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Exercise Can Potentially Cure Parkinson's Disease: A Comprehensive Review

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Abstract

Parkinson's disease is the second most common neurodegenerative disease that negatively affects many American lives. It is characterized by the degeneration of dopamine-secreting neurons in the Substantia Nigra Pars Compacta (SNpc). Individuals with Parkinson's Disease lack motor coordination and experience severe motor impairments. Unfortunately, there is currently no treatment method available that can successfully cure the disease. In fact, all of the mainstream available treatments only eliminate some PD symptoms, and they cause many negative side effects. Although nontraditional, exercise is a side effect free treatment method that can potentially slow the progression of the disease and alleviate some symptoms. This paper first gives a comprehensive overview of the pathology and current treatments of Parkinson's disease. Then this paper reviews the benefits of exercise therapy for PD patients and the potential biological mechanisms that drive the success of exercise therapy.

Introduction

Although not as prevalent as Alzheimers, Parkinsons disease(PD) is the second most common age-related neurodegenerative disorder (Paillard, et. al. 2015, Maiti, et. al. 2017). It occurs in about 1-2% of the population over 65 and has been found to occur even less in younger populations (Maiti, et. al. 2017). Thus, age is considered to be one of the most prevalent risk factors for the development of the disease. Although Parkinson's disease does affect multiple parts of the brain, it is mainly characterized as a neurodegenerative disease that causes the degradation of dopaminergic neurons located in the Substantia Nigra Pars Compacta (SNpc) (Maiti, et. al. 2017, et. al. 2013). In a healthy person, the axons of these neurons extend to the Striatum where they help relay inhibitory signals by secreting dopamine which in return causes the basal ganglia to send inhibitory signals to Globus Pallidus and thalamus. These inhibitory signals help regulate movement by preventing the thalamus from over stimulating the motor cortex and causing impairment of motor coordination (Maiti, et. al. 2017). Due to the degradation of SNpc neurons, patients with Parkinson's disease have a significant decrease of dopamine secretion in the Striatum and as a result they experience significant motor impairments (Petzinger, et. al. 2013, Maiti, et. al. 2017).

Symptoms

PD is a neurodegenerative disorder that slowly worsens over time, thus, individuals with Parkinson disease experience a wider array of symptoms as the disease progresses. It takes around 15 to 20 years for PD symptoms to progress and it is estimated that the first visible symptom is seen only once 80% of the SNcp neurons have died out. Due to the progressive nature of the disease, early symptoms are subtle and often unidentifiable (Sveinbjornsdottir, 2016, Maiti, et. al. 2017). At first, most individuals will experience twitching in their arm, leg, jaw, lips or chin (Maiti, et. al. 2017). This symptom is called a resting tremor and is observed in the early stages of the disease in about 70% of PD patients (Maiti, et. al. 2017) (Moustafa, et al., 2016). It is most commonly found in the arms and the legs, and it usually starts off only on one side of the body. Gradually, this tremor develops bilaterally affecting both sides of the body (Maiti, Manna, & Dunbar, 2017). The second most common symptom is rigidity or stiffness of the muscles and

joints (Maiti, et. al. 2017) (Moustafa, et al., 2016). This side effect causes individuals with PD to feel week and have severe cramping pain (Maiti, et. al. 2017). Individuals with PD also lose their ability to move quickly and experience a symptom called bradykinesia (Moustafa, et al., 2016, Maiti, et. al. 2017). Bradykinesia is characterized by loss of automatic movements, slow handwriting, decreased eye blinking, lower speech volume, difficulty initiating movement and difficulty in stopping continuous movements. In addition, PD patients also experience balance and coordination problems and will often fall. All of the above symptoms are considered to be primary symptoms of Parkinson's Disease and are essential for the diagnoses of the disease (Sveinbjornsdottir, 2016, Maiti, et. al. 2017).

In addition to the above symptoms ,some secondary symptoms may develop. These include continued changes in speech including the slurring of words, the repetition of words and excessively slow or abnormally fast speech. Urination and defecation become exceedingly hard due to the slow movement of smooth muscle in the digestive tract. Swallowing and chewing food becomes very difficult because of the bodies inability to perform peristalsis properly. In addition, PD patients often have a hard time staying asleep at night due to "insomnia, Rem sleep behavior disorder, sleep apnea, sleep attacks and restless leg syndrome (Maiti, et. al. 2017)." Some people with PD also experience depression, mood problems, anxiety, cognitive dysfunction, apathy and Dementia (Chaduri & Schapira, 2009) (Maiti, et. al. 2017).

