Clinical Interventions in Aging

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REVIEW

Understanding Cognitive Decline in Aging: Mechanisms and Mitigation Strategies – A Narrative Review

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Abstract: Cognitive decline is a natural process that accompanies aging. In some cases, such as in sarcopenia-burdened or diseased older adults, the disease course may be more rapid. Declining cognitive function is associated with changes in the central nervous system per se or peripheral triggers that impair cognition. This review discusses issues related to central, central-peripheral, and peripheral factors that enhance cognitive deterioration, such as cortical thickness, cerebral white matter structure and function, blood-brain barrier (BBB) disruption, insulin resistance, inflammation, and vascular dysfunction. BBB permeability appears to be a critical point for factors associated with aging that may accelerate cognitive decline. Thus, we provide an in-depth analysis of the central-peripheral crosstalk. Additionally, we discuss high-intensity interval training (HIIT) as a promising strategy to counteract changes that accompany the aging process. Resistance (RHIIT) and aerobic (AHIIT) may be beneficial for cognitive health among the elderly, but their lack of empirical confirmation is a huge gap in the research.

Keywords: aging, adipose tissue, central nervous system, cognition, exercise, inflammation

Introduction

Healthy aging and quality of life are becoming the goals of gerontological research, as extending the health span and delaying the development of disabilities and chronic diseases are the expectations of aging societies.[1] Unfortunately, by 2020, 1 billion people worldwide were aged 60 years or over and by 2050 that number will exceed 2 billion.[2] Moreover, projections of dementia onset will triple over the next 30 years.[3] This has led to an intensified search for anti-aging treatments.

Aging is a multifactorial process based on cellular senescence,[4] which, through its influence on specific signalling pathways, leads to a progressive decline in tissue and organ function among older people.[5] In addition, negative age-related changes have been observed in the brain tissue, where structural changes have an important impact on cognitive functioning.

Among others, deterioration of skeletal muscles (sarcopenia), attenuation of cardiovascular functions, and pathophysiological metabolic states, such as obesity and/or type 2 diabetes, have been listed as risk factors for cognitive health.[4–6] The key factors associated with cognitive decline are sleep apnea,[7] hearing deficits,[8] atrial fibrillation,[9] vitamin B12 deficiency,[10] but physical activity, in turn, can delay cognitive decline.[11] It has been shown that most affected cognitive domains include short- and long-term memory as well as executive functions which are crucial for everyday functioning.[12]

Moreover, a progressive decline in cognitive function may predict the development of neurodegenerative diseases such as Alzheimer's disease and related dementias,[13] chronic mental health conditions such as depression or anxiety.[14] Furthermore, low-grade inflammation originating from adipose tissue throughout life may accelerate this process.[15]

Interestingly, healthy habits, such as physical activity, balanced nutrition, and social interactions, can delay and prevent negative changes in the body.[16] Moreover, the approach to healthy aging includes both physical and mental aspects, which are partly established.[17,18] However, therapeutic interventions targeting cognitive decline during aging

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require a comprehensive understanding of the underlying functional and structural changes, which would enable formulation of more precise and effective recommendations.

Consequently, the aim of this review was to shed light on current knowledge regarding the mechanisms related to cognitive decline accompanying aging. Simultaneously, high-intensity interval training (HIIT) is also discussed as a promising exercise strategy that has the potential to slow cognitive decline in aging.

Potential Mechanisms of Cognitive Decline

Cognitive decline during aging is a multidimensional issue that deserves a broader perspective. Hence, the division into central, central-peripheral, and peripheral factors/mechanisms seems to be the most appropriate and is summarized in Figure 1.

