BRAIN-BEHAVIOR RELATIONSHIPS IN TYPE 2 DIABETES

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Overview

- Introduction to the concept of executive control
- Brain regions to support executive control
- Significance of executive control for self-management
- A trial to enhance self control resources among those living with T2DM
- Question and answer period.

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Questions to be answered:

1. What are ECRs?
2. Why should we care about them?
3. Under what conditions are they most relevant?
4. How can we increase them?
5. Can we apply this to T2DM?
6. Can you help?

What is self-control?

Often involves suspending an action that would otherwise occur (i.e. suspending a "default").

The act of suspending this default is a behavioral manifestation of "self-control."

… but its also the act of making yourself do something you wouldn't otherwise do.

(also involves suspending a default)

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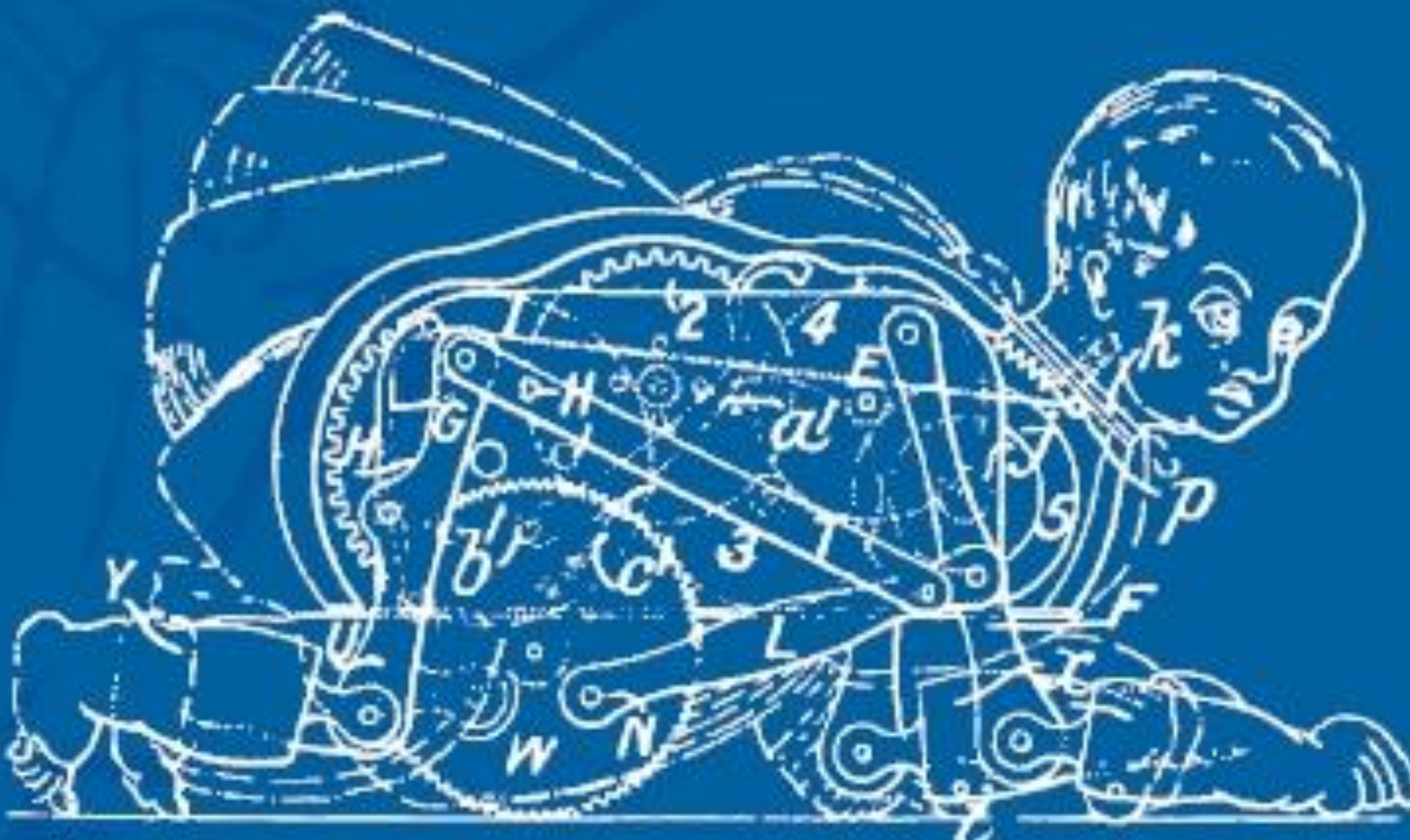
2
4
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Executive control resources (ECRs)

- Brain based resources that enable us to control
  - **Emotions** (e.g., reflexive “default” responses… surprise, anger, fear … even glee).
  - **Cognitions** (e.g., thoughts, images)
  - **Behaviors** (e.g., acts of omission, acts of comission)

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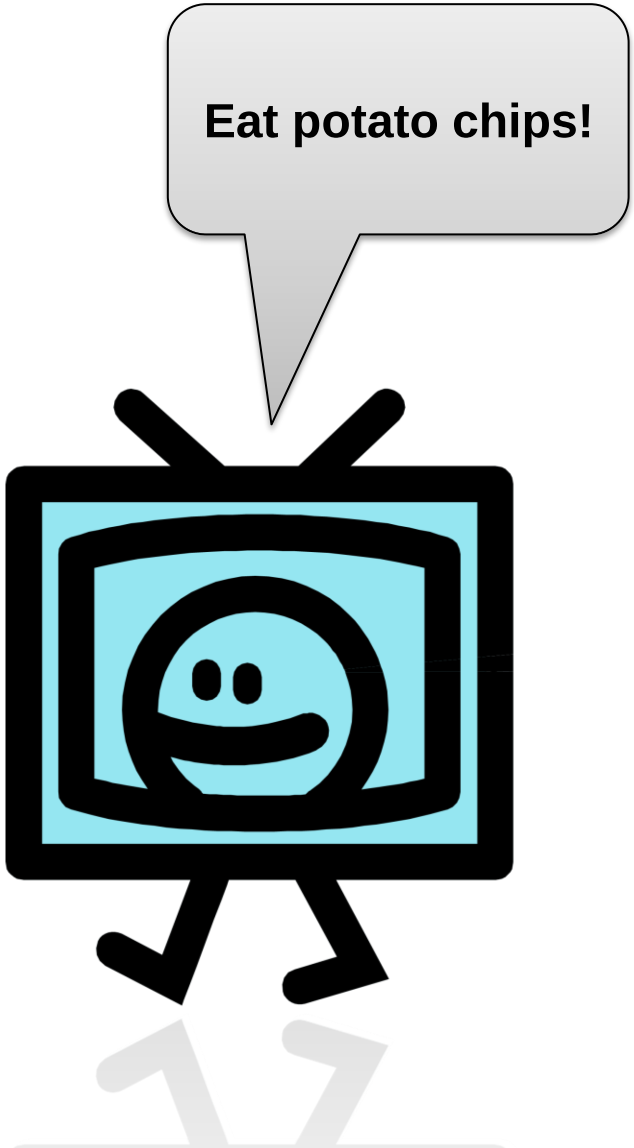
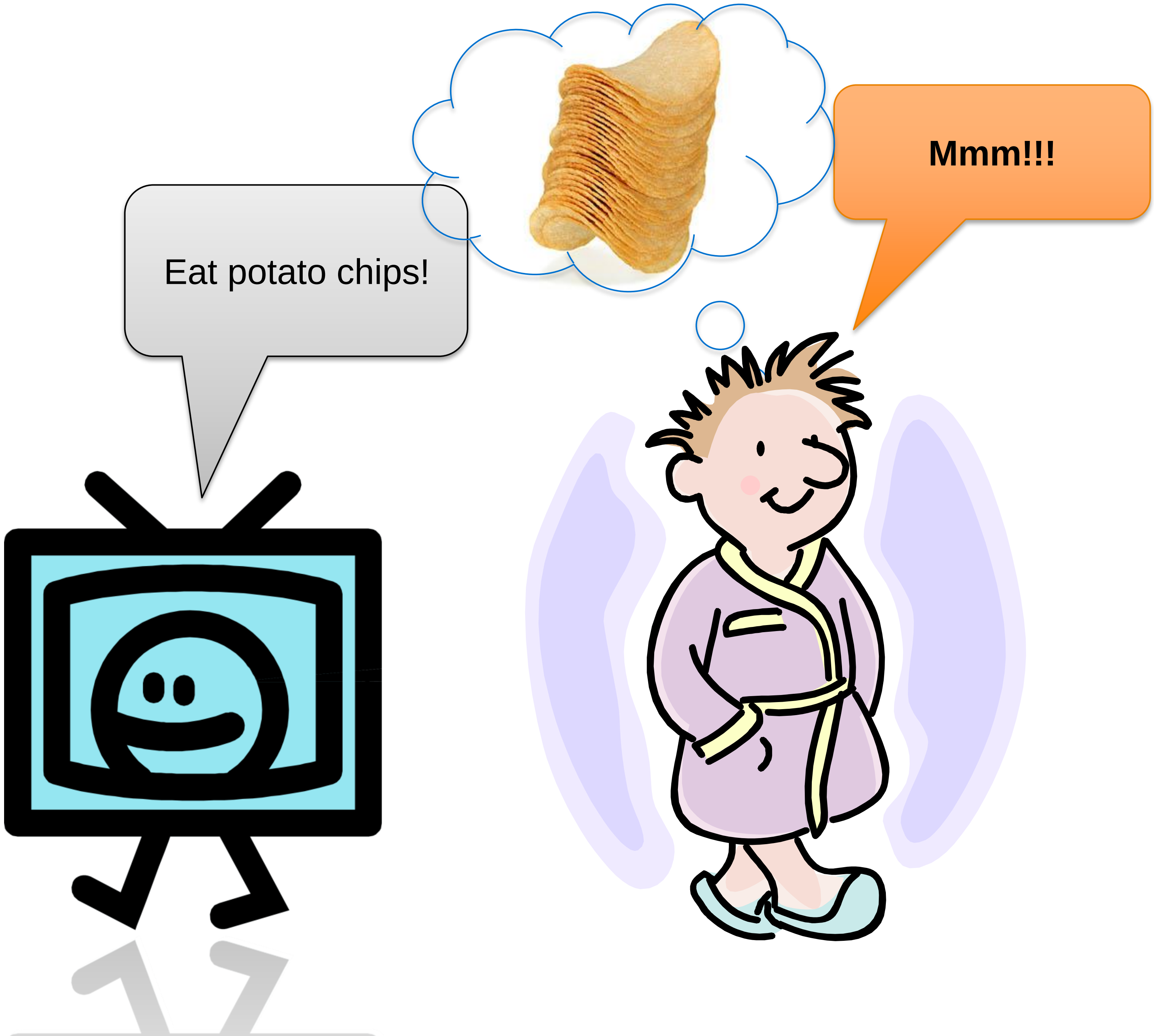
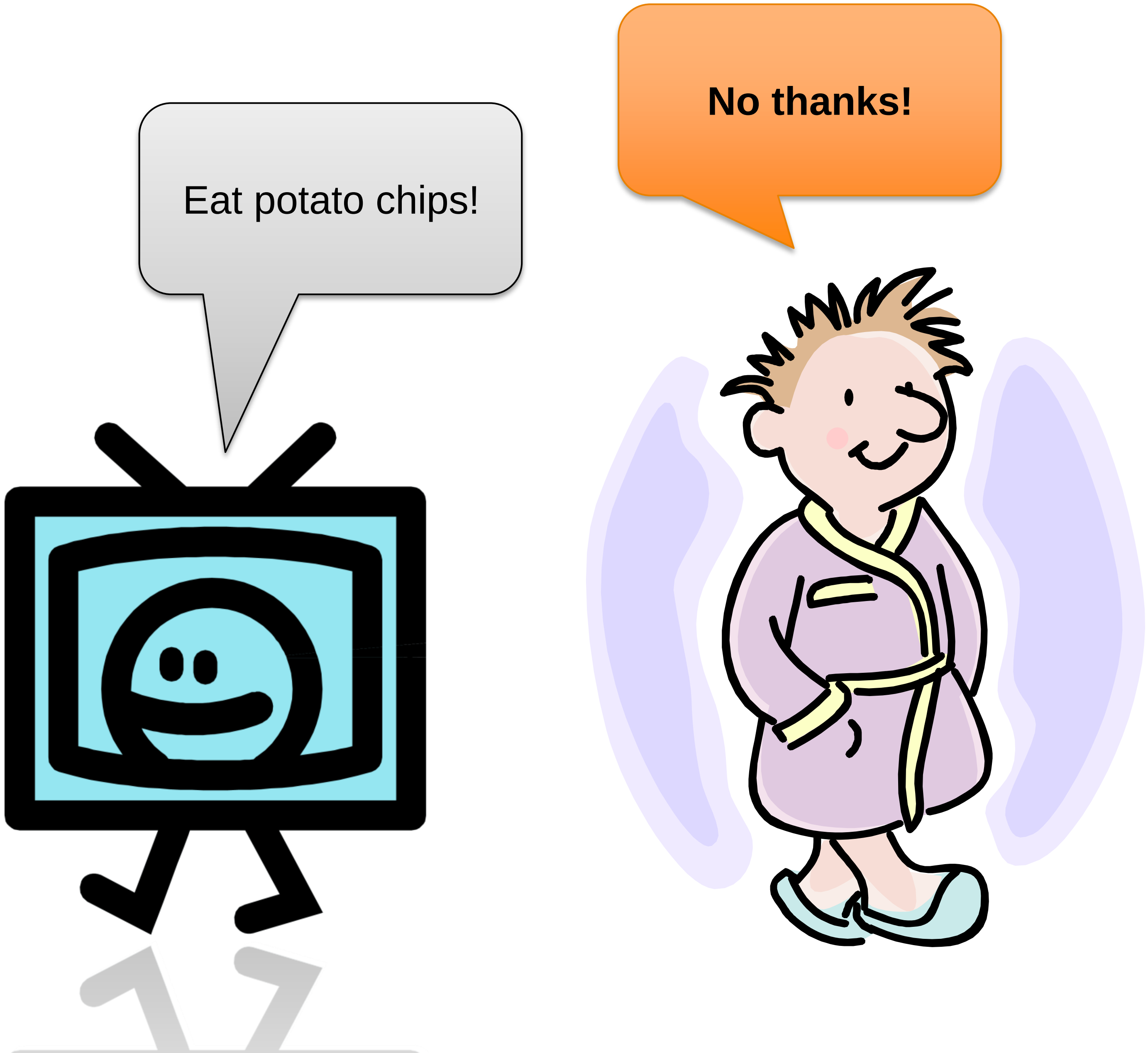

Eat potato chips!

