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for neurological and translational science

Can exercise and attitude change the course of PD?

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Living with PD approx 15 years

Disclosures

- Board member Parkinson's WA
- Chairperson clinical advisory committee and stockholder ARGENICA Therapeutics
- Prior talks for pharmaceutical companied sponsored medical education events

- NOT a movement disorders specialist

  DO see PD

  Adjustment to diagnosis and exercise

Outline

Can the course of PD be modulated?

- Introduction
- Exercise- review basic terms
- Exercise as therapy
- FIGHT-PD results
- Psychological reaction to Dx
- A new image of PD
- Progression of PD
- How can we intervene?

A neurologist with Parkinson's disease

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I could feel Parkinson's disease creeping up on me, so when I finally summoned up the courage to have a colleague assess me and make the diagnosis, it was of no surprise; in fact, it was almost a relief.

In my mid-30s, I had taken up long-distance running, mainly to shed the weight I'd stacked on during training and fellowship years. About 10 years later, I developed a gait disturbance, manifesting as an exercise-induced dystonia in my leg. Initially, it appeared only after running a significant distance, but gradually it became more problematic, eventually leading me to stop participating in competitive events. My leg would spasm, twist and generally tighten up. I knew it was dystonia but told others it was just cramp or a 'hip problem'; that was easier than explaining what this could become.[1] I was otherwise fine and made a concerted effort to keep fit and to continue exercise as best I could. I also abandoned plans to reduce my caffeine intake given the possibility of this being neuroprotective in Parkinson's disease. Sadly, my sense of olfaction became impaired, so the great pleasure of the aroma of coffee was lost.

Within a few years though, other symptoms emerged, including a tremor of my right hand and leg. The first time it caused a problem was at a national conference when I stood to ask a question, and with the nervousness my hand and leg trembled. I don't think it was visible to others, but I sat quickly, shocked to realise that symptoms were making an impact.

Gradually and pervasively, more tasks became difficult. My handwriting was clearly shrinking and at work that was causing problems. The striking issue though, was bradykinesia; when demonstrating rapid alternating movements and finger tapping to patients, it was clear that my dominant hand was inferior, and seemingly becoming slower each month. It became obvious to me that some of my Parkinson's patients were performing better than me. What really started to bother me was the impact on my ability to play golf. Generating club head speed was difficult, again related to bradykinesia. Simply walking the course was becoming a challenge, and getting a tee out of my pocket and placing the ball on it was becoming difficult.

So it was clear that it was time to get onto treatment and that I should have a proper assessment and diagnosis. I spent some time thinking about whom I should consult. I chose a respected colleague who worked in another hospital on the other side of the city. I obtained an MR scan of my brain before this and was struck by how normal it looked. I remember staring at the images, frustrated that the structure looked so normal, but the function was not.

My colleague was kind, sensitive and caring, and agreed completely with the diagnosis. With my nervousness, the tremor was there again, and he skillfully demonstrated some cogwheeling of my right arm, and the bradykinesia was there for us all to see. Straight on to L-dopa was the plan; no fiddling around with a dopamine agonist.

I filled the script for Madopar the next day and took the first tablet late that afternoon. I remember tapping my right hand and fingers to test for a response; 45 min after the dose, I could feel it working. I was almost shocked to feel this. For some reason, my expectations were low, so I felt encouraged. Over the next few days, I started to take it regularly. What I wasn't prepared for was the nausea. The worst part was the worry that this might continue. Thankfully, with time this passed and I've continued to have an excellent symptomic response.


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Exercise and PD

Various lines of evidence

- Epidemiological studies show physical activity and exercise reduce risk of PD
- Clinical observation shows that exercise can reduce motor Sx
- Animal models show appropriately timed exercise can reduce toxin induced damage of nigrostriatal dopamine system

Rationale for endurance exercise

Lamotte et al, *Parkinson's disease 2014*

- Increased DOP metabolism
- Angiogenesis
- Neurogenesis
- Increased VO2 Max
- Neuroplasticity
- Anti-inflammatory
- Improved Mito function
- Increased brain connectivity
- Increased neurotrophic factors; BDNF, clusterin, lactated-PHE

Definition of exercise

- *Exercise is a subcategory of physical activity that is planned, structured, repetitive and purposefully focused on improvement or maintenance of one or more components of physical fitness.*
- Non-exercise activity thermogenesis (NEAT)
- Sports
- Short bursts of vigorous physical activity

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Association of wearable device-measured vigorous intermittent lifestyle physical activity with mortality

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Wearable devices can capture unexplored movement patterns such as brief bursts of vigorous intermittent lifestyle physical activity (VILPA) that is embedded into everyday life, rather than being done as leisure time exercise. Here, we examined the association of VILPA with all-cause, cardiovascular disease (CVD) and cancer mortality in 25,241 nonexercisers (mean age 61.8 years, 14,178 women/11,063 men) in the UK Biobank. Over an average follow-up of 6.9 years, during which 852 deaths occurred, VILPA was inversely associated with all three of these outcomes in a near-linear fashion. Compared with participants who engaged in no VILPA, participants who engaged in VILPA at the sample median VILPA frequency of 3 length-standardized bouts per day (lasting 1 or 2 min each) showed a 38%–40% reduction in all-cause and cancer mortality risk and a 48%–49% reduction in CVD mortality risk. Moreover, the sample median VILPA duration of 4.4 min per day was associated with a 26%–30% reduction in all-cause and cancer mortality risk and a 32%–34% reduction in CVD mortality risk. We obtained similar results when repeating the above analyses for vigorous physical activity (VPA) in 62,344 UK Biobank participants who exercised (1,552 deaths, 35,290 women/27,054 men). These results indicate that small amounts of vigorous nonexercise physical activity are associated with substantially lower mortality. VILPA in nonexercisers appears to elicit similar effects to VPA in exercisers, suggesting that VILPA may be a suitable physical activity target, especially in people not able or willing to exercise.

Physical activity is associated with reduced mortality risk[1], and reduced risk of CVD[1] and certain cancers[2–4]. Recently updated guidelines[4,5], based mostly on questionnaire-derived evidence, recommend 150–300 min of moderate-intensity activity or 75–150 min of vigorous-intensity physical activity (≥6 metabolic equivalents) per week. New emphasis is placed on 'all activity counts' occurring across all life domains and regardless of bout duration. This recommendation contrasts with previous guidelines[6,7] that did not recognize the health value of physical activity bouts

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Main categories of exercise

- Endurance
- Strength
- Balance
- Flexibility

More exercise definitions

- Aerobic (“with air”) ie energy metabolism using 02, usually moderate, steady
- Anaerobic (“without air”), metabolic pathways don’t use O2, usually high intensity and short

Global Recommendations on Physical Activity for Health

65 years and above

These guidelines are relevant to all healthy adults aged 65 years and above, unless specific medical conditions indicate to the contrary, irrespective of gender, race, ethnicity or income level. They are also relevant to individuals in this age range with chronic NCD conditions or with disabilities. Individuals with specific health conditions, such as cardiovascular disease and diabetes, may need to take extra precautions and seek medical advice before trying to achieve the recommended levels of physical activity for older adults.

Strong evidence demonstrates that compared to less active men and women, older adults who are physically active have:

- lower rates of coronary heart disease, hypertension, stroke, diabetes, colon and breast cancer, a higher level of cardiorespiratory and muscular fitness,
- healthier body mass and composition and enhanced bone health; and
- higher levels of functional health, a lower risk of falling, and better cognitive function.

Recommendations:
In older adults of the 65 years and above age group, physical activity includes leisure time physical activity, transportation (e.g. walking or cycling), occupational (if the individual is still engaged in work), household chores, play, games, sports or planned exercise, in the context of daily, family, and community activities.
The recommendations in order to improve cardiorespiratory and muscular fitness, bone and functional health, reduce the risk of NCDs, depression and cognitive decline are:

1. Older adults should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.

2. Aerobic activity should be performed in bouts of at least 10 minutes duration.

3. For additional health benefits, older adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate-and vigorous-intensity activity.

4. Older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week.

5. Muscle-strengthening activities, involving major muscle groups, should be done on 2 or more days a week.

6. When older adults cannot do the recommended amounts of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow.

Inactive people should start with small amounts of physical activity and gradually increase duration, frequency and intensity over time. Inactive adults and those with disease limitations will have added health benefits when they become more active.

For further information see: http://www.who.int/dietphysicalactivity/pa/en/index.html
or contact WHO on dietandhealth@who.int

World Health Organization

Measuring exercise and exercise intensity

Lab based

- VO2 max, lactate thresholds

Field based

Heart rate based

Some studies report % of maximum HR, other % heart rate reserve (some both)

Max HR, Karnoven equation; 220-age

Heart rate reserve (HRR); Max HR- resting HR

HRR used to calculate HR defined exercise zones

Target HR intensity=

(Max-resting x intensity) + resting HR

Moderate ; 50-70%

High; 70-85%

"High intensity" also defined > 80% max HR

Scales and Questionnaires

- Baseline
- Before each exercise session
- During the exercise session
- After the exercise session
- End of 5 week block
- End of the 15 week programme

Borg's Rating of Perceived Exertion (RPE) Scale

Perceived Exertion Rating	Description of Exertion
6	No exertion. Sitting & resting
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

https://www.braininjuryaustralia.org.au/wp-content/uploads/Barry-Willer_2.pdf

High intensity interval training
HIIT

- **HIIT** Form of interval training where short periods (<20 sec) of near maximal effort are mixed with rest
- Intense anaerobic exercise
- ***HIIT may be the threshold for triggering the release of BDNF and other metabolic factors?***
- ***Goal directed practice + aerobic (better still HIT) synergistic to facilitate neuroplasticity***

Taking blood from mice who run and infusing into sedentary mice improves cognition and reduces neuroinflammation

Article

Exercise plasma boosts memory and dampens brain inflammation via clusterin

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Physical exercise is generally beneficial to all aspects of human and animal health, slowing cognitive ageing and neurodegeneration[1]. The cognitive benefits of physical exercise are tied to an increased plasticity and reduced inflammation within the hippocampus[2–4], yet little is known about the factors and mechanisms that mediate these effects. Here we show that 'runner plasma', collected from voluntarily running mice and infused into sedentary mice, reduces baseline neuroinflammatory gene expression and experimentally induced brain inflammation. Plasma proteomic analysis revealed a concerted increase in complement cascade inhibitors including clusterin (CLU). Intravenously injected CLU binds to brain endothelial cells and reduces neuroinflammatory gene expression in a mouse model of acute brain inflammation and a mouse model of Alzheimer's disease. Patients with cognitive impairment who participated in structured exercise for 6 months had higher plasma levels of CLU. These findings demonstrate the existence of anti-inflammatory exercise factors that are transferrable, target the cerebrovasculature and benefit the brain, and are present in humans who engage in exercise.

Physical activity evokes profound physiological responses in multiple tissues across the animal kingdom and is accepted to broadly improve human health[1,5]. The benefits of exercise extend to patients with neurodegeneration and brain trauma[6,7], possibly by reducing neuroinflammation[2]. Long-term voluntary exercise in mouse models of Alzheimer's disease (AD) and related disorders improve learning and memory, and decrease neuroinflammation[3,7,8]. How exercise exerts these beneficial effects is poorly understood. It has been proposed that 'exercise factors'—secreted from muscle and other tissues into the blood—subsequently signal to the brain. Factors including IGF-1 (ref. [9]), VEGF[10] and PF4 (ref.[11]) increase hippocampal neurogenesis in young mice, whereas GPDL1 rescues the age-related loss in neurogenesis and cognition in old mice[12] (Extended Data Table 1). However, it is unknown whether exercise-conditioned plasma contains factors that benefit the young healthy brain, whether these factors are directly transferrable through the plasma, whether such factors mediate the anti-inflammatory effect of exercise and what the key factors are.

Runner plasma improves cognition

Given these beneficial effects of exercise on the hippocampus, we investigated whether plasma from exercising male mice (runner plasma (RP)) transferred into young non-exercising littermates can mimic running: mice without access to a running wheel in their cage generated control plasma (CP) (Fig. 1a; details of the set-up are provided in the Methods). We observed that 28 d of running was sufficient to increase overall cell survival ($BrdU^+$ cells), including neurons($NeuN^+BrdU^+$ cells), the number of neural stem and progenitor cells (NSPCs; $Sox2^+GFAP^-$ cells) and astrocytes ($GFAP^+BrdU^+$ cells) and that this effect was most prominent in mice aged 3 months (Extended Data Fig. 1a–d). Notably, recipient mice that received RP showed a significant increase in total proliferating cells, DCX^+ neuroblasts and surviving cells compared with CP-recipient mice (Fig. 1b, c). Notably, these results are very similar to the direct effects of running described above (Extended Data Fig. 1a–d). Importantly, repeated control injections of saline through the retro-orbital vein under anaesthesia did not significantly alter hippocampal cell proliferation and survival, whereas restraining mice and injecting them through the tail vein reduced proliferation (Extended Data Fig. 1e). Furthermore, RP induced a twofold expansion of surviving NSPCs compared with CP. However, RP did not significantly increase the number of surviving mature neurons and, instead, lead to a twofold increase in the survival of newly produced astrocytes (Fig. 1c). In an independent experiment, RP from mice that had access to a running wheel for 28 d replicated

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Article

An exercise-inducible metabolite that suppresses feeding and obesity

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Exercise confers protection against obesity, type 2 diabetes and other cardiometabolic diseases[1–5]. However, the molecular and cellular mechanisms that mediate the metabolic benefits of physical activity remain unclear[6]. Here we show that exercise stimulates the production of *N*-lactoyl-phenylalanine (Lac-Phe), a blood-borne signalling metabolite that suppresses feeding and obesity. The biosynthesis of Lac-Phe from lactate and phenylalanine occurs in CNDP2$^+$ cells, including macrophages, monocytes and other immune and epithelial cells localized to diverse organs. In diet-induced obese mice, pharmacological-mediated increases in Lac-Phe reduces food intake without affecting movement or energy expenditure. Chronic administration of Lac-Phe decreases adiposity and body weight and improves glucose homeostasis. Conversely, genetic ablation of Lac-Phe biosynthesis in mice increases food intake and obesity following exercise training. Last, large activity-inducible increases in circulating Lac-Phe are also observed in humans and racehorses, establishing this metabolite as a molecular effector associated with physical activity across multiple activity modalities and mammalian species. These data define a conserved exercise-inducible metabolite that controls food intake and influences systemic energy balance.

