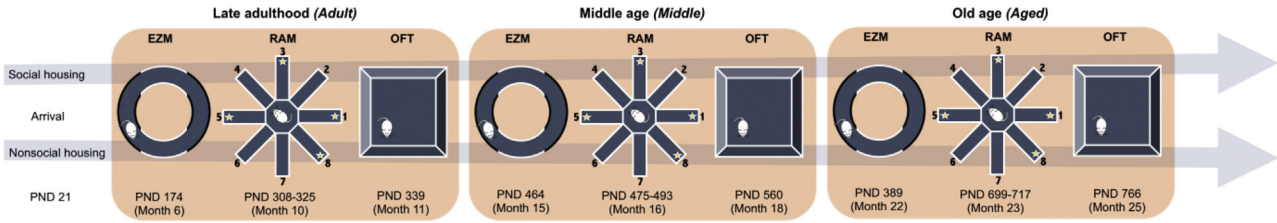


**Fig. 1.** Experimental design and timeline. Rats were maintained in socially housed (SH) or nonsocially housed (NSH) conditions from postweaning to old age. The elevated zero maze (EZM), radial arm maze (RAM), and open field test (OFT) were conducted in 3 ages. White lines indicate walls and black lines indicate open areas. In the radial arm maze (RAM), stars indicate correct arm locations.

total arm entries decreased in middle age compared to adulthood and then increased in old age. Social housing had no effect on total arm entries.

### 3.3. Measures of anxiety

#### 3.3.1. Social housing increased time in center of OFT in old age but did not affect latency to center

For time-in-center, an overall effect of age-by-group ($F_{2,34}$ = 25.008, $p$ = 0.000) followed by post hoc one-way ANOVAs revealed that the SH group spent more time exploring the center of the maze than the NSH group in old age ($F_{1,18}$ = 39.118, $p$ = 0.000) but not in adulthood ($p$ = 0.409) or middle age ($p$ = 0.815) (Fig. 3A). A main effect of age ($F_{2,34}$ = 76.629, $p$ = 0.000) followed by pairwise comparisons also indicated that center exploration for both groups decreased significantly from adulthood to middle age ($p$ = 0.024) and then increased in old age compared to both middle age ($p$ = 0.000) and adulthood ($p$ = 0.000). Unlike time-in-center, latency-to-center did not differ between housing groups ($p$ = 0.957) or age-by-group ($p$ = 0.164), and declined steadily across ages for all rats (Fig. 3B). This decline was confirmed by a main effect of age ($F_{2,34}$ = 31.998, $p$ = 0.000) and by pairwise comparisons showing that latency for both groups decreased significantly from adulthood to middle age ($p$ = 0.003) and decreased again in old age compared to both middle age ($p$ = 0.001) and adulthood ($p$ = 0.000). Thus, time-in-center decreased for both groups in middle age compared to late adulthood, and then increased in old age but more so for SH rats compared to NSH rats. However, latency-to-center declined steadily across ages for both housing groups.

