

Authors and Disclosures

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It Is Not About the Bike, It Is About the Pedaling

Forced Exercise and Parkinson's Disease

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Abstract and Introduction

Abstract

Forced exercise has resulted in neuroprotective effects and improved motor function in animal studies. These promising results have not yet been translated fully to humans with Parkinson's disease (PD), as traditional exercise interventions have not yielded global improvements in function. A novel forced exercise intervention is described that has resulted in improved motor function and central nervous system function in PD patients.

Introduction

The aim of this review is to provide a brief overview of what is known about the effects of aerobic exercise training on the symptoms and motor function in patients with Parkinson's disease (PD) and to detail the impact of a relatively new approach to exercise in human patients with PD, forced exercise (FE). FE, in this case, is defined operationally as a mode of aerobic exercise in which exercise rate is augmented mechanically to assist the participant in achieving and maintaining an exercise rate that is greater than their preferred voluntary rate of exercise. It is important to note that during FE, the participant is contributing actively to the exercise; they are not being moved through the motion passively. Our data indicate that FE leads to a global improvement in PD motor function and an alteration in the CNS function.^[22] These global changes in motor function and altered activation patterns provide strong evidence for the hypothesis that for patients with PD to derive motor benefits from exercise, assistance is required to achieve a rate of exercise that triggers the release of neurotrophic factors or possibly dopamine.

PD is a progressive neurodegenerative disorder affecting nearly 1.5 million Americans, with annual treatment costs approaching \$25 billion. It is caused by selective neuronal loss in the substantia nigra and resultant degeneration of dopaminergic pathways in the basal ganglia. This loss of dopamine alters both inhibitory and excitatory pathways, resulting in its cardinal motor signs: bradykinesia (slowness of movement), tremor, rigidity, and postural instability.^[12] PD impacts movement ability, function, cognition, and quality of life (QOL), all to varying degrees on an individual patient basis. Traditional medical and surgical approaches to managing PD are expensive and associated with a variety of side effects that may further compromise QOL. Utilization of a non-drug, non-surgical therapeutic approach, such as exercise, to improve motor function would provide an attractive adjunct to current PD treatment approaches.

FE and Motor Function in Animal Models of PD

The effects of FE on motor and behavioral function using the 6-OHDA or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) rodent model of PD has been studied extensively.^[11,27,31,32] A typical FE paradigm is motorized treadmill running that requires the animal to maintain a running velocity that is greater than its preferred running velocity.^[19-21,27,32] Failure to keep pace with the motorized treadmill results in a noxious stimulus (contact wire brush or electric current).

Recent data indicate that FE has neuroprotective properties^[27,32] and improves motor function in MPTP-treated mice.^[19-21] FE has been proposed to support angiogenesis and synaptogenesis, increase defense from oxidative stress, and improve mitochondrial performance.^[32] The exact mechanism underlying improved motor function in MPTP-treated animals after FE is

unknown. An emerging and well-supported hypothesis is that FE increases neurotrophic proteins, including brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), and others within the substantia nigra and striatum.^[27,32] Furthermore, an elevation of neurotrophic factors within the basal ganglia has been suggested to protect against cell loss. Forced exercise has been shown to produce an increase in dopamine availability within the dorsolateral striatum.^[19-21] Because the primary role of this area is related to motor function, use-dependent forms of neuroplasticity may explain this regional specificity after a FE intervention.^[19-21] Collectively, the animal data suggest that FE triggers an endogenous release of neurotrophic factors within areas of the basal ganglia, which is likely to increase the level of dopamine within the dorsolateral striatum and facilitate compensatory changes in dopamine handling and neurotransmission.^[11,19-21] Although FE in animals may lead to dopamine sparing, improvements in motor function may require additional afferent input to the CNS of the animal^[11,29] (or human). Significant additional work is required to understand what the animal results mean in terms of potential exercise therapy for patients with PD. These promising results from animal exercise studies have not been translated fully to patients with PD. In fact, a recent meta-analysis concluded that there was insufficient evidence to support or refute the effectiveness of exercise therapy for patients with PD.^[25] We hypothesize that the apparent contradictory results between human and animal experiments are due to differences in the exercise paradigms used. The human experiments utilized voluntary exercise (VE), whereas FE was used in animals.

