Feel the Burn: How exercise shapes cognitive health and brain function

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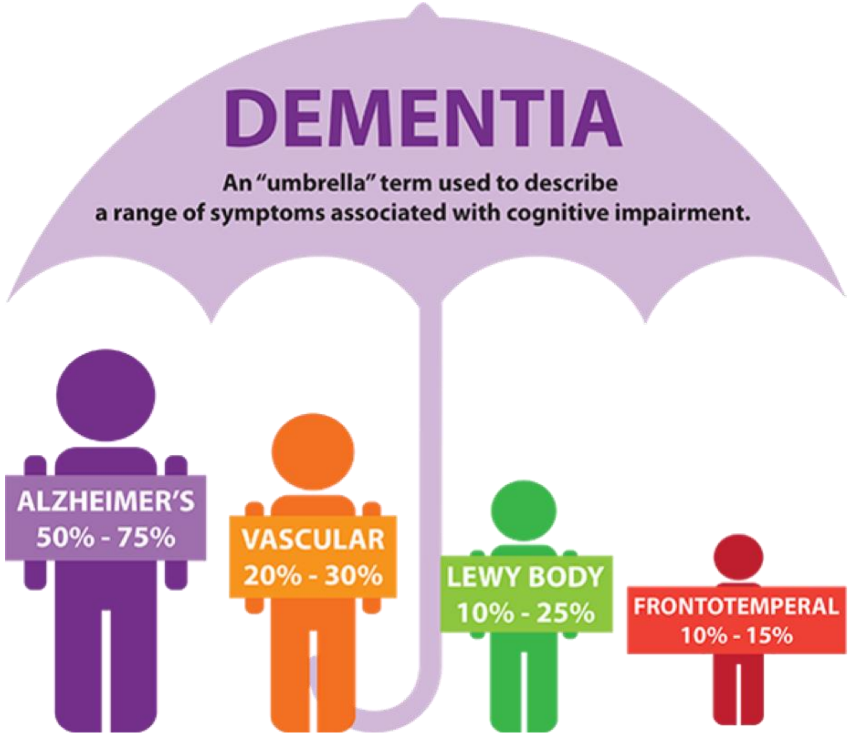
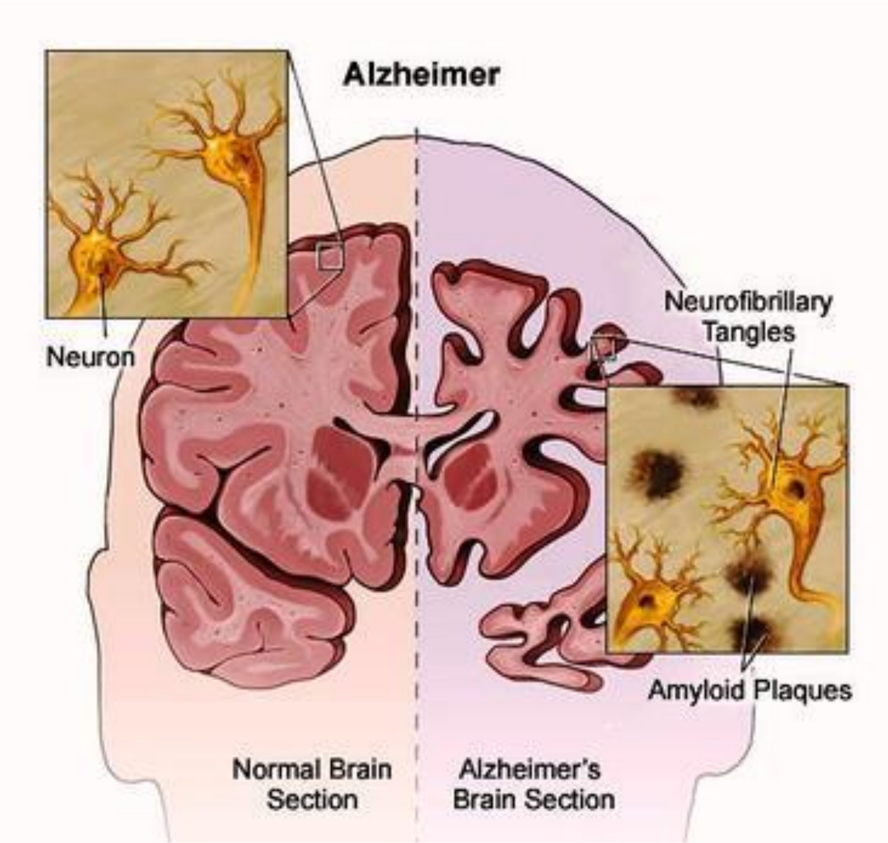
Etiology of cognitive decline



Courtesy: Dementia Friendly America



Your amazing (and hungry) brain

Why is energy so important for brain health?

Every day, your brain needs:

- 1000 Liters of blood
- 72 Liters of oxygen
- 120 grams of sugar (glucose)

To generate energy (ATP)!

Energy metabolism and the brain

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Your brain as a car

- **Fuel (*glucose, lactate, ketones: "metabolic"*)**
  - *Green et al. 2025 PMID 39258961*
  - *Kemna et. al 2025 PMID 41376120*
- **Fuel lines (*blood supply: "vascular"*)**
  - *Morris et al 2024 PMID 38108352*
- **Engine (*mitochondria: "bioenergetic"*)**
  - *Johnson et al 2025 PMID 40250718*

Metabolic, vascular, and bioenergetic function are all critical to generate energy.

Our work focuses on targeting these systems to improve brain health.

History of Exercise in Aging and AD at KU

- BAP *(Brain Aging Project: 2006-2008)*
  - Longitudinal observational study, ND and AD
- TEAM *(Trial of Exercise on Aging and Memory: 2008-2013)*
  - Endurance Exercise trial, cognitively healthy elderly
- ADEPT *(Alzheimer's Disease Exercise Program Trial: 2010-2015)*
  - Endurance Exercise trial, probable AD
- APEX *(Alzheimer's Prevention through Exercise: 2014-2019)*
  - Endurance Exercise trial, at risk older adults
- LeapRx and Leap AHEAD *(2018-2022, 2025-present)*
  - Trial of exercise prescription, long term effects
- rrAD *(2017-2022)*
  - Blood pressure control (exercise and drug)
- IGNITE *(2017-2022 – analyses ongoing)*
  - Aerobic exercise, ND
- COMET *(2020-2026 – complete and pending unblinding!!)*
  - ND, aerobic and resistance training

