Thalamic atrophy in frontotemporal dementia – not just a *C9orf72* problem

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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 *C9orf72*-associated 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	Disease Duration
Clinical	controls	98	44%	63 (12)	--
	bvFTD	152	69%	62 (8)	5 (3)
	PNFA	102	49%	68 (8)	4 (2)
	SD	76	57%	64 (8)	5 (2)
	PPA-NOS	11	64%	63 (6)	3 (2)
	FTD-MND	7	57%	66 (4)	5 (3)
Genetic	*C9orf72*	23	65%	61 (7)	6 (3)
	GRN	15	47%	63 (7)	3 (3)
	MAPT	23	65%	56 (8)	5 (3)
Pathological	TDP-43	60	60%	63 (7)	5 (3)
	Tau	40	73%	59 (9)	5 (3)
	FUS	2	100%	51 (8)	4 (3)

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

Results

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-43opathies had an 11% difference from controls (p<0.0005), and tauopathies 8% (p<0.0005), while the FUSopathies did not show any significant difference from controls.

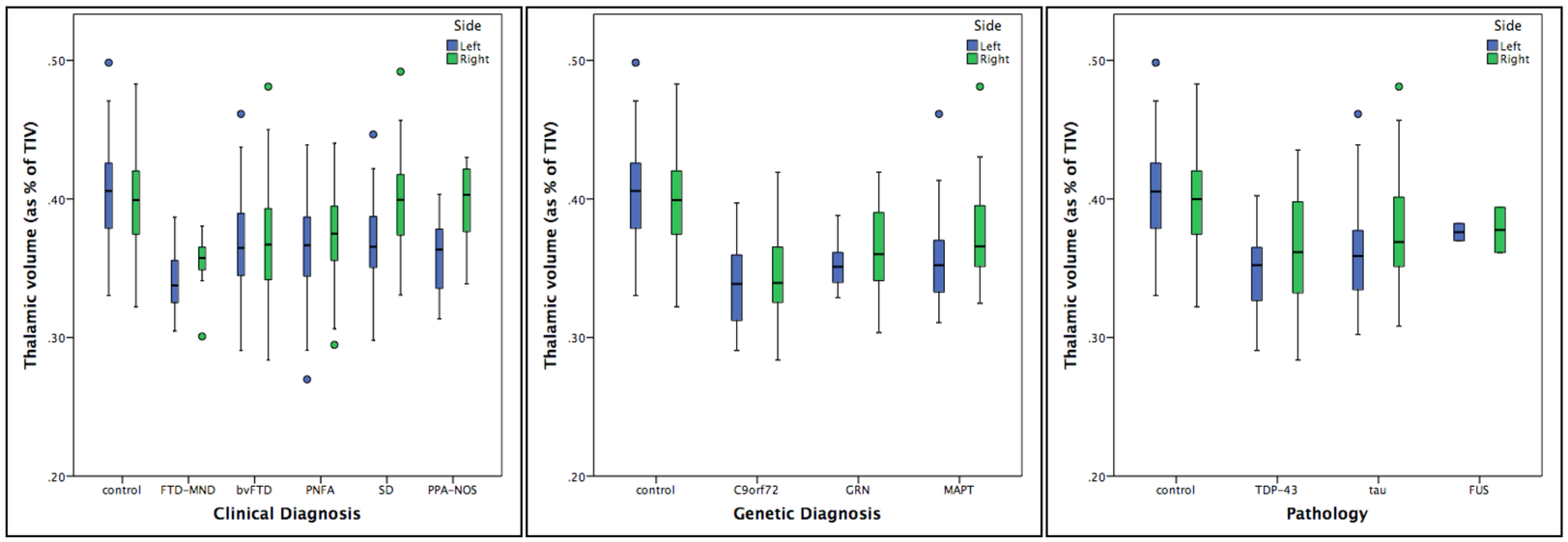

Figure 1. Volume of the left and right thalamus as a percentage of total intracranial volume in 348 FTD patients and 98 controls, by clinical, genetic and pathological groups.

Conclusions

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.

Acknowledgements: The Dementia Research Centre is supported by Alzheimer's Research UK, Brain Research Trust, and The Wolfson Foundation. This work was supported by the NIHR Queen Square Dementia Biomedical Research Unit, the NIHR UCL/H Biomedical Research Centre, and the MRC UK GENFI grant. JDR is supported by an MRC Clinician Scientist Fellowship and a NIHR Rare Disease TRC Fellowship. EG is supported by an Alzheimer's Society PhD Studentship.