# Does vigorous exercise have a neuroprotective effect in Parkinson disease?

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## ABSTRACT

Parkinson disease (PD) is progressive, with dementia and medication-refractory motor problems common reasons for late-stage nursing-home placement. Increasing evidence suggests that ongoing vigorous exercise/physical fitness may favorably influence this progression. Parkinsonian animal models reveal exercise-related protection from dopaminergic neurotoxins, apparently mediated by brain neurotrophic factors and neuroplasticity (predicted from in vitro studies). Similarly, exercise consistently improves cognition in animals, also linked to enhanced neuroplasticity and increased neurotrophic factor expression. In these animal models, immobilization has the opposite effect. Brain-derived neurotrophic factor (BDNF) may mediate at least some of this exercise benefit. In humans, exercise increases serum BDNF, and this is known to cross the blood–brain barrier. PD risk in humans is significantly reduced by midlife exercise, documented in large prospective studies. No studies have addressed whether exercise influences dementia risk in PD, but exercised patients with PD improve cognitive scores. Among seniors in general, exercise or physical fitness has not only been associated with better cognitive scores, but midlife exercise significantly reduces the later risk of both dementia and mild cognitive impairment. Finally, numerous studies in seniors with and without dementia have reported increased cerebral gray matter volumes associated with physical fitness or exercise. These findings have several implications for PD clinicians. 1) Ongoing vigorous exercise and physical fitness should be highly encouraged. 2) PD physical therapy programs should include structured, graduated fitness instruction and guidance for deconditioned patients with PD. 3) Levodopa and other forms of dopamine replenishment therapy should be utilized to achieve the maximum capability and motivation for patients to maintain fitness. *Neurology*® **2011;77:288-294**

## GLOSSARY

**AD** = Alzheimer disease; **BDNF** = brain-derived neurotrophic factor; **GDNF** = glial-derived neurotrophic factor; **MCI** = mild cognitive impairment; **PD** = Parkinson disease; **VEGF** = vascular endothelial growth factor.

Parkinson disease (PD) is progressive. Although the dopaminergic nigrostriatal system receives much attention, progression in nondopaminergic circuits eventually becomes the primary substrate for major PD disability. Nursing home placement is typically the consequence of cognitive impairment/dementia or nondopaminergic motor deficits, especially levodopa-refractory balance and gait problems.[1]

A major focus of PD research has been on "disease-modifying" or "neuroprotective" agents to slow PD progression. No drugs have surfaced, to date, that unequivocally have that property. However, often overlooked in this discussion is the potential benefit of sustained vigorous exercise on PD progression. Exercise is well-known to have general health benefits, including improvement of cardiovascular and cerebrovascular health, reduction of osteoporosis/fracture risk and age-related sarcopenia, improvement of psychological affect, and perhaps even a general anti-inflammatory effect.[2] However, accumulating evidence, albeit indirect, suggests that ongoing vigorous exercise may have a neuroprotective effect in PD, beyond the general salutary effects on age-related afflictions.

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**VIGOROUS EXERCISE** "Vigorous exercise" may be variously defined, but for our purposes consider this to represent aerobic physical activity sufficient to increase heart rate and the need for oxygen. For this to be meaningful, it should be sustained (e.g., perhaps for at least 20–30 minutes at a time) and repeated/ongoing. Ultimately, such sustained and ongoing physical activity should translate into what physiologists term cardiovascular fitness, documented by relatively high oxygen uptake at peak exercise ($VO_2$). Operationally, this would include regular routines such as walking, jogging, swimming, tennis gym exercises, or home activities such as raking leaves, digging, shoveling snow, and so on. These and related activities are often scaled back or neglected in our society with normal aging, and especially by people with PD. Although physical therapy is routinely utilized in PD treatment, this often focuses on gait and balance training, and stretching, but usually is not directed at achieving physical fitness. Evidence from several perspectives suggests that this may be a neglected opportunity for "disease modification" by the PD community.

