Aberrant intrinsic functional network connectivity in Early-Onset Alzheimer’s Disease

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BACKGROUND

- Neurodegeneration in sporadic early-onset Alzheimer’s disease (EOAD) at the stage of MCI and mild dementia is characterized by atrophy most prominently in posterior temporoparietal cortical areas. These “EOAD signature” regions[1] spatially correspond to key nodes of several canonical large-scale functional networks, including the default mode, frontoparietal, language, and dorsal attention networks.
- While current evidence points to abnormal functional connectivity in EOAD compared with healthy controls, prior studies employed small samples and have yielded mixed results.[2,3]

Goal: To investigate alterations in the intrinsic functional organization of the EOAD signature cortical regions among individuals with sporadic EOAD based on a large, well-characterized patient cohort.

Hypotheses: (1) EOAD patients would exhibit disruption of intrinsic functional connectivity involving several functional networks. (2) AD-related connectivity alteration in the EOAD signature cortical regions would be associated with the magnitude of cognitive impairment and of cortical atrophy within the same regions.

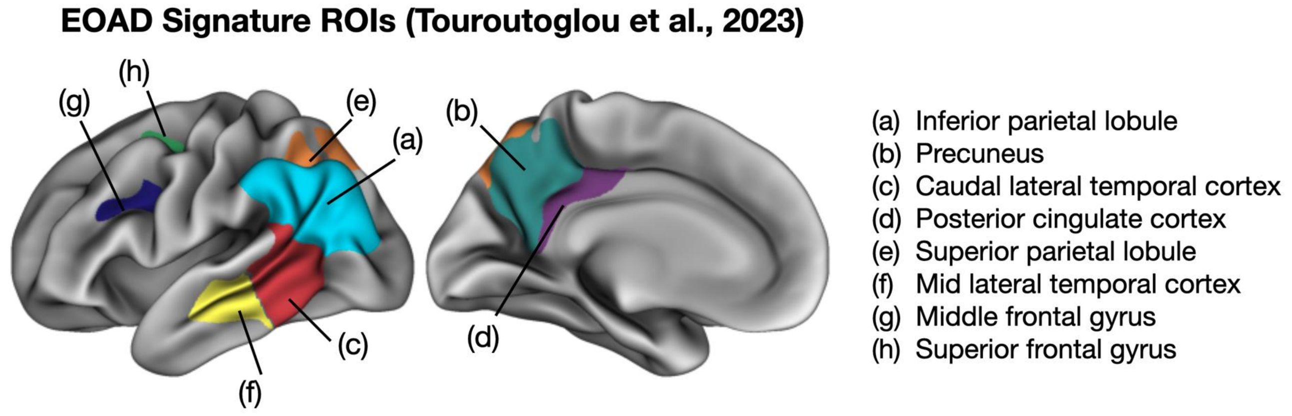
MATERIALS AND METHODS

Participants: We analyzed data collected from 239 patients with sporadic EOAD and 68 low-amyloid cognitively unimpaired (CU) participants from the Longitudinal Early-Onset Alzheimer’s Disease Study[4] (LEADS). All EOAD patients were classified as amyloid positive based on a hybrid approach combining visual reads and quantification of amyloid-PET data.

Neuroimaging: Whole-brain multiband functional MRI data were acquired on a 3T MRI scanner following the ADNI3 protocol (TR = 600 ms, TE = 30 ms, multiband acceleration factor = 8x, 2.5-mm isotropic voxels; acquisition duration = 10 min). Data preprocessing was conducted using fMRIPrep version 24.0.1 with additional surface resampling, geodesic smoothing, and confound regression implemented through in-house custom scripts in python.

Data analysis: Following data preprocessing and quality control, the residual BOLD fMRI timeseries data were used to calculate seed-based functional connectivity of each anatomically distinct cortical region within the EOAD signature (see below). We then compared these seed-based connectivity maps between EOAD and CU participants, while controlling for age, sex, and estimates of in-scanner head motion (i.e., mean framewise displacement). An exploratory analysis of whole-cortex functional connectivity organization was conducted by reducing the dimensionality of BOLD fMRI timeseries data to 400 spatially non-overlapping cortical areas based on the Schaefer parcellation.

