

Age-Related Declines in Neurovascular Coupling Revealed by Nonlinear ASL–BOLD Mutual Information

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Introduction

- Neurovascular coupling (NVC) links neural activity with cerebral blood flow and metabolic support.
- NVC is known to decline with aging and may contribute to dementia risk.
- Arterial spin labeling (ASL) measures cerebral blood flow, while BOLD fMRI reflects hemodynamic responses related to neural activity.
- Simultaneous ASL–BOLD acquisition enables direct assessment of perfusion–BOLD coupling.
- Most studies quantify ASL–BOLD coupling using linear correlation.
- Mutual information (MI) captures nonlinear, model-free dependencies between signals.
- MI may provide greater sensitivity to subtle age-related changes in neurovascular function.

Objectives

- Examine age-related changes in voxelwise ASL–BOLD MI in cognitively normal aging.
- Identify brain regions where ASL–BOLD MI changes with age.
- Test whether ASL–BOLD MI is influenced by sex or age-by-sex interaction.

Methods

Participants

- 120 cognitively normal adults. Mean age: 66.1 ± 8.0 years.
- Age range: 50–87 years; 81 female participants.

Imaging acquisition

- Resting state ASL and BOLD time series were acquired simultaneously using a multiband multi-echo imaging sequence enabling direct assessment of perfusion–BOLD coupling.

Preprocessing

- Standard preprocessing was applied to ASL and BOLD time series.
- BOLD images were distortion-corrected, volume registered, denoised with multi-echo independent component analysis (ME-ICA), and normalized to MNI space.
- ASL timeseries were surround-subtracted to compute the perfusion-weighted signal.

Mutual information analysis

- Voxelwise MI was computed between ASL and BOLD time series.
- MI was estimated using a k-nearest neighbors entropy estimator. This approach captures nonlinear statistical dependence beyond linear correlation.

Statistical analysis

- Voxelwise general linear models tested effects of age, sex, and age-by-sex interaction.
- Multiple comparisons were corrected across voxels using cluster correction.
- Significant clusters were interpreted as regions showing altered ASL–BOLD coupling.