**STUDIES IN HUMANS** **Prospective evidence suggests that midlife, regular exercise reduces the subsequent PD risk years later.** Moderate to vigorous exercise habits in midlife significantly reduced the risk of later-developing PD in 3 large cohorts,[3–5] although confined to men in one study.[3] Among these prospectively tabulated subjects, this PD risk reduction was significant even when restricted to periods well before PD, such as ages 35–39,[5] ages 30–40,[3] or PD onset >4 years following exercise assessment.[4] In 2 other large prospective cohorts, trends suggested a reduced PD risk with exercise, although not significant.[6,7]

A recent meta-analysis of prospective studies confirmed the association of diminished PD risk with moderate to vigorous activities in preceding years.[5] To put this into perspective, the risk reduction documented in this meta-analysis (OR = 0.67) was of a similar order of magnitude to the PD risk reductions previously noted with caffeine consumption or smoking,[8] although presumably by quite different mechanisms.

Obviously, reverse causality cannot be excluded in these studies of exercise and subsequent PD risk; preclinical PD might manifest years before as reduced activities or aversion to exercise. Also, health-conscious people who exercise may be more likely to consult physicians and have PD diagnosed.

**Might exercise slow PD progression?** If midlife vigorous exercise is directly responsible for subsequently reduced PD risk, this may also have implications for PD progression. If this is a bona fide effect, then an attenuating influence on the inciting neurodegenerative process may not necessarily stop when PD clinically manifests. Assuming the pathogenic mechanism continues, the disease-attenuating effect may persist. In other words, if exercise reduces PD risk, it might also slow the progression of PD.

Little direct evidence currently bears on this possibility and there is a paucity of clinical trial data. Cardiovascular fitness (measured by peak $VO_2$) has been associated with better cognitive and motor scores in patients with PD.[9] Vigorous exercise improved corticomotor excitability in a PD cohort, suggesting potential neuroplasticity in one other investigation.[10] Finally, longevity in PD has been associated with physical exercise.[11] However, expanding on these findings is substantial indirect evidence from a variety of sources suggesting that a neuroprotective effect from vigorous exercise in PD is biologically plausible and perhaps even likely, as summarized below.

**Exercise reduces risks of cognitive impairment in the general population.** Cognitive impairment from PD progression is the outcome most feared by patients, and is a major source of eventual treatment-refractory disability. Mild cognitive impairment (MCI) is already present in about a quarter of patients with early PD.[12–14] Dementia eventually develops in most patients with PD with long-term follow-up.[15,16]

The few studies that have assessed the effect of exercise on cognition in patients with PD suggest a favorable effect. As mentioned above, physically fit patients with PD had better cognitive scores than unfit patients with PD.[9] In 2 other studies among patients with PD, exercise was associated with short-term cognitive benefits.[17,18] Unfortunately, there are no randomized, controlled trials of long-term exercise in PD.

There is, however, an ever-increasing literature suggesting that exercise/physical fitness has more pervasive benefits on cognitive outcomes in the general population, as evidenced by the following.

1. Similar to PD risk, regular exercise in mid- or later life reduces the later risk of dementia, as well as Alzheimer disease (AD), documented in recent meta-analyses.[19]
2. Early-life and midlife exercise reduces the subsequent risk of MCI.[20–23]
3. Patients with AD who were physically active had a significantly reduced mortality risk compared to sedentary patients.[24]
4. Seniors with MCI[25,26] or dementia[27] experienced significant cognitive improvement with exercise over those randomized to a sedentary intervention.

5. Aerobic exercise in normal adults significantly improved cognitive performance in a meta-analysis of controlled trials.[28]
6. Physically fit seniors (defined by peak $VO_2$ values on exercise testing) had better cognitive scores than unfit seniors.[29,30]
7. Chronic exercise in seniors appeared to improve functional connectivity or cortical activation in cerebral circuits relevant to cognition, measured by fMRI, as well as improving executive cognitive scores.[29,31]

Caveat: The first 3 entries in the above list could alternatively relate to reverse causality. Those destined to develop cognitive impairment/dementia or earlier mortality may have been less inclined to exercise.

