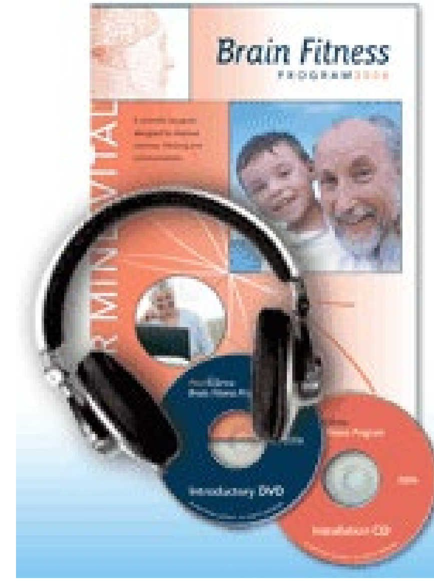
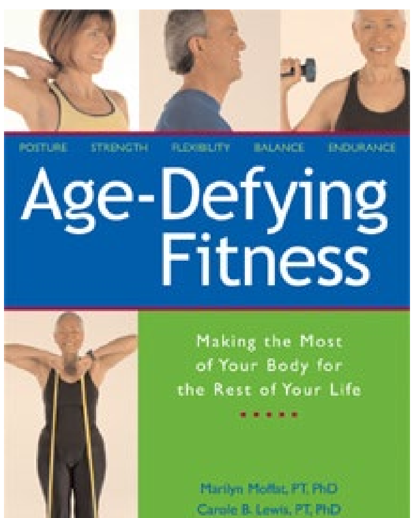
The Influence of Physical Activity on Cognitive & Brain Health of Older Adults: A summary and future directions – including an increasing role for AI

"Try the fish. It's brain food."

Art Kramer & colleagues
Northeastern University,
University of Illinois,
& other collaborators



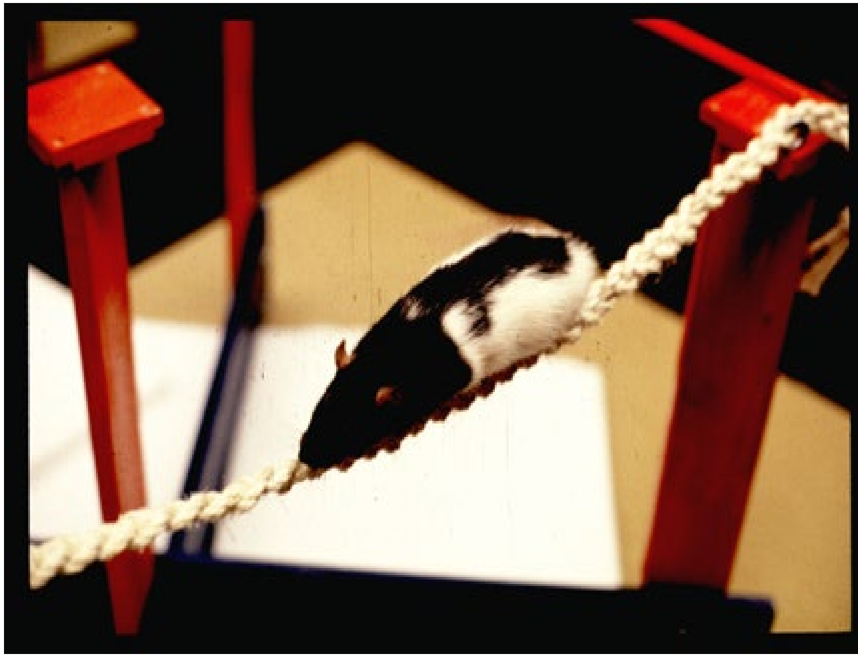


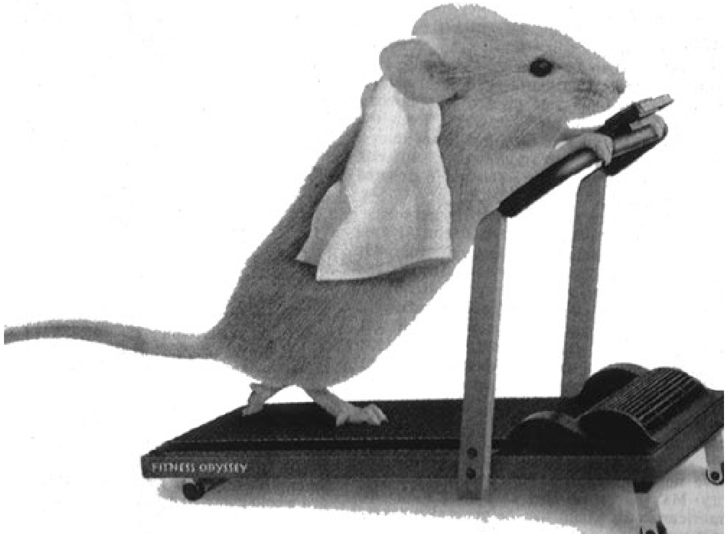
We all live in yellow submarine,
yellow submarine, yellow submarine.
And our friends are all aboard,
Many more of them live next door.

Roadmap for Today …..

- What do we currently know about the molecular and cellular brain mechanisms of physical activity – animal models.
- Meta-analytic studies of physical activity effects on 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 ?

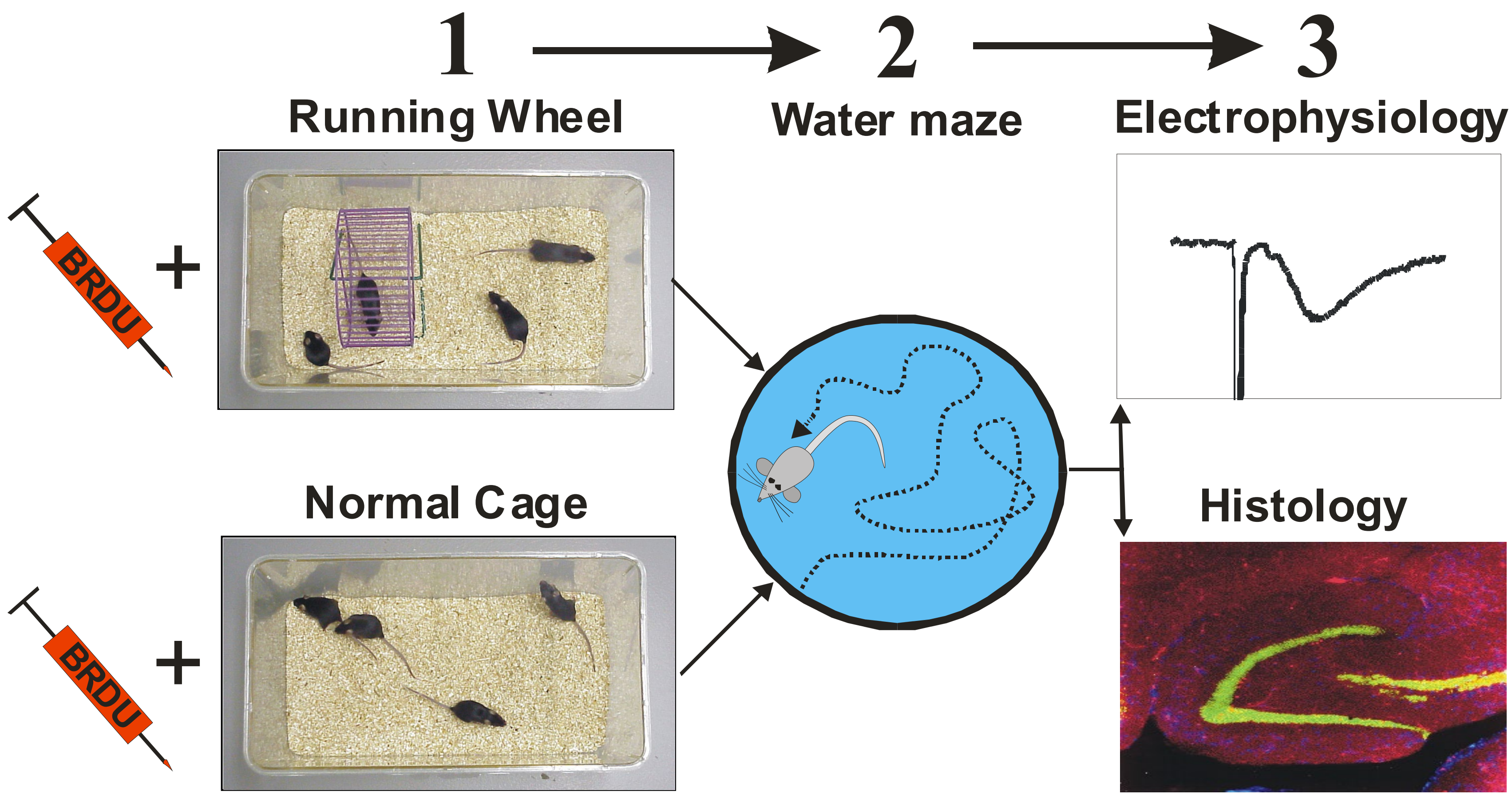
Enriched (complex) environments include:



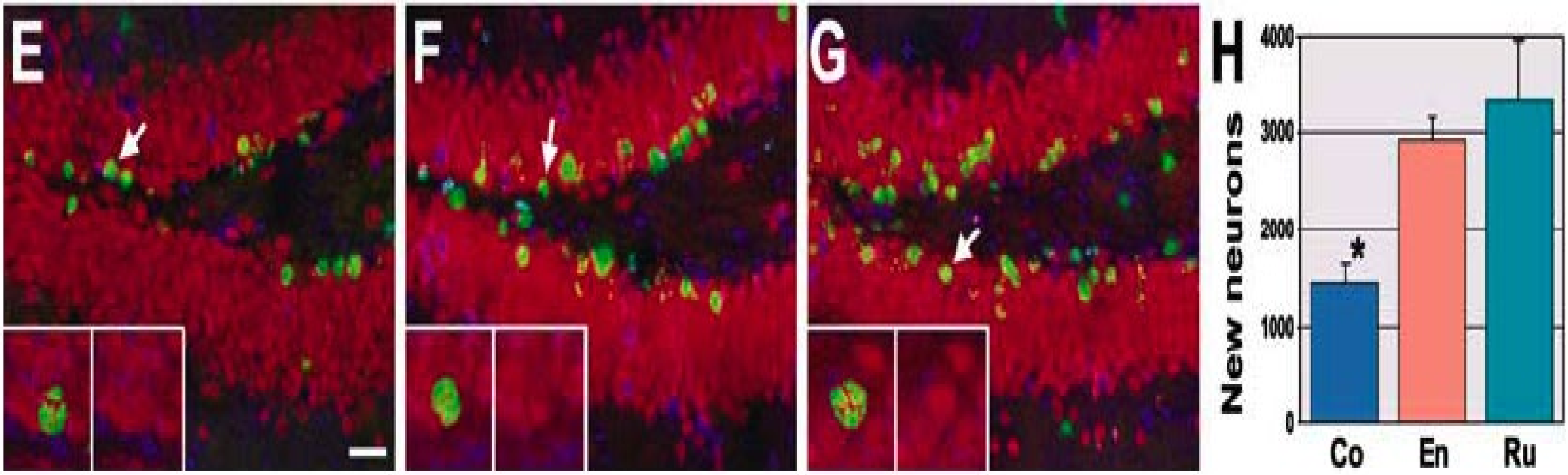


EXPERIMENTAL DESIGN

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 transgene mouse models
- increased telomere length
- increased expression of genes associated with plasticity & mitochondria function, downregulates genes associated with oxidative stress
- enhanced learning & memory

Roadmap for Today .....

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

- Meta-analytic studies of physical activity effects on cognition.

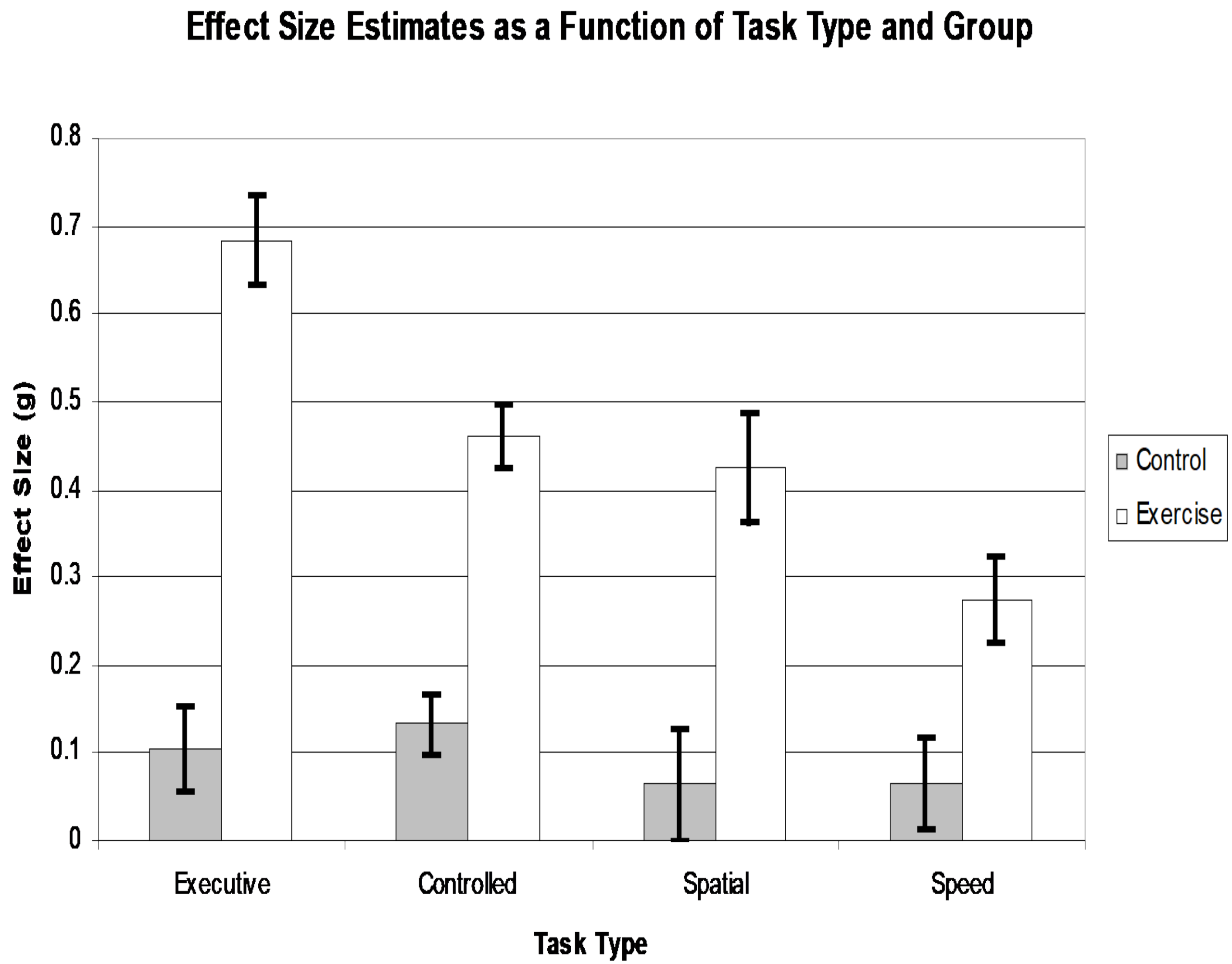
- Exercise and physical activity effects on older human minds & brains – structure, function and functional connectivity.

- 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 ?

• 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 …

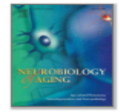


Colcombe & Kramer (2003), Kramer & Colcombe (2018)

There have been lots and lots of additional meta-analyses since 2003 …….

ELSEVIER

Neurobiology of Aging
Volume 79, July 2019, Pages 119-130



Review

Impact of exercise training on physical and cognitive function among older adults: a systematic review and meta-analysis

Ryan S. Falck [a, b, c, 1], Jennifer C. Davis [d, 1], John R. Best [a, b, c], Rachel A. Crockett [a, b, c], Teresa Liu-Ambrose [a, b, c]

Highlights

- Maintaining physical and cognitive function is critical for healthy aging.
- Physical function and cognitive function are linked and share common mechanisms.
- Exercise training improves physical function and cognitive function.
- Exercise-induced improvements in physical and cognitive function are associated.

Cognitive benefits of exercise interventions: an fMRI activation likelihood estimation meta-analysis

Qian Yu[1] · Fabian Herold[2] · Benjamin Becker[3] · Ben Klugah-Brown[3] · Yanjie Zhang[1] · Stephane Perrey[4] · Nicola Veronese[5] · Notger G. Müller[2] · Arthur F. Kramer[6,7] · Liye Zou[1]

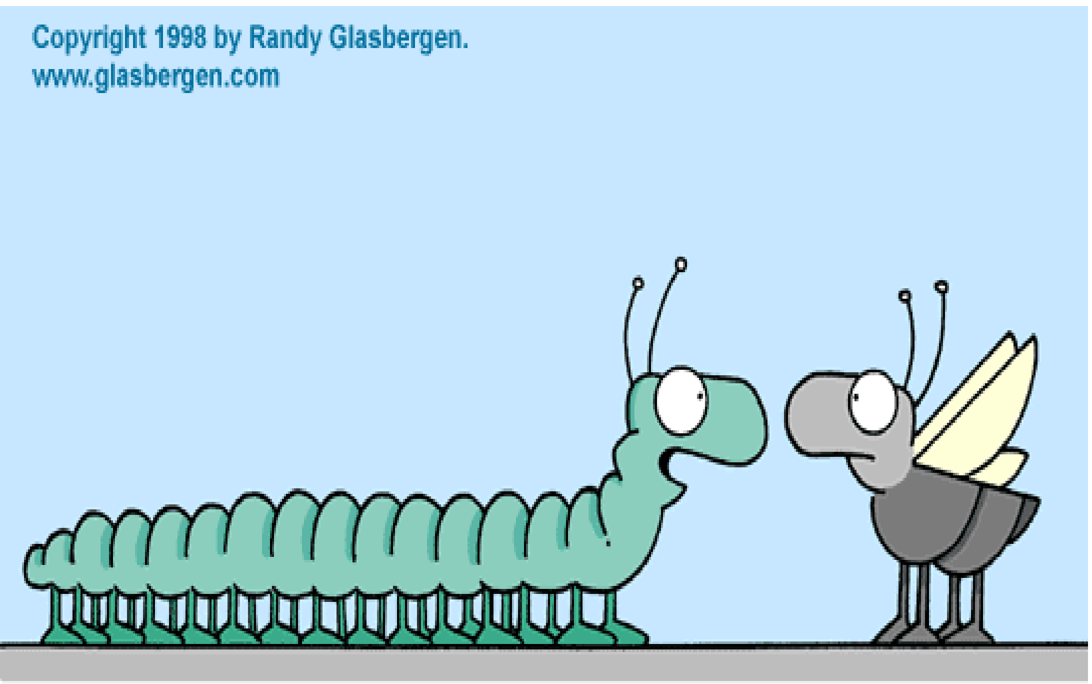
Received: 27 November 2020 / Accepted: 26 February 2021

Shorter exercise intervention durations induced changes with regions connected to frontoparietal and default mode networks while longer duration interventions induced changes with regions connected to frontoparietal and dorsal attention networks

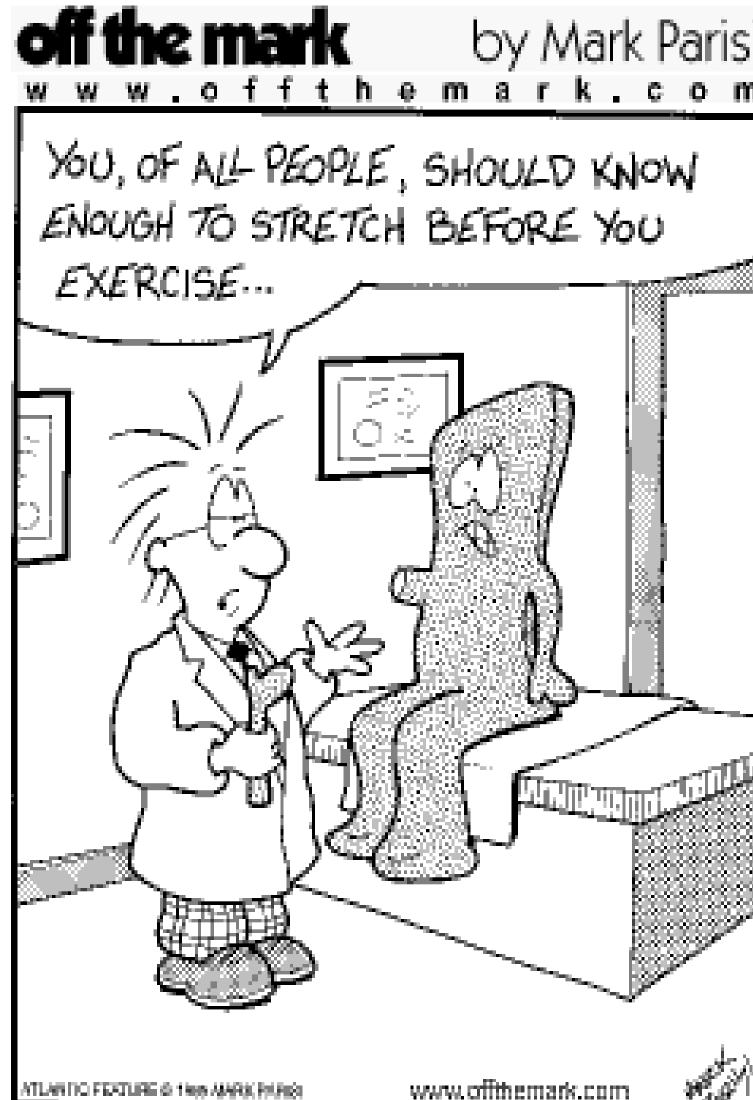
Roadmap for Today …..

