

Reduced Cerebrovascular Reactivity in Mild Cognitive Impairment and Alzheimer's Disease Assessed by CO₂ Challenge fMRI

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BACKGROUND

Cerebrovascular reactivity (CVR) is the brain's ability to regulate blood flow through dilation and and constriction of small arteriole vessels. Reduced CVR is a known hallmark of vascular disease and a risk factor for Alzheimer's Disease (AD). Traditional CVR assessments in older adults use breath-holding or resting-state functional MRI, but these methods may fail to reach a vessel's full dilatory capacity. Here, we employed a strong CO₂ stimulus during functional MRI to map CVR. We investigated whether this robust measure of CVR serves as a marker of vascular impairment and subsequent cognitive deficits.

OBJECTIVES

1. Compare CVR in controls against individuals with Mild Cognitive Impairment (MCI) who are at risk of progressing to AD, and individuals with AD
2. Investigate relationship between CVR and global cognition measured by the Montreal Cognitive Assessment (MoCA)

METHODS

Study Population

- 13 cognitively normal (10F; 67±6 years)
- 12 with MCI (7F; 71±6 years)
- 4 with AD (4F, 73±6 years)
- MCI and AD were diagnosed at the University of Washington Alzheimer's Disease Research Center Consensus Conference using UDS v3.0 and CDR, among other criteria (**Controls:** CDR = 0, **MCI:** CDR = 0.5, **AD:** CDR = 1)

Magnetic Resonance Imaging

- 3D T1-weighted image
- 8-minute functional MRI scan

Analysis

- CVR calculated as change in percent BOLD signal per change in end-tidal CO₂ (mmHg)
- Average CVR in gray matter compared between groups with Wilcoxon rank sum
- Association between MoCA scores and CVR (adjusted for age and sex) evaluated with linear regression