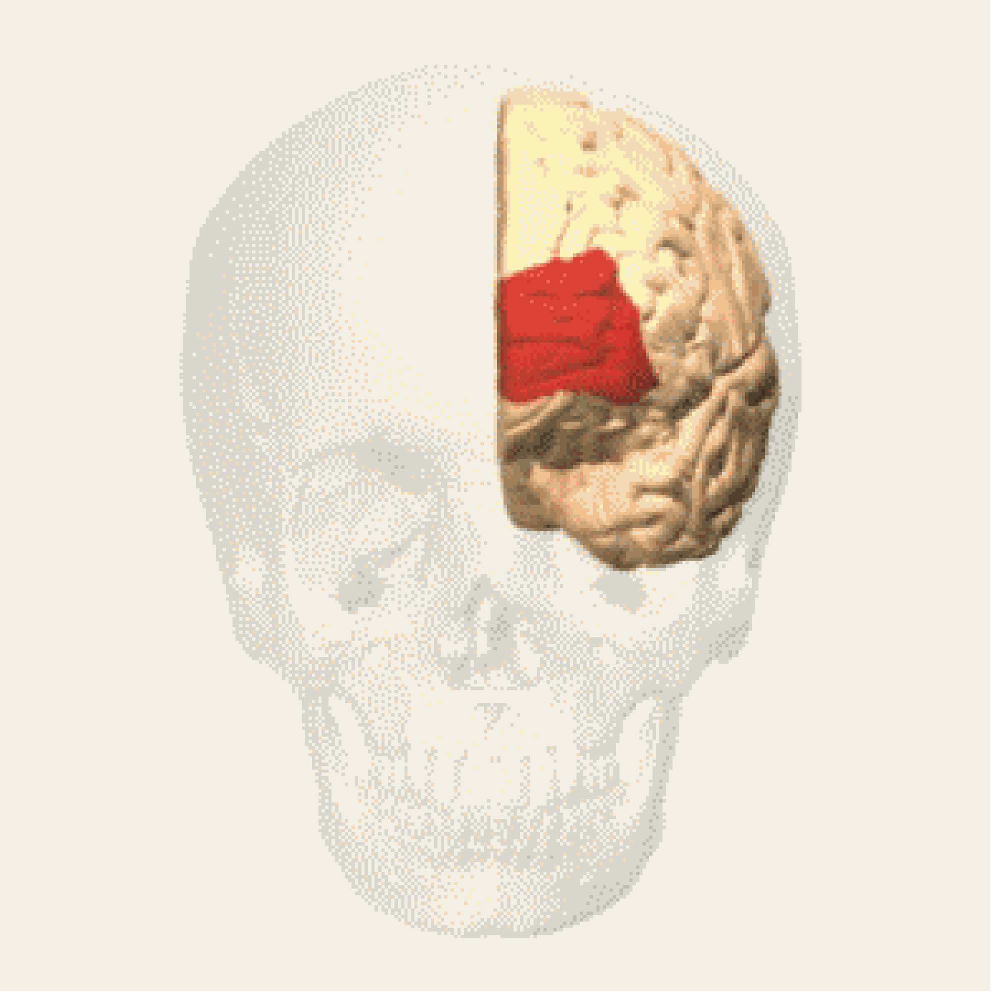

Eat potato chips!
Mmm!!!


Eat potato chips!
No thanks!

What is the "seat" of cognitive control?

- No <u>single</u> structure; only networks of neurons, which connect to other centres/structures.
- But there exist important <u>nodes</u> in these neural networks.
- One very central node is the <u>prefrontal cortex</u>.

Prefrontal cortex (PFC)



How do we measure the operation of the PFC?

- Neuroimaging paradigms (fMRI and EEG)
  - Suitable for small samples … 10-30 participants.

- Reaction time paradigms (Stroop, Go-Nogo)
  - Suitable for larger samples … 100-300.

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ECRs → dietary behavior?

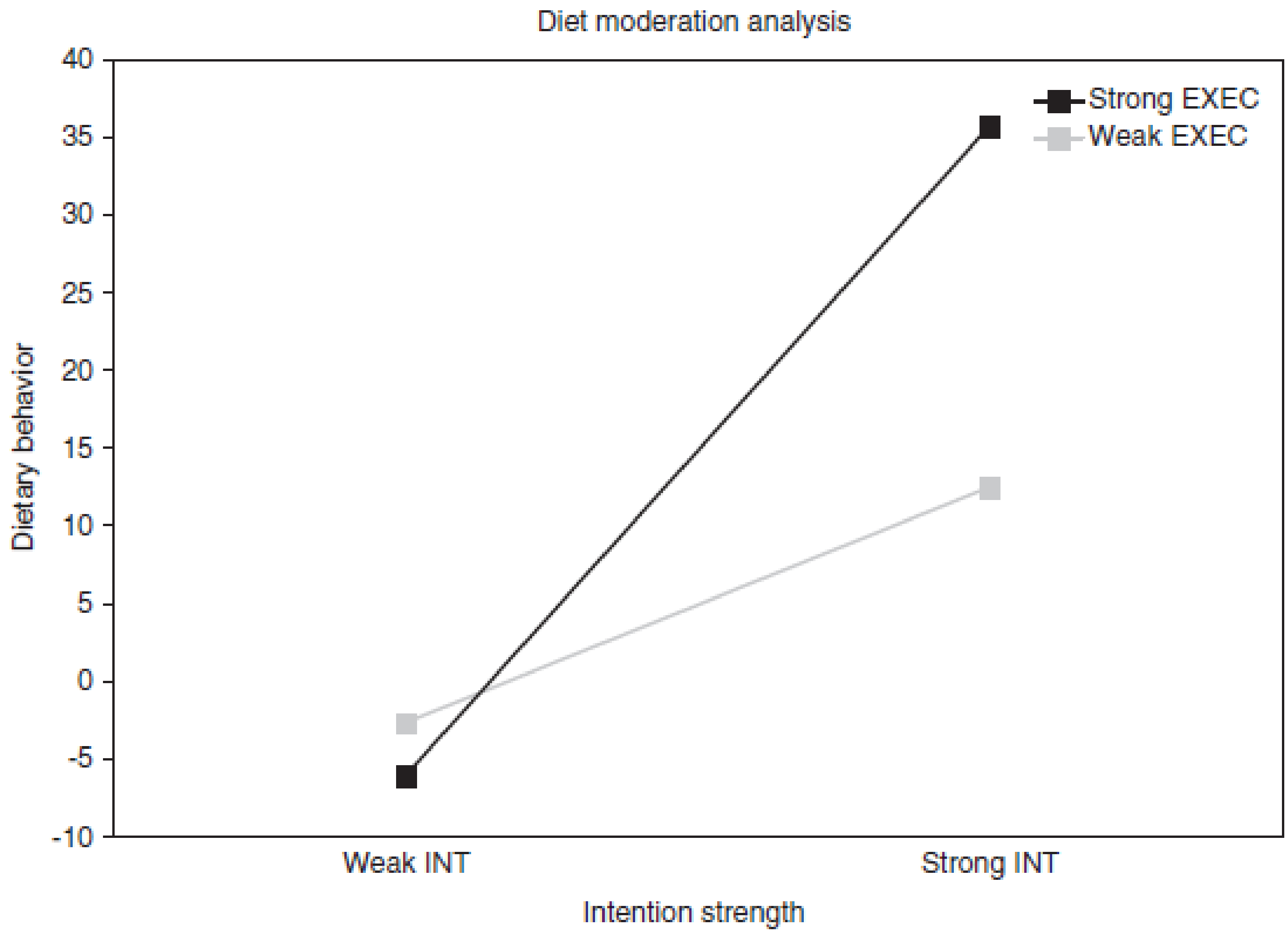
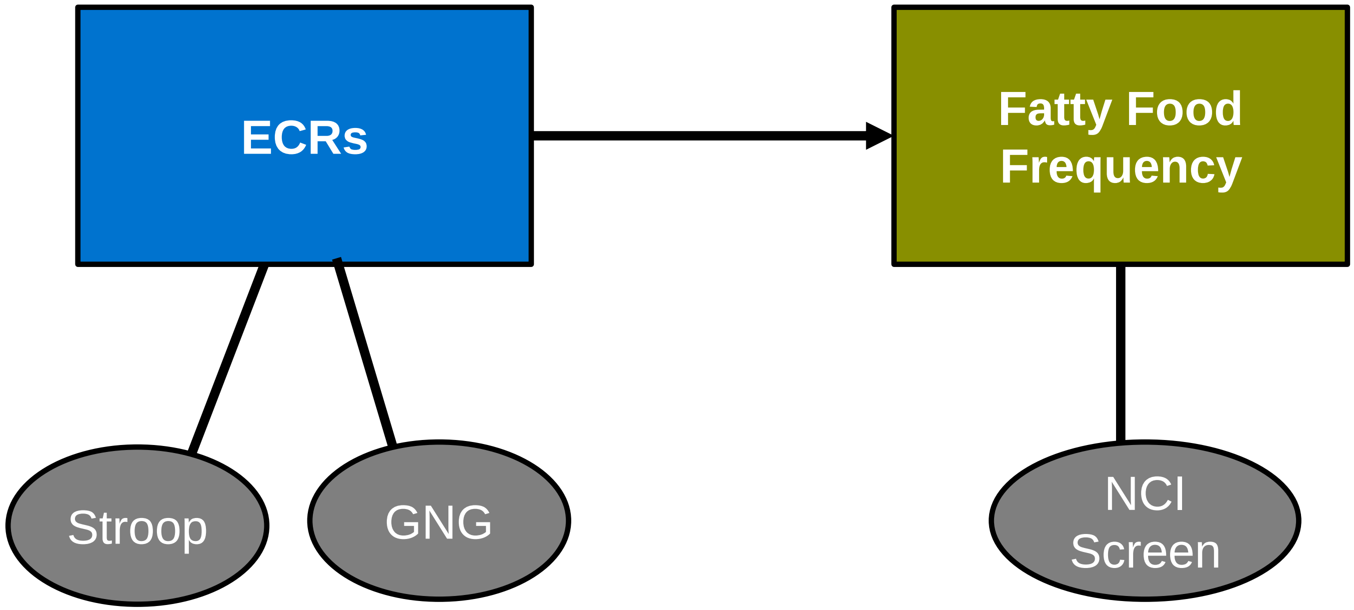


Figure 2. The relation between behavioral intention and healthy dietary choice for high and low executive function participants.

Hall, Epp, Elias et al. (2008)

Do ECRs predict consumption of high calorie foods?



