# A MIND IN MOTION: THE BENEFITS OF EXERCISE FOR MOOD, MEMORY, AND NEUROCOGNITIVE LONGEVITY

by

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## ABSTRACT

Current research in the field of exercise neuroscience has shown several neurological and psychological benefits to adopting a regular exercise routine in addition to the plethora of other physical benefits it confers. Exercise has been found to improve mood by decreasing depressive symptoms, increasing feelings of self-esteem and self-efficacy, decreasing the body's physiological response to stressors, modulating neurotransmitter levels such as serotonin, and increasing the release of endogenous endorphins and endocannabinoids which relieve pain and create positive feelings of euphoria. Additionally, exercise has been shown to increase short-term, long-term, and spatial memory. Proposed mechanisms for these improvements include increased levels of neurotrophic factors that serve to increase neurogenesis, neuroplasticity, long-term potentiation, hippocampal volume, cerebral blood flow, and overall neuron health. Finally, exercise strongly correlates with decreased risk of dementia and a slowed progression of the disease in its early stages. Being active can reduce the deposition of neuron-damaging plaques, increase cerebral blood flow, strengthen and enlarge pertinent brain regions that are targeted by dementia, and increase neurotrophic factors that support neuron health. The numerous beneficial effects of exercise on the brain and the physiological mechanisms behind them are explored.



*Keywords:* exercise, mood, learning, memory, dementia

## DEDICATION

To my parents, Chris and Suzanne, who have supported me and my passions from the very beginning, instilling in me a love of learning and a sense of duty to help those in need.

To my future patients whom I hope to serve and guide, in sickness and in health, one day. May the information I learn and convey in this very paper benefit them and all who read this.

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## LIST OF ABBREVIATIONS

Aß: Amyloid beta
ACTH: Adrenocorticotropic Hormone
AD: Alzheimer's Disease
ADHD: Attention-Deficit/Hyperactivity Disorder
AHA: American Heart Association
AMPA: α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
ATP: Adenosine Triphosphate
BBB: Blood-Brain Barrier
BDNF: Brain-Derived Neurotrophic Factor
CBF: Cerebral Blood Flow
COPD: Chronic Obstructive Pulmonary Disease
CRH: Corticotrophin-Releasing Hormone
GABA: Gamma-Aminobutyric Acid
HHS: Health and Human Services
HIIT: High-Intensity Interval Training
HPA: Hypothalamic-Pituitary-Adrenal
IGF-1: Insulin-like Growth Factor
LTP: Long-Term Potentiation
MCI: Mild Cognitive Impairment
mTOR: Mammalian Target of Rapamycin
NFT: Neurofibrillary Tangle
NMDA: N-Methyl-D-Aspartate
SSRI: Selective Serotonin Reuptake Inhibitor
VD: Vascular Dementia
VEGF: Vascular Endothelial Growth Factor

## I. EXERCISE RECOMMENDATIONS FOR HEALTH BENEFITS

Exercise is often seen as a means for improving cardiorespiratory fitness, building muscle, and preventing chronic health conditions associated with being sedentary such as obesity, hypertension, diabetes, and osteoporosis, but it is not often connected with brain health (Mikkelsen et al., 2017). However, in addition to these bodily health benefits, current research has shown that exercise can also improve mood, reduce depression, facilitate learning and memory, and strengthen brain regions whose degradation is associated with neurocognitive disorders, thus reducing the risk of developing diseases such as dementia.

The U.S. Department of Health and Human Services' [HHS] Physical Activity Guidelines for Americans, 2nd edition (2018) recommends that adults engage in at least 150 minutes (2.5 hours) of moderate intensity aerobic exercise per week, 75 minutes (1.25 hours) of vigorous intensity aerobic exercise per week, or an even mixture of the two. Additionally, adults should engage in muscle-strengthening activities two or more days a week. Exercise beyond these minimum recommendations provides additional health benefits. The American Heart Association [AHA] (2018) supports these guidelines, stating that they are based on current research. They also list some of the general benefits of regular exercise as improving thinking, sleeping, and making daily tasks easier.

## II. PHYSICAL ACTIVITY & EXERCISE: INTENSITIES, TYPES, AND ENERGY PATHWAYS

Physical activity is a broad term that encompasses any movement that requires energy beyond what is required at rest (HHS, 2018). Exercise is a specific type of physical activity in which movement is planned, structured, repetitive, and intended to improve health.

The intensity of exercise is subjective, making it different from person to person depending on factors such as fitness level (Mayo Clinic, 2021). A brisk jog may feel vigorous in intensity to a sedentary person, while feeling low in intensity to an avid runner. The two primary metrics for estimating the intensity of a workout are breathing rate and heart rate. Moderate-intensity exercise quickens breathing, but a person should still be able to comfortably hold a conversation. However, they should not have enough breath to sing. Their heart rate should be around 50-70% of their maximum heart rate (roughly estimated by formulas such as $HR_{max}$ = 220 – Age). Vigorous-intensity exercise will produce deep and quick breathing and should substantially limit a person's ability to speak. It should elevate a person's heart rate to 70-85% of their maximum heart rate.

Exercise is often categorized as either aerobic or anaerobic. These terms refer to the specific energy systems relied most heavily upon by working muscle cells to produce adenosine triphosphate (ATP), the primary source of cellular energy. Aerobic exercise, meaning "oxygen requiring", is defined as rhythmic activity that increases heart rate and breathing for a continuous period of time (Patel et al., 2017). Examples of aerobic exercise include walking, jogging, dancing, cycling, and swimming. These are considered aerobic activities because they maintain a constant elevation of heart rate and breathing, use large muscle groups in rhythmic and repetitive motions, and are carried out at an intensity that can be sustained using aerobic respiration, which uses oxygen to catabolize carbohydrates and fats for energy.

In contrast, anaerobic exercise is often higher intensity activity that is performed in short bursts followed by intervals of rest or activity that does not significantly elevate heart rate. Anaerobic activity utilizes anaerobic (non-oxygen utilizing) energy pathways such as the ATP-phosphocreatine system as well as anaerobic glycolysis and fermentation (Gastin, 2001). This

latter pathway produces a buildup of lactate and other metabolites in the muscles which reduce their ability to contract, eventually leading to cessation of muscle contraction. A period of rest is required to regenerate ATP stores and to clear lactate from the muscles before activity can be resumed. Examples of anaerobic activity are sprinting, resistance training, and high intensity interval training (HIIT).

