Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease

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Exercise interventions in individuals with Parkinson's disease incorporate goal-based motor skill training to engage cognitive circuitry important in motor learning. With this exercise approach, physical therapy helps with learning through instruction and feedback (reinforcement) and encouragement to perform beyond self-perceived capability. Individuals with Parkinson's disease become more cognitively engaged with the practice and learning of movements and skills that were previously automatic and unconscious. Aerobic exercise, regarded as important for improvement of blood flow and facilitation of neuroplasticity in elderly people, might also have a role in improvement of behavioural function in individuals with Parkinson's disease. Exercises that incorporate goal-based training and aerobic activity have the potential to improve both cognitive and automatic components of motor control in individuals with mild to moderate disease through experience-dependent neuroplasticity. Basic research in animal models of Parkinson's disease is beginning to show exercise-induced neuroplastic effects at the level of synaptic connections and circuits.

Introduction

Parkinson's disease is a progressive neurodegenerative disorder that is characterised by the loss of dopamine caused by degeneration of substantia nigra pars compacta dopaminergic neurons. Characteristic features of Parkinson's disease include motor impairment (bradykinesia, rigidity, tremor, gait dysfunction, and postural instability), cognitive impairment (frontal lobe executive dysfunction), and mood disorders. In healthy individuals, motor performance depends on the interaction between automatic (unconscious) and volitional (cognitive) control of movement.[1,2] Conversely, in Parkinson's disease, the early and preferential loss of dopamine in the caudal regions of the basal ganglia (dorsal regions in rodents) leads to diminished automatic and increased cognitive control of movements that include frontal lobe circuitry. Consequently, individuals with Parkinson's disease need to handle and sustain a larger cognitive load to execute either motor or cognitive (eg, working memory) tasks.[2,3] Dopamine replacement therapy alleviates some motor features of Parkinson's disease, but with less beneficial effects observed on cognitive function.[4] In the past decade, mounting evidence has accumulated for the role of exercise in the improvement of motor performance, which might include facilitation of both the cognitive and automatic control of movement.

Epidemiological studies have supported a link between strenuous exercise and reduced risk for Parkinson's disease.[5,6] Additionally, many studies and published reviews on exercise in normal ageing and in Parkinson's disease provide the background that supports the benefits of exercise, physical activity, and environmental enrichment.[7–9] Although research into exercise and Parkinson's disease is continuing, the overall purpose of this Review is to draw attention to published studies in human beings and animal models of Parkinson's disease that might support the beneficial effects of exercise through neuroplastic mechanisms. First, we introduce the notion that exercise, through goal-based and aerobic training, might enhance neuroplasticity, which is important for driving motor and cognitive behavioural improvement in Parkinson's disease. Second, we report findings from studies of animals that show the neuroprotective and neurorestorative capacity of intensive exercise. Finally, we present data on the potential role of exercise in overall brain health that might influence the structural (connectivity) and physiological properties of brain function.

Neuroplasticity is a process by which the brain encodes experiences and learns new behaviours and is defined as the modification of existing neural networks by addition or modification of synapses in response to changes in behaviour or environment, which can encompass exercise.[10] 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.[11] Importantly, exercise-induced benefits on brain health (ie, blood flow, trophic factors, and the immune system) might help to create the optimum milieu needed for neuroplasticity to happen in the injured brain. We highlight exercise approaches used to drive behavioural improvement in individuals with Parkinson's disease and findings in animal studies that support the potential for targeting neuroplasticity.

Exercise and Parkinson's disease

Goal-based exercise

Exercise is the general term for physical activity that is planned, structured, and repetitive for the purpose of conditioning any part of the body. In the past decade, an important direction in the specialty of neurorehabilitation and exercise research in Parkinson's disease has been the application of exercise that incorporates goal-based motor training for the improvement or recovery of impaired or lost motor function. This exercise approach can be termed goal based because it shares fundamental characteristics with other forms of goal-based learning, which is the practice of certain activities that lead to improved

performance. In Parkinson's disease, exercises are often designed or implemented to engage individuals in the practice of motor activities for the improvement of specific motor skills, such as gait and balance. Accordingly, in Parkinson's disease the intent is to use exercises that incorporate parameters important for experience-dependent neuroplasticity that include intensity, repetition, specificity, difficulty, and complexity of practice. These same practice parameters have been shown to be important for neurorehabilitation of stroke and traumatic brain injury.[10] Another component of exercise in Parkinson's disease is cognitive engagement. Prefrontal cognitive circuits are involved in early phases of motor learning and become actively recruited in the early stages of Parkinson's disease (figure 1). Cognitive engagement might be enhanced by feedback (eg, verbal or proprioceptive), attentional demand through cueing or dual tasking (eg, performance of two motor or motor and cognitive tasks simultaneously), and by motivation (eg, reward). We present examples of exercises used in individuals with Parkinson's disease that have incorporated these ideas. These studies have used many different exercise modalities that include, but are not restricted to, treadmill training,[12,13] amplitude training,[14,15] Tai Chi,[16,17] tango dancing,[18,19] boxing,[20] and forced cycling.[21,22]