RESULTS

A. Gas Delivery



B. Group Average Timeseries

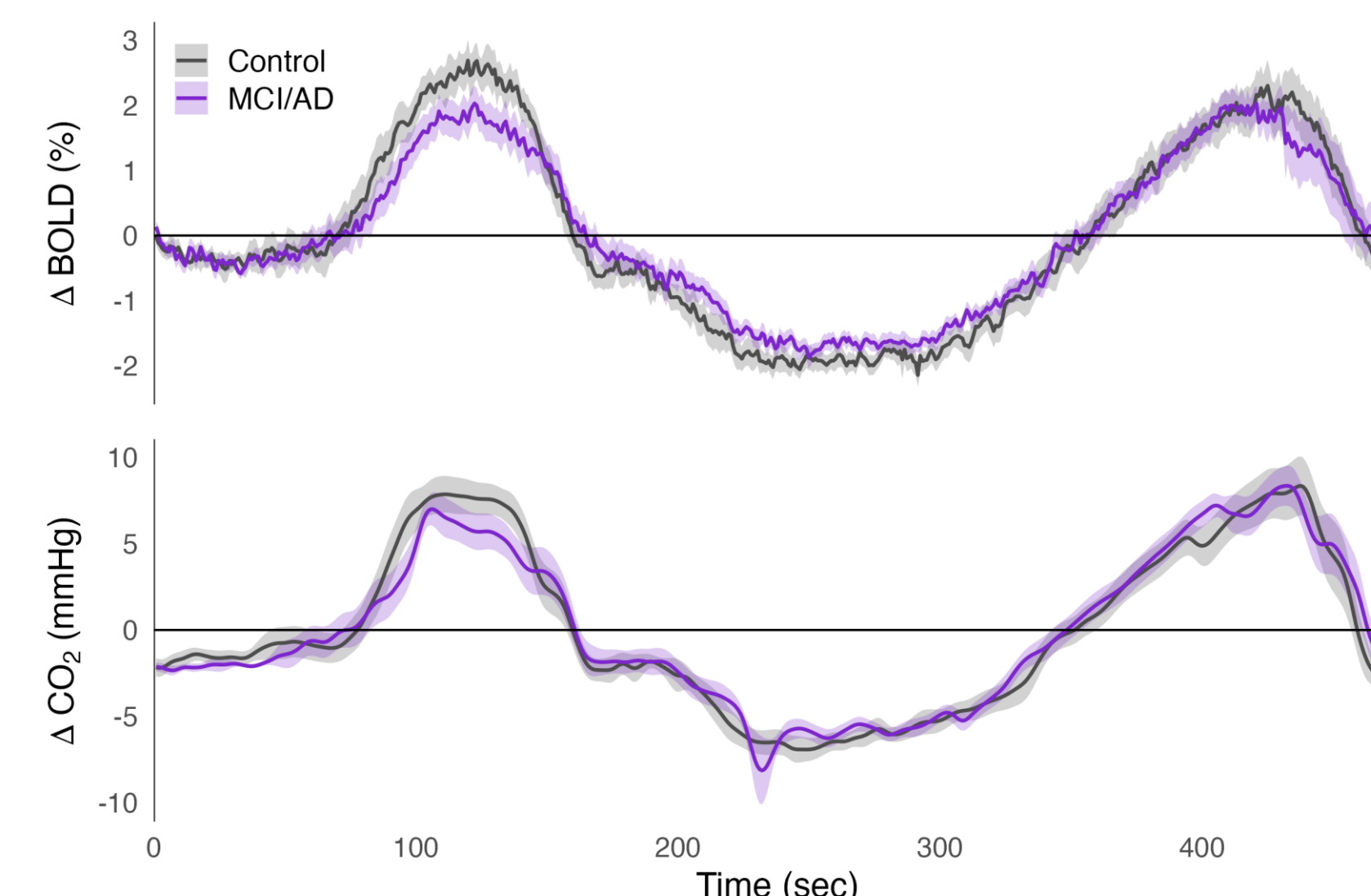


Figure 1: A) Example of the RespirAct™ (Thornhill Medical) gas delivery system worn by participants during an 8-minute fMRI scan. **B)** Group average (Control vs. MCI/AD) blood-oxygenation-level dependent (BOLD) fMRI and end-tidal carbon dioxide (CO₂) traces, shown as mean ± standard error. There were six stages of CO₂ modulation: a 60-second baseline, 60-second hypercapnia (+10 mmHg), 60-second baseline, 60-second hypocapnia (-5 mmHg), 180-second ramp (-5 to +15 mmHg), and a final baseline.

Cerebrovascular reactivity to a strong, dynamic CO₂ stimulus was significantly lower in individuals with MCI or AD.