Covariates:

Age
Sex
SES
BMI
IQ

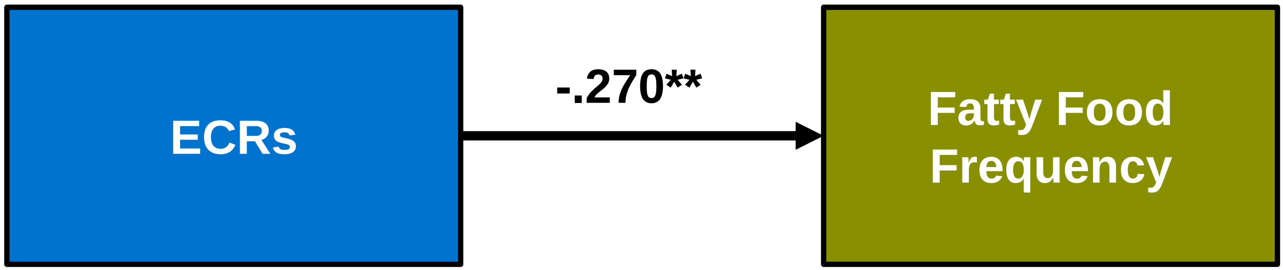
Hall (2012)

Hall (2012)

Covariates:

Age
Sex
SES

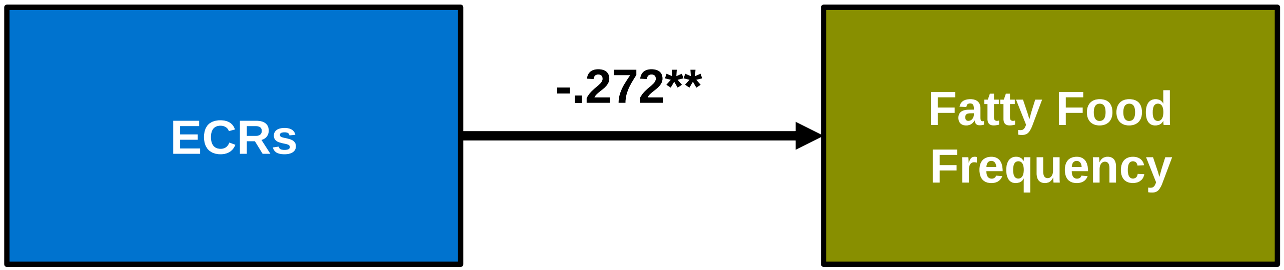
Hall (2012)



Covariates:

Age
Sex
SES
BMI

Hall (2012)

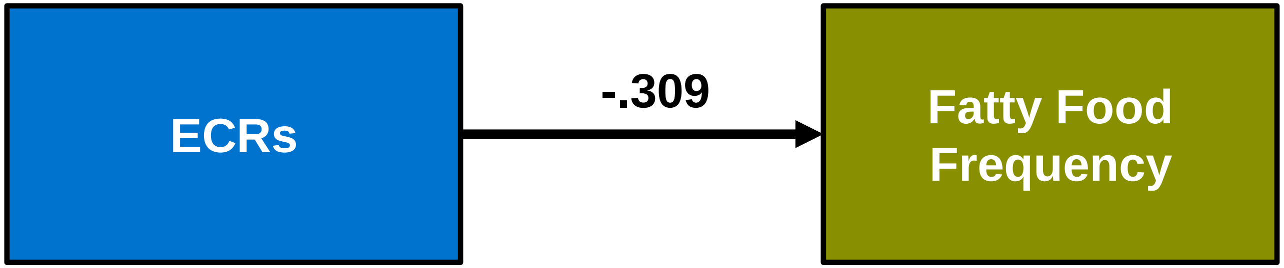


Covariates:

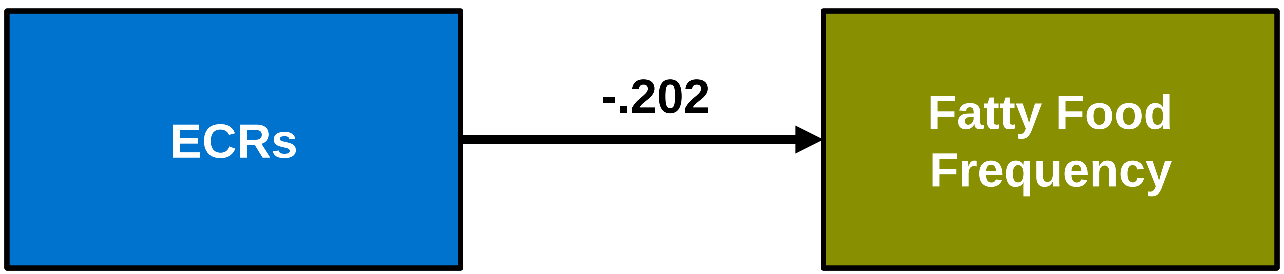
Age
Sex
SES
BMI
IQ

Hall (2012)

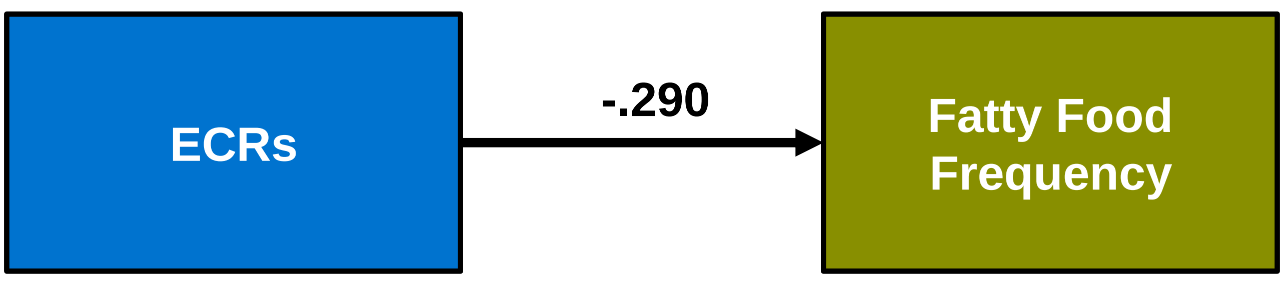
Younger (18-45)



Middle (18-45)



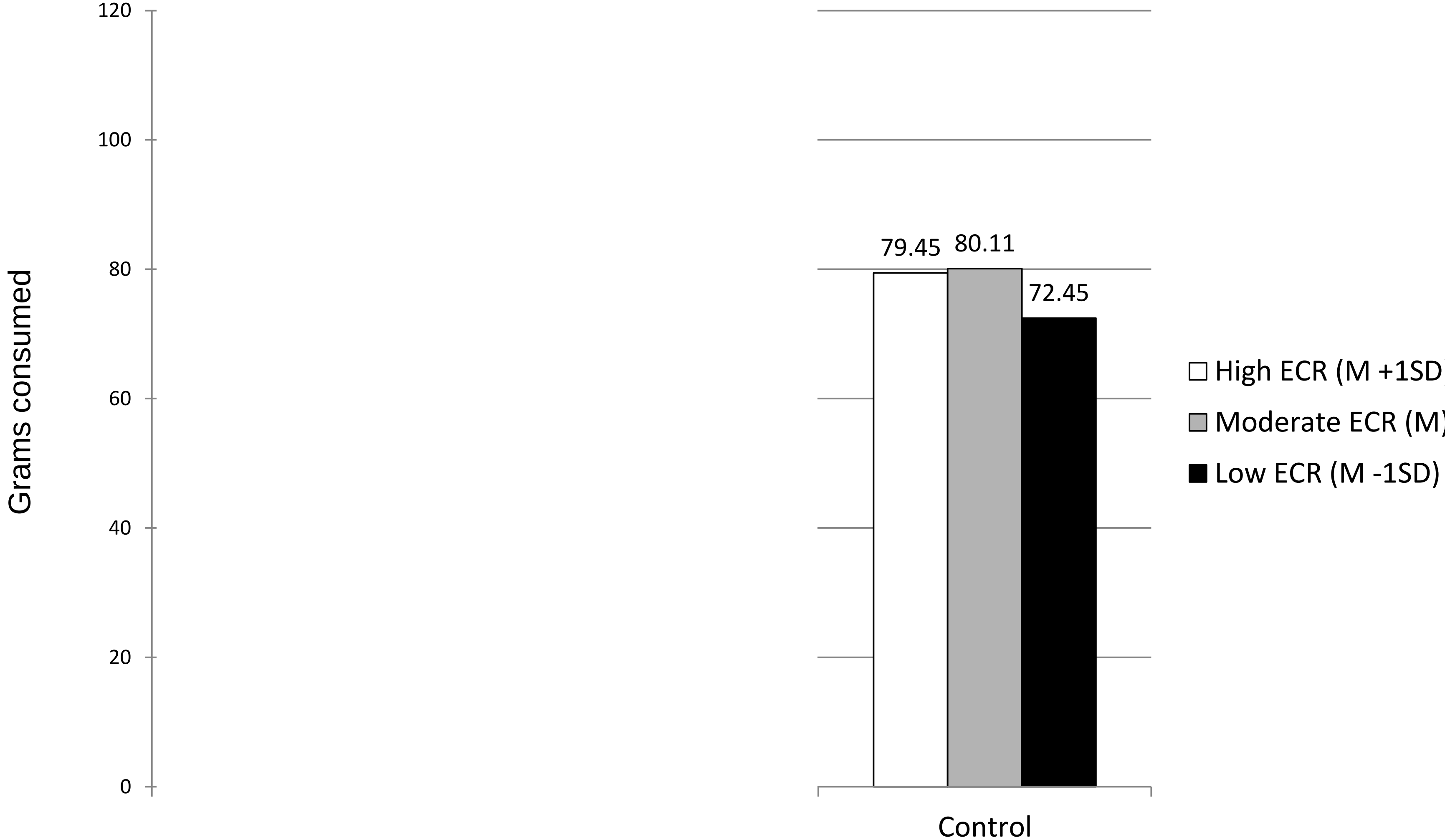
Younger Adults (18-45)



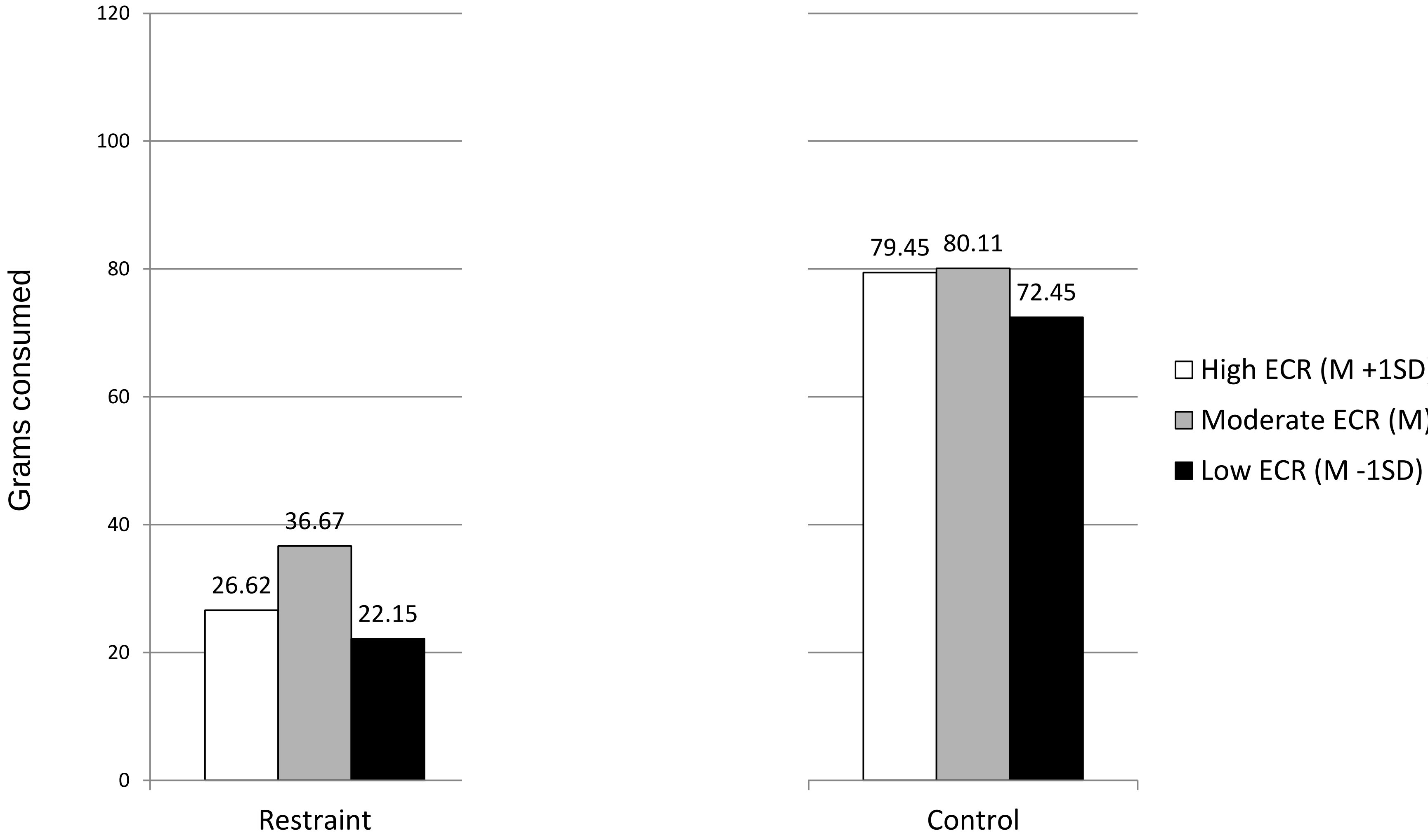
Hall (2012)

Under what circumstances?

