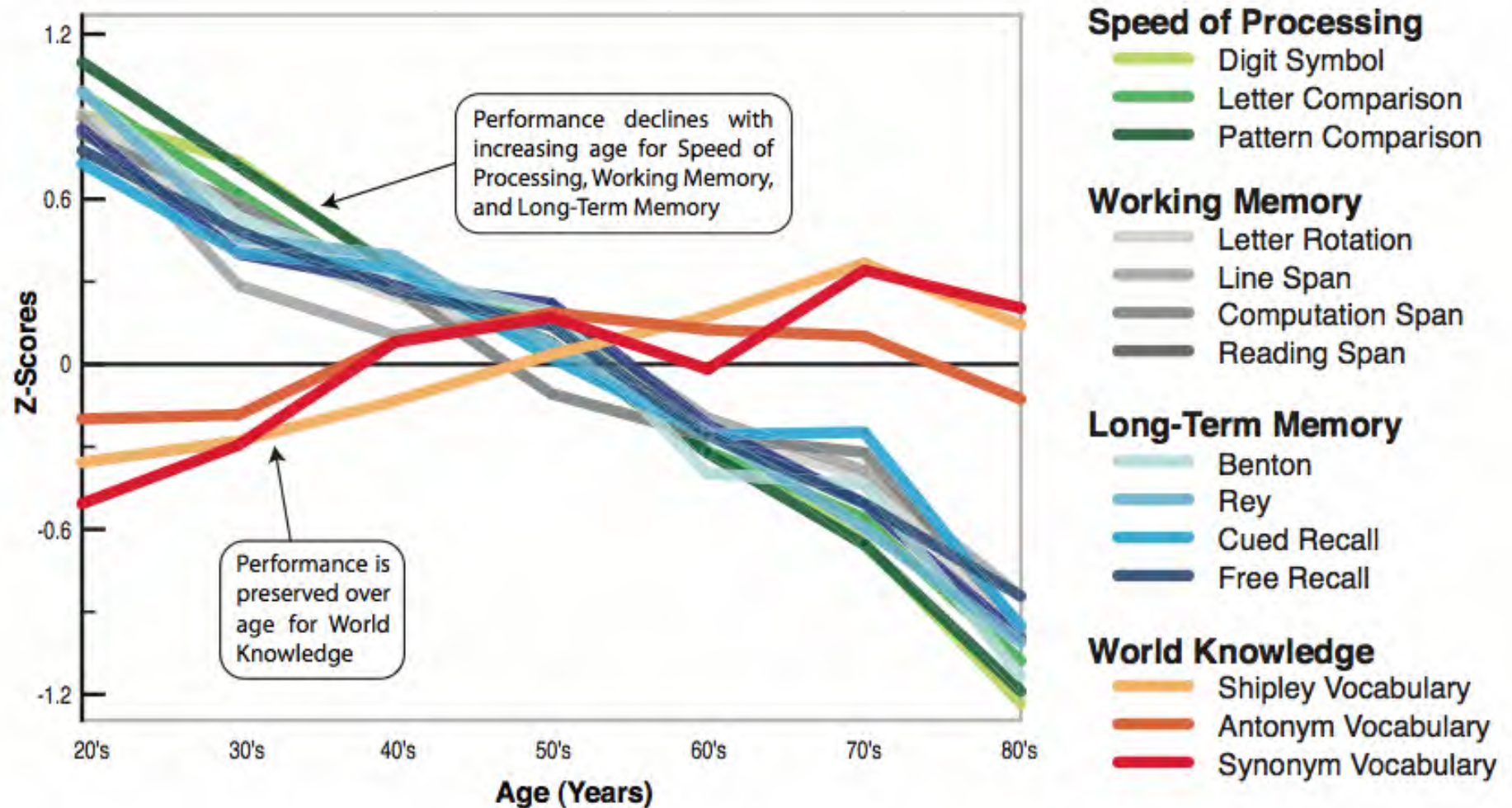


Can Physical Activity Enhance your Brain & Mind ?

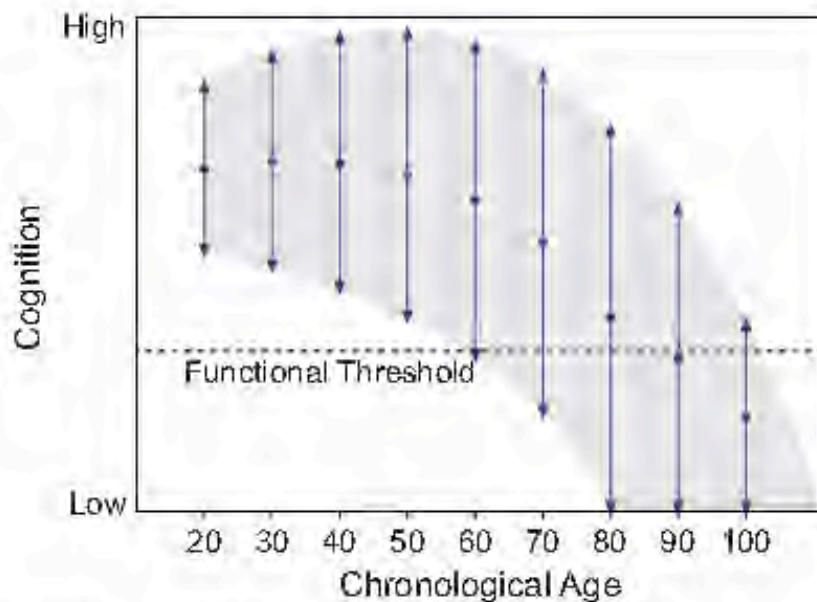
Art Kramer & colleagues
Beckman Institute
University of Illinois
July, 2011



Cognitive decline in healthy aging



*“It’s a fortunate person whose brain
Is trained early, again and again,
And who continues to use it
To be sure not to lose it,
So the brain, in old age, may not wane.”
(Rosenzweig & Bennett 1996)*

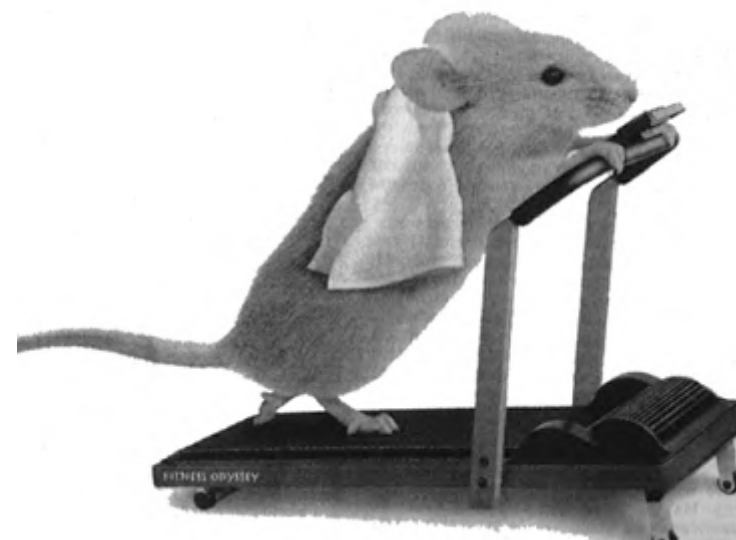


Cognitive Enrichment Hypothesis

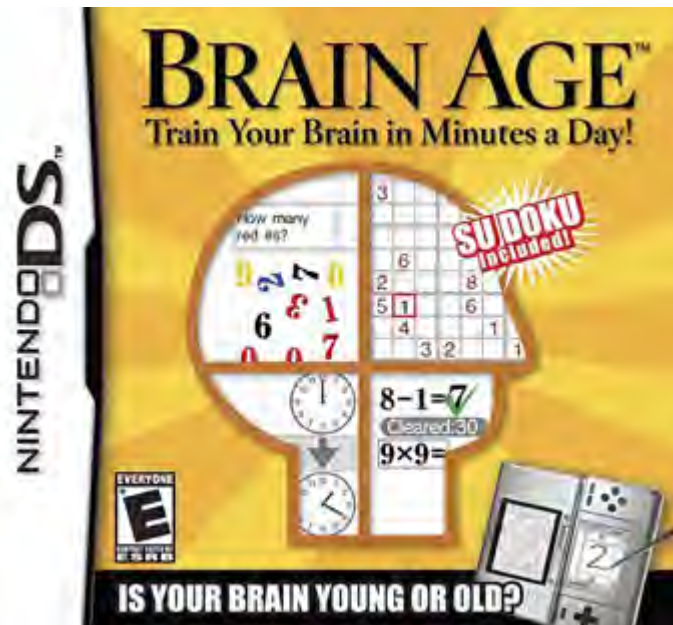
- levels of performance are malleable & open to enhancement throughout the human lifespan
- Upper levels of performance are constrained by the boundaries of biological aging (& how malleable are these biological constraints ... ?)

Hertzog, Kramer, Wilson & Lindenberger (2009)

Enriched (complex) environments include:



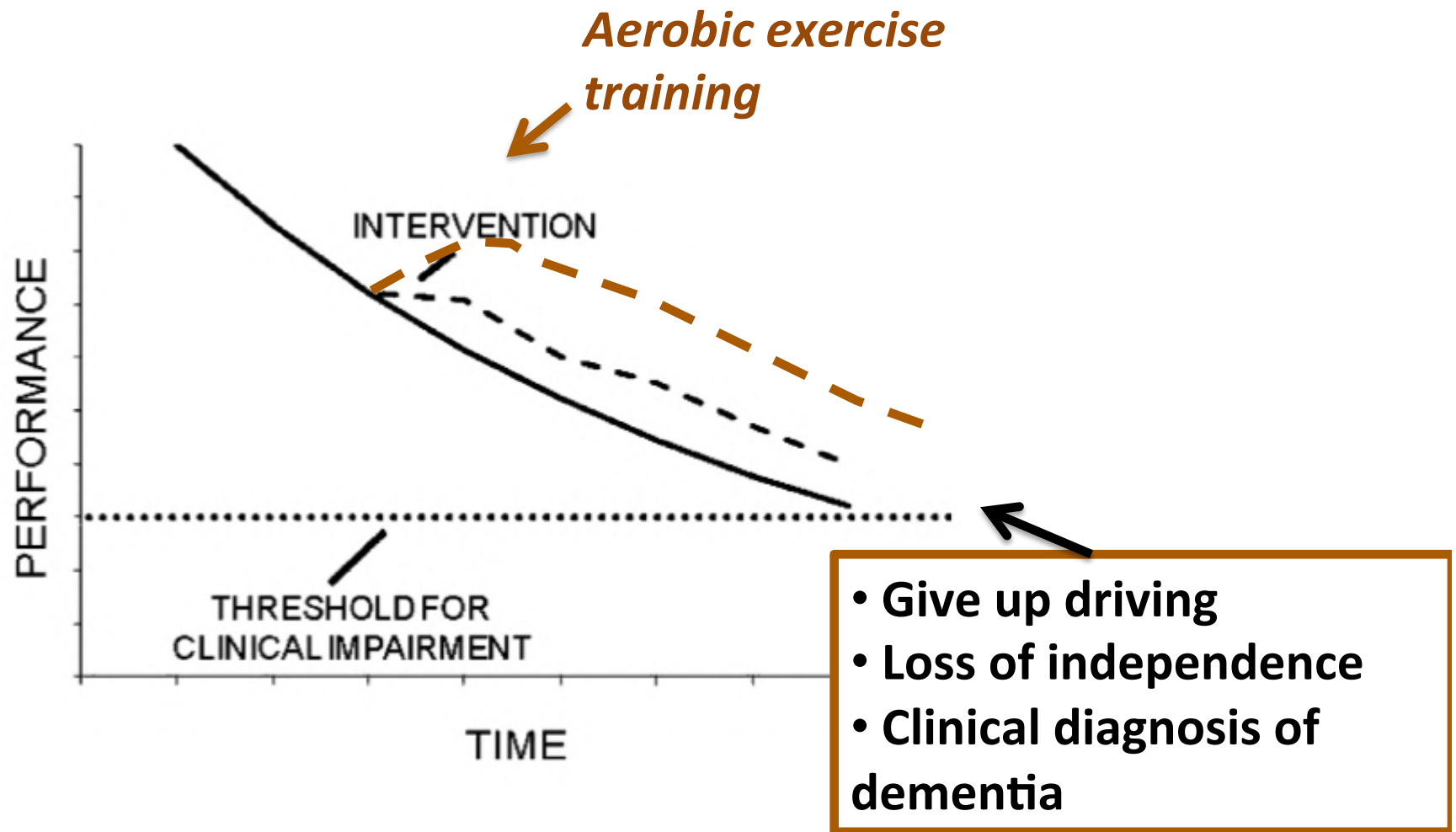
Lots of products to “help” us age successfully