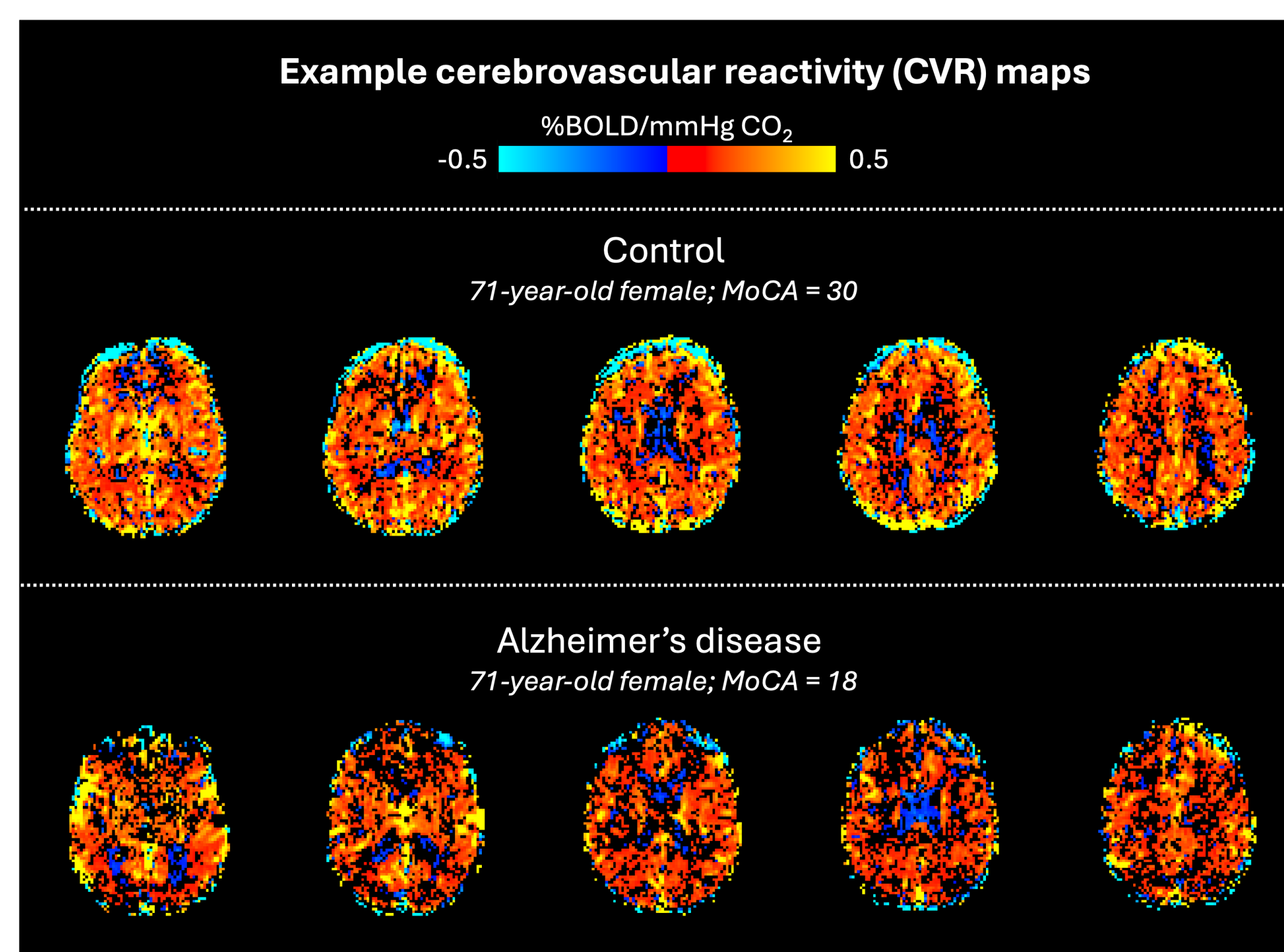


Figure 2: Example CVR maps in an adult with Alzheimer's disease and an age-matched, sex-matched control. CVR is the change in cerebral blood flow to a stimulus, reported here as the percent change in blood-oxygenation-level dependent (%BOLD) fMRI signal per change in CO₂ pressure (in mmHg). Maps show only voxels with a significant fit ($\alpha = 0.05$) between CO₂ and BOLD signals.

