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The Effects of *High-Intensity Interval Training* (HIIT) on Cognitive Function

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ABSTRACT

Introduction : Physical exercise has an important role in the prevention or treatment of cognitive impairment. High Intensity interval training is one of interval training modalities that offers an effective way to improve cognitive function.

Main Text : High intensity interval training (HIIT) defined as intervals of vigorous physical activity followed by short periods of rest. The target intensity of HIIT is typically described as "near maximal," meaning it falls between 80 and 100% of an individual's maximum heart rate (HRmax). This form of exercise has been suggested as a time-efficient intervention for fitness improvement. HIIT induces significant improvements of adaptations in skeletal muscle, cardiovascular, and cerebral function as a result of HIIT. The influence of HIIT on skeletal muscle and cardiovascular function has been found to enhance maximal oxygen utilization (VO2max) which can be associated with improvements in cognitive function, such as memory, attention and executive function. This exercise induces changes in cognitive function by eliciting alterations in greater total grey matter volume, hippocampus, and cortical thickness in frontal, temporal and cingular cortices. The enhancement of cognitive function can also be attributed to the upregulation of specific molecular biomarkers, including BDNF, VEGF, IGF-1, and Irisin. These molecular biomarkers have the potential to enhance cognitive function by modulating changes in the brain's structural and functional plasticity.

Conclusion : This review highlighted the effect of high-intensity interval training (HIIT) in overcoming cognitive impairment by enhancing neuroplasticity, which is facilitated by alterations in molecular biomarkers that directly influence the central nervous system.

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INTRODUCTION

Exercise has a fundamental role in the primary prevention of chronic conditions such as obesity, hypertension, diabetes mellitus, cancer, cardiovascular disease, dementia and depression.(Booth et al., 2012, Atakan et al., 2021) According to evidence-based scientific guidelines, exercise is an innovative non-pharmaceutical strategy for the prevention and management of chronic diseases.(Azadpour et al., 2017, Pedisic et al., 2020) Despite these established positive effects of exercise, approximately 1.4 billion people, or one-third of adults and four-fifths of young adults, do not meet health department guidelines for prescribed levels of exercise, making sedentary behavior a global problem.(Hallal et al., 2012)

The recently upgraded World Health Organization 2020 Guidelines on physical activity and sedentary behavior recommend engaging in at least 150 to 300 min of moderate-intensity

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exercises, or 75 to 150 min of vigorous-intensity aerobic exercise, per week to attain significant improvements in health.(Organization, 2020, Bull et al., 2020) However, lack of sufficient time is the most prevalent obstacle to regular exercise.(Cassidy et al., 2017) Recent research has focused on high intensity interval training models, which consist of relatively short bouts of intense activity performed with a "near-maximal" or "all-out" effort corresponding to 90% of maximal oxygen uptake (VO2max) or >75% of maximal power, mixed with passive or active recovery periods.(Buchheit and Laursen, 2013) This HIIT models can induce similar or even greater physiological adaptations when compared to moderate-intensity continuous training (MICT), which typically consists of 30–60 minutes of moderate-intensity.(Bishop et al., 2019, MacInnis and Gibala, 2017)

There are some strong evidences that HIIT can improve cognitive function. According to research conducted by Dupuy et al., there was an increase in cognitive performance as measured by the Stroop Test reaction time up to 60 minutes after HIIT.(Dupuy et al., 2018) Tsukamoto et al, also came to the same conclusion; the effects of continuous acute exercise on cognitive performance persisted for 30 to 50 minutes after the exercise ended.(Tsukamoto et al., 2016) This improvement of cognitive function caused by some molecular biomarkers such as BDNF, IGF-1, VEGF.(Norling et al., 2020) However, the number of studies examining the impact of HIIT on the molecular biomarker for improving cognitive function is lacking. (Drapeau et al., 2019)

In order to address this knowledge gap, this review will provide an overview of interval training, the physiological adaptation to interval training, and the impact of HIIT on improving cognitive function through some specific molecular biomarkers, including BDNF, IGF-1, VEGF and Irisin.