What do we currently know?

- Normal Populations
- Patient Populations
- On the basis of
 - Prospective observational studies
 - Animal models
 - Human RCT's

Goal: Interventions for cognitive aging

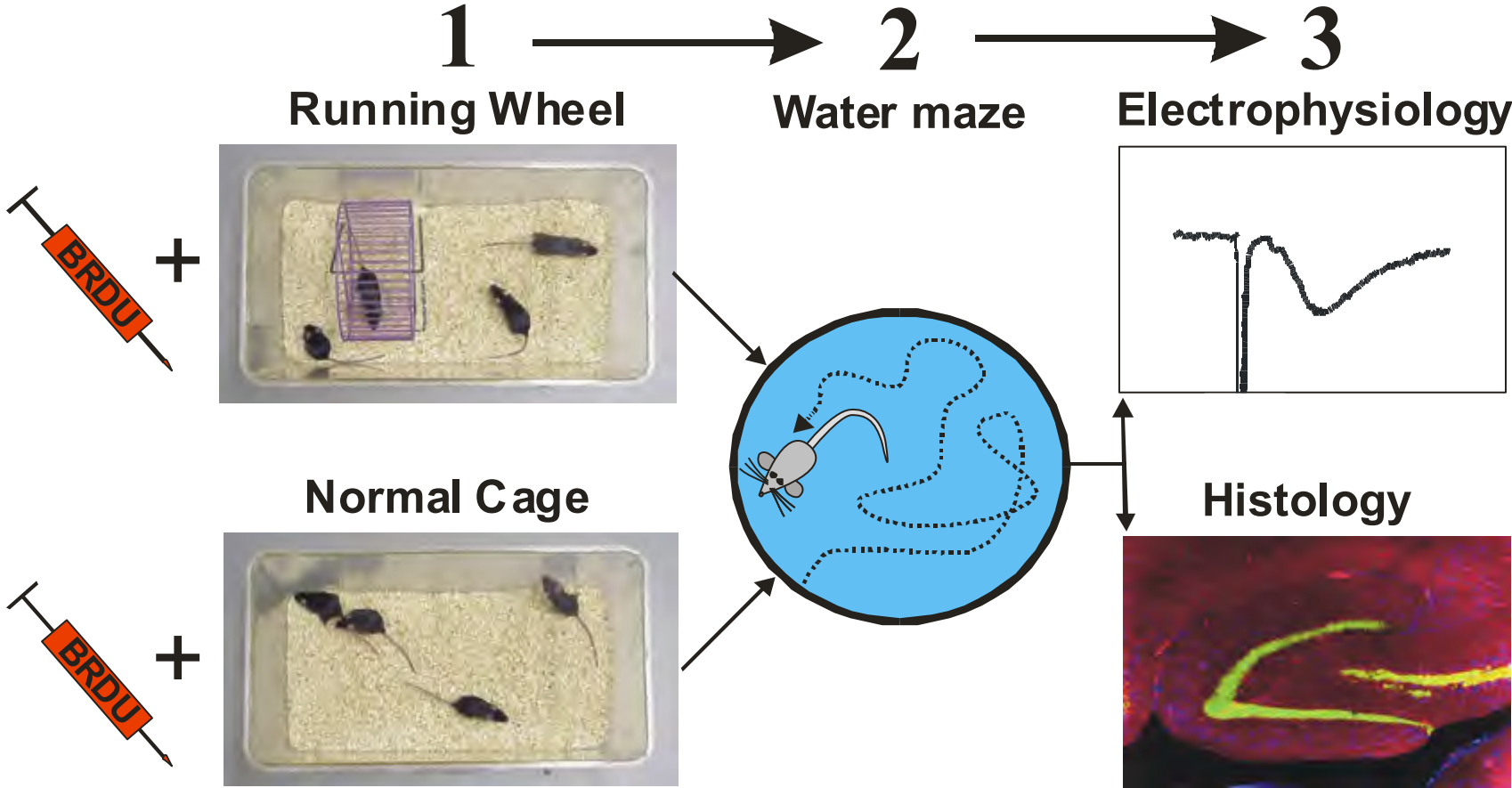


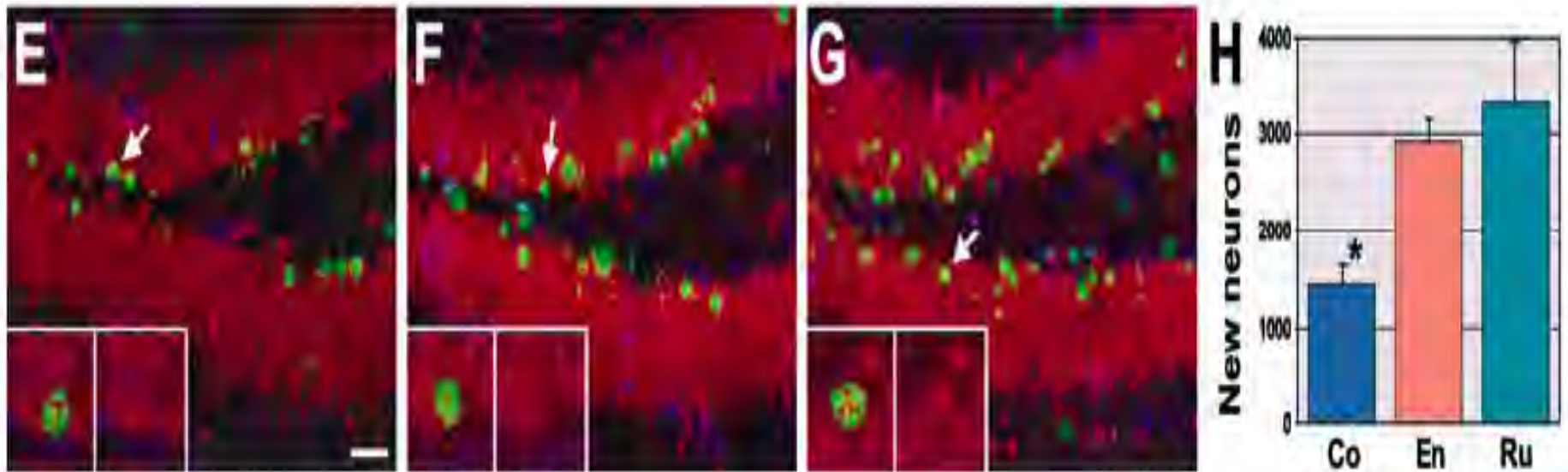
What do we currently know?

- Normal Populations
- Patient Populations
- On the basis of
 - Prospective observational studies
 - Animal models
 - Human RCT's

EXPERIMENTAL DESIGN

Assessing the effects of exercise





Brown et al, 2003

ALSO

- increases in neurotrophins (e.g. BDNF, IGF1, VEGF, etc)
- enhanced synaptogenesis
- enhanced angiogenesis
- increased production of various neurotransmitters
- increased telomere length
- increased expression of genes associated with plasticity & mitochondrial function, downregulates genes associated with oxidative stress
- enhanced learning & memory

Barnes et al, 2003 – 6 yr prospective study

- 349 healthy + 55 year olds
- Objective measures of cardiorespiratory fitness *

Table 2. Cognitive Function by Sex-Specific Tertile of Baseline Peak VO₂

Cognitive Measure	Peak VO ₂ (mL/kg*min ⁻¹)			P-value for trend*
	Lowest Tertile	Middle Tertile	Highest Tertile	
Change in mMMSE [†] from baseline to Year 6, mean (95% CI)	-0.5 (-0.8-0.3)	-0.2 (-0.5-0.0)	0.0 (-0.3-0.2)	.002
Performance at Year 6, mean (95% CI)				
Global cognitive function				
MMSE [†]	28.5 (28.3-28.7)	28.9 (28.7-29.1)	29.2 (29.0-29.5)	<.0001
Attention/executive function				
Trails B, [†] correct/min	12.4 (11.3-13.4)	14.7 (13.6-15.7)	17.0 (15.9-18.0)	<.0001
Stroop, [†] correct/min	39.8 (37.5-42.2)	44.1 (41.9-46.4)	48.2 (45.9-50.4)	<.0001
Digit Symbol, correct/min	23.9 (22.6-25.2)	27.5 (26.3-28.8)	30.2 (28.9-31.4)	<.0001
Verbal memory				
Immediate recall, [†] words	6.6 (6.0-7.2)	7.8 (7.2-8.4)	8.2 (7.6-8.8)	.0002
Delayed recall, [†] words	7.3 (6.7-7.9)	8.5 (7.9-9.1)	8.8 (8.2-9.4)	.0007
Verbal fluency				
Letter "s," words	11.9 (11.1-12.8)	12.6 (11.8-13.4)	13.6 (12.8-14.4)	.005
Animals, words	16.5 (15.6-17.4)	17.2 (16.4-18.1)	18.3 (17.4-19.2)	.006

Note: Values are adjusted for sex. Oxygen consumption at peak exercise (peak VO₂) ranges were: women (n = 172) lowest tertile = 12.3-18.6, middle tertile = 18.7-22.7, highest tertile = 22.8-36.1; men (n = 177) lowest tertile = 14.8-23.4, middle tertile = 23.5-28.9, highest tertile = 29.0-45.7.