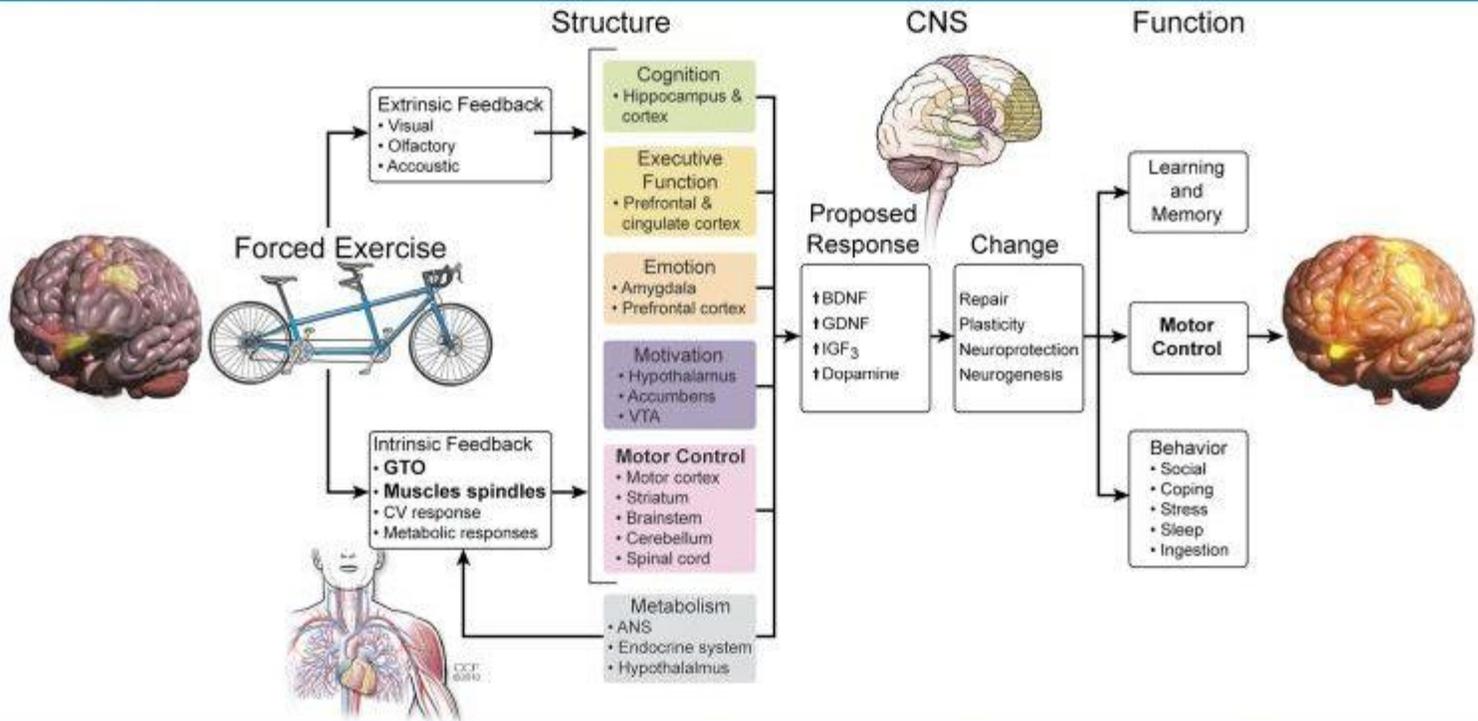
Exercise-induced Neuroplasticity in Humans

Clinical studies in healthy adults have demonstrated the molecular and cellular response to acute exercise in the release of neurotrophins, thought to be the key in supporting neuroplasticity.^[15] A recent systematic review of exercise-induced response of BDNF found that acute aerobic exercise transiently increased basal peripheral BDNF concentrations.^[16] This was evident only with acute aerobic exercise, not strength training, suggesting a relationship between exercise intensity and BDNF response. The release of BDNF into the bloodstream and subsequently into tissues is thought to be responsible for a cascade of neurotrophic and neuroprotective mechanisms, possibly facilitating neuromotor recovery. Specifically, BDNF is thought to facilitate "neuronal protection and survival, axonal and dendritic growth and remodeling, neuronal differentiation, and synaptogenesis".^[16]

In addition to the neuromotor improvements evident with aerobic exercise, the release of endogenous neurotrophins has been associated with improved cognition, learning, and memory.^[6,15] Animal studies have found a similar effect with enhanced behavioral recovery associated with the proliferation of glial cells and changes in neurotransmitter levels.^[15] A functional magnetic resonance imaging (fMRI) study by Burdette and colleagues^[9] found that a 4-month aerobic exercise intervention in a group of healthy but sedentary older adults resulted in increased cerebral blood flow and neuronal connectivity in the hippocampus. To date, these biochemical and neuronal changes as the result of voluntary aerobic exercise have not been shown in patients with PD. We hypothesize that the pathophysiology of PD, which limits sustained high-rate and high-intensity exercise, acts to impede these biochemical and neuronal responses.

Rationale for the Use of FE for the Treatment of PD

A representation of the structure and proposed changes in the CNS associated with FE and PD is provided in Figure 1. This schematic depicts the intrinsic and extrinsic factors associated with exercise in general. A potential differentiating feature of FE from VE is the magnitude of intrinsic feedback as a result of the greater pedaling rate. In particular, assisting patients with PD to pedal at higher rates than they could achieve voluntarily is likely to increase the afferent input from muscle spindles and Golgi tendon organs within the lower extremities (bolded in Fig. 1). It is proposed that this increase in intrinsic feedback may be triggering the release of neurotrophic factors or levels of certain neurotransmitters, such as dopamine in the case of PD, which may impact structure and function. Although the exact central mechanism is unknown, and unlikely to be determined in human studies, it is proposed, based on animal models of exercise and PD, that an increase in neurotrophic factors, such as BDNF, GDNF, insulin-like growth factor-3, and the neurotransmitter dopamine, likely aid in neural repair and neuroplasticity and possibly may provide a framework for neuroprotection or even neurogenesis within the brain. These proposed increases in neurotrophic factors and dopamine make FE a viable adjunct to current treatment regimes especially in those neurological populations that have motor or possibly cognitive declines that may prevent them from exercising at relatively high rates.



