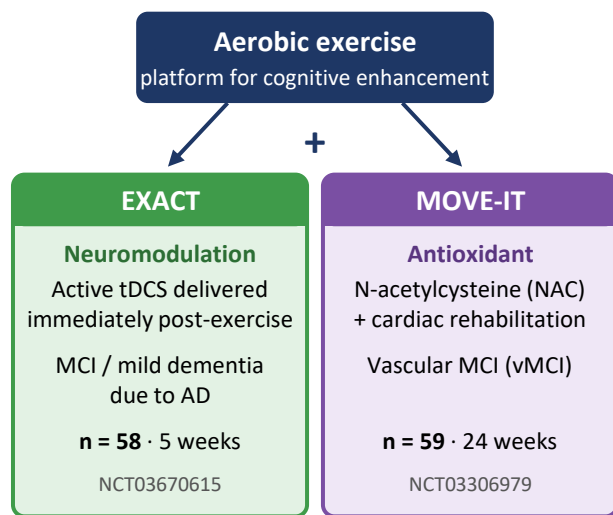


Background

- Aerobic exercise is a promising strategy for mitigating cognitive decline in early Alzheimer's disease (AD), including mild cognitive impairment (MCI) and mild AD dementia.
- However, individual responses are heterogeneous and there is no consensus on how to optimize exercise for cognition.
- This calls for a transition toward **targeted, precision-based exercise paradigms**, with exercise as a platform augmented by a second intervention.

Objective: To explore how exercise can be optimized for cognitive enhancement by comparing two distinct augmentation strategies.

Two Augmentation Strategies



Statistical Approach

- EXACT:** Modified intent-to-treat ANCOVA of endpoint word recognition (WR) errors with planned pairwise contrasts, adjusting for baseline WR and screening MoCA.
- MOVE-IT:** Intent-to-treat linear mixed-effects model of executive function (EF) composite scores over 24 weeks.
- All models adjusted for age, sex, years of education, and trial-specific covariates.
- Timing check (EXACT):** interval-specific sensitivity analysis separated the exercise-only ramp-up (T1→T2) from the stimulation period (T2→T3).
- Safety:** adverse events (AEs) compared between arms using χ^2 or Fisher's exact tests; tDCS side effects logged at every session.

EXACT: Exercise-Primed tDCS

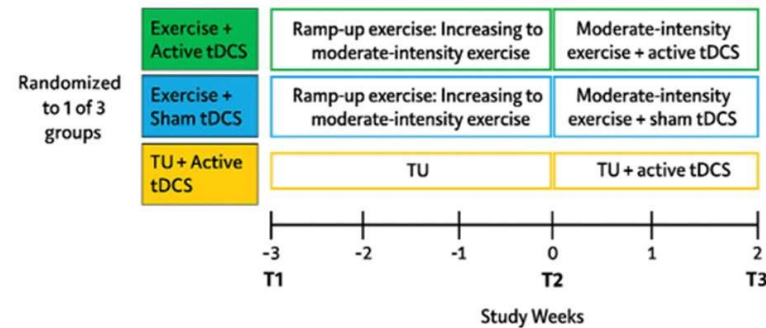


Figure 1. EXACT randomized, parallel-group design; participants blinded to stimulation (active vs sham). T1 = Screening, T2 = Baseline, T3 = Endpoint, TU = Treatment-as-usual.

Participants & Intervention

- Adults ≥ 50 years with MCI or mild dementia due to AD or mixed AD/vascular etiology; MMSE ≥ 19 .
- Exercise:** 30 min at each patient's first ventilatory threshold (VT_1), 5 days/week; 3-week ramp-up, then 2 weeks fully supervised.
- tDCS:** anodal T3/T4 (return at inion), 2 mA, 20 min, 10 sessions over 2 weeks, started *immediately* post-exercise.
- Primary outcome:** ADAS-Cog Word Recognition (WR) errors at endpoint.

Results

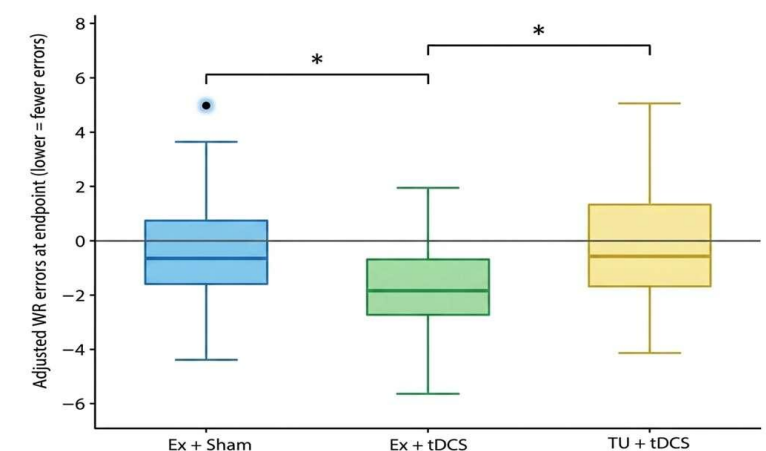


Figure 2. Covariate-adjusted WR errors at endpoint (lower = fewer errors). * $P < .05$

Contrast	B [95% CI]	P
Ex + tDCS vs Ex + Sham	-1.48 [-2.94, -0.01]	.049
Ex + tDCS vs TU + tDCS	-1.71 [-3.20, -0.21]	.026
Ex + Sham vs TU + tDCS	-0.23 [-1.77, 1.31]	.765

Planned contrasts; omnibus group effect $P = .91$. Groups did not diverge during the exercise-only ramp-up; the benefit emerged during the stimulation period. No group differences in word recall, MoCA, or 2-back.

