OhioHealth

Delay the Disease

Continuing Education Course Curriculum

Table of Contents

Evidence-Based Concepts for Planning and Implementing a Community-Based, Parkinson's-Specific Exercise Class Based on the Delay the Disease™ Parkinson's Fitness Program

Course outcome: Enable learners to successfully create and implement an interdisciplinary Parkinson's-specific exercise and wellness program for people with Parkinson's disease.

Continuing education:

+ Continuing Nursing Education*: 10.5 hours
+ Ohio Physical Therapy Association: 11 hours
+ Ohio Occupational Therapy Section: 10.5 hours
+ Ohio Athletic Trainers Section: 10 hours

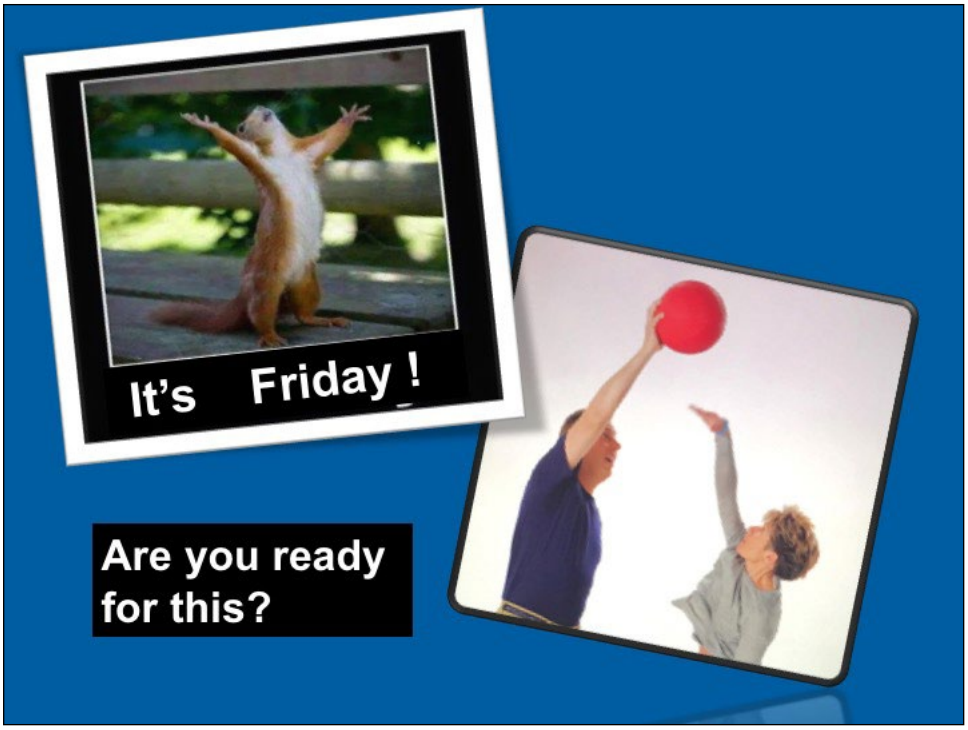
Criteria for successful completion:

+ Attend and participate in at least 90% of the facilitator-led learning event.
+ Attain an 80% or greater on the post course assessment
+ Complete the course evaluation

The planners and presenters for this program have declared no conflict of interest.
This program has no commercial support or sponsorship.

*Central Ohio OhioHealth Continuing Education Review Committee (OH-022/2-1-15) is an approved provider of continuing nursing education by the Ohio Nurses Association (OBN-001-91), an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

I. Jackie Russell, RN, BSN, CNOR



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THE #1 PARKINSON'S EXERCISE PROGRAM

Evidenced Based Concepts for Planning and Implementing a Parkinson's Specific Community Exercise Class using Delay the Disease

Jackie Russell, RN BSN CNOR
Co-Founder -Program Development Coordinator
Delay the Disease / OhioHealth

OhioHealth


IF YOU REST, YOU RUST.
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OBJECTIVES:
❖What is OH Delay the Disease?
❖How can I start a community-based Parkinson's-specific exercise class?


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WE are. . .
WELLNESS.
OhioHealth Delay
OhioHealth


If you follow all the rules, you might miss the fun!
"ONCE YOU START EXERCISING, HONEY, IT'S A WHOLE NEW BALL GAME."
Ernestine Shepard, 78


M. Ali
MJ Fox
Billy Graham
Linda Rondstadt
Robin Williams
Neil Diamond
Hope for a "hopeless" diagnosis
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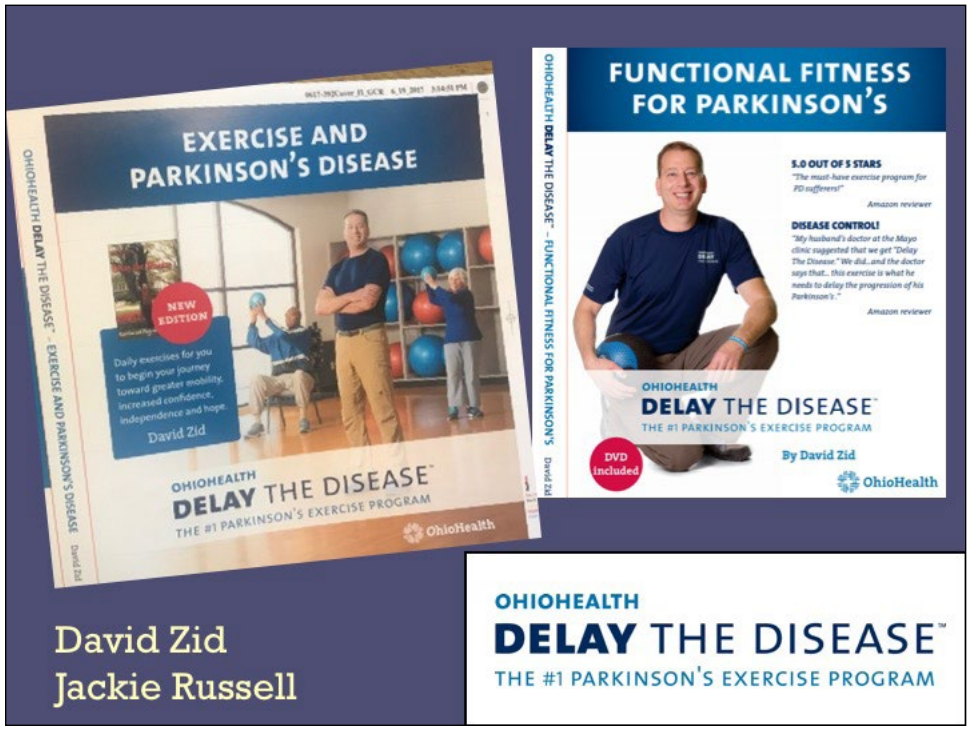
EXERCISE AND PARKINSON'S DISEASE
NEW EDITION
Daily exercises for you to begin your journey toward greater mobility, increased confidence, independence and hope.
David Zid
OHIOHEALTH
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THE #1 PARKINSON'S EXERCISE PROGRAM
OhioHealth
FUNCTIONAL FITNESS FOR PARKINSON'S
5.0 OUT OF 5 STARS
"The must-have exercise program for PD sufferers!"
Amazon reviewer
DISEASE CONTROL!
"My husband's doctor at the Mayo clinic suggested that we get "Delay The Disease." We did...and the doctor says that... this exercise is what he needs to delay the progression of his Parkinson's."
Amazon reviewer
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DVD included
By David Zid
OhioHealth
David Zid
Jackie Russell
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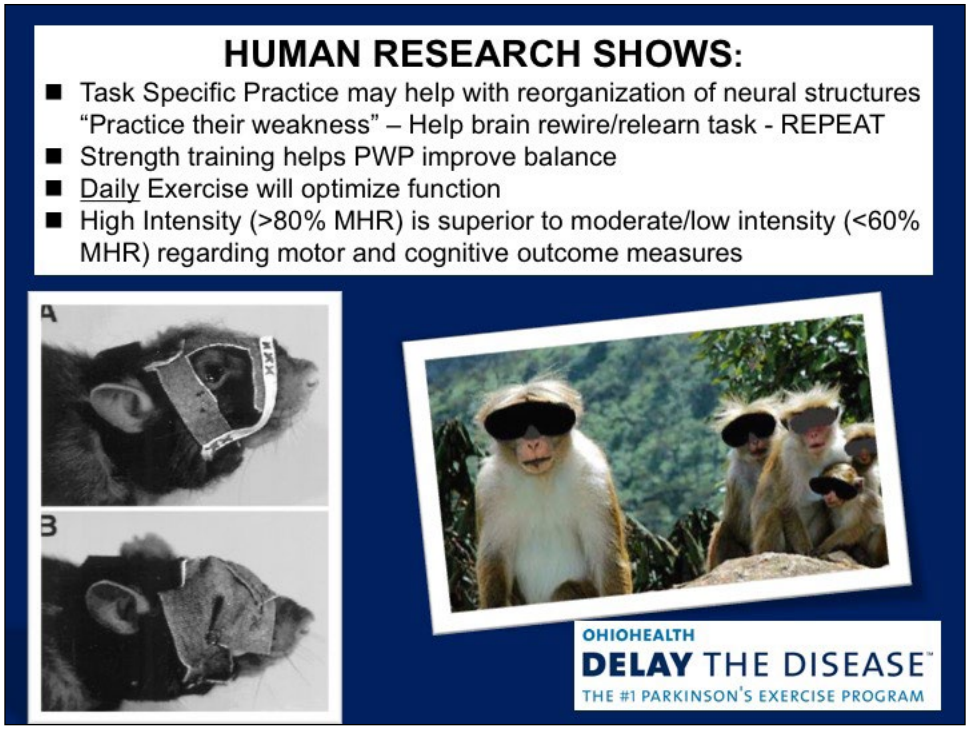
HUMAN RESEARCH SHOWS:
Task Specific Practice may help with reorganization of neural structures "Practice their weakness" – Help brain rewire/relearn task - REPEAT
Strength training helps PWP improve balance
Daily Exercise will optimize function
High Intensity (>80% MHR) is superior to moderate/low intensity (<60% MHR) regarding motor and cognitive outcome measures
A
B
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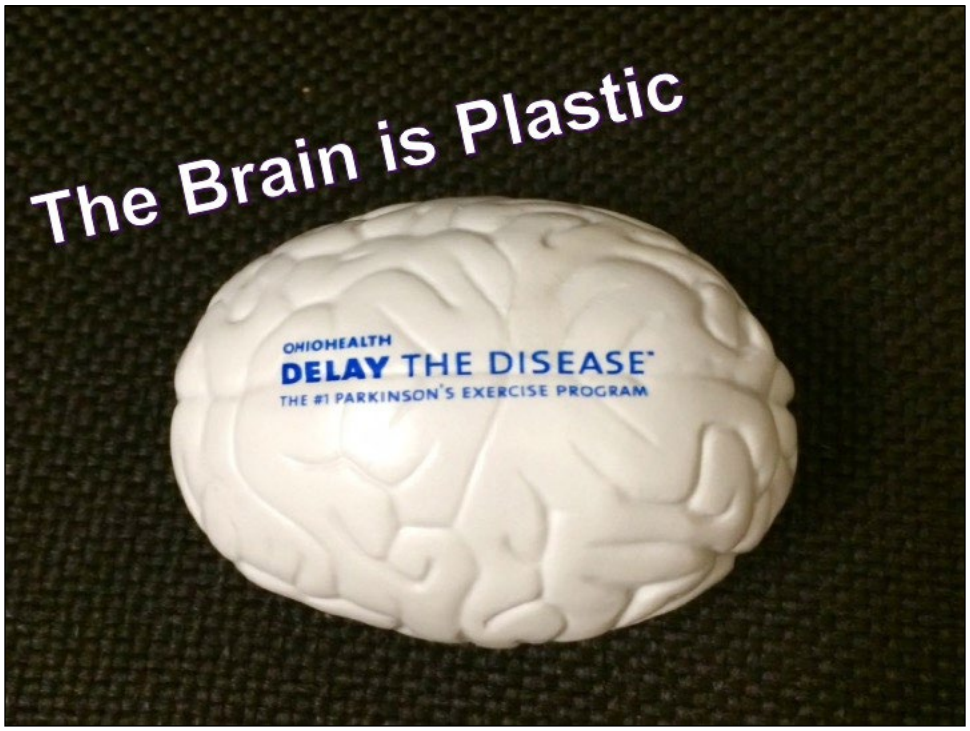
The Brain is Plastic
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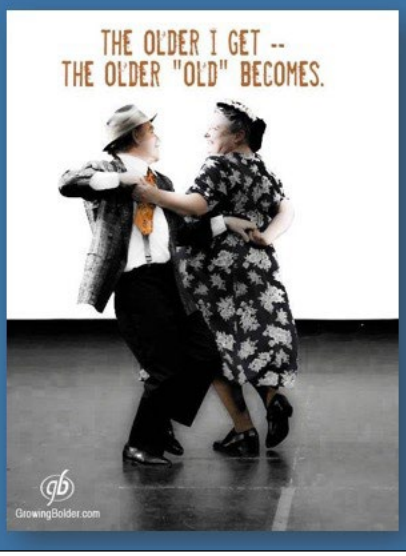
Neuroplasticity

- Brain's ability to reorganize/learn new behaviors by modifying and adding new synapses. Brain becomes more efficient at a task. Life long process.
- Exercise enhances neuroplasticity – WHY?:
- Unclear
  - Upregulates BDNF - neurotrophic factor that improves motor relearning
  - Keeps Dopamine in the synapse longer, improving efficiency and usage
- May protect the brain from further degeneration. NEUROPROTECTION
- Rigorous/Intense = Related to formation of new synapse NEUROGENESIS

WHEN IS THE BEST TIME FOR THE BRAIN TO RELEARN?



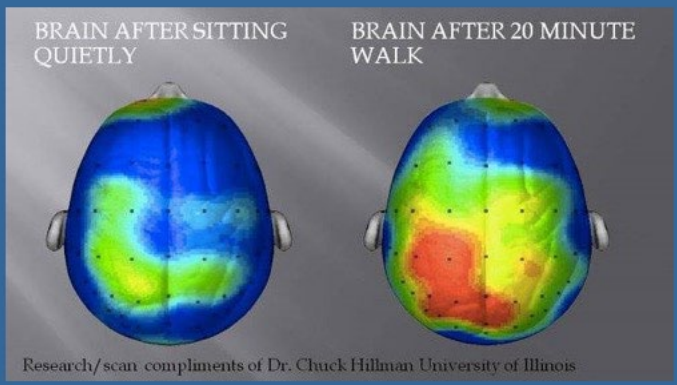
Become Aerobic

Smith, A; Goldsworthy, M: The influence of a single bout of aerobic exercise on short-interval intracortical excitability. Exp Brain Research 2/2014

- 22 participants in mid 30s
- 30 mins high intensity cycle
- Cortical inhibition before and after
- Measured hand muscle excitability

A single bout of exercise may promote cortical environment that is optimal for plasticity.

Aerobic Exercise Primes the Brain for



Inspiration

The ultimate tool for helping another individual to achieve their maximum potential

Exercise can put you in charge of your own morale

You cannot change the cards you are dealt in life, but you can change the way you play your hand

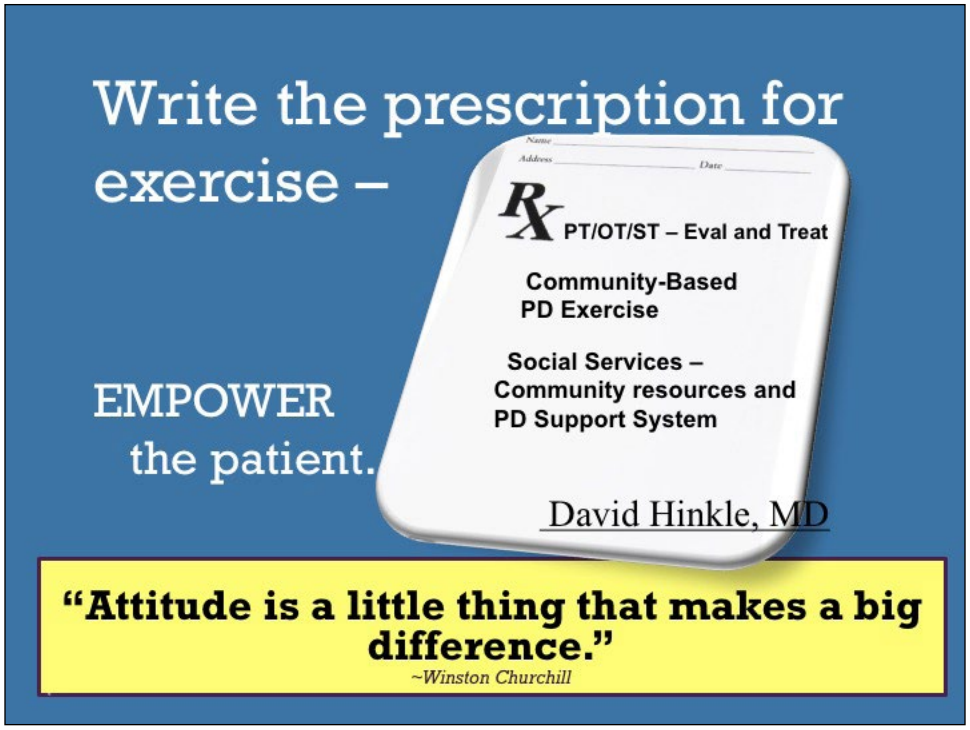
Randy Pausch, "The Last Lecture"

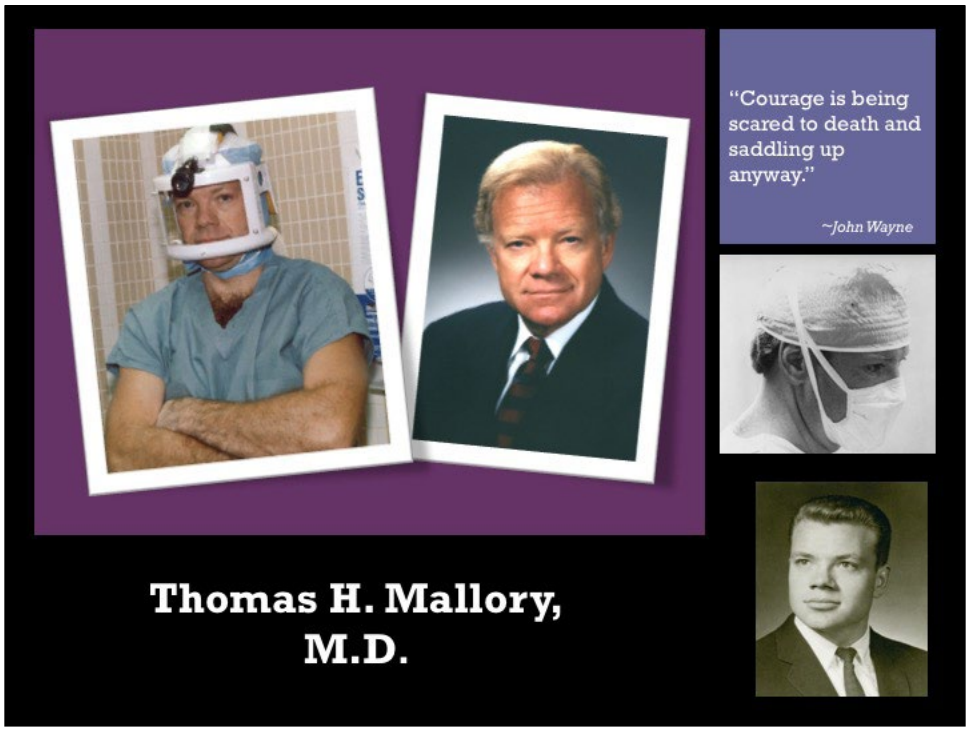
Exercise:

The "trump card".

"One could argue the more important objective research is moving towards the development of drugs that are neuroprotective — that is, medication that may delay or reverse the disease's progression. We believe that exercise is likely such a 'drug.'"

~Michael J. Zigmond, Ph.D., professor of neurology at the Pittsburgh Institute for Neurodegenerative Diseases.


Write the prescription for exercise –
EMPOWER the patient.
Name
Address
Date
Rx
PT/OT/ST – Eval and Treat
Community-Based PD Exercise
Social Services – Community resources and PD Support System
David Hinkle, MD
"Attitude is a little thing that makes a big difference."
~Winston Churchill


"Courage is being scared to death and saddling up anyway."
~John Wayne
Thomas H. Mallory, M.D.


Mallory-Head
Hip System


"The impossible can always be broken down into possibilities"
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- Community–Based PD Exercise Classes
- Local - 50 central Ohio Nationally - 21 States
- Educating Healthcare Professionals CE course
- Patient Education Tools – Book/DVD
- Educating CarePartners
- Educating Home Care Agencies / **Rehab Companies**
- Research

NATIONAL

California
Connecticut
Florida
Georgia
Illinois
Idaho
Iowa
Indiana
Massachusetts
Michigan
Minnesota
New Jersey
Nevada
Nebraska
New York
North Carolina
Ohio
Pennsylvania
South Carolina
Tennessee
West Virginia

** Ontario, Canada

Class Leader Selection

Personality – key to success

Credentials:

DTD Trained
CPR
PT/OT/RN/Ex Phys/AT
(ACE, ISSA, ACSM, NSCA)

The longer I live, the more I realize the impact of attitude on life. . I am convinced that life is 10% what happens to me and 90% of how I react to it."
~Charles Swindoll

Class Location

- Accessibility – 1st Floor, no elevator
- Room size/acoustics
- Comfort – temp, H20, storage

DTD is good for my mental outlook; I like the camaraderie. I am taking control of my illness.

~M.W., class participant

Equipment

Chairs – folding, non-upholstered, armless

Med Balls - Elivate Fitness
https://www.elivatefitness.com/body-sport-medicine-ball

Mats

Agility Ladder - Power Systems, 30 ft
https://www.power-systems.com/shop/product/pro-agility-ladder

Playground balls

Free Weights

Ziddy Sticks (arm swing)

Funding

SOURCES

Participant Charge - Self Sustaining

Grants

Philanthropy – Foundation support

Fund Raising / local community donations

Local PD Organization

YMCA

Neurology / Hospital support

Facilities with DTD

YMCA

Senior Centers/ Community Fitness Centers

Rehab / Skilled Nursing

Independent / Assisted Living

Hospitals

Local gyms

Welcome the community to your facility to increase marketing

Marketing

How To Grow Your Class

- Local PD organizations (APDA, PF) website / newsletters
- Flyers in offices / Neurologists, Family Practice, Gerontologists
- Suburban Newspapers
- TV, radio
- Flyers in local gyms, fitness clubs
- WORD OF MOUTH – most important

- GIVE THEM AN EXPERIENCE – it will bring them back!

Define Intake Process

- Physical Activity Readiness Questionairre (PAR – Q)
  - Demographics / Emergency contact
  - Medical Questions
  - Liability Release (PD specific)
- Participant call – phone screening
- Pre-assessment (in person) to risk stratify

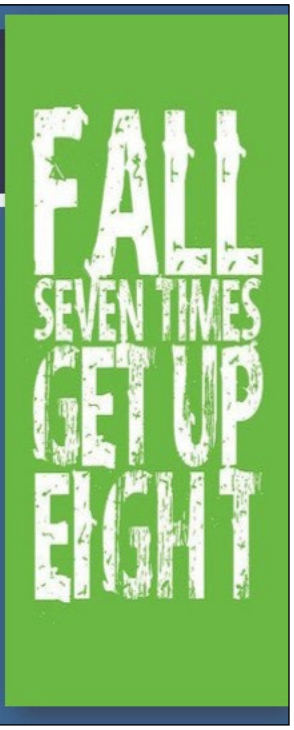
LIABILITY

Protect : Sponsoring Organization
Trainer/Facility

Participant Safety -#1 Goal

Define Instructor – Participant Ratio

PAR-Q Intake Form – MD Evaluation

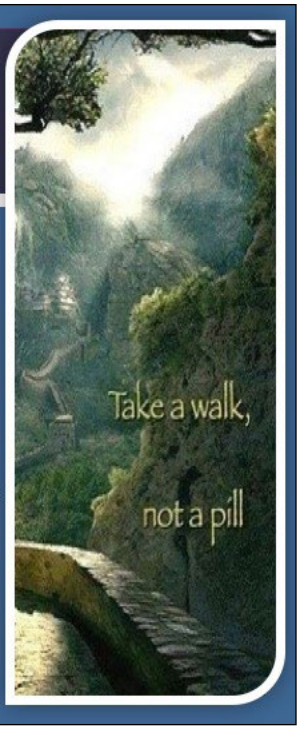


REFERRALS

Rehab Referral Indicators

- ❑ **PT/OT/ST indicators**
- ❑ **Physician Rx for referral**

= SYSTEM RETENTION



Data Collection

PDQ – 39 (PDQoL 37)

Most widely used, nationally recognized, self administered Quality of Life tool /rating scale in Parkinson's disease

Data Subsets:

Mobility	ADL's
Emotional well-being	Stigma
Social support	Cognitions
Communication	Bodily discomfort

Data Collection

12 Week Cycle – Pre- and Post-Testing

Outcome Measures

Single Leg Stance (mini-BEST, Berg) *Balance*
TUG – Timed Up and Go (dual task) *Functional Mobility, Fall Risk, Gait*
Five X Sit to Stand *Strength, Functional Mobility*
10 Meter Walk *Gait Speed, Functional Mobility*
PDQ 39 (PD Qol 37) *Quality of Life*
Beck Depression Inventory (PHQ 9)

DTD Program Stats

Retrospective Look

1 year retrospective look at changes (2 tailed t-test p values):

- Clinically significant improvements in functional mobility, reduced risk for falling and enhanced quality of life.

Make sure you Organize Your Class!

DO THE COMMON THINGS UNCOMMONLY WELL!

- **Communications - Volunteer for ATTENDANCE**
- **Arrive early - BE PREPARED**
- **Phone Tree for cancellations, ill instructor**
- **Bandaids, cups for water, nametags**
- **Celebrations – potluck, holiday parties, "no reason" lunch**

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Recipe for Success:

Intensity – aerobic, slightly breathless
Specific – practice what you want to improve, stay engaged, repeat perfect behavior
Ongoing – daily is best
Complex /Difficult – multitasking, motor and cognitive

Cardio Brain Core

DTD License Agreement

$400 for 2 years

- 12 week program x 2, Boot Camp, Chair based
- Press Release Template
- Discount books/DVDs
- Email/phone support to help you develop and market
- Use of our Logo, call your class "Delay the Disease"
- Door Sticker "DTD Taught Here"
- Outcome Measure Assistance / forms
- Facility holds this agreement

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STAY CURRENT WITH DTD

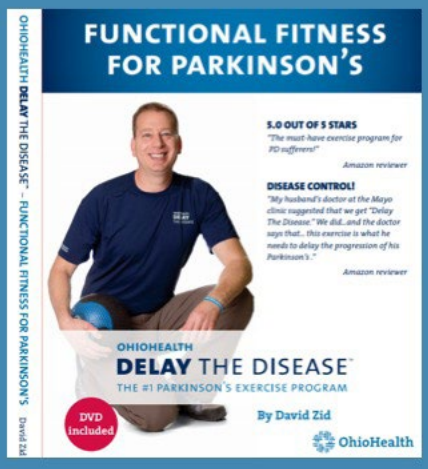
DTD Facebook
YouTube DTD
Delaythedisease.com

Stay Flexible

- Have a back up plan
- PWP may have "off" day
- Be prepared

Functional Fitness

- Getting out of the car
- Getting up off of the floor
- Dressing
- Turning in bed
- Balance
- Getting up from a chair
- Posture
- Rotation
- Incontinence
- Moving about in crowds
- Arm Swing
- Freezing …. And more



The Effects of a formal exercise program on Parkinson's Disease

Parkinsonism and Related Disorders, 2014
A Park, D Zid, J Russell, A. Malone, A. Rendon, X Li

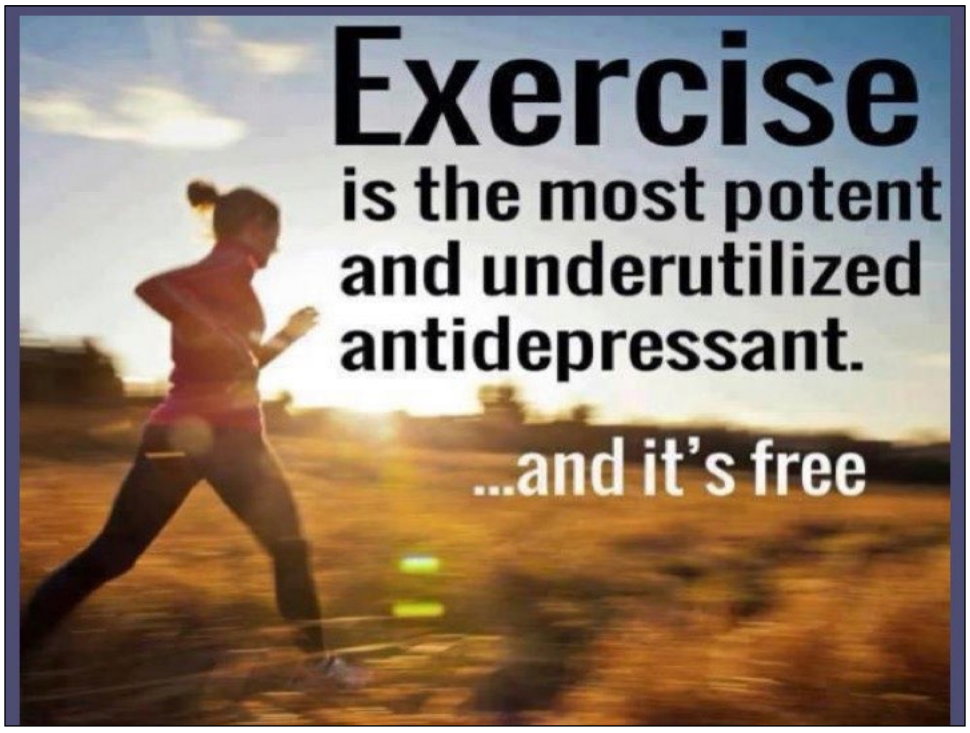
PUBLISHED

Conclusions:

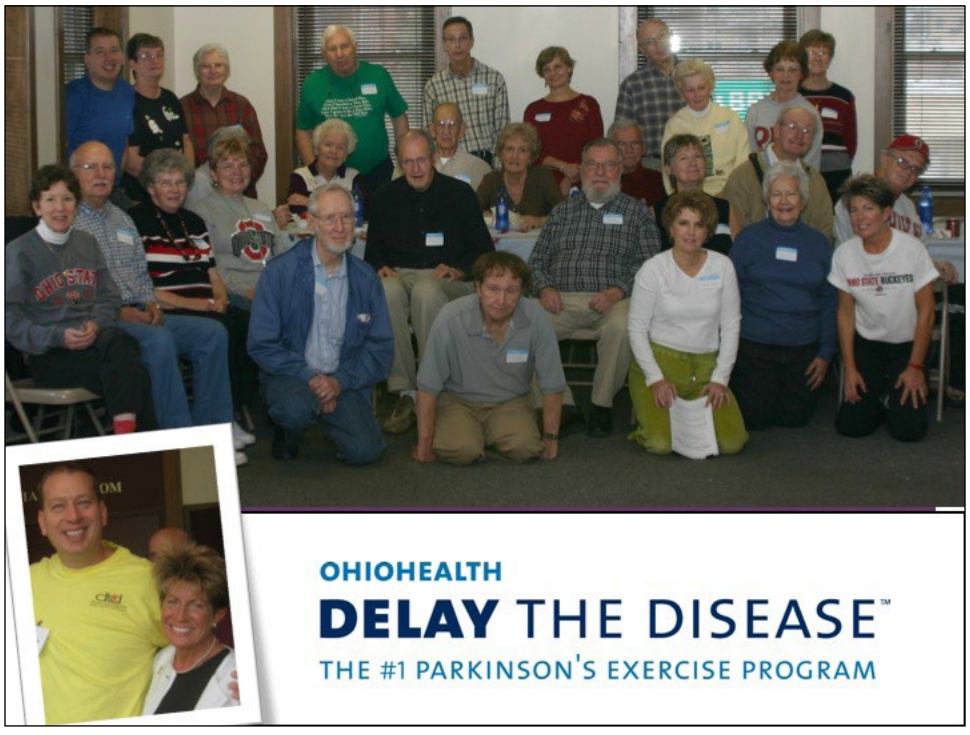
This group exercise program had a significant effect on the symptoms of depression.

Group exercise programs for PD are feasible with minimal drop out and and excellent adherence.

Positive environment of group exercise improved attitudes, fostered optimism, and was a positive force for the patient and the circle of support.




MDS International Congress – Vancouver 2017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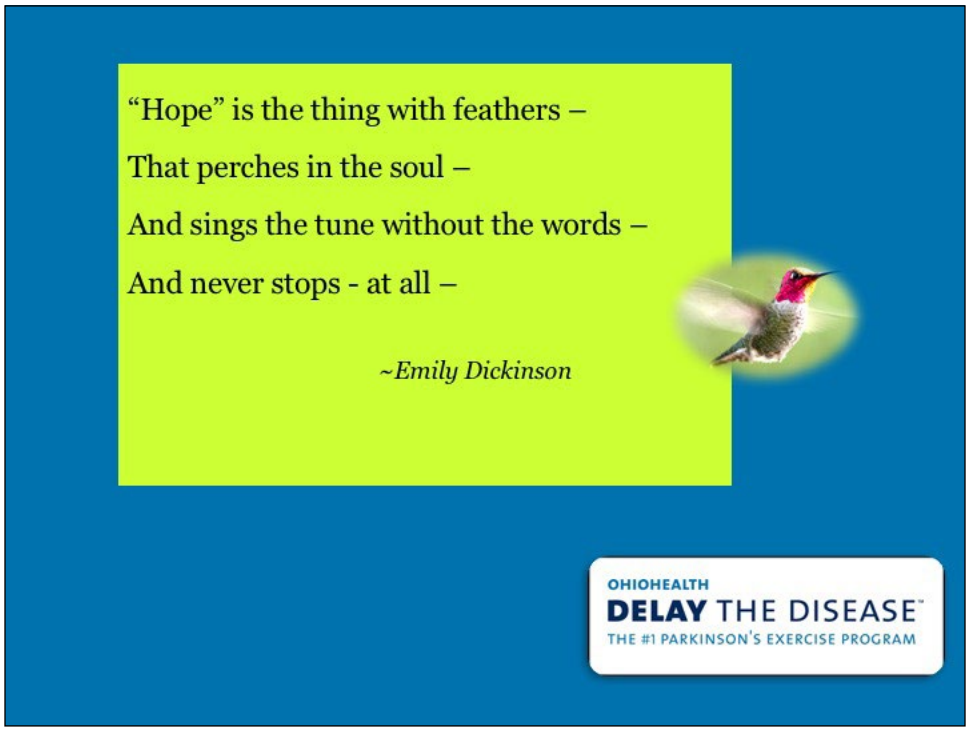
"Hope" is the thing with feathers –
That perches in the soul –
And sings the tune without the words –
And never stops - at all –
~Emily Dickinson
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NEVER TOO LATE TO START,
NEVER TOO EARLY
THANK YOU
60
5
10
15
20
25
30
35
40
45
50
55
DELAY THE DISEASE
The #1 Parkinson's Exercise Program

Consent/Release for PD Exercise Class Participants Delay the Disease™

General Information

Basic information about your class, title of the class, and its purpose.
(i.e., Delay the Disease™ exercise class is a Parkinson's — specific class for all levels of people with Parkinson's disease)

Release

I have read the statements below and release (Name of your parent organization), its members, agents, heirs, successors and assigns, from any and all liability or cause of injury and shall indemnify and hold them harmless from any such liability. I have inspected the building, its environs, and the physical area where the exercise training will be conducted, and they are acceptable to me. Therefore, I release the property owner from any and all liability or cause of injury and shall indemnify and hold them harmless from any such liability.

