# Therapy: targets and approaches to improve cognitive and sensory outcomes

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# Disclosures

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- Conflicts of interest:  None

# Interventions to influence cognitive function

- Exercise interventions (e.g., brisk walking)
- Cognitive training interventions (e.g., multi-task training)
- Dietary interventions (e.g., Mediterranean diet)
- Multi-modal interventions (e.g., combining cognitive training + exercise)

# Intervention types – effects on cognitive function

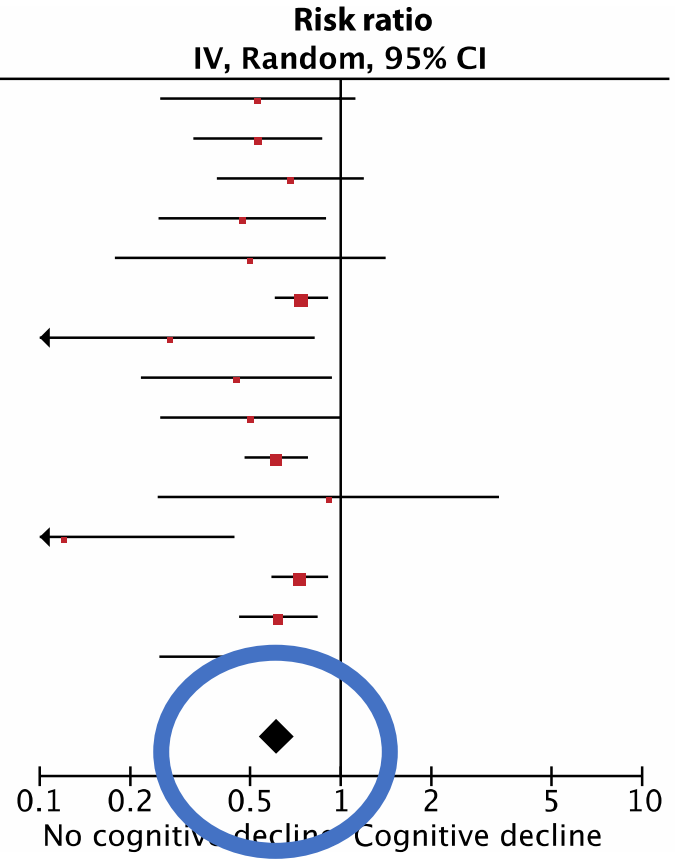
- Exercise interventions (e.g., brisk walking) – Moderate evidence
  - Ongoing clinical trials should be illuminating
- Cognitive training interventions (e.g., multi-task training) – Mixed evidence
- Dietary interventions (e.g., Mediterranean diet) – Modest evidence right now
  - Ongoing clinical trials should help clarify associations
- Multi-modal interventions (e.g., combining cognitive training + exercise)
  - Modest evidence that the multi-modal component adds above and beyond the individual component

# Meta-analyses: epidemiological studies

| Study or Subgroup | Weight | Risk ratio IV, Random, 95% CI |
|---|---|---|
| Ho *et al.*, (M) | 2.7% | 0.53 [0.25, 1.12] |
| Ho *et al.*, (F) | 5.8% | 0.53 [0.32, 0.87] |
| Laurin *et al.*, (M) | 4.6% | 0.68 [0.39, 1.19] |
| Laurin *et al.*, (F) | 3.6% | 0.47 [0.25, 0.89] |
| Schuit *et al.*, | 1.4% | 0.50 [0.18, 1.41] |
| Yaffe *et al.*, | 20.5% | 0.74 [0.60, 0.91] |
| Pignatti *et al.*, | 1.3% | 0.27 [0.09, 0.82] |
| Lytle *et al.*, | 2.8% | 0.45 [0.22, 0.94] |
| Flicker *et al.*, | 3.2% | 0.50 [0.25, 1.00] |
| Singh-Manoux *et al.*, | 16.7% | 0.61 [0.48, 0.78] |
| Sumic *et al.*, (M) | 0.9% | 0.91 [0.25, 3.36] |
| Sumic *et al.*, (F) | 0.9% | 0.12 [0.03, 0.44] |
| Middleton *et al.*, | 19.1% | 0.73 [0.59, 0.91] |
| Niti *et al.*, | 12.6% | 0.62 [0.46, 0.84] |
| Etgen *et al.*, | 3.9% | 0.46 [0.25, 0.85] |
| **Total (95% CI)** | **100.0%** | **0.62 [0.54, 0.70]** |