- What do we currently know about the molecular and cellular brain mechanisms of physical activity – animal models.
- Meta-analytic studies of physical activity effects on 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 ?

TYPICAL FITNESS INTERVENTIONS

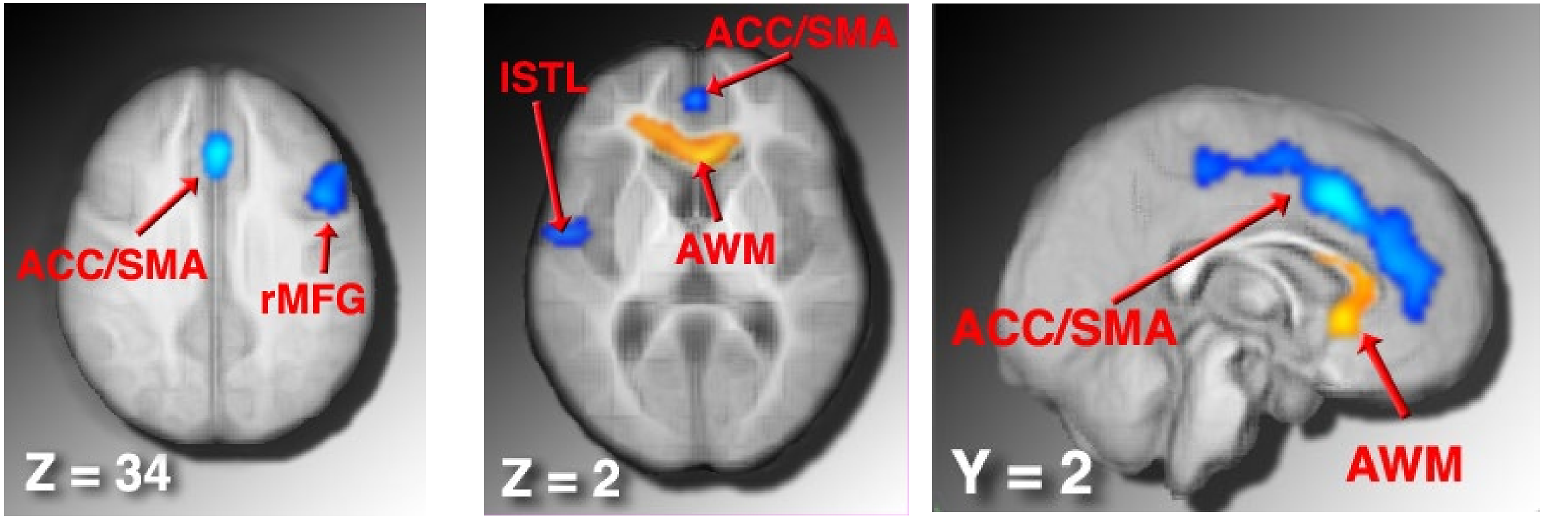


"I tried all the fitness fads, but my doctor was right all along—walking is still the best exercise."

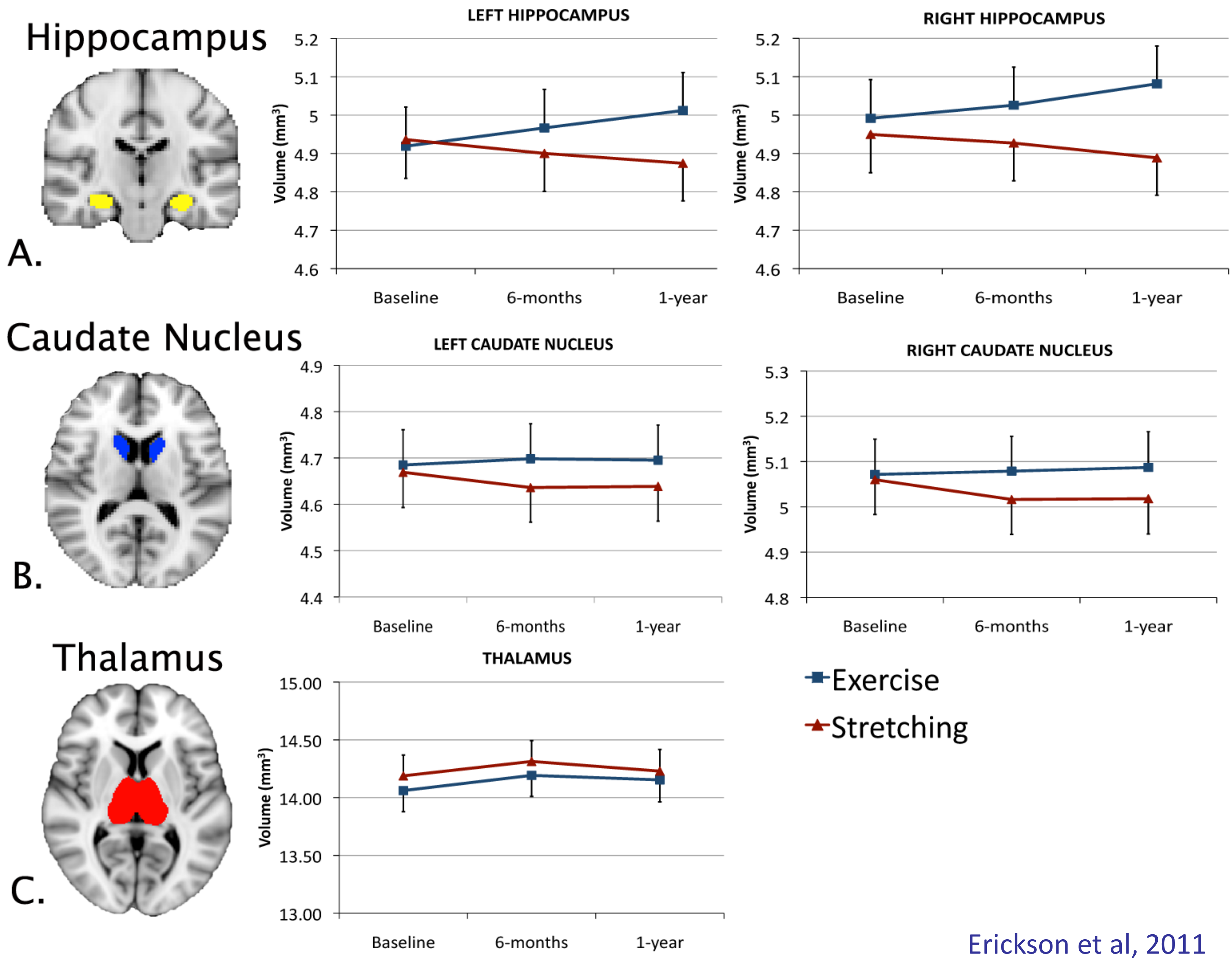


Exercising your brain structure …….

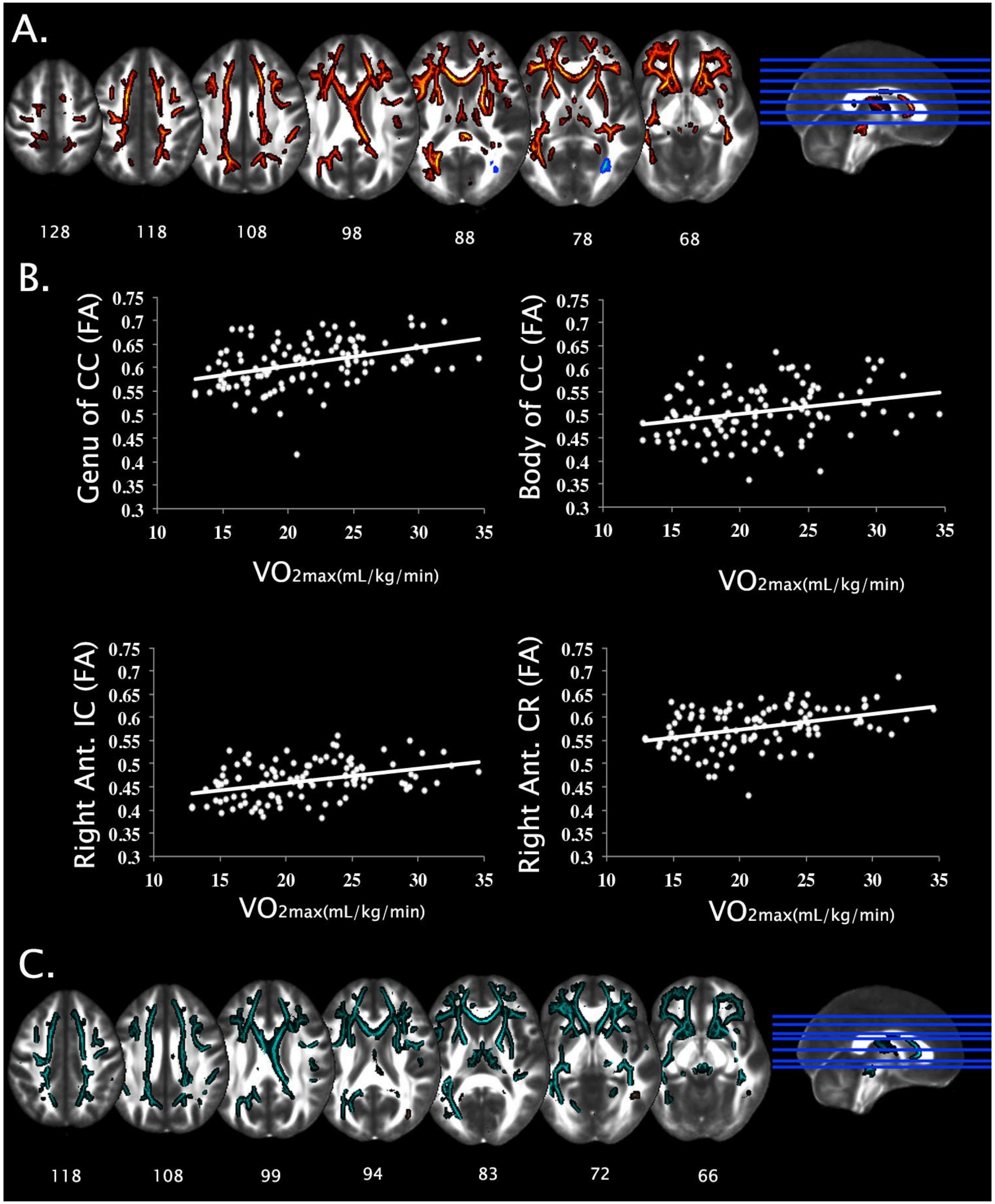
Although much is known about <u>fitness training effects</u> on brain function with non-human animals there is a dearth of knowledge of fitness training effects with humans …….



Colcombe et al, 2006



Erickson et al, 2011



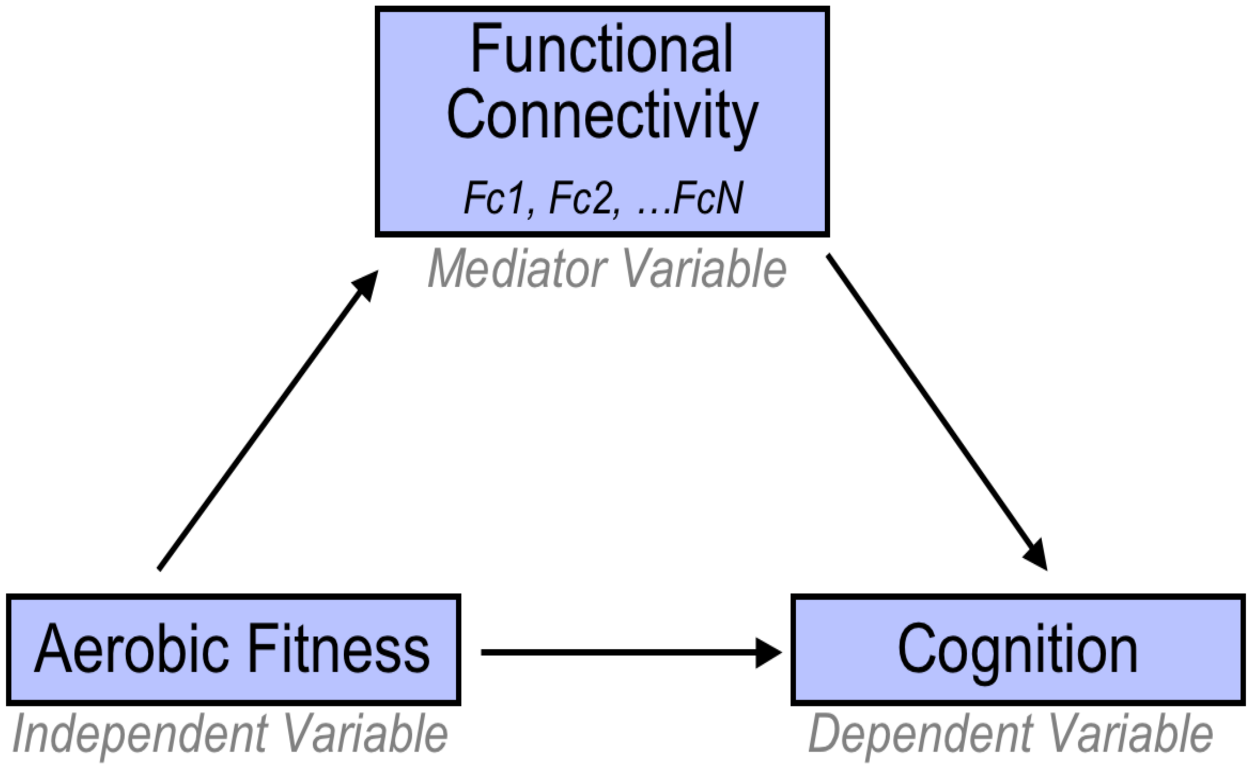
Clusters of voxels where fitness was significantly associated with FA in multiple samples of 100+ older participants.

Mediation analysis showed *significant indirect associations between CRF and spatial working memory* performance through distributed white matter regions, highlighted in cyan in Figure 1C.

Burzynska et al, 2014
Oberlin et al, 2016

Exercising your brain function …….

Is aerobic fitness associated with better Functional connectivity?



