Exercise and AD Research: The Power of Healthy Lifestyle

Carl W Cotman
Neurology, and Neurobiology
Behavior UCI
Goal

• Promote Successful Aging, delay onset and treat AD
• Lifestyle strategies, the new frontier
• Which have the “most impact”?
Physical inactivity is #1 modifiable risk factor
(Barnes and Yaffe, 2011, Alz Assoc)
“Sitting is the new smoking!”
(Mayo Clinic)
Outline

• Age and synapses. Exercise increases BDNF (Brain derived neurotropic factor), “miracle molecule”
• Clinical studies on physical activity and cognition
• Exercise induces a molecular memory for its benefits
• Amount and type (controversy)
• Regulation of genes in human brain
Synaptic failure

Dennis Selkoe: “Alzheimer’s disease is a disease of synaptic failure” (Science, 2002)

- Loss of synapses in AD (Bob Terry, 1989)
- Defective synaptic plasticity caused by amyloid oligomers, eg., impairs long term potentiation (Bill Klein, 1998)
Amyloid (Aβ) oligomers target synapses
Key molecule is BDNF (brain derived neurotrophic factor), a growth or trophic factor.
BDNF (Brain Derived Neurotrophic Factor) is necessary for neuronal health and learning: Exercise?
BDNF (Brain derived neurotrophic factor)

- BDNF promotes neuronal health, survival, protects them from toxins
- Stimulates synaptic function and plasticity
- Essential for Long term potentiation (LTP), a synaptic mechanism for memory at the synapse
- Problem is molecule is a protein so cannot be given peripherally. How can BDNF be increased in brain?
Exercise increases BDNF levels in the hippocampus

HIPPOCAMPUS:

Rats: 1, 4 weeks wheel-running

Berchtold et al., 2002, Adlard et al., 2005
Physical activity and clinical trials. Status?
NHS: Cognitive function and total physical activity

Participation in leisure time activities: survey (Weuve, 2004)

Multivar. Adj
Difference in performance in the global score
An Exercise Intervention Improves Cognitive Performance (Lautenschlager, 2008)

• 119 Subjects with a subjective complaint of memory problems or mild cognitive impairment enrolled; 19 months
• Randomly assigned to home-based physical intervention or usual care
• Average increase in physical activity of 110min./wk
• Significantly improved ADAS-Cog 1.3X
Exercise improves MCI performance
(Baker, 2010)

• Mild cognitive impairment (MCI) subjects 65-85 yrs old
• Aerobic exercise: 3X/wk: 45 min at 60-80% HRR for 6 months
• Improved executive function and biomarkers such as glucose utilization
Issue: Regular exercise is rarely achievable. Likely will miss days, sometimes weeks.

- Can one stop exercising then restart, with no loss of cognitive benefits? What intervals?
- In other words, is there a “molecular” memory for exercise?
- Experiment examine BDNF induction, decay and re-induction with exercise in rodent hippocampus to test idea.
Exercise induces BDNF

• It has to be enough exercise
• BDNF levels go back down eventually after exercise stops, BUT.....
There is a “memory” for BDNF induction by exercise

BDNF can be rapidly reinduced, by just a little bit of exercise!
At this juncture, the importance of exercise seemed non-controversial.

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

• Design & Methods
  - 1,635 physically frail, cognitively normal older adults followed for 24 months to test whether light to moderate exercise can improve physical function (primary aim) and cognition (secondary)
  - 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)

• Results
  - No benefit of physical activity intervention on cognition
  - Caveat: achieved exercise ‘dose’ sufficient to improve physical function, but not cognition?
  - Dose of exercise was too low – need more weekly activity to move cognitive function
  - Weuve study: 90 min/week of moderate walking = <5.2 MET hours activity (e.g. lowest activity quintile in Weuve study, which had lowest cognitive function)
NHS: Cognitive function and total physical activity

Participation in leisure time activities: survey (Weuve, 2004)

Multivar. Adj
Difference in performance in the global score
Most recent results say ....
Aerobic Exercise Effects on Cognition, Blood flow, and CSF AD Biomarkers in Adults with MCI (L. Baker)
Study Design