Observational

Completed Trials

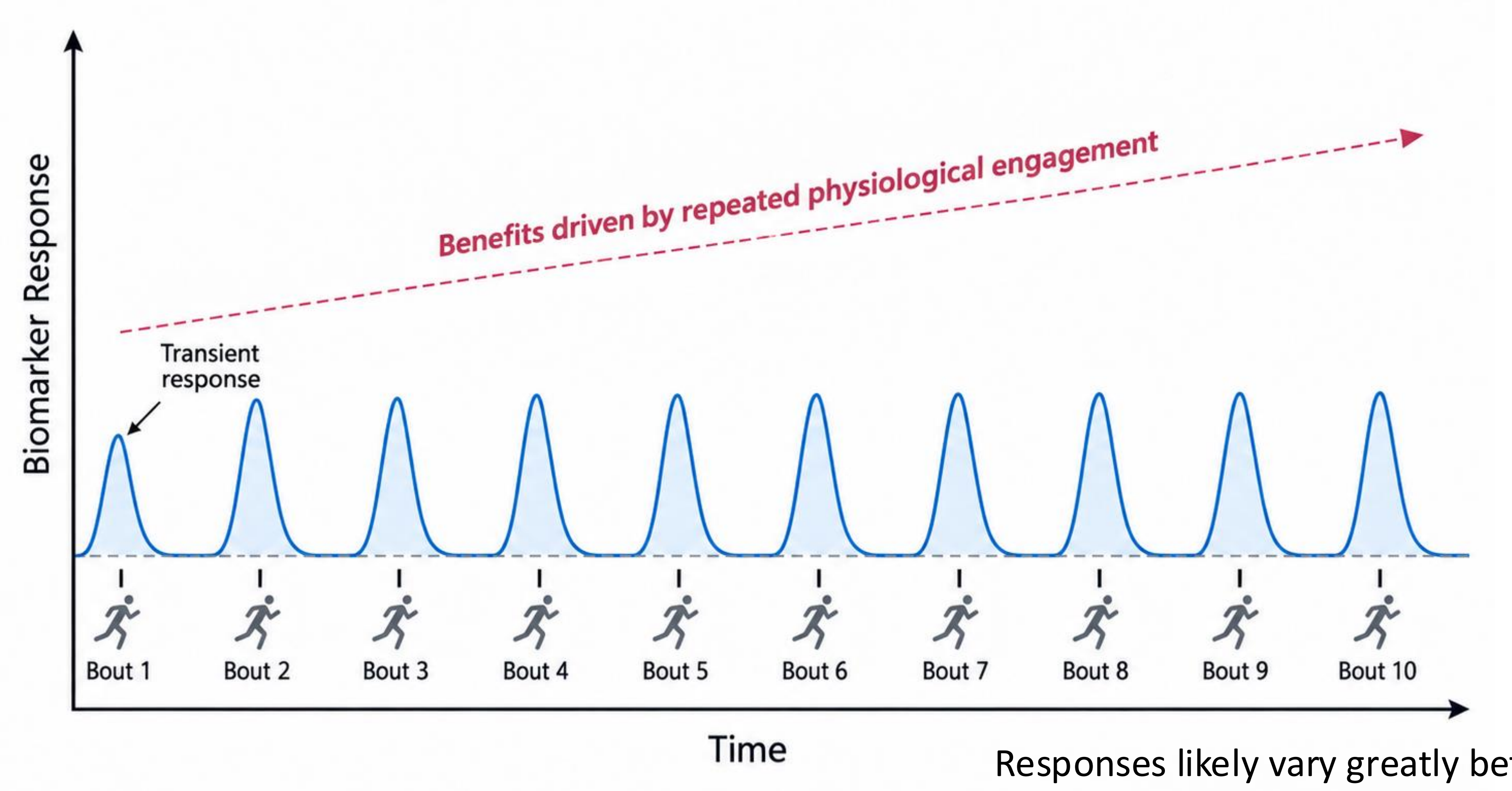
What have we learned?

- Most consistently, trials have shown benefit to:
  - Executive function
  - Fitness
  - Functional Ability
  - *But the effects varied greatly between studies!*

We were telling people to exercise without really knowing what the acute responses to exercise looked like.

We need to better understand factors that contribute to the heterogeneity in response to exercise

Acute biomarker responses may drive physiological benefit



Responses likely vary greatly between individuals!

The brain is highly reliant on glucose, but can use other fuels

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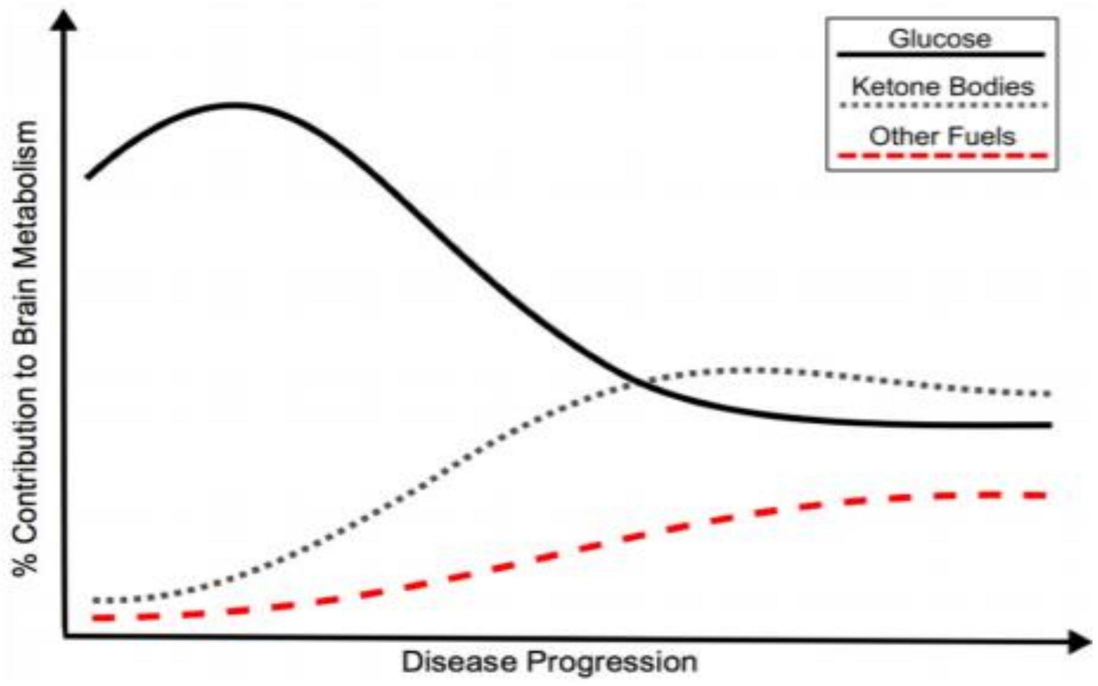
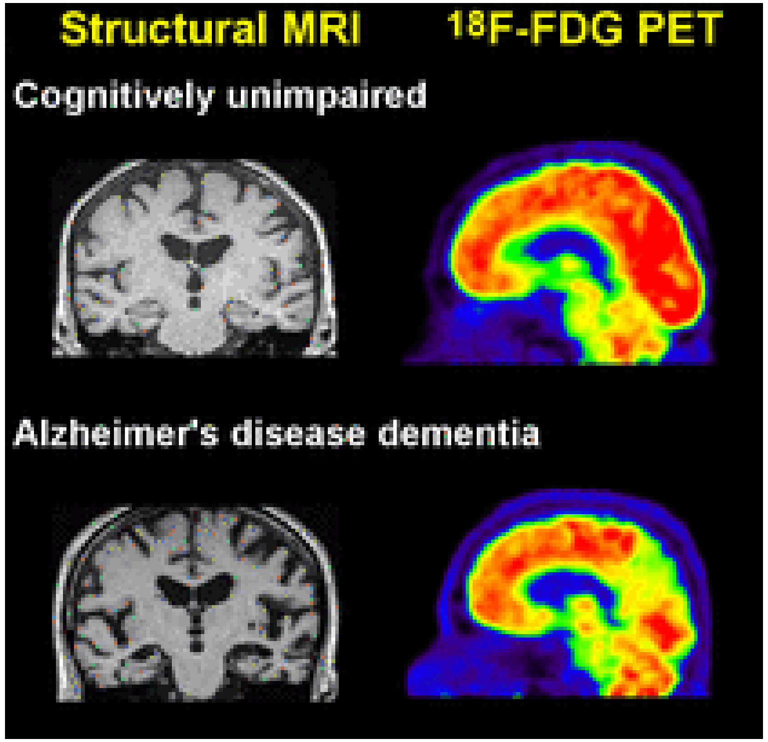




Neth and Craft 2017 *Front Aging Neursci*

Lactate – an understudied effector of brain benefit

Lactate is more than a waste product

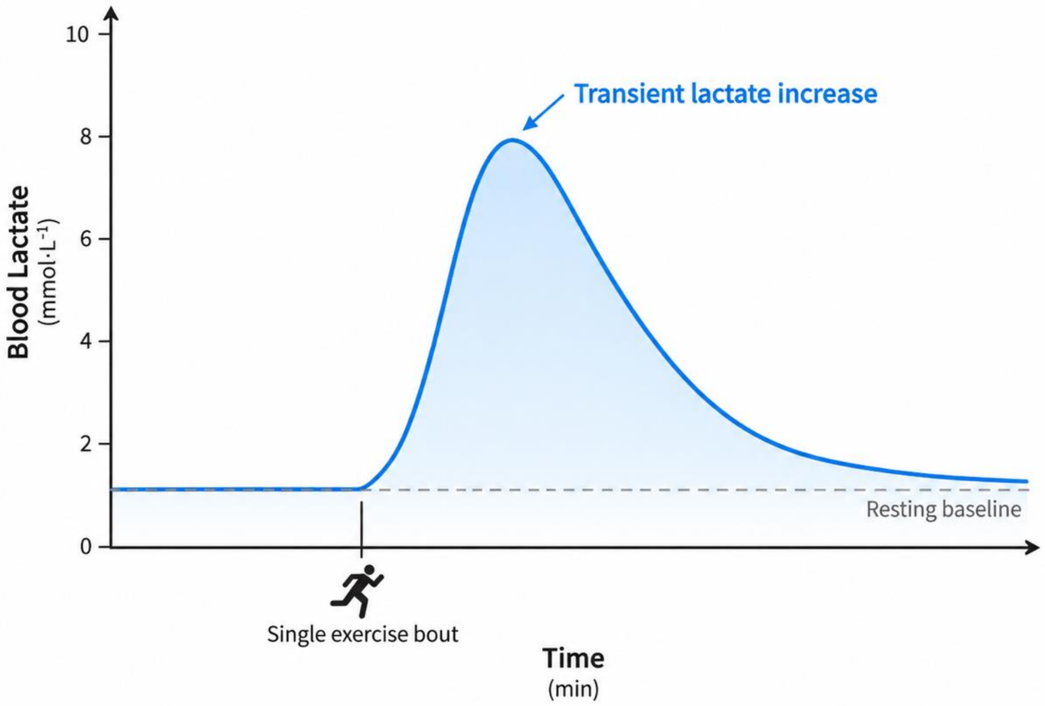
- Acts a buffer
- Can be a signaling hormone
    - BDNF induction
    - Brain blood flow
- Can be used as a fuel