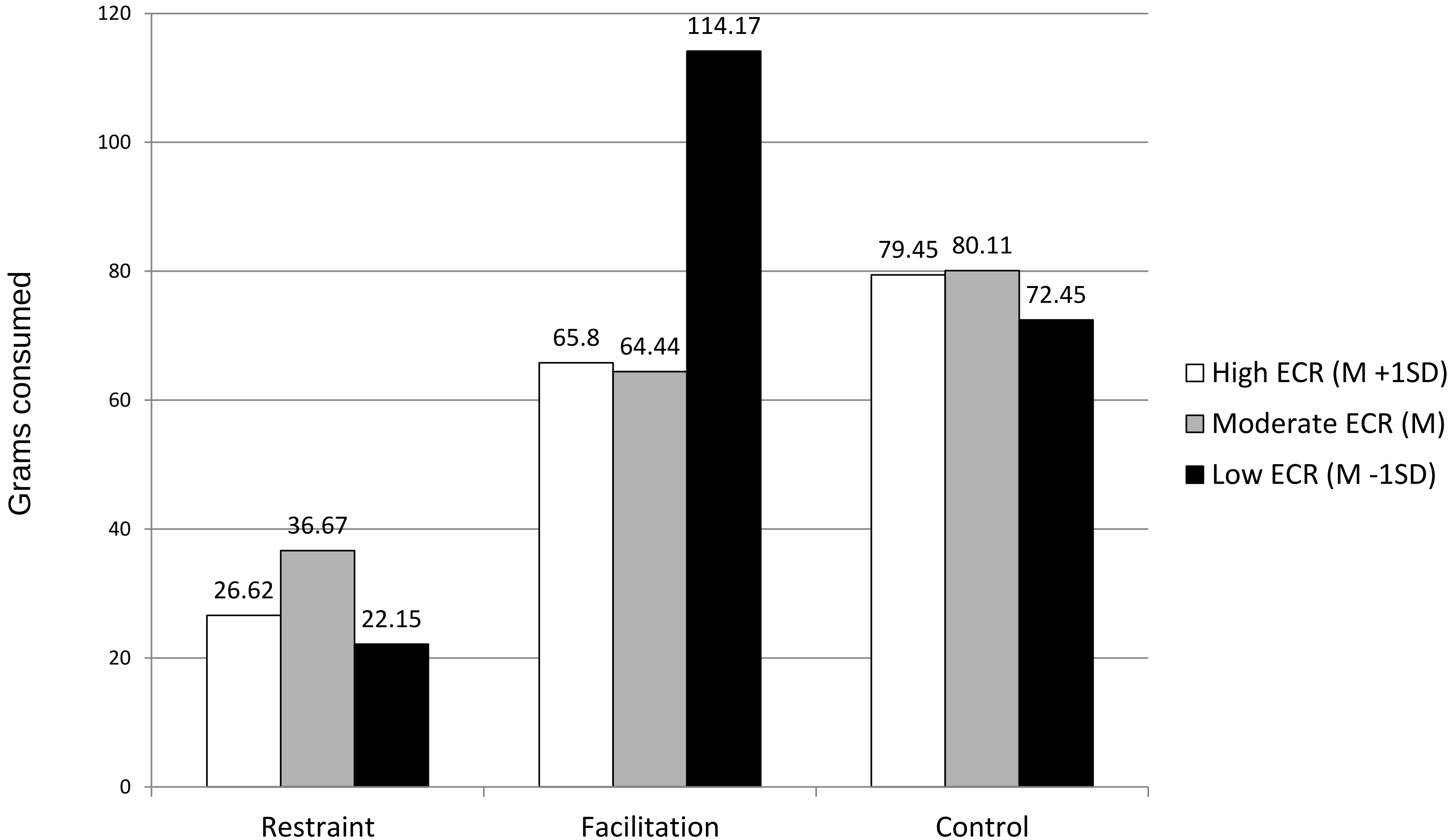
- Restraint
- Facilitation
- Neutral



Hall, Lowe & Vincent (2013)

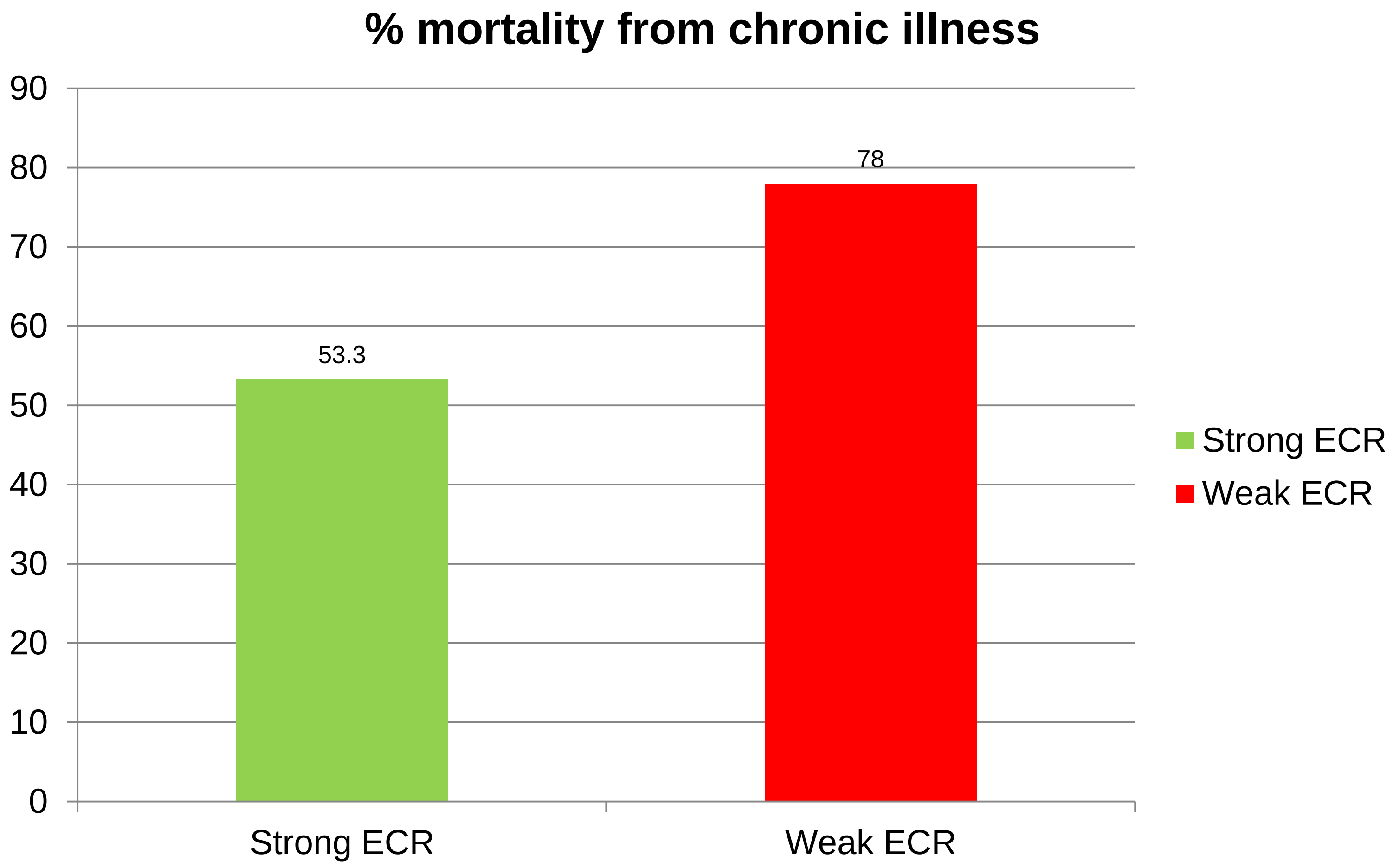


Hall, Lowe & Vincent (2013)

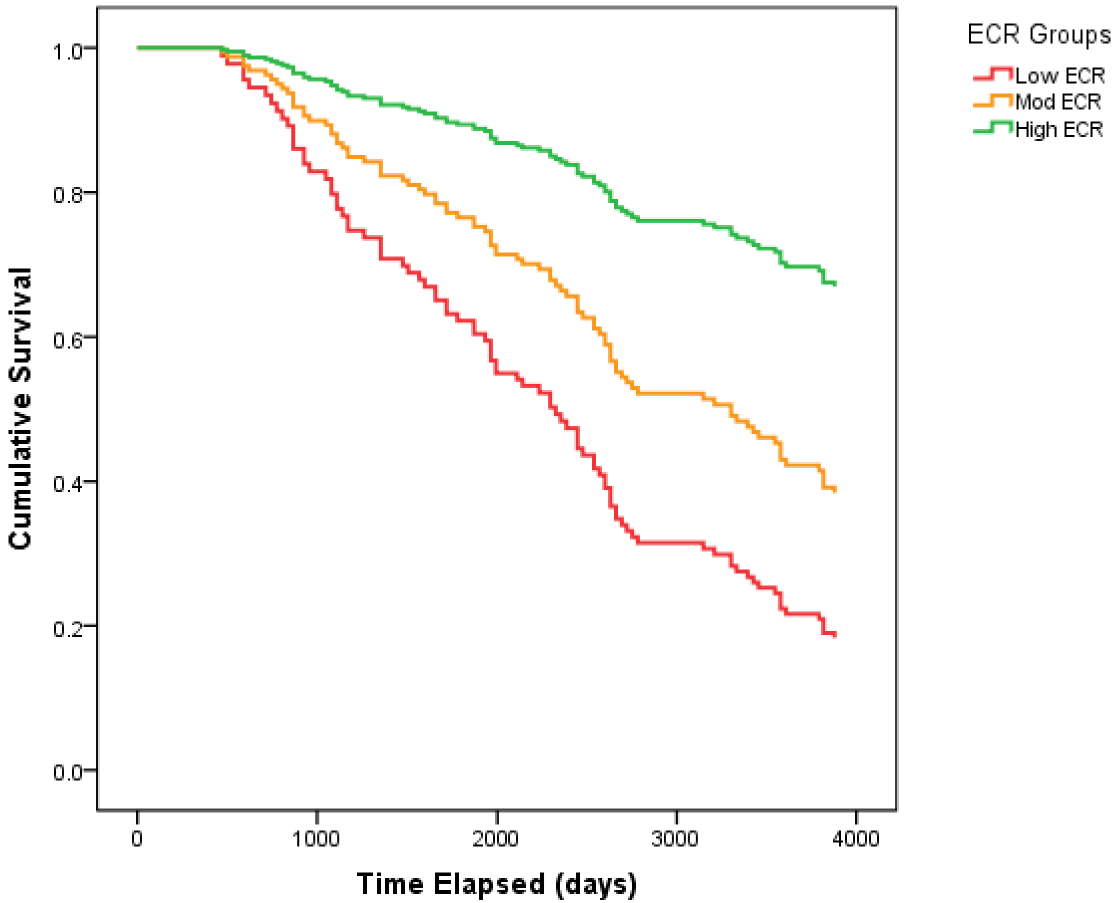


Hall, Lowe & Vincent (2013)

ECRs → other health outcomes?



Hall, Dubin, Holmqvist, Crossley & D'Arcy (2009)



Hall, Crossley & D’Arcy (2010)

Does aging influence ECRs?

- Generally speaking, the brain is no different from other organs in your body.

- As we age, it functions not quite as well!

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Aging and the Human Brain

- However, some functions are affected more than others. Those first to show signs of age are:
  - Memory
  - Executive function

    !!!

How can we bolster ECRs?

Two Types of Exercise:

1. **Aerobic exercise**: builds endurance, continuous, gets your heart beating.
   - Brisk walking, running, cycling.

2. **Resistance exercise**: builds muscle mass, intermittent.
   - Weights, exercise bands.

Aerobic

Resistance

Can Exercise help offset the effects of aging?

Some evidence

Cardiovascular fitness, cortical plasticity, and aging

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*The Beckman Institute, †Neuroscience Program, and Departments of §Psychology, ¶Kinesiology, and ‖Electrical and Chemical Engineering, University of Illinois at Urbana–Champaign, Urbana, IL 61801

Communicated by William T. Greenough, University of Illinois at Urbana–Champaign, Urbana, IL, January 13, 2004 (received for review June 6, 2003)

Cardiovascular fitness is thought to offset declines in cognitive performance, but little is known about the cortical mechanisms that underlie these changes in humans. Research using animal models shows that aerobic training increases cortical capillary supplies, the number of synaptic connections, and the development of new neurons. The end result is a brain that is more efficient, plastic, and adaptive, which translates into better performance in aging animals. Here, in two separate experiments, we demonstrate for the first time to our knowledge, in humans that increases in cardiovascular fitness results in increased functioning of key aspects of the attentional network of the brain during a cognitively challenging task. Specifically, highly fit (Study 1) or aerobically trained (Study 2) persons show greater task-related activity in regions of the prefrontal and parietal cortices that are involved in spatial selection and inhibitory functioning, when compared with low-fit (Study 1) or nonaerobic control (Study 2) participants. Additionally, in both studies there exist groupwise differences in activation of the anterior cingulate cortex, which is thought to monitor for conflict in the attentional system, and signal the need for adaptation in the attentional network. These data suggest that increased cardiovascular fitness can affect improvements in the plasticity of the aging human brain, and may serve to reduce both biological and cognitive senescence in humans.

Several approaches to maintaining or improving cognitive performance in older adults have shown promise. It has long been known that older experts in a variety of domains can maintain high levels of performance into their 70s (1, 2). Also, in some cases, older adults have been shown to benefit as much or more than young adults from formal training of different cognitive abilities (3, 4). However, with few exceptions (4), the beneficial effects of these interventions tend to be limited to the tasks used in training. For example, expertise in typing has little or no effect on one's ability to drive a car, and training in

Additionally, recent neuroanatomical evidence from human populations shows that the same benefits in brain health seen in aging animals may, in fact, extend to aging humans (13). In a cross-sectional study of humans ranging in age from 55 to 79 years, the estimated trajectory of age-related declines in cortical tissue density were significantly reduced as a function of cardiovascular fitness. Moreover, these effects were greatest in the frontal, prefrontal, and parietal cortices. These regions of cortex also show the greatest age-related declines in humans (14). Interestingly, these regions are also thought to support executive cognitive functions; these executive functions also show the greatest behavioral improvement with CFT in aging humans (6, 7).