In Parkinson's disease, exercise is often used to improve gait and balance. Gait impairment includes reduction in speed and step length and increased stride length variability and can affect an individual's quality of life.[23] Treadmill exercise is generally used to improve gait capacity because the treadmill can be easily adjusted for speed (and gradient), thereby increasing intensity and challenge of gait practice. Studies of treadmill exercise (with or without bodyweight support, typically used for safety) have shown that through exercise practice, individuals with mild to moderate Parkinson's disease can improve gait performance, including velocity, stride length, cadence, postural stability, gait rhythmicity, and joint excursion.[24,25] Although most treadmill studies have reported these benefits, a few studies have shown that despite a similar period of practice, no substantial improvement in gait capacity happened.[26] One possible explanation for this discrepancy in gait outcomes could be differences in the amount of feedback and cognitive engagement during practice.[27] Another possible confounder is severity of disease, which might affect cognition. In studies in which improvement of motor function is shown, the challenge to repetitively control dynamic balance in conjunction with the proprioceptive feedback from the moving treadmill are probably important to drive learning. Additionally, verbal feedback or cues that draw attention to the motor task practice might ease cognitive engagement to help consolidation of the learned behaviour that leads to strengthening or modification of existing motor circuits. In treadmill training, the contribution of both repetitive practice and cognitive engagement might contribute to the immediate (upon completion of 4 to 12 weeks of training) and long-term retention (lasting several months) of gait improvements reported after cessation of treadmill exercise.[24,28,29] Benefits of treadmill training, which predominantly engage lower extremity practice, also translate to improvements in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score, a scale for the assessment of simple motor repetitive tasks (eg, finger and foot tapping) in individuals with Parkinson's disease.[28,29] One explanation for the transfer of the benefits of exercise might be related to exercise effects on neuroprotection of dopaminergic neurons or more global effects on the repair or strengthening of overlapping motor circuitry involved in cognitive and automatic components of motor movements.

Many exercise modalities aim to improve balance because balance impairments lead to high morbidity in individuals with Parkinson's disease.[30,31] Similar to treadmill exercise, these modalities incorporate aspects of goal-based skill training while helping with cognitive engagement. For example, in amplitude training, individuals with Parkinson's disease are asked to focus on the generation of large amplitude movements involving the whole body during the practice of a skill. This form of exercise, which incorporates a substantial amount of verbal feedback and attention strategies, results in improvements in both movement speed and amplitude that seem to be analogous to results observed

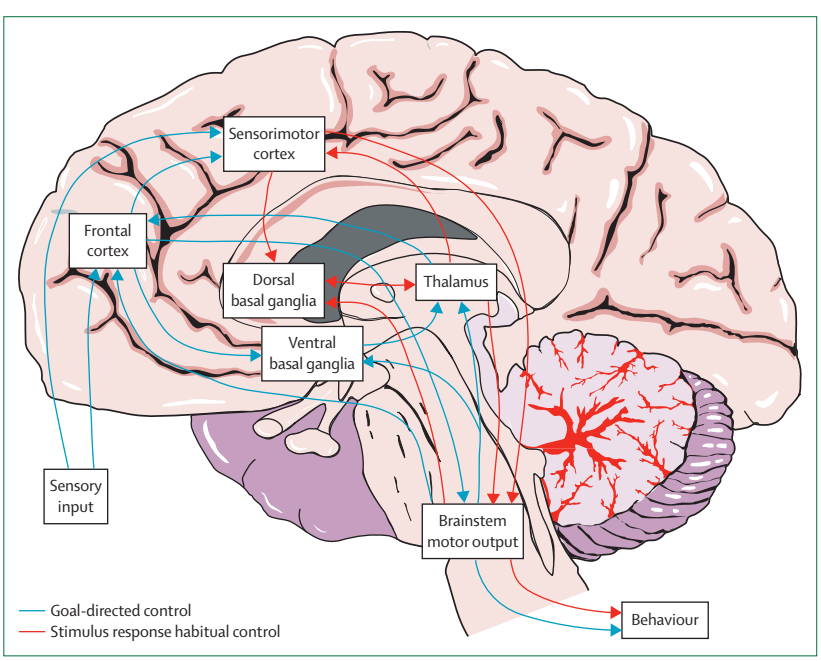

Figure 1: **Cognitive and automatic motor control**
Motor control incorporates many cortical and subcortical structures. Most important are the connections between the basal ganglia and cortex, which are involved in cognitive and automatic aspects of motor control. The blue arrows represent volitional or cognitive (frontal) circuits. The red arrows represent the automatic (unconscious or habitual) circuits. In Parkinson's disease, loss of dopamine in the caudal basal ganglia leads to impaired automaticity involving circuits important in stimulus-based habitual learning (red arrows) and over-reliance on cognitive (volitional) circuits involved in reward-based learning (blue arrows).