Lactate can potentially spare glucose

- Impact on meeting cerebral energy demand
- PPP effects
- Infusion rescues hypoglycemia related cognitive impairment

During exercise

- Brain switches from net release to net uptake
- Nearly all lactate taken up by the brain is oxidized
- *More work is needed to understand acute exercise effects on the brain*

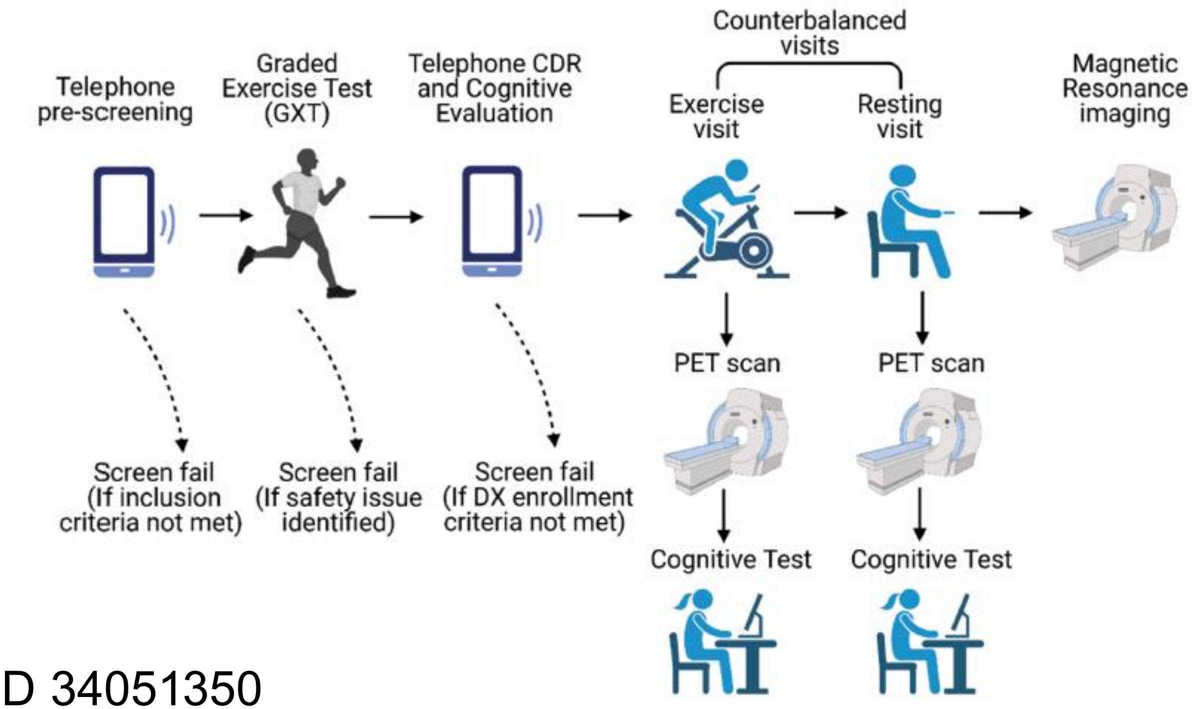


Acute Exercise Response on Brain Imaging and Cognition (AEROBIC)

