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Research report

Translating the impact of exercise on cognition: Methodological issues in animal research

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HIGHLIGHTS

- Measures of oxygen consumption may be a useful tool to compare rodent and human.
- Housing conditions influence the effect size of the impact of exercise on cognition.
- Single-housed rodents may be seen as a model for social isolation.
- Social, physiological or environmental enrichment contribute to cognitive improvement.

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ABSTRACT

Physical exercise and fitness have been proposed as potential factors that promote healthy cognitive aging. Some of the support for this hypothesis has come from animal research. Animal studies are also used to propose the physiological mechanisms underlying the cognitive performance improvement associated with exercise. In the present review and meta-analysis, we discuss several methodological problems that limit the contribution of animal studies to the understanding of the putative effects of exercise on cognitive aging. We suggest that the most likely measure to equate exercise intensity in rodent and humans may be oxygen consumption (VO_2) because observed values are surprisingly similar in young and older rodents and humans. For practical reasons, several animal studies use young rodents kept in social isolation. We show that social isolation is associated with an enhanced impact of exercise on cognitive performance but not on some physiological measures thought to mediate the effect of exercise. Surprisingly, two months or more of exercise intervention appeared to be ineffective to promote cognitive performance compared to shorter durations. We argue that impact of exercise in socially isolated animals is explained by an alleviation of environmental impoverishment as much as an effect of physical exercise. It is possible that the introduction of exercise in rodents is partly mediated by environmental changes. It may explain why larger effects are observed for the shorter durations of exercise while much smaller effects are found after longer periods of exercise.

1. Introduction

There is a growing scientific literature that examines the potential benefits of physical exercise on cognitive functions. Most published human research conclude that physical exercise is beneficial to cognition particularly in older people [1–10]. Similar conclusions have been proposed about the effect of enrichment (cognitive, social and physical) on cognition [11]. In a recent review, we identified some of the methodological limitations in the human literature on this topic with a special emphasis on control groups and the difficulty in dissociating the effects of social, cognitive and physical stimulations in order to attribute causality between exercise and cognition [12]. Within the review, we expressed to hope that this dissociation could be better established in animal research. We now examine some of the methodological aspects of the test of the general hypothesis that physical exercise is beneficial for cognitive functions in rodents with a special attention to the impact of housing environment on the effect of physical exercise on cognition and brain physiology.

In rodents, the impact of physical exercise on cognition and on the brain processes that are involved in brain plasticity has been demonstrated by numerous studies. Taken at face value, the results are very encouraging for translational research and should lead us all to increase our physical activities. The present review

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is not aimed at refuting the current views on the positive impact of exercise on cognition. Rather, we would like to point out some methodological limitations that could temper our translational enthusiasm and possibly introduce additional controls in animal studies. These methodological refinements could provide a closer approximation of the absolute benefits of physical exercise that can be expected in human populations. To this end, we address some of the characteristics of experimental design in rodent experiments that may have an influence on the observed results and examine how experimental environments can either contribute or limit the generalization of the conclusions to humans. In the second part of this review, we used an effect size analysis, and we report that single-housed living conditions in some experiments may lead to an overestimation of the impact of physical exercise on cognition but that effect is less prominent for biological brain plasticity measures. The data does support the hypothesis of an influence of physical activity on the brain but the conditions under which this happens in rodents may not translate as directly in the daily life of most people. We now turn to the first topic of our review in which we explore the influence of the type and intensity of exercise in rodent experiments and how it compares to human exercise.

2. Type and intensity of exercise in rodents

One of the more important translational question about exercise and cognition is to determine which type of exercise and which intensity is the most efficient to improve cognitive processes and promote brain health. There are a number of human experiments that have tackled this issue but animal experiments can offer both better control for the exercise intensity and additional insight in the physiological mechanisms behind any impact of exercise on brain functions. Although there are a large variety of physical activities for humans, the practical choices for animal research are more limited. Most of the studies use running as the exercise modality for rodents. Running in rodents can be either spontaneous, generally in running wheels, or forced, generally on treadmills. Rats and mice appear to prefer running wheels and will spontaneously run long distances in them [13,103], even in old age [95,104]. They also show a preference for the environment where the running wheel is situated [105] and will work to access them [106,107] indicating that rodents find exercise in running wheels rewarding. Conversely, most rodents will not engage in running on a treadmill without extensive training using some form of negative reinforcement such as electric shocks or physical prodding to get them to run continuously. Treadmill running is accompanied by several indices of chronic stress such as adrenal hypertrophy, thymic involution, and suppressed lymphocyte proliferation [14]. Finally, maximal speeds that are attained in a coercive treadmill run can be higher than voluntary wheel running [15].