Mechanisms of Parkinson's Disease

Parkinson's Disease can manifest due to external factors or as a result of inherited genetic mutations. Most cases of PD are considered to be non-genetic forms of PD, that result from environmental stimuli (Maiti, Manna, & Dunbar, 2017). Both genetic forms and sporadic forms of PD follow similar mechanisms of neuronal degeneration. Three of the most probable pathways of neuronal degeneration are death through mitochondrial dysfunction, A-synuclein aggregation, malfunctioning chaperone proteins and Autophagy lysosomal pathway damage.

Mitochondrial dysfunction can be caused by both genetic and environmental factors. Some environmental factors that cause PD include pesticides, herbicides, fungicides, and insecticides. Consequently, farmers and individuals who live in rural areas

are considered to be more susceptible to PD due to direct exposure to these substances through the air and drinking water. Other environmental factors that cause PD included bacterial toxins, viruses and illegal street drugs such as synthetic forms of heroin and rotenone. These environmental factors "inhibit complex one activity and cause dysfunction in the electron transport chain which causes oxidative stress (Maiti, et.al. 2017, p.12)." Gene mutations of the DJ-1 and Pink1 genes also cause mitochondrial dysfunction that can result in oxidative stress by inhibiting the formation of mitochondrial protective proteins. Once initiated by either environmental or genetic factors, oxidative stress causes the phosphorylation of tau proteins which eventually aggregate to form Lewy Bodies. These Lewy bodies accumulate in the cell making it exceedingly hard for the cell to complete basic tasks needed for neuronal function . Lewy bodies also make pores in the cell membrane resulting in "neuronal death via oxidative stress, energy failure, excitotoxicity, and neuronal inflammation. Eventually, the infected neurons begin to die due to their inability to perform tasks essential for survival". In addition to oxidative stress, mitochondrial dysfunction can also directly lead to energy failure. Energy failure refers to the cells inability to produce the chemical energy needed for cell survival. Energy failure causes the degeneration and death of dopaminergic neurons (Maiti, Manna, & Dunbar, 2017).

Mutations in the a-synuclein gene cause an alternative mechanism of neuronal degeneration. This mutation leads to the creation of misfolded α-synuclein proteins that eventually aggregate and develop into Lewy Bodies . Lewy bodies block up the cell making it close to impossible for basic cell functions to be completed. In addition, the Lewy bodies can make holes in the cell membrane which cause cell death by initiating, oxidative stress, energy failure, excitotoxicity, and neuroinflammation (Maiti, et. al. 2017). Thus, the α-synuclein gene mutation directly affects neuronal cell death.

Mutations of the parkin and UCHL1 genes can lead to the death of SNpc neurons by causing the destruction of ubiquitin-proteasome system(UPS) and molecular chaperones (Maiti, Manna, & Dunbar, 2017). The UPS actively brakes down short polypeptides into intracellular plasma membrane proteins, and it also helps with degeneration of "misfolded or damaged proteins in the cytosol, nucleus or endoplasmic reticulum (Maitiet. Al. 2017, p. 9)." Chaperone proteins play an important role in ensuring that proteins are folded properly. Damage to these two systems lead to the accumulation of misfolded proteins and to the impairment of the Autophagy Lysosomal pathway(ALP). The ALP helps degrade large protein debris that cannot be degraded by the UPS. When the UPS, chaperone proteins and ALP fail to complete their respective jobs, misfolded proteins begin to aggregate in the cell and form Lewy bodies (Maiti, Manna, & Dunbar, 2017). The Lewy bodies go on to disrupt cell function leading to the degeneration SNpc neurons.

The Spread of the Disease

Many researchers believe that once Parkinson's disease is initiated, Lewy body infected neurons transmit the disease to adjacent uninfected neurons (Maiti, Manna, & Dunbar, 2017). This method of proliferation is known as the prion hypothesis. Interestingly, many studies have found that α-synuclein begins to aggregate in the enteroendocrine cells of the gastrointestinal tract and then spreads to the brain via prion infection. Although this may be the method of proliferation used in some cases of PD, it is definitely not used in all PD cases since Lewy bodies are not necessary for initiation of PD (Maiti, et. al. 2017).