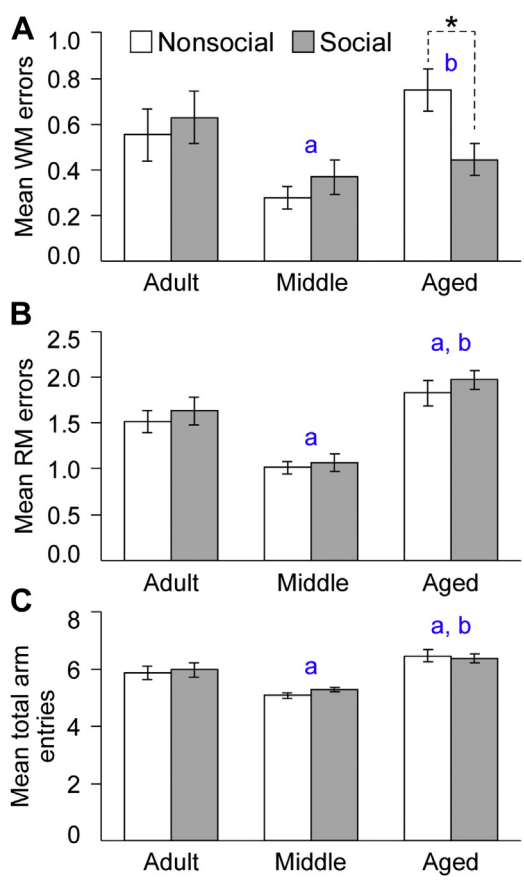


**Fig. 2.** Performance on the radial arm maze (RAM) across ages. (A) Mean WM errors, (B) mean RM errors, and (C) mean total arm entries. Error bars represent standard error of the mean (SEM). * indicates $p < 0.05$ resulting from post hoc one-way ANOVA. Blue letters "a" and "b" indicate main effects of age compared to adulthood or middle age, respectively. Abbreviations: ANOVA, analysis of variance; RM, reference memory; WM, working memory. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

### 3.4. Housing conditions did not affect performance in the EZM

Because the RAM maze does not require subjects to enter open fields, we also tested subjects on the EZM, an anxiety task which more closely resembles the closed environment of the RAM. We analyzed time in open areas and latency to open areas and found no group (time: $p$ = 0.706; lat: $p$ = 0.085) or age-by-group (time: $p$ = 0.550; lat: $p$ = 0.0362) differences. This was similar to latency to center in the OFT. Across ages, time spent in open areas increased steadily while latency to enter the open areas decreased. This is evidenced by a main effect of age (Time: $F_{2,34}$ = 10.688, $p$ = 0.000; Lat: $F_{2,34}$ = 14.764, $p$ = 0.000) and post hoc pairwise comparisons for adulthood versus middle age (time: $p$ = 0.000; lat: $p$ = 0.026) and adulthood versus old age (time: $p$ = 0.000; lat: $p$ = 0.000). Middle age vs. old age was significant for time ($p$ = 0.001) but not for latency ($p$ = 0.155). These data indicate that both SH and NSH subjects explored open areas progressively more across ages and did so progressively sooner. Thus, housing conditions did not influence levels of anxiety as assessed by the EZM.

#### 3.4.1. Housing conditions did not affect corticosterone levels

To complement the behavioral measures assessed in the OFT and EZM, we analyzed corticosterone levels in the SH versus NSH groups (Dallman et al., 2004). Group mean (±SEM) was 107.54 ± 17.01 ng/mL for the SH group and 65.49 ± 17.09 ng/mL for the NSH group, but these were not significantly different from each other ($p$ = 0.103). Thus, corticosterone levels did not indicate a difference in physiological stress as a consequence of housing.

#### 3.4.2. Anxiety is unlikely to account for the observed WM enhancements

Five primary measures were used to assess anxiety: time spent in center of the OFT (Fig. 3A), latency to enter center of the OFT

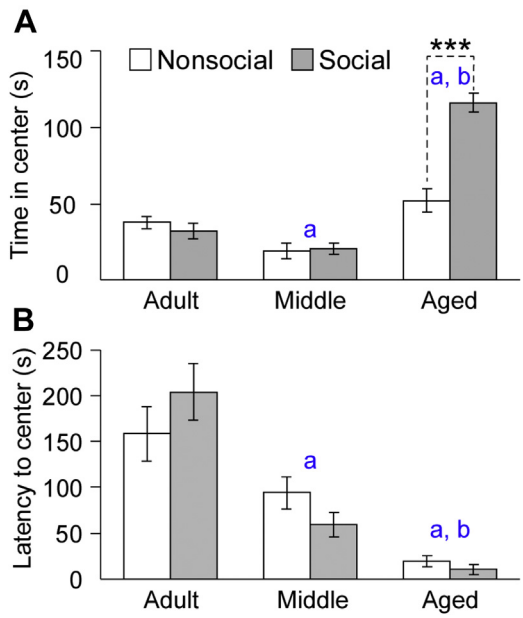


**Fig. 3.** Performance in the open field test (OFT) across ages. (A) Time spent in the center, and (B) latency to enter center. Error bars represent SEM. *** indicates $p < 0.001$ resulting from post hoc one-way ANOVA. Blue letters "a" and "b" indicate main effects of age compared to adult or middle, respectively Abbreviations: ANOVA, analysis of variance; SEM, standard error of the mean. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