with treadmill exercise.[14] Likewise, Tai Chi focuses on dynamic postural control via exercises that involve weight shifting. Individuals also become cognitively engaged while practising the control of their centre of gravity during maximal movements.[32] Findings from these studies show that after 24 weeks of twice weekly sessions, Tai Chi leads to improved stride length and maximum excursion and reduced falls compared with 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 uses cognitive engagement through coordination with a partner in addition to the cueing and increased attention provided by the music and rhythm.[33] Duncan and Earhardt[34] showed that after 12 months of tango dancing, individuals with Parkinson's disease had improved balance, walking, and dual tasking capability. Studies of boxing in individuals with Parkinson's disease have also shown improvement in balance and gait. Boxing incorporates dynamic balance activities with multidirectional movements similar to exercise regimens that specifically target balance practice.[20] Similar to the effects of treadmill exercise on motor learning, individuals with Parkinson's disease show retention of task benefits (especially gait and balance) after a period of time after completion of these exercise modalities.[35] As stated earlier, an additional benefit of these various forms of goal-based practice often includes improvement in other simple motor behaviours, such as finger tapping (as measured through the UPDRS motor subscale), which might occur through the more general effects of exercise on shared motor circuitry.

Thus, a wide range of exercise modalities used in individuals with Parkinson's disease have common elements including goal-based practice for the acquisition of a skill (eg, gait and dynamic balance) in a supervised environment to ease learning through feedback (reinforcement). Feedback challenges patients beyond self-selected levels of perceived capability, maintains motivation, and helps to engage individuals to become cognitively aware of movements that were previously automatic and unconscious. These exercise studies, although in progress, provide a useful platform for the investigation of other parameters of practice in individuals with Parkinson's disease that might contribute to experience-dependent neuroplasticity and motor learning. For example, many studies of exercise have investigated additional strategies to enhance learning through electronic gaming (eg, with the Wii), virtual reality, dual task practice, and auditory and visual cueing.[36,37] Although the ability of exercise to affect motor performance through goal-directed exercise in individuals with Parkinson's disease is encouraging, major gaps remain in understanding the contribution of ageing, cognitive impairment, and disease severity in the restriction of the effectiveness of exercise.[38]

Panel: The development of automatic movements

The basal ganglia contribute to cognitive (volitional) and automatic (unconscious) components of motor skill performance. The basal ganglia and its cortical connections also play an essential part in procedural motor learning, including the acquisition and retention of automaticity.[2,40] 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) and the prefrontal cortex. This early phase of learning involves dopamine and the dopaminergic D1 and D2 receptors. Extended training of a motor skill involves a shift from goal-directed to habitual-based (ie, stimulus response) learning. This latter phase of learning leads to decreased activation of circuits in the prefrontal-rostral basal ganglia and increased activation of circuits in the caudal, also called the sensorimotor, regions of the basal ganglia (dorsal lateral striatum in rodents) and the sensorimotor cortex. Dopamine and the dopamine D2 receptor are important in these latter aspects of learning. Dopamine depletion, predominant in the caudal basal ganglia of individuals with Parkinson's disease, leads to aberrant habitual learning and loss of automatic motor control.

Goal-based plus aerobic exercise

The previous section highlighted the importance of goal-based exercise. In this section we discuss the additional benefits of aerobic exercise—defined as vigorous and sustained activity—in combination with goal-based exercise. The combination of these two types of exercise might provide synergistic benefits not seen with either alone.[39]

A predominant feature of Parkinson's disease is the loss of automaticity of movements such as balance and gait. Exercise has been shown to promote neuroplasticity in ageing healthy individuals and might help restore automaticity in individuals with Parkinson's disease. Automaticity is defined as the ability to perform a skilled movement without conscious attention or volitional control (panel).[41] Early depletion of dopamine within caudal regions of the basal ganglia (dorsal striatum in rodents) results in impaired automatic circuitry. This circuitry involves a balance between the two major afferent basal ganglia projections, the striatonigral (D1 receptor containing or direct) and striatopallidal (D2 receptor containing or indirect) pathways.[42] Specifically, depletion of dopamine results in increased inhibitory drive of the indirect pathway in the striatal-thalamic-cortical circuit attributable to reduced dopamine D2 receptor activation. In the classic model of Parkinson's disease, this increased inhibitory tone induces motor impairments, including

bradykinesia.[43] Furthermore, accumulating evidence suggests that neuroplasticity within this corticostriatal circuit is also impaired under conditions of dopamine denervation,[44–47] which might give rise to aberrant learning that further impairs automatic motor behaviour.[48,49]

Although some studies have shown that individuals with Parkinson's disease can acquire some degree of automaticity after motor skill practice[3,50] (where automaticity is defined by the ability to dual task), the role of exercise in driving neuroplasticity of circuits involved in automaticity (eg, the striatal-thalamic-cortical circuit) is under investigation. Studies of healthy elderly people and individuals with Alzheimer's disease have supported the idea that aerobic exercise might be necessary to promote neuroplasticity as part of the restoration of automaticity in Parkinson's disease.[51] 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. This amount of intensity typically targets a goal of 60% to 85% maximum heart rate. The effect of exercise on restoration of automaticity in Parkinson's disease and the role of an aerobic component require further research. However, some studies are beginning to address this fundamental question.