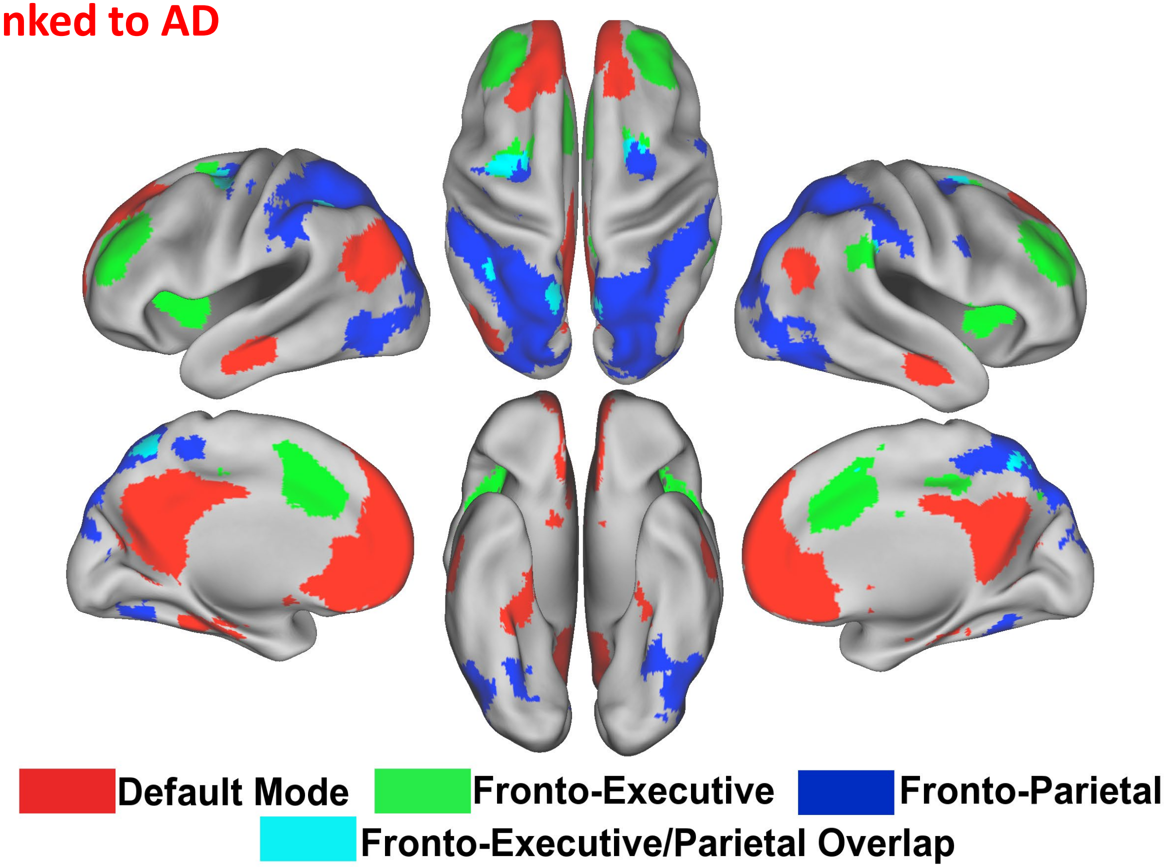
Voss et al., 2010, 2016

Cognitively relevant brain networks

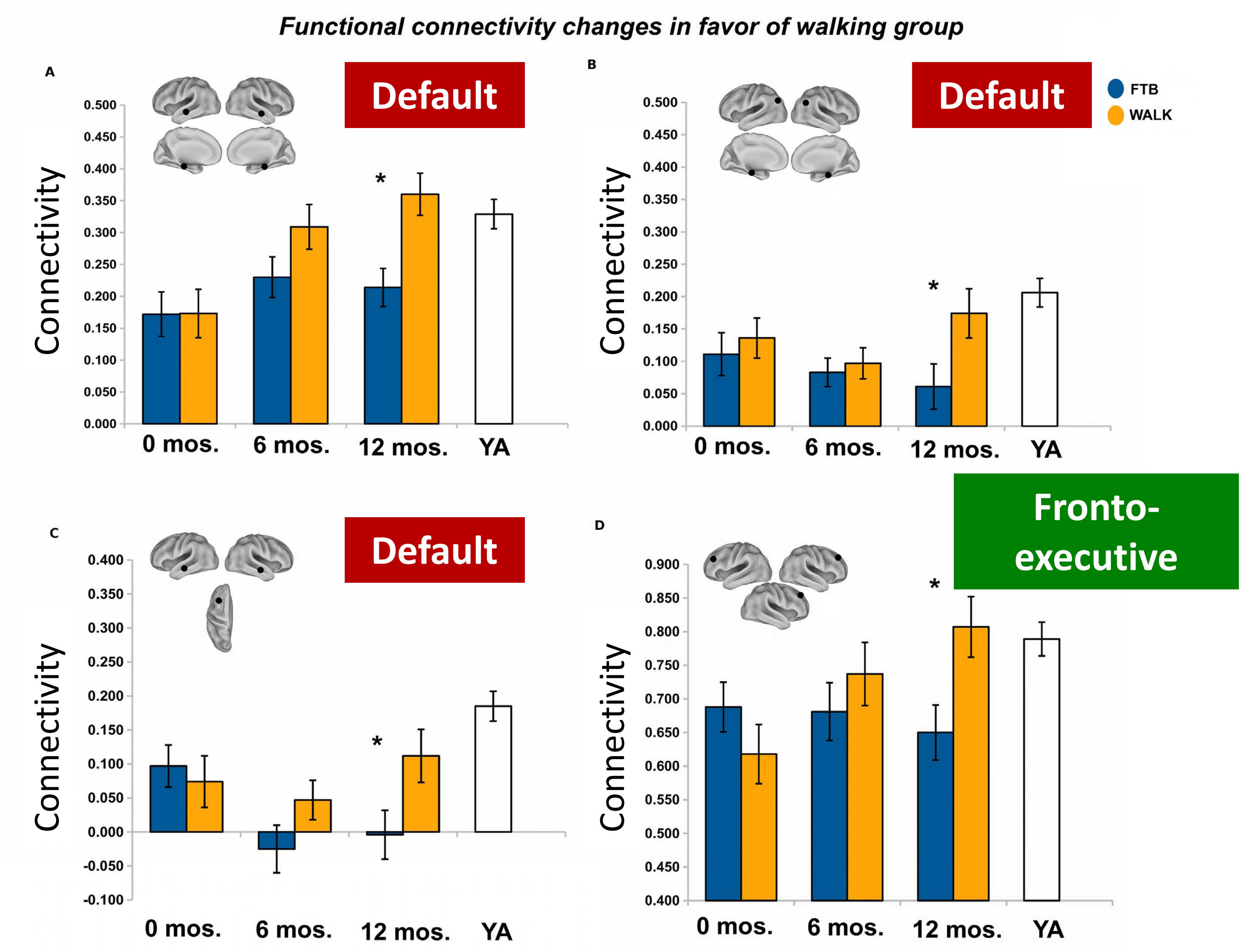
- deactivated during goal-directed attention
- active at rest, inward thought
- ↑ executive functions, speed, memory processes
- dysfunction linked to AD

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

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

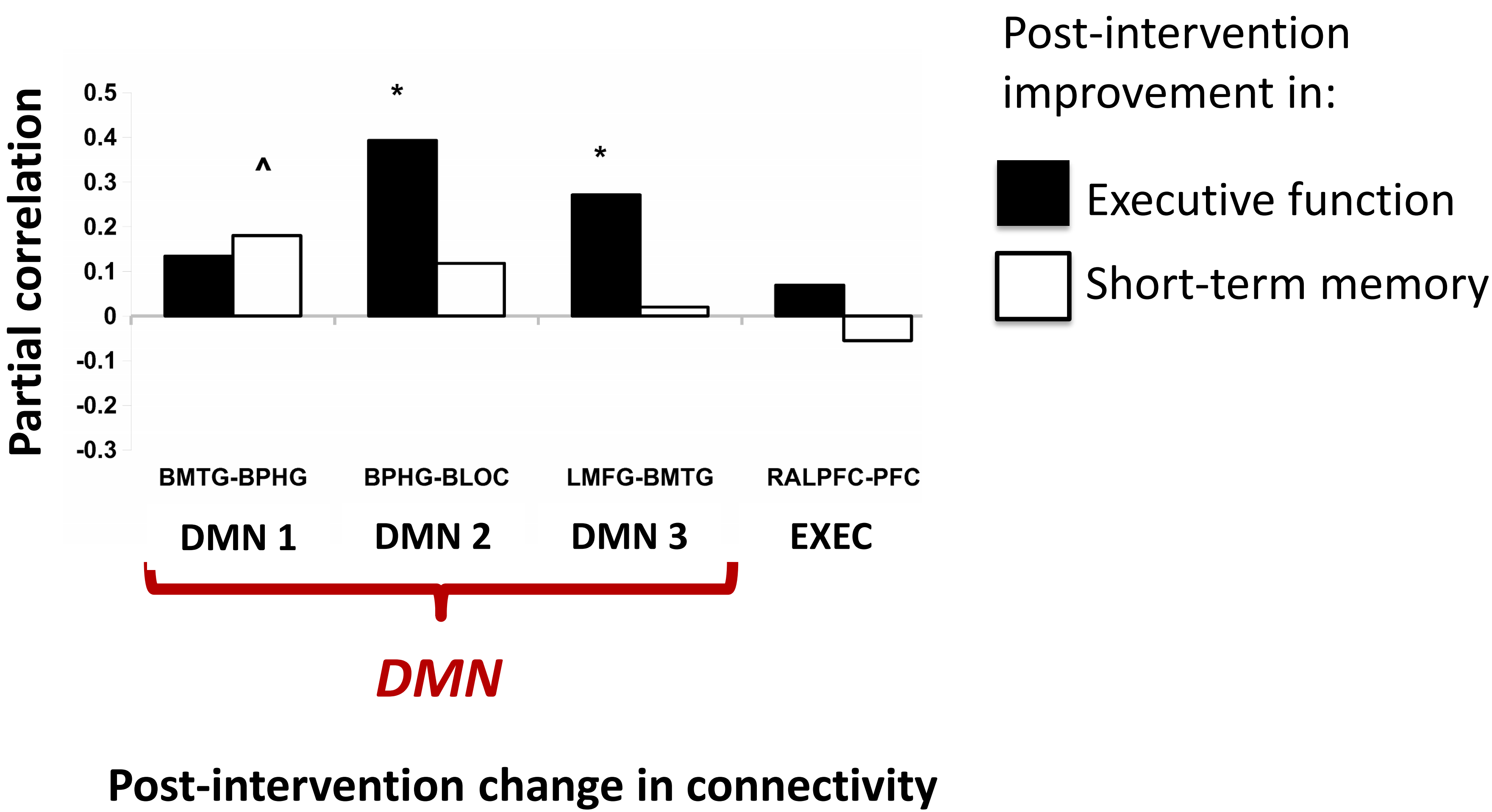


Improvements in networks post-exercise?



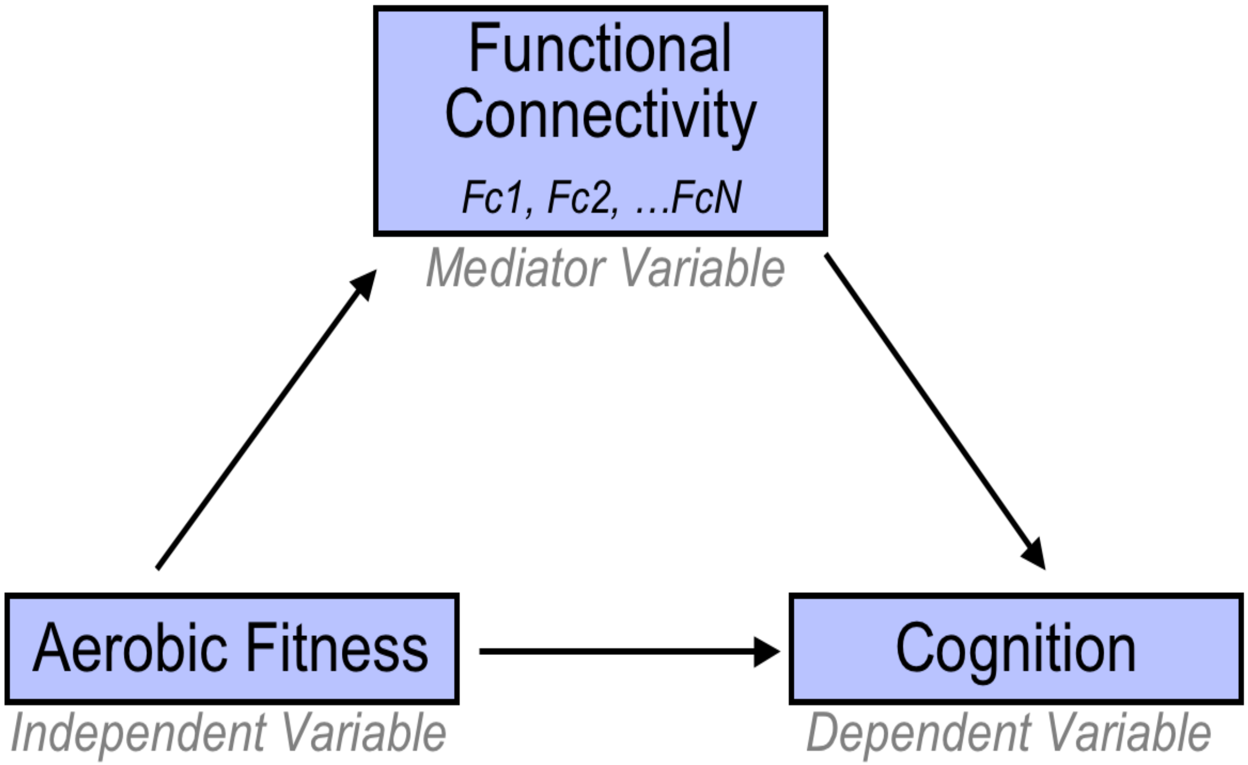
Voss et al., 2010, 2016

Brain-Behavior associations



Voss et al., 2010, *2016*

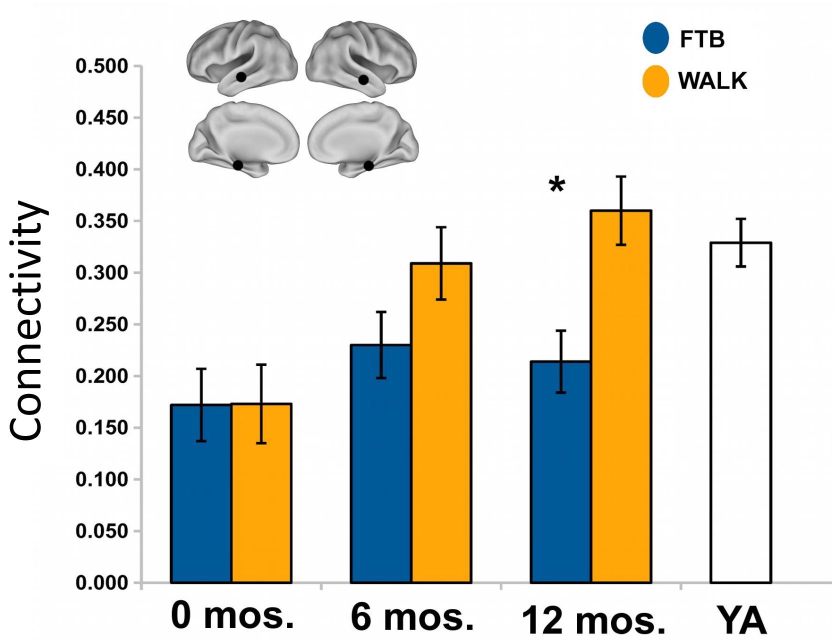
Is aerobic fitness associated with better Functional connectivity?

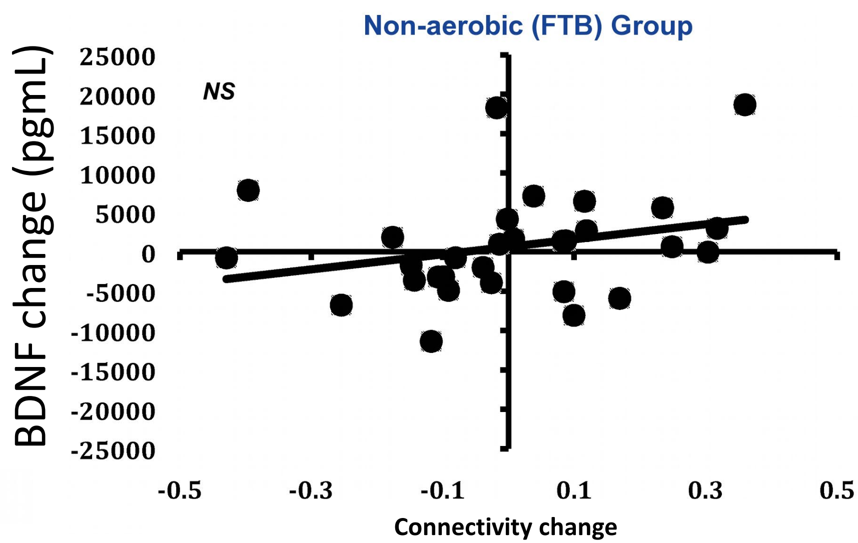


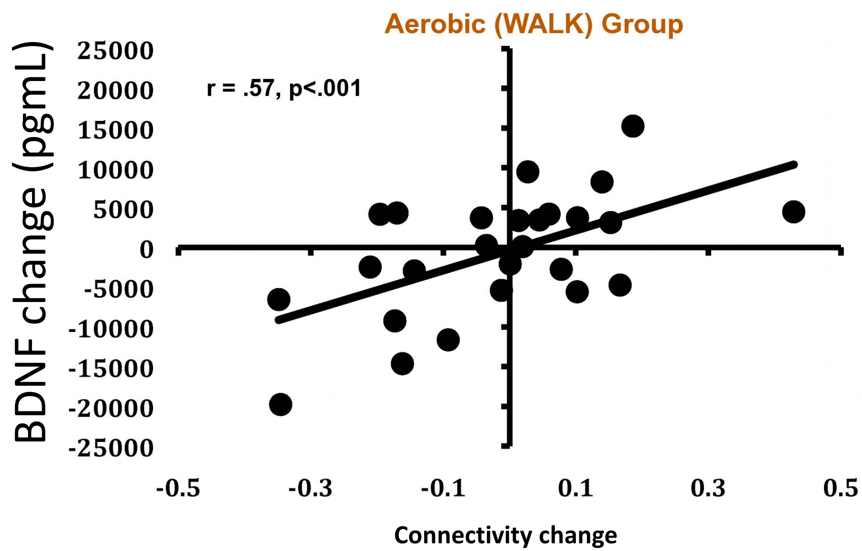
✓ ***Executive function abilities***

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

Brain-Derived Neurotrophic Factor (BDNF)



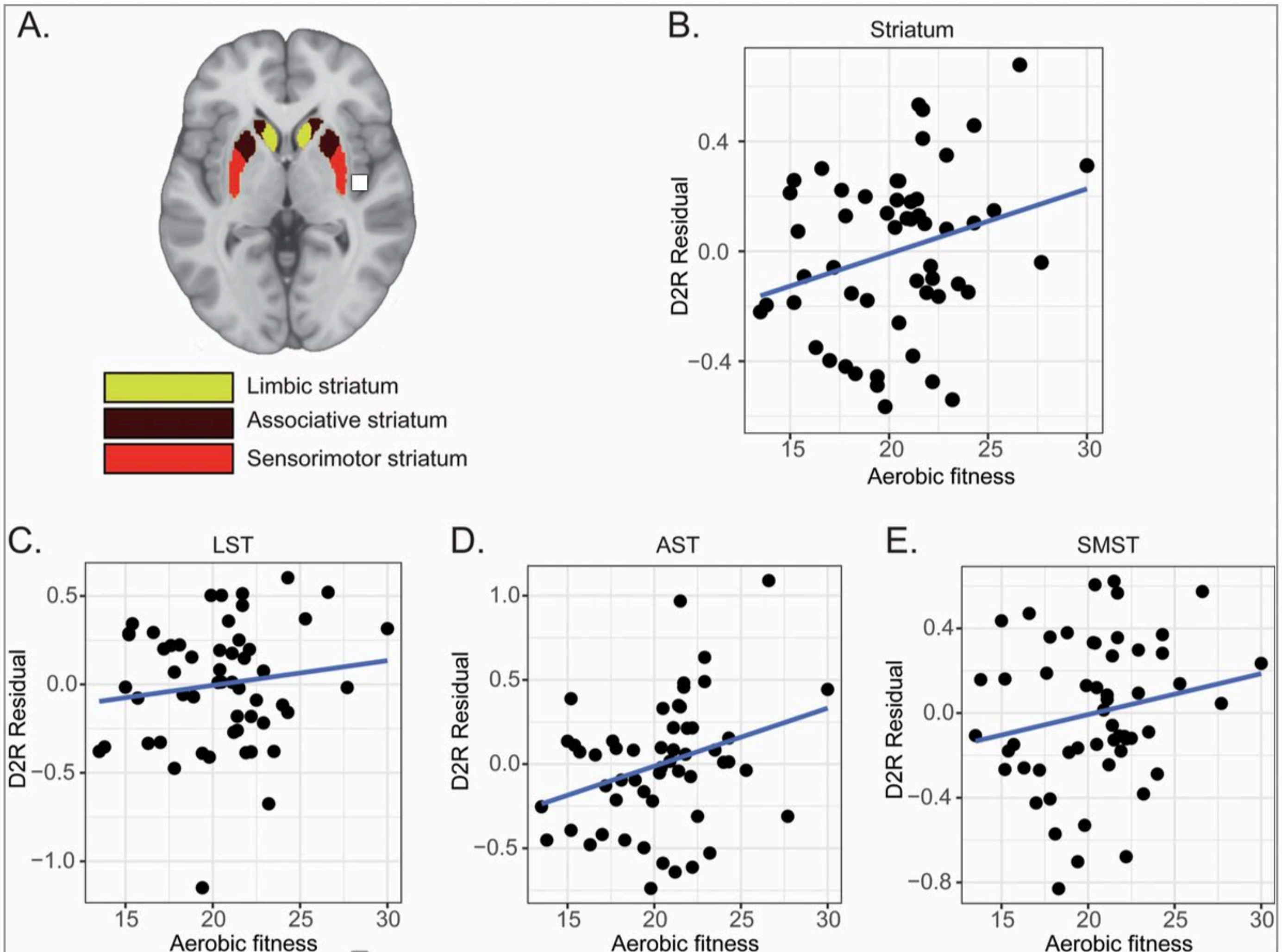




Voss, et al., (2010, 2013, 2016)

Higher striatal D2-receptor availability in aerobically fit older adults

Lars S Jonasson[1234*], Lars Nyberg[124], Arthur F Kramer[56], Jan Axelsson[27], Katrine Riklund[12], CJ Boraxbekk[238]
(2019)



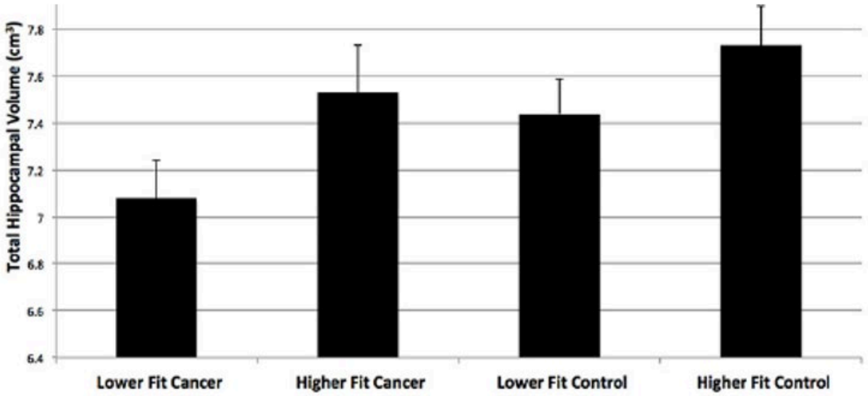
Roadmap for Today .....