Results

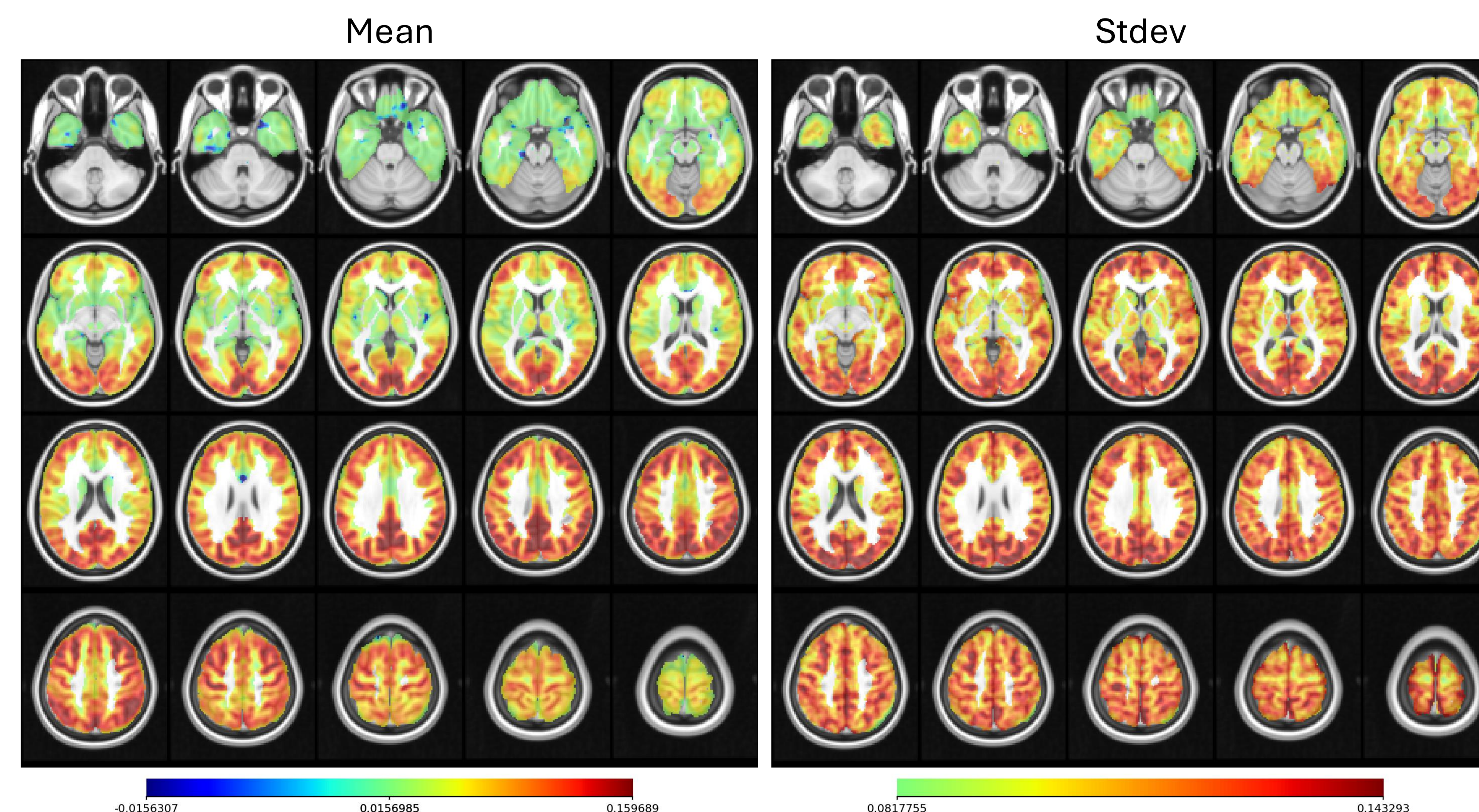


Figure 1. Group ASL–BOLD Mutual Information mean and standard deviation. Group-level ASL–BOLD coupling maps show widespread perfusion–BOLD signal dependence across cortex.