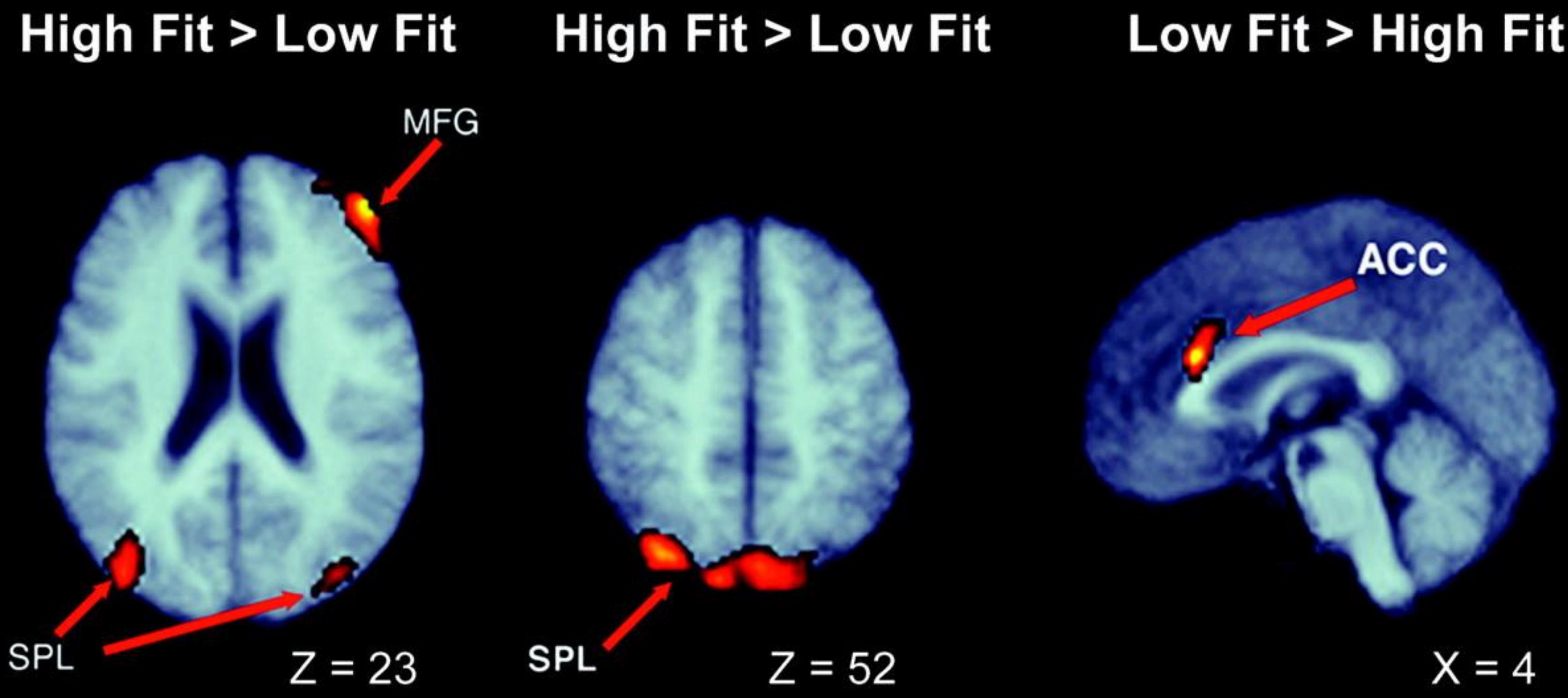
Data from animal models, human behavioral paradigms, and most recently, from human neuroanatomical models, all suggest that cardiovascular fitness should positively affect cortical functioning in aging humans. More specifically, increases in cardiovascular fitness should provide the neural substrates of the aging brain with a degree of flexibility and plasticity that is not present in less-fit counterparts.

The task we chose to address this issue was a modified version of the Ericksen flanker paradigm (ref. 15 and Fig. 1). To make a correct response in the incongruent trials, participants were required to inhibit or filter misleading information provided by incongruent flanking cues. Our primary interest in this study was in the cortical circuitry invoked when generating a response in the incongruent condition, when the misleading flankers must be filtered to make a response, compared with the congruent condition, in which no such filtering is required.

Neuroimaging results in similar tasks have identified several regions involved in selective attention and the resolution of response competition engendered by conflicting response cues. Although a full discussion of this literature is beyond the scope of this paper, it is important to note that regions of the frontal and parietal cortices, particularly the middle frontal gyrus

Study 1 Findings

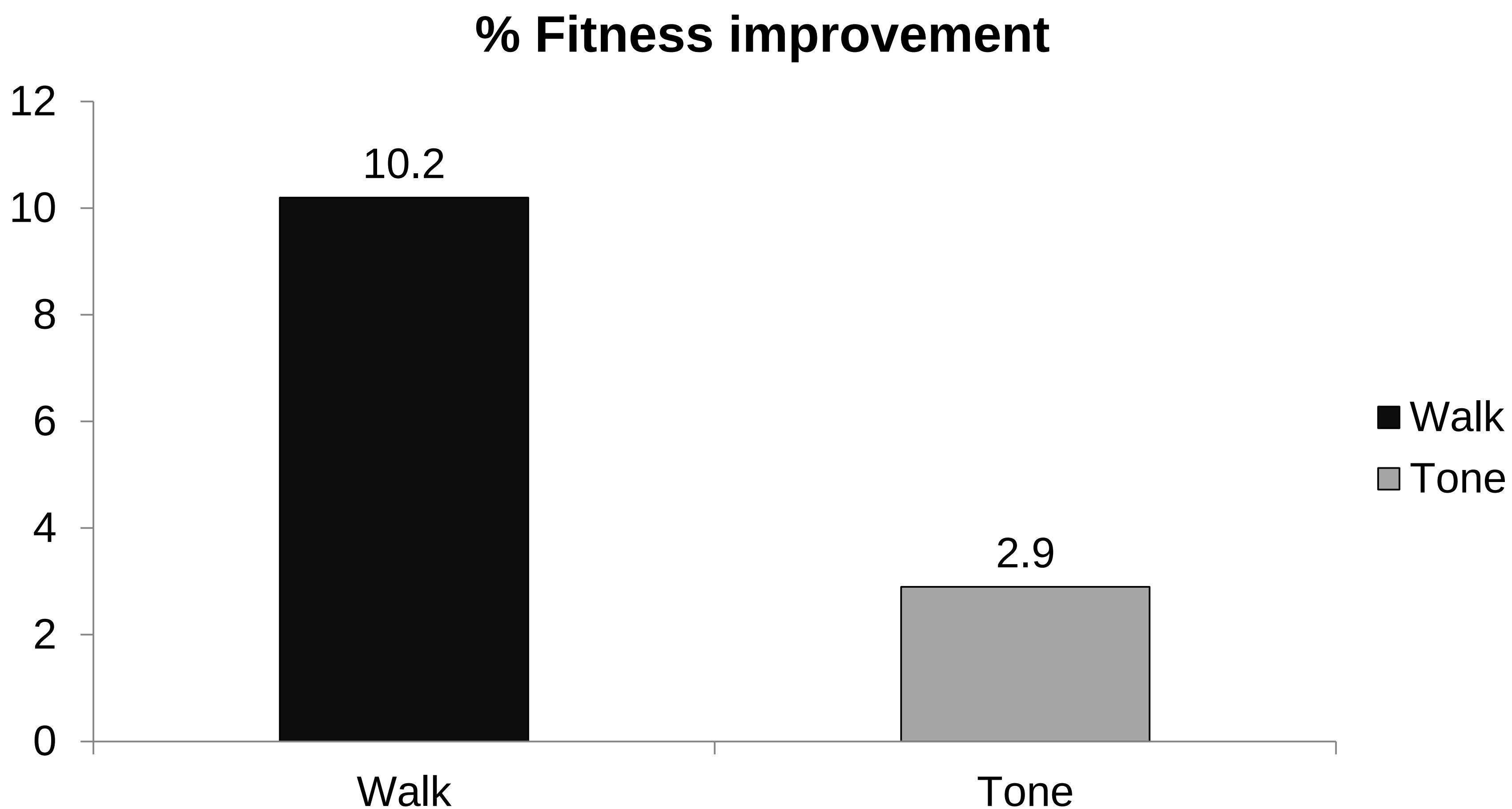
- Those in the Hi Fit group performed significantly better than Lo Fit group.


High Fit > Low Fit
MFG
SPL
Z = 23
High Fit > Low Fit
SPL
Z = 52
Low Fit > High Fit
ACC
X = 4

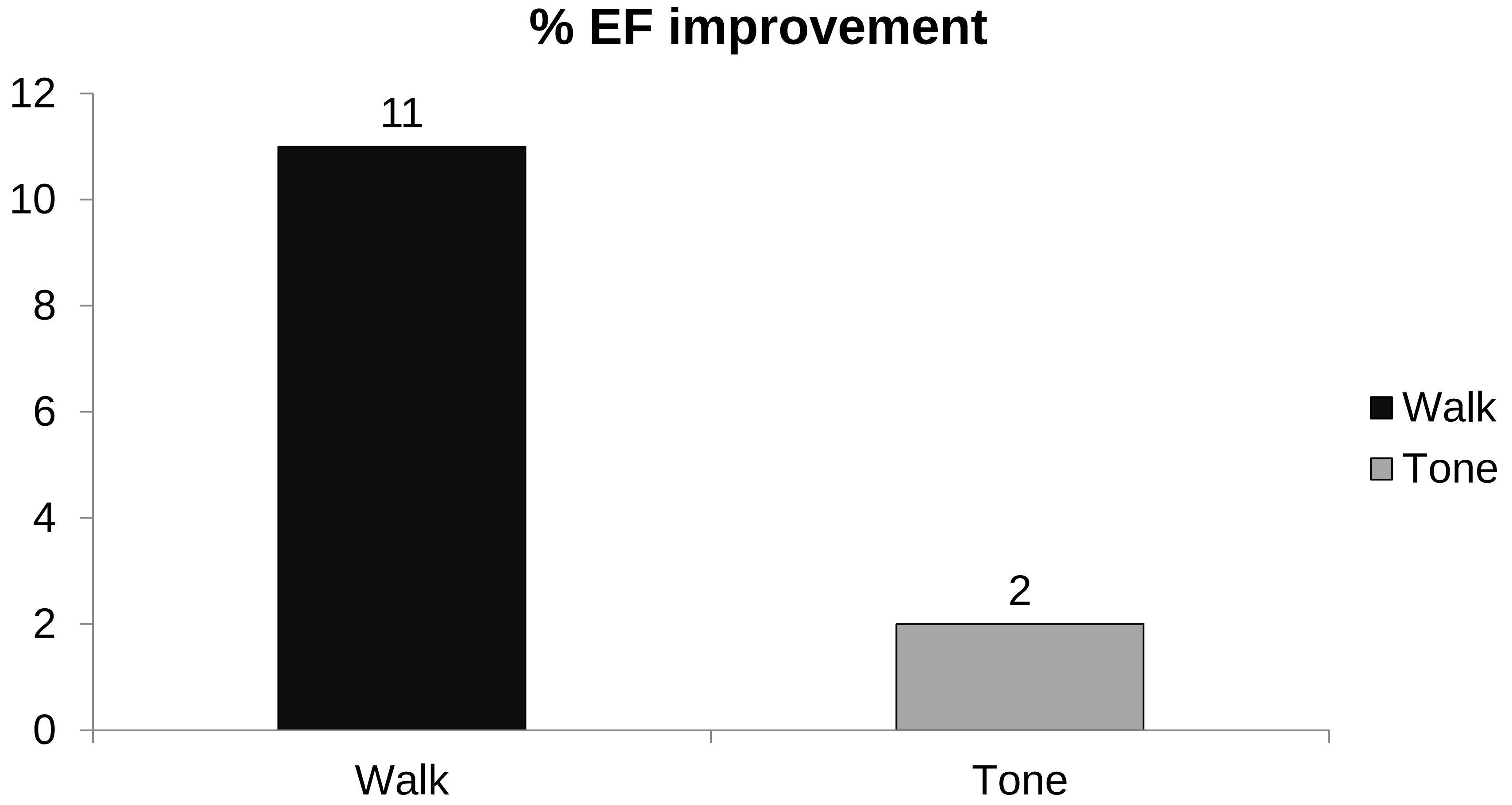
Two Studies (cont'd)

Study 2:

- Experimental design (RCT)
- Randomly assigned older adults to two groups:
  - Aerobic (walking)—6 mo.
  - Anaerobic exercise (toning)—6 mo.
- Assessed EF and brain activity.



