Pattern of progression in *MAPT*-related frontotemporal dementia: results from the GENFI study

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INTRODUCTION

Mutations in the microtubule associated protein TAU (*MAPT*) gene have been linked with frontotemporal dementia (FTD), but little is known of the progression of neurodegeneration in early presymptomatic carriers. We aimed to identify the presence of early brain changes in *MAPT* mutation carriers.

METHODS

3T MRIs from 84 *MAPT* mutation carriers from the Genetic FTD Initiative (GENFI) with 77 age-matched non-carrier cognitively normal controls were included. We divided presymptomatic carriers into two groups based on their expect years to symptom onset (EYO): 'late' (within 10 years of expected onset) and 'early' (more than 10 years from expected onset) (**Table**). A voxel-based morphometry (VBM) analysis was performed to compare 26 symptomatic carriers with 41 age-matched controls to identify regions of interest (ROIs) which were atrophic in the symptomatic stage. Following this, using the automated Geodesic Information Flow algorithm (Cardoso *et al.*, 2015) we extracted the volumes for these ROIs in all 84 carriers and 77 controls (**Figure 1**). Manual segmentation of the hypothalamus was performed following the criteria described in (Bocchetta *et al.*, 2015) to extract hypothalamic volumes (**Figure 2**). We computed w-scores for each ROI from a linear regression model carried out on the controls adjusting for the effect of age, gender, total intracranial volume and scanner type. A w-score of <-1.28 (corresponding to the 10th percentile) was considered as 'abnormal'.

***Table**. Demographics by group. *One subject excluded from VBM analysis due to a cerebellar artefact. Early presymptomatic carriers were classified from -30 to -10 years before expected years to onset. Late presymptomatic carriers were classified as within 10 years of expected age of onset.*

Group	Subgroup	Age Mean(SD)	Gender (% male)	EYO Mean(SD)	Disease duration Mean(SD)
Controls	*All (N=77)*	43.9(13.7)	55.8	-	-
	Symptomatic age-matched controls (N=41)	53.8(9.9)	51.2	-	-
Presymptomatic *MAPT* carriers	*Early (N=35)*	33.9(7.6)	45.7	-19.9(7.9)	-
	Late (N=22)	49.7(8.9)	36.4	-1.3(6.7)	-
Symptomatic *MAPT* carriers	*All (N=27)**	57.9(8.3)	66.6	-	5.4(4.5)

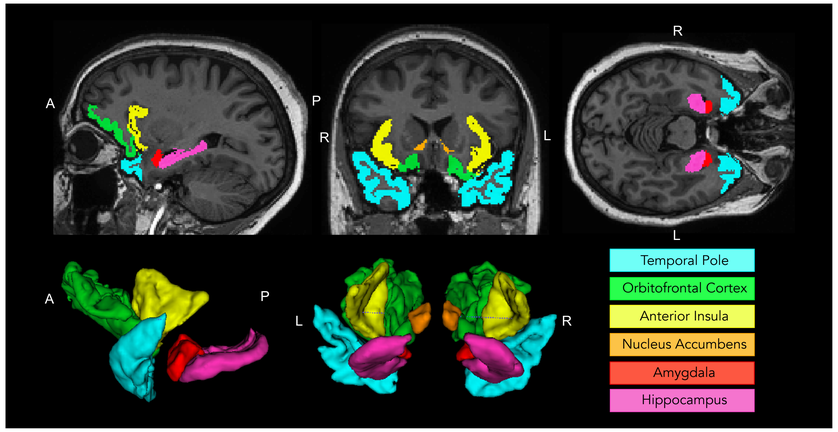

***Figure 1**. Example of the Geodesic Information Flow (GIF) segmentation of the selected regions mapped on a T1-weighted 3T MR of a control subject.*

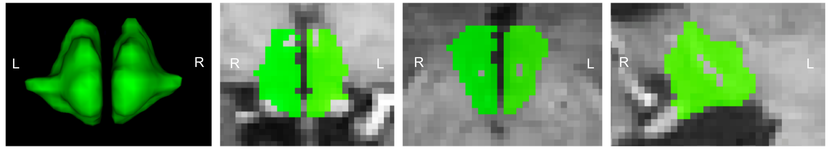

***Figure 2**. Example of the hypothalamic manual segmentation in three planes (coronal, axial and sagittal) of a healthy control subject.*

