EFFECTS OF EXERCISE ON COGNITIVE FUNCTIONING AND MENTAL HEALTH: A MUSCLE - BRAIN CONNECTION

DOI 10.7251/SIZ2201151C
ISSN 1840-152X
UDK 159.95:616.89-008
http://sportizdravlje.rs.ba/
https://doisrpska.nub.rs/index.php/SIZ

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PROFESSIONAL ARTICLE

Abstract: During the last decades, the benefits of regular exercise for brain health, particularly for cognition and mental health, have been well-reported by both observational and experimental human studies. Although many of these studies were focused on the effects of chronic exercise in cognitively impaired subjects, recent investigations have highlighted the role of exercise in improving cognitive abilities and preventing the decline of cognition across the lifespan in healthy individuals. On the other hand, significant evidence exists to suggest that exercise programs can improve treatment outcomes for different mental disorders, especially those that affect mood. However, the mechanisms of acute and chronic exercise-improved brain function are still not completely known. In this context, it is important to consider that exercise induces muscle responses and adaptations that affect remote tissues. Like other secretory cells, myocytes produce cytokines and other peptides called myokines which exert an autocrine function in regulating muscle metabolism as well as a paracrine/endocrine regulatory function on distant organs, such as the gut, liver, and brain. Thus, the aim of this manuscript is to reinforce the potential of exercise as a useful tool to improve cognitive functioning and mental health and how muscle-brain crosstalk could play a key role in these exercise-related benefits.

Keywords: exercise, cognitive functioning, mental health, myokines.

INTRODUCTION

Boosting cognition: the role of exercise on executive functions

To a better understanding of how exercise improves cognition it's necessary first to consider executive functions. First, because they are necessary to develop complex cognitive processes; second, because they are sensitive to exercise-related stress.

Executive functions refer to a family of mental processes needed when you have to concentrate and pay attention, that is, when going on automatic or relying on instinct would be insufficient, or impossible. There is general agreement that there are three core executive functions: inhibition or inhibitory control, including self-control or behavioral control (that is, resisting temptations and not acting impulsively) and interference control (selective attention); working memory, which involves holding information in mind and mentally working with it (this information can be verbal or visual-spatial) and cognitive flexibility (also called mental flexibility), which allows to change perspectives spatially or interpersonally (that is, to see or to think from different points of view). From these interconnected executive functions more complex cognitive abilites are built such as reasoning, problem solving, and planning (Diamond, 2013) (Figure 1).

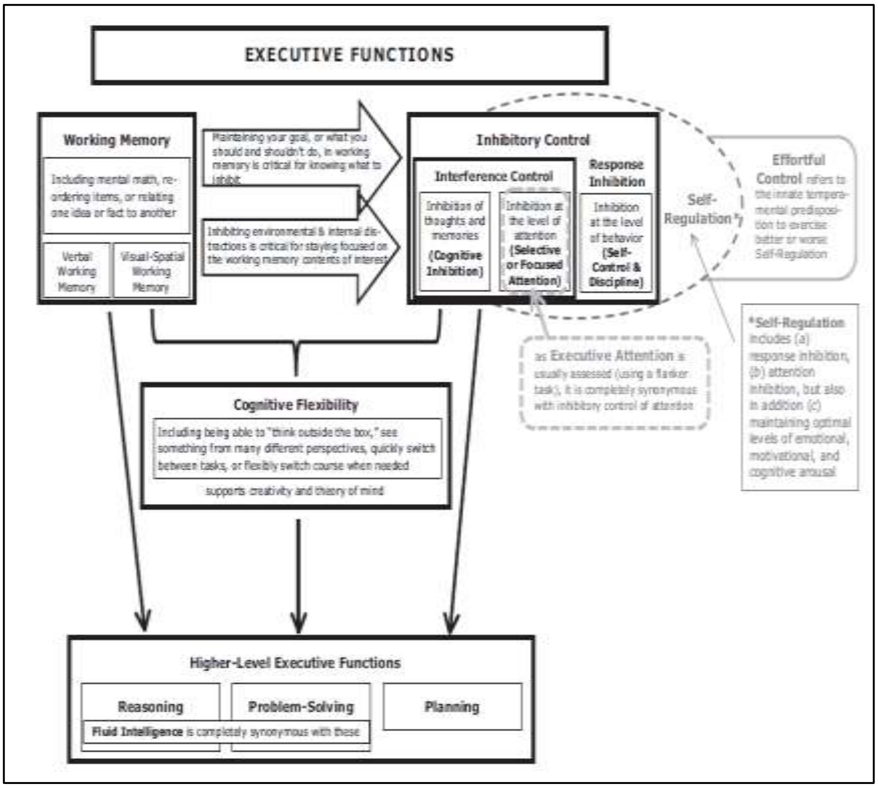

Figure 1. The three core executive functions (modified from Padilla et al., 2014).