Inflammation may also be responsible for the spread of Parkinson's disease (Zhang, et al., 2011) (Phania, et. al. 2012). Neuronal inflammation occurs due to head trauma or the development of pathogenic disease such as PD. Inflammation in the PD brain is characterized by activated microglia cells, astrocyte cells and imported T-cells that crossed the blood-brain barrier (Cebrián & Sulzer, 2017). In the case of Parkinson's disease, the immune response is unbalanced, and instead of eliminating the disease it aids in the progression of the disease.

Microglia cells are activated as a result of α-synuclein accumulation (Cebrián & Sulzer, 2017). Once activated they act as phagocytic cells and participate in the removal of toxins and dead neurons (Vivekanantham, et al., 2015). They also produce "a plethora of pro-inflammatory mediators including prostaglandins, cytokines, chemokines, complement, proteinases, ROSs and RNSs (Vivekanantham, et al., 2015)." These substances initiate cell death by directly causing oxidative stress. In addition, microglia phagocytose extracellular neuromelanin that was released by dying neurons (Cebrián & Sulzer, 2017). During this process cytokines and hydrogen peroxide are released and cell death via oxidative stress is initiated (Zhang, et al., 2011).

Astrocytes are supposed to help regulate the immune response by protecting neurons from oxidative stress. In theory this would allow the microglia cells to participate in the immune responses without initiating neuronal cell death. However, because Parkinson's disease affects a part of the brain that has almost no astrocytes, this regulatory system fails to occur. In addition, many of the astrocytes present in the PD brain contain α-synuclein aggregations and release harmful substances such as cytokines, chemokines, and IFN-T (Cebrián & Sulzer, 2017). Thus, although astrocytes have the potential to be neuroprotective in Parkinson's disease, they are neurodestructive.

In addition to the damage that both astrocytes and microglia cells cause independently, they also work together to proliferate the disease by increasing the permeability of the blood-brain barrier. They accomplish this task by releasing cytokines which actively increase the permeability of the blood-brain barrier. This allows CD4 T cells and CD8 T cells to enter the central nervous system easily. Once the T cells reach the SNcp, they are activated by microglia cells that present antigens on their surfaces

using MHC II molecules and MHC I molecules (Kannarkat, Boss, & Tansey, 2013). This activation causes the release of more cytokines which leads to cytotoxicity and further activation of microglia cells (Kannarkat, et. al. 2013, Federoff, 2014). Thus, infiltrating T cells aid in the progression of Parkinson's disease (Phania, et. al. 2012).

Treatment

Traditional treatment for Parkinson's disease is limited to medications, surgeries, stem cell implantation and gene therapies that are only effective in eliminating side effects and cannot cure the disease. Most of these treatment methods have a multitude of side effects and only work for a limited amount of time or on a small population of Parkinson's patients. Various tratmentoptions and their success in treating PD are reviewed below with a particular focus on their success in treating PD and their adverse side effects.

Medications

Levodopa, a precursor form of dopamine, is perhaps the most common PD medication (Connolly & Lang, 2014) because it can cross the blood-brain barrier where it is converted to dopamine. By increasing dopamine levels in the brain, this medication successfully reduces resting tremors (Maiti, et. al. 2017). Unfortunately, Levodopa has also been found to cause vomiting, nausea, restlessness, drowsiness, low blood pressure, sudden onset of sleep and impulsive control disorders (Connolly & Lang, 2014) (Maiti, et. al. 2017). Additionally, chronic use of levodopa results in dyskinesia and motor fluctuations (Smith, et. al. 2012). Levodopa also has been found to quickly lose its effectiveness because it is converted immediately upon arrival into the central nervous system and by the time it reaches the target area enzymes have already started breaking it down (Maiti, et. al. 2017). Thus, to increase the potency of levodopa, many dopamine agonists are administered in combination with levodopa.

