A prediction framework for evaluating the age dependence of physiologically induced fMRI signal variability

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Background

- Respiration and cardiac activity are important physiological processes involved in brain-body interactions. In this study, we examine the biological significance of physiologically coupled fMRI signals in the context of aging.
- Aging is associated with brain vasculature changes that impact resting-state fMRI signals. While resting-state BOLD variability has been shown to correlate with age [1], both neural and autonomic physiological processes contribute to measures of BOLD variability and are not typically separated.
- Here, we demonstrate that the component of BOLD variability linked with low-frequency respiratory and heart rate fluctuations is predictive of age above chance. In addition, we verified the model's generalizability on an unseen hold-out dataset collected from a different site, further confirming the predictability of age from physiologically induced BOLD signal.

Dataset

- We included 487 samples from the Nathan Kline Institute Rockland Sample [2] (age range 19-85 years; voxel size = 2 mm isotropic; TR = 1400 ms) [*Fig. 1*] and 221 samples from the HRV-ER dataset [3] (117 younger adults, age range 18-30 years; 94 older adults, age range 55-80 years; voxel size = 3 mm isotropic; TR = 2400 ms).

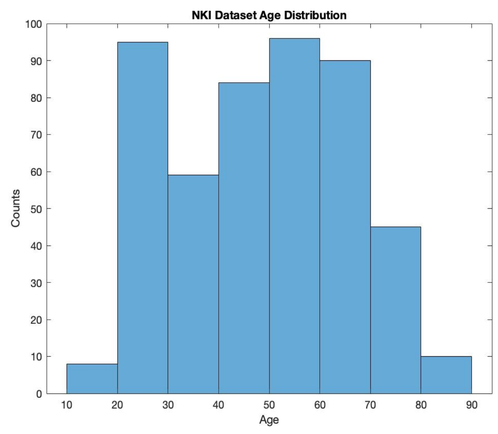

Figure 1. Age distribution for the NKI dataset.

- All data were acquired at 3T and included both resting-state fMRI and physiological recordings.
- Both datasets were registered into MNI space, spatially smoothed, detrended up to the 4th degree polynomial and with 12 motion parameters regressed out.
- We used 4 atlases to extract 497 cortical and subcortical ROIs, including Schaefer Atlas (400 ROIs) [4], Pandora Tractseg Atlas [5], Melbourne Atlas [6] and Ascending Arousal Network Atlas [7], and each ROIs' time series were z-scored.

Method

- Respiratory variation (RV) is represented as the standard deviation (SD) of a sliding window of 6 s centered at each TR, and heart rate (HR) is calculated as the inverse of the mean inter-beat-interval in the same window.
- RV and HR were then each convolved with pre-defined basis functions[8], and the fMRI physiological subspace was extracted by fitting the convolved signals to the z-scored fMRI signals via ordinary least squares. We used SD and MSSD (mean-squared successive differences) to capture the variability of the fitted signals.
- Support vector regression (SVR) model with RBF kernel was used to perform age prediction with ROI-based variance. We first performed 5-fold cross-validation on the NKI dataset to verify the model's performance on the same dataset. In addition, we tested the generalizability of the age prediction model by training the model on the entire NKI dataset and testing the performance on the hold-out HRV-ER dataset.