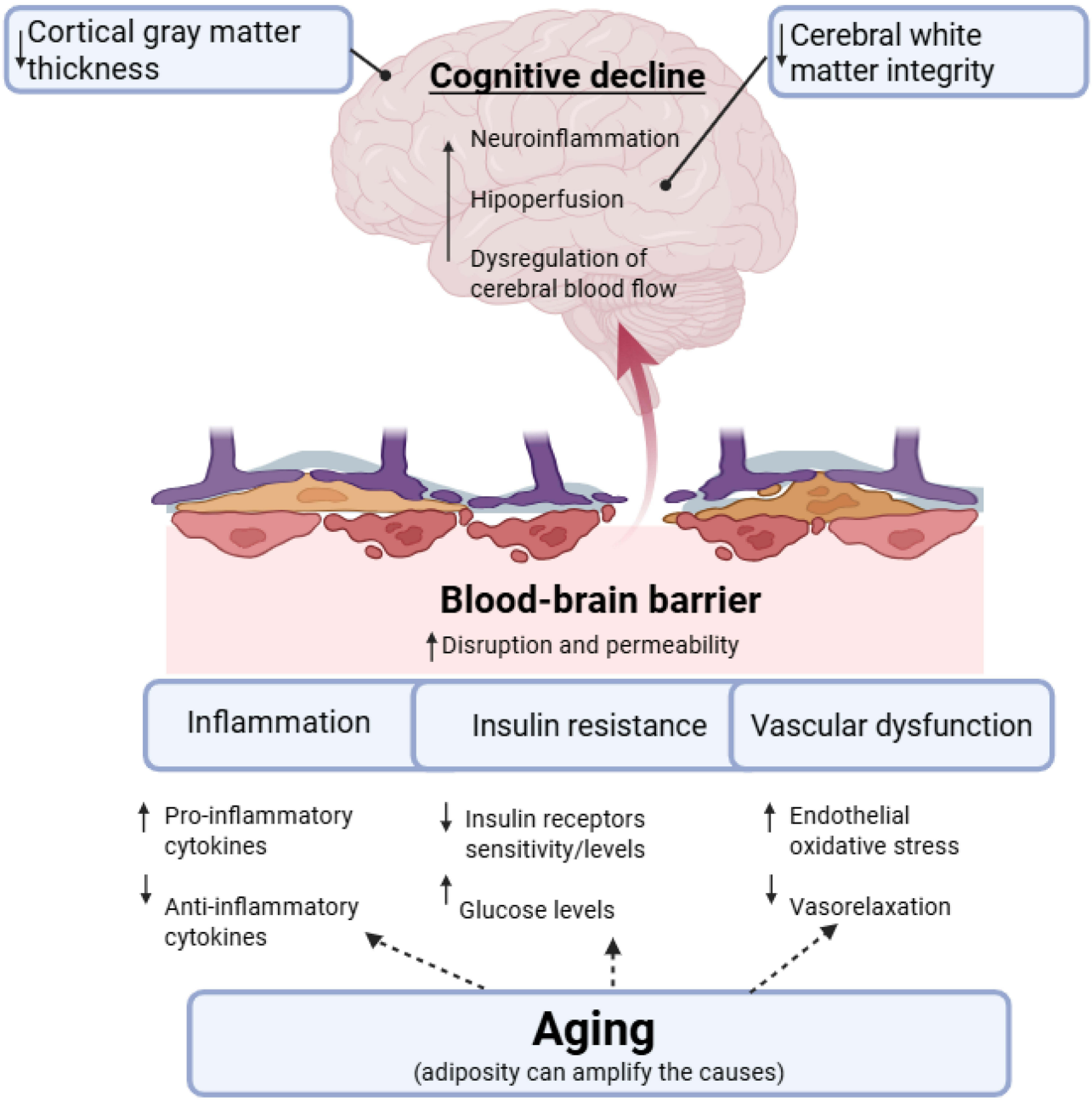

Figure 1 Factors affecting cognitive decline in aging.

Central Mechanisms

Cortical Thickness

The cerebral cortex, particularly the prefrontal cortex, is a region in which cognition-related processes occur.[19] Hence, the greater the thickness of the cerebral cortex, the better is the cognitive performance throughout life.[20] On the other hand, cortical thinning or shrinkage is a natural process that occurs with aging,[21] but the thinning of some regions of the cerebral cortex is accelerated with age (lateral occipital, lingual), and others are slowed down (posteriorcingulate, lateral orbitofrontal).[22] In addition, some cortical regions undergo thinning dependent on genetic and environmental factors.[23] The findings indicate that lifestyle, including moderate to vigorous physical activity, was associated with greater thickness of the cerebral cortex.[24] In addition, a meta-analysis provided by Afanador-Restrepo et al indicated that high-intensity training interventions are sufficient to improve or at least delay the decline in global cognition.[25] Unfortunately, the lack of cortical thickness analyses does not directly indicate a cause-and-effect relationship.

