

Vascular risk as a predictor of treatment response in the EXACT trial

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Background

- Vascular pathology frequently co-occurs with neurodegeneration and may influence response to exercise intervention therapies
- The Exercise Augmenting Cognition tDCS (EXACT) trial demonstrated that moderate-intensity exercise significantly augments the cognitive efficacy of bitemporal transcranial direct current stimulation (tDCS) in patients with early Alzheimer’s dementia (AD)
- It is unclear how the presence of vascular risk factors at baseline influences treatment outcomes

Objectives

- Investigate whether vascular pathology moderates patient response to exercise-primed tDCS
- Clarify mechanisms of treatment resistance and inform personalized neuromodulation strategies.

Methods

- 58 participants with early AD were randomized into one of three 2-week interventions
 - Exercise plus active tDCS
 - Exercise plus sham tDCS
 - treatment-as-usual (TU) plus active tDCS
- Baseline diagnostic etiology was dichotomized via neuroimaging, distinguishing pure AD patients from those with mixed AD/vascular disease
- Baseline vascular risk was dichotomized by the presence of ≥ 1 vascular risk
- ANCOVA evaluated whether etiology/vascular risk moderated treatment effects measured by MoCA and TwoBack D-prime change scores
- Logistic regressions assessed predictors of clinical response, defined by an improvement of test scores of ≥ 1 SD
- All models were adjusted for age, sex, education, and baseline MoCA scores

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Results

Table 1. Participant characteristics

	Exercise + tDCS (n = 20) mean $\pm$ SD or n (%)	Exercise + sham (n = 21) mean $\pm$ SD or n (%)	TU + tDCS (n=19) mean $\pm$ SD or n (%)	p-value
Age (years)	77.2 $\pm$ 8.1	74.9 $\pm$ 7.5	78.4 $\pm$ 7.2	0.34
Sex (female)	9 (45%)	8 (38%)	13 (68%)	0.14
Years of Education	16.2 $\pm$ 3.4	17.1 $\pm$ 2.8	15.3 $\pm$ 1.5	0.12
Baseline MoCA Score	21.2 $\pm$ 3.1	22.6 $\pm$ 3.9	20.4 $\pm$ 4.2	0.17
Obesity	5 (25%)	4 (19%)	2 (11%)	0.48
Hypertension	6 (30%)	8 (38%)	6 (32%)	0.82

Table 1. Baseline characteristics of study cohort stratified by treatment group.

