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Review

Adult hippocampal neurogenesis and memory interference

Gordon Winocur[a,b,c,*], Suzanna Becker[d], Paul Luu[e], Shira Rosenzweig[e], J. Martin Wojtowicz[e]

[a] Rotman Research Institute, Baycrest Centre, 3560 Bathurst Street, Toronto, Ontario, M6A 2E1, Canada
[b] Department of Psychology, Trent University, Peterborough, Ontario, K9J 7B8, Canada
[c] Departments of Psychology and Psychiatry, University of Toronto, Toronto, Ontario, M5S 3G3, Canada
[d] Department of Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, Ontario, L8S 4K1, Canada
[e] Department of Physiology, University of Toronto Medical Sciences Building, Toronto, Ontario, M5S 1A8, Canada

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ABSTRACT

Rats, subjected to low-dose irradiation that suppressed hippocampal neurogenesis, or a sham treatment, were administered a visual discrimination task under conditions of high, or low interference. Half of the rats engaged in running activity and the other half did not. In the non-runners, there was no effect of irradiation on learning, or remembering the discrimination response under low interference, but irradiation treatment increased their susceptibility to interference, resulting in loss of memory for the previously learned discrimination. Irradiated rats that engaged in running activity exhibited increased neuronal growth and protection from memory impairment. The results, which show that hippocampal cells generated in adulthood play a role in differentiating between conflicting, context-dependent memories, provide further evidence of the importance of neurogenesis in hippocampus-sensitive memory tasks. The results are consistent with computational models of hippocampal function that specify a central role for neurogenesis in the modulation of interfering influences during learning and memory.

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1. Introduction

It is well established that new neurons, generated in the dentate gyrus during adulthood, are functionally integrated into existing hippocampal circuitry [1]. The reduction of adult neurogenesis, as seen following treatment with low-dose irradiation, anti-mitotic drugs, or in genetic mutations is associated with impaired performance on tests of hippocampus-dependent learning and memory [2–7]. Conversely, factors that promote neurogenesis (e.g., physical activity, enriched environments) contribute to improved performance on hippocampus-dependent tasks [8,9]. Notwithstanding these advances, the precise role of new cell growth in normal hippocampal function is unresolved.

* Corresponding author at: Rotman Research Institute, Baycrest Centre, 3560 Bathurst Street, Toronto, Ontario M6A 2E1, Canada. Tel.: +1 416 785 2500x3592; fax: +1 416 785 2474.
E-mail address: gwinocur@rotman-baycrest.on.ca (G. Winocur).

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The hippocampus is involved in the formation of flexible, contextually rich memories and there is compelling evidence that discrete neuronal representations within the dentate gyrus form the basis of these memories [10]. An important feature of hippocampus-based memories is that, by virtue of their distinctiveness and contextual richness, they are readily distinguished from other memories. When the hippocampus is impaired, memories become more schematic [11], susceptible to interfering influences [12], and, as a result, subject to inaccuracy.

We have proposed that neurogenesis provides a mechanism for hippocampal plasticity that is critical to the process of representing distinct memories [[3,13]; see also Refs. [7,14]]. It follows that, as part of this process, newly generated cells should also play a role in modulating interfering influences and minimizing the effect of competing memories during selective recall. This view is supported by recently developed computational models [e.g., Refs. [15–17]] which, while differing from one another in several respects, make the common prediction that adult-born hippocampal cells are essential to the process of reducing the adverse effects of interference during learning and memory.

As a direct test of this hypothesis, we used irradiation to suppress neurogenesis in adult rats, and tested them in a novel task that assessed memory for a learned discrimination response under conditions of high and low interference. In addition, half of the rats engaged in running activity, and the other half did not. It is well known that physical exercise can promote new cell growth and improve cognitive function in normal animals [9,18]. We sought to determine if such effects were possible when hippocampal neurogenesis was compromised by irradiation.