Goal: Characterize the effect of acute exercise on brain glucose metabolism

Moderate & “higher” intensity,
cognitively healthy & AD participants

- Primary: Cerebral glucose metabolism
- Secondary: Lactate AUC, BDNF change



Methods paper:
Green et. Al 2021 Contemporary Clinical Trials PMID 34051350

Strict blood draw timecourses in relation to PET

Figure 2A. Resting Visit Timeline

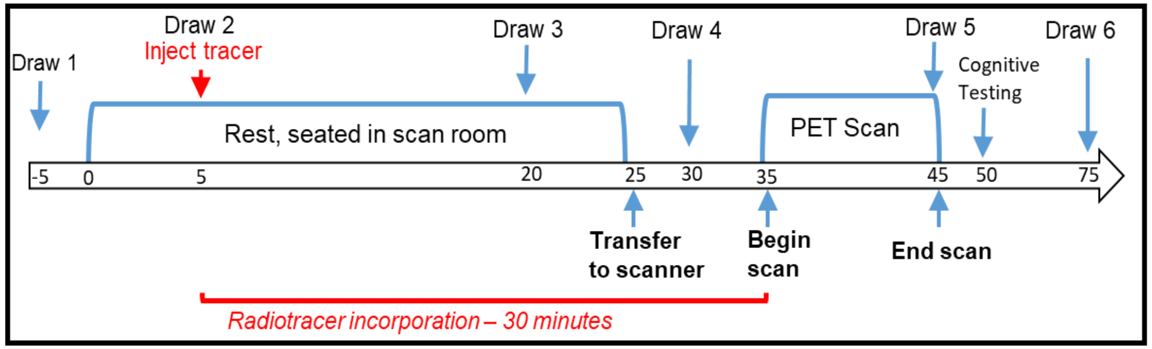
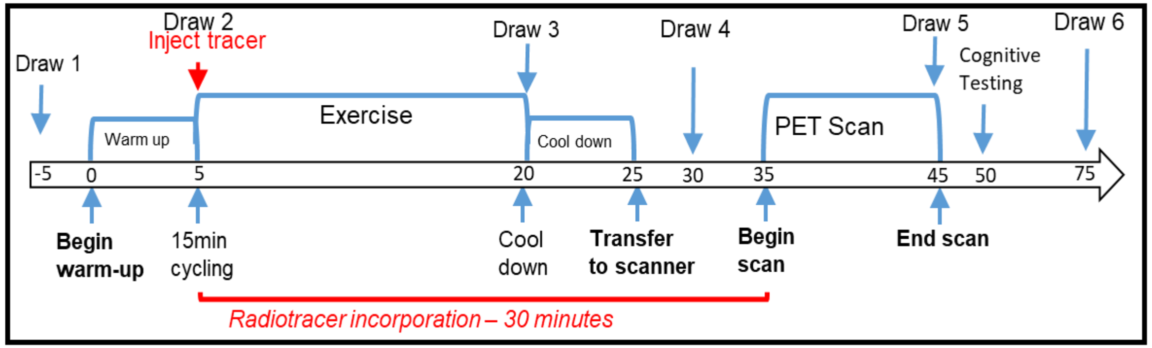
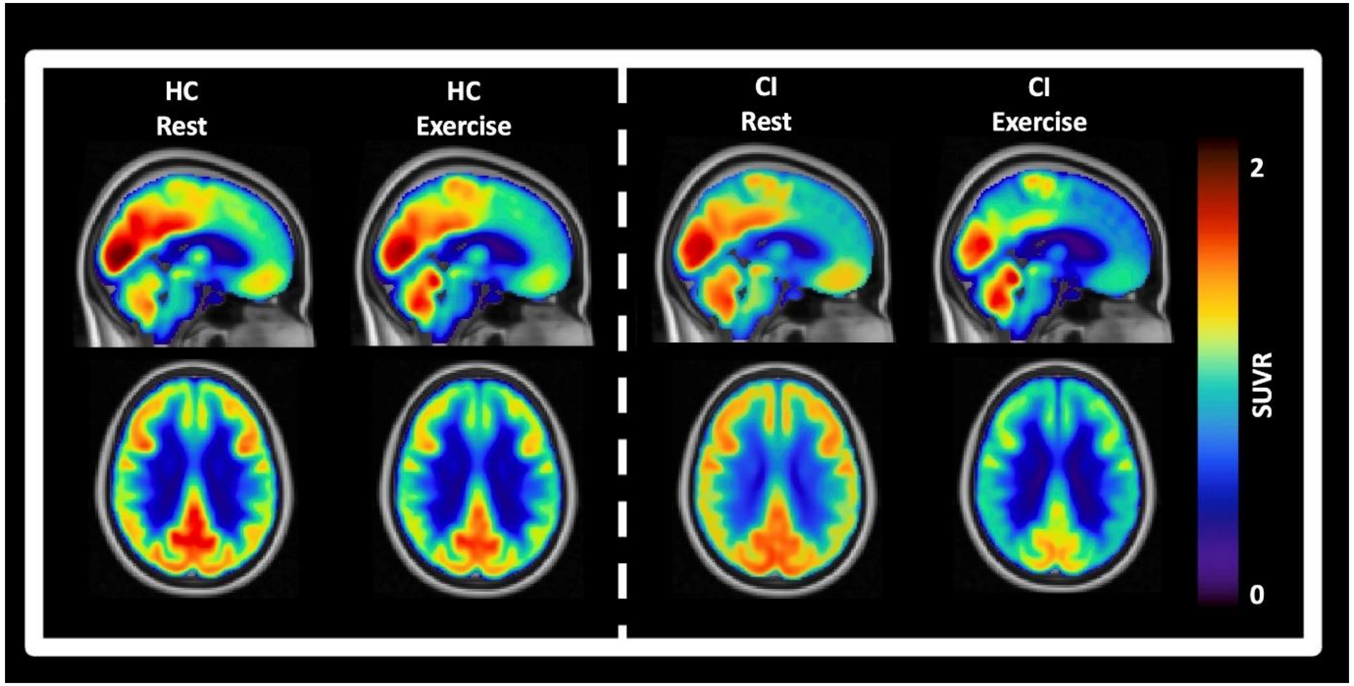
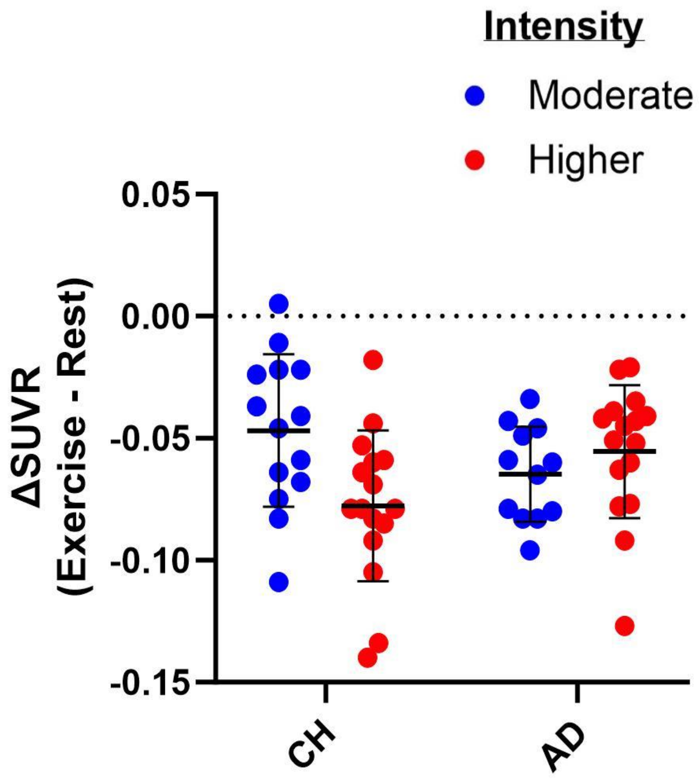


Figure 2B. Exercise Visit Timeline



Changes in fuel utilization during exercise





Changes occur across many regions

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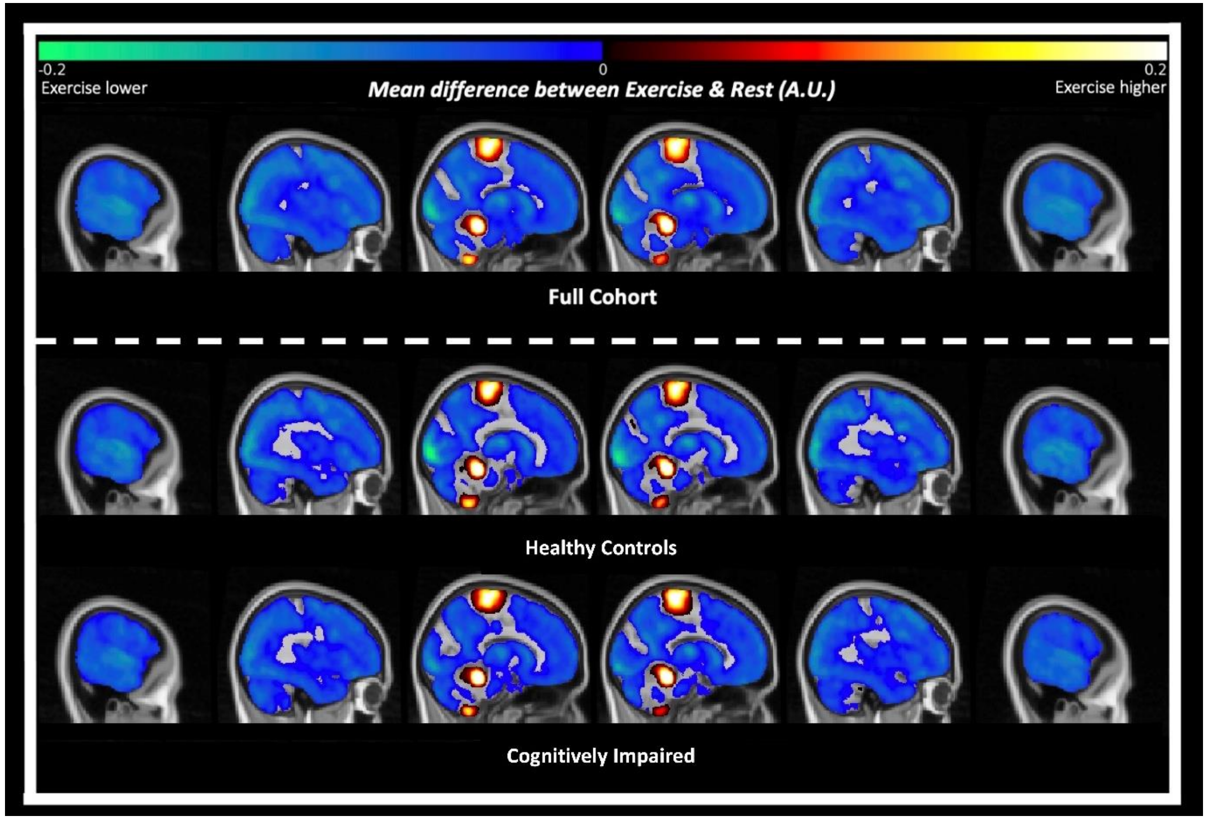