EOAD Signature ROIs (Touroutoglou et al., 2023)

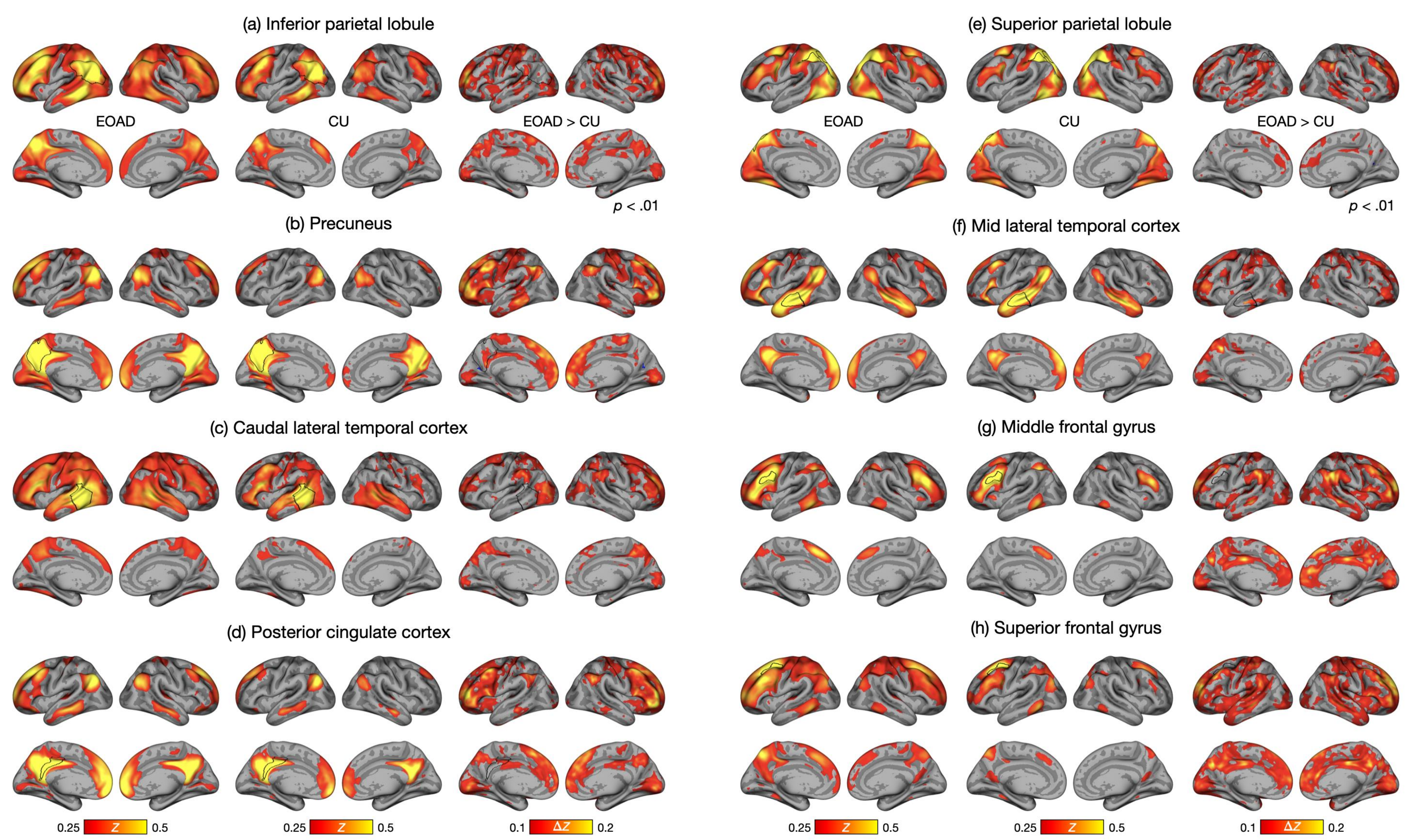


RESULTS

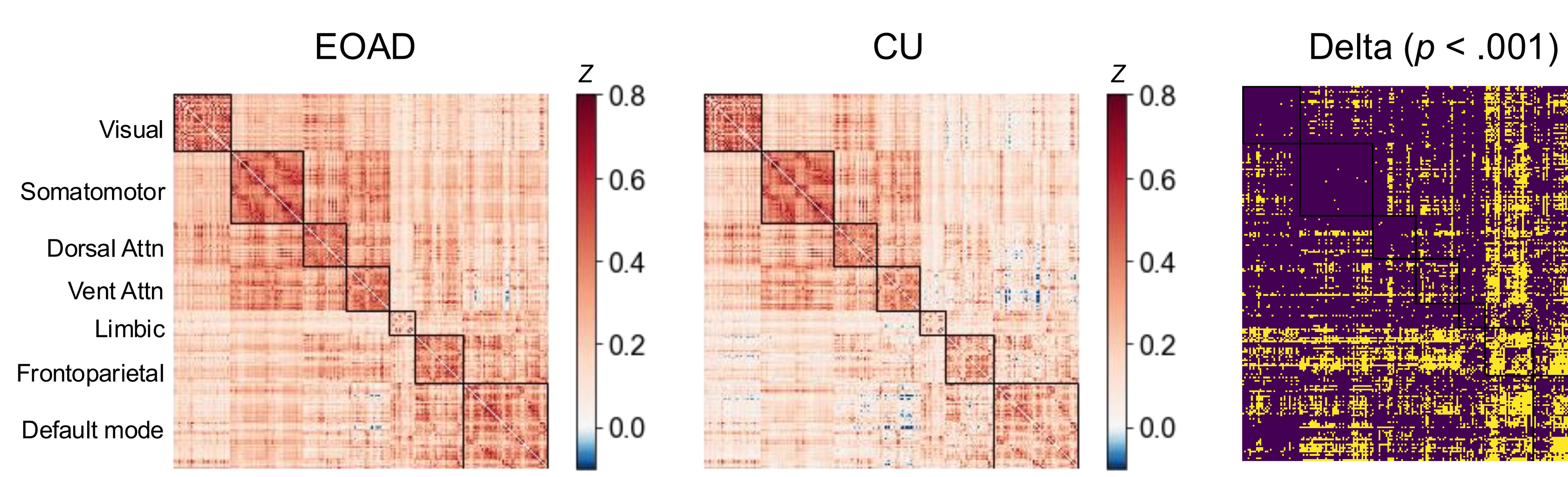
Demographic and clinical characteristics of the sample

	EOAD	CU	*p*
n	239	68	-
Age, years	59.08 ± 3.99	56.07 ± 6.00	**.001**
Sex, % female	60	64.7	.60
Education, years	15.64 ± 2.39	16.81 ± 2.19	**.001**
CDR global, % 0/0.5/1	<1/62/37	100/0/0	-
CDR-SB	3.75 ± 1.80	0	-
MMSE total	21.53 ± 5.09	29.29 ± 0.83	**.001**
ApoE4 status, % known carrier	56	45	.16
Mean framewise displacement	0.14 ± 0.04	0.12 ± 0.05	**.015**

Alterations in seed-based intrinsic functional connectivity of the EOAD signature