Research has primarily focused on how aerobic exercise affects the brain. However, anaerobic exercise modalities, mainly resistance training, have also been studied, although to a lesser extent. Therefore, more research should be done to better understand its effects on the brain.

## III. NEUROPHYSIOLOGY AND NEUROANATOMY

Neurons are nerve cells found in the brain and spinal cord that often send out projections, known as axons, which bundle together to form nerves in the body. Neurons are the main functional units of the nervous system, communicating with one another by sending and receiving signals in the form of chemical messages known as neurotransmitters (Sheffler et al., 2022; Cleveland Clinic, 2022). This chemical linking of neurons to other neurons, muscle, and gland cells allows neurons to regulate bodily processes such as mood, digestion, sleep, memory, learning, muscle movements, hormones, heart rate, blood pressure, and a host of other critical functions. Imbalances in the levels of well-studied neurotransmitters such as dopamine, serotonin, glutamate, and norepinephrine have all been linked to neurological, neurodegenerative, and psychiatric disorders such as Alzheimer's disease (AD), Parkinson's disease, anxiety, depression, attention-deficit/hyperactivity disorder (ADHD) and many other conditions.

The human brain, consisting of around 100 billion neurons and roughly 10 times as many supportive neuroglial cells, is made up of many sections that specialize in controlling different functions, a property known as functional specialization (Herculano-Houzel, 2009; Mahon & Cantlon, 2011). One particular brain region of scientific focus, the hippocampus, is implicated in learning, formation and storage of long-term memories, and spatial navigation (Anand & Dhikav, 2012). This slender, curved extension of neural tissue, named for its resemblance to a seahorse, lies deep within the left and right sides of the brain, known as the temporal lobes, and is highly subject to damage (Bir et al., 2015). Damage or atrophy to this region is observed in neuropsychiatric conditions like Alzheimer's disease, amnesia, and epilepsy. Within the hippocampus, new neurons are created in a process known as neurogenesis. This process is quite rare in the adult human brain, and until recently was thought to not occur at all after the cessation of fetal development (Kumar et al., 2019). It was long thought that the brain became stable after birth with very little capacity for change. However, this scientific paradigm has been dislodged as research discovered the brain's remarkable ability to change and adapt throughout life in response to its environment by creating new neurons and forming new connections between neurons, a quality known as neuroplasticity (Cassilhas et al., 2016). This ability for adult neurogenesis makes the hippocampus a unique region of the brain, capable of growing new neurons to aid in memory and learning (Kumar et al., 2019). The rate of neurogenesis decreases with stress and aging and can be increased with exercise. It has also been observed to occur in other animals such as rats and primates.

The hippocampus also connects with the hypothalamus, an important center for regulation of hormones such as adrenocorticotropin, which triggers the adrenal glands to release cortisol, one of the body's primary stress hormones (Bir et al., 2015). The hippocampus plays a

role in regulating these stress hormones, thus connecting it with stress. It has been observed that people with elevated cortisol levels experience atrophy of their hippocampus. The hippocampus is sensitive to degradation when cortisol levels are chronically high. This creates a positive feedback loop that further damages the hippocampus, weakening its ability to regulate cortisol release. Studies have shown that chronic stress negatively impacts long-term potentiation (LTP), the neurological mechanism by which learning occurs. The hippocampus also contains neurons with receptors for many of the previously mentioned neurotransmitters: serotonin, dopamine, norepinephrine, acetylcholine, and gamma-aminobutyric acid (GABA).

Memory has been linked to the hippocampus for several reasons. For one, the hippocampus contains n-methyl-d-aspartate (NMDA) receptors that are pivotal for learning and LTP. Furthermore, a famous case study of a man initialed HM, who had a bilateral removal of his hippocampus in an attempt to cure his epilepsy, resulted in both retrograde amnesia, entirely forgetting the previous 11 years of his life before the surgery, and anterograde amnesia, the permanent inability to form new memories after the surgery. HM would often repeat himself, asking the same questions and reading the same magazine multiple times (Scoville & Milner, 1957). He could not recall simple facts such as what he had for lunch or the faces of people he had just met because he could not initially encode this information into his long-term memory without his hippocampus. Memory is often categorized as either short-term or long-term (Cowan, 2008). Short-term memory is limited in the amount of information it can hold and the duration with which it can hold onto that information before it is forgotten. Long-term memory, however, can store a virtually unlimited amount of information for years or even indefinitely. Information is initially stored in short-term memory where it is highly accessible but subject to being quickly forgotten. To avoid forgetting, information can then be encoded into long-term

memory, where it can be stored and recalled at a later time. Long-term memory can either be explicit (declarative) or implicit (non-declarative) (Camina & Güell, 2017). Explicit memory, also known as hippocampal-dependent memory, includes consciously remembering facts or events, whereas implicit memory includes unconscious memory used for performing skills, such as riding a bike, or associating two objects with one another based on prior experience, known as associative memory. Although the hippocampus is crucial for long-term memory formation, it is not the only brain structure implicated. HM still had memories from his childhood and adolescent years, and he could still learn and remember novel procedural tasks such as tracing a star with a pencil using only the reflection of a mirror as a visual aid (Squire, 2009). This skill-based, procedural, or implicit memory, was still intact after the removal of HM's hippocampus, indicating that it depended on a different brain region. Additionally, HM's childhood memories, an example of explicit memory, were still present, suggesting the hippocampus helped to initially encode long-term memories, but that it wasn't the ultimate storage location for them. The science of the storage and retrieval of memory is complex and involves several brain regions. However, the hippocampus is one of the most well-studied brain structures by memory researchers and is the primary structure mentioned by most of the literature on exercise and its connection with memory, learning, and dementia.

Atrophy, or decrease in size, of the hippocampus has been linked to diseases such as Alzheimer's disease (AD), and it is still used commonly as a metric for the progression of the disease (Laakso et al., 1996). A loss of 10-15% of hippocampal volume is seen in those with minimal cognitive impairment, a loss of 15-30% is seen in those with early AD, and a loss of up to 50% is seen in those with moderate AD. Furthermore, the deposition of misfolded and altered proteins such as amyloid beta (Aß) and tau in and around neurons within the brain, including the

hippocampus, is observed in Alzheimer's patients. These proteins clump together to form plaques and neurofibrillary tangles (NFTs) that impede neuronal function.

