

Assessment Of Default-Mode Network Effective Connectivity In Presymptomatic Autosomal Dominant Alzheimer's Disease

Gabe M. Yawitch^{1,2} Elizabeth Powell^{1,3} Sam Ereira⁴ Antoinette O'Connor^{5,6} Eli Gibson⁷ Christina Triantafyllou⁸ Natalie S. Ryan^{5,6} Charles Marshall^{9,10} David M. Cash⁵ Nick C. Fox^{5,6} Geoff J.M. Parker^{1,3,11} Phil S.J. Weston^{5,6}

¹Hawkes Inst., UCL ²Mech Eng., UCL ³Med. Ph. & Biomed. Eng., UCL ⁴Wolfson Inst. of Pop. Health, QMUL, ⁵Dementia Research Centre, UCL Queen Square Inst. of Neurology ⁶UK DRI at UCL ⁷Digital Technology & Innovation, Siemens Healthineers, Princeton NJ ⁸Research & Scientific Collaborations GBI, Siemens Healthcare Ltd, Camberley ⁹Centre for Preventive Neurology, QMUL ¹⁰Tower Hamlets Memory Service, ELFT NHS FT ¹¹Bioxydyn, Manchester

1) Introduction

- Entering an era of AD prevention trials, we need improved tools to identify those at greatest risk of imminent decline.
- Assessing **effective connectivity (EC) in the default-mode network (DMN)**, may offer greater sensitivity to early network breakdown compared with measures of brain structure and conventional rs-fMRI measures.

2) Aims

(1) To classify presymptomatic and symptomatic AD cases vs controls and (2) to predict time to symptom onset and compare to familial estimate of time to symptom onset in an Autosomal Dominant Alzheimer Disease (ADAD) cohort where time to symptom onset can be estimated from family history.

3) Methods

- Scans acquired on a 3T MRI scanner (MAGNETOM Prisma Fit, Siemens Healthineers, Forchheim, Germany). Scans preprocessed in SPM25. BOLD signal extracted from 10 pre-specified ROIs representing nodes within the DMN.
- Fully connected dynamic causal model fitted to time-series data to estimate EC between every pair of ROIs.
- Group connectivity modelled as a function of (1) ADAD mutation status, and (2) estimated years to/from onset (EYO).
- Bayesian model reduction generated sparse connectivity matrices used to train elastic-net regression models.

4) Participants demographics

	Controls	Presymptomatic ADAD	Symptomatic ADAD
N	26	26	12
Gender (M/F)	12M / 14F	14M / 12F	7M / 5F
Age at scan	37.5 [29.5 – 43.4]	37.1 [32.5 – 40.9]	48.9 [39.2 – 56.0]
EYO at scan	N/A	10.3 [4.8 – 15.8]	-3.1 [-7.2 – 2.0]
MMSE	29.8 [30.0 – 30.0]	29.8 [30.0 – 30.0]	23.4 [23.0 – 24.0]
Years in education	15.4 [14.0 – 17.0]	14.7 [12.0 – 17.0]	15.3 [14.0 – 17.0]

Table 1. Values are mean [IQR]. MMSE: Mini-Mental State Examination, EYO: Estimated Years to/from Onset. (Positive is prior to expected symptom onset)

