Deleterious effects of physical inactivity on the hippocampus: New insight into the increasing prevalence of stress-related depression

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Abstract Populations worldwide are increasingly becoming physically inactive, which is related to somatic and psychological health problems that are prevalent in modern society. Recent epidemiological studies have indicated that the associations between physical inactivity and depression are bidirectional. Numerous animal studies have demonstrated that exercise improves hippocampal function. Because the hippocampus is a pivotal brain region that exerts inhibitory control over stress responses by affecting the hypothalamus-pituitary-adrenal axis, enhanced hippocampal function by exercise can increase stress resilience, which helps prevent stress-related depression. In contrast, physical inactivity is difficult to model in animal studies, and little is known about the effects of physical inactivity on the rodent hippocampus. To fill this gap, we previously developed a mouse model of habituated voluntary wheel running cessation as a reverse intervention to control physical activity. We found that reducing physical activity by cessation of wheel running impairs hippocampal neurogenesis in mice. Thus, this review discusses the relevant literature and provides a hypothesis that physical inactivity can be a potential risk factor for stress-related depression as it increases stress vulnerability by impairing hippocampal function.

Keywords: physical inactivity, hippocampus, depression, stress vulnerability, neurogenesis

Introduction Two decades have passed since the historical discovery that exercise increases brain-derived neurotrophic factor (BDNF) gene expression in the rat hippocampus, a brain area involved in learning, memory, and stress regulation. Since then, the effects of exercise on the hippocampus have been extensively studied, and the results demonstrate that physical exercise is a powerful, non-pharmacological approach to improve hippocampal function. The specific effects of exercise on the hippocampus have been reviewed in depth elsewhere, and will not be discussed in detail here. In contrast, this review preferentially discusses how physical inactivity affects the hippocampus, especially from the perspective of the risk of depression. This alternative discussion will provide new insight into the relationship between physical activity and brain health.

We begin this review with a summary of the existing research, and present the current view that the associations between physical inactivity and depression are bidirectional. Then, we review studies examining the effects of physical inactivity on the rodent hippocampus and discuss the validity of animal models. Finally, we hypothesize that physical inactivity is a potential risk factor for stress-related depression as it increases stress vulnerability by impairing hippocampal function.

The worldwide pandemic of physical inactivity Health promotion through exercise is now widely accepted, but the deleterious effects of physical inactivity have received less attention. In 2012, The Lancet published a series on physical activity, emphasizing that physical inactivity is a serious global health concern. Evidently, physical inactivity increases the risk of major non-communicable diseases including cardiovascular disease, type 2 diabetes, and some types of cancers. However, a growing proportion of the world’s population is physically inactive, not only in the developed, but also in the developing countries. It is estimated that the global prevalence of physical inactivity, defined as not meeting the current physical activity recommendations (A: 30 min of moderate-intensity physical activity at least 5 days per week, B: 20 minutes of vigorous-intensity physical activity on at least 3 days per week, or C: an equivalent combination achieving 600 metabolic equivalent [MET]-min per week), is around 31% among adults over 15 years old. Furthermore, physical inactivity is the fourth leading risk factor for global mortality (6-10% of all
deaths from major non-communicable diseases\textsuperscript{(15)}, which results in dramatically increased social and economic costs\textsuperscript{(16,17)}.

Exercise has been called a “miracle drug”\textsuperscript{(18)} that has tremendous health benefits and can even extend lifespan\textsuperscript{(19)}. However, these amazing benefits would be observed because inactive people perform exercise. From an evolutionary perspective, humans are born to run\textsuperscript{(20)}, suggesting that a lack of physical activity is, in fact, an abnormality\textsuperscript{(21)}. It would be attractive to be able to discover an exercise pill containing a molecule that can mimic the beneficial effects of exercise\textsuperscript{(22)}; however, it is also important and more realistic to understand the impacts and underlying mechanisms of physical inactivity on human health to further promote physical exercise\textsuperscript{(2,23)}.

**Bidirectional associations between physical inactivity and depression**

Physical inactivity causes both somatic and psychological problems. A number of epidemiological studies have examined the association between physical activity and depression (see review\textsuperscript{(24)}). A 10-year prospective study, of 49,821 women without clinical depression or severe depressive symptoms at baseline, has clearly demonstrated that physical activity is inversely associated with the risk of depression\textsuperscript{(25)}, which is in accordance with most other relevant studies\textsuperscript{(26-28)}. Generally, these studies emphasize the importance of increasing physical activity to decrease the risk of depression. However, the inverse association would indicate that physical inactivity increases the risk of depression. This possibility was raised in a 1991 study by Camacho and colleagues\textsuperscript{(29)}, but it received relatively little attention. Some studies have demonstrated that decreases in leisure-time physical activity\textsuperscript{(30)}, and in intensity of physical exercise\textsuperscript{(31)}, forced withdrawal of regular exercise\textsuperscript{(32)}, and bed rest\textsuperscript{(33)} have been shown to increase the prevalence of depressive symptoms. These findings suggest that physical inactivity or a reduction in physical activity is a causal factor of depression.