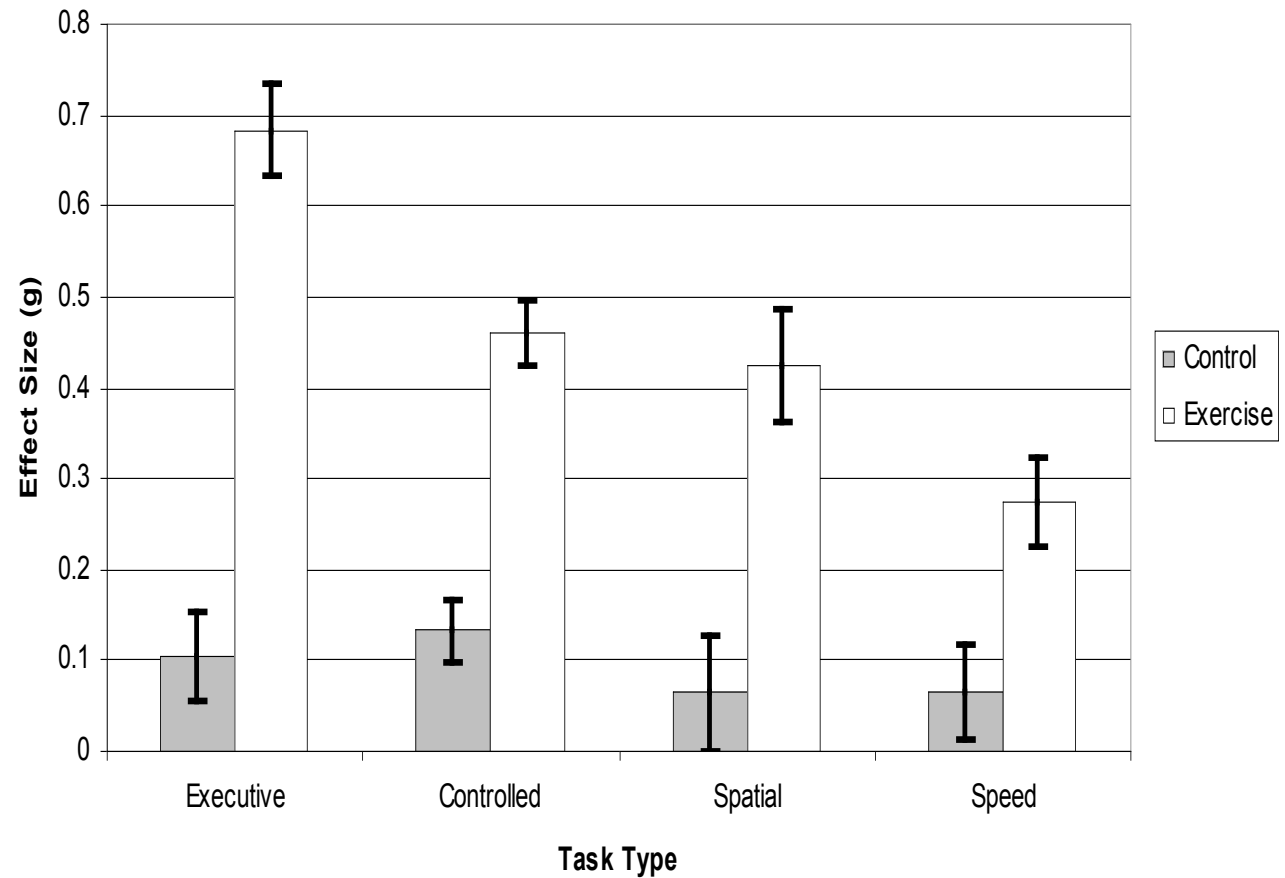
* P-values based on analysis of variance adjusted for sex.

[†]Data were missing as follows: modified Mini-Mental State Examination (mMMSE) change (n = 11), Mini-Mental State Examination (MMSE) (n = 8), Trails B (n = 2), Stroop (n = 3), Verbal memory immediate/delayed recall (n = 4).

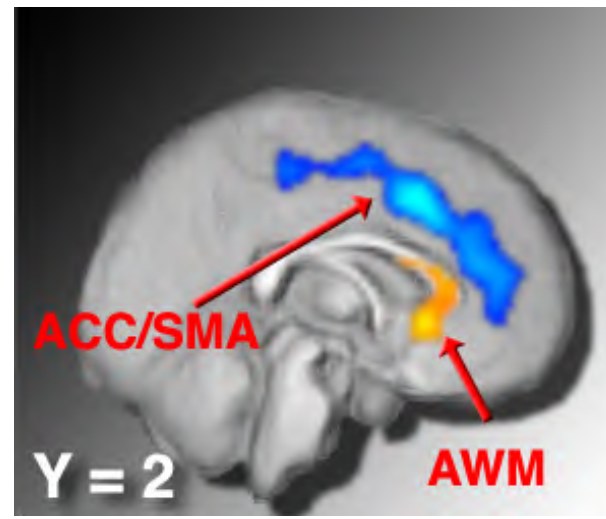
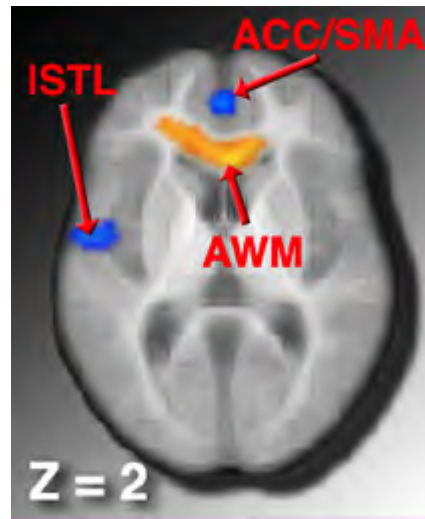
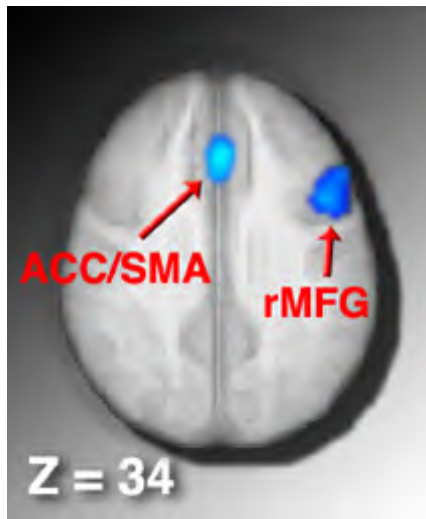
peak VO₂ = oxygen consumption at peak exercise; CI = confidence interval.

Effect Size Estimates as a Function of Task Type and Group

- Across intervention studies (with normal elderly) that find positive effects of fitness training on cognition the cognitive benefits are quite broad – with larger benefits for some cognitive processes ...

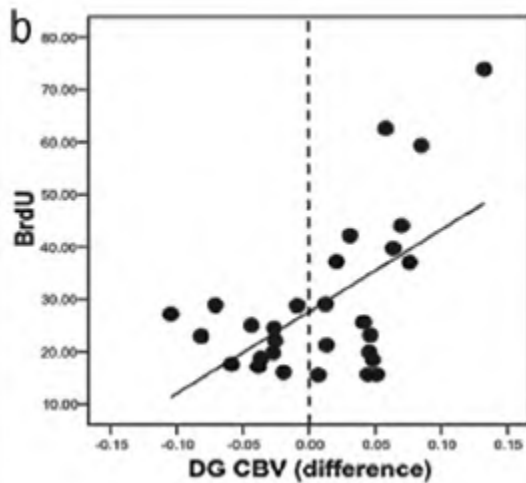


Although much is known about fitness training effects on brain function with non-human animals there is a dearth of knowledge of fitness training effects with humans



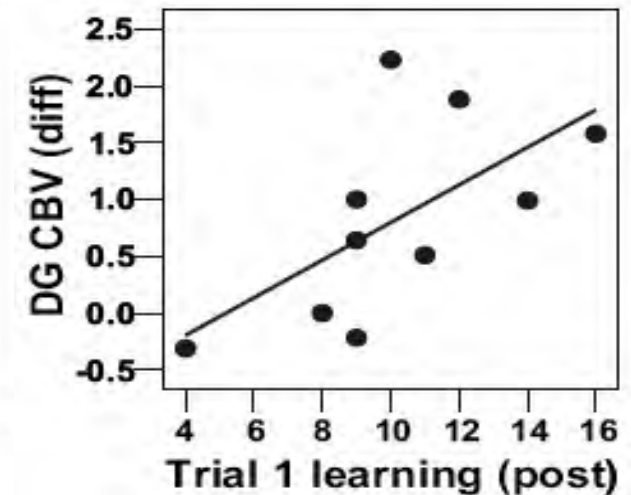
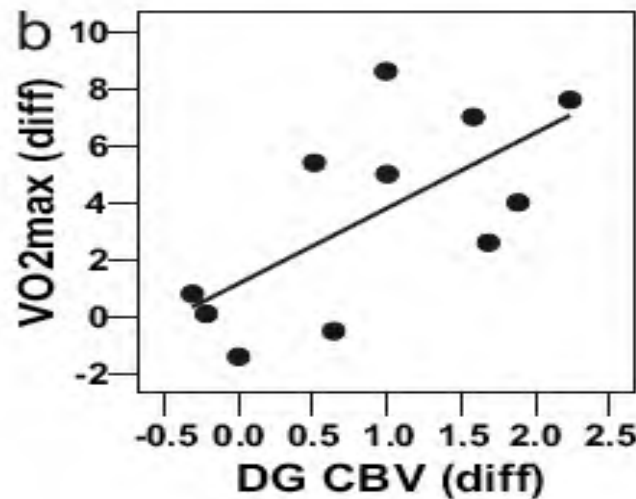
Colcombe et al, 2006

Rodent



Pereira et al, 2007

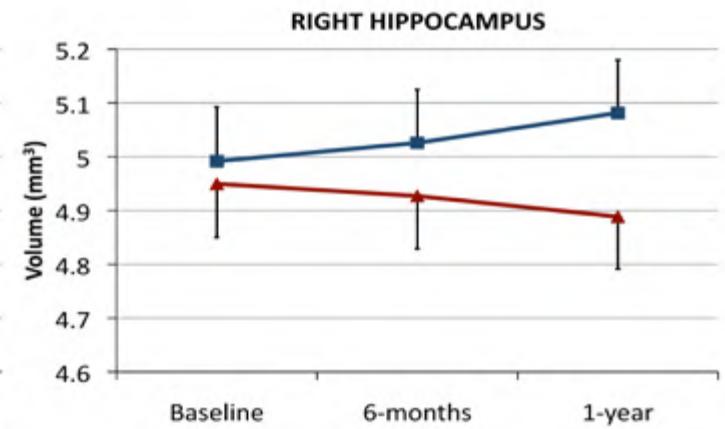
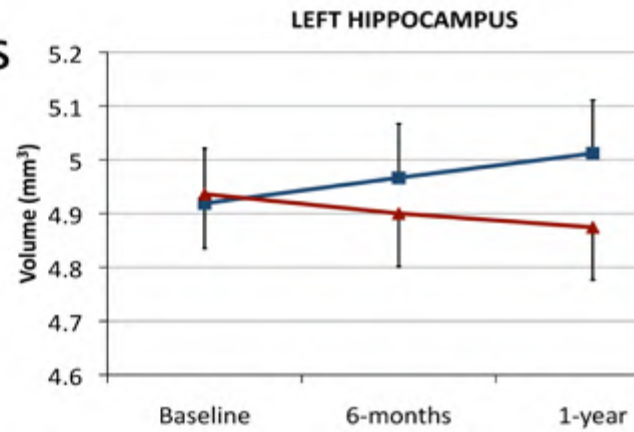
Human



