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Investigating the Putative Mechanisms Mediating the Beneficial Effects of Exercise on the Brain and Cognitive Functions

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Abstract

Introduction: Exercise training is documented to impact many aspects of brain function and has helpful effects on the overall brain, mental health, and performance. The beneficial impacts of exercise on brain performances are the promotion of learning and memory, enhancement of plasticity, protection from neurodegenerative disease, and neuro-rehabilitation following stroke.

Methods: Searching keywords including cognitive functions, exercise, neurodegenerative diseases, neurotrophic factors, and sleep deprivation in Pubmed, Science Direct, and Google Scholar helped us to access approximately 153 articles in this study. Besides, the positive effects of various forms of exercise on the brain function in humans and animal experiments mediated by neurotrophic factors were compared and discussed in this review.

Results: Regular physical activity increases synaptic plasticity by influencing the synaptic organization and potentiating synaptic strength and enhances the expression of certain neurotrophic factors including Brain-Derived Neurotrophic Factor (BDNF) which is the key mechanism intermediating wide benefits of exercise in the brain and animal hippocampus. In addition, exercise improves synaptic plasticity by reinforcing the underlying systems which support plasticity including neurogenesis, metabolism, and angiogenesis. Such structural and functional alteration made by physical activities has been indicated in various parts of the brain. These alternations have been studied more in the hippocampal system.

Conclusion: A variety of brain disorders including alzheimer's disease, parkinson's disease, chronic stress, age-related cognitive decline, psychological disorders have been revealed to avoid, restore, or improve by different procedures of physical exercise.

Keywords: Cognitive Functions, Exercise, Neurodegenerative Diseases, Neurotrophic Factors

Introduction

Exercise is the most effective, successful, and non-pharmaceutical technique to influence approximately every organ in the body.[1] Additionally, it has been indicated that peripheral risk factors such as hypertension, diabetes, and cardiovascular disorders have been diminished by physical training.[1,2] Many studies have stated a strong association among physical training, size of the hippocampus, and cognitive performances. Studies in the elderly people have demonstrated a direct association between regular physical training and advanced cognition, with an increase in the volume of the hippocampus after physical training[3,5] supporting the notion that anatomical and physiological changes in the brain have been mediated by physical activates. Research in schizophrenia patients have confirmed associations among exercise training, the augmented volume of hippocampus, and improved cognitive functions.[6] Likewise, studies in healthy groups have established that high regular physical activities are related to developed hippocampal volume, augmented cerebral blood flow, cognitive function enhancement such as learning and memory, and lowered brain tissue damage.[7]

Exercise in healthy adults causes several advantages, including the synaptic plasticity enhancement and the advancement of learning and memory performance.[8-10] Formerly, results of previous experimental studies indicated that physical training developed the cognitive performances and expression of protein and mRNA level of BDNF in the hippocampal formation of sleep-deprived female animals.[11-15] Some experimental studies indicate that BDNF would have the ability of neural protection, increase in neural plasticity, improvement of learning and memory, and is capable of mediating the profitable effects of exercise on the brain and mental wellness.[16-18]

Induction of Long-Term Potentiation (LTP) by high-frequency stimulation is the continual improvement in synaptic strength and important electrophysiological widely used cellular model of learning and memory carried out in hippocampal pathways in vitro and in vivo in the experimental studies.[13,19-21] However, a meaningful and greater LTP was indicated in the hippocampal dentate gyrus and CA areas of running animals compared to the inactive or control animals.[22,23] The improvement in LTP following running is consistent with an augmentation of BDNF in the hippocampus, which can facilitate synaptic plasticity.[24]

Physical activity may alter the synaptic plasticity of the hippocampal areas through the augmented neurogenesis.[25,26] Neonatal granule cells may have a main role in neural plasticity of the hippocampus, and the role of these newborn cells can be improved with running.[27,28]

Regular physical activity has been frequently indicated to progress cognition and inhibit age-caused cognitive degeneration,[29] predominantly in groups involved with certain types of neurodegenerative disorders such as Alzheimer's, Parkinson 's, and Huntington’s diseases.[30-32] Though, the basic mechanisms which mediate the helpful impacts of physical activity are still unrecognized. Nevertheless, experimental conclusions have suggested that a hippocampal neurogenesis enhancement, synaptic plasticity, neurotransmission improvement, and growth factor gene overexpression may mediate the helpful effects of regular physical training on cognitive performances.[33,34] In the same way, regular physical activity can increase endothelial cell proliferation, vascular growth factor levels, and angiogenesis throughout the brain.[35,36] Nevertheless, considerable research have been accomplished in adult individuals. Several studies in teenagers exhibit helpful associations between exercise and academic functions.[37] Therefore the profits of physical exercise on cognitive functions appear to be extended across all age individuals.

