Therapeutic physical exercise in neural injury: friend or foe?

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Abstract. [Purpose] The intensity of therapeutic physical exercise is complex and sometimes controversial in patients with neural injuries. This review assessed whether therapeutic physical exercise is beneficial according to the intensity of the physical exercise. [Methods] The authors identified clinically or scientifically relevant articles from PubMed that met the inclusion criteria. [Results] Exercise training can improve body strength and lead to the physiological adaptation of skeletal muscles and the nervous system after neural injuries. Furthermore, neurophysiological and neuropathological studies show differences in the beneficial effects of forced therapeutic exercise in patients with severe or mild neural injuries. Forced exercise alters the distribution of muscle fiber types in patients with neural injuries. Based on several animal studies, forced exercise may promote functional recovery following cerebral ischemia via signaling molecules in ischemic brain regions. [Conclusions] This review describes several types of therapeutic forced exercise and the controversy regarding the therapeutic effects in experimental animals versus humans with neural injuries. This review also provides a therapeutic strategy for physical therapists that grades the intensity of forced exercise according to the level of neural injury.

Key words: Neurological injury, Neuroprotective effect, Physical exercise

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INTRODUCTION

Among the many therapeutic strategies used following neurological injuries, physical exercise aids in functional recovery by increasing resistance to nerve injury, enhancing neuron survival, stimulating neurogenesis, increasing learning ability, and improving recognition and memory function¹⁾. A dominant theory regarding the central nervous system (CNS) following neurological injury posited that no reassortment of any type occurs in neuronal populations.

Since the 1990s, however, various studies have identified precursor neural stem cells (NSCs) and demonstrated that neurons are generated continuously within the CNS²⁾. It is now widely accepted that neurogenesis in adults occurs in the subventricular zone of the forebrain and subgranular zone of the hippocampus³⁾, particularly via the proliferation, differentiation, and migration of precursor NSCs. These processes are regulated by neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and basic fibroblast growth factor (FGF-2), which are increased in the brain by physical exercise and sensory stimulation and, in turn, increase the number of surviving new neurons^{4, 5)}. This suggests that neurological disorders, such as stroke, spinal cord injury (SCI), and Alzheimer's disease (AD), are treatable^{6–8)}.

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DIFFERENT EFFECTS OF MILD AND FORCED EXERCISE IN PHYSIOLOGICAL AND NEURAL THERAPY

In animal models, forced exercise, such as treadmill running, and voluntary exercise, like wheel running, are interventions that are used widely to study the effects of physical exercise on the recovery of physiological function in neurological injury⁹⁾. The application of these exercises following neurological injury results in increased angiogenesis in the cerebral cortex¹⁰⁾ and enhanced neurogenesis¹¹⁾ and positively affects neuroplasticity, recognition, and memory function¹²⁾ via neuroprotective actions against the structural injury of nerve cells¹³⁾ and the increased expression of neurotrophic factors^{14, 15)}. Rehabilitation therapies following neurological injury vary, based on the ethological aspects of forced and voluntary exercise, including timing, period, and intensity¹⁶⁾ in terms of the recovery of nerve cells. The intensity of the exercise is an important factor.

Mild exercise is effective for neurological recovery¹²⁾. Exercise intensity influences cell proliferation and neurogenesis in the adult dentate gyrus, and mild exercise is more effective for cell proliferation than high-intensity exercise¹⁷⁾. Mild treadmill exercise increases cell proliferation via the enhancement of insulin-like growth factor (IGF)-1 and FGF-2 levels in the brain¹⁷⁾. Moreover, Lee et al.¹⁸⁾ found that the application of mild exercise in ischemic animal models resulted in a lower infarct volume and greater numbers of astrocytes than high-intensity exercise, indicating that mild exercise is more effective for neurological and functional recovery. Astrocytes are glial cells in the brain and spinal cord that are more active in proximate injury regions and act in the repair and scarring process following neuronal injury¹⁹⁾. These glial cells contribute to functional recovery through the activation of angiogenesis, neurogenesis, and the secretion of neurotrophic factors²⁰⁾. Accordingly, mild exercise is effective for neurological recovery via the induction of astrocyte proliferation. By contrast, forced exercise inhibits the degree of cell proliferation in the adult dentate gyrus, and it also reduces cell proliferation by decreasing the amount of BDNF in the dentate gyrus²¹⁾. Additionally, forced exercise induces stress, which enhances the secretion of glucocorticoids and may initiate increased corticosterone synthesis²¹⁾. Otherwise, long-term voluntary exercise has a considerable impact on hypothalamic-pituitary-adrenal (HPA) axis regulation²²⁾; thus, clarification of the association between exercise intensity and the HPA axis is needed.