Exercise is a powerful physiological intervention that protects against obesity and obesity-associated cardiometabolic diseases[1–5]. By contrast, physical inactivity increases the risk of obesity, metabolic disease and all-cause mortality[4,5]. There has been a growing interest in identifying 'molecular transducers' that might mediate the cardiometabolic benefits of exercise[6]. Although large-scale multi-omics efforts (for example, by the Molecular Transducers of Physical Activity Consortium) have begun to generate molecular maps of the biological molecules regulated by physical activity[6–9], the functional relationships between these molecular changes and physiological outcomes remain poorly defined. In parallel, candidate approaches have uncovered specific functional exercise-regulated signalling molecules[10–14], but the extent to which these candidate molecules represent the most important mediators of physical activity remains unclear. We reasoned that a hybrid approach might be valuable in both providing a global view of the most relevant molecular changes associated with physical activity and designating high-priority, candidate molecular transducers of exercise.

Plasma metabolomics of exercise

To measure exercise-induced circulating metabolites in a global and unbiased manner, we performed both targeted and untargeted metabolomics of blood plasma from mice following an acute bout of treadmill running until exhaustion (Extended Data Fig. 1a). Our targeted metabolomics analysis detected increases in several metabolites, including lactate, fumarate and succinate, which were previously established to be regulated by physical activity[6–8,12,15,16] (Fig. 1a, Supplementary Table 1 and Methods). The metabolite most significantly induced by exercise, however, was found by untargeted metabolomics (Fig. 1a,b). This metabolite had a mass-to-charge ratio (m/z) of 236.0928 that was

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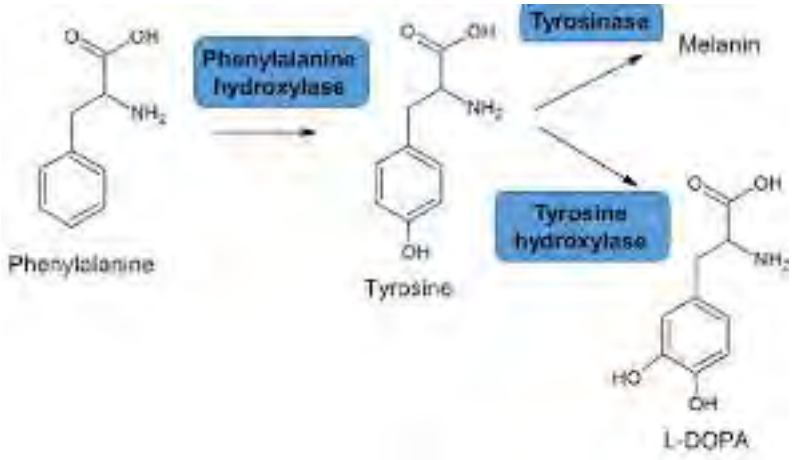
Phenylalanine hydroxylase
Tyrosinase
Melanin
Tyrosine hydroxylase
Phenylalanine
Tyrosine
L-DOPA

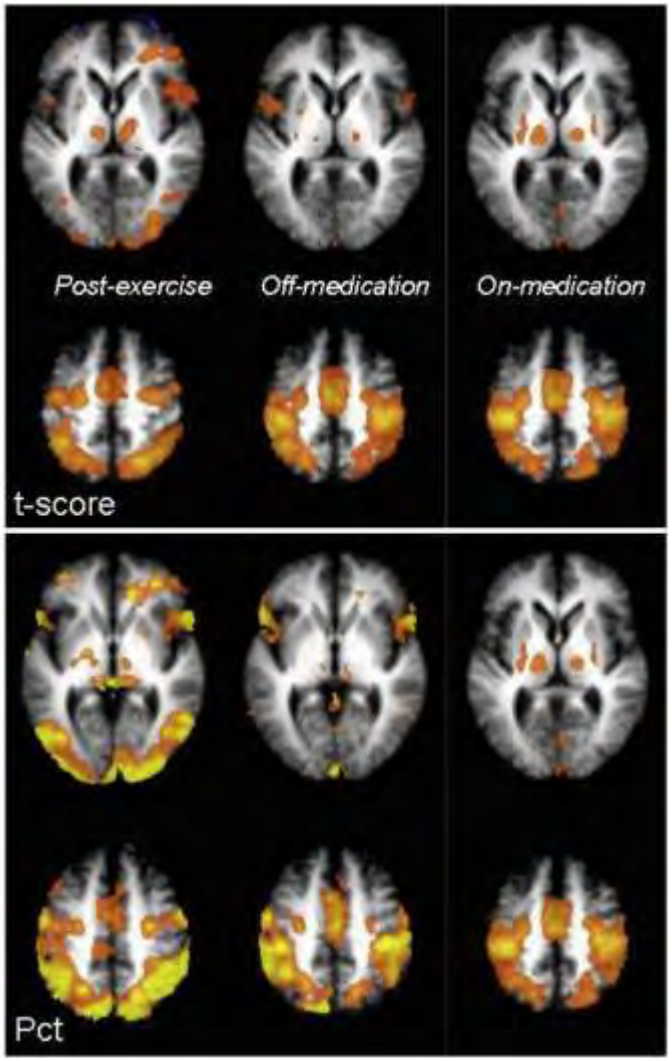

Fig. 1. Bilateral tapping task activation t-score and mean percent signal change (Pct) in each of the 3 states, averaged across patients and shown on Talairach-averaged anatomy. Activation t-score (**top**) was thresholded at 3.5 sigma. Pct (**bottom**) was masked by activation thresholded at 2 sigma.

MEDS + FE, compared to OFF MEDS. Overall, medication improved UPDRS-III ratings by 37% while UPDRS-III ratings improved by 48% in the OFF MEDS + FE relative to OFF MEDS (Table 2).

Analysis of variance (ANOVA) indicated significant difference in UPDRS Motor III scores among the conditions (ON MEDS, OFF MEDS, OFF MEDS + FE) ($F_{2,23} = 14.78$; $P < 0.001$, Fig. 2A). Post-hoc Tukey testing demonstrated that UPDRS-III ratings were significantly ($P < 0.001$) improved when comparing ON MEDS to OFF

Clinical studies

Phase 2 exercise studies in PD

Title Author year	# subjects	Stage of PD UPDRS III	Inter-vention	Intensity	Volume Duration	Result UPDRS motor change
SPARX 2 Schenkman *JAMA* 2018	128 43 HI 45 MI 40 cont	H&Y 1 or 2 < 5 years NO meds Exercise < 3 p/ week 17,16,16	Treadmill walking	HI 80-85% MI 40 control	Aimed for 4 days p/week 2.8 HI 3.2 MI	HI +0.3 MI +3.2 (p=0.03)
PARK-In SHAPE Van der Kolk, Bloem *Lancet N 2019*	130 65 active 65 cont	H&Y 1 or 2 3.2 yeqrs post Dx Stable therapy 29.5 active 27.2 cont	Stationary cycle v stretching	Ave % max HR 76%	3 per week 30-45 min 6 months	Active +1.3 Cont +5.6 MRI substudy
RCT walking Mak et al *Journal of PD* 2021	64 33 active 31 cont	H&Y 2 Ave 2 years 29.7 active 28.7 cont	Outdoor brisk walking	"Moderate" 40-60% HRR	3 per week 60-90 mins 6 months	Active -6.0 Cont -1.4 **NB ave +4.7** **CID = + 4.6** **CID = - 3.3**

JAMA Neurology | Original Investigation

Effect of High-Intensity Treadmill Exercise on Motor Symptoms in Patients With De Novo Parkinson Disease

A Phase 2 Randomized Clinical Trial

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IMPORTANCE Parkinson disease is a progressive neurologic disorder. Limited evidence suggests endurance exercise modifies disease severity, particularly high-intensity exercise.

OBJECTIVES To examine the feasibility and safety of high-intensity treadmill exercise in patients with de novo Parkinson disease who are not taking medication and whether the effect on motor symptoms warrants a phase 3 trial.

DESIGN, SETTING, AND PARTICIPANTS The Study in Parkinson Disease of Exercise (SPARX) was a phase 2, multicenter randomized clinical trial with 3 groups and masked assessors. Individuals from outpatient and community-based clinics were enrolled from May 1, 2012, through November 30, 2015, with the primary end point at 6 months. Individuals with idiopathic Parkinson disease (Hoehn and Yahr stages 1 or 2) aged 40 to 80 years within 5 years of diagnosis who were not exercising at moderate intensity greater than 3 times per week and not expected to need dopaminergic medication within 6 months participated in this study. A total of 384 volunteers were screened by telephone; 128 were randomly assigned to 1 of 3 groups (high-intensity exercise, moderate-intensity exercise, or control).

INTERVENTIONS High-intensity treadmill exercise (4 days per week, 80%-85% maximum heart rate [n = 43]), moderate-intensity treadmill exercise (4 days per week, 60%-65% maximum heart rate [n = 45]), or wait-list control (n = 40) for 6 months.

MAIN OUTCOMES AND MEASURES Feasibility measures were adherence to prescribed heart rate and exercise frequency of 3 days per week and safety. The clinical outcome was 6-month change in Unified Parkinson's Disease Rating Scale motor score.

RESULTS A total of 128 patients were included in the study (mean [SD] age, 64 [9] years; age range, 40-80 years; 73 [57.0%] male; and 108 [84.4%] non-Hispanic white). Exercise rates were 2.8 (95% CI, 2.4-3.2) days per week at 80.2% (95% CI, 78.8%-81.7%) maximum heart rate in the high-intensity group and 3.2 (95% CI, 2.8-3.6; $P = .13$) days per week at 65.9% (95% CI, 64.2%-67.7%) maximum heart rate in the moderate-intensity group ($P < .001$). The mean change in Unified Parkinson's Disease Rating Scale motor score in the high-intensity group was 0.3 (95% CI, −1.7 to 2.3) compared with 3.2 (95% CI, 1.4 to 5.1) in the usual care group ($P = .03$). The high-intensity group, but not the moderate-intensity group, reached the predefined nonfutility threshold compared with the control group. Anticipated adverse musculoskeletal events were not severe.

CONCLUSIONS AND RELEVANCE High-intensity treadmill exercise may be feasible and prescribed safely for patients with Parkinson disease. An efficacy trial is warranted to determine whether high-intensity treadmill exercise produces meaningful clinical benefits in de novo Parkinson disease.

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Supplemental content

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Research Report

Six-Month Community-Based Brisk Walking and Balance Exercise Alleviates Motor Symptoms and Promotes Functions in People with Parkinson's Disease: A Randomized Controlled Trial

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Abstract.
Background: In Parkinson's disease (PD), sustained aerobic exercise is a promising therapy in delaying motor disability. Brisk walking is a moderate intensity aerobic training, which could be translated to community practice at low cost, but its effects on motor symptoms remains unclear.
Objective: To determine the effectiveness of a six-month brisk walking and balance program in alleviating motor symptoms, and promoting functional, gait, and balance performance in people with PD.
Methods: Seventy individuals with mild to moderate PD were randomly assigned to a brisk walking (BW) group or an active control (CON) group. BW group received ten 90-minute supervised brisk walking and balance exercise for six months (weeks 1–6: once/week, weeks 7–26: once/month). CON group received upper limb training. Both groups performed 2-3 self-practice sessions weekly. Primary outcome was Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score. Secondary outcomes were fast gait speed (FGS), timed-up-and-go (TUG) time, six-minute walk distance (6MWD), and Mini-Balance Evaluation Systems Test (Mini-BEST) score.
Results: Sixty-four participants (33 BW/31 CON) completed training. BW group showed greater significant decreases from baseline than CON group in MDS-UPDRS motor score after six weeks (–5.5 vs –1.6, $p < 0.001$) and 6 months (–6.0 vs –1.4, $p < 0.001$) of training. BW group also showed greater significant improvement from the baseline than CON group for TUG time, FGS, 6MWD, and mini-BEST score (all $p < 0.05$).
Conclusion: The six-month brisk walking and balance program alleviates motor symptoms, promotes functional and gait performance, walking capacity, and dynamic balance in people with mild to moderate PD.

Keywords: Parkinson's disease, rehabilitation, aerobic exercise, recovery of function, postural balance

INTRODUCTION

Parkinson's disease (PD) is a chronic progressive disorder affecting around seven million people in the year 2020 [1], characterized by motor symptoms including bradykinesia, rigidity, tremor, and postural

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Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial

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See Comment page 982

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Summary

Background High-intensity aerobic exercise might attenuate the symptoms of Parkinson's disease, but high-quality evidence is scarce. Moreover, long-term adherence remains challenging. We aimed to evaluate the effectiveness of aerobic exercise—gamified and delivered at home, to promote adherence—on relieving motor symptoms in patients with Parkinson's disease with mild disease severity who were on common treatment regimes.

Methods In this single-centre, double-blind, randomised controlled trial (Park-in-Shape), we recruited sedentary patients with Parkinson's disease from the outpatient clinic at Radboudumc, Nijmegen, Netherlands. Patients were made aware of the study either by their treating neurologist or via information in the waiting room. Patients could also contact the study team via social media. We included patients aged 30–75 years with a Hoehn and Yahr stage of 2 or lower, who were on stable dopaminergic medication. Patients were randomly assigned (in a 1:1 ratio) to either aerobic exercise done on a stationary home-trainer (aerobic intervention group) or stretching (active control group) by means of a web-based system with minimisation for sex and medication status (treated or untreated) and permuted blocks of varying sizes of more than two (unknown to study personnel). Patients were only aware of the content of their assigned programme. Assessors were unaware of group assignments. Both interventions were home based, requiring 30–45 min training three times per week for 6 months. Both groups received a motivational app and remote supervision. Home trainers were enhanced with virtual reality software and real-life videos providing a so-called exergaming experience (ie, exercise enhanced by gamified elements). The primary outcome was the between-group difference in the Movement Disorders Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor section at 6 months, tested during the off state (≥12 h after last dopaminergic medication). The analysis was done on an intention-to-treat basis in patients who completed the follow-up assessment, regardless of whether they completed the assigned intervention. Patients reported adverse events directly to their coach and also after the 6-month visit retrospectively. A between-group difference of 3·5 points or more was deemed a-priori clinically relevant. The study is concluded and registered with the Dutch Trial Registry, NTR4743.

