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Exercise-enhanced Neuroplasticity Targeting Motor and Cognitive Circuitry in Parkinson's Disease

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Abstract

The purpose of this review is to highlight the potential role of exercise in promoting neuroplasticity and repair in Parkinson's disease (PD). Exercise interventions in individuals with PD incorporate goal-based motor skill training in order to engage cognitive circuitry important in motor learning. Using this exercise approach, physical therapy facilitates learning through instruction and feedback (reinforcement), and encouragement to perform beyond self-perceived capability. Individuals with PD become more cognitively engaged with the practice and learning of movements and skills that were previously automatic and unconscious. Studies that have incorporated both goal-based training and aerobic exercise have supported the potential for improving both cognitive and automatic components of motor control. Utilizing animal models, basic research is beginning to reveal exercise-induced effects on neuroplasticity. Since neuroplasticity occurs at the level of circuits and synaptic connections, we examine the effects of exercise from this perspective.

Introduction and the Motor Problem in Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized by the loss of dopamine (DA) due to the degeneration of substantia nigra pars compacta (SNpc) dopaminergic neurons. Characteristic features of PD include motor (bradykinesia, rigidity, tremor, gait dysfunction, and postural instability) and cognitive impairment (frontal lobe

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Contributors
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Conflicts of interest
All authors declare that there are no conflicts of interest to report.

Search strategy and selection criteria
References for this review were identified by searches of PubMed using the search terms "exercise" linked to "Parkinson's", "neuroplasticity", "environmental enrichment", "dopamine", "glutamate", "synaptogenesis", "striatum and physiology", " basal ganglia", "physical activity". We mainly selected publications in the past 15 years but we did not exclude commonly referenced and highly regarded older publications. We also searched the reference list of articles identified and selected those we judged relevant.

executive dysfunction), as well as mood disorders. In healthy individuals, motor performance is dependent on the interaction between unconscious (automatic) and volitional (cognitive) control of movement [1, 2]. Conversely, in PD, the early and preferential loss of DA in the dorsal basal ganglia leads to diminished automatic and increased cognitive (frontal cortex) control of motor movements. Consequently, individuals with PD must handle and sustain a larger cognitive load to execute either motor or cognitive tasks[2, 3]. DA replacement therapy alleviates some motor features of PD, but with less beneficial effects observed on cognitive function [4]. In the last decade there is mounting evidence for the role of exercise in improving motor performance that may include facilitating both the cognitive and automatic control of movement.

Epidemiological studies have supported a link between strenuous exercise and reduced risk for PD [5, 6]. Additionally, a number of studies and published reviews on exercise in normal aging and in PD provide the background that supports the benefits of exercise, physical activity, and environmental enrichment [7–9]. While the field of exercise and PD remains an area of ongoing research, the overall purpose of this review is to draw attention to published studies in humans and animal models of PD that may support the beneficial effects of exercise through neuroplastic mechanisms. First we introduce the concept that exercise, through goal-directed and aerobic training may enhance neuroplasticity important for driving motor and cognitive behavioral improvement in PD. Second, we report findings from animal studies demonstrating the neuroprotective and neurorestorative capacity of intensive exercise. Finally we present data on the potential role of exercise in overall brain health that may influence the structural (connectivity) and physiological properties of brain function. Neuroplasticity is a process by which the brain encodes experiences and learns new behaviors and is defined as the modification of existing neural networks by adding or modifying synapses in response to changes in behavior or environment, that encompasses exercise [10]. Neuroplasticity includes a wide spectrum of structural and physiological mechanisms including synaptogenesis, neurogenesis, neuronal sprouting and potentiating synaptic strength, all of which can lead to the strengthening, repair, and/or formation of neuronal circuitry.[11] Importantly, exercise-induced benefits on brain health (blood flow, trophic factors, immune system) may help to create the optimal environmental milieu required for neuroplasticity to occur in the injured brain. This review highlights exercise approaches used to drive behavioral improvement in individuals with PD and findings in animal studies that support the potential for targeting neuroplasticity.

Exercise and Parkinson's disease

Goal-Based Exercise

Exercise is a general term to describe a physical activity that is planned, structured, and repetitive for the purpose of conditioning any part of the body. A major interest in utilizing exercise for neuro-rehabilitation in PD has been that it incorporates many aspects of practice important for goal directed motor skill learning. These elements include repetition, intensity, and challenge which together with skill training lead to improvement in motor performance. Since prefrontal cognitive circuits are critically involved in early phases of motor learning, another important component of exercise in PD is cognitive engagement. Cognitive engagement may be facilitated by (i) feedback (e.g. verbal or proprioceptive), (ii) cueing (i.e. attention), (ii) dual tasking (i.e. attention), and (iv) motivation. The following sections will present studies that have incorporated these concepts. These studies have utilized a variety of different exercise modalities that include but are not limited to treadmill training [12, 13], amplitude training,[14, 15] Tai Chi,[16, 17] tango dancing,[18, 19] boxing[20] and forced cycling.[21, 22]