- 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 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 ?

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

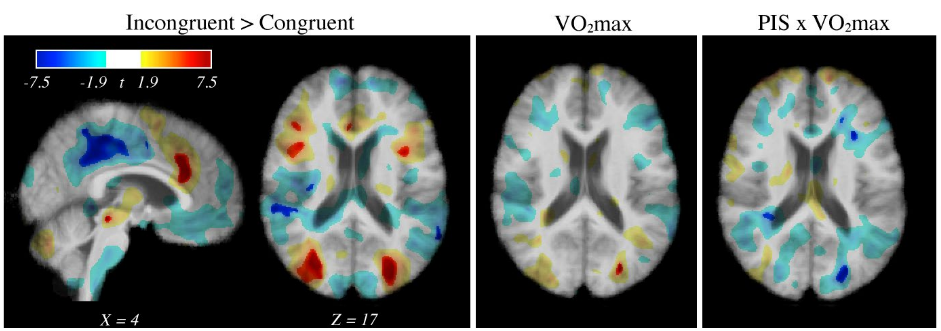
Cancer Patients

Chaddock-Heyman et al, 2015



Parkinson's Patients

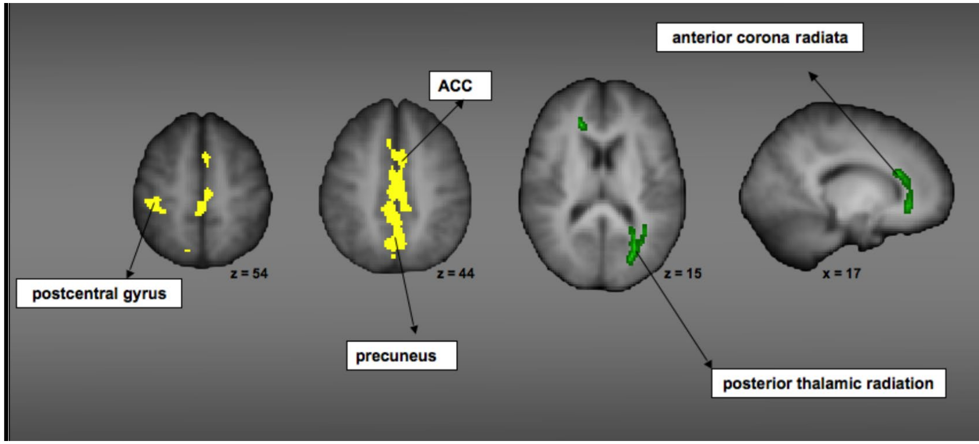
Uc et al, (2008)



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

Prakash et al (2009)

Multiple Sclerosis Patients



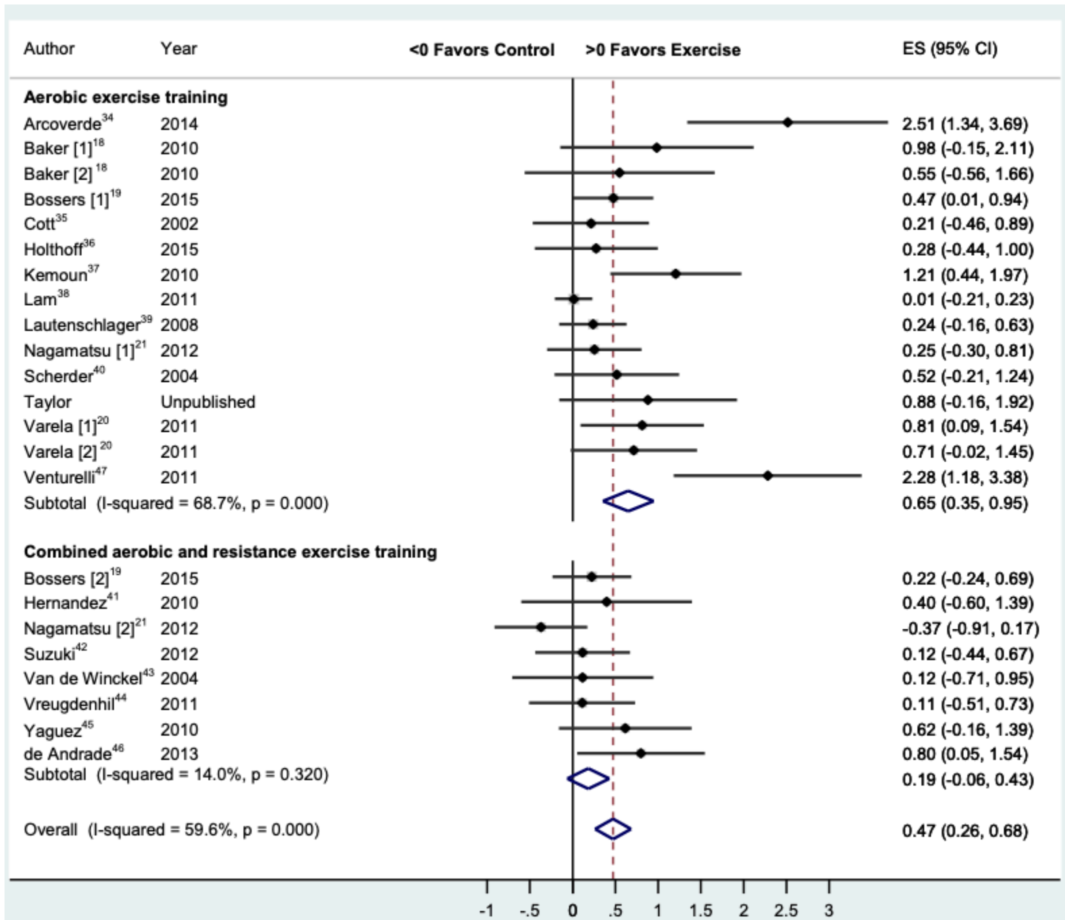
- Differences in gray matter volume & white matter integrity (via DTI) as a function of fitness are correlated with processing speed

What about those at risk for dementia and those with forms of dementia?

What about those at risk for dementia and those with forms of dementia?

Can Exercise Improve Cognitive Symptoms of Alzheimer's Disease?

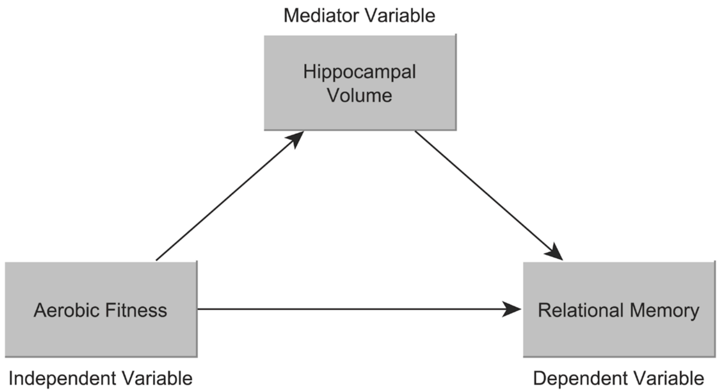
Gregory A. Panza, MS,† Beth A. Taylor, PhD,*† Hayley V. MacDonald, PhD,‡ Blair T. Johnson, PhD,§ Amanda L. Zaleski, MS,*† Jill Livingston, MS,¶ Paul D. Thompson, MD,† and Linda S. Pescatello, PhD** 2018

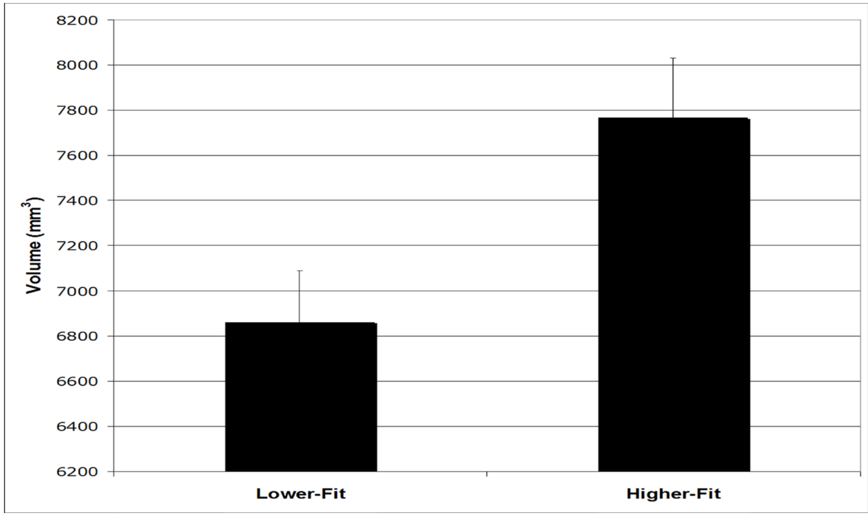


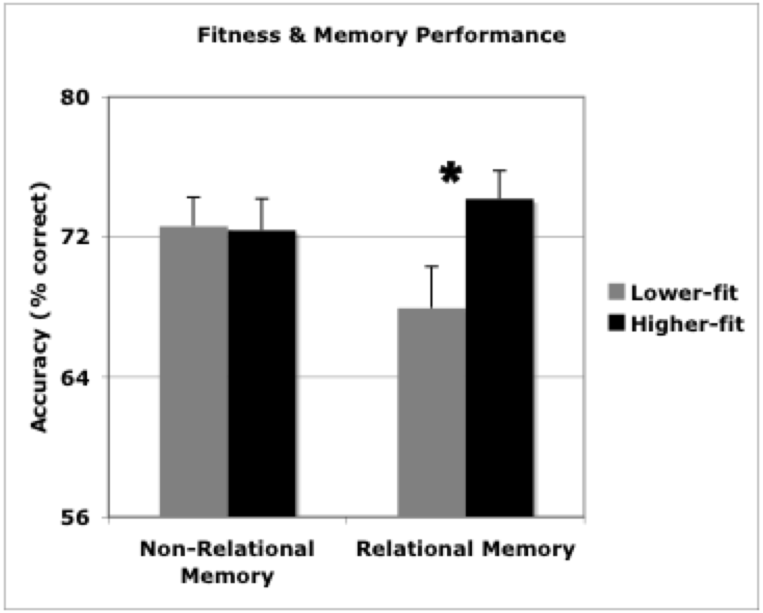
Roadmap for Today .....

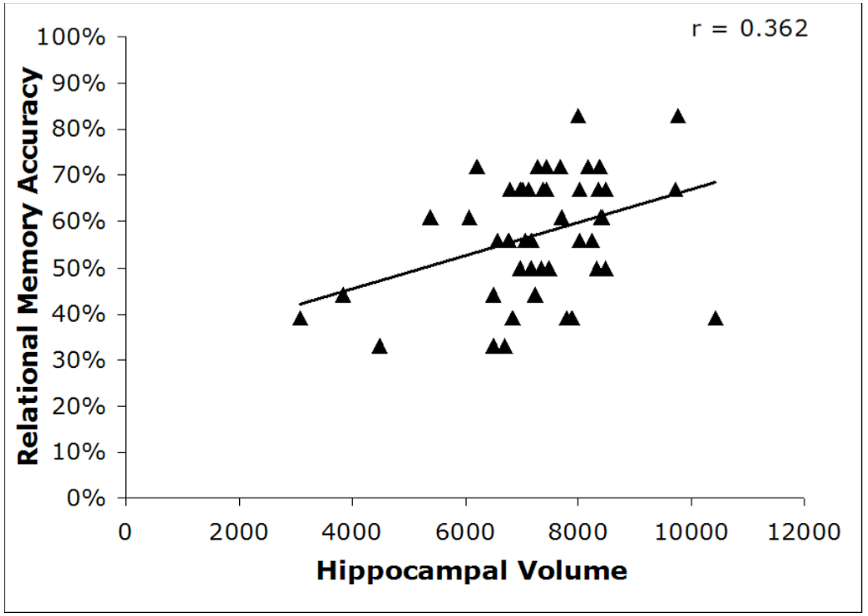
- What do we currently know about the molecular and cellular brain mechanisms of physical activity – animal models.
- Exercise versus cognitive training – and human performance and cognition.
- Exercise and physical activity effects on older human minds & brains – structure, function and functional connectivity.
- 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?







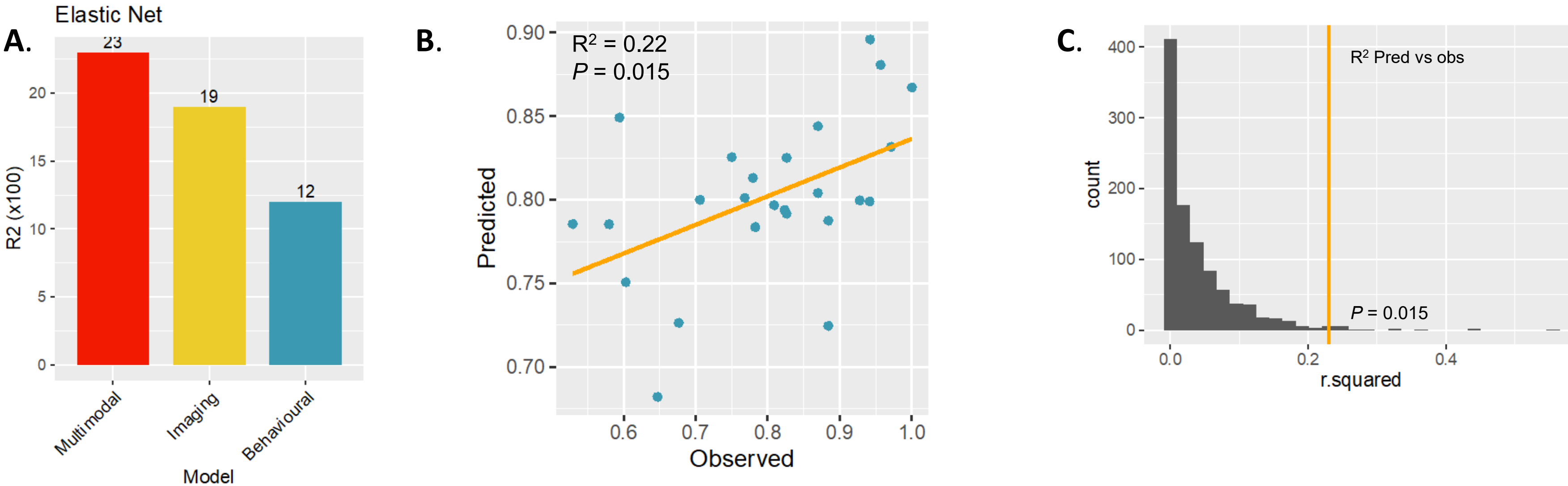


Some examples of how we might enhance our study of lifestyle benefits on healthy brains and minds --

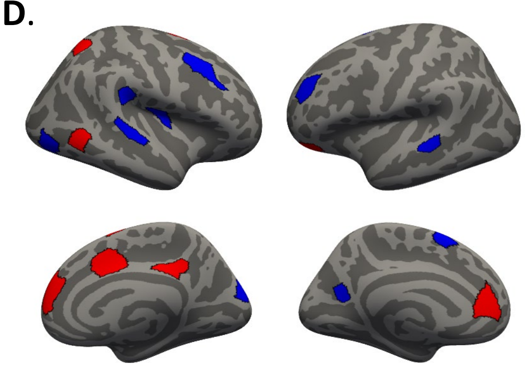
With machine learning and other varieties of Artificial Intelligence

PREDICTING ADHERENCE TO EXERCISE PROGRAMS

Elastic Net models aid prediction

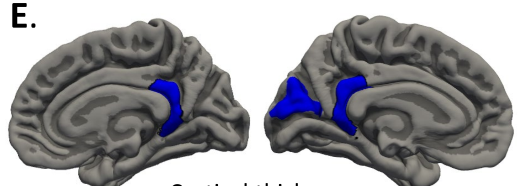


D.



Degree centrality edges

E.



Cortical thickness

Add networks to these edges

F.

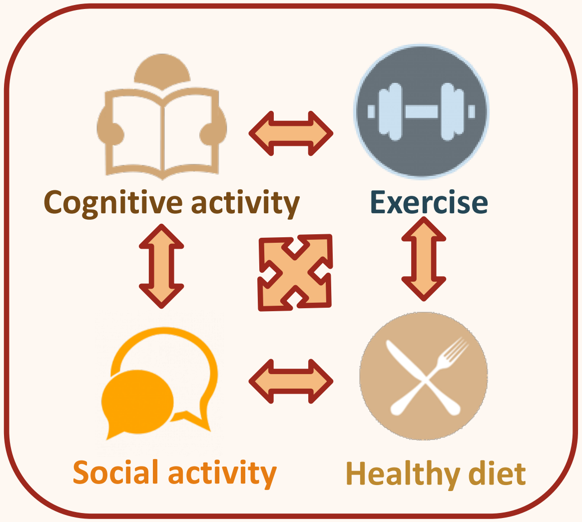
Non-imaging predictors	Direction
Gait-self efficacy	Positive
Big 5 extroversion	Negative
Perceived sleep quality index	Negative
Sex	Negative (female)
Employment	Positive (retired)
Pattern comparison score	Negative

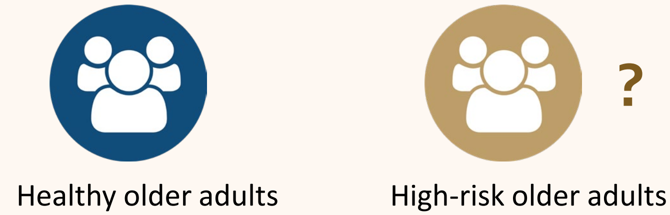
B through **C** illustrates results from the Multimodal model

R^2 represents the squared correlation between the observed (train data) and predicted (test data) values

Morris et al, 2021

To what extent does adherence to good ***lifestyle practices*** (for high risk older adults) relate to brain and mental health?





