Elizabeth Gordon1, Martina Bocchetta1, M. Jorge Cardoso1,2, Sophie Harding3, Sebastien Ourselin1,3, Jason D. Warren1 & Jonathan D. Rohrer1

1 Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK
2 Translational Imaging Group, Centre for Medical Image Computing (CMIC), University College London, UK

BACKGROUND
Targeted 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 (nvPPA); by genetic diagnosis (MAPT, C9orf72 and GRN mutations); or pathological diagnosis (confirmed tauopathy or TDP-43opathy).

RESULTS

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). An automated parcellation technique called geodesic information flows (GIF) extracted grey matter (GM) volumes using the neournomorphometric atlas (Figure 1). 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 change of baseline volume percentage. 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 α = 0.05.

METHODS - Image Analysis

RESULTS - Sample Size calculations

In the clinical subgroups, sample sizes were relatively high for 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).

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.

ACKNOWLEDGEMENTS

Elizabeth Gordon, Sophie Harding, Sebastien Ourselin, Jason D. Warren & Jonathan D. Rohrer

1 Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK
2 Translational Imaging Group, Centre for Medical Image Computing (CMIC), University College London, UK

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.

RESULTS - Table 1. Patient demographics for each subgroup

METHODS - Manual global segmentation

METHODS - Automated regional measure

CONCLUSIONS

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