

Combining Cerebral Blood Flow and Cerebrovascular Reactivity Enhances Multivariate Classification of Mild Cognitive Impairment

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Introduction

- Cerebrovascular dysfunction is increasingly recognized as an early contributor to cognitive decline and may precede or accompany neurodegenerative change.
- Cerebral blood flow (CBF) reflects baseline perfusion whereas cerebrovascular reactivity (CVR) reflects dynamic vascular reserve during hypercapnia.
- Prior work suggests both CBF and CVR are altered in mild cognitive impairment (MCI), particularly in posterior cingulate, precuneus, and parietal cortex
- Multivariate pattern analysis (MVPA) provides a framework for integrating spatially distributed vascular information

Objective

Determine whether combining arterial spin labeling (ASL) -derived CBF and breath-hold CVR improves multivariate classification of clinically defined MCI compared with either modality alone.

Methods

Participants

- 37 clinically-defined MCI and 48 cognitively unimpaired control subjects
- MRI acquisition + preprocessing**
- 3D T1-MPRAGE
- Multi-delay pseudocontinuous ASL (pCASL) for ATT-corrected CBF
- Multiband multi-echo breath-hold BOLD fMRI for CVR.
- Functional images were distortion-corrected, volume registered, denoised with multi-echo independent component analysis (ME-ICA) denoising, and normalized to MNI space
- CVR was estimated with a GLM using the respiration response function (RRF)

Searchlight MVPA

- MVPA (radius=3 voxels) used a support vector machine classifier with k-fold cross-validation
- Performance was evaluated using area under the receiver operating characteristic curve (AUC)
- Feature sets were CBF-only, CVR-only, and concatenated CBF+CVR.

Statistical analysis

- Label-permutation testing (1000 permutations) estimated empirical significance for classifier performance.
- Schaefer-400 ROIs summarized regional mean AUC; top ROIs were ranked by CBF+CVR AUC.
- Multimodal gain was computed as $\Delta AUC = CBF+CVR - \text{best unimodal model}$