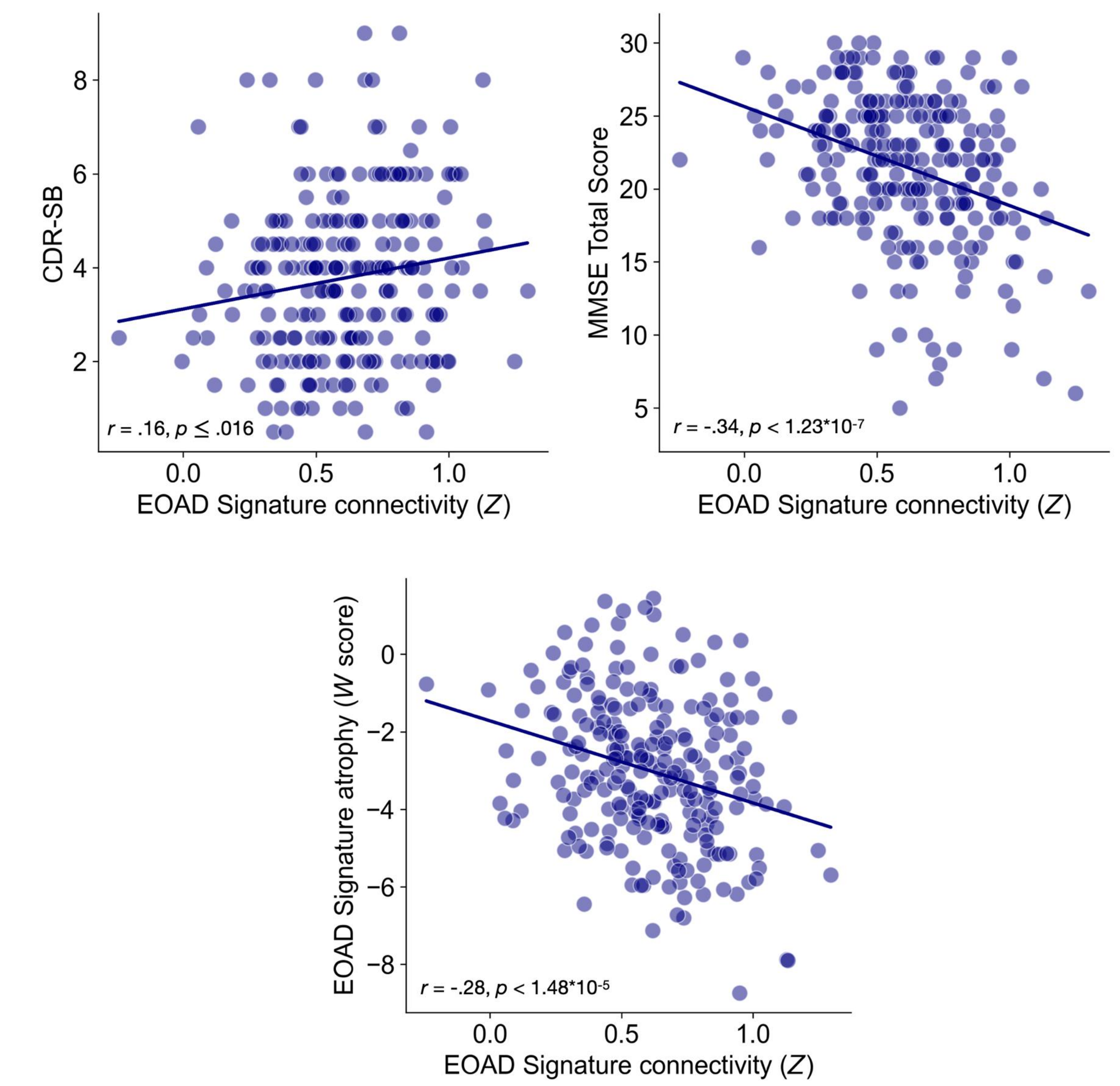


Alterations in whole-cortex intrinsic functional connectome organization



RESULTS, CONT’D

Intrinsic functional connectivity of the EOAD signature in relation to cognitive impairment and cortical atrophy



CONCLUSIONS & FUTURE DIRECTIONS

- EOAD patients showed abnormally stronger connectivity in all EOAD signature regions than CU participants, involving multiple large-scale functional networks.
- A data-driven, whole-cortex analysis further provided evidence for an AD-related increase in connectivity within the default mode and frontoparietal networks as well as between these networks and other networks.
- In EOAD patients, stronger functional connectivity within multiple networks was associated with worse cognitive impairment and greater atrophy in the EOAD signature.
- In patients with sporadic EOAD, phenotypically vulnerable cortical regions exhibit prominent disruption of intrinsic functional connectivity. Our findings support the selective vulnerability of cortical functional networks in EOAD, which may underlie the distinct pattern of AD pathology spreading and cognitive impairment in this AD clinical phenotype.
- Ongoing analyses examine functional connectivity alterations within and between specific functional networks, graph theory-based network properties, and longitudinal changes in connectivity profiles in EOAD.

REFERENCES & ACKNOWLEDGMENTS

[1]Touroutoglou et al. (2023). *Alzheimers Dement*; [2]Adriaanse et al. (2014). *PLOS ONE*; [3]Gour et al. (2014). *Hum Brain Mapp*; [4]Apostolova et al. (2021). *Alzheimers Dement.* We would like to thank all members of the LEADS Consortium. This study was in part generously supported by NIH R56 AG057195, U01 AG6057195, U24 AG021886, K01 AG084820, Alzheimer’s Association LEADS GENETICS-19-639372, Alzheimer’s Association LDRFP-21-818464, Alzheimer’s Association LDRFP-21-824473, Alzheimer’s Association LDRFP-21-828356, and Alzheimer’s Association AARG-24-1309264.