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FORCED AND VOLUNTARY EXERCISE DIFFERENTIALLY AFFECT BRAIN AND BEHAVIOR

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Abstract—The potential of physical exercise to decrease body weight, alleviate depression, combat aging and enhance cognition has been well-supported by research studies. However, exercise regimens vary widely across experiments, raising the question of whether there is an optimal form, intensity and duration of exertion that would produce maximal benefits. In particular, a comparison of forced and voluntary exercise is needed, since the results of several prior studies suggest that they may differentially affect brain and behavior. In the present study, we employed a novel 8-week exercise paradigm that standardized the distance, pattern, equipment and housing condition of forced and voluntary exercisers. Exercising rats were then compared with sedentary controls on measures previously shown to be influenced by physical activity. Our results indicate that although the distance covered by both exercise groups was the same, voluntary exercisers ran at higher speed and for less total time than forced exercisers. When compared with sedentary controls, forced but not voluntary exercise was found to increase anxiety-like behaviors in the open field. Both forms of exercise increased the number of surviving bromodeoxyuridine (BrdU)+ cells in the dentate gyrus after 8 weeks of exercise, although forced exercisers had significantly more than voluntary exercisers. Phenotypic analysis of BrdU+ cells showed no difference between groups in the percentage of newborn cells that became neurons, however, because forced exercise maximally increased the number of BrdU+ cells, it ultimately produced more neurons than voluntary exercise. Our results indicate that forced and voluntary exercise are inherently different: voluntary wheel running is characterized by rapid pace and short duration, whereas forced exercise involves a slower, more consistent pace for longer periods of time. This basic difference between the two forms of exercise is likely responsible for their differential effects on brain and behavior.

Key words: voluntary, forced, anxiety, water maze, dentate gyrus, progenitor cells.

Although evidence of the neural and behavioral benefits of exercise is accumulating, the optimal type, duration and intensity of long-term physical activity have not been established. Laboratory animal models of chronic exercise are highly variable, with many studies utilizing *ad libitum* access to voluntary exercise wheels, while others employ comparably short bouts of forced exercise on a treadmill. Not surprisingly, studies of the same outcome measure produce different results, depending on whether a voluntary or forced exercise paradigm is used (for a recent review of these disparities, see Ang and Gomez-Pinilla, 2007). In addition, it is becoming increasingly recognized that no single exercise paradigm is likely to fulfill all therapeutic needs (Ang and Gomez-Pinilla, 2007; Cotman et al., 2007). Thus, it is imperative to study the neural and behavioral effects of different forms of chronic exercise while holding their parameters constant.

Human studies have attempted to pinpoint the optimal intensity level at which acute exercise maximally benefits cognition (Winter et al., 2007; McMorris et al., 2008, see Brisswalter et al., 2002 for a useful review), event-related brain potentials (ERP's) (Kamijo et al., 2004b, 2007) and arousal level (Kamijo et al., 2004a). The most beneficial intensity, duration and type of long-term physical activity have not been well-studied in laboratory animals, however. The type of exercise may be particularly important, since several lines of evidence suggest that forced exercise and voluntary exercise exert different effects on the brain and behavior. For example, forced and voluntary exercise differentially affect monoamine neurotransmitters (Dishman, 1997), hippocampal parvalbumin expression (Arida et al., 2004), hippocampal brain-derived neurotrophic factor and synapsin-1 expression (Ploughman et al., 2005), longevity and body composition (Narath et al., 2001), taste aversion learning (Masaki and Nakajima, 2006) and open-field behavior (Burghardt et al., 2004). Although these studies suggest that forced and voluntary exercise may not be equivalent in their effects on the brain and behavior, a carefully matched comparison has never been made. In fact, with a few notable exceptions (Dishman, 1997; Dishman et al., 1997; Noble et al., 1999; Greenwood et al., 2003; Burghardt et al., 2004; Ploughman et al., 2005) the two forms of exercise are often treated as if they are equivalent. Even studies that make use of both forced and voluntary exercise paradigms do not attempt to match the distance, duration or intensity of exercise between groups. To illustrate, forced exercisers are usually required to cover only short distances. Mice and rats will voluntarily run long distances (see for example Rodnick et al., 1989; Lambert et al., 1996; Allen et al., 2001; Burghardt et al., 2004; Naylor et al., 2005), yet many studies that use forced exercise paradigms run the animals for only a few hundred

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Abbreviations: BrdU, bromodeoxyuridine; HPA, hypothalamic–pituitary–adrenal axis; NIH, National Institutes of Health; TBS, tris-buffered saline; TBST, 0.3% tris-buffered saline/Triton-X.