INTERVAL TRAINING: DEFINITION AND CLASSIFICATION

Interval training, simply defined as intervals of vigorous activity followed by periods of recovery.(Fox et al., 1973) Interval training regimens have been found to be highly effective in enhancing VO2max, endurance capacity, resting metabolic rate, body composition, insulin sensitivity and cognitive functions, especially among older individuals.(Bouaziz et al., 2017, Drigny et al., 2014, Hsieh et al., 2021) Besides, interval training is a suitable exercise regimen for both healthy adults and individuals with cardiopulmonary disease, breast cancer, vascular disease, osteoartritis and diabetes. (Wormgoor et al., 2017)

Interval training appears to have been investigated in cardiac rehabilitation for the first time in 1972, when patients were encouraged to cycle at high workloads for 60 seconds with a 30 second rest between cycles. The intervals allowed the patients to exercise for at least twice as long as they could when cycling continuously.(Smodlaka, 1972)

In 1977, a study involving healthy participants investigated the effects of a 10-week program that combined interval and moderate continuous training.(Hickson et al., 1977) Contrary to the study's hypothesis that VO2 would plateau over time, Hickson et al discovered a linear increase in maximal oxygen absorption (VO2max) over a 10-week period.(Hickson et al., 1977) Forty years after the first report of interval training in cardiac patients, the interest in Interval high-intensity interval training (HIIT) in patients at higher risk has prompted a number of studies in this area.(Weston et al., 2014)

This review will use the terminology proposed by Weston et al. to distinguish between two fundamental categories of interval training based on exercise intensity(Weston et al., 2014): (1) Sprint interval training (SIT) is characterized by efforts performed at intensities equal to or greater than the tempo that would elicit $V_{O2\ peak}$, including "all-out" or "supermaximal" efforts.(MacInnis and Gibala, 2017) The most common SIT protocol is performed on a cycle ergometer and consists of four 30-second intervals of maximum effort cycling against a high force approximately 170% of VO2max with moderate exercise or rest intervals.(Gillen and Gibala, 2014) (2) High-intensity interval training (HIIT) is defined as 'near maximal' efforts performed at an intensity that elicits ≥80% (but frequently 85–95%) of maximal heart rate. The term moderate intensity continuous training (MICT) is used in comparison to high intensity interval training (HIIT) to describe continuous exercise conducted at a lower intensity.(MacInnis and Gibala, 2017)

It is well documented that HIIT provides a strong stimulus for central cardiovascular adaptations and metabolic stress(Gibala and Jones, 2013), whereas MICT primarily induces peripheral adaptations that contribute to muscular oxygen extraction and metabolic efficiency.(Daussin et al., 2008) According to original research conducted by Thum et al, HIIT induces greater enjoyment than MICT, making interval training a practical and pleasurable mode of exercise for the general population.(Thum et al., 2017) Moreover, due to its time-efficiency and the induced physiological adaptations similar to MICT, HIIT has been ranked first in Worldwide Fitness Trends 2018.(Thompson, 2017)

PHYSIOLOGICAL ADAPTATION OF INTERVAL TRAINING

Exercise physiology mainly focuses on the elucidation of mechanisms underlying training adaptations. The improvements in aerobic energy metabolism are influenced by three types of adaptations that happened after an interval training session.(MacInnis and Gibala, 2017) First, the peripheral adaptations, such as improvement of skeletal muscle mitochondrial content and capillary density.(Holloszy and Coyle, 1984) Second, the cardiovascular adaptation such as increased maximal stroke volume, maximal cardiac output, and blood volume.(Blomqvist and Saltin, 1983) Third, the cerebral adaptation associated with improved cerebral perfusion and cerebrovascular reactivity.(Calverley et al., 2020)

Skeletal Muscle Adaptation to Interval Exercise Training

Fundamental features of exercise biology include molecular and cellular processes that underlie adaptations to exercise, and the responsiveness of these pathways to various exercise stimuli is crucial for understanding how humans adapt to exercise.(Egan and Zierath, 2013) Cellular stress is proportional to exercise intensity, and there is substantial evidence that higher levels of exercise elicit a stronger metabolic signal than moderate levels.(Gibala et al., 2012, Egan and Zierath, 2013)

