

Network Level Analysis Provides a Framework for Biological Interpretation of Machine Learning Results

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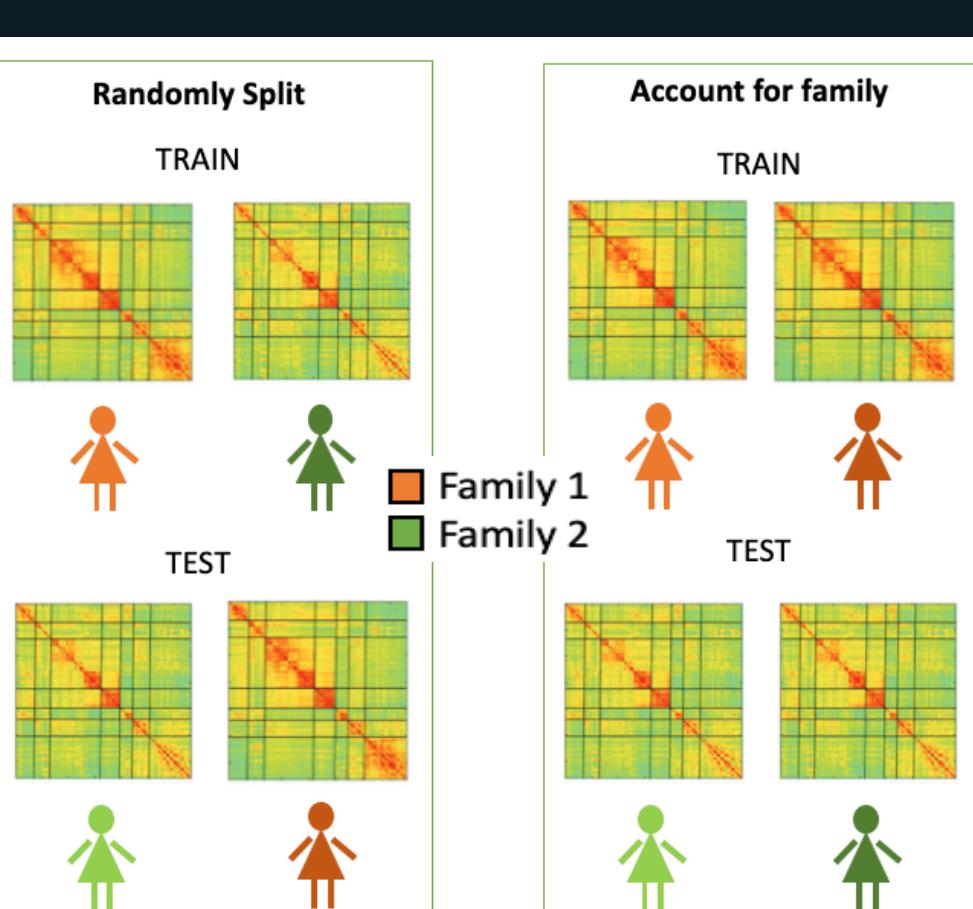
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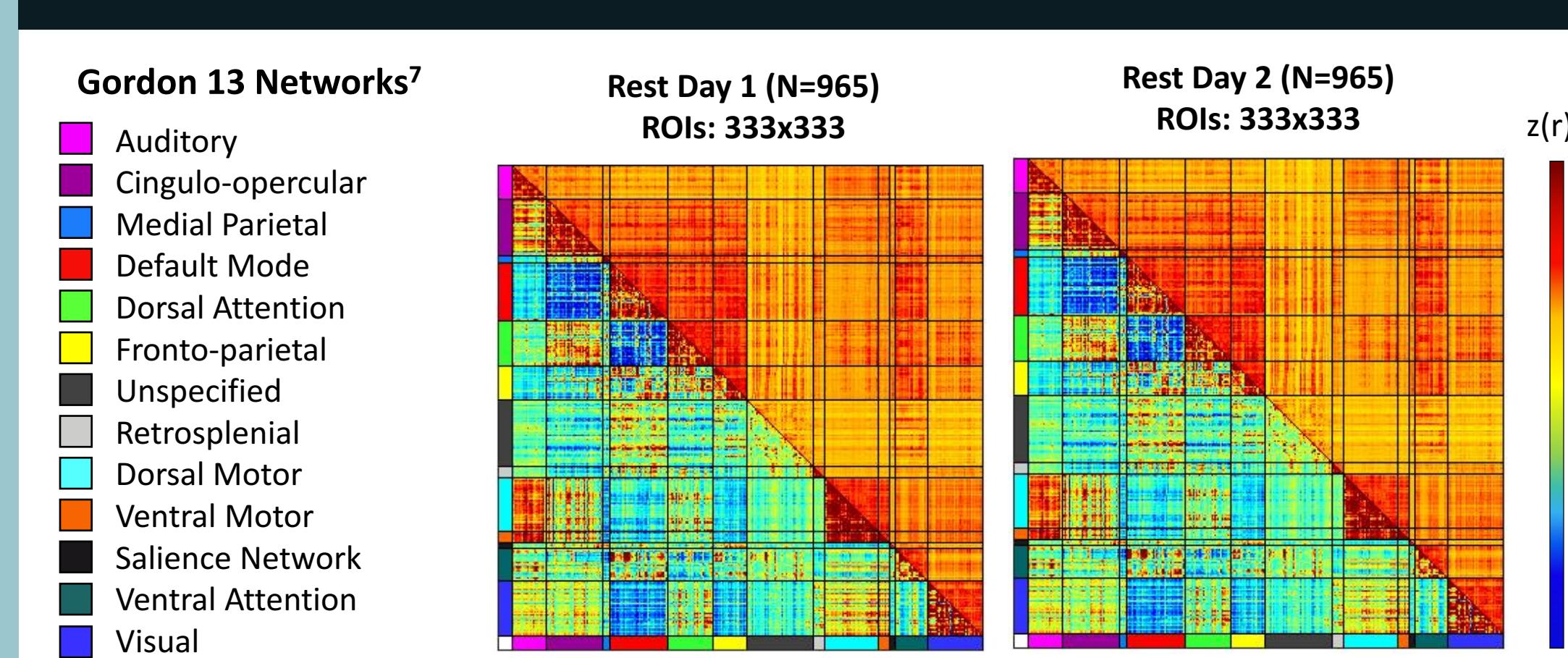
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BACKGROUND