## IV. MOOD

The term "mood" refers to the emotional state of an individual. Moods include feelings such as happiness, sadness, anger, and irritability. Although simple on the surface, moods are quite complex neurobiologically, and research is still searching for detailed explanations of the mechanisms behind emotions (Clark et al., 2018). One theory is that the brain is in a constant, active state of predicting the sensory input it will receive from the environment prior to it actually happening. By doing this, the brain is attempting to reduce surprises, and the stress brought about by them, from the external world. This means a person's mood, in part, depends on their expectations of their environment. For example, if an individual predicts their current or future environment to be unstable, hostile, and unpredictable, then this can result in a depressed or anxious mood state. Conversely, if an individual predicts a stable, safe, and consistent environment, they are more likely to have a positive or excited mood state. A similar psychological concept, learned helplessness, posits that past experiences of failure and negative environments combined with feelings of low self-efficacy (the belief in one's own abilities) can result in mood disorders such as depression. Furthermore, it has been found that people with depression have negative attentional and emotional biases, meaning they tend to focus more on negative stimuli while ignoring positive ones and that they may misperceive neutral stimuli as negative. However, this is only one perspective on perception and mood, and there are likely several neurobiological and psychological mechanisms at play.

Additionally, genetic and epigenetic forces may impact mood and the development of

mood disorders. Disorders such as depression tend to run in families, suggesting that, in addition to environment, there is likely a genetic component involved. Also, it was demonstrated that rat pups who did not receive maternal care after birth had a higher rate of DNA methylation (epigenetic changes to the genome that can turn off normal genes) than pups who were cared for by a mother. This parallels the finding in humans that victims of childhood trauma and neglect have an increased risk of developing mood disorders later in life.

## The Effects of Exercise on Mood

A review by Mikkelsen et al. (2017) detailed several research studies showing that exercise can help improve mood and self-esteem while reducing symptoms of depression and anxiety. Some of the studies showed exercise to be just as psychologically beneficial as typical psychotherapy. It was found that one bout of 20 to 40 minutes of aerobic activity improved mood for several hours, and that improvements were greater in depressed individuals than in those without depression. Many studies have shown both aerobic and anaerobic forms of exercise contribute similar improvements to mental health. A consistent exercise routine correlates with a significant decrease in the rate of depression and anxiety. It is important to note that poor self-image and eating disorders have the potential to lead to exercise obsession and compulsion. This dependence can become a source of psychological stress and, if it results in overtraining, can weaken the immune system and increase the risk of infections and musculoskeletal injuries. This one potential psychological risk for a subset of individuals should not, however, detract from the many psychological benefits of a regular exercise regimen.

## Physiological Mechanisms

### *HPA Axis*

Biologically speaking, an important component of mood disorders is the hypothalamic-

pituitary-adrenal (HPA) axis (Pariante & Lightman, 2008; Guilliams & Edwards, 2010). This system of neural and glandular tissue functions as the stress response system of the body. When the brain perceives a stressor, defined as any stimulus with the potential to disturb the body's homeostasis, the hypothalamus releases corticotropin-releasing hormone (CRH) which triggers the pituitary gland to release adrenocorticotropic hormone (ACTH) into the bloodstream. When ACTH arrives at the cortex of the adrenal glands, they are stimulated to release cortisol into the blood. Cortisol, as previously mentioned, is one of the body's primary stress hormones. It is a natural hormone needed for normal functioning. However, when cortisol levels remain high for extended periods of time, it can have a negative impact on health. High levels of cortisol, known as hypercortisolism, inhibit the release of growth, thyroid, and sex hormones, increase insulin levels and insulin resistance, promote fat accumulation, increase blood cholesterol, and contribute to heart disease and high blood pressure. It also suppresses the immune system, causing increased susceptibility to infections and cancers and increased inflammation and oxidative stress, which contributes to the death of neurons. As stated earlier, high cortisol also damages the hippocampus, negatively impacting memory (Bir et al., 2015). Additionally, the hypothalamus increases activation of the sympathetic nervous system, which causes the adrenal glands to release the hormones epinephrine and norepinephrine, commonly known as adrenaline and noradrenaline. This hormonal cascade results in the "fight or flight" stress response commonly experienced during bouts of acute stress. Individuals with depression, anxiety, and post-traumatic stress disorder have been found to have hyperactivity and dysfunctional regulation of the HPA axis.

Exercise can regulate secretion of CRH and ACTH from the hypothalamus and pituitary gland, thus reducing an individual's response to stress and their ability to regulate the HPA axis

(Mikkelsen et al., 2017). Individuals who exercise regularly can develop a hyposensitivity to physical and mental stress, which can cause a dampened physiological response to other unrelated stressors in life.

### *Inflammation*

Inflammation and its associated diseases have been linked to depression, anxiety, and poor mental health overall (Mikkelsen et al., 2017). It is theorized that inflammatory mediators released in the gastrointestinal system increase neurotoxic metabolites that can impact neurotransmitter production and prevent neurogenesis and neuroplasticity.

Additionally, people with inflammatory diseases such as Alzheimer's disease and chronic obstructive pulmonary disease (COPD) show decreased depressive symptoms with a regular exercise routine. It is proposed that exercise has anti-inflammatory effects by inhibiting pro-inflammatory immune cell signals known as cytokines (which are also linked with depression), stimulating release of anti-inflammatory cytokines, and reducing fat tissue which produces pro-inflammatory cytokines. Additionally, exercise decreases the number of (down-regulates) pro-inflammatory receptors and strengthens the nervous system's activation of the anti-inflammatory cascade in the body. For those with mood disorders caused or worsened by inflammation, exercise may be an appropriate treatment for these reasons.

### *Endogenous Opioids and Endocannabinoids*

Exercise has been demonstrated to increase blood plasma levels of endogenous opioids, a class of neurohormones produced naturally by the body to relieve pain and reduce anxiety. (Mikkelsen et al., 2017; Harber & Sutton, 1984). These endorphins, such as ß-endorphin, are similar in their chemical structure to morphine and heroin, bind to the same opioid receptors as those drugs, and are similarly blocked by opioid overdose medications such as naloxone (Loh et

al., 1976). In fact, ß-endorphin is 18 to 33 times stronger in its effects than morphine when concentrations are equal.

