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A comparison of low- and high-impact forced exercise: Effects of training paradigm on learning and memory

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Abstract

In this study we compared two types of forced exercise—a low impact paradigm to minimize stress, which included speeds up to 10 m/min and a stressful high impact paradigm, with speeds up to 21 m/min. 150 male C57BL/6J mice were randomly assigned to the low impact, high impact, or sedentary control conditions and were tested on the rotorod and Morris water maze (MWM) as indices of motor learning and spatial memory. We found that five weeks of stressful high speed forced exercise led to significant improvement in rotorod performance, as high impact runners outperformed both low impact runners and controls at 15 and 25 RPM speeds. These differences were the result of improved physical fitness due to exercise and likely do not reflect enhanced learning in these mice. In the MWM, five weeks of stressful high impact exercise led to significant impairment in spatial memory acquisition compared to low impact runners and controls. Low impact exercise for 10 weeks significantly improved retention of spatial memory compared to high impact exercise. Results suggested that these two paradigms produced different effects of forced exercise on learning and memory. The low impact paradigm led to some improvements, whereas the stressful high impact program caused significant impairment. Comparison of these two paradigms begins to address the window between the beneficial and detrimental effects of forced exercise, and have suggested a boundary of exercise intensity that leads to impairment in learning.

Keywords

spatial memory; motor learning; forced exercise; mouse; Morris water maze; rotorod

1. Introduction

The goal of this study was to compare the effects of forced exercise intensity on motor learning and spatial memory. The forced exercise paradigm affords greater experimental control by manipulating the duration and intensity of exercise, though studies of voluntary exercise are more prevalent. In humans, exercise can improve physical health [1], increase brain volume [2] and enhance cognition in samples ranging from children [3] to older adults [4, 5]. In animal research, there is little consensus on the appropriate speeds to maximize the benefits of exercise, or conversely, the speeds most appropriate for studying the damaging effects of stress due to exercise. Thus, we compared forced exercise paradigms—low impact

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exercise at slow to moderate speeds and high impact exercise at very high speeds. Few studies exist that address both the cognition-enhancing and the stress-inducing potential of forced exercise. Our goal was to determine if our low impact paradigm, modeled studies examining the benefits of exercise, could improve spatial memory and motor learning. We also examined if a high impact paradigm, incorporating speeds used in stressful exercise research, would impair learning and memory. Finally, we compared the two paradigms—to investigate the different effects of low and high impact forced exercise on learning and memory.

Forced exercise is generally implemented as a stressor, with the goal of disrupting physiological function, including immune and endocrine systems. Stressful forced exercise elevates corticosterone [6], alters inflammatory cytokine expression [7], and increases the susceptibility to infection [8]. Elevated levels of corticosterone can cause atrophy of pyramidal neurons in the hippocampus [9–12], as this structure is particularly sensitive to prolonged exposure to elevated glucocorticoid levels [13]. A behavioral consequence of this hippocampal disruption is impairment on tests of learning and memory. For example, high intensity treadmill running (25 m/min) leads to impairment in spatial learning ability in rats [14]; however, high speed forced exercise can also improve aspects of spatial learning [15]. Few studies of learning that implement forced exercise speeds approaching those used in immune and endocrine system studies exist in mice. In addition, it remains unclear whether high impact forced exercise has beneficial or detrimental effects on learning.

The effects of exercise on learning and memory appear to be more consistent when low impact paradigms are used. In rats, forced exercise at speeds of 8–9 m/min improves spatial learning [16, 17]. Comparable results have also been reported in mice. Speeds ranging from 3–12 m/min improve acquisition of spatial memory, as well as retention [18–20]. These studies incorporate speeds well below those normally considered stressful (17–30 m/min, i.e. [6]) and therefore examine forced exercise apart from a stressful component.

In this study we compared mice that were randomly assigned to a low impact (up to 10 m/min) forced exercise paradigm, a high impact (up to 21 m/min) forced exercise paradigm, or sedentary controls on measures of hippocampus-dependent spatial learning (Morris water maze [MWM]) and cerebellum-dependent motor learning (rotarod). Our goal was to replicate previous low impact studies and extend conclusions to forced exercise using a wheel system rather than a treadmill. Since very few mouse high impact exercise studies exist, another goal was to examine speeds approaching those used in stressful exercise research, though with a focus on behavior rather than immune or endocrine function. Finally, we planned to compare the two types of forced exercise directly. We hypothesized that low impact exercise would improve spatial learning and have no impact on motor learning. We also hypothesized that high impact forced exercise would lead to impairment in the hippocampus, which would impair spatial learning. High impact exercise was not expected to affect motor learning.

