



Sex Differences In Default Mode Network Laterality

Sophia Moret¹, Wen-Xiang Tsai¹, Jordan A. Galbraith¹, Carolyn A. Fredericks¹

¹ Yale School of Medicine, New Haven, CT



Introduction

- Alzheimer's disease (AD) is the leading cause of dementia and two-thirds of those affected are women¹
- The DMN is highly implicated early in AD pathology and shows sex-related differences in midlife, including higher connectivity in women aged 40-50³
- In cognitively impaired individuals, DMN regions, including the posterior cingulate cortex, posterior inferior parietal lobule, and angular gyrus, show reduced left lateralization relative to cognitively normal adults²
- Sex differences in DMN laterality remain largely unexplored, despite its relevance to women's increased AD risk**

Methods

- Cognitively normal adults from the Human Connectome Project-Aging dataset were analyzed⁴
- A 30-component group ICA was run on resting-state fMRI data, followed by dual regression
- Schaefer 2018 DefaultA/B/C masks identified DMN submodule components
- Laterality indices were calculated as (Left – Right) / (Left + Right), with positive values indicating left-lateralization
- Sex and Sex × Submodule effects were tested across DefaultA, DefaultB, and DefaultC

	Female	Male
N	208	197
Age (mean ± SD)	56.1 ± 14.02	58.0 ± 14.01
White Race	69.7%	72.6%
Hispanic or Latino	13.5%	7.1%

Methods: Analysis Pipeline

Fig 1.

