



Exercise and neuroplasticity in persons living with Parkinson's disease

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For many years, exercise was not a recommended rehabilitation strategy for persons with a diagnosis of idiopathic Parkinson's disease (PD). Since it was believed that exercise had no measurable effect on PD, or might worsen the underlying pathology, it was to be avoided. A rich vein of bench and translational research now suggest non-pharmacological approaches, such as exercise or physiotherapy, have a far greater effect on the cardinal features of PD than previously believed. In particular, recent studies utilizing animal models of PD have begun to explore the molecular mechanisms of exercise-induced changes in the pathophysiology of PD. Yet, many clinicians and communities remain unaware of the scientific literature underlying exercise-induced brain repair or reorganization (neuroplasticity) and accompanying behavioral recovery in animal models of PD. The authors will summarize some noteworthy preliminary studies suggesting that continuous, deficit targeted, intensive training may confer neuroprotection and thereby, slow, stop or reverse the progression of the disease or promote neurorestoration through adaptation of compromised signaling pathways. While much work remains and these preliminary results await replication in larger prospective human trials, we believe a major challenge in the field of non-pharmacological, rehabilitative intervention for PD will be the extent to which healthcare providers are able to translate the science of exercise and PD to the level of the community.

KEY WORDS: Parkinson disease - Neuronal plasticity - Rehabilitation - Exercise.

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Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it.
Plato (cited in H. Dawes, p. 867)¹

Parkinson's disease (PD) is marked by progressive loss of motor function with loss of nigrostriatal dopaminergic (DA) neurons. This paper aims to summarize some of the most exciting basic and clinical science studies suggesting exercise may promote brain repair and reorganization (neuroplasticity) in people with PD; and that this exercise-induced neuroplasticity is accompanied by behavioral recovery. Altogether, these data suggest a need for exercise interventions that are intensive, available at diagnosis, that promote continuous exercise (normal use), and that avoid inactivity. It is hoped that clinicians, managed care organizations and other healthcare providers will begin to translate this information to the clinical setting and to the level of the community, where it may benefit the needs of individuals with early PD. Historically, physiotherapy had been seen as an "adjunctive" (*i.e.*, helpful) treatment to the pharmacological management of persons diagnosed with PD.² Physical therapists, sport and recreation specialists, fitness professionals and other educators often participate in the rehabilitation of persons with PD

by developing, administering and assessing the effects of training programs to improve function. Yet, the mainstream approach to the management of the signs and symptoms of individuals living with PD remains the use of pharmacological agents such as levodopa, introduced in the late 1960s, dopamine agonists and, in the later stages of the disease process, neurosurgical interventions such as deep brain stimulation (DBS). While the pharmacological treatment of PD is essential, a growing body of bench and clinical research suggests that adding nonpharmacological approaches to symptomatic management of the disease through exercise and physical therapy enhances function beyond that of medications or surgery alone.³⁻⁵ The authors hope this historical overview may help bring about a paradigm shift that removes barriers to the implementation of evidenced-based PD-specific exercise approaches across disease severity, starting at diagnosis.

In a recent feature edition on rehabilitation and PD⁶ Susan Calne, a leader in the field of allied health for PD, recounted an experience she had while moderating a PD conference session at the first Parkinson Foundation of Canada Educational Meeting in 1982: "...a patient asked the panel of internationally distinguished physicians whether exercise and physiotherapy were useful for PD. One panelist (a giant in the world of PD treatment at the time) told the patient that it was a waste of time..."⁶ At the time the panelist gave his opinion, there were few randomized controlled trials in medicine, and even fewer peer reviewed controlled trials on the effect of exercise or physiotherapy for PD.

In 1994 the American Academy of Neurology came to a different conclusion, recommending physiotherapy and exercise as an adjunctive (*i.e.*, helpful) strategy in early and advancing PD.⁷ Koller *et al.*⁷ urged healthcare professionals to strongly encourage their patients to exercise: "*The optimal approach to the management of early PD includes daily exercise, one of the most beneficial things a patient can do for himself. It can consist of stretching, walking, swimming, or any activity the patient enjoys and will do regularly. More formal cardiovascular programs are also beneficial...*"⁷ For patients with early PD, the guidelines recommended "strengthening with light weights".⁸ In patients with advancing PD the guidelines state "...exercise is also helpful. Although vigorous exercise is not necessary, just doing a few pushups, sit-ups, or isometric exercise is **not** (emphasis added)

enough. Patients must be encouraged to walk as much as several miles a day, if possible, or swim regularly".⁷ Surprisingly, neither of the treatment guidelines provided citations specific to studies demonstrating treatment efficacy of exercise or physiotherapy and the 2001 treatment guidelines⁹ failed to mention exercise altogether.

Despite best efforts by clinicians to encourage patients to exercise, the attitude that physical therapy or exercise had little or no effect on PD, prevailed during the 1980s and 1990s among researchers and clinicians. Dr. Katherine Deane from the Cochrane collaboration was one of the first researchers to systematically summarize the literature on exercise and physical therapy for PD. In a series of highly cited papers conducted in the 1980s and 1990s, Deane *et al.* concluded that there is "*insufficient evidence for the effect of physiotherapy versus no physiotherapy*", and "*no conclusive evidence*" that physiotherapy is beneficial for people with PD, despite individual studies demonstrating measurable treatment effects.¹⁰⁻¹² The authors cautioned about drawing firm conclusions about the effect of PT for PD based on methodological flaws in the quality of trials which may lead to bias. Most clinical trials cited by Deane *et al.* were characterized by methodological flaws in research design and execution, heterogeneity in patient selection within and across studies, failure to use randomization or control groups, lack of detail in describing the ingredients of physiotherapy treatment, use of divergent outcome measures, failure to blind assessors, failure or inappropriate use of statistical tests, lack of follow-up testing and other factors.

Since the Cochrane reviews, the quality and number of published peer reviewed randomized trials on exercise and/or physiotherapy has steadily increased. Many systematic reviews and at least 3 meta-analytic studies (Table I) have reported positive effects of physiotherapy and exercise on the motor¹³⁻³¹ and non-motor³² signs and symptoms of PD. Recently, the Quality Standards Subcommittee of the American Academy of Neurology, and a joint task force of the European Federation of Neurological Societies and the Movement Disorders Society, European Section reviewed the literature on the effects of exercise and/or physiotherapy on improvement in motor symptoms, function, or disability of PD. Both panels independently recommended the use of exercise and physiotherapy in PD,^{20, 33} citing studies published through January 2006 with certain caveats concerning

TABLE I.—*Review and meta-analytic papers on benefits of exercise and physiotherapy in Parkinson's disease.*

