Non-pharmacological approaches and modifiable risk factors in AD

Carl W Cotman
Univ. of California Irvine
What can be done for AD?

• No new FDA approved drugs for AD since 2003 (eg., Namenda) despite over 400 trials

• Lifestyles have emerged as effective strategies for delay of onset and improving symptoms.
Lifestyles that can modify risk for cognitive decline

• Exercise
• Cognitive activity
• Social activity
• Diet

Well-hidden story but gaining ....
Outline

• **Part 1:** Background. (no conflicts of interest)
• **Part 2:** Human epidemiological and clinical studies on lifestyles, recent controversies
• **Part 3:**
  - Multimodal clinical studies, combining lifestyles
  - Impact of lifestyles on gene expression patterns in human brain
How can cognitive decline be prevented?

Physical inactivity is #1 modifiable risk factor (Barnes and Yaffe, 2011)

“Sitting is the new smoking!” (Mayo Clinic)
BDNF is necessary for neuronal health and learning: Exercise?
Exercise increases BDNF levels in the hippocampus

**HIPPOCAMPUS:**

Rats: 1, 4 weeks wheel-running

Berchtold et al., 2002, Adlard et al., 2005
Overall Exercise Counteracts Brain Aging, the “Wonder Drug”!

- Generates BDNF (Brain derived neurotrophic factor) that enhances synaptic function and learning
- Drives formation of new neurons in the hippocampus
- Stimulates vascular growth and blood flow
- Improves cognitive function, particularly executive function
- Reduces rate of hippocampal atrophy
Exercise increases hippocampal volume and improves memory in elderly humans

Erickson et al., PNAS 2011

Cognitive improvement

Aerobic capacity improvement
Transgenic mice exist that include PS1 mutations, to “model” autosomal dominantly inherited disorders (PS1/APP).
Even late life exercise improves learning and reduces B-amyloid in P1/APP mice

Spatial learning

Amyloid levels

![Graph showing spatial learning and amyloid levels comparison between young and aged sedentary (SED) and exercise (EX) groups.](image-url)
Test on learning (Morris water maze) and measure brain β-amyloid
• **Part 2:** Epidemiological and clinical studies on lifestyles including recent controversies.
Nurses Health Study: Cognitive function and total physical activity, 18,000 nurses (Weuve, et al., 2004)

P<0.001

<table>
<thead>
<tr>
<th>level</th>
<th>activity</th>
<th>MET hr value</th>
</tr>
</thead>
<tbody>
<tr>
<td>vigorous</td>
<td>running</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>stair-climbing</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>jogging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bicycling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lap swimming</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tennis</td>
<td>7</td>
</tr>
<tr>
<td>moderate</td>
<td>aerobics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>calisthenics</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>brisk walking (3-4 mph)</td>
<td>4.5</td>
</tr>
<tr>
<td>light</td>
<td>strolling</td>
<td>2.5</td>
</tr>
</tbody>
</table>

For example:
1 hr/wk brisk walking – 4.5 MET-hrs
4 hrs/wk brisk walking = 18 MET-hrs
Exercise improves cognitive performance in those with MCI (Baker, 2010)

• Mild cognitive impairment (MCI) subjects (65-85 yrs old, N=17)
• Aerobic (3X/wk): 45 min at 60-80% HRR
• 6 months intervention
• Improved executive function and biomarkers such as glucose utilization
• Effects strongest in females
Exercise promotes a healthy brain in mice and men
At this juncture, the importance of exercise seemed non-controversial.

