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Research report

Mouse genetic differences in voluntary wheel running, adult hippocampal neurogenesis and learning on the multi-strain-adapted plus water maze

Jennifer R. Merritt[a], Justin S. Rhodes[b,*]

[a] Department of Psychology, Psychology and Interdisciplinary Sciences Building, Emory University, 36 Eagle Row, Atlanta, GA, USA
[b] Department of Psychology, The Beckman Institute, University of Illinois at Urbana-Champaign, 405 North Mathews Avenue, Urbana, IL, USA

HIGHLIGHTS

- Running increased neurogenesis and enhanced plus water maze learning across 5 strains.
- Running, neurogenesis, and learning displayed significant heritability.
- Level of neurogenesis was a poor predictor of learning between strains.

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ABSTRACT

Moderate levels of aerobic exercise broadly enhance cognition throughout the lifespan. One hypothesized contributing mechanism is increased adult hippocampal neurogenesis. Recently, we measured the effects of voluntary wheel running on adult hippocampal neurogenesis in 12 different mouse strains, and found increased neurogenesis in all strains, ranging from 2- to 5-fold depending on the strain. The purpose of this study was to determine the extent to which increased neurogenesis from wheel running is associated with enhanced performance on the water maze for 5 of the 12 strains, chosen based on their levels of neurogenesis observed in the previous study (C57BL/6 J, 129S1/SvImJ, B6129SF1/J, DBA/2 J, and B6D2F1/J). Mice were housed with or without a running wheels for 30 days then tested for learning and memory on the plus water maze, adapted for multiple strains, and rotarod test of motor performance. The first 10 days, animals were injected with BrdU to label dividing cells. After behavioral testing animals were euthanized to measure adult hippocampal neurogenesis using standard methods. Levels of neurogenesis depended on strain but all mice had a similar increase in neurogenesis in response to exercise. All mice acquired the water maze but performance depended on strain. Exercise improved water maze performance in all strains to a similar degree. Rotarod performance depended on strain. Exercise improved rotarod performance only in DBA/2 J and B6D2F1/J mice. Taken together, results demonstrate that despite different levels of neurogenesis, memory performance and motor coordination in these mouse strains, all strains have the capacity to increase neurogenesis and improve learning on the water maze through voluntary wheel running.

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1. Introduction

Evidence has established that incorporating regular exercise into the life routine is critical for maintaining cognitive health throughout the lifespan [1]. Uncovering the neurological mechanisms is currently an active area of research. One consistent finding is enhanced volume of the hippocampus in association with physical exercise in humans [2]. Rodent models have also found certain regions of the hippocampus to enlarge as a result of wheel running exercise [3]. Large ensembles of neurons in the hippocampus become rhythmically active, with the amplitude and frequency of the rhythms closely related to the intensity of the physical activity [4,5]. Expression of immediate early genes including Zif268, Arc, and c-Fos increases in the dentate gyrus in direct proportion to amount of running [6,7]. Given the prominent role of the hippocampus in learning and memory, exercise-induced increases in neuronal activation, immediate early gene induction and

* Corresponding author at: 405 North Mathews Avenue, Beckman Institute, Urbana, IL 61801, USA. Tel.: +1 217 265 0021; fax: +1 217 244 5180.
E-mail address: jrhodes@illinois.edu (J.S. Rhodes).

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associated morphological changes in the hippocampus likely contribute to the broad enhancement in cognitive performance observed from exercise in both humans and rodent animal models.

In 1999, Dr. Henriette van Praag and colleagues reported the seminal discovery that wheel running massively increases adult hippocampal neurogenesis in association with enhanced learning and memory performance on the Morris water maze task in C57BL/6 J (B6) mice [8]. It is likely that the addition of new neurons contributes to the increased volume of the granule layer of the dentate gyrus in association with exercise in rodents and humans [2,3]. Many studies have since confirmed that increased neurogenesis from exercise occurs in parallel with enhanced performance on hippocampal-dependent tasks in the B6 genotype [3,9–15]. Whether or not the increased neurogenesis from running causally contributes to enhanced performance by adding large numbers of highly plastic units to the circuit has proven much more difficult to establish, and remains a hot topic of research and debate [9,16–20].

One piece of information that would be useful for interpreting the significance of the association between running-induced neurogenesis and enhanced learning in B6 is to know the generality of the result for other genotypes besides B6. To the best of our knowledge, few studies have explored whether increased neurogenesis occurs in parallel with enhanced learning and memory in other strains of mice besides B6 in response to wheel running exercise. In at least some of the other strains that have been tested, the association was absent, prompting the need to evaluate the generality of the finding further [21]. For example, in one study, mice from four different lines that were selectively bred for increased voluntary wheel running displayed large increases in adult hippocampal neurogenesis from running but did not show an improvement in learning on the Morris water maze [21]. In fact, if anything, running worsened performance in these mice. These mice are not “normal” in the sense that they are highly physically active and display a number of interesting features including altered dopamine function not typically observed in other mouse strains [22]. Therefore, it would be useful to evaluate the association between exercise-induced neurogenesis and behavioral performance in other standard inbred strains in addition to B6 to resolve the generality of the finding.