**Cortical and hippocampal volume increases with exercise in the general population.** Aging is associated with progressive reduction of gray matter volume, primarily due to progressive loss of synapses and neuropil.[32–34] Several magnetic resonance brain imaging studies suggest that exercise may counter this trend. Thus, less age-related volume loss in cortex[30,35] or hippocampus[36] was found among seniors with documented aerobic fitness, defined by peak $VO_2$ on exercise testing. Prospective studies have documented significantly increased cortical gray matter[37,38] or hippocampal volumes[39] in seniors randomized to 6–12 months of exercise, compared to more sedentary controls. Similarly, walking distances as indices of physical activity were associated with better preservation of gray matter/cortical volumes when followed up 9 years later[40]; this was also associated with a significantly reduced risk of cognitive impairment. Finally, hippocampal dentate gyrus cerebral blood volume was increased at the end of a 3-month exercise program; both this change, as well as cognitive improvement, correlated with changes in aerobic fitness (peak $VO_2$).[41] However, whole brain or temporal lobe volumes in control group subjects did not correlate with aerobic fitness in 2 other studies.[42,43]

**AD brain atrophy is significantly less among those with cardiorespiratory fitness.** Brain MRI volumetric measurements have revealed progressive brain atrophy in AD, especially affecting the temporal lobe. However, this is attenuated with maintained physical fitness, documented by peak $VO_2$ values during exercise testing. Thus, in patients with AD, peak $VO_2$ correlated with whole brain, white matter, and temporal lobe volumes.[42,43] Parenthetically, in a transgenic mouse model of AD, 5 months of exercise significantly reduced brain $\beta$-amyloid concentrations.[44]

**ANIMAL MODELS** Evidence from animal studies indicates that physical exercise enhances brain neuro-

plasticity and elevates certain neurotrophic factors. This may be relevant to patients with PD.

**Protective effect of exercise in animal models of parkinsonism.** Multiple studies have documented that vigorous exercise in animal models of parkinsonism mitigates the effects of the dopaminergic neurotoxins, 6-hydroxydopamine (6-OH-DA) and 1-methyl,4-phenyl,1,2,3,6-tetrahydropyridine (MPTP), with evidence for a neuroprotective effect. In these rat/mouse studies, exercise is controlled, using running wheels or treadmills; in the case of unilateral 6-OH-DA to create hemiparkinsonism, cast immobilization of the good limb forces use of the affected limb. This literature may be summarized as follows.

**Unilateral nigrostriatal 6-OH-DA to induce hemiparkinsonism**

1. Parkinsonian deficits are markedly attenuated or reversed by exercise,[45–47] although with one exception[48]:
2. Parkinsonian deficits are reversed by forced used of the affected limb (casting of the unaffected limb).[49–51]
3. Nonuse via cast immobilization of the parkinsonian side significantly exacerbates the deficit.[50]
4. Markers of integrity of the dopaminergic terminals[45,47,49,50] or neurons[47] suggest a neuroprotective effect from exercise, although this was not confirmed in one study.[46]

**Systemic MPTP to induce generalized parkinsonism**

1. Parkinsonism is attenuated by exercise.[45,52–54]
2. Limb immobilization exacerbates the parkinsonian deficit.[55]
3. Markers of dopaminergic terminal integrity suggest exercise sparing from neurotoxin damage or sprouting of new terminals.[45] Conversely, immobilization results in significant further reductions of terminal markers such as vesicular monoamine transporter–2 (VMAT2).[55] Other studies, however, failed to document increased tyrosine hydroxylase or dopamine transporter expression with exercise.[56,57]
4. Midbrain dopaminergic neuronal counts corroborated a neuroprotective effect from exercise in some,[53,58] but not in all studies.[52,56]
5. There is a dose effect, with exercise duration and intensity each influencing the neurochemical and neuronal count results, as well as the motor-parkinsonism.[53,58]
6. Exercise attenuates the hyperexcitability of striatal (medium spiny) neurons after dopamine depletion, with modulation of glutamatergic receptor subunit expression.[54]

Notably, vigorous exercise in these parkinsonian animal models induces brain neurotrophic factor expres-

sion, which may mediate putative neuroprotective effects. This includes brain-derived neurotrophic factor (BDNF)[47] and glial-derived neurotrophic factor (GDNF).[47,51] Note that both BDNF and GDNF are significantly reduced in the substantia nigra of patients with PD.[59] One other animal model utilized systemically administered lipopolysaccharide to induce nigral cell loss and parkinsonism; exercise blocked these negative outcomes in proportion to the exercise duration, apparently mediated by elevated BDNF levels.[60] Other exercise effects in parkinsonian animal models have included enhanced subventricular zone neural progenitor cell proliferation and migration,[47] as well as reversal of age-related decline in substantia nigra vascularization, apparently mediated by vascular endothelial growth factor (VEGF) expression.[e1]

How such animal models relate to neurodegenerative PD is open to debate. However, they suggest that exercise-induced neuroplasticity is operative in the nigrostriatal and related motor circuits.