Higher intensities exercise produces a greater ATP turnover, which also relies more on carbohydrate oxidation and utilizes more glycogen than lower intensities exercise.(Van Loon et al., 2001) This condition caused a greater accumulation of intracellular lactate, creatine, AMP, ADP, AMPK, and CaMKII.(MacInnis and Gibala, 2017, Rose et al., 2006) Greater activation of these kinases is associated with increased expression of mRNA for PGC-1alpha, a significant regulator of mitochondrial biogenesis that promotes a higher rate of mitochondrial protein synthesis and a higher mitochondrial content.(Gibala et al., 2012)

A study conducted by Perry et al. explore the first temporal patterns of adaptations to high-intensity interval training (HIIT). Their findings revealed that the expression of messenger RNA (mRNA), such as PGC-1α, exhibited a temporary and immediate rise subsequent to each HIIT session.(Perry et al., 2010) Multiple studies have provided evidence indicating that there is a notable increase in mitochondrial content, as evaluated by Citrate Synthase or COX activity, following a regimen of six to seven sessions of high-intensity interval training (HIIT).(Talanian et al., 2007, MacInnis et al., 2017)

Cardiovascular Adaptation to Interval Exercise Training

Effects on VO2max

The influence of interval training programs on cardiovascular structure and function has also been studied. Few studies using low-volume HIIT models for two weeks have shown increases in cardiorespiratory capacity as measured by changes in VO2 max.(Henriksson and Reitman, 1976) The follow-up study found that a high volume of severe interval and continuous training resulted in a significant mean increase in VO2 max in humans, a 44% rise over 10 weeks.(Bassett and Howley, 2000) In cross-sectional investigations, the variation in VO2 max is primarily due to variations in maximal stroke volume (and cardiac output), rather than differences in arteriovenous O2.(Montero et al., 2015)

Studies comparing HIIT to MICT in various populations, including adolescents, healthy adults, persons with obesity, cancer, and metabolic syndrome, have demonstrated that HIIT is a more time-efficient intervention for enhancing aerobic capacity than MICT.(García-Hermoso et al., 2016, Cao et al., 2019, Milanović et al., 2015) According to a meta-analysis by Bacon et al., high-intensity training results in a greater increase in VO2 max than values typically reported in large studies of MICT.(Bacon et al., 2013) Similarly, Weston et al. concluded from a meta-analysis that HIIT was more effective than work-matched MICT for enhancing VO2 max in patients with lifestyle-induced cardiometabolic disease.(Weston et al., 2014) A recent, large randomized controlled trial of different intensities of continuous exercise with obese adults supports these meta-analyses: greater increases in VO2 max were demonstrated

in response to 24 weeks of exercise performed at 75% of VO2max compared to isocaloric exercise performed at 50% of VO2max, with differences evident after 8 weeks of training.(Ross et al., 2015)

Effects on Endurance Capacity

The enhancements in endurance capacity resulting from high-intensity interval training (HIIT) can be attributed to a combination of molecular and physiological mechanisms.(Holloszy and Coyle, 1984) These factors encompass an increase in skeletal muscle blood flow and vascular conductance, an augmentation in lactate carrying capacity and hydrogen ion releasing capacity from active muscles, as well as an improvement in sarcoplasmic reticulum function.(Krustrup et al., 2004, Juel et al., 2004, Ørtenblad et al., 2000)

Additionally, the enhanced maximal oxygen consumption (VO2 max) and oxidative capacity of skeletal muscle resulting from high-intensity interval training (HIIT) significantly contribute to the enhancement of exercise performance.(Hawley et al., 2014, Little et al., 2010) This improvement enables individuals to sustain the same exercise intensity for an extended duration subsequent to the implementation of the training intervention. Another noteworthy observation is that the High-Intensity Interval Training (HIIT) programme has the potential to impact exercise performance by promoting heightened fat burning during physical activity and preserving glycogen levels. These modifications lead to a reduction in the buildup of intracellular metabolites, including lactate, hydrogen ion, inorganic phosphate, adenosine diphosphate, and adenosine monophosphate. This reduction has the potential to enhance exercise performance.(MacInnis and Gibala, 2017, Astorino and Schubert, 2018)