Recently, we measured adult hippocampal neurogenesis in 10 different standard inbred strains and 2 F1 hybrids, housed either with or without a running wheel and found that neurogenesis was massively increased from wheel running in all 12 strains (the increase ranged from 2- to 5-fold, depending on the strain) [23]. A significant percentage of the strain variation in exercise-induced neurogenesis could be accounted for by the distance the animals ran. After removing variation related to distance run, strain still accounted for a significant percentage of the variation in levels of neurogenesis. Taken together, these results imply that the quantitative increase in total number of new neurons resulting from housing the animals with a running wheel differs between strains with some strains showing relatively more new neurons for the same amount of running as compared to others [23]. It would be useful to know whether strains that show relatively larger increases in neurogenesis from running would display relatively greater cognitive enhancement from running. If exercise-induced neurogenesis functionally contributes broadly to the pro-cognitive effects of exercise, one would expect to see a positive correlation between degree of exercise-induced neurogenesis and degree of cognitive enhancement.

The goal of this study was to first determine the generality of the finding that exercise enhances performance on the water maze in parallel with increased neurogenesis in 2 other standard inbred strains besides B6, DBA/2 J (D2) and 129S1/SvImJ (129S1), and their F1 hybrids, B6D2F1/J (B6D2F1), and B6129SF1/J (B6129F1). We included the F1 hybrids along with the parental strains to for two reasons. First, we wanted to determine the pattern of inheritance of the alleles from each strain (e.g., dominant, recessive, additive, or over-dominant) on the running, neurogenesis and learning phenotypes. Second, we aimed to choose strains with a range in levels of exercise-induced neurogenesis and B6D2F1 and B6129F1 displayed among the greatest increases in neurogenesis from running in our previous study [23]. 129S1 and D2 displayed the lowest levels of neurogenesis under baseline sedentary or running conditions. B6 displayed the highest levels of neurogenesis under sedentary conditions, but the smallest increase in neurogenesis from wheel running. Because we hypothesized that exercise-induced neurogenesis is functionally related to enhanced performance on the water maze, we expected the hybrids to display the greatest enhancement in performance, and B6 the least enhancement, with the other strains in the middle.

The reason we used the plus water maze instead of the standard version of the water maze is because it is known that the different strains react to the standard version in ways that make differential behavior (in path length, latency to the platform, or time in target quadrant during the probe trial) difficult to interpret as differences in learning or memory. For example, some strains float rather than swim, or swim around the edge of the maze. The version of the plus water maze used in this study is the version that worked the best for a majority of strains without resulting in interference from idiosyncratic differences related to test reactivity [24].

In addition to the plus maze, we also wanted to measure performance on a behavioral task that has shown improvements from wheel running but not thought to be related to adult hippocampal neurogenesis. For this purpose we chose the rotarod, a motor performance task, thought to rely more on function of the cerebellum than hippocampus [9]. Our expectations for the rotarod were general improvements from wheel running across the strains following a pattern unrelated to levels of adult hippocampal neurogenesis.

2. Materials and methods

2.1. Animals

Male mice from the following strains were purchased from The Jackson Laboratory (Bar Harbor, ME), and arrived at the Beckman Institute animal facility at five weeks of age: (n = 20 or 21 per strain: B6, 129S1, B6D2F1, D2, and B6129F1; n = 102 mice total). Upon arrival, the mice were group housed mice (3 or 4/cage) for one week in standard polycarbonate shoebox cages (dimensions 29 cm × 19 cm × 13 cm; $L \times W \times H$) with corncob bedding, Teklad 7012 (Harlan Teklad, Madison, WI, USA). Rooms were controlled for temperature (21 °C ± 1 °C) and photo-period (12 h L:D; lights on at 10:00 am and off at 10:00 pm). Food and water was provided ad libitum.

2.2. Experimental design

After one week of habituation, the mice were divided into two groups by strain designated as Sedentary or Runner (n = 10 or 11 per group). Sedentary mice were individually housed in standard shoebox cages whereas Runners were individually housed in cages (36 cm × 20 cm × 14 cm; $L \times W \times H$) with a 23-cm diameter wheel mounted to the cage top (Respironics, Bend, OR, USA). Wheel rotations were monitored continuously in 1 minute increments via magnetic switches interfaced to a computer throughout the experiment. The Sedentary mice were not housed in cages with locked wheels because mice climb in wheels and physical activity was intended to be minimal [25].

During the first 10 days of the Runner or Sedentary conditions, all the mice received 10 daily intraperitoneal (i.p.) injections of