Hippocampus



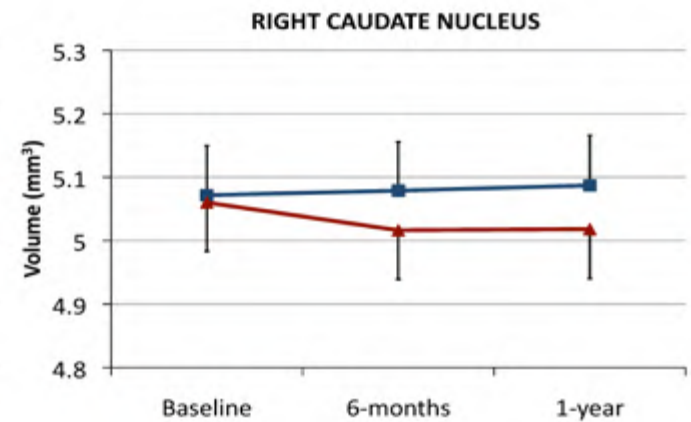
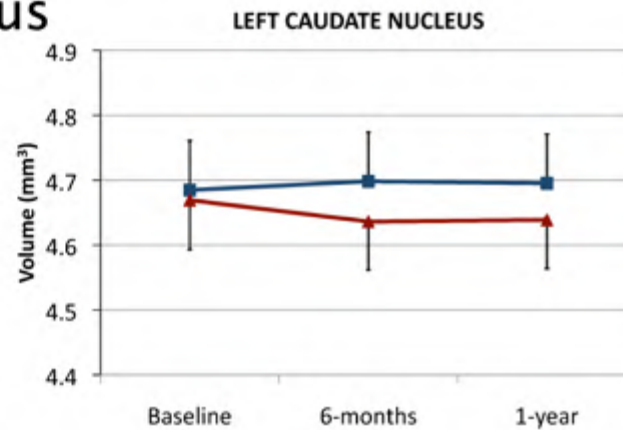
A.



Caudate Nucleus



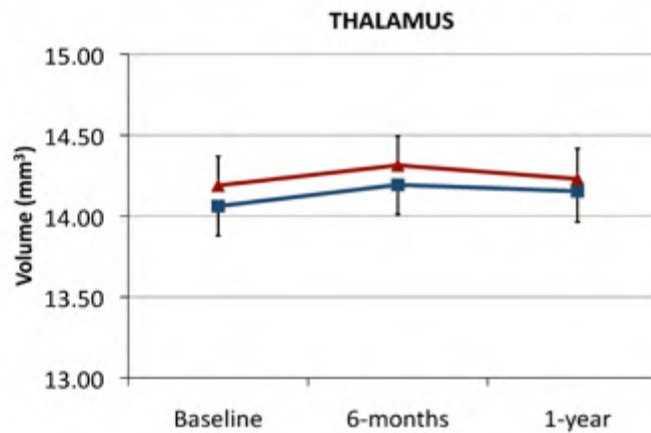
B.



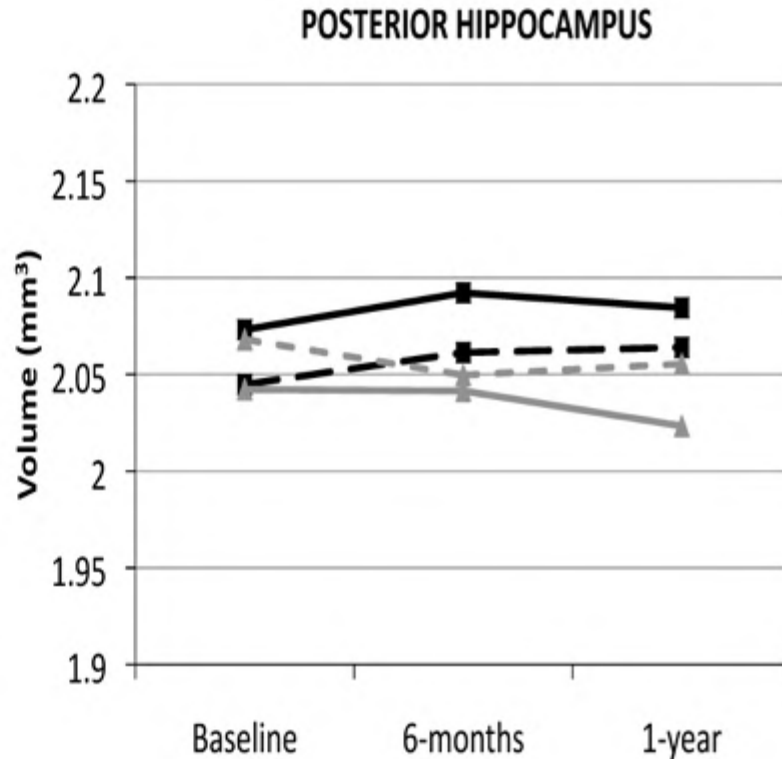
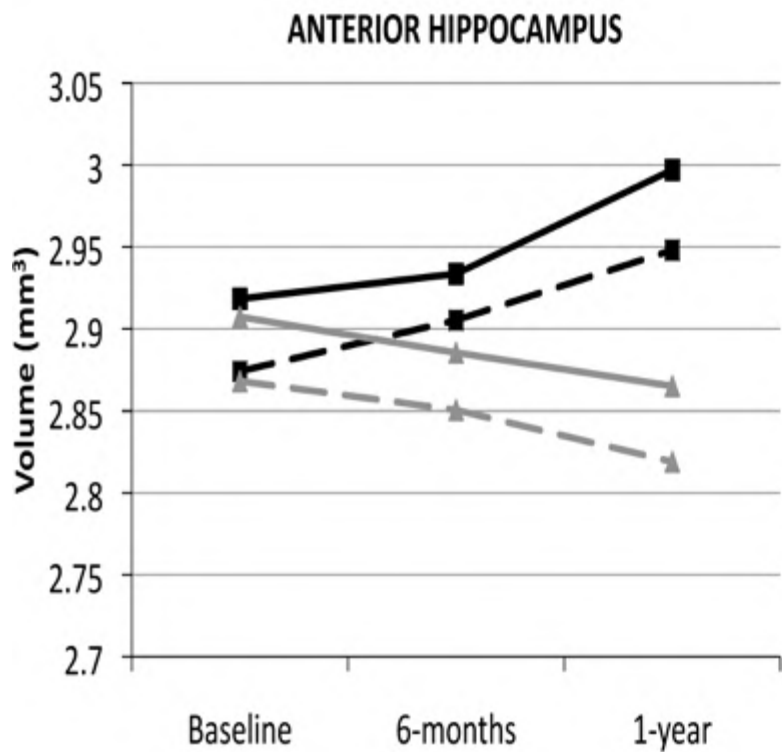
Thalamus



C.



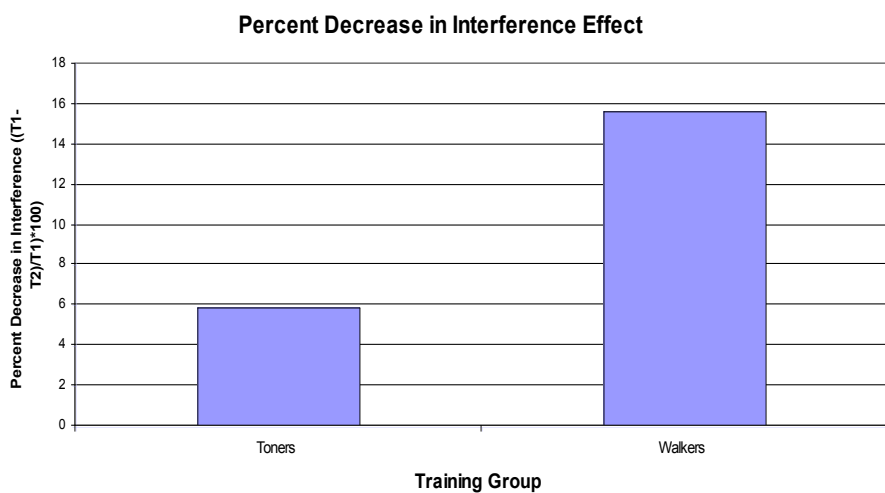
■ Exercise
▲ Stretching



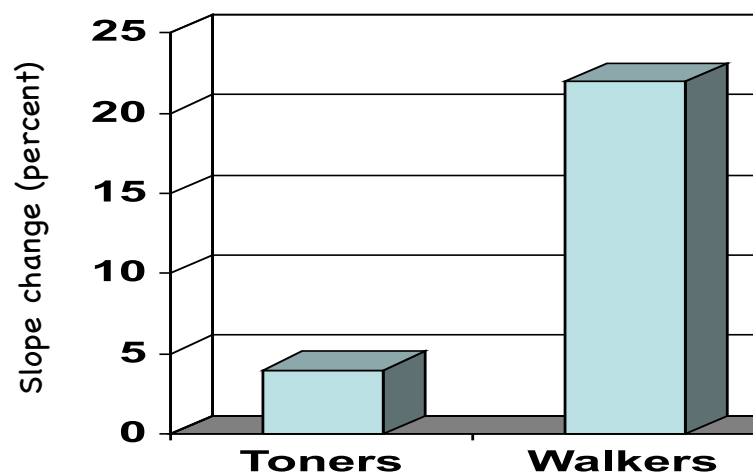
Exercise Left
 Exercise Right
 Stretching Left
 Stretching Right

Effects of fitness training on performance & brain function:

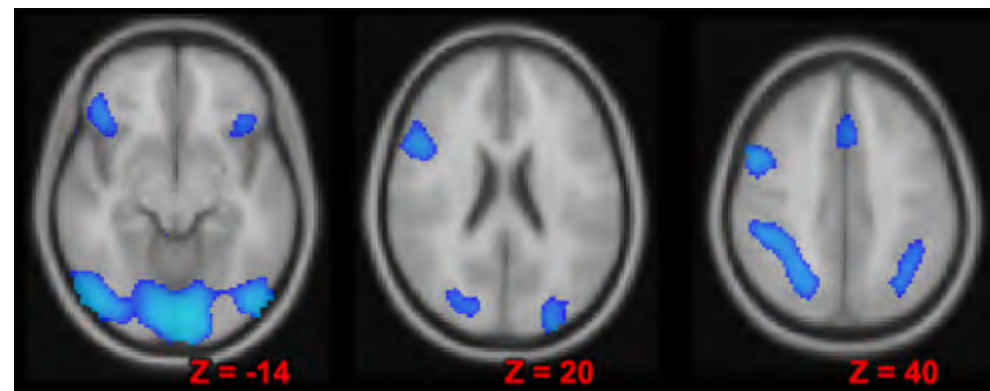
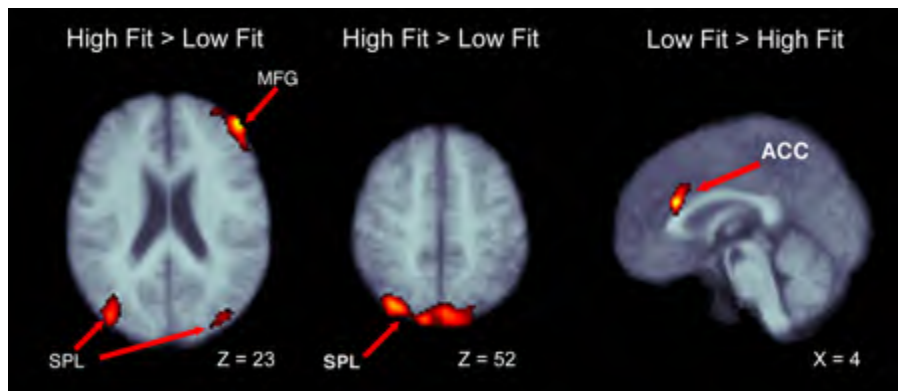
Flanker / Selective Attention Task



