Exercise Intensity and Brain-Derived Neurotrophic Factor: Implications for Mental Health and Neurodegenerative Disease

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Abstract

Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophic factor that helps support neuroplasticity, neurogenesis, neural growth, and neuronal survival within the brain. It plays a critical role in cognitive functions and brain health and has become an important target for research on the treatment and prevention of neurodegenerative diseases and mental disorders. One of the strategies used to increase BDNF without pharmacological treatment is exercise; however the rise in BDNF levels can vary depending on the intensity of the exercise. The purpose of this literature review is: 1) to determine which exercise intensity is the most effective at increasing BDNF while minimizing adverse effects, and 2) to examine how exercise-induced changes in BDNF may influence mental health and neurodegenerative disease. This literature review proposes that moderate-to-high intensity exercise is the most effective for increasing BDNF levels, with high-intensity exercise producing the largest immediate BDNF increase following a single exercise session and moderate-intensity exercise providing more sustainable long-term benefits. However, because of the risk of fatigue and injury associated with high-intensity exercise, pairing it with moderate-intensity exercise provides a more sustainable balance of long term benefits. By promoting neuroplasticity and neurogenesis, exercise-induced BDNF increases may be able to produce neurobiological effects on mental disorders and neurodegenerative diseases similar to medications like antidepressants. However, factors such as sleep, diet, genetics, and individual fitness levels may influence BDNF responses and limit the interpretation of these studies. Reliance on proxy measurements may limit the accuracy of these studies as well. Overall, moderate-to-high intensity exercise appears to be the most effective approach for increasing BDNF and promoting brain health without pharmacological intervention and may potentially slow the progression of mental health disorders and neurodegenerative disease.

Introduction

Mental health disorders and neurodegenerative diseases have been on the rise and represent a growing public health challenge. For example, major depressive disorder (MDD) affects roughly 17% of people at some point in their lives (Hashimoto et al., 2004). Beyond mental health, reports show that global daily counts of neurological disease increased by 18.2% from 1990 to 2021 and now affect more than 40% of the global population (Wang et al., 2024). Neurodegenerative diseases involve the gradual deterioration of neurons, which affects the brain's ability to function, and include Alzheimer's, Parkinson's, and Huntington's diseases (Azman & Zakaria, 2022). They have been a socioeconomic burden, especially in the aging population (Augusto-Oliveira et al., 2023).

Physical activity, exercise, and fitness training can improve cognition, mental well-being, brain structure, and brain function through the increased release of neurotransmitters (chemical messengers that transmit signals across neurons synapse), neurotrophins (proteins that promote growth, survival, and neuroplasticity of neurons), and neuromodulators (chemical messengers that regulate neuronal activity) (Bhattacharya et al., 2023). For example, a rat study found that memory improvements were linked to exercise intensity, with higher-intensity

treadmill exercise improving memory performance and promoting activation of the brain-derived neurotrophic factor (BDNF)–tropomyosin receptor kinase B (TrkB) signaling pathway in brain regions important for cognition (Cefis et al., 2019). BDNF is especially important because it supports neuronal survival and neuroplasticity, and its levels may vary depending on exercise intensity. For this reason, it has become an important focus of research on how exercise may influence cognition and brain health (Cefis et al., 2019; Knaepen et al., 2010).

Given its importance, this present review focuses specifically on the neurotrophin Brain-Derived Neurotrophic Factor (BDNF), given its central role in exercise-induced neuroplasticity. During physical exertion, the brain and muscles trigger the release of BDNF to support energy metabolism, homeostasis, and brain health (Knaepen et al., 2010). Although the connection between exercise and BDNF is established, it still remains unclear which specific exercise intensities trigger the most optimal BDNF release for combatting mental health disorders and neurodegenerative diseases. This review hypothesizes that moderate-to-high-intensity exercise is the most effective range for increasing BDNF levels sustainably. High-intensity exercise may produce the largest increase following an acute exercise session, whereas moderate-intensity exercise may provide more sustainable long-term benefits with fewer risks associated with excessive high-intensity training.