Findings Between Feb 2, 2015, and Oct 27, 2017, 139 patients were assessed for eligibility in person, of whom 130 were randomly assigned to either the aerobic intervention group (n=65) or the active control group (n=65). Data from 125 (96%) patients were available for the primary analysis; five patients were lost to follow-up (four in the intervention group; one in the control group). 20 patients (ten in each group) did not complete their assigned programme. The off-state MDS-UPDRS motor score revealed a between-group difference of 4·2 points (95% CI 1·6–6·9, p=0·0020) in favour of aerobic exercise (mean 1·3 points [SE 1·8] in the intervention group and 5·6 points [SE 1·9] for the control group). 11 patients had potentially related adverse events (seven [11%] in the intervention group, four [6%] in the control group) and seven had unrelated serious adverse events (three in the intervention group [vestibilar disorder, vasovagal collapse, knee injury during gardening that required surgery; 6%], four in the control group [supraventricular tachycardia, hip fracture, fall related injury, severe dyskinesias after suprathreshold dose levodopa in a patient with deep brain stimulation; 7%]).

Interpretation Aerobic exercise can be done at home by patients with Parkinson's disease with mild disease severity and it attenuates off-state motor signs. Future studies should establish long-term effectiveness and possible disease-modifying effects.

Funding Netherlands Organization for Health Research and Development.

Introduction

Parkinson's disease is a progressive neurodegenerative disorder.[1] Pharmacotherapy alleviates symptoms but is limited by response fluctuations with disease progression.[2] Non-pharmacological approaches might offer additional symptomatic relief. High-intensity aerobic exercise appears to be promising with beneficial effects on several functional outcomes (that were often specifically trained

Aerobic Exercise Alters Brain Function and Structure in Parkinson's Disease: A Randomized Controlled Trial

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Objective: Randomized clinical trials have shown that aerobic exercise attenuates motor symptom progression in Parkinson's disease, but the underlying neural mechanisms are unclear. Here, we investigated how aerobic exercise influences disease-related functional and structural changes in the corticostriatal sensorimotor network, which is involved in the emergence of motor deficits in Parkinson's disease. Additionally, we explored effects of aerobic exercise on tissue integrity of the substantia nigra, and on behavioral and cerebral indices of cognitive control.
Methods: The Park-in-Shape trial is a single-center, double-blind randomized controlled trial in 130 Parkinson's disease patients who were randomly assigned (1:1 ratio) to aerobic exercise (stationary home trainer) or stretching (active control) interventions (duration = 6 months). An unselected subset from this trial (exercise, n = 25; stretching, n = 31) underwent resting-state functional and structural magnetic resonance imaging (MRI), and an oculomotor cognitive control task (pro- and antisaccades), at baseline and at 6-month follow-up.
Results: Aerobic exercise, but not stretching, led to increased functional connectivity of the anterior putamen with the sensorimotor cortex relative to the posterior putamen. Behaviorally, aerobic exercise also improved cognitive control. Furthermore, aerobic exercise increased functional connectivity in the right frontoparietal network, proportionally to fitness improvements, and it reduced global brain atrophy.
Interpretation: MRI, clinical, and behavioral results converge toward the conclusion that aerobic exercise stabilizes disease progression in the corticostriatal sensorimotor network and enhances cognitive performance.

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An increasing number of studies suggest that motor symptoms associated with Parkinson's disease (PD) can be improved through physical exercise. We recently completed a clinical trial showing attenuated motor symptom progression in PD following an aerobic exercise intervention (Park-in-Shape trial).[1] Similar findings were observed in a clinical trial that investigated exercise dosage in de novo PD (SPARX trial).[2] These two studies provide strong clinical evidence that exercise can alleviate motor symptoms in PD. However, the cerebral mechanisms underlying this effect remain unclear. Here, we investigated the effect of aerobic exercise on cerebral changes using longitudinal,

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Additional supporting information can be found in the online version of this article.

Exercise and hippocampal volume

- Hippocampal volume shrinks by 1-2% pa in older adults without dementia
- Increases risk for cognitive impairment
- Exercise increases cerebral blood volume and hippocampal perfusion
- Exercise may increase BNDF, which mediates neurogenesis

Erickson et al Aerobic exercise intervention

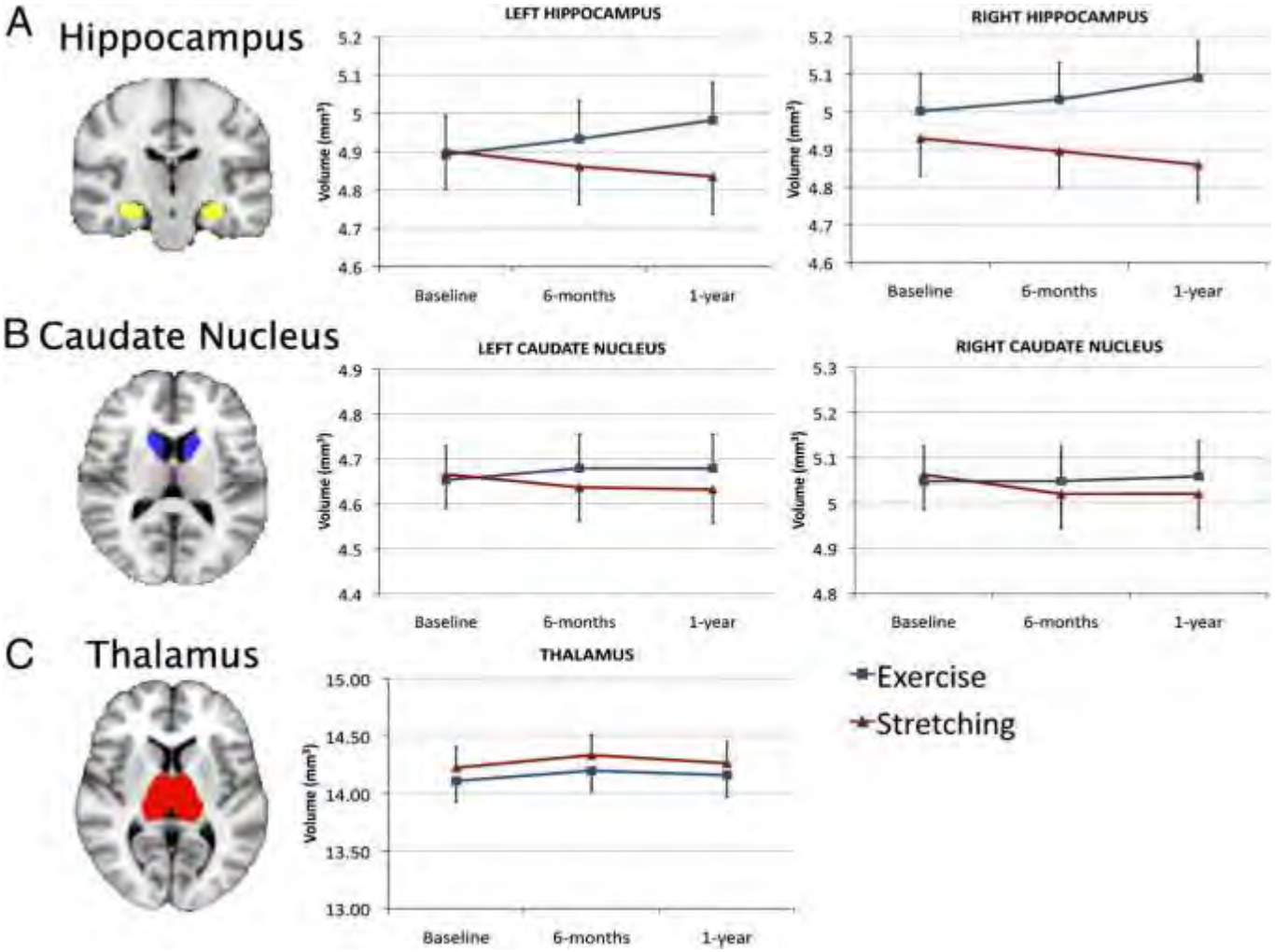
Aerobic exercise

- Walking 10 mins, increasing by 5 mins until 40 mins by week 7
- HR monitors, target 50-60% max HR (220-age) for weeks 1-7, then 60-75% remainder of program
- Exercise log
- Every 4 weeks, summary provided

“79% attendance”; number of sessions per week?

Actual amount of exercise performed?

(A) Example of hippocampus segmentation and graphs demonstrating an increase in hippocampus volume for the aerobic exercise group and a decrease in volume for the stretching control group.



Kirk I. Erickson et al. PNAS 2011;108:7:3017-3022

PNAS

MAYO CLINIC

Aerobic Exercise: Evidence for a Direct Brain Effect to Slow Parkinson Disease Progression

J. Eric Ahlskog, PhD, MD

Abstract

No medications are proven to slow the progression of Parkinson disease (PD). Of special concern with longer-standing PD is cognitive decline, as well as motor symptoms unresponsive to dopamine replacement therapy. Not fully recognized is the substantial accumulating evidence that long-term aerobic exercise may attenuate PD progression. Randomized controlled trial proof will not be forthcoming due to many complicating methodological factors. However, extensive and diverse avenues of scientific investigation converge to argue that aerobic exercise and cardiovascular fitness directly influence cerebral mechanisms mediating PD progression. To objectively assess the evidence for a PD exercise benefit, a comprehensive PubMed literature search was conducted, with an unbiased focus on exercise influences on parkinsonism, cognition, brain structure, and brain function. This aggregate literature provides a compelling argument for regular aerobic-type exercise and cardiovascular fitness attenuating PD progression.

 ■ Mayo Clin Proc. 2018;93(3):360-372

From the Department of Neurology, Mayo Clinic, Rochester, MN.

Parkinson disease (PD) is a relatively common neurologic condition with perhaps 1 million affected people in the United States. Increasingly, their treatment is falling into the hands of primary care physicians, who should be able to provide optimal care to most patients.[1-3] As previously described,[2] appropriate carbidopa/levodopa administration is the single most crucial medication strategy. Herein, the argument is advanced that the other important component of optimal PD treatment is engagement in regular aerobic-type exercise. Although no medications are proven to slow PD progression, there is substantial evidence for vigorous exercise attenuating PD progression, which is the specific focus of this article.

Exercise advice may be skeptically viewed by patients. The lay public is bombarded by health advice, some biologically supported and some that is arbitrary, unsupported, or commercially driven. Exercise is easily dismissed as yet another dictum from health experts. Moreover, regular exercise implies strenuous, time-consuming physical work, which for some people is novel. Thus, an exercise prescription for people with PD is easily discarded, especially in the absence of definite proof.

IMPEDIMENTS TO CLINICAL TRIAL ASSESSMENT OF PD EXERCISE INFLUENCES

Definitive arguments for any health intervention are expected to come from clinical randomized controlled trials (RCTs). The outcome of interest is preventing the slow neurologic decline that occurs with PD. Unfortunately, a valid and reliable RCT of long-term exercise to slow PD progression is not truly feasible for several reasons.

First, PD progression tends to be very slow. Reliable and valid biomarkers of PD progression have yet to be developed. Assessment requires outcome measures that will not be contaminated by medication effects (ie, levodopa and related drugs); this precludes motor outcomes routinely used in PD clinical trials (eg, Unified Parkinson Disease Rating Scale scores). From a patient's perspective, the most important markers of clinical progression are dementia and levodopa-refractory symptoms, which are measureable and not subject to medication influences. However, these problems typically do not develop for many years or decades and, thus, are not amenable to RCTs.

Second is the physical and motivational challenge of longer-term engagement in an

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www.mayoclinicproceedings.org ■ © 2017 Mayo Foundation for Medical Education and Research

Conclusion

- ***Regular aerobic-type exercise tending to lead to fitness is the single strategy with compelling evidence for slowing PD progression***
- ***All patients with PD should be encouraged to engage in regular exercise***
- ***Optimize L-dopa Rx to enable engagement in vigorous exercise***

RESEARCH ARTICLE

Effects of Exercise on Depressive Symptoms in Patients With Parkinson Disease

A Meta-analysis

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Abstract

Background and Objective

The purpose of this study was to provide clear evidence in support of the use of exercise to improve depressive symptoms in patients with Parkinson disease (PD) and to investigate whether this effect differs by exercise type and intensity.

Methods

Three independent reviewers searched for randomized controlled trials (RCTs) that applied exercise interventions with depressive symptoms as an outcome measure for patients with PD on PubMed and Web of Science up to February 28, 2022. Random-effects meta-analyses were performed, in which standardized mean differences (SMDs) between the effects of exercise and control interventions on depressive symptoms with 95% CIs were calculated.

Results

A total of 19 RCTs including 1,302 patients with PD were eligible for meta-analysis, and we obtained 23 comparisons from the included studies for data synthesis. Physical exercise interventions showed significant effects on the reduction in depressive symptoms in patients with PD (SMD = 0.829; 95% CI = 0.516–1.142; $p < 0.001$). Moderator analyses on exercise type revealed significant positive effects for combined exercise interventions (SMD = 1.111; 95% CI = 0.635–1.587; $p < 0.001$), whereas aerobic training alone failed to show significant effects (SMD = 0.202; 95% CI = −0.045 to 0.449; $p = 0.108$). Both light-to-moderate intensity exercises (SMD = 0.971; 95% CI = 0.521–1.421; $p < 0.001$) and moderate-to-vigorous intensity exercises (SMD = 0.779; 95% CI = 0.407–1.152; $p < 0.001$) significantly improved depressive symptoms with a small difference between the exercise intensities.

Discussion

Our results suggest that physical exercise has significant antidepressant effects in patients with PD. These effects seemed to be more closely associated with exercise type than intensity. Different types of exercise interventions may result in greater benefit and require further investigation.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

PLOS ONE

RESEARCH ARTICLE

Effects of physical exercise programs on cognitive function in Parkinson's disease patients: A systematic review of randomized controlled trials of the last 10 years

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Abstract

Background

Given the relative importance of cognitive impairment, there was considerable interest in identifying the cognitive profile of PD patients, in order to ensure specific and appropriate therapeutic interventions.