Author/ Year of Publication	Major content of review	Type of publication		Journal Name
		Review	Meta-analytic	
de Goede ¹³	PT		X	Archives of Physical Medicine & Rehabilitation
Deane ¹⁰	PT	X		Cochrane review
Deane ¹¹	PT	X		Cochrane review
Deane ¹²	Paramedical therapies	X		Movement Disorders
Hirsch ¹⁴	PT	X		Physiopraxis
Ebersbach ¹⁹	PT	X		Aktuelle Neurologie
Schroeteler ¹⁸	PT	X		Nervenheilkunde
Lim ¹⁶	PT/ Cueing Training		X	Clinical Rehabilitation
Smidt ³¹	Exercise	X		Australian Journal of Physiotherapy
Seel ¹⁷	Rehabilitation	X		Neurorehabilitation
Nutt ¹⁵	Medical Management	X		New England Journal of Medicine
Suchowersky ³³	Medical Management	X		Neurology
Rao ³⁴	Medical Management	X		American Family Physician
Horstink ²⁰	Medical Management	X		European Journal of Neurology
Crizzle ²¹	Exercise	X		Clinical Journal of Sports Medicine
Jobges ²⁶	PT & Exercise	X		Parkinsonism and Related Disorders
Keus ⁵¹	PT	X		Movement Disorders
Kwakkel ²³	PT	X		Parkinsonism and Related Disorders
Nijkraake ²⁴	Allied Health Care	X		Parkinsonism and Related Disorders
Reuter ²⁵	Sports Medicine	X		Deutsche Zeitschrift für Sportmedizin
Ebersbach ²⁷	PT	X		Nervenheilkunde
Falvo ²⁸	Resistance Training	X		Movement Disorders
Goodwin ²⁹	PT & Exercise	X	X	Movement Disorders
Dibble ³⁰	PT & Exercise, Balance Training	X		Neurologic Physical Therapy

PT: physiotherapy; Meta-analytic papers: Papers that reported results using meta-analytic techniques; review papers: papers that reported results from review of the literature using non-meta-analytic techniques.

magnitude of effects and long-term benefits. According to these authors: higher levels of exercise may reduce the risk of PD in men (class IV evidence); exercise and physiotherapy that includes practice and task-specific training strategies may improve parkinsonian motor performance, motor impairments and disability (Class II and III evidence), and sensory cueing strategies may improve gait and reduce episodes of freezing in select patients (class III and IV evidence).²⁰ Finally, based on eight class II studies, Suchowersky *et al.*³³ concluded that “*various exercise modalities...are probably effective in improving functional outcomes for patients with PD*”.³³

The previous practice guidelines were included in overall medical guidelines for medical treatment and were brief and not geared towards physiotherapists and other allied healthcare providers. In 2001 the first

evidence based physical therapy guidelines were developed in the UK.³⁴ In 2004 and 2006, these guidelines were updated and supplemented with evidence-based physical therapy practice recommendations by a group in the Netherlands.³⁵ They have continued to be updated with the latest evidence (through December 2007) and are now available online.²² Four specific treatment recommendations reached level 2 evidence (*i.e.*, conclusions supported by a least two independent randomized controlled trials (RCTs) of moderate methodological quality or with sufficient power, or other non-randomized, controlled studies). These included: cueing strategies to improve gait; cognitive movement strategies to improve transfers; exercises to improve balance; and training of joint mobility and muscle power to improve physical capacity.²² To solve the problems with implementation of

evidence-based exercise guidelines into clinical practice they pose the development of community-based networks of dedicated PD-specific experts that undergo intensive training and in turn, train others at more remote sites (fitness professionals and caregivers) to carry out parts of the evidence-based practice or promote ongoing physical activity. The merits of this ParkinsonNet concept are currently being investigated in a large cluster-randomized study.²⁴

Importance of exercise

It is recognized that normal age-related physiological changes and leading a sedentary lifestyle are associated with increased vulnerability towards cardiovascular, metabolic or musculoskeletal conditions among adults such as cerebrovascular and heart disease, cognitive impairment, dementia, depression, osteoporosis, diabetes, obesity and peripheral vascular disease, to name but a few. Recent evidence suggests that exercise has a positive effect on many of the chronic conditions listed above. This prompted the American Medical Association to start a program called "Exercise is Medicine".³⁶ The purpose of the "Exercise is Medicine" program is to educate all physicians about the importance of exercise for their patient so that they will talk to their patients about exercise and encourage them to become physically active. Just as physicians perform routine screenings for other conditions, the "Exercise is Medicine" program provides the incentive for them to ask each patient at each visit if they are exercising and to document the type of exercise they are doing, as well as its frequency and duration. Based on *Healthy People 2010* (HP2010) objectives,³⁷ the American College of Sports Medicine (ACSM) and the American Heart Association released exercise recommendations for adults based on scientific evidence that regular exercise may decrease vulnerability for the above conditions or may improve health substantially among older adults.³⁸ Recommendations include incorporating regular exercise to maintain and increase in the following domains: cardiovascular conditioning, muscle strength, flexibility and balance.

Guidelines specify:

- aerobic activity to be of vigorous or moderate intensity (20 minutes/ 3 days per week or 30 minutes 5 days per week, respectively);
- muscle strengthening consisting of 8-10 exer-

cises involving the major muscle groups with at least 1 set of 10-15 repetitions per muscle group, on at least 2 non-consecutive days per week;

- flexibility exercises consisting of 8-10 exercises involving the major muscle groups (2-4 repetitions per exercise, holding each repetition for 15-30 seconds, 2-3 days per week at minimum, ideally 5-7 days per week);

- balance training exercises.

Only roughly 50% of Americans meet the above guidelines for aerobic exercise. Thus a substantial proportion of the adult population does not reap the benefits of exercise.

There is little information available on the physical activity patterns of people with a diagnosis of PD. It is likely important that people with PD increase their exercise in all domains outlined in HP2010; however, the amount of physical activity people with PD currently receive in each area, barriers to exercise, and the effects of exercise in each domain on functional independence or quality of living is currently unknown. There are a number of good reasons why people living with PD should exercise. Research demonstrates that people with disabilities are less physically active than people without disabilities, although the reasons for this are unclear. People with disabilities are certainly as vulnerable, if not more vulnerable to develop chronic conditions that arise from lack of activity and a sedentary lifestyle. Chronic exercise meeting the HP2010 guidelines could improve cardiorespiratory, neurologic and musculoskeletal function and mobility and enable greater independence in daily activities, and could thereby reduce the burden of care for caregivers of persons with PD. As one spouse of a person with PD who had participated in a two year community-based high intensity training program^{39, 40} noted: "*(because of the program) I am better able to take care of my husband (with PD), feel more relaxed, am in a better mood, and less tired...my husband would not be where he is today without the training program*".⁴¹

Often persons in the early stages of PD do not request a referral to physiotherapy, or they do not ask about how much or what type of exercise to do, as they do not perceive that their function has declined or that their symptoms interfere with normal daily activities. This is not necessarily the case, as impairments in sensory processing underlie bradykinesia and accurate motor plans for movement.⁴² Thus, even at diagnosis, body awareness and perceptions of time

and distance^{43, 44} may be distorted and patients rarely self-correct their smaller/slower everyday movements. While there is remarkable inter-individual variation in the progression of PD and in the perceptions of disability,²⁴ approximately 25% of persons diagnosed with PD reach Hoehn and Yahr stage III within 5 years of diagnosis. Traditionally, it is at this point that referrals to rehabilitation are initiated. This referral model does not allow for a proactive treatment approach during the early postdiagnosis period, prior to loss of postural stability. Animal studies suggest that this is a lost window of opportunity. What follows is meant to summarize the rationale for early referral to PD-specific exercise programs that are intensive, promote normal use, and avoid inactivity and to raise important considerations for practical implementation.