Results

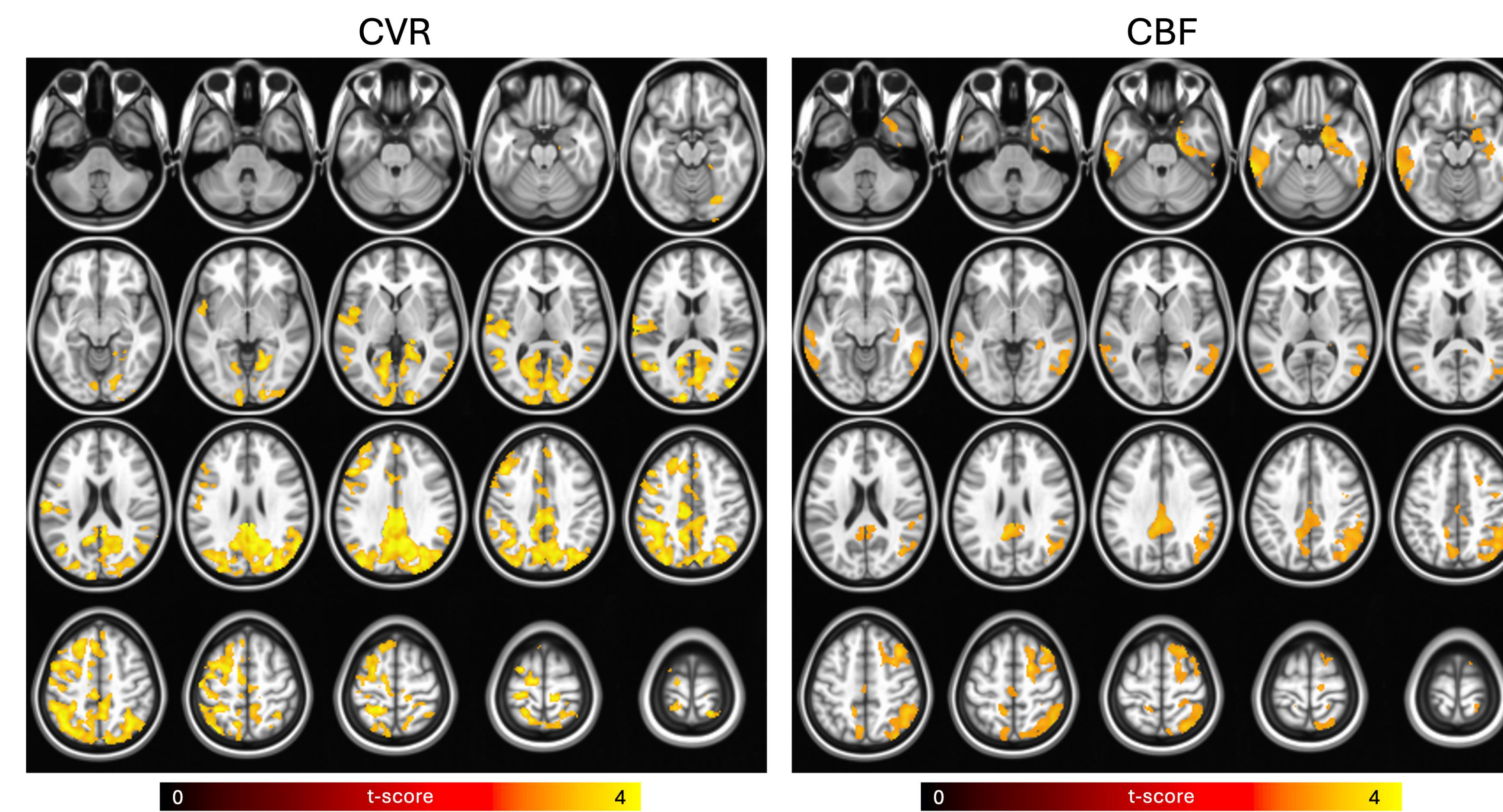


Figure 1. Group differences in vascular metrics. Voxelwise/groupwise comparison between controls and MCI for vascular metrics (CBF and CVR), displayed as t-statistic maps. Positive/negative values reflect higher/lower values in control relative to MCI subjects respectively. Maps were thresholded at $p < 0.05$, cluster-corrected at $\alpha < 0.05$.