Purpose

To determine the effects of physical exercise programs on cognitive function in PD patients, compared with the control group.

Data sources

Medline, Cochrane, Scopus, PEDro and Web of Science (last searched in September 2016).

Study selection

Randomized clinical trials examining the effects of physical exercise programs and cognitive function in PD patients. Nine studies fulfilled the selection criteria and were included in this review.

Data extraction

Characteristics of the publication, characteristics of the participants, test used for cognitive screening, cognitive domain assessed, tools used to assess cognitive function, characteristics of the experimental intervention, characteristics of the control group, mean results and standard deviation of function cognitive. The PEDro score was used to evaluate methodological quality.

“Peripheral progression”

- Neuromuscular
- Cardiovascular

- Note- mitochondrial dysfunction

- Resistance (strength) may provide more benefits than aerobic

Editorial

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Strength and physical functions in people with Parkinson's disease

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Keywords: alternative therapy • exercise • neurophysiology • physical activity • resistance training

Strength & physical functions

Strength refers to the maximum force that a muscle or muscle group can generate, and it is important to be assessed in all populations, young and old, men and women, healthy and with some type of disease. Strength is essential to perform activities of daily living and to have a good quality of life as with diminishing strength, simple tasks start to become hard [1].

Physical functions has various terms to refer it (exercise capacity, physical fitness, physical performance, physical capacity, physical ability, physical limitation, physical disability, functional status, functional capacity, functional ability, physical functional status, health status and so on). Furthermore, all these words must mean the individual's ability to function. Moreover, physical functions related with activities can be split in simple movements (e.g., stand up from a chair) and complex movements (e.g., playing soccer). To perform movements, simple or complex, it is important to have cardiorespiratory fitness, strength, muscle endurance, flexibility and balance [2].

Physical capacities & diseases

Some diseases can alter the individual's physical capacities, such as Parkinson's disease (PD) affects the muscles, thus affecting strength. The diminishing strength in this population occurs because there is a progressive deterioration of the substantia nigra in the midbrain causing a decrease in dopamine production. This reduction in dopamine results in a GABA-mediated tonic inhibition of the thalamus, which in turn reduces the excitation of the thalamus on cortical projection areas. This is manifested as an alteration in somatic motor activities and as a result, a person with PD can have difficulties contracting the muscles, thereby reducing the strength production [3].

The diminished strength in people with PD affects their quality of life, simple tasks such as rising from a chair become difficult, as do all day-to-day tasks [4]. The deficit in central activation of muscles is responsible for muscle weakness [5]. PD affects not only motor symptoms like resting tremor, bradykinesia, freezing, gait disturbance and postural instability but also contributes to diminished maximal force production [6]. Skinner *et al.* [7] verified the effect of PD in 13 individuals and 13 controls after performing maximal and submaximum (5, 10 and 20% of maximum voluntary contractions) isometric force tasks. The results showed that PD individuals demonstrated lower strength in lower limbs when compared with controls. These results reinforce the fact that strength deficits cause impairments in activities of daily living.

The major treatment for PD is oral medication, and the main drug is the levodopa. This drug is the most effective for PD and works increasing dopamine levels in the brain, which reduces motor fluctuations. There is variation from oral levodopa, levodopa intestinal gel, but it is expensive and invasive. Also in medicaments, dopamine agonists are used as alternative that mimic dopamine effects in the brain. The monoamine oxidase inhibitors can be used to prevent the breakdown of brain dopamine by inhibiting the brain enzyme monoamine oxidase B [8]. Furthermore, anticholinergics [9], amantadine [10] and catechol O-methyltransferase inhibitors [11] are alternative medicaments for PD treatment.

Future Medicine

Ideal exercise for PD

<u>Key elements</u>

- Aerobic; moderate and HIT
- Resistance, strength
- Stretching

“Any exercise is good”

“Do exercise that interests you”

“Exercise is medicine”

Parkinson's Foundation

F.I.T.T.-V.P.	Aerobic	Strength	Balance, Agility, & Multi-Tasking	Flexibility
Fre-quency	At least 3 days per week.	2-3 days per week, challenging all major muscle groups on nonconsecutive days.	2-3 days per week focused workout, with daily integration as possible.	≥ 2-3 days/week, with daily being most effective.
Intensity & Progression	Moderate Intensity: 40% - 60% HRR (or VO_2R), RPE of 12-13/20 or 3-4/10. **Progress** to vigorous intensity: 60-85% HRR; RPE 14-17/20 or 5-7/10), when physiologically appropriate and safe. Teach client to self-assess.	40-50% of 1-RM for beginners. 60-70% 1-RM for more advanced exercisers. **Progress** number of repetitions and resistance, working muscles to fatigue.	Appropriate challenge delivered in a safe manner given the setting (individual vs group). **Progress** motor and cognitive challenges as patient improves and can tolerate.	Full extension, flexion, or rotation stretch to the point of slight discomfort. **Progress** as patient can tolerate
Time & Volume	≥30 min of continuous or intermittent exercise per session. Build to at least 150 minutes/week.	10-15 repetitions starting an exercise program. ≥1 set of 8-12 repetitions (~60% 1-RM) and progress to 3 sets of 8 -10 to fatigue. Build to 2-3 hours/week.	30-60 minutes per workout. Build to 2-3 hours/week.	Static Stretching: 15-60 seconds per muscle; 2-4 repetitions of each stretch. Dynamic Stretching: 8-10 movements in each direction.
Type	Prolonged, rhythmic activities using large muscle groups.	Major muscle groups of the upper and lower body using weight machines, resistance bands, or body weight. Focus on extensors. Could use resistance training with instability.	Multi-directional stepping, weight shifting, reaching, large amplitude movements, functional agility (steps, turning, obstacles, backwards, floor activities, sit-to-stand). Multi-task training (motor, cognitive, distractions). Static and dynamic balance with varied surfaces, limb support, perturbations.	Static Stretching: All major muscle groups after exercise, first thing in the morning or before bed. Dynamic stretching/active range of motion: Prior to intense aerobic and strengthening exercise. Include diaphragmatic breathing and meditation.
Disease-Related Considerations	Prioritize safety (ambulatory status, physical assistance, equipment). Risk of freezing of gait. Consider comorbidities (*e.g.* musculoskeletal, cardio-respiratory). Risk of autonomic dysfunction, including orthostatic hypotension, blunted heart rate response to exercise, arrhythmias associated with PD or medications.	Posture and body mechanics. Estimate 1-RM safely. Progressive with high repetitions. Timed for ON periods of optimal functioning. For safety, avoid heavy free weights. Consider comorbidities (*e.g.* spinal stenosis, osteoporosis, osteopenia).	Consider varied ability levels related to cognitive engagement and attention. Allow upper extremity support when needed. Consider comorbidities (*e.g.* peripheral neuropathy, cognitive decline). Risk of freezing of gait. Use of gait belt for safety.	Consider dystonia (tonic or activity-induced) and general worsening of flexed posture with disease progression. Consider comorbidities (*e.g.* osteoporosis, pain, dystonia).
	Consider collaborating with a licensed physical therapist specializing in Parkinson's disease to assist with full functional evaluation and individually-tailored exercise recommendations taking into account complex medical history.			2021

What if I can't exercise

- Note cardiac screening;
  Review of risk factors, symptoms,
  non-invasive testing
  GP review

- Modifications; eg chair yoga,
- Alter the mix; less cardio, more weights

- Research may identifiable injectable factors

PD and Boxing???
Muhammed Ali, Atlanta Olympics 1996
Recently clarified NOT CTE

Rock Steady Boxing

> 43 000 participants in > 830 sites worldwide

frontiers in Neurology

SYSTEMATIC REVIEW
published: 04 December 2019
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Boxing for Parkinson's Disease: Has Implementation Accelerated Beyond Current Evidence?

Meg E. Morris[1,2], Terry D. Ellis[3], Dana Jazayeri[1,2], Hazel Heng[1], Andrea Thomson[1], Arun Prasad Balasundaram[1] and Susan C. Slade[1,2]*

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Background: Exercise and physical activity are argued to promote neural plasticity in Parkinson's disease (PD), with potential to slow disease progression. Boxing for PD is rapidly growing in popularity.

Objectives: (i) To evaluate evidence on benefits and risks of boxing exercises for people living with PD and (ii) to appraise websites for evidence of global implementation of this intervention.

Data Sources: We searched AMED, CINAHL, Cochrane, EMBASE, EMCARE, Health and Medical Collection via ProQuest, MEDLINE, and PEDro electronic databases for the research literature. Websites were also searched for evidence of successful implementation of boxing for PD.

Study Selection: Published research and websites were considered if they reported data on adults with PD and boxing as an intervention.

Data Extraction: For the literature review, two reviewers independently extracted data on study characteristics and intervention content. Risk of bias was assessed with the PEDro scale and Joanna Briggs Checklist. We conducted a quality appraisal of websites using the QUality Evaluation Scoring Tool (QUEST).

Data Synthesis: Two studies, with a total of 37 participants, met the review eligibility criteria for the literature review. Risk of bias was low in these trials. Balance confidence, mobility, and quality of life were reported to improve with community-based boxing training programs delivered in 24–36 sessions over 12 weeks. PD medications were not always documented and some elements of the boxing interventions were incompletely reported against the CERT (Consensus on Exercise Reporting Template). Nine websites advocating boxing programs for PD were also evaluated. The QUEST analysis showed low-level quality, and little scientific evidence verifying findings, despite positive reports.

Limitations: In the published literature, findings were limited due to the small number of included studies and participants. Websites were numerous yet often lacked verifiable data.

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Many unanswered questions

- Dose, timing, intensity, optimal regimen
- Side effects
- Safety and appropriateness at different stages
- Comparison with other exercises
- Impact on disease progression
- Motor v NMS
- Sleep, mood, balance, olfaction
- How to train instructors


GYMMASTER
CORE


STAR TRAC
WOODWAY

Determined to outfox Parkinson's.

OPTIMISM

Pass It On.

VALUES.COM THE FOUNDATION FOR A BETTER LI

FIGHT-PD

Feasibility of Instituting Graduated High intensity Training for Parkinson's Disease

Protocol for a non-contact boxing exercise study

David Blacker- medical director, neurologist, PD patient

Rai Fazio- former Australian amateur boxing champion and boxing trainer

Travis Cruickshank and Mitchell Turner- exercise physiologists

Claire Tucak- neurophysiotherapist

Australian and New Zealand Clinical Trial Registry Number 380492

where hope begins

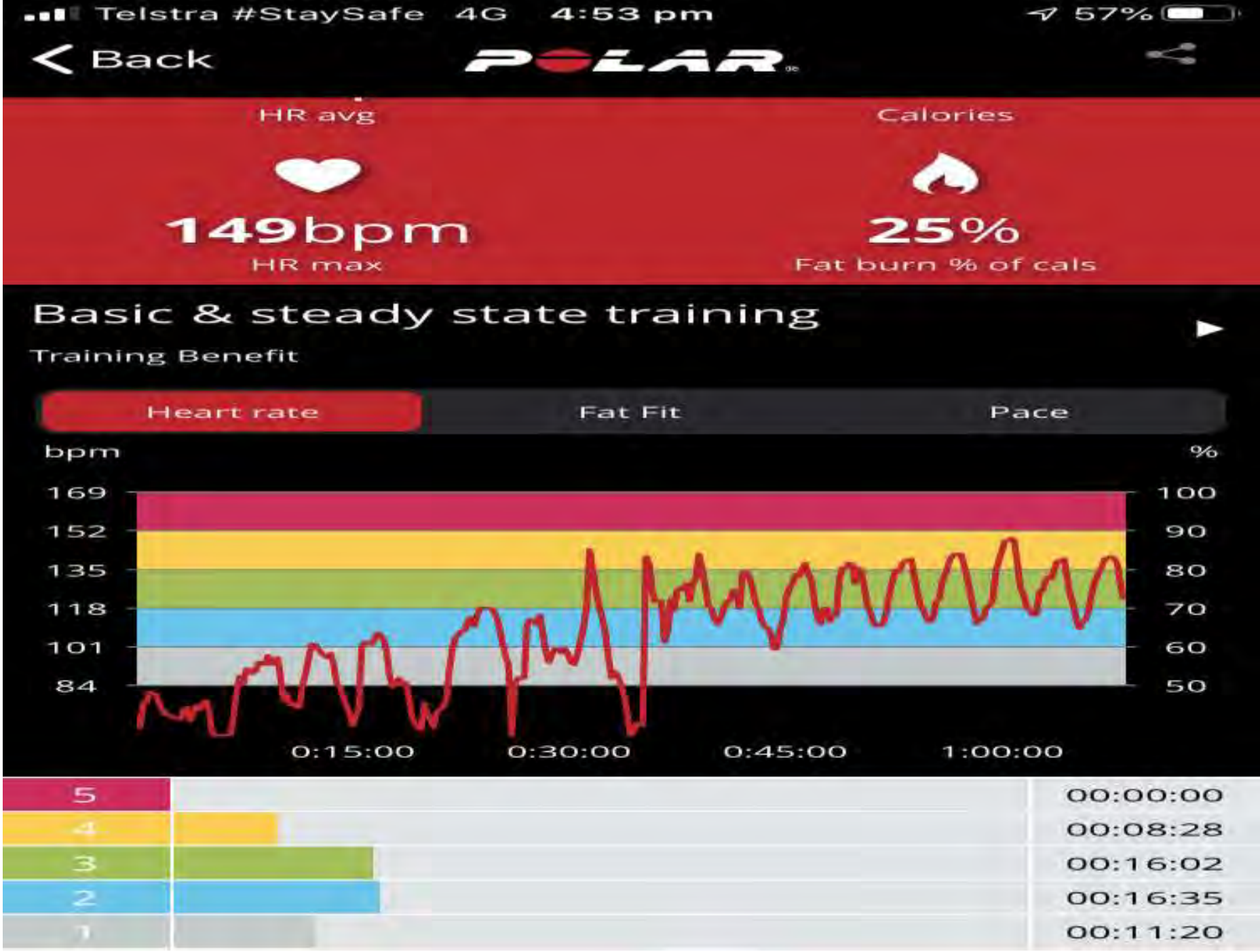
Objectives

1. Feasibility
2. Tolerability
3. Safety

Use principles of exercise science to quantify the components of the program

- Continual HR monitoring
- Rate of perceived physical (RPE) and mental exertion

  Borg scales
- Close monitoring for injury
- Compare standardized PD measures pre/post