Accumulating evidence exists that exercise using both components of intensive and challenging goal-based practice in combination with aerobic training can to some degree restore neuroplasticity in the striatal-thalamic-cortical-motor circuit responsible for automaticity. For example, using body-weight-supported treadmill training, Fisher and colleagues[12] made individuals with early-stage Parkinson's disease engage in gait training at speeds faster than their self-selected pace while maintaining observationally normal execution of movement. Over 8 weeks (24 sessions), as treadmill speeds were gradually increased, researchers asked patients to make corrections in posture, arm swing, and stride length, thus challenging problem-solving operations and increasing attentional demands. Patients reached and maintained a metabolic equivalent of greater than 3·0 Metabolic Equivalent of Task, or 75% of an age-adjusted maximum heart rate. In this study, patients had improved gait and balance parameters, along with a decrease in corticomotor excitability as measured by an increase in the duration of the cortical silent period on transcranial magnetic stimulation.[12] Additionally, using PET imaging with ^{18}F-fallypride, a ligand for dopamine D2/D3 receptors, this same group reported an exercise-induced increase in dopamine D2 receptor binding potential in the caudal basal ganglia of individuals with early-stage Parkinson's disease.[52] These changes in corticomotor excitability with increased dopamine D2 receptor availability might contribute to the mitigation of inappropriate inhibitory drive of the indirect pathway and circuits involved in automaticity. Further supportive evidence for the effects of exercise on neuroplasticity and automaticity has been provided by studies using forced cycling.[53] With a stationary tandem bicycle, Alberts and colleagues[21] forced individuals with Parkinson's disease to achieve pedalling rates that were 30% greater than their preferred rate, thus combining aspects of cognitive engagement with aerobic training.[22] This exercise led to central changes as shown by improved automatic manual dexterity and increased connectivity between corticosubcortical regions that underlie automaticity on functional MRI.

Taken together, these data suggest that exercise paradigms incorporating both goal-based practice and aerobic training might work synergistically to promote neuroplasticity necessary to overcome 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. Although results show preserved motor skill learning in individuals with early-stage Parkinson's disease, studies that use functional MRI show that the acquisition and learning of dual task training in individuals with Parkinson's disease are restricted and happen mainly through compensatory cortical circuits.[3] This is by contrast with healthy individuals in whom dual task training leads to activation of subcortical basal ganglia pathways involved in automatic motor control.[3] Additionally, cognitive impairments common in early-stage Parkinson's disease might hamper other aspects of motor skill learning, including the development of context dependency, defined as the process by which the environment affects cognitive processing and recall and learning of specific motor skills. Context dependency is evident even in the early stages of Parkinson's disease.[54] This finding is shown 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 *vs* blocked) conditions are changed.[54,55]

The beneficial role of exercise, and specifically the incorporation of aerobic training, might promote neuroplasticity and improve motor learning. This process can arise through enhanced blood flow and changes in the brain environment, which are important in the restoration of physiological and structural function. Consistent with this notion, findings from studies in animals have shown that changes to the brain as a result of exercise are distinct from those recorded in learning.[56] Only a few studies have assessed the effects of aerobic training alone that incorporates little or no aspects of skill learning.[13,22,53] Although preliminary, findings from these studies seem to show only modest gains in motor skill performance if aerobic exercise is used without the additional benefits of goal-based exercise. Taken together, these data suggest that although motor learning might be restricted or impaired in the dopamine-depleted state, exercise that uses both aerobic and goal-based strategies might provide synergistic mechanisms to improve basal

ganglia function and its connections. Future research is needed to further identify how different exercise modalities, either alone or in combination, contribute to restoration of behavioural function and automaticity in Parkinson's disease.[57,58]

Effects of exercise on cognition

The loss of dopamine in the basal ganglia not only affects automaticity but also impairs cognitive (executive) functions,[59,60] especially mental flexibility and set shifting related to alterations in frontostriatal connectivity.[61–63] Cognition is affected early and progresses with disease severity and affects many neurotransmitter systems including dopaminergic, serotoninergic, noradrenergic, and cholinergic systems.[64,65] In addition to improvement of motor performance, aerobic exercise might also improve cognitive (executive) function in individuals with Parkinson's disease. The finding that exercise leads to cognitive improvement in normal ageing and Alzheimer's disease is well established.[66–68] In these studies, functional MRI data suggest that aerobic exercise leads to more efficient neuronal activity in the prefrontal regions similarly affected in Parkinson's disease.[69,70] Tanaka and colleagues[71] concluded that after a 6-month aerobic exercise programme, individuals with Parkinson's disease showed improved executive function. Likewise, in a study of aerobic training in individuals with Parkinson's disease Cruise and colleagues[72] reported improvement in cognitive functions such as working memory] and verbal fluency.[73,74] These findings are promising, but have been shown in individuals with minimum to moderate disease severity and who are able to follow the training protocol. With increased disease severity and increased disruption of corticostriatal circuitry, cognitive impairment progresses to dementia.[64] An important gap in our knowledge is whether the benefits of exercise are still evident in patients with dementia and later stages of Parkinson's disease.

