EXERCISE & PARKINSON'S DISEASE: PART II
MEDICAL EVIDENCE FOR A STRONG RELATIONSHIP

Philip W. Tipton, M.D. | Parkinson's ExercisAbilities Conference
November 14, 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
THE STUDY OF EXERCISE & NEURODEGENERATION
WHAT WE WANT TO KNOW...

• Does exercise prevent Parkinson’s disease?
  • How early in life must one begin exercising?
  • What type of exercise is best?
• Does exercise slow progression of PD?
  • What type of exercise?
  • What symptoms are slowed?
  • How does it do this?
    • Are we replacing brain cells?
• Does exercise prevent PD-related cognitive decline?
  • If so, what type of exercise?
• 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
Aerobic Exercise: Evidence for a Direct Brain Effect to Slow Parkinson Disease Progression

J. Eric Ahlskog, PhD, MD

Abstract

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

HURDLES

• How do we answer these questions?
  • Level of evidence
    • Anecdotal
    • Randomized control trials

• Considerations
  • PD is slow
  • Biomarkers are lacking
  • How to measure exercise
    • Reporting bias

• Cost (reality)
  • Exercise isn't profitable
EFFECT OF AEROBIC EXERCISE ON 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

Baseline
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)
Physical activities and future risk of Parkinson disease

Q. Xu, MD, PhD
Y. Park, ScD
X. Huang, MD, PhD
A. Hollenbeck, PhD
A. Blair, PhD
A. Schatzkin, MD, PhD
H. Chen, MD, PhD

MIDLIFE EXERCISE REDUCES LATER PD RISK

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

Fei Yang,1 Ylva Trolle Lagerros,2 Rino Bellocco,1,3 Hans-Olov Adami,1,4 Fang Fang,1
Nancy L. Pedersen1,5 and Karin Wirdefeldt1,6

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

I-Fan Shih 1, Zeyan Liew 2, Niklas Krause 2, Beate Ritz 2,3,*

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2 Department of Neurology, School of Medicine, University of California at Los Angeles, California, USA
Back to the basics: Regular exercise matters in Parkinson's disease: Results from the National Parkinson Foundation QII Registry study

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b Ruerler Center on Aging, Health & Society Northwestern University, Chicago, IL, USA
c Department of Preventive Medicine, Northwestern University, Chicago, IL, USA
d Department of Neurology, Northwestern University, Chicago, IL, USA

Table 1
Baseline demographics and disease characteristics.

<table>
<thead>
<tr>
<th>No exercise</th>
<th>Light exercise</th>
<th>Regular exercise</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex – male</td>
<td>3047 (62.8%)</td>
<td>1739 (35.5%)</td>
<td>773 (15.8%)</td>
</tr>
<tr>
<td>Age at SM</td>
<td>65.0 ± 10.8</td>
<td>66.3 ± 10.8</td>
<td>67.5 ± 10.8</td>
</tr>
<tr>
<td>RFF</td>
<td>217 ± 3.4</td>
<td>230 ± 3.9</td>
<td>213 ± 3.4</td>
</tr>
<tr>
<td>Mobility</td>
<td>412.5 (100.0)</td>
<td>412.8 (100.0)</td>
<td>412.3 (100.0)</td>
</tr>
<tr>
<td>Age at onset</td>
<td>54.0 (10.8)</td>
<td>54.0 (10.8)</td>
<td>54.0 (10.8)</td>
</tr>
<tr>
<td>Living at home</td>
<td>4619 (64.0%)</td>
<td>2554 (56.0%)</td>
<td>1112 (13.8%)</td>
</tr>
<tr>
<td>Care partner – yes</td>
<td>3972 (60.5%)</td>
<td>1112 (13.8%)</td>
<td>3972 (60.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>4186 (27.4%)</td>
<td>2061 (34.0%)</td>
<td>3972 (60.5%)</td>
</tr>
<tr>
<td>Hart 3.3</td>
<td>3660 (27.4%)</td>
<td>3660 (27.4%)</td>
<td>3660 (27.4%)</td>
</tr>
<tr>
<td>History of falls</td>
<td>1355 (20.7%)</td>
<td>1355 (20.7%)</td>
<td>1355 (20.7%)</td>
</tr>
</tbody>
</table>

Table 2
Exercise as a correlate of quality of life, mobility, physical function, and caregiver burden (n = 4860).

