EXERCISE & PARKINSON’S DISEASE: PART III

MEDICAL EVIDENCE FOR A STRONG RELATIONSHIP

Philip W. Tipton, M.D. | Parkinson’s ExercisAbilities Conference
May 22, 2020
TIME LINE

NOVEMBER 14, 2020
1. Introduction to the nervous system
2. Concept of neurodegeneration
3. Studying exercise & neurodegeneration
4. Animal studies

MARCH 20, 2021
1. Rapid review
2. Human studies of Alzheimer’s disease
3. Human studies of Parkinson’s disease

MAY 22, 2021
1. Rapid review & summary of evidence
2. Call to action
INTRODUCTION TO THE NERVOUS SYSTEM
WHAT IS A NEURODEGENERATION?
THE FACES OF NEURODEGENERATIVE DISEASE
Parkinson’s disease
THE STUDY OF EXERCISE & NEURODEGENERATION
NEUROPLASTICITY

Ability for neural networks to change to suit the needs of the individual.
**IMPORTANT TERMINOLOGY**

- **Neuron (86,000,000,000 in the human brain)**
  - One type of brain cell that transmits information in the form of electrical impulses to a synapse
- **Synapse (1,000,000,000,000,000 in the human brain)**
  - The space between a pre- & post-synaptic neuron.
  - Site of neurotransmission.
    1. Neurotransmitters are released from the pre-synaptic neuron
    2. Neurotransmitters travel across the synaptic cleft
    3. Neurotransmitters activate specific receptors on the post-synaptic neuron
- **Neurotrophic factor**
  - Naturally occurring compounds that promote neuroplasticity by pruning and strengthening synapses
  - Ex. Brain-derived neurotrophic factor (BDNF) & Glial-derived neurotrophic factor (GDNF)
NEUROPLASTICITY

- Exercised animals perform better on simple cognitive tasks
- Rats and mice show exercise-related improvement in spatial memory (maze) or object recognition

NEUROPLASTICITY

- Microscopic and neurophysiologic evidence of exercise-related neuroplasticity
- **Neurogenesis** occurs in the hippocampus
  - This may be enhanced with long-term running exercise in rodents.

NEUROPLASTICITY

- Treadmill exercise reverses dendritic spine loss in mouse model of Parkinson’s disease

NEUROPLASTICITY

- PD rat model (6-OHDA)
- “Compulsive” Treadmill exercise 24 hours after 6-OHDA lesion
  - 5 days/wk, 30 min/day, 11 meters/min
- Preservation in dopamine signaling (TH)
- Increased neurotrophic factors (BDNF & GDNF)

EXERCISE MAKES THE HIPPOCAMPUS BIGGER

Exercise training increases size of hippocampus and improves memory

A Hippocampus

B Caudate Nucleus

C Thalamus
EXERCISE INCREASES BDNF IN PD

- Serum BDNF levels significantly increased after 1 month of treadmill exercise in a cohort of patients with PD; the levels were unchanged in the unexercised control patients with PD
  - Cycling physiotherapy 3 hours per day, 5 days per week for 4 weeks.
- In 2 other uncontrolled studies, 8 weeks of cycling exercise significantly increased serum BDNF levels
  - Cycling 1 hour per day, 3 days per week for 8 weeks
  - Cycling interval training (3 × 1-h sessions weekly: 10-min warm-up, 40 min interval exercise, 10-min cool-down)
WHAT WE WANT TO KNOW...

1. Does exercise prevent Parkinson’s disease?
   • How early in life must one begin exercising?
   • What type of exercise is best?
2. Does exercise slow progression of PD?
   • What type of exercise?
   • What symptoms are slowed?
   • How does it do this?
   • Are we replacing brain cells?
3. Does exercise prevent PD-related cognitive decline?
   • If so, what type of exercise?
4. Consider secondary benefits
   • Ex. Exercise to prevent deconditioning to prevent falls or other serious injury which may appear to accelerate the disease
   • Cardiovascular and cerebrovascular benefits
Physical activities and future risk of Parkinson disease

**Physical activity and risk of Parkinson’s disease in the Swedish National March Cohort**

Fei Yang, Ylva Trolle Lagerros, Rino Bellocco, Hans-Olov Adami, Fang Fang, Nancy L. Pedersen, and Karin Wirdefeldt

**Lifetime occupational and leisure time physical activity and risk of Parkinson’s disease**

L-Fan Shih, Zeyan Liew, Niklas Krause, Beate Ritz

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WHAT WE KNOW...