% Fitness improvement
12
10
8
6
4
2
0
10.2
2.9
Walk
Tone
Walk
Tone



% EF improvement
12
10
8
6
4
2
0
11
2
Walk
Tone
Walk
Tone

Exercise training increases size of hippocampus and improves memory

Kirk I. Erickson[a], Michelle W. Voss[b,c], Ruchika Shaurya Prakash[d], Chandramallika Basak[e], Amanda Szabo[f], Laura Chaddock[b,c], Jennifer S. Kim[b], Susie Heo[b,c], Heloisa Alves[b,c], Siobhan M. White[f], Thomas R. Wojcicki[f], Emily Mailey[f], Victoria J. Vieira[f], Stephen A. Martin[f], Brandt D. Pence[f], Jeffrey A. Woods[f], Edward McAuley[b,f], and Arthur F. Kramer[b,c,1]

[a]Department of Psychology, University of Pittsburgh, Pittsburgh, PA 15260; [b]Beckman Institute for Advanced Science and Technology, and [f]Department of Kinesiology and Community Health, University of Illinois, Champaign-Urbana, IL 61801; [c]Department of Psychology, University of Illinois, Champaign-Urbana, IL 61820; [d]Department of Psychology, Ohio State University, Columbus, OH 43210; and [e]Department of Psychology, Rice University, Houston, TX 77251

Edited* by Fred Gage, Salk Institute, San Diego, CA, and approved December 30, 2010 (received for review October 23, 2010)

The hippocampus shrinks in late adulthood, leading to impaired memory and increased risk for dementia. Hippocampal and medial temporal lobe volumes are larger in higher-fit adults, and physical activity training increases hippocampal perfusion, but the extent to which aerobic exercise training can modify hippocampal volume in late adulthood remains unknown. Here we show, in a randomized controlled trial with 120 older adults, that aerobic exercise training increases the size of the anterior hippocampus, leading to improvements in spatial memory. Exercise training increased hippocampal volume by 2%, effectively reversing age-related loss in volume by 1 to 2 y. We also demonstrate that increased hippocampal volume is associated with greater serum levels of BDNF, a mediator of neurogenesis in the dentate gyrus. Hippocampal volume declined in the control group, but higher preintervention fitness partially attenuated the decline, suggesting that fitness protects against volume loss. Caudate nucleus and thalamus volumes were unaffected by the intervention. These theoretically important findings indicate that aerobic exercise training is effective at reversing hippocampal volume loss in late adulthood, which is accompanied by improved memory function.

aging | brain | cognition | plasticity | MRI

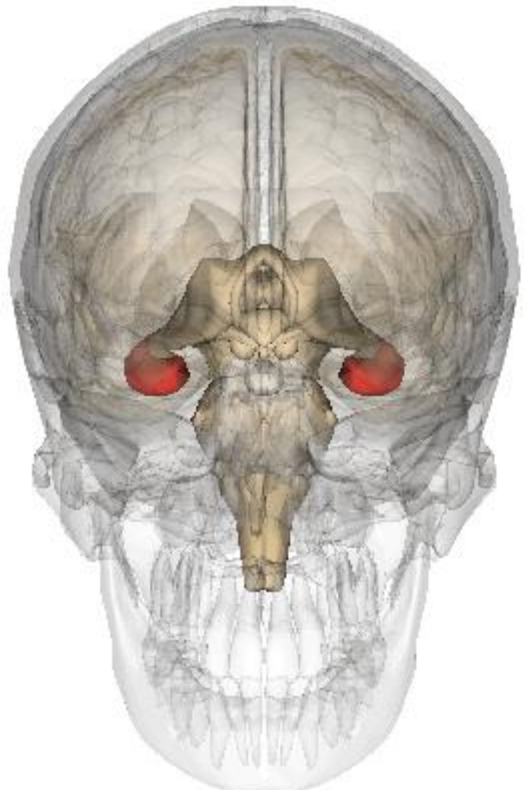
Deterioration of the hippocampus precedes and leads to memory impairment in late adulthood (1, 2). Strategies to fight hippocampal loss and protect against the development of memory impairment has become an important topic in recent years from both scientific and public health perspectives. Physical activity, such as aerobic exercise, has emerged as a promising low-

assigned to receive either moderate-intensity aerobic exercise 3 d/wk or stretching and toning exercises that served as a control. We predicted that 1 y of moderate-intensity exercise would increase the size of the hippocampus and that change in hippocampal volume would be associated with increased serum BDNF and improved memory function.

Results

Aerobic Exercise Training Selectively Increases Hippocampal Volume. One hundred twenty older adults without dementia (Table 1) were randomly assigned to an aerobic exercise group ($n = 60$) or to a stretching control group ($n = 60$). Magnetic resonance images were collected before the intervention, after 6 mo, and again after the completion of the program. The groups did not differ at baseline in hippocampal volume or attendance rates (Table 2 and *SI Results*). We found that the exercise intervention was effective at increasing the size of the hippocampus. That is, the aerobic exercise group demonstrated an increase in volume of the left and right hippocampus by 2.12% and 1.97%, respectively, over the 1-y period, whereas the stretching control group displayed a 1.40% and 1.43% decline over this same interval (Fig. 1*A*). The moderating effect of aerobic exercise on hippocampal volume loss was confirmed by a significant Time × Group interaction for both the left [$F(2,114) = 8.25$; $P < 0.001$; $\eta_p^2 = 0.12$] and right [$F(2,114) = 10.41$; $P < 0.001$; $\eta_p^2 = 0.15$] hippocampus (see Table 2 for all means and SDs).

As can be seen in Fig. 2, we found that aerobic exercise selectively increased the volume of the anterior hippocampus that included the dentate gyrus, where cell proliferation occurs (4, 6, 8), as well as subiculum and CA1 subfields, but had a minimal effect



Background

Hippocampus is implicated in learning and memory. Along with executive function, these abilities decline with presence of Alzheimer's disease and with advancing age.

- Deterioration of memory performance in **Alzheimer's disease** is closely matched by deterioration in the hippocampus. The hippocampus and frontal lobes are the first affected.
- Even in normal aging, hippocampal volume steadily decreases (about **1-2%** of volume per year in older adulthood).
- This volume loss is thought to cause the **deterioration of memory skills** among older adults.

Question: Can we reverse the deterioration of the hippocampus? .. And can exercise help?

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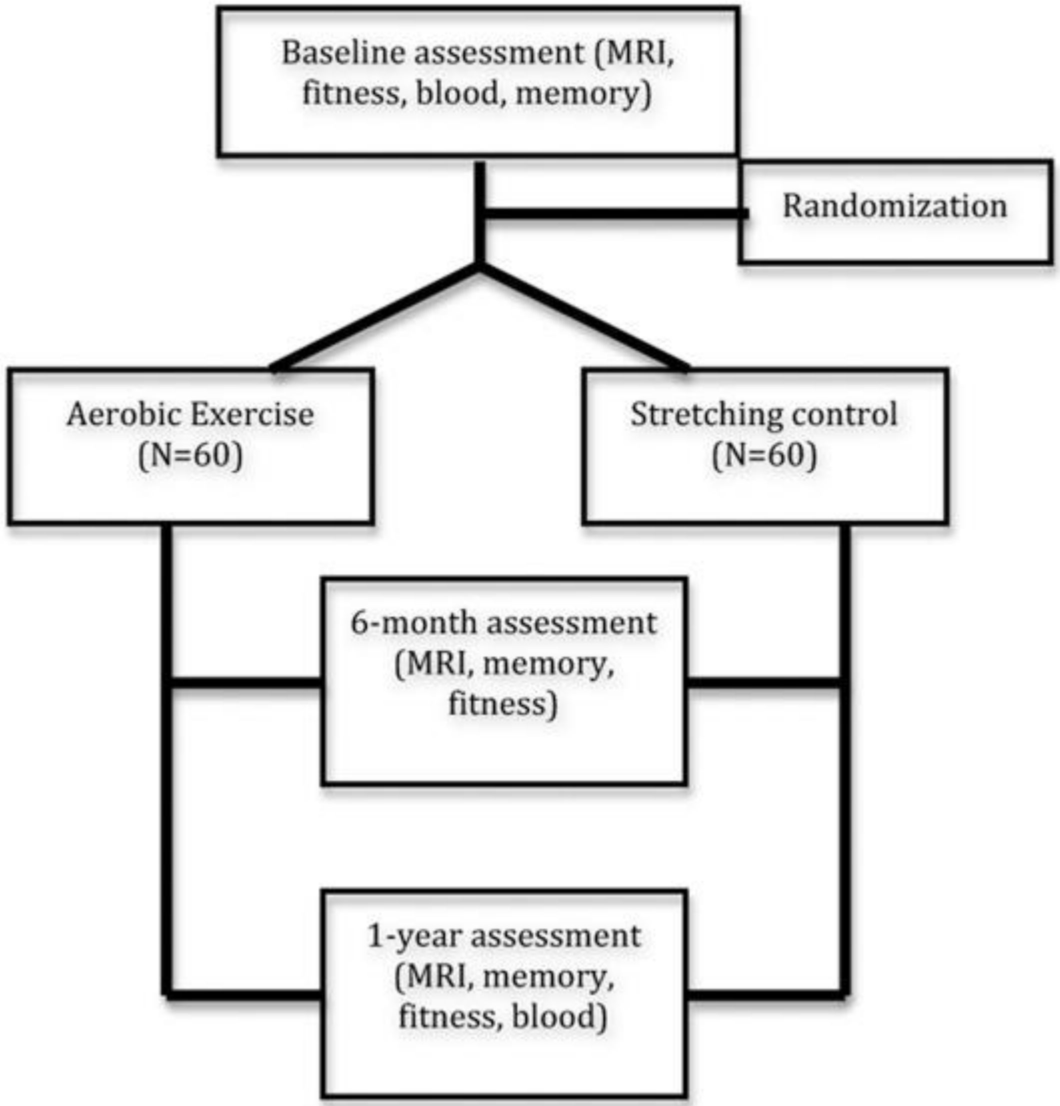
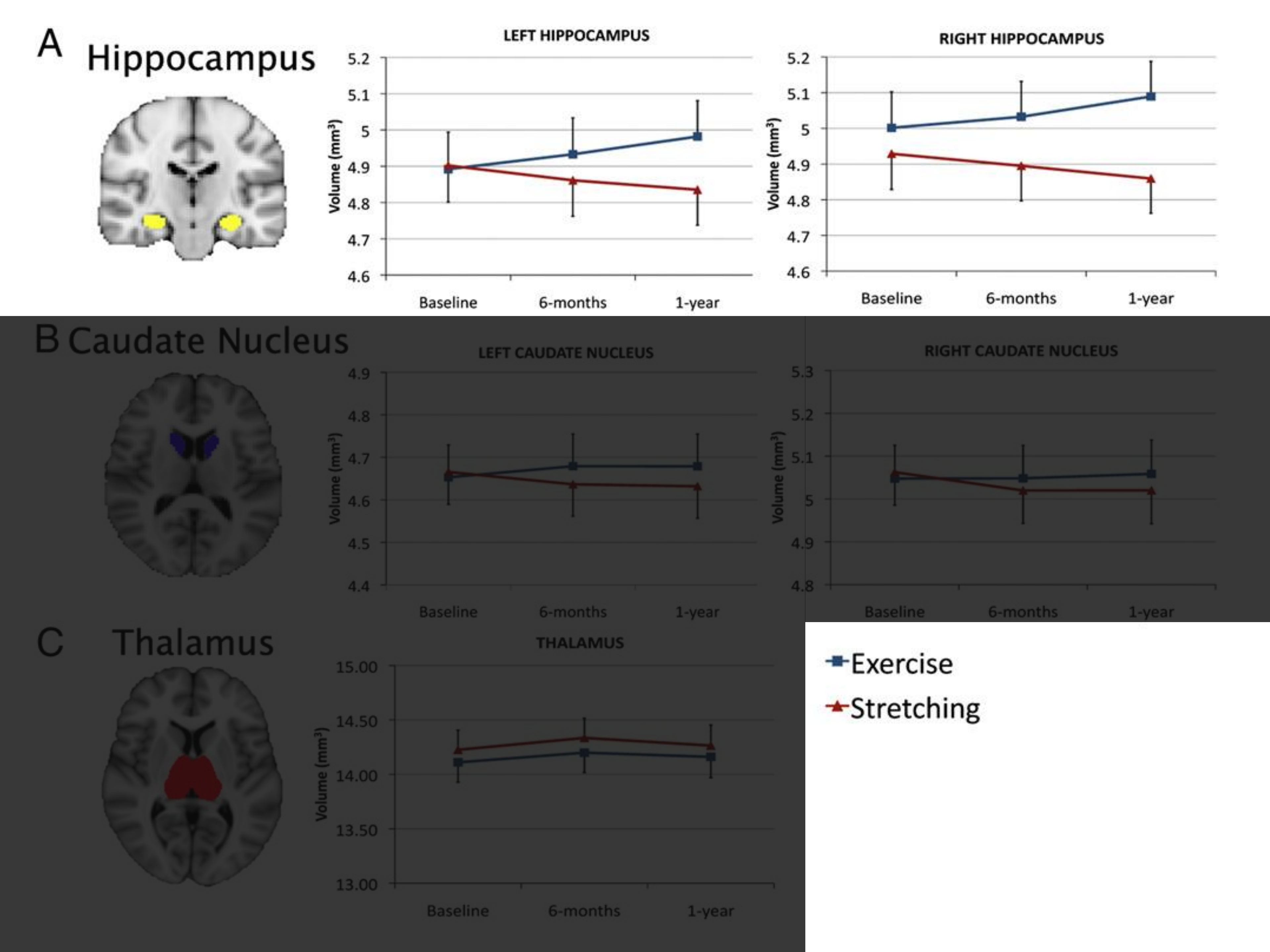
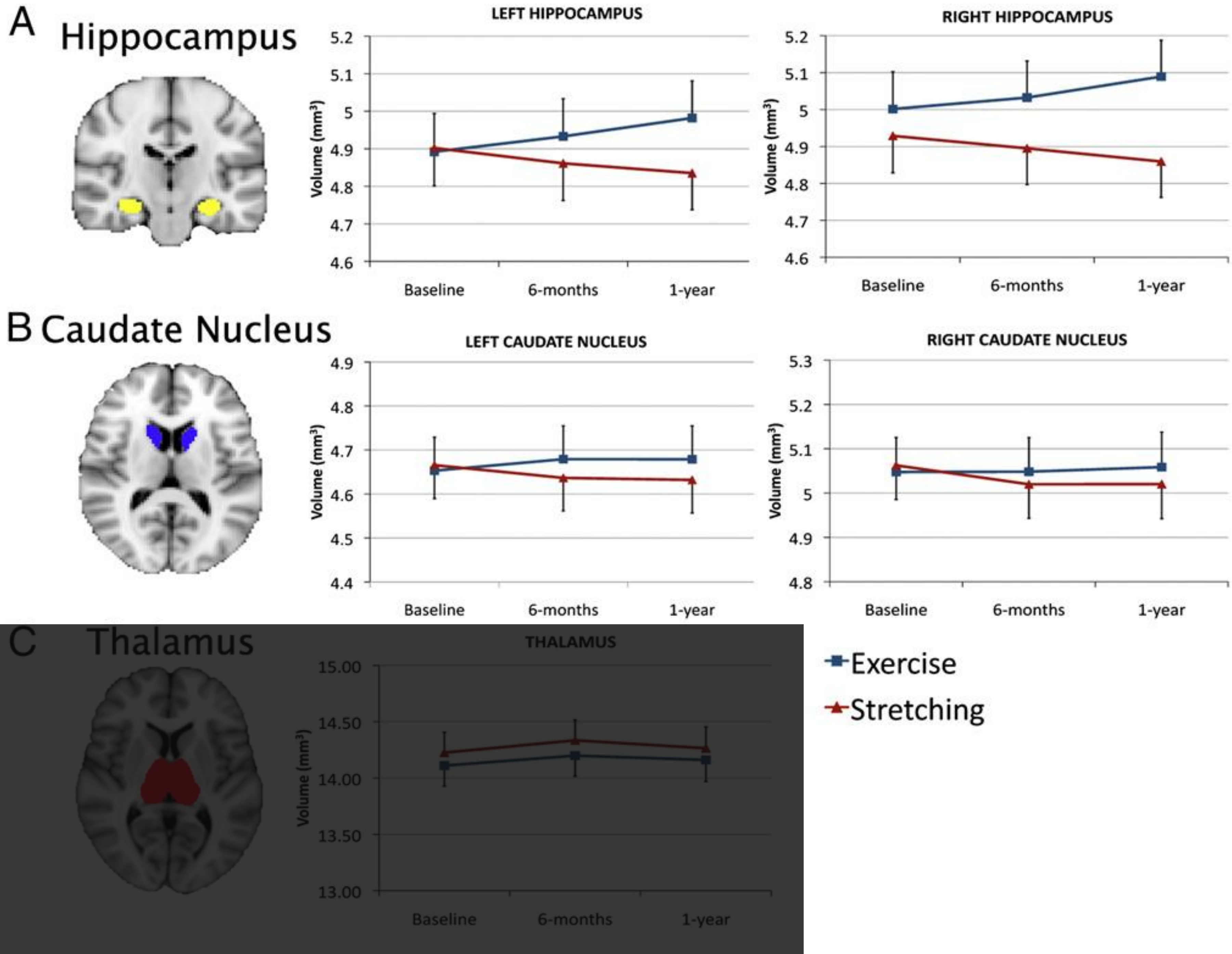
What did they do?