I have been diagnosed with Parkinson's disease. I understand that a common symptom of Parkinson's disease is loss of balance, which can lead to falls. By signing this, I represent that I am physically able to undertake the exercise program and have made full disclosure of any physical problem now existing. I agree that this exercise program will be undertaken at my own risk and that I am responsible for informing (name of parent organization) of any exercise or activity related to the exercise program that causes discomfort and/or pain. I also understand that it is my decision whether or not to continue the exercise program in the event of injury or illness. By continuation of a program, I represent that I am physically able to undertake any and all physical exercise provided.

Signature _____

Date _____

Payment Issues

The Delay the Disease™ exercise class is provided as a service to the community by (Funding Source). The instructors are compensated. While there is no fee for this class, any contribution you wish to make is sincerely appreciated.

Trainers Name _____

Location Trained: (address of facility)

(Name of parent organization) staff members are not, nor do they claim to be, physicians or possess medical knowledge. Therefore, they cannot take responsibility for any injury or illness related to this exercise class. It is recommended that you consult with your family physician prior to beginning this exercise class. If you choose to forgo the above-mentioned physical examination, we cannot be held responsible for any injury related to a pre-existing condition.

PDQ-39 QUESTIONNAIRE

Please complete the following

Please tick <u>one</u> box for each question

Due to having Parkinson's disease, how often <u>during the last month</u> have you....		**Never**	**Occasionally**	**Sometimes**	**Often**	**Always** or cannot do at all
1	Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2	Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3	Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4	Had problems walking half a mile?	☐	☐	☐	☐	☐
5	Had problems walking 100 yards?	☐	☐	☐	☐	☐
6	Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7	Had difficulty getting around in public?	☐	☐	☐	☐	☐
8	Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐
9	Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐
10	Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11	Had difficulty washing yourself?	☐	☐	☐	☐	☐
12	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13	Had problems doing up your shoe laces?	☐	☐	☐	☐	☐

*Please check that you have ticked **one box for each question** before going on to the next page*

Due to having Parkinson's disease, how often <u>during the last month</u> have you....		***Please tick <u>one</u> box for each question***				
		Never	**Occasionally**	**Sometimes**	**Often**	**Always** or cannot do at all
14	Had problems writing clearly?	☐	☐	☐	☐	☐
15	Had difficulty cutting up your food?	☐	☐	☐	☐	☐
16	Had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17	Felt depressed?	☐	☐	☐	☐	☐
18	Felt isolated and lonely?	☐	☐	☐	☐	☐
19	Felt weepy or tearful?	☐	☐	☐	☐	☐
20	Felt angry or bitter?	☐	☐	☐	☐	☐
21	Felt anxious?	☐	☐	☐	☐	☐
22	Felt worried about your future?	☐	☐	☐	☐	☐
23	Felt you had to conceal your Parkinson's from people?	☐	☐	☐	☐	☐
24	Avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25	Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26	Felt worried by other people's reaction to you?	☐	☐	☐	☐	☐
27	Had problems with your close personal relationships?	☐	☐	☐	☐	☐
28	Lacked support in the ways you need from your spouse or partner?	☐	☐	☐	☐	☐
	If you do not have a spouse or partner tick here		☐			
29	Lacked support in the ways you need from your family or close friends?	☐	☐	☐	☐	☐

*Please check that you have ticked **one box for each question** before going on to the next page*

Due to having Parkinson's disease, how often <u>during the last month</u> have you....		***Please tick <u>one</u> box for each question***				
		Never	**Occasionally**	**Sometimes**	**Often**	**Always**
30	Unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
32	Felt your memory was bad?	☐	☐	☐	☐	☐
33	Had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34	Had difficulty with your speech?	☐	☐	☐	☐	☐
35	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐
36	Felt ignored by people?	☐	☐	☐	☐	☐
37	Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38	Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39	Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

*Please check that you have ticked **one box for each question** before going on to the next page*

Thank you for completing the PDQ 39 questionnaire

Name _____ Date_____

The Modified Parkinson's Disease Quality of Life Questionnaire

This questionnaire has 37 questions, which will help us to know how you are feeling. Please do not leave out any questions, it is important that they are all answered. Place a check ✓ in the box that you feel shows how much of a problem each one has been for you *in the past 3 months.*

How often in the last 3 months have you had trouble with:	All the time	Most of the time	Some of the time	A little of the time	Never
1. Stiffness?	☐	☐	☐	☐	☐
2. Feeling generally unwell?	☐	☐	☐	☐	☐
3. Feeling that you are no longer able to do your hobbies?	☐	☐	☐	☐	☐
4. Being tense?	☐	☐	☐	☐	☐
5. Feeling insecure of yourself due to your physical limitations?	☐	☐	☐	☐	☐
6. Shaking of your hand(s)?	☐	☐	☐	☐	☐
7. Feeling worn out or having no energy?	☐	☐	☐	☐	☐
8. Difficulties in doing sport or leisure activities?	☐	☐	☐	☐	☐
9. Clumsiness?	☐	☐	☐	☐	☐
10. Feeling embarrassed about your illness?	☐	☐	☐	☐	☐
11. Shuffling when you walk?	☐	☐	☐	☐	☐
12. Having to postpone or cancel social activities because of your illness?	☐	☐	☐	☐	☐
13. A feeling of extreme exhaustion?	☐	☐	☐	☐	☐
14. Difficulties turning around while walking?	☐	☐	☐	☐	☐
15. Being afraid of possible progressing of the illness?	☐	☐	☐	☐	☐
16. Difficulties writing?	☐	☐	☐	☐	☐
17. Being less able to go on vacation than before your illness?	☐	☐	☐	☐	☐
18. Feeling insecure of yourself around others?	☐	☐	☐	☐	☐
19. Difficulties getting a good night's rest?	☐	☐	☐	☐	☐
20. "On/Off" periods?	☐	☐	☐	☐	☐
21. Difficulty in accepting your illness?	☐	☐	☐	☐	☐
22. Difficulties talking?	☐	☐	☐	☐	☐
23. Difficulties signing your name in public?	☐	☐	☐	☐	☐
24. Difficulties walking?	☐	☐	☐	☐	☐
25. Drooling?	☐	☐	☐	☐	☐
26. Feeling depressed or discouraged?	☐	☐	☐	☐	☐
27. Difficulty with sitting still (for long periods)?	☐	☐	☐	☐	☐
28. Often needing to urinate and/or wetting yourself?	☐	☐	☐	☐	☐
29. Difficulties with transport?	☐	☐	☐	☐	☐
30. Sudden extreme movements?	☐	☐	☐	☐	☐
31. Difficulties concentrating?	☐	☐	☐	☐	☐
32. Difficulties getting up (from a chair)?	☐	☐	☐	☐	☐
33. Constipation?	☐	☐	☐	☐	☐
34. Difficulties with your memory?	☐	☐	☐	☐	☐
35. Difficulties turning around in bed?	☐	☐	☐	☐	☐
36. That your illness inhibits your sex life?	☐	☐	☐	☐	☐
37. Feeling worried about (the possible consequences of) an operation in connection with your illness?	☐	☐	☐	☐	☐

Did you need any help to complete this questionnaire? Yes ☐ No ☐

If Yes, who? Partner/spouse ☐ Friend/neighbor ☐ Family member ☐ Nurse ☐ Other (specify) _____ •

BRIEF PATIENT HEALTH QUESTIONNAIRE (Brief PHQ)

This questionnaire is an important part of providing you with the best health care possible. Your answers will help in understanding problems that you may have. Please answer every question to the best of your ability unless you are requested to skip a question.

Name_____ **Age**_____ **Sex:** ☐ **Female** ☐ **Male** **Today's Date**_____

1. Over the last 2 weeks, how often have you been bothered by any of the following problems?

		Not at all	Several days	More than half the days	Nearly every day
a.	Little interest or pleasure in doing things	☐	☐	☐	☐
b.	Feeling down, depressed, or hopeless	☐	☐	☐	☐
c.	Trouble falling or staying asleep, or sleeping too much	☐	☐	☐	☐
d.	Feeling tired or having little energy	☐	☐	☐	☐
e.	Poor appetite or overeating	☐	☐	☐	☐
f.	Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	☐	☐	☐	☐
g.	Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
h.	Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	☐	☐	☐	☐
i.	Thoughts that you would be better off dead, or of hurting yourself in some way	☐	☐	☐	☐

2. Questions about anxiety.

		NO	YES
a.	In the last 4 weeks, have you had an anxiety attack—suddenly feeling fear or panic?	☐	☐
	If you checked "NO," go to question 3.		
b.	Has this ever happened before?	☐	☐
c.	Do some of these attacks come suddenly out of the blue—that is, in situations where you don't expect to be nervous or uncomfortable?	☐	☐
d.	Do these attacks bother you a lot or are you worried about having another attack?	☐	☐
e.	During your last bad anxiety attack, did you have symptoms like shortness of breath, sweating, your heart racing or pounding, dizziness or faintness, tingling or numbness, or nausea or upset stomach?	☐	☐

3. If you checked off any problems on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

☐ **Not difficult at all** ☐ **Somewhat difficult** ☐ **Very difficult** ☐ **Extremely difficult**

Continued on next page

FOR OFFICE CODING: Maj Dep Syn if answer to #1a or b and five or more of # 1a–i are at least "More than half the days" (count #1i if present at all). Other Dep Syn if #1a or b and two, three, or four of #1a–i are at least "More than half the days" (count #1i if present at all). Pan Syn if all of #2a–e are "YES."

4. In the last 4 weeks, how much have you been bothered by any of the following problems?

		Not bothered	Bothered a little	Bothered a lot
a.	Worrying about your health	☐	☐	☐
b.	Your weight or how you look	☐	☐	☐
c.	Little or no sexual desire or pleasure during sex	☐	☐	☐
d.	Difficulties with husband/wife, partner/lover, or boyfriend/girlfriend	☐	☐	☐
e.	The stress of taking care of children, parents, or other family members	☐	☐	☐
f.	Stress at work outside of the home or at school	☐	☐	☐
g.	Financial problems or worries	☐	☐	☐
h.	Having no one to turn to when you have a problem	☐	☐	☐
i.	Something bad that happened recently	☐	☐	☐
j.	Thinking or dreaming about something terrible that happened to you in the past—like your house being destroyed, a severe accident, being hit or assaulted, or being forced to commit a sexual act	☐	☐	☐

5. In the last year, have you been hit, slapped, kicked, or otherwise physically hurt by someone, or has anyone forced you to have an unwanted sexual act?

NO	YES
☐	☐

6. What is the most stressful thing in your life right now?_____

7. Are you taking any medication for anxiety, depression, or stress?

NO	YES
☐	☐

8. FOR WOMEN ONLY: Questions about menstruation, pregnancy, and childbirth.

a. Which best describes your menstrual periods?

☐ **Periods are unchanged** ☐ **No periods because pregnant or recently gave birth** ☐ **Periods have become irregular or changed in frequency, duration, or amount** ☐ **No periods for at least a year** ☐ **Having periods because taking hormone replacement (estrogen) therapy or oral contraceptives**

		NO (or does not apply)	YES
b.	During the week before your period starts, do you have a serious problem with your mood—like depression, anxiety, irritability, anger, or mood swings?	☐	☐
c.	If YES, do these problems go away by the end of your period?	☐	☐
d.	Have you given birth within the last 6 months?	☐	☐
e.	Have you had a miscarriage within the last 6 months?	☐	☐
f.	Are you having difficulty getting pregnant?	☐	☐

PAR-Q – Delay the Disease
Physical Activity Readiness Questionnaire

Name _____Address_____City_____
Please Print
State: _____ Zip _____

Home Phone: (___) _____ Cell Phone: (___) _____ Work Phone: (___) _____

E-mail Address: _____ Date of Birth _____

Emergency Contact Name _____ Phone Number _____

If you are planning to participate in our exercise program, please answer the seven questions below.
If you are between the ages of 15 and 69, this PAR-Q may indicate if you should check with your doctor before exercising. If you are over 69, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read carefully and answer honestly:

Check YES or NO:

YES NO

☐ ☐ 1. Has your doctor ever said that you have a heart condition *and* that you should only do physical activity recommended by a doctor?

☐ ☐ 2. Do you feel pain in your chest when you do physical activity?

☐ ☐ 3. In the past month, have you had chest pain when you were not doing physical activity?

☐ ☐ 4. Do you ever get lightheaded and lose consciousness?

☐ ☐ 5. Do you have a bone or joint problem that could be made worse by a change in your physical activity?

☐ ☐ 6. Is your doctor currently prescribing any drugs (e.g., water pills) for your blood pressure or heart condition?

☐ ☐ 7. Do you know of *any other reason* why you should not do physical activity?

If you answered:

YES to one or more questions

If you have not recently done so, consult with you physician Before increasing your physical activity and/or taking a fitness Test. Tell your physician about any "YES" answers on this PAR-Q.

NO to all questions

If you answered the PAR-Q accurately, you have reasonable assurance of your stability for our exercise program.

PHYSICAL ACTIVITY

After medical evaluation, seek advice from your physician as to your suitability for:

- Unrestricted physical activity, starting off easily and progressing
- Restricted or supervised activity to meet your specific needs

POSTPONE PHYSICAL ACTIVITY

If you have a temporary minor illness such as a the common cold

If your have answered YES to any of the preceding questions:
Although I have answered yes to one or more questions on the PAR-Q and have identified a potential risk, and have been advised by a fitness center representative to consult a physician before beginning my physical activity, I wish to begin immediately and understand that all physical activity and use of the facilities shall be undertaken buy me at my own risk. I have read, understood and completed the questionnaire. Any questions I have were answered to my full satisfaction.

Participants Signature/Date

Rules and Regulations, Policies and Procedures

1. Attire. Please wear proper clothing. Comfortable shirts and shoes are required in all public and fitness areas.
2. Damages. Any damage to the Center's property by any participant shall be paid by the participant.
3. Children. Children under 14 years of age are not allowed in the Center or the building.
4. Smoking. Smoking will NOT be permitted in any areas of the Center or the building.
5. No Soliciting Allowed. There is no soliciting allowed in the Center or the building.

Your signature below constitutes agreeing to and abiding by the following waiver:

I acknowledge that I have reviewed the Rules and Regulations "policies and procedures" and agree to abide by those policies and procedures and any other regulations that may be posted from time to time. I present, warrant, and acknowledge that I am in good physical condition and I am able to utilize the Center's facilities and preform the exercise recommended by the Center's employees. I understand that all exercise and use of the facilities shall be undertaken by me at my sole risk. In consideration of my use of the Center, I for myself and on behalf of my executor's release and discharge the Center, its owners, officers, employees, agents, assigns, successors and the Center's building owners from any liability, damages, claims, and causes of action, whether known or unknown, for personal injuries to me resulting from or in any way related to or connected with the use of the Center, including but not limited to, use of all fitness and exercise equipment. It is understood that the Center shall not be responsible or liable to me or any third party for articles damaged, lost or stolen in or about the Center, or in lockers, or for loss or damages to any property including, not limited to any contents thereof. Any damages to the premises, facilities, and equipment will be paid for by me.

I have been diagnosed with Parkinson's Disease. I understand that a common symptom, of Parkinson's Disease is loss of balance, which can lead to falls. By signing this, I represent that I am physically able to undertake the exercise programs and have made full disclosure of any physical problem now existing. I agree that the exercise progrtam will be undertaken at my own risk. I am responsible for informing the instructor of any exercise of activity related to the exercise program that causes discomfort and/or pain. I also understand that it is my decision whether or not to continue the exercise program in the event of injury or illness. By continuation of a program, I represent that I am Physically able to undertake any and all physical exercise provided.

Participants Signature/Date

Indicators of Rehabilitation Services for Person with Parkinson's Disease (PWP)

Referral to Speech Therapist is promptly indicated if PWP reports or is observed having:

+ Trouble with swallowing such as coughing when swallowing, trouble getting pills down, feeling like "food gets stuck"
+ Unintended weight loss and/or noted malnutrition

Referral to Speech Therapist is immediately indicated if PWP reports or is observed having trouble in the following areas and has not had ST in the last 6 months:

+ Changes to cognition including word finding, memory, problem solving
+ Reduced voice volume, pitch range, articulation of sounds or syllables

Referral to Occupational Therapist is indicated if PWP reports or is observed having trouble in the following areas and has not had OT in the last 6 months:

+ Need for adaptive equipment to increase independence with activities of daily living (ADLs)
+ Adjusting home environment and interior of the house to make ADL easier or safe
+ The caregiver experiences problems in supervising or supporting the PWP
+ Limitations in ability to perform work responsibilities, housekeeping, hobbies, or driving
+ Impaired PWP's safety and self-reliance with ADLs

Referral to Physical Therapist is indicated if PWP reports or is observed having trouble in the following areas and has not had PT in the last 6 months:

+ Physical impairments limiting functional mobility not consistent with Parkinson's disease process such as back pain or injury sustained during a fall
+ Increased frequency of falls (greater than 2 falls in last month or a fall with injury)
+ Need for 1:1 instruction beyond the scope of fitness and maintenance of function
+ Need for education or interventions to prevent complications of decreased mobility such as pressure sores and contractures
+ PWP or caregiver has need for transfer training
+ Need for information about the consequence of PD especially regarding those limitations in activity that have to do with posture or movement for those recently diagnosed or throughout disease process

Dear Physician,

Your patient _____ has been an active participant in **OhioHealth's Delay the Disease™** exercise program. This program is designed to empower people with Parkinson's disease by optimizing their physical function and helping to delay the progression of symptoms.

This letter is to inform you that your patient has demonstrated, or verbalized, a newly developed physical impairment that may require an outpatient rehabilitation consultation.

- ☐ **Physical Therapy:** Treatment designed to improve gait and balance issues, as well as strength and mobility to help patients function independently. Physical Therapy can address pain issues as well as specific joint, spine and musculoskeletal impairment.
- ☐ **Occupational Therapy:** Treatment designed to return patients to their daily activities, helping them regain necessary skills for getting dressed, bathing, driving and relearning other daily tasks. Occupational Therapists provide patients with new strategies to achieve their personal goals.
- ☐ **Speech Therapy:** Treatment designed to treat speech disorders, including word-finding and speech comprehension issues, facial weakness and speech clarity issues and swallowing impairment.

OhioHealth's Brain & Stroke Rehabilitation is one option for therapy for your patient. This program has treated patients with Parkinson's disease for over two decades. Referrals can be made by calling phone: (614) 566.1139 or fax: (614) 566.1130.

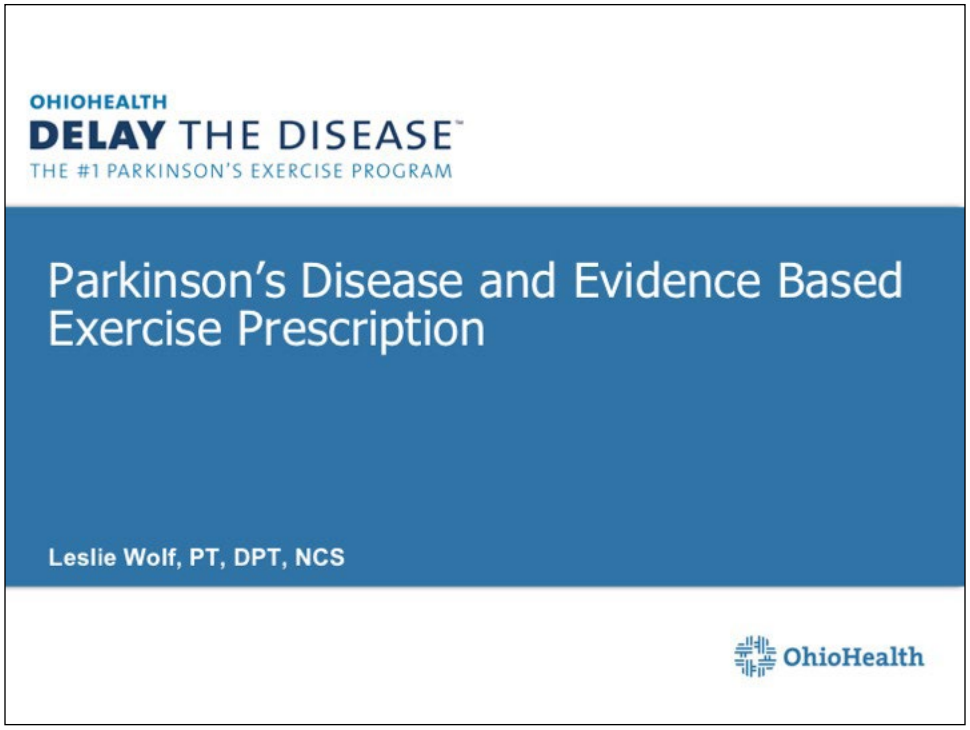
Sincerely,

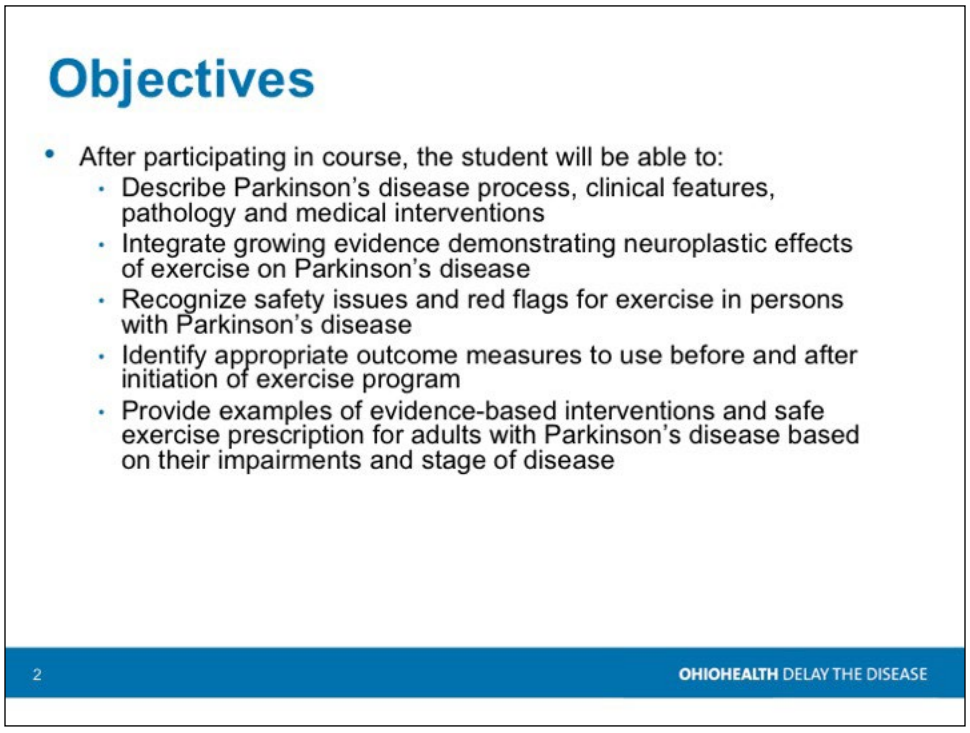
_____

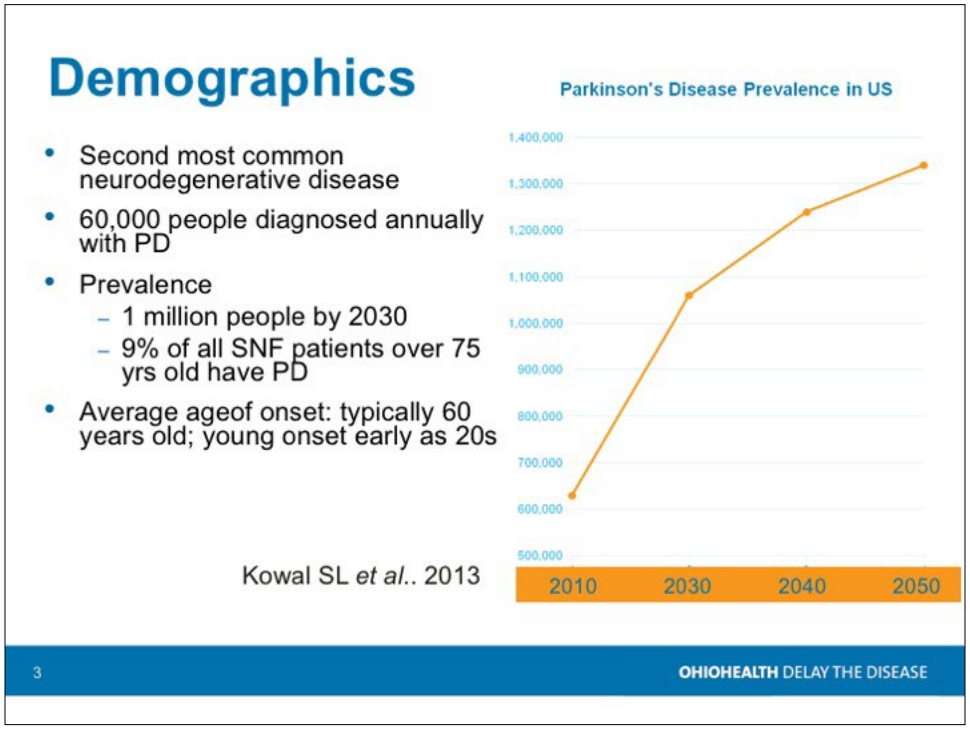
OhioHealth Delay the Disease™

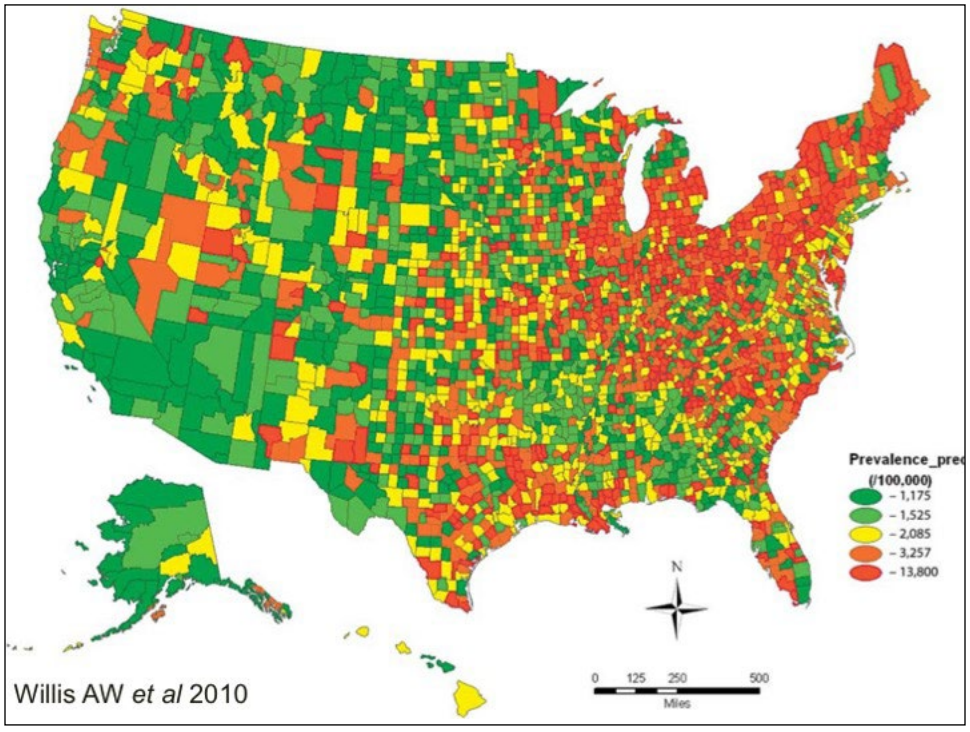
Phone: _____

II. Leslie Wolf, PT, DPT, NCS


OHIOHEALTH
DELAY THE DISEASE™
THE #1 PARKINSON'S EXERCISE PROGRAM
Parkinson's Disease and Evidence Based Exercise Prescription
Leslie Wolf, PT, DPT, NCS
OhioHealth


Objectives
After participating in course, the student will be able to:
Describe Parkinson's disease process, clinical features, pathology and medical interventions
Integrate growing evidence demonstrating neuroplastic effects of exercise on Parkinson's disease
Recognize safety issues and red flags for exercise in persons with Parkinson's disease
Identify appropriate outcome measures to use before and after initiation of exercise program
Provide examples of evidence-based interventions and safe exercise prescription for adults with Parkinson's disease based on their impairments and stage of disease
2
OHIOHEALTH DELAY THE DISEASE


Demographics
Second most common neurodegenerative disease
60,000 people diagnosed annually with PD
Prevalence
1 million people by 2030
9% of all SNF patients over 75 yrs old have PD
Average ageof onset: typically 60 years old; young onset early as 20s
Kowal SL et al.. 2013
Parkinson's Disease Prevalence in US
1,400,000
1,300,000
1,200,000
1,100,000
1,000,000
900,000
800,000
700,000
600,000
500,000
2010
2030
2040
2050
3
OHIOHEALTH DELAY THE DISEASE


Prevalence_pre
(/100,000)
- 1,175
- 1,525
- 2,085
- 3,257
- 13,800
N
0 125 250 500
Miles
Willis AW et al 2010

Risk Factors for Developing PD

- Age
- Men > Women
- Family History
- Decreased estrogen levels
- Agricultural work
- Playing in the NFL
- Air pollution
- Head trauma
- Well water consumption
- Genetic factors
- Low levels of Vitamin B folate

Hubble et al 1993

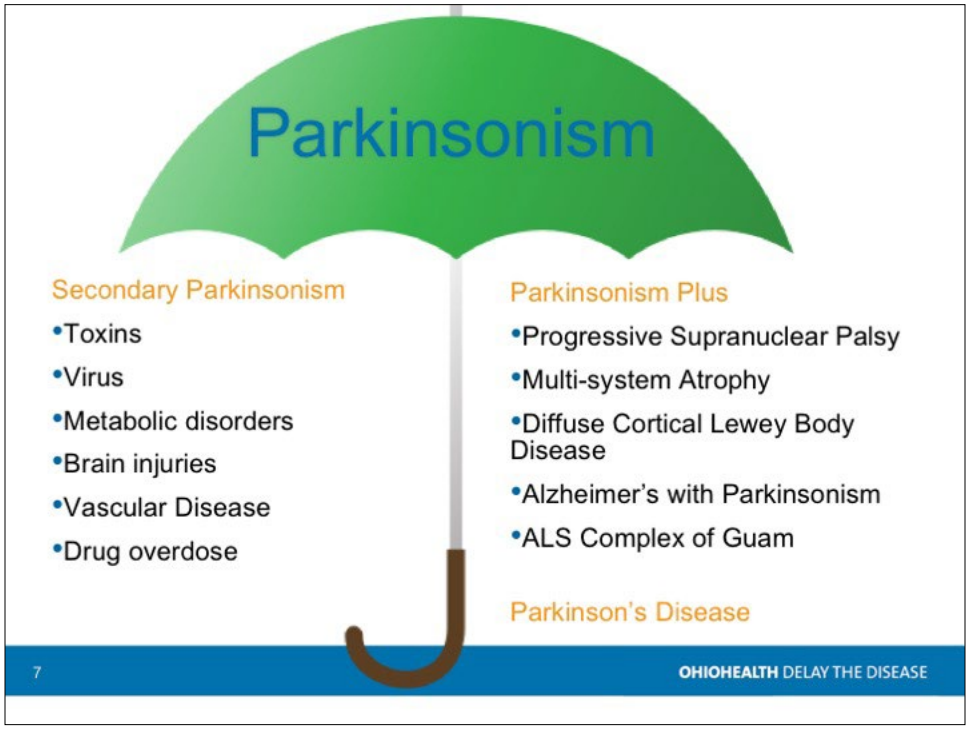
Etiology

Ideopathic PD

- 85% of all cases
- Despite decades of intensive study, the causes of Parkinson's remain unknown
- Likely caused by a combination of genetic and environmental factors, which may vary from person to person
- "*Genetics loads the gun and environment pulls the trigger*"

Familial PD

- 15% of people with Parkinson's report having a relative with the disease
- Often seen with young onset (<50 years old)
- Genes: PARK-1, PRKN, PINK1, LRRK2, DJ-1, SNCA, PARK-7


Parkinsonism
Secondary Parkinsonism
•Toxins
•Virus
•Metabolic disorders
•Brain injuries
•Vascular Disease
•Drug overdose
Parkinsonism Plus
•Progressive Supranuclear Palsy
•Multi-system Atrophy
•Diffuse Cortical Lewey Body Disease
•Alzheimer's with Parkinsonism
•ALS Complex of Guam
Parkinson's Disease
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Cardinal Motor Signs

- **Resting tremor**
  - First symptom for 70% of PWP
  - Pill rolling, less severe when relaxed, diminishes with voluntary effort
- **Rigidity in trunk and limbs**
  - Akinetic-rigid type typically has more rapid course of disease
  - Dementia and cognitive impairments more common
- **Bradykinesia**
  - Slowness and difficulty maintaining movement in speed, range, amplitude
  - Micrographia
  - Freezing of Gait
- **Postural Instability**
  - Rare in early years of PD

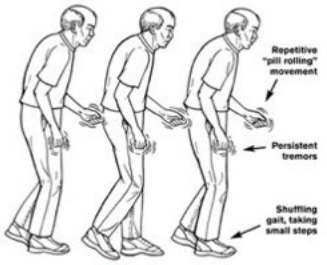


Image courtesy of Dana Foundation www.dana.org

Dopamine

- Dopamine is major neurotransmitter used for movement, coordination, information processing
- Loss of dopamine producing cells in brain (Substantia nigra pars compacta in Basal Ganglia)
- Dopamine cell firing encodes differences between expected movement and obtained outcomes providing implicit "motor motivational" signal for movement based on energy cost of task
  - Gepshtein et al 2014

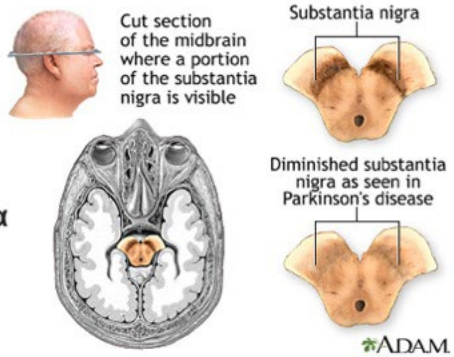


Image courtesy of U of Maryland

α-Synuclein and Lewy Bodies

- α-Synuclein is a protein that becomes abnormally folded and accumulated in human dopaminergic neurons
- Accumulated α-Synuclein form Lewy Bodies

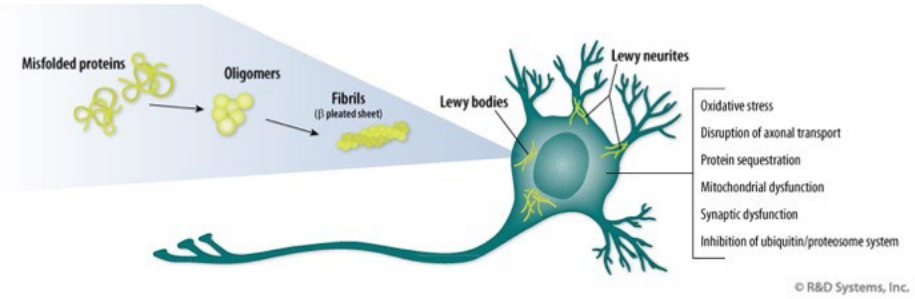
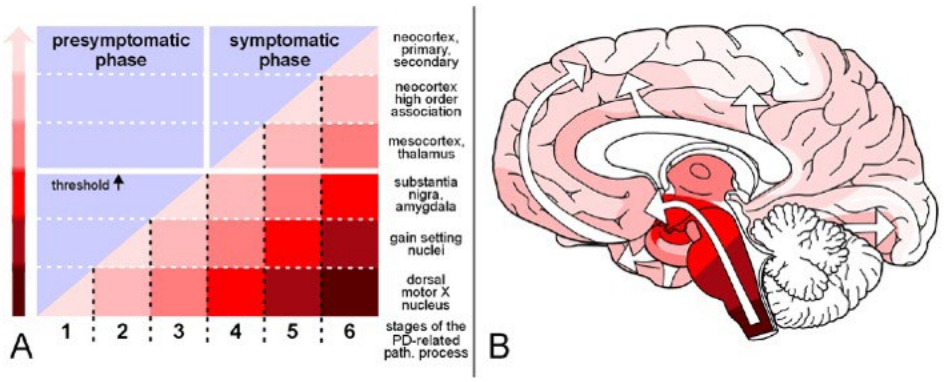


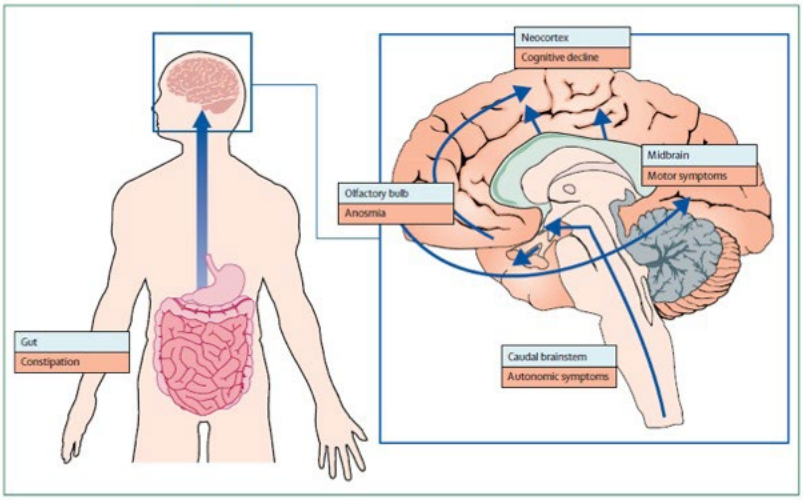
Image by RnD systems, adapted from Lee, V.M-Y. and J.Q. Trojanowski (2006) Neuron 52:33.