		Mean difference (Exercise − Rest)	t-stat	P-value	SD	95% CI of difference	
						Lower	Upper
SUVR normalized to cerebellum	Whole brain grey matter	−0.0596	−13.81	<0.001	0.0329	−0.068	−0.051
	Motor	0.0731	10.95	<0.001	0.0508	0.060	0.086
	ACC	−0.0462	−10.48	<0.001	0.0336	−0.055	−0.037
	Precuneus	−0.0745	−12.26	<0.001	0.0463	−0.087	−0.062
	Superior medial frontal	−0.0638	−13.41	<0.001	0.0362	−0.073	−0.054
	Superior parietal	−0.0660	−12.35	<0.001	0.0407	−0.077	−0.055
	PCC	−0.0709	−14.08	<0.001	0.0384	−0.081	−0.061
	Parahippocampus	−0.0383	−11.80	<0.001	0.0247	−0.045	−0.032
	Hippocampus	−0.0469	−13.97	<0.001	0.0256	−0.054	−0.040
	Pons	*−0.0284*	*−11.12*	*<0.001*	*0.0194*	*−0.034*	*−0.023*
	Cerebeller grey matter	*−0.0012*	*−4.44*	*<0.001*	*0.0021*	*−0.002*	*−0.001*
	Whole cerebellum	*0.0000*	*0.16*	*0.874*	*0.0000*	*0.000*	*0.000*
SUVR normalized to pons	Whole brain grey matter	−0.0286	−4.84	<0.001	0.045	−0.017	−0.040
	Motor	0.1535	16.95	<0.001	0.069	0.172	0.135
	ACC	−0.0131	−2.65	0.011	0.038	−0.003	−0.023
	Precuneus	−0.0395	−4.67	<0.001	0.064	−0.023	−0.056
	Superior medial frontal	−0.0327	−5.20	<0.001	0.048	−0.020	−0.045
	Superior parietal	−0.0400	−6.13	<0.001	0.050	−0.027	−0.053
	PCC	−0.0375	−5.82	<0.001	0.049	−0.025	−0.050
	Parahippocampus	−0.0140	−4.94	<0.001	0.022	−0.008	−0.020
	Hippocampus	−0.0218	−7.77	<0.001	0.021	−0.016	−0.027
	Pons	*0.0000*	*−1.00*	*0.324*	*0.000*	*0.000*	*0.000*
	Cerebellar grey matter	*0.0488*	*9.82*	*<0.001*	*0.038*	*0.059*	*0.039*
	Whole cerebellum	*0.0498*	*10.56*	*<0.001*	*0.036*	*0.059*	*0.040*

Green et al. *J Physiol* 2025 PMID 39258961

Blood lactate responses

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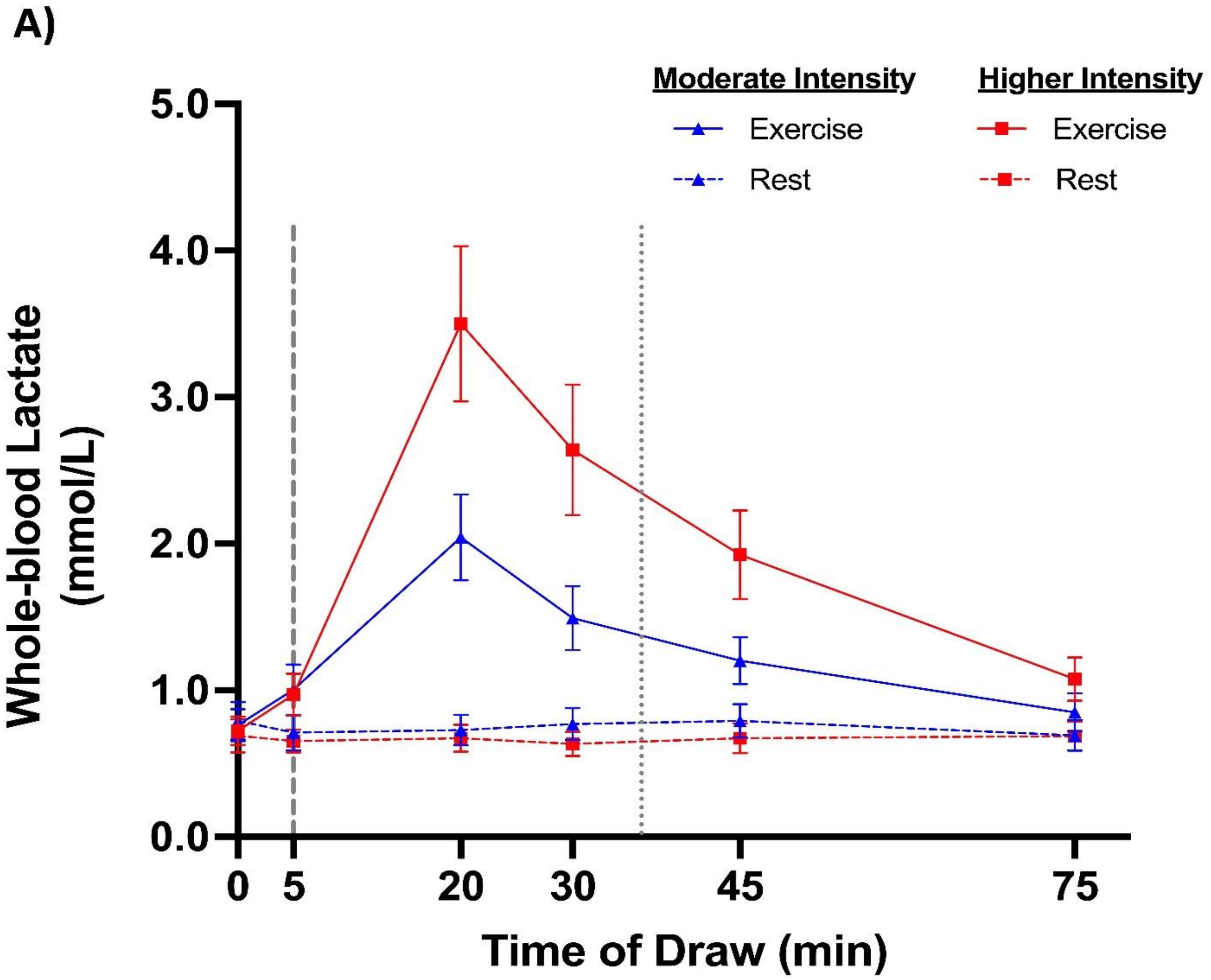