5) Connectivity differences between ADAD cases and controls

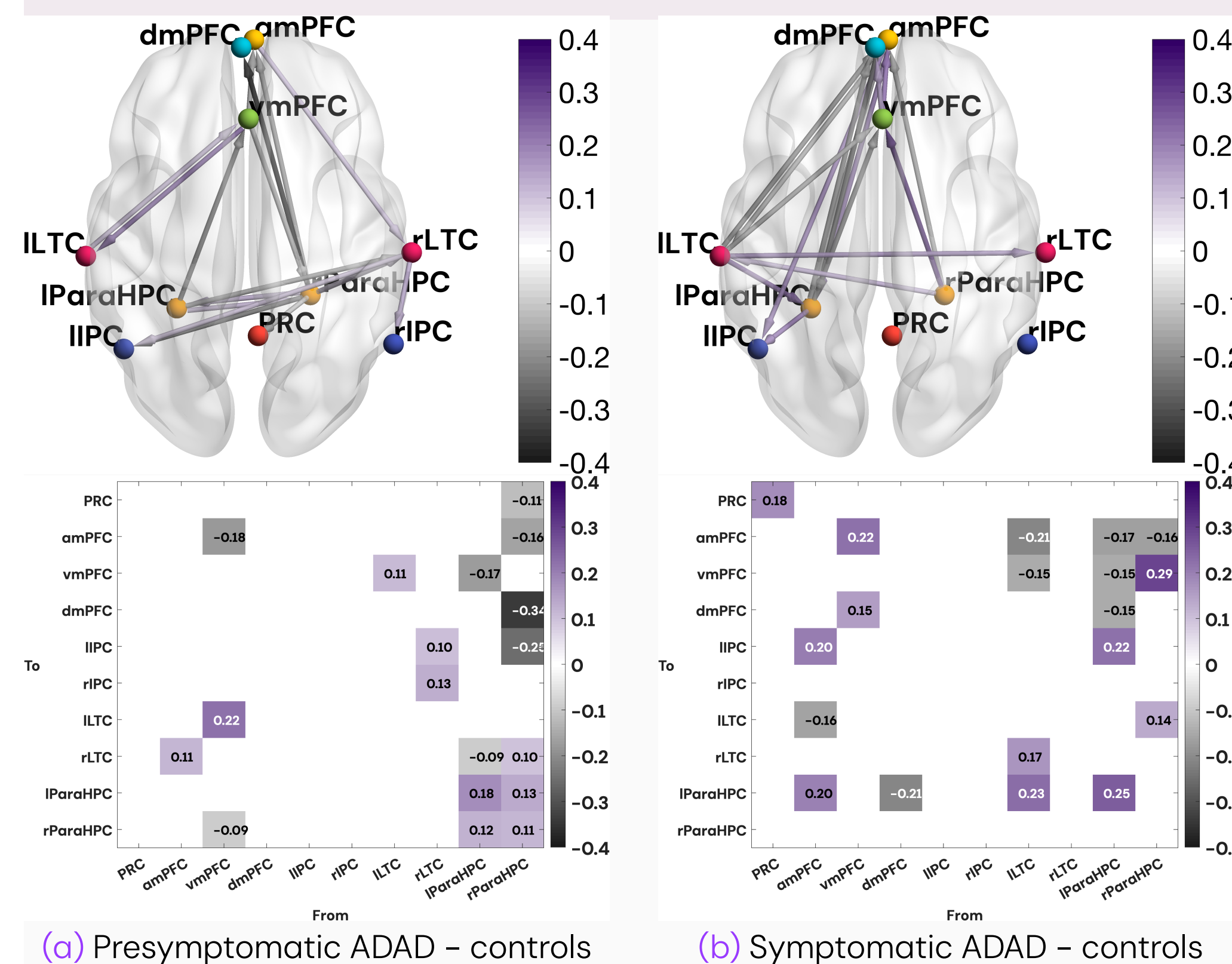


Figure 1. Difference in effective connectivity between (a) presymptomatic ADAD and controls and (b) symptomatic ADAD and controls. Units: Hz; self-connections: unitless log scaling parameters.

6) Classifying presymptomatic ADAD vs controls and symptomatic ADAD cases vs controls