2. Materials and Methods

2.1. Subjects

150 male C57BL/6 mice (Jackson Laboratory, Bar Harbor, Maine), aged 3–5 months ($M = 4.01$ mo, $SD = 1.00$ mo) were randomly assigned as low impact runners ($n = 40$), high impact runners ($n = 35$) or sedentary controls ($n = 75$). Mice were housed in temperature- and humidity-controlled Association for Assessment and Accreditation of Laboratory Animal Care facility with a 12 hr light/dark schedule and *ad libitum* access to food and water. This research was approved by Temple University's Institutional Animal Care and Use Committee.

2.2. Exercise

A Forced Walking Wheel System (Lafayette Instrument Co., Lafayette, IN, Model 80801) with individual running wheels was used to pre-train runners twice daily in 30-minute sessions. All runner mice were pre-trained for several days at low speeds to acclimate to the running wheels. Mice randomly assigned to the low impact runner condition were trained in two 45-minute sessions per day for 5 days/week with speeds progressively increasing to a maximum of 10 m/min. After 10 weeks of training, mice were tested on the rotorod and MWM. High impact runners were trained in two 45-minute sessions per day for 5 days/week with speeds progressively increasing to a maximum of 21 m/min. After 5 weeks of training, mice were tested on the rotorod and MWM. Occasionally, mice that clung to the wheel were gently prodded with paintbrushes to insure they were continually moving during the session. Sedentary control mice were handled for a portion of each session to approximate handling of runners. Ample evidence exists that chronic stressors have detrimental effects on hippocampal neurons in as few as 21 days [21–23]. Thus, the high impact runners were exercised for 5 weeks to maximize stress effects and minimize potential muscle damage due to long-term running exposure. Low impact runners were exercised for 10 weeks to approximate previous studies [18, 19]. High and low impact exercise parameters were determined by a survey of the exercise literature (behavioral, endocrine and immune system effects) and our own experience with forced wheel running [6, 16–20].

2.3. Rotorod

2.3.1. Apparatus—A four-lane motorized rotorod (San Diego Instruments, Inc., San Diego, CA) was used. Each rod was 3 cm in diameter and 11 cm long, and maintained at 46 cm above the foam-covered base. An electronically controlled motor maintained the rod speed. Photo beams detected falling in each lane.

2.3.2. Procedure—Training took place over three days. Each session consisted of eight trials, four at each speed (15 and 25 RPM). There was a five-minute inter-trial interval and 30 minutes between speed changes. On each day, mice were placed in the direction opposite of the rotation of the rod. To avoid falling, mice were required to move forward in a coordinated manner. Trials ended if the subject did not fall after 60 seconds.

2.4. Morris Water Maze

2.4.1. Apparatus—MWM methods have been reported previously [19]. A black circular pool, 100 cm diameter and 60 cm deep contained 16 cm of water maintained between 24–26°C. The pool was surrounded with visual cues. An 11 cm square clear Plexiglas platform was positioned 1 cm below the surface of the water. The same platform was used for cued training marked by a black flag (10 × 7 cm) suspended on a stick. The black interior of the pool, combined with the clear Plexiglas platform, is sufficient to hide the location of the platform and avoids the use of nontoxic paint to make the water opaque [19].

2.4.2. Procedure—Training took five days. Each trial was initiated by placing the mouse in the water in a quadrant either opposite or adjacent to the platform. The platform location was fixed during hidden platform training and varied across the four quadrants in the visible platform task. Each trial lasted 90 seconds or until the mouse located the platform. Mice that did not find the platform were guided to it and given a maximum latency score. Each mouse was required to spend 15 seconds on the platform at the end of each trial. Between blocks mice were placed in individually heated, extra-absorbent paper-lined plastic holding cages.

Training consisted of three blocks of four trials (12 trials/day/mouse) for three consecutive days. On the fourth day, mice were given a probe trial without the platform. After swimming

for 90 seconds the mouse was returned to its holding cage. On the fifth day, mice were given the visible platform task. Trials were recorded using the SMART program (Panlab; Barcelona, Spain).