Monoamine oxidase-B (MAO-B) inhibitors such as selegiline and rasagiline are examples of dopamine agonists that are used in combination with levodopa (Maiti, et. al. 2017). MAO-B is an enzyme that participates in the breakdown of dopamine (Kay et. al. 2013). MAO-B inhibitors help prevent the breakdown of dopamine and increase the potency of levodopa (Smith, et. al. 2012) (Maiti, et. al. 2017). Although these medications have been successful in prolonging the effects of levodopa, they also cause a multitude of negative side effects. Which include, "Dizziness, dry mouth, insomnia, muscle pain, rash, nausea, constipation, severe headache, tachycardia, arrhythmia, hallucinations, chorea, or difficulty in breathing (Maiti, Manna, & Dunbar, 2017, p. 19)."

Another commonly used dopamine agonist is Catechol-O-methyltransferase (COMT) inhibitors (Maiti, Manna, & Dunbar, 2017). These drugs prevent the breakdown of dopamine and increase the efficiency of levodopa (Smith, Wichmann, Factor, & DeLong, 2012) (Maiti, Manna, & Dunbar, 2017). Entacapone and tolcapone are two examples of commonly used COMT inhibitors (Smith, Wichmann, Factor, & DeLong, 2012). Along with increasing the lifespan of dopamine these drugs cause hepatotoxic, nausea, orthostatic hypotension, urine discoloration, dizziness and mitochondrial dysfunction (Maiti, Manna, & Dunbar, 2017).

Dopamine agonists such as pramipexole and ropinirole are examples of drugs that are used instead of levodopa to treat the early stages of Parkinson's disease. They help alleviate Parkinson's symptoms by increasing dopamine levels in the brain. These drugs are not as effective as levodopa, and they cause similar side effects as levodopa. Some of the side effects commonly observed while administering these drugs are hallucinations, low blood pressure, nausea, dizziness, drowsiness, dry mouth, swollen legs and feeling faint upon standing (Maiti, et. al. 2017).

Anticholinergic drugs are also used to treat Parkinson's disease. These drugs inhibit the release of acetylcholine, which is overproduced in the brains of Parkinson's patients due to diminished dopamine inhibitory signaling (Maiti, et. al. 2017). They are successful in alleviating tremor and rigidity in about 50% of patients (Smith, et. al. 2012) (Maiti, et. al. 2017). Their adverse side effects include memory loss, confusion, hallucinations, constipation, urination problems, dry mouth, dry eyes and blurred vision (Smith, et. al. 2012). Due to the limited population that can be helped with anticholinergic drugs and the adverse side effects of these drugs they are less commonly used for the treatment of PD.

Surgical Treatments

Deep brain stimulation(DBS) surgery is a common surgery used to treat the advanced stages of Parkinson's disease. This surgery is only performed once all the medications mentioned above begin to lose their potency (Smith, et. al. 2012). Additionally, this surgery can only be performed on individuals who had success in using levodopa and show no signs of dementia or psychiatric abnormalities (Smith, et. al. 2012) (Okun, 2012). During DBS surgery electrodes are implanted into GPi and STN of the brain (Okun, 2012) (Maiti, et. al. 2017). These electrodes are attached to two batteries that are implanted in the chest directly under the color bone (Maiti, et. al. 2017). Electrical signals are then generated by the implanted batteries and sent to the electrodes in the brain where they stimulate inactive neurons (Okun, 2012) (Maiti, et. al. 2017). Once implanted this device is controlled by an external handheld device (Maiti, et. al. 2017). DBS has been shown to successfully eliminate many motor abnormalities including motor fluctuations. Additionally, because DBS eliminates the need for levodopa it successfully reduces dyskinesia and dystonia (Smith, et. al. 2012) (Maiti, et. al. 2017). Unfortunately, DBS entails a surgery that can cause stroke, hemorrhage, infection, speech issues and balance problems (Okun, 2012) (Maiti, et. al. 2017) (Smith, et. al. 2012). DBS has also been found to

increase depression, mania and suicide risk (Okun, 2012). Thus, although DBS can be helpful in treating PD, it may also cause adverse symptoms that can lead to death.

Another two surgeries which are used to treat Parkinson's disease are pallidotomy and thalamotomy. Pallidotomy is a surgery in which a part of the globus pallidus is destroyed . As a result of this destruction, "the synaptic connections with thalamus or striatum are altered in a way which decreases tremor, rigidity, bradykinesia and posture abnormalities in PD patients (Maiti, et. al. 2017, p. 21)." Thalamotomy is the destruction of the thalamus, which disrupts the connection between the basal ganglia and the motor cortex. This procedure restores neurotransmitter balance and reduces tremor . However, thalamotomy is unsuccessful in alleviating other symptoms such as bradykinesia, rigidity, and dyskinesias (Maiti, et. al. 2017).