Moreover, executive functions are skills essential for mental and physical health, cognitive, social, and psychological development, and also success in school. In fact, improvements in academic performance could reflect increases in executive functions abilities. With the aim to evaluate the relationship between physical fitness and academic achievement, Grissom (2005) compared scores on the FITNESSGRAM battery to reading and mathematics scores on the Stanford Achievement Test in nearly a million students from fifth to ninth grade. Results indicate a consistent positive relationship between overall fitness and academic achievement. That is, as overall fitness scores improved, mean achievement scores also improved. This relationship between fitness and achievement appeared to be stronger for females than males and stronger for higher socio-economic status students.

A recent study was also aimed to examine the association between health-related physical fitness (cardiorespiratory fitness and muscular fitness), skill-related physical fitness (speed-agility test) and cognitive functions (working memory and inhibitory control) in 423 Dutch adolescents (from 12 to 15 years) (Haverkamp, Oosterlaan, Königs, & Hartman, 2021). Physical fitness was assessed using five tests of the Eurofit battery whereas academic achievement was evaluated by two standardized tests assessing mathematic and language skills. The results showed that speed-agility was significantly related to visuospatial working memory and inhibitory control, but not to the other cognitive or academic achievement outcomes. Cardiorespiratory fitness and muscular fitness were also not related to any of the cognitive or academic achievement outcomes.

Exercise and mental health

On the other hand, it has been demonstrated that exercise programs can improve treatment outcomes for different mental disorders, especially those that affect mood and depressive symptoms (Figure 2).

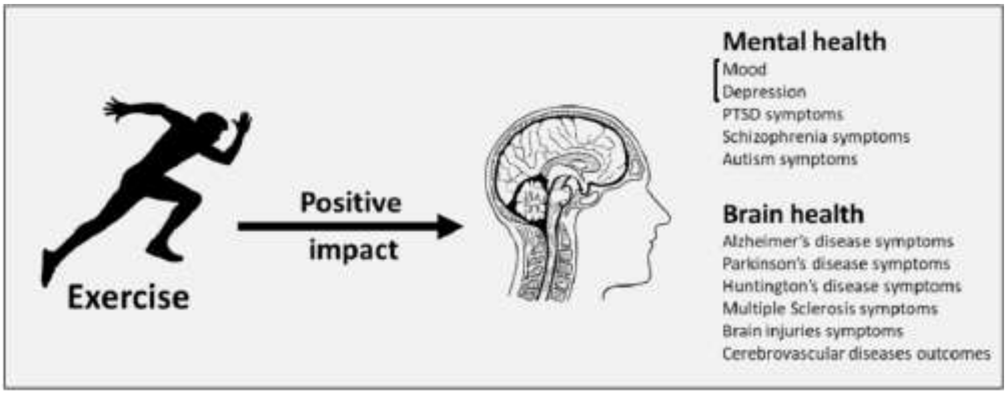

Figure 2. Positive effects of exercise on mental and brain health.

In 2019, a systematic review and meta-analysis on the role of physical activity and sedentary behavior in the mental health of children and adolescents were performed. In this review, studies were included if they included physical activity or sedentary behavior data and at least one psychological ill-being (for example, depression, anxiety, stress or negative affect) or psychological well-being outcomes (for example, self-esteem, self-concept, self-efficacy) in children and adolescents aged 6 to 18 years. Moreover, results of meta-analysis of randomized controlled trials showed a small but significant overall effect of physical activity on mental health (Rodríguez-Ayllón et al., 2019).

Regarding the effects of exercise on brain health, Carvalho et al. (2015) compared the effects of three programs, strength training (ST), aerobic training (AT), and physiotherapy, on motor symptoms and functional capacity in Parkinson disease patients. The 12 weeks strength program was performed at an intensity of 80% of one repetition maximum whereas the intensity of aerobic training was set at 70% of maximum heart rate. Parkinson disease motor symptoms in the group of patients who performed strength training and aerobic training improved by 27.5% and 35%, respectively (what means effect sizes up to 2.6). By contrast, the physiotherapy group showed an improvement of only 3%.

DISCOVERING THE UNDERLYING MECHANISMS: THE MUSCLE-BRAIN CROSSTALK

Up until this point we have seen some direct effects of exercise on cognition and mental health. However, it is important to know what underlying mechanisms are behind these effects.