On the contrary, a sedentary lifestyle and increased fat accumulation can enhance cortical thinning. A longitudinal study by Shaw et al examined nearly 400 mildly overweight older adults (60–66 years of age) and observed that the cortical thickness decreased with age by 0.3% per year over a 12-year study period.[26] Furthermore, a longitudinal study of overweight and obese individuals found that a 1% annual increase in BMI was associated with cortical thinning of up to 0.5%.[27] Similarly, another longitudinal study demonstrated that BMI trajectories over four decades predict a pattern of cortical thinning. Moreover, the authors concluded that a steeper increase in BMI during midlife was linked to a thinner cortex later in life.[28] Several mechanisms may link excessive midlife BMI to neurodegenerative damage, likely through interconnected processes such as vascular and metabolic pathways, inflammatory responses, and potential genetic influences. Therefore, maintaining a healthy body weight (BMI < 24.9) and avoiding excessive adiposity are crucial for long-term health, not just in later life, but at every stage.

Cerebral White Matter

The white matter of the brain integrates areas responsible for cognition. Fluidity-based measurements and crystallization, which characterize speed and knowledge, respectively, differ in terms of aging changes.[29] A few studies have indicated that aging is strictly related to white matter decline and cortical disconnectivity.[30–32] Additionally, variations in BMI during the lifespan are associated with a reduction in white matter integrity, indicating that deteriorated physical health (increased global adiposity) can affect brain function.[33] A significant number of studies have confirmed this hypothesis.[34–36] Moreover, similar conclusions have been drawn from studies involving older adults who were overweight or obese.[37,38] Nevertheless, the mechanisms responsible for these changes are not fully understood. However, some researchers have claimed that it can be associated with low-grade systemic inflammation owing to excessive adiposity or abnormal cardiometabolic and cardiovascular factor levels.[39,40]

Therefore, central mechanisms are involved in shaping the grey and white matter of the brain, which is crucial for cognition in the elderly. Structural, functional, and endocrine changes in peripheral systems and tissues, including the blood-brain barrier (BBB), insulin resistance, adipose tissue-derived inflammation, and vascular function, should also be considered when explaining the mechanisms responsible for the decrease in cognitive performance in older adults.

Blood-Brain Barrier as a Central-Peripheral Mechanism

Cross-environmental homeostasis between the central nervous system (CNS) and blood that connects the rest of the body is rigorously protected by specialized endothelial cells of pericytes, astrocytes, and cerebral microvessels called the BBB.[41] The influx and efflux of energy substrates, metabolites, ions, and other serum-derived factors from the CNS through protein complexes, tight junctions, and glycocalixes are regulated by the BBB to maintain physiological neuronal function.[42] Unfortunately, some pathophysiological conditions, such as diseases of the nervous system, including neurodegenerative and metabolic conditions, cause BBB disruption and increase the permeability to neurotoxic compounds.[43,44] Moreover, impaired efflux, accumulation, and aggregation of amyloid-β (Aβ) in the brain also causes cognitive impairment.[45] However, other factors such as aging and obesity are associated with BBB influx-efflux disruption.[46,47]

Some studies using magnetic resonance imaging (MRI) have shown that BBB disruption is most pronounced in the hippocampus[48] and in the grey and white matter of the brain.[49] It was also indicated that over 12 years, BBB leakage in

the white and grey matter was significantly associated with memory retrieval decline.[50] Unfortunately, aging and excess adipose tissue aggregation, that is, in overweight and obese individuals, show synergistic and negative health effects.[51–53] Low-grade systemic inflammation induced by adipose tissue-derived cytokines can exacerbate the activation of immune cells, such as microglia, causing neuroinflammation and further BBB disruption,[51,54] as summarized in the review by Takata et al.[55] Therefore, obesity-induced chronic peripheral inflammation is associated with impaired hippocampal plasticity in an animal model.[56,57] Interestingly, high-fat diet (HFD)-fed animals by reducing mRNA expression of proteins such as claudin-5 and −12 resulted in impaired BBB integrity. Increased BBB permeability was observed mainly in the hippocampal area, which appears to be particularly vulnerable to BBB disruption.[58] Moreover, HFD-induced obesity interacts with aging, causing neuroinflammation and cognitive decline.[59] HFD also amplifies the negative impact of aging through neuroinflammation-induced increase in microglial activation.[60] Therefore, BBB disturbances caused by peripheral pathophysiological changes such as excessive fat accumulation during aging can pose a danger to cognitive health.