**Cognition in general animal models: Evidence for exercise-induced neuroplasticity.** As mentioned, dementia develops in most patients with PD over the long term[15,16] and is often the reason for nursing home placement. The substrate is proliferation of the Lewy neurodegenerative process.[e2-e4] Animal studies have not specifically addressed the influence of exercise on proliferation of Lewy pathology. However, the influence of exercise on cognition in intact animals has been extensively studied.

Most animal studies investigating exercise influences on cognition have targeted the hippocampus, obviously a crucial brain nucleus for learning. Note that mice/rats voluntarily run for long durations if provided exercise wheels in their cages. Other research paradigms utilize treadmills to control exercise. The outcomes from such studies in mice/rats have been consistent, with evidence of enhanced neuroplasticity in the hippocampus, especially dentate gyrus. These hippocampal findings induced by exercise include the following:

1. Elevated expression of BDNF, which appears to be a key factor mediating the effects of exercise on cognition[e5-e14]
2. Increased expression of the neuroprotective agent, insulin-like growth factor I, which interacts with BDNF to mediate exercise-induced cognitive gains[e15]; exercise-induced production of this factor protects against neurotoxic hippocampal insults[e16] and is acutely elevated by exercise in normal humans[e17]
3. Induction of neuroplasticity-related transcription factors such as intracellular kinase signaling systems

and cyclic adenosine monophosphate response element-binding protein[13,e9,e18]
4. Neurogenesis[e6,e19-e23]
5. Elevated concentrations of synaptic proteins, synapsin I and synaptophysin[e11,e12]
6. Enhanced long-term potentiation, a measure of synaptic efficacy[e6,e14,e19]
7. Increased dendritic length, complexity, and spine density[e22,e24]
8. Increased expression of genes associated with synaptic plasticity and downregulation of genes linked to oxidative stress[e25]

The changes at the molecular and microscopic level within the hippocampus have been associated with improved performance on spatial memory tasks[e7,e10,e13,e15,e19,e23] and object recognition.[e24] In contrast to exercise, hind-limb immobilization had opposite effects, with reductions in both hippocampal BDNF and neurogenesis.[e26] Whereas the above studies involved rodents, normal adult monkeys trained to run on treadmills for 1 hour, 5 days weekly for 5 months, improved their scores on certain cognitive tests, compared to sedentary animals.[e27]

**Elevated BDNF induced by exercise in humans.** Increased expression of BDNF appears to be important for the beneficial effects of exercise on cognition in animals.[e9,e10,e13,e28] BDNF is recognized to be a key protein modulating brain plasticity and is distributed widely throughout the brain.[e29] In humans, serum BDNF concentrations rise after exercise,[e30] and in proportion to the exercise intensity.[e31] Cognition in aging women is correlated with plasma BDNF, although not in men.[e32] These findings in the circulation may be relevant in that BDNF readily crosses the blood–brain barrier.[e33,e34]

**BDNF is localized to neurons affected by PD and is neuroprotective for cultured dopaminergic nigrostriatal neurons.** BDNF expression is widespread in brain, including the dopaminergic substantia nigra, striatum, as well as numerous other nuclei affected by PD.[e29] Note, however, that BDNF expression in the nigra is significantly diminished in PD brains.[e29,e35]

In vitro, dopaminergic cells are protected from spontaneous death by BDNF, and also from specific nigral toxins such as MPP+ or 6-hydroxydopamine.[e29] BDNF applied to cultured neurons also increases neuritic outgrowth and synaptic transmission, not only in dopaminergic cells but also other neuronal types.[e29]

**WHAT IS THIS TELLING US, RELEVANT TO PD?** In the aggregate, these findings do not prove that exercise slows PD progression, but a neuroprotective effect is certainly plausible, if not compelling.