Gait impairments that involve reductions in speed and step length as well as increased stride length variability are common in PD and impact quality of life [23]. Treadmill exercise is commonly used for improving gait capacity since it can be easily adjusted for speed (and gradient) thus increasing intensity and challenge of gait practice. Studies, using treadmill exercise (with or without body weight support typically used for the purpose of maintaining safety) have shown that through exercise practice individuals with mild to moderate stages of PD can improve gait performance, including velocity, stride length, cadence, postural stability, gait rhythmicity, and joint excursion [24, 25]. While the majority of treadmill studies have reported these benefits, a few studies have shown that despite a similar period of practice, no significant improvement in gait capacity occurred. One possible explanation for this discrepancy in gait outcomes may be due to differences in the amount of feedback and cognitive engagement during practice [26, 27]. Severity of disease, which may affect cognition, may also be a confounder. While the challenge of repetitively controlling dynamic balance in conjunction with the proprioceptive feedback from the moving treadmill may be helpful for learning, verbal feedback and/or cues that draw attention and facilitate cognitive engagement to the motor task practice may be what underlies the treadmill training benefits observed in most PD studies. Both immediate (upon completion of training 4 to 12 weeks) and long-term retention (lasting several months) of gait improvements have been reported following cessation of treadmill exercise [24, 28, 29]. Interestingly benefits of treadmill training, a largely lower extremity task, have also been shown to transfer to improvements in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score. For example, the benefits of increased movement amplitude and speed in gait (stride length and velocity) appear to transfer to increased amplitude and speed of finger and foot tapping [28, 29]. One possible explanation for this phenomenon is the following. During gait practice, characteristics of the motor behavior involved in gait training, such as speed and amplitude, and reinforced through cognitive engagement may serve to guide the learning of a general schema for simple motor performance (e.g. finger tapping). Brain regions, including but not limited to the hippocampus, that remain relatively unaffected in PD may contribute to these aspects of learning. Another possible explanation may be related to neuroprotection and/or increased dopaminergic availability that occur with cognitive challenge. Conversely, exercise that is unduly stressful may dampen this effect through similar but contrasting mechanisms. Finally, exercise effects on circuitry involved in cognitive and automatic components of motor movements may be involved in these more general exercise effects (see below).

Exercise and motor training have also been used to improve balance, since balance impairments lead to high morbidity in PD [30, 31]. Some exercise modalities targeting both gait and balance, also incorporate aspects of goal skill training while increasing cognitive engagement. For example, in amplitude training individuals with PD are asked to focus on generating large amplitude movements involving the whole body during the practice of a skill. This form of exercise, which incorporates a significant amount of verbal feedback and attention strategies, results in improvements in movement speed as well as amplitude that appear to be analogous to results observed with treadmill [14]. Similarly, Tai Chi focuses on dynamic postural control via weight shifting to control center of gravity during maximal movements [32]. Findings from these studies show that, following 24 weeks of twice weekly sessions, Tai Chi leads to improved stride length and maximum excursion as well as reduced falls compared to resistance training or stretching. These benefits were retained for at least 2 months [17]. Other forms of exercise approaches that combine skill practice with cognitive engagement include dance, such as the Argentinian Tango, and Boxing. Dance employs cognitive engagement through coordinating with a partner in addition to the cueing and increased attention provided by the music and rhythm [33]. Earhardt and colleagues showed that by the end of 12 months of Tango dancing individuals with PD had improved balance, walking, and dual tasking capability [34]. Finally, studies using boxing have also shown

improvement in balance and gait in individuals with PD. Boxing incorporates dynamic balance activities with multidirectional movements comparable to exercise regimens that specifically target balance practice [20].

Despite a wide spectrum of exercise modalities these studies share common elements including **goal-based practice** for the acquisition of a skill (gait and dynamic balance) in a supervised environment to facilitate **learning through feedback** (reinforcement). Feedback serves several purposes including (i) **challenging** patients beyond self-selected levels of perceived capability, (ii) maintaining **motivation**, and (iii) facilitating the **engagement** of individuals to become cognitively aware of movements that were previously automatic and unconscious. Other factors that could impact exercise effects on motor skill learning include age, cognition, and disease severity [35].

While a number of exercise studies have typically utilized instructors or physical therapists to facilitate goal-directed learning through cognitive engagement, other forms of feedback and attention strategies can also be included in the exercise regimen including virtual reality, electronic gaming (Wii for example), dual task practice and auditory and visual cueing [36, 37]. The fact that individuals with PD show retention of task benefits (especially gait and balance) after a period of time without training is consistent with motor learning and underlying neuroplasticity [38]. As stated earlier an additional benefit of these various forms of goal-based practice may include transfer from one learned behavior to another (i.e. trained behavior to a related untrained behavior).