On the other hand, exogenous supply of substances with antioxidant, anti-inflammatory and prebiotic properties, such as polyphenols, may contribute to strengthening the integrity of the BBB through changes in the composition of the gut microbiome.[61,62] In an association study, elderly people with cognitive impairment had lower abundance of the anti-inflammatory bacteria *E. rectale* and *B. fragilis*, and higher presence of the pro-inflammatory bacteria *Escherichia/Shigella* than those without cerebral amyloidosis - one of the causes of the development of Alzheimer's disease.[63] Other gut bacteria such as *Odoribacter* has been positively associated with white matter volume and the right hippocampus, and *Bacteroides* enrichment has been linked to better cognitive performance among older adults.[64] Dietary polyphenols present in tea and grapes, among others, can improve the composition of the intestinal microbiota, including increasing the abundance of *Bacteroidetes* phyla.[65–67] Therefore, increasing the presence of anti-inflammatory gut bacteria may reduce peripheral inflammation,[68] contributing to a decrease in BBB permeability to inflammatory factors, thereby protecting CNS structure and function. Nevertheless, the exact mechanism underlying the changes in BBB permeability following dietary polyphenol supply requires further experimental studies.

Peripheral Mechanisms

Despite the central mechanisms mentioned above, special attention should also be paid to body-brain crosstalk and its impact on aging-associated cognitive performance decline. Peripheral mechanisms include insulin resistance, low-grade systemic inflammation, and vascular dysfunction.[69–71]

Insulin Resistance

Insulin is a hormone secreted by pancreatic β-cells that plays a key role in the regulation of glucose levels in the body.[72] Interestingly, insulin is also involved in neuronal cell signalling and communication by regulating neurotransmitter secretion in the CNS.[73] Insulin transported from the periphery across the BBB to the CNS influences synaptogenesis and nerve growth,[74] and the consolidation of short- and long-term memory (at least in animal models) is associated with insulin receptor (IR) levels.[75] However, weakening of excitability in response to insulin due to dysfunctions/low levels of IRs, that is, insulin resistance, leads to cognitive deterioration.[76]

Insulin resistance has been linked to memory deficits such as dementia, vascular dementia, and other cognitive dysfunctions such as Alzheimer's disease.[77] However, some studies have attempted to link insulin resistance with cognitive decline as a normal aging-associated process in humans. Indeed, a recently published study by Wei et al showed that the triglyceride glucose (TyG) index of over 660 older adults was strongly correlated with low cognitive function,[78] which also confirmed a previous report.[79] Moreover, data from nearly 3,000 older adults aged > 60 years showed that among participants without obesity, homeostasis model assessment of insulin resistance (HOMA-IR) and insulin were negatively correlated with the Consortium to Establish a Registry for Alzheimer's Disease Immediate Recall (CERAD-IR). In addition, the odds of a low score on the Digit Symbol Substitution Test (DSST), one of a cognitive function test) increased with the number of glucose metabolic risk factors.[80]

Finally, the largest study to date, conducted by Wang et al, with 4,420 participants, found that the TyG index was significantly associated with an increased risk of global cognitive decline, but only in men over 60 years of age (n =

2062).[81] Therefore, a weakened insulin response (insulin resistance) may increase the risk or accelerate a decline in cognitive function during aging.

However, the connection between these factors - low-grade systemic inflammation, reduced IRs, BBB disruption, and increased microglial cytotoxicity along with interventions that enhance insulin responsiveness to elevated glucose levels warrants further investigation in the context of cognitive aging.

Inflammation

Few reviews have been released concerning the association between peripheral inflammation and CNS ie brain and its function.[82–84] In a longitudinal study conducted over 4.5 years, low-grade systemic inflammation originating in the periphery has led to unfavourable changes in brain morphology in older adults. Doubling of circulating interleukin-6 (IL-6) was associated with lower total brain volume and, what is more fascinating, with doubled aging equivalent (9 years).[85] In support of this, a study investigating the risk factors for brain aging in individuals aged 64–100 years found that elevated levels of IL-6 were associated with an increased likelihood of accelerated brain aging. Moreover, in the same study, obesity was associated with brain aging, which seems to demonstrate the synergy between these two factors,[86] confirming the findings of previous studies.[87,88] Hence, body–brain crosstalk, which refers to the communication between factors secreted by peripheral tissues and cells, particularly cytokines released by adipose tissue as well as neuroprotective molecules produced and/or released from skeletal muscles, as well as from the brain, deserves special attention. Indeed, in cognitively unimpaired adults aged slightly above 85 years, higher IL-6 and soluble tumor necrosis factor receptor 2 (sTNFr2) levels are positively associated with greater Aβ deposition in the brain.[89]