2. Materials and methods

2.1. Subjects

Forty-eight, 5-month-old, male Long-Evans rats, weighing 350–400 g at the beginning of the study, were obtained from the Charles River Laboratories in St. Constant, Quebec, and served as subjects. The rats underwent irradiation, or a control procedure (see below) at the Ontario Veterinary College, University of Guelph, and a few days later, they were transferred to Trent University, where they were housed individually with food and water available at all time. Rats were maintained on a 12-h light–dark schedule, with lights on between 8:00 p.m. and 8:00 a.m.

Two weeks before behavioural testing and for the duration of the experiment, rats in the running conditions were allowed free access to a running wheel that was attached to the cage. The wheel, approximately 30 cm in diameter, was equipped with a meter that measured duration, speed, and distance traveled on a daily basis. Rats in the non-running condition were housed in identical cages, but without a running wheel, for the same period of time.

2.2. Irradiation

For the irradiated groups, gamma irradiation was administered under ketamine/xylazine anaesthesia with a Cobalt source (AECL Medical, MDS Nordion Co., Chalk River, Ontario, Canada). As in a previous study [13], irradiation was administered on one day at a dose of 8 Gy. A heavy lead shield was used to restrict the irradiation beam to a 1 cm × 1 cm square area, which was projected to the rear of the brain from above. The irradiation procedure took approximately 20 min per animal. Throughout the duration of the study, there were no noticeable side effects of irradiation in terms of weight loss, or hair loss. Control rats receiving the sham procedure were transported to the irradiation facility, anaesthetized, and handled the same way, but were not administered radiation.

2.3. Behavioural testing

Following irradiation, or sham treatment, the rats were assigned to one of four experimental conditions (see Fig. 1 for experimental design and timelines).