Goal-Based plus Aerobic Exercise

A predominant feature of PD is the loss of automatic control of motor movements such as balance and gait. Automaticity is defined as the ability to perform a skilled movement without conscious attention or executive control [39] (see Box 1). Early depletion of DA, within caudal regions of the basal ganglia (dorsal striatum in rodents), results in impaired automatic circuitry. Specifically DA depletion results in increased inhibitory drive of the indirect pathway in the striatal-thalamic-cortical circuit due to reduced DA D2 receptor (DA-D_2R) activation. In the classic PD model this increased inhibitory tone induces motor impairments, including bradykinesia [40]. However, accumulating evidence suggest that neuroplasticity within this corticostriatal circuit is also impaired under conditions of DA denervation [41–44], which may give rise to an aberrant learning that further impairs automatic motor behavior [45, 46]. While a small number of studies have demonstrated that individuals with PD can acquire some degree of automaticity after simple motor skill practice,[3, 47] the loss and restoration of automaticity in PD in general remains a difficult problem to solve.

BOX 1

The Development of Automatic Movements (Automaticity)

The basal ganglia contribute to cognitive and automatic components of motor skill performance. The basal ganglia and its cortical connections also play an essential role in procedural motor learning, including the acquisition and retention of automaticity (For review see [2, 127]). Motor learning is defined as a practice related change or improvement in motor performance. The initial phase of motor skill learning involves the activation of circuits involved in reward based and goal directed learning. This circuit includes connections between the rostral, also called the associative regions of the basal ganglia (dorsal medial striatum in rodents) with the prefrontal cortex. This early phase of learning involves DA, and the DA-D1 and D2 receptors. Extended training of a motor skill involves a shift from goal directed to habitual (stimulus response) based learning. This latter phase of learning leads to decreasing activation of circuits in the prefrontal-rostral

basal ganglia and increasing activation of circuits in the caudal, also called the sensorimotor regions of the basal ganglia (dorsal lateral striatum in rodents) with the sensorimotor cortex. Dopamine and the DA-D2R are important in these latter aspects of learning. DA depletion predominant in the caudal basal ganglia of individuals with PD, leads to aberrant habitual learning and loss of automatic motor control.

Exercise studies employing both components of intensive and challenging goal-based practice in combination with aerobic training have provided some evidence of restored neuroplasticity in the striatal-thalamic-cortical-motor circuit responsible for automatic motor control. Utilizing body weight supported treadmill training. Fisher and colleagues demonstrated that individuals with early stage PD were capable of engaging in gait training at faster speeds than their self-selected pace while maintaining observationally normal execution of movement [12]. Over an 8-week period (24 sessions total) patients were asked to make corrections in posture, arm swing, and stride length, as treadmill speeds were gradually increased thus challenging problem solving operations and increasing attentional demands. Patients were also instructed to reach and maintain a metabolic equivalent (MET) of greater than 3.0 METS and/or 75% of an age-adjusted maximum heart rate (AAMHR). Along with improved gait and balance parameters, an exercise related decrease in cortico-motor excitability through an increase in cortical silent period duration (CSP) using Transcranial Magnetic Stimulation (TMS) was shown [12]. In addition, using positron emission tomography (PET)-imaging and [^{18}F]fallypride, a DA-D_2/D_3R receptor, Fisher and colleagues reported that 8 weeks of treadmill exercise was accompanied by an increase in DA-D_2R binding potential within the dorsal striatum of individuals with early stage PD [48]. Taken together changes in cortico-motor excitability with increased DA-D2 receptor availability may be associated with mitigating inappropriate inhibitory drive of the automatic circuit. Further evidence for exercise effects on neuroplasticity and circuitry involved in automatic motor control is observed in studies utilizing forced cycling [49]. Using a stationary tandem bicycle Alberts and colleagues “forced” individuals with PD to achieve pedaling rates that were 30% greater than their preferred rate thus combining aspects of cognitive engagement with aerobic training.[21, 22] This led to central changes as evidenced by improved automatic manual dexterity as well as increased connectivity between cortico-subcortical regions involved in automatic control using functional magnetic resonance imaging (fMRI).

Taken together these data support that exercise paradigms incorporating both goal-directed practice and aerobic training may work synergistically to facilitate neuroplasticity necessary for overcoming aberrant circuitry within the basal ganglia. Dual task practice without aerobic exercise provides insight into the role of cognitive motor training without an exercise component. Though studies point to preserved motor skill learning in individuals with early stage PD, fMRI studies demonstrate that the acquisition and learning of dual task training in PD is limited and occurs principally through compensatory cortical circuits. This is in contrast to healthy subjects where dual task training leads to activation of subcortical basal ganglia pathways involved in automatic motor control [3]. Additionally cognitive impairments common in early stage PD may hamper other aspects of motor skill learning, including the development of context dependency. Context dependency occurs after motor skill learning in PD. This is demonstrated through diminished performance of a newly acquired motor skill either when the augmented cues used to learn the task are removed or the environmental or practice (random versus blocked) conditions are altered [50, 51]. The beneficial role of exercise, and specifically incorporating aerobic training, may be to facilitate neuroplasticity and improve motor learning. This may occur through enhanced blood flow and alterations in the brain environment that are important for restoring physiological and structural function (see below). Consistent with this notion, studies in

animals have shown that brain changes seen in exercise are distinct from those observed in learning [52]. Only a few studies have examined the effects of aerobic training alone that incorporate limited or no aspects of skill learning [13, 22, 49]. While preliminary, these studies appear to demonstrate only modest gains in motor skill performance. In general, taken together these findings support several concepts. First that while motor learning may be limited or impaired in PD, exercise may improve both goal directed motor skill practice and ultimately through repair of the basal ganglia and its connections, automaticity. Second that the acquisition and recovery of a lost motor skill in PD through exercise requires cognitive engagement and goal-directed practice. While a few exercise studies have begun to help establish the benefits of both goal directed and aerobic training, future research is clearly needed to further establish how different exercise modalities either alone or in combination may contribute to restoration of behavioral function and automaticity in PD [53, 54].