Similar to its effect on endorphins, exercise also increases blood plasma levels of endocannabinoids, neurotransmitters produced by neurons to regulate pain, sleep, appetite, and mood (Marsicano & Lutz, 2006). These molecules share a similar structure to the cannabinoids found in the cannabis plant. Increases in endocannabinoid levels after exercise were associated with reductions in anxiety and pain for both mice and humans (Mikkelsen et al., 2017). This has led researchers to believe endocannabinoids have some contribution to the sense of euphoria experienced after aerobic exercise, commonly called a "runner's high". It was long believed that endorphins were the driving agent of the runner's high, but recent research has cast doubt on that belief, showing that endocannabinoids are the most likely explanation. Siebers et al. (2021) even demonstrated that using naltrexone to block the opioid receptors where endorphins bind to neurons did not have an effect on the euphoria experienced by subjects post-exercise. The increased release of both endorphins and endocannabinoids during and after exercise further illustrates another possible mechanism by which exercise improves mood and reduces anxiety, thus helping to counter the symptoms of depression and other mood disorders.

### *Mitochondriogenesis*

Exercise has been demonstrated to increase the process of mitochondriogenesis, the creation of new mitochondria, the cellular organelle that breaks down food to produce energy for the cell, with subjects engaging in aerobic exercise having a greater number of mitochondria (Mikkelsen et al., 2017). Mitochondria exist in all active cells, including neurons. Within neurons, mitochondria provide the energy necessary for maintenance of neuronal circuits in the brain, the generation of new pathways through neuroplasticity, and the creation of new neurons

through neurogenesis, all of which place a high demand on the neuron for energy. It is theorized that mood disorders may be caused by decreased neuroplasticity and neurogenesis in the brain, leading to a decreased capacity to respond and adapt to novel, stressful situations. This in turn results in negative mood states. Additionally, reduced neuroplasticity hinders the brain's ability to counter negative structural and physiological changes and impairments that take place due to chronic stress, thus impacting the brain's ability to repair and adapt to maladaptive changes that lead to mood disorders.

### *mTOR*

Mammalian target of rapamycin (mTOR) is a protein kinase responsible for multiple cell functions such as cell growth, metabolism, and division (Mikkelsen et al., 2017). It has been linked with learning, memory, and antidepressant effects. In fact, many neurological diseases are characterized by disruption of mTOR signaling. The anesthetic and antidepressant medication, ketamine, functions by increasing mTOR signaling. Exercise, similarly, has been found to immediately increase mTOR activation in the brain, particularly in regions related to cognition and regulation of emotions and behavior. It also increased the creation of mTOR neurons in regions like the hippocampus and prefrontal cortex. Due to mTOR's antidepressant effects in the brain and exercise's ability to increase mTOR activation, it follows that this may be another mechanism by which physical activity benefits mood.

### *Neurotransmitters*

Many mood disorders such as depression and anxiety have been correlated with abnormal levels of neurotransmitters such as dopamine, serotonin, norepinephrine, and glutamate (Mikkelsen et al., 2017). In depression, for example, low serotonin has long been implicated as a contributor. Often, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) target

this mechanism by blocking the reuptake of the neurotransmitter, causing elevated levels of serotonin to remain in the synapse between two neurons. Subjects assigned to an aerobic exercise treatment had increased levels of both serotonin and tryptophan, an amino acid precursor to serotonin, in their blood. This serotonin increase correlated with lower levels of depression, demonstrating exercise as potentially having an antidepressant effect by acting in a similar mechanism to SSRIs. Recent research has cast doubts on the paradigm that low serotonin is the cause of depression (Cowen & Browning, 2015). However, there still remains a clear link between increased serotonin levels and improvements in depressive symptoms.

### *Psychological Effects*

From a psychological perspective, regular exercise provides an outlet for distraction from negative emotions, acting as a temporary respite from internalized rumination which may further fuel a negative emotional state (Mikkelsen et al., 2017). Additionally, exercise can benefit mood by increasing one's feelings of confidence in themselves (self-esteem) as well as their own capabilities (self-efficacy). The mere act of completing a difficult task, in this case exercising, improves a person's view of themselves and increases their belief in what they can accomplish and succeed at. This by itself can create positive emotions, but increased self-esteem also directly correlates with greater adherence to an exercise regimen and inversely correlates with symptoms of depression. A study of women with heart failure demonstrated increased quality of life and less depressive symptoms for women who participated in the home walking program as opposed to those who just attended educational sessions. Exercise has clear implications in improving psychological wellbeing for people.

## V. MEMORY AND LEARNING

The definitions of memory and learning are still contested to this day, highlighting the complexity and interconnectedness of these two processes. However, the general definitions of memory and learning are a useful foundation for understanding the research surrounding them. Generally, memory is the encoding and storing of perceived information within the brain to be recalled at a later time, whereas learning is the act of acquiring that new information which starts the encoding process (Klein, 2015; De Houwer et al., 2013). The American Psychological Association describes learning as acquiring a skill or knowledge, while memory is the demonstration of that acquired skill or knowledge (Kazdin, 2000). The process of learning is dependent upon memory, and testing memory is a straightforward way to demonstrate that learning has occurred, as most schools and universities around the world test memory and application to assess student learning.

A heavily studied molecular mechanism that is implicated in learning and memory is that of long-term potentiation (LTP) (Lüscher & Malenka, 2012). LTP is the long-term physiological change that occurs in neurons to increase their synaptic strength and efficacy due to repeated stimulation over time. The primary players in this process are the presynaptic and postsynaptic neurons. A presynaptic neuron is the neuron sending a chemical message in the form of a neurotransmitter, while the postsynaptic neuron is the one receiving the signal. Glutamate is one of the primary excitatory neurotransmitters used in the brain. On the postsynaptic neuron, there are several types of glutamate receptors. Two types that are important for LTP are N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. When glutamate is released into the synapse between the two neurons, it binds to NMDA and AMPA receptors, triggering the opening of an AMPA ion channel that allows sodium ($Na^+$) ions to quickly enter the neuron and depolarize it. If the neuron becomes

