1. Background

It is hypothesised that a number of pathophysiological mechanisms are associated with neurodegeneration, including abnormalities in both mitochondrial and synaptic function. Novel radiotracers which enable the quantification of mitochondrial and synaptic proteins in vivo have not previously been explored in frontotemporal dementia (FTD).

2. Methods

$[^{11}]$UCB-J, $[^{18}]$BCPP-EF and $[^{11}]$CSA4503 were used to measure the density of synaptic vesicle protein 2A (SV2A), mitochondrial complex 1 (MC1) and the sigma 1 receptor (S1R) respectively. Six participants with behavioural variant FTD (bvFTD) and 17 healthy controls underwent 90-minute dynamic acquisition PET scans following injection of each of the three tracers, with metabolite corrected arterial input function. Regions of interest were defined on individual MR images using the CIC anatomical atlas. Regional density was evaluated using the $V_r$ corrected for the plasma free fraction ($F_p$) for the S1R, and the regional $V_r$ normalised to the $V_r$ in the centrum semiovale (DVR-1) for SV2A and MC1. Target density of SV2A and MC1 was compared between groups using Mann-Whitney U tests with Bonferroni correction for multiple comparisons. Group comparisons were not performed for S1R as only two FTD scans were free from associated drug interactions at the S1R.

3. Results

Significant comparisons at p≤0.003 marked by *

- People with FTD have significantly lower density of SV2A in multiple cortical and subcortical regions, all p≤0.001
- People with FTD have significant loss/impairment of MC1 in cortical regions related to disease topography, all p≤0.003
- The magnitude of target density loss is greater than the magnitude of volume loss for SV2A and MC1 (Figure 1)

4. Conclusions

Significant reductions in binding of $[^{11}]$UCB-J and $[^{18}]$BCPP-EF in the FTD group compared to controls suggests there is reduced synaptic density and mitochondrial function in disease-relevant regions in FTD. Evaluation of the full MINDMAPS FTD cohort will further investigate the extent of molecular abnormalities in FTD and the relationship between regional densities and cognition.

Affiliations: 1Dementia Research Centre, UCL Queen Square Institute of Neurology, 2Division of Brain Sciences, Imperial College London, 3Invicro LLC, 4Biogen, 5Pfizer, 6Takeda Pharmaceuticals, Cambridge MA, USA, 7Takeda Development Center Japan, Osaka, Japan, 8King’s College London, 9MINDMAPS Consortium

Acknowledgements: We acknowledge the support of the NIHR Queen Square 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. MTMC is supported by a Brain Research UK PhD Studentship. JDR is an MRC Clinician Scientist and has received funding from the NIHR Rare Diseases Translational Research Collaboration.