

BACKGROUND

- Brain clocks quantify brain-age gaps (BAGs) (predicted age minus chronological age calculated from neural features)
- These BAGs can be used to measure accelerated aging, monitoring deviations from healthy brain trajectories
- Most evidence comes from high-income settings, overlooking global diversity
- Diversity shapes brain health, yet few studies pair neuroimaging with biophysical modeling [1]
- Whole-brain models can map gaps to neural mechanisms [2]
- The biophysical mechanisms driving healthy aging deviations remain poorly understood

METHODS

- We used EEG data from participants across ten countries from the global north and the global south (N = 1,399):
 - Healthy controls (HC) (North N = 724, South N = 516)
 - Alzheimer's disease (AD) (South N = 102)
 - Behavioral variant frontotemporal dementia (bvFTD) (South N = 57)
- Countries involved:
 - Global North = Turkey, Greece, Italy, the United Kingdom, and Ireland
 - Global South = Cuba, Colombia, Brazil, Argentina, and Chile
- We used support vector machine (SVM) algorithms to compute BAGs and biophysical semi-empirical modeling to analyze the neural mechanisms driving those BAGs
- Biophysical modeling:
 - Generative whole-brain model fit to each participant
 - Simulates the excitatory/inhibitory balance to check for hyperexcitability and hypoexcitability effects driving BAGs
- Statistical analysis:
 - Student t-tests for comparisons between groups and conditions, Cohen's d for effect sizes
 - Evaluated BAGs associations with diagnosis, country, and sex

RESULTS

- SVM predicting BAGs achieved Pearson's $r = 0.727$, Cohen's $f^2 = 1.118$, mean absolute error (MAE) = 7.723 and root-mean-square error (RMSE) = 9.833
- By categorizing countries into low- and high-income groups based on the median of the income distribution, we observed accelerated brain aging in low-income countries (5.44 BAG difference [2.52, 6.56]_{95%}, $t(1,183) = 7.40$, $P = 2.54 \times 10^{-13}$, $D = 0.45$, FDR-corrected)
- When analyzing variables such as age, income, education, and sex, we observed disparities, with higher BAGs among participants in the global south
- No BAG differences were found between females and males in the global north. However, accelerated aging in females was observed in the global south (-4.78 BAG difference, $[-7.49, -2.07]$ _{95%}, $t(469) = -3.46$, $P = 5.98 \times 10^{-4}$, $D = 0.32$, FDR-corrected P values)
- Accelerated brain aging is more pronounced in AD than HCs (9.12 BAG difference, [6.80, 11.44]_{95%}, $t(217) = 7.72$, $P = 4.16 \times 10^{-13}$, $D = 1.05$, FDR-corrected P values) and in bvFTD (6.88 BAG difference, [4.41, 9.35]_{95%}, $t(174) = 5.08$, $P = 9.34 \times 10^{-7}$, $D = 0.83$, FDR-corrected P values)