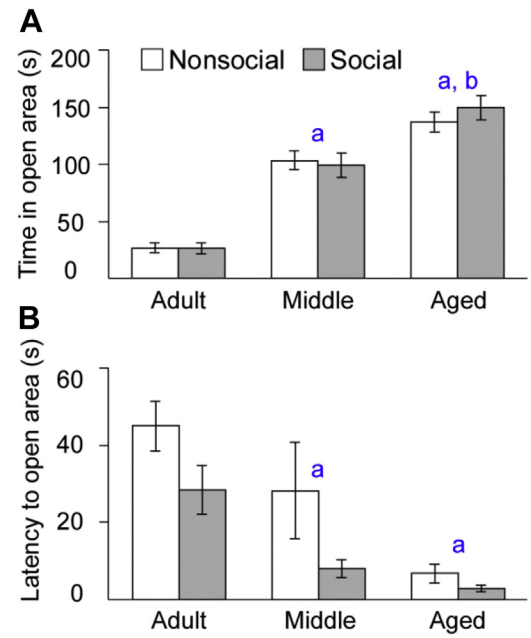


**Fig. 4.** Performance on the elevated zero maze (EZM) across ages. (A) Time spent in the open areas, and (B) latency to enter open areas. Error bars represent SEM. Blue letters "a" and "b" indicate main effects of age compared to adulthood or middle age, respectively. Abbreviation: SEM, standard error of the mean. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(Fig. 3B), time in open areas of the EZM (Fig. 4A), latency to enter open areas of the EZM (Fig. 4B), and blood serum corticosterone levels. Of these, only one (time spent in the center of the OFT) indicated reduced anxiety in the SH compared to the NSH subjects. However, given that the difference in OFT time-in-center was highly significant, we wondered whether there were any parallels between this anxiety measure and WM performance in aged subjects. We used both the raw data for OFT center exploration, and normalized data, which accounted for a slight difference in the distance traveled (Fig. S1). A Pearson correlation revealed that WM errors in old age were not significantly correlated to time-in-center of the OFT for either raw ($r = -0.412$, $p = 0.080$) or normalized OFT data ($r = -0.377$, $p = 0.111$). Thus, although NSH subjects spent less time in the center of the OFT in old age compared to the SH group, it appears unlikely that differences in anxiety can account for group differences in WM.

## 4. Discussion

In this study, we set out to determine how sociality affects cognition throughout the adult lifespan. Rats were either single or group housed and tested on the RAM at 3 time points, adult (10 months), middle age (16 months), and old age (23 months). We found that in old age, sustained social housing provided a protective benefit against age-related WM decline at 23 months. Nonsocial housing, on the other hand, resulted in decreased WM performance in old age, even in the presence of physical enrichment, exercise, extensive handling, and a restricted diet. It is unlikely that these group differences can be explained by differences in anxiety levels. Surprisingly, RM was not affected by housing condition at any time point. Housing conditions did not affect WM or RM in middle age or late adulthood. To our knowledge, this is the first longitudinal study to explore cognition in old age as a consequence of housing conditions divorced of the physical components of EE.

Our results provide the first evidence that sustained social housing facilitates cognition in old age. The independent effects of physical enrichment (Frick and Benoit, 2010; Frick et al., 2003; Frick and Fernandez, 2003; Harati et al., 2011; Harburger et al., 2007a,b), exercise (Albeck et al., 2006; Harburger et al., 2007b), diet (Andres-Lacueva et al., 2005; Markowska and Savonenko, 2002; Pitsikas and Algeri, 1992), and handling (Meaney et al., 1988) on age-related decline have been studied extensively but not those of social housing. Previous work has examined postweaning social isolation compared to group housing in adult rodents (<3 months), but these studies only model extremely impoverished conditions, and results vary widely. One recent study found that exposing aged rats (23–24 months) to one month of EE, but not social housing (without any EE), increased performance and mGluR5-dependent hippocampal long-term potentiation and behavioral performance in the novel object recognition test, the morris water maze, and the radial arm water maze (Cortese et al., 2018). Many possibilities could account for the discrepancy in results obtained here and in this study. It is possible that protective effects of sociality are only achieved when animals are housed throughout their lifespan or that one month of social housing in impoverished conditions (no EE) was simply not powerful enough to reverse impoverished conditions maintained for 2 years of life. Given repeated robust effects observed of EE in the literature, it is likely that EE is simply more powerful than social enrichment. Finally, it is possible that socially housing animals that lived in isolated conditions for 2 years is more stressful than it is beneficial. Many studies find that isolated animals display impaired cognitive performance (An et al., 2017; Leser and Wagner, 2015; Okudan and Belviranli, 2017; Quan et al., 2010; Shao et al., 2015; Yusufishaq and Rosenkranz, 2013), but others find no differences (Grigoryan et al., 2010; Huang et al., 2011), or even enhanced performance among isolated subjects (Grigoryan et al., 2010; Pisu et al., 2011; Wongwitdecha and Marsden, 1996b). Instead of modeling acutely impoverished social conditions, in the present study, we provided all subjects with the

