Multimodal structural imaging analysis of *C9orf72*-associated FTD

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Background

Hexanucleotide repeat expansions in the *C9orf72* gene represent the most common genetic cause of frontotemporal dementia (FTD) and lead to a heterogeneous behavioural and cognitive syndrome.

Methods

Using different multimodal techniques, we investigated the structural changes in grey and white matter in six patients with C9orf72-associated FTD, compared with 17 cognitively normal controls (**Table**). Participants were scanned on a 3T Siemens Trio scanner and groups were matched for age, gender, and education. T1-weighted 3D images were used for voxel-based morphometry (VBM) analysis with SPM12, and, together with T2-weighted 3D images, for manual and automated segmentations using the Neuromorphometrics protocol, to extract cortical and subcortical regions of interest. Using a combination of tools from DTI-TK and NiftyPipe, diffusion-weighted images were pre-processed and analyzed to firstly, extract diffusion measures in white matter (WM) tracts of interest, and secondly perform a tract-based spatial statistics (TBSS) analysis. Volumes were corrected for total intracranial volume (TIV), and VBM analysis was adjusted for age, gender and TIV. Results were corrected for multiple comparisons.

	Controls (n=17)	*C9orf72*-FTD (n=6)	p-value
Gender, male	9 (53%)	5 (83.3%)	0.190
Age at scan (years)	57.2 (14.3)	65.1 (7.2)	0.201
Disease duration (years)	N/A	10.8 (6.4)	---
FRS (/100)	N/A	28 (25) Range 3-67	---
Age at onset (years)	N/A	54.3 (9.8)	---
Education (years)	14.4 (3.1)	13.3 (3.9)	0.494
MMSE (/30)	29.2 (1.3)	24.0 (4.0)	**0.010**
CBI-R Total (/180)	N/A	78.7 (33.4)	---

Table. *Demographic, clinical and behavioural variables for the C9orf72-FTD patients and controls. Values denote mean (standard deviation) or n (%). P-values denote significance on Mann-Whitney U or chi-square test.*

Results

The *C9orf72*-associated FTD group showed significantly lower volumes than controls in the thalamus, superior-posterior region of the cerebellum and habenula, as well as the frontal and insular cortices (9-19%, p≤0.003 on Mann-Whitney U test, **Figure 1**). VBM analysis confirmed involvement of the same regions (**Figure 2**). Both TBSS and regional WM analyses showed involvement of the posterior thalamic radiation, sagittal stratum, fornix, body of the corpus callosum and cingulum (**Figure 3**).

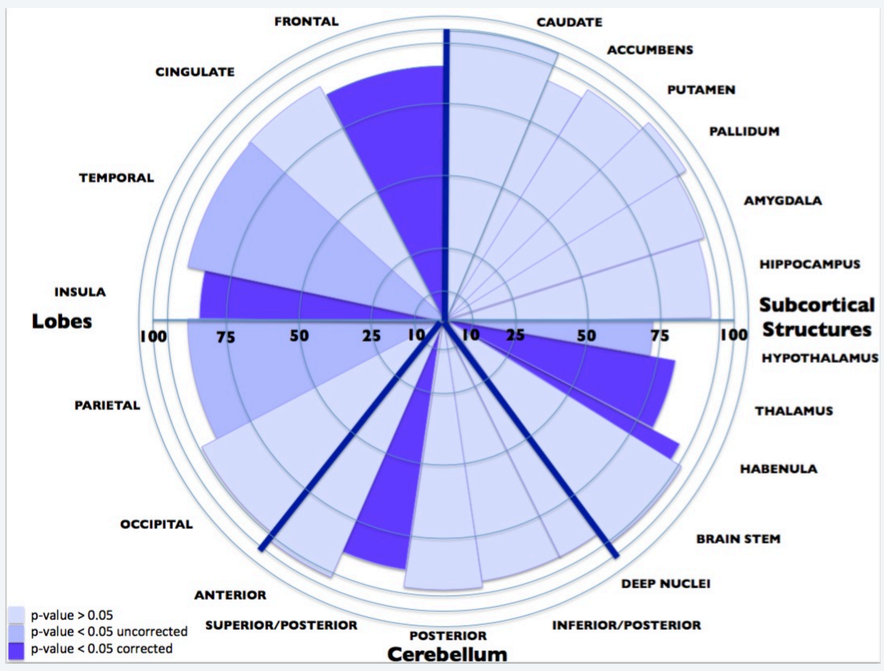

Figure 1. Percentage of volumetric differences between C9orf72-FTD and controls.