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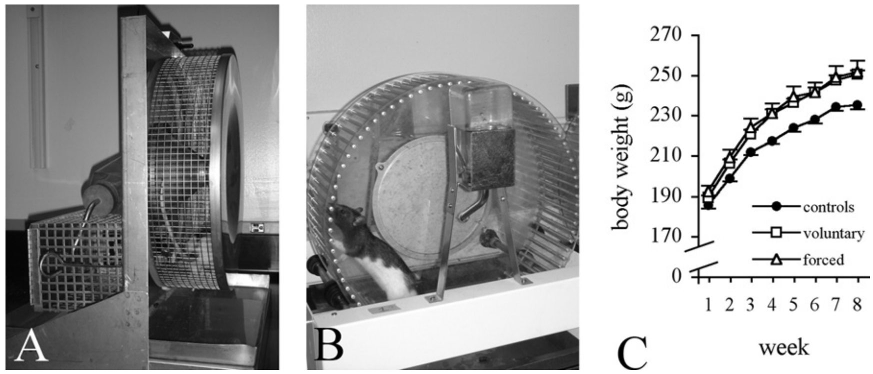

Fig. 1. Rats in the voluntary condition (A) exercised in freely moving wheels, while rats in the forced condition (B) had to maintain the pace of motorized wheels. All rats gained weight during the course of the experiment (C).

meters (Carro et al., 2000; Kim et al., 2002; Ra et al., 2002; Burghardt et al., 2004). Such studies typically also restrict forced runners to about an hour on the treadmill, once or perhaps twice a day, 5 days per week, while allowing voluntary runners 24-h access to running wheels. Thus, in most studies, neither the distance covered nor the time spent running by forced exercisers approximates that of spontaneous exercisers.

In the current study we employed a novel exercise paradigm to test the hypothesis that equivalent amounts of forced and voluntary exercise would exert different effects on physiological, behavioral and neural parameters previously shown to be influenced by exercise, including body weight (Lambert et al., 1996; Moraska et al., 2000; Droste et al., 2007), abdominal fat (Droste et al., 2007), hind-limb musculature (Rodnick et al., 1989), spatial navigation (Fordyce and Farrar, 1991a; van Praag et al., 1999a; Vaynman et al., 2004; Ang et al., 2006), open-field activity (Burghardt et al., 2004; Fulk et al., 2004) and survival and differentiation of hippocampal progenitor cells (van Praag et al., 1999a).

EXPERIMENTAL PROCEDURES

Animals

All experimental procedures were conducted in accordance with the National Institutes of Health (NIH) Public Health Service Policy on Humane Care and Use of Laboratory Animals (NIH 2002), and were approved by the Institutional Animal Care and Use Committee of the University of Houston. Furthermore, animal suffering was minimized where possible and the lowest possible number of animals was used. Thirty-four female Long-Evans rats (Harlan Sprague Dawley, Indianapolis, IN, USA), weighing 170–200 g at the beginning of the experiment were divided into three groups; sedentary controls (n=12), voluntary runners (n=13) and forced runners (n=9). When not exercising, rats were housed in groups of three, on a reversed 12-h light/dark cycle (10:00 h off/22:00 h on) with food and water available *ad libitum*.

Novel exercise paradigm matching distance of voluntary and forced exercise

Rats were exercised daily, 5 days per week, for 8 weeks, beginning at the start of the dark cycle (10:00 h). In order to directly compare the effects of voluntary and forced exercise on body and brain, it was necessary to both limit the distance covered by the voluntary exercisers and lengthen the distance run by the forced exercisers. We limited the distance run by the voluntary exercisers by allowing access to a wheel (see Fig. 1A) only until each rat reached a daily maximum, which was increased weekly during the 8-week exercise period, beginning with approximately 1300 m in Week 1 and gradually increasing to 2300 m in Week 8. The voluntary exercise wheels were equipped with counters that recorded distance traveled, average speed and time spent running. The distance covered by the forced exercisers was matched daily to the average distance run by the voluntary exercisers. The sedentary control rats were placed into immobilized wheels that were otherwise identical to those used by the voluntary runners. All rats had access to water at all times during the exercise period.

We employed four general strategies to standardize the exercise conditions of the forced and voluntary runners. First, we chose not to use a treadmill. Instead, forced exercisers ran in motorized wheels atop rotating axles (Lafayette Instruments, Lafayette, IN, USA) (see Fig. 1B). This strategy ensured that both groups were running in wheels (rather than the forced exercisers running on a belt), and that those wheels were similarly sized. In addition, it ensured that our forced exercisers were not exposed to aversive electric shocks, since commercially available treadmills (but not our motorized apparatus) have an electric shock component that can be used to "encourage" the animals to maintain the pace of the treadmill belt.

Second, the forced exercisers ran in a pattern consistent with the manner in which rats exercise voluntarily—in short bursts of activity interspersed with frequent rests (Eikelboom and Mills, 1988). The motorized wheel apparatus was controlled by a keypad that allowed the speed and duration of exercise, as well as periods of rest, to be pre-set. For example, the motorized axles could be programmed to turn the wheels at 15 m/min for 40 s, followed by a 20 s rest period, during which the wheels stopped turning. This sequence represented a single cycle. The cycle was repeated, and combined with additional cycles of faster or slower speeds (5–30 m/min) until the forced runners had reached the average distance run by the voluntary runners for the day. Thus, the forced exercisers were not running constantly for a fixed amount of time, as they usually are in treadmill exercise studies. We found that rats were reluctant to run at speeds higher than 20 m/min, therefore, higher speeds were used sparingly and for short durations. Rats were observed carefully to ensure that they kept pace with the wheels. One rat was eliminated from the study because it held onto the spokes of the wheel through the entire rotation.

Third, each day the distance covered by the forced exercisers was matched to the average distance run by the voluntary exercisers on that day. This ensured that both groups ran similar distances daily throughout the course of the experiment (see Fig. 2A). The distance that the voluntary exercisers were allowed to