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Figure 1. Schematic depicting the proposed effect of forced exercise (FE) on central nervous center (CNS) structure and function. Diminished neural activity in the Parkinsons disease (PD) brain is depicted on the left portion of the illustration. It is proposed that FE results in an increase in the quantity (high rate of pedaling) and quality (consistent pedaling pattern) of intrinsic feedback from the Golgi tendon organs (GTO) and muscle spindles. This increased afferent information may trigger the release of neurotrophic factors (BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; IGF3, insulin growth factor) and possibly the neurotransmitter dopamine. The elevation of neurotrophic factors and dopamine has the potential to impact CNS structure and function. Proposed structures and function (matched by colors) that may be impacted by an elevation neurotrophic factors and dopamine are shown in the middle of the illustration. For PD, patients FE leads to improvements in motor control and an increase in the cortical activation. These changes in the CNS in PD positively affect the symptoms of this neurodegenerative disease and may serve as a model for the treatment of other neurological conditions. VTA, ventral tegmental area; ANS, autonomic nervous system. (Copyright © 2011 Cleveland Clinic Center for Medical Art & Photography. If you would like to reuse this image, please seek permissions directly from Cleveland Clinic Center for Medical Art & Photography. Used with permission.)

As the left portion of Figure 1 represents, patients with PD exhibit decreased cortical excitability and motor cortical output^[10,30] which are thought to underlie bradykinetic movements and impaired sensory integration. Previous studies have shown that patients with PD experience a decrease in the quantity, quality, and processing of afferent information.^[23] Exercise studies in animal models suggest that an important factor contributing to the positive effects of exercise on PD motor function is exercise rate (e.g., higher rate results in improved motor function and greater dopamine sparing).^[29] Patients with PD, because of diminished motor cortical activation, produce slow and irregular movements that may limit their ability to sustain exercise at the relatively high rates that seem necessary to trigger an endogenous increase in neurotrophic factors that are thought to underlie improved motor function.^[31,32] Therefore, our approach is to augment the VE rate of patients with PD via mechanical assistance (initially with a tandem cycle). It is important to note that our approach augments, but does not replace, the active efforts of the patient with PD. In our studies, under the guidance of an exercise physiologist, the patient actively must contribute sufficiently to the pedaling action that their heart rate is between 60% and 80% of their maximum heart rate using the Karvonen formula. Recent data indicate that active-assist mode of training of the upper^[17] extremities results in increased motor cortical activation, whereas passive training does not.^[28] Our preliminary data indicate that when the exercise rate of patients with PD is increased beyond their VE rate through mechanical assistance, the CNS receives additional afferent input via intrinsic feedback, primarily through an increase in the quantity and quality of intrinsic feedback. The proposed resultant cellular and biochemical responses improve PD symptoms and motor and nonmotor function. Through the induced changes as a result of FE, there is an increase in cortical excitability, which is represented on the right portion of Figure 1 and has been measured in our fMRI work.

Observations on a Bicycle Built for Two

The "discovery" of the positive effects of tandem cycling or FE on PD motor function was serendipitous. In 2003, one of the authors (J.L.A.) captained (front seat) a tandem cycle with a 48-year-old female patient with PD (rear seat stoker) on a week-

long recreational bike ride across Iowa. The purpose of riding tandem with a patient with PD for that week was to demonstrate that PD does not have to be a life-altering disease and that an active lifestyle can, and should, be maintained after diagnosis. After 2 days of tandem riding, the patient reported improvements in her symptoms and exhibited a substantial improvement in her handwriting.

Before the tandem ride across Iowa, the captain and stoker had spent only a minimum amount of time actually riding the tandem cycle together. Rather, each was training separately with the patient exercising on a stationary cycle because of compromised balance. Based on her training records, her voluntary pedaling rate during training was approximately 60 revolutions per minute (RPMs). During tandem cycling, the captain controlled the pedaling rate, which averaged 85 RPMs for the week. After observing the improvements in motor function of the patient and the improved handwriting after a lower extremity exercise, it was reasoned that tandem cycling may be a form of FE for humans. The drivetrain on a standard tandem cycle requires the two riders to pedal at the same rate, as their pedals are linked mechanically via a timing chain on the left side of the cycle. In the case of the ride across Iowa, the captain was "forcing" the patient to pedal about 40% faster than she pedaled during VE training. These "real-world" observations led us to conduct an initial study to assess if a tandem cycle could be used safely to deliver FE to human patients with PD and if a FE intervention of this type actually could improve PD motor symptoms and function.