Figure 1a. MoCA Total Score Change by Treatment Group and Etiology

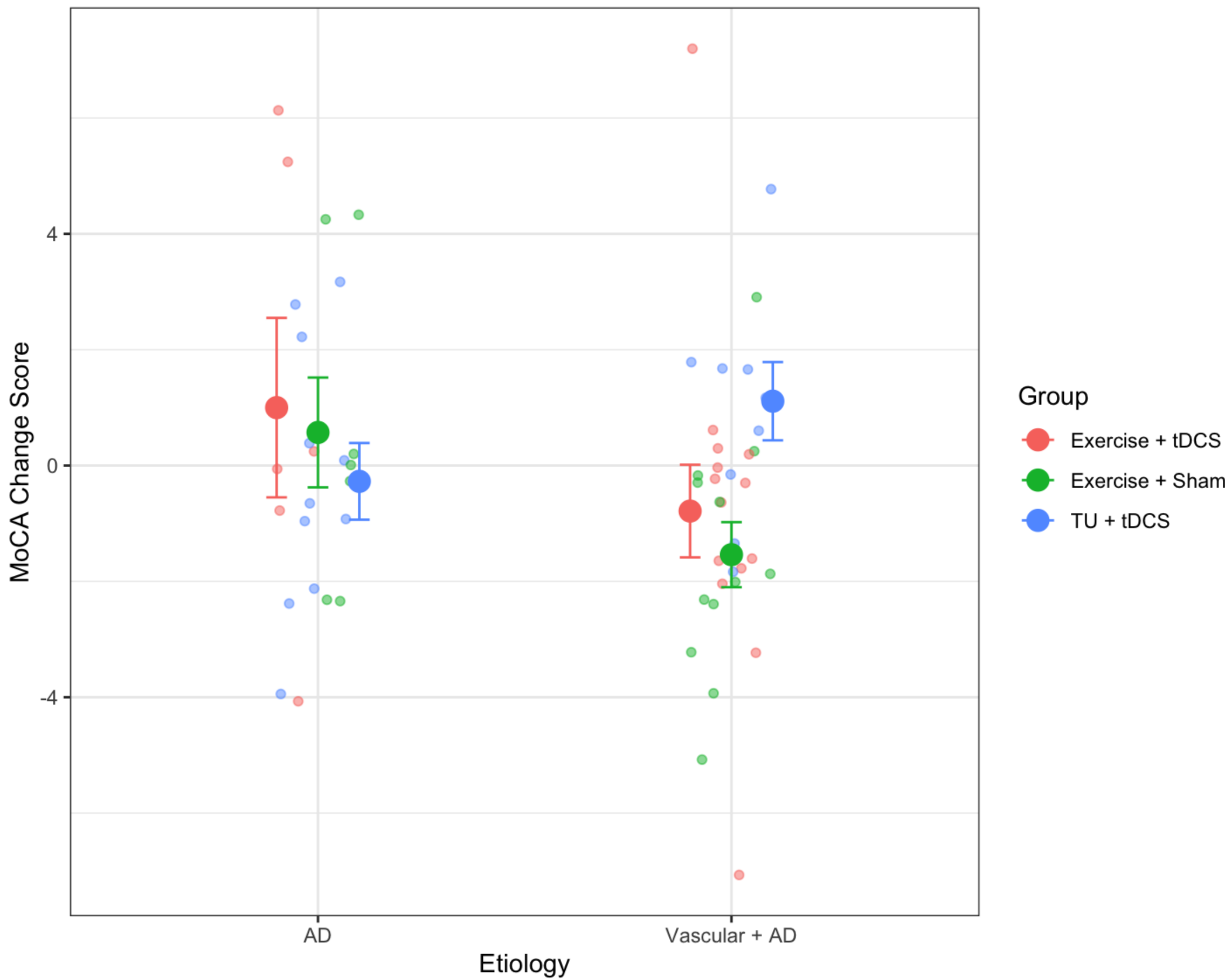


Figure 1a. ANCOVA revealed a significant treatment-by-etiology interaction for MoCA change scores ($F= 3.71$, $P=.034$). Participants with pure AD showed cognitive improvement following exercise-primed tDCS (1.00 ± 3.79). Participants with mixed AD showed cognitive improvement TU + tDCS (1.38 ± 2.00), but declined with exercise-primed tDCS (-0.79 ± 2.99)

