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Network connectivity alterations in presymptomatic and symptomatic *MAPT* mutation carriers

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State of the art: Microtubule-associated protein tau (*MAPT*) gene mutations cause frontotemporal lobar degeneration. Yet, previous studies have not examined network connectivity across this entire *MAPT* clinical continuum.
Methodology: We compared 17 symptomatic (age 54.4±11.9 years) and 39 presymptomatic *MAPT* mutation carriers (age 37.3±11.9 years) to 81 demographically matched controls to investigate intrinsic connectivity network alterations cross-sectionally. We performed: 1) seed-based analyses to examine connectivity within networks associated with the most common *MAPT*-associated clinical syndromes (i.e., salience network, default mode network, corticobasal syndrome and progressive supranuclear palsy syndrome networks); and 2) whole brain approaches to study intra- and inter-network connectivity. We applied K-means clustering to explore heterogeneity in whole-brain connectivity in presymptomatic carriers and examined longitudinal gray matter volume trajectories per subgroup.
Results: Both symptomatic and presymptomatic carriers showed connectivity alterations within *MAPT*-syndromic networks. Within these networks, presymptomatic carriers vs. controls also showed regions of altered connectivity with age within key cortical network hubs, alongside regions of principally higher subcortical connectivity with age. Two presymptomatic subgroups were identified, each exhibiting predominantly either hypoconnectivity (n=28) or hyperconnectivity (n=11) across the whole brain. Compared to controls, the presymptomatic subgroup with hypoconnectivity (at baseline) showed extensive longitudinal gray matter volume decline in *MAPT*-relevant regions, whereas the subgroup with hyperconnectivity had less extensive longitudinal decline.
Conclusion: Our findings suggest that task-free fMRI holds promise for detecting early changes along the *MAPT* clinical continuum. Future longitudinal studies are needed to determine whether presymptomatic carriers with baseline hypoconnectivity pose greater risk for imminent symptomatic conversion.

Conflicts of interest

LZ, TMF, SH, SAC, JB, AL, LP, MLM, MLGT, VS, JY, YC, NG, MG, EDH, ALL, IRM, MFM, EMR, MCT, AWT, SW, LKF, HWH and SEL had no disclosures. BSA has consulted with Acadia, Sangamo, and Ionis and is Medical Director of the CJD Foundation (unpaid). BCD served as a consultant for Acadia, Alector, Arkuda, Biogen, Denali, Eisai, Genentech, Lilly, Merck, Novartis, Takeda, Wave Lifesciences, and received royalties from Cambridge University Press, Elsevier, Oxford University Press. DHG served in scientific advisory boards for AcuraStem and Axial Biotherapeutics, received research support from F. Hoffman-La Roche, and consulted for Covington & Burling LLP and Biogen. NG has participated or is currently participating in clinical trials of anti-dementia drugs sponsored by Bristol Myers Squibb, Eli Lilly/Avid Radiopharmaceuticals, Janssen Immunotherapy, Novartis, Pfizer, Wyeth, Roche. NRGR does not have COI and is also taking part in multicenter studies funded by Biogen, Esai and Lilly. GYRH has received research support as a clinical trials site investigator from Anavax, Biogen, Eli Lilly and Roche, and has received research grants from the Canadian Institute of Health Research, Alzheimer Society of Canada, and NIA/NIH. KK consults for Biogen, receives research support from Avid Radiopharmaceuticals and Eli Lilly, and receives funding from the Alzheimer's Drug Discovery Foundation. IL is a member of the Scientific Advisory Board for Amydis, but does not receive funds and from the Rossy PSP Program at the University of Toronto. She receives salary from the University of California San Diego and as Chief Editor of Frontiers in Neurology. CUO receives research support from Alector and Transposon Therapeutics. EDR has served on scientific advisory boards for Biogen and AGTC and on a DSMB for Lilly. He has received funding from NIH, the Bluefield Project, and Alzheimer's Drug Discovery Foundation. He is an owner of intellectual property related to tau. ZKW is partially supported by the Mayo Clinic Center for Regenerative Medicine, the gifts from the Donald G. and Jodi P. Heeringa Family, the Haworth Family Professorship in Neurodegenerative Diseases fund, and the Albertson Parkinson's Research Foundation. He serves as PI or co-PI on Biohaven Pharmaceuticals, Inc. (BHV4157-206 and BHV3241-301), Neuraly, Inc. (NLY01-PD-1), and Vigil Neuroscience, Inc. (VGL101-01.001 and VGL101-01.002) grants. He serves as co-PI of the Mayo Clinic APDA Center for Advanced Research and as an external advisory board member for the Vigil Neuroscience, Inc. BFB has served as an investigator for clinical trials sponsored by Biogen, Alector, and EIP Pharma. He receives royalties from the publication of a book entitled Behavioral Neurology Of Dementia (Cambridge Medicine, 2009, 2017). He serves on the Scientific Advisory Board of the Tau Consortium and receives research support from the NIH. ALB has served as a consultant for Alector, Arkuda, Arvinas, AZTherapeutics, Boehringer Ingelheim, Denali, GSK, Humana, Oligomerix, Oscotec, Roche, Third Rock, Transposon, TrueBinding and Wave. HJR has been a consultant for Takeda pharmaceuticals, Biogen pharmaceuticals, Ionis, Otsuka, Wave and Eisai. BLM received royalties from Cambridge University Press, Guilford Publications, Inc., Johns Hopkins Press, Oxford University Press, Taylor & Francis Group, Elsevier, Inc. WWS received consulting fees from Guidepoint Global, GLG Council, BridgeBio, and Corcept Therapeutics.