Several useful Exercise-developed Modalities

The beneficial and protective effects of exercise on learning, memory and synaptic plasticity

It has been indicated that physical activity is one of the most potent-pharmacological interventions that can improve learning, memory, and synaptic plasticity.[38,39] Numerous epidemiological and animal investigations have indicated that regular physical training such as running amplifies learning and memory in various conditions, including reducing the risk of age-related neurodegenerative illnesses for instance Alzheimer’s disease and dementia. In addition to helping functional rescue from brain damage, it can also improve hippocampal cell proliferation.[40]

Advanced plasticity is mostly noticeable in the dentate gyrus and the CA1 area of the hippocampus, where physical activity induces both short-term and long-term potentiation.[41,42] Physical activity has been indicated to increase learning and memory, synaptic plasticity and cognitive functions by various methods: expression of neurotrophic factors containing BDNF and insulin-like growth factor-1 (IGF-1), modulation of neurotransmitter and generation of new neurons, new blood vessel formation and plasticity associated molecules including CaMKII,[33,43] TrkB receptor[44] and other signaling molecules.[45] These molecular alterations improve the performance of neural systems, which finally display heightened LTP expression and amended performance in hippocampus related tasks such as the Radial Arm Water Maze (RAWM), Morris Water Maze, and Radial Arm Maze (RAM).[46-49] Therefore, mild to moderate exercise training seems to be the best helpful schedule for increasing the accessibility of key signaling molecules which are critical to acquisition and retention in the hippocampus.

Actually, exercise schedules have a protective role in the improvement of memory impairments[50] and expand LTP[51] in neurodegenerative diseases. Additionally, it has been displayed that physical activity recovers learning and memory during estrogen deprived conditions.[52] Other studies have shown that running can avert the sleep deprivation-induced insufficiency in cognitive function, synaptic plasticity, and signaling molecules in the hippocampal CA1 area in male and female animals.[11-14,48,53] This cognitive disorder was more severe in ovariectomized than intact female rats.[12]

The results of a Morris water maze spatial performance test following treadmill exercise in sleep-deprived (72 hours of sleep deprivation using a multiple platform technique) female rats showed significant protective effects of treadmill exercise on spatial learning and memory impairments induced by sleep deprivation in female animals.[12] This finding indicated that exercise has protective effects on the cognitive function in the elderly especially the menopause groups.

In order to examine the effects of treadmill exercise on the memory formation in sleep-deprived rats, hippocampal LTP in intact and OVX female sleep-deprived rats was measured at the cellular levels.[11] The study indicated significant effects of treadmill exercise on the induction and maintenance of LTP in sleep-deprived female rats.

Exercise Increases Angiogenesis

Brain plasticity or neuroplasticity is not constrained to the changes in neural connectivity and synaptic morphological modification. It has recently been indicated that non-neural components such as glia and capillaries can display a parallel capability for plastic modification. For instance, temporary alterations of blood flow and volume in the brain have been found related to sensory, motor, and cognitive functions.[54,55] Physical activity can enhance brain oxygen perfusion through angiogenesis by improving cerebral blood supply and promoting vasodilation particularly in brain areas essential for task execution.[56] Another study reports that aerobic walking training advances the usage rate of maximum oxygen recovers reaction time, and augments function in tasks of executive working in people.[57,58] Also, physical activity up-regulates angiogenic factors including IGF-1, angiopoietins, and Vascular Endothelial Growth Factor (VEGF) that increase cerebral perfusion and cause improved cognitive function.[59] Additionally, in various areas of the brain in healthy young and aged brains of animals and humans,[60,62] regular physical training expands cerebral blood flow and volume and rescues brain vasculature spatially in neurodegenerative disorders.[63,64]

