Clinical, genetic and pathological stratification in frontotemporal dementia (FTD): implications for clinical trial design

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BACKGROUND

Targeted patient enrolment and biomarker choice is critical to optimising the detection of treatment effects in trials. One of the key challenges in FTD is the significant clinical, genetic and pathological patient heterogeneity of the disease and the marked differences in their resulting neuroanatomical profiles and signatures of change. This heterogeneity not only hinders diagnosis and prognosis, but it also poses a major hurdle to accurate stratification into targeted interventions. Improving our understanding of the effects of varying stratification criteria in this population will help inform trial design both in terms of enrolment criteria as well as optimal biomarker choice, which is likely to vary depending on the characteristics of the patients enrolled.

METHODS - Participants

The current study investigated the effect of varying stratification criteria and volumetric imaging marker on sample size estimates in 140 FTD patients and 21 healthy older controls (Table 1). Patient subgroups were divided by clinical diagnosis: behavioural variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and non-fluent variant (nfvPPA); by genetic diagnosis (*MAPT*, *C9orf72* and *GRN* mutations); or pathological diagnosis (confirmed tauopathy or TDP-43opathy).

	Control	Clinical			Genetic			Pathological	
		bvFTD	svPPA	nfvPPA	*MAPT*	*C9orf72*	*GRN*	Tauopathy	TDP-43opathy
n	**21**	**62**	**42**	**36**	**12**	**8**	**3**	**14**	**23**
Gender (M / F)	47 / 14	47 / 15	22 / 20	18 / 18	6 / 6	7 / 1	2 / 1	7 / 7	17 / 6
Age at Onset	NA	55.8 (9.7)	59.7 (7.7)	61.9 (7.7)	49.4 (7.1)	56.1 (9.6)	57.3 (8.1)	50.1 (6.8)	58.3 (7.9)
Age at Assessment (yrs)	63.0 (7.4)	61.3 (9.5)	64.2 (7.8)	66.3 (8.2)	53.7 (7.4)	62.9 (6.6)	61.6 (9.6)	54.3 (7.0)	63.2 (6.4)
Disease Duration (yrs)	NA	5.3 (3.9)	4.3 (1.7)	4.3 (2.3)	4.3 (3.1)	6.7 (4.4)	4.3 (2.0)	4.2 (2.9)	4.9 (3.1)

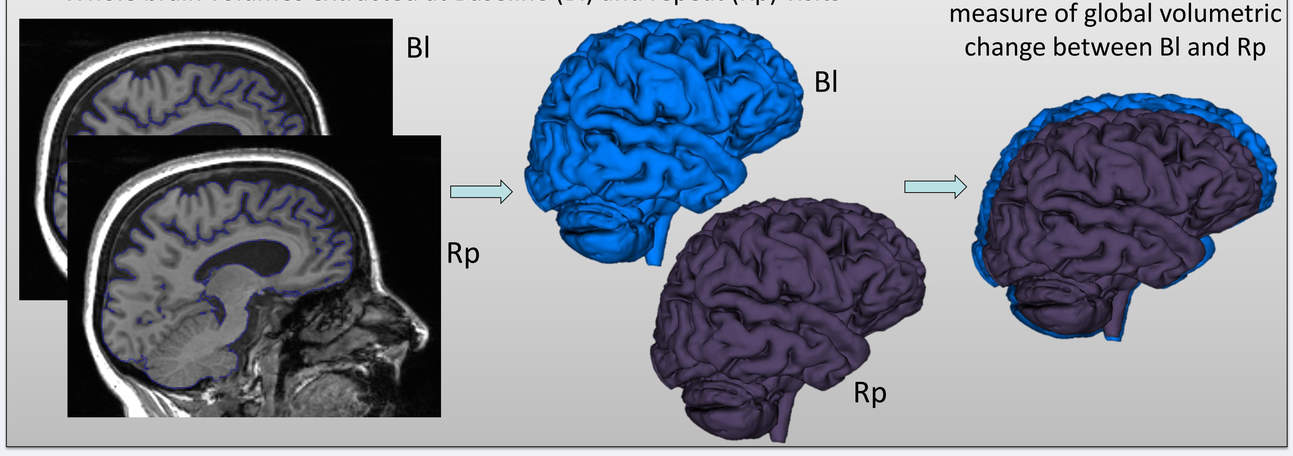
Table 1. Patient demographics for each subgroup