Exercise studies in animal models of Parkinson's disease

Animal models provide an important method to investigate the mechanisms by which exercise induces neuroplasticity in the mammalian brain. Two commonly used models of dopamine depletion are the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned mouse model and the 6-hydroxydopamine (6-OHDA)-lesioned rat model.[75] Both toxins lead to the destruction of nigrostriatal dopamine neurons and the subsequent depletion of dopamine in the dorsal striatum. Exercise improves motor performance, including parkinsonian features, in these models.[76–81] These models are useful to assess the underlying molecular mechanisms involved in exercise-induced neuroplasticity in both neuroprotection and neurorestoration studies (figure 2). Genetic models of familial forms of Parkinson's disease are available, but whether exercise can provide protection from age-related deterioration in dopamine neurotransmission is unknown. Much of what we learn in toxin models is predicted to be applicable to many of the present 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 on the potential neuroprotective effects of exercise have mainly used MPTP or 6-OHDA toxin models of Parkinson's disease. These models have been traditionally

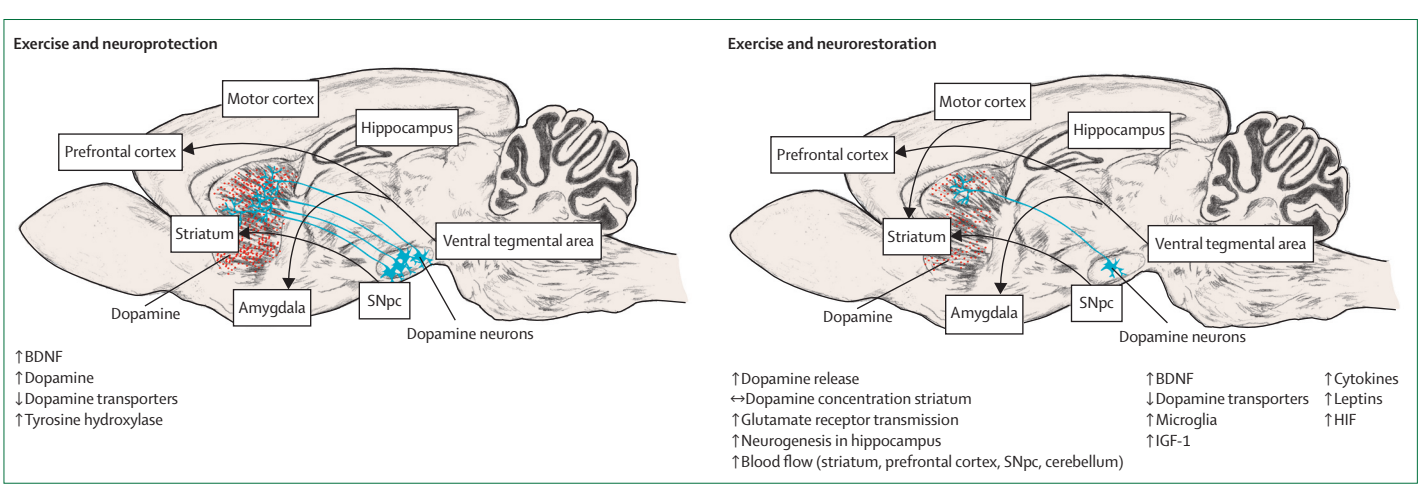

Figure 2: **Exercise, neuroprotection, and neurorestoration in rodent models of Parkinson's disease**
Reported benefits of the effects of exercise in rodent Parkinson's disease neurotoxin models. The left panel shows exercise effects when an animal exercises either before or during the period of toxin-induced (6-hydroxydopamine or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) dopaminergic cell death. Intensive exercise promotes elevation of neurotrophic factors, such as BDNF, and protects from toxin-induced striatal dopamine depletion and cell loss of substantia nigra pars compacta neurons. The right panel shows exercise effects when an animal exercises days to weeks after toxin-induced dopaminergic cell death. Data suggest that intensive exercise can strengthen motor (dorsal basal ganglia) circuits and behavioural performance through mechanisms that include improved dopamine and glutamate neurotransmission and global brain health. The thick black lines indicate dopaminergic circuits from the midbrain. The thin blue lines indicate the nigrostriatal pathway, which is robust in the intact (left) brain but depleted in the lesioned (right) brain. HIF=hypoxia-induced factor 1. IGF-1=insulin-like growth factor 1. SNpc=substantia nigra pars compacta.