Exercise Training Increases Neurogenesis

Various cellular and molecular extrinsic and intrinsic elements can organize the generation of new neurons. The subventricular zone of the olfactory bulb and the subgranular zone of the hippocampal dentate gyrus in the normal brain, comprise two adult fundamental neurogenic areas.[65] Newborn neurons in the SGZ differentiate and incorporate into the functional networks as granule cells of the dentate gyrus. In humans, studies of adult neurogenesis in the SVZ and the dentate gyrus region of postmortem brain sections indicated that almost 700 new neurons are added to the adult hippocampus each day from a study reporting the presence of positive staining for bromodeoxyuridine (BrdU).[66,67] Therefore, the production of new neurons is high in adults and declines with aging.[68]

Improved hippocampal neurogenesis is one of the outstanding influences of physical activity in the brain[69] and might be an important intervention intermediating exercise-associated progress in brain performances. Adult neurogenesis in the hippocampus is folded by physical training.[69,70] Running has effects on all maturation phases of new neurons, containing cell production, differentiation, and survival in the dentate gyrus.[68,71,72] Moreover, new neuron production improved by physical training in adult hippocampal has main effects on cognitive functions such as learning, memory, and synaptic plasticity.[73] In animal models, voluntary exercise training augmented the creation of new neurons in the hippocampus of both young and elder animals.[68] Additionally, a voluntary running program developed the hippocampus-dependent tasks in the MWM and augmented the slope of LTP in the dentate gyrus,[74] demonstrating that improved new neuron production relates to the amended cognitive functions. Moderate physical activity is effective for the promotion of neurogenesis in the adult hippocampus, particularly the amount of matured neural cells which advance the cognitive performances such as spatial learning and memory.[75]

Neuroprotective Effects of Exercise on Age-related Cognitive Impairment

In humans, strong helpful effects of physical activity have been most noticeably indicated in aging populations, where regular activity participation improves learning and memory, recovers executive performances, counteracts age-associated and disease-related mental deterioration, and defends against age-caused atrophy in brain regions critical for greater cognitive processes.[76-78] Additionally, animal studies establish that regular activity can facilitate both learning and memory in young and aged animals in numerous hippocampus-dependent tasks for example the MWM,[79] the RAM,[80] passive avoidance[81,82] and object recognition test.[83]

Cognitive function deterioration is one of the signs of the aging process. Experimental studies have shown that cognitive deterioration in elderly subjects may be related to dysregulation of synaptic plasticity in several parts of the brain.[84,85] Findings of several studies demonstrated that physical exercise can stimulate helpful neuroplasticity, augments cognitive reserve, and advanced neuronal connection density, and causes enhanced cognitive performances.[10] In contrast, physical inactivity decreases cognitive reserve and prevents the development of neuronal connections which lead to reduced cognitive performance.[86] In addition, regular exercise may be more effective in the reduction of degenerative neurological processes speed which causes age-associated cognitive decline and neurodegenerative diseases such as Alzheimer's and Huntington diseases.[64,68,69,79] Neuroimaging studies showed that aged people with developed aerobic fitness have increased hippocampal volumes and recovered scores in cognition schedules.[3,5] Young and elderly animals who accomplished voluntary running exercise, exhibited an improved synaptic plasticity and enhanced functions in hippocampus-related tasks.[25,71,87]

Short and long period physical activity developed cognitive functions such as memory and protected hippocampal deficiencies induced by Alzheimer's disease.[88,89] Furthermore, regular physical activity is helpful to improve some of the neuropathological and behavioral insufficiencies in the Parkinson's disease in the experimental animals[90,91] and clinical studies.[92,93] These studies suggest that regular physical activity may indicate a noninvasive therapeutic intervention to diminish cognitive impairments in neurodegenerative diseases and dementia patients.[94] Animal studies have shown that higher cerebral blood flow velocity was significantly related to a reduced amount of cognitive decline and reduced speed of blood flow was associated with Alzheimer’s disease.[95,96] Besides, atherosclerotic or cerebrovascular conditions that produce cerebral hypoperfusion can cause cognitive decline.[97]

Angiogenesis happens in the brain during growth but declines with aging. Animal studies have indicated that exercise can cause angiogenesis of small vessel vasculature in several parts of the brain.[98,99] Animal experimental research have shown that the hippocampus, which is crucial for memory creation, is extremely oxygen-dependent.[100,101] Therefore, hippocampal angiogenesis may clarify enhancements in cognitive functions following regular physical activity. Another study indicated that decreased levels of BDNF and other signaling molecules were related to age-related deterioration in hippocampal volume, regular exercise augmented BDNF, the volume of the hippocampal and temporal lobe, and spatial memory.[5,10,102]

