Take a Hike: Aging, Activity & Brain Health

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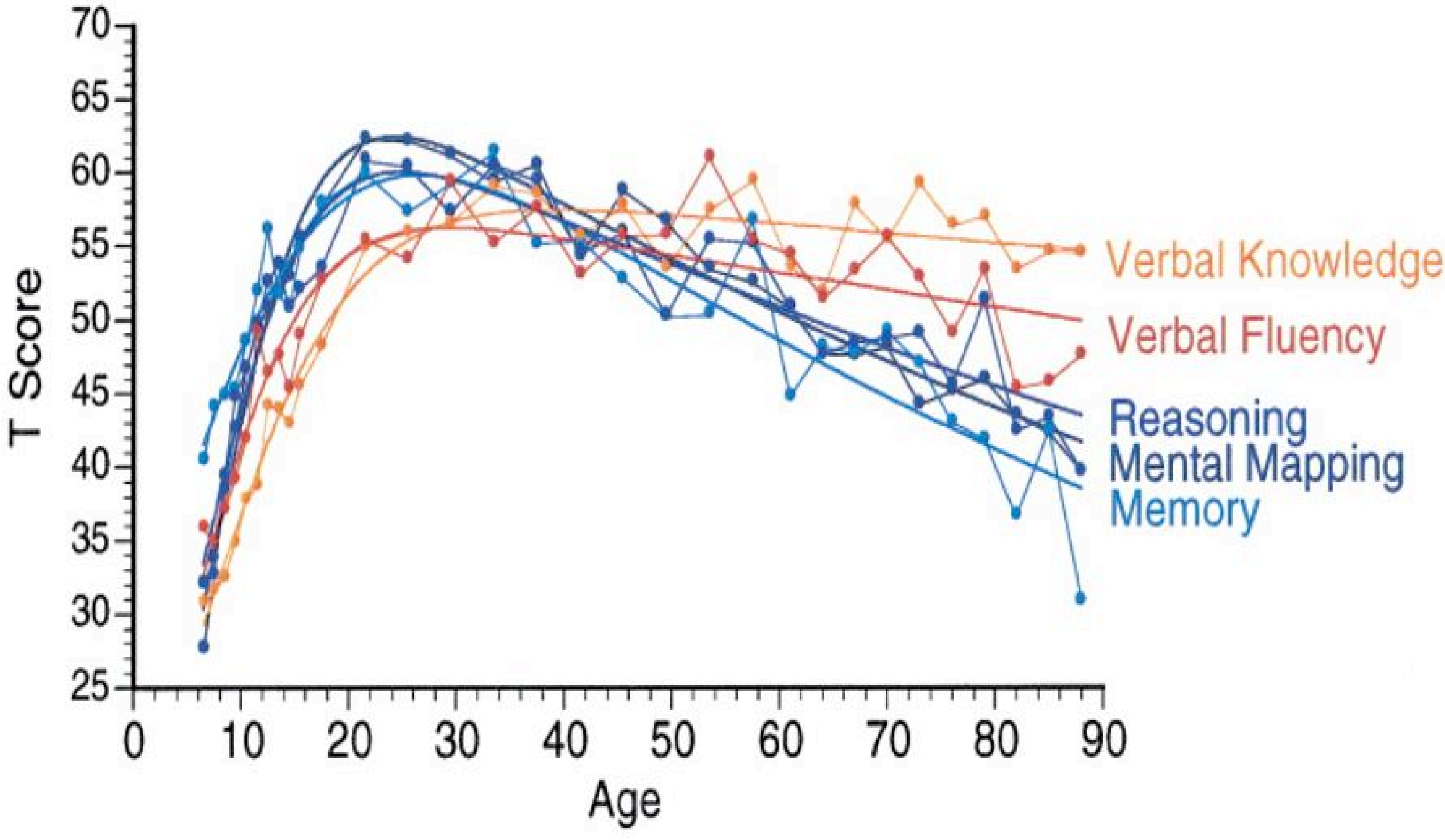
Beckman Institute
University of Illinois
March, 2013

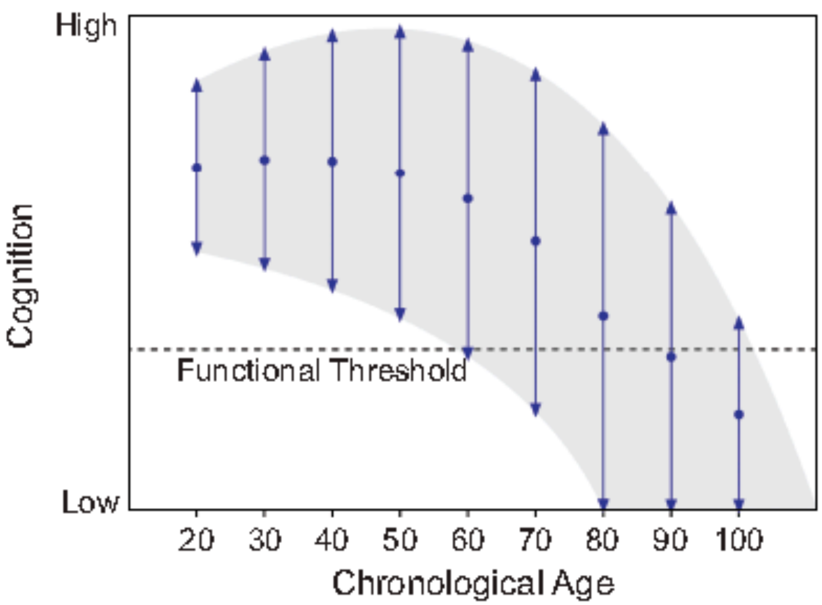
Cognitive differences across the lifespan



Li et al, 2004

"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)



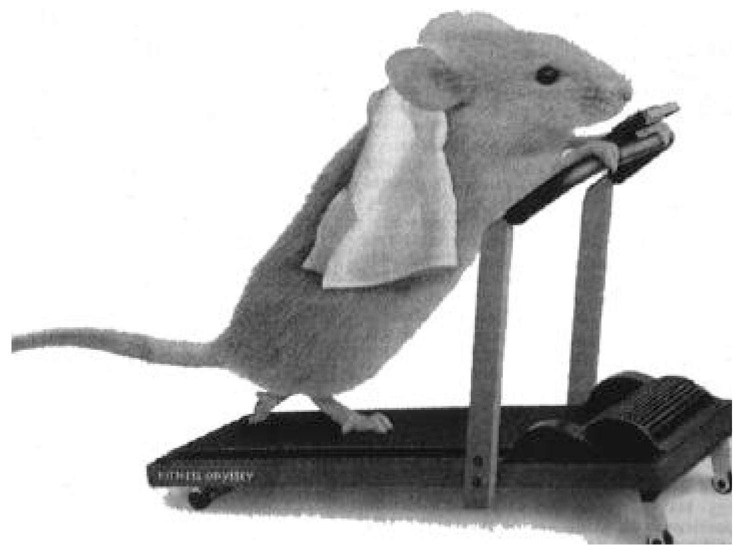
Cognitive Enrichment Hypothesis

- 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:



Roadmap for Today

- What do we currently know about the molecular and cellular brain mechanisms of physical activity – animal models.

- Exercise versus cognitive training – and human performance and cognition.

- Exercise and physical activity effects on older human minds & brains – structure, function and functional connectivity.

- Is there a point of no-return for exercise effects on brain & cognition?

- Fitness effects across the lifespan.

- What studies need to be done to further advance our understanding of the link between exercise & cognition ?

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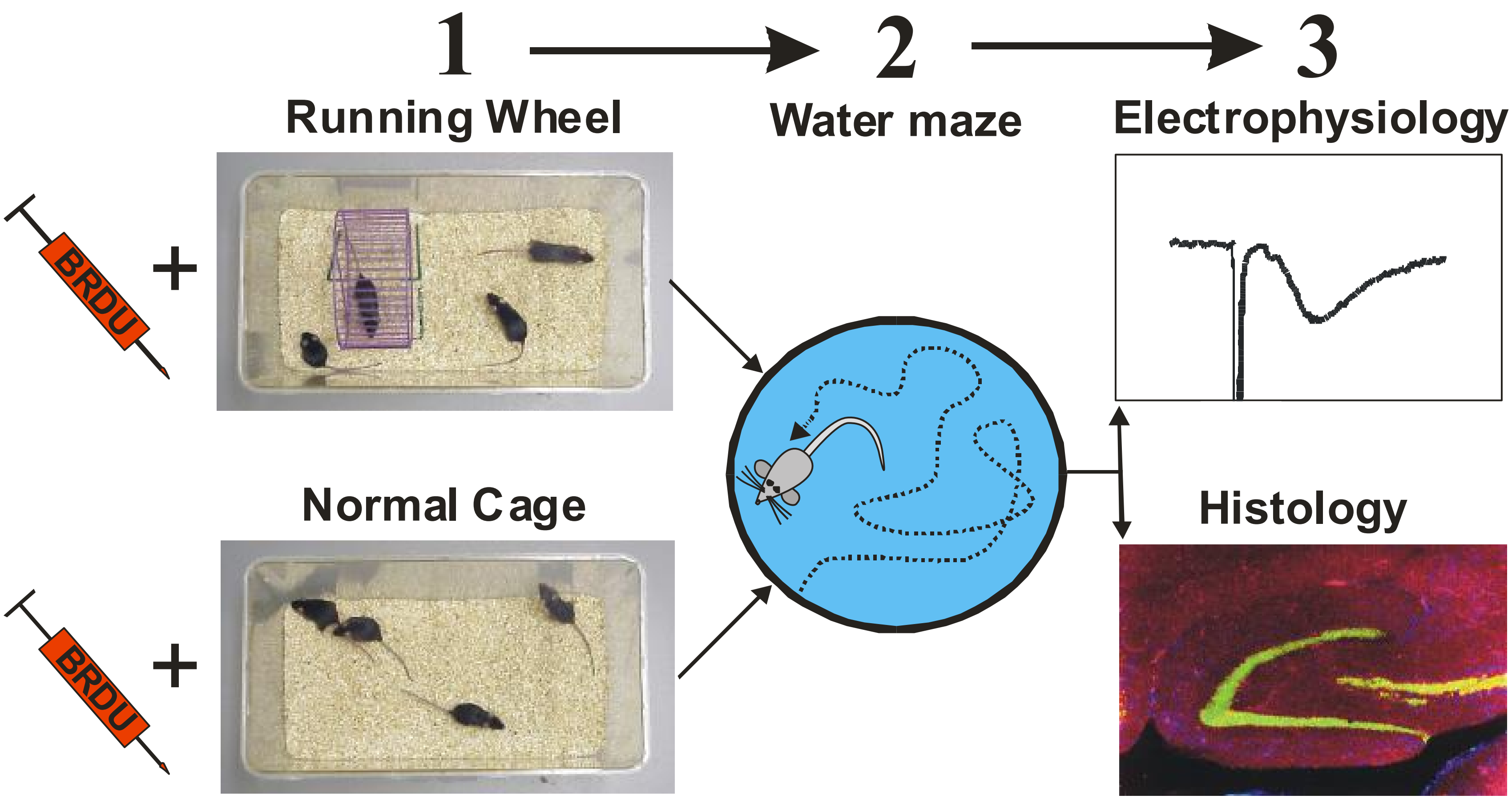
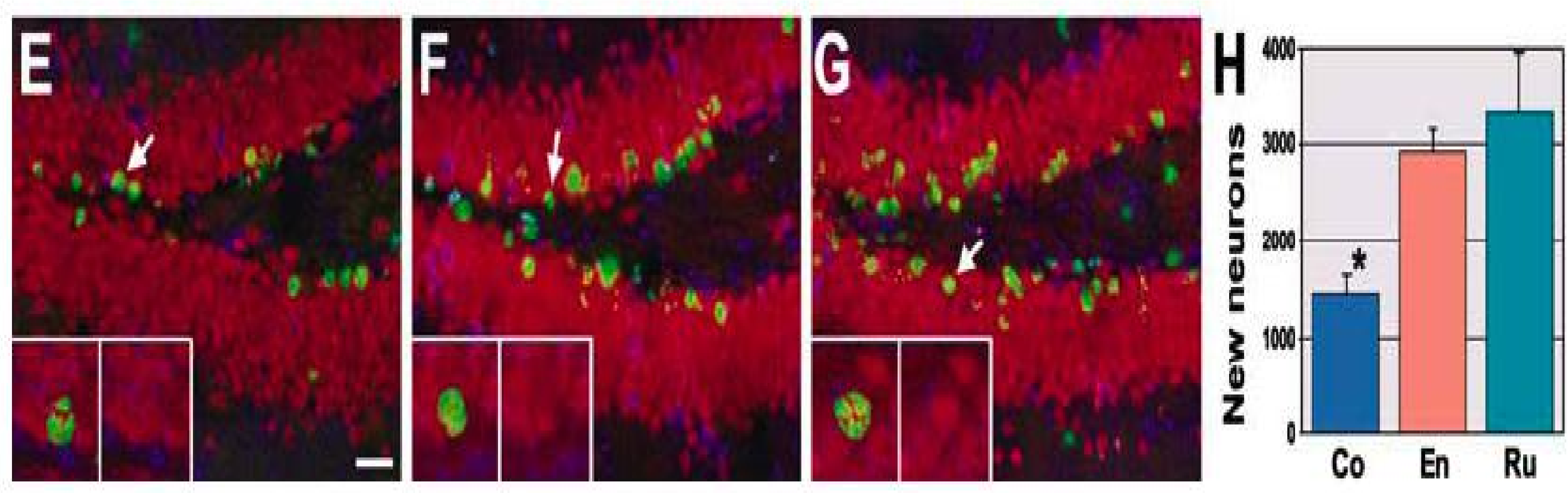
EXPERIMENTAL DESIGN