Cerebral Adaptation to Interval Exercise Training

There is evidence that regular physical activity and improvements in cardiorespiratory fitness can increase cerebral perfusion and vasoreactivity throughout an individual's lifetime.(Davenport et al., 2012) Clinically, moderate to high cardiorespiratory fitness is associated with a significantly reduced risk of stroke mortality and dementia, as well as enhanced cognition.(Singh-Manoux et al., 2005)

The primary mechanisms include : accelerated neurogenesis, especially in the age-vulnerable hippocampal dentate gyrus; decreased-amyloid and neurooxidative-inflammatory-nitrosative stress; and increased brain-derived neurotrophic factor (BDNF), which modulates neuroplasticity by promoting neurite outgrowth and synaptic function.(Brown et al., 2010)

Neuroplasticity is an ongoing phenomenon that facilitates the alteration of preexisting neural networks through the facilitation of structural and functional adjustments in synapses, which are in turn prompted by changes in behavior. Physical activity has the potential to elicit various alterations in the anatomical and functional aspects of the brain.(Lin et al., 2018)

Structural Changes

Macroscopic Changes

The use of resting MRI scans for the assessment of human brain structure has revealed that engaging in aerobic activity for a duration ranging from several months to a year leads to an augmentation in brain volume throughout many regions, including the prefrontal and temporal cortex, as well as the hippocampus.(Colcombe et al., 2006, Erickson et al., 2011) In contrast to sedentary healthy people, athletes of comparable ages exhibit elevated concentrations of gray and white matter clusters in the subgyrus, cuneus, and precuneus regions, as determined using voxel-based analysis.(Tseng et al., 2013)

A study using functional magnetic resonance imaging (fMRI) indicated that engaging in aerobic exercise resulted in increased neural activity throughout brain regions associated with activities related to attentional control.(Colcombe et al., 2006) Furthermore, a duration of twelve months of consistent physical activity resulted in an improvement in the functional connectivity within the default-mode network and the frontal executive network. The observed augmentation in brain regional volume and activity could potentially indicate a modification in the quantity of neurons, synapses, and axonal and dendritic arbors.(Voss et al., 2010) There is also evidence from animal research that exercise can lead to changes in the structure of neurons in many regions of the brain, such as the dentate gyrus (DG) and the cornu ammonis (CA) areas of the hippocampus, amygdala, cortex, striatum, and cerebellum.(Eddy and Green, 2017, Huang et al., 2012)

Microscopic Changes

The impact of physical exercise on the structural characteristics of neurons has been investigated in various regions of the brain. Exercise has been found to have a significant impact on the dendritic length and complexity, as well as the dendritic spine density of neurons in the hippocampal DG and CA regions.(Eadie et al., 2005, Stranahan et al., 2007) At the post-synaptic location, exercise increased the dendritic arborization and spine density in both the CA1 and CA3 regions. The number of dendritic spines and the number of dendritic branches in the apical dendrites of CA1 pyramidal neurons increased after treadmill and wheel-running exercise.(Stranahan et al., 2007, Lin et al., 2012)

Exercise has also been studied in rats and mice for its effect on the structure of amygdalar neurons. After one month of treadmill exercise, the dendritic arborization and spine density of neurons in the basolateral amygdala increased using the single neuron labelling technique.(Lin et al., 2012, Lin et al., 2018) Exercise affects the cytoarchitecture of cortical neurons as well. After 16 months of moderate exercise, nitrergic neurons in the cerebral cortex exhibit larger size and extended dendritic arborization, suggesting that nitric oxide may play a role in exercise-related synaptic plasticity.(Pietrelli et al., 2011)