However, not all scientific evidence unequivocally supports the involvement of pro-inflammatory cytokines in cognitive decline. In a study by Mendelson et al, which analyzed data from nearly 40,000 participants aged 40–70 years from the UK Biobank, a weak association was found between brain structure and levels of C-reactive protein (CRP) in these individuals. In addition, CRP levels were weakly, but negatively, correlated with cognitive function.[90]

Nevertheless, when assessing the relationship between brain function and aging, the total profile of pro-inflammatory cytokines should be considered, as well as single markers that cannot fully demonstrate the association between inflammation and cognitive decline.[91]

Vascular Dysfunction

The mechanisms of vascular aging are likely multifaceted. Vascular dysfunction is usually the main consequence of increased oxidative stress due to decreased mitochondrial density as well as the weakened process of biogenesis observed during aging.[92,93] Elevated levels of reactive oxygen species (ROS), such as superoxide (O^{2-}), are produced by the mitochondrial electron transport chain, resulting in increased expression and activity of NADPH oxidase.[94] Peroxides combine with nitric oxide (NO), a precursor of vasodilation in blood vessels, to form peroxynitrates, which are molecules with strong oxidative effects.[95,96] Moreover, perivascular adiposity in overweight and obese individuals is a source of tumor necrosis factor-α (TNF-α), a molecule that can initiate endothelial oxidative stress signalling, leading to reduced vasorelaxation.[97] Therefore, excess perivascular and global adipose tissue, and aging have both synergistic and negative effects. They trigger an increase in oxidative and nitro-oxidative stress, causing early vascular aging through inflammation, leading to vascular dysfunction.[98]

Vascular inflammation leads to negative structural and functional consequences in the blood and cerebrovascular vessels, such as atherogenesis, aneurysm, vascular rarefaction, and hemorrhage.[99] Therefore, aging induced by excessive adiposity-derived inflammation can be dangerous for cognitive health due to cerebromicrovascular rarefaction, which promotes the dysregulation of cerebral blood flow.[100] Indeed, a decrease in the cerebromicrovasculature causes hypoperfusion of the white matter of the brain, leading to metabolic and functional changes in neuronal dysregulation as well as cognitive decline.[101] Moreover, a much more severe decline in cognitive performance due to cerebral hypoperfusion has been observed in individuals with higher adipose tissue deposition in patients with heart failure,[102,103] and healthy individuals.[104,105] Hence, the search for interventions that induce blood perfusion through organs, including the brain, while from the long-term perspective, reducing low-grade systemic inflammation seems to be a promising direction of research in aged overweight/obese people.

Moreover, focusing on strategies that reduce the resting level of pro-inflammatory cytokines and interventions that slow down aging, that is, maintaining the number and density of mitochondria and increasing the level of anti-inflammatory cytokines, myokines, trophic factors, and neuroprotective metabolites, should be of interest to researchers.

Physical Exercise as a Deaccelerating Strategy in Aging

Strategies to Improve Cognition Through Peripheral Mechanisms – What's Known?

Sarcopenia, along with accompanying changes in body composition (ie, increased adiposity) sometimes referred to as sarcobesity,[106] are part of the aging population. Muscle loss, as well as fat accumulation, promotes the development of pathological conditions such as insulin resistance, inflammation and vascular dysfunction (see above subsections). Since skeletal muscle is known as the largest organ sensitive to insulin and one that secretes pro- and anti-inflammatory factors and has significant vascularization, strategies to enhance the anabolic response are intensively sought. Resistance training (RT) preserves and/or increases skeletal muscle mass by stimulating the protein kinase B/mammalian target of rapamycin (Akt/mTOR) signalling pathway among people of all ages.[107,108] As a result, higher muscle mass can absorb larger amounts of glucose through upregulated IRs sensitivity to insulin, which is often dysfunctional in elderlies. Hence, lowering plasma glucose levels not only promotes a reduction in hyperglycaemia, but also, in the long term, inflammation. Low-grade systemic inflammation caused pro-inflammatory cytokines can be lowered by RT.[109] In addition, contracting skeletal muscles following RT secrete anti-inflammatory factors and exerkines such as brain-derived neurotrophic factor, cathepsin B and irisin, which can cross the BBB.[110] By modulating synaptic plasticity and neuronal migration, exerkines appear to be a key mediator of the crosstalk between peripheral and CNS factors shaping cognition among the elderly. Hence, RT is a promising strategy against cognitive decline.