The loss of DA in the basal ganglia not only impacts automatic behavior but also impairs cognitive (executive) functions[55, 56], particularly mental flexibility and set shifting related to alterations in fronto-striatal connectivity [57–59]. Cognition is affected early and progresses with disease severity and involves a number of neurotransmitter systems including dopaminergic, serotoninergic, noradrenergic, and cholinergic [60, 61]. In addition to improving motor performance, aerobic exercise may improve cognitive function in PD as well. It is well established that exercise leads to cognitive improvement in normal aging and Alzheimer's disease [62–64]. In these studies, fMRI data suggests that aerobic exercise may generate more efficient neuronal activity in the prefrontal regions similarly affected in PD [65, 66]. Tanaka and colleagues showed that following a 6-month aerobic exercise program, individuals with PD showed improved executive function [67]. Similarly, Cruise and colleagues showed cognitive improvement in individuals with PD, including working memory and verbal fluency with aerobic training [68–70]. While promising, these findings have been demonstrated in individuals with minimal to moderate disease severity that are able to follow the training protocol. With greater disease severity and increased disruption of corticostriatal circuitry, cognitive impairment progresses into dementia [60]. A major gap in our knowledge is to determine if the benefits of exercise can still be evident in patients with dementia and later stages of PD.

Exercise Studies in Animal Models of PD

Animal models provide an important tool to investigate the mechanisms by which exercise induces neuroplasticity in the mammalian brain. Two commonly used models of DA-depletion include the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned mouse and the 6-hydroxydopamine (6-OHDA)-lesioned rat models.[71] Both toxins lead to the destruction of nigrostriatal DA neurons and the subsequent depletion of DA in the dorsal striatum. Exercise has been shown to improve motor performance in these models, including parkinsonian features [72–77]. These models have utility in investigating the underlying molecular mechanisms involved in exercise-induced neuroplasticity in both neuroprotection and neurorestoration studies. While genetic models of familial forms of PD are now available it has not yet been established if exercise can provide protection from age-related decline in DA neurotransmission. It is anticipated that much of what we learn in toxin models will be applicable to many of the current genetic models. In the following sections we draw from the basic research literature to show how animal models provide insights and create a framework that can guide translational studies in humans with disease.

Effects of Exercise on Neuroprotection

Studies examining the potential neuroprotective effects of exercise have primarily utilized MPTP or 6-OHDA toxin models of PD. These models have been historically used to examine mechanisms of dopaminergic cell death and therapies that may slow this process.

For the purpose of investigating neuroprotective effects, forced or voluntary exercise is introduced before, during, or immediately after toxin administration. These studies have reported improvement in motor function, along with the preservation of DA neurons and the restoration of dopaminergic terminals, using tyrosine hydroxylase (TH) immunostaining, within the striatum. In these toxin models, neuroprotection has been principally attributed to an exercise-induced increase of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) or glial-derived neurotrophic factor (GDNF) [78–81]. An alternative mechanism for neuroprotection of these models may be though the exercise induced down regulation of DAT, the primary uptake system for 6-OHDA and MPTP [73, 75]. Importantly, other factors that may influence neuroprotective effects of exercise include the relative time frame of exercise initiation to toxin administration, as well as the extent (severe versus mild) of the toxin-induced injury. For example exercise initiated one week post-toxin administration fails to protect from cell death [82]. Additionally, exercise administered to an animal with a mild toxin-induced injury also fails to demonstrate neuroprotection, despite evidence of behavioral recovery. An alternative suggested process for exercise-induced recovery of behavioral function that does not involve neuroprotection is neurorestoration [75].

Effects of Exercise on Neurorestoration

In contrast to neuroprotection, neurorestoration is defined as the brain response to exercise initiated well after toxin induced cell death has been completed. These studies have shown that exercise can increase post-lesion DA neurotransmission by enhancing the vesicular release of DA and increasing synaptic occupancy and decreasing DA clearance through reduced DAT expression. In addition, exercise may alter DA receptor expression. Specifically, intensive treadmill exercise in the MPTP mouse model reverses the reduction of DA-D_2R in the dorsal striatum normally occurring following lesion. Restoration of DA-D_2R, in combination with increase DA release are known to be critically important in the later phase of motor learning when automaticity is developed [83]. Thus, exercise induced increase in DA neurotransmission along with increased DA-D_2R expression observed within the dorsal striatum of the MPTP mouse model may contribute to neuroplastic mechanisms involved in exercise-induced improvement of motor behavior and restoration of automaticity.

