Forced Exercise Holds Promise as Novel Intervention for Parkinson's, Other Neurodegenerative Diseases

By Jay L. Alberts, PhD

Although studies in animal models of Parkinson's disease (PD) have shown that exercise improves motor function and has neuroprotective benefits, results of clinical research investigating the effects of exercise in human PD patients have been less promising. Specific exercise regimens have been associated with a few specific improvements in patients with PD, such as increased strength following weight lifting or increased walking speed after treadmill training. However, the exercise protocols studied failed to produce any type of *global* motor improvements using accepted clinical rating tools such as the Unified Parkinson's Disease Rating Scale (UPDRS) or improvements in parts of the body that were not being exercised.

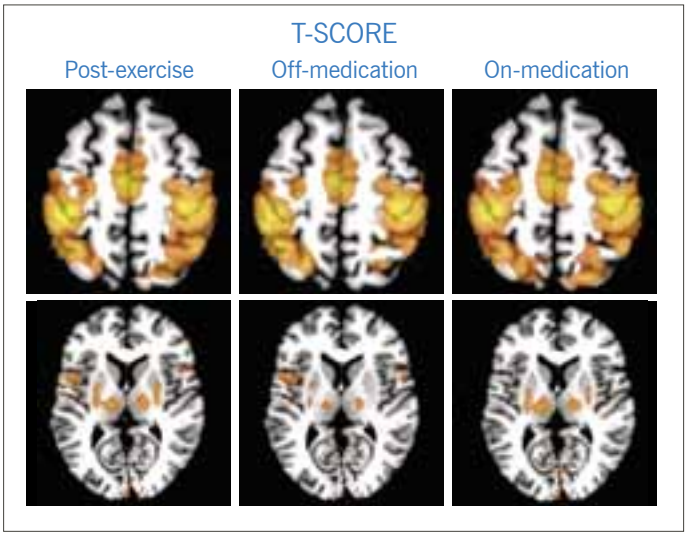
Personal coincidental observations I made on two separate occasions of remarkable symptomatic improvements in PD patients sharing a tandem bicycle with me, a trained cyclist, motivated me to look further to try to understand the discrepancy between the promising results of the animal research and the marginally effective human studies. This interest has led to a clinical study program that we hope will establish exercise as a novel intervention for improving motor function and altering brain function in patients with PD. If successful, the research is exciting, not only because a treatment approach based on exercise will convert patients from a passive role in their disease management to active participation, but also because discovering a treatment that affects brain function might positively alter (i.e., slow) the natural course of PD and, possibly, other neurological diseases.

Exercise Intensity and Motor Function Improvement

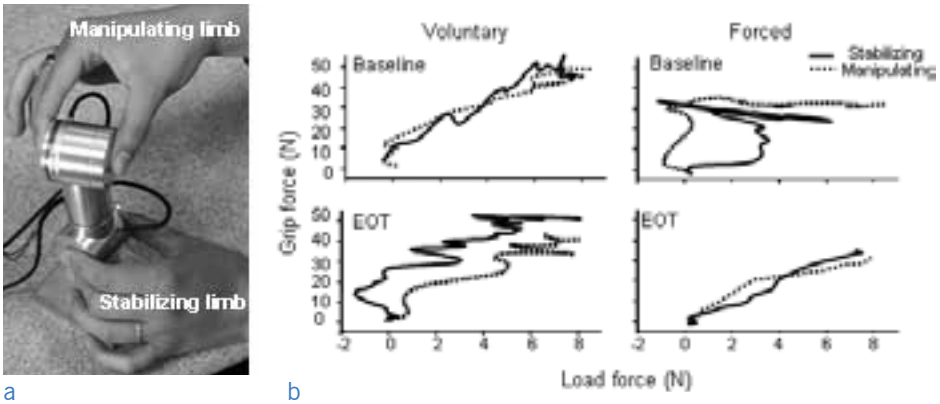
Closer consideration of the research conducted in rodent models of PD revealed that these exercise regimens involved a "forced exercise" paradigm under which the animals were placed on a treadmill and exposed to an external stimulus as needed to assure they maintained a set pace, which was faster than their naturally preferred walking speed. In contrast, exercise intensity for participants in previous clinical studies was under their individual or voluntary control. I postulated that the tandem bicycle riding might be a form of forced exercise that could be responsible for the patient-noted improvements in motor function while cycling. Animal research showing a direct correlation between increasing rate of exercise and the level of global motor function improvement was also consistent with the idea that differences in exercise rate might explain the inconsistency in outcomes between the animal and clinical research.

