

## **Resilience of functional connectomes in presymptomatic frontotemporal dementia**

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**State of the art:** Carriers of frontotemporal dementia-related mutations can maintain cognitive function during the 10-20 years before expected symptom onset, even in the presence of significant progressive atrophy. The integrity of functional organisation during this presymptomatic stage is proposed to determine this functional resilience to the pathology.

**Methodology:** We studied 151 symptomatic and 289 presymptomatic FTD-mutation carriers, and 271 family members without mutations. We analysed functional magnetic resonance imaging using novel gradient mapping technique, to quantify the integrity of the functional connectome, within functional “communities” of cortical and subcortical regions.

**Results:** We confirmed a decrease in network integrity in symptomatic carriers compared to non-carriers. However, there was increased network integrity for presymptomatic carriers compared to non-carriers. The strongest effects were observed in inferior-frontal cortex, dorsal-lateral prefrontal cortex, dorsal anterior cingulate cortex, the intraparietal lobule and superior temporal gyrus. This enhancement of functional connectomes in presymptomatic carriers was behaviourally relevant and independent of the severity of brain-wide atrophy.

**Conclusion:** Our findings suggest that resilience to atrophy may arise from enhanced functional connectomes, protecting against clinical conversion in individuals at risk of dementia. This result has implications for the design of presymptomatic disease-modifying therapy trials, using surrogate markers of brain health rather than clinical end points.

## **Conflicts of interest**

Nothing to declare.