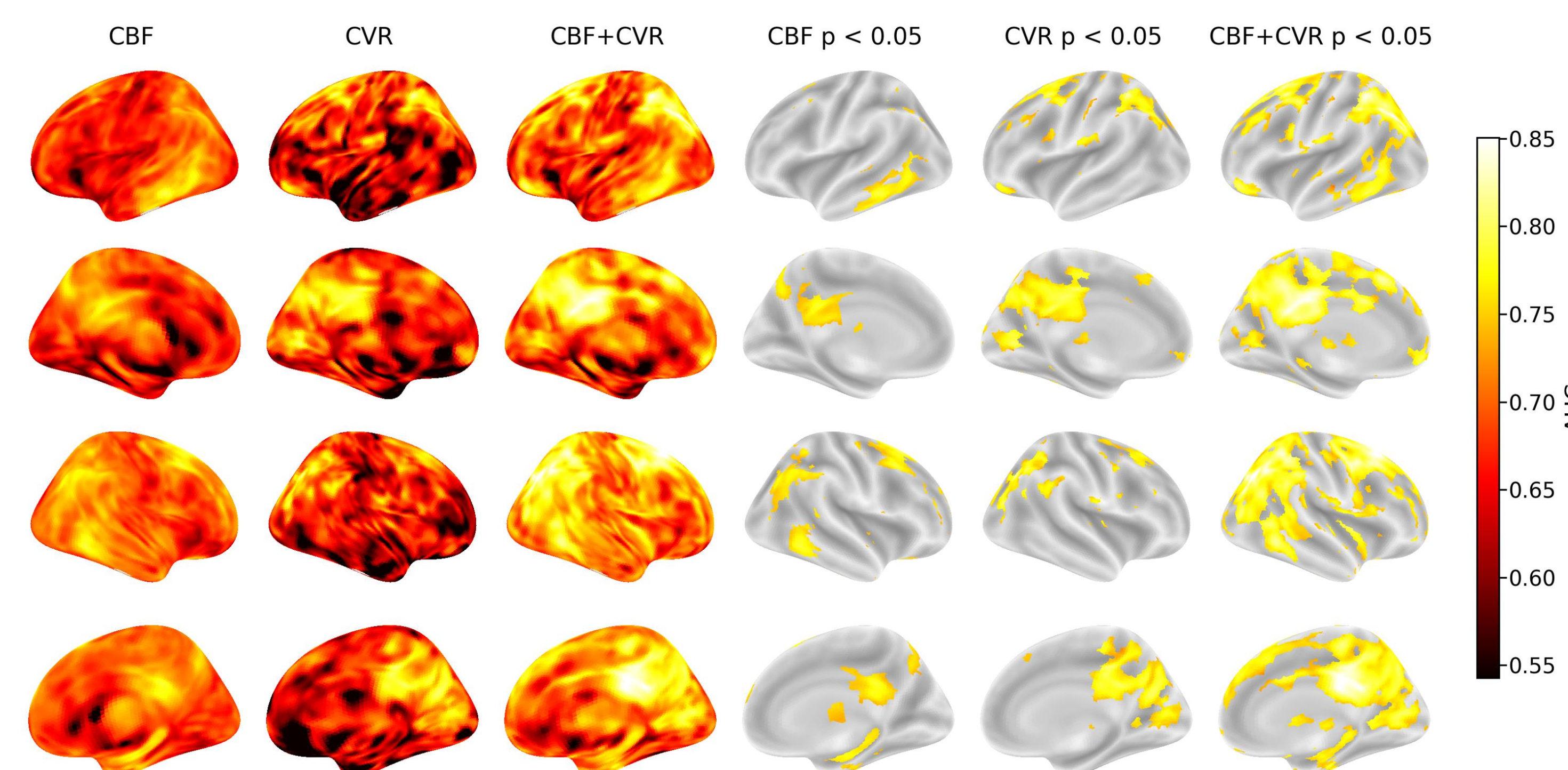


Figure 2. Searchlight MVPA classification performance using CBF, CVR, and combined CBF+CVR. Cortical searchlight maps showing AUC for classifying MCI versus controls. The accompanying thresholded maps display regions surviving the permutation-based significance threshold ($p < 0.05$) for AUC above chance.

Table 1. Mean AUC by metric combination for the 10 highest ROIs and the difference between mean AUC combined metrics and the best single metric (ΔAUC)

ROI	CBF	CVR	CBF+CVR	ΔAUC	p-value
L Control Parietal #4	0.742 $\pm$ 0.017	0.791 $\pm$ 0.031	0.828 $\pm$ 0.021	0.038	0.034
R Precuneus/PCC DMN #6	0.745 $\pm$ 0.022	0.772 $\pm$ 0.024	0.827 $\pm$ 0.023	0.055	0.010
L Control Parietal #5	0.747 $\pm$ 0.011	0.801 $\pm$ 0.033	0.825 $\pm$ 0.028	0.024	0.149
L Precuneus/PCC DMN #8	0.739 $\pm$ 0.019	0.791 $\pm$ 0.014	0.823 $\pm$ 0.019	0.033	0.059
L Control Parietal #1	0.736 $\pm$ 0.014	0.765 $\pm$ 0.027	0.822 $\pm$ 0.023	0.058	0.029
R Control Parietal #3	0.757 $\pm$ 0.014	0.757 $\pm$ 0.027	0.821 $\pm$ 0.022	0.064	0.007
R Posterior Parietal DAN #5	0.737 $\pm$ 0.014	0.755 $\pm$ 0.044	0.819 $\pm$ 0.030	0.065	0.014
R Control Parietal #6	0.763 $\pm$ 0.023	0.750 $\pm$ 0.034	0.818 $\pm$ 0.029	0.055	0.004
R dmPFC DMN #12	0.758 $\pm$ 0.027	0.748 $\pm$ 0.027	0.817 $\pm$ 0.031	0.059	0.004
L Precuneus/PCC DMN #7	0.754 $\pm$ 0.023	0.775 $\pm$ 0.022	0.815 $\pm$ 0.023	0.040	0.019

Abbreviations: PCC: Posterior Cingulate Cortex; DMN: Default Mode Network; DAN: Dorsal Attention Network; dmPFC: Dorsomedial Prefrontal Cortex

