Physical Activity in the Prevention of Cognitive Decline and Dementia

The State of the Science: Human Studies
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Cognitive Decline and Aging

• What happens with cognitive function as we get older?
  — Age-related cognitive decline (Normal cognition)
  — Mild Cognitive Impairment (MCI)
  — Dementia
  — Examples:
    — ARCD – I can’t remember where
    — Dementia – I can’t remember w

Age-related cognitive decline

• Cross-sectional evidence supports a relationship between advancing age and cognitive performance (Salthouse, 2009).

Mild Cognitive Impairment

• MCI is a decline that is > average for age and education level, but not severe enough to be considered dementia.
• More likely to become demented within the next 5 years

Dementia

• a decrease in memory and ≥1 other area of cognition → negatively affects the person’s ability to function in daily life.

Dementia

• Alzheimer’s disease
  — the most common form of dementia
  — memory impairment and cognitive impairment becomes progressively worse over time
Alzheimer’s disease

- Prevalence will reach
  - 65.7 million by 2030 (World Alzheimer Report, 2009)
  - 107 million by 2050 (Brookmeyer et al., 2007).
- Current treatments do not offer a cure for the disease
- Research is focused on preventive strategies that may reduce the risk of or delay the onset of AD.

Physical Activity

- A behavioral strategy that holds promise as a preventative treatment for dementia.
- Length of time until diagnosis with clinical cognitive impairment precludes use of Randomized Controlled Trials (RCTs) with clinical outcomes.
- “holds promise”
  - Evidence with cognitively intact
  - Evidence with cognitively impaired
  - Evidence from epidemiological studies
  - Mechanisms
  - Moderators

Evidence with cognitively intact

Age, Physical Fitness, and Learning

- Acquisition Day
  - Control group performed relatively few trials (n=40)
  - Experimental group performed relatively many trials (n=175)
- Retention Day
  - 24 hours later
  - Performed an additional 20 trials

Age, Aerobic Fitness, and Cognition in COPDers

- Assessed fluid intelligence (Culture Fair Intelligence Test) in older adults with Chronic Obstructive Pulmonary Disease (COPD) at baseline.
- All participants then received a 3 month exercise intervention.
- After 3 months, participants were randomly assigned to either continue to exercise for 15 more months or to return to their normal lifestyle.
Baseline Results
After controlling for depression ($R^2=0.14$) and education ($R^2=0.15$), the distance covered on the 6-min walk test was predictive of fluid intelligence ($R^2=0.17$).

18-month Results
- No change in cognitive performance for short-term exercisers ($ES=-0.03$).
- Significant improvement in cognitive performance for long-term exercisers ($ES=0.47$).
- Significant difference between the two groups at 18-months ($ES=0.99$).

18-month Results
The change in performance on the fluid intelligence task from 3 months to 18 months was reliably predicted by the change in walk distance for the 6-min walk test ($R^2=0.59$).

Evidence with Cognitively Intact
- Evidence supports that physical activity benefits cognitive performance.
- Meta-analytic reviews (statistical summary)
  - Etnier et al. (1997) - 17 RCTs across ages -> $ES=0.18$
  - Colcombe & Kramer (2003) - 18 RCT's with adults 55-80 years of age -> $ES=0.48$

Evidence with Cognitively Impaired
Randomized Control Trial (Lautenschlager et al., 2008)
- Sample: 170 older adults (> 55 years) with MCI
- Control: educational materials on health-related topics
- Exercise: same as control + moderate intensity exercise for ≥150 min/week for six months
- Outcomes: neuropsychological assessments and the ADAS-Cog at baseline, six, 12, and 18 months.
Evidence from Epidemiological Studies

<table>
<thead>
<tr>
<th>Back in Time</th>
<th>First Contact</th>
<th>Subsequent Contact</th>
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<tbody>
<tr>
<td>Retrospective</td>
<td>PA</td>
<td>Cognition</td>
</tr>
<tr>
<td>Case Control</td>
<td>PA</td>
<td>AD</td>
</tr>
<tr>
<td>Prospective Cohort</td>
<td>PA</td>
<td>Cognition</td>
</tr>
</tbody>
</table>

Summary

- Results support that physical activity participation results in cognitive improvements
  - in cognitively normal older adults
  - in cognitively impaired older adults
- Results from epidemiological studies support that physical activity participation is associated with a decreased risk of clinical cognitive impairment

Mechanisms

- Cerebral structure deterioration
  - Some areas show decline after age 30
  - Hippocampus preserved until 50 and then ~1% decline per year in cognitively normal and 3% decline per year in dementia (Jack et al., 1998)
**Designs**

Correlational Study
Erickson et al. (2009)
- Sample: 165 older adults without dementia
- Measures: MRI = the volume of the hippocampus.
- After controlling for age, sex, and education, older adults who were more aerobically fit had larger hippocampal volumes than their less fit peers

Prospective Study
Erickson et al. (2010)
- Sample: 299 adults over the age of 65.
- PA was assessed at baseline (# blocks walked/week).
- MRI data 9 years later

RCT
Erickson et al. (2011)
- Sample: 120 sedentary older adults without dementia
- Exercise: moderate intensity exercise 3 days/week for 1 year
- Control: stretching and toning

**Summary**
- Evidence from a variety of research designs supports that physical activity is associated with/can cause differences/changes in cerebral structure.
- These effects may delay the onset of clinical cognitive impairment.