2.5. Statistical Analyses

All statistical analyses were carried out using the IBM SPSS Statistics (Version 19) software package. The main analysis used was the mixed analysis of variance (ANOVA) to compare the effects of low and high impact forced exercise on dependent measures from the rotorod and MWM. Significance was set at $p < .05$. When appropriate, post-hoc analyses were conducted using the Tukey Honestly Significant Difference (HSD) test incorporating adjusted critical values. A subset of runners ($n = 9$) refused to run during the majority of the five weeks of exercise and instead clung to the wheels. These mice were excluded from all analyses for two reasons: 1) very little running occurred during training and 2) stress effects for these mice were likely different than runners that were not gently prodded as often and were not clinging to the wheels. Some mice were tested as pilot subjects for an accelerating rotorod paradigm (data not included) and were not tested on the standard rotorod. Thus, sample sizes for the rotorod analyses were: control ($n = 45$), low impact runner ($n = 20$) and high impact runner ($n = 20$). Prior to analyses, statistical outliers (mean behavioral performance was at least 1.5 times greater than the interquartile range) were excluded. Final sample sizes for the MWM were: control ($n = 73$), low impact runner ($n = 39$) and high impact runner ($n = 23$).

3. Results

3.1. Rotorod

Latency to fall data were analyzed with a 3 (Group) $\times$ 3 (Training Session) mixed ANOVA. Separate ANOVAs were conducted for the 15 and 25 RPM speeds. At 15 RPM, significant main effects of Group ($F(2, 82) = 6.92, p < .01$) and Training Session ($F(2, 164) = 88.49, p < .001$) were found, as well as a Group $\times$ Training Session interaction, $F(4, 164) = 2.38, p = .05$ (Figure 1). Overall, high impact runners had significantly longer latencies to fall than both low impact ($p < .01$) and control groups ($p < .01$), according to post-hoc tests. To assess the main effect of Training Session, post-hoc tests determined that, for all mice, latency to fall increased significantly from Training Session 1 to 2 ($p < .01$) and from 2 to 3 ($p < .01$). Further post-hoc analyses confirmed that in Training Session 2, high impact runners significantly outperformed controls and low impact runners ($ps < .05$). The same pattern was present in Training Session 3 ($ps < .01$). No significant differences were found in Training Session 1.

At 25 RPM, significant main effects of Group ($F(2, 82) = 10.84, p < .001$) and Training Session ($F(2, 164) = 65.98, p < .001$) were found, as well as a Group $\times$ Training Session interaction, $F(4, 164) = 6.45, p < .001$ (Figure 1). Overall, high impact runners had significantly longer latencies to fall than both low impact ($p < .001$) and control groups ($p < .001$), according to post-hoc tests. To assess the main effect of Training Session, post-hoc tests determined that, for all mice, latency to fall increased significantly from Training Session 1 to 2 ($p < .01$) and from 2 to 3 ($p < .01$). Further post-hoc analyses confirmed that in Training Session 2, high impact runners significantly outperformed controls and low impact runners ($ps < .01$). The same pattern was present in Training Session 3 ($ps < .01$). No significant differences were found in Training Session 1.

3.2. Morris Water Maze

Latency to escape the pool was investigated using a 3 (Group) $\times$ 9 (Training Session) mixed ANOVA. A significant main effect of Training Session was found, $F(8, 1056) = 169.29, p$

$< .001$, as latency to escape tended to decrease significantly across Training Sessions. There was no effect of Group, though a significant Group $\times$ Training Session interaction was found, $F(16, 1056) = 2.36$, $p < .01$ (Figure 2). Post-hoc tests determined that group differences existed in Training Sessions 5 and 7. High impact runners had significantly longer latencies to escape than controls ($p < .01$) and low impact runners ($p < .05$) in Training Session 5. The same pattern was present in Training Session 7 ($ps < .01$).

After hidden platform training, the platform was removed and mice were placed in the pool for one trial as a measure of retention of place learning. The first dependent measure was the number of times the mouse crossed over the area where the location of the platform was learned. A second dependent variable was the amount of time spent swimming in each quadrant. It was expected that the mice would cross the area of the former location of the platform more and spend more time swimming in the quadrant where the platform had been located compared to the other quadrants. Both dependent variables were investigated with 3 (Group) $\times$ 4 (Quadrant) mixed ANOVAs. For the number of platform crossings, results showed a significant main effect of Quadrant, $F(3, 396) = 124.82$, $p < .001$, and Group, $F(2, 132) = 6.04$, $p < .01$, as well as a Group $\times$ Quadrant interaction, $F(6, 396) = 2.37$, $p < .05$ (Figure 3). Overall, mice crossed the location of the platform in the trained quadrant significantly more than the other quadrants ($p < .01$) and high impact runners had significantly fewer platform crossings than low impact runners ($p < .01$). Low impact runners generally had more platform crossings than controls; however, this difference did not achieve statistical significance ($p = .06$).