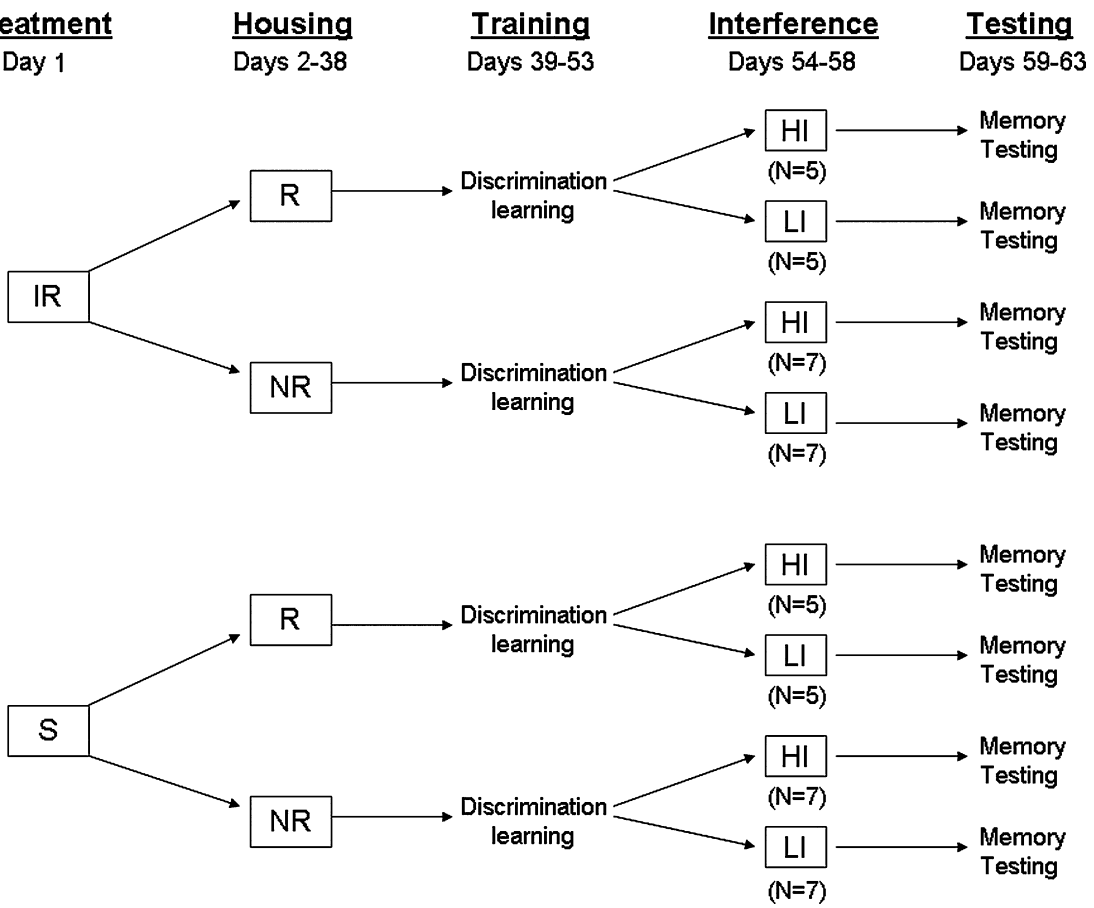

Fig. 1. Experimental design and timeline. Abbreviations: IR – irradiation treatment; S – sham treatment; R – runners; NR – non-runners; HI – high-interference; LI – low-interference; N – number of rats/group.