Stem Cell Implantation

Stem cell implantation therapy involves the implantation of human fetal-derived dopaminergic tissues into the striatum. Implantation of these tissues into the brain results in higher levels of dopamine, which indicates that these stem cells mature properly and are able to create synapses. When porcine-derived dopamine-producing cells are used moderate improvements in symptom control are observed. However, when allogenic human fetal ventral mesencephalic cells are used much greater symptom relief is observed (Maiti, et. al. 2017). "These cells survive and make appropriate synaptic connections, while increasing DA levels within the host cells (Maiti, et. al. 2017, p. 22)." Although stem cell implantation seems promising, it causes many safety issues including unchecked proliferation and tumor development (Smith, et. al. 2012). Thus, more research is needed to develop this treatment technique and increase its safety.

Gene Therapy

Although most cases of Parkinson's disease are sporadic, there are some genetic forms of the disease. Scientists are now starting to develop gene therapy techniques that can cure the genetic forms of PD. Some of the techniques that are being tested are viral vector-mediated gene delivery, AADC-TH -GCH therapy, RNA interference-based therapy and CRISR-Cas-9 gene editing system. Most of these therapies have been successful in animal models, and some have also been used to treat humans successfully. However, most of these therapies must be tested further in order to ensure their safety (Maiti, Manna, & Dunbar, 2017).

Exercise as a Treatment Method for PD

There is no treatment method for Parkinson's disease that is symptom-free. In fact, all of the treatments available for PD are not successful at curing the disease, and when used they generate adverse side effects. Thus, Patients diagnosed with Parkinson's disease often feel helpless and experience depression because

until recently, their diagnosis meant awaiting and experiencing the impending uncontrollable loss of movement until death.

However, in the past two decades, athletic programs such as Boxing, Tai Chi, dancing, treadmill training and forced bicycling have begun to bring hope to Parkinson's patients. These programs are designed in a way that teaches Parkinson's patients physical skills that helps stop the progression of the disease and even allows some individuals to regain full range of movement. Studies have proven the success of these programs, but there is no significant scientific work that can explain how exercise alleviates Parkinson's symptoms on a biological level. In the past couple of years, scientists have turned their attention to discovering the underlying biological mechanism that allows the above exercise programs to be so successful in treating Parkinson's disease. Based on the current scientific research the most probable mechanisms are that exercise promotes neuroplasticity and neuroprotection.

The Two Main Components that make an Exercise Program Successful

Most of the Successful exercise programs incorporate goal based learning and aerobic exercise. The inclusion of these two components helps promote neuroplasticity, which is defined as,

A process by which the brain encodes experiences and learns new behaviors… the modification of existing neural networks by addition or modification of synapses in response to changes in behavior or environment, which can encompass exercise. Neuroplasticity includes a wide range of structural and physiological mechanisms including synaptogenesis, neurogenesis, neuronal sprouting, and potentiation of synaptic strength, all of which can lead to the strengthening, repair, or formation of neuronal circuitry (Petzinger, Fisher, McEwen, Beeler, & Walsh, 2013).

Goal-based learning refers to the incorporation of tasks that are aimed at improving specific skills that are impaired in PD. Intensity, specificity, complexity, repetition, and difficulty are all important aspects of goal-based exercise that help drive. Goal-based exercise also stimulates cognitive engagement of the prefrontal cognitive circuits. These circuits are involved in early motor movement and the development of automaticity. Thus, activation of prefrontal circuits helps patients with Parkinson's disease relearn skills that were previously automatic. Aerobic exercises are similar to goal-based exercise in the fact that it too promotes cognitive engagement and neuroplasticity. "Aerobic exercise is defined as vigorous and sustained physical activity that leads to increased cardiopulmonary function resulting in improved oxygen consumption (maximum oxygen uptake) and blood flow to the brain (Petzinger, et. al. 2013, p. 719)." By increasing blood flow to the brain, aerobic exercise stimulates neuroplasticity and improves cognitive prefrontal cortex function. When goal based and aerobic exercise are combined their effects are compounded, and significant changes in neuroplasticity are observed (Petzinger, et. al. 2013).