sufficiently depolarized by a strong enough chemical signal, a magnesium ion ($Mg^{2+}$) is expelled from the pore of the NMDA receptor, allowing sodium and calcium ($Ca^{2+}$) ions to enter the cell and further depolarize it. This extra step makes NMDA receptors slower to activate upon excitation, but also longer lasting, often remaining open for hundreds of milliseconds. Contrastingly, AMPA receptors activate quickly and remain open for only a few milliseconds. Several regulatory proteins can modify the function and number of AMPA receptors on postsynaptic neurons, thus affecting their sensitivity to signals and their effectiveness at relaying them. If a neuron is regularly activated, it can insert more AMPA receptors into the cellular membrane to better receive such signals in the future, a process known as upregulation. Similarly, if a neuron is not regularly activated, AMPA receptors can be removed to dampen the reception of future signals, a process known as down regulation. Similar receptors on the presynaptic neuron can also become activated by large levels of neurotransmitter or retrograde messenger release and can increase or decrease the amount of neurotransmitter being released by the presynaptic neuron. A change in the amount of neurotransmitter release combined with alterations in the number of postsynaptic receptors contributes to neuroplasticity, as the brain is able to adapt to become more effective with new, stronger pathways that are regularly used and required for the organism to function in its environment.

Additionally, new synapses can form between neurons not previously connected, establishing new neural pathways that also allow for learning and memory to occur. This process is known as synaptogenesis (Qi et al., 2022). These processes of creating new neuronal connections and strengthening frequently used connections are the main biological basis of how organisms learn and form memories.

**The Effects of Exercise on Memory and Learning**

Exercise can improve certain types of memory in both humans and animals. A study of males found that a single bout of aerobic exercise significantly improved visual and motor learning performance and that it likely promoted neuroplasticity (Perini et al., 2016). Additionally, both aerobic and resistance exercise has been shown to improve spatial learning and memory in both humans and animals (Cassilhas et al., 2016). Another study found that middle-aged men who regularly exercised performed significantly better on immediate recall memory tests when compared with their sedentary counterparts (De la Rosa et al., 2019). These improvements can also be seen in rodents, where higher amounts of physical activity correlated with better performance on the Morris water maze task, a test of spatial memory which relies heavily on the hippocampus (Cassilhas et al., 2016). This task involves placing a rat in a small round pool where it must swim to find a hidden platform to rest on. With subsequent trials, the rat learns to associate visual cues with the location of the hidden platform (e.g., the hidden platform is near the red triangle on the pool wall), improving the speed at which they find the platform. Human adolescents with higher levels of physical activity have also shown improved performance on a virtual version of this test. Furthermore, systematic reviews have found that single bouts of exercise improve both short-term and long-term memory and that these improvements were seen in age groups throughout the lifespan, including children, young adults, and older adults (Loprinzi et al., 2021). Exercise also improves procedural memory by improving memory consolidation (Chen et al., 2020). Additionally, regular exercise over time improved short-term memory. However, more research that controls for extraneous factors such as individual differences in genetics, baseline memory performance, forms of exercise, and types of memory tested will be necessary to reach a more conclusive understanding of the magnitude to which exercise improves memory, what types of memory it improves, and what types of exercise

are most effective for creating these changes.

## Physiological Mechanisms

### *Neurotrophins, Neurogenesis, and Neuroplasticity*

Neurotrophic factors, or neurotrophins, are protein growth factors that promote growth of axons, synaptic plasticity, synaptic protein expression, neurotransmission, neurogenesis in the hippocampus, and LTP in neurons, all processes important for learning and memory (De la Rosa et al., 2020). Brain-derived neurotrophic factor (BDNF) is a well-studied neurotrophin that promotes neuron growth, survival, and plasticity. About 75% of the body's BDNF is produced by the brain. Prolonged exercise acutely doubles or triples the amount of BDNF the brain produces. When BDNF binds to its target receptor on neurons, a signal cascade ensues that ultimately promotes neuronal differentiation, proliferation, and survival as well as LTP and other forms of synaptic plasticity (Cassilhas et al., 2016). The aforementioned study of exercised middle-aged men who performed significantly better on the free and cued immediate recall memory tests also had higher levels of BDNF when compared with their sedentary counterparts (De la Rosa et al., 2019). Exercised rodents also demonstrated increased neurogenesis, cell proliferation, and dendritic branching in the hippocampus, all of which are signs of positive neuronal health which support learning and memory (Cassilhas et al., 2016). Additionally, previous studies on birds and rats have found that hippocampal neurogenesis correlates with learning and memory, further highlighting the link between neurotrophins and memory performance.

Another neurotrophin, insulin-like growth factor (IGF-1), is important for preventing death of neurons and other cell types while also promoting neuronal differentiation, proliferation, neuroplasticity, and neurogenesis (Cassilhas et al., 2016). Because of this, IGF-1 blood levels

correlate with improvements in cognitive function. It was found that running induced neurogenesis as well as LTP and reduced the age-related loss of LTP in rats. It also increased gene expression for NMDA receptors that are closely tied with memory. Mice who exercised and performed better on the Morris water maze test also had elevated amounts of BDNF in their hippocampus and other brain regions associated with learning.

In humans, aerobic exercise increases blood BDNF levels but does not appear to influence IGF-1 levels. Conversely, resistance training increases IGF-1 blood levels but does not make a noticeable difference in BDNF levels. This suggests a combination of both aerobic and resistance exercise may be ideal for elevating levels of both of these neurotrophins for brain health. One study found that young males who engaged in a single, short bout of high intensity aerobic cycling had a short-term improvement in hippocampal-dependent memory performance along with elevated blood BDNF levels (Griffin et al., 2011). After five weeks of training, subjects had improvements in cognitive function, blood serum BDNF levels, and cardiorespiratory fitness.

The endocannabinoid system, as mentioned previously regarding mood enhancement, is also linked to neurogenesis (Cassilhas et al., 2016). When this system is blockaded, formation of new neurons in the hippocampus is inhibited. This would directly impact learning and memory since neurogenesis correlates with learning and memory.

### *Angiogenesis and Blood Flow*

Physical activity stimulates the growth of new blood vessels in the brain, a process known as angiogenesis, and appears to maintain these changes long term (Cassilhas et al., 2016). This process is primarily controlled by the neurotrophic factors BDNF, IGF-1, and vascular endothelial growth factor (VEGF). A four-month aerobic exercise routine was found to increase

resting cerebral blood flow and blood volume in the hippocampus in older subjects. Additionally, the exercise group showed greater neural connectivity within the hippocampus and between the hippocampus and other brain regions which could improve cognitive function in older adults. Furthermore, improvements in cognition correlated with aerobic activity, cerebral blood volume, and the number of small vessels in the brain. The exercise-induced brain changes of neurogenesis, increased BDNF and IGF-1 levels, and increased cerebral blood flow all serve a role in supporting neuronal health, and therefore learning and memory.