physical components of EE, including exercise, extensive handling, and cages that are larger than those typically used. Thus, our results show that sociality confers benefits beyond those of EE. The implication for human populations is that the benefits of sociality are not limited to those who are environmentally impoverished but can be extended to human aging populations who lead otherwise healthy lives.

### 4.1. Time point sensitivity of WM enhancements

The finding that social housing preserves WM function in old age but not in late adulthood or middle age is consistent with previous studies showing the effects of short-term EE on spatial acquisition and memory (Harburger et al., 2007a,b), and the effects of long-term EE on attention (Harati et al., 2011). Other studies, however, demonstrate that prolonged EE can afford cognitive benefits earlier, rather than later, for spatial acquisition (Harati et al., 2011; Kobayashi et al., 2002) and object recognition (Leal-Galicia et al., 2008). The fact that long-term social housing does not improve WM in adult or middle aged rats in the present study could indicate a dissociation in the effects of social versus EE. It is possible that social enrichment is protective in old age, as in the present study, whereas EE is protective at younger ages, as in the studies by Harati et al., 2011; Kobayashi et al., 2002; Leal-Galicia et al., 2008. A similar dissociation has been observed with EE and exercise conferring cognitive benefits at different ages (Harburger et al., 2007b). Alternatively, because both housing groups in our study had access to prolonged EE, it is possible that a ceiling effect masked the added benefit of sociality. It is also likely that the difference between our results and previous studies using long-term enrichment reflect the fact that they examine different memory systems and use a cross-sectional rather than a longitudinal design. Either way, it is clear from our data that prolonged social housing protects against WM decline in old age.

### 4.2. Dissociation between RM and WM and possible mechanisms of sociality conferring cognitive benefit

In contrast to WM, RM was not affected by social housing at any time point. This dissociation was unexpected considering that other studies have reported similar rates of decline for both types of memory (Bizon et al., 2009; Kadar et al., 1990; Lindner et al., 1992). However, because EE is known to protect against age-related spatial memory decline (Frick et al., 2003; Frick and Fernandez, 2003; Harati et al., 2011; Harburger et al., 2007a,b), and because both of our housing groups were provided with lifelong EE, it is possible that physical enrichment alone offered ceiling-level cognitive benefits at the ages tested. Had our subjects been reared in standard shoebox cages with neither physical enrichment, extended handling, nor controlled diets, or had we tested them on a fourth age (i.e., 30+ months), we may have detected an effect of social housing on RM. Alternatively, it could be that RM is protected by the physical but not the social aspects of EE. Consistent with this idea, a study in pigs observed a similar dissociation between WM and RM following physical enrichment, while social enrichment was held constant (Elizabeth Bolhuis et al., 2013). In either case, this dissociation provides insight into the underlying physiological mechanisms by which different types of enrichment affect different cognitive functions. In rodent studies, WM has been found to rely on both the hippocampus (Aggleton et al., 1986; Olton and Feustle, 1981; Walker and Olton, 1984; Yoon et al., 2008) and the medial prefrontal cortex (Curtis and D'Esposito, 2004; Lara and Wallis, 2015; Yoon et al., 2008), whereas RM relies primarily on the hippocampus (Clark et al., 2005; Ramos, 2009; Squire, 2004). It is possible, then, that social housing preserved prefrontal rather than hippocampal function. Moving forward, the longitudinal design presented in this study will be useful for investigations into the physiological, electrophysiological, and molecular mechanisms of the cognitive benefits associated with sociality.

