# Thalamic atrophy in frontotemporal dementia – not just a C9orf72 problem Martina Bocchetta<sup>1</sup>, Elizabeth Gordon<sup>1</sup>, M. Jorge Cardoso<sup>2</sup>, Sebastien Ourselin<sup>2</sup>, Jason D. Warren<sup>1</sup>, Jonathan D. Rohrer<sup>1</sup>

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## Background

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder associated with frontal and temporal atrophy. Subcortical involvement has been described too, with early thalamic atrophy being particularly associated with C9orf72associated FTD. We aimed to investigate the thalamic involvement in a large cohort of patients including those with genetic and pathological confirmation.

### Methods

We investigated thalamic volumes in a sample of 348 FTD patients (age: mean(standard deviation) 64(8) years; disease duration: 5(3) years) compared with 98 age-matched controls (age: 63(12) years). We performed a parcellation of T1 MRIs using an atlas propagation and label fusion approach (Cardoso et al., 2015). Thalamic volumes were corrected for total intracranial volumes. We assessed subgroups stratified by clinical diagnosis (152 behavioural variant FTD (bvFTD), 76 semantic dementia (SD), 102 progressive nonfluent aphasia (PNFA), 7 with associated motor neurone disease (FTD-MND) and 11 with primary progressive aphasia not otherwise specified (PPA-NOS), genetic diagnosis (23 with MAPT, 23 with C9orf72, 15 with GRN mutations), and pathological diagnosis (40 tauopathy, 60 TDP-43opathy, 2 FUSopathy). We assessed the diagnostic accuracy based on total thalamic volume.

Groups		n	Gender (male)	Age	
	controls	98	44%	63 (12)	
	bvFTD	152	69%	62 (8)	
	PNFA	102	49%	68 (8)	
	SD	76	57%	64 (8)	
	<b>PPA-NOS</b>	11	64%	63 (6)	
	FTD-MND	7	57%	66 (4)	
Genetic	C9orf72	23	65%	61 (7)	
	GRN	15	47%	63 (7)	
	MAPT	23	65%	56 (8)	
Pathological	TDP-43	60	60%	63 (7)	
	Tau	40	73%	59 (9)	
	FUS	2	100%	51 (8)	

Table 1. Demographic and clinical variables for the FTD patients and controls.

### **Disease Duration** 5 (3) 4 (2) 5 (2) 3 (2) 5 (3) 6 (3) 3 (3) 5 (3) 5 (3) 5 (3) 4 (3)

Overall, FTD patients had smaller thalami than controls (7% difference in volume, p<0.0005, GLM correcting for scanner type). Stratifying by genetics, C9orf72 group had the smallest thalami (14% difference from controls, p<0.0005). However, the thalami were also smaller than controls in the other genetic groups: MAPT and GRN groups showed respectively an 8% and 11% difference (p<0.0005). The C9orf72 group had significantly smaller thalami than the MAPT group (7%, p=0.039), but not the GRN group (p=0.148). ROC analysis showed a relatively poor ability to separate C9orf72 from MAPT (AUC=0.698) and from GRN cases (AUC=0.677). All clinical subtypes had significantly smaller thalami than controls, with the FTD-MND group having the smallest (13%, p=0.005), followed by bvFTD (8%, p<0.0005), PNFA (7%, p<0.0005), PPA-NOS (6%, p=0.018) and lastly SD (4%, p=0.001). However both PPA-NOS and SD showed asymmetric lower volumes in the left more than right thalamus (11 vs 0% and 9 vs 0% respectively compared with controls, p<0.0005). In the pathological groups, the TDP-43 opathies had an 11% difference from controls (p<0.0005), and tauopathies 8% (p<0.0005), while the FUS opathies did not show any significant difference from controls.



and pathological groups.

The thalamus was most affected in C9orf72 genetically, TDP-43opathies pathologically and FTD-MND clinically. However, thalamic atrophy is a common feature across all FTD groups, apart from FUSopathies in which it seems relatively spared.

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### Results

Figure 1. Volume of the left and right thalamus as a percentage of total intracranial volume in 348 FTD patients and 98 controls, by clinical, genetic

### Conclusions