Epidemiologic studies suggest an inverse relationship between activity level and risk of developing PD: moderate or vigorous levels (but not low levels) of physical activity are associated with lower risk of developing PD.^{45, 46} Regular exercise delays the appearance of Parkinsonian features in persons already diagnosed with PD.⁴⁷ Interestingly, studies suggest that following diagnosis, persons with PD reduce their physical activity levels^{48, 49} and only 12-15% of these early diagnosed individuals are referred to physiotherapy. In fact, only a small percentage of individuals with PD (7-57%) report ever being treated by a physiotherapist, although, internationally, there are large differences in healthcare utilization.^{50, 51} It is not known why this is so – but there are most likely many barriers to early referral and access to community-based exercise and physiotherapy. Is it because at the time of diagnosis patients' healthcare providers fail to encourage them to exercise, or encourage them not to exercise? Is it because the sensory deficits of PD interfere with an individual's ability to recognize the significance of their functional deficits? Or, do the non-motor symptoms of motivation and depression interfere with self-efficacy? Is it because the symptoms themselves make it more difficult to exercise? Is it because there is a lack of PD-specific expertise among physiotherapists and other health professions they may encounter? Is there a lack of access to PD-specific community-based exercise programs for people with PD to exercise? Do patients become disenfranchised with exercise programs or PT when they perceive that training does not provide the expected results?⁵¹ Or, are the costs too prohibitive? Understanding these issues is essential to

developing and implementing early intervention and evidence-based guidelines and programs for all individuals with PD.

Exercise and brain health

While exercise guidelines for adults have traditionally focused on achieving musculoskeletal and cardiopulmonary benefits with training, more recent attention has shifted to exercise as a means to maintaining or increasing brain health. Studies on healthy populations of older adults free of central nervous system pathology have already shown that regular aerobic activity triggers plasticity related changes in the central nervous system including synaptogenesis, enhanced glucose utilization, angiogenesis and neurogenesis. Among older adults free of cognitive impairment, aerobic exercise promotes brain health by reducing inflammation, suppressing oxidative stress and stabilizing calcium homeostasis.⁵² Release of endogenous neurotrophins such as brain-derived neurotrophin (BDNF), glia-derived neurotrophin (GDNF), nerve growth factor (NGF) and galanin⁵³ during chronic aerobic exercise is associated with synaptic plasticity, enhanced cognitive ability, learning and memory.⁵⁴ Results from the above human studies are paralleled by studies with lesioned and intact laboratory animals, showing that motor training triggers lasting neuronal changes throughout the brain such as glial cell proliferation, changes in neurotransmitter levels, changes in the expression of endogenous neurotrophic factors such as BDNF and GDNF, the growth of neuronal processes, and neural changes which are associated with enhanced behavioral recovery.⁵⁵⁻⁷⁹

While evidence has elucidated the benefits of exercise among healthy active and inactive populations, scholars⁵³ note that relatively little has been published about the neurobiology of exercise as it pertains to people with neurodegenerative conditions, such as PD. Most of the authors' understanding of activity-dependent or exercise-induced neuroplasticity is derived from studies of brain injury related to stroke and spinal cord injury. Animal models (rodent and nonhuman primate) of stroke suggest that forced-use of the impaired upper limb (small object retrieval) improves motor recovery and results in a reduction in the lesion size and functional reorganization in both

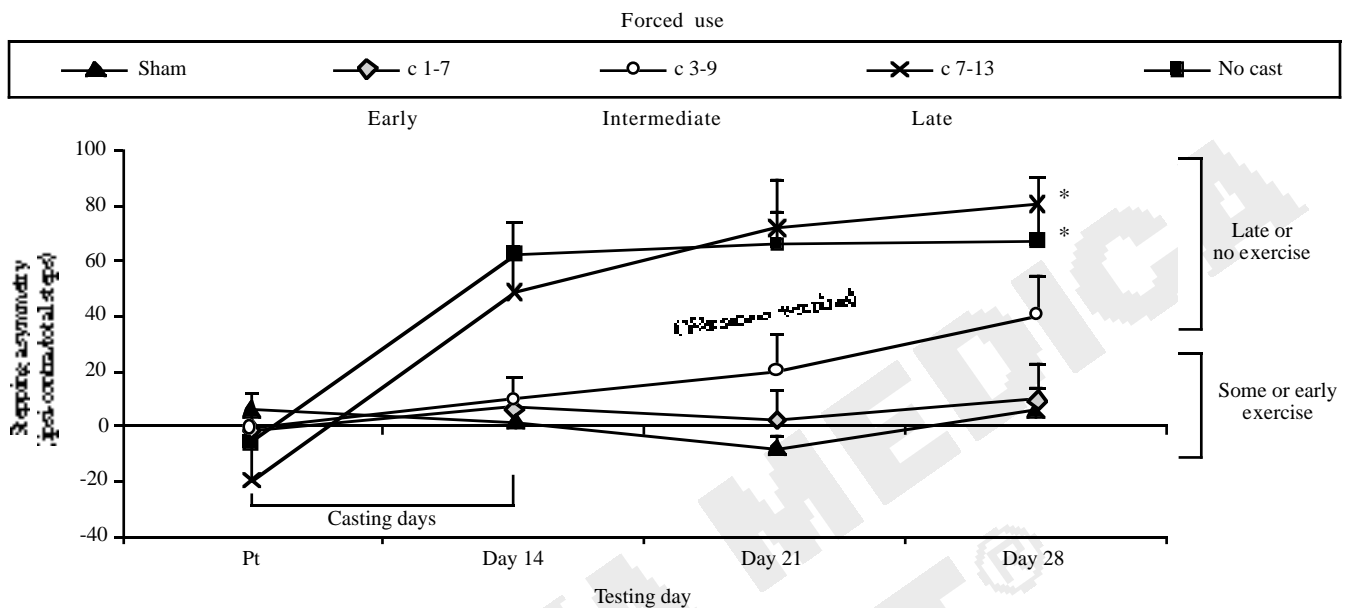


Figure 1.—Forced use of the impaired forelimb on days 1-7 and 3-9 after 6-OHDA exposure ameliorated akinesia. Those animals that did not receive the cast until days 7-13 displayed strong akinetic tendencies as did the animals in the no cast group. Bonferroni *post hoc* analysis indicated significant differences (*) between sham controls (sham) and lesion + no cast (no cast) and lesion + late cast (c7-13) groups. Figure reprinted with permission from Tillerson *et al.*⁸⁸