Acute exercise promotes the release of a pool of neuronal and vascular growth factors mainly from central nervous system but also from other tissues such as skeletal muscle. Some of these factors stimulate the endothelial cell proliferation and play a key role in brain vascular remodeling. Thus, these vascular growth factors allow an increase in brain blood flow increasing both the neurotransmitter circulation and the supply of oxygen and nutrients to neuronal cells. On the other hand, other growth factors called neurotrophins regulate neuronal cells growth, which is known as neurogenesis, and their survival, differentiation, and transformation. If we take all these neuronal changes together, we are referring to neuroplasticity (Figure 3).

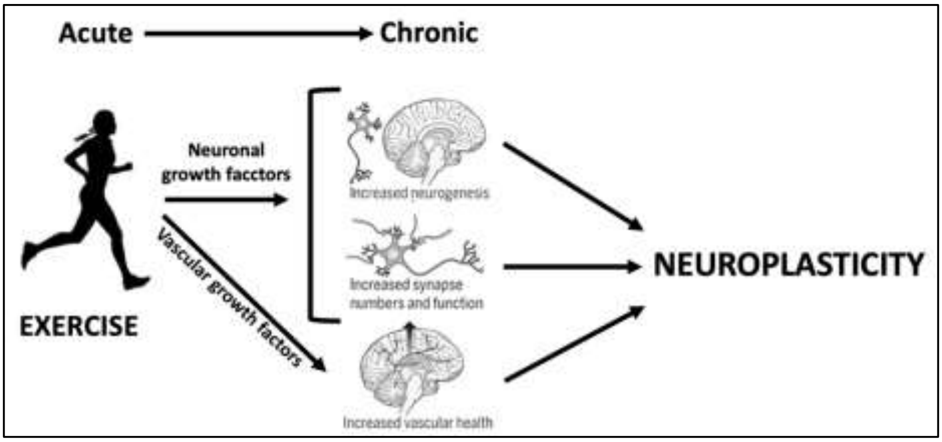

Figure 3. Role of neural and vascular growth factors on exercise-induced neuroplasticity.

To explain what neuroplasticity is, it is necessary to use a case-report image. Figure 4 represents a NMR image of a lateral view of human head. As it can be appreciated, this subject, a young man of 23 years, had a condition named hydrocephalus in which the cerebrospinal fluid replaces a large part of the brain tissue. At this point one could think that this is a disabled subject (with motor and cognitive disabilities) but he is a brilliant student of mathematics at the University of Sheffield (UK) having an intelligence quotient of 126. The question is clear… How is it possible? It is possible thanks to neuroplasticity.

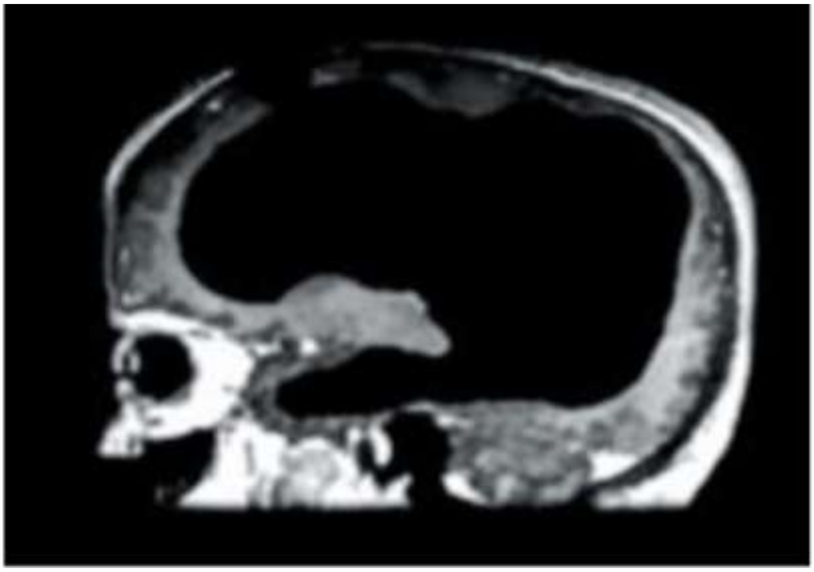

Figure 4. NMR image of a lateral view of human head (case with hydrocephalus).