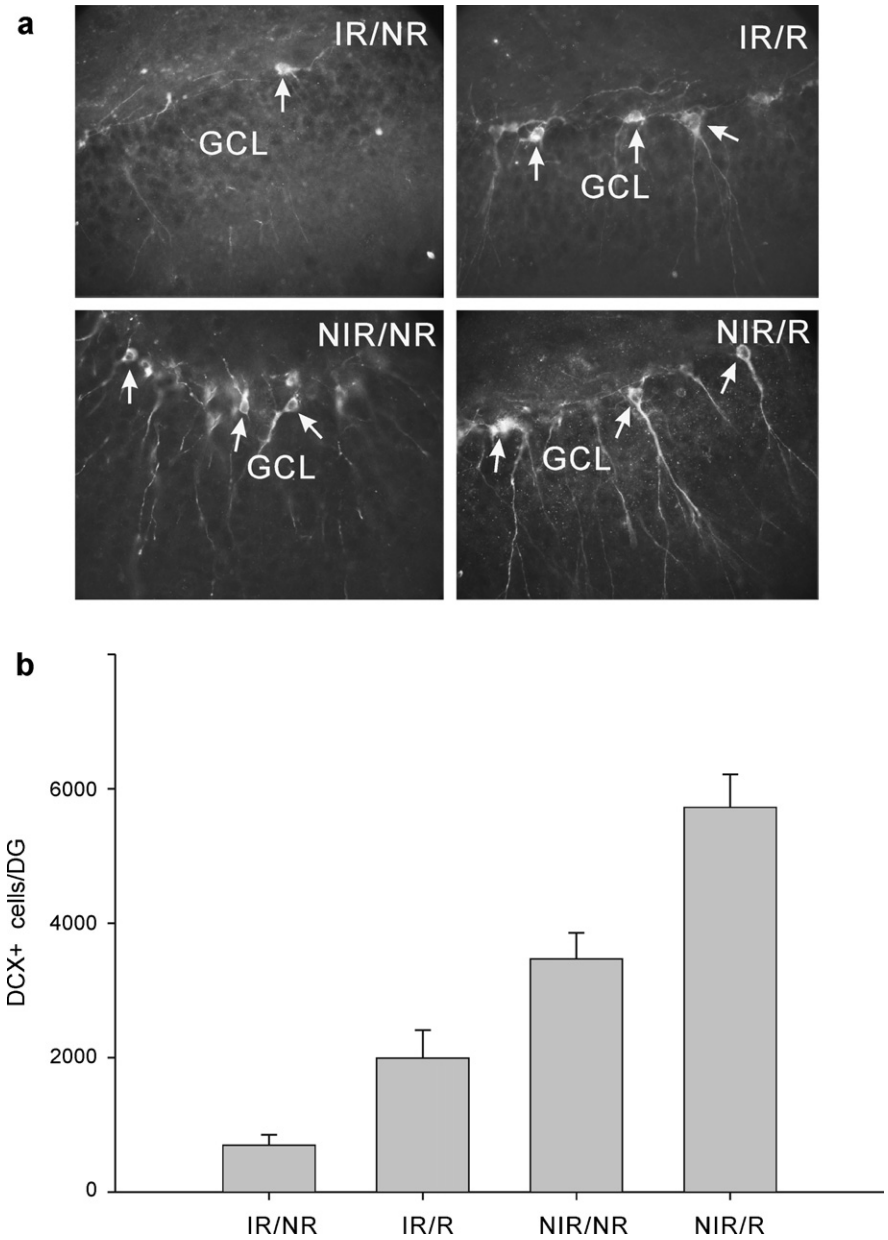

Fig. 2. (a) Neurogenesis in the four experimental groups. Representative images of tissue sections showing doublecortin-stained immature neurons. Arrows point to doublecortin-positive young neurons located in neurogenic subgranular zone. Dendrites of young neurons extend across granule cell layer (GCL) and into the molecular layer. (b) Summary graph illustrating number of immature neurons in dentate gyrus in the experimental groups. Abbreviations: IR/NR – irradiated/non-runners; IR/R – irradiated/runners; NIR/NR – non-irradiated/non-runners; NIR/R – non-irradiated/runners; HI – high-interference; LI – low-interference.

All rats received visual discrimination training in a circular pool that measured 60 cm high, 100 cm in diameter, and was filled with opaque water to a height of 30 cm. The pool was fitted with a cross-maze, in which each arm measured 40 cm long × 20 cm wide and rose 15 cm above the water line. All 4 arms were open throughout discrimination learning and testing. In the centre of the maze, a black cylinder was suspended over the entrance of one of the side arms, and a white cylinder suspended over the entrance of the opposite arm. The cylinders were 28 cm long and 2.5 cm in diameter. The positioning of the cylinders was randomly determined from one trial to the next, although they were always located at the entrance of opposite arms. Each cylinder was positive for half of the rats.

A trial began with the rat placed in the pool at the end of one of the neutral arms and allowed to swim to the centre of the maze. A swimming response toward the positive cylinder led to a 10 cm^2 platform located at the end of that arm and submerged about 2.5 cm below the water line. When the rat found the platform, it could mount it and escape the water for 20 s. If the rat failed to find the platform within 60 s, it was placed on the platform for 20 s. An error was recorded when the rat's full body (less the tail) entered an incorrect arm, or when a rat exited the goal arm before finding the platform. Eight trials/day were administered until the rat reached the criterion of .35 errors/trial, or less, averaged over two consecutive days.

The day after criterion, rats in the high-interference condition received 40 trials (8 trials/day over 5 days) on an unsolvable problem. The procedure was similar to training except that, at the centre of the maze, the rat encountered two identical cylinders painted with alternating black and white bands, suspended over opposite arms. The platform was located randomly at the end of one of the arms. In the low-interference condition, the side arms were sealed, there were no cylinders, and the rat merely had to swim in a straight line to the other end of the pool to find the platform.

The day after the last interference trial, memory for the original black-white discrimination was tested according to procedures followed during training. For this test, the rats received 5 trials/day over 5 days.

2.4. Immunohistochemistry

Two weeks after the completion of behavioural testing, the rats were euthanized with a lethal dose of sodium pentobarbital and perfused using a PBS flush, followed by 100 ml of 4% paraformaldehyde. Following established protocols [19], the hemispheres were separated and fixed in 4% paraformaldehyde overnight at 4 C. The tissue was then transferred to phosphate buffered saline with sodium azide and refrigerated until further processing.

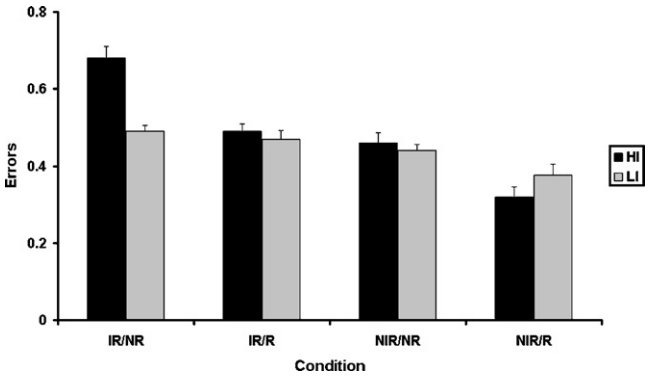

Fig. 3. Memory testing. The number of errors made by all groups in the high- and low-interference conditions averaged over 5 days of testing. Abbreviations for groups and interference conditions are the same as Fig. 2. Error bars represent ± S.E.M.