Not just a Dopamine Problem



Braak *et al* 2004

Dual-Hit Hypothesis



Braak 2007, Shannon 2012, Borghammer 2018

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Common PD Impairments

- Bradykinesia
- Impaired coordination
- Rigidity
- Postural instability
- Autonomic dysfunction
- Sensorimotor and visual-perceptual impairments
- Reduced cognitive function
- Emotional Impairments (motivation, depression)
- Fatigue
- Weakness
- Cardiovascular deconditioning
- Musculoskeletal deformities
- On/Off fluctuations
- Pain
- Impaired divided attention
- Freezing of gait
- Decreased automaticity
- Sleep disorders

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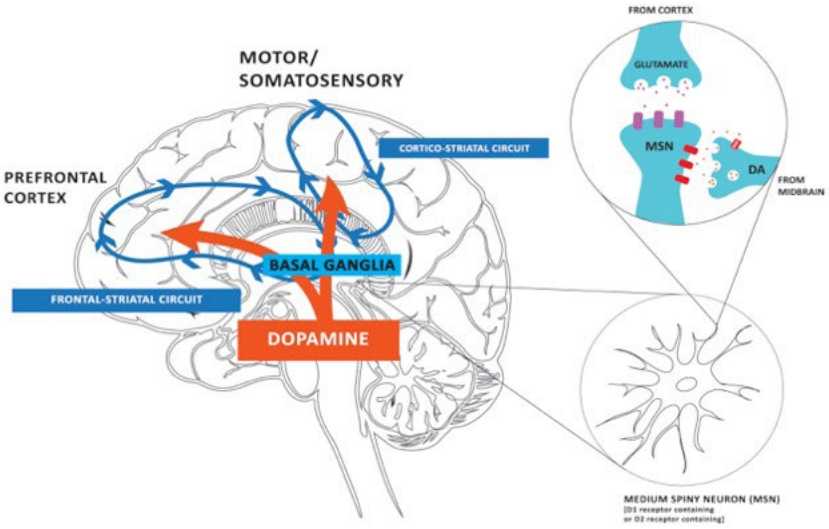

Petzinger et al Brain Plast 2015

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Non-Motor Signs and Symptoms

- Thermoregulatory dysfunction
- Slow papillary responses to light and pain
- Peristalsis frequently resulting in constipation
- Frontal lobe executive dysfunction
- Orthostatic hypotension
- Mood disorders
- Bladder incontinence
- Olfactory dysfunction

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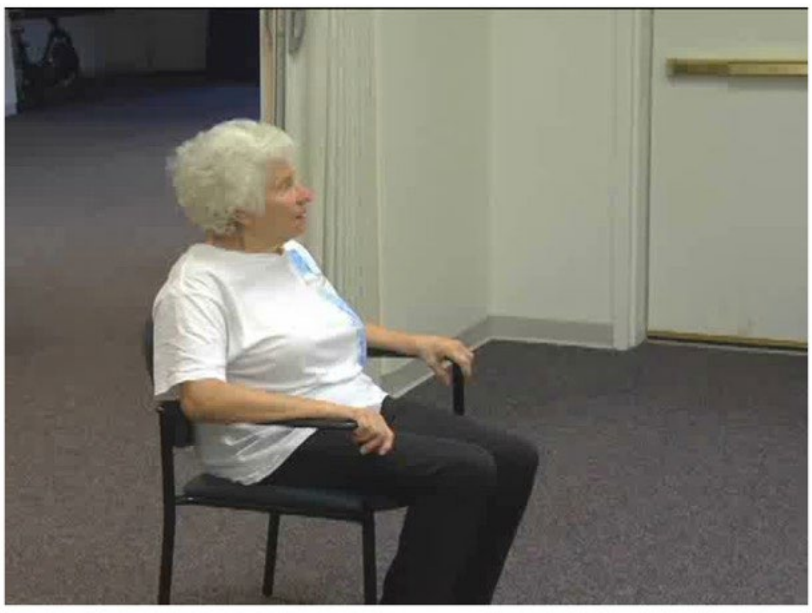
17 OHIOHEALTH DELAY THE DISEASE



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Azulay et al. Visual control of locomotion in PD. *Brain*. 1999;122:111-120.

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Visual-Spatiotemporal Deficits

- PWPs depend on dynamic *visual information* for the control of gait velocity rather than *proprioceptive feedback (*Azulay et al 1999)
- Visual perception deficits in PD contribute to gait problems:
  - Festination of gait
  - Freezing
- Other symptoms of visual hallucinations, double vision, contrast sensitivity deficits, fall risk, gait deficits

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Diagnostic Criteria

Bradykinesia and at least 1 of the following:

- Muscular rigidity
- 4-6 Hz resting tremor
- Postural instability not caused by other health condition

- Signs that support diagnosis of PD
  - Unilateral onset
  - Resting tremor present
  - Progressive disorder
  - Persistent asymmetry affecting the side of onset most
  - Excellent (70%–100%) response to levodopa
  - Severe levodopa-induced chorea
  - Levodopa response for ≥5 years
  - Clinical course of ≥10 years

Image courtesy of Michael J Fox Foundation
UK National Institute for Health and Clinical Excellence (NICE) Parkinson's Disease Guidelines http://www.nice.org.uk/guidance/CG35

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The Hoehn and Yahr Scale is the most commonly-used scale to measure the severity of Parkinson's symptoms, and classifies patients in the following stages:[Goetz 2004]

Stage 1	Stage 1.5	Stage 2	Stage 2.5	Stage 3	Stage 4	Stage 5
Unilateral involvement only	Unilateral and axial involvement	Bilateral symptoms No impairment of balance	Mild bilateral disease with recovery on pull test	Mild to moderate disease Physically independent	Severe disability, still able to walk or stand unassisted	Wheelchair-bound or bedridden unless assisted

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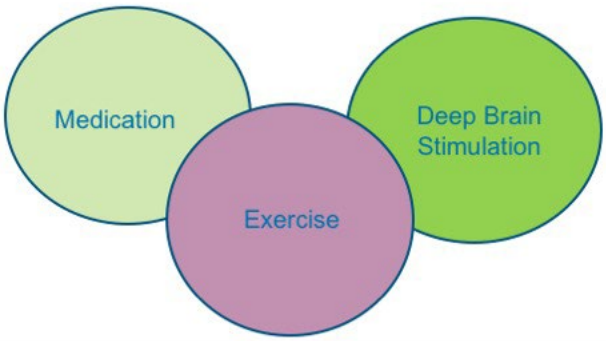
Current Therapeutic Options

- To provide symptomatic relief and improve function
  - Academy of Neurology Practice Guidelines 2006



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Pharmacological Management

- Levodopa
  - Typically administered with carbidopa to allow more drug to enter brain. Alleviates bradykinesia and rigidity with less effect on tremor
  - Sinemet (carbidopa/levodopa)
- Dopamine agonists
  - Administered with L-dopa allowing for lower doses to be administered for moderate to advanced PD
  - Parlodel, Requip, Mirapex
- Anticholinergic Agents
  - Blocks cholinergic function to decrease tremor and rigidity. Has little effect on bradykinesia and postural instability
  - Artane, Cogentin, Parsidol, Kemadrin

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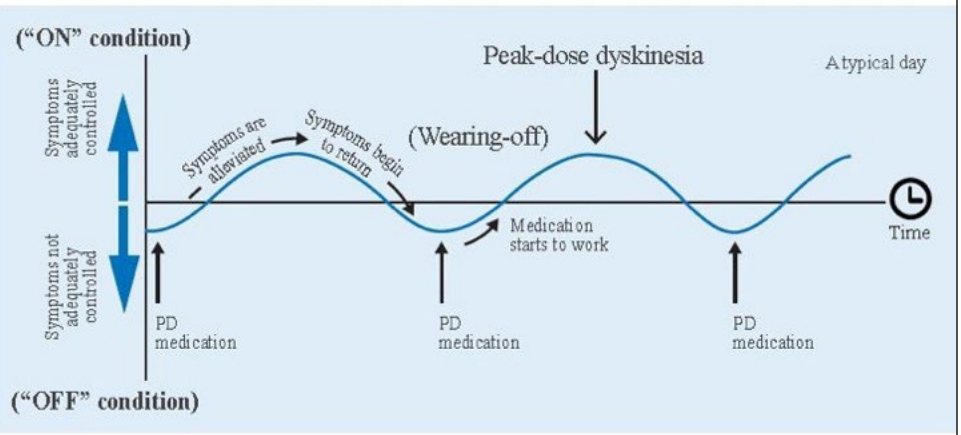
On-Off Phenomenon



Stacy *et al* 2009 adapted from Eriksson *et al* 1984

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Deep Brain Stimulation

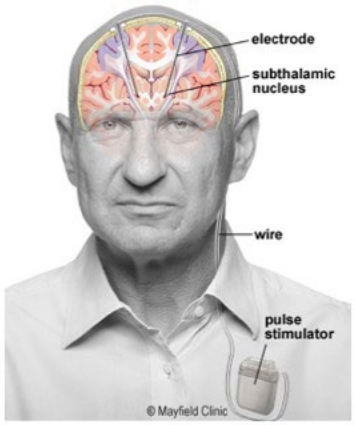

Image courtesy of Mayfield Clinic

- Deep Brain Stimulation
  - Stimulation to Subthalamic Nucleus or Globus Pallidus Internus to decrease tremors
- Best PD surgical candidates:
  - Ideopathic PD for > 4 years
  - Tend to be younger than 69
  - Have positive response to medication but have significant refractory symptoms (wearing off, on-off fluctuations, dyskinesia)
  - Can improve stiffness, tremors but not freezing, non-motor symptoms, and imbalance

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DELAY THE DISEASE™
THE #1 PARKINSON'S EXERCISE PROGRAM

Effects of Exercise in Parkinson's Disease

OhioHealth

Boxing (Combs 2011)

Dancing (Hackney 2009)

Tai Chi (Fuzhong *et al* 2012)

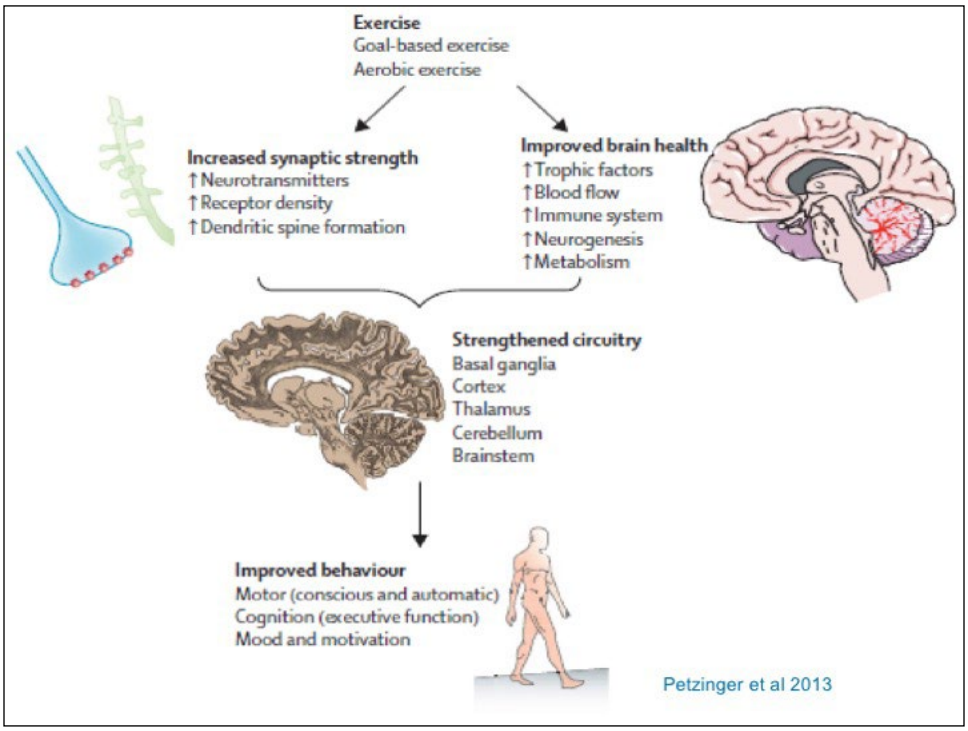
Cycling (Beall 2013, Alberts 2011)

Large Amplitude Training (Farley *et al* 2005)

Resistance Exercise (Dibble 2014)

Exercise in PD Improves:
Timed Up and Go, UPDRS, executive function, gait speed and stride length, fine motor skills and MORE!

Nordic Walking (van Eijkeren 2008)



Petzinger et al 2013

Ingredients for Activity-Dependent Neuroplasticity

- Intensity (Dosage)
  - Frequency and duration of practice
  - Amount of energy expenditure
  - Push beyond self-selected threshold (Ridgel 2009)
- Specificity
  - Target specific PD deficits
- Difficulty/complexity
  - Tasks requiring high level of concentration or attention
  - Adding risks for error
- Saliency
  - Make activities meaningful and goal based!
  - Add social component!
  - Let PWP drive activity

Petzinger *et al* 2010

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Animal models of dopamine depletion

MPTP mice (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)

Oxidative stress
Calcium dysregulation
Exitotoxicity
Mitochondiral toxicity
Proteosme inhibition
α-synuclein aggregation

→ Dopaminergic Nigrostiatal Neurodegeneration → Animal Parkinsonism

6-OHDA rat (6-hydrooxydopamine)

Genetic models including PINK1, Parkin, LRRK2

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Exercise promotes neuroplasticity

Modification of existing neural networks by addition or modification of synapses in response to changes in behavior or environment

Mechanism by which brain encodes information and learns new behaviors

- Includes a wide range of structural and physiological mechanisms including:
  - Synaptogenesis
  - Neurogenesis
  - Neuronal sprouting
  - Potentiation of synaptic strength
- All lead to strengthening, repair, formation of neuronal circuitry

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Exercise Training Results in Changes in the Brain

Petzinger *et al* 2010

- People with PD no more than 3 years post diagnosis were asked to exercise at high intensity 3x/week for 8 weeks using BWSTT
  - 75% HR max > 3.5 METs
  - PD control: typical exercise (25% HR max, < 3 METs including low intensity balance, strengthening, stretching
- Transcranial magnetic stimulation applied over motor cortex while surface EMG measures muscle activity
  - Cortical silent period increased to normal durations after exercise
- One of the first studies to demonstrate exercise induced quantitative cortical changes in humans!
- Shortened CSP durations are among the most consistent and widely reproduced TMS findings among PD patients (surgical and pharmacological interventions)

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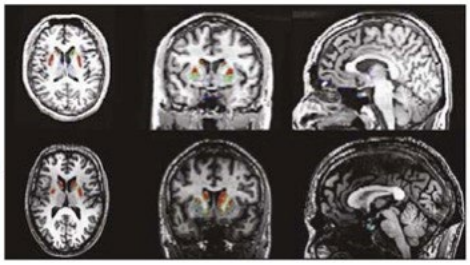
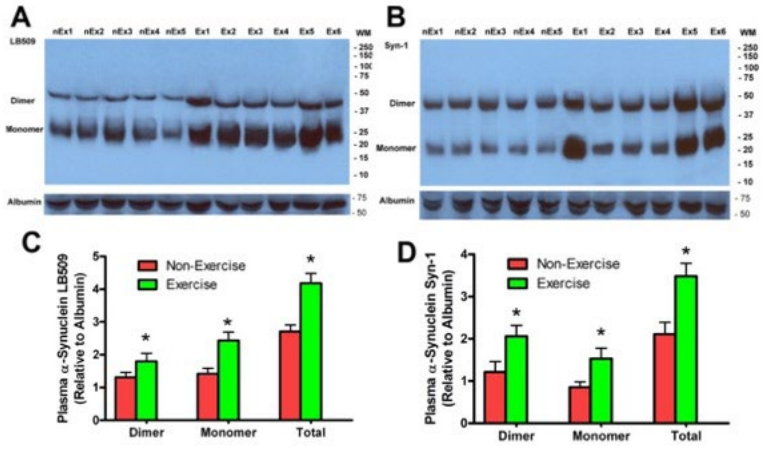
Treadmill exercise improves dopamine handling in brain

- Fisher et al 2013 Translational study
- 4 people with H&Y Stage 1 PD were randomized to receive treadmill training sessions 3x/week for 45 minutes > 3 METs and/or 75% age predicted Max HR
- Results
  - Exercise resulted increased efficiency of dopamine binding potential
  - Postural control improved measured with biomechanical analysis of center of pressure vs center of mass

PET image data= post exercise-pre exercise.
Red = Increased binding potential within the Basal Ganglia (putamen).



Running Wheel-Forced Exercise Reduces Alpha Synuclein Aggregation in Genetic Mouse Model of PD



Zhou et al 2017

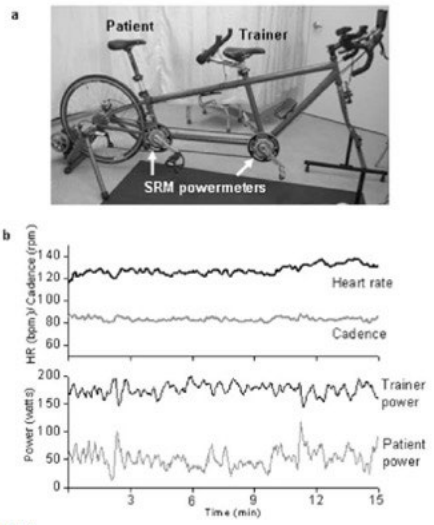
Exercise may reduce PD risk in people

Xu et al 2010

- 213,701 participants of the NIH AARP Diet and Health Study cohort
- Moderate to vigorous activities at ages 35-39 or in the past 10 years as reported in 1996-1997 were associated with lower PD occurrence after 2006 with significant dose-response relationships

Forced Exercise

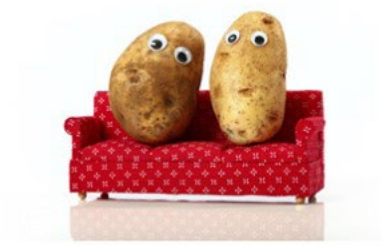
- Forced bicycling stimulates brain PET and MRI activity
- Forced bicycling stimulates electrophysiological indicators of learning plasticity
- Forced treadmill improves motor, skill acquisition, balance, cognition, mood, QOL



Ridgel 2009, Alberts et al Ex SpSci Rev 2011, Singh et al 2014

Inactivity leads to neurodegeneration

- Tillerson et al 2003
  - Cast applied to the hemiparkinsonian side of 6-OHDA rat for 7 days
  - Non-use (immobilization) significantly exacerbated motor deficits
  - Limb disuse led to further neurodegeneration and long term behavioral asymmetry
- Bottom line: Gotta move!



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Role of Exercise in Stages of PD

TIME

HY Stage 1-2	HY Stage 2-4	HY Stage 5
•Prevent inactivity •Start neuro-protection as soon as possible •Address mental and emotional aspects of PD •Maintain or improve physical capacity	•Prevent falling •Reduce limitations on core areas including transfers, posture, reaching and grasping, balance, gait	•Maintain vital functions •Prevent pressure sores •Prevent contractures •Reduce secondary pain from immobility

Keus SH *et al* 2007

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Exercise Precautions in PD

- Follow ACSM Guidelines and risk screening with PAR-Q
- Orthostatic hypotension
- Fall risk
- Know medication schedule! Sinemet reaches peak-dose 1-3 hours after taking
- Know your client's past medical history!
  - Osteoporosis
  - Orthopedic surgeries (ex. total hip replacement, spine)
  - Cardiovascular history
  - Diabetes

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Bone Health Considerations

- Low bone density (osteoporosis and osteopenia) present in up to 61% of men and 91% of women with PD
- 2.61x more likely to receive dx of osteoporosis than age-matched peers
- Reduced BMD at **the femoral neck, lumbar spine, and overall body**
- Bone loss seems to affect the lumbar spine earlier in the disease
  - May be due to decreased axial mobility
  - Postural impairments
- Bone loss associated with:
  - ↓ calcium intake, sunlight exposure and BMI
  - ↑ H&Y stage
  - Possibly higher levodopa intake

(Invernizzi, et al, 2009; Torsney, et al, 2014; Tan, et al, 2014; Dennison, et al, 2012; Gregson, et al, 2014)

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PD Exercise Prescription

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Target PD Impairments!

- Bradykinesia
- Impaired coordination
- Rigidity
- Postural instability
- Autonomic dysfunction
- Sensorimotor and visual-perceptual impairments
- Reduced cognitive function
- Emotional Impairments (motivation, depression)
- Weakness
- Cardiovascular deconditioning
- Musculoskeletal deformities
- On/Off fluctuations
- Pain
- Impaired divided attention
- Freezing of gait

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Benefits of Group Exercise in PD

- Fitness, social support, accountability, fun, motivating!
- Identify decline and refer to Neurologist or Rehab Services
- Can creatively develop programs that are difficult, meaningful, challenging, complex!
- Steffen *et al* 2012
  - Group exercise improves functional outcomes related to walking
- Combs *et al* 2013
  - "Community based exercise can improve balance, mobility, and quality of life in persons with PD"
- States et al 2011
  - Able to maintain moderate to high attendance over 14 months while making functional gains

Exercise Improves Depression in Parkinson's Disease

Park *et al* 2014

- Randomized delayed-start design
  - Rigorous exercise 60 minutes 3/week for 48 weeks 1 group, other group 24 weeks
  - Only 1 drop out
  - The findings demonstrate that long-term, group exercise programs are feasible in the Parkinson's disease population, with excellent adherence and minimal drop out.
- Significant improvement on Beck Depression Inventory for group that exercised for 48 weeks
- **According to National Parkinson Foundation, depression affects health status 2 times as much as motor impairment**

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Aerobic Exercise

- Combination of goal directed exercise and aerobic training may provide benefits not seen with either alone in PD (Petzinger *et al* 2013)
- Improves cognitive functioning such as working memory
- Endurance exercise improves bradykinesia based on UPDRS
  - Improved simple reaction time and fine motor tasks
    (Muhlack et al 2007, Muller and Muhlack 2010, Bergen et al 2012)
- Meta-analysis of aerobic endurance exercise (defined by ACSM) beneficial with noted improvements in UPDRS (Flach et al 2018)
- Use caution due to possible autonomic dysfunction
  - Speelman *et al* 2012
  - 546 sedentary PD patients: more than 50% of patients had an inadequate heart rate increase during submaximal exercise

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Rating of Perceived Exertion Borg RPE Scale

6 7 8 9 10 11	Very, very light Very light Fairly light	How you feel when lying in bed or sitting in a chair relaxed. Little or no effort.
12 13 14 15 16	Somewhat hard Hard	Target range: How you should feel with exercise or activity.
17 18 19 20	Very hard Very, very hard Maximum exertion	How you felt with the hardest work you have ever done. Don't work this hard!

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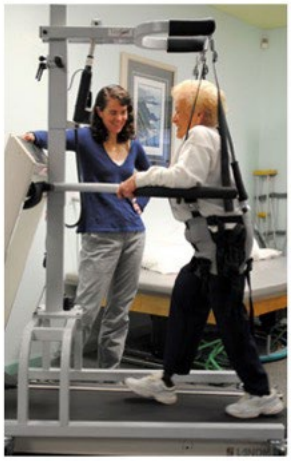
Treadmill Training in PD

- 2010 Cochrane Review
  - Improved gait speed
  - Improved stride length
  - Improved walking distance
  - Treadmill used as an external cue for swing and stride time, promotes motor learning
- PWP expend 20% more energy than healthy peers: TM training improves energy expenditure
  - Protas et al 1996, Canning et al 1997, Schenkman et al 2008
- TM training transfers to TUG, 10MWT, 6MWT, balance, flexibility
  - Pelosin et al 2009



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Strength Training

- Systematic Review (Lima *et al* 2013)
  - PWP of all levels of severity
  - Progressive resistive exercise can improve strength and several measures of function for PWP (ABC scale, 6MWT, TUG)
  - Requires average of 15 weeks and intensity measured by RPE of 13 (somewhat hard)
- Common areas of weakness
  - Neck extensors
  - Postural muscles of trunk
  - Hip extensors, abductors, flexors
  - Knee flexors, extensors
  - Ankle plantarflexors

Image courtesy of bboyscience.com

High intensity *eccentric* resistance training: reduces bradykinesia, improves QOL

- Dibble *et al* 2009
  - 20 people with PD: H& Y 1-3:
    - 10 eccentric group, 10 active controls
  - Both groups participated in stretching, walking on treadmill, riding bicycle ergometer, performing UE PREs on machines and with free weights 3 days per week for 12 weeks
  - Only difference between groups was substitution of high force eccentric training for traditional lower extremity resistance strength training
  - Demonstrated improved muscle force, reduced bradykinesia (measured by gait speed, Timed Up and Go), and improved quality of life (PDQ-39)

Balance and Fall Risk

- Later stages of disease: use of assistive devices, avoid divided attention tasks in high fall risk environments
- Balance impairments usually develop after 2-3 years after symptom onset; Frequent falling usually by10 years.
- Within last 3 months, 50% of PD patients report falling more than once
- Up to 68% of community dwelling individuals with PD fall at least 1x/year
- Need to train dynamic balance!
  - Balance reactions
  - Transition between motor tasks
  - Pivoting/turning
  - Divided attention
  - Backwards walking and side stepping

(Koller, et al, 1989; Wielinski, et al, 2005; Wood, et al, 2002; Cole, et al, 2010)

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Balance Training

- Ashburn et al 2007
  - Reduced risk for falling when PWP performs balance HEP for one hour/day for 6 weeks (Ashburn *et al* 2007)
- Sehm et al 2014
  - 45 minute balance training sessions for 20 PWP and 16 healthy age matched controls 1 time per week for 6 weeks
    - **2 sessions**: changes in gray matter volume in parietal-basal ganglia circuitry
    - **4 sessions**: increase in inferior parietal cortex gray matter
    - **6 sessions**: Increase in right lingual gyrus gray matter and active cerebellum
  - Healthy controls: only training-induced changes were to L hippocampus
  - These changes are clinically related because deficits in parietal-BG circuitry are associated with divided attention and set-shifting impairments

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Flexibility Training

- Address secondary postural changes
- Recommend stretching into rotation and diagonal patterns (combat rigidity)
- Commonly tight muscle groups:
  - Anterior chest
  - Hip flexors, adductors
  - Knee flexors, knee extensors
  - Trunk rotators, extensors
- Know client's orthopedic limitations!
- ***No flexion*** if PWP has osteoporosis!

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Large Amplitude Movements

- Training for amplitude rather than velocity has been shown to induce bigger, faster, and more precise movement while training for velocity only improves speed
  - Ebersbach *et al* 2010
- During tasks that require amplitude and speed, amplitude cues result in both bigger and faster movements that often approach or surpass control values
- Single focus of generalized training of amplitude decreases bradykinesia
  - Farley *et al* 2005

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Dual Task Performance

- Impaired basal ganglia function that was previously responsible for automatic movements
- Gait training with physical or cognitive tasks has been found to improve gait performance
  - Brauer and Morris 2010
- Cognitive working memory tasks (counting, categorical naming) with gait training may result in decline in initial performance but improved gait parameters in *early* stages
  - Wu and Hallet 2009; fMRI simple and complex tasks, motor and cognitive tasks
  - Canning et al 2008; Multi-task gait training
  - Fox and Farley 2006; BIG and LOUD generalized to handwriting
  - Del Olmo 2005, 2006; Temporal variability

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DUALITY study

- 121 patients with PD (H&Y II-III) on medication
- Control: gait and cognitive tasks trained separately
- Experimental Group: gait and cognition trained simultaneously
- Outcomes: Auditory Stroop task, GAITRite
- No significant difference between groups– both improved. Could be due to improved automatization and efficient integration of task-related networks

Strouwen et al 2017

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Motor Learning Considerations

- Motor learning is defined as practice related change or improvement in motor performance
- Basal ganglia contributes to the cognitive and automatic components of motor skill performance and learning of new skills
- Potential for new motor learning depends on stage of disease
  - Petzinger *et al* 2013
  - In PD, dopamine depletion leads to decreased habitual learning and loss of automatic motor control
- Extended training of motor skill involves shift from goal directed to habitual based…in other words practice makes automatic

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The Power of Cuing

- External cues: visual, auditory, vibrational
- Cuing can have immediate and powerful effect on gait performance: speed, step length, step frequency
- RESCUE study
  - H&Y Stages 2-4
  - 3 weeks cuing with gait training, 3 weeks off
  - No carry over of skill retention to other ADLs
  - No improvement in uncued gait
    - Nieuwbore *et al* 2007
- Amount of cuing when exercising depends on stage of disease and cognitive abilities
  - Less cueing for earlier stages of disease!
  - Over-cuing can slow motor learning

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Measure Progress Made through Exercise

Academy of Neurologic PT: PD Edge Wellness Recommendations

- 10 meter walk test (gait speed)
- 6 minute walk test (functional endurance)
- Functional Gait Assessment (balance, mobility)
- Mini BESTest (balance, fall risk)
- 5 Times Sit to Stand
- Timed Up and Go (Cognitive)

Check out rehabmeasures.org for instructions, psychometrics

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Functional Outcome Measures

APTA Neurology Section PD Edge Task Force 2014

Measure	Reported Cut-Off Scores (fall risk)	MCID
Activities Specific Balance Confidence	PD 69%	PD 11-13%
Functional Gait Assessment	PD <19/30 Elderly <23/30	Not established for stroke: 4.2 points
5x Sit to Stand	PD: 16 sec (norm 7.8 sec)	4.2 sec
10 Meter Walk Test	Not established	PD: self selected pace .18m/s, fast pace .25 m/s

Measure	Reported Cut-Off Scores (fall risk)	MCID
Mini-BESTest	PD: <20/28	Not established in PD, varied neuro dx 3.5
Timed Up and Go	PD: 11 sec Early PD: 7.95 sec	PD 11 sec, PD 5 sec
Timed Up and Go (cognitive)	Elderly < 16 sec	Not established
6 Minute Walk Test	Not established, correlations to health status are published	PD: 82 meters (270 feet)
Montreal Cognitive Assessment (MoCA)	Not applicable to fall risk <27/30 mild cognitive impairment, < 22/30 dementia	n/a

Clinical Bottom Line

- Exercise can significantly improve all areas of functioning for people with PD including balance, walking, and QOL
- Basic science research findings suggest that exercise changes the brain and improves function
- PWP who exercise move better and feel better
- Teach patient to exercise safely and how to maximize benefits of exercise specific to PD impairments

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Online Resources

- Delay the Disease www.delaythedisease.com
- National Parkinson Foundation: www.parkinson.org
- American Parkinson Disease Association: www.apdaparkinson.org
- Parkinson's Disease Foundation: www.pdf.org
- Michael J. Fox Foundation: www.michaeljfox.org
- National Institutes of Health: www.ninds.nih.gov/disorders/parkinsons
- Rehabmeasures.org
- PD Edge: www.neuropt.org/professional-resources/neurology-section-outcome-measures-recommendations/

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Questions?

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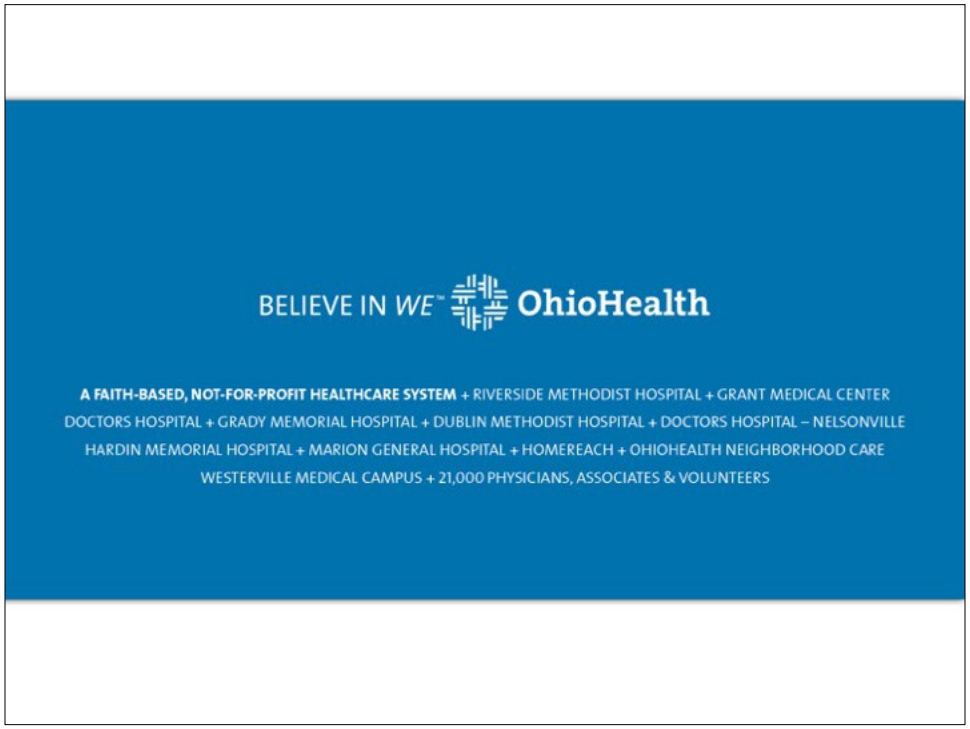
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PD Edge Evidence Based Outcome Measures 2/2014
Neurology Section of American Physical Therapy Association

Standardized Measures – targeting those values reported for Parkinson Disease

Measure	Reported **cut-off scores** - falls risk	Reported MDC	Notes
Activities specific Balance Confidence	PD: 69% Mak & Pang 2009	PD: 11% Del Bello-Haas et al, 2011 PD: 13% Steffen & Seney 2008	
Functional Gait Assessment	PD: ≤ 18/30 Yang 2014 Elderly: ≤22/30 Wrisley 2010	Not established for PD Stroke: 4.2 points Lin et al 2010	
5x Sit-to-Stand	PD: 16 sec Duncan, 2011	4.2 sec Schaubert 2005	
Gait speed 10 meter walk test	Not established	PD: Usual pace 0.18 m/s PD: Fast pace 0.25 m/s Steffen & Seney 2008	
Mini-BEST	PD: ≤19/28 Mak & Auyeung, 2013	Not established for PD Varied Neurol Dx: MDC 3.5; MCID=4pts Godi, 2012	MB total score is 28 Horak, test instructions
Timed Up & Go	PD: 11 sec Nocera et al, 2013 Early PD: 7.95 sec Dibble et al, 2006	PD: 11 sec Steffen & Seney, 2008 PD: 5 sec Dal Bello-Haas et al, 2011	
TUG – Cognitive	Elderly: ≤15 sec Shumway-Cook et al, 2000	Not established	Included in Mini-BEST test with rating adjusted if >10% decline from TUG to TUG-Cog
6 minute walk test	Not established Correlations to health status are published	PD: 82 meters Steffen & Seney, 2008	
9 Hole Peg Test	Not applicable to falls risk	PD: 2.6 sec - dominant hand; 1.3 sec non-dominant hand Earhart 2011	
Montreal Cognitive Assessment (MoCA)	Not applicable to falls risk ≤26/30 Mild cognitive impairment Hoops et al <22/30 Dementia Robbens et al, 2010, Dalyrimple-Alford et al, 2010	---	

Draft created Jan 2014 – These values represent current available evidence with a focus on studies providing specifics for Parkinson Disease (PD). Note that some of these cut points and responsiveness indicators have been established based on a small sample size of those with PD. The stability and strength of these values is expected to improve and change with additional research and require updating. In addition, any individual test psychometric must be used in context of the comprehensive PT exam and reassessment and does not replace clinical judgment.