Neuroplasticity refers to the ability of the brain and central nervous system (CNS) to adapt to environmental change, respond to injury and to acquire novel information by modifying neural connectivity and function. The brain does this through a multitude of mechanisms and can range from changes in synapses to the addition of new adult-generated neurons which is known as neurogenesis. In any case, these adaptations are mediated by neurotrophins and neurotrophic factors. Many of them are secreted by neurons in central nervous system but also in other tissues and cell types.

This is the case of brain-derived neurotrophic factor (BDNF) since it is released from neurons, platelets, and skeletal muscle cells. Considering that BDNF cross the blood brain barrier, it is logical to think that exercise have a facilitating effect on neuroplasticity. In fact, it has been demonstrated that exercise related BDNF responses are associated with hippocampal neurogenesis, increases in number of dendritic spines and consequently increased synaptic function (Figure 5).

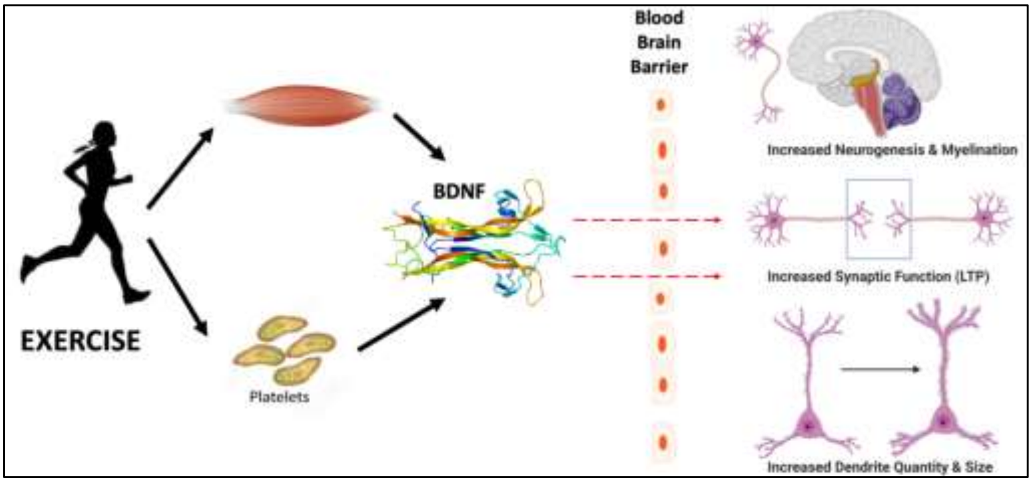

Figure 5. Exercise-related BDNF secretion and its role on brain neuroplasticity.

Just as BDNF, another brain health related proteins are released from myocites so they have been called myokines (in fact, BDNF is conserved one of the most relevant myokines). Myokines are defined as a wide spectrum of active molecules that are directly synthesized and released by skeletal muscle fibers. Myokines exert their effects in either autocrine, paracrine, or endocrine manners (Severinsen & Pedersen, 2020).

From an autocrine perspective, some myokines (especially BDNF, musclin, leukemia inhibitory factor and several cytokines such as IL-6) exert their effect within skeletal muscle itself and are involved in the regulation of muscle mass and muscle metabolism.

The paracrine and endocrine effects of myokines are focused on muscle-surrounding tissues or distant organs. For instance, IL-6 is involved in lypolisis regulation whereas irisin and insulin-like growth factor 1 (IGF-1) seem to be play a key role on bone regeneration.

Anyway, more than six hundred myokines have been identified although the biological function has been described for only 5% of them. During exercise, myokines mediate muscle–organ crosstalk to the brain, adipose tissue, bone, liver, gut, pancreas, and skin.

Nevertheless, and considering the preventive and therapeutic potential of exercise, the muscle-brain crosstalk is perhaps the most relevant connection. The neuro-protective effects of BDNF and irisin against brain and mental disorders make these myokines of additional value in the sports sciences research. In fact, our research group have published two recent manuscripts about the effects of exercise on brain health related myokines.

The first one is entitled "Acute effects of high-intensity interval training on BDNF, cortisol and working memory in physical education college students" and was published in December 2020. The aim of this study was to determine the effects of an acute bout of HIIT on neurocognitive and stress-related biomarkers and their association with working memory capacity in healthy young adults. Twenty-five male college students performed a single bout of HIIT consisting of 10 repetitions of

1 min of cycling at their VO_2peak power output. Plasma BDNF, cortisol levels, and verbal working memory (using the Digit Span Test), were assessed pre-, post- and 30 min post-intervention.

