

Exercise Priming Of tDCS Enhances Cognitive Response: Results From The EXercise Augmenting Cognition tDCS (EXACT) Randomized Trial

Krista Lancot¹⁻³, Julian Schecter^{2,3}, Damien Gallagher², Sandra Black², Jocelyn Charles², Fuqiang Gao², Nathan Herrmann¹, Bradley J. MacIntosh²,

Giovanni Marotta², Susan Marzolini⁴, Sara B. Mitchell², Paul Oh⁴, Tarek Rajji⁵, Mark Rapoport², Mehreen Siddiqui²

¹Department of Psychiatry and Toronto Dementia Research Alliance, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, ²Sunnybrook Research Institute, Toronto, ON, Canada, ³Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada, ⁴University Health Network - Toronto Rehabilitation Institute, Toronto, ON, Canada, ⁵UT Southwestern Medical Center, Dallas, TX, USA.



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Sunnybrook
HEALTH SCIENCES CENTRE

Background

- Transcranial direct current stimulation (tDCS) cognitive benefits in mild cognitive impairment (MCI) and early Alzheimer's disease (AD) are modest and dependent on the state of cortical networks
- Aerobic exercise transiently ↑ cortical excitability and neurotrophic signaling, creating a physiological context to potentially augment neuromodulation

Objective: To determine if moderate-intensity aerobic exercise administered immediately prior to tDCS enhances recognition memory

Methods

- 5-week, randomized, blinded, repeated-session, parallel-group clinical trial (NCT03670615) conducted at SHSC and UHN-TRI

Exercise Prescription: Individualized aerobic intensity prescribed at each patient's first ventilatory threshold to maximize peak cerebral perfusion

Study Participants

- Older adults (≥ 50 years) with a diagnosis of MCI or mild dementia due to AD or mixed AD/vascular etiology
- Baseline MMSE score ≥ 19, reads and communicates in English
- Excluded if recent (< 3 months) cognitive-enhancing/psychotropic medication changes; benzodiazepine use; metal implants (tDCS contraindication); significant neurological or major psychiatric disorders

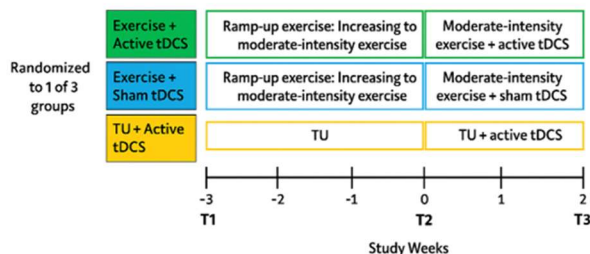


Figure 1. EXACT study design and timeline. T1 = Screening, T2 = Baseline, T3 = Endpoint, TU = Treatment-as-usual

- tDCS parameters:** Soterix Medical mini-CT Stimulator. Bipolar montage over T3 and T4 (20 minutes, 2 mA, 10 total sessions over 2 weeks). tDCS delivered *immediately* post-exercise to capitalize on heightened cortical excitability
- Primary outcome:** ADAS-Cog Word Recognition (WR) Task performance at study endpoint (T3). ANCOVA model evaluating endpoint WR performance, adjusting for baseline WR, screening MoCA, age, sex, and education

Results

Table 1. Screening demographics and clinical characteristics by treatment group

Mean (SD) or n (%)	Ex + tDCS (n = 19)	Ex + Sham (n = 20)	TU + tDCS (n = 19)	P
Age (y)	77 (8.3)	75 (7.7)	76.5 (8.0)	.71
Sex (% female)	8 (42.1%)	8 (40%)	12 (63.2%)	.28
Ethnicity (% white)	15 (78.9%)	11 (55%)	12 (63.2%)	.65
Education (y)	16.2 (3.4)	17 (2.8)	15.3 (1.5)	.16
BMI (kg/m ²)	27.1 (4.0)	26.2 (3.5)	24.8 (4.0)	.17
Baseline physical activity (LTEQ)	33.6 (21.5)	21.7 (19.1)	24.2 (15.0)	.12
Diagnosis (% mild NCD)	15 (78.9%)	16 (80%)	11 (57.9%)	.22
Etiology (% pure AD)	5 (26.3%)	7 (35%)	10 (52.6%)	.23
MMSE score	27.1 (2.5)	27.1 (2.9)	26.1 (2.5)	.43

Figure 2. Covariate-adjusted word recognition errors at endpoint by treatment group

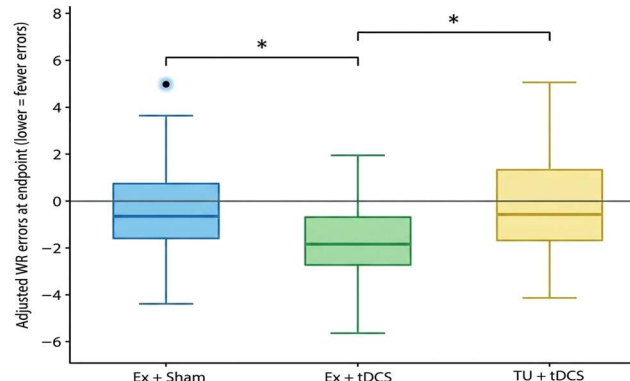


Table 2. Interval-specific planned contrasts in ADAS-Cog word recognition performance

A. Three-week exercise ramp-up (Screening → Baseline)

Contrast	B*	SE*	P*
Ex + tDCS vs TU + tDCS	0.48	0.71	.505
Ex + tDCS vs Ex + Sham	0.21	0.70	.765
Ex + Sham vs TU + tDCS	0.27	0.70	.704

B. tDCS immediately post-exercise intervention period (Baseline → Endpoint)

Contrast	B*	SE*	P*
Ex + tDCS vs TU + tDCS	-1.88	0.70	.008
Ex + tDCS vs Ex + Sham	-1.38	0.69	.047
Ex + Sham vs TU + tDCS	-0.51	0.70	.471

Discussion

- Combining an aerobic exercise primer with active tDCS **significantly reduced word recognition errors** compared to both TU + tDCS and Ex + Sham
- The lack of group divergence during the three-week exercise ramp-up shows that exercise training alone was insufficient to alter memory trajectories before neuromodulation began
- These findings support a sequential model where **exercise acts as a neural primer**, optimizing the cortex to maximize the plastic changes induced by subsequent tDCS
- Selective improvement on the word recognition task**, contrasted with stable MoCA scores, suggests that the intervention preferentially affects specific frontotemporal memory networks

Feasibility: High session compliance (96.9% in all groups) and minimal dropout among all treatment arms confirm that this protocol is practical and well-tolerated by older adults

Safety: No serious adverse events were reported across any of the treatment groups. Mild, transient side effects (mild itching or tingling under the electrodes) were comparable in incidence between the active and sham stimulation conditions

Conclusion

- An exercise primer with active tDCS provides a superior cognitive benefit compared to either intervention component delivered independently
- Ongoing and future analyses of the cohort's blood-based biomarkers will evaluate changes in angiogenesis, inflammation, and oxidative stress pathways to determine the drivers of these cognitive gains
- This multi-modal strategy offers a non-pharmacological framework ready for development to manage memory decline in older adults

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Contact Info: Dr. Krista Lancot, krista.lancot@sunnybrook.ca