III. David Zid, BA, ACE, APG

III — Interactive Demonstration/Lecture

By David Zid, BA, ACE, APG
Director, Movement Disorder and Musculoskeletal Wellness
Parkinson's Fitness Specialist
OhioHealth Delay the Disease™

Methods and Techniques

+ **Class Safety** — encourage health screening prior to class participation, safety is ALWAYS your #1 concern
+ Give them an "Experience"
+ Bring them back to class: your knowledge of PD, fitness and experience with group exercise makes it fun and meaningful

Home Exercises for the Lower-Functioning PWP* (Assisted)

+ Bicycles
+ Arm Pumps
+ Wave Stretches – 2 arm and 1 arm, with/without resistance
+ Wheelchair Leg Press
+ Squats with Assistance

**Always travel to a home with a med ball and a resistance band*

Concepts of Parkinson's Symptoms Related Exercise Agendas

Cardinal signs/symptoms of PD with instruction of exercises applicable to each symptom

Stooped posture *(use med balls)*

Exercises aid return of stature, increases lung capacity

Back line up-sitting, arm circles, back line up-standing, overhead taps, partner pass, swims, TV, pull downs, rows

Decreased arm swing

Ziddy Sticks, weight in one hand

Gait *(med balls)*

+ Decreased stride length and slower stride speed
+ Diminished arm swing
+ Toe walking
+ Problems with turning, changing directions, forward lean with walking

Walking drills, big first step, heel strike, forced walk, walk backwards

Functional Fitness Walking — high knees w/twist, counting steps, calf/Achilles stretch, ladder drills

Freezing *(visual cues, thought process, cognitive) (step over line)*

Ladder drill, tricks/tip to unfreeze-side step, step over, take a step backwards, step counting, relax jaw, tap floor, estimate steps

Demo Class

+ **Wake Up Call–Warm Up** — Head turns, shoulder shrugs, prayers, hand stretch, big pinch, arm pumps, pancake flips, rope pull, high knees, heel/toe, getting out of a chair, quad stretch, hamstring stretch
+ **Multitasking with Voice** — High knees, pancake flips, voice
+ **Balance Drills**
+ **2 minutes of Cardio**
+ **Walking Drills/John Wayne Walking**
+ **Circuit** — Cardio-jumping, 10 loud steps, plank, wall toe taps
+ **Handwriting**
+ **Balloons–Facial expression**
+ **Participant Conversation with PWP After Class**

Multi-Tasking Drills

+ **Driver Lunge** — Opposite arm, opposite leg. Perform near a wall
+ **Wall Drill** — Step in/ step out --whatever foot leads you in, leads you out
+ **Multi-Task Walking**
+ **1 - 2 - 3 Drill**

Functional Fitness Out of Bed — st. leg raise, side-side 2 leg lift, seated stretch, side push up, roll up, funct. abs-side-side

Functional Fitness Off the Floor — hips to all fours, plank, shoulder step up, gluteal stretch, countertop squat, 12-inch box, tricep dip, quad stretch

Functional Fitness Out of the Car — movement begets movement, window trick, seated side steps, side-to-side 2-leg lift, 12-inch box, bicep curls, front pull down, corner trick

Rigidity — exercises focus on rotation, flexibility (med balls)
Wall taps, standing wood chop, high knees w/twist, seated rope pull, seated rotation wood chop, seated rotational driver, night time stretching

Tremor

+ **Strength training** — Full range of motion, 5 sec rep speed, fatigue/ failure in 5-25 reps
+ **Cardio** — BeeHive Jump, Partner Jump
+ **Mindfulness**

Altered balance *(med balls)*

Balance drills — 2 leg, 1 leg, eyes closed, static, dynamic, line walk, 3 second heel-toe walk, 360 hand driver, partner ball pass, perturbation, driver lunge with balance

Decreased facial expression

Smile in the mirror

Low voice volume

Talk to the wall, AHH's and EEE's, first loud word, town hall

Micrographia

4 step handwriting protocol

1. Using blank 8 1/2 x 11 copy paper in the "landscape" direction, draw a sideways line that cuts the paper in half from top to bottom. Using a marker, attempt to draw letters that completely fill the space, touching the line and the edge of the paper.
2. Using a new paper, draw lines in a similar direction (sideways) that cuts the paper into four even sections. Again draw letters that fill each space from top to bottom. If at any time handwriting becomes small, reset by raising hand, stretching arm above head, and replacing to continue writing on paper.
3. Now, using lined paper (legal pad or school paper), attempt to fill the space between two lines, making every letter hit the top and bottom edges of the lines.
4. Using lined paper again, now attempt to fill the single line on the paper

Delay the Disease™ — Functional Fitness Plan XI — Walking

Walking is the most important activity a person can do in life. It allows you to move across the face of the earth; it keeps you from being disabled and maintains independence. If there is only one exercise a person can perform, it is walking. I am passionate about maintaining one's ability to walk; this group of exercises is very important. Practice these daily. Good luck.
— **David**

Rotational Walk — While standing tall, start walking. Lift one knee high and try to touch it with the opposite elbow, keeping elbow flexed at 90 degrees. Don't worry if you cannot touch it, just move your elbow towards your knee. Continue walking with high knees, trying to touch each knee with the opposite elbow. Walk for 10–20 steps.

Counting Steps — Stand in one position and choose a destination about 5 or 10 feet ahead of you; mark that spot with an object. Predict how many steps it will take you to reach that point using big steps. Then start walking towards your destination with big steps, counting your steps and trying to achieve your predicted number of steps. Try to walk that distance again, using one less step. Always make your first step big and think about striking your heel first. This will increase your stride and make all the other steps bigger. Practice this drill 5 times using different distances.

Ladder Drill — Use an agility ladder for the following moves (or create one on the floor with masking tape — simply create a ladder with rungs on the floor with tape). These exercises focus on controlled movements. Using this imaginary ladder on the floor will help your mind think about the task of walking and it will come more naturally to you when moving about in public places. This exercise focuses on "thinking" about the next move.

+ Walk placing one foot inside each ladder opening. Advanced move: walk while skipping every other opening, using a wider step.
+ Walk with shorter step, placing both feet inside each ladder opening.
+ Start with both feet on one side of the ladder, step with the leg closest to the ladder first, placing it inside a ladder opening, follow with the other leg so both feet are inside. Continue stepping in the same direction, until both feet are outside the ladder. Keep stepping in this crisscross pattern, walking from one side of the ladder to the other.
+ Start with both feet inside a ladder opening, facing the edge of the ladder. With a sidestep pattern, step over a rung in a sidestep fashion until both feet are inside the next ladder opening. Continue up the ladder. Facing the same direction, come back down the ladder using the same technique.
+ Step in a sideways pattern — one foot per opening

Walking Backwards — Take about 4-6 steps forward using big steps. Then take 4–6 steps backwards, using slow deliberate motion. You may need to use a partner as a spotter for this one — always perform in a safe place. Focus on making the steps big, and slow. No need to rush this one.

Calf/Achilles Stretch — Stand facing a wall or counter, leaning into the wall with your hands and arms outstretched. Place one leg (back leg) straight back, heel pressing down into the floor, and the other leg (front leg) slightly flexed at the knee and forward. Lean toward wall, keeping the back heel on the floor and feel a stretch low in back leg. Keeping the back leg straight targets the calf muscle. Hold this stretch for a 10 count. Repeat on the opposite leg.

Delay the Disease™ — Functional Fitness Plan IV — Freezing While Standing

By David Zid

Freezing is a problem for many. When you are frozen, your anxiety level goes up because you feel like you need to move. The harder you try, the harder it is to move. Sound familiar? Things that contribute to freezing may be a closed in space or crowds, external distraction and noise. When you are frozen, your mind must think about a new and different movement, then perform that alternate activity and the freezing episode should resolve. For example, when you are frozen in a particular movement, stop that activity and try to perform a completely different task. Then try to return to the original activity at a later time. Here are some ideas that may help. Good luck, and relax.
— **David**

Relax Your Jaw — This may sound funny, but if you relax your jaw the rest of your body will relax also, allowing you to start moving. Unless there is a bus coming at you, there is no real hurry. If there is a bus coming at you, get out of the way! If you are in line at the bank or grocery store, no one is going to die if you can't move right away. So relax your jaw, this is the first thing you must do before trying any of the following alternate movements.

Step Backwards — Take a big step backwards or sideways and then try to step forward with the same foot. Remember to make your first step a big one because the following steps will tend to be large also. If your first step is small, the rest of your steps will tend to be smaller.

Big First Step — If you are frozen, stop thinking about moving forward and try to tell yourself to take a big first step.

Step Over an Object — Find something on the ground, a crack, a dot, a pattern on the carpet, even a piece of gum. Then try stepping over it. Practice this at home using a sock, napkin, or something else that won't put you in danger if you step on it. Practice this over and over at home, then when you are out in public, visualize that napkin or sock and step over it.

Tap the Floor — Try to bend down and attempt to pick up an imaginary object off the floor, or simply tap the floor with a finger. This allows your brain to focus on a completely different activity, thereby allowing you to take a step and "unfreeze." Remember to always make your first step a big one.

Step Counting — Just count, estimate steps, decreasing numbers

Ladder Drills — Agility ladder drills

Delay the Disease™ — Functional Fitness Plan VIII — Getting Out of a Chair

By David Zid

Getting up and out of a chair independently is a struggle for many. A few tips to think about include avoiding the chair that is too low or too soft. Try to sit in a chair with armrests. Always attempt to scoot out to the edge of the chair before you attempt to get up. Your quadriceps need to be strong and flexible to get up without help. Perform these exercises daily and you will soon find that getting out of a chair is a piece of cake.
— David

Sit to Stand — Breaking this task down into 3 simple steps really helps.
+ Scoot to edge of chair
+ Tuck feet underneath you in a wide stance
+ Lean forward, with your "nose over your toes"

Now slowly stand up, hold a few seconds, and sit back down in a controlled fashion, don't 'plop' into the chair. As you sit down, lead with your hips and place your butt in the chair first.
Repeat 5 times.

Squats — The best way to practice getting out of a chair is to practice getting out of a chair! Stand in front of a chair. Start to sit back into the chair, lowering yourself as far as you can go without touching the chair. Return to a standing position. If this is easy for you, start by adding light weights in both hands. Repeat 5–10 times.

Advanced One-Legged Squat Out of a Chair — Try to get out of a chair using just one leg for support. Use your arms at first to assist, then as you progress, try to get up without the help of your arms.

Wall Squat — Lean against the wall with your back. Slide down into a sitting position as you walk your feet away from the wall. Your feet should be 2 to 4 inches apart and your knees should be above your ankles. Pretend that you are sitting on an air bench. Hold this position for as long as you can up to one minute. Do not go beyond your tolerance.

Quadriceps Stretch — While sitting in a chair, bend one knee and place foot as far back as possible on the floor. Lean back in the chair and feel the stretch in the front part of your leg.
Hold for a count of ten. Repeat 2–5 times.

Delay the Disease™ — Functional Fitness Plan I — Getting Out of Bed

By David Zid

This is the first in a series of functional fitness plans for people with Parkinson's disease. Each set of exercises is designed to assist you with a particular task or activity of daily living that may be difficult for you. Perform all exercises in the set at least 3 to 4 times a week. Make each exercise challenging by either increasing the repetitions or adding weight to the exercise. I promise this agenda will help you remain independent longer. With this set, you will be able to practice exercises that will give you the ability to get out of bed without assistance, and perhaps avoid waking your partner in the middle of the night. To be able to get off of a mattress, you need upper body and core strength. Good luck.
— David

Always think about BIG movements

Side Push Up — Lie on your side on your elbow, legs straight and feet stacked. Place other hand on floor in a comfortable position. Perform a "push up" lowering your chest to the floor and back up from this side lying position. Perform 5–10 reps. Change sides and repeat.

Roll Up — Lie flat on back with hands over the head, legs straight and flat against the floor. Starting with your head and neck, slowly roll up bringing one vertebrae off the floor until you are in a seated position. Slowly roll back down to the floor. Perform 5–10 reps.

Functional Abs — Side to Side — Lie on back on floor, with a ball, cushion or pillow between your knees, feet off the floor. Move knees side to side, going towards the floor to tolerance. Perform 5–10 reps.

Straight Leg Raise — In a seated position, straighten one leg in front of you, the other leg flexed at the knee with feet on the floor. Lift straight leg off of the floor as high as you can, keeping the knee as straight as possible. Perform 5–10 reps. If this is easy, try using both legs at once.

Side to Side Two Leg Lift — In a seated position with feet flat on the floor, using both hands to hold onto the sides of the chair, pick up both knees and swing them to the left side of the chair. Then pick up knees and swing to the right side of chair. Perform 5–10 reps.

Seated Stretch — Sit on the floor, with your hips close to the wall. Push your head and shoulders into the wall; push your legs into the floor. Relax your hands in your lap, toes pointed toward the ceiling. Hold for 2 minutes, relax and breathe.

Delay the Disease™ — Functional Fitness Plan III — Getting off of the Floor

By David Zid

Let's imagine that you have fallen and you are lying on the floor. First, make certain that you are not severely injured, or have sustained a bone fracture. Once you are sure that you are safe to move, relax, take a deep breath; you are safe on the floor. You do not need to get up quickly. Here is the process for moving from the floor. Become familiar with this process, and then practice the following exercises that will make the process easier for you. Don't hesitate to use a partner for help at first. Good luck.
— David

There are several ways to get up off the floor. Practice both of these techniques; the following exercises will help you get off the floor easier. Initially, roll from your position to a side lying position, with your bottom arm above your head. Bend your knees up and push up onto the elbow that is over your head. Try to get both knees underneath you by turning your hips, using both elbows and hands for support — you should be on "all fours" in a crawling position. From this position:

Off the Floor Using a Chair

+ Now you can crawl over to a chair to try to help pull yourself up.
+ Grab the edge of the chair with your hands or place elbows on the seat of the chair.
+ Pull your knee up and place one foot flat on the floor.
+ Shift your weight onto your arms on the seat of the chair and bring the other knee up, standing on that foot. Stand up slowly.

Off the Floor Unassisted (No Chair)

+ Pull one knee up and place that foot flat on the floor. Place both hands on the knee that is raised. Push off knee as you stand up.
+ Pull one knee up and place that foot flat on the floor. Keeping both hands on the floor, bring the other knee up and place that foot flat on the floor. Now you are in a deep squat position, so just stand up slowly.

Exercises

Hips Up to All Fours — Practice makes perfect. Start on the floor in a seated position with most of your weight on one hip, legs stacked. You can be leaning on your elbow, or sitting upright. From here, practice bringing your bottom knee underneath you, come up onto both knees, swinging up to an all-four position. Return slowly and with control back to your seated position without "plopping." Repeat this exercise 2–5 times on each side.

Plank — Lie facedown on floor with elbows bent, supporting your upper body. Go into a plank — push up position (legs straight, weight supported on your forearms and toes). Hold position for a 10 count, try to work up to a minute.

Shoulder Step Up — From the plank position, place knees on the floor. Now step up onto your hands with your arms extended. At the top of this movement, your weight should be evenly distributed between your arms (extended with palms on the floor) and your knees. Perform this movement from elbows to hands with arms extended 5 times on each side (5 with right hand leading, then 5 with the left hand leading).

Countertop Squat — Stand facing the kitchen sink with your hands holding onto the edge of the sink. Now bend your knees and perform a "squat," going as low as you can to tolerance. Return to starting position. Work up to 20 repetitions.

12-Inch Box (advanced) — Find a 12–16 inch high box, step, or bench. A fireplace hearth works well. Stand with your back to this box and squat down as far as you can without touching it. Return to a standing position. Repeat 2–5 times.

Tricep Dip — While sitting on the edge of your chair, place the palms of your hands on the front or sides of the seat. Support your body weight on your hands and bring your body out in front of the chair; your knees are bent. Put as much weight on your hands as possible, using your legs for backup support. Now slowly lower your hips while supporting yourself on your hands and arms. Return to starting position. Try to work up to 20 repetitions.

Quadriceps Stretch — While sitting in a chair, bend one knee and place foot as far back as possible on the floor. Lean back in the chair and feel the stretch in the front part of your leg. Hold for a count of 10. Repeat 2–5 times.

Gluteal Stretch — While lying on your back (on the floor or even in bed), straighten one leg while bending the opposite knee. Pull the bent knee up and across your body, towards the opposite shoulder. You should feel a stretch in you low back, glutes and even hamstrings. Hold for a count of 10. Repeat 2–5 times.

Delay the Disease™ — Functional Fitness Plan IX — Getting Out of a Car

This topic brought up more discussion in our weekly exercise class than any other functional exercise plan. Getting out of a car is difficult for most with Parkinson's. The seat is low and frequently hard to slide across. Our class had an open discussion of their opinions of personal struggles with this move. Based on their thoughts and my ideas, we came up with a few tricks and corresponding exercises that might make it easier for you to get out of your car. Practice all of the following; they will help you maneuver in tight space, unfreeze after a period of sitting, and increase your flexibility and ability to rotate yourself out of the car seat. Good luck.
— David

Tips

Movement Begets Movement Trick — Many have problems moving and rotating their feet out of the car after sitting for a long time. A few minutes before you get to your destination, start moving any body parts. Roll your shoulders, move your feet or legs. This can help with the larger movement of getting your legs out of the car.

Window Trick — You will need a partner to perform this. If you are seated in the front passenger seat, roll the window all the way down. Open the car door and rotate yourself so that you are facing the open door, with your feet out of the car. Your partner now will close the door partially, so that the door is barely touching your legs. With both hands, grab the bottom opening of the window. Now have your partner open the door as you continue to hold on, thus pulling out of the seat into a standing position.

Corner Trick — This trick will help you maneuver into the tight space of a car, where frequently people become frozen. Walk to a corner of a room and stand for a minute. Take a big, rotational step and open your stance, making sure you are not crossing your legs as you step. Now walk out of the corner. Repeat 5 times, turning both directions.

Exercises

Seated Side Steps — Start in a seated position on the edge of your chair with feet flat on the floor. Using high knees walk your feet around to the right side of the chair, rotating your head and shoulders with your legs. Using the same motion, walk your feet around to the left side of the chair. Perform 5–10 reps.

Side to Side Two Leg Lift — In a seated position with feet flat on the floor, using both hands to hold onto the sides of the chair, pick up both knees and swing them to the left side of the chair. Then pick up knees and swing to the right side of chair. Perform 5–10 reps.

12-Inch Box (Advanced) — Find a 12–6-inch high box, step, or bench. A fireplace hearth works well. Stand with your back to this box and squat down as far as you can without touching it. Return to a standing position. Repeat 2 –5 times.

Bicep Curls — Hold hand weights, a weighted bar, or even soup cans in each hand. Stand with knees slightly flexed, or remain seated. Keeping your elbows close in at your sides, curl weights up to chest level with palms up. Slowly return down to starting position, with control. Repeat 7–10 times. Now repeat the same move with palms facing in towards the body; repeat 7–10 times.

How to Plan/Design Your Class Weekly Agenda

+ Delay the Disease scripted classes
+ 12-week — one time a week
  - 12-week — two times a week
  - Chair level
  - Bootcamp level
+ Class feedback — what do they need, what do they want, was this helpful?
+ Make the class the most important part — avoid equipment sales, nutritionist, etc.
+ Share important information with them at your discretion
+ Functional Fitness — choose one or two functional fitness plans for one class

Testing/Skill Implementation

Each participant will design a fitness agenda based on a PD symptom; return demonstration with partner work.

Question and Answer — Course Evaluation

Summary and Closing

With this information, you will now be able to successfully create and implement an interdisciplinary exercise program for people living with PD. You will motivate, inspire and grow the program to empower the Parkinson's community in your area.

If you get home and have questions or comments, feel free to contact us!

Delay The Disease™ Program Development Coordinator: Jackie Russell, RN, BSN, CNOR
(614) 975.5874 or Rocco Presutti (614) 566.1189

Direct your questions to David Zid, Rocco Presutti or Jackie Russell. You can email any one of us at the email addresses below.

David.Zid@ohiohealth.com (David)

Rocco.Presutti@ohiohealth.com (Rocco)

Jackie.Russell@ohiohealth.com (Jackie)

Good Luck, Keep Moving!

Board Information

Delay the Disease Education Course

Instructors:

David Zid, BS, ACE, APG Director Movement Disorders/Musculoskeletal Wellness, OhioHealth Delay the Disease/Co-Founder Delay the Disease

Jackie Russell, RN, BSN, CNOR Video Program Development Coordinator, OhioHealth Delay the Disease/Co-Founder Delay the Disease

Leslie Wolf, PT, DPT, NCS Board Certified Neurologic PT, OhioHealth Outpatient Neurologic Rehabilitation

This course will provide evidenced based updates on the effects of exercise on the symptomatic management of Parkinson's Disease (PD). Each participant will be able to:

- Integrate this knowledge along with teaching techniques to create and lead a comprehensive community-based PD-specific exercise program based on the Delay the Disease fitness agenda.
- Select appropriate assessment tools and outcome measures for the evaluation of people living with PD.
- Understand the importance of motivation, enthusiasm, optimism and methods of teaching when designing a fitness agenda to treat a specific symptom related to PD.
- Acquire knowledge to successfully create and implement an interdisciplinary exercise and wellness program for people with PD.

IV. Bios/Bibliography

Jackie Russell, RN BSN CNOR

In her 35-year career as a registered nurse, Jackie Russell boasts a dedicated interest in the treatment of People with Parkinson's (PWP) and their caregivers/care-partners. Credentialed with professional achievement in perioperative nursing (CNOR) and ACLS certified, she is a graduate of The Ohio State University and has been employed in a variety of surgical nursing specialties (neurologic, orthopaedic, cardiac, and oculoplastic surgery). She is currently nursing supervisor for Michael McShane, M.D., at Orthopedic One, a specialty total joint replacement practice in Columbus, Ohio, as well as Co-Founder/ Program Development Coordinator for OhioHealth Delay the Disease™.

Touched by PD when her mother-in-law battled the disease, Jackie became professionally involved in the PD community while working for Dr. Thomas Mallory, who became afflicted with PD while in orthopaedic surgical practice. Her collaborative effort to help translate and spread the Delay the Disease™ exercise program to all PWP is a message of hope. She joined forces with David Zid to create this program in 2005.

She has been a featured speaker with David at many Parkinson's conferences throughout the country. She functioned as an editorial assistant for Dr. Mallory in writing his memoirs, The Man Behind the Mask — Journey of an Orthopaedic Surgeon, published by The University of Missouri Press in 2007. This book is an inspiring account of his life as a renowned hip replacement surgeon whose career came to an abrupt halt with the diagnosis of Parkinson's disease. His response to this diagnosis is an exemplary lesson for all. Russell authored an article in Today's Caregiver magazine in 2006 and was honored to author an article in the Summer 2008 issue of European Parkinson's Nurses Network, a European medical journal circulated throughout the world entitled "Exercise: the Positive Effects." She again published in the Sept/Oct 2009 and Feb 2010 issue of AgingWell Magazine. She continues to have an interest in Parkinson's research and is an author on the peer review study in Parkinsonism and Related Disorders (2014) entitled "Effects of a Formal Exercise Program on Parkinson's Disease: A Pilot Study Using a Delayed Start Design." Jackie and David presented a poster of their DTD outcomes June 2017 at the International Movement Disorder Congress in Vancouver, BC.

Jackie Russell was voted one of central Ohio's 20 Outstanding Women You Should Know (January 2009) for her work with the Parkinson's community. She and David grew Delay the Disease to a national program in 21 states and Canada with instructional courses for healthcare professionals, rehab companies, and home care companies. They joined the OhioHealth Family in 2013 and became the first wellness program in the OhioHealth system. As program development coordinator, she oversees all local classes, develops risk stratification protocols, coordinates research and helps national classes stay up to date with what is new in Delay the Disease.

Jackie has found a special niche with the development of an instructional seminar geared to caregivers and PWP. Train the Caregiver provides methods and functional fitness techniques for the care-partner to help their loved one with a daily home PD exercise program. She also focuses on the importance of "caring for the caregiver." Jackie advocates that daily exercise can empower people to face this disease with a proactive attitude, encouraging them to believe "I may have Parkinson's, but it does not have me." Exercise may just be the newest drug in the treatment of this disease.

Leslie Wolf, PT, DPT, NCS

Leslie Wolf is a board-certified neurologic physical therapist with interest in neuromuscular and neurodegenerative diseases including Parkinson's Disease. Leslie has neurologic rehabilitation experience in the acute care, inpatient rehab, and outpatient rehab and is Neuro-Developmental Treatment certified. She has participated in advanced Parkinson's disease training including the National Parkinson Foundation Allied Team Training for Parkinson, PWR! Training, and LSVT BIG certification. Leslie earned her Doctor of Physical Therapy degree from The Ohio State University in 2010 and her BS in Exercise Science from Miami University in 2007. In addition to patient care, Leslie is the Clinical Coordinator of the Ohio University-OhioHealth Neurologic PT Residency Program, serves on the APTA Movement System Diagnosis Task Force as well Academy of Neurologic Physical Therapy Practice Committee. In her spare time, enjoys traveling with her husband and kids, reading, and cycling.

BIO
David Zid, BA, ACE, APG

David Zid is a graduate of The Ohio State University and has been a professional fitness instructor in Columbus, Ohio, since 1997. Certified through ACE and APG as a personal trainer and functional fitness trainer, respectively, he is the owner and president of Total HealthWorks, a personal training company that he started in 1999. As an energetic coach for hundreds of clients and other personal trainers, he has developed a special interest in the older adult client, and now the Parkinson's client. He is currently the Director for Movement Disorders and Musculoskeletal Wellness at OhioHealth Delay the Disease™.

His focus on Parkinson's disease clients has been very rewarding. He is the leader and co-founder of Delay the Disease™ — group exercise classes specifically designed for people with Parkinson's disease, starting in 2005 when he joined forces with Jackie Russell. He is the author of the book and corresponding DVD "Delay the Disease™ — Exercise and Parkinson's Disease" and "Delay the Disease™ — Functional Fitness for Parkinson's" which highlights short exercise agendas that are based on a functional task that may be challenging to the Parkinson's individual (i.e., freezing, getting out of the car, getting out of bed, getting off the floor).

Zid and Russell helped pioneer the creation of an instructional certification course for Delay the Disease™, targeting healthcare professionals. It is an evidenced based program with detailed information on starting a community-based Parkinson's-specific exercise program, as well as a "train the trainer" component that instructs techniques for teaching and creating the exercise programs. Additional instructional courses include seminars for homecare agency personnel, and rehab companies. He and Jackie Russell co-instruct their Carepartner Seminar that focuses on the needs of the caregiver. David has been a featured symposium speaker both in the U.S. and internationally (including London, Ontario and Melbourne, Australia).

Delay the Disease has grown since joining forces with OhioHealth healthcare system in 2013. Classes locally are now risk stratified to include chair, basic, mixed, advanced, and boot camp levels. More than 500 OhioHealth Delay the Disease classes are now available in 20 states and Canada. People with Parkinson's come from around the country to train one-on-one with David so that he can create a personalized fitness agenda based on their needs.

David has an ongoing interest in Parkinson's research and is an author on the peer review study in *Parkinsonism and Related Disorders (2014)* entitled "Effects of a formal exercise program on Parkinson's disease: A pilot study using a delayed start design." Jackie and David presented a poster of their DTD outcomes June 2017 at the International Movement Disorder Congress in Vancouver, BC. Current prospective research protocols using the program are in the planning stages. Additional information about David's work with Parkinson's patients is available on the Delay the Disease™ website at DelaytheDisease.com.

Delay the Disease: Train the Trainer Course Parkinson's Disease and Evidence-Based Exercise Prescription

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V. Articles

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Effects of a formal exercise program on Parkinson's disease: A pilot study using a delayed start design

A. Park [a,*], D. Zid [b], J. Russell [b], A. Malone [a], A. Rendon [a], A. Wehr [c], X. Li [c]

[a] Department of Neurology, The Ohio State University, Columbus, OH 43210, USA
[b] Columbus Health Works, Columbus, OH 43212, USA
[c] Center for Biostatistics, The Ohio State University, Columbus, OH 43210, USA

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ABSTRACT

Introduction: Parkinson's Disease (PD) is a progressive neurodegenerative disease. Increasing evidence shows that physical exercise is beneficial for motor and non-motor symptoms of PD, and animal models suggest that it may help slow progression of disease.
Methods: Using a randomized delayed-start design, 31 patients were randomized to an early start group (ESG) or a delayed start group (DSG) exercise program. The ESG underwent a rigorous formal group exercise program for 1 h, three days/week, for 48 weeks (November 2011–October 2012). The DSG participated in this identical exercise program from weeks 24–48. Outcome measures included the Unified Parkinson's Disease Rating Scale (UPDRS), Walking Test (get-up-and-go), Tinetti Mobility Test, PDQ-39 Questionnaire, and the Beck Depression Inventory.
Results: There was minimal attrition in this study, with only one patient dropping out. Results did not show improvement in total UPDRS scores with early exercise. At week 48, the mean change from baseline total UPDRS score was 6.33 in the ESG versus 5.13 in the DSG ($p = 0.58$). However, patients randomized to the ESG scored significantly better on the Beck Depression Inventory, with a mean improvement of 1.07 points relative to those in the DSG ($p = 0.04$).
Conclusions: The findings demonstrate that long-term, group exercise programs are feasible in the Parkinson's disease population, with excellent adherence and minimal drop out. While the outcome measures used in our study did not provide strong evidence that exercise has a neuroprotective effect on motor function, earlier participation in a group exercise program had a significant effect on symptoms of depression.

1. Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative condition in the United States, characterized by the motor symptoms of bradykinesia, rigidity, and resting tremor. It has been estimated that approximately 630,000 people in the United States had the diagnosis of PD in 2010, and prevalence of PD is expected to double by 2040, which will substantially increase the economic burden of this disease [1]. While motor symptoms and the dopaminergic system have long been the primary focus of this disease, it is now recognized that widespread involvement of various non-dopaminergic pathways also contribute to the symptoms of PD. Furthermore, it is increasingly clear that the non-motor symptoms of PD, including depression and anxiety, are often more bothersome to patients than their motor symptoms. Recently, the National Parkinson's Foundation Quality Improvement Initiative (QII) data demonstrated that the depression affects health status almost twice as much as motor impairment [2].

Countless studies have shown that a variety of exercises improve the symptoms of PD, including home based exercise [3], treadmill [4], resistance exercise [5], tango dancing [6], tai chi [7], and robot-assisted gait training [8]. The LSVT®BIG therapy is derived from the Lee Silverman Voice Treatment, and focuses on intensive exercising of high-amplitude movements. This therapy has been shown to be an effective technique for improving motor performance in patients with PD, with significant improvements seen in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores [9]. At this time, there are no specific recommendations on

* Corresponding author. Madden Center for Parkinson's Disease and Related Disorders, Wexner Medical Center at The Ohio State University, 395 W. 12th Avenue, Columbus, OH 43210, USA. Tel.: +1 614 293 4969; fax: +1 614 293 6111.
E-mail address: ariane.park@osumc.edu (A. Park).

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what type of exercise is most beneficial in PD, leading most clinicians to suggest any routine leading to improved physical fitness.

While there has been a strong research interest in identifying potential "neuroprotective" therapies that might slow down progression of PD, currently none have proven clinically effective. Large cohort studies have shown that vigorous exercise in midlife significantly reduces risk of developing PD [10–12]. In addition, longevity in PD has been associated with exercise [13]. Thus, if exercise may be involved in reducing the risk of PD, it is possible that it may play a role in slowing down disease progression. In 6-OH-DA rodent models of PD, studies have shown that parkinsonian deficits are attenuated by exercise [14]. Conversely, nonuse via cast immobilization of the parkinsonian side significantly exacerbates motor deficit [15], suggesting that limb disuse may lead to further neurodegeneration. In MPTP rodent models, exercise appears to have a protective effect on dopamine neurons from acute MPTP toxicity [16]. Additional findings have suggested that exercise may attenuate the hyperexcitability of striatal neurons seen after dopamine depletion, possibly via modulation of glutamatergic receptor subunit expression [17]. It is known that vigorous exercise induces brain neurotrophic factor expression [18], and both brain derived neurotrophic factor (BDNF) and glial cell line-derived neurotropic factor (GDNF) have been shown to be decreased in the substantia nigra of patients with PD [19]. It may be that neurotrophic growth factors reduce the vulnerability of DA neurons, thus conferring neuroprotective benefit.

To our knowledge, this is the first study to look at the feasibility of conducting a long-term formal group exercise program in PD, using a randomized delayed start design. This type of study design aims to separate disease modifying/neuroprotective effects from symptomatic effects. Thus, our goal was to gain information on the potential neuroprotective effects of exercise, with the primary outcome measure being total UPDRS score. Furthermore, we explored whether early exercise may confer non-motor benefit in terms of depression and quality of life.

2. Methods

Thirty-one patients with idiopathic PD were selected over a six month period. All consecutive patients referred to our movement disorder center who met inclusion criteria were approached for enrollment. The following inclusion criteria were chosen: 1) Age 40–70 years old diagnosed with PD within three years of symptom onset with a Hoehn and Yahr stage 1 or 2, 2) Participants met the UK Parkinson's Disease Brain Bank criteria [20], 3) Subjects could be on either no anti-parkinsonian medications, or could be taking amantadine, monoamine oxidase B inhibitors, and/or dopamine agonists, and 4) All subjects must have had adequate vision and English sufficient for compliance with testing and surveys. Exclusion criteria were: 1) Hoehn and Yahr stage 3 or higher, 2) Atypical or secondary parkinsonism, 3) Any other condition (other than the primary indications) which in the opinion of the investigators might contribute to gait or balance impairments or complicate its assessment, and 4) Subjects who have been or are on any formulation of levodopa.

