Aging, Exercise, and Brain Health

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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
Brain and cognition in adults without dementia

Kennedy, Erickson, Rodrigue, Voss, Colcombe, Kramer, Acker, Raz, 2009
Age-related decline: ubiquitous?

1. Individual differences
   - What are the factors contributing to this variation?

2. Interventions
   - Is it possible to develop methods to help maintain cognitive function and reverse or prevent atrophy?
     
     - Aerobic Exercise or physical activity
The promise of physical activity

1. **Spirduso et al. (1975)** – higher fit older adults outperformed their more sedentary peers.

2. **Black et al. (1990)** – animal studies identified the molecular pathways by which exercise influences brain function.

3. **Kramer et al. (1999)** – intervention studies find that 6-months of exercise improve executive control (task-switching, flanker, n-back).

4. **Podewils et al. (2004)** – epidemiological studies find that greater amounts of physical activity reduce the risk of dementia.
Exercise improves cognitive function in older adults

Colcombe & Kramer, 2003
Could cardiorespiratory fitness explain variation in hippocampal volume?

- Hippocampus plays a dominant role in memory formation.
- Deterioration predicts conversion to Alzheimer’s disease.
- Physical inactivity is a significant risk factor for dementia.
- Exercise unequivocally affects the hippocampus in rodents.
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, Wojcicki, McAuley, Kramer, 2009
Fitness, spatial memory, hippocampal volume

Hippocampus volume

Cardiorespiratory fitness ($VO_{2\text{peak}}$)

Volume (cm$^3$)

Erickson, Prakash, Voss, Chaddock, Hu, Morris, White, Wojcicki, McAuley, Kramer, 2009
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
- **Follow-up assessments**

- **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
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<th>Stretching Control</th>
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Erickson, Voss, Prakash, et al. (2011).
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Hippocampus

Caudate Nucleus

Thalamus

Erickson, Voss, Prakash, et al. (2011)
Interim summary

• Meta-analyses show that exercise improves memory and executive functions.

• Cross-sectional studies have documented that higher fitness levels are associated with larger hippocampal volumes.

• Randomized intervention increases the size of the hippocampus.
Effects of exercise or fitness on prefrontal cortex?

Are brain regions that support executive functions, including the prefrontal and parietal lobes, associated with fitness or exercise?
Voxel-Based Morphometry measuring brain morphology
Exercise, fitness, and brain volume

6-months of exercise increased prefrontal cortex volume

Higher fitness levels are associated with greater prefrontal cortex volume

Colcombe et al., 2006

Weinstein et al., 2012
We know:
✓ Brain areas associated with fitness and exercise.
✓ Cognitive processes most influenced by exercise interventions.
✓ 6-months is sufficient for detecting effects.

Many unanswered questions:
1. How long are the effects retained?
2. What kinds of exercises are most efficacious for promoting a healthy brain?
3. What are the dose-response effects?
4. What do volumetric differences reflect on a cellular level?
Mechanisms

• Molecular pathways
  – Brain Derived Neurotrophic Factor (BDNF)
  – Inflammation
  – Amyloid deposition

• Cognitive Neuroscience pathways
  – Functional networks
  – Volumetric networks

• Behavioral pathways
  – Mood and self-efficacy
  – Sleep patterns
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
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Question:
Could differences in volume be mediating the fitness-cognition links or exercise-cognition links?
General Mediation Model

Volume

Fitness/Exercise

Executive function
Volume-cognition mediation

Links between fitness/exercise, volume, and cognitive performance

- Erickson et al. (2009) – hippocampus and spatial memory
- Chaddock et al. (2010) – basal ganglia and flanker performance
- Erickson et al. (2011) – hippocampus and spatial memory
- Verstynen et al. (2012) – caudate nucleus and task switch performance
- Weinstein et al. (2012) – prefrontal cortex volume and stroop and spatial memory.
Whole brain mediation approach

- Previous studies have been limited to examining regions-of-interest.

- Most cognitive tasks require a network of areas.

- Could we examine on a voxel-by-voxel level the areas that mediate the link between fitness and any cognitive task?
Gray matter volume mediates association on a point-by-point basis

Weinstein et al., in preparation
Mechanistic summary

• We still know very little about the molecular pathways in humans that link exercise to enhanced cognition.

• BDNF is one possible molecular pathway – there are probably many more.

• Associations with volume appear to mediate the fitness-cognition associations.
  – More results from randomized trials are forthcoming that should more explicitly assess these associations.
Physical activity moderates the effect of APOE*4 on risk for dementia and amyloid deposition.
Overall – the next steps

- We need **longer interventions** with larger samples, multiple sites, to determine if incident rates change.

- **Longer follow-up** periods to determine persistence of benefits

- A better understanding of the **mechanisms** in humans – for clearer translation to animal models.

- A better understanding of **moderators** and the **combination of treatments**.

- The possibility of developing **targeted interventions** that might be tailored based on characteristics of the person.
Specific Conclusions

- Cardiorespiratory fitness explains individual variation in hippocampal and prefrontal cortex volume.

- One year of exercise is sufficient for increasing the size of the hippocampus and prefrontal cortex.

- Fitness – memory associations are mediated by increased prefrontal cortex and hippocampal volume.

- Physical activity offsets effect of BDNF polymorphism on working memory function.
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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Thank you!