However ....
LIFE Study (Sink et al, JAMA 2015)

- Subjects: 1,635 physically frail, cognitively normal older adults followed for 24 months to test whether light to moderate exercise can improve physical and cognitive function

- Intervention: light to moderate physical activity (30 min walking + light resistance training, 3x/wk) vs. health education control

- Cognitive outcomes: Digit Symbol (primary), List Learning (Hopkins)
Outcome of Life Study

- Physical activity improved gait and reduced physical disability
- However, no effect on cognition….
- Exercise ‘dose’ may have been sufficient to improve physical function, but not cognition?
- More activity/wk to improve cognitive function?
NHS: Cognitive function and total physical activity (Weuve, 2004)

**Life Study:** 90min/wk light to moderate, which = <5.2 MET hours/wk activity (e.g. lowest activity quintile in Weuve Study, which had lowest cognitive function)
Direct test:
6m aerobic exercise (40 min, 4x/week) vs stretching

<table>
<thead>
<tr>
<th>mean (SD)</th>
<th>Aerobic</th>
<th>Stretch</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>64 (8)</td>
<td>66 (8)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28 (2)</td>
<td>29 (2)</td>
</tr>
</tbody>
</table>

400 m Walk Test, DEXA (%fat), Blood Collection
Lumbar Puncture (AD Biomarkers in CSF)
Brain MRI (volume, CBF)
Cognitive Assessment

Laura Baker
Aerobic Exercise: Effects on Cognition

Executive Function Composite

Sum Z Scores ~ Change from Baseline ~

ANOVA, p=0.009

Stretch

Aerobic
The enemy: plaques (brown), tangles (black) in a brain with Alzheimer's disease.

Can exercise reduce tangle accumulation?
Aerobic Exercise Effects on AD Biomarkers in CSF

Exercise Reduced pTau Levels in the OLDEST Adults

pTau Protein (pg/ml)
~Change from Baseline~

* Group x Age: p=0.01
Clinical translation

• Currently Dr. Laura Baker (Wake Forest) and I are carrying out a 300 subject multisite NIA trial of exercise on those with mild cognitive impairment (MCI) EXERT
• Involves collaboration with National and Local YMCAs
• Goal to stimulate more people to exercise. Enable physicians to write a “prescription” for exercise!
MY WHOLE ROUTINE LASTS AN HOUR AND A HALF.

15 MINUTES OF CARDIO, 15 MINUTES OF WEIGHTS, AND AN HOUR OF TALKING MYSELF INTO IT.
Late life cognitive activity preserves global cognition (Wilson, 2013)
Cognitive activity is linked to lower amyloid accumulation (Landau, 2012)
Social Engagement

• Social engagement is a key part of life and has many benefits, eg., DIAN network, etc.

• A higher level of social engagement is related to better cognitive function (social networks, activities, support) (Barnes, et al., 2004; Kruger, et al., 2009; Bryan, et al., 2011)
Recent exciting advances on Diet
Which Diet?

- MIND diet
- Mediterranean
- DASH (Dietary approaches to stop hypertension)

• The 3 diets are all beneficial
• Strongest cognitive protection from MIND diet.
• (Support from a higher animal model, aged dog)

Morris et al. 2015
MIND Diet is the most effective approach

MIND Diet consists of:

• Mediterranean Diet, plus

• DASH (Dietary Approaches to Stop Hypertension)
# MIND Diet

<table>
<thead>
<tr>
<th>Include These</th>
<th>Limit These</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Green leafy vegetables: every day</td>
<td>• Red meats</td>
</tr>
<tr>
<td>• Other vegetables: at least once per day</td>
<td>• Butter and stick margarine: less than 1 tablespoon per day</td>
</tr>
<tr>
<td>• Nuts: every day</td>
<td>• Cheese: less than one serving per week</td>
</tr>
<tr>
<td>• Berries: at least twice per week</td>
<td>• Pastries and sweets: limit</td>
</tr>
<tr>
<td>• Beans: every other day</td>
<td>• Fried or fast food: less than one serving per week</td>
</tr>
<tr>
<td>• Whole grains: three times per day</td>
<td></td>
</tr>
<tr>
<td>• Fish: at least once per week</td>
<td></td>
</tr>
<tr>
<td>• Poultry: at least twice per week</td>
<td></td>
</tr>
<tr>
<td>• Olive oil</td>
<td></td>
</tr>
<tr>
<td>• Wine: one glass per day</td>
<td></td>
</tr>
</tbody>
</table>
+++ Berries and Greens
Part 3: Multi-domain effects on lifestyles and gene expression patterns in human brain
Recent Multi-domain Lifestyle Trial (Finger)  
(Nagandu, 2015)