used to examine mechanisms of dopaminergic cell death and treatments that can slow this process. To investigate neuroprotective effects, forced or voluntary exercise is introduced before, during, or immediately after toxin administration. These studies have reported an improvement in motor function, along with the preservation of dopamine neurons and the restoration of dopaminergic terminals in the striatum with tyrosine hydroxylase immunostaining. In these toxin models, neuroprotection has been attributed mainly to an exercise-induced increase of neurotrophic factors such as BDNF or GDNF.[82–85] An alternative mechanism for neuroprotection in these models might be the exercise-induced downregulation of the dopamine transporter (DAT), the main uptake system for 6-OHDA and MPTP.[77,79] Other factors that might influence the neuroprotective effects of exercise include the relative timeframe of exercise initiation to toxin administration and the extent (severe *vs* mild) of the toxin-induced injury. For example, exercise initiated 1 week after toxin is given fails to protect from cell death.[86] Additionally, despite evidence of behavioural recovery, exercise in an animal with a mild toxin-induced injury also fails to induce neuroprotection. Neurorestoration is suggested as an alternative process for exercise-induced recovery of behavioural function that does not involve neuroprotection.[79]

Effects of exercise on neurorestoration

By contrast with neuroprotection, the neurorestorative effects of exercise are defined as the brain's response to exercise when initiated well after the completion of toxin-induced cell death. Studies have shown that exercise can increase post-lesion dopamine neurotransmission by the enhancement of vesicular release of dopamine, increase of synaptic occupancy, and decrease of dopamine clearance through reduced DAT expression. Additionally, exercise might change the expression of the dopamine receptor. Specifically, intensive treadmill exercise in the MPTP mouse model reverses the reduction of dopamine D2 receptors in the dorsal striatum, which usually happens after lesioning.[76] Restoration of dopamine D2 receptors, in combination with increased release of dopamine, is crucially important in the late phase of motor learning when automaticity is developed.[87] Thus, exercise-induced increase in dopamine neurotransmission along with increased dopamine D2 receptor expression recorded in the dorsal striatum of the MPTP mouse model[76] might contribute to neuroplastic mechanisms involved in exercise-induced improvement of motor behaviour and restoration of automaticity.

Exercise might also modulate glutamatergic neurotransmission. Glutamate and its receptors contribute to neuroplasticity and synaptic strengthening during the learning process. Depletion of dopamine in the striatum induces hyperexcitability in the indirect pathway in response to alterations in glutamatergic receptor expression and neurotransmitter release and underlies crucial aspects of motor impairment in individuals with Parkinson's disease.[88] Studies in the MPTP mouse model have shown that intensive exercise can restore aspects of glutamate receptor expression, including the expression of AMPA receptors.[89] Changes to the AMPA receptor and its subunits have been reported in many neurological disease states and are deemed a viable target for drug treatment.[90] In addition to its effects on glutamate receptors, exercise can also alter the storage and release of glutamate in presynaptic terminals, which might also improve circuit function and diminish the increased inhibitory drive of the dopamine-depleted striatum.[44–47] Although additional effects of exercise on cortical and striatal function are probably involved, taken together, these data suggest that exercise (through its effects on neurotransmitters and their receptors) might help to restore neurophysiological properties of synapses within the injured striatum that are needed for normal motor learning and behaviour.

Effects of exercise on dendritic spines

Depletion of dopamine in the striatum leads to the loss of dendritic spines on striatal medium spiny neurons in animal models[91–93] and in individuals with Parkinson's disease.[94] These morphological changes are indicative of the loss of synapses and hence reduction in neurotransmission not only in Parkinson's disease, but in a wide range of brain disorders including Alzheimer's disease and fragile X syndrome.[95] Spine loss arises predominantly on striatal medium spiny neurons of the indirect pathway that contain dopamine D2 receptors, consistent with the dysfunction in neurotransmission in this circuitry.[96,97]

Although the effects of exercise on dendritic spines in Parkinson's disease and in animal models are yet to be fully addressed, studies in healthy rodents subjected to different exercise regimens have shown experience-dependent increases in dendritic spine density in several regions including the hippocampus and cerebellum.[74,98] One hypothesis to be explored in models of Parkinson's disease is that exercise can reverse dendritic spine loss in striatal neurons containing dopamine D2 receptors.