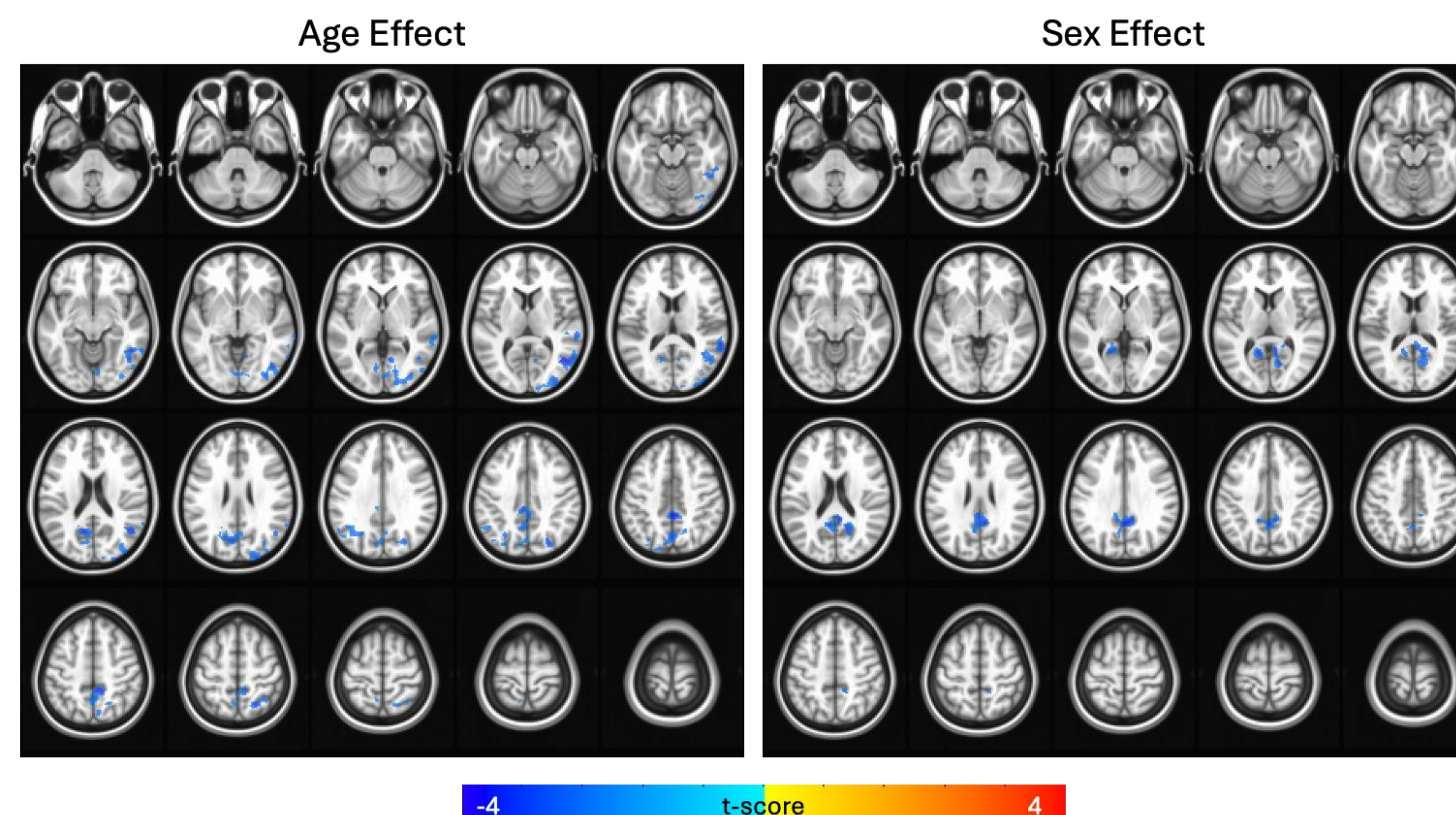


Figure 2. ASL–BOLD coupling age and sex effects. Voxelwise age-effect maps demonstrate significant reductions in MI with increasing age, particularly in posterior cortical, visual, parietal, and posterior default mode regions. Blue clusters indicate negative age effects, supporting widespread age-related neurovascular uncoupling in cognitively normal adults. There was also a significant sex effect in posterior cingulate cortex. Blue represents males < females.

- ASL–BOLD coupling was spatially widespread across gray matter, with high coupling values observed throughout cortical regions.
- Voxelwise statistical maps showed significant age-related reductions in ASL–BOLD coupling in posterior cortical regions and sensorimotor regions, consistent with broad age-related decline in neurovascular coupling.
- Females displayed higher coupling compared to males.

Conclusions

- ASL-BOLD MI revealed significant age-related reductions in neurovascular coupling across multiple cortical regions.
- The strongest age effects were observed in brain networks vulnerable to aging and dementia, including:
 - Default mode network
 - Motor cortex
 - Visual cortex
- Sex effects were observed in the posterior cingulate cortex with females showing higher coupling compared to males.
- Mutual information captures nonlinear ASL–BOLD signal dependencies that may not be fully appreciated using traditional linear correlation.
- These findings support ASL-BOLD MI as a sensitive, noninvasive marker of neurovascular coupling integrity in cognitively normal aging.
- With further validation, ASL-BOLD MI may help identify early neurovascular dysfunction and support risk stratification in studies of cognitive decline and dementia.
- Prior work demonstrates sex-related differences in cerebrovascular metrics, including higher CBF and BOLD CVR in females relative to males, supporting sex as an important cerebrovascular covariate when interpreting ASL–BOLD coupling effects

References

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