Assessing the effects of exercise



Van Praag et al, 1999



Brown et al, 2003

ALSO ……

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

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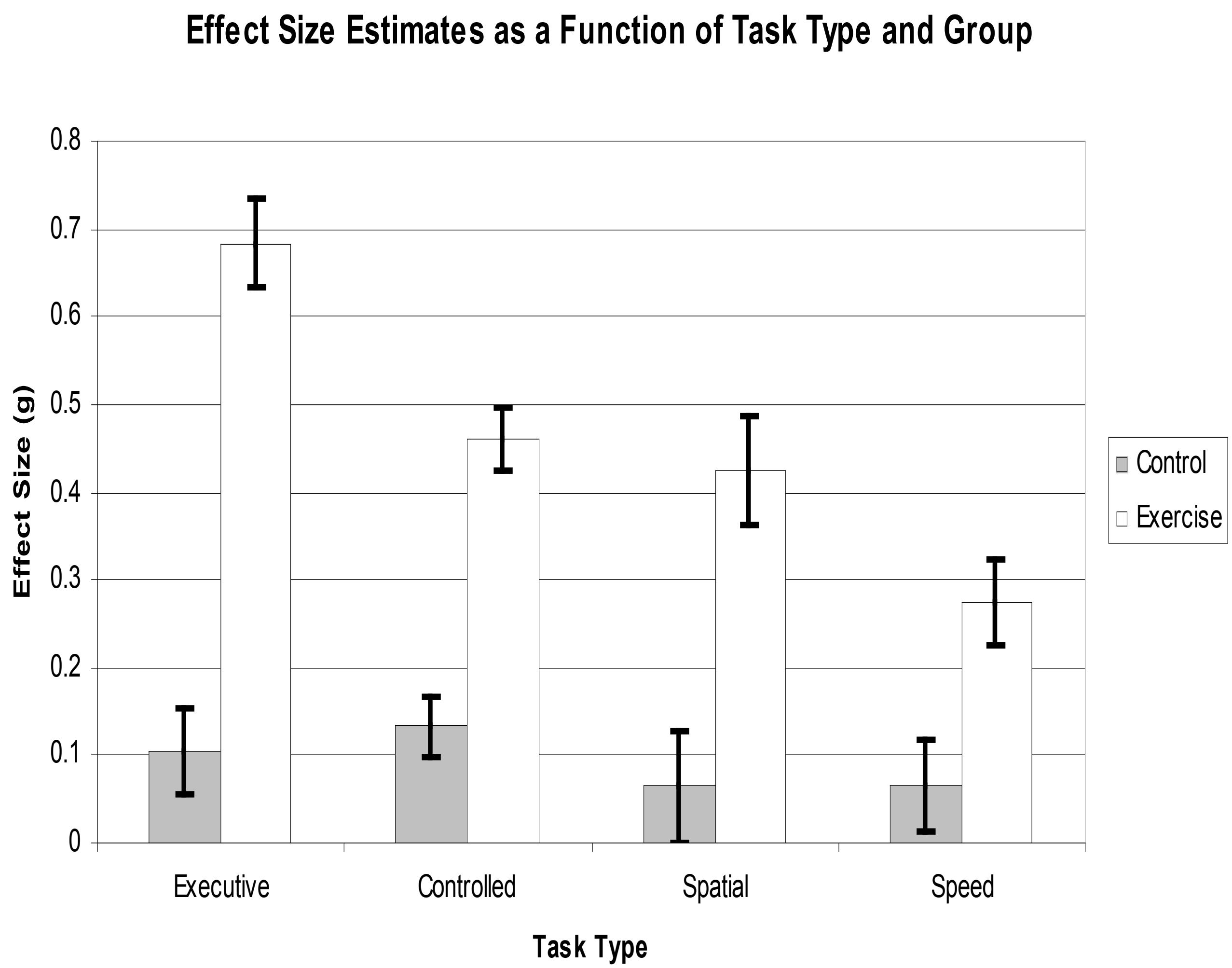
- Across intervention studies (with normal elderly) that find positive effects of fitness training on cognition the cognitive benefits are quite broad – with larger benefits for some cognitive processes …



Colcombe & Kramer (2003)

An illustration of the specificity of cognitive training effects, with the training of individual processes, from the largest randomized trial of cognitive training programs.

Ball et al (2002)

Net Effect of ACTIVE Training on Proximal Outcome Composites

	Memory Training	Reasoning Training	Speed Training
Memory Composite (+), PT	**0.2566*** **	-0.0197	-0.0449
", A1	**0.2085*** **	0.0178	-0.0499
", A2	**0.1751*** **	0.0431	-0.0324
", A3	**0.2207*** **	-0.0103	0.0062
Reasoning Composite (+), PT	-0.0019	**0.4797*** **	0.0014
", A1	-0.0039	**0.3998*** **	-0.0296
", A2	-0.0228	**0.2568*** **	-0.0402
", A3	0.0132	**0.3812*** **	-0.0370
Speed Composite (+), PT	-0.0089	-0.0262	**-1.4541*** **
", A1	-0.0201	-0.0032	**-1.2000*** **
", A2	-0.0503	-0.0192	**-0.8616*** **
", A3	0.0456	0.0053	**-0.9538*** **

Net effect size defined as [Training Mean - Control Mean at indicated time] - [Training mean - Control mean at baseline] divided by intra-subject standard deviation of the composite. (±) indicates direction of positive response.
*** $p < 0.0001$ testing for net effect significantly different from zero.

Some transfer to self-reported IADL's after 5 years (reasoning group)

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Barnes et al, 2003 – 6 yr prospective study

- 349 healthy + 55 year olds
- <u>Objective</u> measures of cardiorespiratory fitness *

Table 2. Cognitive Function by Sex-Specific Tertile of Baseline Peak VO_2

Cognitive Measure	Peak VO_2 (mL/kg^*min^{-1}) Lowest Tertile	Middle Tertile	Highest Tertile	*P*-value for trend*
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 VO_2) 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 VO_2 = oxygen consumption at peak exercise; CI = confidence interval.

See also: Middleton et al, 2011 – for the value of objective fitness measures in observational studies

Physical activity predicts gray matter volume in late adulthood

The Cardiovascular Health Study

Erickson et al (2010)

Figure 1 Subject inclusionary criteria and sample sizes

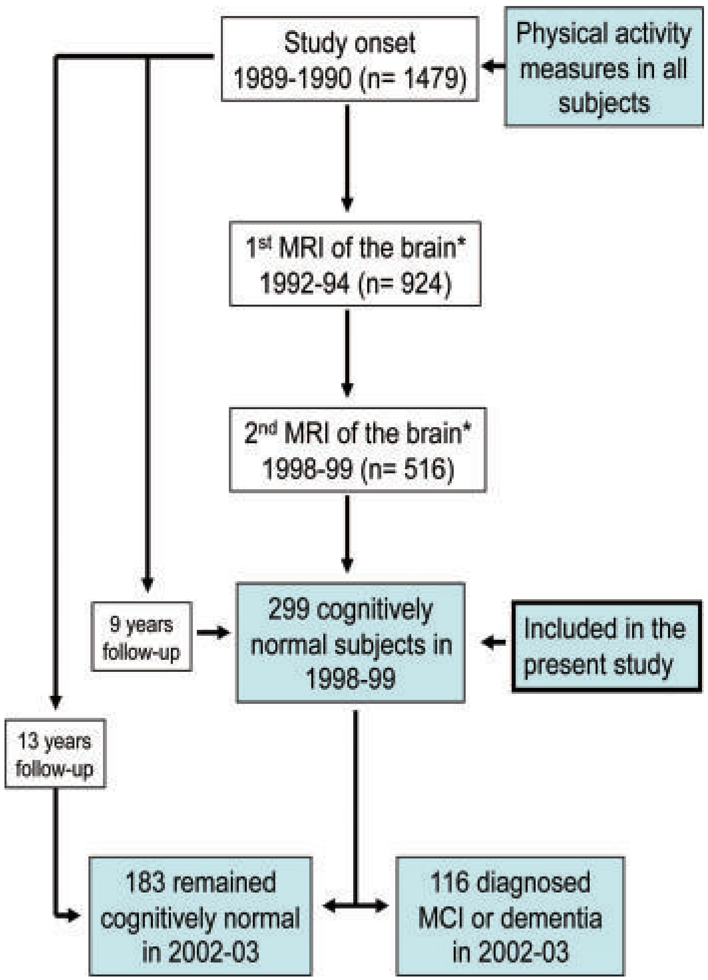
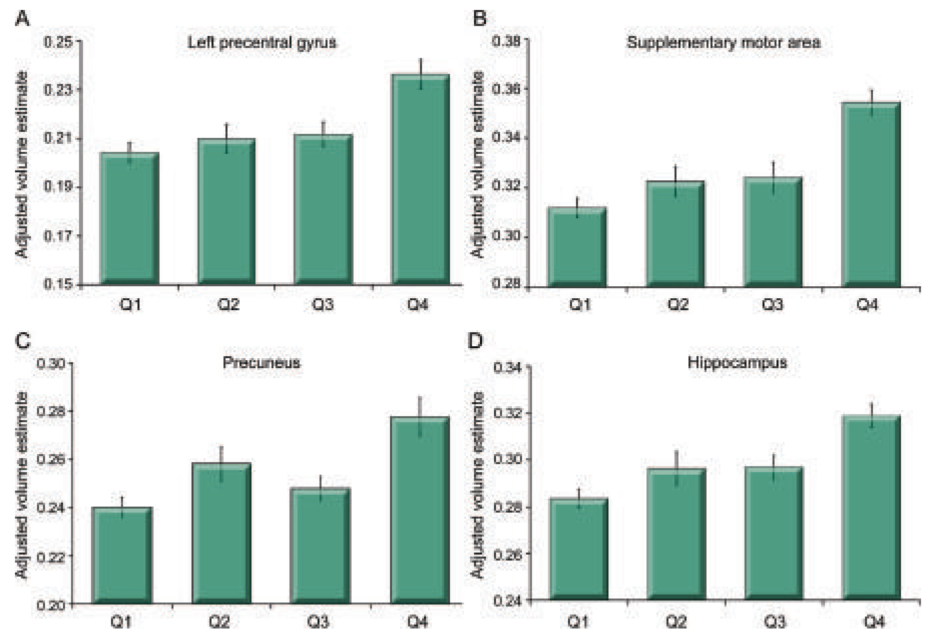
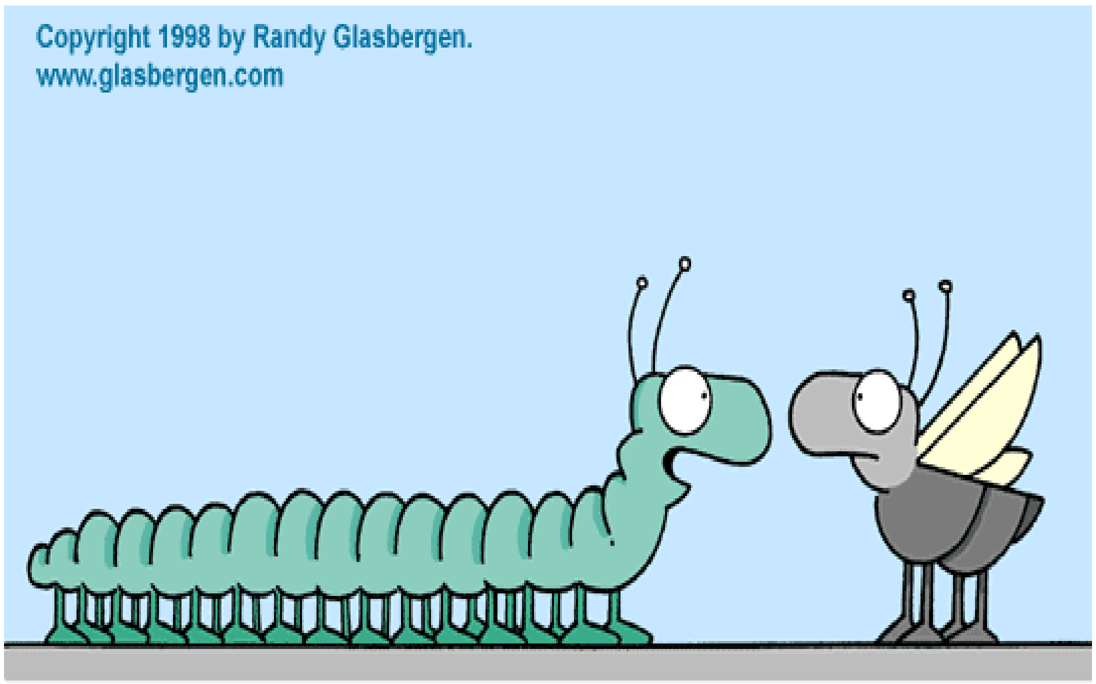