However, some studies have found that high-intensity exercise has more positive effects on neurological recovery and neuroprotection. Hayes et al.¹³⁾ reported that forced exercise, with a stressful component, was neuroprotective after nerve injury via upregulation of the expression of the stress-induced heat shock protein (Hsp)27 and Hsp70 genes. Hsp27 and Hsp70 have been identified in many areas of the brain¹³⁾, cartilage²³⁾, and skeletal muscle²⁴⁾. In addition, these genes exhibit altered expression following exposure to different environmental stresses, such as heat, exercise, infection, inflammation, ischemia, and oxidative stress^{23–25)}. Hsp27 and Hsp70 act as intracellular chaperones for other proteins with physiologically neuroprotective activities^{25, 26)}. In par-

ticular, Hsp70 regulates apoptotic cell death by interfering with apoptosis-inducing factors and increasing the expression of anti-apoptotic proteins via the inhibition of caspase and cytochrome *c* (Cyt *c*) release^{27, 28)}. The expression of the Hsp27 and Hsp70 genes increased significantly following forced exercise, compared with voluntary exercise, and their expression could play an important role in neuroprotection¹³⁾. Kinni et al.²⁹⁾ investigated cerebral metabolism using the expression of glucose transporter (GLUT)-1 and GLUT-3, phosphofructokinase (PFK), lactate dehydrogenase (LDH), and adenosine monophosphate kinase (AMPK) mRNA and protein and found significantly greater increases following forced exercise versus mild exercise. These authors suggested that forced exercise was more effective for neuroprotection.

Physical exercise facilitates functional recognition and memory recovery after nerve injury and improves short-term and spatial memory by repressing apoptotic neuronal cell death and enhancing newborn cell survival in the hippocampal dentate gyrus^{30, 31)}. Shimada et al.¹²⁾ investigated the recovery of memory function following different levels of exercise intensity and found that mild exercise resulted in greater improvements in memory function than high-intensity exercise by increasing the number of neurons in the hippocampal dentate gyrus and enhancing microtubule-associated protein (MAP) expression. Similarly, low-intensity exercise enhanced neurogenesis and significantly increased the expression of neurotrophic factors, such as BDNF, N-methyl-D-aspartate receptor type 1 (NMDAR1), and vascular endothelial growth factor (VEGF), in the dentate gyrus of the hippocampus, compared with high-intensity exercise³²⁾. Increased BDNF gene expression effectively increases neurogenesis and neuroplasticity, which may have a positive effect on the structural and functional recovery of neurons. By contrast, although the method of exercise was different, Ogonovszky et al.³³⁾ found that overtraining of swimming exercise in rat with neurological disturbance improved memory and increased BDNF expression.

Although these studies showed some discrepancies regarding the physiological and ethological effects of voluntary versus forced exercise during neurological treatment, exercise intensities should be compared very carefully. They are similar, have been applied in a variety of ways by different studies, and are associated with many other factors that are not yet understood. Determining an appropriate exercise strategy to aid recovery following neurological injury also depends not only on the exercise intensity but also on the timing and period.

