Ageing, Exercise and Brain Plasticity

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Perspectives on Aging

• *The afternoon knows what the morning never suspected.*
  – Robert Frost

• *When I was younger, I could remember anything, whether it had happened or not; but my faculties are decaying now and soon I shall be so I cannot remember any but the things that never happened. It is sad to go to pieces like this but we all have to do it.*
  – Mark Twain
Meta-analyses: risk for cognitive decline

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk ratio IV, Random, 95% CI</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ho et al., (M)</td>
<td>2.7%</td>
<td>0.53 [0.25, 1.12]</td>
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<tr>
<td>Ho et al., (F)</td>
<td>5.8%</td>
<td>0.53 [0.32, 0.87]</td>
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<tr>
<td>Laurin et al., (M)</td>
<td>4.6%</td>
<td>0.68 [0.39, 1.19]</td>
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<tr>
<td>Laurin et al., (F)</td>
<td>3.6%</td>
<td>0.47 [0.25, 0.89]</td>
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<tr>
<td>Schuit et al.,</td>
<td>1.4%</td>
<td>0.50 [0.18, 1.41]</td>
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<tr>
<td>Yaffe et al.,</td>
<td>20.5%</td>
<td>0.74 [0.60, 0.91]</td>
<td></td>
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<tr>
<td>Pignatti et al.,</td>
<td>1.3%</td>
<td>0.27 [0.09, 0.82]</td>
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<tr>
<td>Lytle et al.,</td>
<td>2.8%</td>
<td>0.45 [0.22, 0.94]</td>
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<tr>
<td>Flicker et al.,</td>
<td>3.2%</td>
<td>0.50 [0.25, 1.00]</td>
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<tr>
<td>Singh–Manoux et al.,</td>
<td>16.7%</td>
<td>0.61 [0.48, 0.78]</td>
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<tr>
<td>Sumic et al., (M)</td>
<td>0.9%</td>
<td>0.91 [0.25, 3.36]</td>
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<tr>
<td>Sumic et al., (F)</td>
<td>0.9%</td>
<td>0.12 [0.03, 0.44]</td>
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<tr>
<td>Middleton et al.,</td>
<td>19.1%</td>
<td>0.73 [0.59, 0.91]</td>
<td></td>
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<tr>
<td>Niti et al.,</td>
<td>12.6%</td>
<td>0.62 [0.46, 0.84]</td>
<td></td>
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<tr>
<td>Etgen et al.,</td>
<td>3.9%</td>
<td>0.46 [0.25, 0.85]</td>
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Total (95% CI) 100.0% 0.62 [0.54, 0.70]

Heterogeneity: $\tau^2 = 0.01; \chi^2 = 16.94, df = 14 (P = 0.26); l^2 = 17\%$

Test for overall effect: $Z = 7.49 (P < 0.00001)$

Sofi et al., 2011
Meta-analyses: risk for Alzheimer’s disease

Scarmeas et al. [15] 20.73% -0.46 [-0.82, -0.11]
Buchman et al. [8] 7.74% -0.63 [-1.22, -0.05]
Scarmeas et al. [13] 9.20% -0.73 [-1.27, -0.20]
Larson et al. [14] 14.96% -0.37 [-0.79, 0.05]
Lindsay et al. [12] 24.18% -0.37 [-0.70, -0.04]
Podewils et al. [7] 11.94% -0.36 [-0.83, 0.11]
Abbott et al. [16] 4.86% -0.80 [-1.54, -0.06]
Yoshitake et al. [17] 1.77% -1.71 [-2.94, -0.49]
Ravaglia et al. [18] 4.62% -0.36 [-1.11, 0.40]

FE Model 100.00% -0.49 [-0.65, -0.32]

Figure 2 Caption: physical activity and the reduction of risk in developing Alzheimer's disease.

Beckett et al., 2015
**Stroke**

Oberlin, et al., 2017

**MCI**

Song et al., 2018

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**Fig. 2.** Meta-analysis of exercise effects on global cognition in comparison to control conditions. Box size represents study weighting. Diamond represents overall effect size and 95% CIs.
Exercise training improves cognitive function in older adults

Colcombe & Kramer, 2003
What’s happening in the brain?
Could cardiorespiratory fitness explain variation in hippocampal volume?