Figure 3 Threshold effects on brain volume

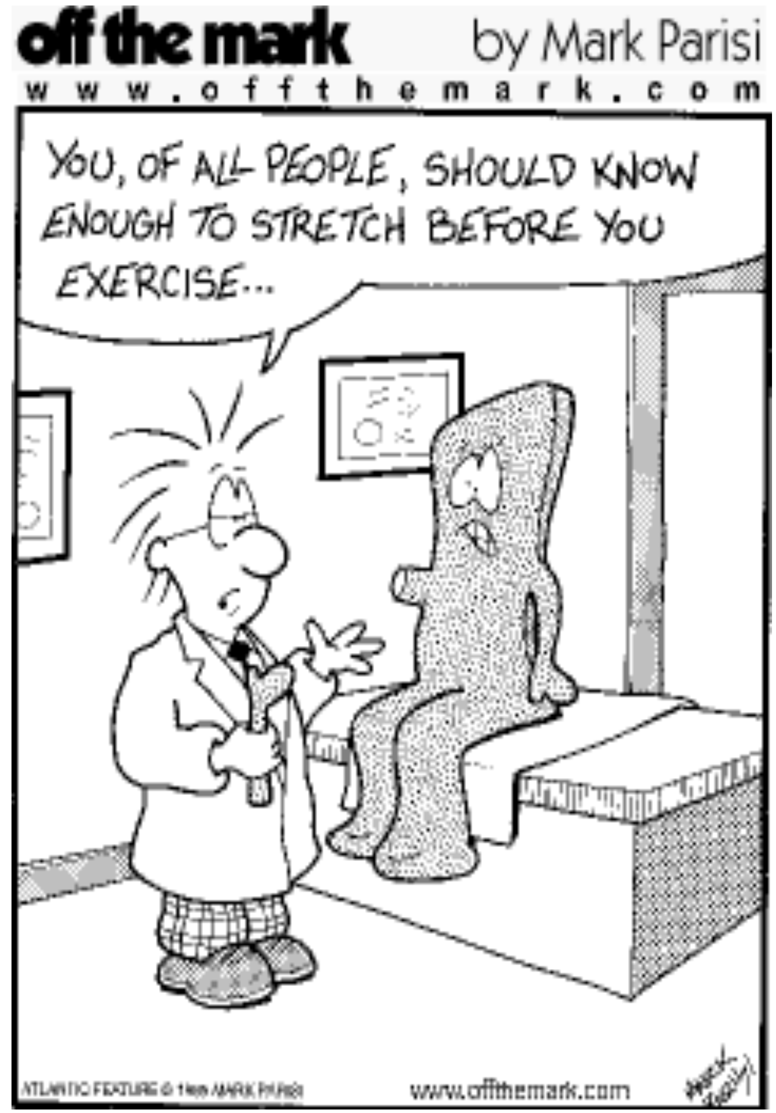


And .... Walking (and subsequent brain volume differences) reduced the risk of cognitive impairment twofold at 13 year follow-up

TYPICAL FITNESS INTERVENTIONS

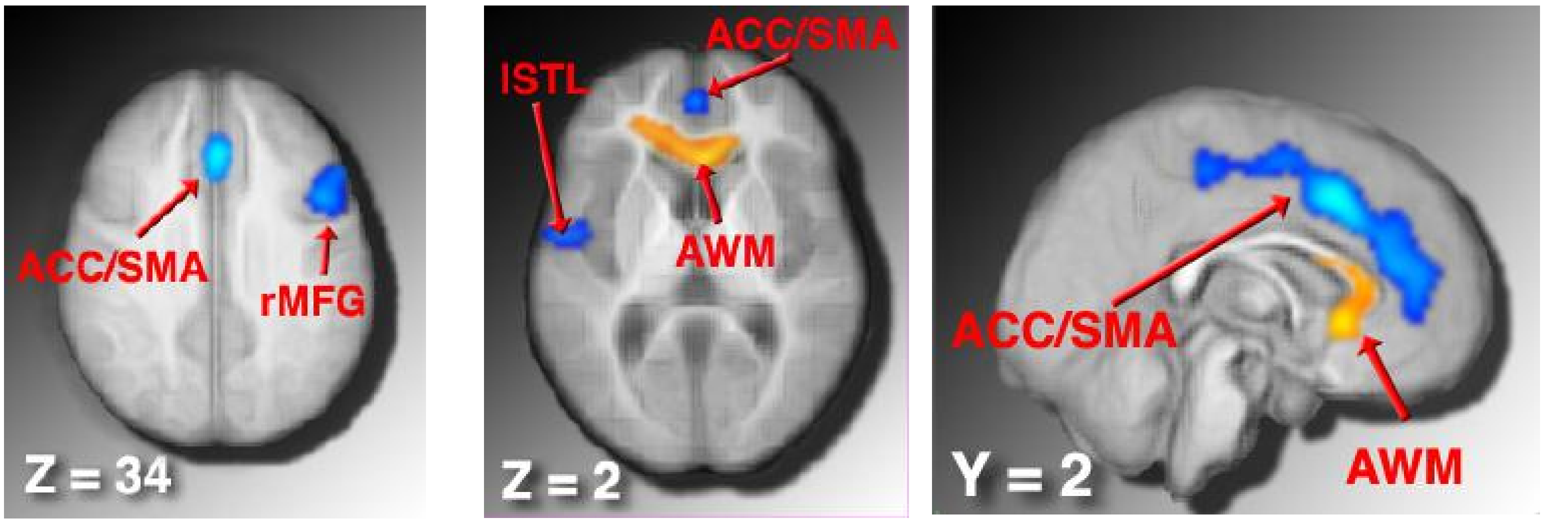


"I tried all the fitness fads, but my doctor was right all along—walking is still the best exercise."



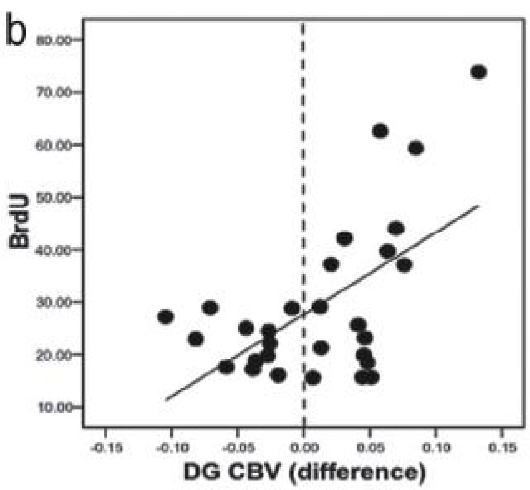
Physical activity interventions in humans have positive effects on brain function & structure – and in turn cognition?

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 …….