Effects of exercise on brain health

Although exercise might have very targeted effects on specific basal ganglia circuits (eg, in corticostriatal neurotransmission through glutamate and its modulation by dopamine), exercise can also have more global effects on factors that influence general brain health.These include blood flow through vascularisation and angiogenesis, activation of beneficial effects of the immune system, induction of neurotrophic factors, and neurogenesis.[99]

Exercise and blood flow

Exercise increases blood flow in the healthy brain in several animals undergoing various exercise regimens.[100,101]

Thus, exercise might promote neuroplasticity by affecting the vasculature of the CNS through angiogenesis and altered blood–brain barrier permeability. Exercise, through increasing blood flow, might also promote the delivery of peripheral signalling molecules originating from muscle or adipose tissue, including insulin; angiogenic factors such as VEGF; hypoxia-mediated factors such as hypoxia-induced factor 1; leptin; and neurotrophic factors including BDNF.[102]

Few studies support the effects of exercise on cerebral vasculature in animal models of Parkinson's disease. Studies in healthy rodents have shown that exercise can alter hippocampal cerebral blood flow and increase hippocampal, striatal, and substantia nigra levels of VEGF,[103–105] a mediator of angiogenesis, cell growth, and neuroprotection. One study in 6-OHDA rats showed that exercise elicits changes in regional blood perfusion of underlying motor circuits, which might contribute to changes in brain connectivity related to synaptogenesis and circuitry.[106] Rodents that have undergone aerobic exercise have an increased density of capillaries in the cerebral motor regions and show improved cortical-related behaviours, without an increase in the number of synapses.[56] Conversely, rodents learning new motor skills have an increased number of synapses per neuron within the motor cortex, without an increase in capillary density.[100,107,108] This relation between blood flow, synaptic function, and synaptogenesis underscores the complexity of mechanisms through which exercise might promote brain circuitry and its function in the dopamine-depleted brain.

Exercise and the immune system

Most of our understanding of exercise and its effects on the immune system is derived from studies in healthy individuals, including athletes.[109] Generally, studies support an exercise-induced beneficial effect of the immune system in the CNS.[110–113] Very few studies exploring the association between exercise and the immune system in individuals with Parkinson's disease have been done. However, a strong immune component in Parkinson's disease exists.[114] Exercise (eg, cycling) can increase plasma concentrations of the anti-inflammatory cytokine interleukin 10 in individuals with Parkinson's disease and also improve motor performance.[115,116] Additionally, the cytokine interleukin 6, although generally regarded as a pro-inflammatory marker in Parkinson's disease that is associated with functional impairment (eg, decreased walking speed), might have an anti-inflammatory role in the context of exercise. Specifically upon exercise, interleukin 6, which originates in skeletal muscle, elicits 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 tumour necrosis factor alpha.[117–119]

Another recently identified role of exercise on the function of the immune system might be through the modulation of cells of the myeloid lineage including monocytes, macrophages, and CNS resident microglia.[109,120,121] 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 close to neurons, suggesting that these cells interact with numerous CNS cell types and circuits.[122] Important questions about the role of exercise and the immune system in individuals with Parkinson's disease include whether the pro-inflammatory stereotypical response to injury and CNS inflammation can be affected by distinct stimuli such as exercise, thus reversing their deleterious effects.[123] For example, can classically activated myeloid cells, termed M1-type cells, which are believed to contribute to the pathology of Parkinson's disease, be converted through exercise into M2-type myeloid cells that secrete cytokines believed to have beneficial consequences that enhance neuroplasticity? The finding that exercise induces a conversion of M1-type to M2-type myeloid cells in adipose tissue macrophages coupled with inhibition of M1-type macrophage infiltration supports this hypothesis.[124] Because peripheral macrophages 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 the expression of BDNF and other chemo-attractants to enhance neuroplasticity and repair at sites of injury and disease.[125]

Exercise and neurogenesis

The adult mammalian brain including that of human beings shows a high degree of neurogenesis. However, neurogenesis is restricted by both age and to a very limited number of anatomical sites including the regions adjacent to the lateral ventricle and hippocampus.[126] Exercise and environmental enrichment in normal rodents have several important effects on neurogenesis: increasing the rate of newborn cell numbers and their survival and affecting the proportion that differentiate into neurons and the proportion that is incorporated into neuronal circuits.[127] Few reports exist that directly address the interactions of neurogenesis, exercise, and dopamine 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.[128] Although decreased gliosis is recorded in these regions with exercise,[129] no reports support increased neurogenesis in the basal ganglia with exercise. The fact that exercise enhances the survival and integration of transplanted cells in animal models of Parkinson's disease is indicative of the importance of experience in influencing cell integration into circuits that are potentially meaningful for functional motor behaviour.[130]

Animal models have played a major part in the improvement of our understanding of the underlying mechanisms of exercise and its effects on restoration of motor behaviour in the dopamine-depleted brain. Most findings are beginning to highlight the importance of focusing on the synapse as the crucial therapeutic target. Exercise can restore important circuits in motor behaviour by modulation of dopamine and glutamate neurotransmission and also affects general brain health.