Exercise may modulate glutamatergic neurotransmission as well. Glutamate and its receptors are known to contribute to neuroplasticity and synaptic strengthening during the learning process. DA depletion in the striatum induces hyper-excitability in the indirect pathway in response to alterations in glutamatergic expression (receptors and neurotransmitter release) and underlies critical aspects of motor impairment in PD [84]. Studies in the MPTP mouse model have demonstrated that intensive exercise can restore aspects of glutamate receptor expression, including the glutamate receptor subtype AMPA [85]. Alterations in AMPA receptor and its subunits have been reported in many neurological disease states and are considered a viable target for drug therapy [86]. In addition to its receptors, exercise can also alter the storage and release of glutamate in presynaptic terminals that may also improve circuit function and diminish the increased inhibitory drive of the DA depleted striatum [41–44]. While additional effects of exercise on cortical and striatal function are likely to be involved, taken together these studies support that exercise through its effects on neurotransmitters and their receptors may help to restore neurophysiological properties of synapses within the injured striatum needed for normal motor learning and behavior.

Effects of Exercise on Dendritic Spines

DA-depletion in the striatum leads to the loss of dendritic spines on striatal medium spiny neurons (MSNs) in both animal models[87–89] and in PD[90]. These morphological changes

reflect the loss of synapses and hence reduction in neurotransmission not only in PD but a wide spectrum of brain disorders including Alzheimer's disease and Fragile-X syndrome [91]. Spine loss occurs predominantly on DA-D_2R-containing MSNs of the indirect pathway, reflecting the dysfunction in neurotransmission in this circuitry [92, 93].

While an important question in exercise yet to be fully addressed in PD and its animal models, studies in healthy rodents subjected to different exercise paradigms have demonstrated experience-dependent increases in dendritic spine density in a number of regions including the hippocampus and cerebellum [70, 94]. One hypothesis to be explored in models of PD is that exercise can reverse dendritic spine loss in DA-D_2R containing striatal neurons.

The Effects of Exercise on Brain Health

While exercise may have very targeted effects on specific basal ganglia circuits such as those highlighted in corticostriatal neurotransmission through glutamate and its modulation by DA, the effects of exercise also have more global effects on factors that influence general brain health. These include (i) blood flow through vascularization and angiogenesis, (ii) activation of beneficial affects of the immune system, (iii) induction of neurotrophic factors, and (iv) neurogenesis [95].

Exercise and Blood Flow

Exercise increases blood flow in the healthy brain in a wide range of animal species undergoing various exercise regimens [96, 97]. Thus exercise may facilitate neuroplasticity by influencing the vasculature of the central nervous system (CNS) through angiogenesis and altered blood brain barrier (BBB) permeability. The delivery of peripheral signaling molecules originating from muscle or adipose tissue including insulin, angiogenic factors such as vascular endothelial growth factor (VEGF), hypoxia mediated factors such as hypoxia-induced factor 1 (HIF-1), leptin, and neurotrophic factors including BDNF[98] can be promoted.

While there are currently no studies supporting the effects of exercise on the cerebral vasculature in animal models of PD, studies in healthy rodents have shown that exercise can alter hippocampal cerebral blood flow and elevate hippocampal, striatal, and substantia nigra levels of VEGF,[99–101] a mediator of angiogenesis, cell growth, and neuroprotection. Long-term exercise elicits change in regional blood perfusion of underlying motor circuits that may contribute to changes in brain connectivity related to synaptogenesis but also enhance synaptic function [102]. Interestingly, rats that have undergone aerobic exercise have an increase in the density of capillaries in the cerebral motor regions, without an increase in the number of synapses, but display improved cortical related behaviors[52]. Conversely, rats learning new motor skills have a greater number of synapses per neuron within the motor cortex, without an increase in capillary density.[96, 103, 104] This relationship between blood flow, synaptic function, and synaptogenesis underscores the complexity of mechanisms that exercise may utilize to promote brain circuitry and its function in the DA-depleted brain.

Exercise and the Immune System

The vast majority of our understanding of exercise and its effects on the immune system is derived from studies in healthy individuals, including athletes.[105] In general, studies support an exercise-induced beneficial effect of the immune system in the CNS.[106–109] Currently there are very few studies exploring the relationship between exercise and the immune system in individuals with PD. Yet it is well recognized that there is a strong immune component in PD [110]. Reports have shown that exercise (cycling) can increase plasma levels of the anti-inflammatory cytokine IL-10 in individuals with PD along with improved motor

performance.[111, 112] In addition, the cytokine IL-6, while generally considered a pro-inflammatory marker in PD that correlates with functional impairment (decreased walking speed), may in the context of exercise, play an anti-inflammatory role. Specifically, IL-6, which originates in skeletal muscle, has been shown with exercise to elicit an anti-inflammatory response that includes elevated expression of a number of factors including IL-10 and IL-1RA, and as well as inhibition of factors like tumor necrosis factor alpha (TNF-alpha).[113–115]