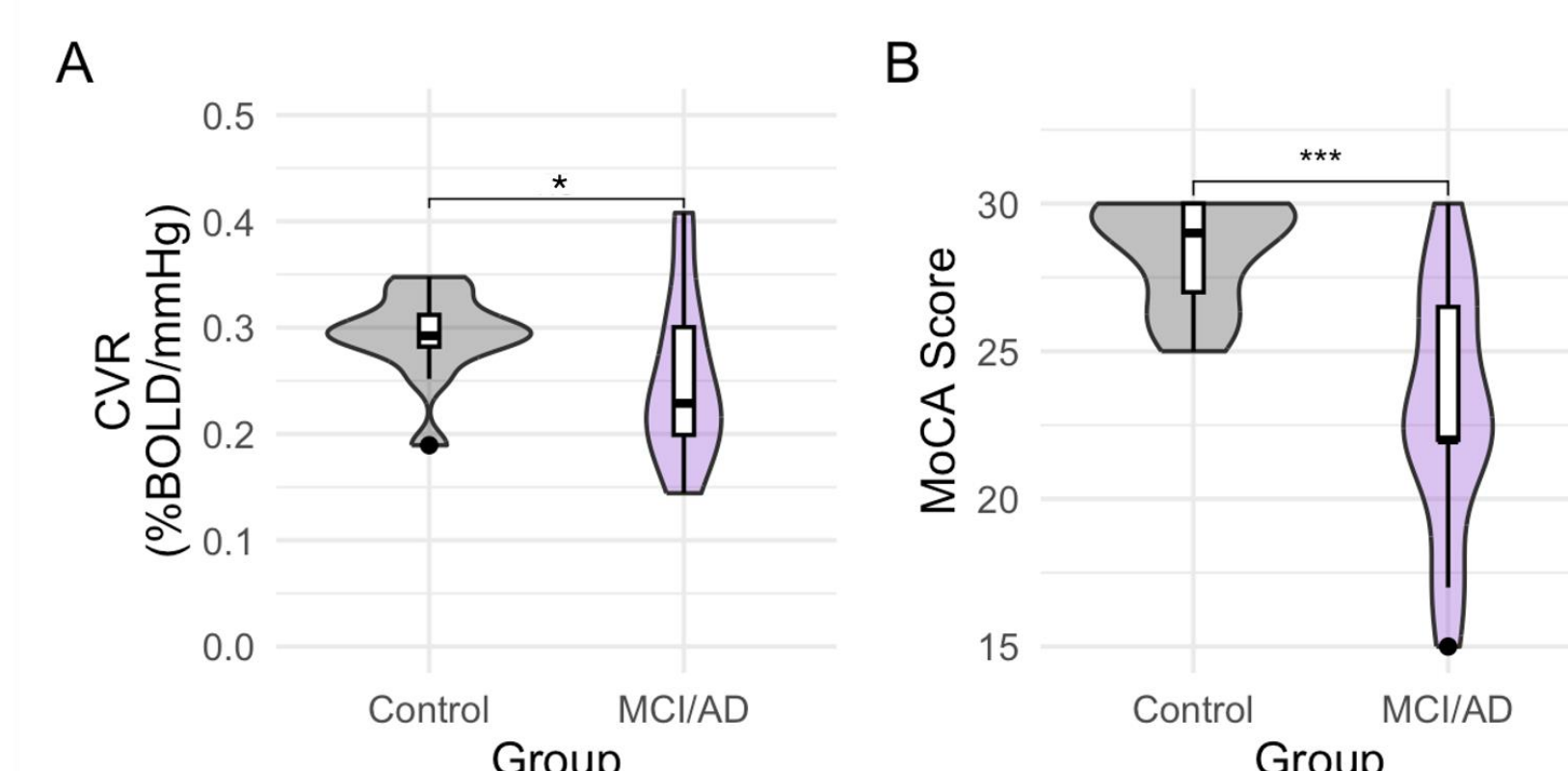


Figure 3: A) Comparison of CVR, averaged in gray matter. The lowest CVR value in the control group is an outlier based on Grubb's test ($G = 2.54$, $p=0.02$) and was removed from statistical testing. **B)** Comparison of MoCA scores.

DISCUSSION

Cerebrovascular Reactivity

- Deficit in MCI/AD appears to be impairment of vascular reaction speed, rather than lack of vasodilatory capacity. The normal response to the gradual ramp suggests vessels can still dilate fully when given ample time to adapt.
- Lower CVR in MCI/AD groups is consistent with previous studies and supports role of vascular dysfunction in disease progression
- CVR can be impaired even while resting cerebral perfusion is maintained, making it a potential early biomarker for cognitive decline

Association of CVR and MoCA Scores

- We did not observe a significant relationship between CVR and MoCA scores, although this has been reported in the literature
- This may be due to our sample size, or the nature of our CO₂ stimulus

Future Work

- Explore association of CVR with executive function, a well-known impairment in individuals with cerebrovascular disease
- Explore relationship between CVR & markers of endothelial health (VEGF, E-selectin)
- Compare CVR delay (the timing of the blood flow response) between groups

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