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# Environmental enrichment restores neurogenesis and rapid acquisition in aged rats

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**Abstract**

Strategies combatting cognitive decline among the growing aging population are vital. We tested whether environmental enrichment could reverse age-impaired rapid spatial search strategy acquisition concomitantly with hippocampal neurogenesis in rats. Young (5–8 months) and aged (20–22 months) male Fischer 344 rats were pair-housed and exposed to environmental enrichment ($n$ = 7 young, 9 aged) or housed individually ($n$ = 7 young, 7 aged) for 10 weeks. After 5 weeks, hidden platform trials (5 blocks of 3 trials; 15 m inter-block interval), a probe trial, and then visible platform trials (5 blocks of 3 trials; 15 m inter-block interval) commenced in the water maze. One week after testing, rats were given 5 daily intraperitoneal bromodeoxyuridine (50 mg/kg) injections and perfused 4 weeks later to quantify neurogenesis. Although young rats outperformed aged rats, aged enriched rats outperformed aged individually housed rats on all behavioral measures. Neurogenesis decreased with age but enrichment enhanced new cell survival, regardless of age. The novel correlation between new neuron number and behavioral measures obtained in a rapid water maze task among aged rats, suggests that environmental enrichment increases their ability to rapidly acquire and flexibly use spatial information along with neurogenesis.


*Keywords:* Adult neurogenesis; Learning; Memory; Enrichment; Water maze; Age-related; Fisher 344; Neural progenitor cell; Hippocampus

## 1. Introduction

Altered hippocampal function likely contributes to age-related changes in cognitive ability because hippocampus-dependent tasks are sensitive to age-related cognitive decline (Foster, 1999). Decades ago, the standard Morris water maze task revealed impaired performances among some senescent rats (Gage et al., 1984; Rapp et al., 1987). More recent behavioral assessments have sought to increase task sensitivity to age-related cognitive decline (Kennard and Woodruff-Pak, 2011), so that the deficits and their underlying mechanisms can be better characterized and potentially manipulated. Here we employ a rapid water maze task sensitive to age-related cognitive decline to test whether daily exposure to an enriched environment can reverse the effects of age on hippocampal function concomitantly with hippocampal neurogenesis.

Neurogenesis is a striking form of neural plasticity that persists throughout life in the hippocampus and olfactory bulbs of all mammals investigated, including humans (Altman and Das, 1965; Cameron et al., 1993; Eriksson et al., 1998). Although the precise role that new neurons play in hippocampal integrity is debated, new neuron number in young animals generally correlates with their performance measures in hippocampus-dependent tasks (Deng et al., 2010; but see Epp and Galea, 2009). Manipulations that attenuate neurogenesis chronically associate with impaired performance (Madsen et al., 2003; Raber et al., 2004; Saxe

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et al., 2006; Shors et al., 2002; Snyder et al., 2005; Winocur et al., 2006) while those that potentiate neurogenesis associate with better performance (Ormerod et al., 2004; van Praag et al., 2005; Dalla et al., 2009). Postmortem signs of hippocampal neurogenesis in human patients who exhibited profound memory impairments are scarce (Coras et al., 2010; Correa et al., 2004; Crossen et al., 1994; Monje et al., 2007; Roman and Sperduto, 1995; Siffert and Allen, 2000).

Hippocampal neurogenesis declines with age in rodents primarily because neural progenitor cells (NPCs) become increasingly quiescent and NPCs that do divide may be less likely to produce surviving neuronal progeny (Cameron and McKay, 1999; Hattiangady and Shetty, 2008; Kempermann et al., 1997; Kuhn et al., 1996; Lichtenwalner et al., 2001; Nacher et al., 2003). While several studies have related new neuron number and cognitive measures in aged rats (Drapeau et al., 2003, 2007; Driscoll et al., 2006; Lemaire et al., 2000), dogs (Siwak-Tapp et al., 2007), and nonhuman primates (Aizawa et al., 2009), the strength of this relationship among aged rats tested in the water maze varies. For example, new neuron number appears unrelated to the performance of aged rats in water maze tasks that distribute training across 8–10 days (Bizon and Gallagher, 2003; Bizon et al., 2004; Merrill et al., 2003) but related in protocols that mass training across 2–3 days (Drapeau et al., 2003; Driscoll et al., 2006). Moreover, new neuron survival in the hippocampi of aged rats is enhanced by their participation in early but not later trials of the distributed water maze protocol (Drapeau et al., 2007). These results suggest that the strength of the relationship between neurogenesis and water maze performance in aged rats may depend upon the speed of learning demanded by the task.