There is also evidence that depression affects physical activity levels. Roshanaei-Moghaddam et al. systematically reviewed prospective studies that examined an association between baseline depression and subsequent levels of physical activity, and suggested that depression can lead to physical inactivity\textsuperscript{(34)}. This finding had been a common clinical observation, but experimental verification was lacking\textsuperscript{(35)}. Recent prospective studies have shed light on this issue and confirmed that associations between physical activity and depression are bidirectional\textsuperscript{(16,37)}. Hence, it is plausible that physical inactivity and depression form a negative chain reaction (Fig. 1). Because physical inactivity increases the risk of major non-communicable diseases, individuals should try to meet daily physical activity recommendations. This could be facilitated by ensuring that populations understand the impacts of physical inactivity on brain function and depression.

**Reconfirming a multilevel concept of physical activity**

Public health measures are shifting their focus to physical inactivity rather than physical activity or exercise; however, we think that this is not accurately modeled in animal studies. To fill this gap, researchers using laboratory rodents would need to reconfirm a multilevel concept of physical activity (Fig. 2)\textsuperscript{(5)}. Sports are structured, competitive, and the most intense form of physical activity. Conversely, exercise is a subset of physical activity performed with the aim of improving or maintaining health or fitness. It should be noted that physical activity encompasses all movements including housework and walking to school/office in humans, and ambulatory activity for rodents. Importantly, this concept comprises physical inactivity (or sedentary behavior), implying that physical inactivity can be avoided by increasing total physical activity without exercise or sports. Indeed, a recent systematic review by Mammen et al. introduced the promising possibility that even low levels of physical activity (walking <150 min/week) can protect against depression\textsuperscript{(38)}.

Researchers usually examine the effects of exercise on the brain following voluntary wheel running, a common method to increase total physical activity in laboratory rodents\textsuperscript{(39)}. Conversely, rodents confined in a standard/control cage might be regarded as physically inactive. Indeed, Dishman et al. pointed out that it is important “to reconsider the use of forced inactive animals as normal controls in studies of physical activity and exercise”\textsuperscript{(40)}. The issue that experimental control conditions are not normal for rodents and hamper scientific discovery is persuasively discussed elsewhere\textsuperscript{(41-43)}, although further discussion is obviously necessary.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{Fig_1.png}
\caption{Bidirectional associations between physical inactivity and depression.}
\end{figure}
Impacts of physical inactivity on rodent hippocampus

Numerous studies have demonstrated the beneficial effects of exercise on the hippocampus of laboratory rodents. In contrast, few studies have been specifically designed to examine the effects of physical inactivity on the hippocampus, presumably due to the difficulties of limiting laboratory rodent physical activity when they are already confined to standard cages.

Some previous studies have used a model of hindlimb suspension to mimic physical inactivity and demonstrated an increase in depressive symptoms and reduced hippocampal neurogenesis. However, hindlimb suspension is known to trigger stress responses and increase glucocorticoid levels, which can, in turn, suppress hippocampal neurogenesis. Although hindlimb suspension did not significantly increase the weight of the adrenal gland and plasma corticosterone level in the latter studies, the increasing trends did not exclude the possibility that this was a false-negative result.

A recent study examined whether long-term spaceflight, an extreme form of physical inactivity, affects gene expression in mouse brain, and found no significant changes in hippocampal mRNA levels of BDNF or its receptors (TrkB and p75). However, it should be noted that these mice were decapitated about 6 h after landing. The time delay might have resulted in acute changes in gene expression, which might have been a confounding variable. Although the results of this study are intriguing, there are clear difficulties in repeating the experiments performed in a spaceflight model, and other designs are needed to obtain further evidence.