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REFERENCES

- 1) Cotman CW, Berchtold NC: Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci*, 2002, 25: 295–301. [[Medline](#)] [[CrossRef](#)]
- 2) Kukekov VG, Laywell ED, Suslov O, et al.: Multipotent stem/progenitor cells with similar properties arise from two neurogenic regions of adult human brain. *Exp Neurol*, 1999, 156: 333–344. [[Medline](#)] [[CrossRef](#)]
- 3) Hsu YC, Lee DC, Chiu IM: Neural stem cells, neural progenitors, and neurotrophic factors. *Cell Transplant*, 2007, 16: 133–150. [[Medline](#)]
- 4) Jeon YK, Ha CH: Expression of brain-derived neurotrophic factor, IGF-1 and cortisol elicited by regular aerobic exercise in adolescents. *J Phys Ther Sci*, 2015, 27: 737–741. [[Medline](#)] [[CrossRef](#)]
- 5) Yong MS, Hwangbo K: Skilled reach training influences brain recovery following intracerebral hemorrhage in rats. *J Phys Ther Sci*, 2014, 26: 405–407. [[Medline](#)] [[CrossRef](#)]
- 6) Zhang L, Hu X, Luo J, et al.: Physical exercise improves functional recovery through mitigation of autophagy, attenuation of apoptosis and enhancement of neurogenesis after MCAO in rats. *BMC Neurosci*, 2013, 14: 46. [[Medline](#)] [[CrossRef](#)]
- 7) Krityakiarana W, Espinosa-Jeffrey A, Ghiani CA, et al.: Voluntary exercise increases oligodendrogenesis in spinal cord. *Int J Neurosci*, 2010, 120: 280–290. [[Medline](#)] [[CrossRef](#)]
- 8) Mirochnic S, Wolf S, Staufenbiel M, et al.: Age effects on the regulation of adult hippocampal neurogenesis by physical activity and environmental enrichment in the APP23 mouse model of Alzheimer disease. *Hippocampus*, 2009, 19: 1008–1018. [[Medline](#)] [[CrossRef](#)]
- 9) Ma Q: Beneficial effects of moderate voluntary physical exercise and its biological mechanisms on brain health. *Neurosci Bull*, 2008, 24: 265–270. [[Medline](#)] [[CrossRef](#)]
- 10) Kleim JA, Cooper NR, VandenBerg PM: Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. *Brain Res*, 2002, 934: 1–6. [[Medline](#)] [[CrossRef](#)]
- 11) van Praag H, Kempermann G, Gage FH: Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci*, 1999, 2: 266–270. [[Medline](#)] [[CrossRef](#)]
- 12) Shimada H, Hamakawa M, Ishida A, et al.: Low-speed treadmill running exercise improves memory function after transient middle cerebral artery occlusion in rats. *Behav Brain Res*, 2013, 243: 21–27. [[Medline](#)] [[CrossRef](#)]
- 13) Hayes K, Sprague S, Guo M, et al.: Forced, not voluntary, exercise effectively induces neuroprotection in stroke. *Acta Neuropathol*, 2008, 115: 289–296. [[Medline](#)] [[CrossRef](#)]
- 14) Chen X, Li Y, Kline AE, et al.: Gender and environmental effects on regional brain-derived neurotrophic factor expression after experimental traumatic brain injury. *Neuroscience*, 2005, 135: 11–17. [[Medline](#)] [[CrossRef](#)]
- 15) Koo HM, Lee SM, Kim MH: Spontaneous wheel running exercise induces brain recovery via neurotrophin-3 expression following experimental traumatic brain injury in rats. *J Phys Ther Sci*, 2013, 25: 1103–1107. [[Medline](#)] [[CrossRef](#)]
- 16) Leasure JL, Jones M: Forced and voluntary exercise differentially affect brain and behavior. *Neuroscience*, 2008, 156: 456–465. [[Medline](#)] [[CrossRef](#)]
- 17) Kim YP, Kim HB, Jang MH, et al.: Magnitude- and time-dependence of the effect of treadmill exercise on cell proliferation in the dentate gyrus of rats. *Int J Sports Med*, 2003, 24: 114–117. [[Medline](#)] [[CrossRef](#)]