Ilana Tokarsky

The Successful Programs and how they Incorporate Goal Based Learning and Aerobic Exercise

"Tai Chi, as a mind-body exercise, consists of a series of dance-like movements linked in a continuous sequence, flowing slowly and smoothly from one movement to another that emphasizes weight transfer and movement of the body." (Yan Yang, 2015, p. 2) It has been shown to improve dynamic postural control, balance, gait, and quality of life (Petzinger, et. al. 2013, Yan Yang, 2015). In one study, scientists observed improved stride length, stability and maximum excursion in patients who had participated in tai chi classes twice a week for 24 weeks (Petzinger, Fisher, McEwen, Beeler, & Walsh, 2013). Tai chi incorporates cognitive engagement by practicing combinations of movements and control of an individual's center of gravity (Yan Yang, 2015). However, it does not include intense aerobic exercise, and it is not clear if this lowers its success rate compared to other exercise debilitation programs.

Dance is an aerobic form of exercise that has also shown promise as a potential treatment for Parkinson's Disease. Dance enhances motor learning by making people pay attention to music and rhythm (Blandy, Beevers, Kerry, & Morris, 2015) (Petzinger, Fisher, McEwen, Beeler, & Walsh, 2013). In addition, partner dancing further stimulates cognitive engagement by teaching people partner coordination (Petzinger, Fisher, McEwen, Beeler, & Walsh, 2013). By incorporating both cognitive and aerobic exercise, dance has been found to improve gait, motor impairment and balance (Blandy, Beevers, Kerry, & Morris, 2015).

Boxing therapy has become a very popular form of exercise therapy for PD in the past couple of years. In 2006 The Rocksteady boxing foundation located in Indiana opened the first noncontact boxing program for PD Patients. Since then, Rocksteady boxing programs have been established across the United States. Boxing therapy takes a whole-body approach by including dynamic balance activities and multi-directional reaching and stepping. These programs also include jump rope and framework activities that help improve people's ability to initiate movement (Combs, et al., 2011). Boxing helps improve balance, gait, parkinsonian symptoms and quality of life (Combs, et al., 2011) (Petzinger, et. al. 2013). Scientists have reported that the benefits of boxing last for a long time even if patients stop participating in as many classes as they originally did. The boxing programs included aerobic exercise and goal-based exercise by incorporating fast-paced multi-directional body movement (Combs, et al., 2011). Thus, boxing is one of the most promising forms of exercise therapy available for PD patients.

Cycling training is another popular form of exercise rehabilitation. Both forced cycling and voluntary cycling programs have been found to help improve PD symptoms (Nadeau, et al., 2017). In forced cycling PD patients are placed on an electric bike and forced to pedal at a speed that is above their comfort level (Ridgel, et. al. 2009). This system helps recruit cognitive involvement and has been shown to improve neuroplasticity in the human brain. In addition, forced cycling helps improve tremor and bradykinesia. Voluntary cycling has been shown to improve cardiovascular capacity, executive function, motor learning and walking speed (Nadeau, et al., 2017). Both voluntary and forced cycling are promising treatment options for Parkinson's Disease, and scientist still have not determined which form of cycling is more successful.

Treadmill training, when used to treat mild to moderate PD, helps improve, "velocity, postural stability, gait rhythmicity and joint excursion (Petzinger, Fisher, McEwen, Beeler, & Walsh, 2013, p. 717)." Some studies have reported treadmill training to be completely infective at treating Parkinson's disease. This inconsistency may be a result of improper feedback during workouts, which is supposed to promote cognitive engagement and enhance motor learning (Petzinger, et. al. 2013). Thus, treadmill training is a prime example of an exercise program that must include both goal based and aerobic exercise in order to be effective.

Neuroprotection

Neuroprotection is the driving force behind the neuroplastic effects that both goal based and aerobic exercise exert on the PD brain. Exercise provides neuroprotection by increasing dopamine release and dopamine receptor expression, decreasing dopamine clearance from the synaptic terminals, stimulating the release of neuroprotective factors and initiating an anti-inflammatory response.