Telstra #StaySafe 4G 4:53 pm
57%
Back
POLAR
HR avg
149bpm
HR max
Calories
25%
Fat burn % of cals
Basic & steady state training
Training Benefit
Heart rate
Fat Fit
Pace
bpm
169
152
135
118
101
84
%
100
90
80
70
60
50
0:15:00
0:30:00
0:45:00
1:00:00
5
4
3
2
1
00:00:00
00:08:28
00:16:02
00:16:35
00:11:20

Scales and Questionnaires

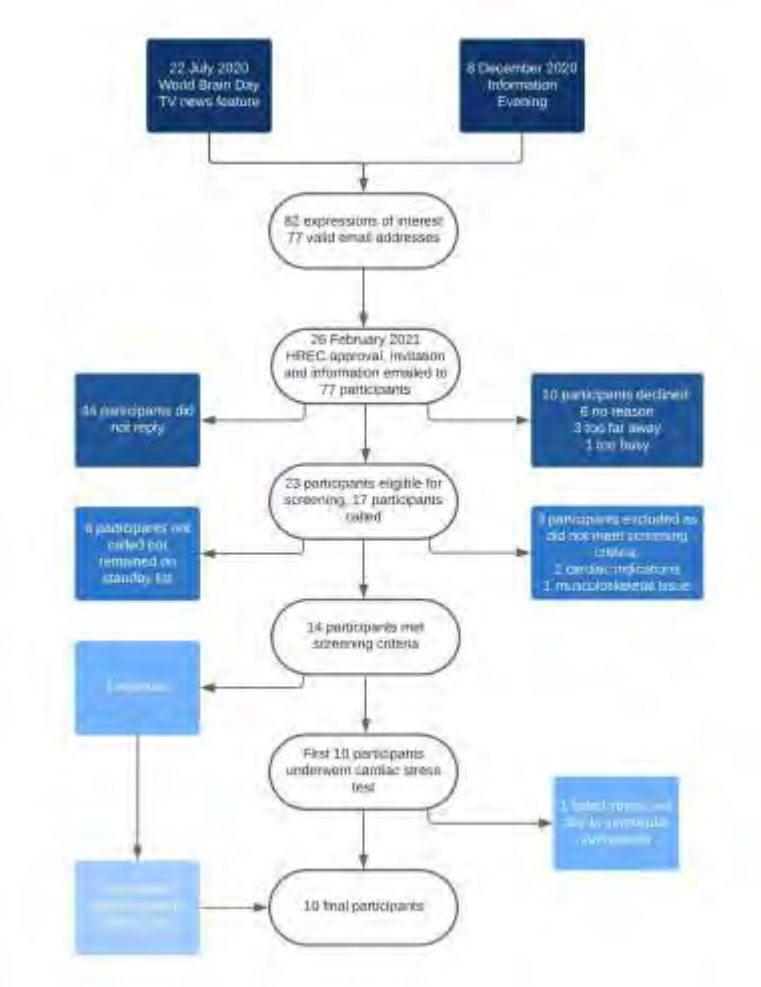
- Baseline
- Before each exercise session
- During the exercise session
- After the exercise session
- End of 5 week block
- End of the 15 week programme

Borg's Rating of Perceived Exertion (RPE) Scale

Perceived Exertion Rating	Description of Exertion
6	No exertion. Sitting & resting
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

https://www.braininjuryaustralia.org.au/wp-content/uploads/Barry-Willer_2.pdf

Participant Selection



10 subjects

- 6M, 4 F
- Ages 45-67; mean 60
- UPDRS motor;6-32

  6,7,10,14,15 and 18,24,25,25,32

  Mean 8.8 mean 24.8

  overall mean 16.6
- Sx duration < 5 years in 7
- All except one on therapy

CODE	AGE/ SEX	WEIGHT (KG)	HEIGHT (CM)	MOCA	UPDRS	BP - LAYING	BP - STANDING	SYMPTOM ONSET	DIAGNOSIS DATE	DATE OF FIRST MEDS	CURRENT PD MEDS	PD SUBTYPE	PREDOMINANT SIDEDNESS	H & Y STAGE
FPD1 - 001	65 M	87	179	30	25	175/ 86	133/ 83	2008	2010	2010	Pramipexole Stalevo	Tremor	RIGHT	2
FPD1 - 002	45 M	79	180	26	6	137/ 80	135/ 87	2015	2016	2016	Stalevo Rotigone patch	Tremor	LEFT	1
FPD1 - 003	52 M	100	182	22	25	169/ 94	137/ 76	2019	2020	2020	Pramipexole	Tremor	LEFT	1
FPD1 - 004	65 F	60	165	30	24	149/ 91	136/ 95	2016	2018	2000	Madopar	PIGD	LEFT	2
FPD1 - 005	66 F	65	154	28	18	140/ 83	123/ 85	2016	2018	N/A	Nil	PIGD	LEFT	1
FPD1 - 006	63 M	87	183	29	32	170/ 93	131/ 82	2017	2020	2020	Rasagaline	Tremor	LEFT	1
FPD1 - 007	67 F	73	167	29	15	155/95	144/ ***	2014	2015	2015	Madopar Pramipexole	PIGD	RIGHT	1
FPD1 - 008	56 F	73	175	30	14	117/ 81	88/ 71	2017	2018	2018	Madopar	Tremor	RIGHT	1
FPD1 - 009	56 M	82	183	29	7	128/ 88	127/ 88	2018	2019	2019	Stalevo Safinamide	PIGD	RIGHT	1
FPD1 - 010	65 M	81	183	30	10	125/ 90	130/ 94		2019	2019	Madopar Pramipexole	PIGD	RIGHT	1

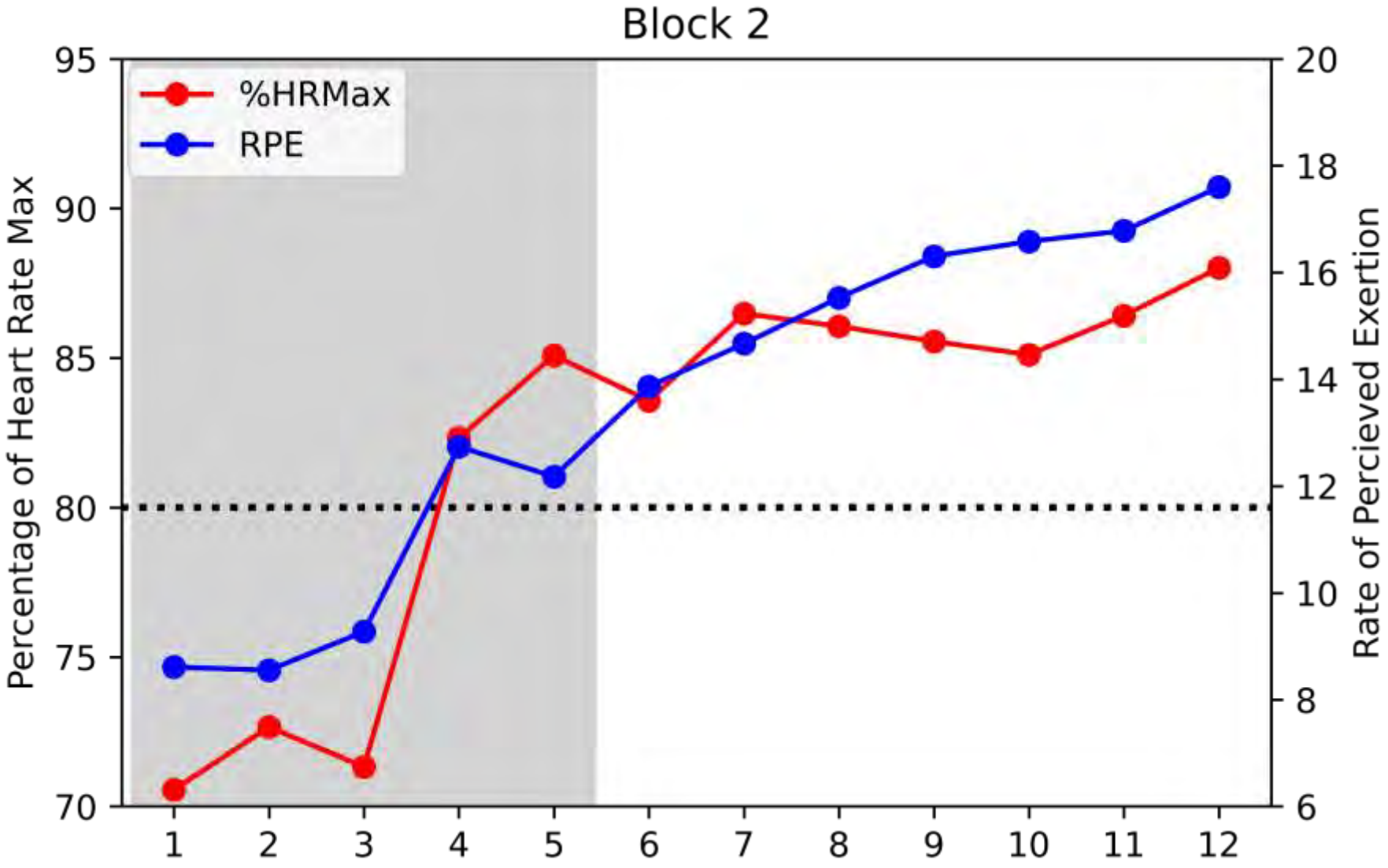
Training Program	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15
	Boxers Development					Boxers Cardio					Boxers Brain				
	Physical Load		Cognitive Load			Physical Load		Cognitive Load			Physical Load		Cognitive Load		
	<70% APMHR <13 RPE		<7 RPME			>80% APMHR >15 RPE		<7 RPME			70-80% APMHR 13-15 RPE		>7 RPME		

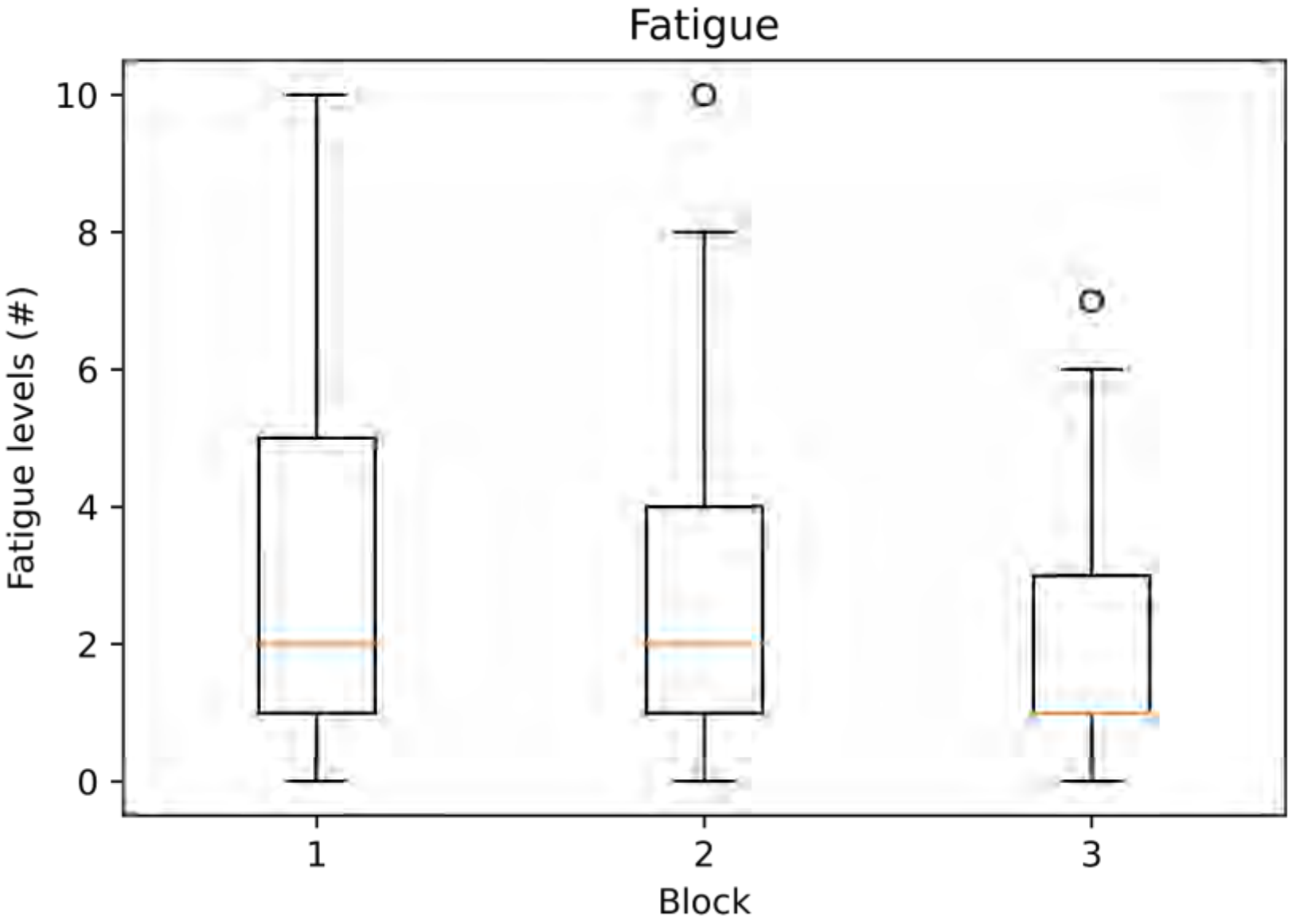
Example Block	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12
	UB	C	LB	CA	CA	Boxing						
	Boxers Movement											

W, week; APMHR, age-predicted maximum heart rate; RPE, rate of perceived exertion; RPME, rate of perceived mental exertion; R, round; APMHR, age-predicted maximum heart rate; RPE, rate of perceived exertion; RPME, rate of perceived mental exertion