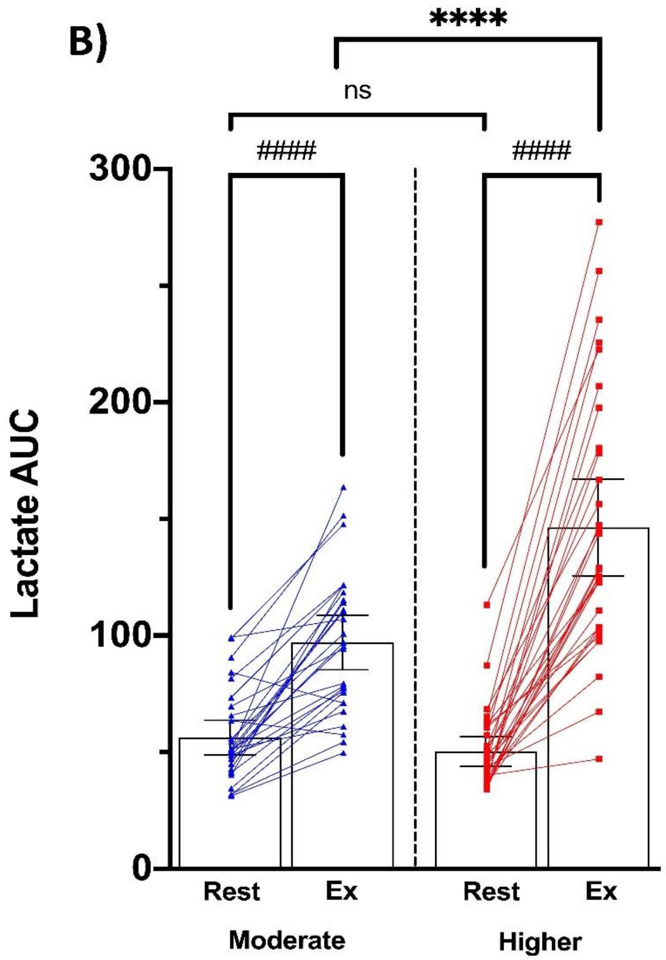

Brain glucose metabolism change tracks with lactate response

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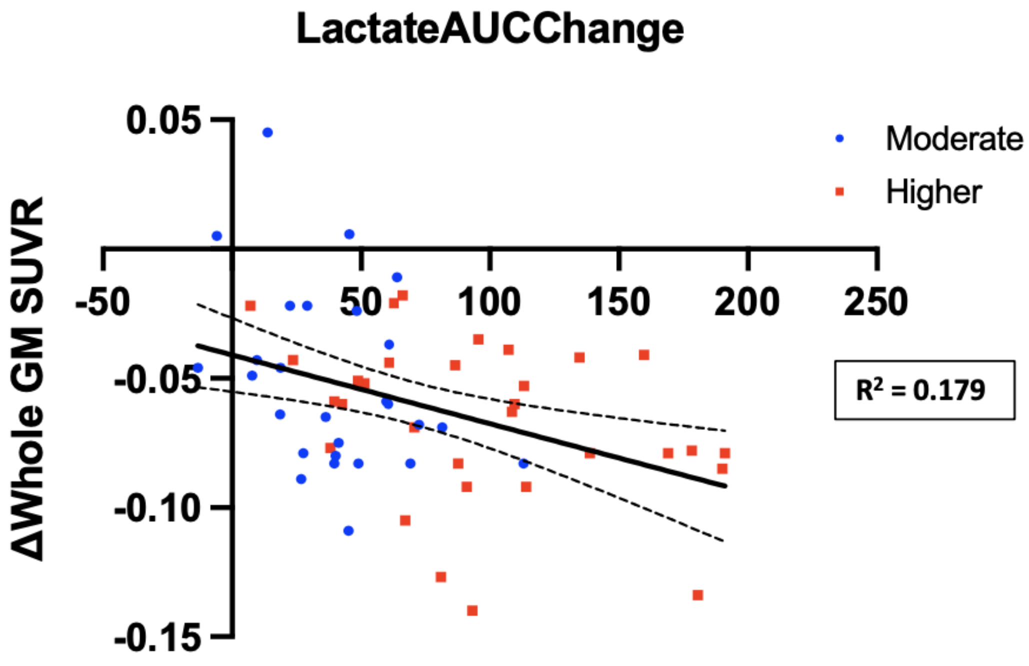
A)



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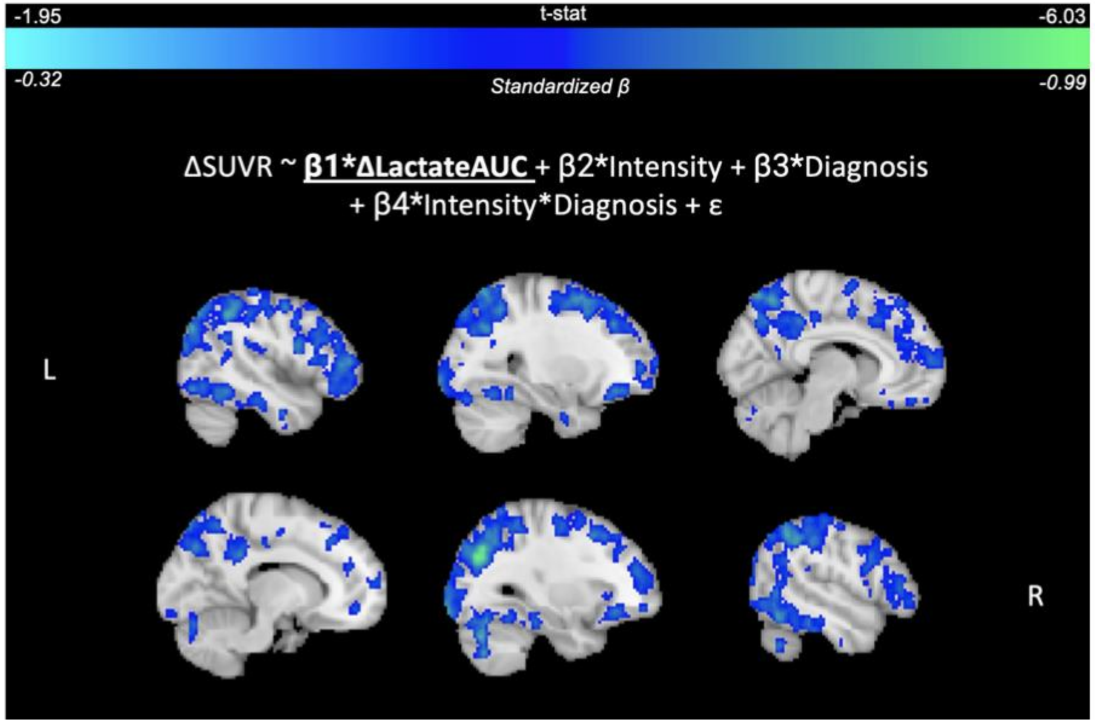

BDNF is released during exercise (PPP)

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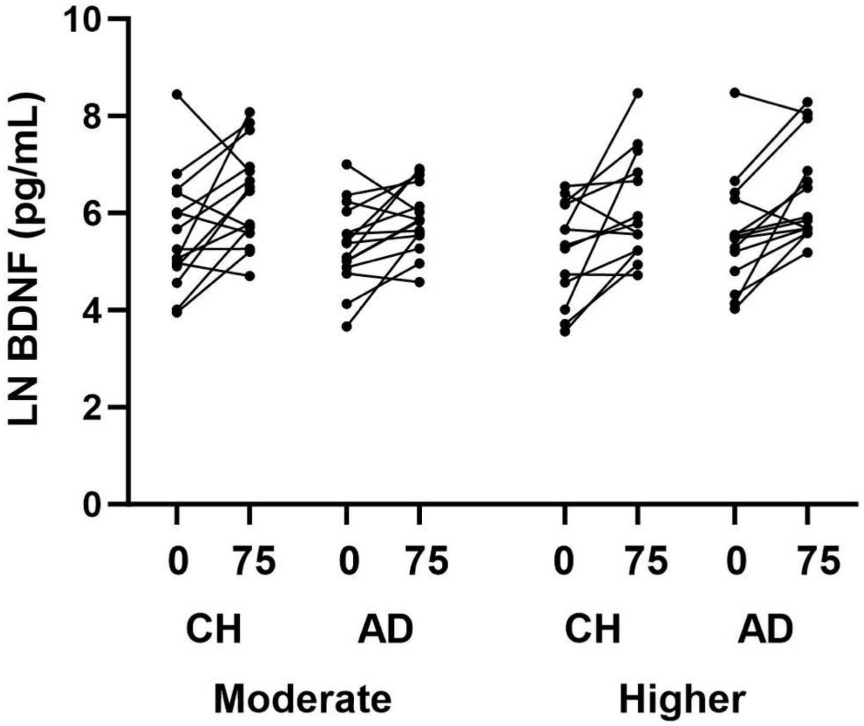
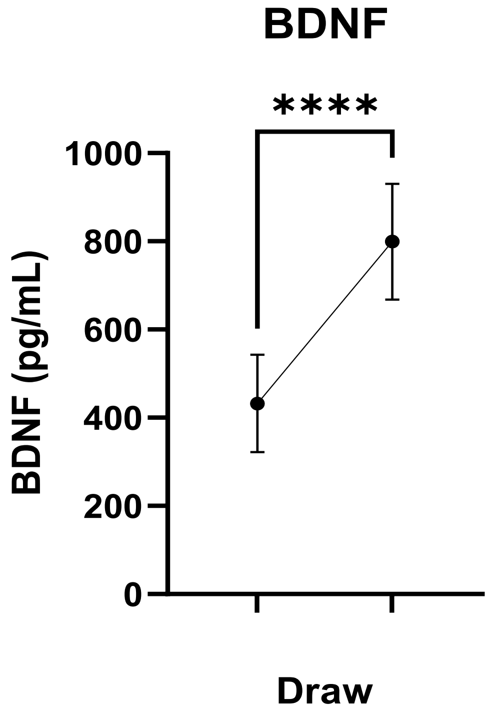
Blood processing matters!!





Summary of AEROBIC study

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- Brain metabolism is acutely affected by exercise
- Lactate increases with increasing exercise intensity
- Change in brain metabolism appears to be mediated by blood lactate concentrations (calculated here as AUC)
- BDNF increases post exercise

But what about Lactate by itself?