- Randomly assigned 120 older adults to:
  - Yes! You got it… Aerobic (walking) exercise—12 mo.
  - Anaerobic (toning) exercise—12 mo.
- Structural MRI scans completed at:
  - Pre-Tx
  - Mid point (6 mo)
  - Post-Tx (12 mo.)
- Assessed volume of the hippocampus (target area) plus two control regions.


Baseline assessment (MRI, fitness, blood, memory)
Randomization
Aerobic Exercise (N=60)
Stretching control (N=60)
6-month assessment (MRI, memory, fitness)
1-year assessment (MRI, memory, fitness, blood)



A Hippocampus
LEFT HIPPOCAMPUS
RIGHT HIPPOCAMPUS
Volume (mm³)
5.2
5.1
5
4.9
4.8
4.7
4.6
Baseline
6-months
1-year
B Caudate Nucleus
LEFT CAUDATE NUCLEUS
RIGHT CAUDATE NUCLEUS
4.9
4.8
4.7
4.6
4.5
4.4
5.3
5.2
5.1
5
4.9
4.8
C Thalamus
THALAMUS
15.00
14.50
14.00
13.50
13.00
Exercise
Stretching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C Thalamus
THALAMUS
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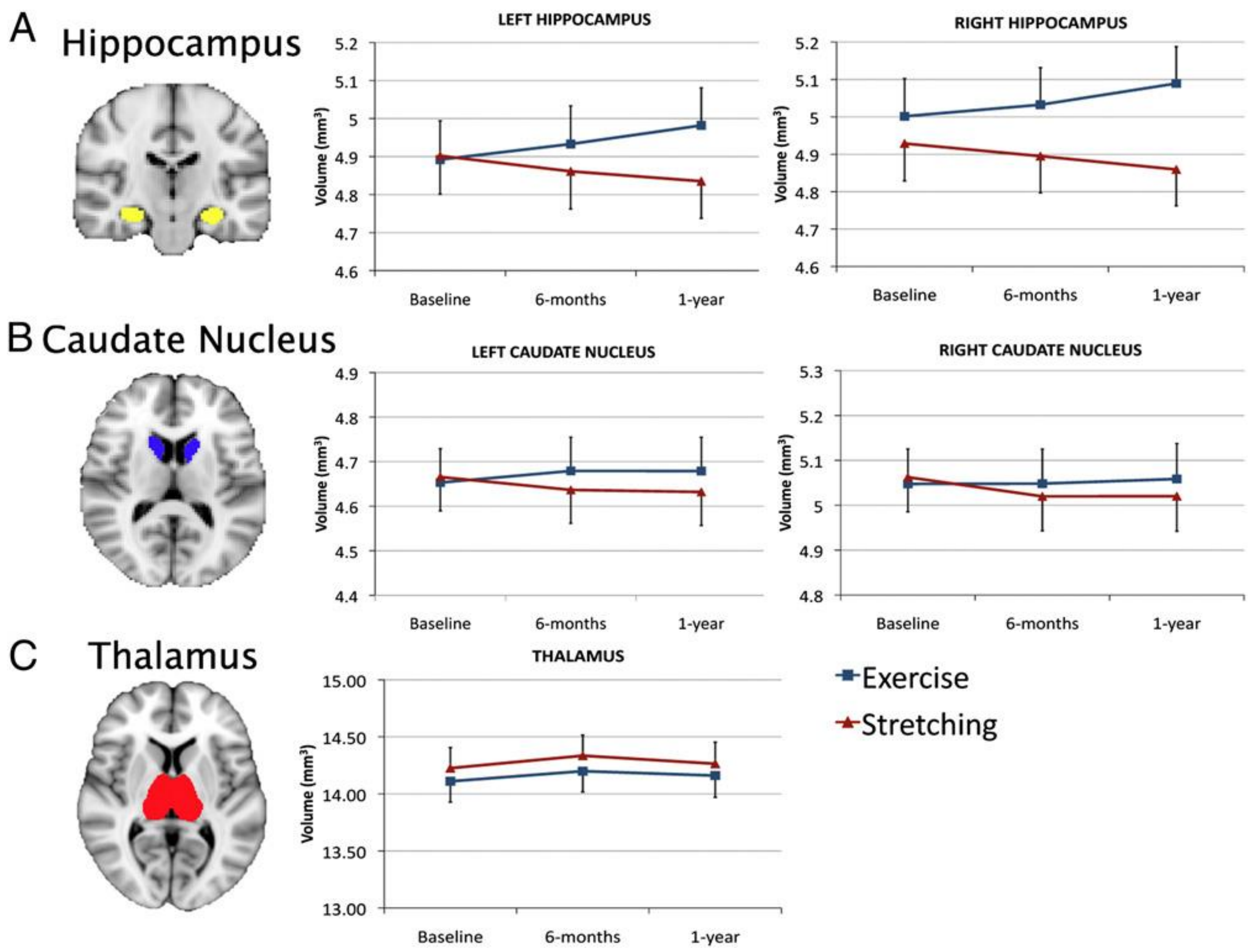
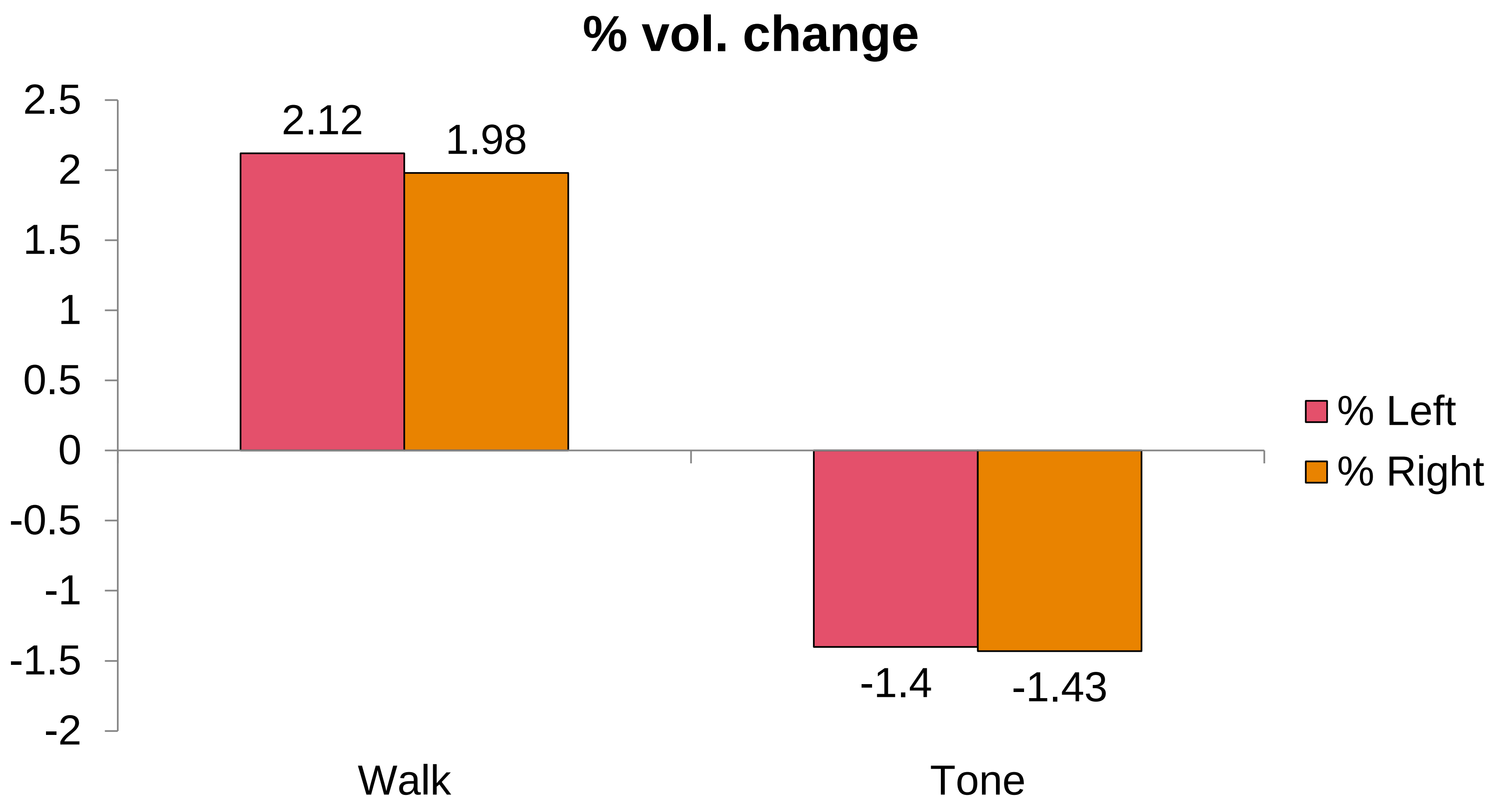
Exercise
Stretching



A Hippocampus
LEFT HIPPOCAMPUS
RIGHT HIPPOCAMPUS
Volume (mm³)
5.2
5.1
5
4.9
4.8
4.7
4.6
Baseline
6-months
1-year
B Caudate Nucleus
LEFT CAUDATE NUCLEUS
RIGHT CAUDATE NUCLEUS
4.9
4.8
4.7
4.6
4.5
4.4
5.3
5.2
5.1
5
4.9
4.8
C Thalamus
THALAMUS
15.00
14.50
14.00
13.50
13.00
Exercise
Stretching

1 yr Vol. Changes



THAT’S ABOUT THE SAME AS THE AVERAGE 1-2 YR LOSS!