Cardiovascular Effects of Exercise

Physical activity has beneficial effects on the cardiovascular system including improved exercise capability, changes in lipid profile, decreased obesity indices, augmented degrees of heart rescue and variability, decreased relaxing pulse, and hemodynamic.[103] Furthermore, suitable levels of physical activity are crucial for developed small vessel state,[104] improved flow of cerebral blood, and delivery of nutrients.[98] In addition, the mentioned issues are believed to mediate developed brain health. In support of this main notion, findings from Colcombe et al. (2003) indicated that physical activity prevented reductions of gray and white matter, principally in the prefrontal, superior parietal, and temporal cortices.[7] Likewise, experimental animal findings have confirmed that running training motivates progress in vascular perfusion and creation of new vessels in the motor cortex and increases vascular growth in the central nervous system especially in the cerebellum.[105] Whereas another research about the association between cardiovascular capability and cognitive performance has indicated weak relationships between the two factors.[106] Actually, robust and reproducible helpful relationships have been steadily indicated in the aged subjects.[107] Therefore, these results recommend that exercise is the main modulator of cognitive functions across the life cycle, however the influence of cardiovascular capability for supporting healthy cognition increases with age.

The Beneficial Effects of Exercise Training Following Stroke and Brain Ischemia

Physical activity improves motor and cognitive ability which is related to the creation of learning and memory following brain ischemia.[108,109] Among several exercise programs, the public running models comprised forced treadmill exercise and voluntary running have been demonstrated to augment cognitive performance and promote neural rehabilitation following brain injury and stroke. Animal experimental studies have established profits through running programs in the early phase (24 h) following stroke or ischemia.[17,110] The quality of movement, motor performance, and the devolvement of the neural network may be improved after rehabilitative training programs following ischemia.[111] Physical training may provide prominent neuroprotection against ischemic stroke damage by reducing cerebral edema, recovering cerebral blood flow, and increasing cerebral microvascular endothelial cell apoptosis in animals, which may be the probable defensive mechanisms of the physical training.[99,112] It was indicated that running programs augmented the expression of basic Fibroblast Growth Factors (bFGF) and vascular endothelial growth factors. These mechanisms induce neurogenesis, angiogenesis, and stimulated neurological recovery, and reduce infarct volume compared to non-exercised after focal ischemic stroke in animals.[113,114] Another study revealed that BDNF has a beneficial role in the rehabilitation process after stroke and physical activity to augment BDNF which may be a probable intervention to progress functional rescue following stroke.[115,116] Running training may increase cognitive functional recovery with further augmentation of BDNF expression and cell proliferation and decrease apoptosis.[117,118] Luo et al. have exhibited that functional recovery may be amended by physical activity in ischemic stroke animals, which might be because of an increase in the production of neural stem cells and movement of these new cells from the subventricular zone region to the ischemic area.[115] Another study has indicated that several brain regions which help the rescue procedures produce a fundamental alteration in synaptic plasticity-related expression of genes through exercise training.[42] Therefore, physical training could control the process of brain edema, cell apoptosis, stem cells, and other mechanisms to apply neuroprotection for the brain. In conclusion, physical exercise training is an important neural recovery technique after brain ischemia and stroke. Also, regular physical activity can cause the rehabilitation of neural systems.

The Effects of Exercise on Mental Disorders

Findings of both experimental and clinical documentation suggest that regular aerobic running reduces the severity of problems and recovers cognition performance in psychosis and schizophrenia. Exercise interventions have been shown to improve cardiorespiratory fitness and markers of cardiometabolic health in schizophrenia patients.[119] Problems of psychological disorder patients such as schizophrenia, depression, and anxiety have been shown to improve.[120,121] A systematic review of exercise interventions articles in psychosis subjects indicated general reductions in the severity of co-morbid mood disorders and both positive and negative psychosis symptoms in response to exercise.[122] Neurocognitive profits of exercise training have occurred particularly in the field of working memory, social cognition, and attention/vigilance.[123] Findings of other studies suggest that an increase in exercise mediated hippocampal volume was associated with improvements in the short term and long term memories and other cognitive functions.[6]