Aerobic Training vs. Stretching Control

Month 0

Month 6

Diagnostic Evaluation & Consensus

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

<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>
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~

Stretch
Aerobic

<70 yrs
>=70 yrs

* Group x Age: p=0.01
Aerobic Exercise Increases Cerebral Blood Flow (CBF)

Whole Brain: Mean CBF

*p < 0.05; means adjusted for age, baseline BMI
Aerobic Exercise Increases Blood Flow in Regions Compromised by Aging & AD

* means adjusted for age, baseline BMI
Aerobic Exercise Effects on Cognition

Executive Function Composite

Sum Z Scores
~ Change from Baseline ~

ANOVA, p=0.009

Aerobic

Stretch
Need to understand fundamental way exercise improves brain health and cognitive function.

• Thus exercise even with MCI can remodel brain and boost function
• Let’s shift to the molecular level and fundamental mechanisms
• What synaptic molecular systems fail in human brain?
Mechanism...

• To identify possible mechanisms, we focused on gene activity related to synapses in the human brain.

• What happens to synaptic genes in normal aging? Is there synaptic weakening or failure?

• Do exercise and other lifestyle variables counteract age-related gene changes?
How do synaptic gene expression patterns change with age in the human brain?
Neurotransmitter receptors: gene expression for young, aged, AD

(Berchtold, Cotman, 2013 Neurobio Aging)

- Greater gene downregulation in aging, little additional change in AD
- Hippocampus is the exception

Because there is little cortical synaptic loss in Aging, the extensive gene downregulation suggests that the synaptic machinery in existing synapses in the cortex is less functional.
Can Lifestyle Variables Counteract these aging-trends?

- Exercise
- Cognitive stimulation
- Social stimulation
Lifestyle variables and Gene Expression....

- Examine postmortem cases from individuals who have been followed longitudinally, from Rush Memory and Aging Project (MAP).
- Age 85 ± 10 yrs., cognitively intact cases (n=36)
- Annually assessed for:
  - Cognitive function
  - Social activity
  - Cognitive frequency
  - Physical activity (measured using actigraphy)
Study Design

Microarray study (Affymetrix, HgU133 plus 2.0)
Synaptic function genes (340 genes)
  - analyzed by Multi-variate linear regression
  - data adjusted for age, education, depression
Which measure has greatest impact??
Cognitive, Social, Physical, All about equal?
For the hippocampus:
Physical activity is more salient than cognitive and social activity

Hippocampus and Synaptic Genes
synaptic genes with significant association between expression and physical activity:

![Graph showing positive and negative correlations between synaptic genes and physical activity.](image)
Gene Expression in the physically active

In the RUSH-Memory and Aging population:

• Total level of physical activity is inversely correlated with the rate of cognitive decline (p=0.007) (Buchman et al., 2012)

• Our data shows that physical activity changes synaptic gene expression in the hippocampus

• What aspects of synaptic function are changed by physical activity?
Physical activity globally reprograms synaptic function and structure

Presynaptic release machinery
- Ca^{2+} sensors: neurotransmitter release
- Vesicle trafficking and release
- Voltage gated channels

Neuromodulators
- SST, NPY, Opioid R, NOS1

Postsynaptic plasticity
- Neurotransmitter receptors
  - Glutamate
  - GABA
  - Acetylcholine
  - Dopamine

Synapse stabilization

Builds synaptic machinery, modulating plasticity and synaptic strength
Neurotransmitter receptor genes associated with physical activity