BDNF is Important to Brain Health and Cognitive Functions

To understand how exercise influences brain health, it is first necessary to examine BDNF and its cellular mechanisms. BDNF was discovered as a protein that supports the survival of dorsal root ganglion cells, which are sensory neurons located in clusters along the spinal cord's dorsal roots. (Barde et al. 1982). BDNF is initially synthesized as a precursor and is later converted into mature BDNF. These forms can produce different cellular effects, with mature BDNF playing an especially important role in neuronal survival and synaptic plasticity. BDNF is widely expressed in both the developing and adult mammalian brain and plays a critical role in cognitive function and overall brain health (Murer et al., 2001). It is important for cognitive development and function because within the hippocampus and prefrontal cortex, it promotes neurogenesis and supports synaptic plasticity, meaning it helps neurons grow, differentiate, and form new connections (Silakarma & Sudewi, 2019). This makes it essential for learning and memory in the adult brain. It has been shown that restoring BDNF levels after depletion can help restore performance in learning and memory tasks, indicating its crucial role in long-term memory (Lin et al., 2012). These functions help explain why BDNF has become an important focus of research on mental health disorders and neurodegenerative diseases (Hashimoto et al., 2004; Azman & Zakaria, 2022).

Associations Between BDNF and Mental Health Disorders and Neurodegenerative Disease

Blood BDNF levels, which are the closest proxy for brain BDNF levels, have been associated with both risk and severity of Alzheimer's disease. In Parkinson's disease, BDNF has shown to contribute to survival of substantia nigra neurons. These specialized cells in the midbrain produce dopamine and are responsible for controlling movement and coordination and to provide protection against neurotoxic challenges (Azman & Zakaria, 2022).

Furthermore, research suggests that lower levels of BDNF are associated with mental disorders such as MDD and bipolar disorders, and an increase in BDNF levels may be associated with improved clinical outcomes and could serve as a target for future therapeutic

care (Hashimoto et al., 2004). For example, studies with rodents show that chronic treatment with antidepressants such as fluoxetine and other SSRIs leads to an increase in BDNF levels in the brain (Silakarma & Sudewi, 2019). Although a causal relationship has not been established, these findings suggest that an increase in BDNF levels may contribute to antidepressant efficacy.

Since BDNF activity is consistently elevated in regions tied to mood and cognition, it has become a key target in research on treatments for mental health disorders, like depression and anxiety disorders (Hashimoto et al., 2004), and neurodegenerative diseases, like Alzheimer's and Parkinson's diseases (Azman & Zakaria, 2022). Clinical studies have tested this neurotrophin for therapeutic potential. For example, one large randomized controlled trial gave BDNF to patients with amyotrophic lateral sclerosis (ALS), a neurodegenerative motor neuron disease. The treatment did not find any significant improvement in outcomes overall, however subgroup analyses suggested that some patients (those who had digestive side effects from the treatment or who already had breathing problems before the study began) seem to benefit more than others (Stansberry & Pierchala, 2023). In mental health research however, a double-blind randomized controlled trial found that eight weeks of psychobiotic supplementation increased serum BDNF levels and improved depressive symptoms in patients with low-to-moderate depression (Heidarzadeh-Rad et al., 2020). These studies suggest that BDNF plays an important role in health, but treating patients by directly changing their BDNF levels is complicated. This is part of why scientists have become more interested in natural ways to increase BDNF, such as exercise.

Measuring BDNF During Exercise

BDNF levels during exercise are typically measured by tracking neurochemical changes in the brain using both rodent models (e..g, wheel running paradigms) and human participants (performing aerobic tasks) (Arazi et al., 2022; Knaepen et al., 2010). Most research measures BDNF by observing levels of mRNA in brain tissue, often finding consistent increased activity in areas like the hippocampus and cerebral cortex (Silakarma & Sudewi, 2019). However, it is important to account for the fact that there are two types of BDNF: blood BDNF and brain BDNF. Brain BDNF is produced in the brain and helps with neuroplasticity and neuron survival. Blood BDNF is stored in and released by platelets, and is influenced by muscles, platelets, and other tissues, and while it may be able to cross the blood-brain barrier, this relationship is unclear and not a confirmed pathway for delivering BDNF to the brain. Therefore the usage of blood-derived BDNF for the measurement of brain BDNF in the central nervous system is not as accurate, though commonly used in studies (Silakarma & Sudewi, 2019). This distinction is particularly relevant for interpreting the human studies reviewed here, as most rely on blood sampling rather than direct measurement of BDNF in the central nervous system, or brain.

The Relationship Between Exercise and BDNF

Acute aerobic exercise, which includes a single session of physical activity at a moderate intensity (Basso & Suzuki, 2016), are one of the ways researchers have explored to increase BDNF. It has been shown to increase blood BDNF concentration in approximately 69% of studies on healthy participants and 86% of studies involving participants with chronic disease or disability such as depression, anorexia nervosa, and allergic asthma (Knaepen et al., 2010). It is also important to note that acute exercise refers to aerobic exercise rather than strength-based exercise. Studies have suggested that aerobic exercise elevates circulating BDNF more reliably