FE Using a Tandem Cycle

In developing this study, it was necessary to measure the active contribution of the patient during FE on a tandem to determine if they were contributing actively to the pedaling action or just having their legs moved passively through the pedaling range of motion. Therefore, we developed a method to quantify the work performed by the captain and stoker during stationary tandem cycling. A standard tandem bicycle was modified to quantify the real-time and average power output of each rider (Fig. 2A). Standard cranksets were replaced with Schoberer Rad Messtechnik (SRM) Powermeter cranksets (Science version, Germany). The SRM has eight strain gauges within the crankset that measure metal displacement within the crankset. Displacement is converted into a power value proportional to pedal force. The SRM system is considered reliable and accurate.^[7] A custom rear axle/hub was built, and a PowerTap (CycleOps) was installed to measure overall power at the rear wheel. The PowerTap has been shown to be reliable in measuring power in laboratory settings.^[8]

The total, captain, and stoker power data for a 25-min test session are provided in Figure 2B. During the first 5 min, the stoker was instructed to be "passive," maintaining contact with the pedals but not assisting or resisting pedaling. When the stoker was passive, the captain produced approximately 15 more watts than the total power recorded at the rear wheel. This additional power was necessary to rotate the legs of the stoker. Thus, if a patient is passive during FE, their power output will be close to zero, and the power produced by the captain will be greater than that measured at the rear wheel. During the remaining 20 min, the stoker actively contributed at various self-selected exertion levels. High and low exertion of both captain and stoker are evident as their curves have clear maximums and minimums. For this 20-min period when both individuals were pedaling actively, the average total power (measured at the rear wheel) was 340 watts. On average, the captain produced 276 watts, approximately 80% of the total, whereas the stoker produced 68 watts or 20% of the total work (there is nearly a 2% loss in combined stoker and captain power compared with the overall power due to drivetrain energy loss). This experimental setup was used to deliver and monitor the contribution of the patient during FE.

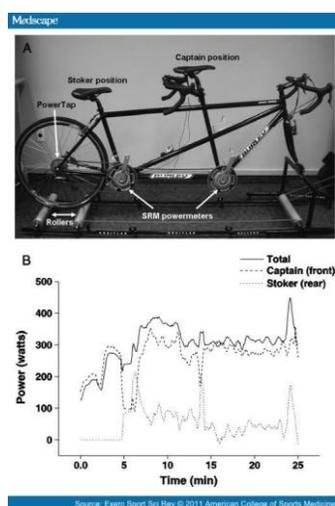


Figure 2. A. Tandem cycle used to deliver forced exercise (FE). B. Total power measured at the rear wheel (solid line) and power produced by the captain (dash line) and stoker (dotted line) for a 25-min test session. The stoker was passive for the first 5 min of the session.

Ten mild-to-moderate idiopathic patients with PD completed an 8-wk exercise intervention. Patients were randomized to a voluntary ($n = 5$) or forced ($n = 5$) exercise group. Table 1 contains patient demographics and group averages for exercise performance variables. In an effort to minimize the potential fluctuations in medication impacting either exercise groups'

ability to participate in the study, patients performed the three 1-h exercise sessions per week while on antiparkinsonian medication. Each session consisted of a 10-min warm-up, 40-min main exercise set, and 10-min cool-down period. Patients were able to rest whenever requested during the 40-min main exercise set. Both groups exercised at similar aerobic intensities (e.g., 60%-80% of their individualized target heart rate (THR)). The THR was calculated using the Karnoven formula, where maximum heart rate was defined as 220 minus the patient's age.

Table 1. Participant characteristics and average exercise performance variables across the 8-wk intervention.

	Forced	Voluntary
	(n = 5)	(n = 5)
Age (yr)	58 ± 2.1	64 ± 7.1
Duration of Parkinson's disease (yr)	7.9 ± 7.0	4.4 ± 4.0
Cadence (rpm)	85.8 ± 0.8	59.8 ± 13.6
Power (watts)	47 ± 16	67 ± 24
Heart rate (bpm)	116.8 ± 4.8	121.2 ± 20.5
Estimated $\dot{V}O_{2max}$ (mL kg ⁻¹ min ⁻¹)		
Baseline	26.1 ± 6.1	22.5 ± 2.0
EOT	29.0 ± 3.2	26.3 ± 2.2

Values are mean ± SD.

bpm, beats per minute; EOT, end of training; rpm, revolutions per minute.

Table 2 outlines the subject demographics, exercise parameters, and clinical ratings from our initial study. Patients randomized to the voluntary group exercised on a stationary bicycle equipped with a power measuring system. Patients were informed of their THR zones and asked to maintain their heart rate within that zone by adjusting resistance or pedaling rate. An exercise supervisor provided encouragement during the session and ensured the patient maintained their THR. No instructions regarding pedaling rate were provided; the rate was selected voluntarily. Patients randomized to the FE group cycled on a stationary tandem bicycle with an able-bodied trainer throughout the 8-wk study. The trainer ensured that the THR was maintained throughout the main exercise set. The trainer controlled the pedaling rate, 80–90 RPMs, and modulated the resistance to ensure that the patient's heart rate remained within the specified range. The patients' voluntary efforts were being augmented by the trainer to achieve a pedaling rate greater than they could produce during voluntary pedaling. The rationale for selecting 80–90 RPMs was based on our field observations that patients with PD experienced relief of motor symptoms when pedaling at this rate. Both groups exercised at identical relative intensities (e.g., 60%–80% of their individualized THR zone) during the 40-min main exercise set. Both groups were expected to show improvements in fitness; however, based on results of animal studies, improvements in motor performance were expected only for the forced group. These results would support the hypothesis that exercise rate is an important factor if motor function is to improve following exercise.

Table 2. Patient demographics, medication, forced-exercise performance, and clinical evaluation.