The aversive component associated with treadmill running is probably due in part to the lack of control of running initiation and intensity. Also, unless animals are kept in a reverse light cycle, treadmill running is usually done during the animals' rest period, which corresponds to the night period in humans and adds to the stress of the experimental situation. The fact that each activity is not hedonically neutral is problematic because reward and aversion influence cognition [16–18], brain morphological changes [19] and adult neurogenesis [20]. Still, each type of exercise paradigm has its benefits for researchers. Treadmill running is used when the experimenter wants to precisely control the amount and intensity of short duration exercise whereas running wheels are used in experiments that examine the impact of longer bouts of exercise over a longer period of time. Conversely, wheel running intensity is variable within groups of rodents and across strains and species and the resulting data can be more variable. For example, within 7 mouse strains, running wheel use during the night period ranged from 2 to 5 h and average speed increased with training [15]. When animals are housed in groups, each individual animal's running wheel activity becomes more difficult to measure. For obvious ecological reasons, voluntary exercise has the best translational value despite the difficulty to control for exercise intensity or duration. A caveat to that last statement is that running does not appear to be as universally motivating to humans as it appears to rodents in captivity.

Since animal studies are aimed at understanding the neural and physiological impact of exercise on the human brain, it is important to determine as much as possible the equivalency of the rodent exercise regimens to human exercise activities. This is particularly important because the results of animal studies are used to determine the impact of exercise not only on brain physiology, morphology but also on cognitive functions. These results, in turn, are used to explain the biological basis of the benefits on brain function observed in humans. It is clear that finding equivalence is fraught with difficulties considering the difference in size between rodents and humans as well as the running stance and physiology of each species [21]. We address in the next paragraph, some issues associated with solutions to calculate an approximate equivalency between rodent and human treadmill running.

A first way to establish this equivalency in the case of running is to compare the distance covered by unit of time and the speed scaled to take into account the size difference and the physiological effort necessary to cover a scaled standard distance. The translation of rodent running performance to human equivalent is challenging if only because rodents run on four paws. Several alternatives can be entertained. A simple equivalency between the amounts of time could be used whereas one hour of rodent exercise is equivalent to one hour of human exercise. This solution does not take into account the amount of energy expanded to perform one hour of running by each species. Also, there is very little information about how age influences the time and running speed of older rodents. Additionally, the ability and extent to which an average older human can run at the same intensity is not entirely clear. Table 1 presents the results of some treadmill rodent studies to illustrate this point. In Table 1, studies that reported animals' speeds but did not report and/or did not have an initial acceleration in each exercise session were also used. Both Toscano-Silva et al. [22], and Ang et al. [23], report familiarizing the animals to the treadmills by beginning at a lower speed and increasing until the top speed in subsequent exercise sessions. However, because there was no acceleration reported in each individual session, the top speed from both papers was used in calculations. The calculations indicate that, overall, animals ran at an average speed of 1.24 km/h and for an average distance and time of 84.2 km in 64.7 days, respectively.

We can use a slow jogging speed (9 km/h) as a (arbitrary, but reasonable) reference for human running [117] to approximate the running performed in rodent treadmill studies presented in Table 1. This translates to a human running distance of 609.8 km, which would take 67.8 h at a speed of 9 km/h. If this distance was to be run in 64.7 days as well, this means that a human must run about 1 hour a day per day at 9 km/h to approximate the regimen used in rodents. This would be an attainable goal for younger humans but might prove more challenging for older adults. In one experiment, it was found that the distance run voluntarily in a running wheel by older (24 mo) rats was half of the distance run by younger rats (9 mo) [24] suggesting that both older rodents and humans find it more difficult to retain the same level of running intensity with advancing age. This age-related reduction should be taken into account in designing experiments in younger animals and translating the results to older humans.