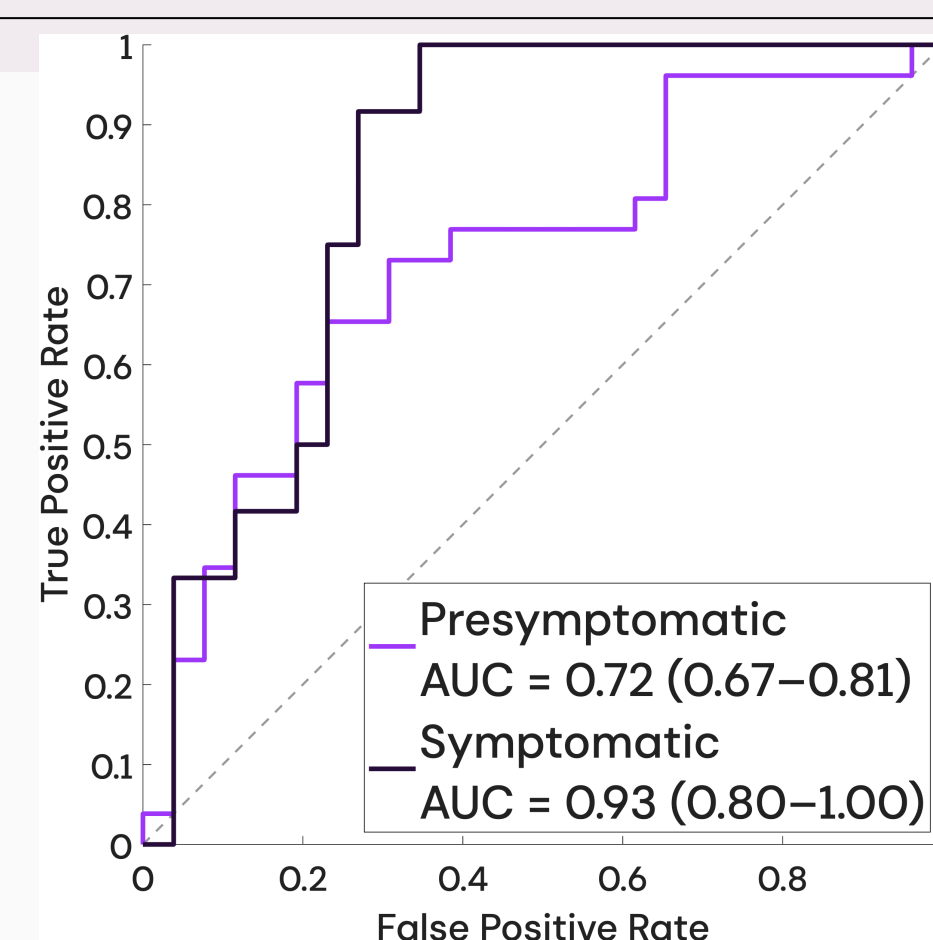


Figure 2. Area under the Curve (AUC) is median AUC value from median iteration of cross-validation. 5 inner folds, 5 outer folds and 9 iterations of cross-validation were used.

7) Connections associated with estimated years to/from symptom onset

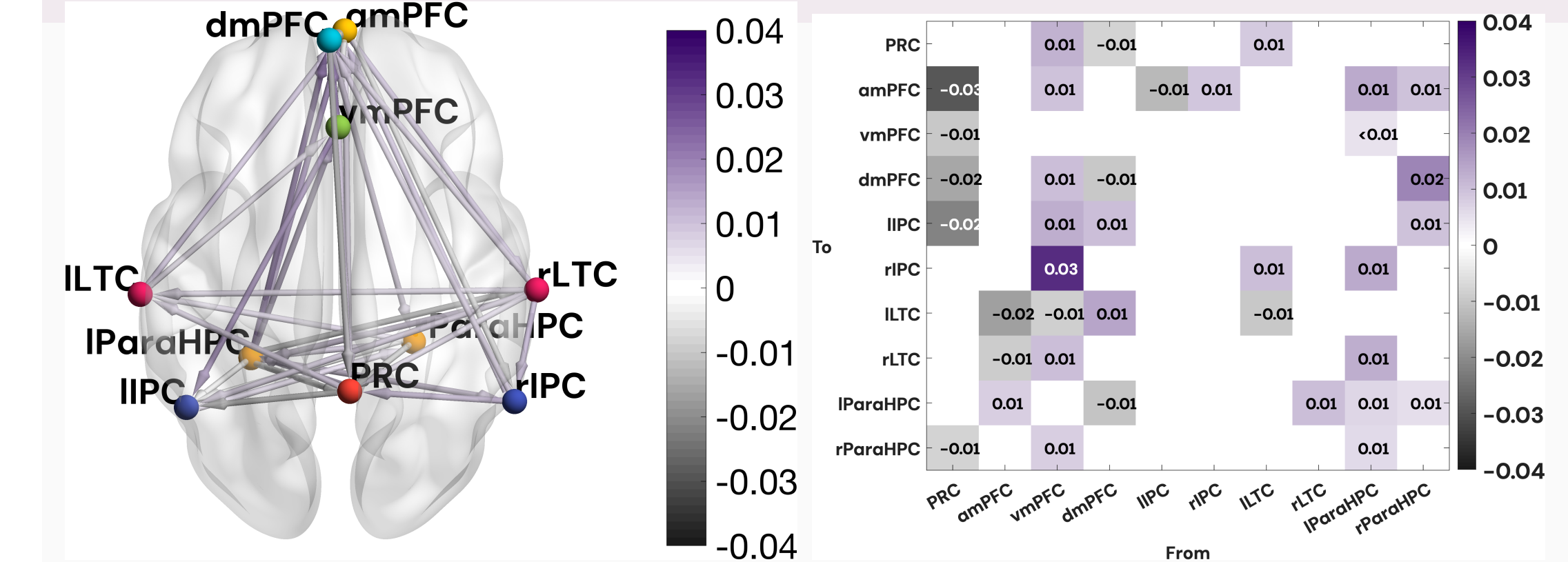


Figure 3. Connectivity parameters associated with estimated years to/from symptom onset. Units: Hz; self-connections: unitless log scaling parameters.