In aged rodents, daily exposure to environmental enrichment primarily stimulates neurogenesis by increasing the probability that new neurons survive to maturity (Kempermann et al., 1997, 1998, 2002; Leal-Galicia et al., 2008; Segovia et al., 2006) and improves the rapid acquisition of spatial information in a condensed water maze task (Kumar et al., 2012). Here we tested the hypothesis that daily exposure to environmental enrichment would reverse age-related impairments in rats' abilities to rapidly acquire a spatial search strategy concomitantly with ongoing rates of neurogenesis.

## 2. Methods

### 2.1. Subjects

Young (5–8 months old) and aged (20–22 months old) sexually naive male F344 rats obtained from the National Institute of Aging colony at Harlan Sprague Dawley (Indianapolis, IN, USA) were treated in accordance with University of Florida and federal policies regarding the ethical use of animals for experimentation. Rats exhibiting signs of aggression (bites and scratches) or age-related health problems (poor grooming, hunching, excessive porphyrin secretion, weight loss, and tumors) were euthanized humanely.

### 2.2. Differential experience: environmental enrichment and individual housing

For the 10-week experiment, the rats were housed in a 12:12 hour light cycle with access to food and water *ad libitum* either individually ($n = 7$ young [YI] and $n = 7$ aged [AI]) or pair housed with 2–3 hours of access daily to an enriched environment ($n = 7$ young [YE] and $n = 9$ aged [AE]). The goal of the differential experience protocol was to provide opportunities for the enriched group to engage in a variety of hippocampus-dependent behaviors while limiting them for the individually housed group. The enriched environment consisted of a large wooden box, empty water maze tank, or large wire cage containing assorted 3-dimensional toys (e.g., plastic tubes, balls, and various objects), food, and water. The environment and toys were randomly rotated daily to maintain novelty. Daily exposure to this environment modifies hippocampal electrophysiology and facilitates the rapid acquisition of a spatial search strategy in aged rats (Foster and Dumas, 2001; Kumar et al., 2007, 2012). Behavioral testing commenced in the 4th week of differential experience and bromodeoxyuridine (BrdU) injections commenced 1 week after behavioral testing was completed. The rats were perfused 4 weeks after the final BrdU injection to quantify neurogenesis (Fig. 1).

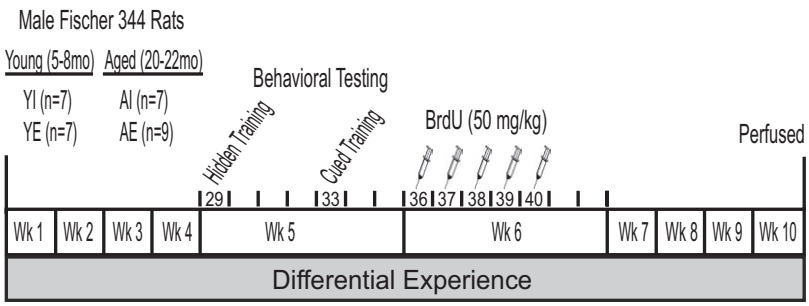


Fig. 1. Experiment timeline. Rats were housed individually ($n = 7$ young, $n = 7$ aged) or in pairs and exposed to an enriched environment daily ($n = 7$ young, $n = 9$ aged) for 10 weeks. In the 5th week, rats were trained and tested on hidden platform trials and then visible platform trials 3 days later. Beginning 1 week after testing, rats were injected daily with bromodeoxyuridine (BrdU; 50 mg/kg) over 5 days and then perfused 4 weeks later to quantify neurogenesis.