• Nearly all studies for cognitive impairment and AD have been single domain!
• Successful prevention trials for cardiovascular disease have emphasized the importance of a multi-domain approach.
• Finland study (2 yrs): 1260 at risk mildly impaired subjects (60-77yrs, Non-demented)
• **Control group vs Multi-domain intervention with:**
  – Diet and nutrition
  – Exercise
  – Cognitive training
  – Social activity with groups
Multi-domain Finnish study

Global cognitive score

- Intervention
- Control

Baseline | 12 months | 24 months

p = 0.03
Multi-domain Finish study

Processing speed

- Intervention
- Control

p=0.03

Baseline 12 months 24 months

Executive functioning

- Intervention
- Control

p=0.04

Baseline 12 months 24 months

Abbreviated memory score

- Intervention
- Control

p=0.038

Baseline 12 months 24 months
Question: Does physical/cognitive activity program genes in the human brain?

• Brain function is dictated by its gene expression patterns
• Does physical activity or cognitive or social activity program expression patterns? Which one(s)? All?
Microarray Analysis on Postmortem Human Hippocampus

• Used a set of postmortem tissues with known physical activity (Actical), cognitive activity and social activity. Followed regularly for 10+yrs (Bennett, Rush)

• Evaluated gene expression patterns via microarrays in well characterized cases.

• 76-100 yrs old, non-demented, N=36
Case distributions across lifestyle variables

ACTICAL predicted metabolic cost *

50,000 counts:
~ 10 min moderate/high activity (3.5 mph)
~ 60 min low activity (1.5 mph)

500,000 counts:
~ 100 min moderate/high activity (3.5 mph)
~ 6 hrs low activity (1.5 mph)

METs and accelerometry of walking in older adults: standard versus measured energy cost.
Cognitive and physical activity are salient lifestyle modalities.

Significant probesets:
- Cognitive: 4000 (increased), 1500 (decreased)
- Physical: 4000 (increased), 500 (decreased)
- Social: 1000 (increased), 500 (decreased)
What gene classes are targeted?

Main Gene Classes Up-regulated with Physical and Cognitive activity:

• Enhanced mitochondrial function
  – Electron transport, mitochondrial translation* (cog activity especially)

• Synaptic genes

• Increased protein trafficking and degradation
  – Ubiquitin-proteasome genes, ER to Golgi transport, trans-Golgi
Lifestyle enhances mitochondrial energy production

Significantly increased with physical activity

Significantly increased with cognitive activity
Anti-Aging effects of lifestyle?
Lifestyle counteracts gene expression changes in Aging and AD

What percentage of significant genes are anti-aging genes?

- Physical activity: 40% of all significant genes = anti-aging
- Cognitive activity: 28% of all significant genes = anti-aging
Summary

• **Exercise** slows HC atrophy, synapse loss reduces Aβ, “Wonder” drug

• **Cognitive, social activity** and **diet** (“Mind”) also slow rate of cognitive decline and counteract brain aging including gene expression patterns

• Most studies are “descriptive”. Recent Finnish **multimodal Lifestyle** intervention slows rate of cognitive decline over 2yrs by 25 % !!

• **Lifestyles build brain health**
Practice Healthy Lifestyles and have Fun! Spread the secret – lifestyles work!
Acknowledgements

Funding provided by NIA, Brain Research Fdn. No conflicts.
“If we could give every individual the right amount of nourishment and exercise we would have found the safest way to health.”

Hippocrates (ca. 460 BC – ca. 370 BC)