In 2007, we initiated a proof-of-concept study to investigate the hypothesis that PD patients might derive motor function benefits from physical exercise, if given the opportunity to exercise at rates higher than they could normally achieve. The results were recently published in a leading rehabilitation journal.[1] The study randomized 10 PD patients into voluntary and forced exercise groups, the former riding a stationary single bicycle at a voluntary rate and the other riding a stationary tandem bicycle with a trained cyclist. The tandem group was assisted at pedaling between 80 and 90 revolutions per minute, while the voluntary group pedaled at its preferred rate.

Patients in both groups completed one-hour exercise sessions, three days a week for eight weeks at similar aerobic intensities. Assessments were made at baseline, at the end of the exercise program and four weeks after its completion, and included a fitness evaluation of maximal oxygen uptake (VO_2max) and motor function evaluations using clinical ratings (the UPDRS Part III motor score) and a biomechanical assessment of manual dexterity. The latter was included as a specific measure of motor function in the non-exercised upper extremities to explore the concept that forced exercise produced global effects and resulted in positive changes in central motor control processes.



Cortical and subcortical activation maps across participants, showing that the pattern of neural activation following forced exercise is similar to the pattern with medication.



(a) Illustration of bimanual dexterity task. (b) Representative grip-load coordination plots for stabilizing and manipulating limbs. Grip-load relationships in Parkinson's disease are typically uncoupled and irregular. After eight weeks of exercise, grip-load relationships appear more coupled in the forced exercise group but are unchanged after voluntary exercise. EOT indicates end of treatment.

Imaging Shows Increased Brain Activation

After eight weeks of exercise, patients in both groups achieved significant improvements in aerobic fitness. However, motor function benefits were observed only in the forced exercise group. After eight weeks of the forced exercise program, patients exhibited a 35 percent improvement over baseline UPDRS III scores, which was statistically significant. While their scores worsened four weeks later, they still showed an improvement over baseline that approached statistical significance.

More strikingly, the forced exercise group showed a significant improvement in manual dexterity that was maintained at the follow-up examination four weeks after cessation of the exercise program. The latter changes included improved coupling of grasping forces, interlimb coordination and rate of force production. There were no significant changes from baseline UPDRS III or manual dexterity scores in the voluntary exercise group immediately after exercise ceased or at the follow-up visit.

Encouraged by these results that indicate the forced exercise program may be having a disease-modifying impact and not just a symptomatic effect, we undertook a short-term follow-up study to examine changes in brain function using functional magnetic resonance imaging (fMRI). Conducted in collaboration with Micheal Phillips, MD, Department of Neurosciences, and Mark Lowe, PhD, Department of Diagnostic Radiology, the study had a crossover design in which PD patients underwent imaging on three separate occasions: 1) three to four hours after completing a forced exercise session, 2) three to four hours after taking their anti-PD medication and 3) when there was no exposure to exercise or medication. The order in which the different test situations were conducted was randomized across subjects. The fMRI scans showed that compared with the control visit, exercise and medication produced similar neural responses in terms of increasing activation levels in both the cortical and subcortical areas of the brain.

New Data Forthcoming

We have expanded our research into a larger clinical trial being conducted at the Cleveland Clinic main campus and at our Lou Ruvo Center for Brain Health in Las Vegas. Our goal is to recruit 60 patients who will be randomized to a no-exercise control group or to an eight-week program of voluntary or forced exercise, with a follow-up assessment again after four weeks. Endpoints include the same clinical and biomechanical measurements assessed in our pilot study, along with additional biomechanical measurements of lower extremity function and postural stability. This trial also includes an imaging component that will provide the first data on possible long-term effects of forced or voluntary exercise on brain function. Patients in the forced exercise group are using a motorized stationary single bicycle that would be more practical for adaptation to clinical or home use.

The mechanism(s) by which forced exercise produces the neural and motor changes we have observed are unknown. However, there is evidence that peripheral nerve stimulation increases excitability in the motor cortex, and animal research indicates that forced exercise is associated with increased brain levels of dopamine and/or neurotrophic factors (GDNF or BDNF). If forced exercise induces these neurochemical changes, it may have exciting potential to slow disease progression and delay the need for medical therapy in patients diagnosed with PD. Looking ahead and considering that these neurotrophic factors have established importance in the acquisition of motor skills, the opportunity to positively alter their levels by forced exercise has us thinking about future research investigating this intervention in Alzheimer's disease, rehabilitation for stroke and other neurodegenerative disorders.

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REFERENCE

1. Ridgel AL, Vitek JL, Alberts JL. Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabil Neural Repair.* 2009;23(6):600-608.