Another investigation reported that the hippocampus, a central area for memory and learning, shriveled in patients with psychosis compared to the matched healthy controls.[124] Hippocampal volume reductions are present during the first episode of psychosis, before antipsychotic exposure and predate the onset of illness.[125,126] The volume of hippocampal formation rises after regular exercise.[5] Animal research has demonstrated that the cellular basis for improvement in memory after exercise is associated with exercise-induced hippocampal neurogenesis.[127]

The potential mechanism of exercise, mediated hippocampal function improvement in psychosis patients remains unknown.[6] A vast body of evidence revealed that aerobic running and treadmill exercises are helpful and cost-well-organized treatments for several anxiety and mood disorders,[128,129] such as anxiety-like behavior.[128] The beneficial effects of exercise on the brain and cognitive functions have been summarized in figure1 (Figure 1).

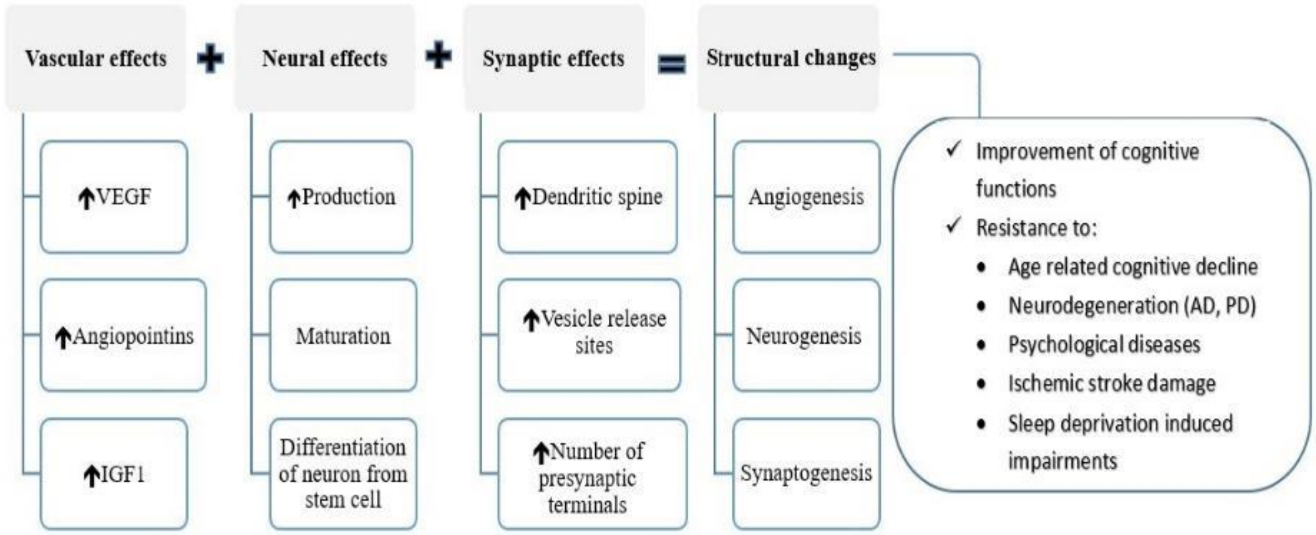

Figure1: This figure summarizes the beneficial effects of exercise on brain and cognitive functions. VEGF; Vascular endothelial growth factor, IGF; Insulin like groth factor1, AD; alzheimer's disease, PD; Parkinson's disease

Trophic Factors Signaling Mediates the Helpful Effects of Exercise

Neurotrophins

Enhanced trophic factor signaling has been reflected as the greatest common theory in order to describe the helpful influences of exercise training on cognition. Neurotrophins (NTs) are consisted of a group of polypeptides that regulate a variety of neuronal functions including production, vitality, migration, and differentiation of new neurons.[130] There are some NTs in the mammalians such as BDNF, Nerve Growth Factor (NGF), and IGF-1 .The aim cells can generate mentioned NTs, principally in the form of pre-pro-protein. Also, the biological functions of NTs have been mediated by two classes of receptor systems, the low-affinity P75NTR receptor and the tropomyosin related kinase (Trk) group of high-affinity tyrosine kinase receptors. After binding these NTs to their receptors, NTs, and receptor complex transport to the cell soma via retrograde axonal transport where they begin multiple positive effects within the nucleus.[24,131] Brain-Derived Neurotrophic Factor (BDNF) is the most important neurotrophin which is most commonly expressed in the brain, causing neuronal survival, differentiation, axonal pathway-finding,[132] regulation of dendritic trafficking to postsynaptic densities[133] defending against neuronal loss in the hippocampus, and the generation and preservation of late-phase long-term potentiation.[24] Administration of BDNF to postnatal hippocampal slice cultures can augment spine density in the CA1 area of the hippocampus. Furthermore, injection of human BDNF in the hippocampal formation of rats causes important enhancement in the cognitive function in these experimental animals.[134,135] These data indicated that BDNF is one of the critically important factors of the cellular and subcellular mechanisms that mediate cognitive function improvement. Notably, it has been confirmed that plasma BDNF is certainly a reliable biomarker for diminished memory in humans.[136]