METHODS - Image Analysis

All participants underwent two 3D T1-volumetric MR image sessions (mean interval = 1.7 (0.9) years). Whole-brain volumes were manually segmented and annual rates of change calculated using the brain boundary shift integral (BBSI)[1]. An automated parcellation technique called geodesic information flows (GIF) extracted grey matter (GM) volumes using the neuromorphometric atlas (Figure 1)[2,3]. These regional GM volumes were summed appropriately to provide a measure of the frontal, temporal, parietal, occipital, cingulate and insula cortices at each timepoint and rates of change calculated as annual percentage of baseline volume change. Sample sizes were calculated using these global and regional rates of change markers to detect a 30% reduction in annual volume loss, with 90% power and $\alpha = 0.05$.

Manual global segmentation

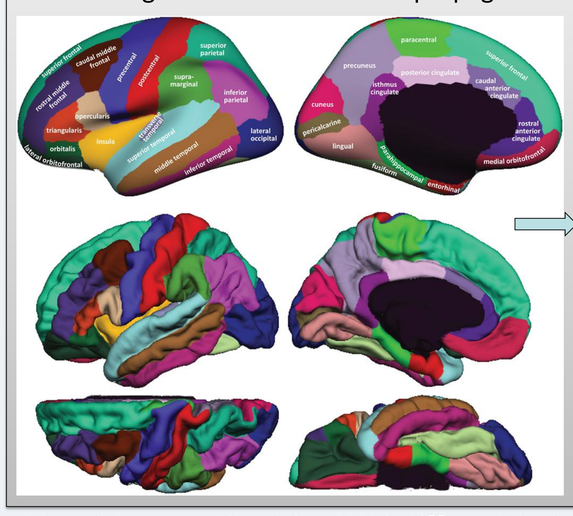
Whole brain volumes extracted at Baseline (Bl) and repeat (Rp) visits

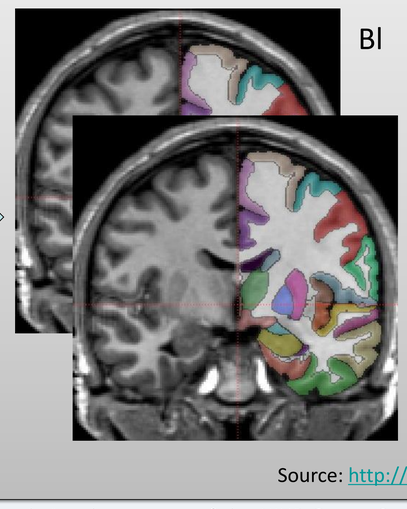


BBSI derives a robust measure of global volumetric change between Bl and Rp

Automated regional measure

GM regional atlas labels were propagated onto Bl and Rp MRI scans using GIF and volumes extracted





Volumes summed to produce composite regional GM measures for:

Frontal
Temporal
Parietal
Occipital
Cingulate and Insular cortices

Source: http://www.neuromorphometrics.com/

RESULTS

Annualised rates of change

Global and regional annual rates of volumetric change are shown in Table 2, expressed as mean (standard deviation) % change from baseline volume.