As discussed previously, an important question to answer in future studies is how sociality leads to decreased WM errors in old age. Although we can only speculate on the mechanism for the neuroprotective effect, we suspect that social housing may parallel the neuronal integrity achieved by exercise and EE, preserving long-term potentiation (e.g., Cortese et al., 2018). One study found that, as compared to young rats, aged rats tested in the RAM exhibited more WM errors when baited arms were adjacent than when they were nonadjacent (Gracian et al., 2013). These findings are consistent with a large literature in humans and animals that cognitive aging impairs spatial interference and pattern separation (e.g., Ces et al., 2018; Johnson et al., 2016; Leal and Yassa, 2015; Stark and Stark, 2017). Unfortunately, we did not evaluate adjacent versus nonadjacent arms in the RAM, as all baited arms were nonadjacent. Had we tested subjects on conditions with higher spatial interference (e.g., adjacent arms), perhaps, we would have seen a more dramatic group difference in WM or even group differences in RM. This would implicate neuroanatomical structures dedicated to spatial processing, such as the hippocampus, as susceptible to plasticity as a result of social housing. Further hypothetically speaking, if such group differences across levels of spatial interference were not observed, this would instead suggest that the mechanism responsible for the group difference observed is not spatial. Although rats here were only tested on nonadjacent arms, we still found a difference in WM errors in SH versus NSH animals, suggesting that the effects of social housing are robust and extend beyond particularly difficult spatial tasks. In addition, because no differences were observed in RM, but were observed in WM, we have no reason to believe the mechanism responsible for group differences is spatial in nature. We find it more likely the benefit is in executive processing that underlie WM. We look forward to future studies that investigate such mechanisms, including but not limited to spatial versus nonspatial accounts.

### 4.3. Relationship between anxiety and cognition

Previous studies have shown that anxiety and stress can impair cognition in rodents (Lupien et al., 2009; McEwen and Sapolsky, 1995), and that social isolation is associated with increased anxiety (Ago et al., 2014; Fone and Porkess, 2008). Our data showed that although both groups experienced reduced anxiety in old age compared to middle age and late adulthood, the social group spent more time in the center of the OFT than the nonsocial group in old age. This suggests that the social group experienced an exaggerated prototypical decrease in anxiety with age. However, 4 other measures did not confirm that the social group was less anxious than the nonsocial group in old age (i.e., OFT latency to center, EZM time in open, EZM latency to open, and corticosterone). Moreover, the correlation between OFT time-in-center and WM errors was marginal at best ($p = 0.080$).

We leave open the possibility that the social group was less anxious than the nonsocial group in old age, and that reduced anxiety had some influence, perhaps additive, on cognitive performance. The open spaces of the OFT may have provided a more extreme measure of relative anxiety than the closed quarters of the EZM. And because the corticosterone measurements were taken at the time of death, they may not have been directly indicative of anxiety levels during cognitive testing. Thus, it could be that the other measures of anxiety were not sensitive enough to detect a group difference. Furthermore, although there was no strong correlation between OFT time in center and WM errors ($p = 0.080$),

this is not surprising considering the human literature. For one, the effects of acute anxiety in old age are temporary and not predictive of future cognitive decline (Bierman et al., 2008). In addition, although anxiety is associated with impaired cognition in the healthy aging population (Bierman et al., 2005, 2008; Bunce et al., 2012; Fung et al., 2018; Yochim et al., 2013), this relationship follows a U-shaped curve such that mild and severe anxieties tend to impair cognition, although moderate anxiety is often associated with improved performance (Bierman et al., 2005, 2008; Dotson et al., 2014). Although further investigation is required to determine the specific mechanism by which sociality confers cognitive benefits, we conclude that in the present study, anxiety alone was unlikely to account for WM enhancements in SH rats. Determining if, and the extent to which, anxiety might contribute to cognitive decline in rodent models of aging will be an important area of investigation for future research.