Another recently identified role of exercise on the function of the immune system may be through the modulation of cells of the myeloid lineage including monocytes, macrophages and CNS resident microglia.[105, 116, 117] These cells generate a vast repertoire of soluble factors including cytokines, chemokines, and growth factors. The large number of CNS resident microglia and perivascular macrophages form an integrated network in close proximity with neurons suggesting that these cells interact with numerous CNS cell types and circuits.[118] An important series of questions involving the role of exercise and the immune systems in PD include determining if pro-inflammatory stereotypic response to injury and CNS inflammation respond to distinct stimuli including exercise thus reversing their deleterious effects.[119] For example, can classically activated myeloid cells, termed M1-type cells, which are thought to contribute to the pathology of PD, be converted through exercise into M2-type myeloid cells that secrete cytokines thought to have beneficial consequences that enhance neuroplasticity. The fact that exercise has been shown to induce a conversion of M1-type to M2-type myeloid cells in adipose tissue macrophages coupled with inhibition of M1-type macrophage infiltration support this hypothesis.[120] Since peripheral macrophages have been shown to infiltrate the brain from the periphery, it is intriguing to speculate whether activated peripheral macrophages can infiltrate the CNS, and promote beneficial effects such as BDNF expression and other chemo-attractants to enhance neuroplasticity and repair at sites of injury and disease [121].

Exercise and Neurogenesis

It is well established that the adult mammalian brain including humans displays a high degree of neurogenesis, the birth of newborn cells. However, neurogenesis is limited by both age and to a very limited number of anatomical sites including the regions adjacent to the lateral ventricle and hippocampus {Feliciano, 2013 #43937}. Exercise and environmental enrichment in normal rodents have been shown to have a number of important influences on neurogenesis including increasing (i) the rate of newborn cell numbers, (ii) the fraction that differentiate into neurons, and (iii) the proportion that incorporate into neuronal circuits [122]. Currently, there are few reports in the literature directly addressing the interactions of neurogenesis, exercise, and DA-depletion in animal models. The fact that exercise increases neurogenesis in the hippocampus and subventricular zone does not necessarily translate into the potential role of exercise in increasing neuron numbers in important basal ganglia circuitry within the striatum, cortex, or thalamus [123]. While decreased gliosis is observed in these regions with exercise there are no reports supporting elevated neurogenesis in the basal ganglia with exercise. The fact that exercise have been shown to enhance the survival and integration of transplanted cells in animal models of PD reflects the importance of experience in influencing cell integration into circuits potentially meaningful for functional motor behavior [124].

In conclusion, animal models have played a major role in allowing us to better understand the underlying mechanisms of exercise and its effects on restoring motor behavior in the DA-depleted brain. The majority of findings are beginning to highlight the importance of focusing on the synapse as the critical therapeutic target. Exercise can restore important circuits in motor behavior by modulating DA and glutamate neurotransmission as well as influencing general brain health.

Overall Conclusions and Impact on Clinical Care

Over the last decade, a primary focus of neuro-rehabilitation has been to alleviate the motor deficits of PD through exercise [10, 125]. The general idea is that exercise incorporating goal based motor skill learning improves motor skill performance in PD and that this may be enhanced through cognitive engagement. More importantly, studies suggest that combining goal based with aerobic training the possibility for improving automatic with cognitive motor control may be possible and thus reduce the attentional demands of consciously processing behaviors such as walking.[126] Aerobic exercise may contribute to more general improvement in brain health and repair, through the recruitment of the immune system and/or increasing blood flow and trophic factor signaling as examples. These aerobic exercise benefits are likely to impact connectivity through *priming* the brain environment conducive for promoting synaptic neuroplasticity leading to altered circuitry. This review raises another fundamental question, which is can an individual learn themselves out of PD? Based on published studies, and current understanding of the detrimental effects of DA loss on brain circuitry, the most obvious response is no. However, exercise studies may be pointing towards potential and important neuroplastic mechanisms that through restoring some degree of basal ganglia circuitry provide a window of opportunity to improve motor learning and behavioral performance.

Based on published studies in both animals and individuals with PD, exercise has been shown to be important in improving motor function in PD and to facilitate neuroplasticity. Future research will continue to add to exercise related mechanisms of neuroplasticity. Thus, exercise should be considered an essential treatment for PD, particularly in individuals with mild to moderate disease. Ongoing research is required, however, to address large gaps in knowledge. Specifically studies with non-invasive neuroimaging are still needed to discern the relative contribution of either goal based or aerobic exercise alone or in combination and their effect on brain function, connectivity and motor behavior. In addition, the important role of exercise in individuals with more advanced disease and with more severe cognitive impairment is needed. By elucidating the precise exercise-induced mechanisms of neuroplasticity, we can begin to better understand its role in disease modification and identify novel therapeutic targets including pharmacological approaches to supplement exercise for improved treatment and potentially a cure in PD.