165 adults between 59-81 years of age
Free of dementia
Spatial memory assessment
Aerobic fitness assessment (VO$_2$ peak) treadmill test.
MRI assessment
Volumetric assessment of the hippocampal formation

Erickson, Prakash, Voss, Chaddock, Hu, Morris, White, Wojciki, McAuley, Kramer, 2009
Fitness and hippocampal volume

Erickson, Prakash, Voss, Chaddock, Hu, Morris, White, Wojcicki, McAuley, Kramer, 2009
49 preadolescent children; 9-10 yrs old


34 males; 15-18 yrs old

Herting & Nagel, 2012
71 early stage Alzheimer’s Disease patients

Honea et al., 2009

29 breast cancer survivors

Chaddock-Heyman et al., 2015
What are the effects of a randomized exercise intervention on hippocampal volume?
The Design of Exercise Intervention

- Older sedentary adults
- Baseline assessments
- Randomization
- 6-months or 1-year of treatment
- Fitness
  - MRI
  - Cognitive testing
  - Blood biomarkers
- Brisk Walking
- Stretching/Toning control
- Both groups receive physical activity around a track
- Both groups receive laboratory based treatment in groups
- Both groups come to the lab 3 days per week for 30-45 minutes
- Differences: Intensity and type of physical activity
- Follow-up assessments
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<td>67.6 (5.81)</td>
<td>65.5 (5.44)</td>
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<td>Sex (% female)</td>
<td>73%</td>
<td>60%</td>
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Erickson, Voss, Prakash, et al. (2011).
Are improvements in fitness associated with changes in volume?

Erickson, Voss, Prakash, et al. (2011).
6-months of exercise increased prefrontal cortex volume

Higher fitness levels are associated with greater prefrontal cortex volume
Mechanisms

Physical activity → Level 1 Cellular and molecular changes → Level 2 Structural and functional brain changes → Level 3 Behavioral/Socioemotional changes → Cognitive functioning

Stillman et al., 2016
Effects of exercise in rodents

- Exercise in rodents
  - Induces angiogenesis & neurogenesis
  - Induces synaptogenesis
  - Enhances learning and memory
  - Increases production and secretion of brain-derived neurotrophic factor (BDNF) among others
  - Is neuroprotective against damage from stroke, depression
  - Reduces inflammation
  - Reduces amyloid deposition
Hippocampus, exercise, and brain-derived neurotrophic factor

Increased volume was associated with increased BDNF levels.

Erickson, Voss, Prakash, et al. (2011).
Other mediators

- Insulin/glucose regulation (Jeong et al., 2018; Yau et al., 2017)
- Insulin-like Growth Factor (IGF-1) (Carro et al., 2000; Maass et al., 2016)
- Vascular Endothelial Growth Factor (Fabel et al., 2003)
- Inflammation (Allen et al., 2015; Di Benedetto et al., 2017)
- Cathepsin B (Moon et al., 2016)
- Cerebrovascular effects (Maass et al., 2015; Tyndall et al., 2013)
- Oxidative stress (Friedenreich et al., 2016)
Moderating factors
Example: Gender

• Benefits greater for females:
  – Interventions with more females show larger effect sizes (Colcombe & Kramer, 2003).
  – Females with mild cognitive impairment (MCI) showed greater benefits across a variety of cognitive tasks (Baker et al., 2010).
  – Female rats show greater changes in capillary structure after exercise (Huang et al., 2013).
  – In the Health and Retirement Study – only females showed reduced depressive symptoms with greater physical activity (Carrol et al., 2010).
  – Greater physical activity was associated with reduced depressive symptoms – only in females (Gujral et al., 2014).
Example: APOE genotype

Head et al., 2012
Erickson, et al. (2013)
More on Moderation

• Challenge: Most studies on moderators have been done in cross-sectional studies
  – Requires larger sample sizes so most RCTs are insufficiently powered to test moderators

• Other moderators:
  – Hormone therapy use (Erickson et al., 2007)
  – Omega-3 intake (Leckie et al., 2014)
  – BDNF genotype (Erickson et al., 2013)
  – Baseline fitness or PA levels? Duration or intensity of activity? Intellectual stimulation? Etc.
Many unanswered questions:
1. How long are the effects of exercise retained?
2. What types of exercise are most effective?
3. What are the dose-response effects?
4. What do volumetric differences reflect on a cellular level?
• Phase III randomized clinical trial of cognitively normal older adults
• 639 participants; 12 month supervised intervention
• Dose response (150 minutes; 225 minutes)
$31 million investment by the National Institutes of Health

5 collaborating institutions

1755 people screened

352 people randomized

6,180 hours procedures
- 3,293 hours of cognitive testing
- 1,015 hours of cardiovascular and anthropometric testing
- 1,336 hours of brain imaging
- 536 hours of labs

20,148 hours exercise prescribed
- 17,126 hours of exercise completed (85% adherence)

37,071 miles covered
- Enough to walk from Oslo to Seoul 7.5 times!

1755 people screened
352 people randomized
Introducing the *Physical Activity Guidelines for Americans, 2nd edition*

Information adapted from the Physical Activity Guidelines for Americans, 2nd edition. Available at health.gov/PAGuidelines.
General Conclusions

• Exercise has widespread effects on the brain.

• Moderate intensity exercise several days a week is sufficient for improving brain health.

• Starting to exercise in late life is not futile: even those who are sedentary can improve function.

• Exercise may have long term health consequences for diseases of the brain.
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Collaborators
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Pete Gianaros

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Cathy Bender
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Thank you!