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- Lots of things change with exercise
- Concentrations don't tell the whole story: uptake and use

Follow up study: lactate infusion in the resting state

Collaboration w/ Ben Miller @ OMRF

Lactate for Energy and Neurocognition (LEAN) Study

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Lactate clamp procedure

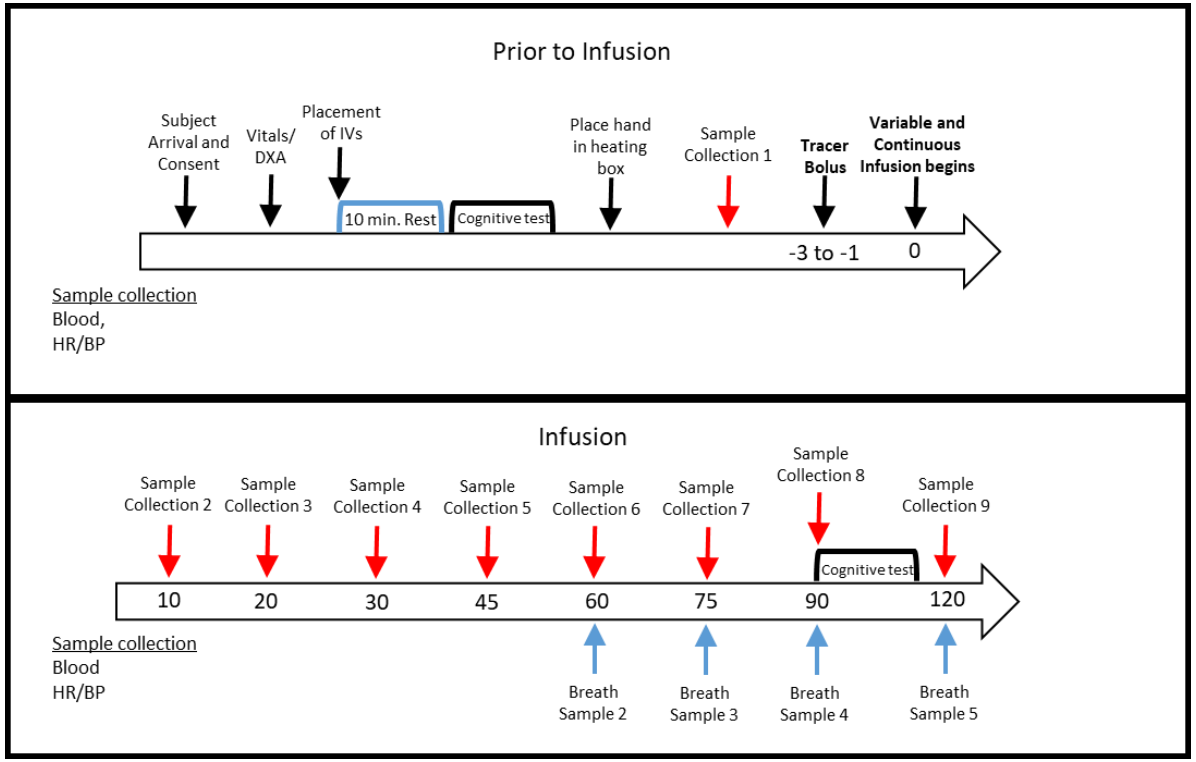
- 24 Cognitively healthy older adult or AD participants (from AEROBIC)
- Stable isotope infusion
- Blood and breath collection

Circulating lactate brought to 4-5mM @ rest

- Mimic effects of "exercise" without the exercise

Cognitive testing pre/post

Blood biomarker outcomes



No overall differences in lactate clearance (MCR) between CH and AD

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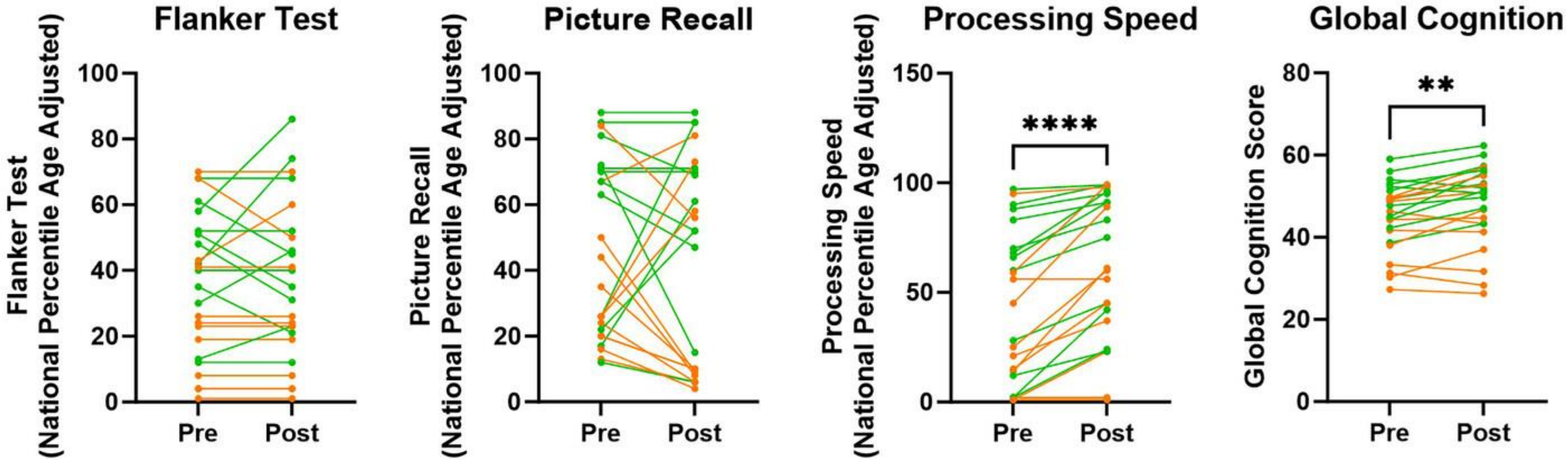
Measure	Cognitively Healthy	Alzheimer's Disease	P-value
Sex (#, % male)	7 (58%)	6 (50%)	0.682
Age (yrs)	67.6 [5.4]	78.9 [7.6]	0.000
APOE4 (#, %)	6 (50%)	6 (50%)	0.682
Lactate MCR (mg/kg/min)	22.9 [12.4]	22.8 [8.6]	0.516
Glucose MCR (mg/kg/min)	2.77 [1.0]	2.73 [1.4]	0.939
HbA1c (%)	5.67 [0.4]	5.67 [0.3]	0.399
RER (resting)	0.76 [0.1]	0.74 [0.1]	0.311