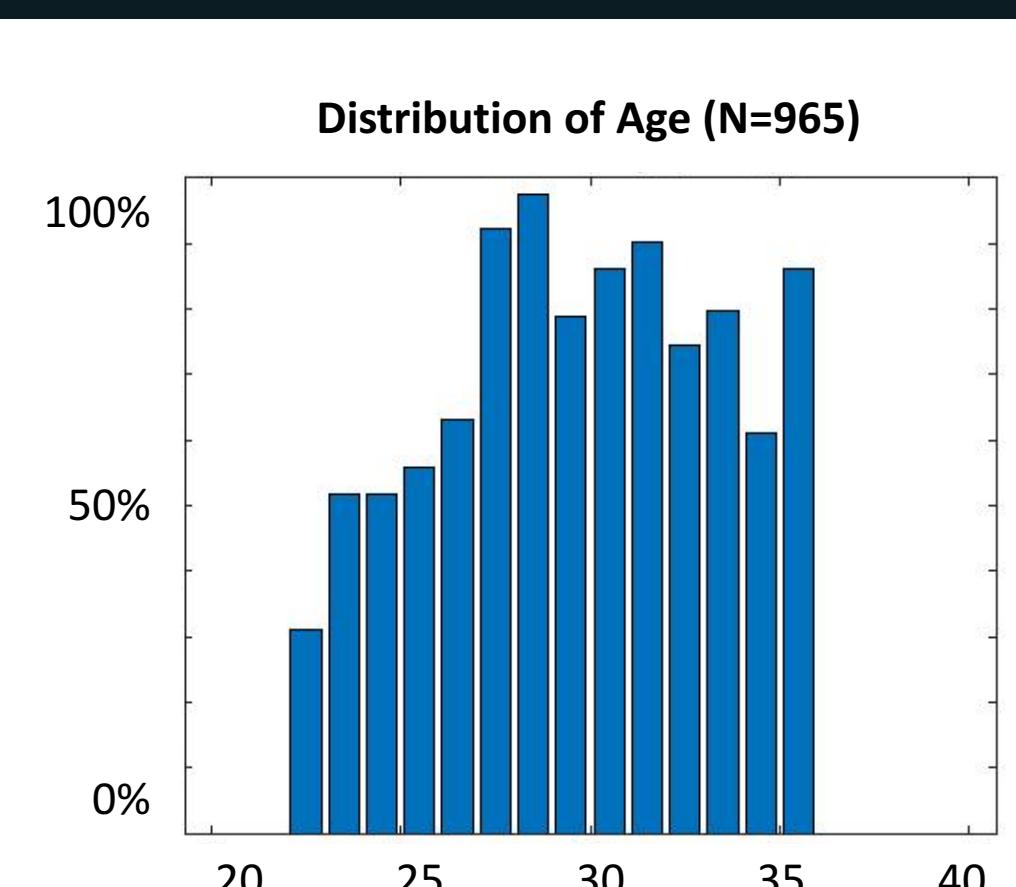


- ☐ Challenges of predicting age (behaviors) by connectome:
 - I. How to account for **shared variance¹** among siblings/families?
 - II. Will **feature filters²** reduce performance of ML models?
 - III. How is **reliability³** of ML models across different days and individuals?
 - IV. Can we provide **biological interpretations⁴** for ML prediction results?
- ☐ Our contributions:
 - I. Develop a **cross-validation⁵** to model shared variance among related subjects like families
 - II. Evaluate **marginal Pearson feature filter** applied ahead of ML models
 - III. Quantify reliability of ML models across **two different days and all subjects**
 - IV. Apply **Network-Level Analysis⁶** on ML results to provide biological interpretations