Attendance

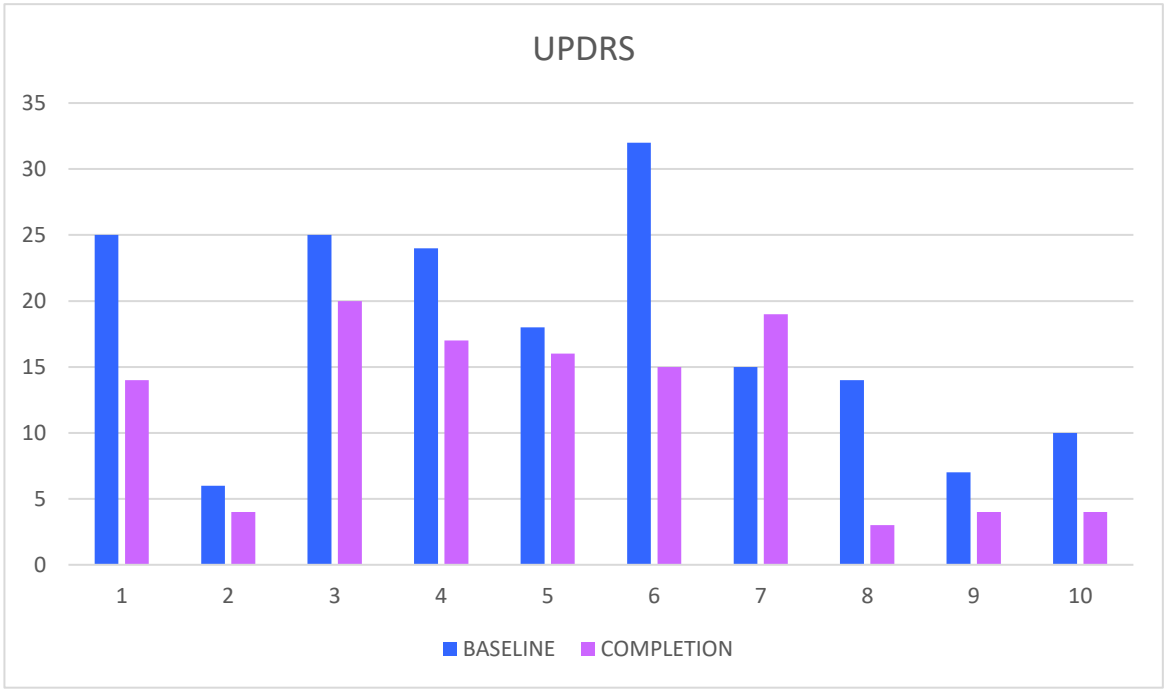
Workouts	Subjects	Subtotal	Reason for absence
36	4	144	Not applicable
35	3	105	*1 knee strain 1 unwell post COVID-vax 1 sick pet
34	2	68	1 hospital (SAE) 1 travel issue due to COVID lockdown
31	1	31	*3 calf muscle strain 2 travel issue due to COVID lockdown
		348	348/360= 96.7% **<u>* 4 sessions lost due to injury</u>**


Block 2
%HRMax
RPE
Percentage of Heart Rate Max
Rate of Percieved Exertion
95
90
85
80
75
70
20
18
16
14
12
10
8
6
1
2
3
4
5
6
7
8
9
10
11
12



Self-reported fatigue levels decreased as indicated by median values (orange line)

UPDRS pre/post



UPDRS pre/post

- 9/10 showed reduction; ie improvement
- Overall mean fell from 16.6 to 11.6
- 4/5 in baseline lower reduced, but one increased so mean remained 8.8
- All 5 in higher group reduced; mean falling from 24.8 to 14.4
- Note; -3.3 indicates “clinically meaningful” improvement

Future FIGHTs

- Later stage PD- stage 3+ possibly targeting those requiring walking aids, focus on balance and falls reduction; discussions with OPH
- Instructional video; telehealth applications
- Rural zoom groups
- Refined short exercise program
- Comparison with other exercise, controlled for aerobic output; eg bike v boxing
- PD gymnasium; + other therapies, eg yoga

Psychological reaction to Dx

“You have PD”

Incurable, progressive, neurodegenerative

- Shock, grief
- Loss of future
- Reactive depression
- Insomnia
- Apathy
- Demoralization

- Image of “future self” has to be revised

Reaction could impact on progression

- Poor psychological reaction could enhance apathy, decrease motivation, decrease physical activity
- Further accelerate deterioration

VIEWPOINT

Time for a New Image of Parkinson Disease

Melissa J. Armstrong, MD, MSc
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Michael S. Okun, MD
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Parkinson disease is now the fastest growing neurological disorder globally.[1] An estimated 6.1 million individuals worldwide had a Parkinson disease diagnosis in 2016, 2.4-fold higher than in 1990.[1] The most common representation of Parkinson disease continues to be the 1886 sketch by Sir William Richard Gowers, MD, published in his book *A Manual of Diseases of the Nervous System* (Figure, A).[2] Other Parkinson disease images remain largely based on Gowers' famous sketch: older white men who are frail, hunched forward, and shaking.

This commonly used image fails to accurately reflect a contemporary view of Parkinson disease and the heterogeneity in age at onset, sex, race/ethnicity, and disease experience. The incidence of Parkinson disease is highest in individuals aged 70 to 79 years,[3] and the prevalence peaks between ages 85 and 89 years.[1] However, these groups are considered to be late-onset Parkinson disease (70 years or older).[4] In one large study,[4] late-onset Parkinson disease accounted for only 39% of the people with Parkinson disease compared with 51% for middle-onset Parkinson disease (aged 50 to 69 years) and 10% for young-onset Parkinson disease (younger than 50 years).

Additionally, the male predominance of Parkinson disease, while well supported, may be overemphasized. Global analyses have shown a male to female ratio of 1.4.[1] In a separate analysis, the incidence of Parkinson disease was statistically higher in men only in those aged 60 to 69 years and 70 to 79 years.[3] Overall, the incidence was 37.16 per 100 000 person-years for women and 44.21 per 100 000 person-years for men,[3] demonstrating that Parkinson disease is common in both sexes.

In the US, Parkinson disease is more frequently diagnosed in white non-Hispanic populations. Using 1995 and 2000 to 2005 Medicare data, the incidence ratio of Parkinson disease among black vs white individuals was 0.74 (95% CI, 0.732-0.748). The prevalence ratio was 0.58 (95% CI, 0.575-0.581).[5] While Parkinson disease was less commonly diagnosed in black populations, the mean (SD) prevalence was still 1036.41 (86.01) per 100 000 Medicare recipients in this group.[5] An accurate view of Parkinson disease must include individuals from different backgrounds.

The frailness and disability shown in Gowers' 1886 picture is also not an accurate rendering of the modern experience of people with Parkinson disease. Recent subtyping identified the disabling diffuse malignant form of Parkinson disease in only 16% of cases.[6] A mild motor-predominant Parkinson disease phenotype was the most common presentation (49%), followed by the intermediate form (35%).[6] While all phenotypes are progressive, the mean (SD) time from diagnosis to first milestone (regular falls, wheelchair dependence, dementia, or residential/nursing home placement) was 14.3 (5.7) years for the mild motor-predominant form, 8.2 (5.3) years for the intermediate form, and 3.5 (3.2) years for the diffuse malignant form. Mean (SD) survival after diagnosis was 20.2 (7.8) years for the mild motor-predominant form, 13.2 (6.7) years for the intermediate form, and 8.1 (5.4) years for the diffuse malignant form.[6] This suggests that people with Parkinson disease are living for many years without the profound disability implied by Gowers' sketch. Current approaches to Parkinson disease subtyping have limitations, and consensus on optimal categorization is lacking. However, it is clear that the experiences of individuals with Parkinson disease are varied and include mild and slow disease progression.

Does it matter? Almost certainly. Images are an increasingly important part of medical teaching. However, medical textbooks continue to have biases relating to age, sex, and race/ethnicity. These biases result in inadequate and unrealistic information.[7] For example, based on existing research, it is possible that images emphasizing the male predominance of Parkinson disease contribute to delays in women with Parkinson disease receiving specialty care. It is similarly possible that the classic picture of advanced Parkinson disease leads to lack of recognition of early Parkinson disease symptoms, especially within primary care settings.

Images such as Gowers' figure also contribute to public assumptions that Parkinson disease is an illness of old, frail individuals. This adds to the stigma reported by people with Parkinson disease, and stigma is a significant contributor to the quality of life of people with Parkinson disease.[8] Research outside Parkinson disease also suggests that expectations can be a self-fulfilling prophecy: negative perceptions of aging at baseline were associated with worse gait speed, decrements in verbal fluency, and impaired self-rated memory after 2 years of follow-up.

No single image can encapsulate the range of motor and nonmotor symptoms experienced by individuals with Parkinson disease, and there is no one common path. However, it is time that our medical images reflect modern people with Parkinson disease (Figure, B-D): young and old; male and female; active and debilitated; working, retired, or disabled; and with various symptoms and circumstances. While no single image can reflect the diversity of backgrounds, phenotypes, and experiences in Parkinson disease, it is important that our images are consistent with the advances in Parkinson disease that have occurred in the more than 130 years since Gowers' sketch. Improving the image to include a broad diversity of

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From: **Time for a New Image of Parkinson Disease**

JAMA Neurol. 2020;77(11):1345-1346. doi:10.1001/jamaneurol.2020.2412

Figure Legend:

Images of Parkinson Disease: 1886 and 2020A, Illustration of Parkinson disease by Sir William Richard Gowers, MD, published in his book A Manual of Diseases of the Nervous System. B, Individuals with mild motor-predominant Parkinson disease often present at a young age (ie, in their 50s to 60s). They have mild motor symptoms and few nonmotor symptoms, slow progression, and a good response to medications. Because of this, others may not be able to tell that the person has Parkinson disease other than the presence of tremor, mildly decreased facial expression, and sometimes foot dystonia (dotted circle). C, Individuals with the intermediate Parkinson disease phenotype have more prominent movement symptoms, including decreased facial expression, stiffness, slowness, and tremor, often with a modest response to medication. While the symptoms are more obvious than in the mild

Problems with a stereotyped image

- 1. Diagnostic Bias
- 2. Doesn’t account for important non- motor symptoms

You don't look like you have PD!

PwPD

- Often feel frustrated negative about this
- " Don't they believe me?"
- " They think I'm not that unwell"

Speaker

- Just trying to be supportive
- Don't know what else to say

Main problem with image

- Trigger negative reaction and downhill path
- Self fulfilling prophecy

PLOS ONE

RESEARCH ARTICLE

Negative Perceptions of Aging and Decline in Walking Speed: A Self-Fulfilling Prophecy

Deirdre A. Robertson[1]*, George M. Savva[2], Bellinda L. King-Kallimanis[1], Rose Anne Kenny[1,3]

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Citation: Robertson DA, Savva GM, King-Kallimanis BL, Kenny RA (2015) Negative Perceptions of Aging and Decline in Walking Speed: A Self-Fulfilling Prophecy. PLoS ONE 10(4): e0123260. doi:10.1371/journal.pone.0123260

Academic Editor: Antony Bayer, Cardiff University, UNITED KINGDOM

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Data Availability Statement: Full dataset available at the Irish Social Sciences Data Archive (ISSDA) (http://www.ucd.ie/issda/data/tilda/), based at the UCD Geary Institute, Ireland.

Funding: Funding was gratefully received from the Atlantic Philanthropies (www.atlanticphilanthropies.org), the Irish Government, the Health Research Board (www.hrb.ie). TILDA is funded by the Department of Health and Atlantic Philanthropies, along with support from Irish Life in the form of a charitable gift. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This does

Abstract

Introduction

Walking speed is a meaningful marker of physical function in the aging population. While it is a primarily physical measure, experimental studies have shown that merely priming older adults with negative stereotypes about aging results in immediate declines in objective walking speed. What is not clear is whether this is a temporary experimental effect or whether negative aging stereotypes have detrimental effects on long term objective health. We sought to explore the association between baseline negative perceptions of aging in the general population and objective walking speed 2 years later.

Method

4,803 participations were assessed over 2 waves of The Irish Longitudinal Study on Ageing (TILDA), a prospective, population representative study of adults aged 50+ in the Republic of Ireland. Wave 1 measures – which included the Aging Perceptions Questionnaire, walking speed and all covariates - were taken between 2009 and 2011. Wave 2 measures – which included a second measurement of walking speed and covariates - were collected 2 years later between March and December 2012. Walking speed was measured as the number of seconds to complete the Timed Up-And-Go (TUG) task. Participations with a history of stroke, Parkinson's disease or an MMSE < 18 were excluded.

Results

After full adjustment for all covariates (age, gender, level of education, disability, chronic conditions, medications, global cognition and baseline TUG) negative perceptions of aging at baseline were associated with slower TUG speed 2 years later (B=.03, 95% CI = .01 to 05, $p < .05$).

Conclusions

Walking speed has previously been considered to be a consequence of physical decline but these results highlight the direct role of psychological state in predicting an objective

JAMA Neurology comment

- **July 28, 2020**
- **Thanks for the Image Update- I can see myself**
- **David Blacker, MB BS, FRACP | Perron Institute for Neurological and Translational Science**

- **Thanks to Armstrong and Okun for this compact, informative and timely article, co-inciding with the week of the World Federation of Neurology World Brain Day (July 22nd), which this year highlights Parkinson Disease. What we say as doctors to patients is highly impactful; words need to be chosen carefully and perceptions of illness count. I suspect that mental perception of PD may even influence progression; if a negative, nihilistic image is formed around the time of diagnosis, the self-fulfilling prophecy concept, combined with apathy, could contribute to lack of engagement in physical therapy and mobility, which I suspect accelerates progression.**

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Declining Quality of Life in Parkinson Disease Before and After Diagnosis

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Abstract

We sought to assess the quality of life in PD patients before the diagnosis, in comparison to age-matched individuals free of PD, among participants in two large prospective cohorts of men and women. Components of the Short-Form Health Status Survey (SF36) were administered to all participants in 1996 and 2008 in the Health Professionals Follow-up Study (HPFS), and in 1992, 1996, 2000 and 2004 in the Nurses' Health Study (NHS). We used scores in 7 health-related quality of life-dimensions, that were rated from 1(worst) to 100(best) points. We fitted a multivariate mixed-effect model with repeated measures to estimate the expected decline with age and compared that to the decline observed among PD cases by time to diagnosis. 454 men and 414 women with PD contributed data to the analyses. A decline in physical function in PD patients relative to the whole cohort began approximately 7.5 years prior to diagnosis in women and 3 years prior to diagnosis in men, and continued to decline thereafter with a rate of 2.35 and 1.43 points per year in women and men respectively ($p < 0.001$ for both). For comparison, the average yearly decline in individuals without PD was 0.42 and 0.23 points per year in women and men respectively. Other measures of quality of life (only available in women) declined in a similar pattern to physical function. In summary, the quality of life in PD patients begins to decline years before the diagnosis.