RESULTS

Seven structures were identified from the VBM analysis as significantly atrophic in symptomatic carriers, including the nucleus accumbens, amygdala, hippocampus, orbitofrontal cortex, temporal pole, anterior insula and hypothalamus (**Figure 3**). We found that 14% of early presymptomatic carriers had an abnormal w-score for the nucleus accumbens and hippocampus, with 20% of the group having an abnormal orbitofrontal cortex w-score. 36% of the late group showed abnormal amygdala and temporal pole scores, whilst 27% of the group had abnormal hippocampal scores, 32% had an abnormal anterior insula score and 9% having an abnormal hypothalamus score. The percentages in the symptomatic group were much higher with the hippocampus and temporal pole showing abnormal w-scores in 85% of cases, in 93% for the anterior insula, 56% for the orbitofrontal cortex, and 48% for the hypothalamus (**Figure 4**).

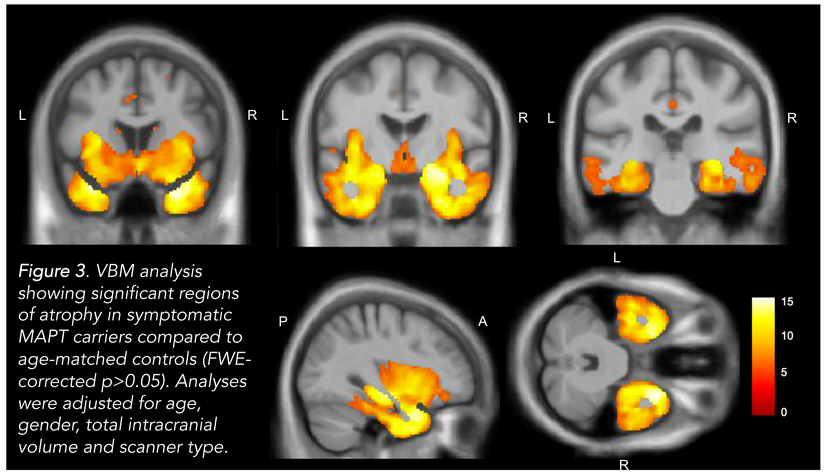

***Figure 3**. VBM analysis showing significant regions of atrophy in symptomatic MAPT carriers compared to age-matched controls (FWE-corrected p>0.05). Analyses were adjusted for age, gender, total intracranial volume and scanner type.*

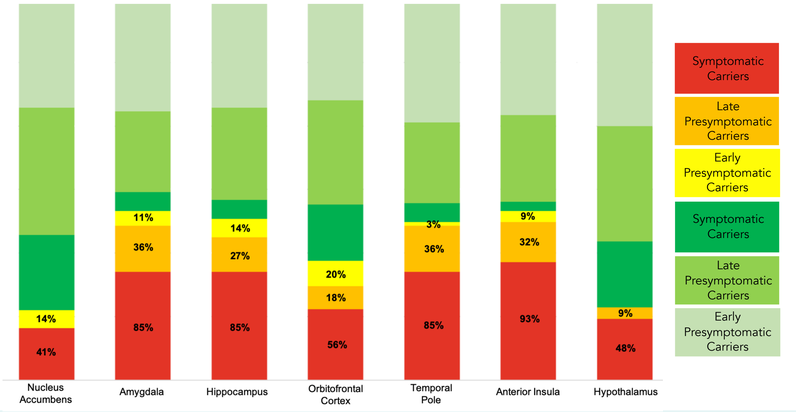

***Figure 4**. Graph showing the percentage of each carrier group with abnormal (red/orange/yellow) or normal w-scores (green) for each ROI.*

CONCLUSION

Abnormal limbic regions are a frequent feature in presymptomatic *MAPT* mutation carriers, showing early structural changes before symptom onset. Further investigations of the associated cognitive and white matter changes are ongoing.

Acknowledgements: The Dementia Research Centre is supported by Alzheimer's Research UK, Alzheimer's Society, Brain Research UK, the Wolfson Foundation. This work was supported by the NIHR Queen Square Dementia BRU, UCLH BRC, LWENC Clinical Research Facility, UK DRI, MRC UK GENFI grant, Italian Ministry of Health, Canadian Institutes of Health Research, Bluefield Project and JPND GENFI-PROX grant. MB is supported by the Alzheimer's Society and the UK DRI. JDR is an MRC Clinician Scientist and has received funding from the NIHR Rare Diseases Translational Research Collaboration, Bluefield Project and Association for Frontotemporal Degeneration.