Significant post-exercise increases in circulating BDNF and cortisol levels were observed coinciding with the highest working memory performance (Figure 6); however, no statistical associations were found between cognitive and neurophysiological variables. Moreover, Digit Span Test scores obtained 30 min after exercise remained higher than those assessed at pre-exercise (Martinez-Dijaz, Escobar-Muñoz, & Carrasco, 2020).

	Pre Mean (SD)	Post Mean (SD)	Post 30 min Mean (SD)	Friedman Test (p)
BDNF (pg/mL)	424.66 (91.05)	1271.07 * (342.93)	437.04 (101.32)	<0.001
CORT (ng/mL)	132.33 (35.88)	181.41 ‡ (107.26)	234.45 † (109.63)	<0.001

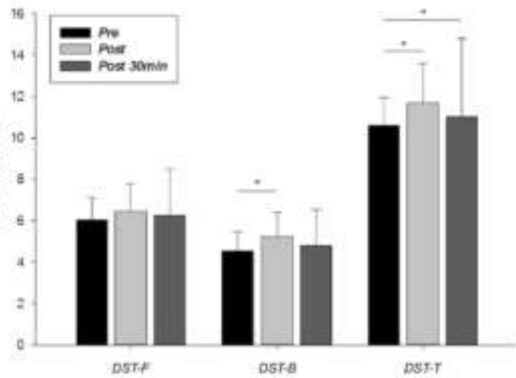

Figure 6. BDNF, cortisol (CORT) and working memory performance (Digit Span Test -DST-), before, just after and 30 min post HIIT intervention (modified from Martínez-Díaz et al., 2020).

The second manuscript, entitled "Effects of padel competition on brain health related myokines" was published last year. As it is well-known, padel is becoming one of the most widespread racket sports with potential health benefits. Considering that several myokines mediate the crosstalk between skeletal muscles and the brain exerting positive effects on brain health status, this study was designed to evaluate the responses of BDNF, leukemia inhibitory factor, and irisin to padel competition in trained players and to determine whether these responses were sex-dependent (Pradas, Cádiz, Nestares, Martínez-Díaz, & Carrasco, 2021). Twenty-four trained padel players (14 women and 10 men with a mean age of 28 years) participated voluntarily in this study, where circulating levels of these myokines were assessed before and after simulated padel competition (mean real playing time 28 min; relative intensity, 75% maximum heart rate).

Except for BDNF responses observed in female players, no significant changes in leukemia inhibitory factor and irisin concentrations were reported after padel competition. In addition, and as you can see, no sex-related differences were found (Figure 7).

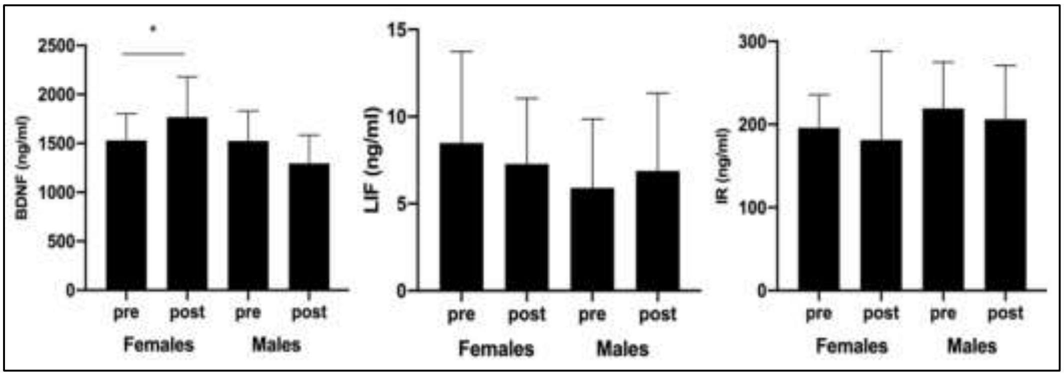

Figure 7. BDNF, leukemia inhibitory factor (LIF) and irisin (IR) plasma levels before and after padel match (modified from Pradas et al., 2021).

CONCLUSIONS

Concluding, it can be said that 1) Although there is strong evidence that exercise can improve cognition, more research is needed to determine what type is most appropriate to improve executive functioning and academic performance. Is dual-task high-intensity exercise the best option? We must clarify if exercise programs combined with cognitive training are more efficient than single-task interventions (that is, exercise or cognitive training performed alone) it. 2) Exercise should be considered as a safe and effective treatment against brain injuries and mental disorders. 3) The assessment of brain-health related myokines could serve as a valid tool to evaluate the potential for exercise (and sports) to have effects on cognition and mental health.

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Received:15.12.2022.

Approved:28.12.2022.

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