

## Coupling between cerebral blood flow and grey matter volume relates to cognition in presymptomatic genetic frontotemporal dementia

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**State of the art:** Frontotemporal dementia (FTD) is a highly heritable neurodegenerative disease, with diverse cognitive changes. Neurobiological changes evident by brain imaging evolve during the presymptomatic stage. Better understanding of the disease trajectory, especially in the presymptomatic stage, would inform accurate staging and facilitate clinical trials. Here we consider the relationships between brain structure, cerebral blood flow (CBF), functional network and cognition, using multi-modal linked independent component analysis (LICA).

**Methodology:** We included 43 symptomatic carriers of *MAPT*, *GRN* or *C9orf72* mutations, 199 relatives without mutations, and 234 relatives who were presymptomatic carriers. The grey matter volume (GMV), CBF, and resting-state network maps were co-analysed using LICA. We used group independent component analysis to define the topography of four large-scale functional networks – salience, default mode, and left/right frontoparietal networks. The expression of LICA components was compared across groups using Kruskal-Wallis tests. Subject loadings of each component were correlated with performance on Digit Symbol Substitution test using linear regression.

**Results:** The principal LICA components were dominated either by a single functional network or an integration of GMV with CBF; component loadings showed significant differences between presymptomatic and symptomatic carriers. A subset of components was cognitively-relevant across all groups. A component reflecting atrophy and hypoperfusion in frontal-temporal cortex correlated with Digit Symbol test performance in presymptomatic carriers ( $\beta=0.33$ ,  $p<0.001$ ) but not in symptomatic carriers ( $\beta=0.098$ ,  $p=0.56$ ).

**Conclusion:** Cognitive function at presymptomatic stage of FTD depends on the joint maintenance of CBF with GMV, although this correlation breaks down after symptom onset.

### Conflicts of interest

No conflict of interest.