than strength-based exercise because strength-based exercise may require greater effort to trigger an increase in BDNF (Knaepen et al, 2010). For example, BDNF increases during or immediately after acute exercise, particularly after high-intensity aerobic exercise such as running, cycling, or rowing. These activities can produce an increase of 100-365% in BDNF levels (Knaepen et al, 2010). BDNF levels typically return to baseline within 10-60 minutes after exercising (Basso & Suzuki, 2016). During this transient increase, BDNF activates the intracellular signaling pathways by binding to TrkB receptors. This promotes synaptic plasticity, neuronal survival, neurogenesis, and long-term potentiation. These signaling pathways may continue to affect neuronal function even after circulating BDNF levels have returned to baseline (Binder & Scharfman, 2004). Aerobic exercise has been linked to improvements in cognitive functions such as attention, working memory, inhibitory control, cognitive flexibility, decision-making, problem-solving and verbal fluency, and these improvements may be associated with exercise-induced increases in BDNF (Basso & Suzuki, 2016). Overall, these findings suggest that acute aerobic exercise may produce a meaningful increase in BDNF and contribute to cognitive benefits, which raises the question of which exercise intensity can produce the greatest and most sustainable increase in BDNF levels.

How Exercise Intensity Affects BDNF

The studies reviewed in this section use different designs to examine how exercise intensity affects BDNF, cognition, and brain related outcomes. Jeon and Ha (2017) conducted a study on 40 male middle school students who did low, moderate, or high intensity treadmill exercise or stretching four times per week for 12 weeks. By measuring serum BDNF and working memory through the Wechsler Intelligence scale for children, Antunes et al. (2020) studied 28 adult men who did randomized acute exercise sessions at low, moderate, and high intensities, with BDNF and lactate measured before and after exercise. Cefis et al. (2019) used a rat model to examine rats running on treadmill for seven days at different intensities to determine whether it affected memory performance and activation of the BDNF and TrkB pathway in the hippocampus and prefrontal cortex. Reitlo et al. (2023) studied older adults from the generation 100 randomized controlled trial to compare high-intensity exercise, moderate-intensity continuous training, and national physical activity guideline based exercise to study hippocampal outcomes, though BDNF was not directly measured. Together, these studies help show how exercise intensity may influence BDNF responses, cognition, and brain structure.

Low-intensity exercises are usually exercises that are light and do not significantly raise your heart rate or breathing rate. The heart rate is typically below 50-65% of your maximum heart rate, and the VO2 (oxygen consumption) level is low to moderate. In one study, low intensity exercise produced a small, non-significant increase in BDNF and it did not improve cognitive function on the working memory subtest of the Wechsler Intelligence Scale for Children (Jeon & Ha, 2017). This means that an increase in these biochemical markers may not always translate to better thinking or memory. It is possible that greater activation of neuroplasticity pathways and involvement of additional brain regions are needed to observe cognitive benefits.

Moderate intensity exercise follows the national physical activity guidelines of more than 30 minutes moderate physical activity more than five days a week. Moderate exercise uses 50-70% of maximum heart rate, 40-60% of VO2 max, and are typically activities such as jogging, cycling or swimming. The result of these moderate-intensity exercises showed a

moderate rate increase in BDNF, however it was less than the increase made by high-intensity exercise (Antunes et al., 2020). In line with these findings, the moderate-intensity exercise group showed improvement in the working memory test. However, after 12 weeks, this increase was not statistically significant (Jeon & Ha, 2017).

High-intensity exercise is usually classified as having a 70-90% maximum heart rate (HRmax) and 70-90% of VO2 max. Both in animals and humans, high intensity exercise has shown to increase the most BDNF out of all other intensities (Cefis et al., 2019; Antunes et al., 2020). The high intensity exercise group also achieved the highest working memory scores with an increase of 3.0 points, which was statistically significant after 12 weeks, demonstrating the greatest improvement from baseline among all three exercise intensity groups (Jeon & Ha, 2017). However, it is important to note that high intensity exercise is not as optimal as moderate intensity exercise. Due to its physical demands, performing high-intensity exercise every day can result in physical and mental fatigue, increased injury risk, and negative mental health effects when taken to extremes (Matta Mello Portugal et al., 2013). Therefore, although high-intensity exercise produces the largest acute BDNF increases, these gains may be offset by the physical and psychological costs of unsustainable training loads.

Additional research shows that moderate exercise that followed the national guidelines was associated with more favorable hippocampal outcomes than higher intensity supervised training (Reitlo et al., 2023). Although this research did not specifically measure BDNF, it is important to consider other factors that may affect neuroanatomy based on exercise intensity.