Keywords

Parkinson; Progression; Epidemiology; Quality of Life

Introduction

There is growing evidence that Parkinson disease (PD) often starts with non-motor symptoms that precede the diagnosis by several years[1,2] but there are no data on the physical and social functioning of PD patients before the disease is diagnosed. In a recent study, newly diagnosed PD patients showed evidence of limitations in the UPDRS Activities

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QOL before and after Dx of PD

Two large longitudinal population health studies

- Nurses Health study

  121 701 women followed from 1976

- Health professionals follow up study

  51 539 men from 1986

Biannual questionnaires re lifestyle, health issues

Surveys every 4 years

SF36-measures health related QOL

Decline in QOL before Dx of PD

- Questions about Dx of PD from 1988
- 2008 analysis;

  PD Dx in 454 mean and 414 women

A decline in physical function began;

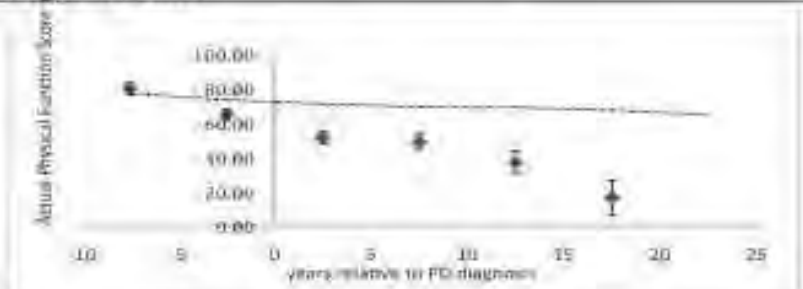
7.5 years before PD Dx in women

3.0 years before PD Dx in men

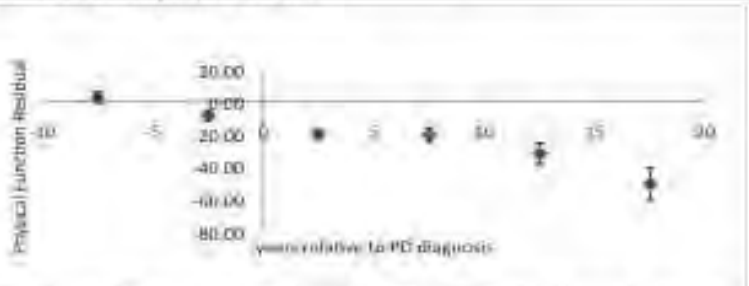
SF 36

WOMEN

A. Physical Function Among PD Cases by Time to Diagnosis,*NHS

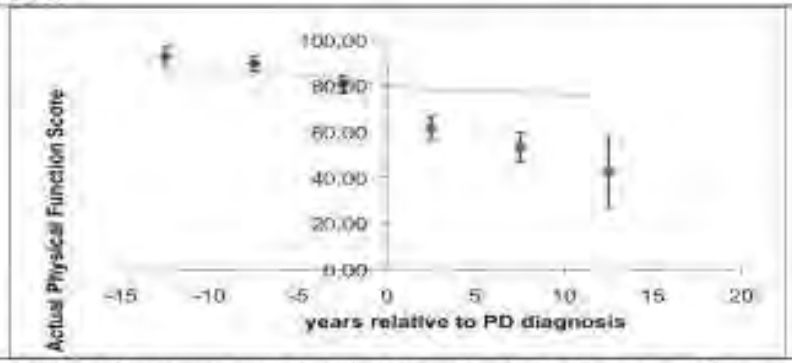


B. Relative Physical Function (Residual) of PD Cases Compared to Non-Cases of the Same Age, Gender and Smoking History by Time to PD Diagnosis, NHS

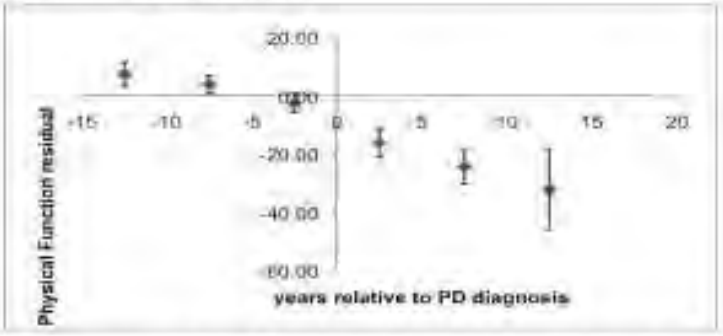


MEN

C. Physical Function Among PD Cases by Time to Diagnosis,* HPFS



D. Relative Physical Function (Residual) of PD Cases Compared to Non-Cases of the Same Age, Gender and Smoking History by Time to PD Diagnosis, HPFS



*Dashed line represents physical functioning of persons of same age as the PD patients in each time-to-diagnosis strata, based on model adjusting for age in 5 year groups

Decline in QOL after Dx of PD

- ***Rates of yearly average decline are 5 to 7 times faster in PD, compared with non-PD matched for age and gender***
- ***QOL worse in PD than;***

  diabetes, MS, SCI, angina, depression

- ***Can this be altered?***

What we say as doctors is highly impactful

Don’t just say;

- See you in 6 months to consider medications
- Have some brochures
- Try to get to a newly diagnosed seminar

- *<u>Patients want more!</u>*

POSSIBLE INTERVENTION

Education

- Correct misperceptions; time course of neurodegenerative conditions, myths about L-dopa

Support

- Early follow up
- E-mail accessibility

Early dopamine replacement

- To optimize exercise
- Don't miss out of benefits

Healthy lifestyle

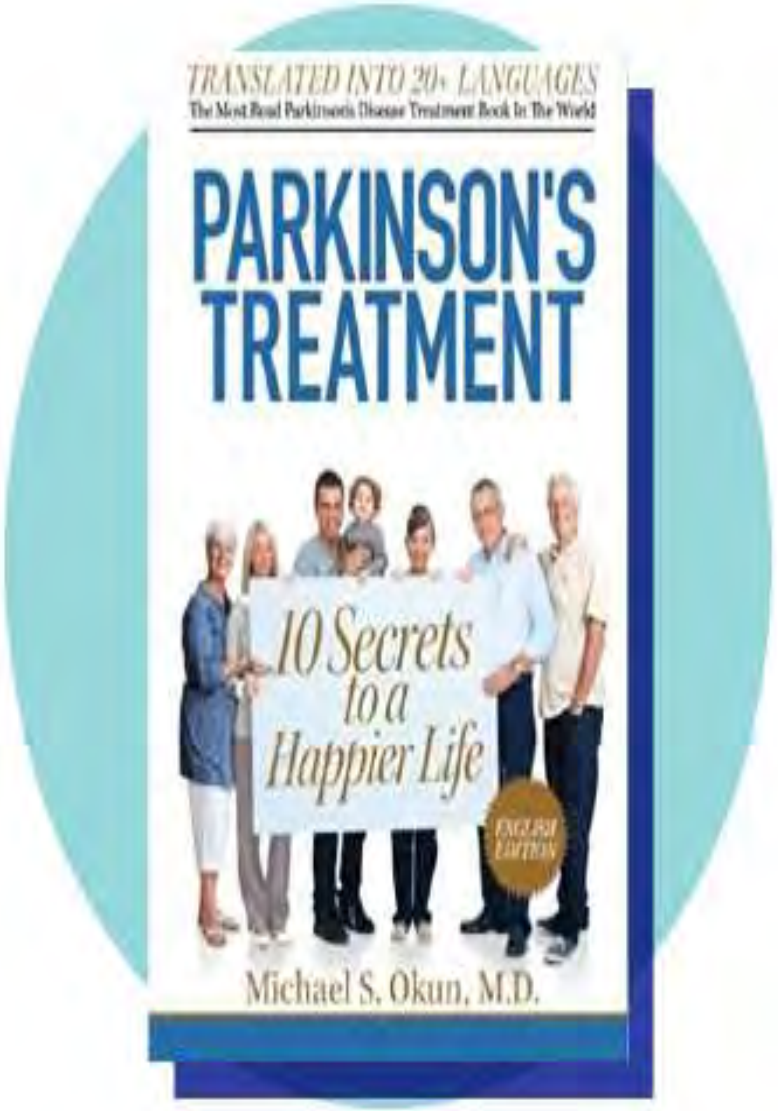
Exercise

Peer group counselling

Focus on "bucket list"

Could actually improve!

"Honeymoon boost"



Hindawi
Journal of Aging Research
Volume 2018, Article ID 2126368, 10 pages
https://doi.org/10.1155/2018/2126368

Research Article

Positive Mental Attitude Associated with Lower 35-Year Mortality: The Leisure World Cohort Study

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Academic Editor: Carmela R. Balistreri

Background. Although emerging research has suggested that "positive psychological well-being" is associated with better health outcomes, studies of long-term health and mortality in the elderly are limited. This study assessed the relationship of mental attitude and mortality in older adults followed up for 35 years. *Methods*. In the 1980s, the Leisure World Cohort Study recruited residents of a California retirement community to a prospective cohort study of health promotion and disease prevention. Participants completed a postal survey including seven positively worded items from the Zung self-rating depression scale. Age-adjusted and multivariable-adjusted (for lifestyle behaviors and disease conditions) hazard ratios (HRs) for death were calculated using Cox regression for 8682 women and 4992 men (median age at entry, 74 years). During follow-up (1981–2016), 13,405 participants died (median age at death, 88 years). *Results*. In both women and men, HRs for death were significantly related to mental attitude with increasing risk with decreasing positive responses for total attitude and the seven individual items. The multivariable-adjusted HR (95% CI) for death for individuals in the lowest vs. highest quarter of total attitude was 1.24 (1.16, 1.32) for women and 1.30 (1.19, 1.41) for men. Some attenuation in the observed associations occurred after adjustment for potential confounders and after elimination of the first five years of follow-up. *Conclusions*. Our study suggests that persons with negative attitude have an increased risk of death even after many years of follow-up. Research into strategies to improve mental outlook may help improve the quantity as well as the quality of life.

1. Introduction

The number of elderly adults continues to increase as does the need for them to lead lives in good mental and physical condition. Although "positive mental attitude," "psychological well-being," "life satisfaction," and "happiness" are vague concepts, emerging research suggests that they are associated with better health outcomes [1–5] while their opposites "negative mental attitude," "life dissatisfaction," "pessimism," and "depression and depressive symptoms" are associated with poorer outcomes [6–9].

Studies of mental attitude and long-term health (including mortality) in the elderly are limited by sample size and length of follow-up. Four prospective cohort studies of all-cause mortality in the elderly have included more than 10,000 participants [10–13], and only one of these included both sexes [10]. Follow-up has been greater than 10 years in only three studies [10, 14, 15]. Thus, little is known about whether positive mental attitude has any predictive value in old age over a long-time span.

In 1981, we undertook a prospective cohort study of nearly 14,000 elderly women and men in a California retirement community with the aim of studying factors associated with longevity and successful aging. We report here the results of positive mental attitude (seven items from the Zung self-rating depression scale [16]) on all-cause mortality

Effects of dispositional optimism on quality of life, emotional distress and disability in Parkinson's disease outpatients under rehabilitation

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Federica Rizza, PhD[a]
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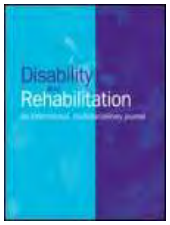
Summary

This study was performed with the aim of assessing dispositional optimism (DO) in a sample of Parkinson's disease (PD) patients, in order to evaluate its association with clinical outcomes and its impact on rehabilitation.
Before entering an outpatient rehabilitation program, 58 participants suffering from idiopathic PD completed the Life Orientation Test-Revised (LOT-R) to evaluate their level of DO, the WHO-5 scale to evaluate their health-related quality of life (HR-QoL), the Hospital Anxiety and Depression Scale (HADS) to identify emotional distress, and the Barthel Index to evaluate their level of disability.
All the measures were repeated four months later, at their discharge from the program. Disease stage and severity measures (Unified Parkinson's Disease Rating Scale) were also taken into consideration. Correlations and multivariate regression analyses compared DO with the health-related variables.
On admission a high level of DO was found to be associated with less severe disease, a better quality of life (QoL) and lower emotional distress, but not with level of disability (Barthel Index). Consistent results were found at discharge. The level of DO did not change after rehabilitation, while anxiety was significantly reduced, especially in subjects with low LOT-R and high HADS scores. The Barthel Index values significantly improved. At discharge, participants with high DO showed the best improvements in disability and in QoL.
In conclusion, a high level of DO was associated with QoL, HADS and UPDRS both on admission and at discharge. The level of DO remained stable after rehabilitation, while disability and anxiety were reduced. Participants with high DO generally had better QoL, and better clinical and psychological performances.