8) Predicting time to symptom onset

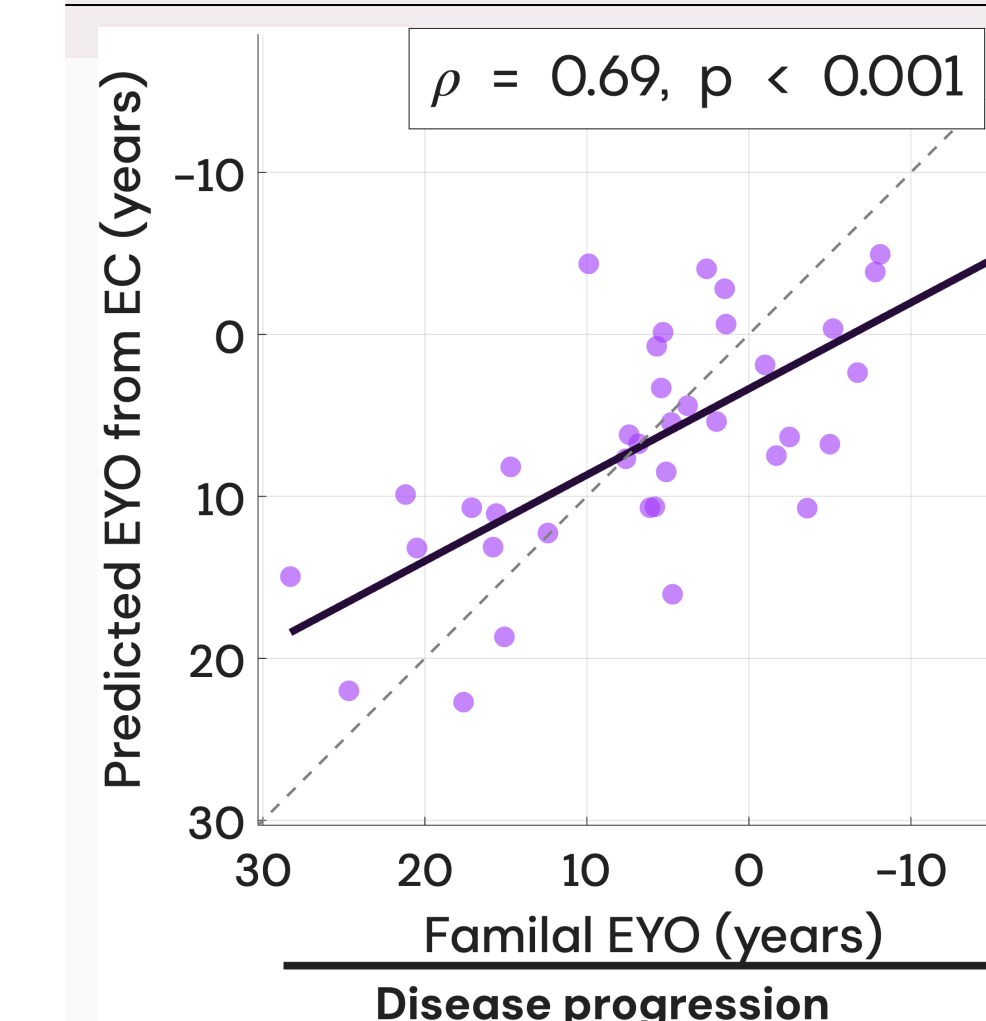


Figure 4. Predicted EYO from EC vs familial EYO. Familial EYO is used as pseudo-ground truth.

9) Conclusion

- DMN EC detects dysconnectivity before symptoms develop** in presymptomatic ADAD pathology, and **estimates proximity to symptom onset**.
- DMN EC may be a useful tool for stratifying individuals at greatest risk from imminent AD-related decline, who may benefit from emerging treatments.



Personal website for updates to manuscript in preparation.

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