Using a delayed start design, participants were randomized to receive either the exercise intervention for both of the 24-week phases (early start group or ESG), or to receive the exercise intervention in the second phase, weeks 24–48, only (delayed start group or DSG). The two phases were designed to capture any symptomatic benefit of the exercise intervention at the end of the first phase, and also any sustained benefit by the end of the study. Research visits were done at baseline, and at weeks 8, 16, 24, 32, 40 and 48 weeks. Attendance was taken at each exercise session, and all participants were required to participate in at least 70% of the exercise sessions in order to remain in the study. At each visit, participants provided a home exercise diary and an updated list of current PD medications. In addition, blinded clinicians conducted the Unified Parkinson's Disease Rating Scale (UPDRS) [21], Timed Walk [22] to monitor speed of movement and the Tinetti test [23], which assesses gait and balance status, and has been associated with changes in fall risk [24]. To minimize inter-rater variability, only three clinically experienced raters were used for these tests at all visits. During the baseline visit and at the 48-week visit, participants filled out the PDQ-39 questionnaire [25], which is a disease-specific measure of subjective health status, and the Beck Depression Inventory [26], an instrument to assess the severity of depression. In addition, at the baseline visit participants completed a brief demographic survey, and at week 48, participants filled out a brief post-exercise program survey.

The formal group exercise program was led by a personal trainer, and was based on two, 12-week fitness cycles as follows.

2.1. First 12-week cycle (done in a group setting)

Weeks 1–6 concentrated on each participant achieving a baseline fitness level to allow each person to safely begin the formal strength program. This portion of the fitness agenda consisted of a cardiovascular, core strength, and joint integrity plan.

During weeks 7–12, formal strength training was added with a focus on increasing weight intensity while repetitions decrease (repetition numbers from 25 decreasing to 15). The goal was that each participant came to muscle fatigue/failure with each set.

2.2. Second 12-week cycle (done in a group setting)

Weeks 13–14 consisted of cardio/core/joint integrity work without formal strength training.

During weeks 15–24, formal strength training was added, however weight intensity increased further as repetitions decreased to a smaller number (repetition numbers from 25 decreasing to 10), again with the goal of muscle fatigue/failure with each set.

All sessions lasted 1 h, and occurred three times per week for 48 weeks. These 12-week cycles were identical for both the ESG and DSG. After week 24, the ESG repeated the two, 12-week cycles over again. During cardiovascular training, attempts were made to have each participant achieve 75%–85% of their maximum heart rate for a 1-min interval. A CPR/ACLS certified RN was in attendance during each exercise session to further ensure participant safety.

Ethical permission to conduct this study was obtained from the Institutional Review Board of The Ohio State University. Written informed consent was obtained from each participant prior to enrollment. This study was conducted in full accordance with the Declaration of Helsinki.

3. Statistical analysis

For all the randomized subjects, baseline demographics and clinical characteristics were summarized between groups. For each outcome measure, group mean and standard deviation of the change in scores from baseline was reported at each post-randomization visit.

Our primary outcome was change in total UPDRS score from baseline. To assess neuroprotective effect in this delayed start design [27], we tested three endpoints simultaneously, each at the 0.05 significance level. This was done to determine whether any differences seen between the groups was enduring (as would be expected with a disease-modifying effect) and not diminishing (as would be expected with an intervention that had a prolonged

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and cumulative symptomatic effect). The objective was to test the following hypotheses: (1) superiority of ESG over DSG at week 24 using data from the first phase, (2) superiority of ESG over DSG at week 48 using data from the second phase, and (3) non-inferiority of the rate of change for ESG to DSG for the second phase. Using the upper limit of the one-sided 95% confidence interval (CI) for change in total UPDRS scores between the ESG and DSG during phase 2, a margin of 3.6 UPDRS points was used (0.15 points per week). Endpoints were analyzed through linear mixed effects models [28], using group, week, week-by-group interaction, and the baseline UPDRS score as the fixed effects. Within-subject correlation among the repeated measures was taken into account by an unstructured variance covariance matrix. Other secondary repeated outcomes were analyzed in a similar way. For BDI and PDQ-39, analysis of covariance (ANCOVA) was used to compare the change in score from baseline between groups. All statistical analyses were conducted in SAS (version 9.2, SAS Institute Inc., Cary, NC).

4. Results

Fifteen participants were randomized to the ESG and sixteen to the DSG. For the 48-week course of the study, only one patient dropped out at week 32 due to extensive travel resulting in missing too many visits. All other patients completed the study and had no missing data. There were no adverse events. Patient baseline characteristics were comparable between the two intervention groups in terms of age, gender, weight and employment status. Other characteristics such as hours of exercise per week and previous PD exercise education were not as comparable. The ESG reported more exercise per week at baseline than the DSG (mean number of hours of exercise per week being 6.8 and 4.6 for the ESG and DSG, respectively). Also, the ESG had fewer participants with previous PD exercise education than the DSG (31% and 53%, respectively) (Table 1). Neither of these observed differences was statistically significant.

Changes in outcome variables are summarized in Table 2. The group mean plot showed no clear separation between the groups over time (Fig. 1A). For total UPDRS, although the ESG tended to improve more at week 16 (-1.19 ± 5.98) compared to the DSG (2.27 ± 7.35), this was not significant ($p = 0.15$), and this difference diminished by week 24 (1.31 ± 6.29 for the ESG and -0.13 ± 8.43 for the DSG, $p = 0.65$). At week 48, both groups had higher UPDRS scores, but the DSG had less increase in total UPDRS (5.13 ± 8.75) than the ESG (6.33 ± 7.49). This was not statistically significant ($p = 0.58$). During the second phase of the study, the ESG showed a smaller rate of increase in UPDRS scores between weeks 32 and 48 than the DSG (raw mean difference being 5.53 ± 1.84 versus 6.40 ± 1.84 for the ESG and DSG, respectively). The 95% one-sided confidence interval for this difference of -0.87 was (-5.70, 3.57). Given that the upper limit of 3.57 is less than the pre-specified margin of 3.6 UPDRS points over weeks 32–48, this indicates the non-inferiority of the ESG to DSG. A similar pattern was observed looking at change in UPDRS III scores (Fig. 1B). Results of the comparisons, and estimates with upper confidence interval limits for non-inferiority testing are listed in Table 2.

For Timed Walk, the ESG tended to have better scores during the entire study period (Fig. 1C). They demonstrated improved performance at the end of the first phase (-0.76 ± 1.28) compared to the DSG (-0.17 ± 1.16), but this was not statistically significant ($p = 0.08$). This trend was not sustained for the duration of the study ($p = 0.86$). For Tinetti, the group mean plot shows that the ESD did better (Fig. 1D), but none of the superiority tests achieved statistical significance ($p = 0.69$ at week 48).

ANCOVA results showed that at the end of the study, the Beck Depression Index mean change from baseline values decreased more in the ESG (-2.67) versus the DSG (-1.60), and this was statistically significant ($p = 0.04$).

Home exercise diary data was analyzed, and out of 168 days (i.e. the total number of days the DSG had prior to starting the formal exercise program), the DSG had an average of 69 days of exercise, compared to 45 days in the ESG. Using the Wilcoxon Rank Sum Test, this was not statistically significant ($p = 0.15$).

In the post-exercise program survey, patients were asked to rate how they liked the exercise class overall on a scale from 1 to 5, 5 being the best, and all but one participant answered 5 (the other answered 4).

Table 1
Baseline demographics and clinical characteristics of the 31 study participants.

Variable	Level	Group		Total
		DSG ($N = 15$)	ESG ($N = 16$)	
Age	Mean (SD)	60.1 (6.6)	59.8 (6.3)	59.9 (6.3)
	(min, max)	(50, 73)	(51, 69)	(50, 73)
Weight (in pounds)	Mean (SD)	176.8 (20.4)	178.1 (36.0)	177.5 (29.1)
	(min, max)	(150, 235)	(110, 230)	(110, 235)
Falls in last month[a]	No Falls	12 (80%)[a]	14 (88%)	26 (84%)
Falls in last 6 months[a]	No Falls	10 (67%)[a]	13 (81%)	23 (74%)
Hours of exercise per week	Mean (SD)	4.6 (3.3)	6.8 (5.2)	5.8 (4.5)
	(min, max)	(0, 12)	(1, 17)	(0, 17)
Gender	Male	10 (67%)	10 (63%)	20 (65%)
Currently driving	Yes	14 (93%)	15 (94%)	29 (94%)
Length of diagnosis	<1 year	3 (20%)	1 (6%)	4 (13%)
	1 to <5 years	11 (73%)	11 (69%)	22 (71%)
	5–10 years	1 (7%)	4 (25%)	5 (16%)
Dyskinesia	Yes	2 (13%)	2 (13%)	4 (13%)
Depression	Yes	4 (27%)	2 (13%)	6 (19%)
Anxiety	Yes	3 (20%)	4 (25%)	7 (23%)
Tobacco use	No	8 (53%)	12 (75%)	20 (65%)
	Previous	6 (40%)	4 (25%)	10 (32%)
	Current	1 (7%)	0 (0%)	1 (3%)
Previous PD exercise education?	Yes	8 (53%)	5 (31%)	13 (42%)
Currently attend physical therapy	Yes	1 (7%)	3 (19%)	4 (13%)
Ever competed in a sport	Yes	10 (67%)	12 (75%)	22 (71%)
Marital status	Married	14 (93%)	12 (75%)	26 (83%)
Currently working	Yes	8 (53%)	10 (63%)	18 (58%)

[a] Note: One patient from the DSG reported having fallen 10 times in the last month and 25 times in the last 6 months.

5. Discussion

Physical activity has been shown to have a positive influence in neurodegenerative diseases, with exercise being correlated with a reduced incidence of cognitive decline and Alzheimer's disease, and an improvement of motor symptoms in PD. It is possible that these benefits occur via mechanisms that reduce inflammation in the central nervous system, thus promoting neuronal resilience. Furthermore, animal models suggest that exercise may confer a "neuroprotective" benefit in PD, possibly delaying disease progression. This randomized clinical trial uses a delayed start design to see if long-term group exercise is, 1) feasible in Parkinson's disease patients, and, 2) if this analysis could detect a neuroprotective effect in the early exercise group versus the delayed exercise group.

We were able to demonstrate that patients could adhere to a long-term group exercise program for 48 weeks, with only one patient dropping out. Furthermore, the enthusiasm that these PD patients had for this group exercise program was sustained based on the results of the post-exercise program survey. Many of these patients continue to exercise as a group after the completion of this study.

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Table 2
Summary statistics of the efficacy outcomes in the early start group (ESG) and the delayed start group (DSG).

Outcome variable	Group[a]	Baseline raw score (SD)	Mean raw score (SD)						Mean change from baseline (SD)								
			Phase 1			Phase 2			Phase 1				Phase 2				Non-inferiority (NI)[d]
			Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	Week 8	Week 16	Week 24	*p*-0value[b]	Week 32	Week 40	Week 48	*p*-value[c]	
Total UPDRS	ESG	21.88 (6.73)	20.19 (7.68)	20.69 (9.34)	23.19 (8.54)	23.07 (11.99)	23.93 (11.30)	28.60 (11.20)	−1.69 (4.22)	−1.19 (5.98)	1.31 (6.29)	0.65	0.80 (7.62)	1.67 (7.93)	6.33 (7.49)	0.58	−0.87 3.57
	DSG	26.07 (9.95)	24.40 (11.33)	28.33 (11.56)	25.93 (12.09)	24.80 (11.92)	29.53 (13.21)	31.20 (13.69)	−1.67 (6.23)	2.27 (7.35)	−0.13 (8.43)		−1.27 (6.55)	3.47 (9.76)	5.13 (8.75)		
UPDRS III	ESG	14.00 (5.73)	13.38 (5.97)	14.56 (6.87)	16.13 (6.86)	16.53 (7.97)	16.80 (7.74)	20.40 (7.01)	−0.63 (3.58)	0.56 (3.37)	2.13 (5.43)	0.49	1.93 (5.09)	2.20 (4.33)	5.80 (4.02)	0.80	−0.93 2.56
	DSG	16.60 (7.02)	16.00 (7.11)	19.47 (8.43)	16.60 (8.72)	17.07 (8.49)	21.47 (9.68)	21.87 (10.43)	−0.60 (5.25)	2.87 (7.37)	0.00 (7.45)		0.47 (5.82)	4.87 (8.31)	5.27 (7.42)		
Tinetti	ESG	26.00 (3.52)	26.69 (3.50)	27.31 (1.99)	27.31 (2.02)	27.07 (2.09)	27.13 (2.59)	26.73 (3.13)	0.69 (1.40)	1.31 (1.85)	1.31 (1.78)	0.80	1.20 (2.04)	1.27 (1.49)	0.87 (1.68)	0.69	−0.47 0.23
	DSG	26.27 (3.17)	27.40 (2.06)	26.33 (2.41)	27.33 (1.59)	27.00 (1.56)	27.00 (1.46)	27.13 (1.46)	1.13 (1.92)	0.07 (1.58)	1.07 (2.12)		0.73 (1.87)	0.73 (2.28)	0.87 (2.10)		
Timed Walk	ESG	6.04 (1.95)	6.16 (2.03)	5.46 (1.68)	5.29 (1.24)	5.31 (1.15)	5.97 (2.37)	6.21 (2.41)	0.12 (1.07)	−0.58 (1.37)	−0.76 (1.28)	0.08	−0.81 (1.35)	−0.16 (1.16)	0.08 (1.39)	0.86	0.41 1.12
	DSG	6.26 (2.04)	6.39 (1.83)	6.27 (1.98)	6.09 (1.85)	5.89 (1.66)	6.63 (2.02)	6.37 (1.74)	0.13 (1.08)	0.01 (1.08)	−0.17 (1.16)		−0.37 (1.15)	0.37 (1.37)	0.11 (1.08)		
BDI	ESG	6.81 (4.13)	–	–	–	–	–	3.87 (2.56)	–	–	–	–	–	–	−2.67 (2.55)	0.04	–
	DSG	9.53 (4.79)	–	–	–	–	–	7.93 (4.73)	–	–	–		–	–	−1.60 (3.42)		
PDQ-39	ESG	12.55 (8.03)	–	–	–	–	–	7.27 (6.42)	–	–	–	–	–	–	−5.05 (6.49)	0.21	–
	DSG	15.51 (12.26)	–	–	–	–	–	13.29 (12.82)	–	–	–		–	–	−2.73 (9.08)		

[a] DSG: $n = 15$, ESG: $n = 16$, 1 patient withdrew at week 32.
[b] *p*-value is for the between group comparison of the change from baseline to week 24.
[c] *p*-value is for the between group comparison of the change from baseline to week 48.
[d] The top number is the estimate for the difference in the chang e between weeks 32 and 48 between the ESG and DGS. The bottom number is the upper limit of the one-sided 95% confidence interval for that estimate.

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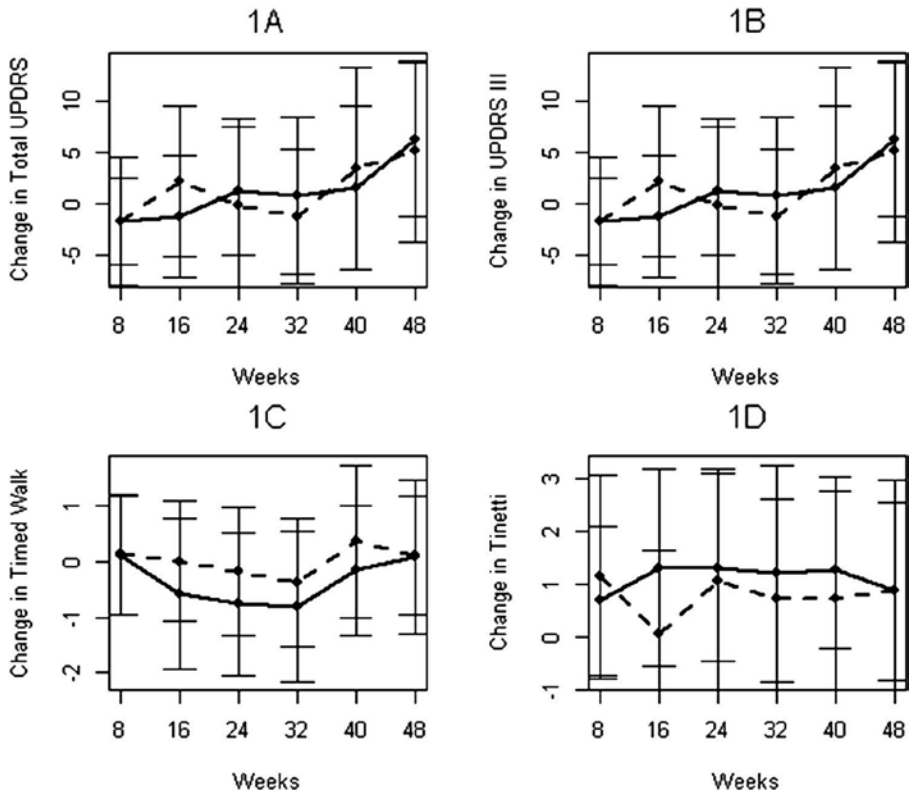

Fig. 1. Longitudinal mean changes in four efficacy outcomes (1A. Total UPDRS; 1B. UPDRS III; 1C. Timed Walk; 1D. Tinetti) in the early start group (solid line) and delayed start group (dashed line).

While this study did not provide strong evidence that the exercise program utilized is neuroprotective, at least as measured by objective change in total and motor UPDRS scores, the lack of effect may have been partially explained by the relatively small sample size for a study of this duration. Another study limitation is that this was a single-blinded study, however this was inevitable since the participants had to be aware of whether they were in the ESG or DSG. The home exercise diary data did not show that the DSG exercised significantly more than the ESG before they started the formal exercise program on week 24, however our home exercise diary data was limited in that we only collected information on whether participants exercised on a particular day or not. We do not know what kind of exercise, the duration or the activity level. Therefore, any exercise done outside of the formal exercise program is a potential confounding issue, and could explain the lack of differences seen between groups in this study.

Finally, it is important to note the inherent difficulties in assessing a neuroprotective effect in PD, as currently we only have indirect measures of progression, and no reliable biomarker. Given that PD is known for its variable progression and heterogenous presentation, despite using a delayed-start design for a long duration, capturing this "neuroprotective" effect may remain elusive and further studies are recommended.

Exercise has been shown to be helpful for mood disorders such as anxiety and depression [29], behavioral symptoms that are common in PD. Exercise has been hypothesized to improve depression through a number of mechanisms of action, including regulation of central monoamines (serotonin, noradrenaline and dopamine), balancing hypothalamic–pituitary–adrenal axis functioning, and increasing levels of β-endorphin. Recently it has been shown that Parkinson's patients doing higher levels of physical activity had significantly less fatigue, and trends for less apathy and depression [30]. Our study demonstrated that patients who started the group exercise earlier had significantly fewer self-reported symptoms of depression than those in the delayed start group. As the National Parkinson's Foundation Quality Improvement Initiative (QII) data has noted, depression affects health status almost twice as much as motor impairment [2]. Thus, the differences noted in this study support early interventions of this type. However, the present study cannot differentiate between the benefits of exercise compared to the benefits of the support of the regular group peer meetings on symptoms of depression, as these may also have impacted feelings of isolation or depression.

It is a common recommendation for PD patients to get regular exercise, and while this study was conducted on relatively early onset PD patients, individual exercise regimens can be tailored to one's physical capabilities and limitations, even in more advanced disease. Not only can PD patients adhere to a long-term group exercise program, exercise can be an inexpensive and fun intervention free of the side effects of current anti-parkinsonian medications. The positive and supportive environment provided by a formal group exercise program cannot be ignored, as it helped to improve attitudes, fostered optimism and was a positive force for not only the patients with PD, but their circle of support as well.

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Paige Pancake, RN, Clinical Research Coordinator.

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Does vigorous exercise have a neuroprotective effect in Parkinson disease?

J. Eric Ahlskog

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ANIMAL MODELS Evidence from animal studies indicates that physical exercise enhances brain neuroplasticity and elevates certain neurotrophic factors. This may be relevant to patients with PD.

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

Unilateral nigrostriatal 6-OH-DA to induce hemiparkinsonism

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

Systemic MPTP to induce generalized parkinsonism

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

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

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

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

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

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

1. Elevated expression of BDNF, which appears to be a key factor mediating the effects of exercise on cognition[e5-e14]
2. Increased expression of the neuroprotective agent, insulin-like growth factor I, which interacts with BDNF to mediate exercise-induced cognitive gains[e15]; exercise-induced production of this factor protects against neurotoxic hippocampal insults[e16] and is acutely elevated by exercise in normal humans[e17]
3. Induction of neuroplasticity-related transcription factors such as intracellular kinase signaling systems and cyclic adenosine monophosphate response element-binding protein[13,e9,e18]
4. Neurogenesis[e6,e19-e23]
5. Elevated concentrations of synaptic proteins, synapsin I and synaptophysin[e11,e12]
6. Enhanced long-term potentiation, a measure of synaptic efficacy[e6,e14,e19]
7. Increased dendritic length, complexity, and spine density[e22,e24]
8. Increased expression of genes associated with synaptic plasticity and downregulation of genes linked to oxidative stress[e25]

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

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

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

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

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

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

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

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

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

Exercise as a specific treatment for PD. This overall body of evidence suggests that vigorous exercise should be accorded a central place in our treatment of PD. It should be encouraged and emphasized as potential strategy for a more favorable disease course. There are 2 fundamental components to this strategy.

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

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

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

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

AUTHOR CONTRIBUTIONS

Dr. Ahlskog: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

DISCLOSURE

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Does vigorous exercise have a neuroprotective effect in Parkinson disease?

J. Eric Ahlskog

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Exercise and neuroplasticity in persons living with Parkinson's disease

M. A. HIRSCH [1], B. G. FARLEY [2]

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

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

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Corresponding author: M. A. Hirsch, PhD, Carolinas Rehabilitation, Department of Physical Medicine and Rehabilitation, 1100 Blythe Blvd Charlotte, North Carolina, 28203.
E-mail: mark.hirsch@carolinashealthcare.org

[1]Carolinas Rehabilitation
Department of Physical Medicine and Rehabilitation
Charlotte, North Carolina, USA
[2]University of Arizona, College of Medicine
Department of Physiology, Tucson, AZ, USA

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

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

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

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

In 1994 the American Academy of Neurology came to a different conclusion, recommending physiotherapy and exercise as an adjunctive (i.e., helpful) strategy in early and advancing PD.[7] Koller et al.[7] urged healthcare professionals to strongly encourage their patients to exercise: "The optimal approach to the management of early PD includes daily exercise, one of the most beneficial things a patient can do for himself. It can consist of stretching, walking, swimming, or any activity the patient enjoys and will do regularly. More formal cardiovascular programs are also beneficial…".[7] For patients with early PD, the guidelines recommended "strengthening with light weights".[8] In patients with advancing PD the guidelines state "…exercise is also helpful. Although vigorous exercise is not necessary, just doing a few pushups, sit-ups, or isometric exercise is not (emphasis added) enough. Patients must be encouraged to walk as much as several miles a day, if possible, or swim regularly".[7] Surprisingly, neither of the treatment guidelines provided citations specific to studies demonstrating treatment efficacy of exercise or physiotherapy and the 2001 treatment guidelines [9] failed to mention exercise altogether.

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

Since the Cochrane reviews, the quality and number of published peer reviewed randomized trials on exercise and/or physiotherapy has steadily increased. Many systematic reviews and at least 3 meta-analytic studies (Table I) have reported positive effects of physiotherapy and exercise on the motor [13-31] and non-motor [32] signs and symptoms of PD. Recently, the Quality Standards Subcommittee of the American Academy of Neurology, and a joint task force of the European Federation of Neurological Societies and the Movement Disorders Society, European Section reviewed the literature on the effects of exercise and/or physiotherapy on improvement in motor symptoms, function, or disability of PD. Both panels independently recommended the use of exercise and physiotherapy in PD,[20, 33] citing studies published through January 2006 with certain caveats concerning

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

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

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

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

The previous practice guidelines were included in overall medical guidelines for medical treatment and were brief and not geared towards physiotherapists and other allied healthcare providers. In 2001 the first evidence based physical therapy guidelines were developed in the UK.[34] In 2004 and 2006, these guidelines were updated and supplemented with evidence-based physical therapy practice recommendations by a group in the Netherlands.[35] They have continued to be updated with the latest evidence (through December 2007) and are now available online.[22] Four specific treatment recommendations reached level 2 evidence (i.e., conclusions supported by a least two independent randomized controlled trials (RCTs) of moderate methodological quality or with sufficient power, or other non-randomized, controlled studies). These included: cueing strategies to improve gait; cognitive movement strategies to improve transfers; exercises to improve balance; and training of joint mobility and muscle power to improve physical capacity.[22] To solve the problems with implementation of

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

Importance of exercise

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

Guidelines specify:

— aerobic activity to be of vigorous or moderate intensity (20 minutes/ 3 days per week or 30 minutes 5 days per week, respectively);

— muscle strengthening consisting of 8-10 exercises involving the major muscle groups with at least 1 set of 10-15 repetitions per muscle group, on at least 2 non-consecutive days per week;

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

— balance training exercises.

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

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

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

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

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

Exercise and brain health

While exercise guidelines for adults have traditionally focused on achieving musculoskeletal and cardiopulmonary benefits with training, more recent attention has shifted to exercise as a means to maintaining or increasing brain health. Studies on healthy populations of older adults free of central nervous system pathology have already shown that regular aerobic activity triggers plasticity related changes in the central nervous system including synaptogenesis, enhanced glucose utilization, angiogenesis and neurogenesis. Among older adults free of cognitive impairment, aerobic exercise promotes brain health by reducing inflammation, suppressing oxidative stress and stabilizing calcium homeostasis.[52] Release of endogenous neurotrophins such as brain-derived neurotrophin (BDNF), glia-derived neurotrophin (GDNF), nerve growth factor (NGF) and galanin [53] during chronic aerobic exercise is associated with synaptic plasticity, enhanced cognitive ability, learning and memory.[54] Results from the above human studies are paralleled by studies with lesioned and intact laboratory animals, showing that motor training triggers lasting neuronal changes throughout the brain such as glial cell proliferation, changes in neurotransmitter levels, changes in the expression of endogenous neurotrophic factors such as BDNF and GDNF, the growth of neuronal processes, and neural changes which are associated with enhanced behavioral recovery.[55-79]

While evidence has elucidated the benefits of exercise among healthy active and inactive populations, scholars [53] note that relatively little has been published about the neurobiology of exercise as it pertains to people with neurodegenerative conditions, such as PD. Most of the authors' understanding of activity-dependent or exercise-induced neuroplasticity is derived from studies of brain injury related to stroke and spinal cord injury. Animal models (rodent and nonhuman primate) of stroke suggest that forced-use of the impaired upper limb (small object retrieval) improves motor recovery and results in a reduction in the lesion size and functional reorganization in both

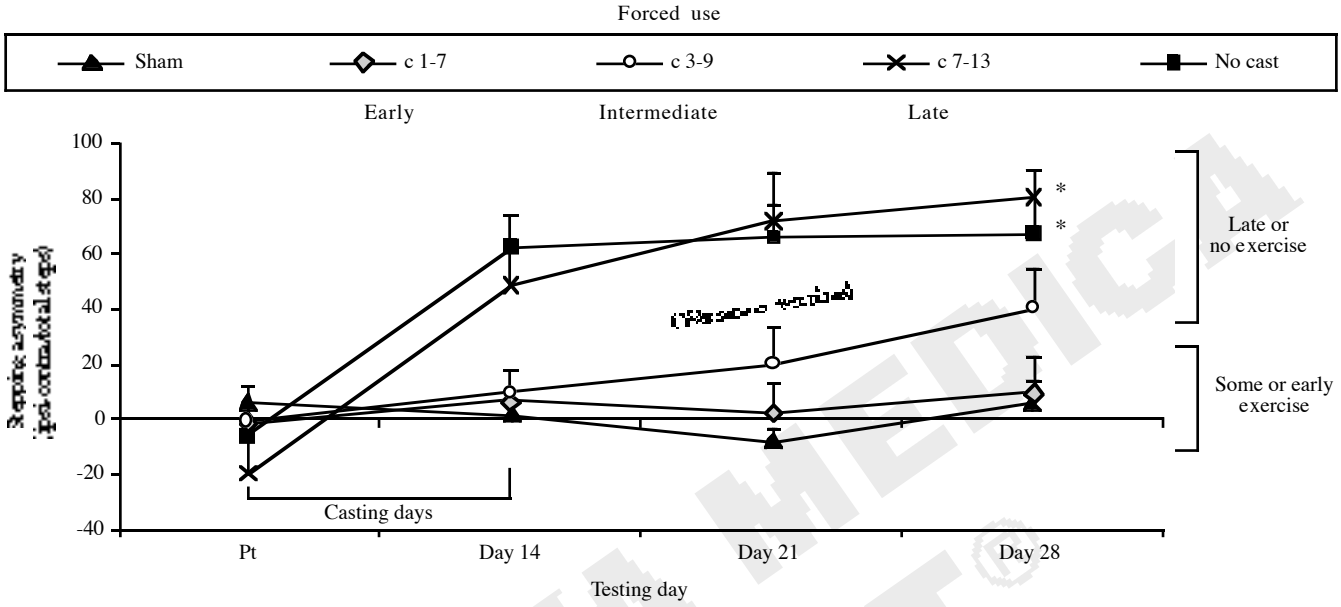

Figure 1.—Forced use of the impaired forelimb on days 1-7 and 3-9 after 6-OHDA exposure ameliorated akinesia. Those animals that did not receive the cast until days 7-13 displayed strong akinetic tendencies as did the animals in the no cast group. Bonferroni post hoc analysis indicated significant differences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

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

Two widely used experimental rodent models of PD will be discussed that use the neurotoxins 6-hyroxydopamine (6-OHDA) in rats, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice, to study the effects of exercise prior to, or following a lesion that leads to progressive dopaminergic cell death and motor deficits typical of PD.[91] Unilateral infusion of 6-OHDA into the medial forebrain bundle leads to unilateral depletion of nigrostriatal DA neurons, followed by asymmetrical forelimb use, akinesia, and impaired placing. MPTP-induced parkinsonism induced by sequential intraperitoneal injections leads to a bilateral depletion of nigrostriatal DA neurons. The behavioral deficits resemble human parkinsonism; bradykinesia, hypokinesia, and akinesia and can be observed during open field activity monitoring and balance tasks (rotorod).

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

to which the behavioral characteristics and pathology mimic the human condition. For example, while the 6-OHDA model serves primarily as a model of striatal dopamine dysfunction, the MPTP model manifests alterations in other catcholaminergic neurons and neurotransmitter systems, more like the human condition. In both models, despite the cell death; partial or complete behavioral recovery occurs. This suggests these animals possess robust molecular mechanisms for plasticity in response to injury – which can be useful for studying the effect of exercise that may enhance recovery.[83, 91] The degree and time course of recovery is dose-dependent and varies across age, species and mode of toxin injections. Thus, it is important that recovery in exercised animals is always compared to recovery in exercised control groups to differentiate how exercise enhances the spontaneous recovery that occurs in controls.