## VI. DEMENTIA

Dementia is a disorder that affects the brain, causing a progressive loss of cognitive abilities in areas such as memory, language, attention, and judgement. Those with dementia tend to struggle with remembering recent events and conversations, the location of items, completing routine tasks, finding the right words, or following directions (Arvanitakis & Bennett, 2019). This can dramatically impact an individual's ability to live independently. Dementia is more of a syndrome than a disease because it is an umbrella term for a set of symptoms that can be caused by a variety of neurological, psychiatric, or vascular diseases, or even by strokes, chronic alcoholism, traumatic brain injuries, or tumors (Gale et al., 2018). A person's risk of developing dementia rises as they age. According to the Alzheimer's Association (2022), roughly 6.5 million Americans have Alzheimer's disease, the most common form of dementia, in 2022. By 2050, a projected 12.7 million Americans will have Alzheimer's if no new treatments are developed, not including all other types of dementia. The disease continues to progress in severity over time and can eventually lead to death. One in three seniors die with a form of dementia. Alzheimer's disease is the fifth leading cause of death for adults aged 65 or older, according to the Centers for

Disease Control and Prevention (2022). With statistics as staggering as these, researchers across the world are working to better understand the etiologies, progression, prophylactics, and viable treatments for such a debilitating and common disorder. The current recommendations to reduce the risk of dementia center around being physically, mentally, and socially active, eating a healthy diet, and getting sufficient, high-quality sleep. With the currently aging "Baby Boomer" generation, the U.S. will be facing the challenge of treating millions of individuals with dementia who may eventually depend on the constant supervision and care of others. In addition to the development of new medications, research is currently being done on exercise as a preventative and potential treatment for dementia.

## Types of Dementia and their Pathophysiologies

As previously discussed, dementia is used as an umbrella term for several similar diseases. They may present with similar and overlapping symptoms, but their underlying causes vary (Raz et al., 2016). This makes diagnosis of a subtype of dementia challenging because of such overlap of symptoms and because people can develop a mixture of more than one type of dementia.

### *Alzheimer's Disease*

Alzheimer's disease (AD), named after one of the pioneers in early dementia-related research, Alois Alzheimer, is the most common form of dementia, accounting for about 60-70% of all dementia cases (World Health Organization, 2022; Raz et al., 2016). It is characterized by the accumulation of protein plaques such as Aß outside of neurons and NFTs inside of neurons. These cell-damaging proteins are connected with memory problems early in the development of Alzheimer's disease, and increased levels of these proteins impair LTP, promote long-term depression (the opposite of LTP), and remove NMDA receptors from neurons, causing a

weakening of synapses and a loss of neuroplasticity (Lüscher & Malenka, 2012; Kamenetz et al.2003). These plaques are also associated with neuronal degeneration, neuroinflammation, dysfunction of the blood brain barrier (BBB), and cognitive decline. AD also has characteristic vascular changes such as a decrease in brain blood vessel density and deposition of Aß plaques in such vessels, causing them to narrow and restrict blood flow to brain tissue. These plaques also weaken the walls of blood vessels, making the BBB more permeable and increasing the incidence of microhemorrhages, which can further damage the brain. Some individuals are genetically predisposed to such plaque deposits later in life due to a mutation in the gene Apolipoprotein E.

***Vascular Dementia***

Vascular dementia (VD) contributes to around 10-20% of all cases, making it the second most common form of dementia behind Alzheimer's (Queensland Brain Institute, n.d.; Raz et al., 2016). Unlike other forms of dementia, vascular dementia is not caused by an aggregation of proteins in the brain, rather, it is the result of a reduction in the amount of blood flow to the brain, which causes deprivation of oxygen and glucose, resulting in the death of neurons. Risk factors for VD are strokes, buildup of fatty plaques on the inside lining of blood vessels (atherosclerosis), and hardening of blood vessel walls (arteriosclerosis).

***Lewy Body Dementia***

Dementia with Lewy bodies makes up about 4% of all dementia cases and is caused by aggregation of the synaptic protein α-synuclein in neurons (Queensland Brain Institute, n.d.; Raz et al., 2016). These are referred to as "Lewy bodies" and cause dysfunction and atrophy of certain brain regions concentrated with dopaminergic neurons, causing alterations of mood and motor impairments similar to the symptoms seen in Parkinson's Disease. The accumulation of

Lewy bodies causes a deficiency in VEGF, leading to decreased brain vascular density and cerebral blood flow. This fuels a destructive cycle as decreased blood flow, also known as hypoperfusion, deprives neurons of oxygen and glucose, further promoting Lewy body deposition.

### *Frontotemporal Dementia*

Frontotemporal dementia accounts for about 10% of dementia cases and is a varied group of different dementias that impact and atrophy the frontal and temporal lobes of the brain (Queensland Brain Institute, n.d.; Raz et al., 2016). Tau and other proteins aggregate, causing the disease. Additionally, loss of neurons, holes in neural tissue of the cortex (cortical spongiosis), and proliferation of glial cells (gliosis) are present in the disease. It occurs earlier in life, often affecting people in their 40s or 50s. Early symptoms appear as changes in personality and behavior rather than the memory loss characteristic of Alzheimer's disease. Roughly half of affected individuals are impacted by genetic factors.

## Exercise as a Preventative for Dementia

Research has found that regular exercise often correlates with a reduced risk of developing dementia, offering a promising, cheap, at-home preventative that most people can adopt. A study from the United Kingdom examined data from fitness trackers and health records for 78,430 adults between the ages of 40 and 79, and found that those who walked 3,800 steps (~2 miles) per day had a 25% reduction in risk of all-cause dementia and that those who walked 9,800 steps (~5 miles) per day had a 51% reduction in risk of all-cause dementia even when adjusting for factors such as age, sex, race, education, socioeconomic status, smoking, alcohol use, fruit and vegetable consumption, family history of cardiovascular disease and cancer, and medication use (Del Pozo Cruz et al., 2022). Although many factors were accounted for, an

observational study like this cannot necessarily prove causation. However, the correlation between exercise and lower risk of dementia is a promising area of research that should continue to be pursued.