the adjacent (injured) and contralateral (undamaged) cortical regions.^{65, 66} Noninvasive imaging in the human brain now offers evidence that activity-dependent plasticity occurs in the human brain after a stroke in response to exercise (forced use) and skill learning.^{80, 81} Forced use, task-specific, and intensive exercise approaches have recently been transferred to work with animal models of PD. The following section will summarize some of these studies suggesting that exercise may exert neuroprotection (slow, stop or reverse the neurodegenerative process), be pro-degenerative (exacerbate the neurodegenerative process), and promote neurorestoration (adaptation of compromised signaling pathways).⁸²⁻⁹⁰

Two widely used experimental rodent models of PD will be discussed that use the neurotoxins 6-hydroxydopamine (6-OHDA) in rats, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice, to study the effects of exercise prior to, or following a lesion that leads to progressive dopaminergic cell death and motor deficits typical of PD.⁹¹ Unilateral infusion of 6-OHDA into the medial forebrain bundle leads to unilateral depletion of nigrostriatal DA neurons, followed by asymmetrical forelimb use, akinesia, and impaired placing. MPTP-induced parkinsonism induced by

sequential intraperitoneal injections leads to a bilateral depletion of nigrostriatal DA neurons. The behavioral deficits resemble human parkinsonism; bradykinesia, hypokinesia, and akinesia and can be observed during open field activity monitoring and balance tasks (rotorod).

Studies with laboratory animals have certain advantages: genetic differences, which may confound results in human studies, can be reduced by using litter mates; lesioning can be systematically titrated and controlled to produce a range of Parkinsonian symptoms from preclinical and mild to severe; life span conditions such as social interaction and the amount, type and timing of physical activity or stimulation relative to when a lesion is made, as well as the age and level of fitness of the animal at the time of lesioning can be controlled more precisely; animals can be randomly assigned to different experimental conditions, and their brains can be studied in detail. However, caution is necessary in extrapolating to humans the results of well-controlled studies using laboratory animals.^{92, 93} The primary disadvantages of these models include the spontaneous behavioral recovery that occurs in affected animals despite a significant loss of dopamine neurons, and the degree

to which the behavioral characteristics and pathology mimic the human condition. For example, while the 6-OHDA model serves primarily as a model of striatal dopamine dysfunction, the MPTP model manifests alterations in other catecholaminergic neurons and neurotransmitter systems, more like the human condition. In both models, despite the cell death;

partial or complete behavioral recovery occurs. This suggests these animals possess robust molecular mechanisms for plasticity in response to injury – which can be useful for studying the effect of exercise that may enhance recovery.^{83, 91} The degree and time course of recovery is dose-dependent and varies across age, species and mode of toxin injections. Thus, it is important that recovery in exercised animals is always compared to recovery in exercised control groups to differentiate how exercise enhances the spontaneous recovery that occurs in controls.

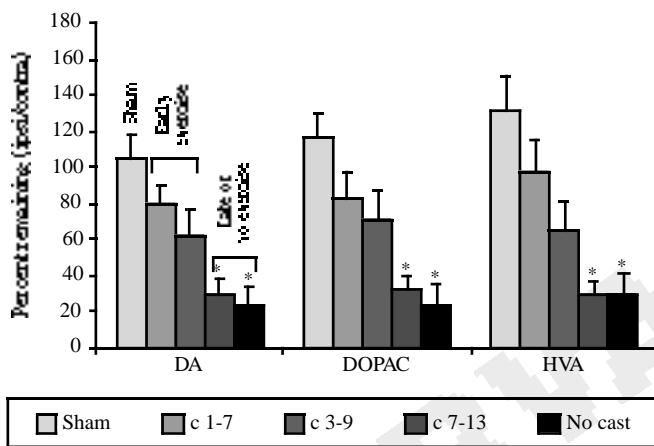


Figure 2.—Animals receiving early casts (days 1-7) and sham animals do not show significant differences in DA, DOPAC or HVA levels. Animals receiving casts on days 3-9 show intermediate DA levels, although still not significantly different from sham. Animals with late casts (days 7-13) and animals not receiving casts show significantly lower (*) DA levels when compared with sham-treated animals. Figure reprinted with permission from Tillerson.⁸⁸

Exercise as neuroprotection

Could there be a sensitive period after PD symptoms first surface during which intense exercise could reduce, halt, or reverse the neurodegenerative process? Early studies on forced-use exercise paradigms using animal models of PD were conducted by Tim Schallert *et al.* at the University of Texas at Austin. In the first of a series of studies,⁸⁸ Long-Evans male rats were randomized into four lesioned groups after receiving unilateral 6-OHDA lesion: (N=54; lesioned plus no cast; lesioned plus cast on postoperative days 1-7 [early casts]; lesioned plus casts on postoperative days 7-13 [late casts]; lesioned plus casts on postoperative days 3-9 [intermediate casts]), or three sham-treated groups (N=16;