Sternberg Memory Search Task

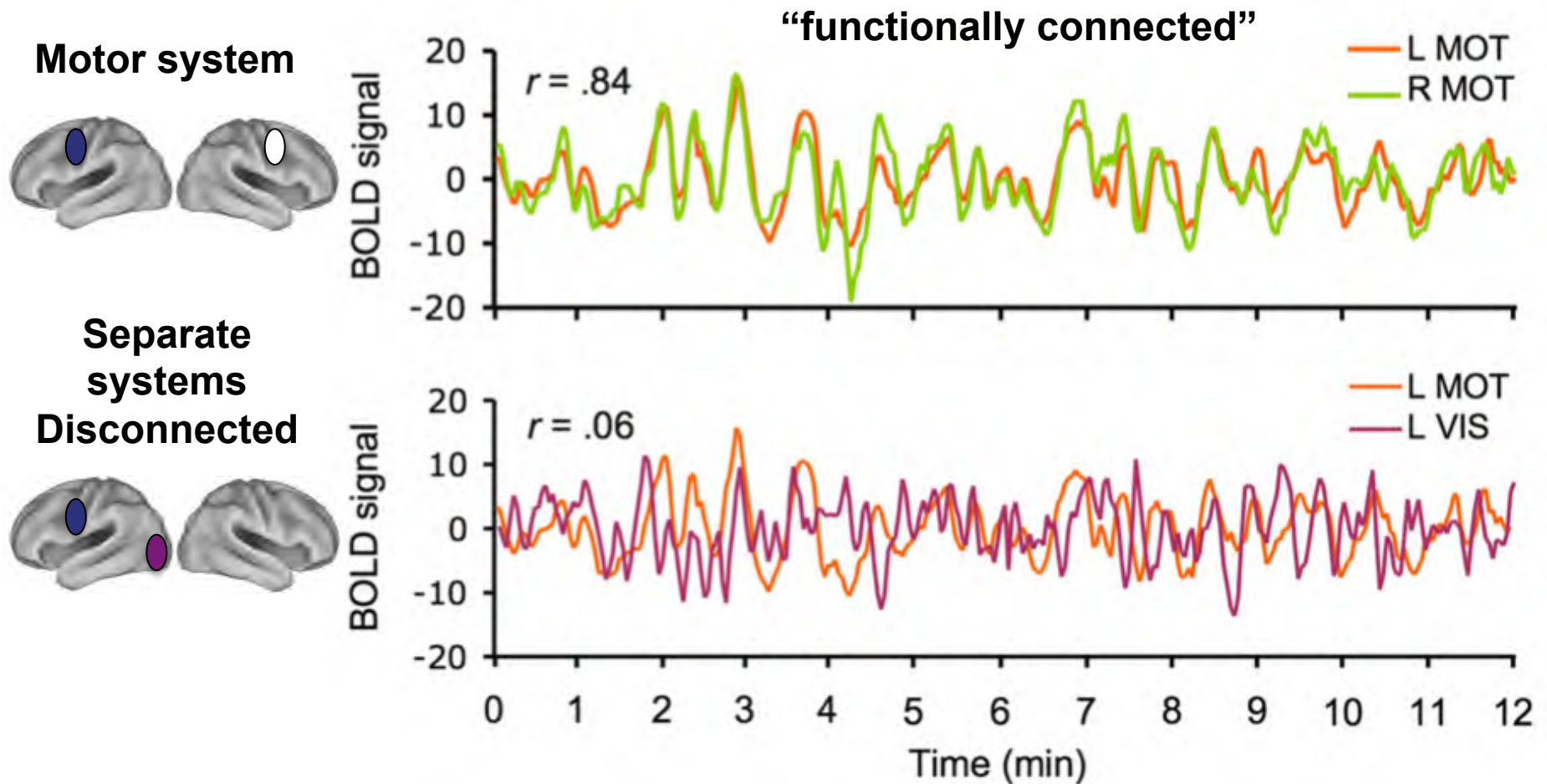


Colcombe et al., 2004



Brain “networks”

Goal: Characterize how brain regions typically co-activate to support behavior

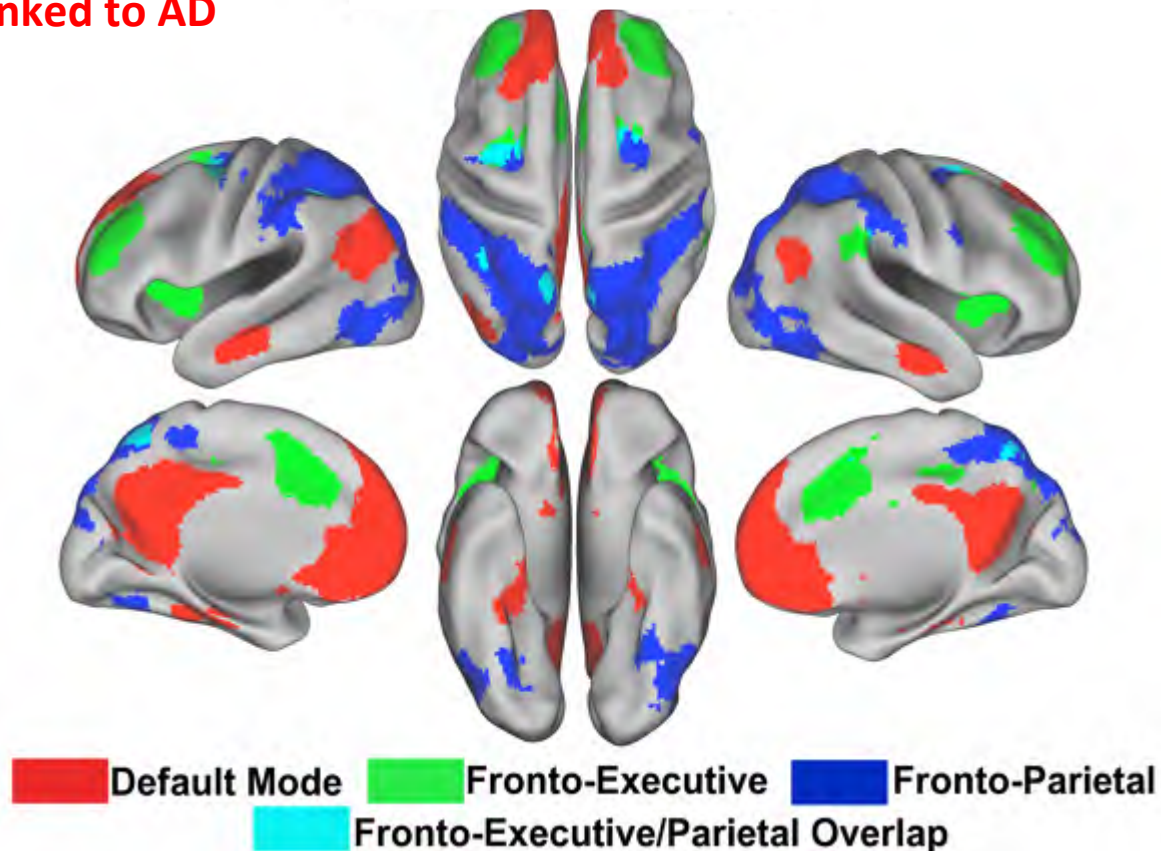


Cognitively relevant brain networks

- deactivated during goal-directed attention
- active at rest, inward thought
- ↑ executive functions, speed, memory processes
- dysfunction linked to AD

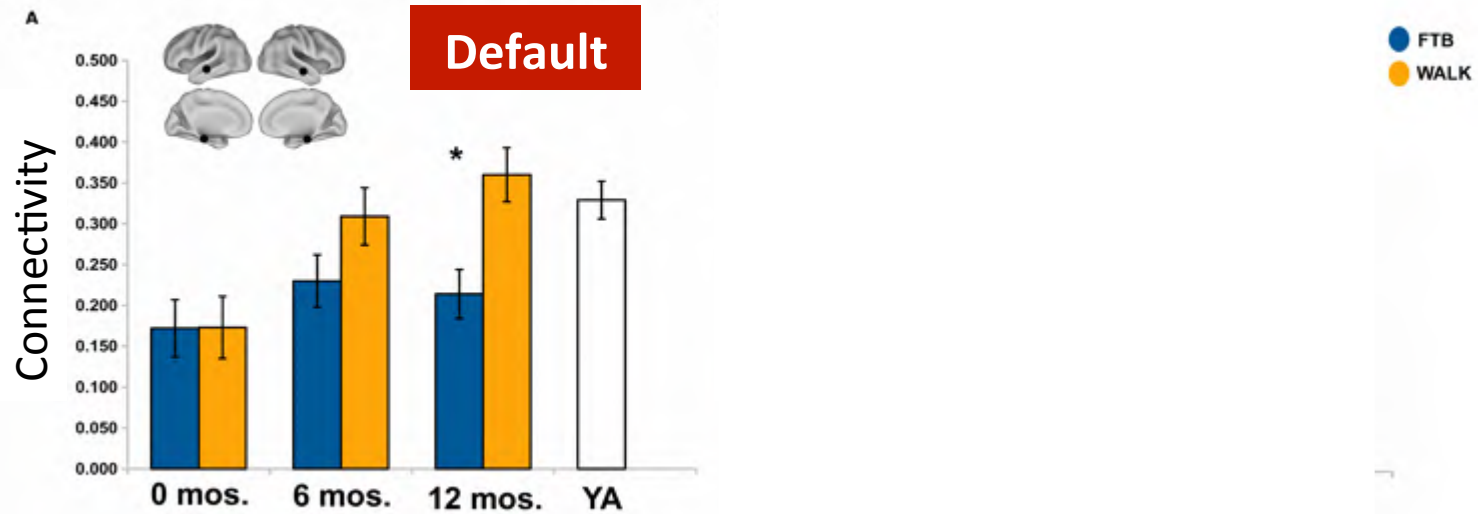
- stable, sustained maintenance of task set
- monitor for errors
- maintain associations between action-outcome