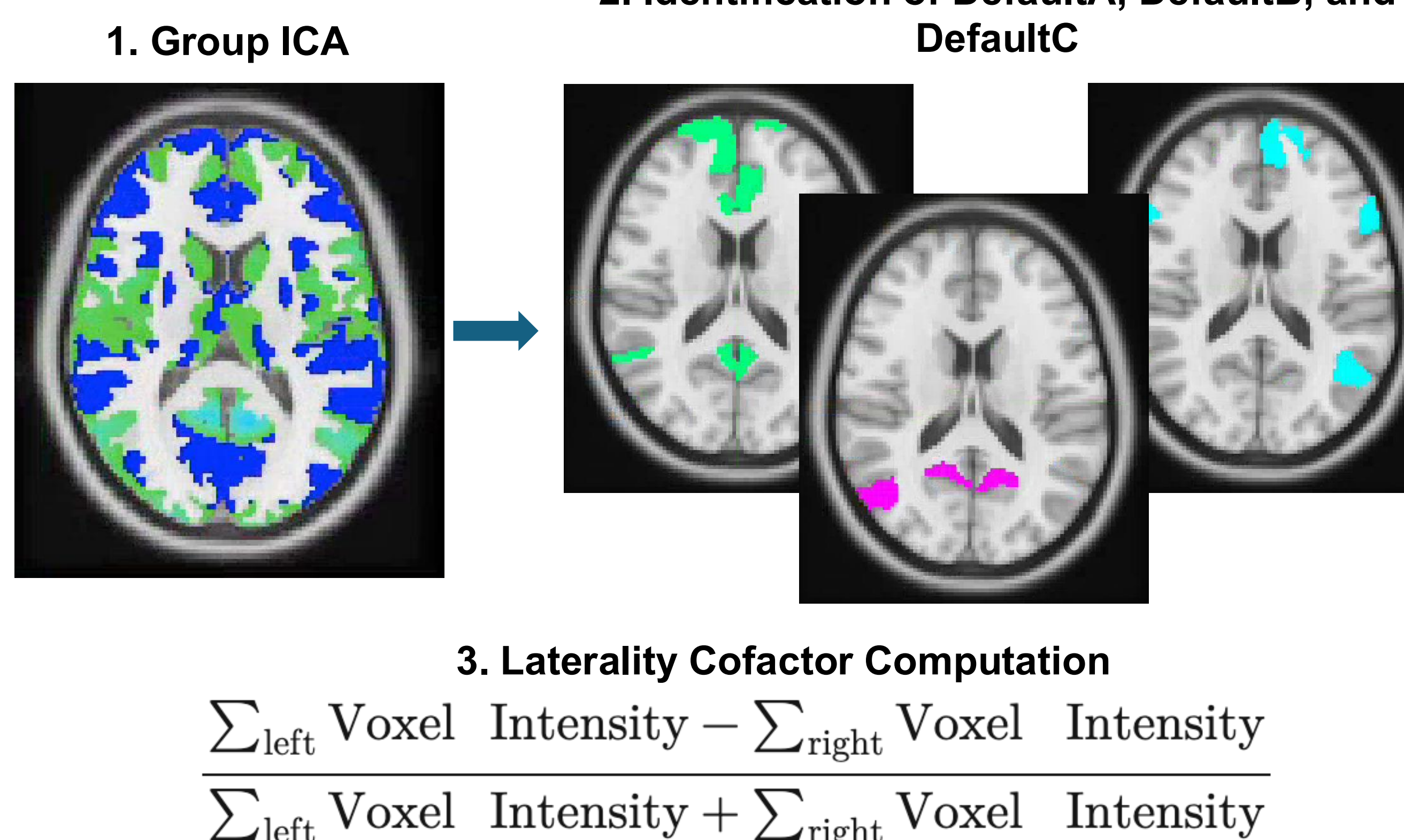


Figure 1. Analysis pipeline

Conclusion

- DMN submodules showed distinct lateralization profiles across males and females**
- DefaultA was right-lateralized, while DefaultB and DefaultC were left-lateralized
- Sex differences were modest, with males showing significantly greater rightward DefaultA laterality than females
- DefaultA includes DMN areas previously linked to altered lateralization in cognitive impairment
- Findings suggest DMN laterality is submodule-specific, with **sex-related differences most apparent in DefaultA**

Results

Fig 2.