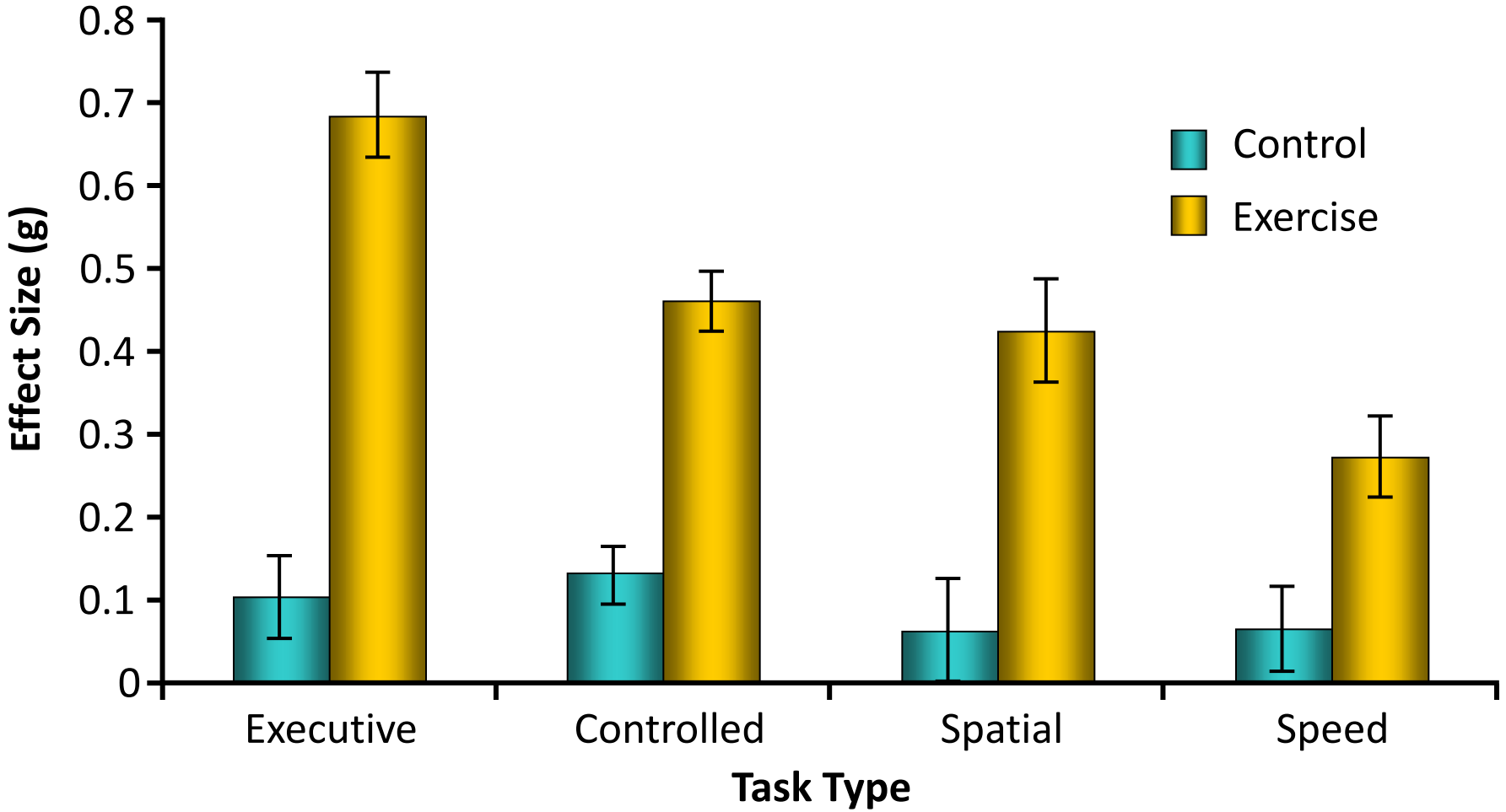
Heterogeneity: Tau$^2$ = 0.01; $\chi^2$ = 16.94, df = 14 ($P$ = 0.26); $I^2$ = 17%

Test for overall effect: $Z$ = 7.49 ($P$ < 0.00001)