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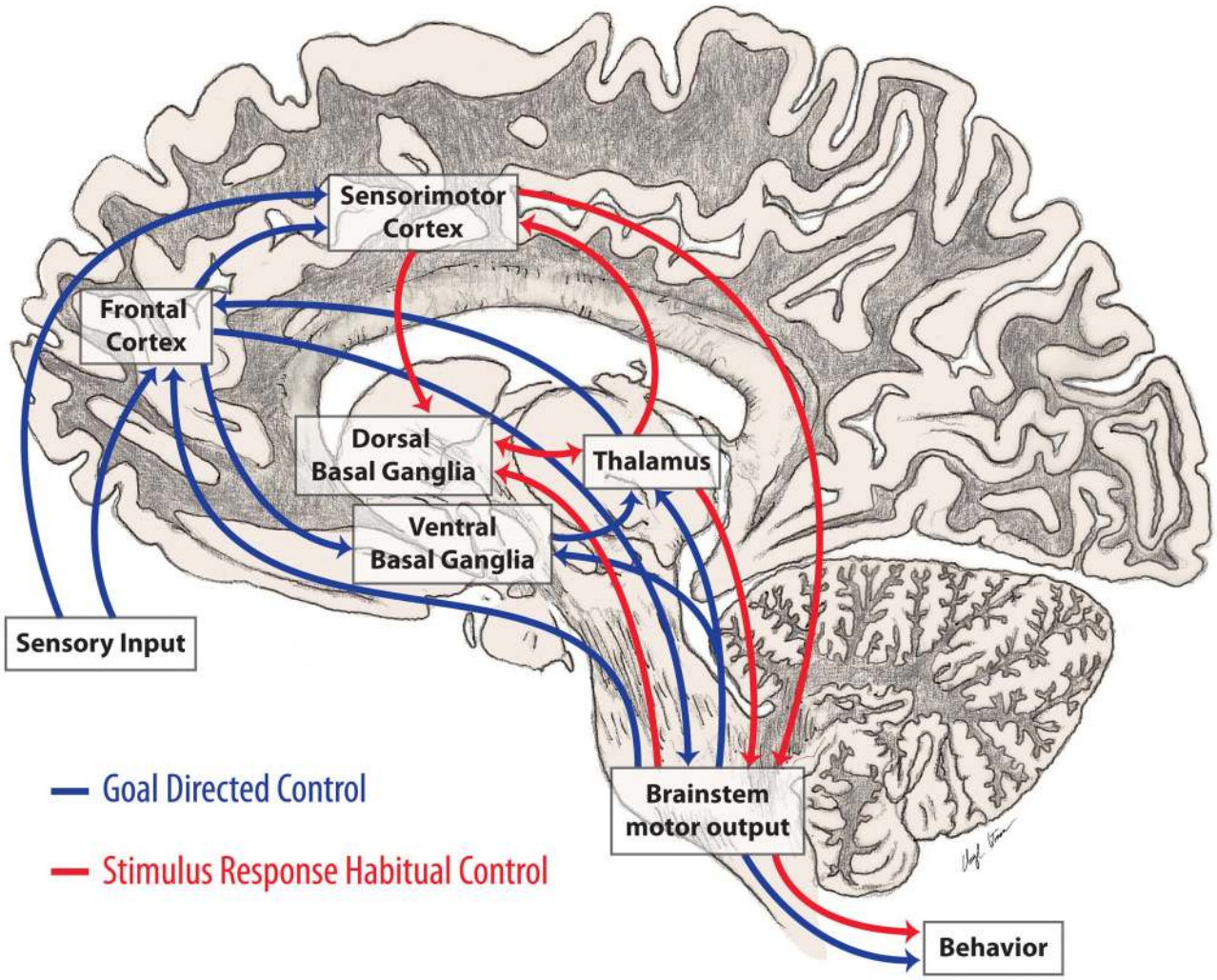

Figure 1. Cognitive and Automatic Motor Control

Motor control incorporates multiple cortical and subcortical structures. Most important are the connections between the basal ganglia and cortex that are involved in cognitive and automatic aspects of motor control. In PD, loss of DA in the caudal basal ganglia leads to impaired automatic movements involving circuits important in stimulus based habitual learning (red arrows) and over-reliance on cognitive components of motor control and circuits involved in reward based learning (blue arrows).

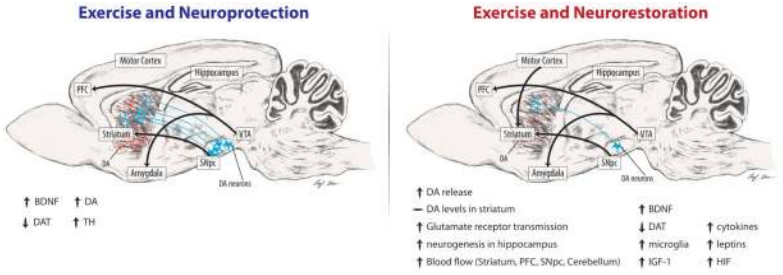

Figure 2. Exercise and Neuroprotection and Neurorestoration in Rodent Models of PD

The figure highlights some reported benefits of the effects of exercise in rodent PD neurotoxin models. The left panel indicates exercise effects when exercise is delivered either before or during the period of toxin-induced (6-OHDA, or MPTP) dopaminergic cell death. Intensive exercise promotes elevation of neurotrophic factors, such as BDNF, and protects from toxin-induced striatal DA depletion and cell loss of SNpc neurons. These findings are consistent with epidemiological data reporting the effect of intensive exercise in lowering the risk for PD. The right panel indicates exercise effects when exercise is administered days to weeks after toxin-induced dopaminergic cell death. Studies suggest that intensive exercise may strengthen motor (dorsal basal ganglia) circuits and behavioral performance through mechanisms that include improved DA and glutamate neurotransmission and global brain health. These data are consistent with the potential role of exercise in modifying the course of PD.