								Clinical Evaluation				
				Medication	Forced-Exercise Session			UPDRS-III			UPDRS Improvement (%)	
Patient	Sex	Age (yr)	Parkinson's Disease Duration (yr)	LEDD (mg)	Average Cadence (rpm)	Average Power (W)	Average Heart Rate (bpm)	Off Meds	On Meds	Off Meds + FE	Off Meds to on Meds	Off Meds to off Meds + FE
1	Male	57	2	900	84	73	108	49	31	33	36.73	32.65
2	Male	79	1	300	83	18	90	50	–	31	–	38.00
3	Male	65	5	225	79	95	138	58	26	27	55.17	53.45
4	Female	44	2	550	85	10	136	49	27	24	44.90	51.02
5	Male	61	5	550	89	98	133	46	23	22	50.00	52.17

6	Female	51	5	500	85	35	135	23	22	7	4.35	69.57
7	Female	61	6	650	86	33	133	51	21	25	58.82	50.98
8	Male	69	3	532	86	21	97	47	30	19	36.17	59.57
9	Male	62	2	160	85	49	115	37	50	21	– 35.14	43.24
Mean		61.00	3.44	485.22	84.54	46.96	120.43	45.56	28.75	23.22	31.38	50.07
SD		10.06	1.81	228.52	2.70	34.46	18.55	10.08	9.32	7.60	31.75	11.09

bpm, beats per minute; FE, forced exercise; LEDD, levodopa equivalent daily dose; UPDRS-III, Unified Parkinson's Disease Rating Scale, Part III.

The voluntary group's average wattage during each 40-min session was 67 watts, whereas the forced group averaged 47 watts per session. These differences in average watts across sessions were not different significantly between the two groups ($P > 0.1$). On average, the trainer riding the tandem cycle with the patient with PD averaged 144 watts across the 40-min exercise sessions. Collectively, the power output of the trainer and patient averaged nearly 200 watts; the relative contributions of the trainer and the patient with PD during cycling were 73% and 24%, respectively, with an average drivetrain loss of 3%. Individual patient analysis of power production data indicated that all patients in the forced group were contributing actively to the pedaling action, albeit less than the trainer; the relative contribution for patients with PD in the FE group ranged from 14% to 32%. Thus, patients with PD were not passive during FE, despite pedaling at a greater than voluntary rate.

Cardiorespiratory fitness was assessed using the YMCA submaximal cycle ergometer test at baseline and end of treatment (EOT). Briefly, heart rate-workload values were obtained at four points and extrapolated to predict workload at the estimated maximum heart rate. The $\dot{V}O_{2max}$ then was estimated from the predicted maximum workload using the formulas of Storer and colleagues.^[26] Estimated $\dot{V}O_{2max}$ improved for both groups after the exercise intervention. The type of exercise did not have a significant impact on estimated $\dot{V}O_{2max}$ after the voluntary or FE treatment period, as estimated $\dot{V}O_{2max}$ improved by 17% and 11%, respectively, from baseline to postexercise testing.

FE Improves Global Motor Function in Patients With PD

Our hypothesis was that FE alters the central motor processes in patients with PD and results in improvements in global motor function. Specifically, improvements in upper extremity function or in the cardinal signs of PD, which cannot be explained using motor learning theories, would be indicative of a global cortical response to a lower extremity exercise intervention. Motor function was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) Part-III motor examination and manual dexterity assessments. The UPDRS universally is the accepted rating scale for patients with PD, and it has been shown to be a valid and reliable clinical rating tool for PD symptoms.^[13,18] The UPDRS-III is a collection of 14 items in which an experienced clinician assigns a numerical score, ranging from 0 (normal or no impairment) to 4 (unable to perform or complete). The UPDRS-III is designed to assess the cardinal symptoms of PD: bradykinesia (slowness), postural instability and gait dysfunction, tremor, and akinesia (difficulty initiating movement). All UPDRS-III examinations were performed by a movement disorders neurologist who was blinded to group assignment, while the patients were practically defined off antiparkinsonian medication (e.g., 12 h since last dose). Patients were evaluated while off medication to better determine the effects of each type of exercise while minimizing possible confounds that could be related to fluctuations or effectiveness of antiparkinsonian medications.

As shown in Figure 3, blinded UPDRS-III ratings improved by 35% from baseline to EOT for the FE group ($P = 0.002$), whereas no improvements were observed for the VE group ($P > 0.17$). An improvement in the cardinal motor signs of PD also was evident, with the FE group demonstrating a 41% improvement in rigidity, 38% improvement in tremor, and a 28% improvement in bradykinesia after the 8-wk intervention. Midpoint evaluations were conducted, and although the FE group did experience an improvement after 4 wk of exercise, this improvement was not significant statistically. In terms of the duration of improvements in motor function, 4 wk after exercise cessation, clinical ratings had nearly returned to baseline levels for the FE group; however, these improvements at the 4-wk postexercise intervention approached significance ($P = 0.09$). This return to preexercise levels in clinical ratings was examined further by analyzing individual symptom ratings, which indicated that tremor ratings were back to baseline levels, whereas measures of bradykinesia and rigidity were, for the most part, maintained. Although we cannot rule out that some clinical improvements may have been due to the differences between human interaction for the two groups, every attempt was made to engage and encourage both groups of patients equally. Had the potentially greater social interaction effect occurred in those riding the tandem cycle been responsible for improvements in clinical ratings, then it would be expected that this social interaction effect certainly would have dissipated after exercise cessation, and those in the FE group would have returned to baseline at the 2-wk follow-up evaluation. Nevertheless, there is always a possibility that any intervention (actual or sham) can result in improvements, simply because of the subject's perception and expectation that they should improve, and all the participants in the study reported that they enjoyed participation and the interaction with the trainers.

