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Longitudinal Changes in Brain Structure Reflect Differential Patterns of Behavioural and Neuropsychiatric Symptom Change in Genetic Frontotemporal Dementia

Paul Tristin Best, Jonathan D. Rohrer, James B. Rowe, Barbara Borroni, Daniela Galimberti, Pietro Tiraboschi, Mario Masellis, Maria Carmela Tartaglia, Elizabeth Finger, John C. van Swieten, Harro Seelaar, Lize Jiskoot, Sandro Sorbi, Chris R. Butler, Caroline Graff, Alexander Gerhard, Tobias Langheinrich, Robert Laforce, Raquel Sanchez-Valle, Alexandre de Mendonça, Fermin Moreno, Matthis Synofzik, Rik Vandenberghe, Isabelle Le Ber, Johannes Levin, Adrian Danek, Markus Otto, Florence Pasquier, Isabel Santana, Matthias L. Schroeter, Anne Remes, Maria Landqvist Waldö, Yolande Pijnenburg, Jorgen Nielsen, Tim Van Langenhove, Mallar Chakravarty, Simon Ducharme

Neuropsychiatric symptoms emerge in mid-adulthood in genetic frontotemporal dementia (FTD), which is caused primarily by one of three genetic mutations: chromosome 9 open reading frame 72 (*C9orf72)*, progranulin (*GRN),* and microtubule-associated protein tau (*MAPT)*. The neuroanatomical changes associated with these symptoms are largely based on cross-sectional or pseudolongitudinal analyses. Thus, we examined the relationship between longitudinal brain atrophy and the development of neuropsychiatric symptoms in FTD-related mutations.

We used T1-weighted structural MRI and behavioural and neuropsychiatric symptom measures from the Cambridge Behavioural Inventory-Revised from subjects with FTD-related mutations (n = 140) and controls (n = 101). We assessed within-subject change at approximately two years by estimating voxel-wise volume change using deformation-based morphometry. Using partial least squares correlation separately for each mutation and controls, we examined the relationship between neuroanatomical change and changes in neuropsychiatric and behavioural symptoms over 2 years.

For each mutation carrier group, we obtained one significant latent variable (LV) ($p < 0.01$) and none for controls. The *C9orf72* LV showed associations between sporadic atrophy and behavioural and psychotic deficits. The *GRN* LV highlighted associations between atrophy in frontal and parietal cortices and behavioural and mood deficits. The *MAPT* LV illustrated associations between atrophy in frontal and temporal cortices and behavioural deficits.

Despite heterogeneity in clinical phenotypes, one LV linking cerebral volume loss to neuropsychiatric symptoms was found per mutation. These findings highlighted brain atrophy patterns unique to each mutation that reflected differential changes in neuropsychiatric symptoms, including cerebral changes being linked to psychosis emergence in *C9orf72* carriers.

Conflicts of interest

N/A