The cerebellum and striatum are integral components of a distributed system that governs the regulation of motor functions.(Laforce Jr and Doyon, 2001) Research has demonstrated that physical exercise has the capacity to enhance the density of dendrites and dendritic spines in the cerebellar Purkinje cells of various animal species.(Pysh and Weiss, 1979, González-Burgos et al., 2011) The alterations in the structural characteristics of dendritic spines may be associated with the modulation of excitability in Purkinje cells as a consequence of motor activity.(González-Burgos et al., 2011) Moreover, it has been observed that exercise has a selective effect on enhancing the thickness of the molecular layer in the cerebellum. This finding suggests that there are morphological adaptations occurring in the basket and stellate cells.(Pysh and Weiss, 1979)

Functional Changes

Functional alterations in neurons (e.g., synaptic activity) are strongly associated with structural alterations in neurons (e.g., spine density, dendritic complexity, and newborn neuron maturation in the adult hippocampus) induced by exercise.(O’Callaghan et al., 2007) LTP is a form of synaptic plasticity characterized by a sustained increase in synaptic efficacy in response to a patterned stimulus.(Van Praag et al., 1999) Numerous studies have demonstrated that physical activity effectively increases LTP amplitude in the DG region.(Radahmadi et al., 2016, Patten et al., 2013) The effect of exercise on the enhancement of long-term potentiation (LTP) is time-dependent (number of running days). Patten et al. examined the expression of LTP in animals that received varying amounts of exercise and discovered that LTP expression gradually increased in the DG from days 7 to 28 of the exercise period, reaching a significant level after 56 days of running.(Patten et al., 2013)

EFFECT OF HIIT IN COGNITIVE FUNCTION THROUGH MOLECULAR BIOMARKERS

The mechanisms underlying exercise-induced neuroplasticity involve several neurotrophic and growth factors such as BDNF, VEGF, Irisin and IGF-1.

1. Brain-Derived Neurotrophic Factor (BDNF)

Brain-Derived Neurotrophic Factor is a member of neutrophin that is found in the nervous system and peripheral organs such as skeletal muscle. BDNF is a protein consisting of 247 amino acids, synthesized and folded in the endoplasmic reticulum as pre-proBDNF (32-35 kDa).(Foltran and Diaz, 2016) After translocation to the Golgi apparatus, the signal sequence of the preregion is rapidly cleaved to form the proBDNF isoform (28–32 kDa). Then Pro BDNF will be cleaved to reach the mature BDNF isoform (mBDNF, 13 kDa).(Colucci-D'Amato et al., 2020, Kowiański et al., 2018) Pro BDNF and mBDNF will produce physiological responses mediated by 2 different classes of transmembrane receptors, namely pT75 NTR and TrKB.(Silakarma and Sudewi, 2019)

In neuronal cells, proBDNF and mBDNF are released following cell membrane depolarization.(Dieni et al., 2012) The balance between proBDNF and mBDNF is determined by the stage of brain development and specific brain regions. In the early postnatal period, concentrations of proBDNF were found to be higher and an important factor for modulating brain function. While mBDNF is usually found in adults and is important for neuroprotection function and synaptic plasticity.(Colucci-D'Amato et al., 2020)

Human and animal studies collectively suggest that exercise is an active strategy to upregulate the expression of BDNF, which plays an essential role in exercise-induced neuroplasticity. BDNF is a well-characterized mediator of neuronal growth, plasticity, and survival, which binds to its receptor, tropomyosin receptor kinase B (TrkB) which increases the phosphorylation levels of cAMP response-element binding (CREB) and the translation of synaptic plasticity-related proteins.(Lin et al., 2018, Jimenez-Maldonado A, 2018)

The activation process of the BDNF signaling pathway is mainly regulated by tropomyosin-related receptor kinase B(TrkB). A previous study showed that the activation of TrkB affects neuronal dendritic afforestation, spinogenesis, dendritic growth, and spinal morphogenesis which leads to improvements in brain functionality.(de Sousa Fernandes et al., 2020)

HIIT is an exercise characterized by relatively short bursts of vigorous activity, interspersed with rest or low-recovery exercises. The effect that HIIT has on human physiology is that it acts on physical performance, metabolism, and brain function.(Pontes and De Sousa, 2016) HIIT is an effective model for improving spatial cognitive function by increasing hippocampal BDNF signaling, even with lower exercise volume and time. (Foster, 2015)