- Rapid, online filtering of attention
- top-down control
- working memory

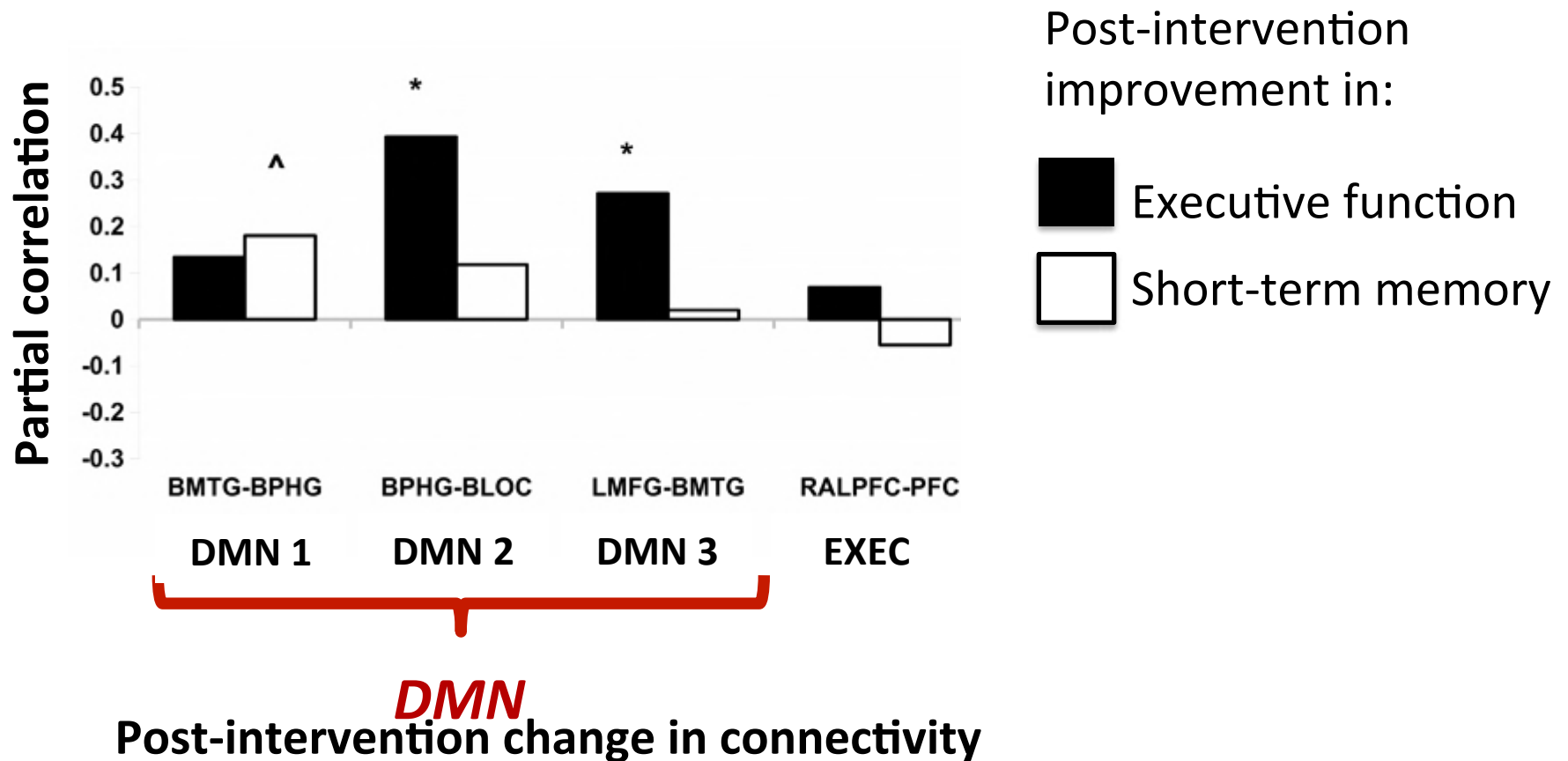


Improvements in networks post-exercise?

Functional connectivity changes in favor of walking group



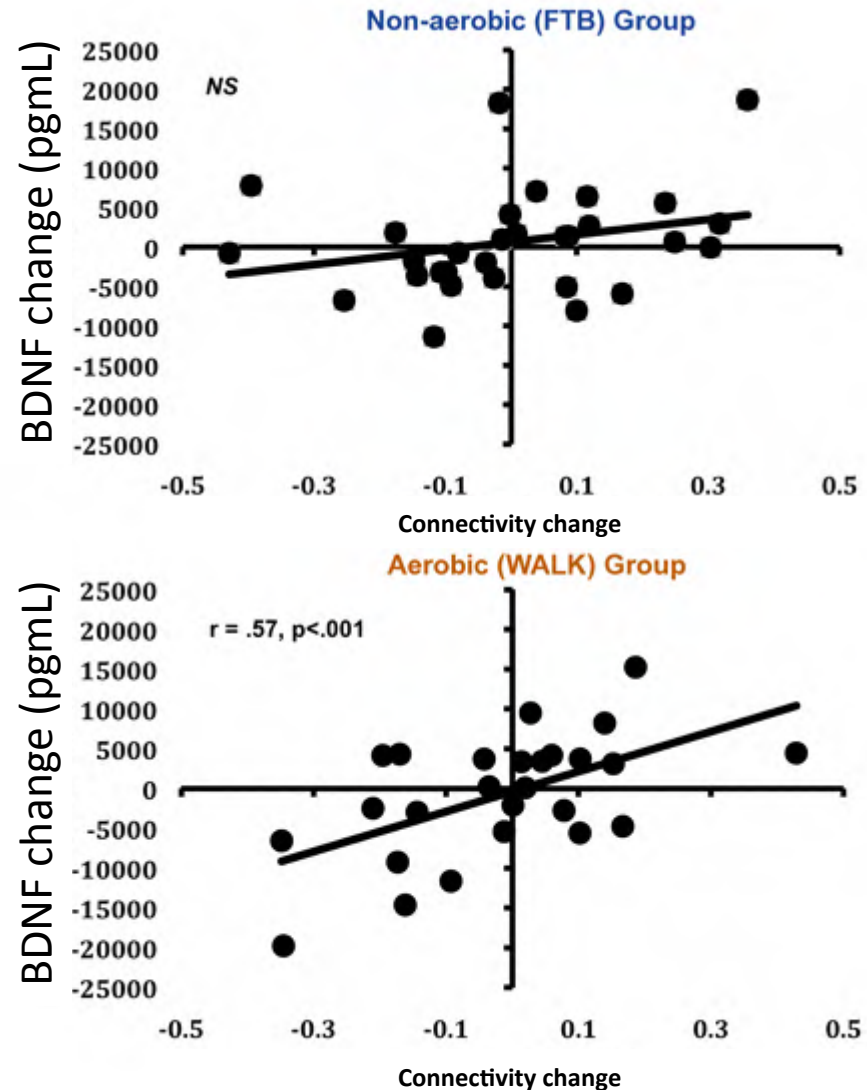
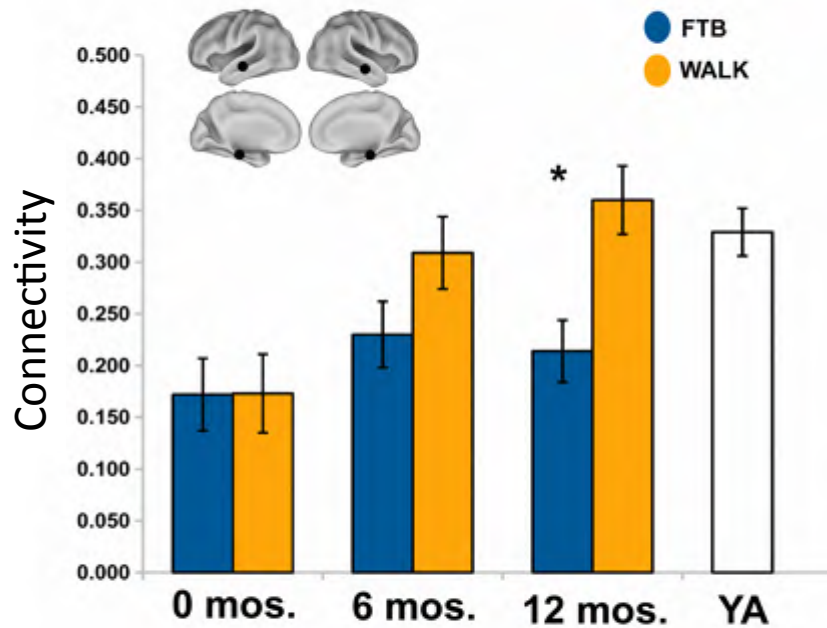
Brain-Behavior associations



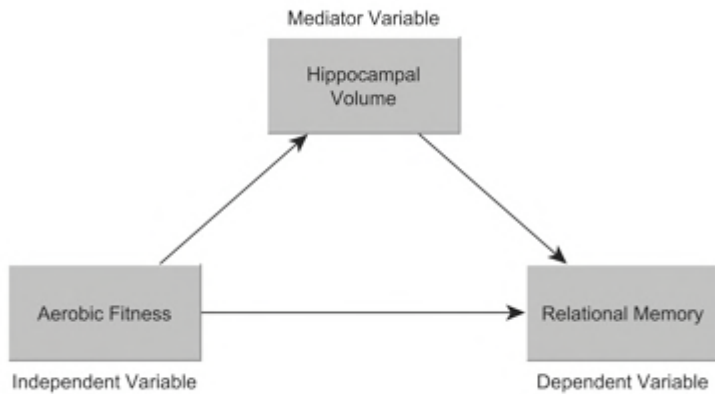
Voss et al., 2010, *Frontiers in Aging Neuroscience*

What are the neurobiological mechanisms for exercise-induced brain plasticity?

