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NEUROIMAGING

Structure-function decoupling in genetic frontotemporal dementia

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Abstract

Background: Functional network integrity is important for maintaining cognitive performance during the 10-20 year presymptomatic period of frontotemporal dementia (FTD), conferring resilience to advancing neuropathology and atrophy. The extent to which functional integrity relies on preserved structural connectivity is unclear. Here, we test the relationship between functional connectivity and structural connectivity, termed structure-function coupling, against genetic risk for FTD and disease progression.

Method: We studied 56 symptomatic and 165 pre-symptomatic FTD-mutation carriers, and 141 family members without mutations, from the GENFI cohort. Diffusion weighted imaging and functional magnetic resonance imaging (Siemens MR platforms) were acquired and analysed using established approaches to quantify participant-level structural and functional connectomes (Figure 1-(1)). Connectomes were defined in the Brainnetome Atlas and re-mapped onto a subcortical network and seven resting-state networks based on the Yeo Networks (Figure 1-(2)). An inter-subject regularized canonical correlation analysis (CCA) with permutation-based cross-validation was used to jointly analyse the structural and functional connectomes (Figure 1-(3-4)). Second-level analysis with robust multiple linear regression models tested for differences between non-carriers, pre-symptomatic carriers and symptomatic carriers in the strength of association between structural and functional CCA subject scores. Age, sex, head motion and scanner site were included as covariates.

Result: Canonical correlation analysis identified significant components linking structural and functional connectivity. The first component ($r=0.656$, $p<0.001$) reflected a structural connectivity pattern with high within- and between-networks loadings (Figure 1-(5)) with strong within-networks functional connectivity and weak-to-negative between-network functional connectivity (Figure 1-(6)). This component associated structural integrity with function segregation, whereby individuals with high structural connectivity within and between networks exhibit greater functional

network segregation as shown by strong within-network functional connectivity and weak between network connectivity. The strength of this structure-function coupling was greater for non-carriers compared to pre-symptomatic carriers (Figure 1-(7)). Symptomatic carriers showed minimal relationship between structural and functional scores, indicating structure-function decoupling, consistent with the hypothesis that cognitive decline is triggered by critical decoupling of previously synergistic neural systems.

Conclusion: Our findings demonstrate progressive de-coupling between structural connectivity and functional segregation over the course of genetic frontotemporal dementia. These results have implications for designing pre-symptomatic disease-modifying 'preventative' trials, supported by imaging-based surrogate markers of neural system dynamics.