- 18) Lee SU, Kim DY, Park SH, et al.: Mild to moderate early exercise promotes recovery from cerebral ischemia in rats. *Can J Neurol Sci*, 2009, 36: 443–449. [[Medline](#)] [[CrossRef](#)]
- 19) Mabuchi T, Kitagawa K, Ohtsuki T, et al.: Contribution of microglia/macrophages to expansion of infarction and response of oligodendrocytes after focal cerebral ischemia in rats. *Stroke*, 2000, 31: 1735–1743. [[Medline](#)] [[CrossRef](#)]
- 20) Liberto CM, Albrecht PJ, Herx LM, et al.: Pro-regenerative properties of cytokine-activated astrocytes. *J Neurochem*, 2004, 89: 1092–1100. [[Medline](#)] [[CrossRef](#)]
- 21) Otawa M, Arai H, Atomi Y: Molecular aspects of adrenal regulation for circadian glucocorticoid synthesis by chronic voluntary exercise. *Life Sci*, 2007, 80: 725–731. [[Medline](#)] [[CrossRef](#)]
- 22) Droste SK, Schweizer MC, Ulbricht S, et al.: Long-term voluntary exercise and the mouse hypothalamic-pituitary-adrenocortical axis: impact of concurrent treatment with the antidepressant drug tianeptine. *J Neuroendocrinol*, 2006, 18: 915–925. [[Medline](#)] [[CrossRef](#)]
- 23) Nam KW, Seo DY, Kim MH: Pulsed and continuous ultrasound increase chondrogenesis through the increase of Heat Shock Protein 70 expression in rat articular cartilage. *J Phys Ther Sci*, 2014, 26: 647–650. [[Medline](#)] [[CrossRef](#)]
- 24) Kim MY, Lee JU, Kim JH, et al.: Phosphorylation of Heat Shock Protein 27 is increased by cast immobilization and by serum-free starvation in skeletal muscles. *J Phys Ther Sci*, 2014, 26: 1975–1977. [[Medline](#)] [[CrossRef](#)]
- 25) Santoro MG: Heat shock factors and the control of the stress response. *Biochem Pharmacol*, 2000, 59: 55–63. [[Medline](#)] [[CrossRef](#)]
- 26) Nishikawa M, Takemoto S, Takakura Y: Heat shock protein derivatives for delivery of antigens to antigen presenting cells. *Int J Pharm*, 2008, 354: 23–27. [[Medline](#)] [[CrossRef](#)]
- 27) Charette SJ, Lavoie JN, Lambert H, et al.: Inhibition of Daxx-mediated apoptosis by heat shock protein 27. *Mol Cell Biol*, 2000, 20: 7602–7612. [[Medline](#)] [[CrossRef](#)]
- 28) Samali A, Robertson JD, Peterson E, et al.: Hsp27 protects mitochondria of thermotolerant cells against apoptotic stimuli. *Cell Stress Chaperones*, 2001, 6: 49–58. [[Medline](#)] [[CrossRef](#)]
- 29) Kinni H, Guo M, Ding JY, et al.: Cerebral metabolism after forced or voluntary physical exercise. *Brain Res*, 2011, 1388: 48–55. [[Medline](#)] [[CrossRef](#)]
- 30) Sim YJ, Kim SS, Kim JY, et al.: Treadmill exercise improves short-term memory by suppressing ischemia-induced apoptosis of neuronal cells in gerbils. *Neurosci Lett*, 2004, 372: 256–261. [[Medline](#)] [[CrossRef](#)]
- 31) Luo CX, Jiang J, Zhou QG, et al.: Voluntary exercise-induced neurogenesis in the posts ischemic dentate gyrus is associated with spatial memory recovery from stroke. *J Neurosci Res*, 2007, 85: 1637–1646. [[Medline](#)] [[CrossRef](#)]
- 32) Lou SJ, Liu JY, Chang H, et al.: Hippocampal neurogenesis and gene expression depend on exercise intensity in juvenile rats. *Brain Res*, 2008, 1210: 48–55. [[Medline](#)] [[CrossRef](#)]
- 33) Ogonovszky H, Berkes I, Kumagai S, et al.: The effects of moderate-, strenuous- and over-training on oxidative stress markers, DNA repair, and memory, in rat brain. *Neurochem Int*, 2005, 46: 635–640. [[Medline](#)] [[CrossRef](#)]