Conclusions

In the past decade, a main focus of neurorehabilitation has been to alleviate the motor deficits of Parkinson's disease through exercise.[10,131] The general idea is that exercise that incorporates goal-based motor skill learning improves motor skill performance in Parkinson's disease and that this might be enhanced through cognitive engagement. Importantly, exercise that combines goal-based with aerobic training might work synergistically to promote automatic and volitional components of motor control (figure 3).[132] Aerobic exercise might contribute to more general improvement in brain health and repair, for example, through the recruitment of the immune system or increased blood flow and trophic factor signalling. These aerobic exercise benefits are likely to result from the promotion of synaptic neuroplasticity leading to altered circuitry. Another interesting question is whether an individual could learn themselves out of Parkinson's disease: on the basis of published studies, and present understanding of the detrimental effects of dopamine loss on brain circuitry, the most obvious response is no. However, exercise studies might be pointing towards potential and important neuroplastic mechanisms that, through restoration of some degree of basal ganglia circuitry, provide an opportunity to improve motor learning and behavioural performance.

Findings from published studies in both animals and individuals with Parkinson's disease show that exercise is important in the improvement of motor function in Parkinson's disease and the facilitation of neuroplasticity. Future research will continue to add to exercise-related mechanisms of neuroplasticity. Thus, exercise should be regarded as an essential treatment for Parkinson's disease, especially in individuals with mild to moderate disease. However, continuing research is needed to address large gaps in knowledge. Specifically, studies with non-invasive neuroimaging are needed to discern the relative contribution of either goal-based or aerobic exercise alone or in combination and their effects on brain function, connectivity, and motor behaviour. Furthermore, research on the important role of exercise in individuals with more advanced disease and with more severe cognitive impairment is needed. Elucidation of the precise exercise-induced mechanisms of neuroplasticity will lead to a better understanding of the role of neuroplasticity in disease modification and enable identification of novel therapeutic targets including pharmacological approaches to supplement exercise for improved treatment in Parkinson's disease.

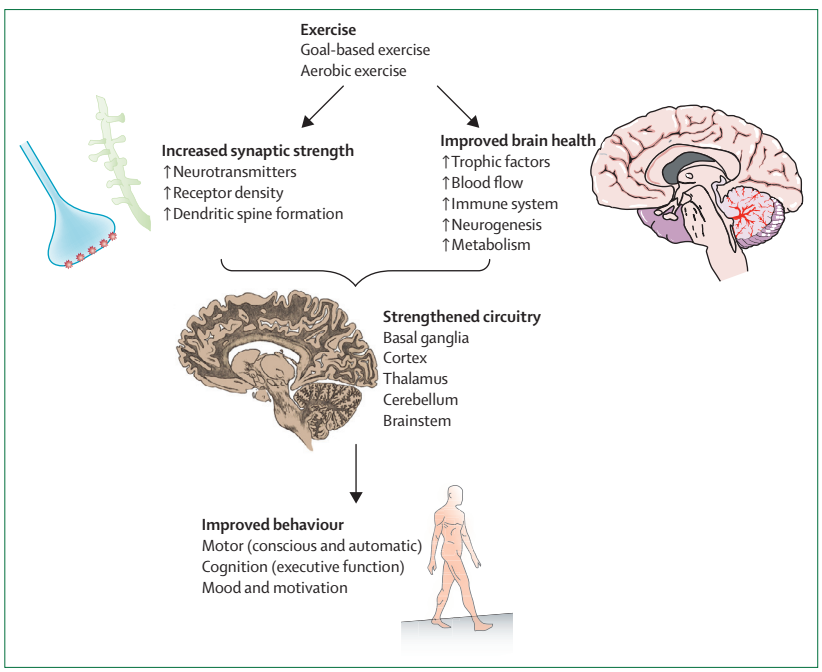

Figure 3: **Exercise and neuroplasticity in Parkinson's disease**
Clinical and basic research studies support the effects of exercise on neuroplasticity in Parkinson's disease. Neuroplasticity is a process by which the brain encodes experiences and learns new behaviours, and is defined as the modification of existing neural networks by addition or modification of synapses. Evidence is accumulating that both goal-based and aerobic exercise might strengthen and improve motor circuitry through mechanisms that include increased synaptic strength resulting from raised dopamine and glutamate neurotransmission within the basal ganglia accompanied by increased dendritic spine formation. Exercise leads to improved generalised brain health including increased expression of neurotrophic factors, increased blood flow, altered immune response, increased neurogenesis (especially within the hippocampus), and altered metabolism (ie, improved mitochondrial health). Such changes might lead to enhanced neuronal circuitry between the basal ganglia and its cortical and thalamic connections, which ultimately result in improved motor, non-motor, and cognitive behaviour in patients with Parkinson's disease.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed using the search terms "exercise" linked to "Parkinson's", "neuroplasticity", "environmental enrichment", "dopamine", "glutamate", "synaptogenesis", "striatum and physiology", " basal ganglia", and "physical activity". We mainly selected papers published between Jan 1, 1998, and Dec 31, 2013, in English, 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.

Contributors
All authors contributed to the conception and design, acquisition of data, or analysis and interpretation of data discussed in this paper; drafted or revised the paper; and approved the final version to be published.

Conflicts of interest
We declare that we have no conflicts of interest.

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