*Sofi et al., 2011*

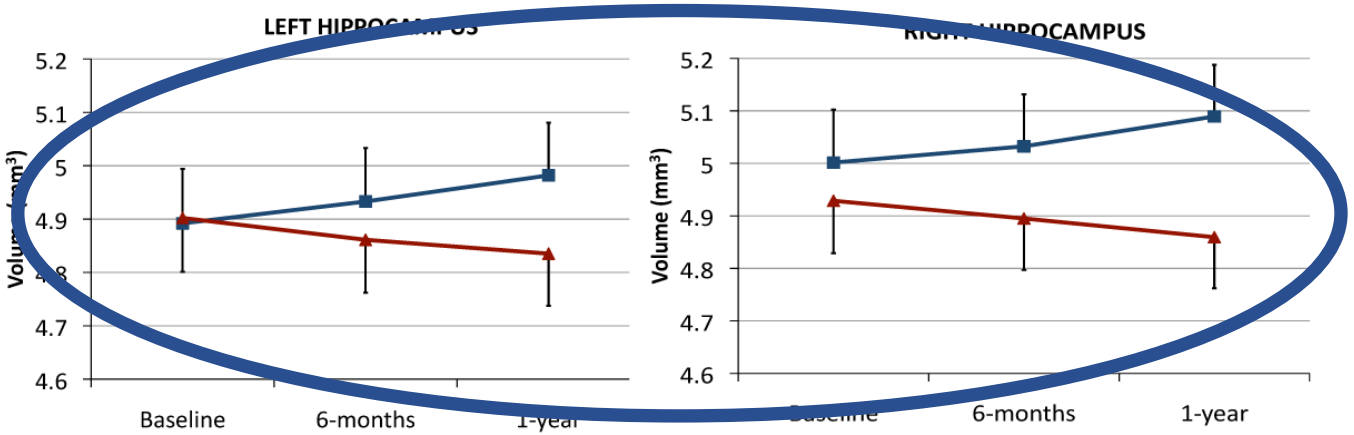
# Exercise training improves cognitive function in older adults



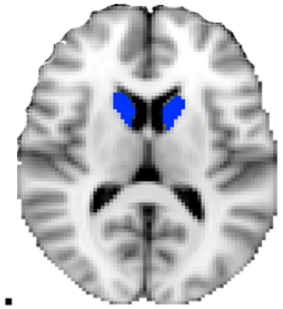

*Colcombe & Kramer, 2003*

## Hippocampus

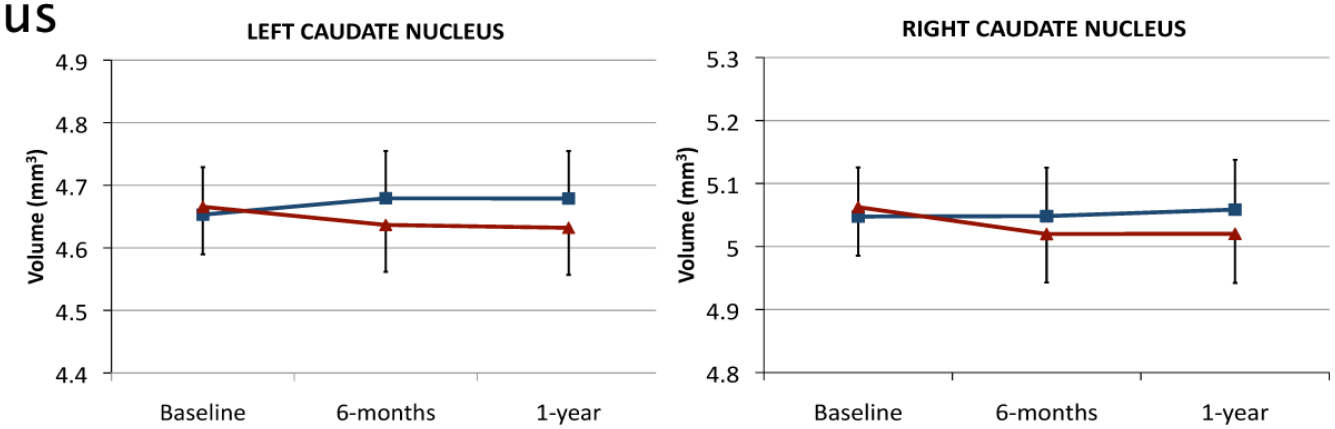
A.



