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

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:
Assessing the effects of exercise

1. Running Wheel
2. Water maze
3. Electrophysiology

Experimental Design

Van Praag et al., 1999
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 & 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), Kramer & Colcombe (2018)
There have been lots and lots of additional meta-analyses since 2003 …...

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.
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“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 **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
Hippocampus

A.

Caudate Nucleus

B.

Thalamus

C.

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.
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

**Default Mode**  **Fronto-Executive**  **Fronto-Parietal**
**Fronto-Executive/Parietal Overlap**
Improvements in networks post-exercise?

**Functional connectivity changes in favor of walking group**

A. Default

![Bar graph showing connectivity changes over time](image)

B. Default

![Bar graph showing connectivity changes over time](image)

C. Default

![Bar graph showing connectivity changes over time](image)

D. Fronto-executive

![Bar graph showing connectivity changes over time](image)

Voss et al., 2010, 2016
Post-intervention improvement in:

- Executive function
- Short-term memory

Post-intervention change in connectivity

Voss et al., 2010, 2016
Is aerobic fitness associated with better Functional connectivity?

- Aerobic Fitness (Independent Variable) → Mediator Variable → Functional Connectivity ($Fc_1, Fc_2, ... Fc_N$) → Cognition (Dependent Variable)

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

**Brain-Derived Neurotrophic Factor (BDNF)**

Higher striatal D2-receptor availability in aerobically fit older adults

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• 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?

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

**Cancer Patients**

*Chaddock-Heyman et al, 2015*

**Multiple Sclerosis Patients**

*Prakash et al (2009)*

**Parkinson’s Patients**

*Uc et al, (2008)*

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>&lt;0 Favors Control</th>
<th>&gt;0 Favors Exercise</th>
<th>ES (95% CI)</th>
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<tr>
<td><strong>Aerobic exercise training</strong></td>
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<tr>
<td>Arcoverde⁷⁴</td>
<td>2014</td>
<td></td>
<td></td>
<td>2.51 (1.34, 3.68)</td>
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<tr>
<td>Baker [1]⁶⁸</td>
<td>2010</td>
<td></td>
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<td>0.88 (-0.15, 2.11)</td>
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<tr>
<td>Baker [2]³⁹</td>
<td>2010</td>
<td></td>
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<td>0.55 (-0.56, 1.66)</td>
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<tr>
<td>Bossers [1]⁵⁰</td>
<td>2015</td>
<td></td>
<td></td>
<td>0.47 (0.01, 0.94)</td>
</tr>
<tr>
<td>Cot¹⁰</td>
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<tr>
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<td></td>
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<td>1.21 (0.44, 1.97)</td>
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<td>Lam⁴⁸</td>
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<tr>
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<td></td>
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<td>Scherder⁴⁵</td>
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<tr>
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<td>Subtotal (I-squared = 68.7%, p = 0.000)</td>
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<td><strong>Combined aerobic and resistance exercise training</strong></td>
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<td>Bossers [2]³⁵</td>
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<td>Hernandez¹¹</td>
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<td>Suzuki³⁷</td>
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<td>0.12 (-0.44, 0.67)</td>
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<td>Van de Winckel³²</td>
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<td>0.12 (-0.71, 0.95)</td>
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<tr>
<td>Vrouwenhof⁴⁶</td>
<td>2011</td>
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<td>0.11 (-0.51, 0.73)</td>
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<td>Vaguez⁴⁶</td>
<td>2010</td>
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<td>0.62 (-0.16, 1.39)</td>
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<tr>
<td>de Andrade⁴⁶</td>
<td>2013</td>
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<td>Subtotal (I-squared = 14.0%, p = 0.320)</td>
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<td><strong>Overall (I-squared = 59.6%, p = 0.000)</strong>*</td>
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<td>0.47 (0.26, 0.68)</td>
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</tbody>
</table>
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- **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
Elastic Net models aid prediction

R² represents the squared correlation between the observed (train data) and predicted (test data) values

**Non-imaging predictors**

<table>
<thead>
<tr>
<th>Non-imaging predictors</th>
<th>Direction</th>
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<tbody>
<tr>
<td>Gait-self efficacy</td>
<td>Positive</td>
</tr>
<tr>
<td>Big 5 extroversion</td>
<td>Negative</td>
</tr>
<tr>
<td>Perceived sleep quality index</td>
<td>Negative</td>
</tr>
<tr>
<td>Sex</td>
<td>Negative (female)</td>
</tr>
<tr>
<td>Employment</td>
<td>Positive (retired)</td>
</tr>
<tr>
<td>Pattern comparison score</td>
<td>Negative</td>
</tr>
</tbody>
</table>

R² 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?

- **Cognitive activity**: Prevent up to 40% dementia risk
- **Exercise**: Younger structure-based brain age
- **Social activity**: Greater functional connectivity in frontal, temporal and motor areas
- **Healthy diet**: Lower Aβ burden and higher global functions

Ai et al, 2023
Do individuals have different profiles of multidomain lifestyle adherence?