As the performance in the trained quadrant is the strongest index of spatial memory retention, we planned to examine exercise effects only in this quadrant. In the trained quadrant, low impact runners crossed the former platform location significantly more than the high impact runners ($p < .05$). Low impact runners had numerically more platform crossings relative to controls, but the difference was not statistically significant. In addition, high impact runners had numerically fewer platform crossings than controls, but the difference was not statistically significant.

An analysis of the time spent swimming showed a significant main effect of Quadrant, $F(3, 396) = 65.01$, $p < .001$. Mice spent significantly more time swimming in the trained quadrant than the other quadrants. No significant effects of Group or interactions were found.

For visible platform training, a flag was attached to the platform to mark its location. A 3 (Group) $\times$ 3 (Training Session) mixed ANOVA with latency to escape as the dependent variable revealed significant main effects of Training Session, $F(2, 264) = 90.33$, $p < .001$, and Group, $F(2, 132) = 13.75$, $p < .001$. Post-hoc tests determined that latency to escape in all mice improved significantly from Training Session 1 to 2 ($p < .01$) and 2 to 3 ($p < .01$). Low impact runners took significantly longer than controls ($p < .01$) and high impact runners ($p < .05$) to find the visible platform. In addition, low impact runners covered significantly more distance ($p < .01$) and had a significantly faster swim speed ($p < .01$) than high impact runners.

4. Discussion

In this study we examined motor learning and spatial memory in mice exercised at moderate or high speeds and sedentary controls. Rotorod performance was enhanced by chronic high impact forced exercise, as these mice significantly outperformed sedentary controls and low impact runners at both 15 and 25 RPM speeds. This result was not expected, but is likely due to training effects in the high speed runners. High intensity wheel running may have led

to increased muscle mass and enhanced physical fitness, which would have allowed the mice to stay on the rotarod longer. Low impact runners also displayed slightly longer latencies to fall on the rotarod, perhaps indicating conditioning effects from the slower speeds, though low impact runners were not significantly different from sedentary controls. Previous research has shown that superior physical fitness due to wheel running improves rotarod performance, but does not alter the rate of learning [24]. In addition, physical exercise is not generally associated with changes in cerebellar plasticity. Motor skill learning can alter the number of synapses per Purkinje neuron, whereas physical exercise only leads to increases in blood vessel density [25–27]. Therefore, the most likely explanation for rotarod performance differences appears to be improved physical fitness and not enhanced learning capacity.

Spatial learning was differentially affected based on forced exercise paradigm. High impact runners were significantly impaired relative to both controls and low impact runners during MWM acquisition. Low impact runners showed no observable improvement in spatial learning acquisition, but did demonstrate enhanced retention of spatial memory compared to high impact runners. Neither exercise group was significantly different from control mice in spatial memory retention, though the difference between low impact runners and controls approached significance ($p = .06$). This suggests that the effects of exercise (positive or negative) on spatial memory retention may not be particularly large. An alternative explanation for the spatial learning results of this study may be due to the large number of acquisition trials given to mice (12 trials/day for 5 days). Fewer training trials per day, thus increasing task difficulty, may have maximized the detection of impairment in high impact runners and improvement in low impact runners.

Several studies have found that low impact exercise (both forced and voluntary) can improve retention of spatial memory [15, 17, 19, 28, 29], though it should be noted that not all studies report enhanced spatial memory retention after exercise [30]. A potential explanation for our results, especially compared to studies incorporating voluntary wheel running, involves the differences between the two types of exercise, which include running speed, time spent running and effects on neurogenesis [31]. For example, mice with voluntary running wheels usually complete about 20,000 – 40,000 revolutions in a single day [32] and, can average 2.21 km/day [33]. In comparison, the mice from the present study ran approximately 900 m/day (low impact) and 1.89 km/day (high impact).