Similarly, a Canadian study of over 9000 men and women over 65 found that compared with sedentary individuals, those who exercised had a decreased risk of cognitive decline and all types of dementia, with greater amounts of physical activity correlating directly with greater cognitive protection (Laurin et al., 2001). Likewise, a meta-analysis of almost 34,000 subjects found that low, moderate, and high levels of physical activity provided a 35-38% protection against cognitive decline (Sofi et al., 2011). Furthermore, a 44-year-long longitudinal study of 1,462 middle-aged and older Swedish women found that those with high fitness had an 88% reduction in dementia risk when compared to those of medium fitness, demonstrating that additional cognitive protective benefits can be conferred by higher levels of fitness beyond just having average fitness (Hörder et al., 2018).

Research has also found a correlation between aerobic fitness and increased size and blood volume in the hippocampus (Burdette et al., 2010). Even for older individuals who haven't been active in the past, it was found that just one year of exercise at moderate intensity (40 minutes of exercise 3 times a week) increased hippocampal size and spatial memory (De la Rosa et al., 2020). Also, a 6-month exercise routine (1 hour, 3 times a week) increased the number of neurons and neuronal connections in regions of the brain where atrophy is implicated in various forms of dementia (Tan et al., 2013). Resistance training also demonstrated improvements in measures of cognition and executive functions.

A set of nine risk factors, one of which being low physical activity, are responsible for roughly 35% of dementia cases. A meta-analysis comprising 16 studies and over 160,000

subjects discovered that those who regularly engaged in physical activity had a 45% lower risk of developing Alzheimer's, and a prospective study of 716 older individuals found that those who reported low daily physical activity had a 53% increase in development of Alzheimer's. These many, broad studies suggest that exercise, and the additional positive lifestyle habits that may accompany it, lowers one's risk of developing dementia.

**Exercise as a Treatment for Dementia**

For those with mild cognitive impairment (MCI), the preclinical stage to dementia, regular aerobic exercise can improve performance in memory, executive functions, and cognitive tests (De la Rosa et al., 2020). This can help slow or potentially even stop the progression of dementia in older individuals.

For adults in the early stages of Alzheimer's disease, aerobic exercise, sometimes in combination with cognitive stimulation, improved certain cognitive functions. Less research has been done for the effects of resistance training on dementia, but one study found that six months of resistance training improved memory, attention, and executive functions in individuals aged 55 to 86 with MCI, and that those improvements were consistent even a year after the training ended. Studies of exercise treatments for patients actively experiencing AD have inconsistent results, requiring more research to further assess its effects. Some studies have found that 16 weeks of moderate to high intensity aerobic exercise did not increase cerebral blood flow (CBF) or reduce the levels of plaque-causing proteins. Results may become more conclusive as different varieties, intensities, frequencies, and durations of exercise are tested on populations with AD. This highlights the importance of adopting and maintaining a consistent exercise routine before dementia develops or progresses, as many of the benefits of exercise are observed in healthy or mildly cognitively impaired individuals early in the disease process.

Some studies have shown that exercise can improve cognitive function, slow cognitive decline, decrease neuropsychiatric symptoms, and slow the loss of ability to perform activities of daily living in affected individuals (Cass, 2017). In contrast, other studies have not found improvements in cognition, further highlighting the importance of more, well-designed studies assessing the effects of exercise on those with dementia, and what forms of exercise provide the most benefit. One challenge to these studies is the low level of compliance and adherence to the exercise plan, particularly if the exercise intervention is long and intense. This makes it difficult to assess if benefits could be observed if subjects continued participation for longer than a few months.

## Physiological Mechanisms

### *Angiogenesis and Blood Flow*

As people age, cognitive function and cerebral blood flow decrease (CBF) (De la Rosa et al., 2020). People with AD can have a reduction of up to 40% in CBF as compared to healthy individuals. Aß plaques can be deposited in cerebral blood vessels, which decreases CBF. Regular exercise has been shown to increase CBF in many brain regions, including the hippocampus, as well as improve function in blood vessels. Even just a 12-week program of three hours of aerobic exercise a week increased resting CBF in multiple brain regions, including the hippocampus, in healthy, middle-aged subjects. However, these increased CBF levels can fall even with short periods of inactivity, highlighting the importance of maintaining a regular exercise routine.

Exercise also decreases the formation of Aß plaques and NFTs (De la Rosa et al., 2020). In transgenic mice models who were given mutations to cause development of AD, exercise lowered the number and size of Aß plaques and NFTs in the brain, including the hippocampus,

sometimes correlating with improved learning and memory in the mice. Even after just 10 weeks of voluntary exercise, these mice had improvements in spatial memory, less neuronal death, and more neurogenesis in the hippocampus. An important finding from this type of research is that exercise treatments need to be started at early stages in the disease, as they cannot remove deposited plaques or the resultant neurodegeneration after it has already occurred, further demonstrating the role of exercise as more of a preventative than a treatment.

In healthy older people, higher levels of physical activity were associated with lower brain and blood concentrations of Aß proteins that lead to plaques. Furthermore, in those with MCI, six months of aerobic exercise lowered Aß blood levels by 24%. These findings suggest exercise can aid in the turnover of these harmful proteins, reducing one of the primary etiologies of dementia.

***Reduced Neuroinflammation***

It has been found that the immune system reacts to the accumulation of Aß plaques by activating microglia, supportive cells that act as the brain's immune system to remove cell debris, pathogens, and protein deposits from the central nervous system (De la Rosa et al., 2020). However, this chronic proinflammatory state decreases the effectiveness of microglia to clear the Aß plaques, stimulating the release of cytokines and cell-damaging free radicals which further promote the formation of Aß plaques and NFTs. This causes more neuronal death which furthers the progression of Alzheimer's and the cognitive decline associated with it.

An increase in chronic proinflammatory responses in the central nervous system is widely believed to be a precursor and marker of Alzheimer's. Exercise has been shown to benefit systemic-wide inflammation markers including in brain tissue. Three weeks of exercise in an AD mouse model reduced proinflammatory cytokines like IL-1ß and TNF-α and increased immune

response proteins in the hippocampus, having an overall anti-inflammatory effect on the brain. In humans, exercise has also been observed to lower inflammatory markers, which correlates with improved performance on cognitive tests. Rats who exercised for just 10 days had a boost in anti-inflammatory cytokines and reductions in proinflammatory cytokines in the hippocampus. They also had a reduction in the inflammatory response of microglia and a prevention of decline in hippocampal BDNF levels. The anti-inflammatory effects of exercise make it a prime option for treating a disease characterized by excessive neuroinflammation such as AD.