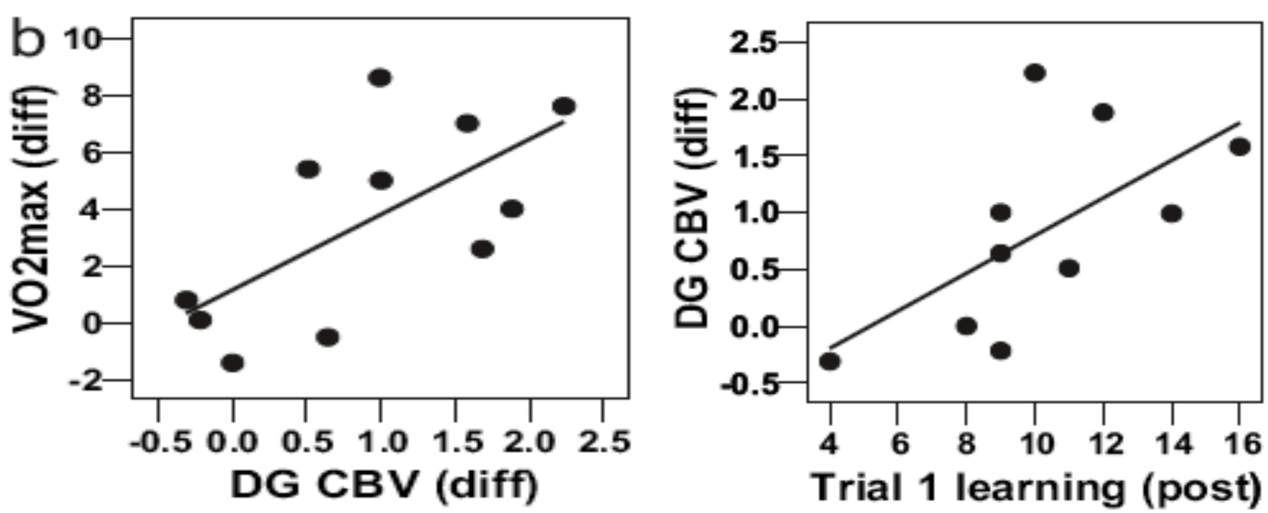
Colcombe et al, 2006

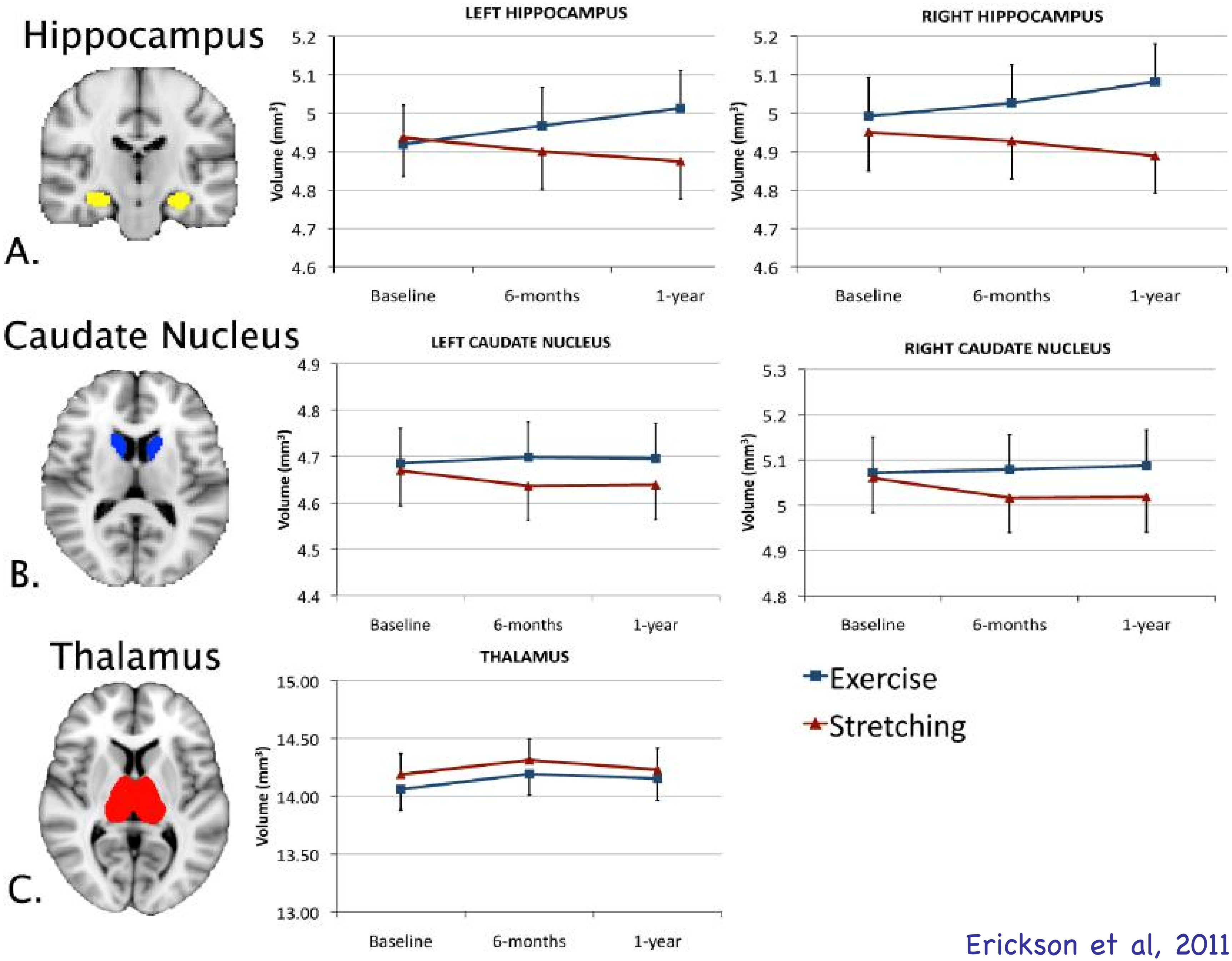
Rodent



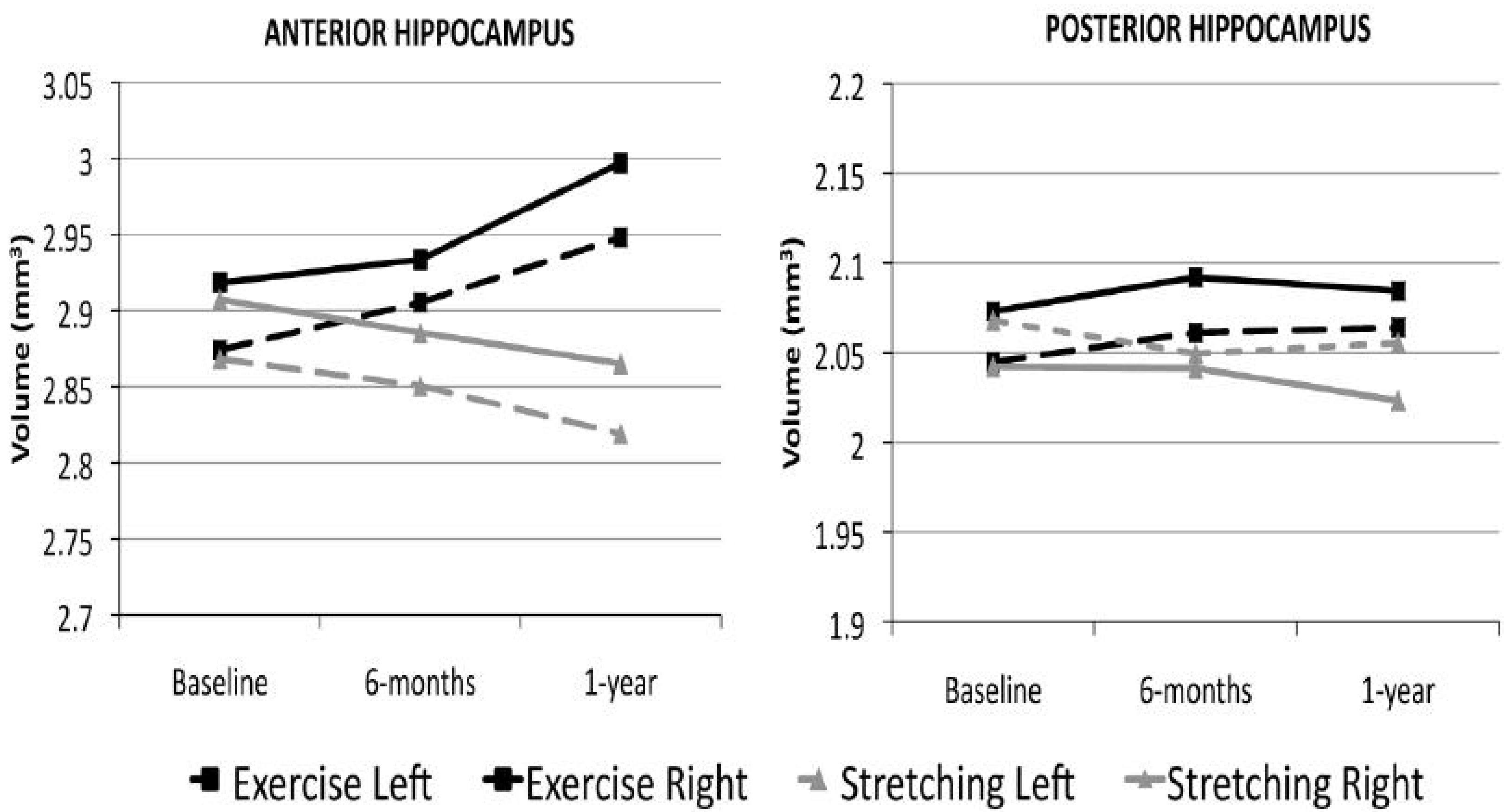
Human

Pereira et al, 2007

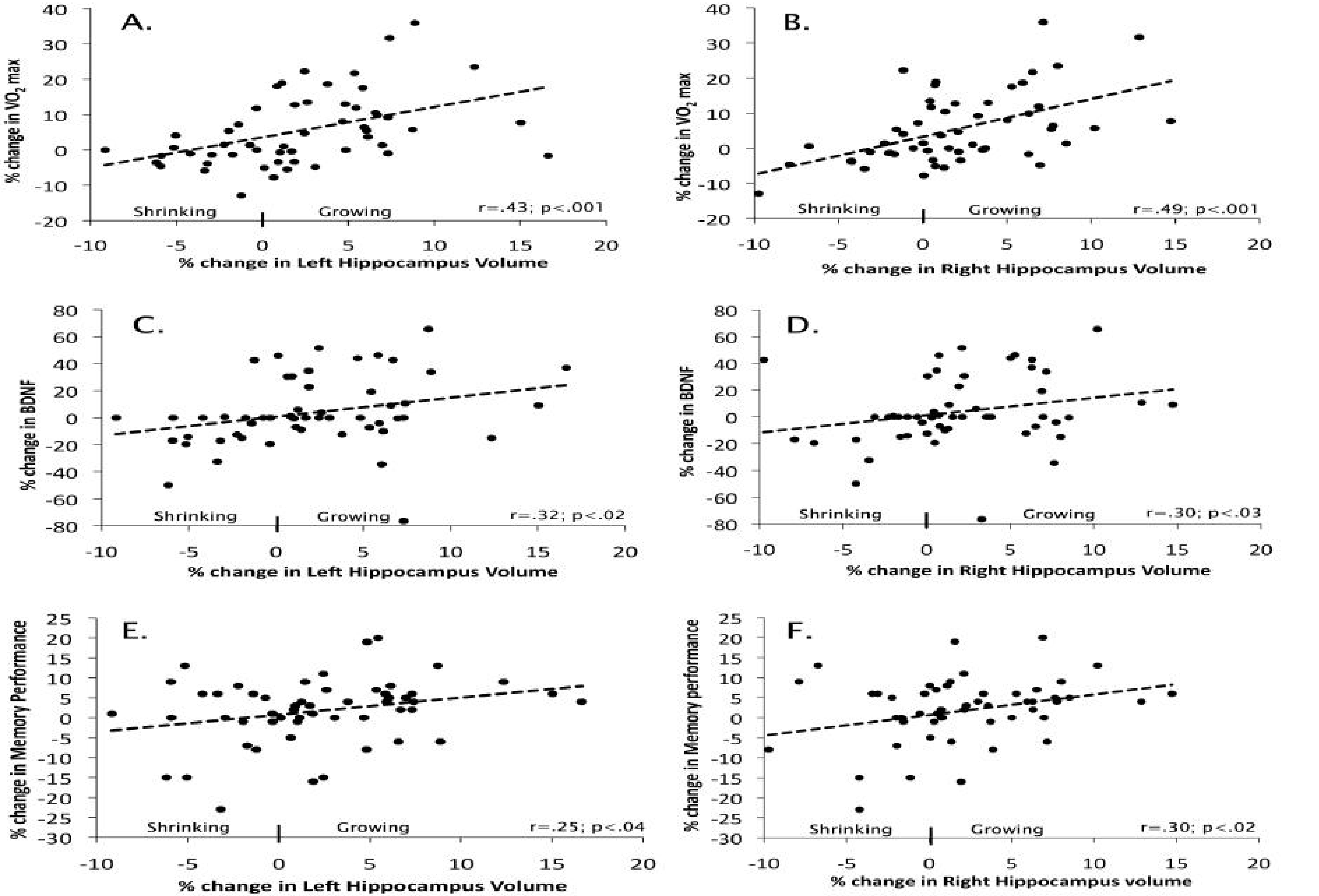




Erickson et al, 2011

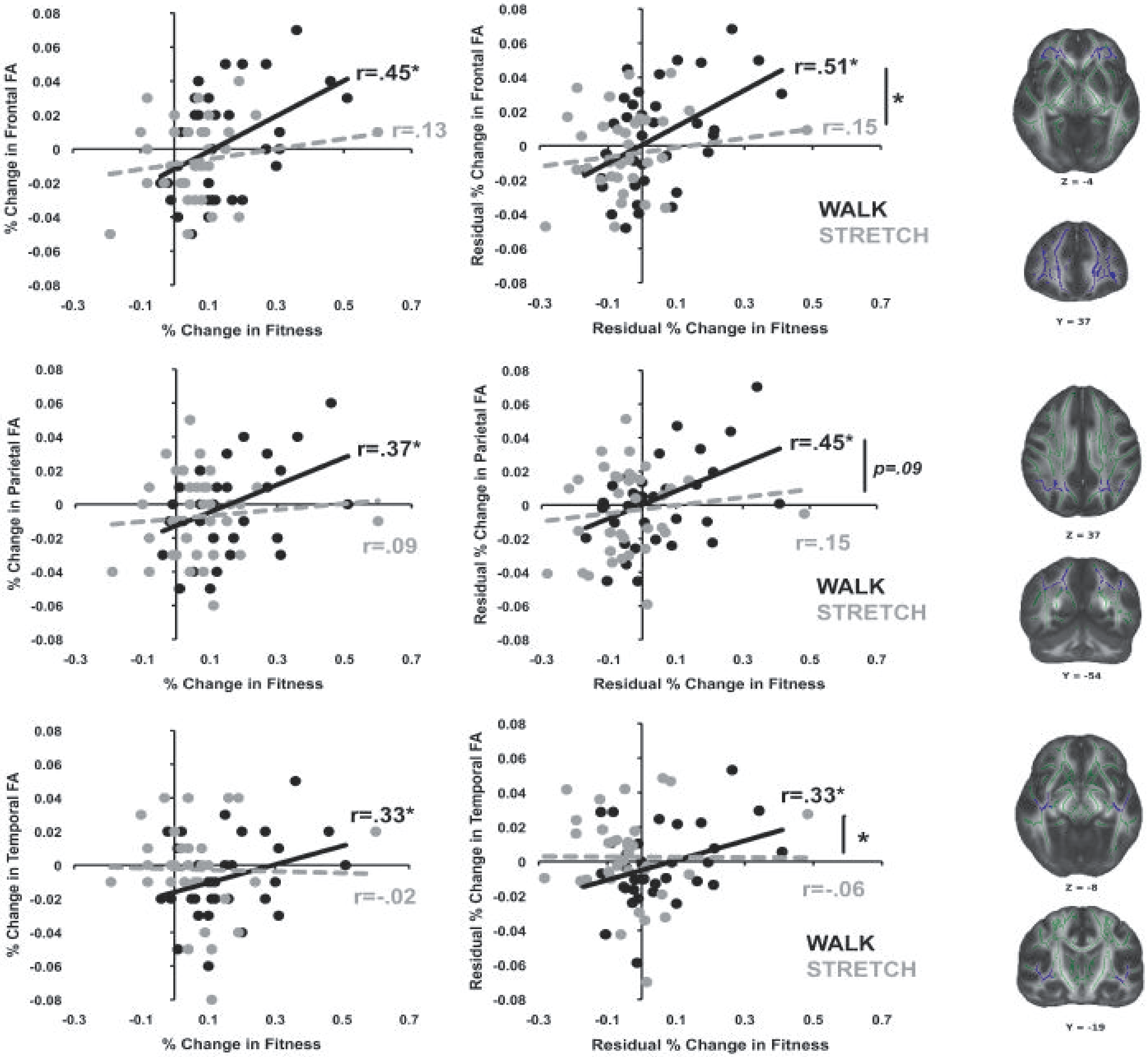


ANTERIOR HIPPOCAMPUS
POSTERIOR HIPPOCAMPUS
Volume (mm³)
3.05
3
2.95
2.9
2.85
2.8
2.75
2.7
2.2
2.15
2.1
2.05
2
1.95
1.9
Baseline
6-months
1-year
Exercise Left
Exercise Right
Stretching Left
Stretching Right



A.
B.
C.
D.
E.
F.
% change in VO_2 max
% change in BDNF
% change in Memory Performance
% change in Memory performance
Shrinking
Growing
r=.43; p<.001
r=.49; p<.001
r=.32; p<.02
r=.30; p<.03
r=.25; p<.04
r=.30; p<.02
% change in Left Hippocampus Volume
% change in Right Hippocampus Volume
% change in Right Hippocampus volume

Correlated change in white matter and aerobic fitness

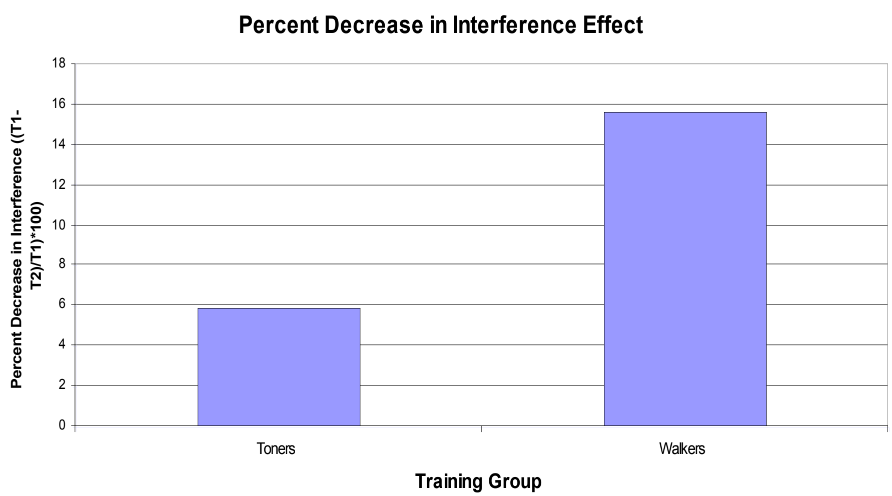


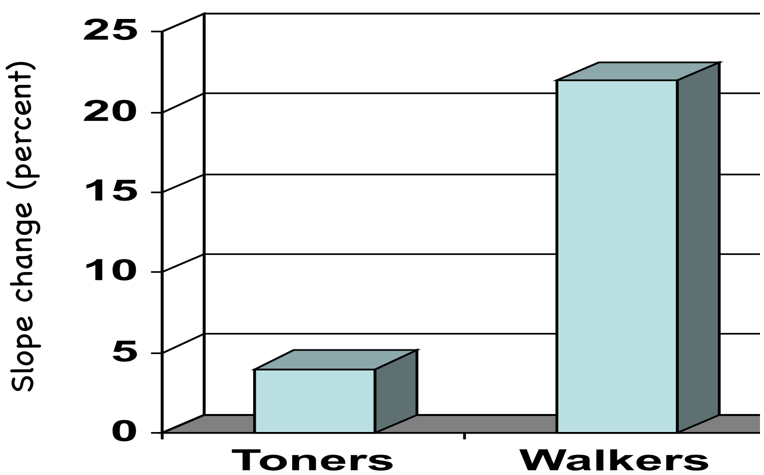
Voss et al,
In press

Effects of fitness training on performance & *brain function*:

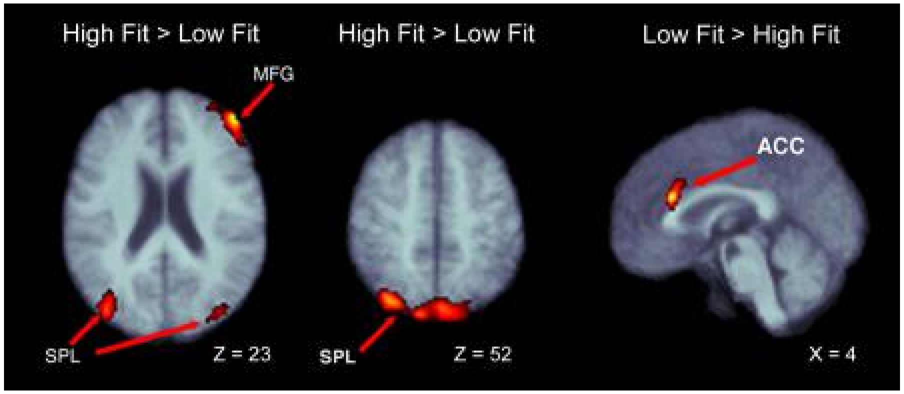
Flanker / Selective Attention Task

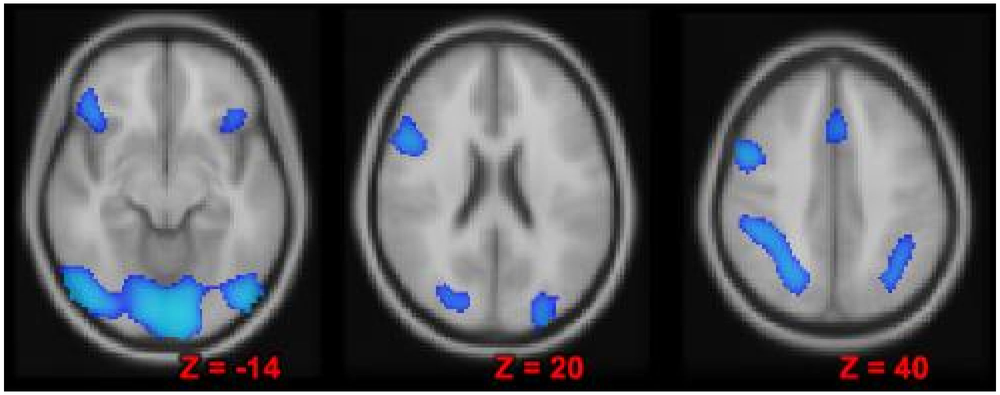
Sternberg Memory Search Task



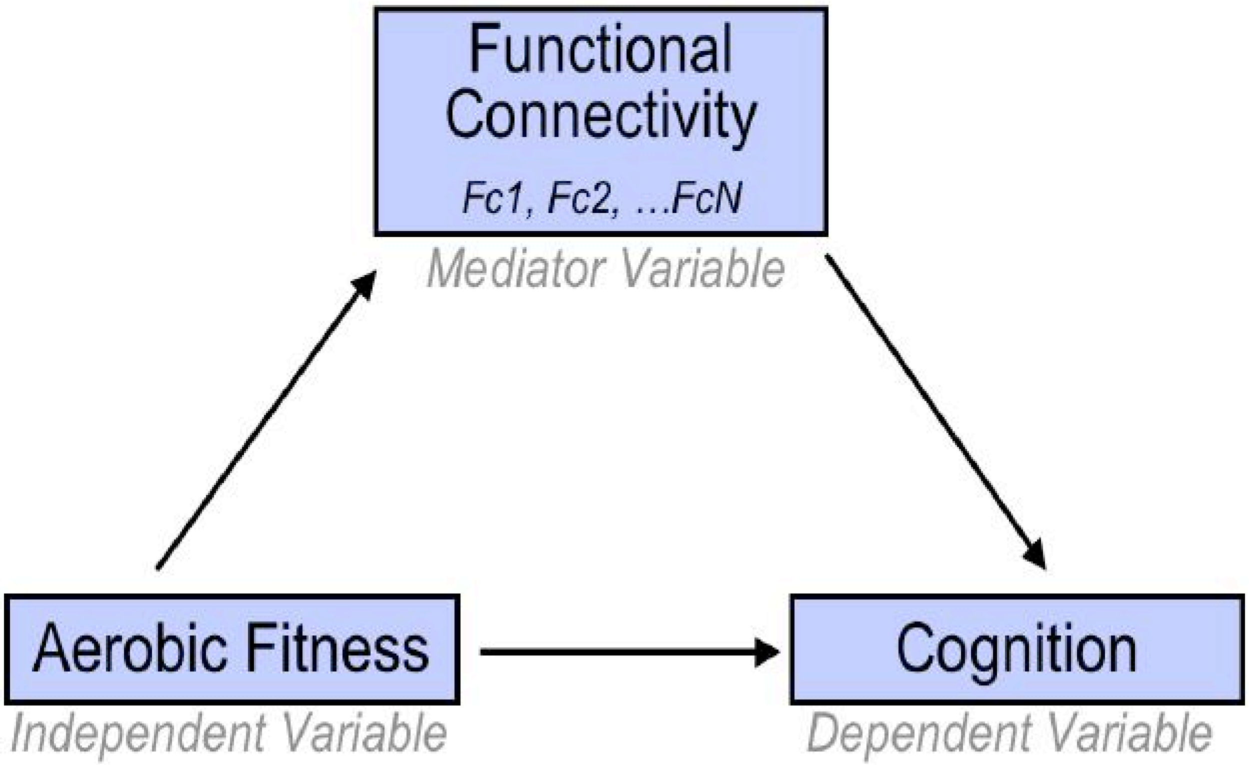


Colcombe et al., 2004





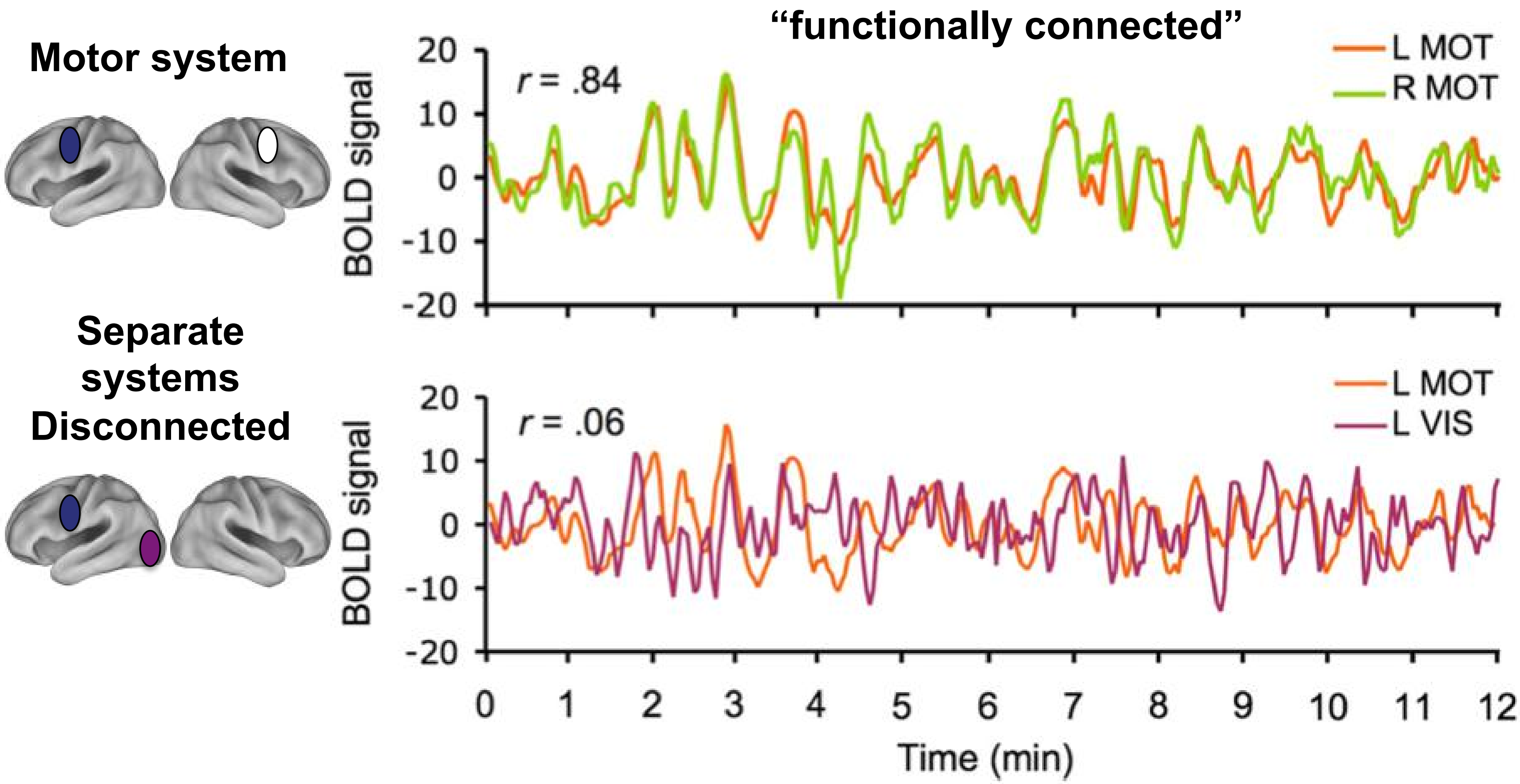
Is aerobic fitness associated with better Functional connectivity?



Voss et al., 2010, *Neuropsychologia*

Brain "networks"

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

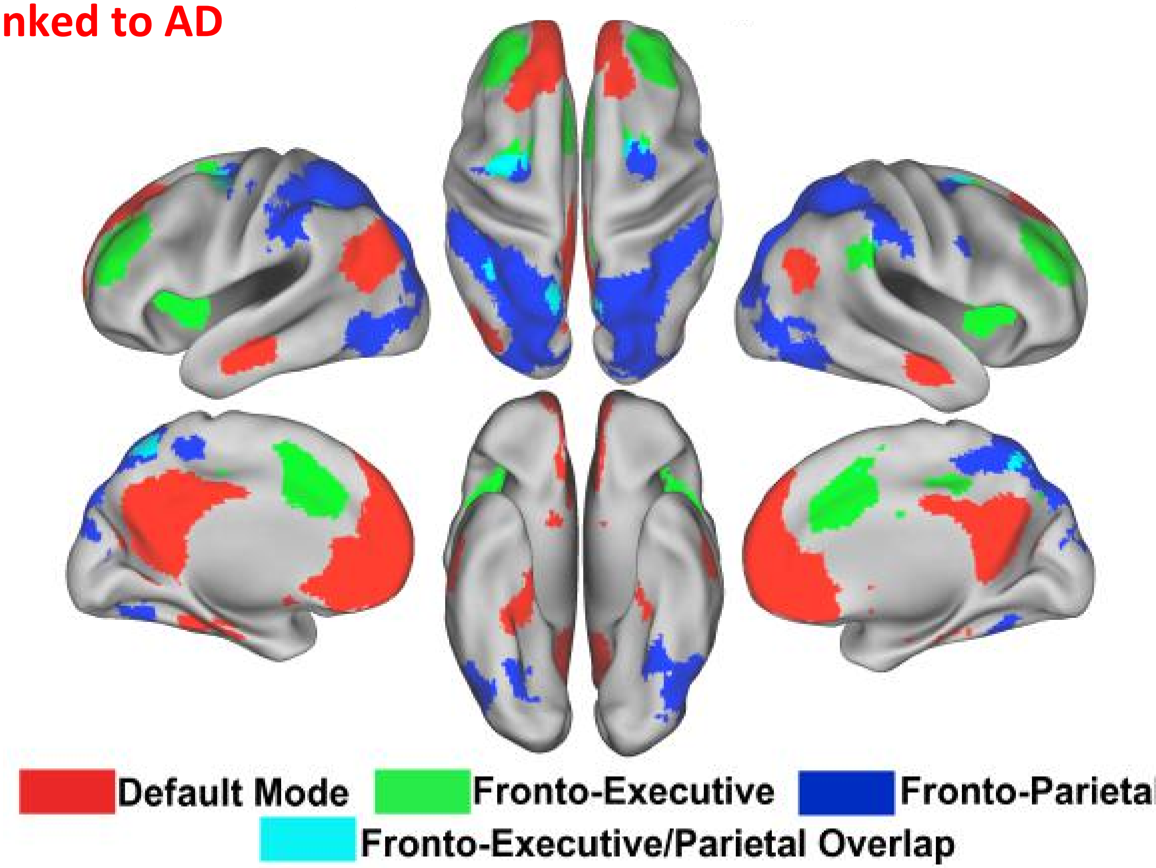


Cognitively relevant brain networks

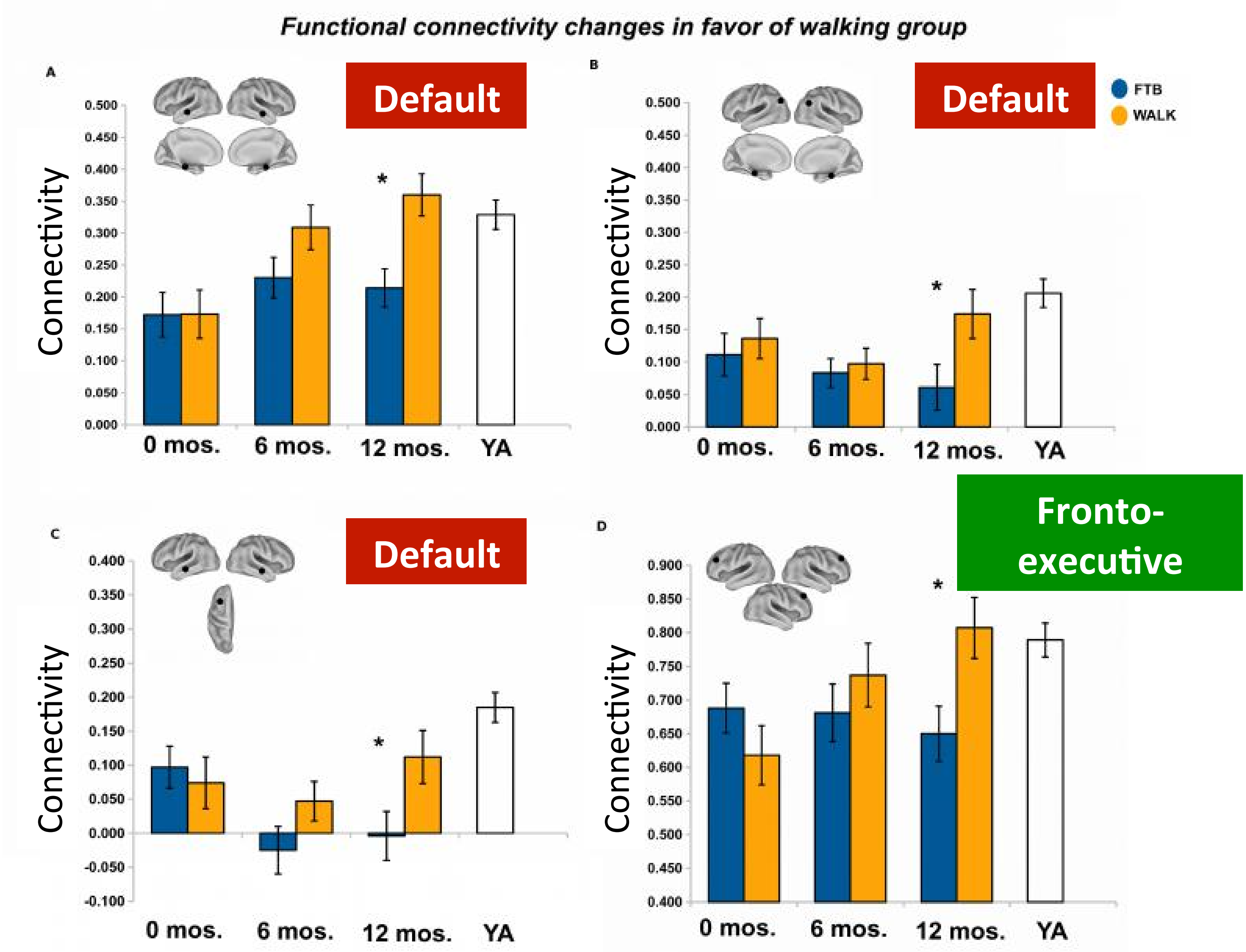
- deactivated during goal-directed attention
- active at rest, inward thought
- ↑ executive functions, speed, memory processes
- dysfunction linked to AD

