Trajectory of apathy, cognition and neural correlates in the decades before symptoms in frontotemporal dementia

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Background
In frontotemporal dementia (FTD), apathy is reported to negatively impact the prognosis and survival of patients. The study of genetic FTD in its pre-symptomatic period permits the investigation of markers in the early stages of disease progression. Therefore, in pre-symptomatic gene carriers in the multicentre Genetic FTD Initiative (GENFI), we examined longitudinal apathy changes in association with cognitive decline over time, and baseline measures of atrophy.
Method
Six hundred participants from Data Freeze 4 (2019) were included: 304 pre-symptomatic mutation carriers, and 296 family members without mutations. Clinical assessment and a structural MRI scan were undertaken at baseline, and annually for at least 2-years. Latent Growth Curve modelling (LGCM) was used to assess: 1) longitudinal changes in apathy, as measured by the apathy subscale of the Revised Cambridge Behavioural Inventory; 2) the relationship with longitudinal changes in executive function; 3) the association with baseline regional grey matter volumes. The time to the expected year of symptom onset was included as a covariate.
Result
Univariate LGCM identified a significant linear increase in apathy scores for pre-symptomatic carriers (estimate= 0.51, se=0.18, z scores= 2.88, p=0.004), but not in non-carriers (estimate= 0.08, se=0.08, z scores=1.04, p=0.30). An equality constrained comparison suggested a significant group difference in the progression of apathy (i.e. the slope) ((Δ χ2=10.14; p=0.0015). Pre-symptomatic carriers also had a significant decline in executive functions (est=-0.07, se=0.03, z scores=-2.49, p=0.017), which was predicted by baseline apathy (standard estimate=-0.40, p=0.008). In pre-symptomatic carriers only, the annual rate of change in apathy was significantly associated with brain volume in frontal lobe (standard estimate=-0.47, p=0.008) and cingulate cortex (standard estimate=-0.29, p=0.05) at the baseline.
Conclusion
Apathy progresses significantly in pre-symptomatic FTD and predicts a sub-clinical deterioration of executive performance in gene carriers. Apathy changes over 2 years are associated with volume in the frontal lobe and cingulate gyrus measured at the baseline. We suggest that apathy may be a modifiable factor to protect function and cognition in those with, or at risk of, frontotemporal dementia.