Ideally, this would be assessed in a prospective clinical trial, with patients with PD randomized to regular aerobic exercise vs a passive intervention. However, this is challenging because of practical issues. First, variations in PD drug therapy and exercise compliance would tend to confound the outcomes. Second, PD progression is slow and patients would need to be followed for long durations, with potential for substantial dropouts. Third, we have no reliable biomarker of PD progression and would have to rely on indirect indices. Hence, we currently are primarily left with indirect evidence, as summarized above. Despite these challenges, clinical trials directed at chronic vigorous exercise as a treatment strategy deserve serious consideration.

**Exercise influences on general health, well-being, and limitations.** Exercise benefits for patients with PD should also be viewed from a broader perspective, given the general health influences of exercise. PD tends to develop in seniors, who also have risks of various age-related afflictions that are known to benefit from exercise. This especially includes vascular health, both cardiac and cerebral. Numerous other concurrent medical conditions benefit from vigorous exercise including diabetes mellitus, hypertension, hyperlipidemia, obesity, and osteoporosis.[2,e36,e37] In the general population, more vigorous physical activity habits in midlife have been associated with significantly longer survival in prospective analysis, controlling for a variety of covariates.[e38]

Depression[e39] and anxiety[e40] are common in PD. Meta-analyses of clinical trials in the general population have documented significant improvement in both depression[e41] and anxiety[e42] with physical exercise. Moreover, a greater antidepressant effect has been associated with more vigorous exercise.[e43]

Unlike medications, side effects from an exercise prescription are very limited. Those with angina or uncompensated major organ failure may not be good exercise candidates, and medical clearance from a medical specialist would be advisable for such patients. Certain exercise routines may predispose to falls; hence, patients with imbalance will need to choose exercises that minimize such risks. Beyond this, exercise side effects primarily relate to orthopedic injuries, except for those susceptible to an unsuspected cardiac dysrhythmia. On balance, given the benefits of exercise, the implications for clinicians treating patients with PD are clear.

**Exercise as a specific treatment for PD.** This overall body of evidence suggests that vigorous exercise should be accorded a central place in our treatment of PD. It should be encouraged and emphasized as potential strategy for a more favorable disease course.

There are 2 fundamental components to this strategy.

First, clinicians should specifically counsel patients with PD to engage in regular exercise, sufficient to establish and maintain physical fitness. The choice of exercise should not only be tailored to the patient's capabilities, but also their interests, so that they will be motivated to maintain a regular routine. Physicians may utilize physical therapists to design programs for deconditioned patients who need a graduated program. The instructions to the physical therapy team should be clear in stating a goal of physical fitness, beyond simply stretching, gait training, and balance exercises. Although age-related orthopedic conditions may limit some activities, the array of exercise equipment in local gyms and health centers allow many exercises tailored to such problems, including machines where exercises are done while seated.

In recent years, a variety of exercise routines have been publicized, such as bicycling/tandem bicycling or vigorous dancing. The literature summarized above does not intuitively endorse any one specific type of exercise, but rather vigorous exercise in general. Any routine ultimately leading to physical fitness should be beneficial.

Second, clinicians must facilitate exercise by appropriately aggressive use of PD drugs. Over the last 2 decades, very conservative symptomatic medical treatment has often been advised, "saving" the best PD treatments for later and arbitrarily limiting dosage. There is no compelling evidence that medication responses can be saved for years later, and similarly there is no good evidence that low doses convey some beneficial effect in the long term. Rather, this approach may translate into lost opportunities. A reasonable goal when prescribing PD medications is to maximize patients' capabilities to engage in physical activities and potentially achieve the best level of physical fitness possible.

Perhaps we have already seen evidence of the benefits of physical activity for PD in the mortality statistics published shortly after levodopa was introduced 4 decades ago. All 8 independent studies comparing longevity immediately before to just after levodopa availability documented substantially improved lifespans.[e44-e51] Although this might reflect some neuroprotective effect of levodopa, per se, it is more likely reflective of mobilizing a generation of sedentary patients with PD. There may be a lesson in this early experience from the beginning of the levodopa era: mobilization and physical activity should not be underestimated in the treatment of PD.

## AUTHOR CONTRIBUTIONS

## DISCLOSURE

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