The findings showed moderate to high intensity exercises appear to be the most sustainable and effective intensity for promoting long term BDNF secretion and cognitive benefits. Although high-intensity exercise produces more BDNF, excessive training may contribute to physical fatigue and distress which can override BDNF benefits over time. On the other hand low-intensity exercise may increase BDNF but it does not consistently produce a significant result in cognitive performance. In order to maximize potential benefits while minimizing negative side effects, it is generally most effective to emphasize doing moderate-intensity exercise with occasional high-intensity bouts. However, age and sex may determine what is most appropriate, and more studies are needed to discern this.

The Effects of Exercise-Induced BDNF on Mental Health Disorders and Neurodegenerative Disease

By exercising consistently at a moderate-high intensity, individuals may achieve increases in BDNF levels that can promote neuroplasticity and neurogenesis. These neurobiological changes may contribute to the benefits of exercise as an adjunct to pharmacological treatment. With these effects, exercise-induced BDNF may help both reduce anxiety and depression symptoms and contribute to their prevention (Portugal et al., 2013). Supporting this relationship, a meta-analysis of 36 randomized controlled trials found that exercise interventions significantly increased BDNF levels in patients with depression. Combined aerobic and resistance exercise, and yoga showed the strongest effects, and the study found a nonlinear dose-response relationship, suggesting exercise volume influences the extent of BDNF increases in individuals with depression (Yuping et al., 2024) .

In addition to its effects on mental health, moderate to high intensity exercise may support the maintenance of healthy neural networks in neurodegeneration, since optimal BDNF level is associated with neuronal survival, synaptic plasticity, and preventing neurodegenerative disease. Reduced BDNF levels have been linked to several neurodegenerative diseases,

including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS) (Azman & Zakaria, 2022). Therefore, exercise-induced increase in BDNF may offer a behavioral strategy for supporting brain health and potentially slowing the onset or progression of neurodegenerative disease.

Limitations

Peripheral/blood BDNF, is used as a proxy marker to measure BDNF in humans and rats. However it can be influenced by muscles, platelets, and other tissue, and may not directly reflect brain BDNF concentration, because it is extremely difficult to measure brain BDNF in humans (i.e., requires acquiring brain tissue). Measuring brain BDNF in rodents' brains is more feasible, since exercise protocols and the environment are tightly controlled, but brain structure and complexity differ from humans, so results do not fully translate. Further, it is important to note that BDNF is also influenced by genetics, fitness, which can introduce variability across studies (Knaepen et al., 2010).

Another limitation is that many studies within this paper identify relationships among exercise, increased BDNF levels, and improved cognitive or mental health outcomes without establishing that BDNF directly causes these benefits. Although controlled exercise studies can show that exercise intensity affects BDNF levels, they often do not directly manipulate BDNF signaling. Therefore, improvements in cognition or mental health may also result from other biological effects of exercise rather than from increased BDNF alone.

Mixed findings of BDNF levels across exercise intensities can make it difficult to determine whether exercise-induced increases in BDNF are linked to improvements in mental disorders or changes in neurodegenerative disease progression. Some studies discussed above suggest that higher intensity aerobic exercise may produce a greater increase in BDNF. However, other studies conclude there is no significant difference between intensities ranging from 60-100% VO2 max (Knaepen et al., 2010). This may be caused by genetics, sleep, or diet factors that can affect BDNF responses.

Another limitation is the differences between short-term and long-term BDNF levels. BDNF may spike during the acute exercise or after but within 10-60 minutes it returns to the baseline. This can cause short term studies to overestimate the effect of it on the brain, if long term tracking is not measured. Long-term effects depend on consistency, exercise type and intensity, and also individual factors which can be difficult to calculate.

Furthermore, BDNF is only one component of the neurobiology system behind exercise-induced brain changes. Improvement in mental health and cognitive functions are not only mediated by BDNF, it also includes other neurotrophins such as nerve growth factor, neurotrophin-3, and neurotrophin-⅘ (Silakarma & Sudewi, 2019), which can also contribute to neuronal survival and neuroplasticity. Exercise also influences neurotransmitters, growth factors, myokines, inflammatory cytokines, and hormones which all can affect mental health and neurodegenerative disease.

Conclusion

It can be concluded that moderate-to-high intensity exercise appears to be the most effective range for increasing BDNF levels in the brain. Exercise-induced BDNF can support neuroplasticity, neurogenesis, neuroprotection, cognitive function such as memory, and maintenance of the neuronal network. Exercise has intriguing potential as a that is, it may be used as a non-pharmacological method to prevent neurodegenerative disease or slow down its

progression. It may also be used as a useful therapeutic strategy to help relieve anxiety or depression symptoms. However, these effects are influenced by multiple factors, and BDNF only represents a singular part of a broader neurobiological system in brain health that is affected by exercise.

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