The group differences in the visible platform portion of the MWM are difficult to explain. Low impact runners took longer to find the visible platform, covered more distance and showed a faster swim speed compared to high impact runners. Increased swim speed could be attributed to enhanced physical fitness from chronic exercise, although it would be expected that high impact runners would show the fastest swim speeds due to the most intense exercise training. Another potential explanation is that the high impact runners may have suffered from some sort of muscle damage due to the chronic high speed running. This damage could account for the longer latencies to escape during acquisition and the slower swim speed compared to the low impact runners that benefitted from enhanced physical fitness but avoided damage from high speeds. This explanation is insufficient for two reasons. First, a muscle damage hypothesis could not account for the reduced retention of the platform location exhibited by the high impact runners, as this portion of the task does not rely on swim speed but instead more precise spatial localization. By the end of acquisition, high impact runners were indistinguishable from low impact runners and controls, which would suggest comparable levels of learning. Secondly, the high impact runners showed the largest training effects on the rotarod. If muscle damage was expected due to high intensity of exercise, then high impact runners should have shown impairment. On the contrary, the high impact runners significantly outperformed controls and low impact

runners at both speeds of the rotorod. Thus, neither physical conditioning, nor the damaging effects of high speed exercise on the muscular system can sufficiently account for the differences reported in the visible platform section of the MWM.

Another potential explanation involves priming of the stress and inflammatory response systems [34]. Acute stress has been found to “prime” the immune system and lead to a greater response to subsequent stressors in both the periphery and CNS. As the MWM is stressful and leads to elevation of corticosterone [35], it is possible that chronic exercise stress primed the immune system and led to an enhanced response to the stress of MWM training. The enhanced inflammatory and stress system response may have interfered with acquisition, resulting in larger latencies and decreased swim speed in the high impact runners. Since low impact runners were trained at non-stressful speeds, they may not have been affected by the priming response of the immune system.

5. Conclusions

Despite some difficulties in drawing conclusions from comparisons between runner and control mice, there were clear differences in learning and memory between low impact runners and high impact runners. The lack of significant improvements in spatial memory acquisition in low impact runners may be addressed by increasing running speed to maximize the effects of several potential underlying neural mechanisms that can support hippocampal plasticity and facilitate spatial memory. Several studies have reported increases in neurogenesis in response to forced exercise [31] that accompany improvements in spatial learning [30, 36, 37]. In addition, improvements in learning and memory may be supported by increases in angiogenesis [38, 39]. Low impact runners had more platform crossings than controls, but for the paradigm to be more effective, the intensity of running may need to be increased to better approximate speeds recorded with voluntary running wheels. Our results suggested that high impact runners showed evidence of spatial memory impairment—in acquisition as well as retention. Learning in these animals was impaired in a similar manner to previous studies of chronic stressors [14, 40, 41]. Our results have narrowed the window between the beneficial and detrimental effects of forced exercise, and suggested a boundary for exercise intensity that leads to impairment. Further work is needed to refine the low impact paradigm to maximize benefits.

Highlights

- We compared low- and high-impact forced running on motor learning and spatial memory
- We expected improvement from low- and impairment from stressful high-impact running
- Differential effects on learning and memory were dependent on running paradigm
- High speed running improved rotorod performance and impaired water maze acquisition
- Low speed running improved water maze retention

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Figure 1.

Rotorod performance in mice randomly assigned to a low impact exercise, high impact exercise or sedentary control condition tested at 15 and 25 revolutions per minute (RPM) over three days. At both speeds, learning is expressed by all groups. Overall, high impact runners had significantly longer latencies to fall than both controls and low impact runners at 15 RPM ($p < .01$) and 25 RPM ($p < .001$). * high impact runners significantly different from control and low impact ($p < .05$).

Figure 2.

MWM acquisition in mice randomly assigned to a low impact exercise, high impact exercise or sedentary control condition. Overall, all groups showed evidence of learning in that latency to escape decreased across nine Training Sessions. High impact runners had significantly longer latencies to escape compared to low impact runners and sedentary controls in Training Sessions 5 and 7. Values are mean $\pm$ SEM. † high impact runners significantly different from controls ($p < .01$); high impact runners significantly different than low impact runners (* $p < .05$; ** $p < .01$).

Figure 3.

MWM retention in mice randomly assigned to a low impact exercise, high impact exercise or sedentary control condition. All mice crossed the area in the trained platform quadrant more times than the same area in untrained adjacent and opposite quadrants. Within the trained quadrant, low impact runners crossed the former platform location significantly more than high impact runners. Values are mean $\pm$ SEM. ** low impact runners significantly different from high impact runners ($p < .01$).