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

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

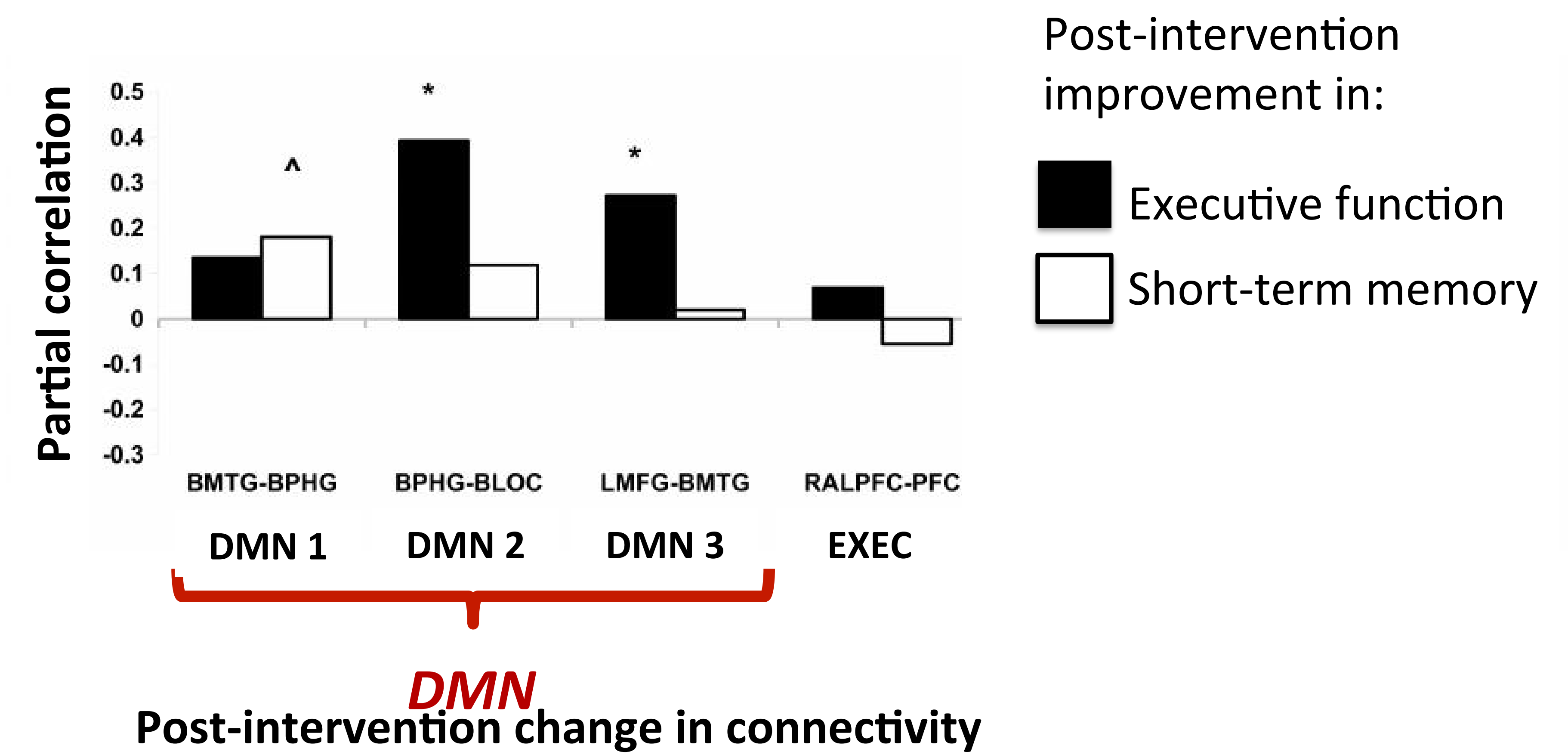


Improvements in networks post-exercise?



Voss et al., 2010

Brain-Behavior associations



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

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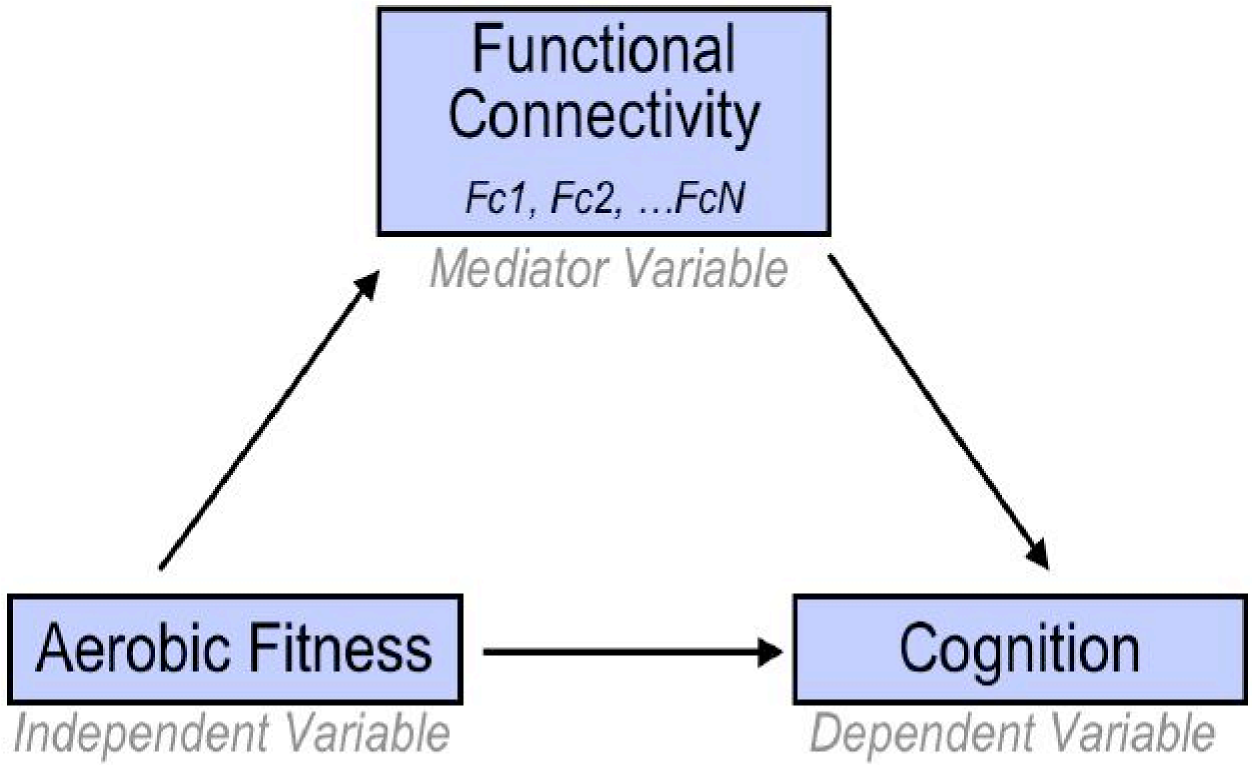


✔ ***Executive function abilities***

Voss et al., 2010, *Neuropsychologia*

What about networks modeled as ***one complex system***?

***Complex network systems analysis* – mathematical models based on graph theory for characterizing large systems of interacting components**

Networks:

Node

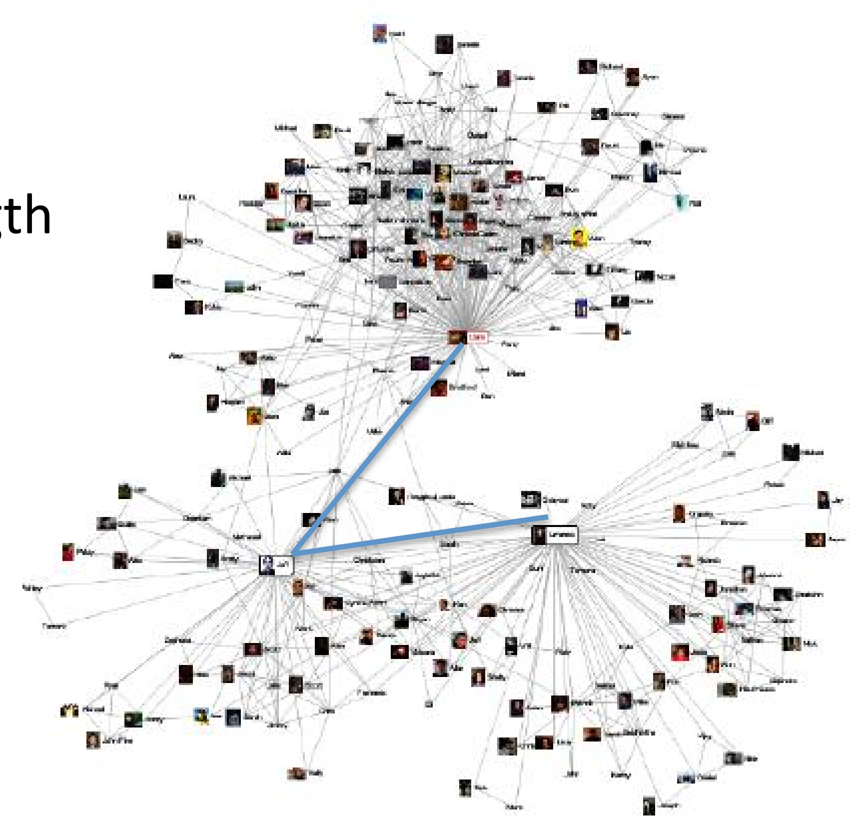
Edge/link

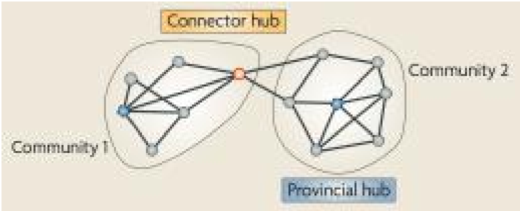
Distance/path length

Cliques

Hubs

Social networks





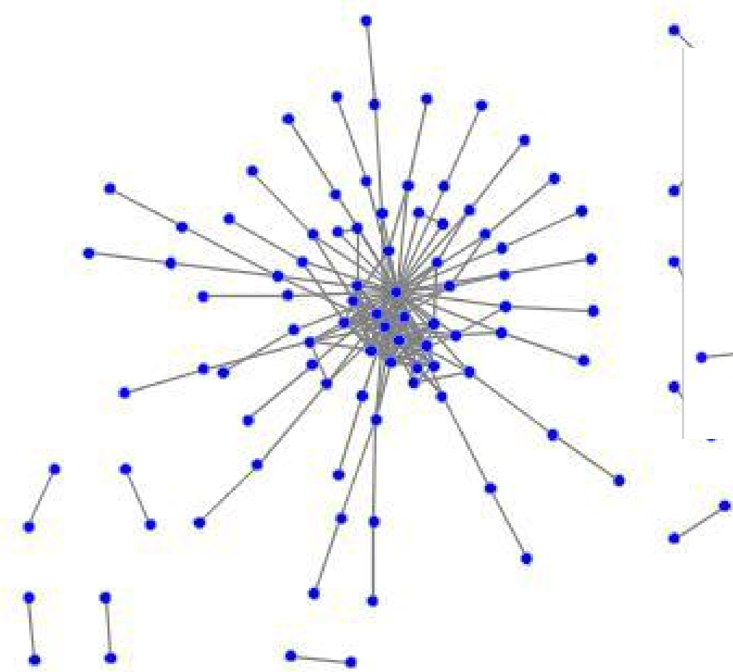
Hubs have MANY connections, but most other nodes don't