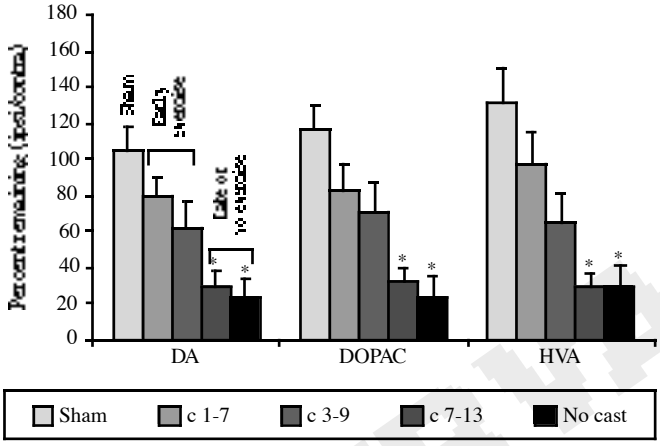

Figure 2.—Animals receiving early casts (days 1-7) and sham animals do not show significant differences in DA, DOPAC or HVA levels. Animals receiving casts on days 3-9 show intermediate DA levels, although still not significantly different from sham. Animals with late casts (days 7-13) and animals not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

Exercise as neuroprotection

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

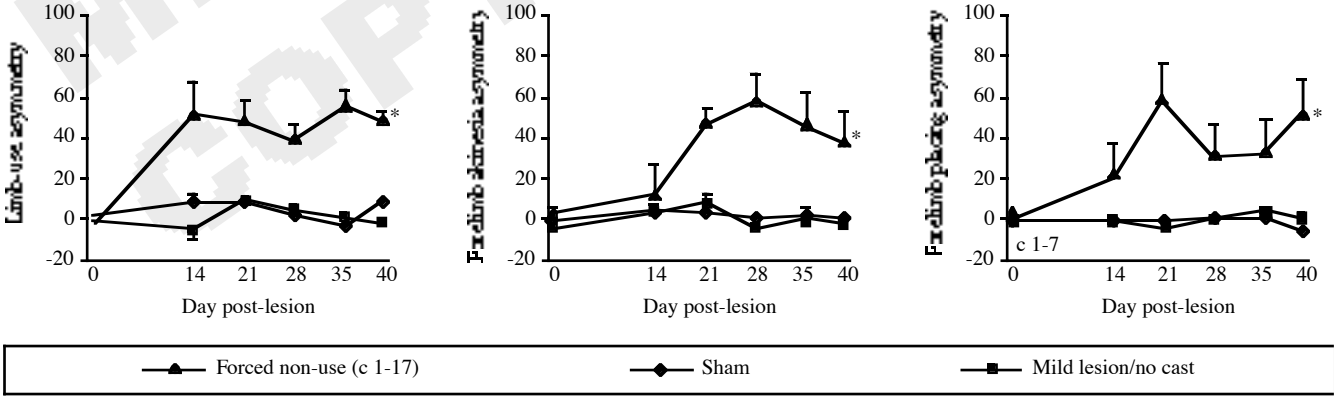

Figure 3.—Behavioral asymmetries after forced nonuse in animals with mild lesions. A) Animals given mild unilateral lesions did not display significant limb use asymmetry; when animals were forced to not use the impaired forelimb for the first 7 days after lesioning, they demonstrated limb use asymmetry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

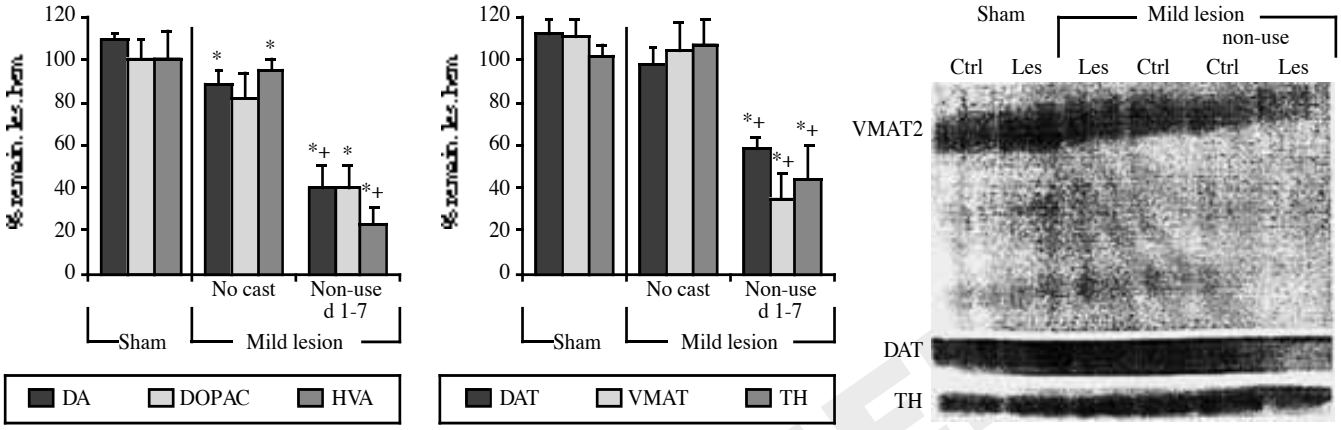

Figure 4.—Effect of forced nonuse of the impaired forelimb after mild 6-OHDA lesion. A) A 5 µg infusion of 6-OHDA resulted in only a mild loss of DA and HVA in striatal tissue when values were compared with the intact hemisphere; In contrast, forced nonuse of the impaired forelimb for the first 7 days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

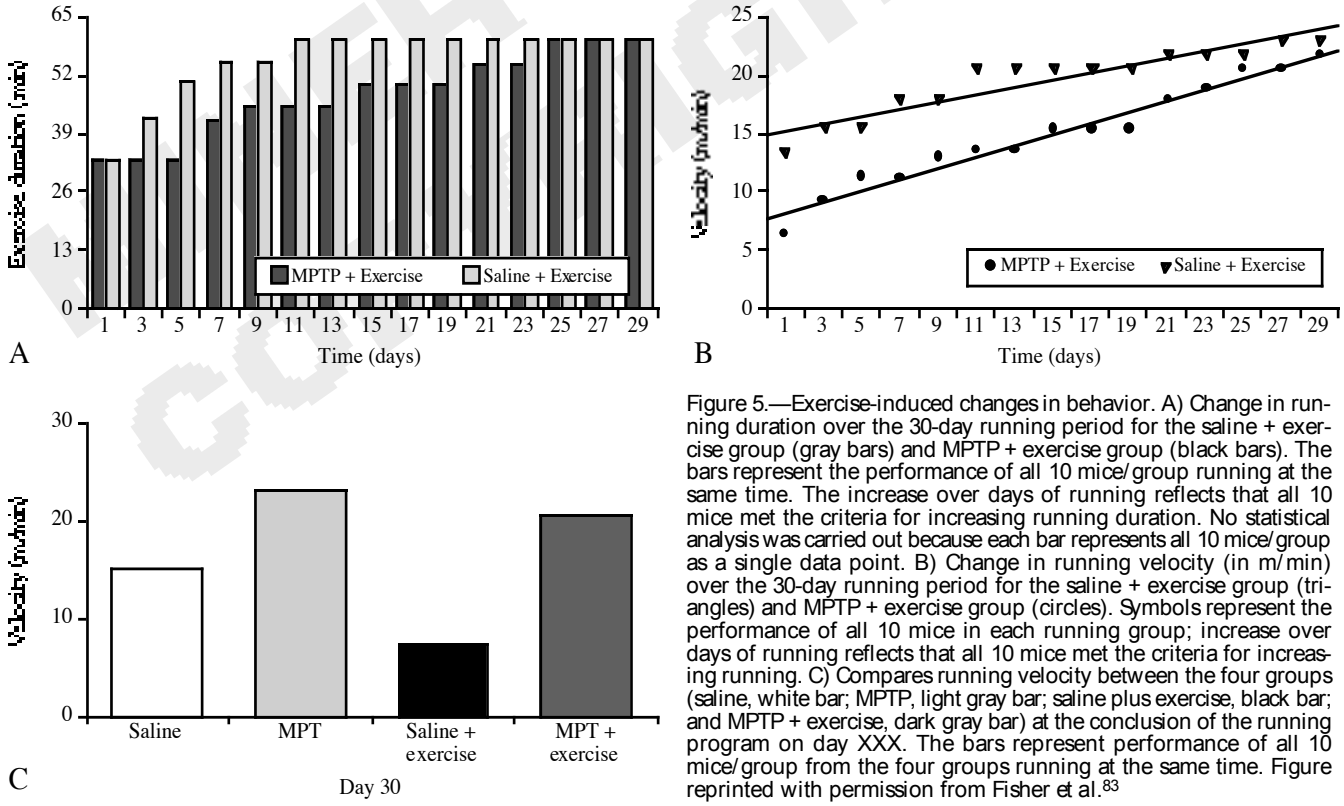

Figure 5.—Exercise-induced changes in behavior. A) Change in running duration over the 30-day running period for the saline + exercise group (gray bars) and MPTP + exercise group (black bars). The bars represent the performance of all 10 mice/group running at the same time. The increase over days of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

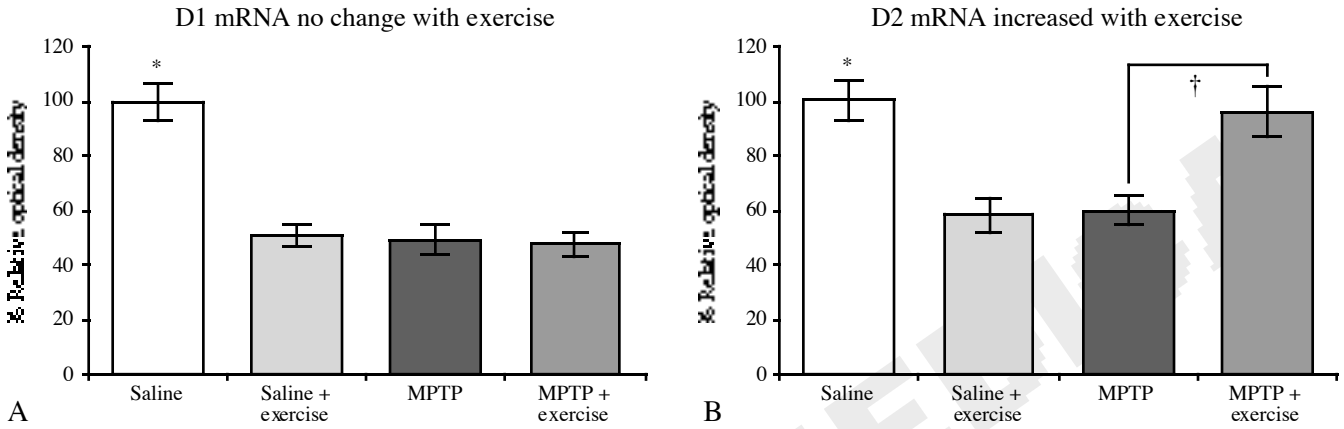

Figure 6.—Analysis of the relative striatal dopamine D1 and D2 receptor mRNA using in situ hybridization histochemistry. The relative optical density of autoradiographic grains above the dorsal striatum were determined from at least three mice from each treatment group using at least 12 sections/mouse.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

sham and no casts; sham and casts on postoperative days 1-7, or sham and casts on postoperative days 7-13). Casted groups were fit with plaster of Paris casts after surgery to immobilize the ipsilateral (non-impaired) forelimb for 7 days beginning 24 hours, 3 or 7 days postsurgery. Animals were then placed in their cages with playmates and forced to rely on their impaired forelimb during everyday exploration and movement. Neurochemical analyses for DA, DA metabolites (dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and vesicular monoamine transporter (VMAT2), a reliable marker for the integrity of DA terminals, were performed in the striatum of the lesioned hemisphere 65-80 days after surgery. Behavioral tests assessed forelimb asymmetry during: movement initiation (forelimb akinesia), voluntary exploration (limb-use asymmetry) and vibrissae-elicited placing (forelimb placing) and were performed before surgery and on days 14, 21, 28, 40 and 60 days after surgery. 6-OHDA lesions in uncasted animals caused chronic behavioral deficits and no neurochemical protection against the loss of striatal DA (Figures 1-2).[88] Early forced use (~24 hours) spared behavioral function and striatal DA levels, metabolites, and VMAT2 expression in the striatum (not shown here),[88] was no different than sham controls. Behavioral and neurochemical benefits were sustained across testing days despite removal of the cast after 7 days (Figure 1). In animals casted on days 3-9, the behavioral deficits were reduced during the period of forced-use, but gradually worsened over time, suggesting lingering asymmetry may have been exacerbated after removal of the cast. In contrast, in day 7-13 casted animals, behavioral deficits persisted. The degree of forelimb asymmetry was correlated with the level of DA (and metabolite) depletion. Altogether, those data suggest that exercise may delay or prevent PD in healthy individuals,[46] and in early PD, slow disease progression and thereby, motor deterioration.

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

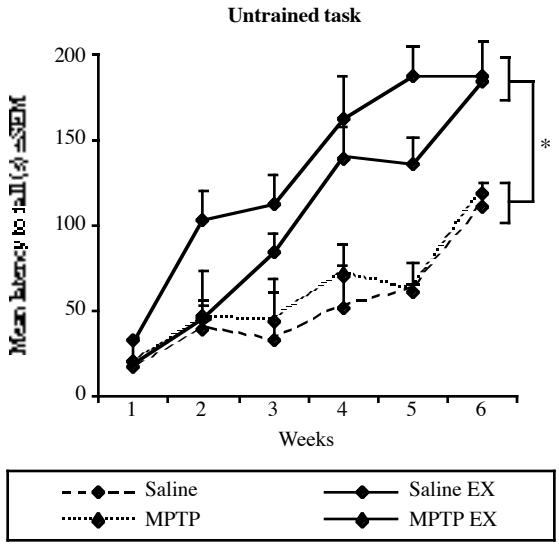

Figure 7.—Analysis of behavior on rotarod mice from all groups were tested once a week for latency to fall from an accelerating rotarod (mean and SEM in seconds per week). There was a significant effect of exercise (treadmill running) on the mean latency to fall (in seconds) from the accelerating rotarod,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

investigation, Cohen [85] demonstrated that a potent neurotrophic factor for the survival of DA neurons, glial cell line-derived neurotrophic factor (GDNF), was upregulated in the striatum corresponding to the exercised limb. More recently, exercise has been shown to induce the generation of GDNF producing cells (glia) in the substantial nigra where DA cells reside.[96] In summary, exercise may be prophylactic (preventative) and capable of protecting DA neurons from toxic events depending upon timing, severity of DA loss, and availability of neurotrophic factors. A combination of regimes (i.e., skilled learning vs aerobic training) may be better than one specific task to trigger multiple mechanisms (i.e., nourishing neurotrophic factor expression and focal synaptogenesis), and force continuous use of nigrostriatal circuits involved in a variety of salient behaviors to extend the neuroprotective benefits, and avoid their decline.

Inactivity as prodegenerative

As indicated above, a period of inactivity or stress may reverse the protection and behavioral benefits of exercise. In addition, decreased physical activity, which is often a precursor of the diagnosis of PD and worsened by the symptoms of bradykinesia, fatigue or weakness, may be prodegenerative, contributing to further motor deterioration and pathogenesis of PD. Using a forced nonuse paradigm, Tillerson [89] revealed that inactivity is not only a symptom of PD, but a catalyst in the degenerative process. Highlights from their study are illustrated in Figures 3,4.[89] Behavioral testing and neurochemical analysis was similar to their previously described forced-use experiments and also incuded neurochemical analysis of tyrosine hydroxylase (TH), a rate-limiting enzyme in DA biosynthesis. In this study animals were given a mild (preclinical) unilateral dose of 6-OHDA and then randomly assigned to sham (no cast or contralateral cast), mild lesion and no cast, or mild lesion and contralateral cast on days 1-7 (forced nonuse paradigm). Animals given a mild lesion with no activity restrictions (no cast) were no different from shams on limb use asymmetry tests or neurochemical indicators of striatal DA loss. These effects were sustained across testing, suggesting exercise (continuous normal use) protects DA neurons from the neurotoxic event. However, restricting activity of the impaired limb in animals immediately after a mild lesion triggered significant limb use asymmetry, exacerbated loss of striatal DA (and metabolites), and loss of DA terminals (VMAT2, DAT, TH protein were measured to provide an index of striatal DA terminal integrity).

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

require continuous normal use or exercise to be maintained.

Exercise and neurorestoration

In the previous mentioned studies [88-90] investigating exercise as neuroprotection, forced use or treadmill training exercise paradigms were begun immediately after neurotoxin injection (2 hours, 6-OHDA; 24 hours, MPTP). This resulted in sparing of behavioral function and striatal DA loss. Since 6-OHDA and MPTP neurotoxins take several days to complete DA cell death, exercise may have interfered with the uptake or metabolism of the neurotoxin or initiated molecular events that helped the cells survive. However, the fact that the withdrawal of exercise (forced non use) unmasked behavioral deficits and striatal DA loss after behavioral recovery in both a mild-lesion and severe lesion, suggests that a threshold level of normal use or activity is required to hold the degenerative processes at bay after exposure to a neurotoxin.

To investigate the neurorestorative effect of exercise on the injured PD brain, recent studies were conducted that manipulated 1) the timing of the start of exercise after nigrostriatal cell loss was complete; 2) the intensity of exercise; and 3) added exercise to control groups to compare the effect of exercise on the noninjured and injured brain.[83, 87] In the initial study, Fisher [83] initiated an intensive and progressive 30-day treadmill training protocol for both the saline controls and MPTP mice to reach a target goal (20.5 to 23 m/min; 30 min; 2x/day), 5 days after four intraperitoneal injections of MPTP. Using this administration protocol, cell death (60-70% loss) is complete by day 3 and persists beyond 30 days postlesioning. Despite a 90% loss of striatal DA, spontaneous behavioural recovery and partial restoration occurs 2-3 months postlesioning. Thus, the researcher's addressed the clinically relevant question if and how exercise may accelerate the restorative process that occurs spontaneously in these animals and how this process may differ between injured (MPTP) and noninjured brains exposed to exercise. Animals were randomized into four groups: MPTP with or without exercise and saline with or without exercise. Both exercised groups (MPTP and saline) significantly improved motor performance (duration and velocity of running) (Figure 5).[83] The MPTP exercise group reached the same maximal performance levels as the saline exercise group, although it took the MPTP group longer to reach this level (day 25 vs. day 11). However, the MPTP lesioned, non-exercised group, did not spontaneous improve motor performance over the 30 days (gait velocity on day 30 was no different from baseline) (data notshown here).

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

In a follow-up study, Petzinger [87] explored changes in the dopaminergic system both at the level of total striatal dopamine levels and localized release. The same intensive treadmill training protocol, group allocation, lesioning, etc, were followed as per the Fisher [83] study discussed above. In addition to behavioural improvements in running velocity, Petzinger et al.[87] demonstrated improvements on a transfer skill requiring balancing on an accelerating rod (rotarod). Following treadmill training, both the MPTP plus exercise and saline plus exercise animals stayed on the rotarod longer (increased latency of fall) (Figure 7). The improvements in motor performance on trained and untrained tasks was accompanied by improvements in overall striatal DA levels only in the saline

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

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

Conclusions

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

Future clinical and translational research of exercise and PT for PD should focus on several key areas. As health-care professionals, we have a tremendous opportunity and a duty to help educate our PD patients on the benefits of exercise. The scientific bases for exercise prescription in PD should be taught at medical and physiotherapy schools and residency programs. However, education and advocacy are not the sole responsibility of the diagnosing physician, but requires an ongoing team effort. The goal should be to educate all healthcare professionals about the benefits of exercise and PD, starting with physiatrists, neurologists, primary care physicians, therapists, and geriatricians as well as our policy makers and legislators. Just as physicians and physiotherapists perform a history and physical exam, every patient should be asked at every office visit about exercise. However, even if we encourage our PD patients to exercise, we still need to create safe places for them to exercise. One approach would be to develop community-based programs where people can exercise in science-based programs under appropriate supervision. However, presently few such efforts are underway. For example, the city of Charlotte, North Carolina is one of the largest cities in the state of North Carolina, USA, with a population of approximately 600 000. To date, there is one community-based exercise program for people with PD. Having one community-based facility that offers PD specific exercise programs is like having only one bank, one gas station or one grocery store. If this were the case, there would surely be public outrage. A good way to remedy the situation would be to develop a grass roots train-the-trainers program, so that any facility could develop a standardized PD exercise program in the persons' community. A few Parkinson's associations and individuals' in the United States and Europe have begun to develop such programs; however these efforts are isolated and poorly coordinated. Funding for these efforts is still limited. The success of these programs is certainly dependent on collaboration between all health care professionals, bench and applied researchers and will most certainly require support through policy makers and legislation that changes how rehabilitation and physiotherapy are applied in PD. Once places to exercise are established we must research their efficacy. The factors that encourage persons with PD to begin or end exercise, as well as the factors that encourage persons with PD to stay highly active, are still poorly understood.

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

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

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Community-based rehabilitation for Parkinson's disease: From neurons to neighborhoods

Mark A. Hirsch*

Carolinas Rehabilitation, Carolinas Medical Center, Department of Physical Medicine and Rehabilitation, Charlotte, NC, USA

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SUMMARY

This paper describes a model for developing early, community-based exercise interventions for people with Parkinson's disease (PD). The model being described is novel in that it advocates collaborative development of the program by multiple stakeholders (i.e., researchers, people with Parkinson's disease, caregivers, Parkinson's associations and healthcare providers), utilizing a community-based participatory research (CBPR) approach, and peer-to-peer training by caregivers and person's with PD. Opportunities and challenges of creating community-based exercise programs are discussed.

1. Introduction

Scholars agree that "more has been learned in the past 10 years about nerve cell recovery from injury than in the past 10 centuries" [1]. It is certainly true that exciting advances have been made in the neuroscience of rehabilitation. We are closer to understanding the molecular and behavioral mechanisms underlying exercise-induced neuroplasticity and are possibly approaching a paradigm shift how exercise is used as a physiologic tool to treat individuals with Parkinson's disease PD [2]. Animal models of PD and exercise now suggest intense sensorimotor training (a) triggers behavioral and biochemical recovery, (b) slows the disease progression and motor deterioration, (c) may be prophylactic (capable of protecting dopaminergic neurons and metabolites from toxic events), while (d) leading a sedentary lifestyle (inactivity) or stress may reverse the positive effects of exercise on the pathophysiology of the disease [3]. This evidence is beginning to be corroborated by high intensity studies with human PD [4–8]. These data suggest individuals at all stages of PD, who do not display contraindications to exercise, should be encouraged to exercise [9].

People with PD are more vulnerable to adopting a less physically active lifestyle after diagnosis than other populations so encouraging an active lifestyle at diagnosis is particularly important in PD. In PD sedentary lifestyles trigger functional impairments and an increased mortality rate [10,11]. The reasons why people with PD do not exercise are not understood and many questions remain. Do reduced physical activity (PA) levels precede the PD diagnosis or are they a result of basal ganglia pathology? To what extent do environmental factors – such as lack of opportunity to exercise – result in reduced exercise participation? If persons with PD and caregivers were more aware of the benefits of exercise and physicians began referring patients to exercise right after diagnosis, would this increase exercise participation? Difficulty with daily activities, walking and transferring are reported by patients at the early stages of the disease and the frequency of these reports increases with advancing disease and co-morbidities [12,13]. However, only a fraction of patients (34%, according to one study) are prescribed physical therapy or medication for PD within the first 6 months after initial PD diagnosis [14]. The animal data would suggest that failure to begin a high-intensity exercise program early after diagnosis or failure to exercise continuously are lost windows of opportunity.

People with PD could try to find opportunities to exercise in their community. However evidence suggests individuals with PD have difficulty accessing and participating in recreational and leisure activities in their community [15]. Data from a recent nationwide telephone poll on PA patterns among 197 persons with early to mid stage PD suggest less than 1% of persons with PD exercise at a community-based fitness facility (e.g., YMCA) while 87% of respondents reported they would be more likely to participate in regular exercise if they had access to a community-based PD exercise program [16].

2. Creating neuroplasticity- and evidence-based programs

A goal to strive for is to create evidence-based exercise programs that cater to the needs of all individuals with PD. Many PD exercise programs are on the market and some have not been tested scientifically for efficacy. There is also considerable debate about what constitutes efficacious treatment and no consensus on the

* Correspondence: Mark A. Hirsch, PhD, Carolinas Rehabilitation, Carolinas Medical Center, Department of Physical Medicine and Rehabilitation, 1100 Blythe Blvd, Charlotte, NC 28203, USA
Tel.: +1 704 355 7673.
E-mail address: mark.hirsch@carolinashealthcare.org (M.A. Hirsch).

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best mode, intensity or duration of exercise. Components of a PD exercise program could include education on the disease itself, general conditioning and impairment specific training. Exercise programs should also provide specific supports and strategies for avoiding inactivity.

The American College of Sports Medicine (ACSM) recommends PD exercise that "maintain strength and capacity to perform as many ADL's as possible" [17]. These may not be suitable goals for individuals who are in the early stages of the disease and who tend to be younger and have more physiologic reserve than those who are older and have more severe PD. As the animal and human data suggest, high intensity may ameliorate the signs and symptoms and neurometabolic pathophysiology of PD, while training at a lower intensity does not necessarily result in physiologic gains [3]. Unless training is oriented towards principles of motor learning, i.e., long enough to achieve gains, intensities are suitably high, exercise is salient to the individual, permits repetitive, task oriented practice of real world skills, and with appropriate feedback – some patients may not experience physiologic gains at all, and may, instead, become disenfranchised with exercise. This is exactly the situation we are trying to avoid. Any program that aims to be successful in the long run – should therefore try to provide an environment that fosters motor learning. Of interest, recent data suggest that once PD exercisers are enrolled in a program, social aspects of the exercise program, such as social interaction (i.e., exercising with other people who are living with the same disease), is a stronger predictor to *continue* an exercise program than an individuals motivation to improve muscle strength [18]. This data is consistent with studies suggesting social support as a strong predictor of exercise adherence among individuals with cerebral palsy, adults with multiple sclerosis, cystic fibrosis and cancer [19–22]. While evidence-based guidelines for prescribing PA for PD have been developed for physiotherapists, physiotherapists traditionally work with clients in the mid to late stages of the disease. Prescribing exercise according to these guidelines might not trigger exercise-induced neuroplasticity among persons at early stages of the disease. Furthermore, while research suggests certain modes of training are beneficial for motor and non-motor signs and symptoms of PD, not all training is equally beneficial, many training approaches are used without evidence for efficacy and few interventions have demonstrated a longer-term effect [3].

Because of the uncertainty associated with what constitutes the optimal mode and intensity to trigger physiologic gains, creating efficacious community-based exercise programs can become a long and arduous process. While there are evidence-based practice guidelines for physiotherapists, there are none geared towards staff at Parkinson's Association, PD foundations, consumers or community-organizations to develop community-based exercise interventions for people with PD. Without consumer guidelines to implement evidence-based programs it will be difficult to develop programs that are evidence-based.

Another important step in developing evidence- and community-based exercise programs is to survey the exercise needs and habits of people with PD in your community. Determine where people exercise, who exercises and who doesn't and why. This information could be useful to persuade administrators to allocate resources to develop a program. Determine available community infrastructure and resources (space, trained personnel etc). Are there facilities in the community that already offer exercise programs for special populations? If so, these facilities might make good partners. Which stages of PD should the program target? Are there staff in place that could potentially administer these programs? Also, facilities will be unlikely to develop new programs unless there is a reasonable return on investment. What incentives are in place to encourage staff to develop new exercise programs? Do facilities have the space and equipment needed to facilitate group and/or personal training? Could classes be held at specific times of day, in group or individual sessions, at peak or off-peak times, are adaptive equipment available?

3. Train-the-PD-trainer

The many needs of caregivers are rarely acknowledged in the literature on caregiving in PD and caregivers are rarely directly involved in providing exercise or physical therapy. Traditionally, this has been the domain of physical therapists. However, according to one study [16], nearly 90% of caregivers of persons with PD would be interested in exercising along with their partner if an exercise program for PD were available in their community. This is information that is key to developing community-based exercise programs because few facilities will have the staff to provide one-on-one training for all PD clients. Some organizations have now begun to recognize the potential contribution that caregivers can make and have begun to provide train-the-PD-trainer workshops to caregivers.

Since a majority of the care of community-dwelling individuals with PD usually falls on a family member anyway, training caregivers to provide supervision and encouragement during exercise seems like a natural extension. However, caregiving is associated with high levels of hypertension, and fatigue, has a deleterious effect on caregivers' mood, sleep patterns, cognition and disease related stress, results in feeling of loss of control and caregiver burden increases as the partners disease progresses [23]. Increasing caregiver duties to include exercise supervision may amplify these issues. However, regular (aerobic) exercise has positive effects on cognition and sleep, and may therefore be therapeutic in this situation. In one study, caregivers were used to monitor and correcting walking [24]. The researchers did not examine how this affected caregiver burden. In another study, carers and several person's with PD were utilized as trainers of persons with PD during a high intensity resistance and balance training program conducted at a public health club. One of the caregivers noted her experiences with exercise: "(because of the program) I am better able to take care of my husband (with stage III PD), feel more relaxed, am in a better mood, and less tired … my husband would not be where he is today without the training program" [25].

Another participant with young onset PD (Hoehn and Yahr stage 1) noted:

> "I was 52 years old when I was diagnosed with Parkinson's disease [in February of 2008]. I did not know what Parkinson's was. My wife and I began researching this condition on the Internet and I did not like what I was reading. My neurologist arranged for several sessions with a physical therapist to help my mobility. Then through a local support group I found out about the Parkinson's Early Intervention Exercise Program offered at the YMCA. I talked to my doctor about it and he agreed to refer me to the program. This was the beginning of a new chapter in my life. The program consisted of weight training, cardio exercise, and nutrition education. Of course, there was regular check-ins to record my progress. I was also lucky enough to meet [Dr. Hirsch] at one of the support group meetings. Through regular meetings with the training staff and additional more specific instructions from [Dr. Hirsch] I have adopted a new life style. Previously, I was not very active. I did some outside work around the house but nothing aerobic. Now I exercise regularly. My routine includes intense weight training, cycling (spinning) or other cardio work and of course watching what I eat. My wife had always been more "into" exercise than me. This change in lifestyle has also had a positive impact on her and our relationship. Now I feel better than I have felt in years.
>
> [Personal communication, 04/28/2009]

In this individual, exercise did enhance self-perceived control over the disease, consistent with reports among individuals with early PD that exercise confers a greater sense of control [26]. Exercise certainly seems to have been an empowering experience

for this individual who went from being fairly sedentary to leading an active lifestyle consisting of high intensity exercise 6 days per week at a local YMCA. When the individuals' children noticed the impact exercise had on their parents' relationship, they also began exercising and today the family exercises together. If we knew more about these family experiences, we might learn more about what motivates people with PD to continue to exercise.

Whether caregivers, persons with PD or other professionals provide supervision during training, trainers' knowledge of exercise physiology and their ability to use effective teaching and learning strategies are important if the program is to be successful. These skills can be learned by caregivers and individuals with PD who want to become PD trainers [25]. While there is ample scientific literature on effective teaching strategies when working with healthy adults, there is scant data on effective teaching strategies when working with people with PD [27]. Trainers may have limited experience working with individuals early after a PD diagnosis, or may have no experience at all. These issues need to be addressed before the program can be implemented.

There are no guidelines for credentialing peer-trainers (caregivers or persons with PD as trainers). Some Parkinson's Associations and Foundations offer train-the-PD-trainer workshops for caregivers. These efforts are poorly coordinated and no one offers training for persons with PD as personal trainers, an idea that was first piloted by our group in 1994 [27]. Sometimes train-the-PD-trainers workshops offer some type of certification. These workshops tend to be costly and some do not certify workshop participants unless they are licensed physiotherapists. Obviously, if this practice continues, it will limit the number of caregivers or other consumers getting credentialed and this will likely affect the number of persons with PD who can be served.

All trainers should undergo a train-the-PD-trainers workshop. Periodic refreshers should also be offered. The workshop curriculum should include training on exercise physiology and first aid as well as hands-on clinical training. Trainers could learn how to perform baseline evaluations, prescribe exercise, ensure exercises are conducted safely and effectively, and should be able to recognize emergency situations and take appropriate action when emergencies do occur during training. In addition, trainers should learn how to develop and administer programs that target the cardinal motor signs and symptoms including exercise prescription and evaluation of balance and/or gait impairment for the different stages of PD, as well as medication interactions and contraindications. For many trainers this will be unfamiliar territory. It is important to establish ties to the PD participants' primary care physician or neurologist to assist with the screening of participants that may have contraindications.

Another important question involves the issue of liability insurance [Becky G. Farley, personal communication, 09/24/2009]. Many, if not most centers should have adequate coverage in place for staff as well as personal trainers. However, what is the situation if family members, caregivers, or persons with PD – who are not on staff – function as personal trainers and an accident or injury occur? Some centers ask members to sign release waivers; however, this is an area that should be clarified before a peer-to-peer program is started.

4. Future directions

Accelerating the translation of medical research into the community is one of the central themes of the Obama administration healthcare reform. A variety of challenges must be overcome, including limited research on community-based exercise and PD, limited services directed to the needs of the PD community, and limited participation by communities in translating research into clinical practice.

In response to this situation, the US Department of Health and Human Services (DHHS) issued the Surgeon General's Call to Action [28]. The Call to Action emphasizes the critical role that community organizations play to increase PA behaviors among people with disabilities and recommends community-based organizations develop partnerships with researchers, people with disabilities and disability advocacy groups *to jointly develop community-based healthcare and wellness programs for people with disabilities and research their efficacy*. The Agency for Healthcare Research and Quality [29], Institute of Medicine [30] and the National Institutes of Health (NIH) [31] support the Surgeon General's Call to Action. The NIH supports community participation in research, termed, c*ommunity based participatory research* (CBPR). The NIH has issued several funding mechanisms to support researchers and communities develop infrastructure to, for example, develop community-based exercise programs using CBPR (http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-09-010.html).

CBPR is an approach to research that creates equitable partnerships between patients, physicians and communities. During CBPR stakeholders are empowered to participate in all aspects of medical research from grant writing, collecting data, data analysis and interpretation and dissemination. The advantages to doing CBPR are that it produces rapid translation of research into practice. CBPR is useful in projects trying to bridge the gap between medical centers and the community and can be very useful in improving continuity and quality of care. CBPR builds community capacity and sustainability and adds validity to the study results.

CBPR could be used to increase public awareness and education about PD, teach communities that exercise is neuroprotective and neurorestorative in PD, that it fosters control over the disease and that inactivity is pro-degenerative. While CBPR holds tremendous promise in the area of community-based exercise, CBPR has rarely been used in neurological populations and has never been used in PD. Workshops on conducting CBPR with the aim of developing sustainable avenues for exercise will help physicians, researchers and communities become more aware of the potentials of community-based exercise for PD and of the use of CBPR.

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Conflict of interests

None declared.

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What's Hot in Parkinson's Disease Column
February 2009

Breaking a Sweat: Is Exercise On Its Way Back Into the Armamentarium for Treatment and Protection Against Parkinson's Disease?

Michael S. Okun, M.D.
National Medical Director, National Parkinson Foundation

Many years before adequate medication treatments were developed to address the symptoms of Parkinson's disease, some doctors recommended exercise, staying busy, and when engaging in activities being as "physical" as possible. There are stories of institutionalized Parkinson's disease patients (prior to the levodopa era) who were asked to push the chart cart for doctors on rounds, or to fold towels for hospital staff. Early observations about improvement in Parkinson's disease patients following task specific physical exertion have contributed to the belief that exercise may be beneficial. For years in my own practice, I have expressed to patients that exercise is "like a drug," and that a daily stretching and exercise routine may be of significant benefit. I have also noticed that patients who receive physical therapy the hour prior to their appointment with me, seem brighter and more optimistic. Though, I personally believe in exercise for Parkinson's sufferers, we have until now, lacked a strong scientific rationale to prescribe it.

Smith and Zigmond reviewed the topic of whether exercise could be neuroprotective or disease modifying in Parkinson's disease in article in Experimental Neurology. These investigators began studying the effects of exercise in a 6-hydroxydopamine model of Parkinson's disease in the animal. Forced exercise in their animals seemed to reduce their vulnerability to developing Parkinson's disease symptoms. They speculated that exercise increased certain chemicals in the brain called trophic factors, and this change may have resulted in protection of brain cells(Smith and Zigmond 2003).

Beth Fisher and colleagues have now moved their research group's recent observations on exercise and Parkinson's disease from an animal model into a human study. Published in July 2008 in the Archives of Physical Medicine and Rehabilitation, this group aimed to "obtain preliminary data on the effects of high-intensity exercise on functional performance in people with Parkinson's disease." They also wanted to determine whether improved performance was accompanied by positive physiological alterations in the brain. In this study there was a small improvement in the motor subscale for Parkinson's disease (called the UPDRS). More importantly though, "the high-intensity group of subjects showed post-exercise increases in gait speed, step and stride length, and hip and ankle joint excursion during self-selected and fast gait and improved weight distribution during sit-to-stand tasks. Improvements in gait and sit-to-stand measures were not consistently observed in low- and zero-intensity exercise groups. The high-intensity group also revealed positive physiological changes in the brain." The findings were supportive of symptomatic benefits, particularly with high intensity

exercise. Perhaps we should be telling our patients that regardless of the exercise program, they need to break a sweat!

Canning, Murray and colleagues reported in the January issue of the Journal BMC Neurology their intentions of performing a randomized study of fall prevention in Parkinson's disease utilizing exercise as their intervention. "The main objective of this randomized controlled trial (of 230 patients) will be to determine whether fall rates can be reduced in people with Parkinson's disease using exercise-- targeting three potentially remediable risk factors for falls (reduced balance, reduced leg muscle strength and freezing of gait). In addition we will establish the cost effectiveness of the exercise program from the health provider's perspective." Participants will be randomly allocated to a usual-care control group or an intervention group which will undertake weight-bearing balance and strengthening exercises and use cueing strategies to address freezing of gait. The intervention group will choose between the home-based or support group-based modes of the program(Canning, Sherrington et al. 2009)." This large study will address symptomatic benefits of exercise, especially with falling.

Nowadays in Parkinson's practices all over the world, exercise is being prescribed more and more. The evidence trail seems to be pointing toward beneficial effects, but more studies are needed. Hopefully these studies will reveal to us what kind of exercise, at what intensity, and at what frequency will be best. Although many practitioners believe that prescribing exercise earlier in the course of Parkinson's disease may yield disease modifying or neuroprotective benefits, this remains unknown (Fisher, Wu et al. 2008). Exercise seems to offer the possibility of both motor and non-motor benefits, as well as general health benefits--- it is therefore reasonable to consider a daily exercise program but remember, if you don't break a sweat it probably doesn't count as exercise!

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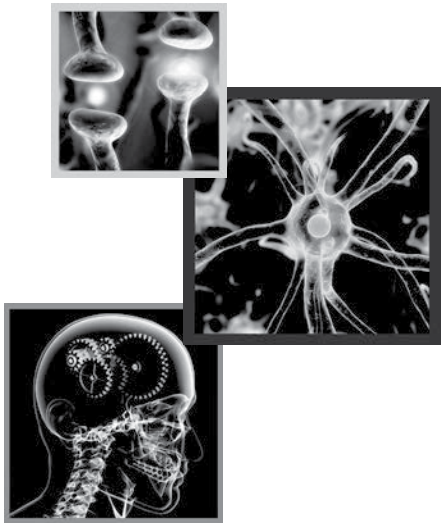
SPECIAL REPORT

Promoting exercise in Parkinson's disease through community-based-participatory-research



Mark A Hirsch[†1], Sanjay S Iyer[2], Danielle Englert[2] & Mohammed Sanjak[2]

Practice Points

- Physical therapy and exercise interventions are important adjunctive treatments in Parkinson's disease (PD).
- Animal data suggest physical activity is associated with neuroplasticity mechanisms. Some studies of exercise and PD demonstrate a lack of neuroplasticity with or without behavioral recovery. More research is necessary in this area.
- At diagnosis and at every office visit, physicians should talk to their patients about exercise interventions and of the potential dangers of inactivity.
- At diagnosis, referrals to physiotherapy and community-based exercise programs should be made where patients exercise under appropriate supervision.
- Healthcare professionals should partner with community-based wellness facilities and should participate in development and implementation of exercise interventions for patients with PD who do not exhibit contraindications to exercise.
- Healthcare professionals, patients and other stakeholders should partner in community-based participatory research interventions.