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHRNA5</td>
<td>cholinergic receptor, nicotinic, alpha 5</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GABARAPL1</td>
<td>GABA(A) receptor-associated protein like 1</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GABBR1</td>
<td>gamma-aminobutyric acid (GABA) B receptor, 1</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GABRA2</td>
<td>gamma-aminobutyric acid (GABA) A receptor, alpha 2</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GABRA4</td>
<td>gamma-aminobutyric acid (GABA) A receptor, alpha 4</td>
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<tr>
<td>GABRB3</td>
<td>Gamma-aminobutyric acid (GABA) A receptor, beta 3</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GABRD</td>
<td>gamma-aminobutyric acid (GABA) A receptor, delta</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GABRG3</td>
<td>gamma-aminobutyric acid (GABA) A receptor, gamma 3</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GRIA4</td>
<td>Glutamate receptor, ionotrophic, AMPA 4</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GRIK2</td>
<td>glutamate receptor, ionotropic, kainate 2</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GRIN2A</td>
<td>glutamate receptor, ionotropic, N-methyl D-aspartate 2A</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GRM7</td>
<td>glutamate receptor, metabotropic 7</td>
<td>positive correlation</td>
</tr>
<tr>
<td>GRM8</td>
<td>glutamate receptor, metabotropic 8</td>
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<tr>
<td>DRD1IP</td>
<td>dopamine receptor D1 interacting protein</td>
<td>positive correlation</td>
</tr>
<tr>
<td>CHRM3</td>
<td>cholinergic receptor, muscarinic 3</td>
<td>negative correlation</td>
</tr>
</tbody>
</table>
Thus physical activity can counteract age-related decline in synaptic gene expression?
Physical activity counteracts both aging and AD-related trends in synaptic gene profiles

**Neurotransmitter Receptors:** GABBR2, GABRA4, GABRB3, GABRD, AMPA4, KA2, mGluR7

**Neurotransmitter vesicle trafficking/release:**
- dynamin 1, VAMP2 (synaptobrevin 2), RAB14, SEC22A

**Neuromodulators:** SST, NPY

**Channels:**
- voltage-gated Ca$^{2+}$ (CACNA1B)
- voltage-gated K$^+$ (KCNC4, KCNK3)
- voltage gated Na$^+$ (SCN2B)

Berchtold et al., Neurobiol Aging 2013
Berchtold et al, under review
Physical activity counteracts aging-AD declines in synaptic gene expression

<table>
<thead>
<tr>
<th>Function</th>
<th>Gene</th>
<th>Gene Name</th>
<th>Physical activity</th>
<th>aging-AD</th>
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<tbody>
<tr>
<td>neurotransmitter trafficking and release</td>
<td>VAMP2</td>
<td>vesicle-associated membrane protein 2 (synaptobrevin 2)</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<td></td>
<td>SYT1</td>
<td>Synaptotagmin I</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<td>SEC22B</td>
<td>SEC22 vesicle trafficking protein homolog B (S. cerevisiae)</td>
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<td>decreasing expression</td>
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<td>DNM1L</td>
<td>dynamin 1 like</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<td>PARK7</td>
<td>Parkinson disease (autosomal recessive, early on set) 7</td>
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<td>decreasing expression</td>
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<td>SEC22A</td>
<td>SEC22 vesicle trafficking protein homolog A (S. cerevisiae)</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<td>SNCA</td>
<td>synuclein, alpha (non A4 component of amyloid precursor)</td>
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<td>decreasing expression</td>
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<tr>
<td></td>
<td>SNCB</td>
<td>synuclein, beta</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<tr>
<td>Neurotransmitter receptor</td>
<td>GRIA4</td>
<td>Glutamate receptor, ionotrophic, AMPA 4</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<td></td>
<td>GRK2</td>
<td>glutamate receptor, ionotropic, kainate 2</td>
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<td>GRM7</td>
<td>glutamate receptor, metabotropic 7</td>
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<td>decreasing expression</td>
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<td>GABBR2</td>
<td>gamma-aminobutyric acid (GABA) B receptor, 2</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<tr>
<td></td>
<td>GABRA4</td>
<td>gamma-aminobutyric acid (GABA) A receptor, alpha 4</td>
<td>positive correlation</td>
<td>decreasing expression</td>
</tr>
<tr>
<td></td>
<td>GABRB3</td>
<td>Gamma-aminobutyric acid (GABA) A receptor, beta 3</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<tr>
<td></td>
<td>GABRD</td>
<td>gamma-aminobutyric acid (GABA) A receptor, delta</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<tr>
<td>glutamate receptor trafficking</td>
<td>GCC2</td>
<td>GRIP and coiled-coil domain containing 2</td>
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<td>decreasing expression</td>
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<td>HOMER1</td>
<td>Homer homolog 1 (Drosophila)</td>
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<td>decreasing expression</td>
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<td>CA1</td>
<td>islet cell autoantigen 1, 69kDa</td>
<td>positive correlation</td>
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<td>SLC1A6</td>
<td>solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6</td>
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<td>decreasing expression</td>
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<tr>
<td>synapse stabilization</td>
<td>EPHA3</td>
<td>EPH receptor A3</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<td></td>
<td>NLGN1</td>
<td>Neuroligin 1</td>
<td>positive correlation</td>
<td>decreasing expression</td>
</tr>
<tr>
<td></td>
<td>NPTN</td>
<td>neuroplastin</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<tr>
<td></td>
<td>NRXN1</td>
<td>Neurexin 1</td>
<td>positive correlation</td>
<td>decreasing expression</td>
</tr>
<tr>
<td></td>
<td>PLDN</td>
<td>Pallidin homolog (mouse)</td>
<td>positive correlation</td>
<td>decreasing expression</td>
</tr>
<tr>
<td>channel</td>
<td>CACNA1B</td>
<td>Calcium channel, voltage-dependent, N type, alpha 1B subunit</td>
<td>positive correlation</td>
<td>decreasing expression</td>
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<td>KCN4</td>
<td>Potassium voltage-gated channel, Shaw-related subfamily, member 4</td>
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<td>decreasing expression</td>
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<td>KCNK3</td>
<td>potassium channel, subfamily K, member 3</td>
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<td>decreasing expression</td>
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<td>SCN2B</td>
<td>Sodium channel, voltage-gated, type II, beta</td>
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<tr>
<td>neuromodulator</td>
<td>NPY</td>
<td>neuropeptide Y</td>
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<td>decreasing expression</td>
</tr>
<tr>
<td></td>
<td>SST</td>
<td>somatostatin</td>
<td>positive correlation</td>
<td>decreasing expression</td>
</tr>
</tbody>
</table>
Microarray conclusion