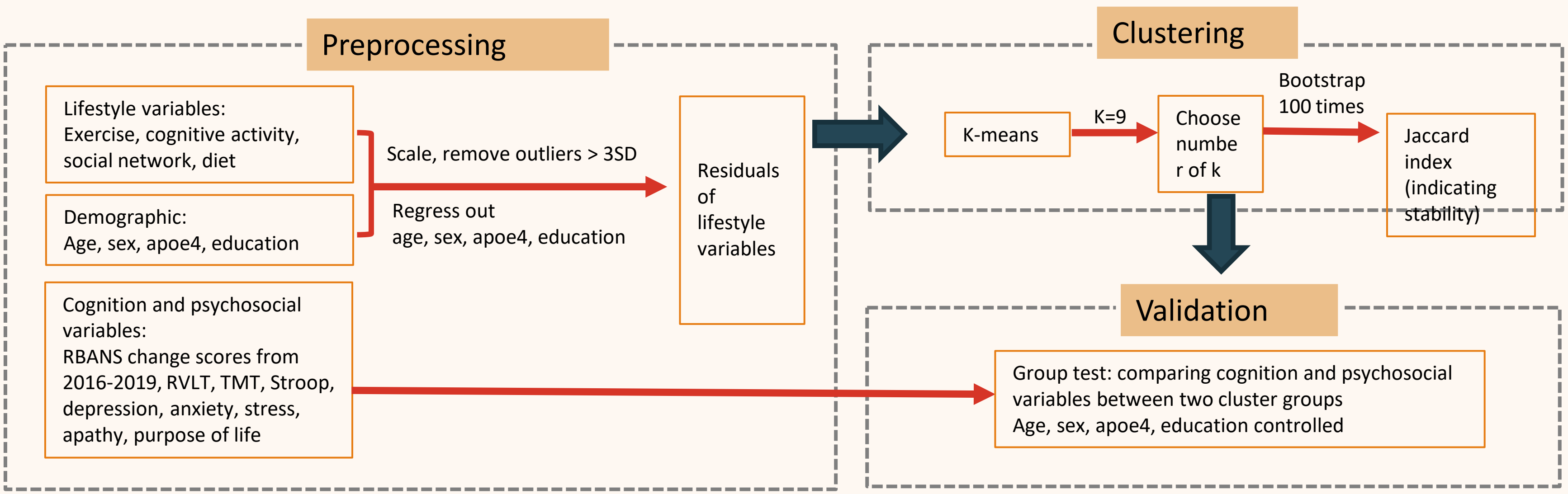
- Prevent up to 40% dementia risk
- Younger structure-based brain age
- Greater functional connectivity in frontal, temporal and motor areas
- Lower Aβ burden and higher global functions

Ai et al, 2023

Study One

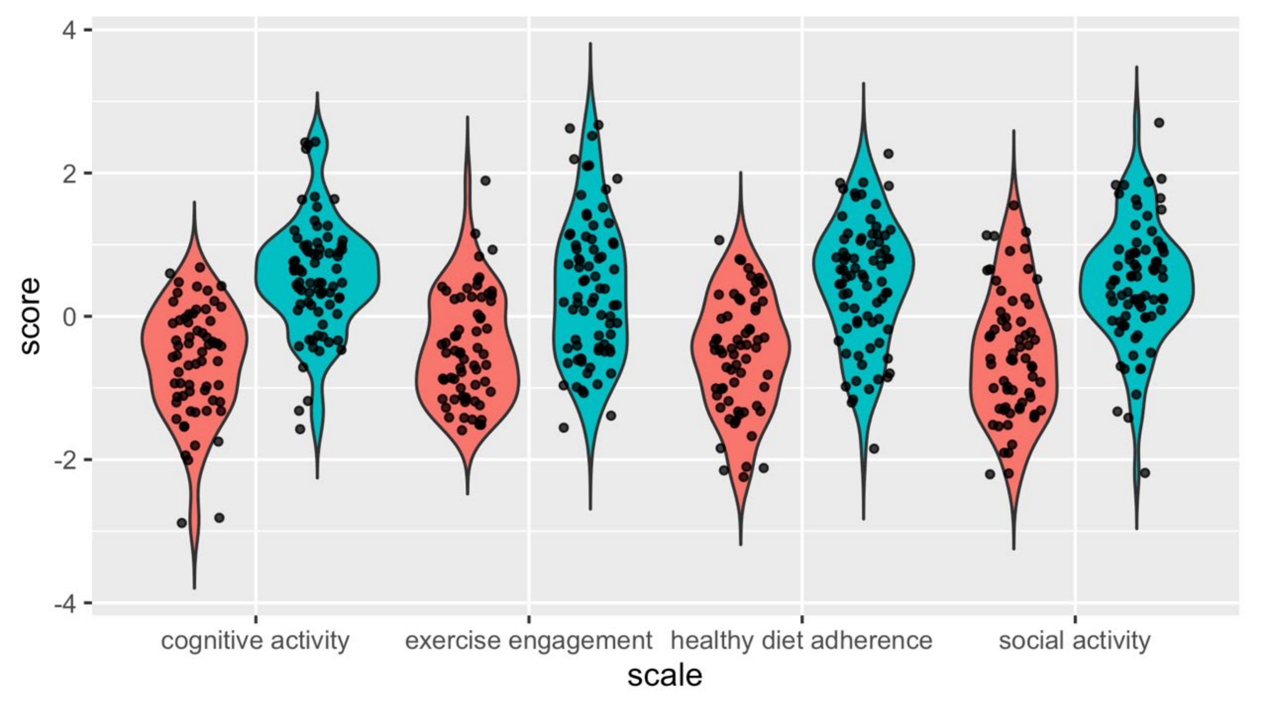
Do individuals have different profiles of multidomain lifestyle adherence?

K-means clustering process



Individuals have different profiles of multidomain lifestyle adherence

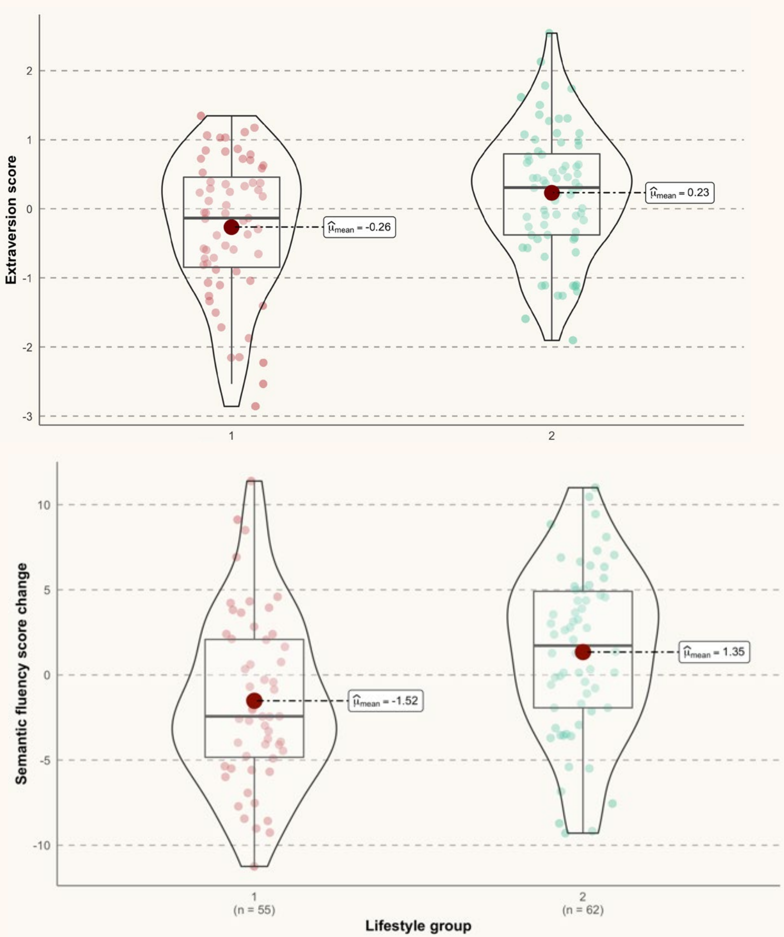
K-means results

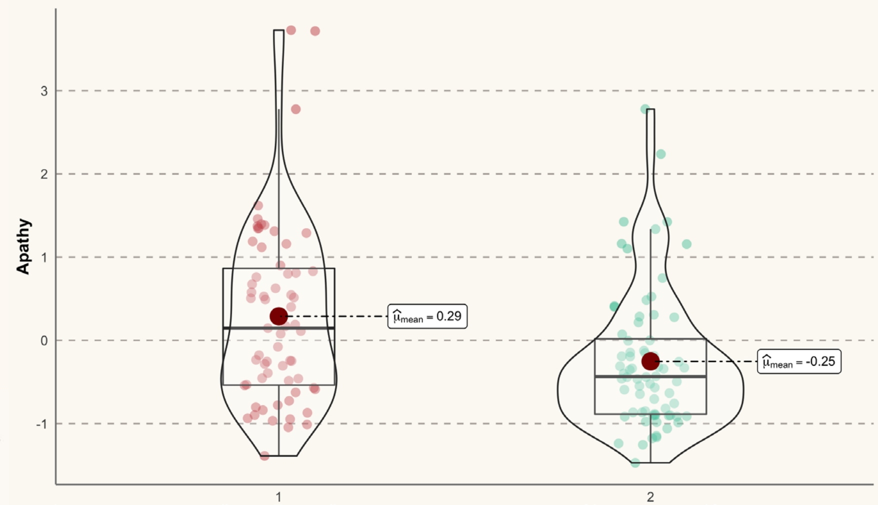


- Adherence group
- Non-adherence group

Study One

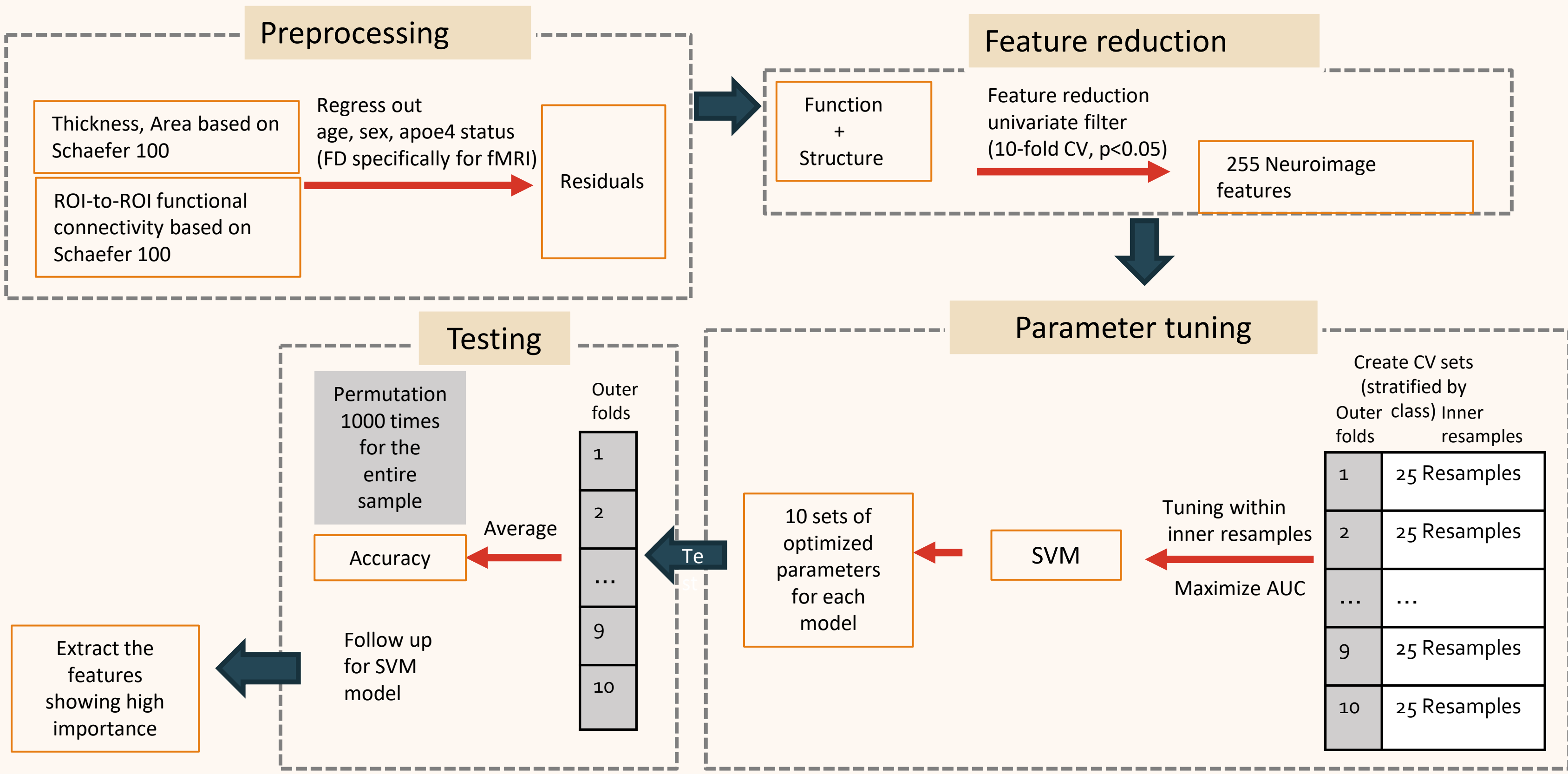
Different profiles of multidomain lifestyle adherence are associated with different features of mental health and cognition





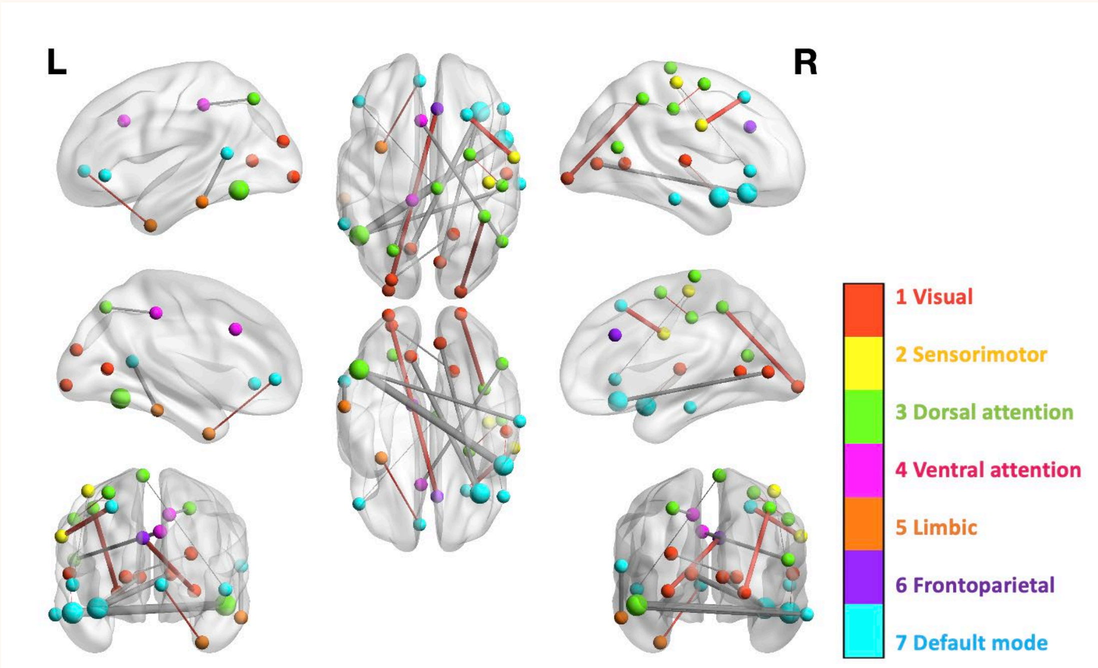
- Non-adherence group
- Adherence group

Do distinct lifestyle profiles show neurobiological differences ?



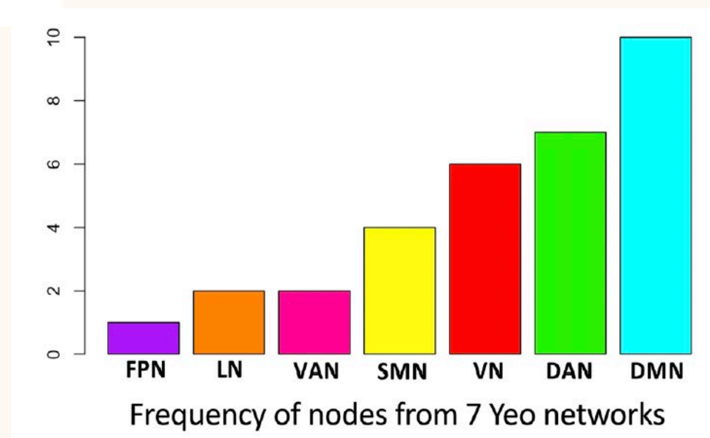
Do lifestyle profiles have neurobiological distinctions?

Study One



Red edges:
Adherence group had greater functional connectivity values than Non-adherence group

Grey edges:
Non-adherence group had greater functional connectivity values than adherence group



Multidimensional Digital Biomarker of Cognitive Health:

Unobtrusive and Continuous Monitoring of Cognitive Changes Using Smartphones

Maciej Kos

F99/K00 NIH Fellow

Why is cognitive health important? Trajectories of cognitive impairments

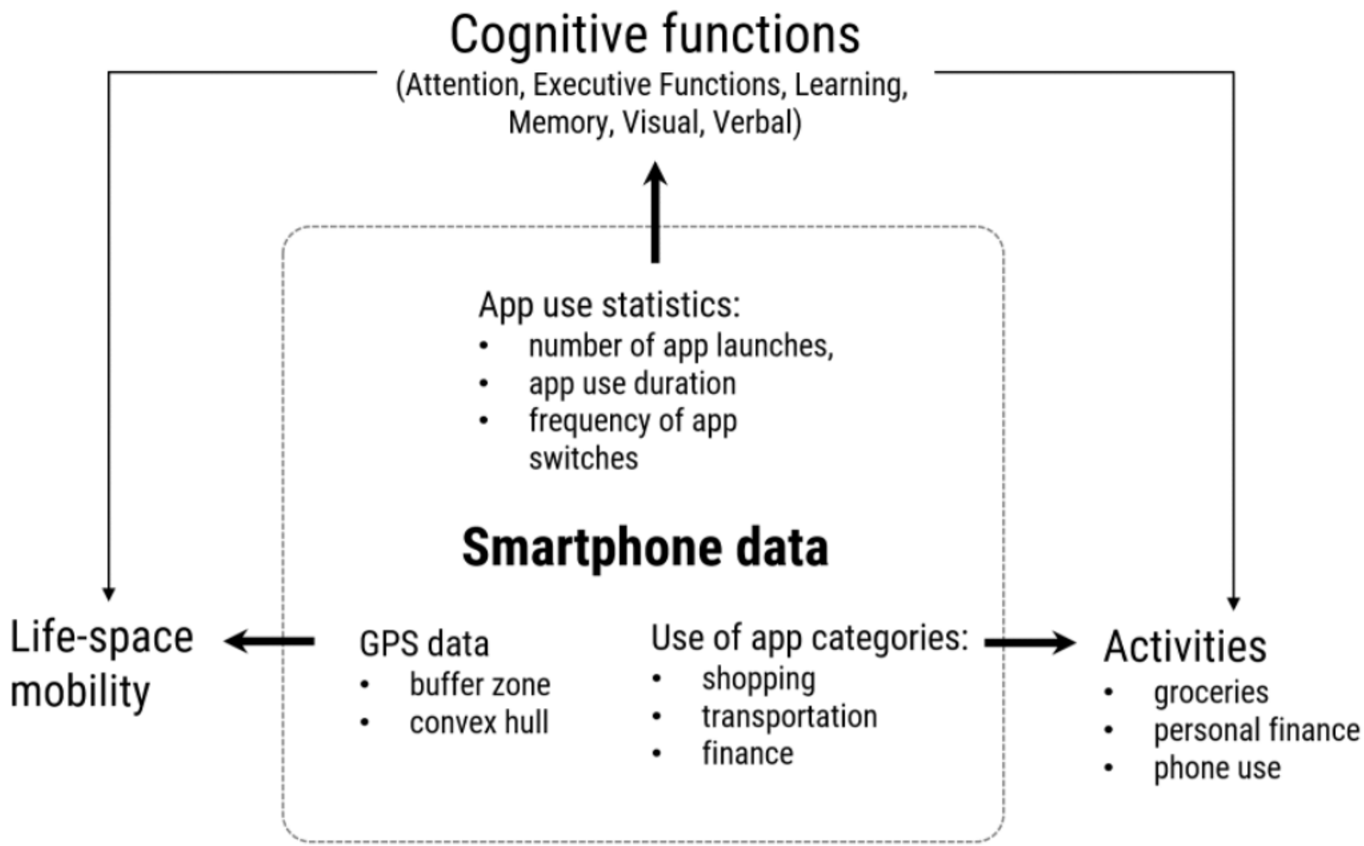
Subjective cognitive impairment	Mild cognitive impairment	Alzheimer's disease