Bullmore et al, 2011, review

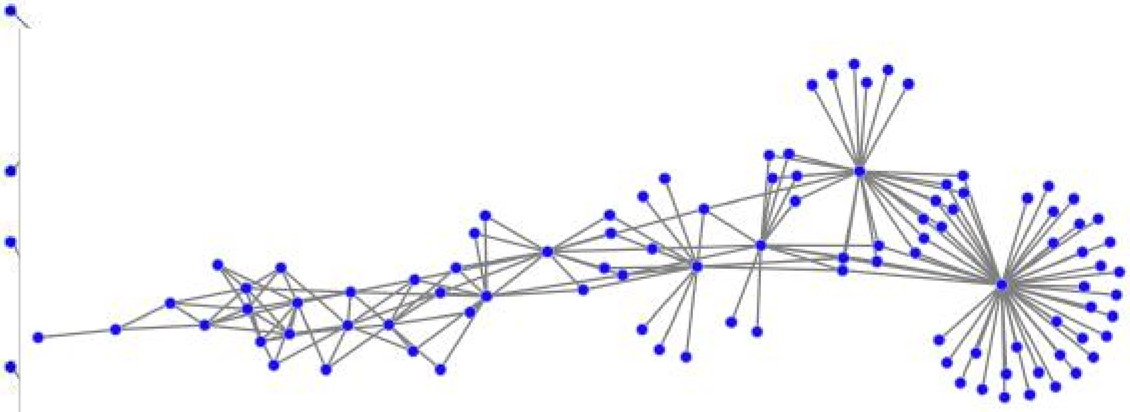
Network topology measures from graph theory

Assortativity correlation of degree of two nodes on end of an edge; measure of network **resilience**

assortive



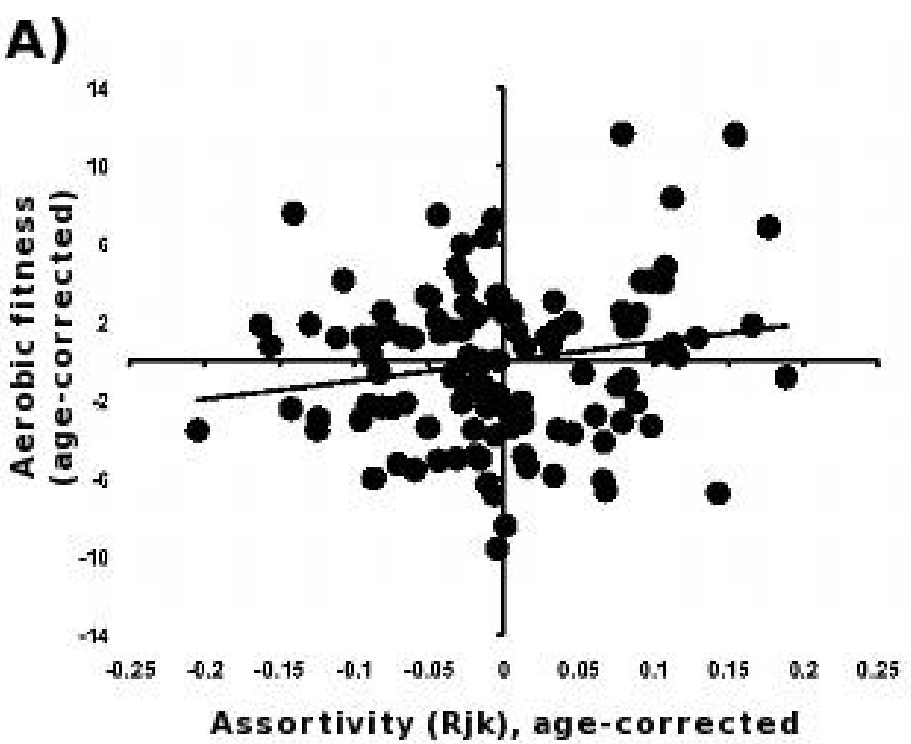
dissassortive



assortativity ➔ greater capacity for redistributing workload in hubs if damaged

Newman et al., 2002

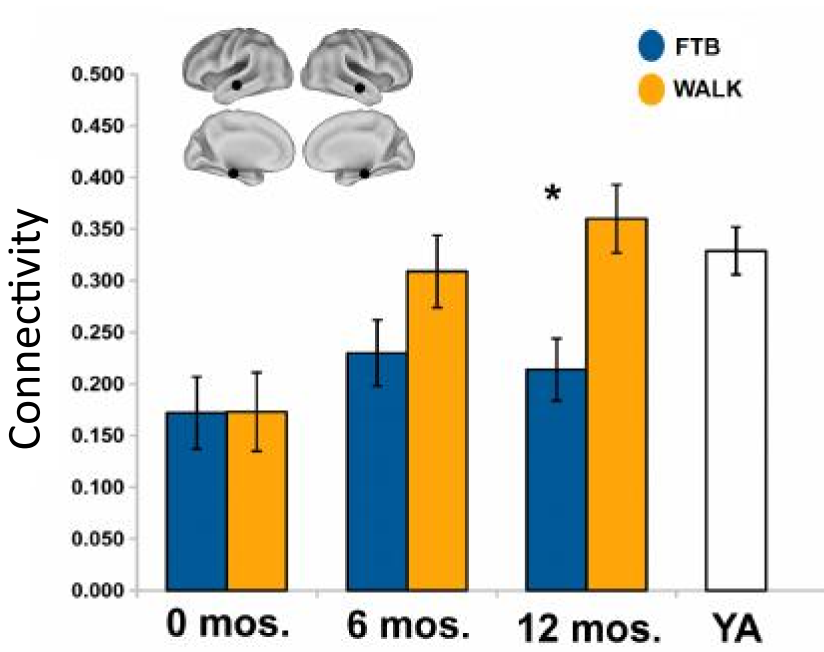
Effects of exercise on network **resilience**

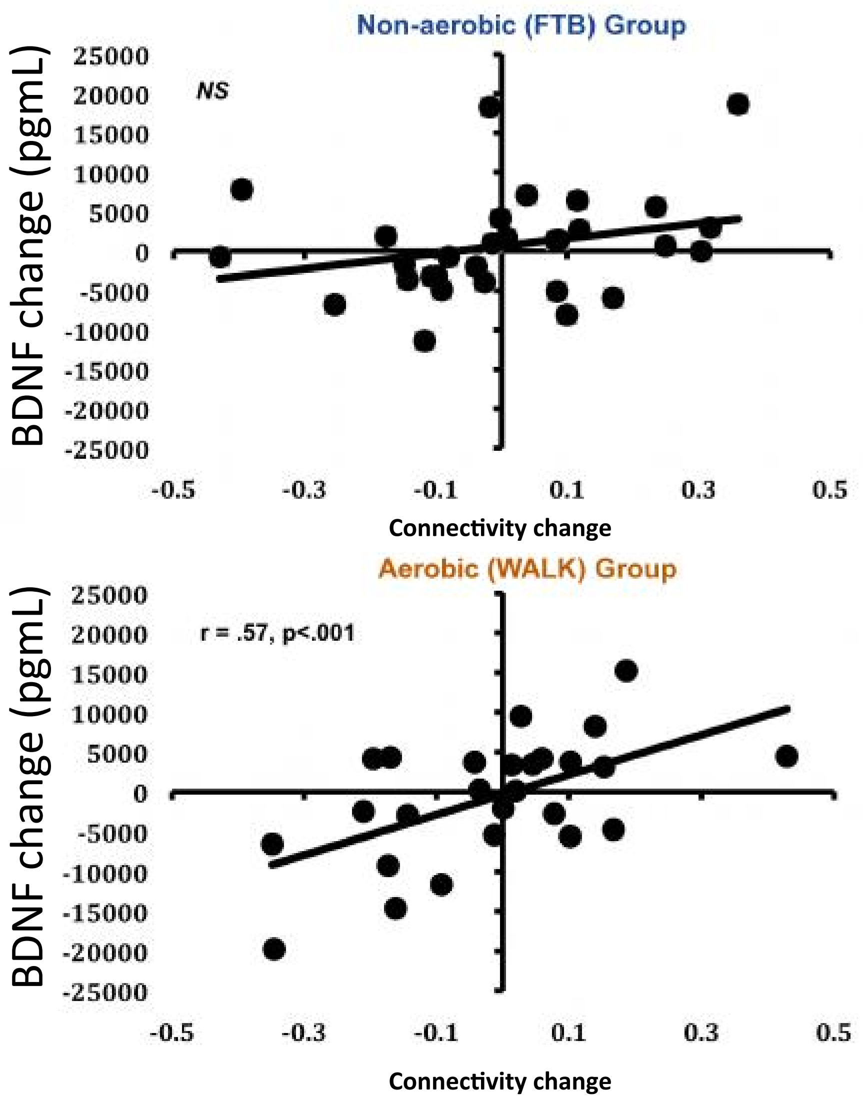


pr = .19*, p<.05 (2-tailed)

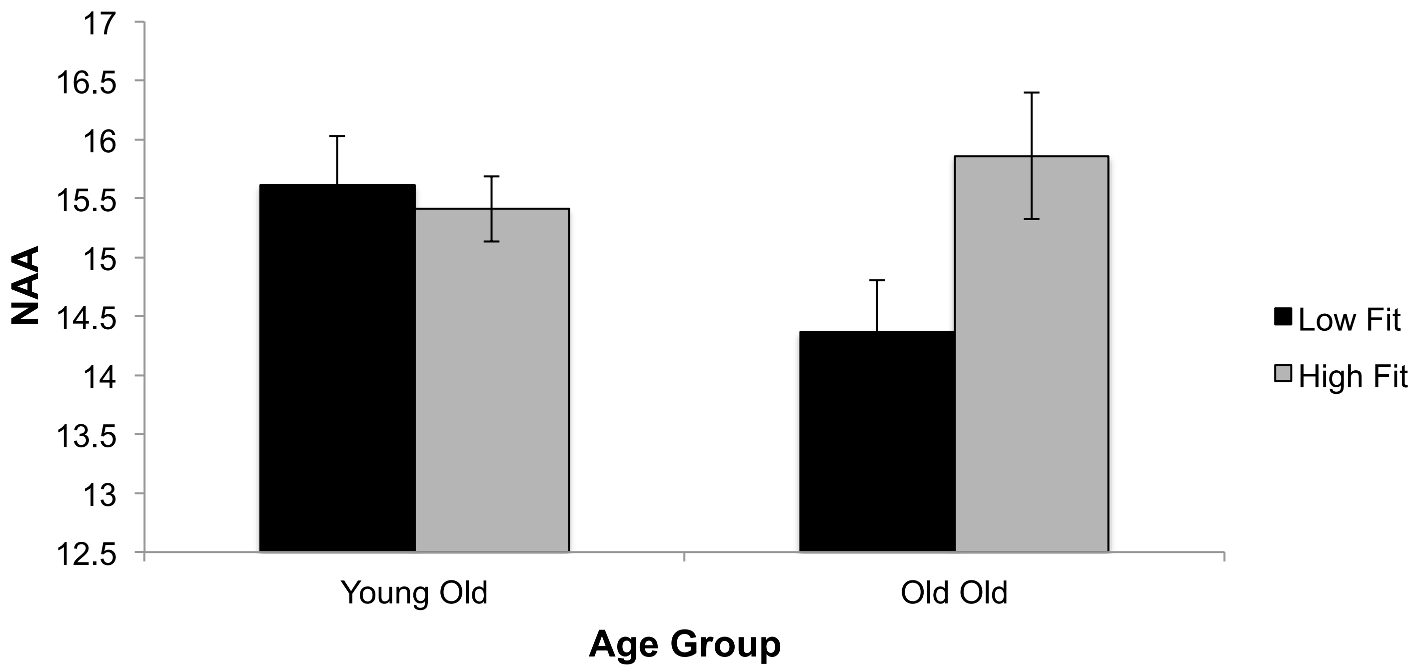
What are the neurobiological mechanisms for exercise-induced brain plasticity?

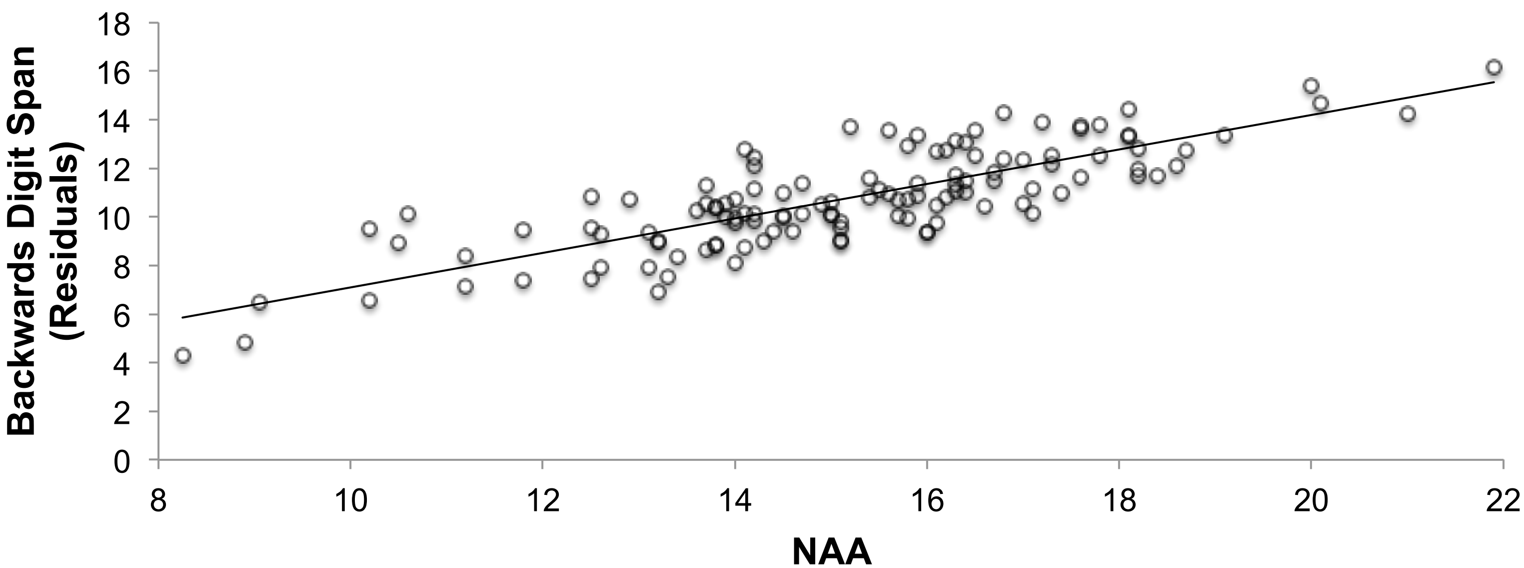
Brain-Derived Neurotrophic Factor (BDNF)





Voss et al, in press





Erickson et al (2012)

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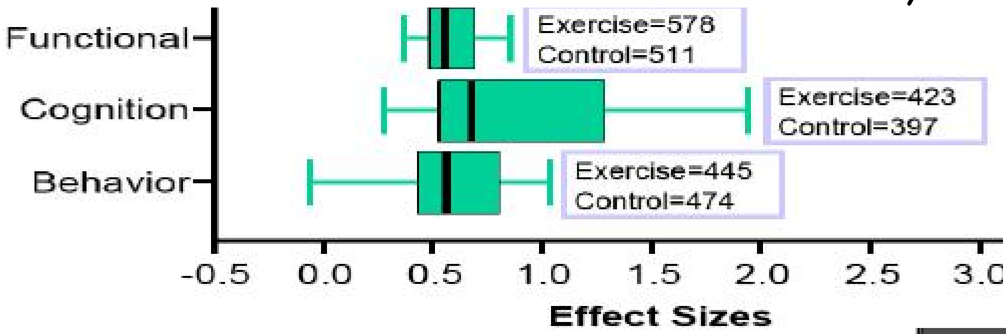
Is there a point of no-return with regard to exercise benefits on cognition and brain?