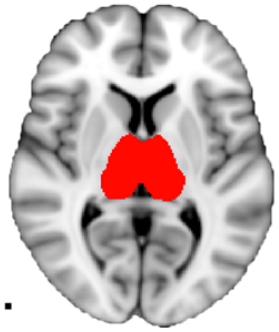

## Caudate Nucleus



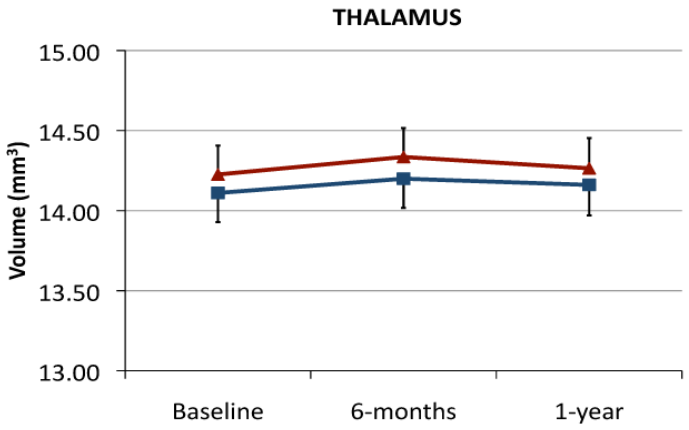
B.




## Thalamus



C.

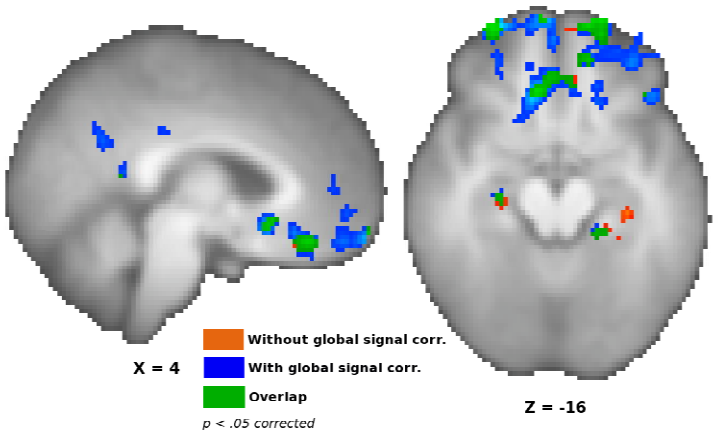



Exercise

Stretching

*Erickson, Voss, Prakash, et al. (2011)*

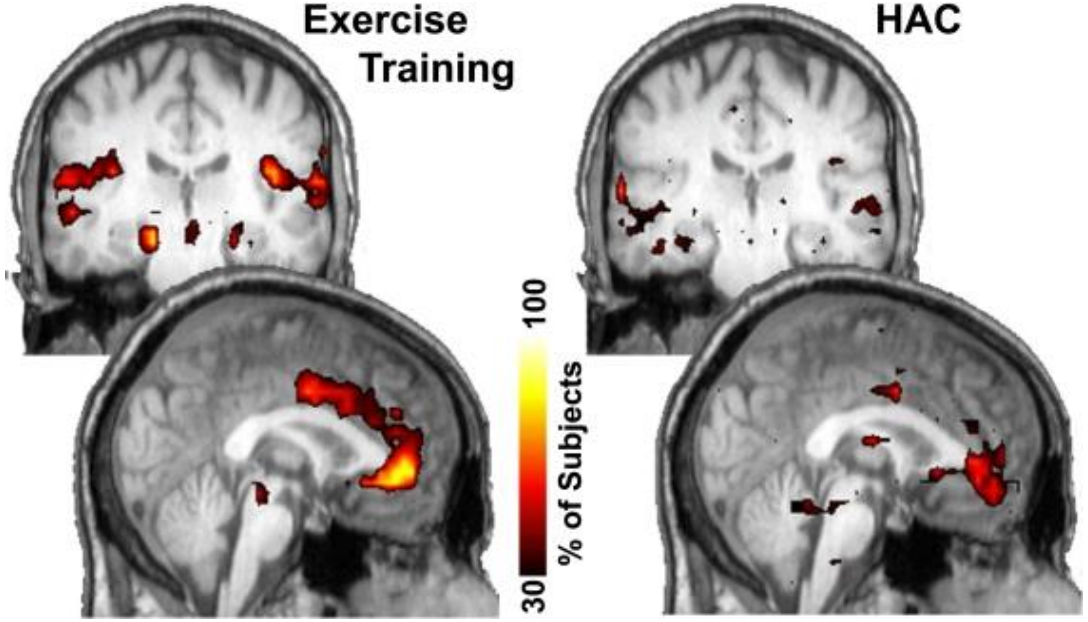
# Physical Activity increases fronto-temporal-parietal connectivity