One alternate possibility is that the difference in time-in-center was actually indicative of motivation rather than anxiety. In longitudinal studies, unenriched rodents typically lose interest in the familiar arena with repeated exposure, as evidenced by decreased distance across ages (Fowler and Muma, 2015; Galeano et al., 2014). The fact that our socially enriched rats spent more time in center and also traveled greater distances in old age (Fig. S1) suggests that social housing prompted a novel increase in exploratory behavior in old age. Whether our results indicate that social housing caused enhanced age-related anxiety reduction or increased motivation to explore familiar environments, or both, remains an open question. Although we leave open the possibility that the social group was less anxious in old age than the nonsocial group, and that reduced anxiety had some influence, perhaps additive, on cognitive performance, it is clear that anxiety alone was unlikely to account for the observed WM enhancements.

### 4.4. Limitations

A significant limitation to this study is the fact that activity levels in the home cage were not monitored throughout the animals' lifespan. Unfortunately, it was beyond the scope of this study to quantify activity and exercise levels in each group. It is therefore possible that the SH rats spent more time exercising in their home cages than NSH rats and that this difference in activity levels could mediate or moderate the purported effect of sociality. Although only anecdotal, experimenters who visited the colony room multiple times a day noticed much more resting and napping in groups in the SH groups than in the NSH cages. It is important to note that the EE and cages were similar in both social and nonsocial cages, allowing for identical room for movement across groups. Nonetheless, if social housing afforded more exercise, it would be nonetheless interesting that sociality indirectly confers cognitive benefit. Here, we cannot confirm with absolute certainly that sociality directly rather than indirectly, affects cognition. Although we find this possibility of more physical activity accounting for cognitive benefits observed here unlikely, we look forward to future studies that examine this hypothesis.

### 4.5. Longitudinal versus cross-sectional study

Translating the results of animal models to human populations requires close scrutiny of experimental design. Although aged subjects in cross-sectional studies tend to be naïve to cognitively demanding tasks, aged subjects in longitudinal designs have been repeatedly exposed to one or more cognitive tasks, in our case, a whole battery of them. The effects of this experience are evident, for instance, in the fact that subjects perform better in middle age than in late adulthood in our study and other longitudinal ones (Algeri, S. et al., 1991; Beatty et al., 1985; Bierley et al., 1986; Caprioli et al., 1991; Chrobak et al., 1995; Dellu et al., 1997; Pitsikas and Algeri, 1992; Pitsikas et al., 1991), while cross-sectional studies yield impaired performance in middle age (Barnes, 1979; Barnes et al., 1980; Bizon et al., 2009; Frick et al., 1995; Gallagher and Burwell, 1989; Kadar et al., 1990; LaSarge et al., 2007; Lindner et al., 1992; Rapp et al., 1987; Robitsek et al., 2008; Rowe et al., 1998; Villarreal et al., 2004; Weiss and Thompson, 1991; Wyss et al., 2000). Although there are arguments that the effects of practice in human longitudinal studies can yield misleading results (Salthouse, 2014), prior training in rodent studies could be desirable because it models a lifestyle filled with cognitive stimulation, a factor known to protect against age-related cognitive decline in humans (Ardila et al., 2000; Nexo et al., 2016). With this in mind, our results imply that even aging humans who are cognitively active and have prior experience in a particular task are susceptible to age-related WM decline in the absence of healthy social interactions.

## 5. Concluding remarks

In this study, we provide the first evidence that lifelong social interactions in a rodent model contribute to the retention of WM in old age and that the benefits of social enrichment go beyond those of physical enrichment. Results from this study provide proof of concept for the use of rodent longitudinal aging designs with housing condition as an independent variable. In addition, this design should provide a springboard for future biomedical studies aimed at identifying the neural mechanisms underlying preserved cognitive functioning achieved with unique behavioral, housing, and phenotypic histories. Isolating the cognitive and neural mechanisms responsible for protective benefits of sociality has the potential to directly and positively affect both preventative care and treatment in aging humans.

## Disclosure

There are no conflicts of interest to disclose.

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All procedures performed were in accordance with the ethical standards of the Animal Care and Use Committee of Providence College and the experiments comply with US Law.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2018.11.016.

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