K-means clustering process

Preprocessing

Lifestyle variables:
- Exercise, cognitive activity, social network, diet

Demographic:
- Age, sex, apoe4, education

Cognition and psychosocial variables:
- RBANS change scores from 2016-2019, RVLT, TMT, Stroop, depression, anxiety, stress, apathy, purpose of life

Scale, remove outliers > 3SD
Regress out age, sex, apoe4, education

Residuals of lifestyle variables

Clustering

K-means
K=9
Choose number of k
Bootstrap 100 times
Jaccard index (indicating stability)

Validation

Group test: comparing cognition and psychosocial variables between two cluster groups
Age, sex, apoe4, education controlled
Individuals have different profiles of multidomain lifestyle adherence

- Adherence group
- Non-adherence group
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?

**Preprocessing**
- Thickness, Area based on Schaefer 100
- ROI-to-ROI functional connectivity based on Schaefer 100
- Regress out age, sex, apoe4 status (FD specifically for fMRI)

**Feature reduction**
- Function + Structure
- Feature reduction univariate filter (10-fold CV, p<0.05)
- 255 Neuroimage features

**Testing**
- Permutation 1000 times for the entire sample
- Outer folds: 1, 2, ..., 10
- Average Accuracy
- Follow up for SVM model
- Te

**Parameter tuning**
- Create CV sets (stratified by Outer class) Inner folds resamples
- 10 sets of optimized parameters for each model
- SVM
- Tuning within inner resamples
- Maximize AUC
- 1 to 10
- 25 Resamples
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**
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- Beyond the laboratory door ….

Davis et al, 2011
INSIGHT
A Comprehensive, Multidisciplinary Brain Training System
INSIGHT Project Phase 1a

Cognitive Training

Brain Stimulation

Physical Fitness

Barbey and colleagues
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

<table>
<thead>
<tr>
<th>Transfer</th>
<th>Intervention</th>
<th>Cohen’s $d$ (0.50)</th>
<th>Measure</th>
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<tbody>
<tr>
<td>Decision Making</td>
<td>Fitness only</td>
<td>0.74</td>
<td>Composite Score</td>
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<tr>
<td>Decision Making</td>
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<td>0.57</td>
<td>Social Norms</td>
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<td>Under/over Confidence</td>
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<td>Decision Making</td>
<td>Mind Frontiers + Fitness</td>
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<td>Composite Score</td>
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<tr>
<td>Decision Making</td>
<td>Mind Frontiers + Fitness</td>
<td>0.49</td>
<td>Social Norms</td>
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<td>Decision Making</td>
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<td>Composite Score</td>
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<tr>
<td>Decision Making</td>
<td>Mind Frontiers + Fitness + Meditation</td>
<td>0.86</td>
<td>Resist Sunk Cost</td>
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<tr>
<td>Analogical Reasoning</td>
<td>Fitness only</td>
<td>0.50</td>
<td>Accuracy</td>
</tr>
</tbody>
</table>

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 What
Different types of exercise may benefit cognitive and brain health outcomes. The moderating role of training parameters such as frequency, intensity, and session duration remains unclear.

The Who
Trials have focused on those with and without overt cognitive impairment. Less is known about individuals with specific risk factors, including those with cerebrovascular pathology, early β-amyloid accumulation, or cardiometabolic diseases.

The When
Investigations have targeted individuals in late-life. Evidence for the effects of exercise in mid-life is limited. Interventions in mid-life could more successfully delay the onset of cognitive impairment and reduce dementia risk.

The How
Knowledge of the mechanisms underlying the effects of exercise on cognition is still limited. Trials have focused on adaptations in grey matter structure. Other candidates include white matter structure, neural activation, and cerebrovascular function.

Next Steps
The effect of exercise is small, which may reflect variability across studies in training parameters, participant characteristics, outcome assessment, and control conditions. Evidence from diverse samples is also very scarce. Future trials need to address these limitations.

Methodology and reporting
Sex, gender, race/ethnicity, and socioeconomic status

Angiogenesis and neurovascular coupling
Axonal sprouting, myelination, and overall white matter integrity
Dendritic branching and synaptic plasticity
Regular Tai Chi Practice Is Associated With Improved Memory as Well as Structural and Functional Alterations of the Hippocampus in the Elderly

Chunlin Yue¹, Qian Yu², Yanjie Zhang³, Fabian Herold⁴, Jian Mei⁵, Zhaowei Kong⁶, Stephane Perrey⁷, Jiao Liu⁸, Norger G. Müller⁹, Zonghao Zhang¹, Yuliu Tao¹, Arthur Kramer¹,², Benjamin Becker⁸ and Liye Zou¹,¹⁰* 2020

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

Aishwarya Rajesh¹,²*, Tony Noice³, Helga Noice³, Andrew Jahn⁴, Ana M. Daugherty⁶, Wendy Heller¹,² and Arthur F. Kramer¹,⁶ 2021
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 …..
Fig 4. Path model testing the effect of aerobic fitness on relational memory mediated by hippocampal $\xi'$ 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?
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- 6 month exercise intervention, 4 groups, 60 to 85 year olds, composite measure of Executive Function, 100+ participants.
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- 6 month exercise intervention, 4 groups, 60 to 85 year olds, composite measure of Executive Function, 100+ participants.

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

Brain (White Matter)
- 16,313 voxels

Macrostructure

Microstructure
- Peak VO₂ = 16

Good Aerobic Capacity