**Whole-brain regional fitness analysis: Comparison of preprocessing with and without global signal correction**

*Voss et al., 2010*

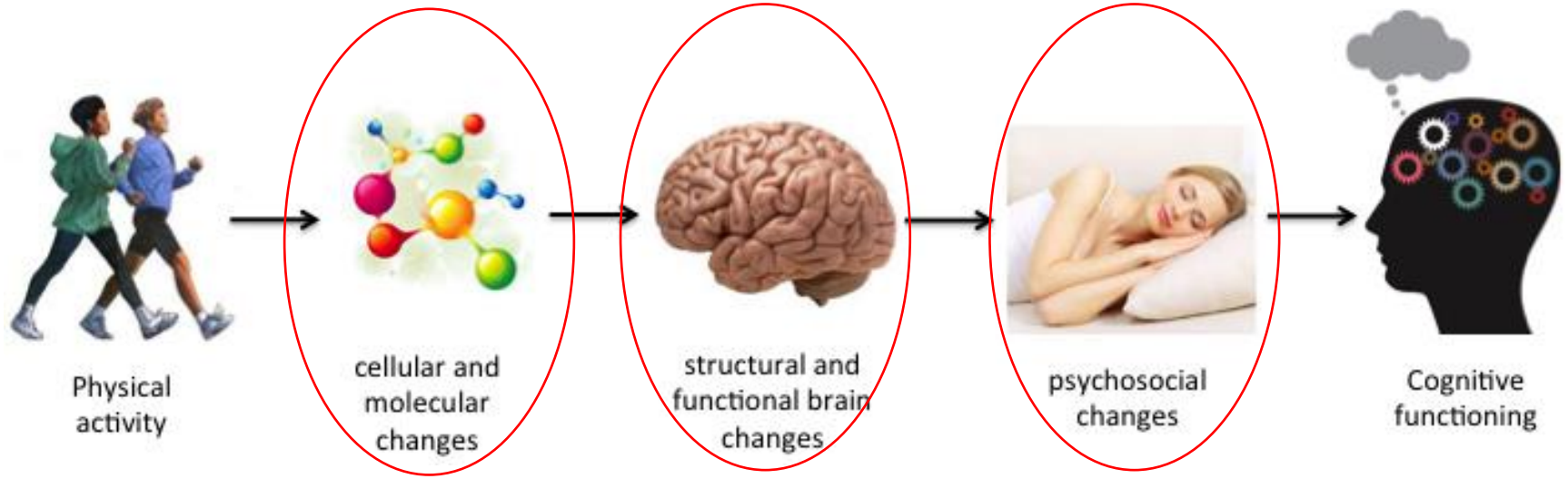
Walking increases functional connectivity between prefrontal and hippocampal regions.




Exercise increased network community structure in the hippocampus and anterior cingulate cortex

*Burdette et al., 2010*

# Mechanisms?




*Stillman et al., 2016*

# Interventions:  What?

- What kind of intervention is best?
- What kind of exercise?  Mode of activity?
- What is the most effective dose, frequency?
- How long do the effects persist?

# Interventions:  When?

- Do critical periods, sensitive periods, or windows-of-opportunity matter?

- Is it ever “too late”?  A “point of no return”?

# Interventions:  moderators and mediators

- Understanding mechanisms and individual differences has a direct impact on therapeutic strategies and impact:
  - Without this we could be targeting the **wrong population** with the **least effective approaches** for the **weakest effects** at the **most inopportune times**.

- A more targeted approach in terms of risk, brain phenotypes of interest, projected outcomes, etc. is necessary to move this field forward

# What can we be certain about?

1. Greater amounts of physical activity are associated with reduced cognitive decline in late adulthood.

2. The brain changes with prolonged exposure to physical activity – with regional specificity

3. Only modest amounts of exercise are sufficient for detecting effects.

# 10 remaining questions

1. Dose of activity – frequency, duration, intensity?
2. Type of activity – walking, tennis, strength?
3. Prevention, delaying, treating cognitive decline?
4. Specificity to certain populations?
5. Cognitive domains most affected?
6. Importance of neuroimaging outcomes?
7. Mechanisms?
8. Individual differences – moderators of the effects?
9. Maintenance of the effects – how long do they last?
10. Comparing effectiveness to other interventions