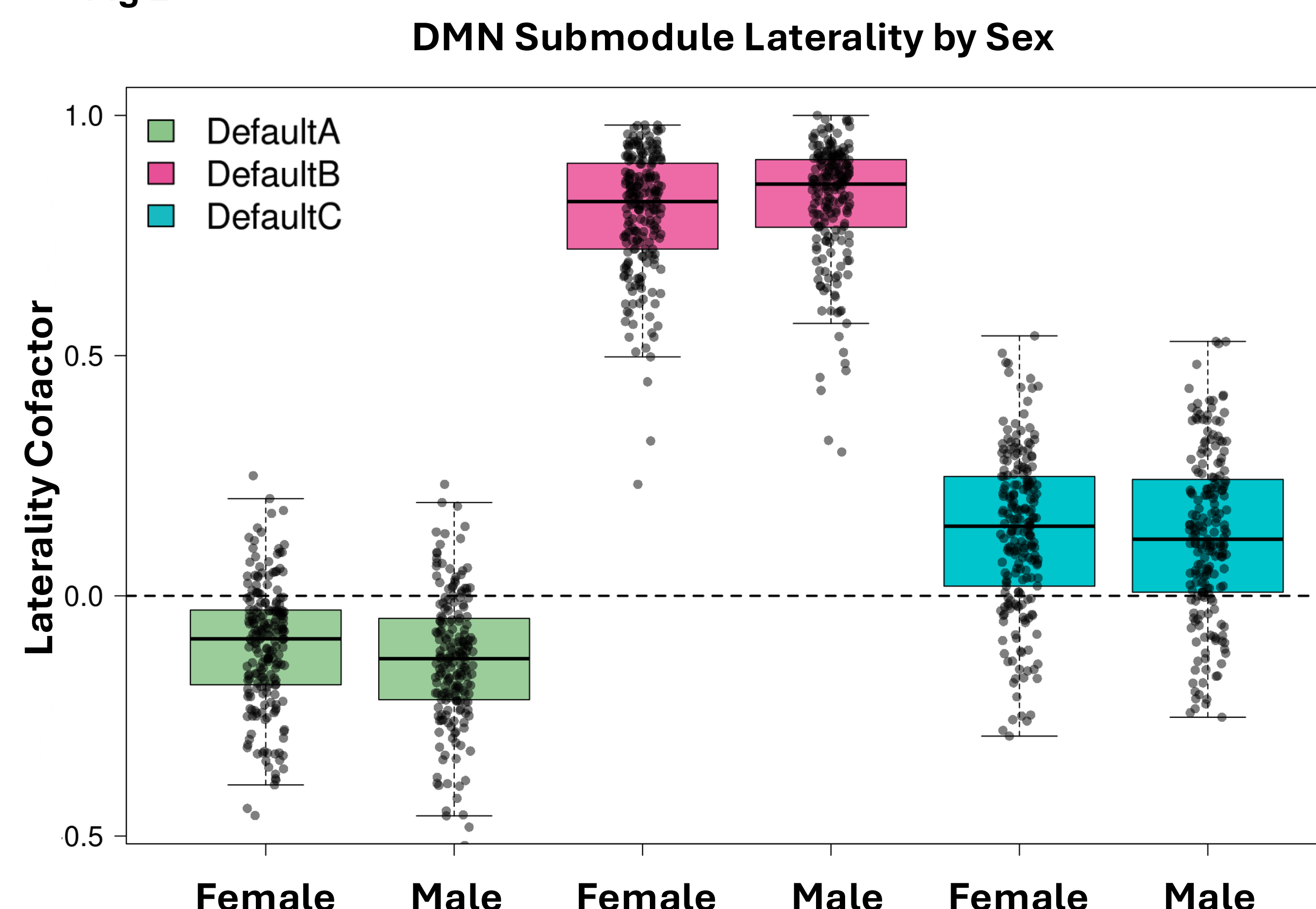


Figure 2. Laterality cofactors are shown for Schaefer atlas DefaultA, DefaultB, and DefaultC submodules in females and males. DefaultA showed a significant sex difference, with males showing greater rightward laterality than females, $p = .025$. Sex differences in DefaultB and DefaultC were not significant.

Future Directions

- Test associations between DMN submodule laterality and hormone levels
- Explore whole-network DMN connectivity beyond hemispheric laterality

References

- Alzheimer's Association. (2013). 2013 Alzheimer's disease facts and figures. *Alzheimer's & dementia*, 9(2), 208-245.
- Banks, S. J., Zhuang, X., Bayram, E., Bird, C., Cordes, D., Caldwell, J. Z. K., Cummings, J. L., & Alzheimer's Disease Neuroimaging Initiative (2018). Default Mode Network Lateralization and Memory in Healthy Aging and Alzheimer's Disease. *Journal of Alzheimer's disease : JAD*, 66(3), 1223–1234. <https://doi.org/10.3233/JAD-180541>
- Ju, S., Horien, C., Shen, X., Abuwarda, H., Trainer, A., Constable, R. T., & Fredericks, C. A. (2023). Connectome-based predictive modeling shows sex differences in brain-based predictors of memory performance. *Frontiers in dementia*, 2, 1126016. <https://doi.org/10.3389/frdem.2023.1126016>
- Harms, M. P., Somerville, L. H., Ances, B. M., Andersson, J., Barch, D. M., Bastiani, M., ... & Yacoub, E. (2018). Extending the Human Connectome Project across ages: Imaging protocols for the Lifespan Development and Aging projects. *Neuroimage*, 183, 972-984.

Acknowledgements

- This project was supported by the National Institute of Health (5K23AG059919-04), the Alzheimer's Association (2019-AACSF-644153)), and the McCance Foundation
- The HCP-A data that support the findings of this study are publicly available through the NIMH Data Archive (https://nda.nih.gov/edit_collection.html?id=2847)
- Special thank you to my mentors Dr. Carolyn Fredericks and MD/PhD student Jordan Galbraith