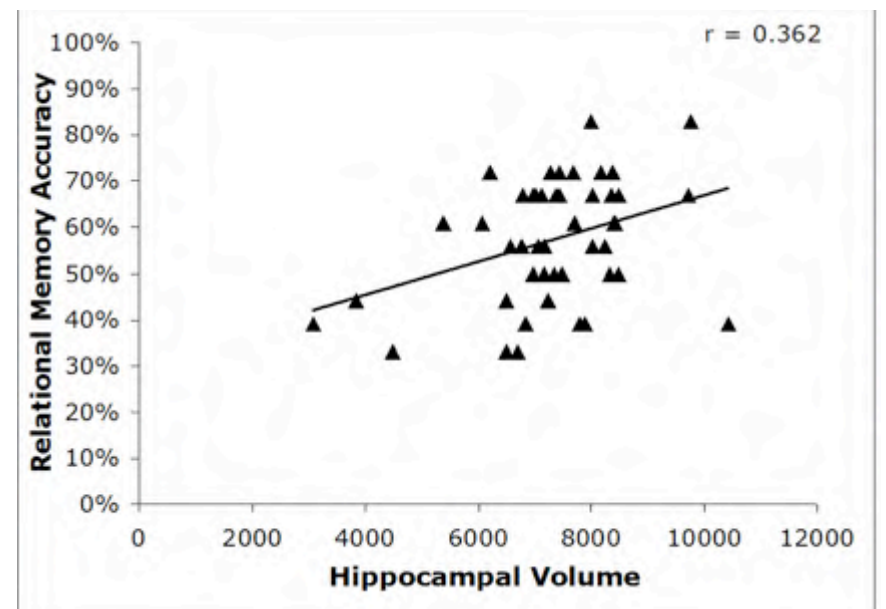
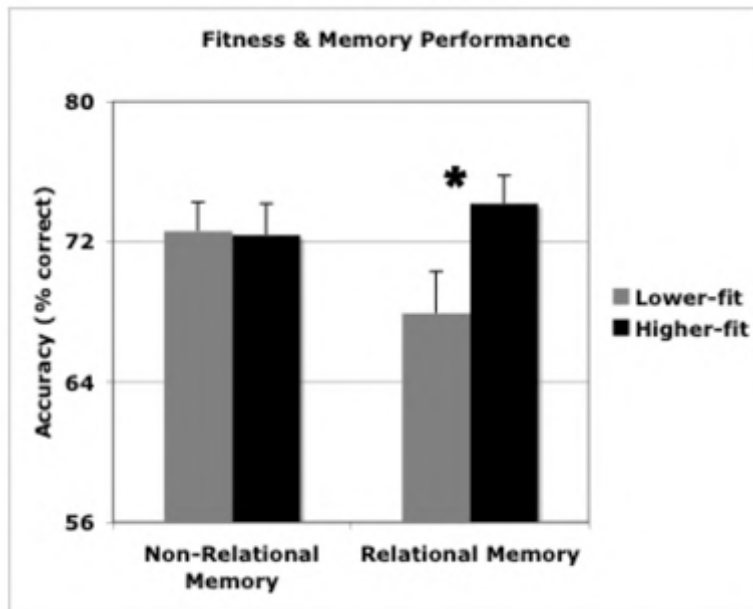
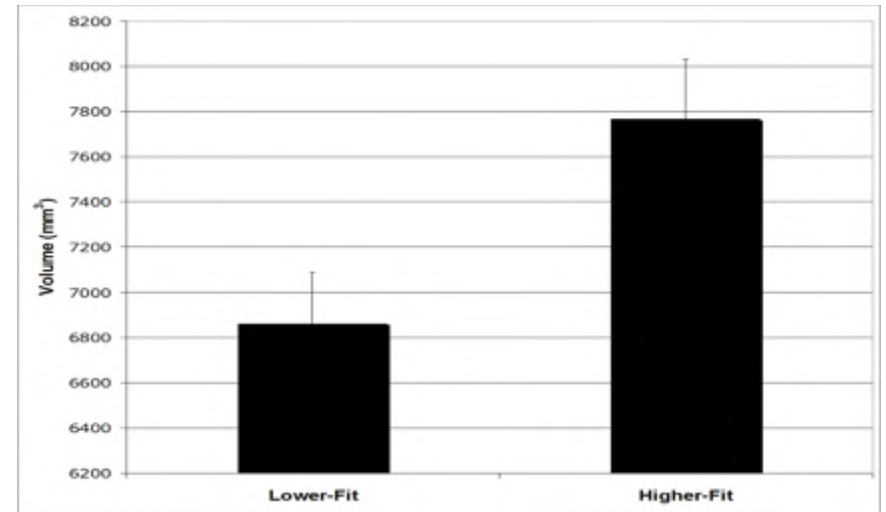
Brain-Derived Neurotrophic Factor (BDNF)



What about exercise effects on brain & cognitive function of children?



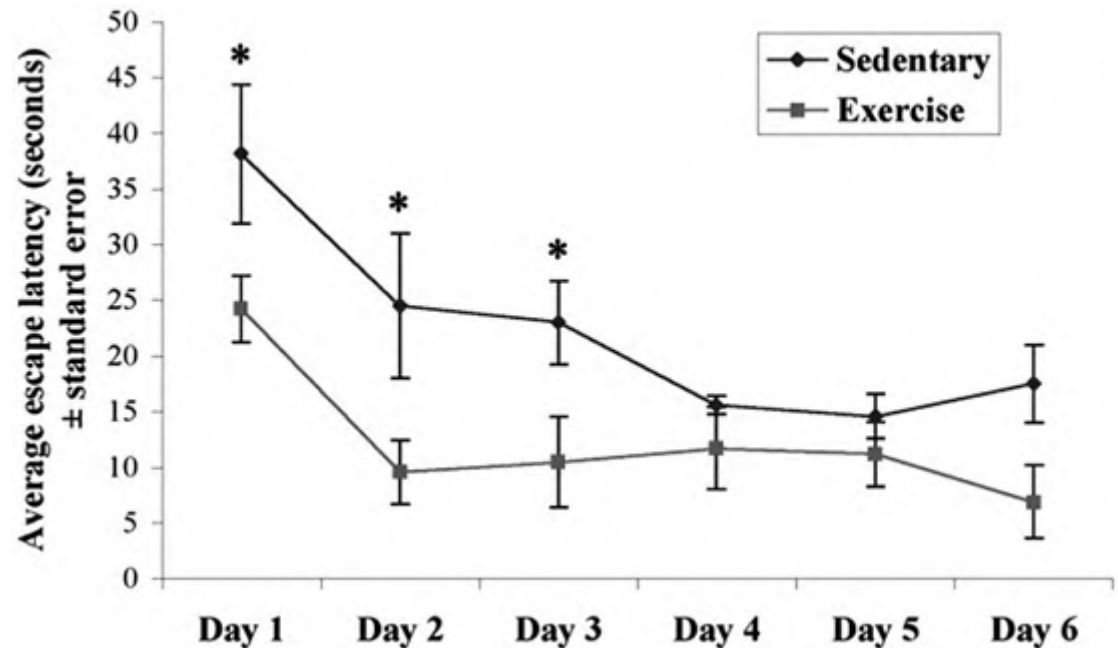
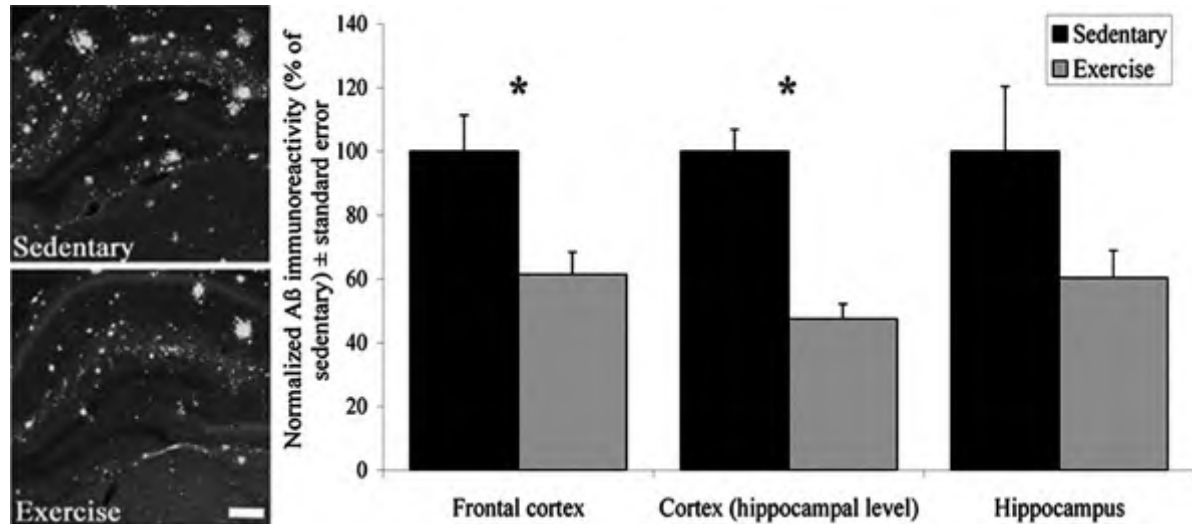
Chaddock et al (2010)



What do we currently know?

- Normal Populations
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 - Prospective observational studies
 - Animal models
 - Human RCT's

Exercise effects in transgenic mice



Adlard et al (2005)

Karp et al (2006)

a study of 776 > 75 year olds over the course of 6 years - activities at time 1, dementia at time 2.

Type of activity	Scores	
	mental	physical
Reading literature	3	0
Handicraft: needlework, weaving, knitting	2	1
Doing crossword puzzles	3	0
Political or cultural interests	3	1
Playing cards or chess	3	0
Visiting the summerhouse	2	2
Attending courses	3	1
Watching TV	2	0
Going to theatres or concerts	3	1
Doing sport	1	3
Going to exhibitions or museums	3	1
Meeting friends, participating in groups	2	1
Walking	1	3

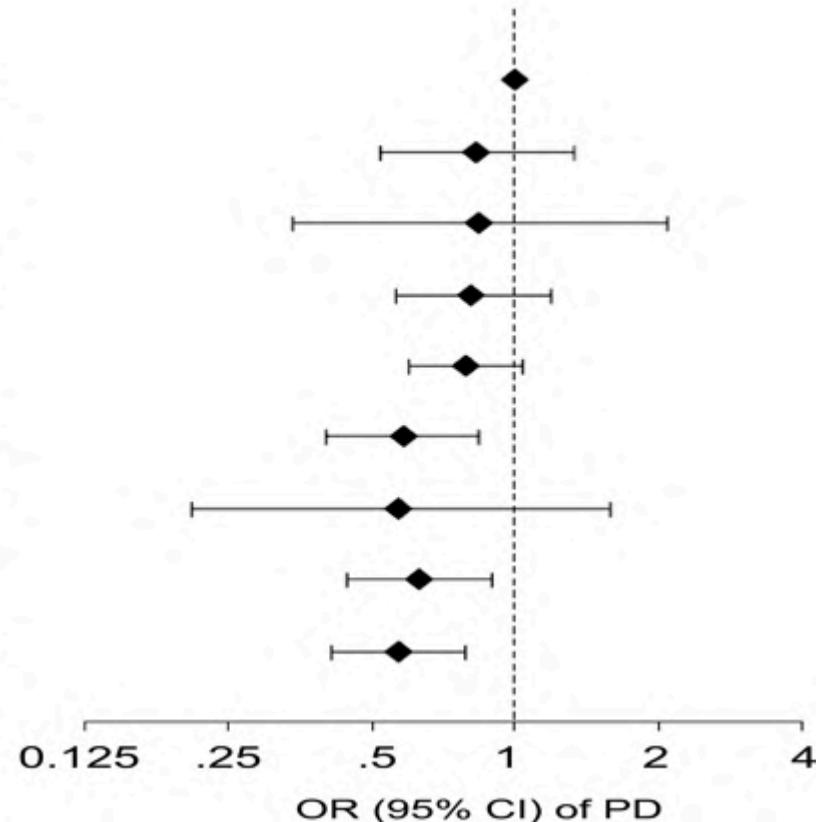
	n	Dementia cases	RR (95% CI) ¹	RR (95% CI) ²
Physical component score sum				
0	285	67	1.0	1.0
1	165	22	0.55 (0.34-0.89)	0.58 (0.36-0.95)
2-3	182	24	0.61 (0.38-0.99)	0.64 (0.40-1.04)
4 or more	100	10	0.51 (0.26-0.99)	0.59 (0.30-1.16)

Physical activities and future risk of Parkinson disease

Xu et al (2010 in Neurology)

Methods: We evaluated physical activity in relation to PD among 213,701 participants of the NIH-AARP Diet and Health Study cohort. Physical activities over 4 periods (ages 15–18, 19–29, and 35–39, and in the past 10 years) were noted in 1996–1997, and physician-diagnosed PD was reported on the 2004–2006 follow-up questionnaire. Only cases diagnosed after 2000 (n 767) were included in the analyses.