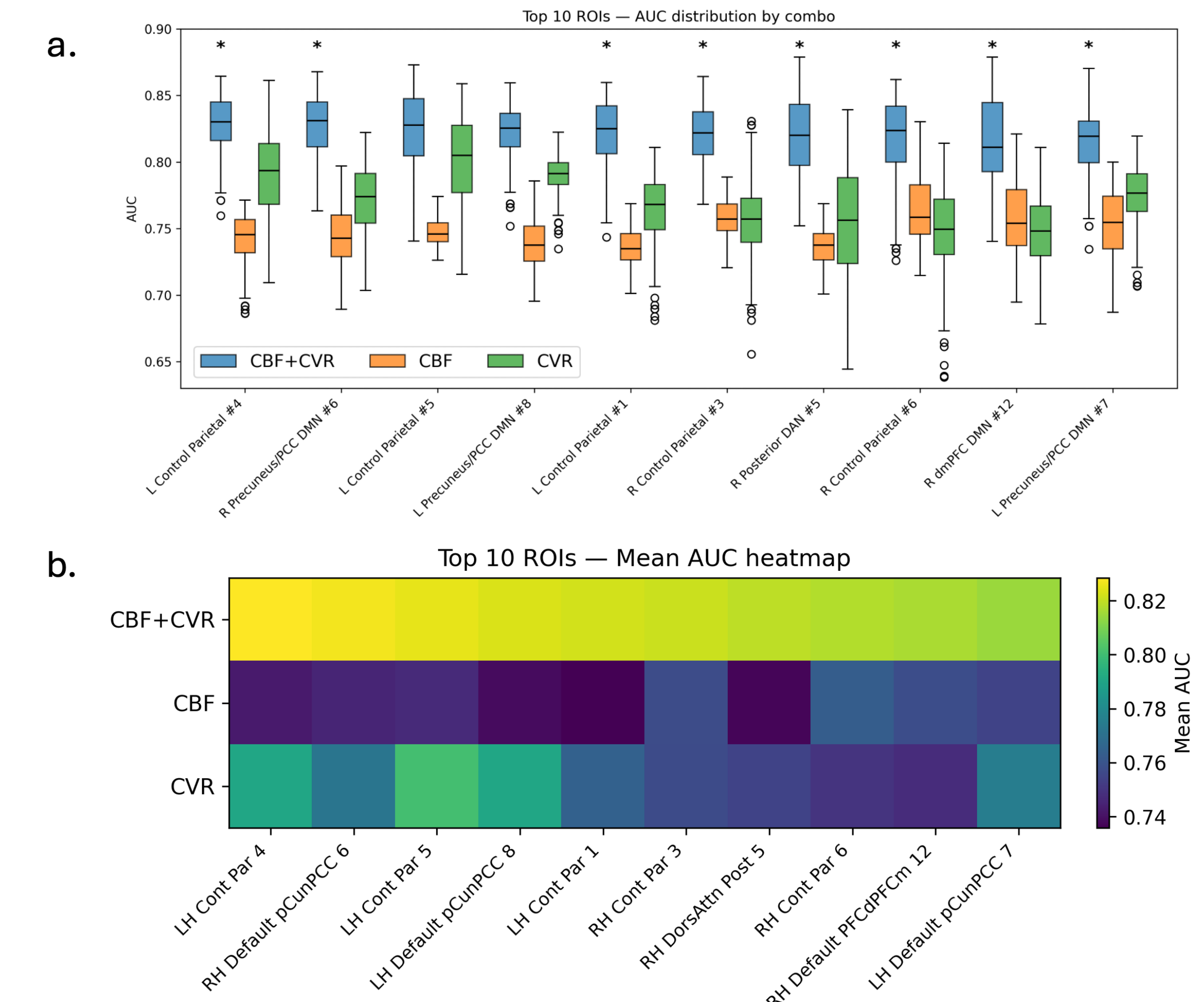


Figure 3. ROI summaries of multimodal gain in classification performance. **a.** Box plots summarizing mean AUC for CBF, CVR, and combined CBF+CVR models for the top 10 ROIs. **b.** A heat map representation of mean AUC for the three combinations. (Note: * indicates CBF+CVR is significantly greater than the highest single modality at $p < 0.05$).

Conclusions

- In general, CVR was the best performing single metric, supporting vascular-first models of cognitive impairment and identifying CVR as a sensitive marker of early disease-related changes.
- Integrating complementary vascular measures enhances the detection of cognitive impairment beyond single metrics.
- Combining CBF and CVR provides a more comprehensive characterization of vascular dysfunction that may precede overt neurodegeneration.
- Future work will evaluate whether MVPA-derived vascular signatures predict progression from MCI to AD and associate with clinical metrics.

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