Figure 1b. Twoback D-prime Score Change by Treatment Group and Etiology

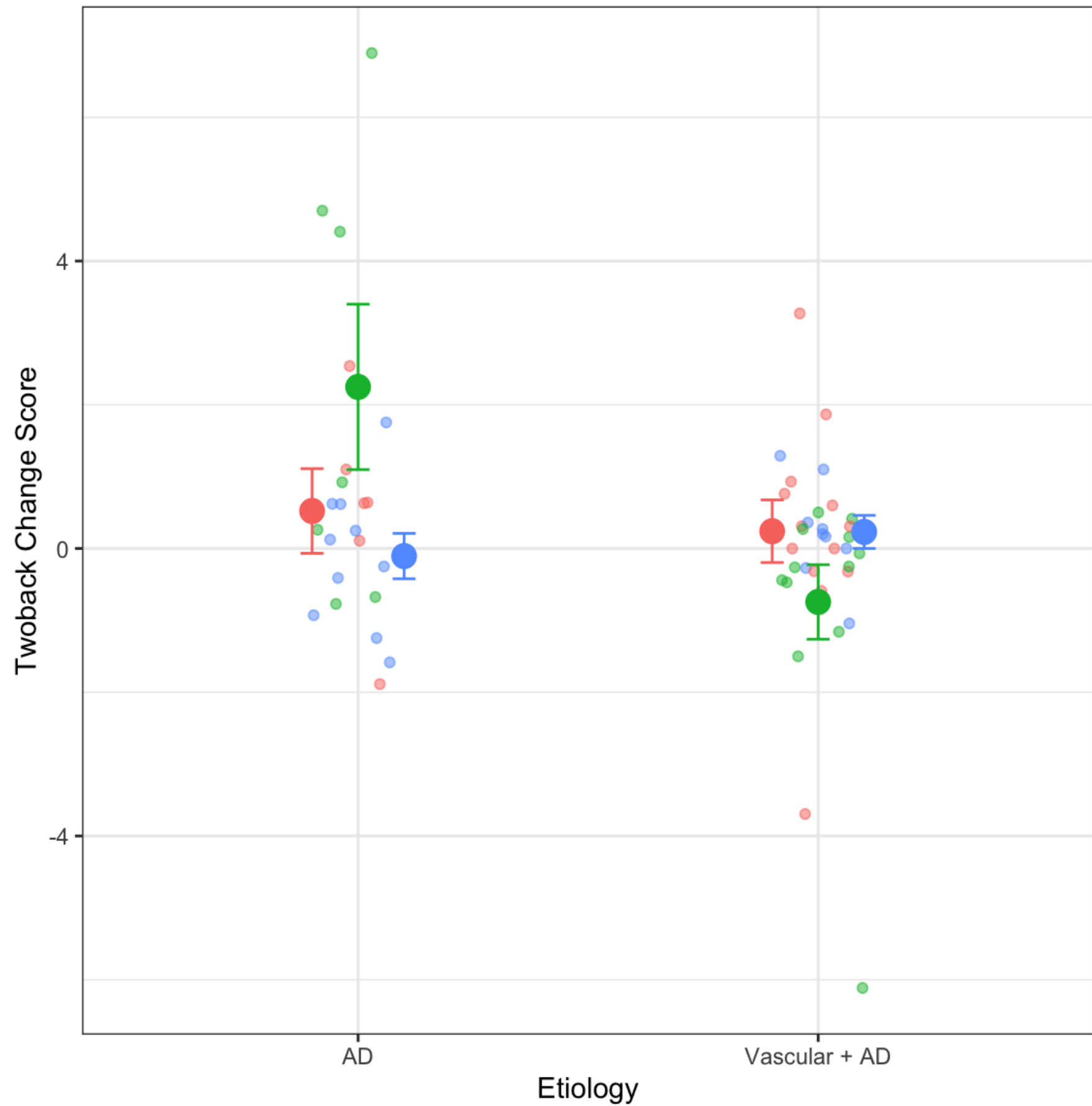


Figure 1b. ANCOVA showed a significant treatment-by-etiology interaction ($F= 3.53$, $P=.037$). Participants with pure AD showed greater improvement in working memory following exercise treatments (0.52 ± 1.44 , 2.23 ± 3.04), whereas participants with mixed AD showed little change regardless of treatment.