Exercise therapy promotes the release of dopamine, decreases dopamine clearance from the synaptic cleft and facilitates the binding of dopamine to D2 receptors in the dorsal striatum. Exercise has been found to increase dopamine synthesis and release in both human and mice models (Horak & King, 2009). One theory for how this is accomplished is that exercise increases tyrosine hydroxylase (TH) levels in the PD brain. TH is an enzyme that increases dopamine levels by converting L-tyrosine to L-dopa (a precursor form of dopamine) (Morgan, Corrigan, & Baune, 2015). TH has also been found to decrease aggregated a-synuclein proteins, which play a primary role in neuronal death in PD (Petzinger, Fisher, McEwen, Beeler, & Walsh, 2013). In addition, exercise decreases DAT levels, which participates in the degradation of dopamine in the synaptic clefts. This increases the dopamine available to bind to dopamine receptors. D2 receptors in the Putman are activated with intensive exercise and are available to bind to dopamine (Jakowec, Wang, et. al. 2016). D2 receptors play an important role in cortical-striatal glutamatergic modulation and are essential for motor learning (Jakowec, et. al. 2016) (Petzinger, et al., 2015).

Exercise plays a role in modulating the inflammatory response in the Parkinson's diseased brain. It is well known that exercise

reduces inflammation and oxidative stress (Shu, et al., 2014). One of the ways that physical activity reduces inflammation is by increasing anti-inflammatory cytokine interleukin 10. Exercise also increases interleukin 6 which usually acts as an inflammatory substance, but in the case of exercise, its effects are anti-inflammatory. Interleukin 6 accomplishes its job by eliciting, "an anti-inflammatory response that includes increased expression of several factors including interleukin 10 and interleukin 1 receptor antagonists, and inhibition of factors such as tumor necrosis factor alpha (Petzingeret, et. al. 2013, p. 722)." In addition, exercise reduces the proliferation of astrocytes and microglia cells which secrete harmful inflammatory cytokines. Physical activity also may drive the conversion of activated microglia cells from M1 myeloid cells which secret harmful cytokines to M2 myeloid cells which helpful secret cytokines (Jakowec, et. al. 2016). This may mean that exercise not only reduces inflammation but also stimulates the development of a positive immune response.

Exercise also increases the secretion of neuronal protective factors, which include brain-derived neurotrophic factor (BDNF), Galia cell-derived neurotrophic factor (GDNF) and hypoxia-inducible factor 1 alpha (HIF-1α). Both BDNF and GDNF promote neuronal growth, prevent neuronal death and help the neurons function properly (Paillard, Ronlland, & Barreto, 2015) (Morgan, Corrigan, & Baune, 2015). BDNF, in particular, is activated by aerobic exercise and has been found to reduce rigidity and muscle stiffness (Morgan, Corrigan, & Baune, 2015) (Jakowec, Wang, Holschneider, Beeler, & Petzinger, 2016). Skilled based exercise increases cortical-striatal function, which results in an increased demand for oxygen. The lack of oxygen activates transcription factor HIF-1α. This transcription factor increases neuronal health by regulating genes that control, "Metabolism, mitochondrial integrity … and signaling cascade pathways involved in nitric oxide synthase and glutamine synaptogenesis (Jakowec, Wang, Holschneider, Beeler, & Petzinger, 2016, p. 41)." Thus, both aerobic and skill-based exercise help increase the release of neuroprotective factors.

Conclusion
Parkinson's Disease is the second most common neurodegenerative disease, and its prevalence is expected to double by 2040 (Ridgel, et. al. 2015). There is no cure for Parkinson's Disease. All the available mainstream treatments cause adverse side effects and are only successful at eliminating a small number of symptoms. However, alternative therapies such as exercise have been found to reduce targeted symptoms, without causing negative side effects. Unfortunately, exercise therapy although growing in popularity is not being used by most primary doctors to treat Parkinson's Disease. Educating affected individuals and medical practitioners on the benefits of exercise programs can potentially help improve the lives of many individuals. Why should medications that cause a plethora of side effects be prescribed when we can use exercise programs instead? Why tell patients that there is no hope in sight for them, when in fact exercise can potentially stop the progression of Parkinson's disease and in some cases eliminate all Parkinson's disease symptoms. It is time for medical professionals to change their outlook on Parkinson's Disease, instead of relaying a message of helplessness they should relay a message of hope.

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