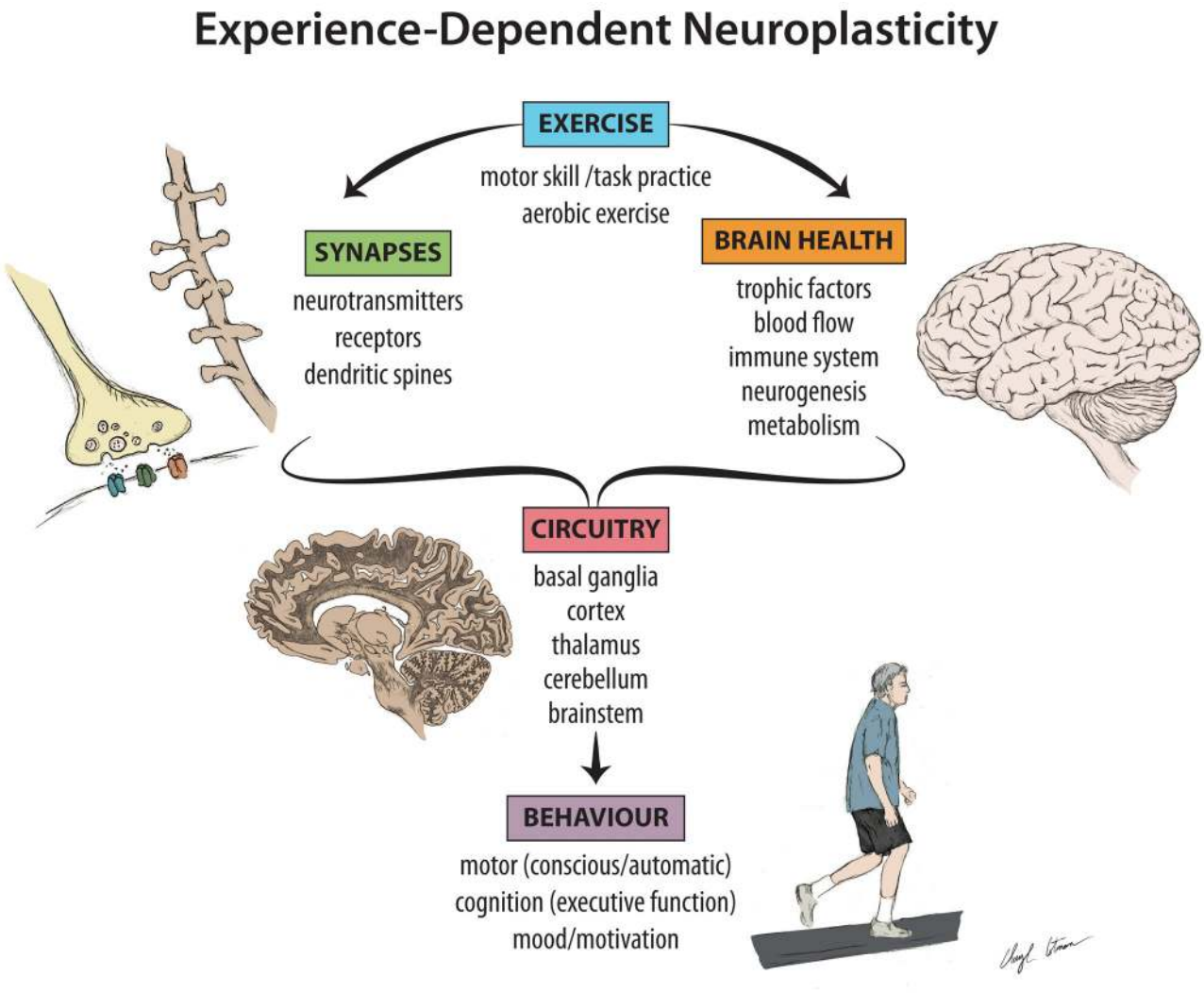

Figure 3. Exercise and Neuroplasticity in PD

Clinical and basic research studies support the effects of exercise on neuroplasticity in PD. Neuroplasticity is a process by which the brain encodes experiences and learns new behaviors and is defined as the modification of existing neural networks by adding or modifying synapses. Evidence is accumulating that both goal directed and aerobic exercise may strengthen and improve motor circuitry through mechanisms that include but are not limited to alterations in DA and glutamate neurotransmission, as well as structural modifications of synapses. In addition, exercise may promote neuroprotection of substantia nigra neurons and their existing connections. Finally, exercise-induced alterations in blood flow and general brain health may promote conditions for neuroplasticity important for facilitating motor skill learning, including cognitive and automatic motor control and overall behavioral performance. While more studies are clearly needed, taken together these findings are supportive of a disease modifying effect of exercise in PD.