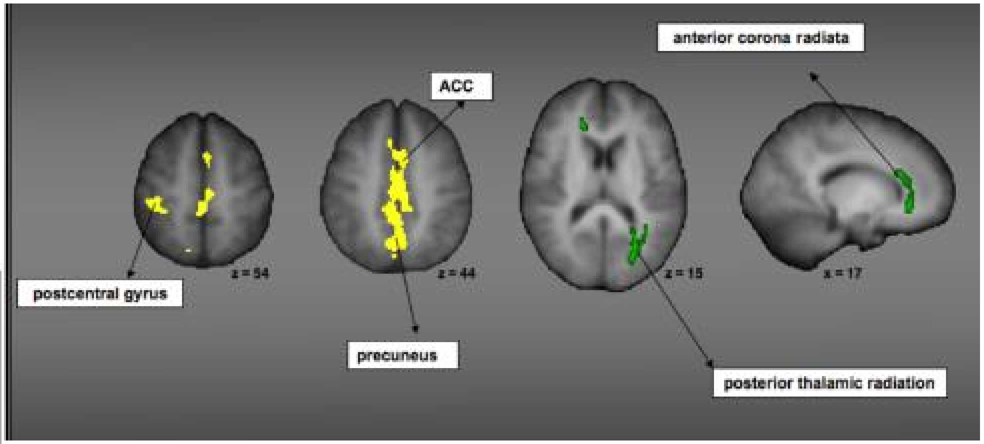
Early Alzheimer's Patients

Heyn et al (2004)



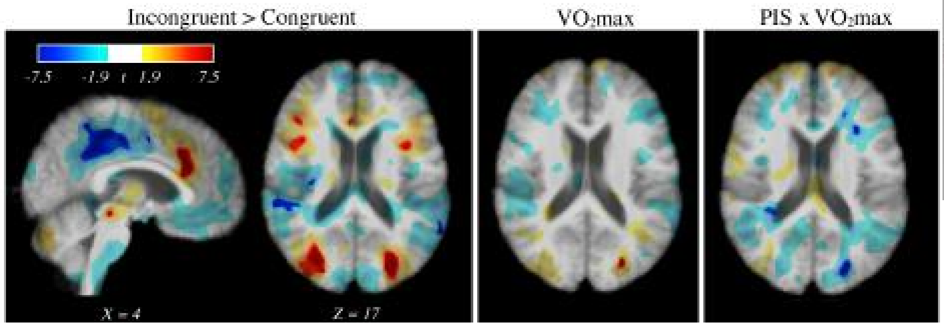
Prakash et al (2009)

Multiple Sclerosis Patients



Parkinson's Patients

Uc et al, (2008)



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

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

Is it known what kinds of physical activity & what durations & frequencies of such activities produce the greatest changes in brain & cognition?

- Aerobic activities have been main focus of fitness training research (given link to animal research) but … (***resistance training***)

TABLE 4. Neuropsychological tests.

	Change (post − pre) Control ($N = 23$)	Change (post − pre) Experimental Moderate ($N = 19$)	Change (post − pre) Experimental High ($N = 20$)	Experimental Moderate vs Control P
Digit span (score)				
Forward	−0.47 ± 0.19	0.51 ± 0.20	0.50 ± 0.19	<0.001*
Backward	−0.14 ± 0.18	−0.12 ± 0.17	−0.10 ± 0.19	0.18
Corsis block-tapping (score)				
Forward	0.18 ± 0.24	0.29 ± 0.20	0.30 ± 0.23	0.87
Backward	0.0 ± 0.24	0.97 ± 0.25	0.95 ± 0.22	0.01*
Similarities (score)	−2.75 ± 0.18	1.08 ± 1.32	1.05 ± 1.45	0.02*
Toulouse–Pieron (score)				
Cancellations numbers	6.67 ± 3.48	4.85 ± 6.27	6.90 ± 5.69	0.17
Errors	5.52 ± 1.40	0.15 ± 0.22	−4.85 ± 6.27	0.28
Rey Osterrieth figure (score)				
Copy	6.10 ± 1.28	6.45 ± 0.90	6.45 ± 0.89	0.18
Immediate recall	5.17 ± 0.98	8.38 ± 1.26	8.31 ± 1.22	0.02*

* $P < 0.05$. ANCOVA test values expressed as mean change ± SE.

Cassilhas et al, 2007

Table 2. Physiological Falls Risk, Functional Mobility, and Executive Functions at Baseline and 6-Month Follow-Up (N = 52)

Outcome Measures	OEP Group (n = 28) Baseline	OEP Group (n = 28) Six Months	Control Group (n = 24) Baseline	Control Group (n = 24) Six Months
	Mean ± Standard Deviation			
Physiological Profile Assessment *z*-score	2.0 ± 1.3	1.9 ± 1.2	1.9 ± 1.3	1.9 ± 1.2
Timed Up and Go Test, seconds	14.2 ± 4.6	13.6 ± 4.3	17.4 ± 10.4	18.1 ± 10.5
Trail Making Test Part B, seconds	222.4 ± 200.1	203.1 ± 262.3	224.7 ± 106.4	232.9 ± 127.1
Verbal Digits Backward Test (maximum 14 points)	3.8 ± 2.0	3.9 ± 2.3	3.1 ± 1.8	2.8 ± 1.8
Stroop Color-Word Test, seconds	157.6 ± 83.0	137.4 ± 49.5	151.7 ± 44.0	167.2 ± 103.4*

* Significantly different from Otago Exercise Program (OEP) group at $P = .05$.

Liu-Ambrose et al, 2008

Roadmap for Today

- What do we currently know about the molecular and cellular brain mechanisms of physical activity – animal models.

- Exercise versus cognitive training – and human performance and cognition.

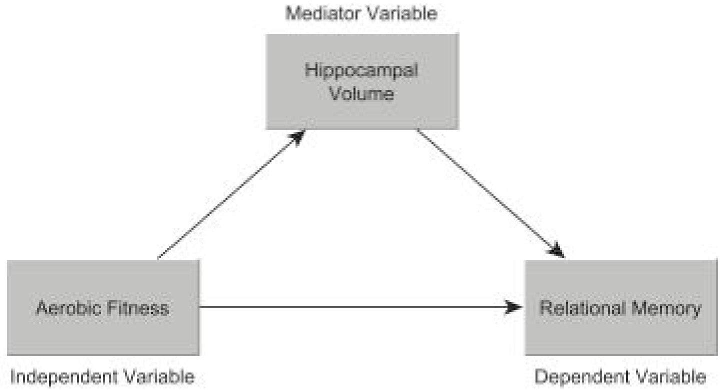
- Exercise and physical activity effects on older human minds & brains – structure, function and functional connectivity.

- Is there a point of no-return for exercise effects on brain & cognition?

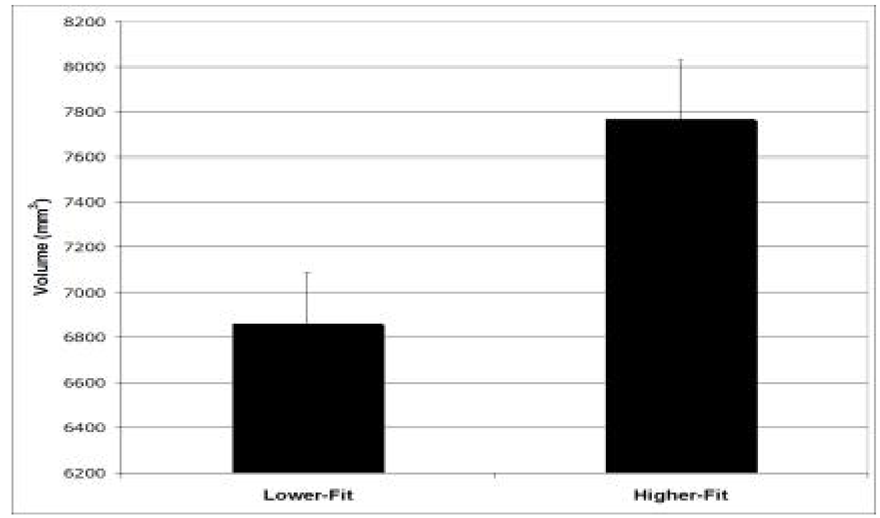
- Fitness effects across the lifespan.

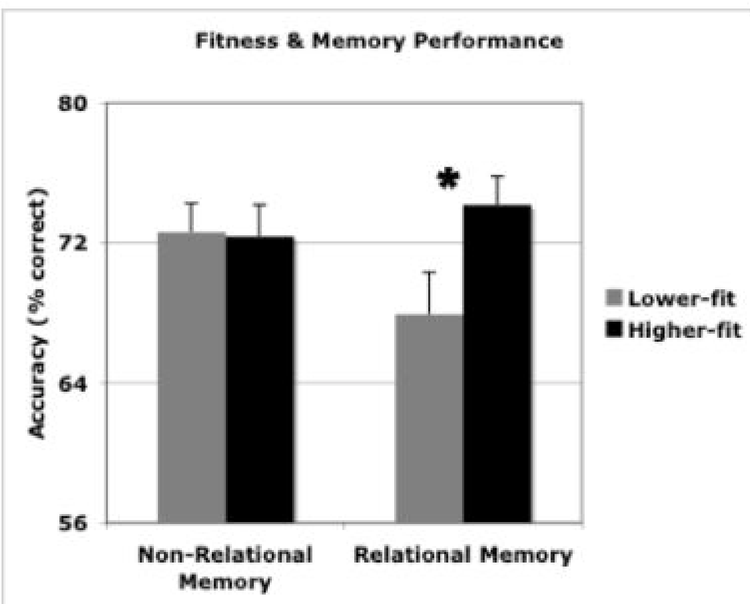
- What studies need to be done to further advance our understanding of the link between exercise & cognition ?

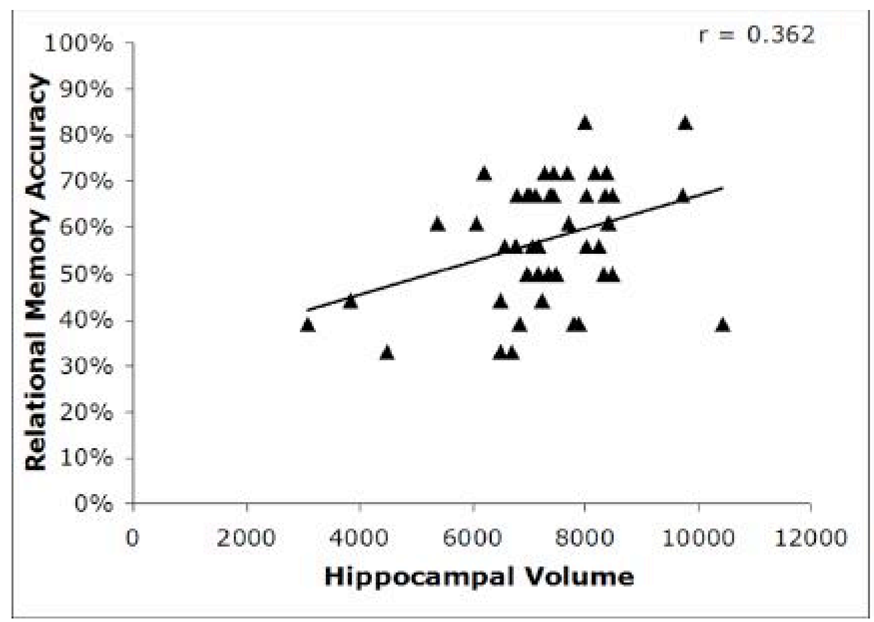
What about exercise effects on brain & cognitive function of children?



Chaddock et al (2010)







To summarize:

Relatively brief fitness interventions (with older couch potatoes – and hi & low fit kid's ….):

- Improves a variety of perceptual & cognitive abilities
- Increases brain volume in regions which normally show age-related decline - including the hippocampus (and increases are correlated with performance improvements)
- Changes functional brain networks, often in the direction of younger adults, associated with improvements in cognition & performance.
- Promising fitness cognitive & brain effects with children.
- Not covered today but …. exercise decreases anxiety and depression and increase self esteem & self efficacy