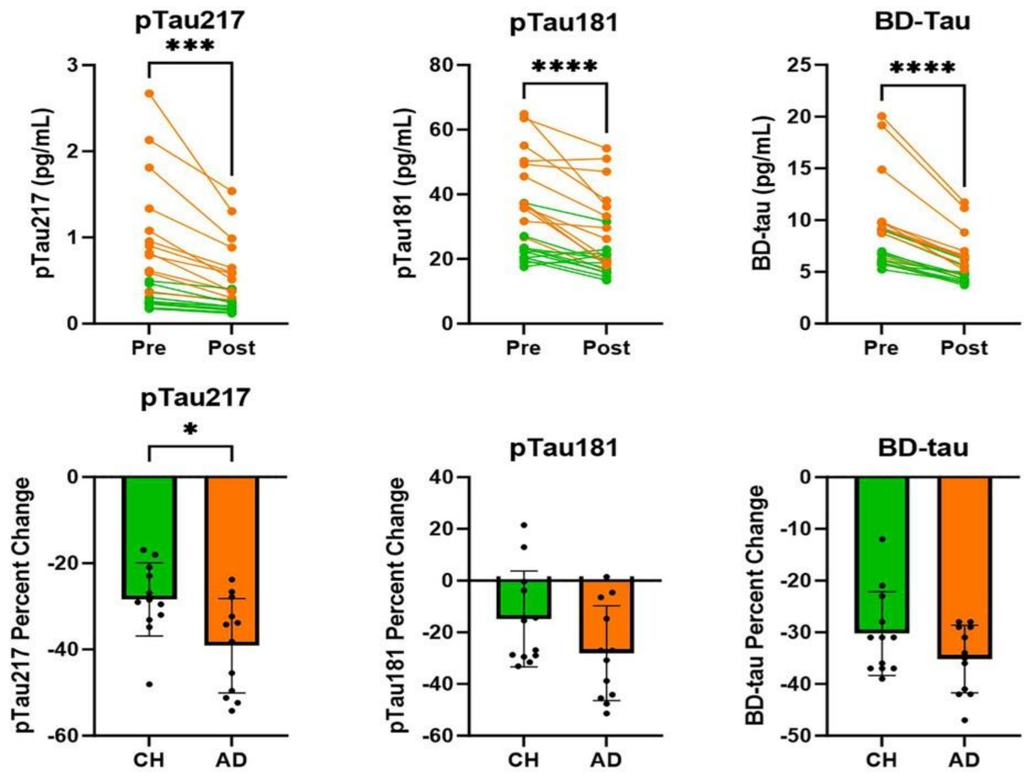
Kemna et. al 2025
PMID 41376120

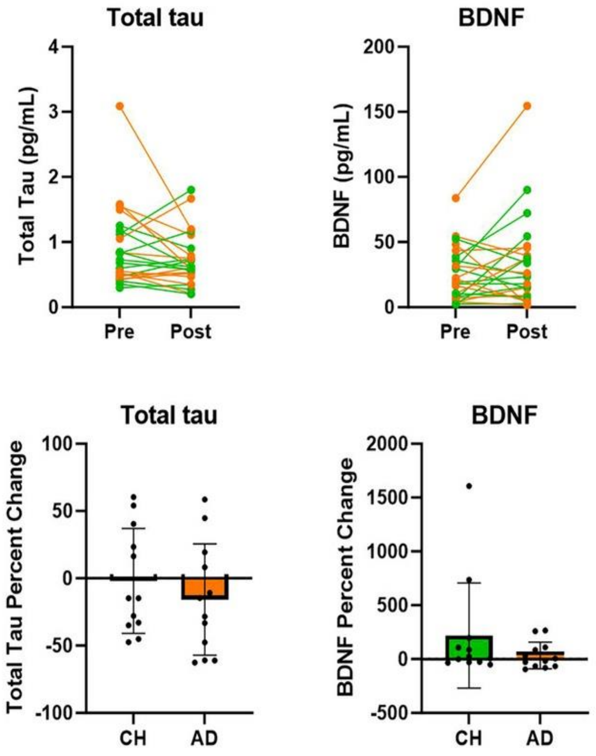
Global cognition improves post-infusion



Green: CN
Orange: AD

AD biomarkers decrease post-infusion

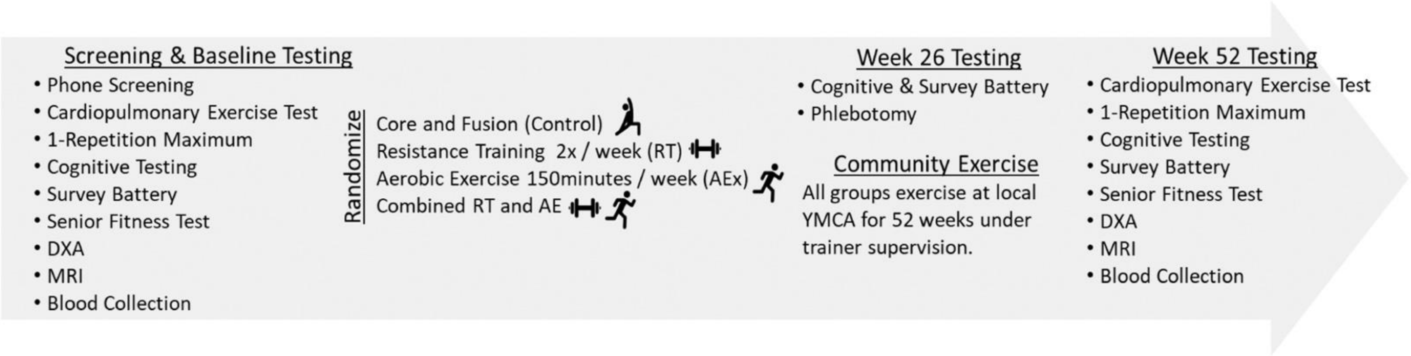




Summary of lactate infusion

- No differences in lactate turnover between diagnosis groups
- Improvement in cognitive performance
  - Control group needed to rule out practice effect
- Large changes in AD-related blood biomarkers with lactate infusion
  - Likely not due to changes in blood volume or kidney function
- Need to investigate mechanisms

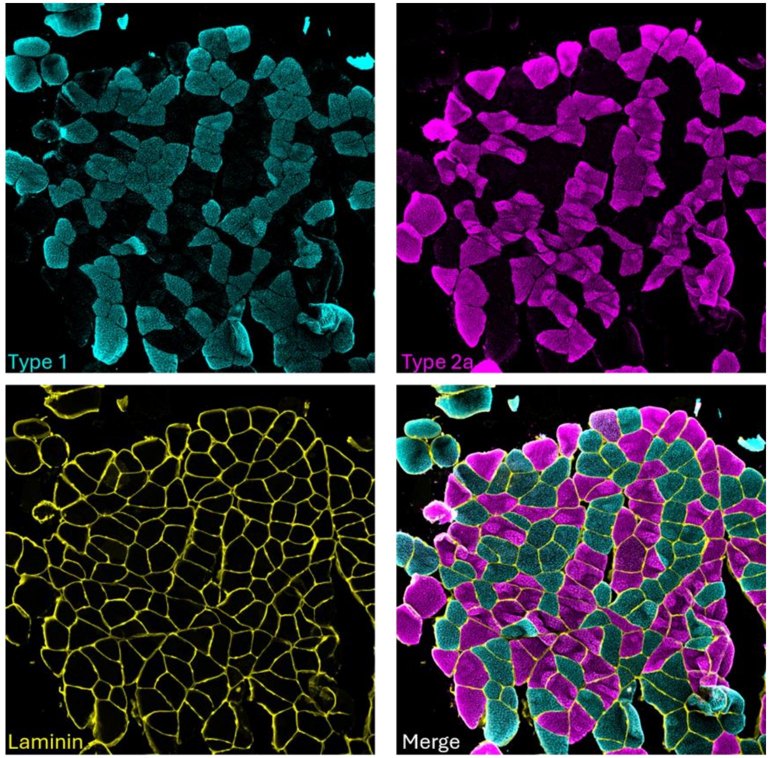
New Directions



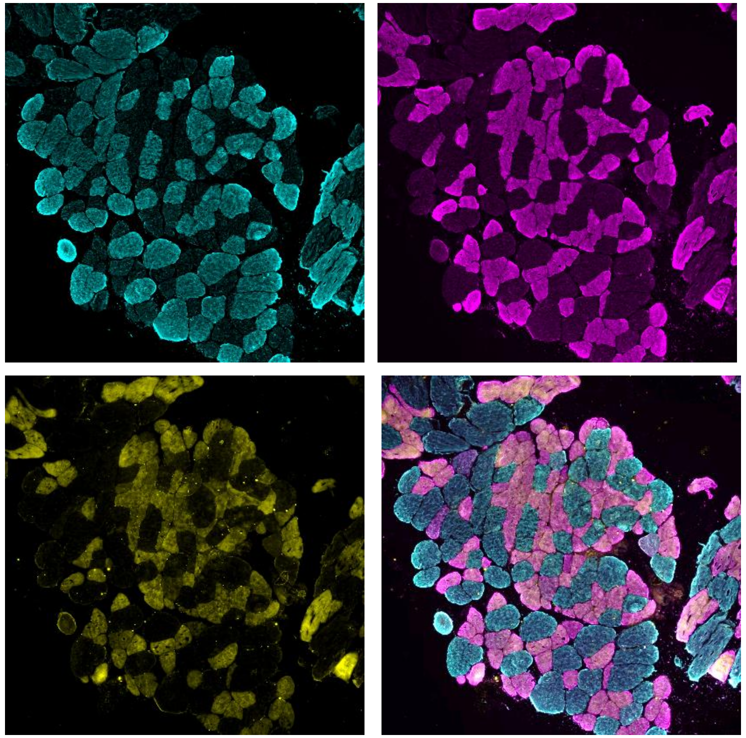
- Modalities
  - Combined Exercise Trial (COMET; NCT04848038)
  - Recruitment is complete. Acute responses pre/post - unblinded soon!
- Experimental designs
  - Can we harness acute differences to create personalized programs that are more effective at the individual level?
- Exercise “mimetics”
  - Heat therapy; NCT06023407

Emerging molecular mechanisms

- Muscle fiber types and energy use



- Type 1 fibers – Cyan
- Type 2a fibers – Lavender
- Yellow - Laminin



- Type 1 fibers – Cyan
- Type 2a fibers – Lavender
- Yellow – BD tau

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Thank you!

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Casey John, MS
Riley Kemna
Paul Kueck
Jenae Pennington
Hana Mayfield
Rachel Reaves
Raechel Camones
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Russell Swerdlow, MD
Benjamin Miller, PhD (OMRF)

Funding

NIH R01 AG062548
NIH R01 AG081304
NIH P30 AG035982 (KU ADRC)
Dickinson Family Foundation
Peg McLaughlin & Lydia Walker

Our Participants

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Intensity

GXT-determined HR ranges

Moderate

- 45-55% HRR

Higher

- 65-75% HRR