We have been attempting to understand the impact of physical inactivity on the hippocampus by using a model of cessation of habituated voluntary wheel running, a reverse intervention to control mouse physical activity. Briefly, post-weaned mice are reared in a cage with a running wheel until early adulthood (8 weeks, from 4 to 11 weeks of age) and subsequently placed in a standard laboratory cage (Fig. 3A). This intervention causes a relative reduction in physical activity without any physical restraint. We have confirmed that wheel running cessation does not induce chronic stress symptoms (e.g., adrenomegaly, thymus atrophy, and increased plasma glucocorticoid levels) (unpublished data). With this approach, reduced physical activity following cessation of...
wheel running attenuated the neuronal differentiation of new born cells, an important component of hippocampal neurogenesis, compared to that in age-matched sedentary controls (Fig. 3B)\(^{49}\). This finding suggests the surprising possibility that hippocampal changes in response to physical inactivity are not merely a reverse adaptation to beneficial changes due to prior exercise; rather, it is more likely that a reduction in physical activity can impair hippocampal function.

To address this possibility, we reviewed previous studies examining how cessation of exercise affects the rodent hippocampus; even those studies were originally designed to examine how long the effects of exercise last. Berchtold et al. studied both rats\(^{50}\) and mice\(^{51}\) and found that hippocampal BDNF protein levels following 3-4 weeks of wheel running remained elevated at 1 week but not at 2 weeks after the cessation of running compared to levels in age-matched sedentary controls. Similarly, Merkley et al. demonstrated that the number of immature neurons positive for doublecortin, a validated neurogenesis marker, was significantly higher at 1 week, but not at 5 weeks after cessation of 30-day wheel running\(^{52}\). Together with the results of other studies\(^{53,54}\), these findings indicate that the positive effects of physical exercise are reversible, which is in agreement with the basic principles of physical training.

Several studies have reported that exercise cessation negatively affects the hippocampus. For example, Radak et al. demonstrated that the hippocampal levels of BDNF and nerve growth factor (NGF) in rats that had experienced swimming exercise for 4 weeks and subsequent normal housing for an additional 4 weeks were significantly lower than those in sedentary controls\(^{55}\). Notably, the author described the findings as “a negative re-bound in BDNF and NGF content after detraining”\(^{55}\). Similarly, Hopkins and colleagues reported that hippocampal BDNF protein levels at 2 or 4 weeks after cessation of a 4-week wheel running protocol (starting from 32 days old) were significantly lower than those measured in age-matched sedentary controls\(^{56}\). They also performed the same experiment in adult rats that started wheel running at 9 weeks old and did not find a significant reduction in BDNF protein levels following exercise cessation, suggesting that the effects might depend on the age that the animals experienced wheel running. Collectively, these results support our current findings that hippocampal adaptation to physical inactivity may not be a simple reversal of a prior adaptation to physical exercise, which could impair hippocampal function\(^{49}\).

**Physical inactivity as a risk for depression – A hypothesis**

Stress is a major risk factor for depression, but there are clear individual variations; some people are resilient to stress, while others are vulnerable. Recently, increasing efforts have been made to elucidate the neural substrates underlyng stress resilience/vulnerability\(^{57}\). One of the promising regulators of stress resilience/vulnerability is the hippocampus, because it exerts inhibitory control over the hypothalamus-pituitary-adrenal (HPA) axis, a pivotal regulator of stress responses\(^{56,57}\). That is, enhanced hippocampal function decreases stress vulnerability, but impaired hippocampal function increases stress vulnerability (Fig. 4).

Exercise is one of the most effective interventions for enhancing hippocampal function, and animals that have exercised are more resilient to stress exposure\(^{58}\). In contrast, this review suggests that physical inactivity or a reduction of physical activity might impair hippocampal function. This led to the novel hypothesis that physical inactivity is a risk factor for depression because it increases stress vulnerability by impairing hippocampal function. This hypothesis nicely fits the state of modern societies that face dual pandemics of physical inactivity and depression. Further studies in appropriate animal models are required to examine whether physical inactivity increases stress vulnerability.

![Fig. 4](image-url)  
Hippocampal function is inversely linked to stress vulnerability. Physical activity is known to enhance hippocampal function, which decreases stress vulnerability. Our recent finding demonstrated that physical inactivity impairs hippocampal function, which might increase stress vulnerability.
Conclusion

The bidirectional association between physical inactivity and depression may explain the increasing prevalence of stress-related depression in our modern, physically inactive society. From a medical perspective, another issue gaining more attention is that depression is a major complication of various diseases including stroke, cancer, and type 2 diabetes. It is noteworthy that breast cancer survivors with physical inactivity experience mood deterioration (higher levels of anger, fatigue, depression, and confusion) compared to survivors who get an adequate amount of physical activity. Thus, we propose to first demonstrate how physical inactivity and exercise can harm and improve mental health, respectively. We hope that this will also stimulate a constructive discussion about reconsidering the control conditions for physical inactivity studies using laboratory rodents.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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