Several potential molecular factors might associate with the effects of HIIT on the process and/or cognitive improvement, because the higher the intensity of physical exercise activity, the higher the body's metabolic rate which shifts towards anaerobic metabolism. Endurance training activities for a long time will stimulate type II muscle fibers (white muscle fibers or fast twitch) which use the anaerobic energy system and will form lactic acid. (Hoshino et al., 2016)

An increase in blood lactate concentrations is frequently correlated with upregulation in serum BDNF levels, motor cortex excitability, and motor learning in healthy humans.(Hoshino et al., 2016) Current research has also demonstrated that high intensity exercise increases peripheral lactate and BDNF levels, while lactate infusion during rest can increase both central and peripheral BDNF levels. Lactate and BDNF can induce neuroplasticity that can improve cognitive function.(Müller et al., 2020)

Some studies using mice found that lactate from active muscles can enter the neuron through the MCT2 receptors to stimulate BDNF by promoting the SIRT1 pathway.(El Hayek et al., 2019) The expression of BDNF in the hippocampus and its high-affinity receptor tropomyosin receptor kinase B (TrkB) are well known to promote neurogenesis, neuronal survival, synaptic plasticity, and long term potentiation. This improvement in hippocampal LTP is often associated with memory and cognitive function.(Lisman et al., 2018) In the same studies, using healthy rodents with repeated lactate injection to mimic high-intensity exercises, can induce higher BDNF and/or VEGF expression that promotes neurogenesis and angiogenesis which improve memory and cognitive function.(Hugues et al., 2021, El Hayek et al., 2019)

Another study discussed that HIIT increased hydrogen peroxide (H202) and tumor necrosis factor-alpha (TNF-α) concentration in the brain, these molecules activate the signaling of peroxisome proliferator-activated receptor γ coactivator (PGC-1α) to induce the synthesis of BDNF neuron.(Jimenez-Maldonado A, 2018)

Moreover, recent evidence has shown that gene expression of fibronectin type III domain-containing 5 (FNDC5) in skeletal muscle after physical exercise, can release an endurance exercise-induced myokine called Irisin. This myokine can cross the blood brain barrier and activate BDNF genes in the hippocampus to improve neurogenesis and cognition.(Hugues et al., 2021, Boström et al., 2012)

Furthermore, another factor associated with the effects of HIIT on neuroplasticity is the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which regulates the subgranular zone (SGZ) niche of the stem cells.(Molteni et al., 2002) The decline in GABA after exercise can elevate BDNF levels that mediate neurogenesis, this theory has been proven with transcranial magnetic stimulation (TMS) in human studies indicate a decrease in synaptic GABA functions, parallel with improvements in motor memory consolidation after HIIT.(Jimenez-Maldonado A, 2018, Stavrinos and Coxon, 2017)

2. Insulin-Like Growth Factor 1 (IGF-1)

IGF-1 is an insulin-like polypeptide that promotes cell proliferation, cell differentiation, bone synthesis and metabolism. IGF-1 was primarily produced by the liver and secreted into the circulation. IGF-1 in plasma can enhance bioavailability and prolong half-life by binding to IGF binding protein (IGFBP), and it can be actively transported to the central nervous system (CNS) through the choroidal membrane and across the blood–brain barrier.(Labandeira-Garcia et al., 2017)

IGF-1 was then isolated from IGFBP via an enzymatic process and bound with high affinity to the IGF-1 receptor (IGF-1R), activating the downstream signalling pathway to carry out the corresponding functions.(Al-Samerria and Radovick, 2021) In addition to peripheral IGF-1, the cortex, hippocampus, cerebellum, hypothalamus, subventricular zone, and dentate gyrus of the CNS produced IGF-1, which regulated neuronal growth, development, metabolism, and neuroplasticity.(Dyer et al., 2016)