Who benefits the most?
MODERATORS
Moderators

- Variables that may influence the extent to which physical activity benefits an individual in terms of mechanisms, behavioral outcomes (cognition), or both.
- Apolipoprotein E (epsilon 4 allele)

Moderators

- Apolipoprotein E (ApoE) genotype (epsilon 4 allele) – predictive of late onset cognitive decline and of the experience of Alzheimer’s disease (AD)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>In NA of European descent</th>
<th>Chance of AD by 80</th>
<th>Age of onset of AD</th>
</tr>
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<tbody>
<tr>
<td>ε4/ε4</td>
<td>~2%</td>
<td>50%</td>
<td>67</td>
</tr>
<tr>
<td>ε4/ε3</td>
<td>~25%</td>
<td>8.1%</td>
<td>72</td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>~55%</td>
<td>3.1%</td>
<td>73</td>
</tr>
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Correlational Study

- Etnier et al. (2007)
- N=75 adults (51-77 years of age)
- Three measures of memory and one of attention

Prospective Studies

- Schuit et al. (2001)
- N=347 men
- M age = 74.6 years
- 3 year follow-up for MMSE drop >3 points
- Active = >1 hour / day

- Rovio et al. (2005)
- N=1149 adults
- Age range = 65-79 years
- 11-26 year follow-up for AD
- Active = moderate PA for 20-30 min >2x/week
Can physical activity protect cognitive function in those at greatest risk for Alzheimer’s disease?

**ON-GOING CHRONIC STUDY**

**Etnier et al. (NIH 1 R21AG040310-01A1)**

- Goal: Recruit 60 cognitively normal young-older adults (50-65 years) with a family history of AD to be enrolled in an 8-month PA program

**Etnier et al. (NIH 1 R21AG040310-01A1)**

- 10.2.2013 – 56 participants enrolled
- Exercise: Walking and strength training for 45-60 min/day, 3 days/week for 8 months

**Tests at Baseline, Pretest, Midtest, and Posttest**

- Mini-mental status exam – to further confirm cognitive normality
- Geriatric Depression Scale
- CHAMPS

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<tr>
<th>Cognitive Tests</th>
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<tbody>
<tr>
<td>AVLT Symbol Digit</td>
</tr>
<tr>
<td>TOL CFT</td>
</tr>
<tr>
<td>PASAT Digit Span</td>
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<tr>
<td>Stroop TMT</td>
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<tr>
<td>Perceived Cognitive Symptoms TOL</td>
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- Submax fitness at all except baseline

**Hypotheses**

- ApoE e4 non-carriers serve as the comparison group.
- Expect both groups to show improvements, but the improvement in cognition will be greater for the ApoE e4 carriers
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- ApoE e4 non-carriers serve as the comparison group.
- Expect both groups to show improvements, but the improvement in cognition will be greater for the ApoE e4 carriers.
- Follow-up on prospective studies and lay work for subsequent RCT.

Progress Report

- 131 interested in participating
- 116 completed telephone screening
- 63 qualified for the study
- 21 participants began in Feb, 2013 (lost 2 for reasons not related to the study)
- 8 participants began in April, 2013
- 26 began in September, 2013

Preliminary Results – AVLT controlling for Education

Summary

- PAAD Study is going very well!
- Social support is huge component
- If data support cognitive benefits, will use to support proposal for an R01 in which a control group is included.

Overall Conclusions

- RCTs with cognitively intact individuals and in MCI patients: PA -> improved cognitive performance.
- Epidemiological studies: PA is associated with decreased risk of cognitive decline and of AD.
- Correlational, Prospective, and RCTs: PA -> changes in cerebral structure associated with better cognitive performance.
- Prospective and correlational evidence: PA might be most important for those at genetic risk for AD.
- Evidence that PA is an effective preventative therapy for AD “holds promise”

Why is prevention important?

- A therapy that delays the development of AD by 5 years could reduce the risk of AD by 50%.
- PA is low cost, has relatively few negative side effects, and has additional mental and physical health benefits, thus the total benefit of PA in relation to cost and risk is potentially very high.
Future Directions

• Learn more about dose-response relationship so we can actually “prescribe” exercise

• Improve our understanding of mechanisms
  – Helps with prescription
  – Helps with multimodal treatments

• Learn who might benefit the most from PA so we can target PA interventions to those individuals