	Control	bvFTD	SD	PNFA	*MAPT*	*C9orf72*	*GRN*	Tauopathy	TDP-43
BBSI	0.5 (0.6)	2.8 (2.7)	3.2 (2.2)	3.1 (1.9)	3.9 (3.9)	3.0 (2.2)	4.6 (2.1)	3.8 (3.6)	2.9 (2.2)
Frontal	1.6 (7.8)	1.4 (2.4)	2.1 (1.8)	2.6 (1.8)	1.8 (2.0)	1.0 (2.9)	3.2 (0.3)	2.3 (1.9)	2.0 (2.4)
Temporal	0.9 (5.3)	2.0 (2.5)	4.1 (2.0)	2.6 (1.8)	1.9 (1.0)	0.4 (0.9)	4.1 (0.4)	2.4 (1.0)	2.6 (2.3)
Parietal	0.8 (2.1)	1.2 (3.0)	1.8 (1.6)	2.4 (1.8)	1.4 (2.0)	1.4 (3.1)	5.5 (5.2)	1.8 (2.3)	2.1 (3.0)
Occipital	1.2 (5.8)	0.6 (2.5)	1.0 (3.1)	0.6 (2.1)	0.2 (2.2)	1.3 (1.1)	1.9 (2.6)	0.2 (2.4)	1.3 (2.7)
Cingulate	0.8 (4.2)	1.9 (2.9)	2.0 (1.9)	1.8 (1.6)	1.1 (1.0)	-0.1 (1.8)	6.6 (2.5)	1.5 (0.9)	1.6 (2.9)
Insula	1.4 (7.0)	2.8 (3.2)	4.8 (2.9)	2.6 (2.5)	2.3 (2.5)	1.0 (2.1)	5.4 (2.5)	3.5 (2.3)	3.6 (3.4)

Table 2. Mean (sd) global (BBSI) and regional annualised volumetric change (% of baseline volume)

RESULTS

Sample Size calculations

In the clinical subgroups, sample sizes were relatively high for the bvFTD with the BBSI measure providing the smallest values with 221 participants per treatment arm (Table 3). In PPA smaller sample sizes were required to detect a similar treatment effect. Stratifying by genetic diagnosis resulted in fewer required participants than in the more heterogenous clinical bvFTD cohort. In the *C9orf72* subgroup, BBSI resulted in sample sizes of 118, whereas for the *MAPT* and *GRN* patients temporal lobe measures performed best with only 68 and <10 participants per arm respectively. Finally, pathological stratification also differentially affected estimates (tauopathy = 42 but TDP-43opathy = 177 participants for temporal lobe measures).

Annual measure of change	bvFTD	SD	PNFA	*MAPT*	*C9orf72*	*GRN*	Tauopathy	TDP-43opathy
BBSI	221	107	98	225	118	24	168	128
Frontal	668	167	113	314	1758	5	155	327
Temporal	362	56	110	68	1425	5	42	177
Parietal	1610	183	139	435	1189	205	358	482
Occipital	4574	2350	2625	29911	149	427	28856	1044
Cingulate	533	205	184	195	37216	34	90	773
Insula	315	87	222	272	1123	49	100	205

Table 3. Sample size estimates per treatment arm to detect a 30% reduction with 90% power at α=0.05

CONCLUSIONS

Varying patient stratification significantly affected sample size estimates and influenced which marker of volumetric change was optimal as the outcome measure. Fully automated methods of parcellating and extracting regional measures produced promising results and sample size estimates suggest *GRN* mutation carriers are an attractive population for intervention given the consistently high rates of change and resulting decreased to detect a meaningful treatment effect.

References:

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Acknowledgements: EG, MB, SH, XXXX CMIC?? and JDR acknowledge the support of the NIHR Queen Square Dementia Biomedical Research Unit, Leonard Wolfson Experimental Neurology Centre, and the University College London Hospitals NHS Trust Biomedical Research Centre. The Dementia Research Centre at UCL is an Alzheimer's Research UK co-ordinating centre and has also received equipment funded by Alzheimer's Research UK and the Brain Research Trust. EG is supported by an Alzheimer's Society PhD Studentship and The Healthcare Management Trust. JDR is an MRC Clinician Scientist and has received funding from the NIHR Rare Diseases Translational Research Collaboration.