Results

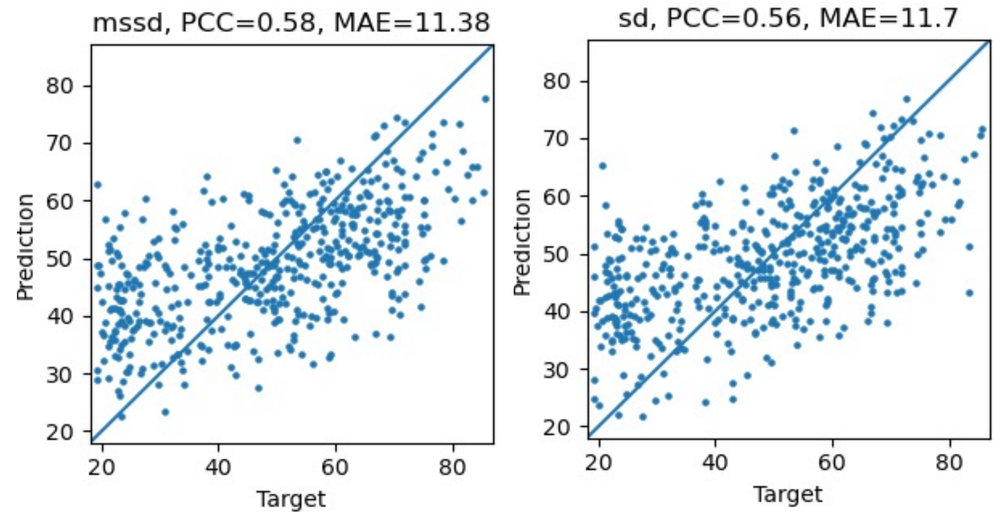

Figure 2. Age prediction test results on the NKI dataset with all 5 test sets concatenated. We achieved an MAE of 11.38 and PCC of 0.58 for the MSSD metric (left), and MAE of 11.70 and PCC of 0.56 for the SD metric (right).

- MAE (mean absolute error) and PCC (Pearson correlation coefficient) are used to evaluate the prediction results.
- When training and testing on the NKI dataset, we achieved an MAE of 11.38 for the MSSD metric, and 11.70 for the SD metric with all 5 test sets concatenated [*Fig. 2*].
- Both results were significant ($p<0.01$) compared to a permutation test (100 iterations) which was carried out by extracting the physiological subspace by fitting a different, random subject's RV/HR to their fMRI data, and using the same SVR model to predict age with the same 5-fold split.

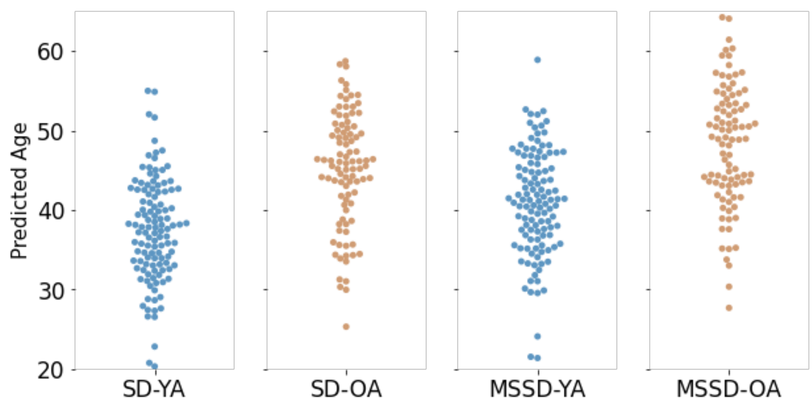

Figure 3. Age prediction test results on the HRV-ER dataset. The model gave significantly higher ($p<0.001$) age predictions for the older adults.

- When training on the NKI dataset and testing on the HRV-ER dataset, the model yielded significantly higher age predictions ($p<0.001$) for older adults for both metrics (SD: PCC=0.51, MAE=17.28; MSSD: PCC=0.48, MAE=17.71), despite the two datasets having different TRs [*Fig. 3*].

Conclusions

- We are not only able to predict age using the variability of fMRI physiological subspace, but the age prediction model is generalizable to a hold-out unseen dataset.
- In summary, these results indicate that physiological components of BOLD signal variability contain useful information about how different brain regions change over lifespan and may contribute a potential biomarker.

Reference

[1] Garrett, D. D., et al., 2017; [2] Nooner, K. B., et al., 2012; [3] Yoo, H. J., et al., 2022; [4] Schaefer, A., et al., 2018; [5] Hansen, C.B., et al., 2020; [6] Tian, Y., et al., 2020; [7] Edlow, B.L., et al., 2012; [8] Chen, J. E., et al., 2020