1. Does exercise prevent Parkinson’s disease?
   • *Exercise is protective against PD.*
   • How early in life must one begin exercising?
     • *Earlier likely is better*
     • Yesterday is better than today, but today is better than tomorrow.
   • What type of exercise is best?
     • *Aerobic exercise, i.e. hot, sweaty, tired*
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AEROBIC EXERCISE DELAYS SYMPTOMS OF ALZHEIMER’S DISEASE

- **Who:** 275 people with AD mutations
- **What:**
  - Longitudinal study assessing
    - AD biomarkers
    - Cognitive scores (MMSE)
  - Exercise level evaluation
  - Self-reported average time (min/wk) in various exercise activities during the preceding 12 months
    - Stratified based on WHO & ACSM of 150 min PA per week
Back to the basics: Regular exercise matters in Parkinson's disease: Results from the National Parkinson Foundation QII Registry study

O. Ogwu, A. Eisenstein, M. Kwasny, T. Simuni

- Who: 4866 People with PD
  - 2252 patients with 1 yr follow up
- Non-exercisers (0 min/week)
- Low exercisers (1-150 min/week)
- Regular exercisers (>150 min/week)

- Regular exercisers at baseline had better:
  - quality of life
  - Mobility
  - physical function

- Regular exercisers at 1 year had less:
  - Progression of disease
  - Caregiver burden
  - Less cognitive decline
LSVT BIG STUDY

Comparing Exercises in Parkinson's Disease—The Berlin LSVT® BIG Study

Gregory D. Marzolf, MD, Amy Zehnder, MD, Robert Ryan, MD, and Christian Schlotz, MD

Habilitation, Therapy, and Rehabilitation Science, Department of Rehabilitation Medicine, University of Wisconsin

Background: Parkinson's disease (PD) is a degenerative neurological disorder that results in a progressive loss of dopamine-producing cells in the substantia nigra. This loss leads to a variety of motor and non-motor symptoms, including bradykinesia, tremor, rigidity, postural instability, and cognitive and psychiatric impairments. LSVT BIG is a rehabilitation program that aims to improve speech, voice, and non-verbal communication in people with PD. The program consists of a series of exercises designed to address the motor impairments associated with PD, focusing on increasing the amplitude, frequency, and intensity of movement.

Methods: The study compared the effectiveness of three different exercise programs: LSVT BIG, WALK, and HOME. Participants were randomly assigned to one of these groups and underwent supervised exercise sessions for 12 weeks. The primary outcome measure was the change in the PDQ-39 quality-of-life scale, which assesses the impact of PD on various aspects of daily life, including mobility, physical functioning, emotional well-being, stigma, and fatigue.

Results: The results showed significant improvements in quality of life for participants in the LSVT BIG group compared to the WALK and HOME groups. Participants in the LSVT BIG group demonstrated an increase in the PDQ-39 quality-of-life scale, indicating improved quality of life in various domains.

Conclusion: The findings suggest that LSVT BIG is an effective exercise program for improving quality of life in people with PD. Further research is needed to explore the long-term effects of LSVT BIG and to identify the most effective exercise strategies for improving quality of life in people with PD.

LSVT LOUD has been documented to improve vocal loudness, breath support, voice quality, intonation, and speech articulation (Mahler et al., 2015). The goal is always healthy vocal loudness.
FMRI BRAIN ACTIVATION AND CONNECTIVITY IMPROVED WITH EXERCISE IN PD

Motor sequence learning (MSL) effect in PD patients before and after aerobic training

Changes in aerobic fitness (VO2peak) predict MSL-related changes in functional brain activity in PD patients

Greater MSL-related functional brain changes in PD patients than in healthy controls after ACT
WHAT WE KNOW...