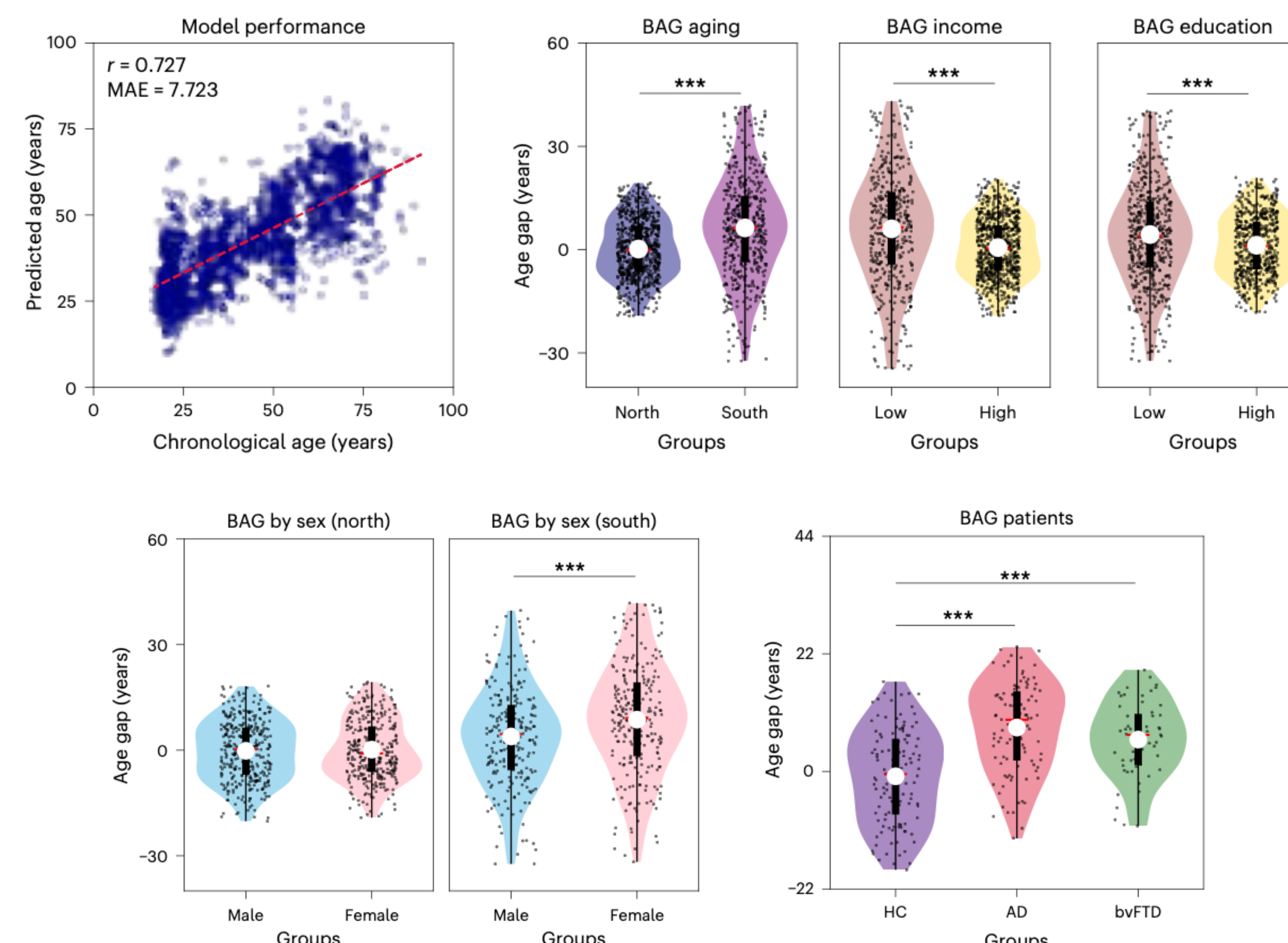


Figure 1. Diversity-sensitive brain-age gaps. Model performance estimating BAGs, and regional differences with aging, income, education, sex, and groups.

- The biophysical model showed that the participants with higher BAGs had higher firing rates/hyperexcitability ($P = 0.00014$).
- In patients, we observed that AD is characterized by a global shift towards lower firing rates/hypoexcitability ($P = 0.008$)

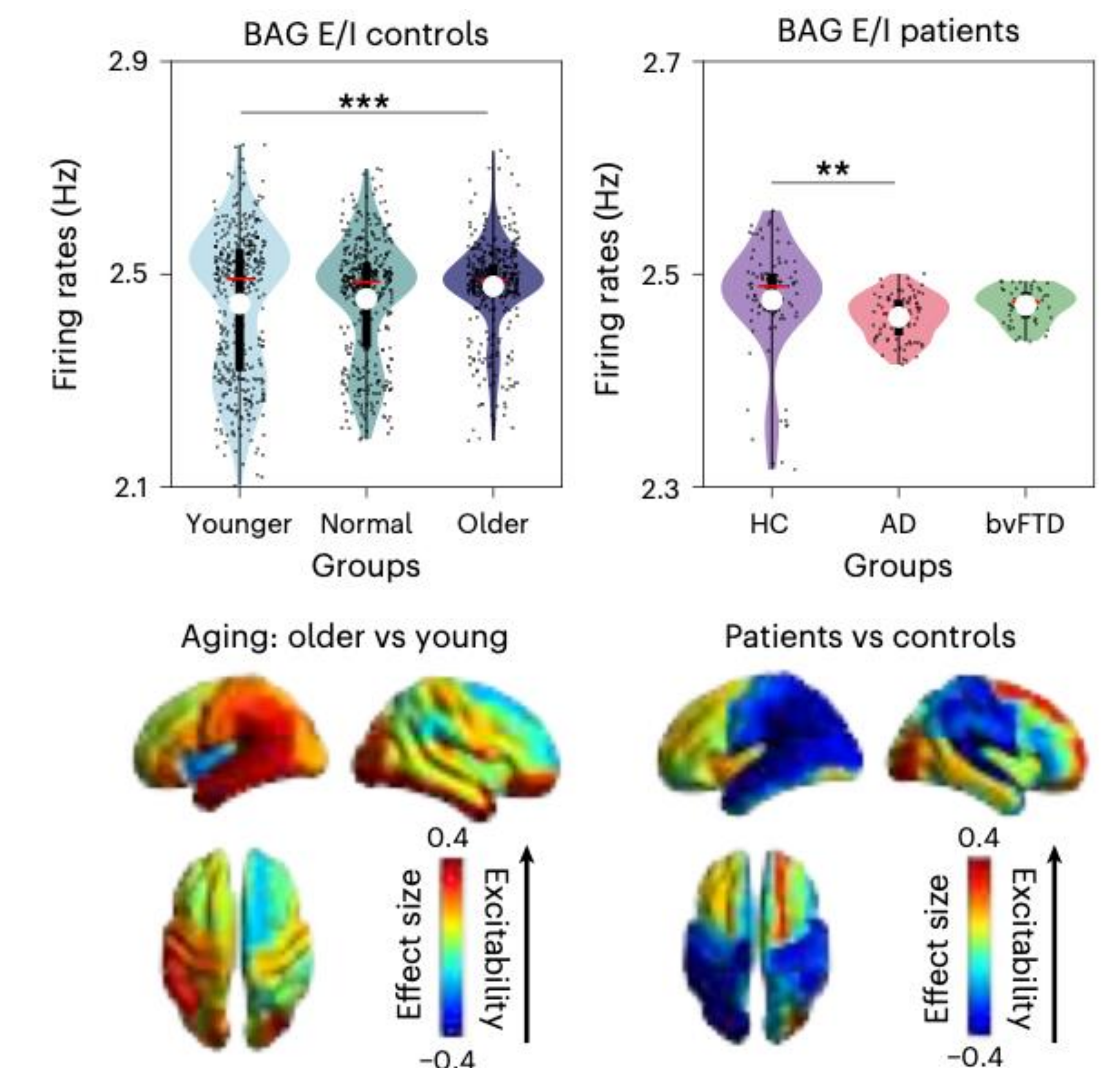


Figure 2. Biophysical mechanisms. Generative whole-brain modeling separates accelerated healthy aging (hyperexcitability) from dementia (hypoexcitability).

CONCLUSIONS

- Brain clocks capture diversity and burden across aging and dementia
- The results suggest that, in dementia, neurodegeneration is characterized by global hypoexcitability

REFERENCES

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