



Role of physical activity on human brain functions

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Abstract

***Mens sana in corpore sano.** This famous sentence has been around for almost 2000 years. Back in the first and second century a.d., Decimus Iunius Juvenalis, a Roman poet spoke of health, mental and physical, and their dependence on one another. But, it was not until the 1990.s, when science allowed us to find proof for this idea, and until the discovery of neurotrophic factors which changed around the way physical activity and brain plasticity is viewed. In 1986 Rita Levi Montalcini and Stanly Cohen received a Nobel Prize in medicine for the discovery of neurotrophins. Neurotrophins are proteins, belonging to a group of growth factors with special effect on neurons. They signal nerve cells to grow, survive, and differentiate. It is one neurotrophic factor in particular, the Brain Derived Neurotrophic Factor (BDNF), which is important for long term memory, affects neurons in central and peripheral nervous system, helps survival of existing neurons, growth and differentiation of new neurons and synapses, and its secretion is encouraged by physical activity.*

Scientists for centuries believed in the possibility of human brain to change. William James, in 1890, was among the first to suggest that human brain is capable for continuous functional changes, which he showed in his work *Principles of Psychology* (1). It is important to keep our brain healthy as well as the body. Brain health has become a very important and recognized public health issue with a growing and aging population. Interventions are necessary from middle age further on, where we face a growing incidence of Alzheimer's disease, and other neurodegenerative disorders. Many recent studies have shown the benefits of exercise in aging populations, not only on physical health, but on brain health and functions. Exercise has become fundamental in improving and maintaining cognitive functions (2, 3).

Physical activity is associated with lower risk of cognitive impairment, Alzheimer's disease, and dementia in general (4, 5). Also, a retrospective analysis showed that physical activity and behavioral stimulation reduced the risk for developing Alzheimer's disease (6, 7). Animal research has gone a step further, studies have shown that exercise improves neuronal survival and brain vascularization, stimulates neurogenesis, enhances learning and memory, and helps maintain cognitive function during aging (8, 9, 10, 11).

During the 1990s, popular belief was that exercise's positive effect on the brain comes from its positive effect on overall health, especially among aged subjects. Today, we are aware of existence of neurobiological basis of these benefits, and we know that exercise has a direct effect

on molecular structure of the brain. The most important and probably the most studied is the brain-derived neurotrophic factor (BDNF) which is held responsible for survival and growth of many neuronal subtypes, including glutamatergic neurons, synaptic efficacy, neuronal connectivity and use-dependant plasticity (12, 13, 14, 15, 16, 17).

Neurotrophin-mediated response to exercise is not restricted to motor-sensory systems as expected by researchers, but showed increased levels of BDNF in the hippocampus (18). Hippocampus is a highly plastic structure associated with higher cognitive function, rather than motor activity. New hippocampal neurons make specific contributions to learning and memory, in part as a result of their unique neural circuitry (19). Within days of exercise, changes in BDNF mRNA levels were found in neurons of the gyrus dentatus, hilus and CA3 region. They were present in both male and female rats, sustained even after several weeks of exercise (20, 21). Apart from the hippocampus, levels of BDNF mRNA increased in the lumbar spinal cord, cerebellum and cortex (22, 23).

Human studies have shown that exercise improves brain plasticity. Learning is a high-order brain plasticity activity, increases BDNF gene expression, and BDNF in turn facilitates learning (24) (25).

Peripheral mechanisms show growing importance in activity-dependent induced changes in levels of BDNF mRNA in the brain. Components influencing this peripheral control include estrogen, corticosterone and insulin-like growth factor-1 (IGF-1).

Steroid hormones such as estrogen influence brain aging, particularly in post-menopausal women. Reduced levels of estrogen seem to compromise neuronal function, survival of neurons and decrease hippocampal availability of BDNF (21, 26). It seems that in females, benefits of exercise are estrogen dependent. Following a two-month estrogen deprivation, BDNF mRNA nor the protein were no longer elevated by exercise (animal model). But, when exercise was combined with estrogen replacement, BDNF protein levels showed a greater increase than in response to estrogen alone (21). In females, the presence of estrogen might be necessary for exercise-induced regulation of availability of BDNF. But, it seems that estrogen works both ways. During absence of estrogen, animals were less active; there was less voluntary physical activity (21).

Just like estrogen has a positive effect on neuroplasticity, there are some factors causing negative neuroplasticity. Prolonged exposure to stress causes elevated levels of stress hormones (i.e. corticosteroids) which can be harmful to neuronal survival in hippocampus. As a response to stress (acute and chronic), neurons undergo morphological changes, dendritic atrophy and spine reduction, which have a negative impact on brain plasticity (27). It is common belief that exercise relieves stress, reduces de-

pression and anxiety (in humans) (28). Corticosteroids decrease BDNF availability in the hippocampus, but exercise before a stressful event can counteract this down-regulation.

Insulin-like growth factor-1 (IGF-1), is structurally related to pro-insulin, and is a potent survival factor for neurons and oligodendrocytes, participates in neuronal growth and differentiation in the brain (29) IGF-1 may be a mediator of BDNF gene upregulation, neurogenesis and the ability of exercise to protect the brain from injury (30). Following exercise, levels of IGF-1 increase in the brain and the periphery, and part of this increase in the brain is due to increased transport from the periphery through the blood-brain barrier (31).

The effect of exercise on genes encoding neurotrophins predict that exercise could regulate downstream anatomical changes, supporting neuroplasticity. Exercise increases the number of new neurons in gyrus dentatus of adult animals (32). Trophic factors like IGF-1, BDNF, fibroblast growth factor (FGF-2), mediate this effect.

Literature shows that experience and behavior activate brain plasticity mechanisms and remodel neuronal circuitry in the brain. Exercise and behavioral enrichment paradigms, such as environmental enrichment, rehabilitation training and learning, affect common endpoints in the brain, including regulation of growth factors, neurogenesis and structural changes. Similarities between these effects and exercise support the idea of existing common mechanisms regulating plasticity (3).

Exercise is simple, free, and widely practiced activity that activates molecular cascades participating in neuroplasticity. It induces BDNF encoding, neurogenesis, enhances brain vascularization, functional changes in neuronal structure and neuronal resistance to injury. Exercise increases the level of hippocampal BDNF, a brain region responsible for learning and memory. By inducing BDNF and other molecules, exercise strengthens neuronal structure, facilitates synaptic transmission, preparing activated cells for encoding.

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