The hippocampus was extracted from the right hemisphere and sectioned extensively along the dorso-ventral extent at 30 μm using a vibratome. Fifteen sections were sampled evenly along the dorso-ventral axis from each animal and incubated with primary anti-doublecortin [DCX, Santa Cruz, (C-18, sc-8066), 1:200, 24 h at 4 C], or anti-Ki67 [(Vector labs, VP-K451), 1:200, 18 h at room temperature] antibodies. This was followed by incubation with appropriate, fluorescently tagged secondary antibodies [3]. The number of new cells in the hippocampus was counted under a fluorescent microscope at 40×. The average cell number per section in each animal was multiplied by the total number of sections to yield the number of cells per dentate gyrus.

3. Results

3.1. Immunohistochemistry

Images from the four experimental groups illustrate typical doublecortin (DCX) – expressing new neurons lining the subgranular zone of the dentate gyrus. Irradiation treatment produced an 80% reduction in the number of immature neurons expressing DCX in the dentate gyrus (Fig. 2a). Running increased neurogenesis about equally in irradiated, as well as non-irradiated rats (Fig. 2b). Statistical analyses confirmed a significant difference between the four experimental groups ($F_{3,46} = 35.39$, $p < .001$), with all groups being different from each other (Holm-Sidak test, $p < .05$). There were no differences in neurogenesis between high and low-interference sub-groups. The relative differences between levels of neurogenesis in the four groups as measured by DCX were confirmed using Ki-67 (not illustrated). The two markers combined showed a robust decrease in proliferation and neuronal differentiation resulting from irradiation.

3.2. Behavioural

Rats required an average of about 60 trials to reach the specified criterion during original discrimination learning and there was no difference between groups on this measure ($F < 1$; see Table S.1).

Since there were no main effects, or interactions involving days ($p > .05$ for all comparisons), for purposes of presentation, the performance of groups during memory testing is represented in Fig. 3 as the mean number of errors across the 5 days of testing (see Fig. S.1). There was an overall main effect of irradiation treatment ($F_{1,40} = 31.86$, $p < .0001$) that was driven largely by the poor performance of irradiated rats in the high-interference memory test. A significant irradiation × interference interaction ($F_{1,40} = 7.10$, $p < .02$) confirmed that the difference in the numbers of errors made in the high- and low-interference conditions was significantly greater in the irradiated than the non-irradiated rats.

The adverse effect of irradiation on memory in the high-interference condition was virtually eliminated in the irradiated group that engaged in running. This was confirmed in separate analyses of performance by the irradiated and non-irradiated groups. There was a significant main effect of running in both groups (irradiated: $F_{1,20} = 10.49$, $p < .01$; non-irradiated: $F_{1,20} = 9.18$, $p < .01$) that, in the irradiated groups, was modified by a significant interference × running interaction ($F_{1,20} = 7.54$, $p < .01$). The interaction reflected significantly improved performance in irradiated runners in the high-interference test (Group IR/R HI), relative to irradiated non-runners on the low-interference test (Group IR/NR LI). Amongst non-irradiated rats, runners generally made fewer errors than non-runners during memory testing ($F_{1,20} = 9.18$, $p < .01$), but in these rats there was no interference × running interaction ($F < 1$). Thus, running selectively improved memory performance of irradiated animals.

The same pattern of results was seen on another recall measure that was minimally affected by relearning of the discrimination response. This measure was a savings score that expressed the mean number of errors by each rat on the first day of testing as a percentage of the mean number of errors made on the final day of training. Irradiated, non-running rats exhibited less savings in the high- than in the low-interference condition ($F_{1,12} = 5.06$, $p < .04$), but this difference disappeared in the irradiated, running group ($F < 1$). As well, on this measure, the irradiated, running group did not differ from any of the non-irradiated groups.