IGF-1 is another important growth factor that is increased as a result of exercise.(Yau et al., 2016) Chronic exercise-enhanced adult hippocampal neurogenesis, learning, and memory performance have been attributed to IGF-1 signaling in the hippocampus.(Lin et al., 2018) The 4-week voluntary exercise of mice upregulates the expression of IGF-1 and promotes hippocampal neurogenesis, and this effect of exercise is mediated by IGF-1, as inhibiting the effect of IGF-1 by intraperitoneal injection of an IGF-1R inhibitor significantly inhibited learning memory ability and hippocampal neurogenesis in mice.(He et al., 2023) There may also be regional variations in the effect of exercise on IGF-1 abundance. According to the study by Yu et al., 15 days of voluntary exercise increased the expression of IGF-1 and promoted hippocampal neurogenesis in healthy adult rodents compared to the non-exercise group, but only in the DG region.(Yu et al., 2014)

Recent studies shown that high-intensity interval training (HIIT) improves cardiorespiratory fitness and vascular function more than moderate-intensity continuous training (MICT).(Ramos et al., 2015) According to Brown et al., the intensity of physical activity may be more crucial than the quantity for enhancing cognitive functions.(Brown et al., 2012) The intensity variable appears to play a significant role in generating increased IGF-1 stimulation. Low-to-moderate intensity exercise has demonstrated long-term benefits for IGF-1 concentration and executive function. In contrast, high-intensity exercise has been shown to improve both variables.(Kercher et al., 2021) In older individuals, Kovacevic et al. discovered that 12 weeks of HIIT improved cognitive function (e.g., working memory) more than moderate-intensity continuous exercise.(Kovacevic et al., 2020)

HIIT has been shown to provide a greater stimulus for the synthesis of brain-derived neurotrophic factor (BDNF), a neurotrophic factor that plays a significant role in cognitive processes. In addition, cognitively declining individuals typically have lower levels of insulin-like growth factor 1 (IGF-1).(Angelini et al., 2009) Herbert et al. found that six weeks (one session every five days) of HIIT (6x30 s at 140% of PPO interspersed with three minutes of active recovery) increased systemic IGF-1 levels.(Herbert et al., 2017) Recently, Guadagni et al. demonstrated that six months of MICT (three times per week for 20–40 minutes at 30–70% heart rate reserve) enhanced executive function, and this enhancement was associated with enhanced cerebrovascular regulation.(Guadagni et al., 2020)

3. Vascular Endothelial Growth Factor (VEGF)

VEGF, also known as VEGF-A or vascular permeability factor, is renowned for its role in angiogenesis, in which it stimulates the proliferation and migration of endothelial cells and increases vascular permeability.(Claesson-Welsh, 2012) Members of the VEGF family have also been implicated in lymphangiogenesis (formation of lymphatic vessels), monocyte recruitment, haematopoiesis, and proliferation or survival of non-vascular cell types expressing VEGFRs or NRPs, including neuronal cells.(Ruiz de Almodovar et al., 2009)

VEGF regulates the formation of blood vessels and directs neuronal migration and axonal pathfinding in the central nervous system.(Mackenzie and Ruhrberg, 2012) VEGF is the primary regulator of CNS blood vessel development. Later in development, VEGF orchestrates the ingrowth of vessel sprouts into the neural tube to create the vasculature of the brain parenchyma.(James et al., 2009)

VEGF promotes neurogenesis and stimulates neural stem cell (NSC) proliferation. VEGF plays a crucial role in cognitive function by stimulating neurogenesis and neuronal differentiation, induces axon extension and branching, and promotes synaptic plasticity.(Lange et al., 2016)

VEGF-A secretion is increased by several pathways mediated by hypoxia-inducible factors (HIFs), peroxisome proliferator-activated receptor- coactivator (PGC)-1, tumor necrosis factor (TNF)-, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) during hypoxia, inflammation, or mitochondrial stress. This condition can be induced by interval training such as HIIT or MICT.(Zhou et al., 2021)

Recent research indicates that HIIT is more effective than moderate-intensity continuous training (MICT) for increasing serum BDNF and VEGF-A levels in young men in good health.(Ferris et al., 2007, Weaver et al., 2021) In addition, Weaver et al. report that a bout of 4 x 30s 200%Wmax sprint interval training (SIT) results in higher serum BDNF and VEGF-A levels in healthy adolescents than a bout of 65%VO2peak MICT.(Weaver et al., 2021)