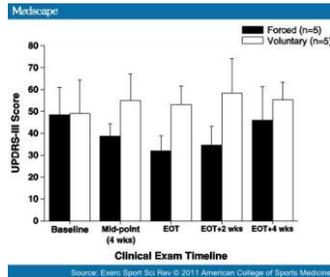


Figure 3. Blinded clinical ratings Unified Parkinsons Disease Rating Scale, Part III Motor Section (UPDRS-III) scores for patients in the voluntary exercise (VE; open bars) and forced exercise (FE; filled bars) groups at baseline, midpoint (4 wk of exercise), end of treatment (EOT). EOT + 2 wk exercise cessation and EOT + 4 wk exercise cessation.

To determine whether FE leads to global improvements in motor function (perhaps indicative of CNS changes), fine motor function was quantified during a bimanual dexterity task. Enhanced fine motor function of the upper extremities after lower extremity exercise would support the hypothesis that FE alters central motor processing. Dexterity was assessed using a paradigm developed in our laboratory (Fig. 4A).^[3,5] This paradigm is modeled after common dexterity tasks performed daily (e.g., fastening buttons or opening a container). The goal of the task is to disconnect two objects; the lower limb serves to stabilize the object, whereas the upper limb performs a manipulating action. The device consists of two identical force/torque transducers that measure normal (grip), tangential (lifting), shear forces and their associated torques (accuracy of 0.5 N). Resistance between the transducers, controlled via an electromagnet, was set at 8 N. Patients performed 10 trials of this task after the UPDRS examination.

Typical grasping force coupling plots (grip vs load) are shown for two representative patients in Figure 4B. Before the intervention, all patients with PD exhibited a decoupling of grasping forces characteristic of PD manual dexterity.^[3,5] Namely, the grip-load relationship was irregular and inconsistent from trial to trial. Voluntary exercise did not improve coupling of grasping forces for either limb. A persistent decoupling of grasping forces suggests that patients' utilized feedback to modulate grasping forces.^[3,5] After 8 wk of FE, the grip-load coupling of patients with PD became more linear, similar to what we have reported after deep brain stimulation.^[3,4] This linear relationship reflects the use of a feed-forward or predictive mode of controlling digit forces.^[14] Improved coupling of grasping forces persisted for the FE group 4 wk after exercise cessation. Improved grip-load coupling during this upper extremity task suggests that FE leads to a fundamental change in motor control for patients with PD. The transition from feedback to feed-forward control after FE, but not with VE, suggests that FE may be enhancing central motor processing and control functions of the basal ganglia.

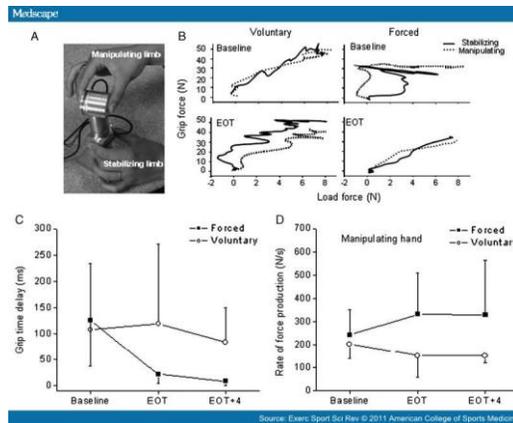


Figure 4. A. System used to objectively quantify bimanual upper extremity function. The goal of the task is to disconnect the two force transducers from one another. The upper transducer is held by the manipulating hand, whereas the lower transducer is grasped by the stabilizing hand. B. Representative grip-load coordination plots for the stabilizing (solid lines) and manipulating (dotted lines) limbs for a patient in the voluntary exercise (VE) (left) and forced exercise (FE) (right) groups at baseline and at end of training (EOT). Grip-load relationships in Parkinsons disease (PD) typically are uncoupled and irregular. After 8 wk of FE, grip-load relationships seem more coupled but unchanged after VE. C. Mean changes in grip time delay (grip onset manipulating-grip onset stabilizing). Delays were reduced significantly in the FE group from baseline to EOT and EOT + 4. Standard deviations also were reduced after the intervention. No changes in grip time delay were noted in the VE group. D. Mean changes in rate of force production in the manipulating hand at baseline, EOT, and EOT + 4. Rates of force production were increased significantly after 8 wk of FE but were reduced slightly after VE. Error bars = standard deviations. (Reprinted from (22). Copyright © 2009 Society for Neuroscience. Used with permission.)