SUMMARY Parkinson's disease (PD) is a chronic, progressive, as-of-yet incurable, neurodegenerative condition affecting the nigro–striatal dopaminergic system. Emerging evidence suggests the importance of exercise in improving the trajectory of PD. Yet few people with PD are physically active. One challenge that healthcare professionals face in the 21st century is how to deliver physical activity programs to the population of individuals living with PD. A novel approach to delivering physical activity to people with PD is introduced – termed community-based participatory research (CBPR) – which engages people with PD and patient advocates as co-researchers in the development and implementation of community-based exercise programs. The authors describe the CBPR approach and provide several recent examples of community exercise programs that are steps in the direction of developing the CBPR model. This is followed by a discussion of what a more fully realized CBPR model might look like. Finally, the authors describe some obstacles to conducting CBPR and suggest strategies for overcoming them. It is argued that people with PD are an integral component of delivering the exercise intervention.

[1]Carolinas Rehabilitation, Department of Physical Medicine & Rehabilitation, 1100 Blythe Blvd, Charlotte, NC 28203, USA
[2]Carolinas Medical Center, Department of Neurology, Center for Parkinson's Disease & Movement Disorders & Carolinas Neuromuscular/ALS-MDA Center, 1010 Edgehill Rd North, Charlotte, NC 28207, USA
[†]Author for correspondence: Tel.: +1 704 355 7673; Fax: +1 704 355 0709; mark.hirsch@carolinashealthcare.org

part of Future Medicine fsg

We believe that one of the most pressing challenges healthcare professionals face in the 21st century is how to deliver physical activity programs to the individuals living with Parkinson's disease (PD). In this article, we introduce a novel approach to delivering physical activity to people with PD – termed community-based participatory research (CBPR) – which engages people with PD and patient-advocates as co-researchers in the development and implementation of community-based exercise programs. In the first section, we present neuroscience evidence supporting the importance of exercise in improving the trajectory of PD and review the literature on physical activity levels of individuals with PD. We will then describe the CBPR approach and provide several recent examples of community exercise programs that are steps in the direction of developing the CBPR model. This is followed by a discussion of what a more fully realized CBPR model might look like. Finally, we describe some obstacles to conducting CBPR and suggest strategies for overcoming them.

Parkinson's disease is a chronic, progressive, as-of-yet incurable, neurodegenerative condition affecting the nigro–striatal dopaminergic system, with effects on motor, cognitive, social and emotional domains [1]. Treatment includes administration of medication (levodopa and other dopaminergic agents) and, in the later stages of the disease, neurosurgical approaches such as deep brain stimulation (DBS). Levodopa and neurosurgery have revolutionized the treatment of PD, but there are no established therapies that can stop or slow the underlying neurodegenerative disease process.

Exercise treatment

Historically, nonpharmacological approaches such as exercise or physiotherapy have been viewed as 'adjunctive' (i.e., helpful) in the management of PD. There is ongoing debate as to the efficacy of exercise or physiotherapy [2–5]. A rich vein of evidence now suggests that exercise or physiotherapy have positive effects on PD function including physiologic capacity, gait, balance, range of motion, muscle strength, cognition and quality of life [6–10]. Gait and balance impairment, the cardinal motor features of PD that generally become more prominent with disease severity, are associated with increased mortality [11,12]. Recently, the American Academy of Neurology Quality Standards Subcommittee noted that "exercise may be helpful in improving motor function in people with PD" [13]. While the evidence that exercise or physiotherapy are beneficial for PD is certainly a cause for hope, slowing down of disease progression remains a major unmet need in PD therapy [14,15]. Even with optimal pharmacological and surgical intervention, scholars believe that the underlying disease process inevitably progresses, resulting in increased disability in most PD patients over time [16].

Recent, groundbreaking neuroscience studies using animal models of exercise and PD seriously challenges this view of PD suggesting the physiologic use of exercise may be a curative model (Box 1). Together, the animal studies suggest that forced and/or voluntary exercise interventions confer neuroprotective and neurorestorative effects on nigro–striatal circuitry with or

Box 1. Plasticity mechanisms in animal models of Parkinson's disease and exercise.

Exercise-induced upregulation of *D2* mRNA, downregulation of DAT and increased dopamine release in dorsolateral striatum [66–68].
Exercise-induced sparing of striatal DA neurons and metabolites [69–71].
Exacerbated loss of striatal DA levels, metabolites and DA terminals with forced nonuse [72].
Exercise-induced increase in *GDNF* mRNA with downregulation of striatal *DAT* and *VMAT2* [73].
Parkinson's disease is characterized by reduced levels of GDNF [74].
Exercise-induced upregulation of striatal GDNF and production of GDNF producing cells (glia) and prevention of downregulation of BDNF signaling pathway in SN and striatum [75–77].
Exercise-induced partial restoration of TH-labeled neurons in SNpc [78].
Lower net DA SNpc neuronal loss with environmental enrichment [79].
Exercise-induced increase in net DA SNpc neurons [80].
Exercise-induced improved mitochondrial function [81].
Exercise-induced striatal angiogenesis [82].
Exercise-induced improved forelimb function without sparing of DA terminals [83].
Exercise-induced loss of TH positive neurons in SNpc [84].
Exercise-induced cardiorespiratory and metabolic adaptations without effects on nigrostriatal DA function [85].
Exercise induced reduction in DA loss without amelioration of behavioral deficits [86].

BDNF: Brain-derived neurotrophic factor; D2: Dopamine receptor type 2 (DA-D2R); DA: Dopaminergic; DAT: Dopamine transporter; GDNF: Glia cell line-derived neurotrophic factor; VMAT2: Vesicular monoamine transporter; SN: Substatia nigra; SNpc: Substantia nigra pars compacta. TH: Tyrosine hydroxylase.

without behavioral recovery [17–19]. Studies using the potent neurotoxins, 6-hydroxydopamine in rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice, report intense, continuous sensorimotor training before or after diagnosis can alter the neurodegenerative and behavioral effects of these toxic agents, while inactivity may be prodegenerative (i.e., amplify the neurodegenerative disease progression).

The mechanisms underlying the effects of exercise-induced neuroplasticity or behavioral recovery in animal models of exercise and PD are yet to be fully understood [19]. Some of the animal studies of exercise and PD suggest neuroprotective or neurorestorative effects of exercise, while other studies suggest behavioral effects without neuroplasticity. Part of the difficulty in generating conclusions from these divergent results may be owing to methodological issues, differences in studies' experimental design, amount or location of neurotoxin used, the timing, mode or amount of exercise, or the animals' age or gender (for overview see [20–23]). While insights from the animal models await replication in human trials, and this may take years, the value of animal models of exercise and PD is that they may lead to new treatment directions. If exercise is as important as the animal studies hint, one of the pressing issues at hand is how to ensure that patients at all stages of PD become more physically active [24,25]. Optimal care which includes development of exercise infrastructure administered by multidisciplinary healthcare teams is one option [24,25]. However, these approaches share a common theme: they place the patient as more-or-less passive recipient of care and not as an active leader. In this article, we describe a novel approach to multidisciplinary care that aims to empower patients as equal partners in all aspects of their care and also may increase physical activity seeking behaviors (Figure 1).

Exercise levels

There is a small but growing number of studies on physical activity levels in PD. Animal models hinted that 'the amount of voluntary physical activity is regulated at least in part by the dopamine system' [26], and now studies in human PD suggest people with PD are prone to exhibiting a more or less sedentary lifestyle [27–31]. In one of the largest studies on daily physical activity patterns that included 699 patients with PD and 1959 controls, Nimwegen and colleagues [28] report those with PD were 29% less physically active than healthy controls. In an ongoing study by Nimwegen and colleagues (the ParkFit trial [32]), 64% of participants with PD (mean age = 64.1 years, SD = 7.6 years; Hoehn and Yahr [33] stage ≤3), who were screened for physical activity levels at baseline, were classified as being 'sedentary'. This was defined by the authors using standardized criteria as: less than three times a week of vigorous-intensity physical activity for <60 min; or <three times a week moderate-intensity physical activity for <150 min [34]. Busse and colleagues [29] report reduced 7-day physical activity patterns (measured by step activity monitor) among adults with neurological conditions compared with healthy controls. The ten PD patients in their study had lower step/day counts than healthy adult control subjects. Using accelerometers, Hale and colleagues [30] extended these results demonstrating that people with PD are less physically active than even healthy sedentary adults (Figure 1) [30].

Functional factors

With little research having been conducted on physical activity in PD, factors associated with physical activity levels remain elusive. A number of studies [32,35] report high correlations between number of daily steps taken, postural instability and disease severity, with the lowest number of steps taken among patients at mid to higher disease stage (stage 3 and 4). Mak and Pang [35] and Garber [36] report that low scores on standardized measures of PD balance and balance self-efficacy correlate with less distance walked on a standardized test of walking (6-min walk test). Jones and colleagues postulate that cardinal motor characteristics of PD such as step-hesitation, freezing and problems with balance and dyskinesias may interfere with physical activity seeking behaviors [37]. The authors qualitative study investigated the experiences (e.g., patients' thoughts and feelings) associated with walking among people with PD. Patients experienced walking as an integral component of their self-esteem and independence, and identified walking as integral to their connection with society and feeling like a human being. Results suggest people with PD dislike walking in public, especially negotiating stairs and walking in crowded environments, with the greatest concerns expressed over problems with balance, which could be misconstrued as drunkenness [37]. Prior studies have reported associations

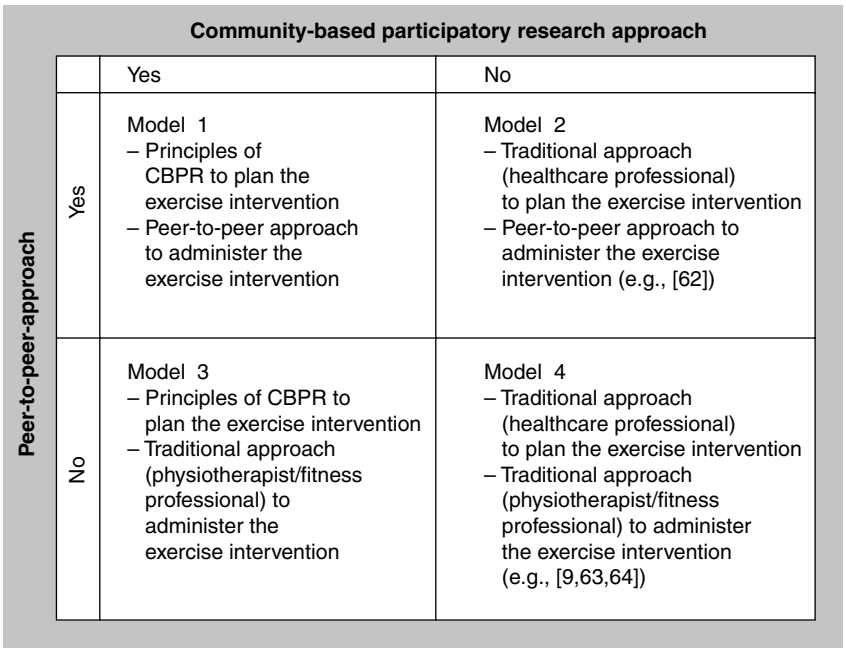


Figure 1. Models to plan and deliver community-based exercise interventions for people living with Parkinson's disease.
CBPR: Community-based participatory research.

between PD, fears of being publicly humiliated [38] and anxiety over interacting socially [39]. These fears are understandable as individuals who might be trying to conceal their symptoms in public settings might be experiencing considerable anxiety and would be less likely to exercise in public. These factors could be exacerbated in community-based public health settings unless strategies are taken to address them.

Several studies report associations between physical fatigue, one of the most disabling symptoms of PD [42], and physical activity levels across disease severity [36,40,41]. Using activity monitors, Rochester and colleagues report patients with PD spent a significant portion of their time sedentary – and these patients displayed the greatest amount of physical fatigue on standardized tests but no statistical relationship was noted between fatigue and physical activity (walking) [41]. Using a cross-sectional design with self-report and standardized measures of physical function, Garber and Friedman report high levels of fatigue correlated with low performance on physical capacity (i.e., maximal oxygen consumption) and associations between high levels of leisure activity and low levels of fatigue [36]. In a recent prospective, longitudinal study on the effect of cueing training in PD [43] in which patients wore activity monitors for 12 weeks, Elbers and colleagues developed a mathematical model of fatigue and physical activity [40]. The authors found greater amounts of fatigue associated with getting less physical activity, however, fatigue explained only 2% of the variability in the amount of physical activity [40]. The authors did not report if the cueing intervention resulted in greater physical activity levels.

One logical avenue to increasing physical activity would be through referrals. Haas and Okun add the following: "most patients with PD are treated by clinicians without specific PD-based training" [25]. According to one study, 25% of PD treating neurologists fails to talk to their PD patients about leading a physically active lifestyle [101]. In addition, "in reality, many patients have limited access to PD services" [25]. Only 34% of PD patients are prescribed medication or physical therapy at diagnosis or within the first year [44], and patients with PD lack awareness for the places in their community to participate in exercise [45,46].

Therefore, people with PD are at special risk toward inactivity and low physical activity levels are an early and ongoing feature of PD. If this situation does not improve, communities with PD could stay disenfranchised from exercise.

Future perspective

A vital component to improving healthcare among people with PD is to educate the community about evidence-based treatment such as exercise, and at the same time, it is important to test the efficacy of exercise intervention for PD, which involves the PD patients themselves as equal partners in the delivery of the interventions (Figure 1). We question whether it is enough for healthcare professionals to ask patients whether or not they exercise and then to expect them to do it, or to send patients home with a brochure or a booklet with community resources and then to hope for the best. We believe that substantial investments in community-based infrastructure – supportive and empowering places to exercise – and novel strategies for developing and implementing community-based exercise programs are necessary if we are to expect individuals with PD to exercise for the long-term starting at diagnosis, and, we must all work together in multidisciplinary rehabilitation teams with patients and patient advocates in order to achieve this vision.

Why is greater patient involvement in delivery of exercise interventions necessary? In most developed countries, populations of older adults

will continue to grow well into the middle of the 21st century, and it is feared that the number of older adults will far outgrow the number of physicians and other allied healthcare professionals needed to provide high-quality care for people with PD [47,48]. With the looming caregiver and professional shortages, we argue that one avenue to solving the problem is to develop collaborative efforts involving the multiple lay stakeholders (e.g., patient, care-partner or fitness professionals) to develop and implement community-placed exercise interventions. We are concerned that ultimately, our inability to develop collaborative efforts leaves populations with PD with limited resources **(Table 1 & Figure 2)**.

In the following section, we highlight recent initiatives that could serve as potential blueprints for developing community-placed exercise interventions. There were reasons that were felt to be important as to why these models were chosen for highlighting and not others. The efforts we describe represent an emerging paradigm change in the delivery of health services. This change involves administration of therapy according to evidence-based guidelines of physiotherapy for PD with collaboration by lay-experts. We wish to emphasize that the models are not directly related to the discussion of the PD animal models of exercise but serve as potential models for population-wide programs to empower patients with PD to lead more physically active lifestyles. The amount of detail provided by the models is felt to be a very important reason as to why these initiatives were chosen and not others, as it is felt that the amount of detail provided about the components of the intervention facilitates translation to the community level.

While there is a growing number of well-designed studies on the efficacy of physiotherapy for PD, the field of physical therapy or exercise for PD is marked by a dearth of studies examining implementation of evidence-based knowledge to the community level. In one of the handful of studies examining whether the physical activity patterns of the PD populations could be affected by an intervention, Rochester and colleagues used objective measures (accelerometers) to examine physical activity levels (defined as the continuous sequence of periods spent sitting/lying, standing and walking at different cadences) [49] before and after DBS of the subthalamic nucleus. A total of 6 months after DBS surgery, there was no change in the patients' volume of physical activity.

Other recent approaches aim to increase physical activity behaviors of patients by making evidence-based physiotherapeutic treatment more accessible by providing services in the patients' home, neighborhood community, instead of the traditional approach of providing services linked to the clinic or hospital. The ParkinsonNet cluster randomized controlled trial is the first and largest study of its kind to bring evidence-based physiotherapy to neighborhoods [50]. Elements of the ParkinsonNet initiative are described in detail in the following section, of which include [51]:

- Training of physiotherapists through intensive training workshops according to Dutch evidence-based physiotherapy guidelines
- Facilitating communication and collaboration with referring physicians by developing standardized forms to improve the referral into physiotherapy
- Web-based and educational materials accessible to patients and healthcare professionals

Results of the ParkinsonNet initiative include reduced healthcare costs among ParkinsonNet clusters compared with patients treated with the usual care [50]; as well as improved PD-specific knowledge of evidence-based care among healthcare professionals involved; enhanced referral process; increased patient volume per treating therapist; and enhanced stakeholder collaboration (cited in [24]). The physiotherapeutic training of the ParkinsonNet professionals, who were licensed physical therapists, was provided by physicians and physical therapists (for more information, see [102] and for practical guidelines to the Dutch evidence-based recommendations for physiotherapy in PD, see [103]).

Using the ParkinsonNet infrastructure [51], the Dutch group followed up with ParkFit [32], a 2-year multicenter, randomized controlled, single-blind trial with 586 sedentary PD patients enrolled. The primary outcome variable of ParkFit is to increase voluntary physical activity [32]. Secondary outcomes are to monitor the effect of exercise on standardized measures of disease progression (United Parkinson's Disease Rating Scale [UPDRS]), gait, fatigue, anxiety, depression, bone mineral density, aerobic fitness, falls, quality of life and healthcare utilization. Participants are screened for contraindications and randomized into one of two interventions:

Table 1. Potential obstacles to conducting community-based participatory research.

Potential obstacle to conducting CBPR	Suggestions for addressing obstacles
The true needs of the community are rarely known to researchers	Healthcare professionals could make efforts to get involved politically as patient advocates in Parkinson's policy (such as the Parkinson Action Network, in the USA) or, at the local level, with community organizations (i.e., local or national Parkinson Associations, disability-rights groups), volunteering time to serve on association boards and attending board functions to get to know the issues facing the Parkinson's disease community with translation of programs into policies. Healthcare professionals could make efforts to regularly attend Parkinson support group meetings, interact with support group leaders, patients, care-partners and their families. These social interactions can give academicians and clinicians a ground-zero view of the lives of people with PD from the perspectives of the patients and the care-partners own experiences. These are valuable opportunities for developing research partnerships that healthcare professionals and researchers might not otherwise have.
Researchers may be unaware of CBPR resources (e.g., funding mechanisms or people in their community currently conducting CBPR)	Contact community-based participatory researchers in your community by signing up to the CCPH blog and information on their website [109]. To obtain a list of federally funded North American community-based participatory research projects and principal investigators, the NIH maintains a search engine, the Research Portfolio Online Searching Tool [108]. Using keywords, 'community-based participatory research' or CBPR, current and past grant awards can be searched online. Examples of federal and foundation supports for CBPR funding include: – National Institute for Health Research (UK) website promoting public involvement in public health and social care research [110] – Agency for Healthcare Research and Quality (USA) [111] – WK Kellogg Foundation (USA) [112] – CDC (USA) [114]
Communities are rarely aware of the research interests of researchers or of the research infrastructure that is available right in their own community	Solicit research ideas by organizing regular town hall meeting or focus groups attended by community leaders. These meetings and agendas should be cofacilitated by researchers and patients. These could aim to identify research topics and research questions of importance to the stakeholders. Develop interactive worldwide web sites or blogs and invite consumers and researchers to interact for the purpose of generating ideas for research.
CAB	A basic element of CBPR is the formation of a CAB comprised of community leaders, patients, patient advocates and other key stakeholders who provide leadership to the study. CABs could meet monthly throughout the year. For a synthesis of best practices of developing CABs in public health research settings, see the following citation [114].
Professionals use technical language (i.e., postural reflex impairment, dyskinesia etc.) or specialized phrasing (e.g., statistical power, external validity and sampling strategy). This may potentially disenfranchise consumers from partnering with researchers in the research process	In planning community-based participatory projects, it is important to provide consumer educational workshops on research methods (data collection, data analysis, data interpretation). While conducting these workshops for consumers (with intact CNSs) might be challenging enough, designing teaching and learning curricula for people with PD – who may have cognitive and communication impairments – adds further layers of complexity to teaching research skills.
A key element of a successful CBPR project is to capture the degree of shared decision making during the research project	Team meetings could be cofacilitated/cochaired by healthcare providers/researchers and patients; team meeting agendas can be developed with substantial input from nonresearchers, and at the end of each team meeting, anonymous questionnaires to determine team members' satisfaction with the amount and quality of participation could be administered. Meeting minutes should be kept and distributed to the group following the meetings. Team meetings could be audio taped or video taped and transcribed. The transcripts could be examined and analyzed for the level of participation using participatory codes. Ensure that the CAB is comprised of mostly patients and community leader representatives. Ensure that the research team committee has consumer and community leader representation.

CAB: Community advisory board; CBPR: Community-based participatory research; CCPH: Community-Campus for Health Partnership.

- Physical therapy focusing on training on how to become more physically active (ParkFit)
- Physical therapy with focus on safety and quality of movement (ParkSafe)

In both interventions, patients are treated by ParkinsonNet experienced physiotherapists in years 1 and 2, they receive equal number of sessions, brochures with educational materials and a biannual newsletter. In ParkFit, patients interact with therapists schooled in evidence-based behavior modification strategies using the transtheoretical model of health behavior change; they receive educational brochures listing specific exercises, specific strategies to overcome barriers to increasing physical activity in the community such as education about the advantages of leading a physically active life and the dangers of inactivity, encouraging patients to set goals and develop social alliances, and a behavioral health contract, which the patient and the therapist sign before the program begins (for further details on treatment procedure, see [32]).

We believe that community-based exercise provides opportunities for developing social networks that might not develop as readily in clinic or hospital-based settings. Research suggests that social networking may increase physical activity participation in the early stages of the disease [52] and broadening the social network may result in improved compliance with exercise, reduced anxiety or phobic behavior; however, studies have not examined this. In ParkFit, patients interact with a physical therapist who is assigned as a lifestyle coach to the participant, who guides the participant in making healthy lifestyle choices and partake in personal training sessions. Patients are trained in exercise goal setting and they receive an ambulatory biofeedback activity monitor with access to a website to track their physical activity patterns to compare results with others. Hopefully, this will provide feedback on the individuals amount of physical activity in comparison with others in the trial and could serve as a further motivator to engage in social networks with a more motivated physical activity-seeking behavior. In ParkSafe, patients receive educational brochures on the benefits of exercise, safety and aims of physical therapy, and are assigned a physical therapist who treats the patient according to agreed upon goals (for further details and rationale of the interventions, see [32]).

Figure 2. Peer trainers with Parkinson's disease are members of the community-based participatory research team. The photograph shows two individuals with Parkinson's disease who participated in the first authors randomized controlled trial on high-intensity resistance (80% of a four repetition maximum was defined as high-intensity resistance training) and balance training [62]. The study took place at a public fitness facility in Tallahassee, FL, USA. Clinicians might shudder at the thought of two patients serving as peer-trainers. The photograph shows two individuals; one individual is on the foam, while the other individual is leading the balance intervention. At the time the photograph was taken, both individuals were at Hoehn and Yahr stage 2. The photograph is shows the feasibility of implementing research models that incorporate traditional approaches to planning the exercise program and utilize nontraditional (e.g., peer-to-peer) approaches to deliver the exercise intervention (model 2, Figure 1). We wish to emphasize that there are other important models of community-based exercise that are emerging in the literature that are important (for examples see Gruber [63] who uses physioptherapists as personal trainers or King and Horak [64] who employ trained exercise professionals as personal trainers (presumably model 4, Figure 1).
Reproduced with permission from [65].

We believe that initiatives such as those previously mentioned should definitely be developed in other healthcare system. However, caution is warranted when translating the ParkinsonNet model directly to other population regions. Future studies should examine how successful ParkinsonNet initiatives are when implemented in more densely populated regions. With 16,485 square miles, The Netherlands is approximately the size of the state of Maryland (MD, USA) and half the size of the state of South Carolina (SC, USA) but has a higher population density (over three times the population of Maryland). So the generalizability of the ParkinsonNet concept might be more applicable to densely populated regions where there is a greater number of physiotherapists per capita, more access to public transportation, and in which patients have shorter travelling time to the therapists, which might increase compliance. Public transportation in the USA, for example, is not as plentiful as in some other European countries. In some communities, individuals with PD may live in more rural settings, with fewer resources available (i.e., lack of public transportation). Future studies will need to be conducted to investigate whether the ParkinsonNet concept can be applied in these remote settings.

Community-based participatory approaches

'Community' may be defined by geographic location, as the place where individuals live, work, play or study. Other definitions of community might be any group with common interests, including sexual orientation, religious, ethnic or political affiliation, medical specialty, disease or diagnosis [104]. A hallmark feature of medical care is that lay-communities are often not as directly involved in decisions about their disease management as clinicians would like them to be. In our opinion, this extends to the rehabilitation research world where patients are often involved in research as 'subjects' or 'objects' of the research, but rarely as 'colleagues'. Scholars note that rehabilitation researchers have been criticized for doing things to patients rather than with them [53]. Post and colleagues add that: "a challenge is to involve patients more closely in the healthcare process, empowering them to actively participate in the management of their own disease. Effective multidisciplinary care for PD comes with the recognition that patients and their advocates are indispensable members of the healthcare team, with an important role in decision making" [24]. Post and colleagues proceed to state that little progress has been made in translating research to the level of the community, owing to the fact that multidisciplinary team approaches [24] face the formidable challenge of obtaining research funding for partnership building.

In the USA, health services research rests on three pillars; bench-to-bedside translational research (T1); clinical trials (T2); and population-based and implementation research (T3; research that aims to translate knowledge from academic centers to community-settings). Researchers that aim to translate the evidence-base to community levels (T3) have historically been under-funded, with the majority of federal support from the NIH in the USA going towards basic science research (including Phase I and II clinical trials) and human clinical research (including controlled observational studies and Phase III clinical trials that aim to translate from the bench to the bedside). The T1 and T2 funding resources have yielded tremendous progress in our understanding of the efficacy of evidence-based physiotherapeutic treatments on PD by increasing the number of meta-analytic studies, systematic reviews and guideline development in PD treatment.

Traditionally, scientists make most, if not all, of the decisions in what to research and how to research it, with little or no community input. Since many of these critical decisions are made in isolation, researchers may be unaware of true community needs. At the same time, communities are often not unaware of the research resources in their community. To address this issue, in 2004 the NIH, Agency for Healthcare Research and Quality and the CDC inaugurated a new stream of funding known as community participation in research (T3), to encourage healthcare providers and patients to work collaboratively to build healthier communities using an approach to research and interventions such as CBPR. The first steps for encouraging academic and lay-expert involvement in CBPR is not an easy task, as summarized in Table 1 and elsewhere [54–57,104–107].

Community-based participatory research initiatives are patient-centered approaches to research that foster collaborative research partnerships between patients, healthcare professionals and communities. During traditional biomedical research, the academically trained

researcher develops the idea, writes the grant, collects, analyzes, interprets and disseminates the data. CBPR aims to develop community capacity for research by empowering patients and patient advocates as co-researchers in every step of the research process from generating the idea and writing the grant, to data analysis, data interpretation and dissemination of the results [54–57].

In recent years, funding for CBPR has increased dramatically. In 2004, there were 38 CBPR-funded NIH studies. In 2010, there were 263 studies with a CBPR component and a total of over US $114 million in funding [108]. While CBPR has gained acceptance in North America and internationally as an important approach to improve public health [57], no studies have demonstrated benefits of CBPR to health outcomes and only a few CBPR studies have been conducted with neurological populations [58–61].

Models of community-based participatory research & exercise

As far as we know, there are no published guidelines available for conducting CBPR in populations with neurological or neurodegenerative conditions. As a first step, Table 1 lists the potential obstacles (as well as potential strategies in overcoming obstacles) in conducting CBPR approaches. Particularly in the early stages of developing CBPR studies, it can be challenging to find funding resources and people with expertise in doing CBPR. A good strategy in getting started with CBPR is to identify CBPR researchers in the community. Websites with information for CBPR are becoming more plentiful. A resource to tap into is Community-Campus Partnerships for Health (CCPH). CCPH is a nonprofit, world-wide network of over 2000 participatory researchers. A webpage and blog are maintained with up-to-date research and tools for conducting CBPR [109]. These resources are invaluable sources of information on CBPR, research and community partnering. It is hoped that healthcare professionals and rehabilitation researchers will begin to collaborate with lay-communities in developing and testing exercise interventions for all patients with PD across disease severity, using CBPR approaches.

As suggested in Figure 1, there are numerous options for researching the relationship between traditional and CBPR approaches or peer-to-peer and traditional approaches to delivering the exercise interventions. These might include using principles of CBPR in planning the exercise intervention (e.g., using a CBPR approach involving lay experts such as patients, care-partner, and exercise trainers, and others in making decisions that evidence-based training exercises to include in the community-based setting (models 1 and 3, Figure 1); using traditional approaches to planning the exercise intervention (e.g., therapists and clinicians) (models 2 and 4, Figure 1); using peer-to-peer approaches (e.g., patients as trainers) to delivering the intervention (models 1 and 2, Figure 1); or traditional approaches to delivery of the exercise intervention (e.g., physiotherapist or exercise professional; models 3 and 4, Figure 1).

Goodwin and colleagues recently reviewed randomized controlled trials on the effects of exercise interventions on PD [9]. The authors reported that in ten out of 14 studies, the delivery of the exercise intervention was led by medical professionals (e.g., physiotherapists; model 4, Figure 1). In the remainder of the studies, the exercise interventions were delivered by trained exercise leaders (including QiGong teacher and a student nurse) [9]. Presumably, none of the studies reported by Goodwin had substantial input from patients with PD [9]; however, patient involvement in protocol development was not reported. The amount of healthcare professional involvement in delivery of exercise interventions is unlikely to change in the near future, but it does not mean that lay-experts should not or cannot be empowered to work with the healthcare professionals to jointly deliver (and/or develop) the exercise training protocol.

Since research has not examined the effect of CBPR participation on health outcomes in PD, it is conceivable that participating in the planning and implementation of exercise interventions could have a positive or a negative effect on physical activity participation. For example, one hypothesis might be that peer-to-peer approaches to delivery of exercise result in more injuries and generally poorer compliance and poor outcomes. People who are vulnerable to falls and secondary disabling injuries might be especially prone to injuries if they are given too much responsibility for each others safety without taking appropriate steps to protect both the trainer and the trainee from falls. Using some common sense in selecting peer-to-peer trainers (such as selecting peer-to-peer trainers who are in the early stages of the disease before falls and gait problems develop) may be a good strategy before asking people with greater disability and impairment to

assist individuals in whom falls are likely to occur during training. It is also possible that peer-to-peer approaches might empower individuals with PD to become physically active. Research suggests that in PD, exercise settings can serve as social networks. By participating in settings with people who have a common interest, community-based exercisers develop social networks that become more important to the individual than, for example, increasing muscle strength. Peer-to-peer approaches to delivering exercise interventions might thus serve to further increase the social network bonds. It is hoped that future research will examine these relationships and the associations of CBPR with peer-to-peer training and health outcomes in greater detail.

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Enhancing Neuroplasticity in the Basal Ganglia: The Role of Exercise in Parkinson's Disease

Giselle M. Petzinger, MD,[1,2]* Beth E. Fisher, PhD,[2] Jon-Eric Van Leeuwen, BSc,[1] Marta Vukovic, MSc,[1] Garnik Akopian, MD,[3] Charlie K. Meshul, PhD,[4] Daniel P. Holschneider, MD,[5] Angelo Nacca, PhD,[6] John P. Walsh, PhD,[3] and Michael W. Jakowec, PhD[1,2]

[1]*The George and MaryLou Boone Center for Parkinson's Disease Research, Department of Neurology, University of Southern California, Los Angeles, California, USA*
[2]*Division of Biokinesiology and Physical Therapy, University of Southern California, Los Angeles, California, USA*
[3]*Andrus Gerontology Center, University of Southern California, Los Angeles, California, USA*
[4]*Department of Behavioral Neuroscience, Oregon Health and Science University/VA Medical Center, Portland, Oregon, USA*
[5]*Department of Psychiatry, University of Southern California, Los Angeles, California, USA*
[6]*Department of Radiology, University of Southern California, Los Angeles, California, USA*

Abstract: Epidemiological and clinical trials have suggested that exercise is beneficial for patients with Parkinson's disease (PD). However, the underlying mechanisms and potential for disease modification are currently unknown. This review presents current findings from our laboratories in patients with PD and animal models. The data indicate that alterations in both dopaminergic and glutamatergic neurotransmission, induced by activity-dependent (exercise) processes, may mitigate the cortically driven hyper-excitability in the basal ganglia normally observed in the parkinsonian state. These insights have potential to identify novel therapeutic treatments capable of reversing or delaying disease progression in PD. © 2010 Movement Disorder Society

Key words: dopamine; MPTP; animal models; treadmill; glutamate; electrophysiology; PET imaging

INTRODUCTION

Parkinson's disease (PD) is characterized as a progressive neurodegenerative disease with no known cure. The primary pathology of PD is loss of substantia nigra pars compacta neurons accompanied by loss of striatal dopamine. Exercise has been shown to be beneficial in PD, yet the question remains whether exercise leads to central nervous system (CNS) compensatory or neuroprotective changes with potential to alter the natural course of the disease. Studies have demonstrated that the adult brain is altered by experience including exercise.[1–4] This phenomenon termed "activity-dependent neuroplasticity" is defined as modifications within the CNS, in response to physical activity that promotes a skill acquisition process.[5] As such (1) intensity; (2) specificity; (3) difficulty; and (4) complexity of practice appear to be important parameters for driving neuroplasticity and a potential lasting effect on both brain and behavior.[6,7] Although the importance of these parameters have been primarily established in healthy brain and in brain injury secondary to stroke, this framework has more recently been adopted to study activity-dependent neuroplasticity in neurodegenerative diseases, including PD, and to examine its potential to modify disease progression (Table 1).[8–21]

Using a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-(MPTP)-lesioned mouse model of PD, we have examined the effects of intensive treadmill exercise on activity-dependent neuroplasticity within the striatum. Our studies have focused on exercise-induced changes

*Correspondence to: Dr. Giselle M. Petzinger, Department of Neurology, MCA-241, Keck School of Medicine, University of Southern California, Los Angeles, CA, 90033.
E-mail: gpetzinger@surgery.usc.edu

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TABLE 1. *Practice variables important for evoking activity-dependent neuroplasticity- examples in brain injury (PD, stroke, spinal cord injury)*

Practice variable	Animal study	Human study
Intensity	Petzinger et al., 2007[20]; Tillerson et al., 2001[21]	Liepert, 2006[13]; Liepert et al., 2000[14]
Specificity	Fisher et al., 2004[19]; De Leon et al., 1999[18]; Tillakaratne, 2002[17]	Forrester et al., 2006[12]; Dobkin et al., 2004[11]
Difficulty	Friel and Nudo, 1998[16]	Wittenberg et al., 2003[10]; Johansen-Berg et al., 2002[9]
Complexity	Jones et al., 1999[15]	Winstein et al., 1997[8]

in dopaminergic and glutamatergic neurotransmission. Interactions between these systems are important for normal basal ganglia function. Both dopaminergic neurons from the substantia nigra as well as glutamatergic afferents from the cerebral cortex and thalamus synapse in close proximity on medium spiny neurons (MSN) of the striatum and together dictate the electrophysiological properties of these cells.[22,23] There is compelling data that the loss of nigral dopaminergic neurons is responsible for an increase in glutamatergic corticostriatal drive at the level of the MSNs, contributing to the motor deficits in PD.[24–27] One possible mechanism by which exercise may drive activity-dependent neuroplasticity in PD may be through mitigating corticostriatal hyperactivity (i.e., hyperexcitability), by modulating dopaminergic signaling, and/or diminishing glutamatergic neurotransmission.