Figure 2. Clinically Meaningful MoCA Improvement by Treatment Group and Etiology

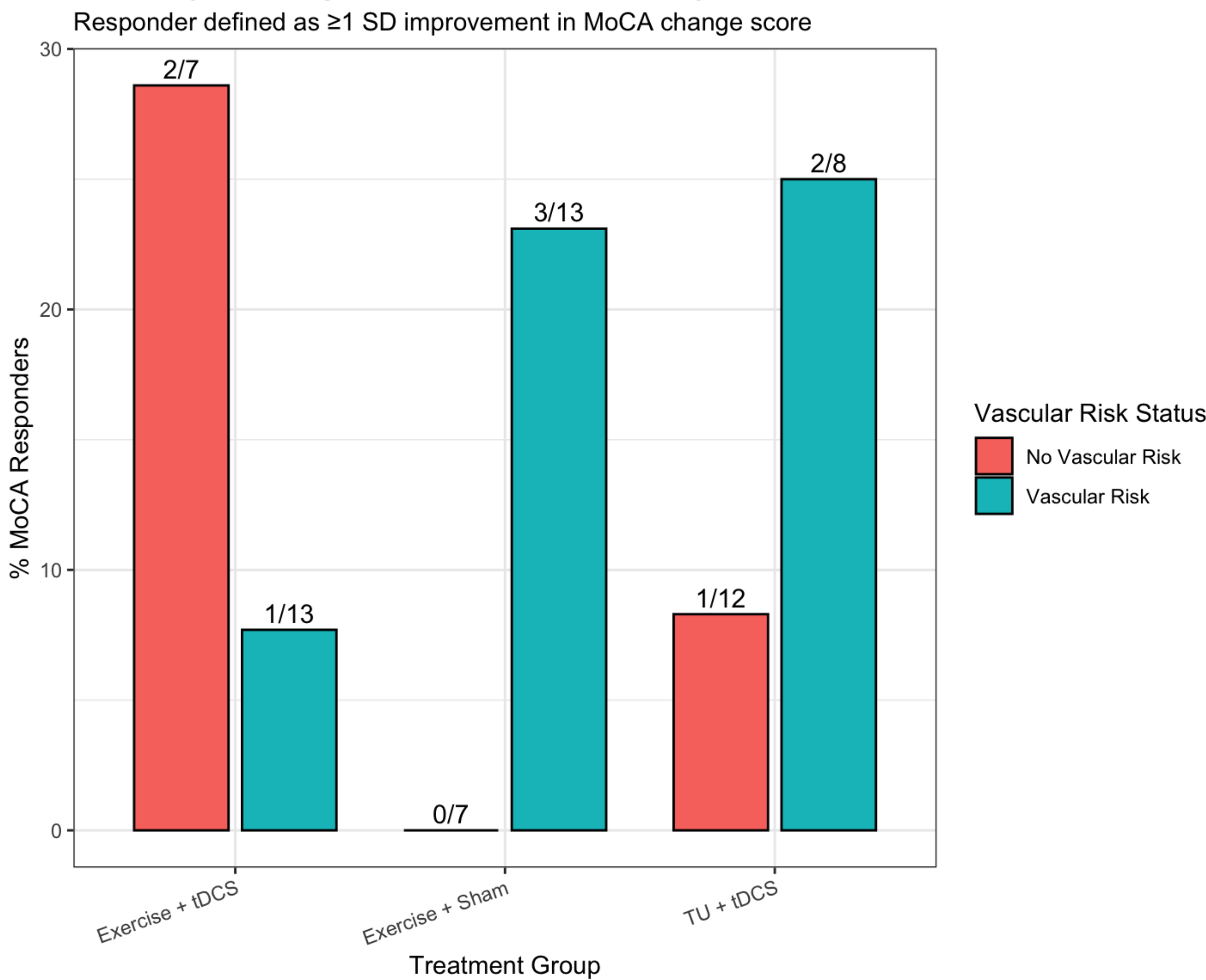


Figure 2. MoCA responders were defined as participants with ≥ 1 SD MoCA improvement. No-risk participants most frequently responded to exercise + tDCS, while participants with vascular risk factors showed higher response in non-combined treatments($T= 1.97$, $P=.050$).

Table 2. Proportion of MoCA Improvements by Treatment Group and AD Etiology

Treatment Group	Etiology	Total n	Improved n
Exercise + tDCS	AD	6	2 (33.3%)
Exercise + tDCS	Probable VaD	14	2 (14.3%)
Exercise + sham	AD	7	2 (28.6%)
Exercise + sham	Probable VaD	13	1 (7.7%)
TU + tDCS	AD	11	3 (27.3%)
TU + tDCS	Probable VaD	8	6 (75.0%)

Table 2. Logistic regressions confirmed a significant interaction predicting responder status ($P=.011$). 75% of mixed AD participants responded to TU + tDCS versus 14% in the exercise-primed group.

Conclusions

- Baseline etiology and vascular risk moderated treatment response
- Participants with mixed AD/vascular disease benefitted from active tDCS + TU, while those without vascular pathology required active aerobic exercise priming to achieve benefit
- Patients with mixed AD may require a longer initial exercise ramp-up period before combined treatment begins, allowing sufficient time for cerebrovascular remodeling and reductions in arterial stiffness that may be necessary for effective priming.
- Accounting for vascular profiles is critical to understanding treatment resistance and personalizing treatment protocols in early dementia