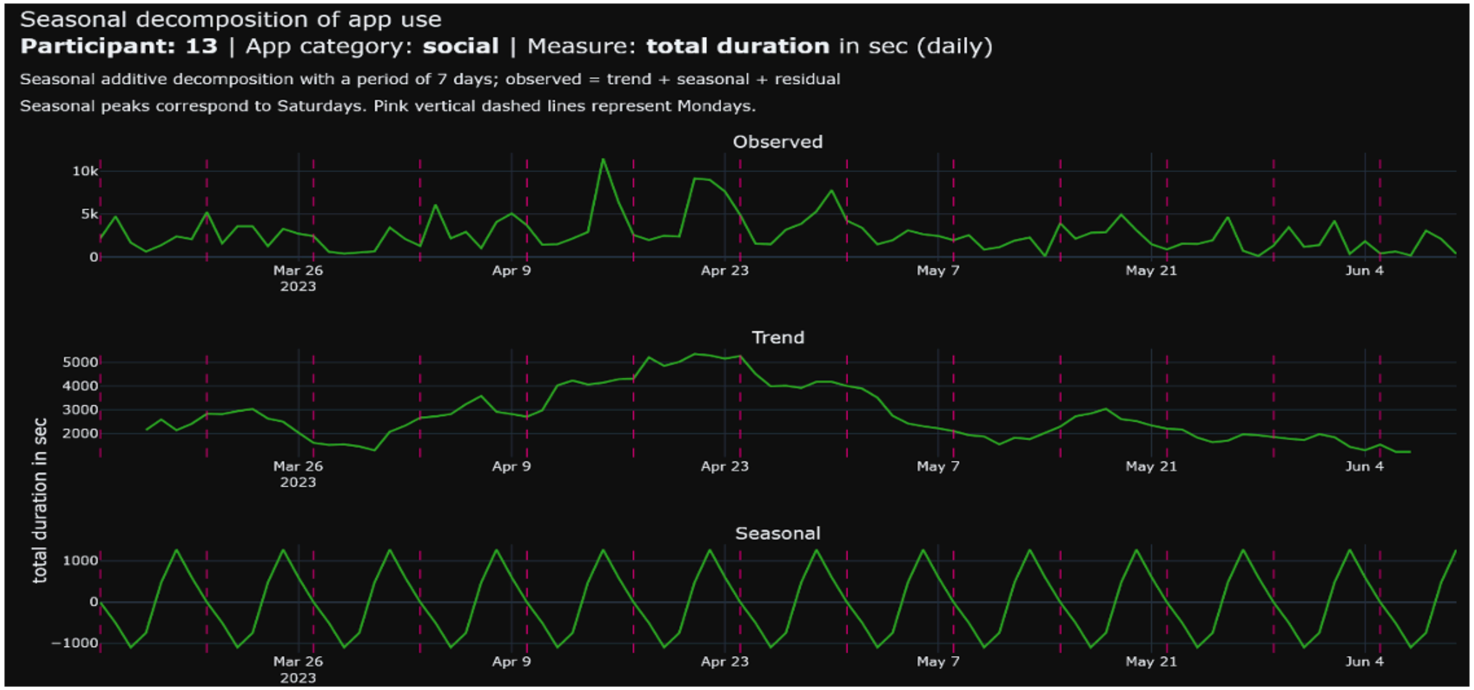
Problem:
No robust and affordable way to monitoring subtle changes in cognitive functions over time to:

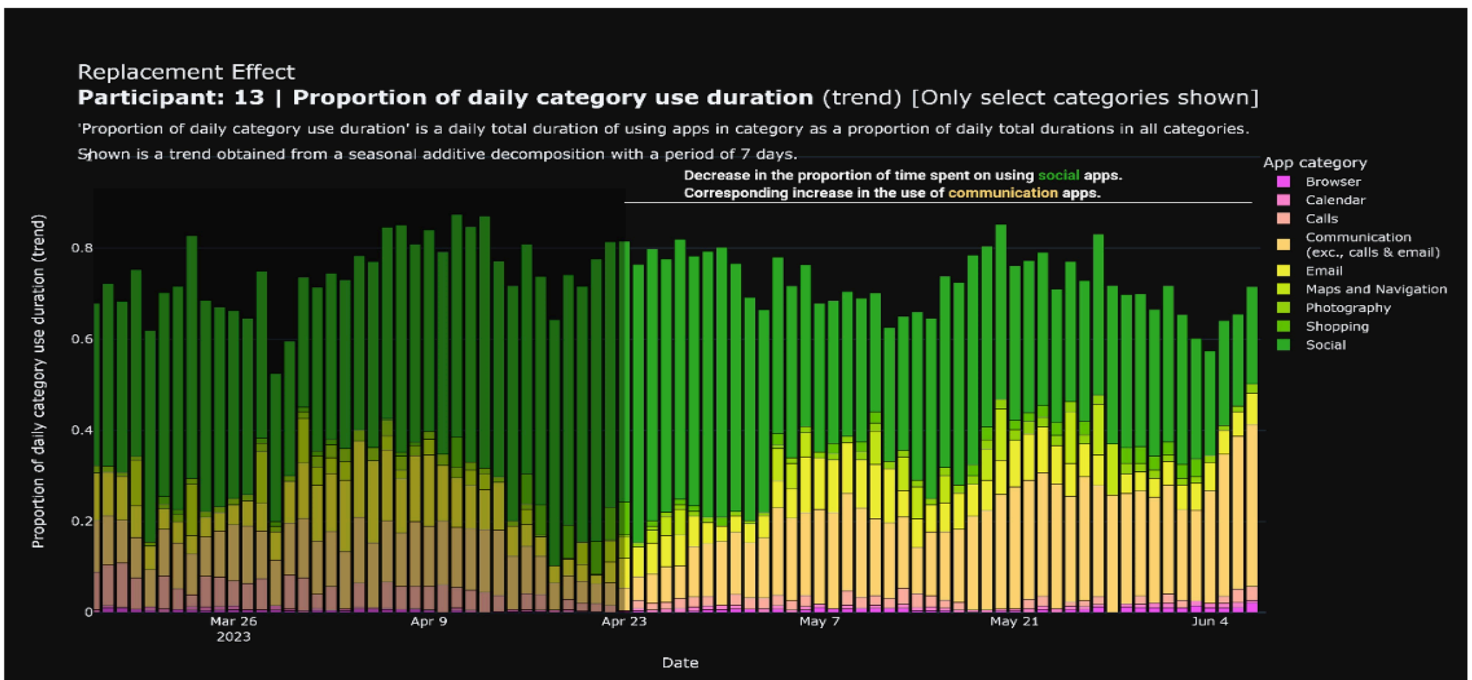
- develop efficacious therapeutics
- personalize treatments

Proposed solution (long term):
Multidimensional digital biomarker of cognitive changes to augment existing methods:

- combines AI/ML methods with mechanistic modeling
- based on smartphone data collected continuously and unobtrusively


Cognitive functions
(Attention, Executive Functions, Learning, Memory, Visual, Verbal)
App use statistics:
• number of app launches,
• app use duration
• frequency of app switches
Smartphone data
Life-space mobility
GPS data
• buffer zone
• convex hull
Use of app categories:
• shopping
• transportation
• finance
Activities
• groceries
• personal finance
• phone use





Smartphone based estimates of IADLs significantly correlate with self-reports of IADLs.

To summarize:

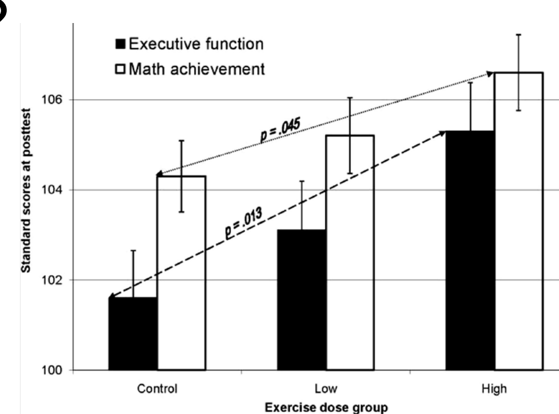
Relatively brief fitness interventions (with older couch potatoes – and hi & low fit kid’s ….):

- Improve a variety of perceptual & cognitive abilities
- Increase brain volume in regions which normally show age-related decline - including the hippocampus (and increases are often correlated with performance improvements)
- Change 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

Where to go from here?

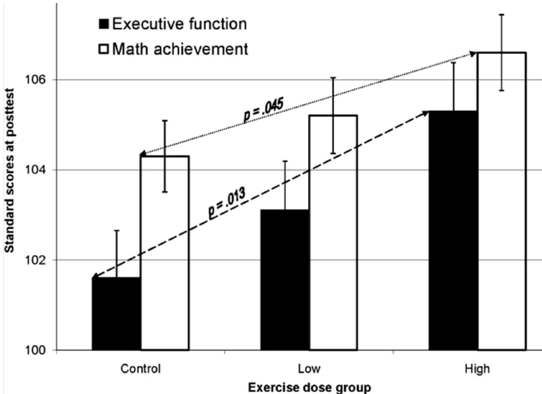
- Understanding boundary conditions on exercise effects (e.g. Sink et al., 2015 – 24 month RCT)
- More study combining different interventions
  - Social, physical activity, cognitive activity, diet ….
  - When, how much, sequence …..
  - Common or separate mechanisms/pathways?
- Genetic moderators of the relationship between interventions and cognition & brain
- What factors predict adherence to exercise?
- Beyond the laboratory door ……

Davis et al, 2011

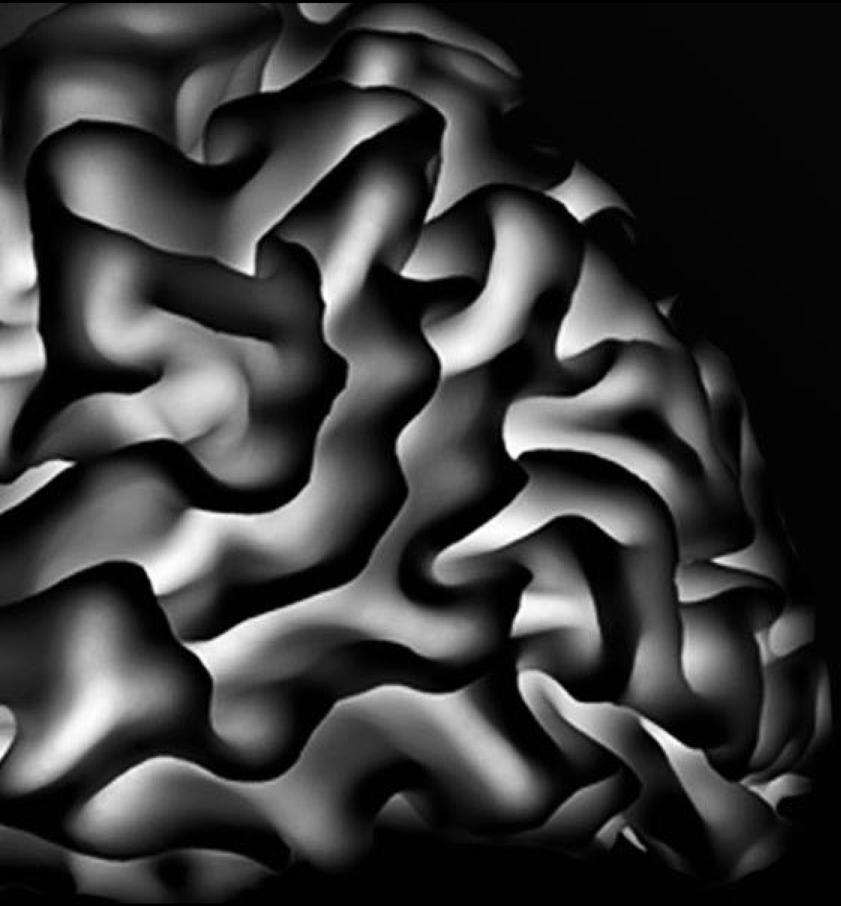


Where to go from here?

- Understanding boundary conditions on exercise effects (e.g. Sink et al., 2015 – 24 month RCT)
- Combining different interventions
  - Social, physical activity, cognitive activity, diet ….
  - When, how much, sequence …..
  - Common or separate mechanisms/pathways?
- Genetic moderators of the relationship between interventions and cognition & brain
- Beyond the laboratory door ……



Davis et al, 2011



INSIGHT

A Comprehensive, Multidisciplinary Brain Training System

BECKMAN INSTITUTE FOR ADVANCED SCIENCE AND TECHNOLOGY
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Abbott A Promise for Life

APTIMA® Human-Centered Engineering

CUNY The City University of New York

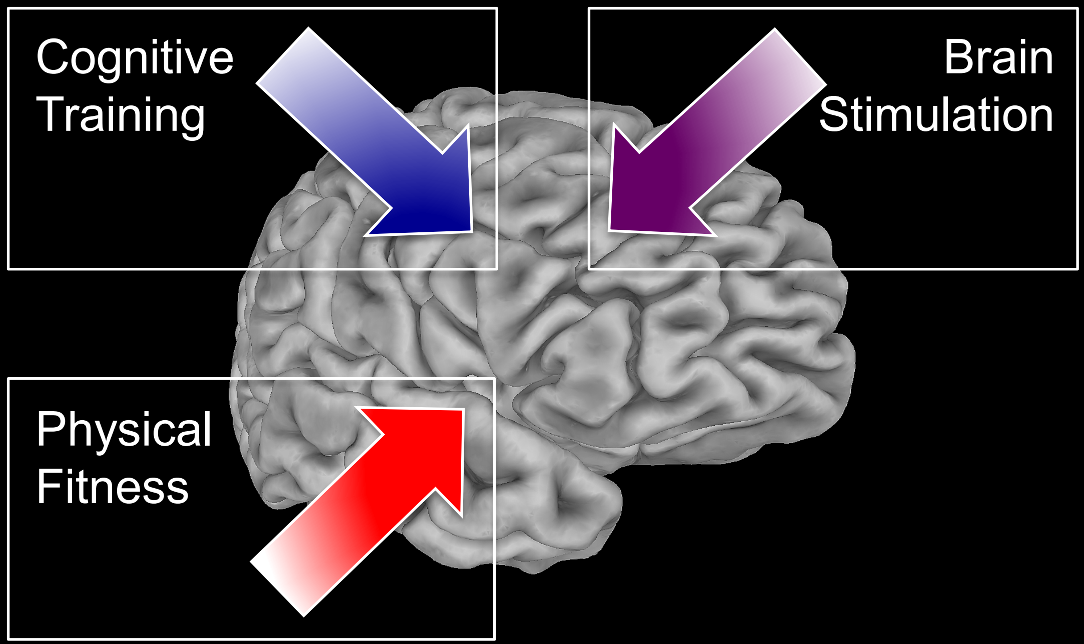
CIRSINUS

Georgia Tech

Soterix medical BETTER. SMARTER.

UAM UNIVERSIDAD AUTONOMA DE MADRID

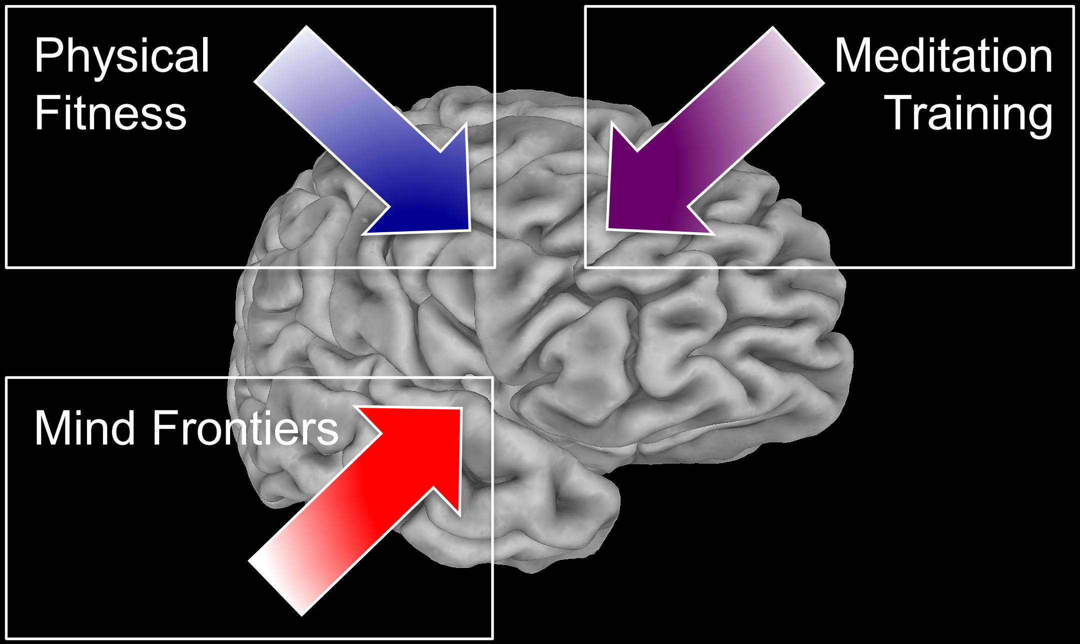
INSIGHT Project Phase 1a



Experimental Design: Phase 1b

- Three experimental groups

    1. Physical Fitness
    2. Physical Fitness + Mind Frontiers
    3. Physical Fitness + Mind Frontiers + Mindfulness Meditation



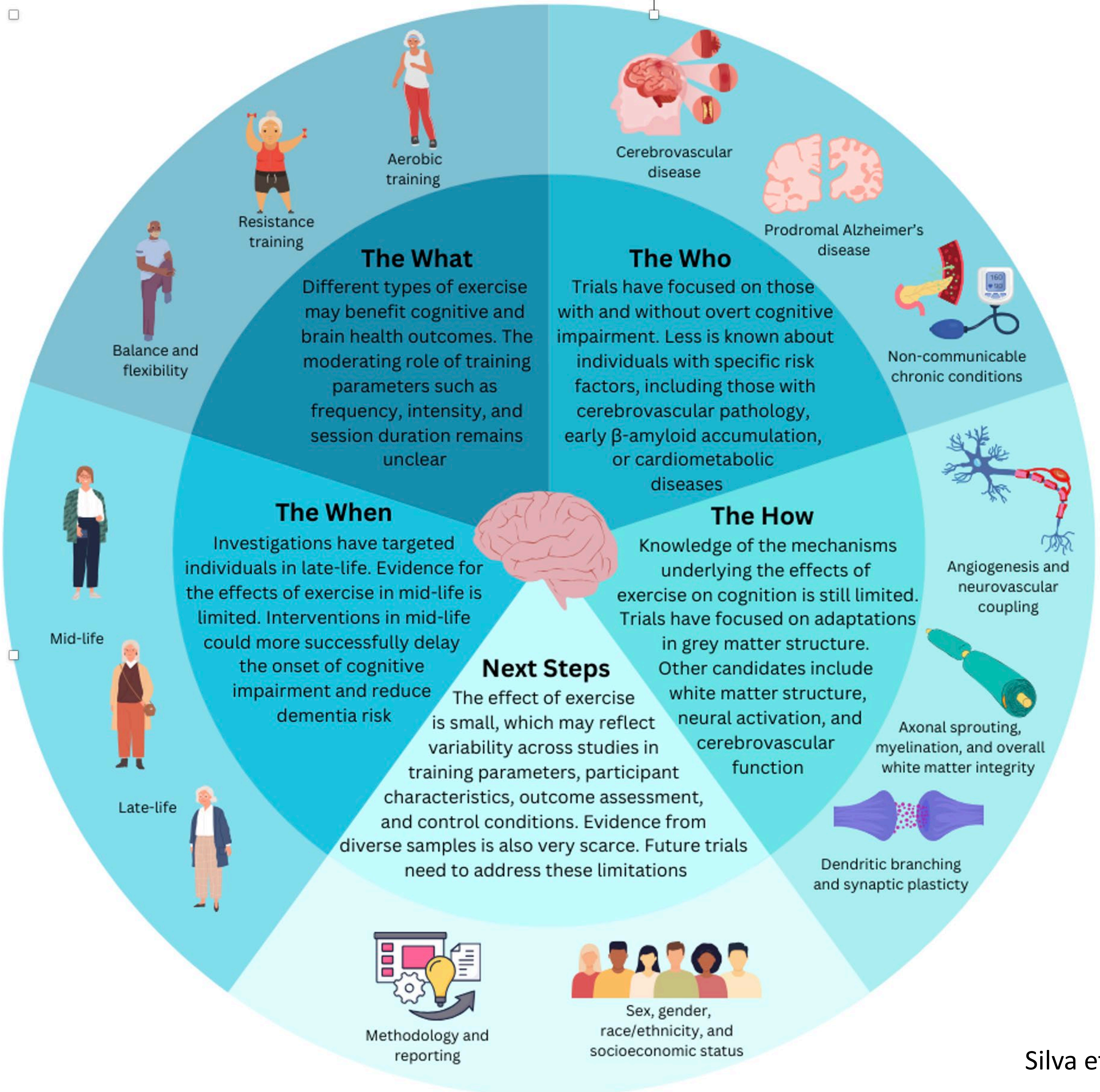
Summary – INSIGHT brain health study

Transfer	Intervention	Cohen's *d* (0.50)	Measure
Decision Making	Fitness only	0.74	Composite Score
Decision Making	Fitness only	0.57	Social Norms
Decision Making	Fitness only	0.47	Under/over Confidence
Decision Making	Mind Frontiers + Fitness	0.58	Composite Score
Decision Making	Mind Frontiers + Fitness	0.49	Social Norms
Decision Making	Mind Frontiers + Fitness + Meditation	0.45	Composite Score
Decision Making	Mind Frontiers + Fitness + Meditation	0.86	Resist Sunk Cost
Analogical Reasoning	Fitness only	0.50	Accuracy