<table>
<thead>
<tr>
<th></th>
<th>Univariate m ± SD</th>
<th>p-Value</th>
<th>Adjusted m ± SE</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDQ – total</td>
<td>48.4 ± 28.2</td>
<td>&lt;0.001</td>
<td>54.7 (14.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>45.4 ± 27.8</td>
<td>52.2 (15.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>34.9 ± 24.5</td>
<td>47.5 (14.1)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MDQ - mobility</td>
<td>15.8 ± 11.9</td>
<td>&lt;0.001</td>
<td>19.3 (5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>14.6 ± 11.5</td>
<td>18.0 (5.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>9.8 ± 9.9</td>
<td>15.9 (5.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>TUG</td>
<td>12.6 ± 4.7</td>
<td>&lt;0.001</td>
<td>14.2 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>12.4 ± 4.7</td>
<td>13.0 (3.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>11.2 ± 4.0</td>
<td>13.2 (3.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MCI total</td>
<td>14.7 ± 12.1</td>
<td>&lt;0.001</td>
<td>14.3 (8.8)</td>
<td>0.026</td>
</tr>
<tr>
<td>Low</td>
<td>14.6 ± 11.3</td>
<td>14.3 (8.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>11.6 ± 10.8</td>
<td>13.2 (8.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

- Adjusted for cognition, disease duration, severity, age, gender, values are the least square means and (standard errors).

• 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
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 for 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 for with background music
• 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group</th>
<th>Baseline</th>
<th>One month</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAB-14</td>
<td>Intervention</td>
<td>14.00 (11.00, 15.00)</td>
<td>16.00 (14.00, 17.00)</td>
</tr>
<tr>
<td>6MWT (metres)</td>
<td>Control</td>
<td>14.00 (14.00, 16.00)</td>
<td>14.00 (14.00, 15.73)</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>Intervention</td>
<td>310.22 (83.28)</td>
<td>346.67 (80.70)</td>
</tr>
<tr>
<td>MoCA (3-32)</td>
<td>Control</td>
<td>286.75 (101.31)</td>
<td>307.25 (89.47)</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>Intervention</td>
<td>24.00 (19.50, 27.00)</td>
<td>25.50 (20.50, 29.62)</td>
</tr>
<tr>
<td>TMT-A (seconds)</td>
<td>Control</td>
<td>23.00 (20.25, 26.00)</td>
<td>24.50 (22.00, 26.75)</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>Intervention</td>
<td>141.00 (113.90)</td>
<td>120.67 (104.59)</td>
</tr>
<tr>
<td>TMT-B (seconds)</td>
<td>Control</td>
<td>123.50 (101.27)</td>
<td>134.75 (108.55)</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>Intervention</td>
<td>200.00 (86.19)</td>
<td>149.86 (89.32)</td>
</tr>
<tr>
<td>Mil (0-9)</td>
<td>Control</td>
<td>6.50 (6.05, 7.16)</td>
<td>5.50 (4.60, 6.74)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>Intervention</td>
<td>10.00 (1.50)</td>
<td>7.81 (1.50)</td>
</tr>
<tr>
<td>10MWT (seconds)</td>
<td>Control</td>
<td>9.41 (3.00)</td>
<td>9.30 (2.42)</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>Intervention</td>
<td>11.00 (8.00, 25.00)</td>
<td>6.00 (3.00, 16.05)</td>
</tr>
<tr>
<td>BED (0-60)</td>
<td>Control</td>
<td>13.00 (9.25, 25.00)</td>
<td>13.00 (7.00, 15.79)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>Intervention</td>
<td>40.00 (33.50, 45.50)</td>
<td>37.00 (30.00, 43.00)</td>
</tr>
<tr>
<td>UPDRS (0-147)</td>
<td>Control</td>
<td>42.00 (33.75, 43.75)</td>
<td>40.50 (34.25, 42.75)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>Within-group comparisons</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
EXERCISE IN EARLY PD AND LATER DEMENTIA