HCP DATA

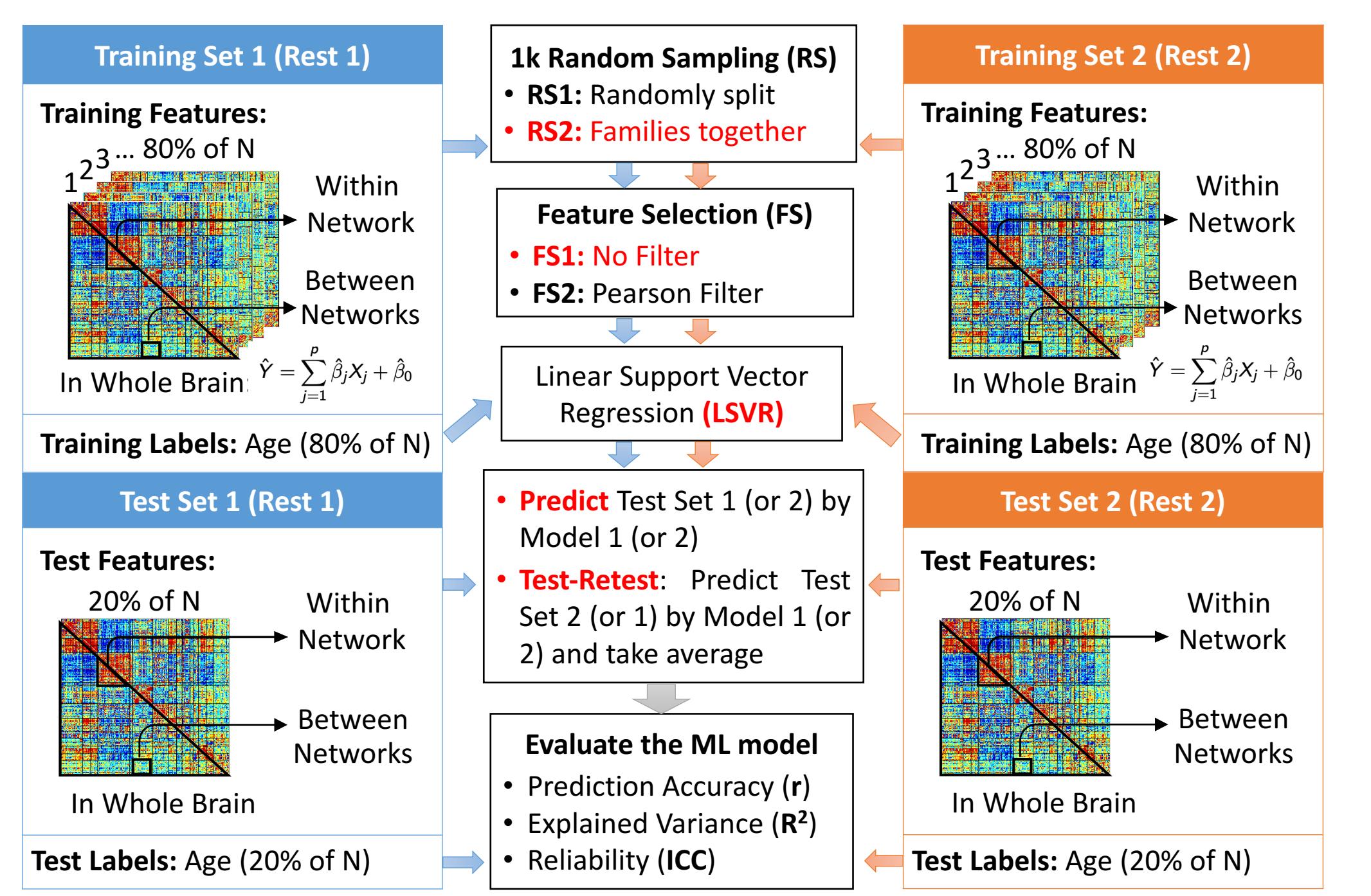


- 10 min of low motion rs-fMRI data on **two separate days**
- lower triangle: mean; upper triangle: SD;
- 965 Human Connectome Project (HCP) subjects: healthy adults (420 families included)