Interlimb coordination, as assessed by grip time delay, improved significantly for the FE group ($P = 0.01$) but did not change for the VE group (Fig. 4C). The rate of grip force ($\Delta\text{force}/\Delta\text{time}$) has been suggested to reflect the level of voluntary neural activation.^[1] A slight but nonsignificant decrease in the rate of grip force in the manipulating limb was observed for the VE group from baseline to EOT ($202.8\text{--}151.6\text{ N}\cdot\text{s}^{-1}$) with no change from EOT + 4 wk ($151.6\text{--}150.4\text{ N}\cdot\text{s}^{-1}$) (Fig. 4D). However, patients in the FE group showed a significant increase in rate of grip force production for the manipulating limb from baseline

to EOT (242.4–331.4 N·s⁻¹). A group × time interaction was present for the rate of grip force for the manipulating limb ($F_{2,36} = 6.195$, $P = 0.005$); the FE group increased rate significantly ($P = 0.006$). The rate of force produced by the manipulating limb increased approximately 37% from baseline to EOT. These improvements in the rate of grip force production were maintained for the FE group at the EOT + 4 evaluation.

Digit placement on the upper and lower object was determined using the forces and torques to calculate the average center of pressure (COP) during the task (for details related to this calculation, see previous work^[3,4]). Figure 5 contains the average COP for both the manipulating and stabilizing limbs (which corresponds to digit placement) for all trials at baseline, EOT, and EOT + 4 evaluations for both groups. Consistency of digit placement was quantified by calculating the area of an ellipse that captured 95% of the COP data; smaller area corresponds to more consistent digit placement.^[4] The COP analyses were performed for each limb for each patient on an individual patient basis. A significant group × time interaction was present for area of COP for the manipulating ($F_{2,36} = 7.85$, $P < 0.001$) and stabilizing ($F_{2,36} = 6.41$, $P < 0.001$) limbs. At baseline, patients in both groups, on average, were variable in digit placement for both limbs. The average area of the ellipse for the manipulating and stabilizing hand was 4.1 and 3.1 cm², respectively, for the FE group, whereas the voluntary group had areas of 3.8 and 3.1 cm² for the manipulating and stabilizing hands, respectively. In general, the VE group did not exhibit any improvement in consistency of digit placement: at EOT, 2.9 and 2.8 cm² for the manipulating and stabilizing limb, respectively, and at EOT + 4, 2.9 and 2.4 cm². FE resulted in a significant improvement in the consistency of digit placement for both limbs. At EOT, area of the ellipse decreased to 1.1 and 1.0 cm² for the manipulating and stabilizing limbs, respectively. These improvements were maintained at EOT + 4-wk evaluation as area was 1.74 and 0.89 cm². Overall, these results provide additional support that FE may be resulting in a change in motor control with greater reliance on feed-forward control processes, allowing for patients to preprogram their movements, which leads to more consistent digit placement.

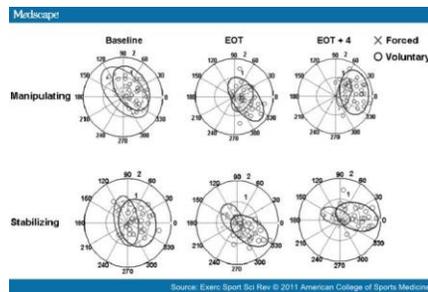


Figure 5. Center of pressure for all dexterity trials for patients in the forced exercise (FE) (x) and voluntary exercise (VE) (o) groups at baseline, end of training (EOT), and EOT + 4 wk. The upper limb performs the manipulating action, whereas the lower limb acts to stabilize the device. Ellipses define the area of spread to encompass 95% of the data. Forced exercise resulted in significantly less spread in center of pressure (COP) than VE. Smaller ellipses indicate less variability in COP and digit placement. (Reprinted from (22). Copyright © 2009 Society for Neuroscience. Used with permission.)

Improved grip-load coupling, more consistent digit placement, faster movements, improved interlimb coordination, and increased rate of grip force production indicate that FE improves the upper extremity motor performance and may lead to a fundamental change in movement control strategy. Before the intervention, all patients' kinematic and kinetic variables were characteristic of a reliance on feedback control,^[3,5] likely to compensate for variability in motor output.^[2,24] VE did not improve any biomechanical variable characterizing manual dexterity. Therefore, improvements in aerobic fitness associated with VE do not lead to improved motor function. However, after FE, patients appeared to rely more on feed-forward to control grasping forces. Increased rate of grip force production with FE may reflect an increased, albeit indirect, level of motor cortical activation.

Immediate and sustained improvements in objective biomechanical measures of upper extremity function in patients with PD after FE, but not VE, suggest that aerobic exercise alone may not be sufficient to produce global changes in motor function. Rather, these initial data suggest that patients with PD may require assistance in achieving a pedaling rate that is sufficient to elicit a change in central motor processing. These results from the FE group parallel previous findings in which rodents forced to exercise at high rates demonstrated improvements in motor function and increased concentrations of BDNF and GDNF compared with controls.^[11,19] Although the exact mechanism(s) for these improvements in upper extremity motor function after a lower extremity exercise intervention cannot be determined solely through biomechanical measures, the fundamental change in the motor control strategies, from feedback to feedforward, used in the control and coordination of grasping forces is strong evidence for a change in CNS function. Further support for a change in CNS function after FE is that improvement in the control and coordination of grasping forces was present not only after the intervention ended but also 4 wk after exercise cessation, and these improvements occurred while the patients were off antiparkinsonian medication. To further investigate the possible mechanism responsible for these changes in motor control patterns, we sought to compare the effects of acute FE and antiparkinsonian medication on the pattern and level of cortical and subcortical activation in PD patients.