Exercise-primed active tDCS **reduced word recognition errors** compared with either component alone.

MOVE-IT: NAC-Augmented Cardiac Rehab

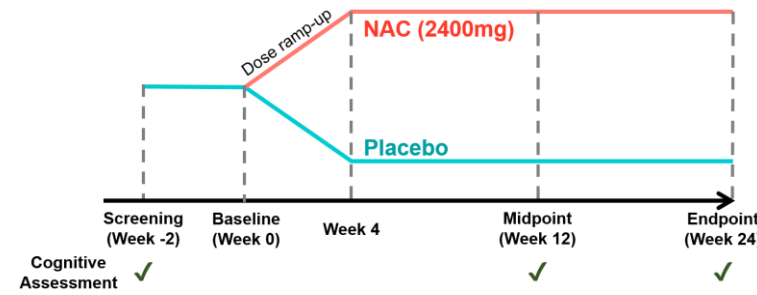


Figure 3. MOVE-IT 24-week, randomized, double-blind, placebo-controlled design. All participants were enrolled in exercise-based cardiac rehabilitation (CR).

Participants & Intervention

- Adults 55–85 years with coronary artery disease (CAD) or vascular risk factors enrolled in CR at UHN-TRI; vMCI (MoCA ≤ 27 and ≥ 1 SD below norms in ≥ 1 cognitive domain).
- CR:** supervised aerobic and resistance training, weekly in-person sessions plus home exercise.
- NAC:** titrated from 600 mg/day to 2400 mg/day by week 4, vs matching placebo.
- Adherence:** pill adherence 78.5% (NAC) vs 84.0% (placebo); CR attendance 70.7% vs 65.1% (both ns).
- Primary outcome:** EF composite (Trail Making Test B, Digit Symbol Coding, FAS fluency) at weeks 0, 12, 24.

Results

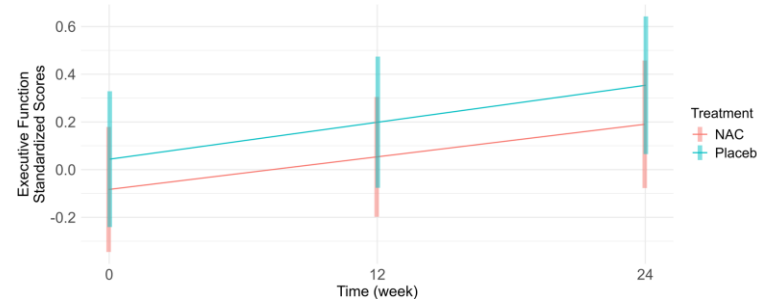


Figure 4. Standardized EF composite scores over time by treatment group. Estimated marginal means (95% CI) from a linear mixed-effects model adjusting for age, sex, and education.

Effect	B [95% CI]	P
EF: time (all participants)	0.31 [0.14, 0.48]	< .001
EF: NAC $\times$ time	-0.04 [-0.28, 0.20]	.80
Non-verbal memory: time	0.58 [0.35, 0.81]	< .001
MoCA: time	2.2 [1.1, 3.3]	< .01
VO _{2peak} : time (all participants)	4.02 [2.29, 5.76]	< .001

No NAC $\times$ time effect on any outcome (attention, working memory, verbal or non-verbal memory, MoCA). Nausea was more frequent with NAC (14.3% vs 0% during ramp-up).

Cardiac rehabilitation improved executive function and fitness, but **NAC conferred no additive benefit**.

Head-to-Head Summary

	EXACT	MOVE-IT
Population	MCI / mild dementia due to AD	vMCI
Exercise	Individualized aerobic	Cardiac rehab
Augmentation	tDCS right after exercise	NAC 2400 mg/day
Target	Cortical excitability	Oxidative stress
Tolerability	No serious AEs; $\uparrow$ burning sensation	No serious AEs; $\uparrow$ nausea
Additive benefit?	✓ Yes	✗ No

Discussion

- The clinical utility of exercise for cognition is **not uniform**, it depends on the chosen augmentation strategy.
- Exercise appears to open a **transient physiological window** that maximizes the brain's response to tDCS, which directly modulates cortical excitability.
- NAC added nothing to exercise, possibly because exercise already boosts antioxidant defences. Augmentation may work best when it targets a mechanism exercise does not.
- Both strategies were well-tolerated with no serious AEs. Mild burning under electrodes was more common with tDCS alone, and nausea with NAC.

Conclusion & Future Directions

- Pairing exercise with **timed neuromodulation** is a promising precision-based approach to cognitive enhancement in early AD.
- Exercise itself is a robust foundation, improving executive function, memory and fitness in vMCI.
- Future work should define the **optimal temporal dosing** of exercise and neuromodulation and test the **durability** of effects in larger, more diverse clinical populations.

Acknowledgements

We thank all participants. Supported by the Canadian Institutes of Health Research.



Trial registration: EXACT NCT03670615 · MOVE-IT NCT03306979
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