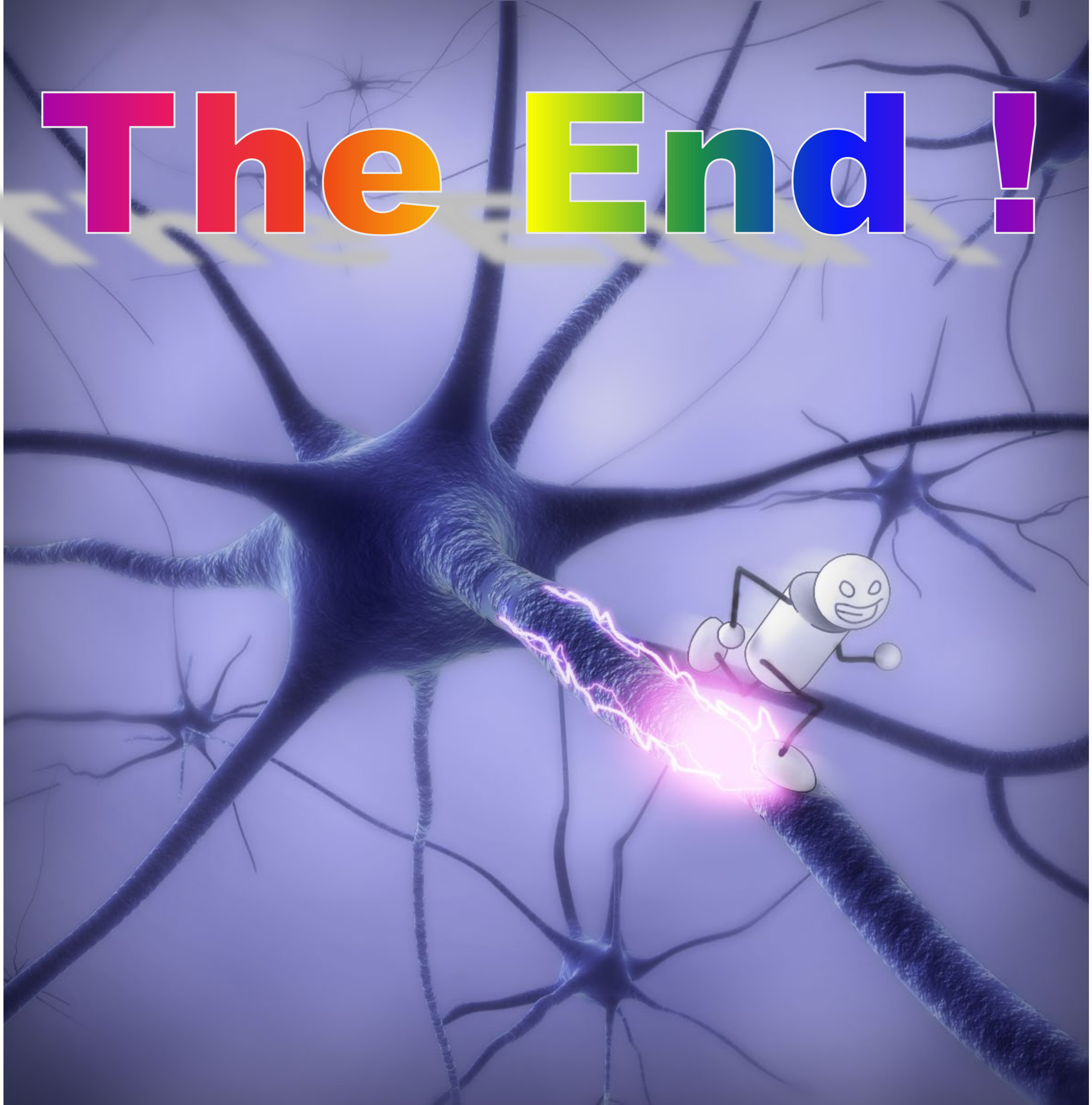
Significant effect size increases of up to 0.86

(relative to the active control) in multiple measures of transfer to **Adaptive Reasoning and Problem Solving**

> 250 18 to 44 year old participants

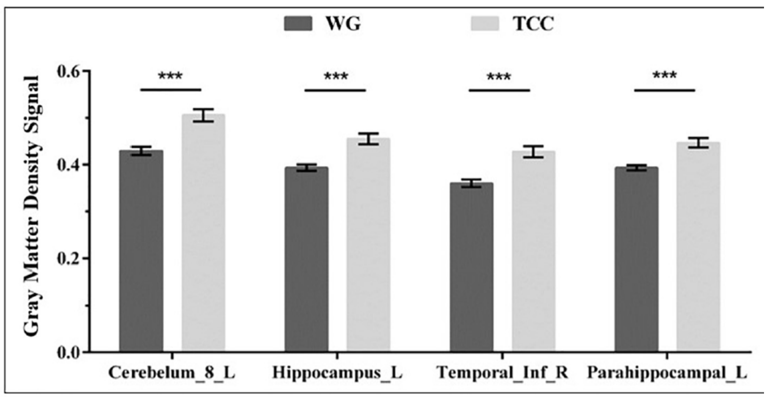


Silva et al, 2024


The End !

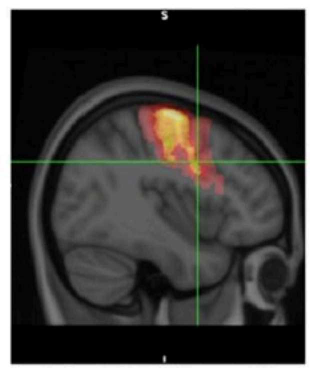
Regular Tai Chi Practice Is Associated With Improved Memory as Well as Structural and Functional Alterations of the Hippocampus in the Elderly

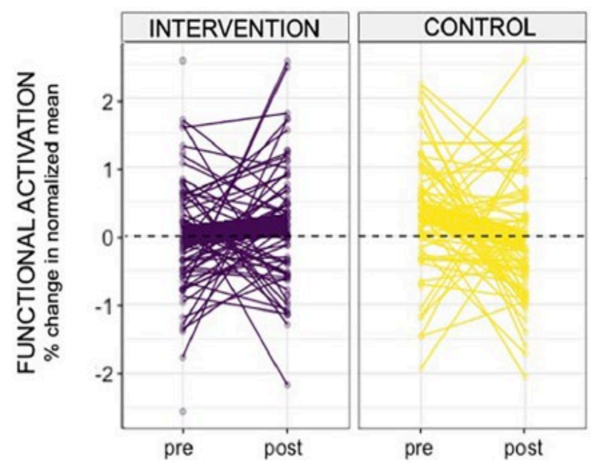
*Chunlin Yue[1], Qian Yu[2], Yanjie Zhang[2], Fabian Herold[3], Jian Mei[1], Zhaowei Kong[4], Stephane Perrey[5], Jiao Liu[6], Notger G. Müller[3], Zonghao Zhang[1], Yuliu Tao[1], Arthur Kramer[7,8], Benjamin Becker[9] and Liye Zou[2,10]** 2020



Can a Theater Acting Intervention Enhance Inhibitory Control in Older Adults? A Brain-Behavior Investigation

Aishwarya Rajesh[1,2], Tony Noice[3], Helga Noice[3], Andrew Jahn[4], Ana M. Daugherty[5], Wendy Heller[1,2] and Arthur F. Kramer[1,6]* 2021


Crosshair at (40, 5, 34)



Center for Cognitive & Brain Health

OVERARCHING VISION:

To use our knowledge of brains, minds & bodies to guide current and future generations to happier healthier lives through novel interdisciplinary interventions.

To accomplish this, we investigate the effects of lifestyle, early life experiences, the arts, the aging process, demographics, genetics and health behaviors on brain and cognition.

We bring to bear multiple perspectives and methodologies to explicate mechanisms of brain health and disease to improve the lives of individuals across the lifespan:

- computational modeling
- state of the art multimodal neuroimaging
- sophisticated behavioral paradigms
- Interventions
- analyses of large data sets

Currently include 18 interdisciplinary faculty (and lots of post-doc's and students) from 4 different colleges – with more to come ……

Collaborators

University of Illinois

- Aga Burzynska
- Laura Chaddock
- Neal Cohen
- Eddie McAuley
- Sean Mullen
- Brad Sutton
- Aron Barbey
- Jeff Woods
- Neha Gothe
- Dominika Pindus

University of Pittsburgh

- Kirk Erickson

Ohio State

- Ruchika Prakash

University of Umea

- L. Jonasson, L. Nyberg et al

Northeastern Univ.

- Chuck Hillman
- Meishan Ai
- Tim Morris
- Sue Whitfield-Gabrieli
- Maya Geddes

Johns Hopkins

- Michelle Carlson
- George Rebok

University of Grenada

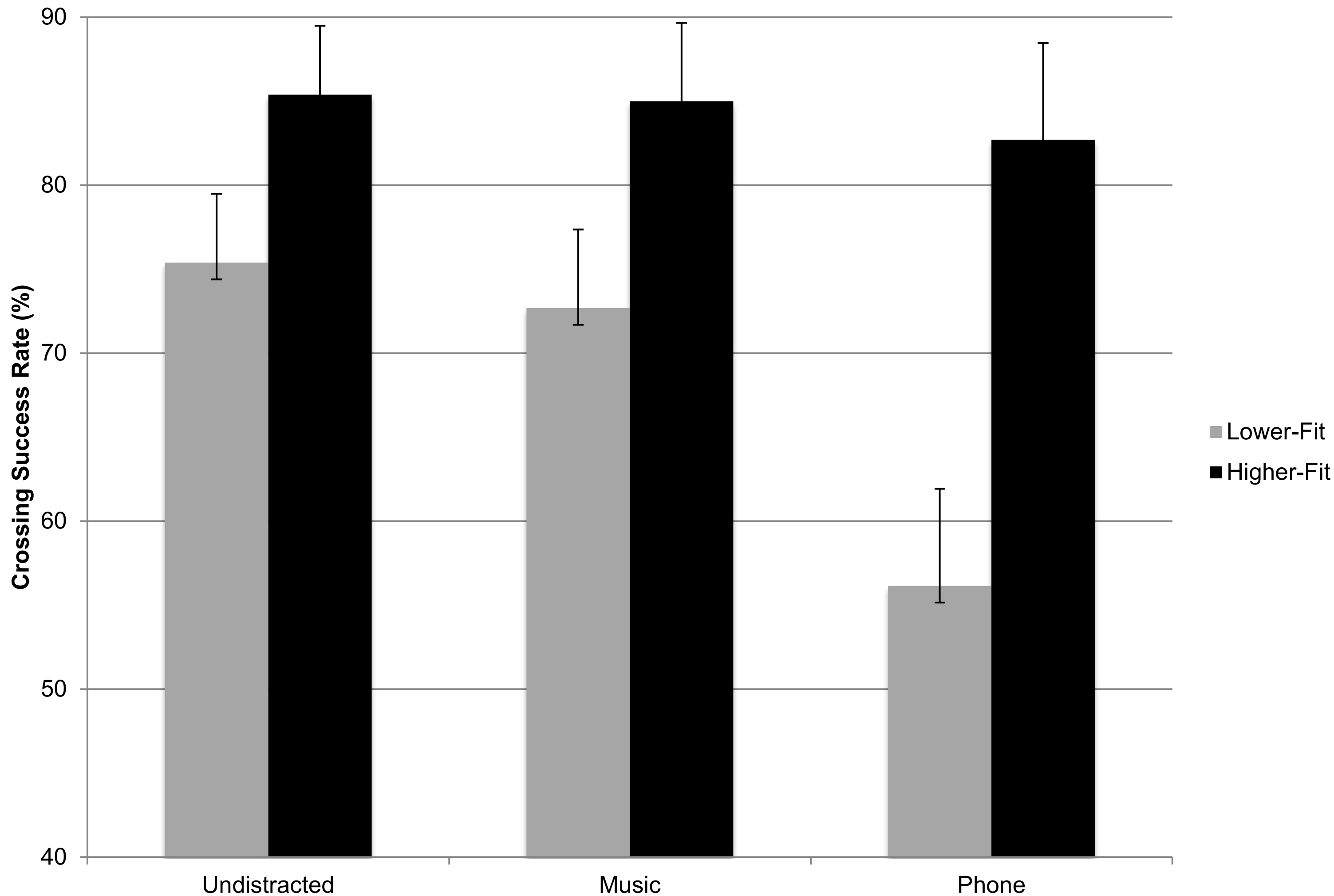
- F. Ortega, I. Esteban-Cornejo, P. Sollis-Urra and many other team members

University of Iowa

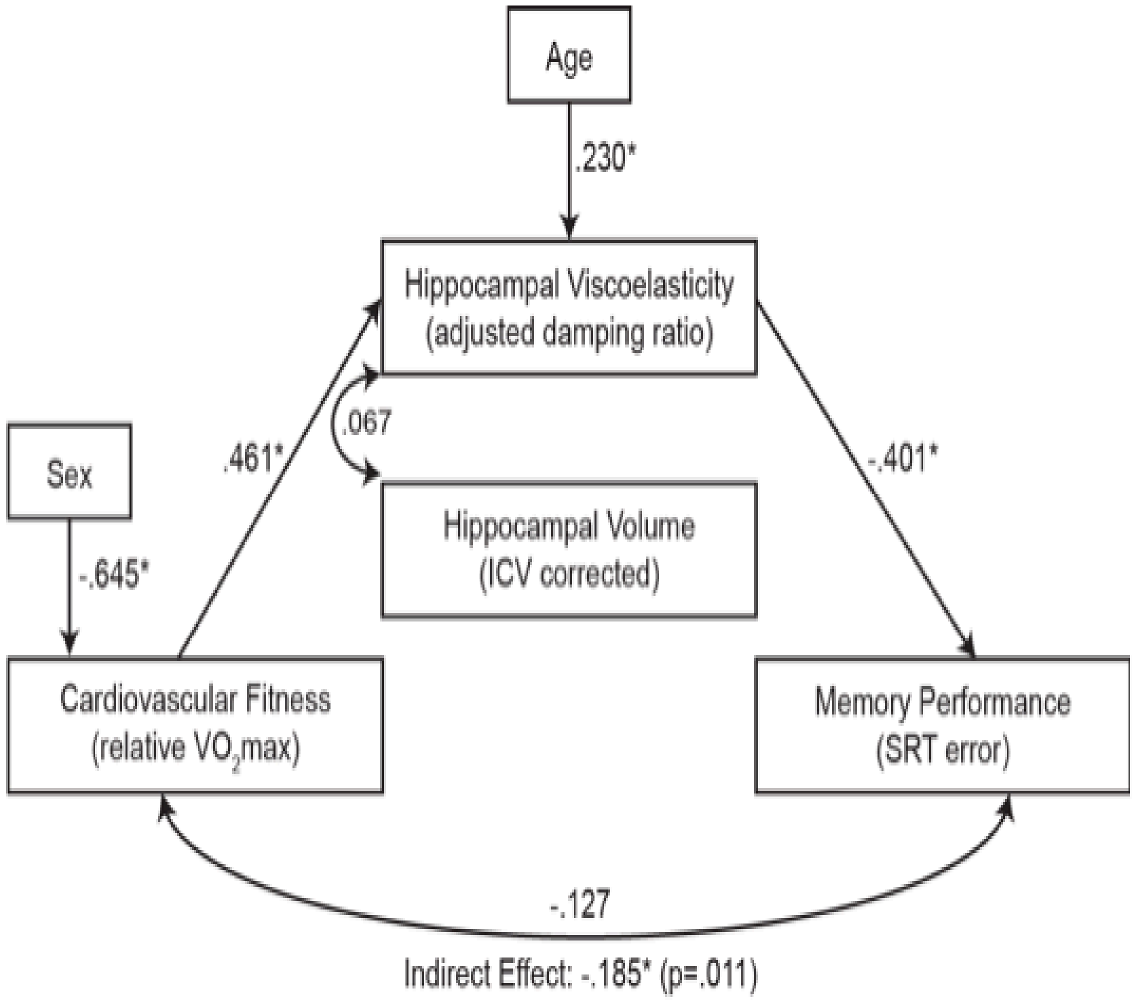
- Michelle Voss

What about implications for the real-world ?

What about implications for the real-world ?