Examination of the running data for the IR/R and NI/R groups predictably showed that, over the course of the experiment, distance traveled each day correlated significantly with running speed ($r^2 = 0.56$, $p < .001$) and time spent running ($r^2 = 0.49$, $p < .001$). There was an unexpected finding in that the IR/R group engaged in more running than the NI/R group. For example, the IR/R group averaged 8.4 km/day over the entire study, as compared to 3.6 km/day by the NI/R group ($t_{18} = -3.65$, $p < .002$). The other running measures yielded the same difference.

4. Discussion

Memory loss associated with hippocampal impairment in many species [12], including humans [20], is especially pronounced under conditions of high interference. In demonstrating that blocking the generation of new neurons in the dentate gyrus has similar effects, the present study showed that neurogenesis functions as part of the mechanism that controls interference in memory.

While suppressing neurogenesis disrupted memory for the learned discrimination in the high-interference condition, it had no effect on acquisition, or recall of the discrimination in the absence of interference. This result parallels the findings of similar studies involving animals with surgical lesions to the hippocampus [21,22]. It is widely held that, when presented with visual discrimination problems, animals with hippocampal damage compensate by depending more on a context-independent, stimulus-response strategy to learn the task. This strategy does not require the hippocampus but, rather, is thought to be mediated by striatal neural circuitry [23,24]. Information learned by following a stimulus-response strategy is extremely vulnerable to the effects of interference, primarily because such learning does not produce the type of representations that readily distinguish between conflicting events. To accomplish this, the animal must employ a hippocampus-based stimulus-association strategy in which a learning event is uniquely linked to contextual features of the environment [25,26]. If, on another occasion, a potentially interfering event is introduced into the same environment, such as the unsolvable problem in the present experiment, the hippocampus is involved in forming a new set of contextual associations that help to differentiate the two experiences. When required to recall the original learning, the intact animal is able to separate the con-

flicting experiences and efficiently retrieve the correct memory. The present research points to the conclusion that, within the hippocampus, newly generated dentate gyrus cells are implicated in the formation of those contextual associations.

Another explanation relates to the physical similarity of the stimuli used in the learning/memory tests and the interference condition. If the irradiated, non-running group failed to disambiguate these stimuli and learned, during the interference condition, that the stimuli were no longer predictive, it is possible that they generalized this new learning to the memory test. This is an interesting possibility that, in fact, was considered in our early research involving surgically induced hippocampal lesions and similar discrimination learning paradigms [27,28]. In those studies, rats with hippocampal lesions were consistently impaired in high-interference situations in which tasks were modified within the same context. When the learning and interfering tasks were administered in distinctively different and novel contexts, the lesioned rats did not exhibit inter-task interference. This suggested that their impairment was related to an inefficiency in forming associations with learned responses when the learning events occurred in overlapping contexts, and not to a basic difficulty in stimulus discrimination. While we favour the 'contextual-association' hypothesis, the two ideas could be tested in irradiated rats using the present paradigm, but administering the learning and memory tests in a context that contrasted with the interference condition.

The selective effect of irradiation treatment on memory in the presence of high interference is predicted by computational models of hippocampal function that attribute a central role to newly generated hippocampal cells in the control of interference during learning and memory [e.g., Refs. [15–17]]. While the various models differ in their points of emphasis [see Ref. [7]], they are all based on the premise that differentiated inputs from newly formed dentate gyrus cells to CA3 help to encode event-specific information and create contextualized memories that are represented in the hippocampal network. Distinctive memories, formed in this way, are essential for successful performance on hippocampus-dependent tasks including, for example, trace conditioning [2], contextual fear conditioning [3], and delayed-non-matching-to-sample [3]. Moreover, because the contextually distinct memories can be distinguished from other memories that share contextual features, potentially interfering effects of similar experiences, as encountered in the present task as well as tasks that require separation [29] or integration [17] of fine patterns, can be resisted. It should be noted that current computational models are based on the controversial notion that newly born cells are preferentially recruited for hippocampus-dependent tasks. In fact, while there are reports that new neurons of different ages are preferentially recruited for specific tasks [30–33], the exact nature of activation, age of young neurons, and their location within the hippocampus are all still under debate [34]. While computational models represent a significant advance toward understanding the functional significance of adult neurogenesis, the ultimate usefulness of this approach will depend on further confirmation of preferential recruitment at appropriate timelines.

