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Background

Studies have previously shown evidence for presymptomatic cortical atrophy in genetic frontotemporal dementia (FTD). Whilst initial investigations have also identified early deep grey matter volume loss, little is known about the extent of subcortical involvement, particularly within subregions, and how this differs between genetic groups. We aimed to examine the specific pattern of subcortical changes (including specific subregions), to determine which areas were impaired across the different disease stages of genetic FTD.

Methods

480 mutation carriers from the Genetic FTD Initiative (GENFI) were included (198 GRN, 202 C9orf72, 80 MAPT), together with 298 non-carrier cognitively normal controls (NC) (Table). Cortical and subcortical volumes of interest were generated using automated parcellation methods on volumetric 3T T1-weighted MRI scans. Mutation carriers were divided into three disease stages based on their global CDR® plus NACC FTLD score: asymptomatic (0), possibly mildly symptomatic (0.5) and fully symptomatic (1 or more).

Results

In all three groups, subcortical involvement was seen at the CDR 0.5 stage prior to phenocconversion, whereas in the C9orf72 and MAPT mutation carriers there was also involvement at the CDR 0 stage (Figure). In the C9orf72 group the earliest volume changes were in thalamic subnuclei (particularly pulvinar and lateral geniculate, 9-10%) cerebellum (lobules VIIa-Crus II and VIIb, 2-3%), hippocampus (particularly presubiculum and CA1, 2-3%), amygdala (all subregions, 2-6%) and hypothalamus (superior tuberal region, 1%). In the MAPT group changes were seen at CDR 0 in the hippocampus (subiculum, presubiculum and tail, 3-4%) and amygdala (accessory basal and superficial nuclei, 2-4%). GRN mutation carriers showed subcortical differences at CDR 0.5 in the presubiculum of the hippocampus (8%).

Conclusions

C9orf72 expansion carriers show the earliest and most widespread changes including the thalamus, basal ganglia and medial temporal lobe. By investigating individual subregions, changes can also be seen at CDR 0 in MAPT mutation carriers within the limbic system. Our results suggest that subcortical brain volumes may be used as markers of neurodegeneration even prior to the onset of prodromal symptoms.

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