Conclusions

- Exercise is good for your brain!
- It enhances two types of brain function that are crucial to diabetes management:
  - Executive function
  - Memory
- Including both aerobic and resistance training has the potential to help you live a better life, and also manage your condition.
- **There is still a lot left to learn**! We are conducting studies here at UW to find out more about the link between exercise and brain function in those living with diabetes.

What does this have to do with diabetes?

1. Some evidence that T2DM accelerates age related cognitive decline.

2. The cognitive functions most effected in T2DM are those associated with the PFC.

3. Executive functions are necessary for self-care behavior performance.

Want to help out?

- We are recruiting people with Type 1 and 2 diabetes for exercise studies at the University of Waterloo!

- We need people who currently exercise AND those who do not currently exercise.

- On your table you will find a card that you may fill out to provide your contact info.
  - If you want to be contacted to participate, pls fill out and return before you leave tonight.

UPCOMING INTERVENTION TRIAL:

DETEC trial

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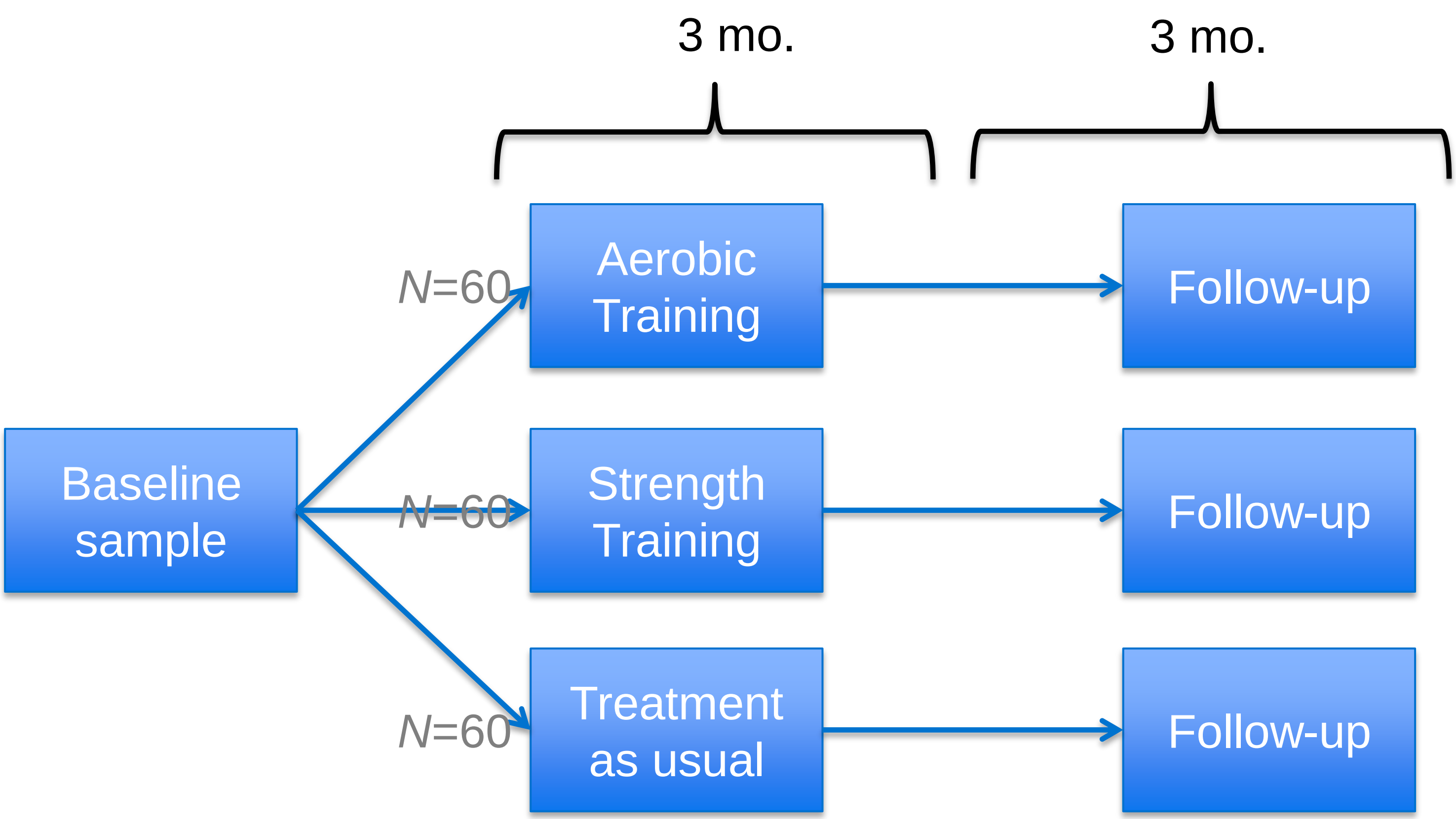
DETEC Trial



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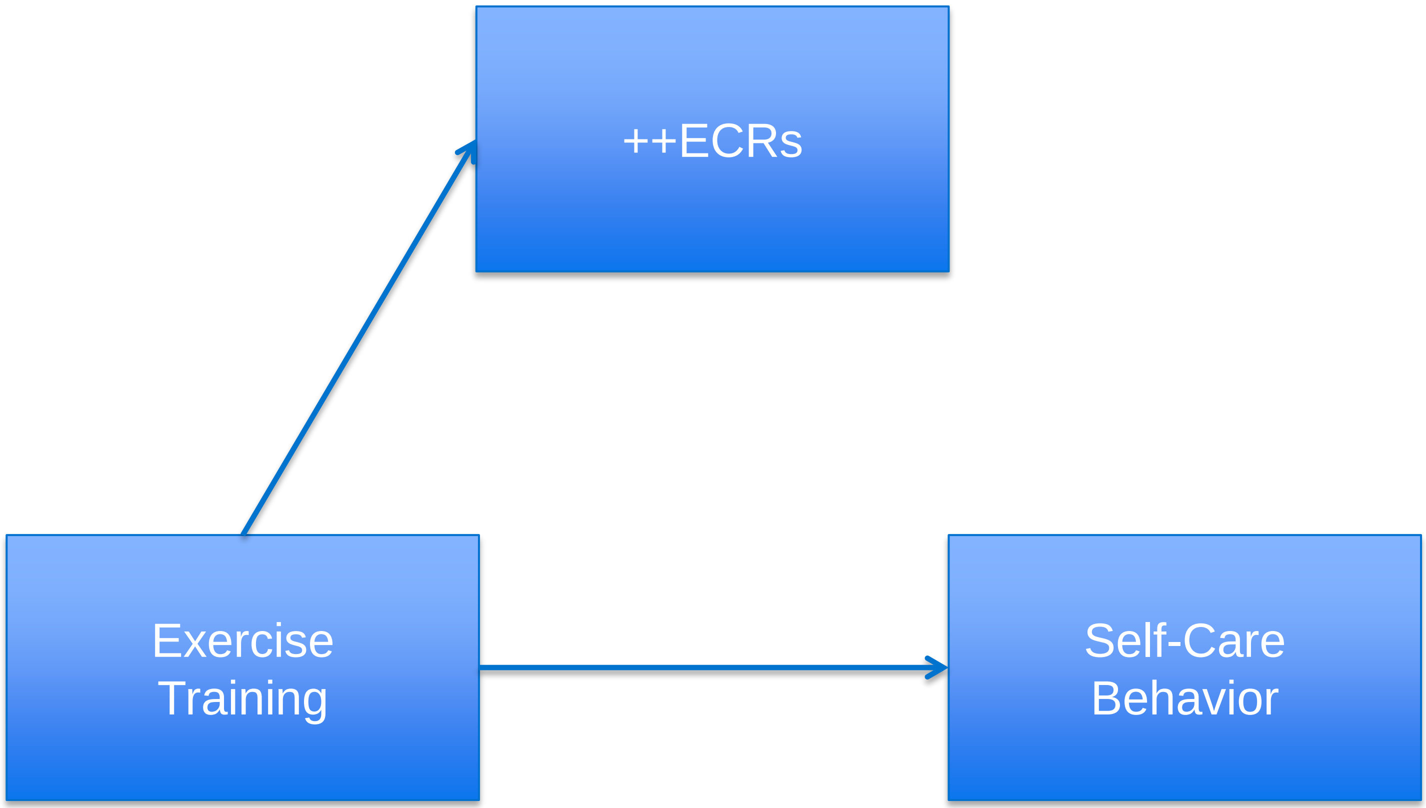
Outcomes

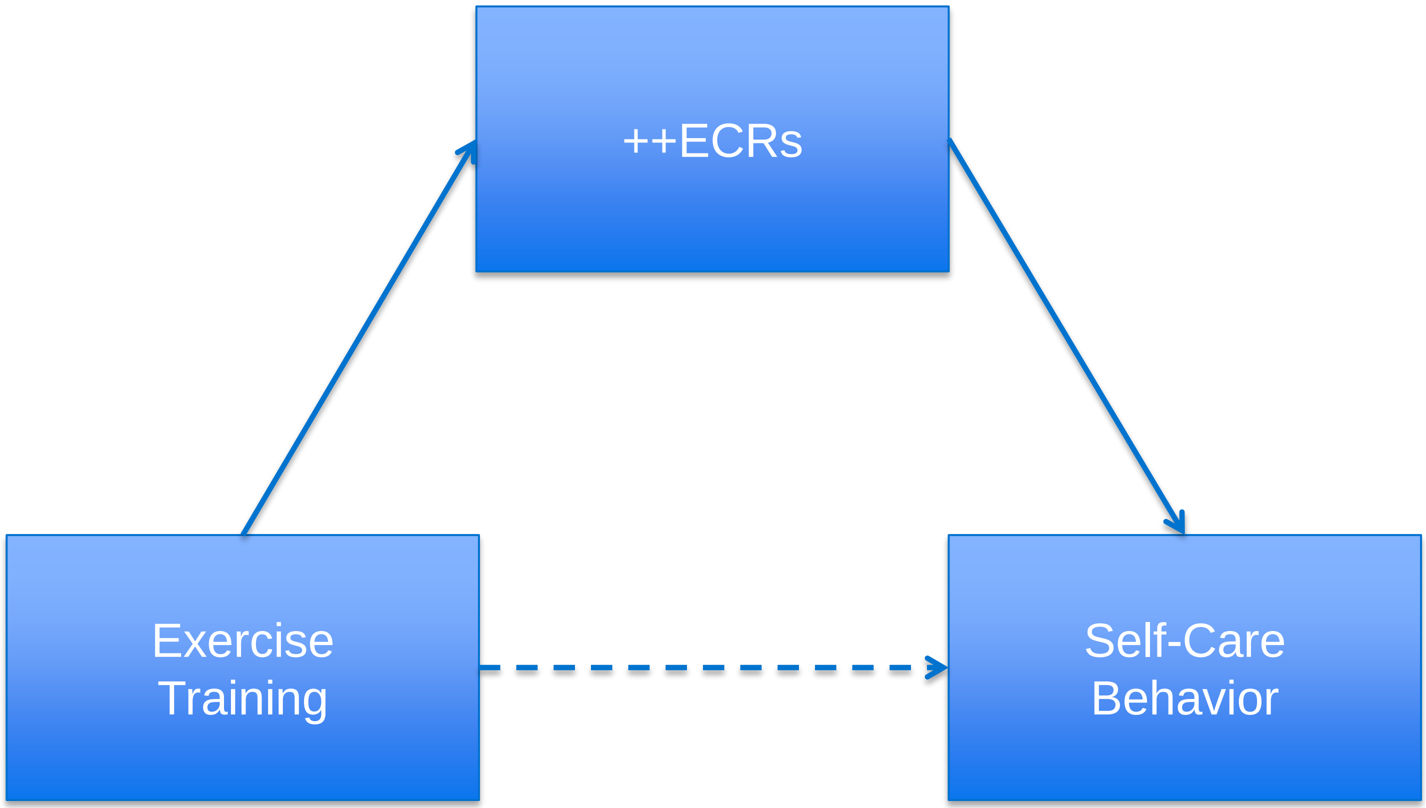
1. **Cognitive function**
   - Executive control resources
   - Global cog function
   - Memory

2. **Glycemic control (A1C)**

3. **Self care behaviors**
   - Medication adherence
   - Dietary behavior
   - Foot care behaviors


Exercise Training
Self-Care Behavior


++ECRs
Exercise Training
Self-Care Behavior


++ECRs
Exercise Training
Self-Care Behavior

Details

WHO?

- Over 55 years of age
- Diagnosis of T2DM (no T1s involved in this trial).
- A1C over 7.0
- Currently taking hypoglycemic medications (Metformin etc.).

WHEN?

- Recruitment starting in May of 2013.

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Where?

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Benefits?

- Learn more about the potential utility of exercise in enhancing outcomes

- Potential to build evidence base on facilitating factors for dietary change, and medication adherence.

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Pilot Study

- MA project: Corrie Vincent (SPHHS student)
- Recruiting 20 participants with T2DM.
- We could use your help!

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THANK YOU!

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