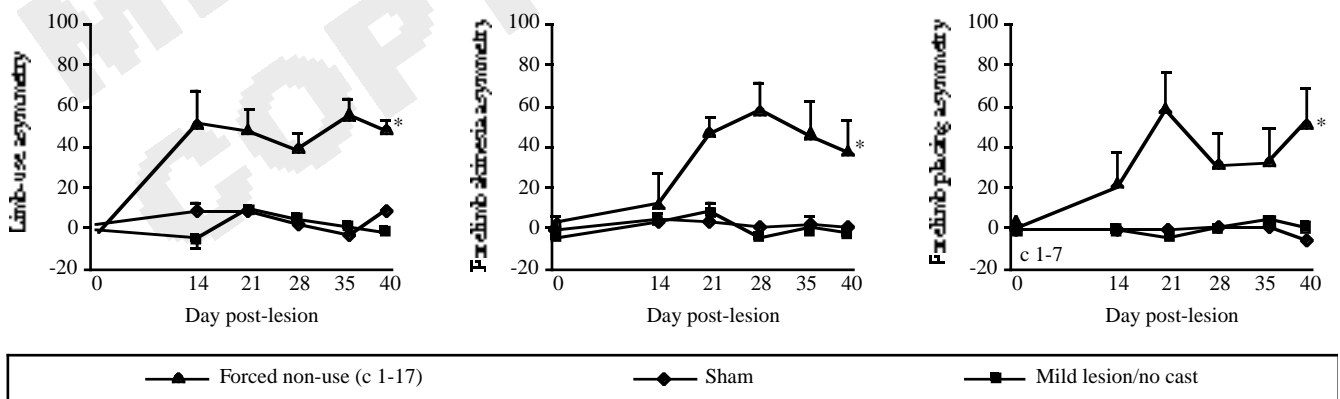


Figure 3.—Behavioral asymmetries after forced nonuse in animals with mild lesions. A) Animals given mild unilateral lesions did not display significant limb use asymmetry; when animals were forced to not use the impaired forelimb for the first 7 days after lesioning, they demonstrated limb use asymmetry that persisted across testing days; B) animals given mild unilateral lesions did not display significant forelimb akinesia; When animals were forced to not use the impaired forelimb for the first 7 days after lesioning, they demonstrated forelimb akinesia that persisted across testing days; C) animals given mild unilateral lesions did suffer placing deficits; when animals were forced to not use the impaired forelimb for the first 7 days after lesioning, they demonstrated significant placing deficits that persisted across testing days (*P<0.01 compared with lesion only). Figure reprinted with permission from Tillerson *et al.*⁸⁹

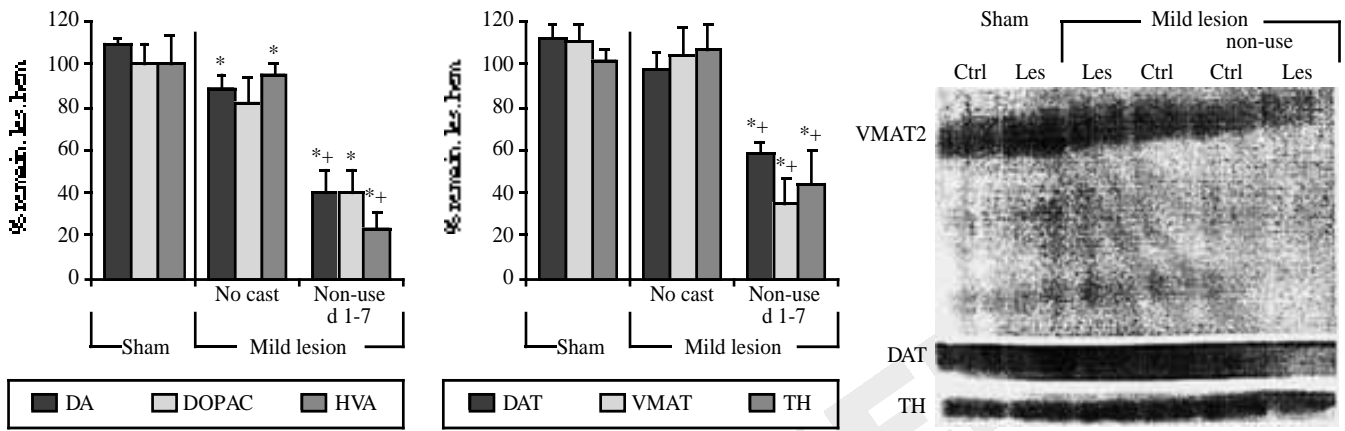


Figure 4.—Effect of forced nonuse of the impaired forelimb after mild 6-OHDA lesion. A) A 5 µg infusion of 6-OHDA resulted in only a mild loss of DA and HVA in striatal tissue when values were compared with the intact hemisphere; In contrast, forced nonuse of the impaired forelimb for the first 7 days after lesioning resulted in significantly greater loss of DA and its metabolites when compared with both sham animals and animals lesioned but not casted; *P<0.05 compared with sham; +P<0.01 compared with lesion /no cast; B) immunoreactivity of DAT, VMAT2, and TH was not reduced after mild lesioning (calculated as percentage remaining in lesion hemisphere); In contrast, forced nonuse of the impaired forelimb for the first 7 days after lesioning resulted in significant declines in DAT, VMAT2, and TH immunoreactivity; *P<0.01 compared with sham; +P<0.02 compared with lesion/no cast; C) representative blots of VMAT2, DAT, and TH for sham, mild lesion, and mild lesion and nonuse groups. Ctrl: Control; Les: lesion. Figure reprinted with permission from Tillerson *et al.*⁸⁹