We propose that the gene changes associated with physical activity:

• Globally enhances synapse machinery
• This makes the brain more ready to encode (learn)
• Net result is that individuals can benefit more from cognitive and social activity because synapses stronger and more ready
ADCS MCI Exercise trial

**Goal**
- 1 yr, 4x/wk, 45 min/session (includes warm up & cool down)

**Gradually ramp up activities over 1st 6 wks**

**Continuous enrollment**

**Activities carried out at local YMCAs** (or other suitable facility)

**daily activities supervised locally by trainer & centrally by designated “specialty” staff**

**Subjects encouraged to enroll with an “activity buddy”**

**activities performed in groups whenever possible**

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**Interventions**

**Non-Aerobic Exercise**
- <30% HR reserve for duration of session (stretching, yoga, tai chi)
  - HR < ~90 beats/min

**Aerobic Exercise**
- 70-80% HR reserve (maintain intensity at least 20 min/session)
  - HR ~120-135 beats/min
If you wish to be considered for this study, please contact:

Beatriz Yanez, R.N.
949-824-3250
byanez@uci.edu

Vanessa Lin
949-824-6187
Vanessa.lin@uci.edu
Conclusions: Add more Life to years

- Animal studies and human clinical trials demonstrate benefits of exercise for promoting cognition and healthy brain aging.
- Exercise needs to be aerobic
- Can be intermittent and tap into molecular memory mechanisms
- Builds synapses in human brain “fights off synaptic failure”
“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)
Acknowledgements

Funding provided by NIA

Nicole Berchtold, Ph.D.
Aleph Prieto, Ph.D.
Paul Adlard, Ph.D.
Shikha Snighda, Ph.D.
Michael Valenzula, Ph.D.
Laura Baker, Ph.D.
Bill Milgram, Ph.D.
David Bennett, MD
Aron Buchman, MD
Kate Nichol, Ph.D.
Sean Deeny, Ph.D.
Patrick Sullivan, Ph.D.
Alan Butterfield, Ph.D.
M. Fahnestock, Ph.D.
Christina de Rivera
Karlie Intlekofer, Ph.D.
Dan Gillen, Ph.D.
Malcolm Dick, Ph.D.