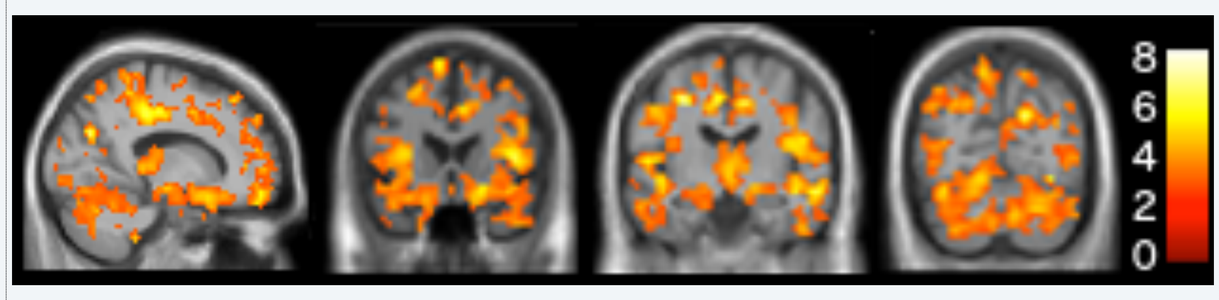

Figure 2. VBM analysis on GM regions. *Statistical parametric maps were thresholded at p<0.05 after FDR correction. Analyses were adjusted for age, gender and TIV. The colour bar indicates the t-values.*

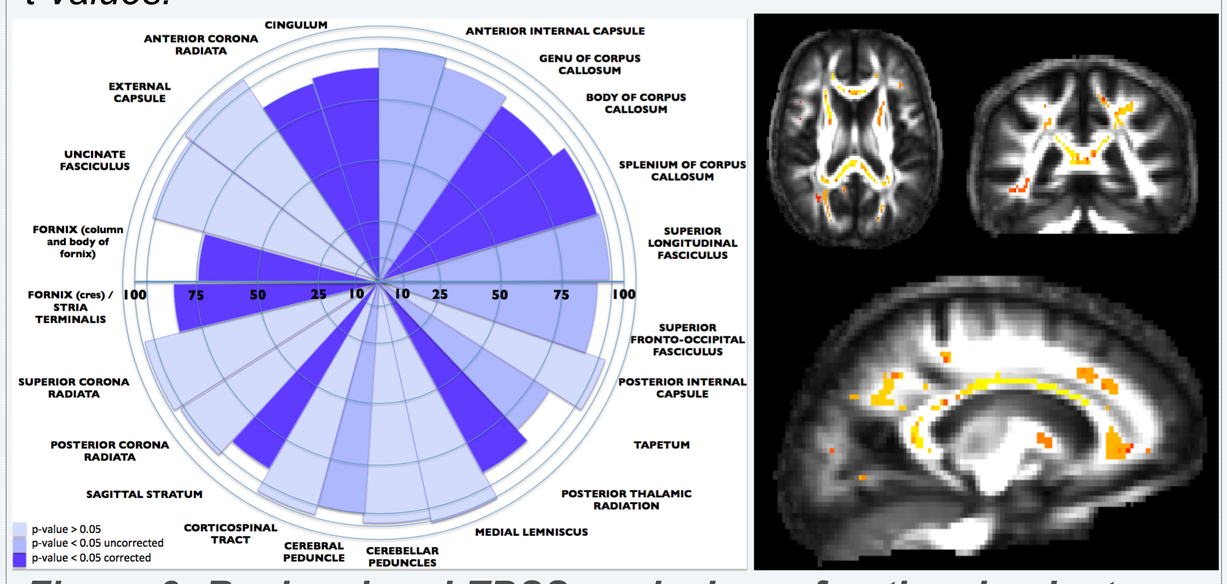

Figure 3. Regional and TBSS analysis on fractional anisotropy. *FA maps show lower FA values in C9orf72-FTD than in controls. Map were thresholded at p<0.05 after FWE correction.*

Conclusions

Multimodal structural analysis of *C9orf72*-associated FTD reveals degeneration of widespread regions within the brain but particularly involving a cortico-thalamic-cerebellar network, specific to this genetic subtype of FTD.

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