Who
- 43 people with PD

Intervention
- Continuous Training (n=10)
- Interval Training (n=10)

Findings
- Exercise improved cognition on Wisconsin card sorting test
CHANGES IN BRAIN FUNCTIONAL CONNECTIVITY IN PARKINSON’S DISEASE

Figure 2
Changes in resting-state functional connectivity in patients with Parkinson disease over time

Brain regions show decreases in resting-state functional connectivity (synchronization likelihood) values in patients with Parkinson disease (n = 38) over time. Coronal, transverse, and sagittal views are shown (X = -91, Y = -109, Z = -91). Orange: p < 0.01; red: p < 0.05; paired samples t test.

Table 2
Association over timepoints between global cognitive performance (CAM COG) and functional connectivity (SL) in patients with Parkinson disease for the 13 brain regions showing the most significant changes in SL

<table>
<thead>
<tr>
<th>Brain region (bilaterally)</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior frontal gyrus, orbital part</td>
<td>0.129</td>
<td>0.008</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>0.193</td>
<td>0.003</td>
</tr>
<tr>
<td>Parsa centralis lobula</td>
<td>0.261</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>0.198</td>
<td>0.001</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>0.184</td>
<td>0.004</td>
</tr>
<tr>
<td>Superior parietal gyrus</td>
<td>0.242</td>
<td>0.002</td>
</tr>
<tr>
<td>Superior occipital gyrus</td>
<td>0.219</td>
<td>0.005</td>
</tr>
<tr>
<td>Middle occipital gyrus</td>
<td>0.237</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior occipital gyrus</td>
<td>0.207</td>
<td>0.004</td>
</tr>
<tr>
<td>Calcarine cortex</td>
<td>0.207</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cuneus</td>
<td>0.206</td>
<td>0.002</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>0.184</td>
<td>0.004</td>
</tr>
<tr>
<td>Median (pars) cingulate gyrus</td>
<td>0.185</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Abbrevoations CAM COG = Cambridge Cognitive Examination; SL = synchronization likelihood. β Coefficients are standardized in order to facilitate interpretability.

Figure 3
Distribution of functional connectivity changes in patients with Parkinson disease over time

Distribution of reduced functional connectivity with other brain regions (synchronization likelihood, p < 0.05; paired samples t test) for the paracentral (A), superior parietal (B), middle occipital (C), and superior temporal (D) regions in patients with Parkinson disease (n = 38) over time. Coronal, transverse, and sagittal views are shown (X = -91, Y = -109, Z = -91).
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 (VO_{2max}) predict MSL-related changes in functional brain activity in PD patients.

Changes in aerobic fitness (VO_{2max}) and MSL-related changes in functional brain activity.

Fig. 1. Motor sequence learning (MSL) effect in PD patients before and after aerobic training.

Fig. 2. Changes in aerobic fitness (VO_{2max}) predict MSL-related changes in functional brain activity in PD patients.
FMRI BRAIN ACTIVATION AND CONNECTIVITY IMPROVED WITH EXERCISE IN PD

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 55.9 15.4</td>
<td>Right superior temporal gyrus</td>
</tr>
<tr>
<td>2</td>
<td>535</td>
<td>24.6 -19.6 15.5</td>
<td>Right thalamus</td>
</tr>
</tbody>
</table>
**TIME LINE**

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  2. Concept of neurodegeneration
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  2. Human studies

- **MAY 22, 2021**
  1. Rapid review & summary of evidence
  2. Call to action (Exercise & More)
QUESTIONS
THANK YOU