The present study also examined the impact of running activity on the performance of irradiated and control rats in our behavioural task. There is considerable evidence that physical exercise can lead to improved memory function in aged animals [35] and in animals with hippocampal damage [18]. The present results show that increased running confers similar benefits in rats whose hippocampus has been compromised by irradiation treatment. It is also well known that physical exercise promotes the production of new dentate gyrus cells in normal animals [8,9], but here we demonstrate that exercise-induced neurogenesis can rescue hippocampus-dependent function in hippocampally impaired animals. This finding extends previous reports involving postnatal- [36] and adult- [37] irradiated mice, where the behavioural tasks were quite different and did not involve manipulations of memory interference. Interestingly, in the present study, both irradiated and non-irradiated rats exhibited increased neurogenesis following running and both groups performed better than non-runners. While physical exercise is known to have non-neurogenic effects [38,39] that could have contributed to improved performance in the runners, the present results provide evidence that increased cell growth is an important factor in the functional benefits derived from such activity, specifically in high interference conditions.

A recently completed study provides indirect evidence that improved cognitive function following exercise is also associated with enhanced neurogenesis in humans [40]. In that study, a group of young adults was administered a series of cognitive tasks before and after a rigorous, six-week program of aerobic exercise. A gadolinium enhanced MRI scanning technique [41] measured changes in dentate gyrus regional cerebral blood volume (rCBV) that are known to correlate with changes in hippocampal neurogenesis. The results showed a significant increase in dentate gyrus rCBV that selectively correlated with improved performance on hippocampus-dependent learning and memory tasks.

Other research suggests that the relationship between activity, neurogenesis, and cognition is not straightforward. In two studies [42,43], physical activity was found to improve spatial memory in normal mice. Irradiation that reduced hippocampal neurogenesis did not affect the performance of mice raised in standard housing conditions, but physical exercise affected the irradiated mice in different ways. Clark et al. [42] found that, in contrast to normal mice, the performance of irradiated mice on the spatial task did not benefit from increased activity, suggesting that neurogenesis was necessary to realize the cognitive benefits of exercise. The opposite conclusion was drawn by Meshi et al. [43] who found that arresting neurogenesis through irradiation did not affect performance, regardless of activity level. The reasons for the discrepancies are unclear but research into this question will need to consider several factors, including task, species, and procedural differences, as well as the amount of neurogenesis suppression following treatment and the recovery of cell production associated with increased activity.

Related to the running effect in the present study, it is notable that the IR/R group exhibited more running than the NI/R group. Hyperactivity was not observed in our previous work that examined various running parameters before and after irradiation [13], nor was it observed in a recent study by Naylor et al. [36]. Interestingly, the latter investigators did report irradiation-induced hyperactivity in an open-field, an effect that also has been associated with hippocampal damage [21,44]. With respect to the higher running levels in the IR/R group, it is interesting to speculate that it may have contributed to recovery of neurogenesis. The effect of irradiation on activity levels would appear to warrant further investigation.

In summary, the present results extend the range of hippocampus-sensitive tasks that appear to depend on adult-generated neurons in the dentate gyrus of the hippocampus. The modulation of interfering influences during various types of learning and memory is a well-established feature of hippocampal function and it is now clear that newly born dentate gyrus cells are an essential part of this process. At a more fundamental level, there is growing evidence that this and other memory-related functions can be seen as an expression of the role that new cells play in the formation of hippocampus-dependent contextualized memories. That the importance of neurogenesis to the formation of such memories can be influenced by external variables, such as physical exercise, speaks to the degree of plasticity within the system.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbr.2011.05.032.

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