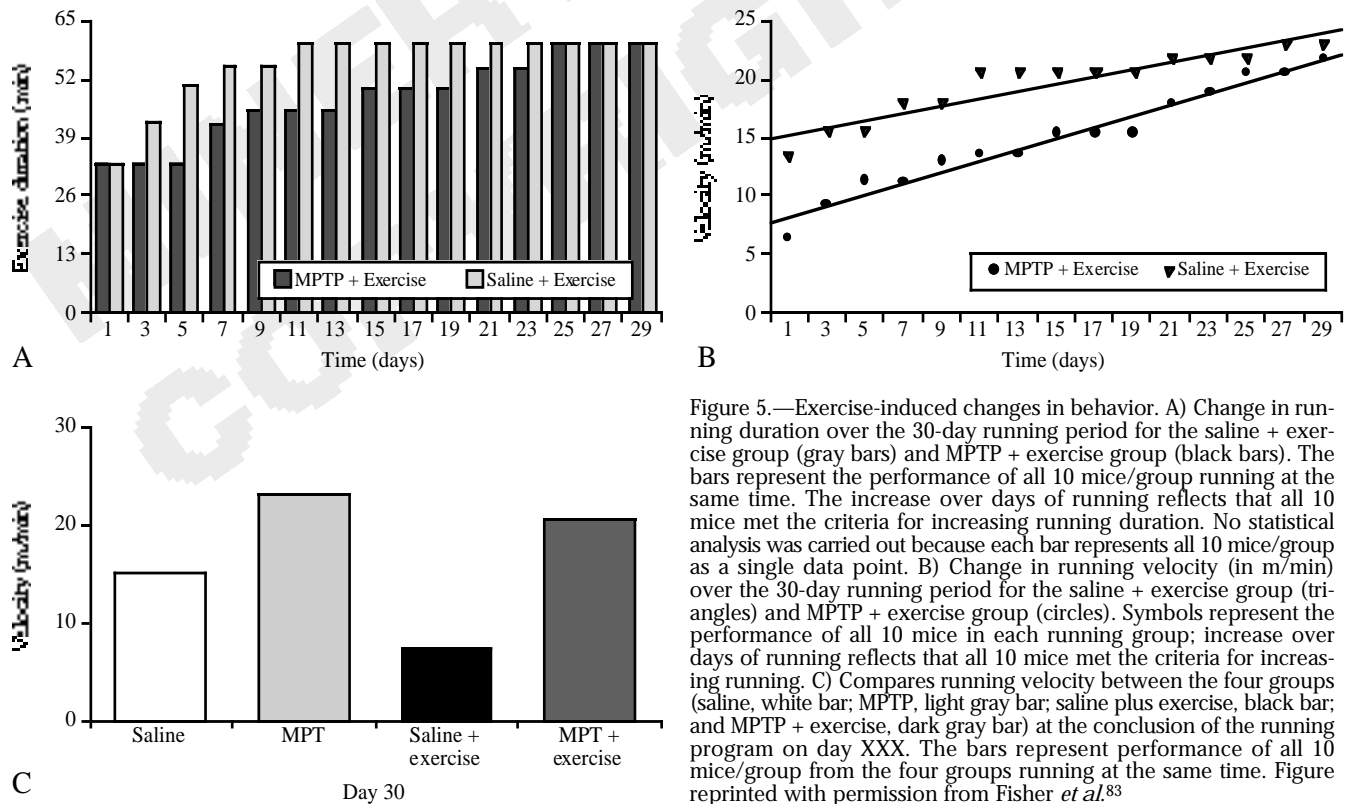


Figure 5.—Exercise-induced changes in behavior. A) Change in running duration over the 30-day running period for the saline + exercise group (gray bars) and MPTP + exercise group (black bars). The bars represent the performance of all 10 mice/group running at the same time. The increase over days of running reflects that all 10 mice met the criteria for increasing running duration. No statistical analysis was carried out because each bar represents all 10 mice/group as a single data point. B) Change in running velocity (in m/min) over the 30-day running period for the saline + exercise group (triangles) and MPTP + exercise group (circles). Symbols represent the performance of all 10 mice in each running group; increase over days of running reflects that all 10 mice met the criteria for increasing running. C) Compares running velocity between the four groups (saline, white bar; MPTP, light gray bar; saline plus exercise, black bar; and MPTP + exercise, dark gray bar) at the conclusion of the running program on day XXX. The bars represent performance of all 10 mice/group from the four groups running at the same time. Figure reprinted with permission from Fisher *et al.*⁸³

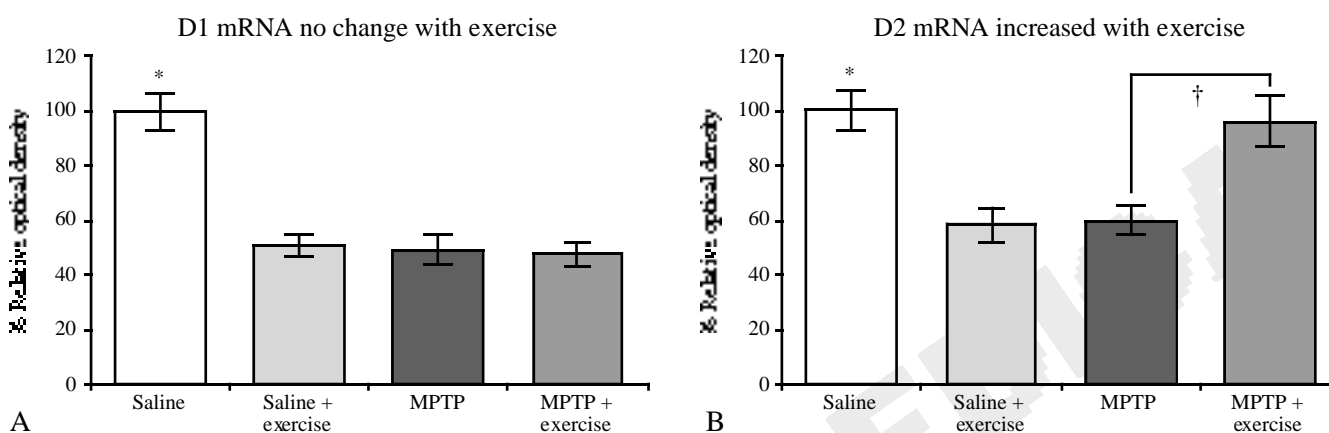


Figure 6.—Analysis of the relative striatal dopamine D1 and D2 receptor mRNA using in situ hybridization histochemistry. The relative optical density of autoradiographic grains above the dorsal striatum were determined from at least three mice from each treatment group using at least 12 sections/mouse. For comparison, the saline group was set arbitrarily at 100% and all other groups normalized against it for both dopamine receptors D1 and D2 mRNA. A) compared to the saline group, expression of D1 mRNA was reduced significantly with exercise and MPTP lesioning (saline, 100.0±6.9%; saline + exercise, 51.9±3.9%; MPTP, 50.1±5.7%; MPTP + exercise, 48.6±4.2%; $P<0.0001$); B) the expression of dopamine D2 mRNA was reduced as a result of either exercise (saline + exercise) or MPTP lesioning (MPTP group) compared to that in saline group (saline, 100.0±7.6%; saline + exercise, 58.5±6.4%; MPTP, 60.3±5.3%; $P<0.002$); the expression of dopamine D2 mRNA was increased significantly in the MPTP + exercise group when compared to that in the MPTP group (MPTP + exercise, 95.9±9.4%; $P<0.005$). Figure reprinted with permission from Petzinger *et al.*⁸⁷

sham and no casts; sham and casts on postoperative days 1-7, or sham and casts on postoperative days 7-13). Casted groups were fit with plaster of Paris casts after surgery to immobilize the ipsilateral (non-impaired) forelimb for 7 days beginning 24 hours, 3 or 7 days postsurgery. Animals were then placed in their cages with playmates and forced to rely on their impaired forelimb during everyday exploration and movement. Neurochemical analyses for DA, DA metabolites (dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and vesicular monoamine transporter (VMAT2), a reliable marker for the integrity of DA terminals, were performed in the striatum of the lesioned hemisphere 65-80 days after surgery. Behavioral tests assessed forelimb asymmetry during: movement initiation (forelimb akinesia), voluntary exploration (limb-use asymmetry) and vibrissae-elicited placing (forelimb placing) and were performed before surgery and on days 14, 21, 28, 40 and 60 days after surgery. 6-OHDA lesions in uncasted animals caused chronic behavioral deficits and no neurochemical protection against the loss of striatal DA (Figures 1-2).⁸⁸ Early forced use (~24 hours) spared behavioral function and striatal DA levels, metabolites, and VMAT2 expression in the striatum (not shown

here),⁸⁸ was no different than sham controls. Behavioral and neurochemical benefits were sustained across testing days despite removal of the cast after 7 days (Figure 1). In animals casted on days 3-9, the behavioral deficits were reduced during the period of forced-use, but gradually worsened over time, suggesting lingering asymmetry may have been exacerbated after removal of the cast. In contrast, in day 7-13 casted animals, behavioral deficits persisted. The degree of forelimb asymmetry was correlated with the level of DA (and metabolite) depletion. Altogether, those data suggest that exercise may delay or prevent PD in healthy individuals,⁴⁶ and in early PD, slow disease progression and thereby, motor deterioration.