2. Does exercise slow progression of PD?
   - *This is unclear, but it is associated with better mobility, physical function and quality of life*
   - What type of exercise?
     - *Regular exercise (>150min/wk of aerobic exercise)*
     - *LSVT BIG*
   - What symptoms are slowed?
     - Lower UPDRS motor scores (LSVT)
     - Physical activity/mobility (aerobic)
   - How does it do this?
     - *Likely by enhanced neuroplasticity.*
     - Are we replacing brain cells?
       - *Likely not.*

Caveat:
None of these studies are actual proof that we are slowing the disease process.
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Exercise and Parkinson’s benefits for cognition and quality of life

- Who
  - 28 people with PD
- Intervention
  - Exercise Intervention Program (n=15)
    - Combination of strength & cardiovascular training
    - 2 one hour sessions per week for 12 weeks
  - Control (n=13)
- Findings
  - Exercise improved frontal lobe-based executive function
EXERCISE IN EARLY PD AND LATER DEMENTIA

• Who
  • 24 people with PD
• Intervention (6 months)
  • Individualized exercises (n = 8)
  • Group exercises (n = 8)
  • Monitoring (n = 8)
• Measurement
  • Executive function assessment with Wisconsin card sorting test & the Raven colored progressive matrices
• Findings
  • Exercise improved frontal lobe-based executive function on the Raven

Exercise sessions
• 10 min: muscular stretching with background music
• 25 min: Variety of proprioceptive & strength activities
• 25 min: Walking and balancing with different support bases and directions
• 10 min: muscular stretching with background music
EXERCISE IN EARLY PD AND LATER DEMENTIA

- **Who**
  - 17 people with PD

- **Intervention**
  - Treadmill (n=9)
    - 12 45-minute sessions (1 per day, 3 day/wk for 4 weeks)
  - Control (n=8)
    - Required to have “regular social interactions”

- **Measurement**
  - Frontal Assessment Battery-Italian version (FAB-it)
  - 6-minute walking test (6MWT)

- **Findings**
  - Treadmill improved cognition & motor features
EXERCISE IN EARLY PD AND LATER DEMENTIA

- Who
  - 20 people with PD

- Intervention
  - Trained (n=10)
    - Aerobics (moderate intensity over long duration)
    - 60-min sessions, 3x per wk for 6 months
  - Control (n=10)

- Findings
  - Exercise improved cognition on Wisconsin card sorting test
WHAT WE KNOW...

3. Does exercise prevent PD-related cognitive decline?
   • *It protects against cognitive decline*
   • If so, what type of exercise?
     • *Aerobic exercise*
WHAT ARE THE NEXT STEPS?
Levodopa is the most effective medication for Parkinson’s disease. Discuss with your doctor whether you are on the optimal dose.

**STEP 1**

**STEP 2**
Find an accountability partner(s)

**STEP 3**
Work towards at least 150 min of aerobic exercise per week

**STEP 4**
Consider participating in a formal program

**STEP 5**
HAVE FUN!!
BRAIN CONNECTIVITY IMPROVED WITH EXERCISE IN PD
HOW FAST YOU PEDAL MATTERS

Baseline

EOT

EOT + 4wks

EOT

EOT + 4wks

TABLE 3. COORDINATES OF CLUSTERS SHOWING SIGNIFICANT CORRELATION BETWEEN CADENCE AND CHANGE IN FC WITH *M1 AT EOT +4

<table>
<thead>
<tr>
<th>Cluster</th>
<th>No. of voxels</th>
<th>Coordinates</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>547</td>
<td>55.9, 15.4</td>
<td>Right superior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>temporal gyrus</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>535</td>
<td>24.6, 15.5</td>
<td>Right thalamus</td>
</tr>
</tbody>
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MAY 22, 2021
QUESTIONS
THANK YOU