KEY WORDS: disability, dispositional optimism, mood, Parkinson's disease, quality of life, rehabilitation

Introduction

Parkinson's disease (PD) is a disabling and progressive disease. Nevertheless, dispositional optimism (DO) has recently become a topic of growing interest and research within the field of PD. The mental attitude, or outlook on life, of individuals with DO is characterized by positive expectations and confidence in a secure future. They also view events and situations, including difficulties, in a positive light. In recent years, there has been an increase in studies exploring emotional responses, adaptive behavior and coping strategies under stressful conditions (see Chiesi et al., 2013).
Three early studies investigated the role of DO on disability and health-related quality of life (HR-QoL) in PD. While a longitudinal study in 12 PD patients found no significant relationship between disease severity and DO (Shifren, 1996), the Global Parkinson's Disease International Survey (2002) found a statistically significant effect of DO on HR-QoL in 1020 PD patients. Several years later, the presence of low DO or high pessimism was found to be associated with reduced QoL in 99 PD patients (Gruber-Baldini et al., 2009). More recently, we found high DO to be associated with a satisfactory quality of life (QoL), low emotional distress, and reduced disease severity in PD (Gison et al., 2014). None of the above studies considered the effect of rehabilitation.
The present study was conducted with two aims: i) to evaluate the presence of correlations between PD patients' levels of DO and major measures of well-being, both on admission to and at discharge from an outpatient rehabilitation program; ii) to examine the effect of baseline DO (on admission) on the rehabilitation outcome.



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Post-traumatic growth in people living with a serious medical condition and its relations to physical and mental health: A systematic review

Tatjana Barskova & Rainer Oesterreich

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behavioral sciences

MDPI

Article

A Qualitative Study on the Impact of First Steps—A Peer-led Educational Intervention for People Newly Diagnosed with Parkinson's Disease

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Abstract: *Aim:* The dual aim of this research was to consider the impact of providing the First Steps program on the stories of people with Parkinson's Disease (PD) and to investigate the psychosocial and emotional mechanisms which may explain this impact. *Methods*: A qualitative study using a subtle realist paradigm and hermeneutic phenomenological methodology was undertaken. A single semi-structured interview was used to consider the impact and experiences of people with PD who completed either the intervention (2-day peer-led behavior intervention using storytelling 6–8 weeks apart) or received telephone support calls as part of the active control group. Descriptive statistics and a narrative analysis were undertaken on the results. *Results:* Forty-two participants were invited to participate, forty of whom completed the interview. This included 18 from the intervention group and 22 from the active control group. The intervention group identified the value of the program as worth-while, demonstrating improved exercise behavior and coping mechanisms following the intervention. Three major stories (the affirmed, the validated and the transformed story) identified the impact of the intervention. Three internal mechanisms (perceived control, hope and action, and the individual's mind set) alongside three social mechanisms (social comparison, social control and the first opportunity to share with peers) appeared to explain this impact. *Conclusion*: This study provides exciting and novel evidence of the impact of a peer-led psycho-educational intervention for people newly diagnosed with PD. Further research is needed to consider the impact of stories-based approaches on participants and consider a critical evaluation of the mechanisms which may explain changes in stories and self-reported behaviour.

First steps Peer –led Educational Intervention for newly Dx PD

- Major problem in care of PD at Dx is lack of social support
- Educational programs important
- Some have shown improvements in self-reported mood and QOL
- Program of interviews and workshops
- Based in Oxford, UK

PATH-PD Program

Positive **A**ttitude **T**owards **H**ealth

Soon after diagnosis or first visit

Session with PD nurse psychologist

Lead through package of information

Where to find support, trials, websites, books, video, medication advice, driving, insurance

Can effect be measured?

- Excellent longitudinal data sets
- MJ Fox Foundation PPMI- progressive Parkinsons markers initiative
- TONiC- Trajectory of Outcome in Neurological conditions

  Based in UK, started with MS and MND

  Prof Sluv Koks, Perron, TONiC -PD

frontiers in Aging Neuroscience

REVIEW
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Exercise-Induced Neuroprotection of the Nigrostriatal Dopamine System in Parkinson's Disease

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Epidemiological studies indicate that physical activity and exercise may reduce the risk of developing Parkinson's disease (PD), and clinical observations suggest that physical exercise can reduce the motor symptoms in PD patients. In experimental animals, a profound observation is that exercise of appropriate timing, duration, and intensity can reduce toxin-induced lesion of the nigrostriatal dopamine (DA) system in animal PD models, although negative results have also been reported, potentially due to inappropriate timing and intensity of the exercise regimen. Exercise may also minimize DA denervation-induced medium spiny neuron (MSN) dendritic atrophy and other abnormalities such as enlarged corticostriatal synapse and abnormal MSN excitability and spiking activity. Taken together, epidemiological studies, clinical observations, and animal research indicate that appropriately dosed physical activity and exercise may not only reduce the risk of developing PD in vulnerable populations but also benefit PD patients by potentially protecting the residual DA neurons or directly restoring the dysfunctional cortico-basal ganglia motor control circuit, and these benefits may be mediated by exercise-triggered production of endogenous neuroprotective molecules such as neurotrophic factors. Thus, exercise is a universally available, side effect-free medicine that should be prescribed to vulnerable populations as a preventive measure and to PD patients as a component of treatment. Future research needs to establish standardized exercise protocols that can reliably induce DA neuron protection, enabling the delineation of the underlying cellular and molecular mechanisms that in turn can maximize exercise-induced neuroprotection and neurorestoration in animal PD models and eventually in PD patients.

Keywords: basal ganglia, dendritic spine, dopamine, glutamate, medium spiny neuron, neuroprotection, neurotrophic factor, physical activity

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INTRODUCTION

Parkinson's disease (PD) is a common, age-dependent degenerative neurological disorder caused by a severe loss of the nigrostriatal dopaminergic projection (Kish et al., 1988; Hornykiewicz, 2001; Braak et al., 2004; Kordower et al., 2013), leading to the characteristic motor deficits and symptoms including resting tremor, a slowness and paucity of movements, muscle rigidity, and postural

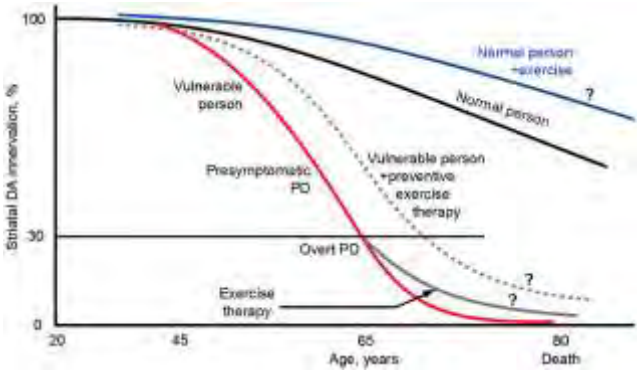


FIGURE 1 | Diagram illustrating that PD has a long presymptomatic period and that exercise may reduce PD risk, delay the appearance of the symptoms, and slow the disease progression. ? indicates that the illustrated possibilities are suggested by indirect evidence but direct evidence is lacking. The diagram is based on Kish et al. (1988), Hornykiewicz (2001), Braak et al. (2004), Gaig and Tolosa (2009), Hawkes et al. (2010), Savica et al. (2010), Coelho and Ferreira (2012), Burke and O'Malley (2013), Goedert et al. (2013), Kordower et al. (2013), Del Tredici and Braak (2016), Noyce et al. (2016) and Salat et al. (2016). The curves and values are approximate because published data are incomplete and variable. Original illustration of Fu-Ming Zhou.

symptom progression, less caregiver burden and less cognitive decline (Oguh et al., 2014; Rafferty et al., 2017). It has also been reported that a 24-week Tai Chi exercise improved balance and gait function while reducing falls in PD patients (Li F. et al., 2012, 2014), although another study indicated that a 16-week Tai Chi exercise failed to produce detectable beneficial effect on the motor function in PD patients (Amano et al., 2013). Additional studies have indicated that that exercise can play an important role in slowing the physical and cognitive decline resulting from PD (Corcos et al., 2013; LaHue et al., 2016; Reynolds et al., 2016; Dipasquale et al., 2017). Physical exercise has also been reported to produce synergistic benefits with L-dopa for improving motor functions in PD patients (Kang et al., 2012).

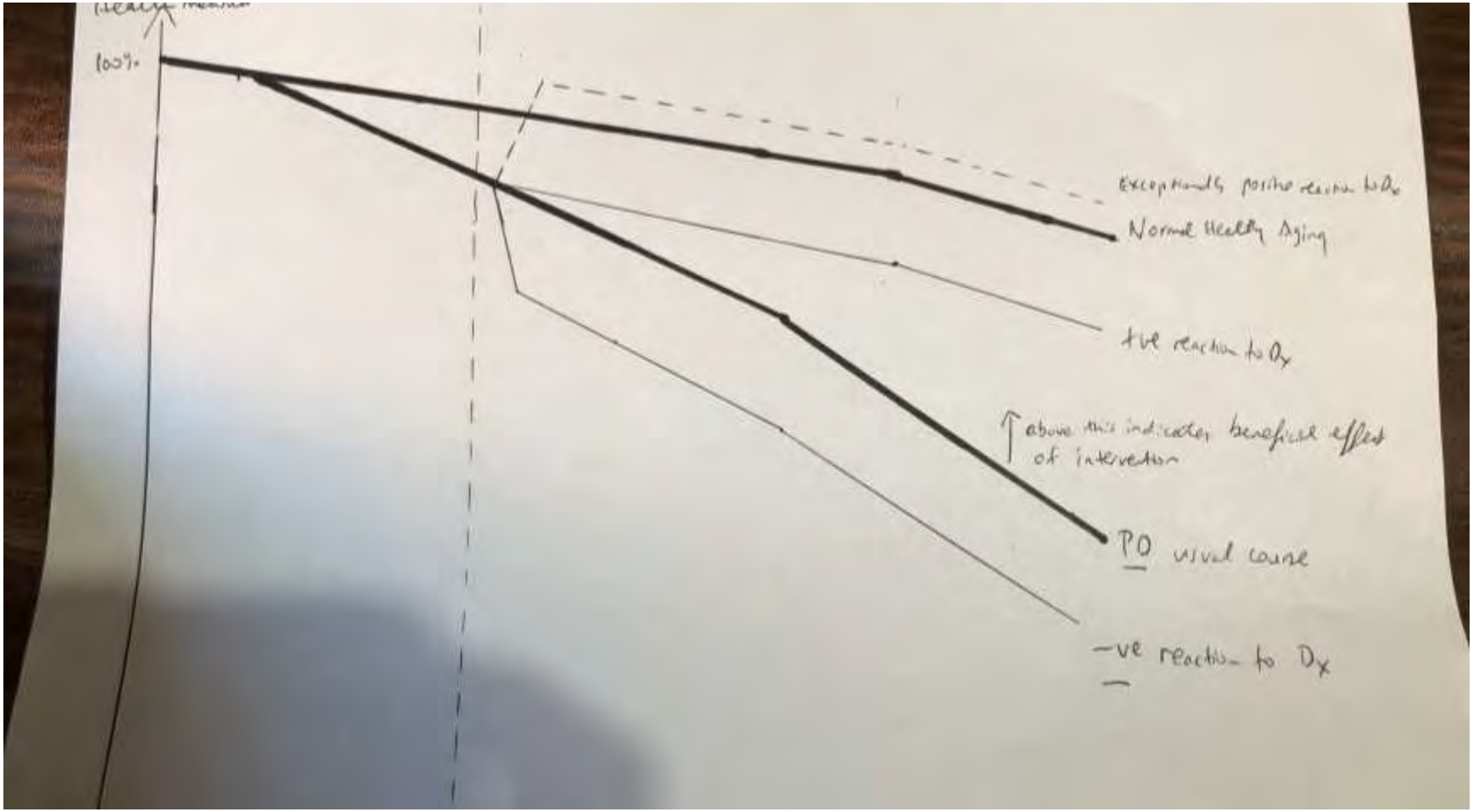
Taken together, these clinical and epidemiological studies have provided evidence supporting the conclusion that exercise not only has a significant preventive effect on PD, but also has therapeutic value by reducing the symptoms and slowing the symptom and disease progression (**Figure 1**), and should be promoted to the general population, PD vulnerable population in particular (Burley et al., 2016; Jackson et al., 2016; Lauzé et al., 2016). These studies also indicate that physical exercise needs to be prescribed to PD patients and be an essential component of the treatment for PD (Ahlskog, 2011; Vina et al., 2012; Shulman et al., 2013; Bloem et al., 2015; Pedersen and Saltin, 2015; LaHue et al., 2016; Lauzé et al., 2016; Reynolds et al., 2016) (**Figure 1**). Indeed, the highly respected International Parkinson and Movement Disorder Society has designated exercise as an adjunct therapy for PD (Fox et al., 2011).

Although much remains to be understood, exercise's benefits for PD are likely to be mediated partly by exercise-induced improvement of the general health (e.g., increasing the cardiovascular and cerebrovascular function), the function of the skeletal musculature and also the function of the broad motor control neural systems including cerebral motor cortices, BG, the cerebellum and the thalamus (Beall et al., 2013; Petzinger et al., 2013; Singh et al., 2014; Wang et al., 2015a,b; Alberts et al., 2016; Burley et al., 2016; Jackson et al., 2016; Shah et al., 2016). Additionally, because of the known importance of the nigrostriatal DA system and the cortico-BG circuitry in motor function, a large number of studies have examined how exercise directly affects these neural systems. Below, we will summarize and synthesize these studies, starting with describing the basic anatomy and physiology of the nigrostriatal DA system and cortico-basal ganglia circuits, likely key neural targets for exercise intervention.

ANATOMY OF THE NIGROSTRIATAL DA SYSTEM AND THE BASAL GANGLIA

Components of the Basal Ganglia and the Nigrostriatal DA System

The basal ganglia (BG) are a group of interconnected subcortical nuclei including the striatum, globus pallidus external segment (GPe) and internal segment (GPi), the subthalamic nucleus (STN), the substantia nigra pars compacta (SNc), and pars reticulata (SNr) (Gerfen and Bolam, 2017; Zhou, 2017) (**Figures 2A,B**). In primates, the striatum comprises the caudate nucleus and putamen. The striatum is the major input nucleus for the BG receiving glutamatergic inputs from motor and somatosensory cortices and other cortical areas (Deng et al., 2015) and the thalamus (Smith et al., 2014). The GABAergic medium spiny neurons (MSNs), comprising 90% of the striatal neurons, are the projection neurons of the striatum and critical to


100%
Exceptionally positive reaction to Dx
Normal Healthy Aging
+ve reaction to Dx
above this indicates beneficial effect of intervention
PO usual course
-ve reaction to Dx