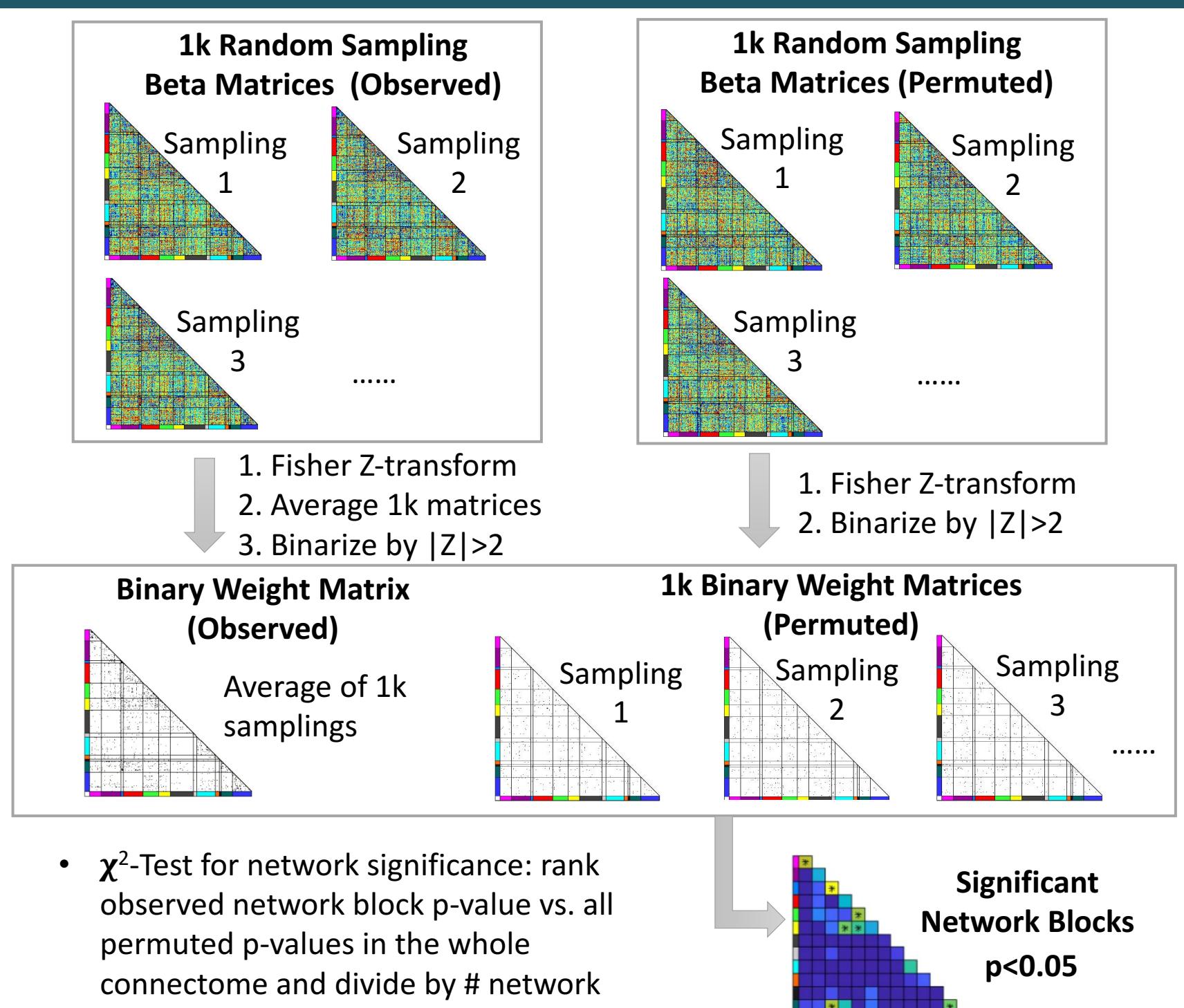


METHODS

Pipeline of Machine Learning Model

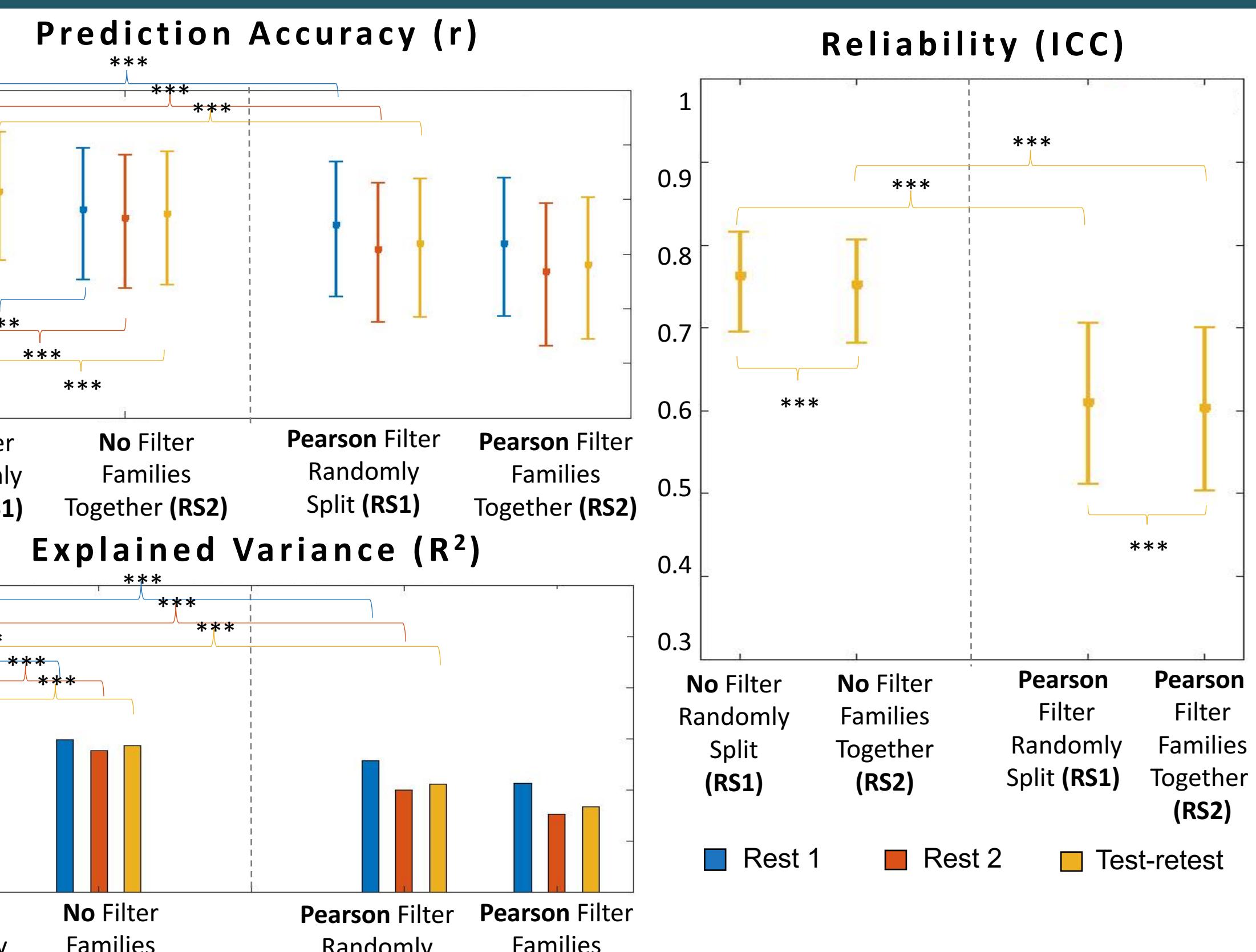


Network-Level Analysis⁶



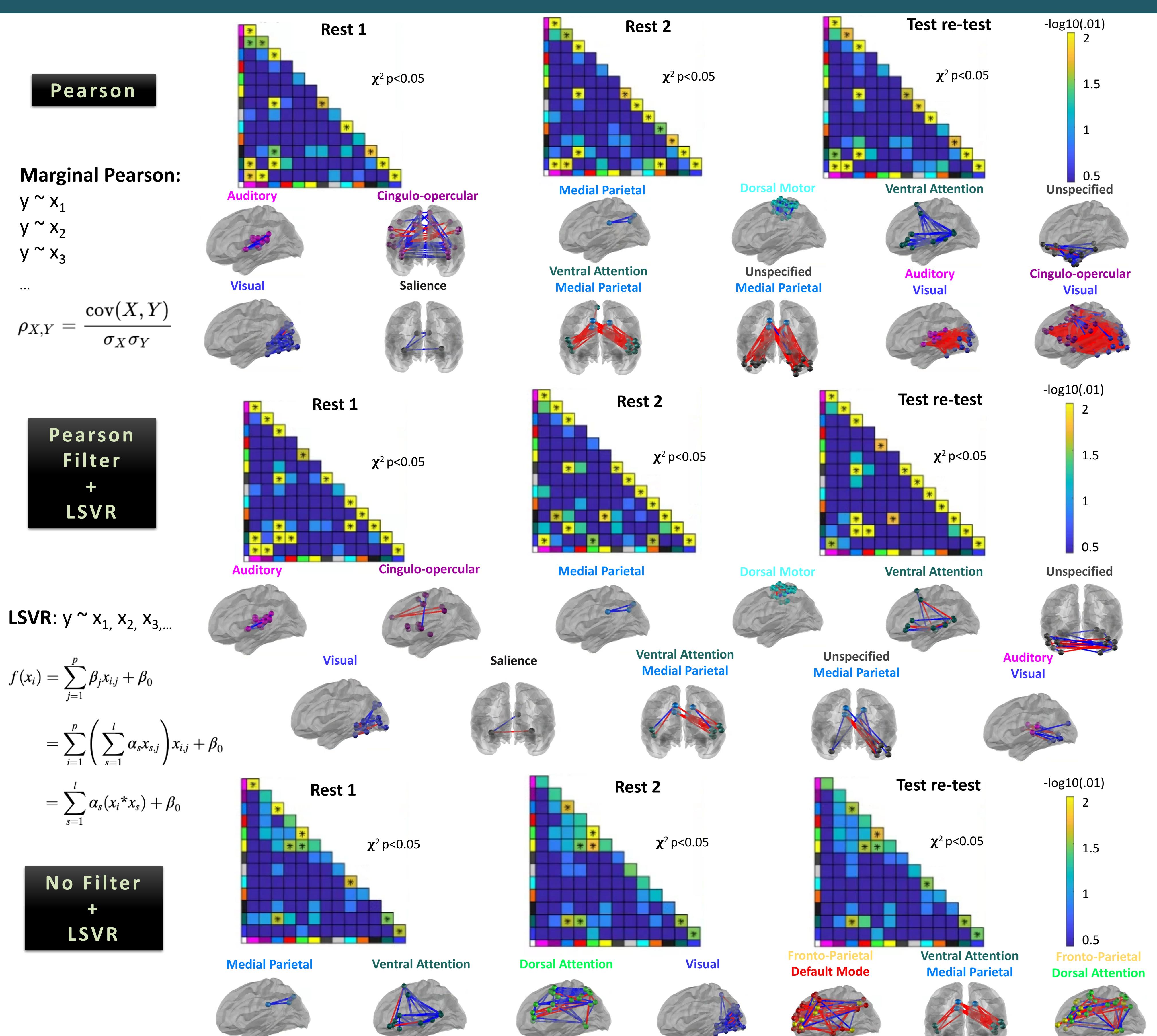
RESULTS

Evaluation of ML Models



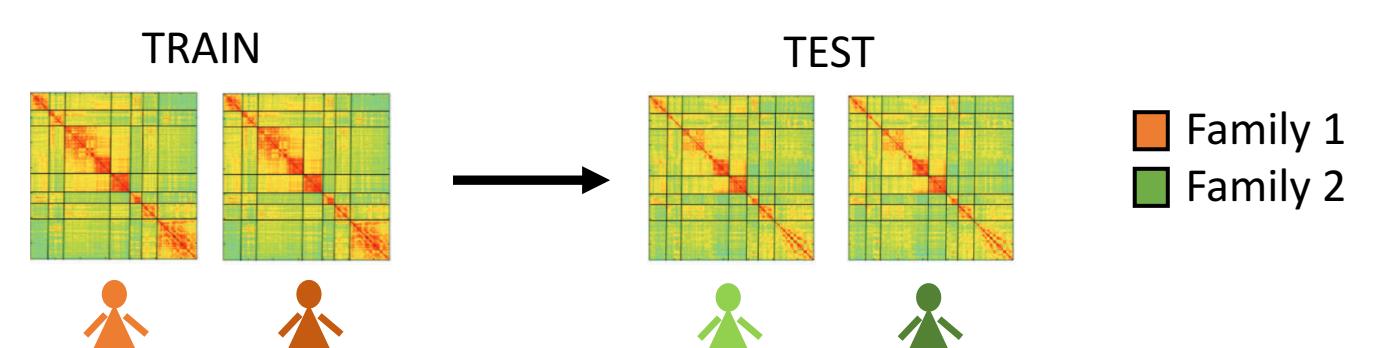
***: Significantly different ($p < 0.001$)

Significant Network Blocks Selected by Pearson vs. Pearson + LSVR vs. LSVR



CONCLUSIONS

- ☐ To address the shared variance of **related subjects**
 - Random resampling while keeping **families in the same set**: training or test set
 - The falsely inflated prediction performance is **corrected**
 - The **reliability** across different days implied by ICC is not much worse.