Several studies have replicated these data using treadmill exercise, environmental enrichment, and voluntary running paradigms in the same animal models with similar results.^{90, 94-96} Exceptions in these, and other studies suggest that age,⁹⁰ type of motor training (skilled *vs.* aerobic), and extent of lesion may affect the degree of protection, behavioral recovery, or generalization of training.⁹⁷⁻¹⁰⁰ Finally, stress and removal of activity (forced non-use paradigms) in these animal models of PD can decrease or reverse the beneficial effects of exercise.^{89, 101} In a follow-up

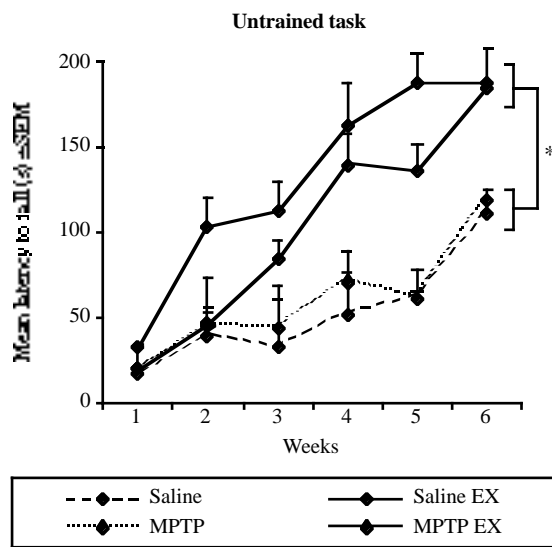


Figure 7.—Analysis of behavior on rotarod mice from all groups were tested once a week for latency to fall from an accelerating rotarod (mean and SEM in seconds per week). There was a significant effect of exercise (treadmill running) on the mean latency to fall (in seconds) from the accelerating rotarod, where the asterisk represents significant difference between the exercise and no exercise groups ($F_{(3,44)}=9.587$; $P<0.0001$). Both MPTP plus exercise and saline plus exercise mice performed better on the rotarod compared with the nonexercised groups. There was no significant effect of MPTP on mean latency to fall ($F_{(3,44)}=0.851$; $P=0.504$) and no significant interaction between exercise and MPTP on mean latency to fall ($F_{(3,44)}=0.965$; $P=0.435$). Figure reprinted with permission from Petzinger *et al.*⁸⁷

investigation, Cohen⁸⁵ demonstrated that a potent neurotrophic factor for the survival of DA neurons, glial cell line-derived neurotrophic factor (GDNF), was upregulated in the striatum corresponding to the exercised limb. More recently, exercise has been shown to induce the generation of GDNF producing cells (glia) in the substantia nigra where DA cells reside.⁹⁶ In summary, exercise may be prophylactic (preventative) and capable of protecting DA neurons from toxic events depending upon timing, severity of DA loss, and availability of neurotrophic factors. A combination of regimes (*i.e.*, skilled learning *vs* aerobic training) may be better than one specific task to trigger multiple mechanisms (*i.e.*, nourishing neurotrophic factor expression and focal synaptogenesis), and force continuous use of nigrostriatal circuits involved in a variety of salient behaviors to extend the neuroprotective benefits, and avoid their decline.

Inactivity as prodegenerative

As indicated above, a period of inactivity or stress may reverse the protection and behavioral benefits of exercise. In addition, decreased physical activity, which is often a precursor of the diagnosis of PD and worsened by the symptoms of bradykinesia, fatigue or weakness, may be prodegenerative, contributing to further motor deterioration and pathogenesis of PD. Using a forced nonuse paradigm, Tillerson⁸⁹ revealed that inactivity is not only a symptom of PD, but a catalyst in the degenerative process. Highlights from their study are illustrated in Figures 3,4.⁸⁹ Behavioral testing and neurochemical analysis was similar to their previously described forced-use experiments and also included neurochemical analysis of tyrosine hydroxylase (TH), a rate-limiting enzyme in DA biosynthesis. In this study animals were given a mild (preclinical) unilateral dose of 6-OHDA and then randomly assigned to sham (no cast or contralateral cast), mild lesion and no cast, or mild lesion and contralateral cast on days 1-7 (forced nonuse paradigm). Animals given a mild lesion with no activity restrictions (no cast) were no different from shams on limb use asymmetry tests or neurochemical indicators of striatal DA loss. These effects were sustained across testing, suggesting exercise (continuous normal use) protects DA neurons from the neurotoxic event. However, restricting activity of the impaired limb in animals immediately after a mild lesion triggered significant limb use asymmetry, exacerbated loss of striatal DA (and metabolites), and loss of DA terminals (VMAT2, DAT, TH protein were measured to provide an index of striatal DA terminal integrity).

These same results occurred in animals given a severe lesion (data not shown) who were then forced to rely on their impaired limb (forced-use paradigm) during the first week of training and then, 1-2 weeks after recovery of behavioral and neurochemical deficits, they were forced to *not* use the impaired limb (forced non-use). In animals who received forced-use followed by forced-non-use behavioral and neurochemical deficits returned following forced-non-use.⁸⁹ These data suggest, to us at least, that periods of inactivity, which may be typical for older adults with PD who do not exercise regularly or continuously, and failure to engage damaged systems (impairment-related or self-imposed) may be prodegenerative contributing to further degradation of function and disease progression. In addition, the molecular mechanisms underlying this protection (and recovery) may

require continuous normal use or exercise to be maintained.

Exercise and neurorestoration

In the previous mentioned studies⁸⁸⁻⁹⁰ investigating exercise as neuroprotection, forced use or treadmill training exercise paradigms were begun immediately after neurotoxin injection (2 hours, 6-OHDA; 24 hours, MPTP). This resulted in sparing of behavioral function and striatal DA loss. Since 6-OHDA and MPTP neurotoxins take several days to complete DA cell death, exercise may have interfered with the uptake or metabolism of the neurotoxin or initiated molecular events that helped the cells survive. However, the fact that the withdrawal of exercise (forced non use) unmasked behavioral deficits and striatal DA loss after behavioral recovery in both a mild-lesion and severe lesion, suggests that a threshold level of normal use or activity is required to hold the degenerative processes at bay after exposure to a neurotoxin.