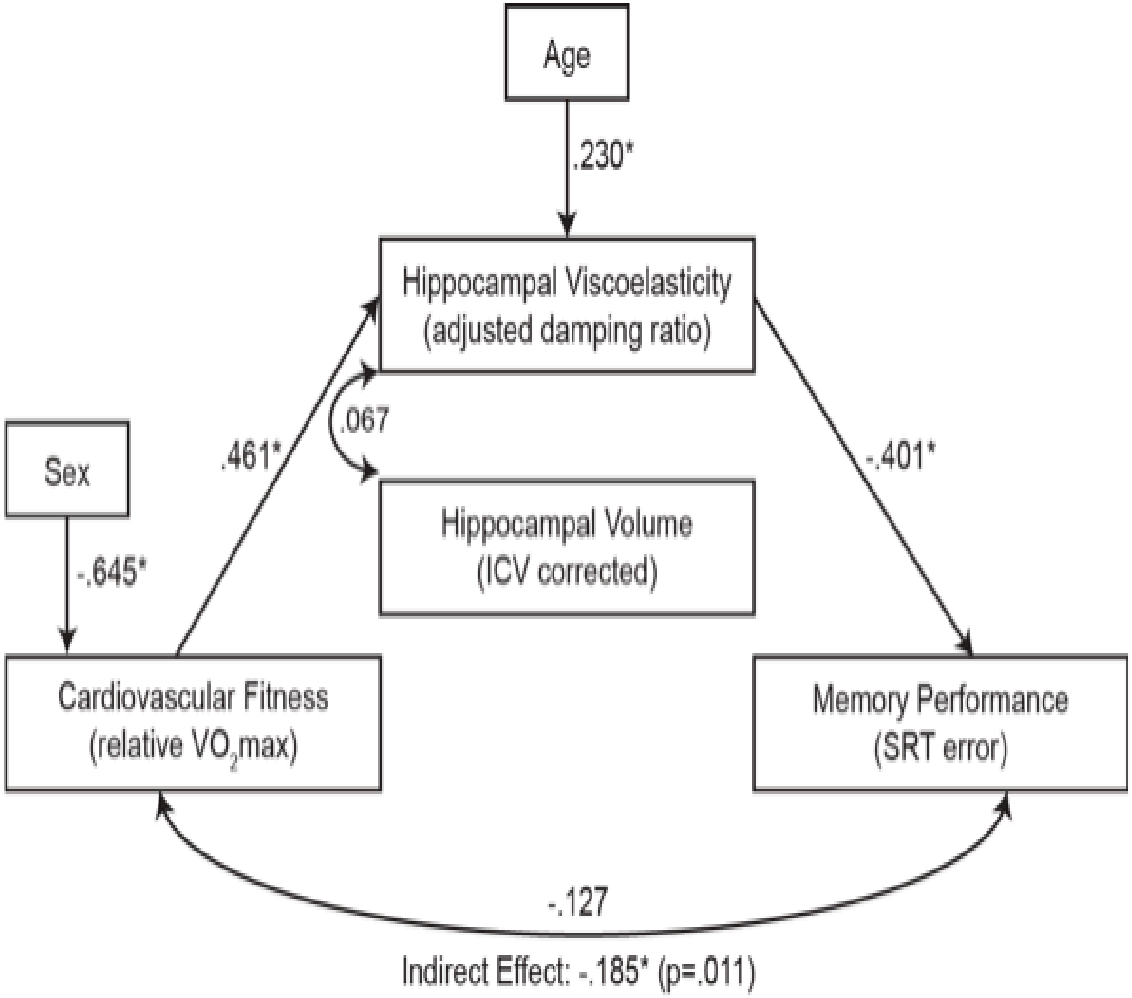


Some new tools & measures for studying, fitness, brain and cognition and ……



Schwarb et al (2017)

Fig 4. *Path model testing the effect of aerobic fitness on relational memory mediated by hippocampal ξ′ accounting for hippocampal volume. Regression path values are standardized coefficients. Asterisks indicate significance (p<.05).*



Also individual differences in variability in the fMRI (BOLD) signal is useful in predicting & tracking exercise benefits for cognitive & brain health

Fig 4. *Path model testing the effect of aerobic fitness on relational memory mediated by hippocampal ξ′ accounting for hippocampal volume. Regression path values are standardized coefficients. Asterisks indicate significance (p<.05).*

Can we predict future benefits of fitness training on cognitive and brain health ?

Can we predict future benefits of fitness training on cognitive and brain health ?

- Brain networks exhibit a modular organization, comprised of separable sub-networks or modules.
- Networks with high modularity have dense connections within networks and sparser connections between networks.
- More modular networks allow for more efficient & greater adaptive reorganization in response to changing demands.

- *We propose* that network modularity may predict outcomes of interventions including when baseline behavioral measures may not reliably distinguish between individuals or cannot be reliably obtained.

    - Consistent with the literature on cognitive training benefits for younger adults, older adults, and TBI patients.

What about exercise-related executive function gains for older adults?

What about exercise-related executive function gains for older adults?

- 6 month exercise intervention, 4 groups, 60 to 85 year olds, composite measure of Executive Function, 100+ participants.

What about exercise-related executive function gains for older adults?

- 6 month exercise intervention, 4 groups, 60 to 85 year olds, composite measure of Executive Function, 100+ participants.

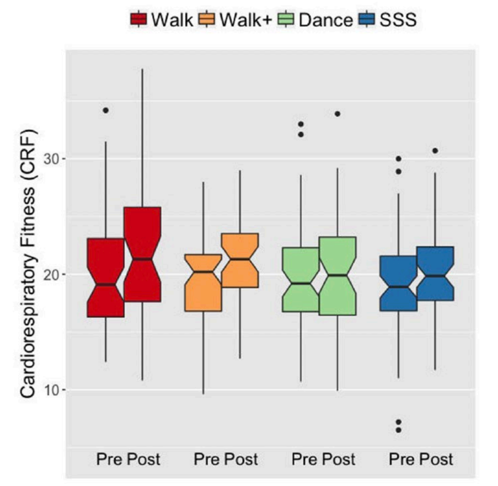
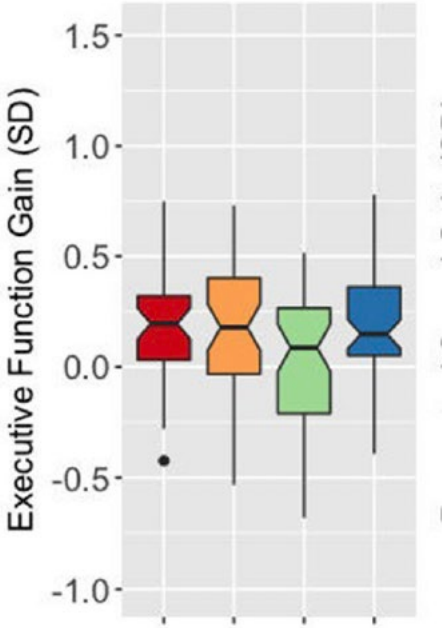


FIGURE 1 | Notched box plots show the distribution of CRF values before and after the intervention. The horizontal line marks the median. The notches extend to ±1.58 IQR/sqrt(n). The upper and lower hinges correspond to the first and third quartiles. The whiskers extend from the hinge to ±1.5*IQR of the hinge. IQR, inter-quartile range.

What about exercise-related executive function gains for older adults?

- 6 month exercise intervention, 4 groups, 60 to 85 year olds, composite measure of Executive Function, 100+ participants.



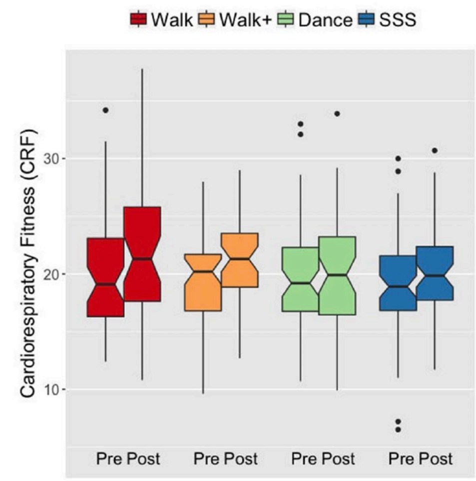


FIGURE 1 | Notched box plots show the distribution of CRF values before and after the intervention. The horizontal line marks the median. The notches extend to ±1.58 IQR/sqrt(n). The upper and lower hinges correspond to the first and third quartiles. The whiskers extend from the hinge to ±1.5*IQR of the hinge. IQR, inter-quartile range.

What about exercise-related executive function gains for older adults?

- 6 month exercise intervention, 4 groups, 60 to 85 year olds, composite measure of Executive Function, 100+ participants.

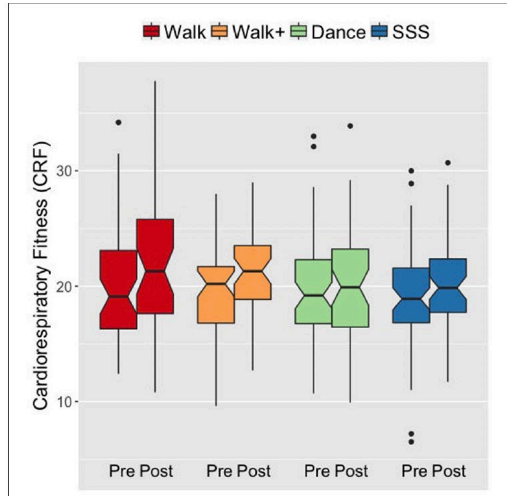
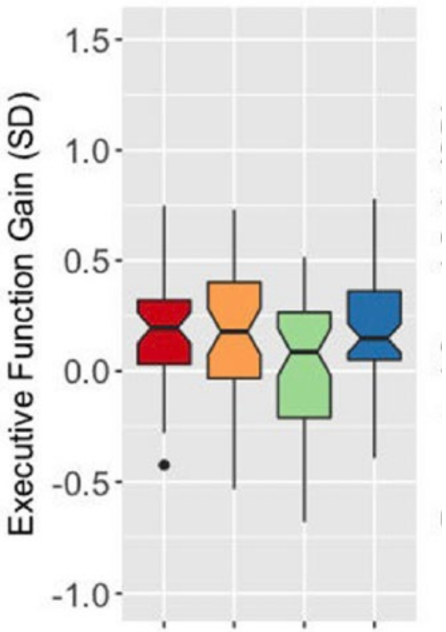
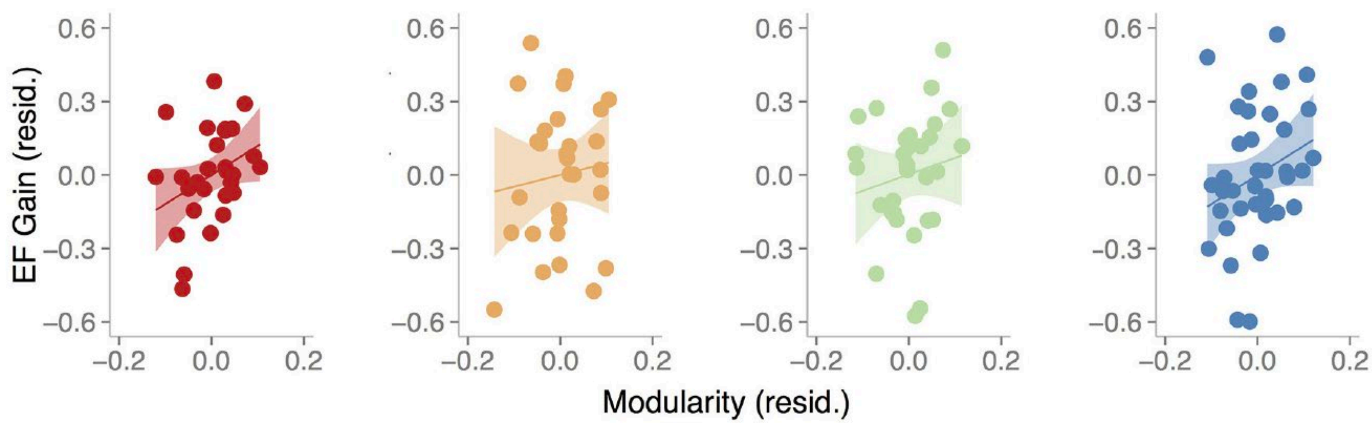


FIGURE 1 | Notched box plots show the distribution of CRF values before and after the intervention. The horizontal line marks the median. The notches extend to ±1.58 IQR/sqrt(n). The upper and lower hinges correspond to the first and third quartiles. The whiskers extend from the hinge to ±1.5*IQR of the hinge. IQR, inter-quartile range.





What about exercise-related executive function gains for older adults?

- 6 month exercise intervention, 4 groups, 60 to 85 year olds, composite measure of Executive Function, 100+ participants.

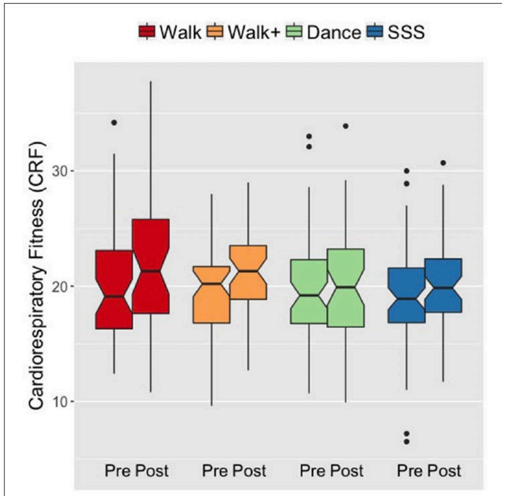
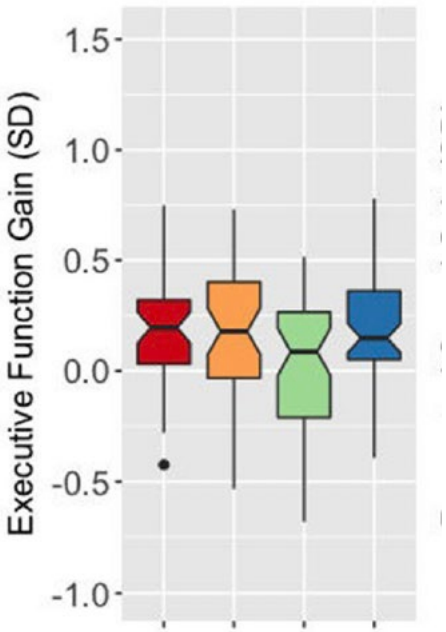
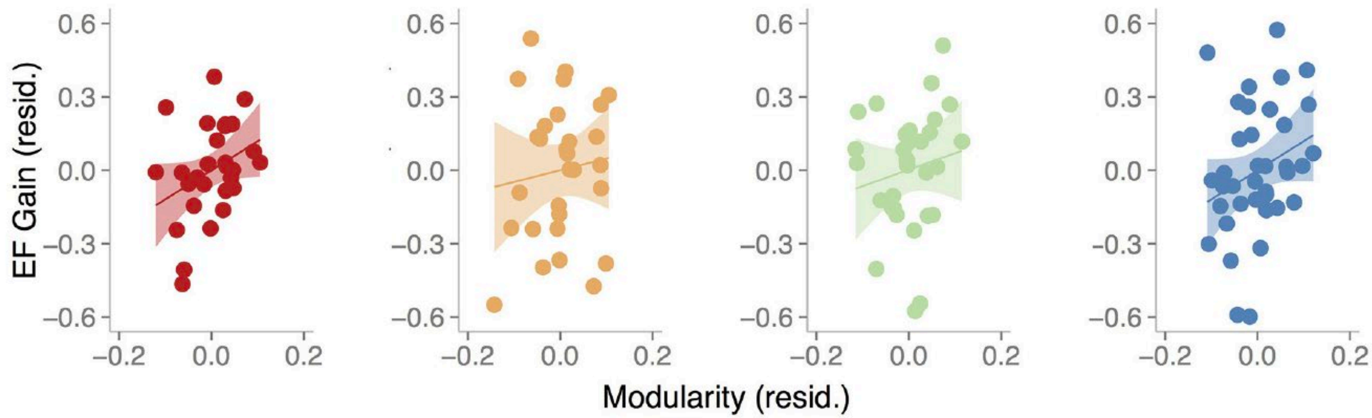


FIGURE 1 | Notched box plots show the distribution of CRF values before and after the intervention. The horizontal line marks the median. The notches extend to ±1.58 IQR/sqrt(n). The upper and lower hinges correspond to the first and third quartiles. The whiskers extend from the hinge to ±1.5*IQR of the hinge. IQR, inter-quartile range.

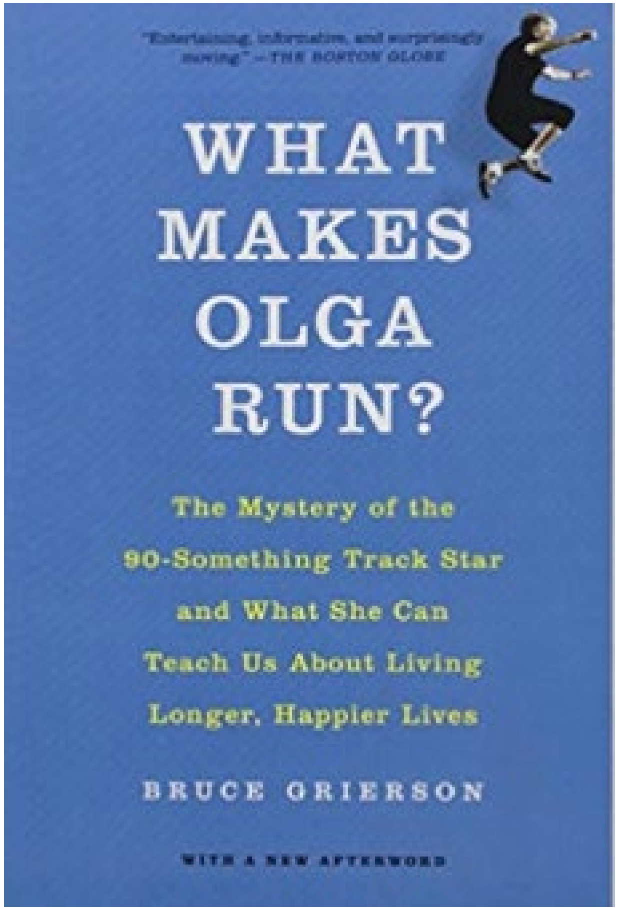




So …. Generalizable effects across populations and intervention types …..

Baniqued et al, 2018

An exemplar of successful aging …….



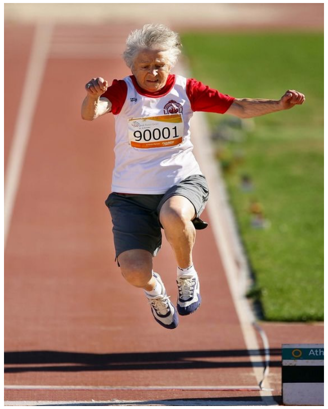
Olga Kotelko – 95 years of age (30 world records since 75 years of age)

Olga Kotelko vs. 60 older women

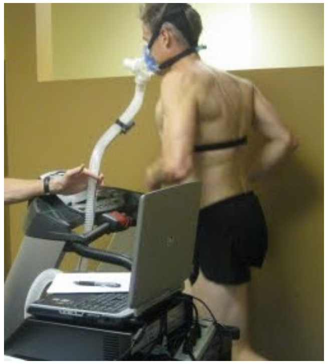
WHOLE BODY

30 world records
Started at age 75

~5 hours light
~1 hour vigorous



PHYSICAL ACTIVITY



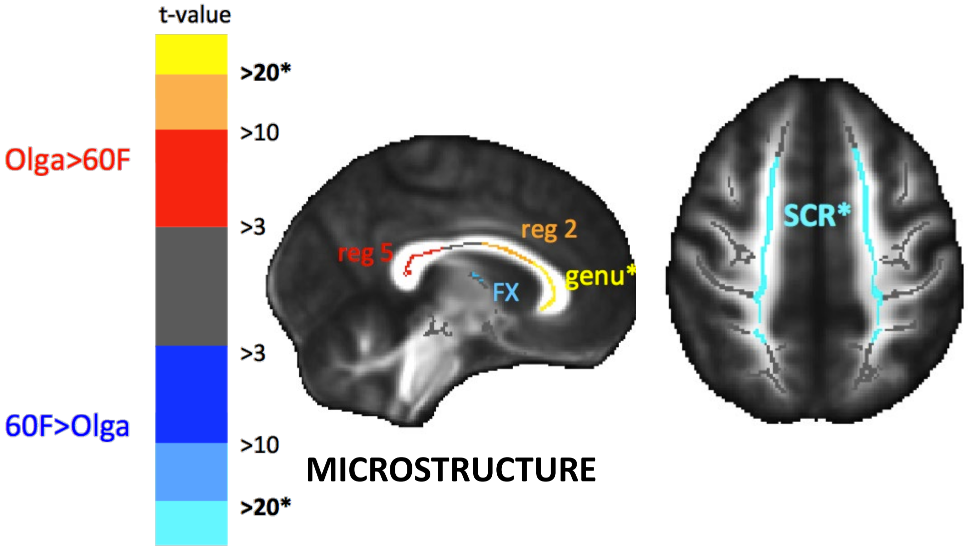
GOOD AEROBIC CAPACITY

Peak VO_2 = 16

BRAIN (WHITE MATTER)

16313 voxels

MACROSTRUCTURE



MICROSTRUCTURE