- ☐ Downsides of utilizing a **feature selection** as a pre-step ahead of ML
 - Correlation among predictors could fool the feature selection via marginal Pearson correlation²
 - Some significant features may **fail to survive** the marginal variable screening
 - The prediction accuracy and **reliability** decreased when a feature selection applied

- ☐ Alternative variable screening methods
 - Iterated Sure Independent Screening⁹ (ISIS)
 - General correlation¹¹
 - Quantile partial correlation¹²

- ☐ To provide an accessible **biological interpretation** of ML results
 - Traditional method for examining ML models fit on single network pairs should be interpreted carefully
 - While models may perform better than permuted data, individual networks rarely perform better than same size randomly selected features across the whole connectome¹⁰
 - Prediction accuracy (R^2) converges as # of features in the model¹⁰ goes to 1K

- ☐ Network-Level Analysis (NLA software⁶) is a promising alternative method for biological interpretation
 - NLA is applied to the whole connectome ML results and then determines network-level significance

FUTURE DIRECTIONS

- ☐ Interpret **structural patterns** in permuted weight matrices, may be related to the SD structure in connectivity matrix and principle components
- ☐ Build ML models on other behavioral scores, e.g. motor or cognitive abilities
- ☐ Evaluate **alternative feature filters** accounting for correlations among predictors, e.g. ISIS⁹

ACKNOWLEDGEMENTS

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REFERENCES

1. Cui and Gong (2018) NeuroImage
2. Wang et al. (2021) Statistical Analysis and Data Mining
3. Taxali et al. (2021) Cerebral Cortex
4. Smith et al. (2021) Brain Connectivity
5. Feilong et al. (2021) eLIFE
6. Wheelock et al. (2020) Cerebral Cortex
7. Gordon et al. (2017) Cerebral Cortex
8. Rudolph et al. (2018) Nature Neuroscience
9. Fan and Lv (2008) Journal of Royal Statistical Society Series B
10. Nielsen et al. (2019) Cerebral Cortex
11. Hall and Miller (2009) Journal of Computational and Graphical Statistics
12. Ma, Li, and Tsai (2017) Journal of the American Statistical Association