FE Improves Cortical and Subcortical Activation

The effects of acute FE on brain activation pattern were studied in nine mild-to-moderate patients with PD, not part of the long-term study, using a magnetic resonance imaging (MRI) protocol including whole brain T1-weighted anatomic images and a set of fMRI scans. Subjects were scanned under three conditions: 1) off meds, 2) on meds, and 3) after FE while off

meds. The order of scan sessions was randomized across subjects. Each session was separated by 5–7 d. On the FE day, subjects performed 40 min of FE, showered (to maintain blinding of the neurologist), rested, and ate a light snack and were evaluated 3 h later. After the UPDRS-III, subjects were transported by wheelchair to the scanner. During scanning, subjects performed a constant or sinusoidal force-tracking task, which we have used previously. All subjects were fitted for a bite bar to restrict head motion during scanning.

Figure 6 shows activation maps averaged across subjects for two axial slices (showing subcortical and cortical regions) in Talairach space, displayed on averaged T1 anatomic image. Regions of interest (ROI) were drawn in bilateral putamen, globus pallidus, thalamus, primary motor, and supplementary motor area. The effect of FE (vs off medication) was compared with the effect of medication by examining the percent signal change in the side contralateral to the task, as shown in Table 3. In all five regions, strong correlations were observed, indicating a similar change in BOLD MRI response for FE and medication. Blinded UPDRS-III ratings in these same patients decreased 35% and 32% after FE and on medication compared with off medication, respectively. Imaging data indicate a significant correlation between FE and medication for regions in the basal ganglia and cortex. These results indicate that FE and medication utilize similar pathways to produce symptomatic relief. We are unaware of any other data that demonstrates that exercise in PD leads to an increase in cortical and subcortical activation.

Table 3. Correlations in subcortical and cortical regions of interest between effect of medication and effect of exercise.

	Linear Correlation	
	Contralateral Side	P
Putamen	0.527	4.76 E-03
Globus pallidus	0.551	2.90 E-03
Thalamus	0.891	4.94 E-10
Primary motor	0.494	8.85 E-03
Supplementary motor area	0.580	1.50 E-03

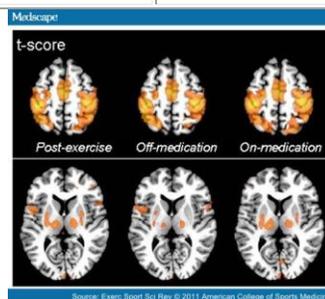


Figure 6. Cortical and subcortical activation maps across subjects. Highlighted areas indicate areas in the brain where increased blood flow, or cortical activation is present with hand movement tasks during scanning. This figure is an average of nine patients with Parkinsons disease (PD) under three conditions: on antiparkinsonian medication, off antiparkinsonian medication, and 3-h post forced exercise (FE) while off antiparkinsonian medication. The pattern of cortical and subcortical activation was similar while patients were on medication and following FE while off medications.

Future Directions and Summary

A randomized controlled trial currently is underway as a follow-up to the initial tandem cycling study. Subjects are randomized to one of three groups: no exercise, VE, and FE. However, in the current trial, a motor-driven cycle, which we have developed is being used to safely deliver FE. A model-based controller was developed to replicate the "feel" of the human interaction that occurs during tandem cycling (e.g., real-time alteration of motor contribution, pedaling rate, and monitoring of heart rate). The controller model approximates the dynamics of the cycle interacting with the rider during an exercise session. This trial includes clinical testing and neuroimaging 8 wk after exercise cessation to help determine the long-term effects of FE and VE in patients with PD. We also are engaged in a preliminary study with deNovo patients with PD in which they will exercise for 6 months in their home. Weekly cognitive and motor assessments will be made and compared with a group of deNovo patients with PD who are not exercising. Collectively, these studies will provide greater information regarding the potential mechanisms underlying any improvements in cognitive or motor function in patients with PD after FE or VE, the possible duration of motor or symptom benefits and initial data regarding the potential for exercise to slow the progression of PD.

Although the exact components and dosage of optimal exercise interventions have not been determined for patients with PD, evidence from the animal studies and our data suggests that intensive aerobic FE may have neurorestorative and neuroprotective properties possibly through the endogenous release of neurotrophins or alteration of dopamine. Animal and our preliminary human data suggest the ability to influence cognition, metabolism, and potentially, the progression of

neurodegenerative diseases through these mechanisms. Even the hint of neurorestoration associated with FE warrants the testing of this intervention in other neurologic conditions such as stroke and Alzheimer disease, as the "side effects" of exercise include improved cardiovascular fitness and increased energy. Future studies will help delineate the optimal dosage of FE or VE for neurologic patients. Furthermore, a clearer understanding of the use of FE as a neuroprotective or neurorestorative adjunct to pharmacological or surgical interventions offers these patients a rare opportunity to participate actively in the treatment of their disease with minimal risks or side effects.

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