Moreover, the combination of RT with aerobic training (AT) ie concurrent training (CT) is as effective with its cardiorespiratory fitness (CRF) enhancing effect as AT alone.[111] Furthermore, the increase in CRF is closely linked to improvements in global white matter volume and local integrity,[112] which together promote the preservation of cognitive function. Although it is known that AT and RT are hugely beneficial for brain health in elderly, current recommendations do not specify the nature of the exercises performed in the first place.

Physical Exercise – Facts and Recommendations

Scientific reports have clearly indicated that physical exercise leads to the improvement or preservation of physical fitness components, especially during aging.[113] However, the proper implementation of aerobic- or strength-based protocols needs to be adapted to the level of physical and cognitive fitness of older people.[114,115] In addition, many positions/recommendations for prescribing training programs can be found in literature,[116,117] but the specifics are not fully standardized. At the same time, the World Health Organization guidelines assume that at least 150–300 minutes of moderate-intensity or 75–150 minutes weekly of vigorous-intensity aerobic physical activity should be performed by adults aged > 65 years.[118] Studies indicate that most adults are aware of the importance of physical activity on most days of the week, but do not meet the minimum guidelines, mainly due to lack of time.[119,120]

Furthermore, the often-recommended traditional endurance exercises may be perceived as boring and consequently discourage further exercise activities. Recently, increasing attention has been paid to HIIT, which is supposed to be a non-pharmacological, decelerative cognitive decline treatment for aging.[121]

HIIT as a Remedy to Aging – A Future Direction

HIIT is a strategy that was originally compared in terms of adaptation to classic, moderate-intensity continuous endurance training (MICT),[122] as well as in terms of cell signalling,[123] and metabolic changes.[124] Similar training adaptations following HIIT and MICT have prompted a cascade of subsequent experiments on HIIT and its effects on individuals with type I and II diabetes,[125,126] cardiovascular system dysfunction,[127,128] and its impact on cognitive function.[129,130]

Safety issues of interventions that induce significant physiological and metabolic stress often raise questions. HIIT is highly safe among older adults, as summarized in a recent review paper.[131] Moreover, even among patients with coronary

heart disease,[132] and chronic stroke,[133] HIIT is very well tolerated, and the number of participants withdrawing from continuation of the experiment, including personal reasons, is similar to the groups performing lower-intensity workouts and controls.

To date, only the impact of classical resistance training on physical fitness among older adults has been studied.[134,135] It is also believed that dividing HIIT into two models, depending on the nature of the work undertaken, resistance (RHIIT) and aerobic (AHIIT), can be beneficial for cognition. RHIIT may inhibit sarcopenia by activating the mTOR/insulin-like growth factor-1-dependent signalling pathways, resulting in a hypertrophic response in the skeletal muscle. Preserving and/or increasing muscle mass and postural muscle and limb muscle balance responsible for locomotion leads to an increase in quality of life in older adults.[136] RHIIT also leads to improvements in aerobic capacity due to adaptations to physical training at the skeletal muscle level in older adults.[137] However, an increase in aerobic capacity is the main outcome of AHIIT,[138] and may lead to an increase in cognitive performance. Thus, both RHIIT and AHIIT appear to be promising interventions for aging; however, many issues remain unclear.

Conclusion

In conclusion, at least in theory, RHIIT and AHIIT may be beneficial for cognitive health among older adults. The lack of experimental studies comparing the effects of the two forms of HIIT is a major gap in the research. In this review we highlight the mechanisms underlying cognitive aging that may be improved following different types of HIIT. However, validating these innovative ideas require providing empirical evidence.

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Disclosure

The authors report no conflicts of interest in this work.

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