CHANGES IN DOPAMINERGIC NEUROTRANSMISSION WITH EXERCISE

Our MPTP model consisted of administration of four intraperitoneal injections of 20 mg/kg (free-base) at 2-hour intervals for a total administration of 80 mg/kg, which leads to 60–70% of nigrostriatal dopaminergic neuronal death. Five days post-lesioning, when cell death is complete, mice were subjected to exercise on a motorized treadmill for 30 days (5 days/week). Task specific benefits were observed as improvements in both running velocity and endurance. Improvement was also observed on a motor task that was designed to assess balance.[20] These benefits were accompanied by increased dopamine availability, revealed as an increase in stimulus-evoked release and a decrease in dopamine decay as measured by fast-scan cyclic voltammetry. Interestingly this exercise effect of dopamine release was most pronounced within the dorsolateral striatum. Since the primary role of this area is in motor function, use-dependent forms of neuroplasticity may explain this regional specificity in an exercise-induced effect. Additionally, we observed an increase in expression of dopamine D2 receptor mRNA and down regulation of the dopamine transporter (DAT) protein within the striatum, changes that are consistent with increased dopaminergic signaling.[19] A primary role of DAT is to clear dopamine from the extracellular space. Down-regulation of DAT protein leads to increased synaptic dopamine availability for dopamine receptor binding.[28] The binding of dopamine to both the D1 and D2 receptors are required in the normal brain to elicit a motor response. After basal ganglia injury, however, this synergy is lost and dopamine binding to either D1 or D2 may elicit a motor response.[29] In addition, dopamine binding to the D2 receptor alone may elicit a robust response that may be attributed to its heightened sensitivity after lesioning.[30] Thus, an exercise-induced increase in D2 receptor expression coupled with an increase in the synaptic availability of dopamine may be sufficient to elicit increased dopaminergic neurotransmission and improved motor function. Preliminary Positron Emission Tomography (PET) imaging studies in our lab using 18F-Fallypride, a benzamide ligand with high affinity for the D2 receptor, have demonstrated an exercise-induced increase in binding affinity within the striatum, confirming our D2 receptor findings. Interestingly, we observed no exercise-induced changes in either the total level of striatal dopamine, as measured by HPLC in tissue homogenates, or the number of dopaminergic substantia nigra neurons, measured by immunohistochemistry. These findings suggest that high intensity exercise leads to compensatory changes in dopamine handling and neurotransmission.[20]

CHANGES IN GLUTAMATERGIC NEUROTRANSMISSION AND EXERCISE

Studies in our laboratory also suggest that exercise-induced neuroplasticity of the glutamatergic system may diminish corticostriatal hyperexcitability and underlie the motor improvement observed in our exercised mice. Specifically, using immuno-electron microscopy, we have observed that treadmill exercise reversed the MPTP-induced increase level of *presynaptic* glutamate immunolabeling within striatal terminals, suggesting that exercise reduced the amount of glutamate available for release.[19] In addition, new studies in our lab demonstrate that treadmill exercise modulates postsynaptic AMPA receptor (AMPAR) subunit expression through an increase in both GluR2 and phosphorylation of GluR2 at serine 880.[31] The poten-

tial process by which these changes may lead to decreased glutamatergic hyperexcitability could involve a general reduction in glutamatergic neurotransmission and synaptic strength (i.e., long-term depression). We have been interested in examining exercise induced changes in the AMPAR, as it is responsible for the majority of fast excitatory neurotransmission in the CNS and it mediates activity-dependent processes that alter synaptic strength.[32,33] Located on the postsynaptic MSN, the AMPAR is an ionotropic channel that converts the chemical signal of presynaptically released glutamate into a postsynaptic electrical signal through the mobilization of cations such as Na^+ and Ca^{2+}.[34] The AMPAR is a heteromeric tetramer consisting of four subunits GluR1–4; the most abundant in the striatum are GluR1 and GluR2.[32,35] Alterations in GluR2 expression and phosphorylation have been associated with diminished synaptic strength (i.e., long-term depression).[32,36–38] Increased expression of the GluR2 subunit within the tetrameric complex of the AMPAR, as seen in our exercised mice, creates an additional positive charge within the channel pore, which impedes cation flow, lowers calcium conductance and thus diminishes synaptic strength.[34,39] Another means of regulating AMPAR transmission occurs via trafficking and removal of the AMPAR from the membrane. This may be regulated through phosphorylation of AMPAR subunits, including GluR2. Specifically, phosphorylation of serine 880 on the GluR2 subunit leads to internalization of the entire receptor and decreased synaptic strength (i.e., long-term depression).[33,40] Studies in our laboratory reveal that treadmill exercise increases the phosphorylation state of GluR2 at serine 880 in MPTP-lesioned mice. Additional electrophysiological studies indicate that exercise-induced changes in the expression of GluR2 subunit lead to decreased excitability in the MSNs, demonstrated by reduced EPSCs generated by cortical stimulation. They have also shown reduced polyamine sensitivity and loss of rectification in AMPAR conductance at depolarized membrane potentials of MSNs. These findings provide further evidence that changes in GluR2 expression are the basis for the exercise-induced reduction in the EPSCs of MSNs.[34,39] Finally, consistent with an exercise mediated attenuation of corticostriatal hyperexcitability, we have also observed an exercise induced decrease in cerebral blood flow in corticostriatal regions using cerebral perfusion studies in rats with basal ganglia injury.[41] Collectively our data in both mouse and rat models of basal ganglia injury indicate that exercise training attenuates the over-activation in basal ganglia-cortical circuits.

In summary, these findings suggests that alterations in both dopaminergic and glutamatergic neurotransmission through activity-dependent processes modulates cortical hyper-excitability of the basal ganglia. Modulation of cortical hyper-excitability may be what underlies exercise-induced behavioral improvement. An important next step is to translate these findings to humans, and to investigate whether high intensity exercise has similar benefits in PD.

ACTIVITY-DEPENDENT NEUROPLASTICITY AND PARKINSON'S DISEASE

As our studies in animal models suggested that high intensity is a characteristic of exercise that may be specifically important in promoting activity-dependent neuroplasticity, we designed a study to the use of Body-weight supported treadmill training (BWSTT) to drive intensity of practice in individuals with PD. BWSTT involves the use of an overhead harness that allows exercise intensity to be safely escalated by increasing treadmill velocity. Thus, subjects are able to walk at higher gait speeds than they are able to obtain over-ground. They also experience high repetition of stepping, are actively engaged in the training, and have the sensory experience of normal gait kinematics. Patients with PD, no more than 3 years from initial diagnosis were asked to exercise at high intensity, 3 times per week for 8 weeks using body-weight BWSTT. Outcomes consisted of measures of motor performance, including gait kinematics, sit-to-stand, and stair climbing. Unique to this human trial, and directly related to our animal finding, was the inclusion of measures of cortical excitability using transcranial magnetic stimulation (TMS). TMS is a noninvasive method of stimulating the brain and provides a tool for assessment of excitability of the corticospinal motor system. Single TMS pulses are applied over the motor cortex while recording surface electromyography (EMG) responses over a contralateral target muscle. If the target muscle is preactivated (contracted), the TMS pulse induces a characteristic transient period of EMG silence called the cortical silent period (CSP). Importantly for this study, single pulse TMS studies have shown systematic abnormalities of CSP and other corticoexcitability measures in individuals with PD. In general, these abnormalities reflect cortical hyper-excitability in PD compared to non-PD control subjects.[42,43] As CSP represents inhibitory influences on cortical excitability, higher excitability would be evident as a shortened CSP duration. In fact, shortened CSP durations are among the most consistent and widely repro-

duced TMS finding amongst PD patients.[44] Further, symptomatic treatment of PD with surgical or pharmacological interventions is associated with lengthening of the CSP towards levels seen in control subjects.[45,46] Thus, CSP duration could underlie symptomatic improvement, such as improved motor performance. Thus, not only is TMS an excellent tool to measure CSP duration and to examine possible exercise-induced changes in PD, but more importantly TMS may be used to support the existence of CNS changes in response to different exercise parameters including intensity. After 24 sessions of BWSTT subjects demonstrated improved walking performance including increased gait velocity, stride length, step length, and hip and ankle joint excursion, and improved weight distribution during sit-to-stand. More importantly, these subjects also showed reversal of cortical hyper-excitability indicated by increased CSP. In fact, every subject undergoing BWSTT showed exercise-induced lengthening of CSP. To our knowledge, this was the first demonstration of exercise-induced cortical changes in the brain in individuals with PD.

FUTURE DIRECTIONS

We have shown that exercise may influence activity-dependent processes in the basal ganglia through alterations in dopaminergic and glutamatergic neurotransmission. In addition, we demonstrate that exercise-induced behavioral benefits may be in part due to changes in cortical hyper-excitability normally observed in the dopamine depleted state, as in PD. Although we have demonstrated the potential impact of BWSTT on the human condition, a critical next step is to determine whether exercise induces or is associated with a disease modifying effect in PD. The implications for our understanding of the impact of exercise in PD are broad. Not only is there potential to develop new insights into mechanisms of neuroplasticity and motor recovery in PD, but also the study of exercise may lead to the development of novel therapeutics, perhaps even nonpharmacological approaches to delay or reverse disease progression in PD.

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Author Roles: GP, BF, JW, MJ: responsible for concept and design. GP, BF: responsible for initial draft. GP, BF, JV, MV: responsible for editing and revision of text. All authors contributed to data acquisition and analysis reported in this paper.

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Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease

Beth E. Fisher[a,d], Quanzheng Li[b], Angelo Nacca[c], George J. Salem[a,d], Jooeun Song[a], Jeanine Yip[a], Jennifer S. Hui[d], Michael W. Jakowec[a,d] and Giselle M. Petzinger[a,d]

We have previously demonstrated changes in dopaminergic neurotransmission after intensive exercise in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of Parkinson's disease (PD), including an increase in the dopamine D_2 receptor (DA-D_2R), using noninvasive PET imaging with the radioligand [^{18}F]fallypride. The purpose of this feasibility and translational study was to examine whether intensive exercise leads to similar alterations in DA-D_2R expression using PET imaging with [^{18}F]fallypride in individuals with early-stage PD. In this pilot study, four patients with early-stage PD were randomized to receive intensive exercise (treadmill training sessions three times/week for 8 weeks) or no exercise. Two healthy age-matched individuals participated in treadmill training. Alterations in the DA-D_2R binding potential (BP) as a marker for receptor expression were determined using PET imaging with [^{18}F]fallypride. Turning performance in the patients with PD as a measure of postural control and the Unified Parkinson's Disease Rating Scale scores pre-exercise and postexercise were determined. Our data showed an exercise-induced increase in [^{18}F]fallypride BP as well as improved postural control in patients with PD who exercised. Changes in DA-D_2R BP were not observed in patients with PD who did not exercise. These results suggest that exercise can lead to neuroplasticity in dopaminergic signaling and contribute to improved function that may be task specific (postural control) in early-stage PD. *NeuroReport* 24:509–514 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]Division of Biokinesiology and Physical Therapy, [b]Viterbi School of Engineering, Departments of [c]Radiology and [d]Neurology, University of Southern California, Los Angeles, California, USA

Correspondence to Giselle M. Petzinger, MD, Department of Neurology, 1333 San Pablo St., MCA-241, University of Southern California, Los Angeles, CA 90033, USA
Tel: +1 323 442 1057; fax: +1 323 442 1055;
e-mail: gpetzinger@surgery.usc.edu

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Introduction

Exercise studies have demonstrated beneficial effects of exercise in individuals with Parkinson's disease (PD) [1–3], and epidemiological studies have suggested a protective effect of exercise throughout life from degenerative disorders like PD [4,5]; however, the underlying mechanisms linking exercise with neuroplasticity and PD are unknown. In our laboratories, we have been interested in understanding how exercise in the form of intensive treadmill running can enhance motor performance and neuroplasticity in individuals with PD.

Our published studies on the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned mouse model of PD demonstrate that intensive treadmill exercise leads to (i) improved motor performance, (ii) increased dopaminergic signaling through an increase in striatal dopamine (DA) release, (iii) reduced DA reuptake and hence increased synaptic occupancy, and (iv) elevated DA-D_2 receptor (DA-D_2R) expression (but not DA-D_1R) as measured by protein and transcript expression levels [6]. The loss of DA leads to an imbalance in the inhibitory and excitatory projection pathways of the basal ganglia, specifically the striatopallidal (indirect pathway) DA-D_2R-containing medium spiny neurons and the striatonigral (direct pathway) DA-D_1R-containing medium spiny neurons, respectively [7]. This imbalance includes overactivation and increased inhibition of the DA-D_2R pathway on the basal ganglia–thalamus–cortical loop, which leads to parkinsonian features and the loss of motor skills [8,9]. Therefore, we hypothesize that the potential effects of exercise are attenuation of the overactive indirect DA-D_2R-containing pathway and improvement of motor performance in the MPTP mouse model of PD through an increase in DA signaling (through increased DA release and DA-D_2R expression). These findings on the effects of exercise on DA signaling were subsequently confirmed by our group in the MPTP mouse model of PD by noninvasive *in vivo* PET imaging with [^{18}F]fallypride, a DA-D_2/D_3R specific ligand [10]. The purpose of this pilot study was to translate our exercise findings in animals to examine the effects of intensive treadmill exercise on DA-D_2R binding potential (BP) using PET imaging with [^{18}F]fallypride in individuals with early-stage and unmedicated PD. We also measured exercise-induced changes in (i) motor performance, specifically turning behavior (a sensitive measure of

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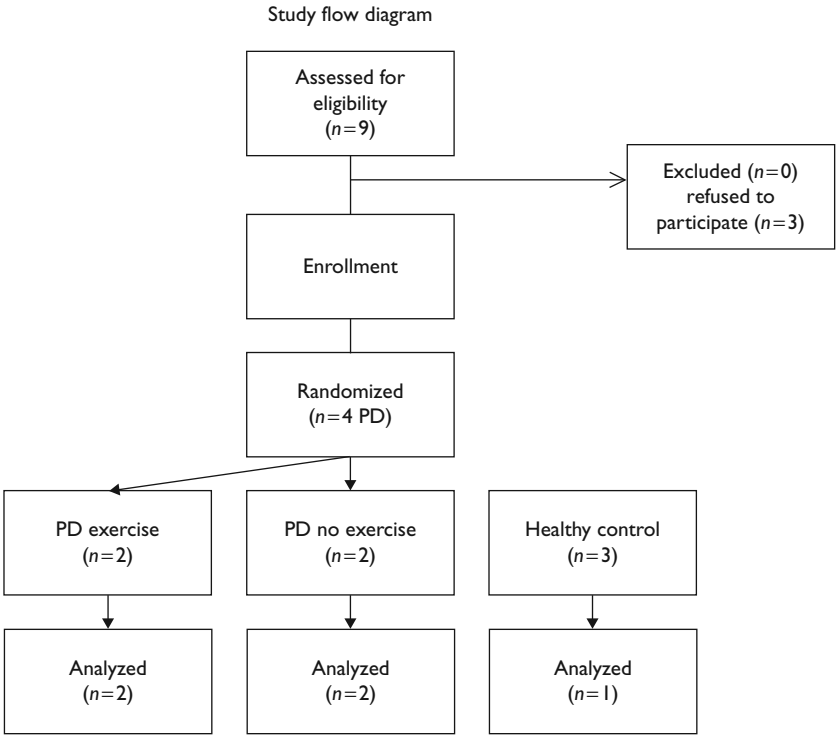
Fig. 1



Flow chart of patient numbers and their assignments.

deficits in individuals with early-stage PD) [11] and (ii) the Unified Parkinson's Disease Rating Scale (UPDRS) scores [12].

Methods

Four individuals within 1 year of diagnosis with PD and two healthy controls (HCs) were recruited for the study. Two participants with PD (S1 and S2) and the two HCs (S5 and S6) underwent intensive treadmill exercise, whereas two participants with PD (S3 and S4) did not receive treadmill training. Demographics of patients with PD and HCs (sex/age) were as follows: S1: M/52, S2: M/55, S3: M/63, S4: F/50, S5: M/58, and S6: F/53. Patients with PD were diagnosed by a neurologist who was fellowship trained as a PD specialist. All patients met orthopedic and cardiac criteria for rigorous exercise. No participant was receiving any medication for PD. Informed consents approved by the Institutional Review Board of the University of Southern California were obtained. A flow chart of the patient assignment is shown in Fig. 1. Treadmill training consisted of three 1-h sessions/week for 8 weeks at progressively increasing speeds [1]. Participants were challenged to walk and/or run faster than their self-selected speed but within the constraints of an observationally normal gait pattern. Participants were fitted with a harness used for safety purposes only, with no unweighting, and were trained with the assistance of a physical therapist. The goal of each treatment session was to reach and maintain a metabolic equivalent of task (MET) level greater than 3.0 METS and/or 75% of an age-adjusted maximum heart rate using proper gait kinematics for stance and swing (upright posture, extending and flexing the hip, knee, and ankle, and coordinating limb movements to achieve symmetric limb cadence and equal step length). The end goal for each participant was to run on the treadmill continuously for 45 min within the above MET level. Progression on the treadmill occurred with the following parameters scaled up: (i) increased treadmill speed, (ii) decreased verbal feedback, and (iii) increased treadmill time. A trained physical therapist was responsible for decisions on progression including monitoring the upright posture, manual or verbal feedback on pelvic position, weight shift, stride characteristics, and cadence.

Exercise (S1, S2, and S5) and nonexercise (S3 and S4) participants underwent PET imaging at baseline and at completion of the 8-week study. PET imaging was carried out on a Siemens Biograph TruePoint whole body PET/CT scanner (Siemens Medical Solutions USA Inc., Knoxville, Tennessee, USA) with a 16.2 cm axial field of view and a spatial resolution of 2 mm, providing 81 slices

of 2 mm thickness. DA-D_2/D_3 receptor BP was assessed using [^{18}F]fallypride, a radioligand with high affinity for D_2/D_3 receptors [13]. Participants were supine, with the brain centered in the transaxial field of view. Dynamic PET scanning was initiated with a 30-s bolus (0.07 mCi/kg) of [^{18}F]fallypride infusion. The first dynamic scanning sequence consisted of six frames at 30 s, seven frames at 1 min, five frames at 2 min, four frames at 5 min, and four frames at 10 min; this was followed by a 20-min break and a second dynamic sequence with eight frames at 10 min each, yielding a total study time of 3 h. Modeling studies have demonstrated stable fits using the reference region method in all brain regions from 180 min or more [14]. The PET imaging data were acquired in the list mode and reconstructed using the Siemens HD-software OSEM3D algorithm (six iterations, 16 subsets) with normalization, attenuation, and scatter correction.

For a structural definition of the brain, a single T1-weighted MRI scan was acquired on a GE 1.5 T scanner (GE Healthcare, Waukesha, Wisconsin, USA) using a three-dimensional SPGR sequence with parameters (TE = 5, TR = 24, NEX = 1, 1.2 mm slice thickness/contiguous, $256 \times 256 \times 128$ matrix size). Coregistration of [^{18}F]fallypride PET images to magnetic resonance (MR) anatomic images was performed with VINCI (CPS Innovations Inc., Knoxville, Tennessee, USA) and a template-matching algorithm using the software program AIR, available from UCLA Laboratory of Neuroimaging (LONI; *http://bishopw.loni.ucla.edu/AIR5/*). Before coregistration, the MR images were processed to extract brain volume from the skull and connective tissue using the BrainSuite software (*http://brainsuite.usc.edu/*).

The regions of interest (ROIs) were drawn within the boundaries of the dorsal putamen on the structural MRI, an area of the basal ganglia important in motor control and affected by exercise [6,15,16]. The ROI and cerebellum (reference region) in the anatomical MRI image were mapped to all the PET images on the basis of the PET–MRI registration. The time–activity curves of all voxels in each ROI and the cerebellum were averaged and used to compute the distribution volume ratio (DVR) [17]. Binding potential, BP = DVR – 1, was computed using a multilinear method.

Postural control was analyzed before and at the completion of the study as our previous published work demonstrated it to be a sensitive motor measure in early PD [11]. Participants walked straight and turned at a 'self-selected, comfortable pace' at the designated stanchions at a right angle toward their dominant leg and then continued walking in the new direction. The task is shown in Fig. 3a. A total of three turning trials were recorded. For analysis, 90° turns were selected as these turns are associated with navigation along corridors, around street corners, and in other common walking activities. Three consecutive steps during the turn, (i) the 'approach' step, (ii) the 'pivot' step, and (iii) the 'acceleration' step, were used to define two phases of turning: (i) defined from heel strike of the approach step to heel strike of the pivot step and (ii) defined from heel strike of the pivot step to heel strike of the acceleration step.

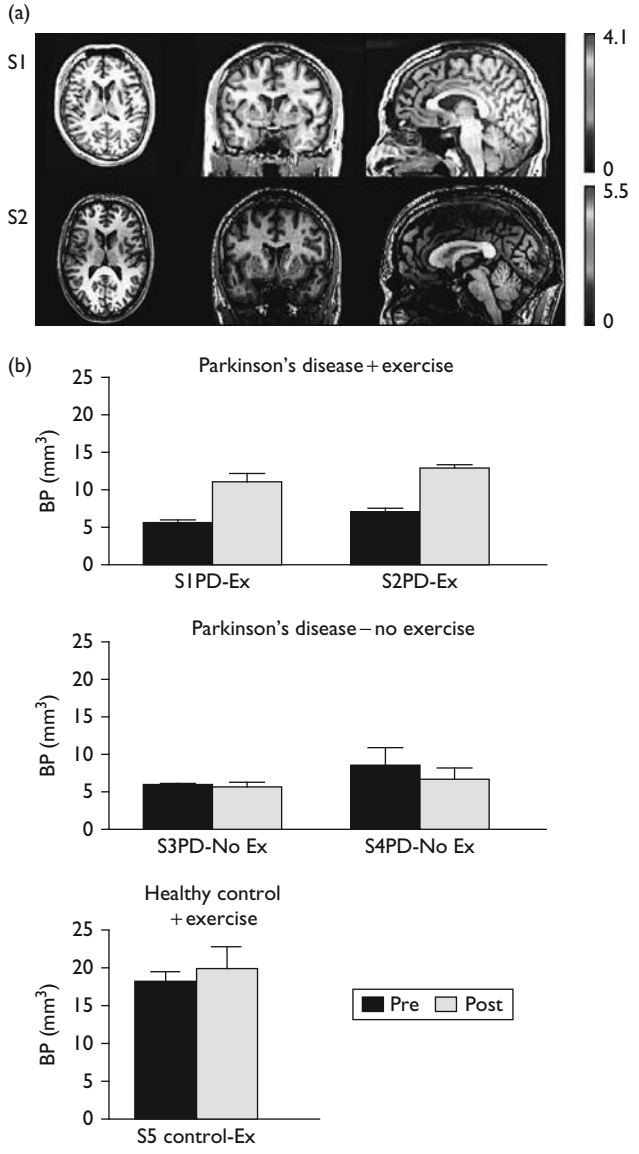
Using previously reported kinematic methods, postural control during turning was quantified as the peak distance between the center of pressure (COP) of the supporting foot and the extrapolated center of mass (eCOM) [11]. Separation of the COP and the eCOM creates the momentum necessary for successful turning. Greater separation, however, requires increased neuromuscular control (e.g. neural drive, muscle force, and joint power) to redirect and control this momentum. Previous studies have demonstrated that persons with early PD have difficulty with turning and reduced COP and eCOM distances during a turn [11]. All tests were performed by a biomechanist blinded to the treatment groups. The UPDRS serves as the gold standard measure of disease severity in PD and UPDRS scores were assessed before and at the completion of the study. We report both the total score and motor subsection score of the UPDRS.

Results

Individuals S1 and S2 with PD who participated in exercise demonstrated a marked increase in [^{18}F]fallypride BP, as shown in the representative coregistration of MRI and PET imaging (Fig. 2a). Data are graphically depicted in Fig. 2b. The pre-exercise average BP for S1 in the dorsal putamen was 5.58 ± 0.43, whereas the post-exercise BP was 11.0 ± 1.09. For S2, pre-exercise and postexercise average BPs were 7.14 ± 0.36 and 12.9 ± 0.47, respectively. Conversely, there was either no change or a decrease in the BPs in individuals S3 and S4 with PD who did not exercise. The average baseline BP for S3 was 5.94 ± 0.18 and that after 8 weeks was 5.74 ± 0.53. For S4, the baseline BP was 8.64 ± 2.31 with a BP of 6.64 ± 1.49 eight weeks later. The pre-exercise average BP for the HC S5 was 18.26 ± 1.31, which is within the range that has been previously reported in healthy individuals of the same age [18]. Postexercise BP was 19.92 ± 3.03 for HC S5. HC S6 moved while in the PET imager and reliable data were not available for analysis.

Individuals with PD demonstrated improved turning performance (S1 in both phases; S2 in phase 1) after intensive exercise, whereas minimal change was observed in the two nonexercise patients (Fig. 3b). Data are shown in Table 1. Over the study period, no study participant demonstrated any appreciable change in UPDRS total or motor component scores. Baseline UPDRS scores (total/motor) were: S1: 32/12; S2: 15/13; S3: 31/21; and

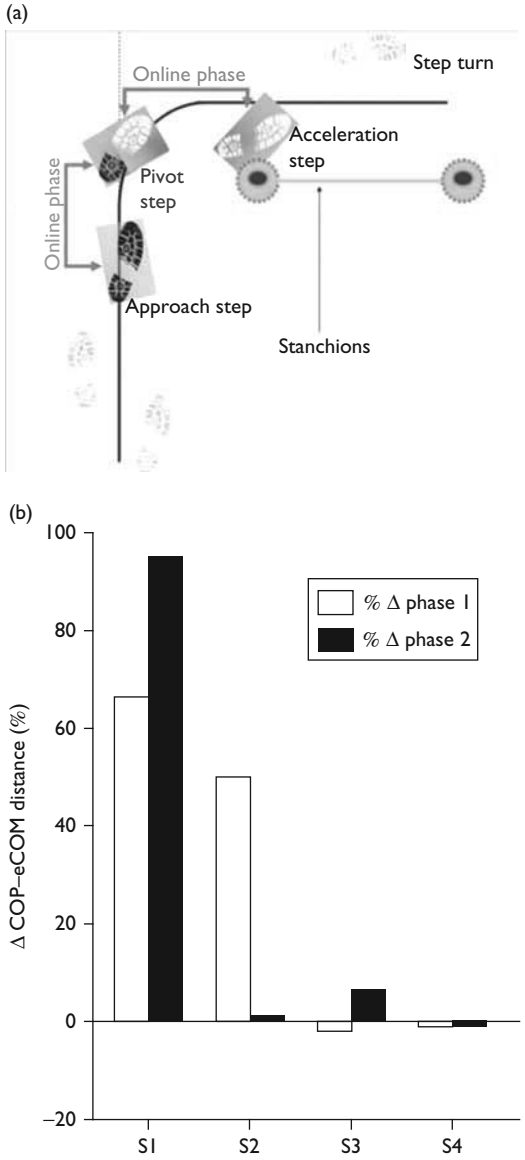
Fig. 2



PET imaging using the dopamine D2/3 specific ligand [^{18}F]fallypride. (a) Representative coregistration of MRI and PET imaging. PET imaging data were derived from subtraction of the postexercise from the pre-exercise [^{18}F]fallypride binding potential (BP). Increased BP is indicated by red color within the basal ganglia. (b) BP for [^{18}F]fallypride in the putamen for all participants including S1 and S2 [Parkinson's disease (PD) plus exercise], S3 and S4 (PD no exercise), and S5 (control plus exercise). Pre-exercise (black bar) and postexercise (gray bar) BPs were compared. The top graph shows a pre-exercise average BP for S1 in the putamen of 5.58±0.43 and postexercise BP of 11.0±1.09. For S2, the pre-exercise average BP in the putamen was 7.14±0.36 and the postexercise BP was 12.9±0.47. The middle graph shows a baseline BP of 5.94±0.18 for S3 (no exercise) in the putamen and an unchanged BP of 5.74±0.53 after 8 weeks. S4 had a baseline BP of 8.64±2.31, and after 8 weeks the BP was 6.64±1.49. The bottom graph shows a BP of 18.26±1.31 at baseline for S5 (control) and a postexercise BP of19.92±3.03. Graphs show mean±SEM. S1 and S2, exercise; S3 and S4, no exercise; S5, control. Ex, exercise; No Ex, no exercise.

S4: 19/14; post-UPDRS scores were: S1: 34/13; S2: 14/13; S3: 33/23; and S4: 19/16.

Fig. 3



Turning task for postural control. (a) Schematic representation of the turning task. Phase 1 is defined from heel strike of the approach step to heel strike of the pivot step. Phase 2 is defined from heel strike of the pivot step to heel strike of the acceleration step. (b) Percentage change in the resultant eCOM–COP distance in meters (postexercise–pre-exercise/pre-exercise × 100) for S1 and S2 (exercise) and S3 and S4 (no exercise). The percentage change in phase I performance is shown by the open bars and the percentage change in phase 2 performance is shown by the solid black bars. eCOM, extrapolated center of mass; COP, center of pressure.

Discussion

Previous studies in our laboratories have shown that in the dopamine-depleted striatum, intensive treadmill exercise leads to an increase in the expression of striatal DA-D_2R protein and mRNA *in vitro*, which reflects increased BP (a reflection of DA-D_2R availability) on in-vivo PET imaging using the DA-D_2R-specific

Table 1 Raw data for the turning task for postural control

	Phase 1		Phase 2	
	Baseline	Post	Baseline	Post
S1-Ex	0.25±0.03	0.41±0.01	0.22±0.02	0.42±0.04
S2-Ex	0.34±0.02	0.52±0.05	0.36±0.02	0.37±0.02
S3-No Ex	0.33±0.03	0.33±0.05	0.28±0.04	0.30±0.01
S4-No Ex	0.40±0.03	0.39±0.01	0.41±0.01	0.40±0.03

Mean (m)±SD for three trials; Ex, exercise; No Ex, no exercise.
Raw data=mean (m)±SD.

radioligand [^{18}F]fallypride [6,15]. The primary goal of this pilot study was to determine whether high-intensity treadmill exercise leads to increased [^{18}F]fallypride BP (DA-D_2R availability) in patients with early-stage unmedicated PD. Specifically, we found that exercise led to an 81 and 98% increase in [^{18}F]fallypride BP in two of the patients with PD, respectively. In contrast, nonexercise patients with PD showed no change (3%) or a decrease (23%) in DA-D_2R BP during this same time period. This exercise effect appears specific to PD as only a slight increase was observed in HCs (9.2%) and the pre-exercise and postexercise values were within the range reported for healthy nonexercised individuals [18]. These preliminary findings are important because they demonstrate that similar outcome measures are observed in both an animal model of DA depletion and in individuals with PD, suggesting that similar mechanisms may be occurring when the two are subjected to intensive exercise. Larger studies are needed to confirm these preliminary results.

[^{18}F]fallypride is a highly selective DA-D_2/D_3R antagonist, shown to be a highly specific and sensitive ligand whose BP reflects an in-vivo measure of available striatal and extrastriatal receptors (B_{max})/binding affinity (K_d), which is thought to be independent of DA levels, especially in the context of striatal DA depletion [19]. In this current pilot study, we observed baseline DA-D_2R BPs in PD patients to be lower than those in HCs; this is consistent with observations in nonhuman primate models of PD [20]. Findings with [^{18}F]fallypride are in contrast to what has been reported in early-stage PD using the DA-D_2R-specific ligand [^{11}C]raclopride [21]. Such differences between studies may reflect differences in duration of the disease: patients in our study were in the early stages of the disease (within 1 year), whereas those reported by Rinne *et al.* [21] had a disease duration of greater than 1 year. In addition, differences may also be the result of the ligand used, as the binding affinity of [^{11}C]raclopride can be influenced to a greater degree by DA levels within the brain, where decreased levels of DA lead to increased binding of [^{11}C]raclopride [22,23].

PD is characterized by DA loss, resulting in the overactivation of the DA-D_2R indirect striatopallidal pathway and consequently an imbalance in the DA-D_1R direct striatonigral pathway [24,25]. This imbalance leads to an overall inhibitory influence on the basal ganglia–thalamic–cortical loop, which underlies the motor dysfunction associated with PD including slowness, stiffness, and deficits in gait and postural control. Acting principally through the DA-D_2R to enhance DA signaling, we hypothesize that exercise may serve to attenuate the overactivation of the DA-D_2R-containing indirect pathway and restore the balance between the direct and indirect projection pathways of the basal ganglia, thus leading to improved motor performance. An exercise-induced increase in [^{18}F]fallypride early in the disease may reflect a beneficial compensatory mechanism by the DA-D_2R to boost DA signaling within the indirect (striatopallidal) pathway of the dorsal striatum under conditions in which DA levels are low. In addition, as DA levels do not change significantly with exercise in MPTP-lesioned mice or 6-hydroxydopamine-lesioned rats, our pilot study suggests that compensatory changes in the DA-D_2R may be important for the exercise-related improved motor performance that we, and others, have reported [6,26]. Although mechanisms that modulate this effect of exercise on DA-D_2R expression are unknown, one possibility is through neurotrophic factors, such as brain-derived neurotrophic factor.

This study also demonstrates that exercise improves an early and sensitive motor feature in PD, namely postural control. This exercise-induced improvement in postural control may be explained through a potential compensatory effect of the DA-D_2R within the basal ganglia; this may also involve other related motor circuitry such as the cerebellum or the cerebral cortex [27,28]. In contrast, there were no marked exercise-induced changes in UPDRS scores. The UPDRS serves as a standard scale to assess the principal motor features of PD, namely bradykinesia, tremor, and rigidity [12]. Our exercise findings on postural control suggest a possible task-specific benefit of treadmill exercise in early-stage PD in that treadmill practice requires and thus improves control of dynamic balance through circuits involved in motor skill learning, especially those involving the prefrontal cortex. By comparison, the UPDRS takes into consideration more general whole body motor performance, which may not be impacted by more specific motor skilled training of gait and balance in early-stage patients. Thus, the more generalized UPDRS may not have the sensitivity to detect changes in motor behavior in such a small study. Larger studies examining specific motor components of the UPDRS may be necessary to detect any changes with exercise.

Conclusion

This pilot study demonstrates an exercise-induced increase in DA-D_2R expression in the basal ganglia of patients with early-stage and unmedicated PD, supporting similar findings in a rodent model of PD. This strengthens the validity of translating findings from the

laboratory to meaningful clinical practice, impacting patients' quality of life. In addition, this study demonstrates feasibility for intensive and challenging exercise in unmedicated and early-stage PD patients and supports the need for larger studies. In terms of clinical policy, our findings support the implementation of exercise as standard of care for individuals newly diagnosed with PD. Finally, establishing the impact of exercise on other dopaminergic circuits involving nonmotor behaviors affected in PD including cognition, depression, anxiety, and executive function, warrants investigation and can be designed into larger clinical studies in humans.

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Concept and study design: B.E.F., G.M.P., G.J.S.; study execution: B.E.F., G.M.P., Q.L., A.N., G.J.S., J.S., J.Y., J.H.; data analysis: B.E.F., G.M.P., Q.L., A.N., G.J.S., J.S., J.Y., M.W.J.; manuscript writing of draft: B.E.F., G.M.P., G.J.S., M.W.J.; manuscript editing and final approval: B.E.F., G.M.P., Q.L., A.N., G.J.S., J.S., J.Y., J.H., M.W.J.

Conflicts of interest

There are no conflicts of interest.

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Contact information

Rocco S. Presutti

Manager Business Operations
Neuroscience
OhioHealth Delay the Disease
500 Thomas Lane
Columbus, Ohio 43214
(614) 566.1189 cell | (614) 800.7060
rocco.presutti@ohiohealth.com
DelayTheDisease.com

Jackie Russell, RN BSN CNOR

Co-Founder / Program Development Coordinator
OhioHealth Delay the Disease
500 Thomas Lane
Columbus, Ohio 43214
(614) 975.5874
jackie.russell@ohiohealth.com
DelayTheDisease.com

David Zid BA, ACE, APG

Co-Founder OhioHealth Delay the Disease
Director, Movement Disorder and MSK Wellness
500 Thomas Lane
Columbus, Ohio 43214
(614) 419.4678
david.zid@ohiohealth.com
DelayTheDisease.com