Various sections of the central nervous system produce BDNF in different situations. This trophic factor that comprises of 250 amino acid deposits has been produced as a precursor molecule with a length twice the size compared to mature BDNF.[137] The production of BDNF and its high-affinity receptors has been revealed to happen in the hippocampus, frontal, parietal, and entorhinal cortex areas in cognitive function. Physical activity has also been revealed to increase serum BDNF levels in young people[138] and neurodegenerative disease patients.[139] In humans, it has been indicated that four hours of regular activity increases levels of plasma BDNF.[140,141] Also, significant useful effects of exercise on improvement of BDNF mRNA expression level has appeared in the hippocampus in the experimental animals. In addition, the creation of trophic factors has been induced by regular physical training in the perirhinal cortex.[142] The review of the mentioned data demonstrated that the helpful effects of physical activity are mediated by BDNF.[143] Another study has demonstrated that blocking the influences of BDNF on TrkB receptors reduced the helpful effects of physical activity on cognitive performances.[44,144]

Another study indicated that BDNF is the most important candidate to mediate the useful effects of exercise on cognitive function in sleep-deprived female rats. The results of this study showed that protein and mRNA expression of BDNF significantly decreased after sleep deprivation. Furthermore, sleep-deprived ovariectomized rats under exercise conditions had a significant up-regulation of the BDNF protein and mRNA in the hippocampus.[11] The review of the mentioned studies indicates the protective effects of exercise on cognitive functions.

Insulin-like Growth Factor 1

The IGF-1 which is a 70 amino acid polypeptide chain is released by the liver and is one of the influential trophic factors for growth and metabolic responses.[145] Besides, the entrance of this growth factor to the CNS through the CSF system,[146] perivascular macrophages and microglia, endothelial cells of the blood vessels, and vascular smooth muscle cells are the main cells enable to produce IGF-1 in the brain.[146,147] Intracerebroventricular administration of IGF-1 in the old animals was capable of repair object recognition.[24] Besides, the application of IGF-1 can increase the neurogenesis in the hippocampal dentate gyrus of the rats.[148] It has been indicated that the peripheral production of IGF-1 is the main element in neurogenesis in the DG as prolonged administration of anti-IGF-1 antibody stopped the valuable impacts of physical activity in the experimental animal studies.[149] Overexpression of IGF1 in transgenic mice can increase the size of the brain and the density of neurons.[150] This data indicates that IGF1 is a main factor in neurogenesis in the adult brain. Additionally, peripheral injection of IGF-I applies powerful therapeutic effects on neurodegenerative diseases[151,152] and hippocampal related diseases.[148] Furthermore, IGF-I improves memory impairments in old animals.[153]

Conclusion

Exercise training is a prominent intervention that is capable of producing changes throughout the organization of the body. In recent times, numerous outcomes in the basic sciences have indicated the brain as a structure that directly profits from physical activity. Regular exercise training has valuable effects on the hippocampal formation as a critical region for learning, memory, and cognitive functions. In this critical region for cognitive function, the physical activity begins alterations in molecular mechanisms supporting the health and improving the brain plasticity. Abilities of BDNF and other trophic factors are important for many of these helpful mechanisms. Animal model studies have revealed that running training decreases the amount of impairment after brain damage. Moreover, human investigations suggest that regular activity can delay the beginning of neurodegenerative diseases. There is an urgent necessity to advance non-pharmacological and pharmacological techniques to recover neurodegenerative disorders. Regular activity suggests a reasonable and helpful technique to recover cognitive performances in all ages, predominantly the old people who are most susceptible to neurodegenerative sicknesses.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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