### *Increased Neurotrophic Factors*

As previously discussed in detail, exercise increases the levels of multiple neurotrophins such as BDNF, IGF-1, and VEGF that support the growth and survival of neurons. BDNF levels have been shown to decrease naturally with age as well as with stress, removing the protective barrier BDNF creates against neuronal cell damage, and people with AD also show lower than average levels of BDNF (Laasko et al., 1996; De la Rosa et al., 2020). Exercise increases BDNF levels in the blood and brain and which often correlates with improved cognitive function. In healthy, older adults, aerobic exercise increased the size of the hippocampus and correlated with higher blood BDNF levels and a lower risk of developing AD.

In several AD mice models, exercise promoted hippocampal neurogenesis and increased BDNF levels, improving their cognitive function by allowing for the creation and maintenance of new neurons, countering the neuronal loss of AD. Similarly, in mice with accelerated aging, four weeks of moderate intensity exercise improved their memory recognition and hippocampal BDNF levels.

## VII. CONCLUSIONS

Current research in the field of exercise neuroscience has shown several neurological and psychological benefits to adopting a regular exercise routine in addition to the plethora of other physical benefits it confers. A brief summary of the benefits discussed in this review are as follows:

**Mood**

Exercise has been found to improve mood by decreasing depressive symptoms, increasing feelings of self-esteem and self-efficacy, decreasing the body's physiological response to stressors, modulating neurotransmitter levels such as serotonin, and increasing the release of endogenous endorphins and endocannabinoids which relieve pain and create positive feelings of euphoria.

**Memory & Learning**

Additionally, exercise has been shown to increase both short-term and long-term memory, spatial memory, and hippocampal-dependent memory. Proposed mechanisms for these improvements include increased levels of neurotrophic factors such as BDNF, IGF-1, and VEGF that serve to increase neurogenesis, neuroplasticity, LTP, hippocampal volume, CBF, and overall neuron health. This supports neurons which can benefit memory and overall cognitive function.

**Prevention and Treatment of Dementia**

Finally, exercise strongly correlates with decreased risk of dementia and a slowed progression of dementia in those with MCI or early-stage dementia. Being active can reduce the deposition of neuron-damaging plaques, increase CBF, strengthen and enlarge pertinent brain regions that are targeted by dementia, and increase neurotrophic factors that support neuron health. The current literature shows physical activity can help as a preventative for dementia as well as a treatment for slowing the disease progression in those early in the disease process.

However, exercise cannot remove plaques or reverse the damage to neural tissue if it has already occurred. Further research on this topic will provide valuable insight on the most effective exercise prescriptions for preventing and treating the debilitating host of neurodegenerative diseases referred to as dementia.

**Current Recommendations**

Most of the adult population can reap the physical and mental benefits of exercise, some of which have been detailed in this paper, by following the exercise guidelines outlined and agreed upon by major health organizations such as the HHS and AHA. It is recommended that those with pre-existing health conditions, which may be exacerbated by exercise, talk with their physician before starting a new exercise regimen. The current physical activity guidelines are:

- at least 150 minutes (2.5 hours) of moderate intensity aerobic exercise per week

  OR

- at least 75 minutes (1.25 hours) of vigorous intensity aerobic exercise per week

  OR an even mixture of both moderate and vigorous intensity aerobic exercise

  AND

- muscle-strengthening activities at least twice a week.

According to the AHA (2018), only roughly 20% of adolescents and adults meet the minimum physical activity guidelines to maintain good health. For individuals who are currently sedentary, defined as not meeting these requirements or walking less than 5,000 steps a day, it is recommended to start small, focus on building a habit of regular exercise, and to only gradually increase the duration and intensity of exercise as your fitness improves (Petrie, 2020). Going for a 10-minute walk or bike ride at a low to moderate intensity can be a sufficient start. As the individual's schedule and body adapts to this change, provided no hindering health problems

arise, they can increase the minutes they exercise, eventually reaching the 150 minutes per week guideline, and even surpassing it, as 2.5 hours per week is only a minimum recommendation and further health benefits can be garnered by exercising beyond it.

Additionally, engaging in resistance training at least twice a week, whether with weights, body weight, or water resistance, combined with a proper warm up, cool down, and stretching routine can yield additional benefits for muscle strength, endurance, appearance, and flexibility.

## VIII. EPILOGUE

The power of the human mind is remarkable, and its effects are ever reaching. It has written complex symphonies, put people on the moon, built cities full of skyscrapers and motor vehicles, and created treatments for the many things that ail us, even going so far as to successfully transplant a foreign heart into a patient. The very computer that allowed for the writing and reading of this paper was created from the ingenuity of the human mind. Every thought and innovation ever conceived of has been the result of the complex firing of billions of interconnected neurons inside a soft, delicate organ roughly the size of two fists. Our brains are so central to what makes us human that brain death is the defining metric of cessation of life, even if the rest of the body is completely healthy. It is the unsurpassed brainpower of *Homo sapiens,* Latin for “wise man”, that has enabled our species to thrive and shape the very world we inhabit in a way no other creature has managed to do. Why wouldn’t we explore every possible avenue to maximize our brain’s health, performance, and longevity, and search for every effective preventative and treatment for debilitating brain conditions like dementia? Perhaps there would be an influx of sharp, independent 70 to 100-year-olds if we did. As for what we can do today, maybe taking a break from our work to go for a brief walk would help us more than we

know.

Newton's first law of motion states that an object in motion will tend to stay in motion, an idea that moving objects have momentum which allows them to resist forces that attempt to stop or redirect them. Although he was describing the physics of moving objects, perhaps in a similar way, a body that stays in motion will create the momentum necessary to allow a mind to stay in motion for several decades into the future; a mind in motion that can resist the forces, such as aging and disease, that attempt to stop it in its tracks.

Humans have talked about, and even scoured the world looking for, a fountain of youth that will bring youth and immortality to its partakers. Although this likely doesn't exist, exercise may be the closest humanity will ever come to finding a fountain of youth.

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