In the current study, both 20 and 30 minutes of HIIT increased serum VEGF-A immediately after HIIT. In the 20min HIIT group, serum VEGF-A returned to baseline 30 minutes after HIIT, whereas serum VEGF-A decreased substantially in the 30min HIIT group.(Li et al., 2022) Hebisz et al. reported a comparable finding that cyclists' serum VEGF-A was downregulated following sprint interval training (4 30s all-out repetitions separated by 90 s of rest).(Hebisz et al., 2019) Serum VEGF-A has been reported to perform a role in tissue repair. It is hypothesized that the body is under a high level of metabolic stress and that this downregulation is due to local tissue damage 30 minutes after HIIT.(Tischer et al., 1989) Moreover, the decreases in serum BDNF and VEGF-A following HIIT suggest that these proteins are utilized for local tissue repair.(Hebisz et al., 2019)

4. Irisin

Irisin is a 112 amino acid polypeptide proteolytically cleaved from FNDC5, which is glycosylated and then secreted into the bloodstream.(Waseem et al., 2022) Fibronectin type III domain-Containing Protein 5 (FNDC5) protein is composed of 209 amino acid residues comprising an N-Terminal signal. This peptide consisting of 29 amino acids, an irisin/fibronectin III domain with 94 amino acids, a linking peptide region consisting of 28 amino acids, a transmembrane domain consisting of 19 amino acids, and a cytosolic domain consisting of 39 amino acids.(Elizondo-Montemayor et al., 2018)

Irisin has an important role in the central nervous system. Irisin secretion is closely related to physical activity, which activates the PGC1/FNDC/BDNF pathway. Following an increase in PGC-

1alpha expression in the brain and periphery induced by exercise, FNDC5 gene expression will increase.(Boström et al., 2012) Then, irisin is synthesized and found in Purkinje cells, the hypothalamus, and cerebrospinal fluid; it also crosses the blood-brain barrier. Upon crossing the blood-brain barrier, irisin will stimulate the expression of BDNF, resulting in enhanced memory, cognitive function, and learning ability.(Lourenco et al., 2019) BDNF is extensively expressed in the brain and exerts a significant influence on synaptic activity. Microglia and astrocytes secrete BDNF, which stimulates synapse plasticity, increases neuronal differentiation ability, and promotes neuronal survival.(Peng and Wu, 2022)

According to research by Daskaloupulou et al., the increase in irisin levels after a maximal workload protocol was considerably greater in fitter individuals who exercised for longer durations and attained higher percentages of VO2 max and MET peaks after exercise.(Daskalopoulou et al., 2014) Similarly, previous research conducted by Kim et al, suggests that HIIT may mobilize more type II muscle fibers and increase irisin levels compared to MICE protocol.(Kim et al., 2016)

Furthermore, based on previous research, acute exercise may immediately and substantially increase circulating irisin and BDNF levels. Both acute MICE and HIIT modes with different protocols may induce varying physiological (e.g., cerebral hemodynamic and heart rate dynamics/variability) and circulating molecular biomarker responses.(Archundia-Herrera et al., 2017)

CONCLUSION

High intensity interval training can improve cognitive function by increasing some molecular biomarkers that play a role in enhancing neuroplasticity in brain. These molecular biomarkers, such as BDNF, IGF-1, VEGF and Irisin, might influence neuroplasticity in brain by enhancing neurogenesis, synaptogenesis and neuronal proliferation.

BDNF activated by binding with TrkB receptor, resulting in dendritic growth, and spinal morphogenesis which leads to improvements in neuroplasticity. Similar with BDNF, IGF-1 also activated by binding with its receptor IGF-1R and enhanced adult hippocampal neurogenesis. Meanwhile, Irisin acts indirectly by stimulating the expression of BDNF, which resulting in enhanced memory, cognitive function, and learning ability. VEGF also plays a crucial role in cognitive function by stimulating neurogenesis, neural stem cell (NSC) proliferation and neuronal differentiation. Some of these mechanisms can explain the effects of high intensity interval training in enhancing cognitive function as a prevention to chronic condition problems such as depression and dementia.

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