Reconfigured metabolism brain network in asymptomatic microtubule-associated protein tau mutation carriers: A graph-theoretical analysis

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Abstract

Background: Studies exploring topologic properties of the metabolic network in the presymptomatic stage of genetic frontotemporal dementia (FTD) are scarce, which may be important for understanding brain function and disease pathogenesis. This study aimed to explore FTD-specific patterns of metabolism topology reconfiguration in asymptomatic microtubule-associated protein tau (MAPT) mutation carriers.

Method: Six asymptomatic carriers of MAPT P301L mutation were compared with 12 non-carriers who were all from the same large family of FTD. For comparison, we included 32 behavioral-variant FTD (bvFTD) patients and 33 unrelated healthy controls. Each participant underwent neuropsychological assessments, genetic testing, and hybrid PET/MRI scan. Voxel-wise gray matter volume and standardized uptake value ratio were calculated and compared for structural MRI and FDG-PET, separately. The sparse inverse covariance estimation (SICE) method was applied to topologic properties and metabolic connectomes of brain functional networks derived from ¹⁸F-fluorodeoxyglucose PET/MRI data. Independent component analysis was used to explore metabolic connectivity in the salience (SN) and default mode networks (DMN).

Result: The mean estimated years from symptom onset was 8.33 ± 1.875 years in the mutation carrier group. The asymptomatic MAPT carriers show no significant differences in cognitive tests, gray matter volume and FDG uptake compared to non-carriers. They also retained normal global parameters of metabolism network, but not for bvFTD patients. However, we revealed lost hubs in the ventromedial prefrontal, orbitofrontal, and anterior cingulate cortices and reconfigured hubs in the anterior insula, precuneus, and posterior cingulate cortex in asymptomatic carriers, which is consistent with the findings in bvFTD patients. Similarly, significant differences in local parameters of these nodes were observed in asymptomatic carriers. The reduction in connectivity was marked in lost hub regions during the asymptomatic stage. Functional connectivity within the SN and DMN was enhanced in asymptomatic carriers, while reduced in bvFTD patients.

Conclusion: Our findings showed that asymptomatic MAPT carriers were initially involved in medial prefrontal areas and actively compensated in task-related regions.
Topologic properties of the metabolic network may contribute to further investigations and monitoring of the earliest stages of FTD in individuals with genetic backgrounds.