<u>Ages 35-39</u>	<u>Past 10 years</u>	<u>No. of cases / controls</u>
Low	Low	59 / 12,739
Low	Medium	25 / 5,744
Low	High	5 / 1,012
Medium	Low	50 / 13,062
Medium	Medium	399 / 103,589
Medium	High	58 / 17,390
High	Low	4 / 1,567
High	Medium	64 / 21,892
High	High	94 / 33,480



There have been several RCT's

Baker et al (2010)

- Small 6 month trial with 33 MCI patients
- More robust cognitive effects for women than for men

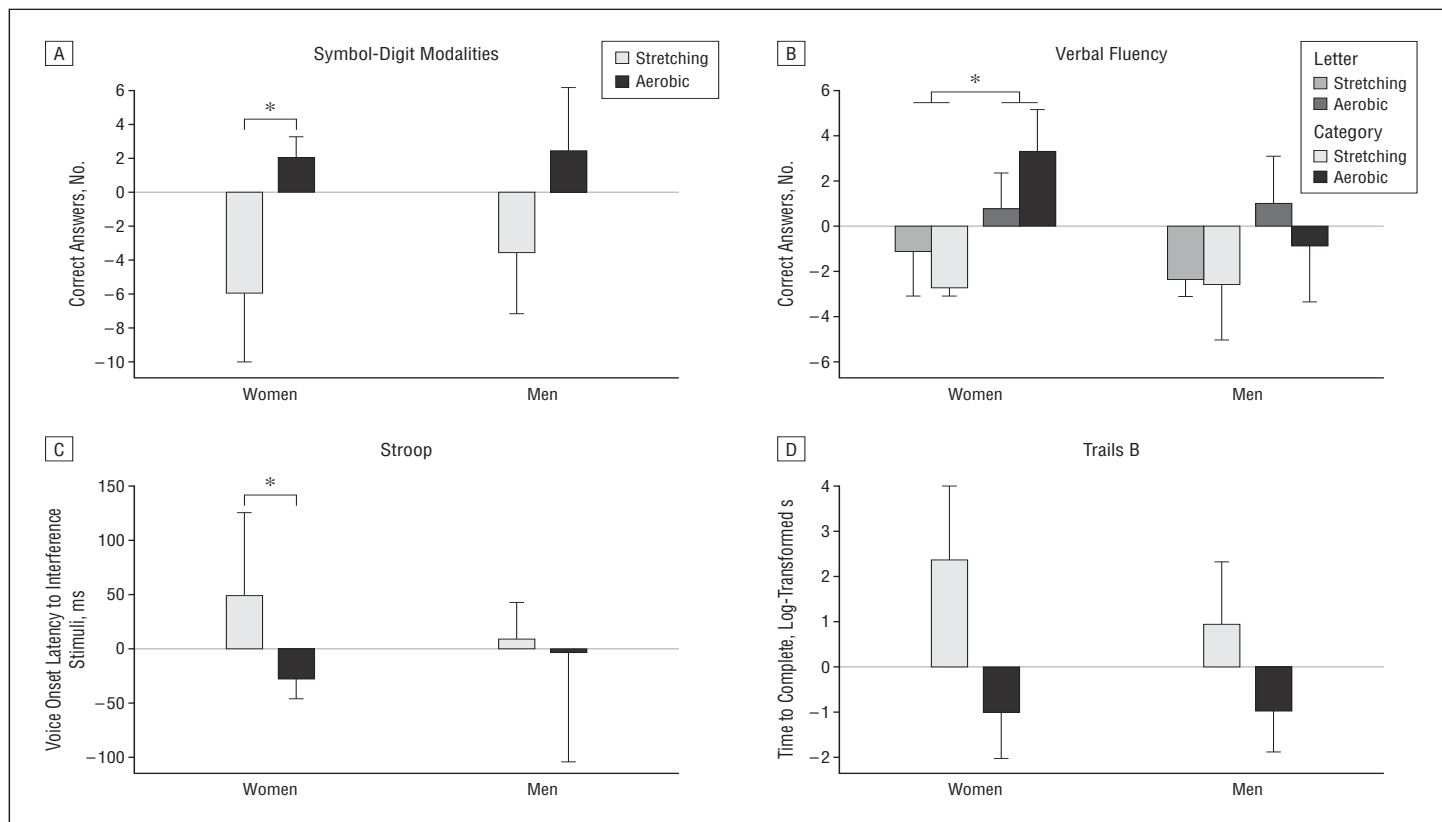
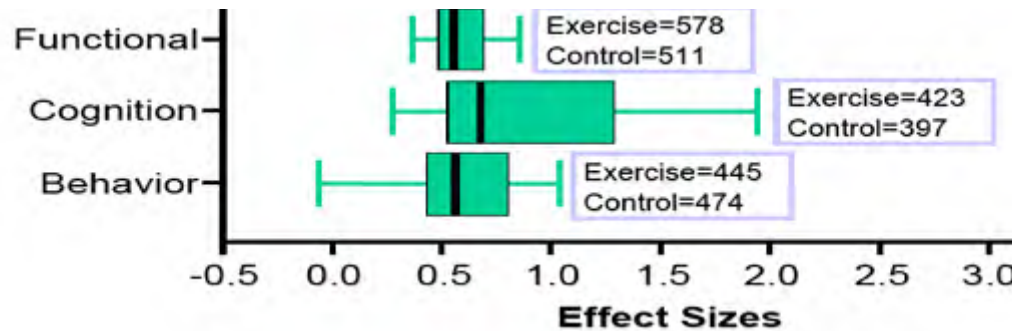


Figure 2. Mean (standard error of the mean) values representing the change from baseline for cognitive measures, expressed as residual scores. A, For the Symbol-Digit Modalities test, the number of correct responses (in 120 seconds) increased for those in the aerobic group relative to the stretching group ($P = .05$); this effect was more pronounced for women ($P = .04$) than men ($P = .33$). B, For the Verbal Fluency test, word generation was increased for those in the aerobic group relative to the stretching group ($P = .04$). For women only, aerobic exercise increased category fluency ($P = .01$). C, For the Stroop test, voice onset latencies to interference stimuli were reduced for women in the aerobic exercise vs stretching group ($P = .02$). D, For the Trails B test, aerobic exercise reduced the time to complete the task ($P = .04$), and this effect was comparable for women ($P = .09$) and men ($P = .05$). * $P < .05$.

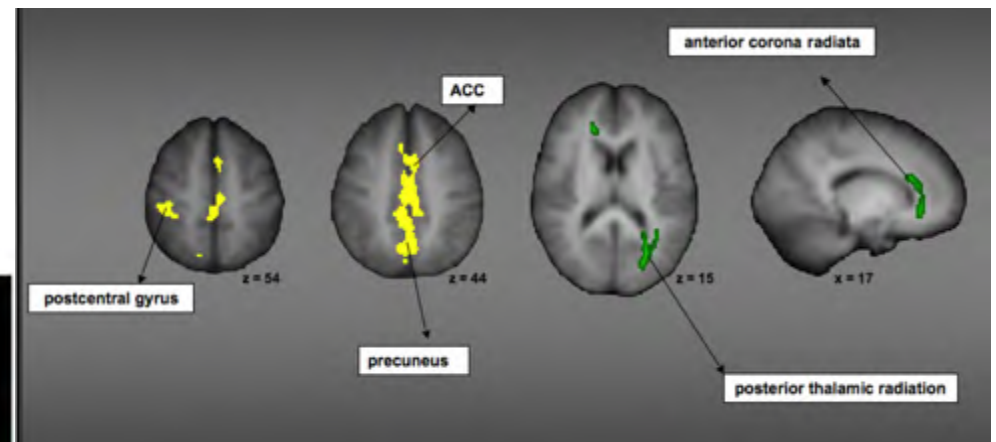
Early Alzheimer's Patients

Heyn et al (2004)



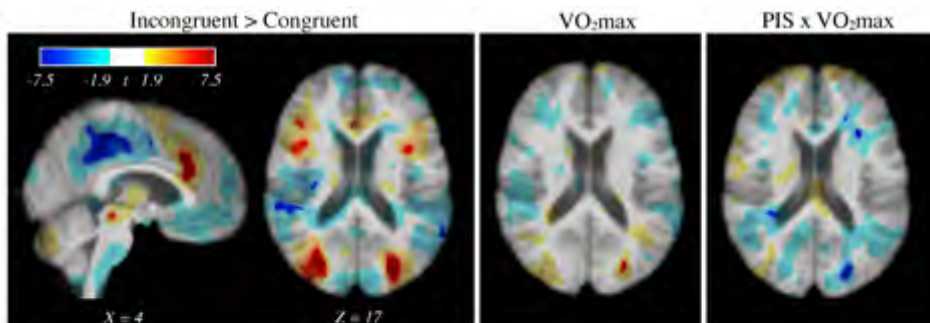
Prakash et al (2009)

Multiple Sclerosis Patients



Parkinson's Patients

Uc et al, (2008)



- Fitness related differences in fMRI activation pattern are correlated with measures of attentional control and inhibition

- Differences in gray matter volume & white matter integrity (via DTI) as a function of fitness are correlated with processing speed

Some caveats & ideas for the future

- There is some consistency but far from universal agreement in most of the effects that were discussed.
 - Clearly a need to examine boundary conditions with regard to:
 - Length, intensity and type of physical activity / exercise
 - Outcome measures – brain and cognition
 - Potential moderators – age, gender, health history, exercise history, type and stage of dementia
 - Potential genetic moderators – apoe, thus far
 - Transfer beyond the lab
 - Need for theoretically-based multimodal assessments
 - Need for retention assessments – any “free lunch”?
 - Need to assess potential synergistic effects with other lifestyle choices (intellectual, social, diet, other behaviors)

In terms of Parkinson Disease

Eric Ahlskog in his 2011 review (in Neurology) entitled "Does vigorous exercise have a neuroprotective effect in Parkinson disease" stated that

In terms of Parkinson Disease

Eric Ahlskog in his 2011 review (in Neurology) entitled "Does vigorous exercise have a neuroprotective effect in Parkinson disease" stated that

" This overall body of evidence suggests that vigorous exercise should be accorded a central place in our treatment of PD".

Collaborators

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- Eddie McAuley
- Brad Sutton
- Michelle Voss
- Jeff Woods

University of Pittsburgh

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Ohio State

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New York University

- Stan Colcombe

Rice University

- Chandramilika Basak

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University of Iowa

- Ergun Uc

University of British Columbia

- Teresa Liu-Ambrose
- Lindsay Nagamatsu

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“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”