To investigate the neurorestorative effect of exercise on the injured PD brain, recent studies were conducted that manipulated 1) the timing of the start of exercise after nigrostriatal cell loss was complete; 2) the intensity of exercise; and 3) added exercise to control groups to compare the effect of exercise on the noninjured and injured brain.^{83, 87} In the initial study, Fisher⁸³ initiated an intensive and progressive 30-day treadmill training protocol for both the saline controls and MPTP mice to reach a target goal (20.5 to 23 m/min; 30 min; 2x/day), 5 days after four intraperitoneal injections of MPTP. Using this administration protocol, cell death (60-70% loss) is complete by day 3 and persists beyond 30 days postlesioning. Despite a 90% loss of striatal DA, spontaneous behavioural recovery and partial restoration occurs 2-3 months postlesioning. Thus, the researcher's addressed the clinically relevant question if and how exercise may accelerate the restorative process that occurs spontaneously in these animals and how this process may differ between injured (MPTP) and noninjured brains exposed to exercise. Animals were randomized into four groups: MPTP with or without exercise and saline with or without exercise. Both exercised groups (MPTP and saline) significantly improved motor performance (duration and velocity of running) (Figure 5).⁸³ The MPTP exercise group reached the same maximal performance levels as the saline exercise group, although it took the MPTP group longer to reach this level (day

25 vs. day 11). However, the MPTP lesioned, non-exercised group, did not spontaneously improve motor performance over the 30 days (gait velocity on day 30 was no different from baseline) (data not shown here).

This degree of behavioral recovery and improved motor performance in the exercised groups (MPTP and saline) resulted in a down-regulation of the DA transporter (DAT), a primary mechanism for the clearance of DA from the extracellular space (data not shown here).⁸³ This alteration in DAT may have contributed to behavioral improvement by increasing DA availability by allowing for greater diffusion and time in synaptic occupancy. In contrast to a similar response in DAT regulation in the injured (MPTP) and non injured (saline) models above, exercise had a differential effect on DA receptor expression in these two groups (Figure 6).⁸³ In saline animals, exercise suppressed dopamine D1 and D2 receptor mRNA levels. In the MPTP group, exercise had no effect on already reduced D1, but increased D2 mRNA levels. This may be significant, as D2 receptor activation is associated with medium spiny neurons in the striatum and is an important modulator of corticostriatal glutamergic inputs. Interesting, terminal glutamate immunogold labeling only changed in the MPTP group, first increasing with MPTP lesion, and then decreasing back to control levels after exercise (data not shown here).⁸³ This suggests that glutamate release may have been enhanced by exercise in the MPTP group and that this may have contributed to alterations in D2 receptor expression. Thus, intensive treadmill exercise initiated after a period of neurotoxin-induced cell death improved motor performance, and alterations in glutamate-dopamine interactions and neurotransmission may be molecular mechanisms that underlie the restoration (repair) observed in this study.

In a follow-up study, Petzinger⁸⁷ explored changes in the dopaminergic system both at the level of total striatal dopamine levels and localized release. The same intensive treadmill training protocol, group allocation, lesioning, etc. were followed as per the Fisher⁸³ study discussed above. In addition to behavioural improvements in running velocity, Petzinger *et al.*⁸⁷ demonstrated improvements on a transfer skill requiring balancing on an accelerating rod (rotarod). Following treadmill training, both the MPTP plus exercise and saline plus exercise animals stayed on the rotarod longer (increased latency of fall) (Figure 7). The improvements in motor performance on trained and untrained tasks was accompanied by improvements in overall striatal DA levels *only* in the saline

exercised group.⁸⁷ In contrast, the improvements in motor performance in the MPTP exercised group was due to an increase in dopamine release, which was localized to the dorsolateral striatum, a motor region that becomes repetitively engaged in forelimb/hindlimb movement on the treadmill (data not shown here).⁸⁷

In summary, these studies suggest that in animal models of PD that are more typical of the human condition at diagnosis, exercise may restore motor function *beyond* that of baseline unexercised controls, but comparable to exercised controls. This remarkable capacity for motor performance occurred through a variety of molecular repair mechanisms from within the damaged basal ganglia circuits; however, progressively higher intensity, longer duration practice, and task-specific paradigms may be required to achieve these results in human PD.

Conclusions

These studies suggest an enormous capacity of the PD brain to reshape itself in response to self-produced activity and provide a plausible rationale for exercise-induced plasticity-related mechanisms in humans with PD. The animal data suggest that multiple time-dependent mechanisms (*i.e.*, neuroprotection, neurorestoration) are capable of contributing to behavioral recovery in PD (or potentially exacerbating the process further). Currently, a growing number of studies utilizing higher intensity training paradigms are being reported in humans with early and later stages of PD.^{5, 40, 102, 103} The results of these studies are beginning to corroborate earlier studies on the importance of exercise intensity in PD and suggest that PD patients without specific contraindications should be encouraged to begin exercise training programs that focus on achieving a higher training intensity, beyond what they may self-select.

Future clinical and translational research of exercise and PT for PD should focus on several key areas. As health-care professionals, we have a tremendous opportunity and a duty to help educate our PD patients on the benefits of exercise. The scientific bases for exercise prescription in PD should be taught at medical and physiotherapy schools and residency programs. However, education and advocacy are not the sole responsibility of the diagnosing physician, but requires an ongoing team effort. The goal should be to educate all healthcare professionals about the

benefits of exercise and PD, starting with physiatrists, neurologists, primary care physicians, therapists, and geriatricians as well as our policy makers and legislators. Just as physicians and physiotherapists perform a history and physical exam, every patient should be asked at every office visit about exercise. However, even if we encourage our PD patients to exercise, we still need to create safe places for them *to* exercise. One approach would be to develop community-based programs where people can exercise in science-based programs under appropriate supervision. However, presently few such efforts are underway. For example, the city of Charlotte, North Carolina is one of the largest cities in the state of North Carolina, USA, with a population of approximately 600 000. To date, there is one community-based exercise program for people with PD. Having one community-based facility that offers PD specific exercise programs is like having only one bank, one gas station or one grocery store. If this were the case, there would surely be public outrage. A good way to remedy the situation would be to develop a grass roots train-the-trainers program, so that any facility could develop a standardized PD exercise program in the persons' community. A few Parkinson's associations and individuals' in the United States and Europe have begun to develop such programs; however these efforts are isolated and poorly coordinated. Funding for these efforts is still limited. The success of these programs is certainly dependent on collaboration between all health care professionals, bench and applied researchers and will most certainly require support through policy makers and legislation that changes how rehabilitation and physiotherapy are applied in PD. Once places to exercise are established we must research their efficacy. The factors that encourage persons with PD to begin or end exercise, as well as the factors that encourage persons with PD to stay highly active, are still poorly understood.

There are other challenges. Laboratory-based exercise programs utilize highly academically educated, skilled trainers to conduct the PD training and interventions. Can similar improvements in exercise capacity, symptom reduction and brain health be achieved by community-based training programs staffed by non-PT professionals? Greater collaboration between communities is called for. We must test the efficacy of community-based programs and staff in delivering programs through prospective trials; we must develop train-the-trainers programs that utilize, not-only, skilled physiotherapists and other health care pro-

fessionals as trainers, but also train people with PD, spouses and caregivers to become trainers themselves. And we must work together to examine the effects of community-based peer training. We firmly believe that once we translate these data to human clinical trials, we can integrate them into a new era of clinical practice for people with PD.

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