Imaging synaptic and mitochondrial function in frontotemporal dementia using [^{11}C]UCB-J, [^{18}F]BCPP-EF and [^{11}C]SA4503 PET

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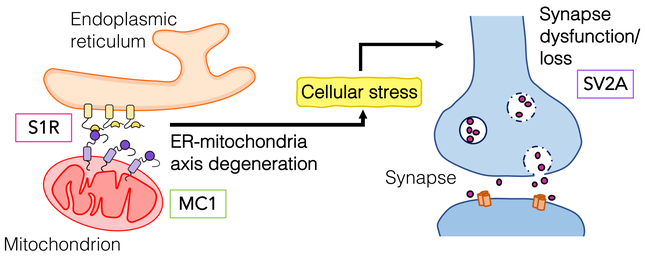
1. Background

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}C]UCB-J, [^{18}F]BCPP-EF and [^{11}C]SA4503 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_T corrected for the plasma free fraction (f_P; V_T/f_P) for the S1R, and the regional V_T normalised to the V_T 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.

Group	*N*	Age at scan [years *M* (SD)]	Gender [*Male:Female*]
bvFTD	6	61.8 (5.4)	5:1
Healthy controls	17	63.7 (12.5)	8:9

3. Results

*Significant comparisons at p≤0.003 marked by **

Region		[^{11}C]UCB-J [DVR-1 *M* (SD)]			[^{18}F]BCPP-EF [DVR-1*M* (SD)]		
		FTD	Controls	*	FTD	Controls	*
Cortical	Frontal	1.43 (0.32)	2.12 (0.28)	*	0.66 (0.38)	1.06 (0.27)	*
	Temporal	1.60 (0.25)	2.38 (0.25)	*	0.74 (0.28)	1.05 (0.27)	*
	Parietal	1.57 (0.23)	2.16 (0.31)	*	0.87 (0.25)	1.14 (0.30)	
	Insula	1.86 (0.18)	2.67 (0.29)	*	0.88 (0.24)	1.19 (0.31)	*
	Anterior cingulate	1.64 (0.38)	2.59 (0.28)	*	0.71 (0.37)	1.14 (0.29)	*
	Posterior cingulate	1.77 (0.35)	2.53 (0.26)	*	0.97 (0.32)	1.34 (0.34)	*
Subcortical	Hippocampus	0.88 (0.38)	1.54 (0.24)	*	0.47 (0.34)	0.81 (0.22)	
	Amygdala	1.43 (0.49)	2.11 (0.24)	*	0.64 (0.35)	0.91 (0.24)	
	Caudate	0.52 (0.53)	1.20 (0.49)		0.20 (0.56)	0.71 (0.42)	
	Putamen	2.30 (0.39)	2.72 (0.24)		1.62 (0.38)	1.78 (0.46)	
	Thalamus	0.55 (0.13)	0.98 (0.25)	*	0.49 (0.26)	0.90 (0.28)	*
	Brainstem	0.13 (0.10)	0.27 (0.08)		0.31 (0.21)	0.47 (0.14)	
	Cerebellum	1.43 (0.21)	1.84 (0.20)	*	1.27 (0.33)	1.51 (0.39)	

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

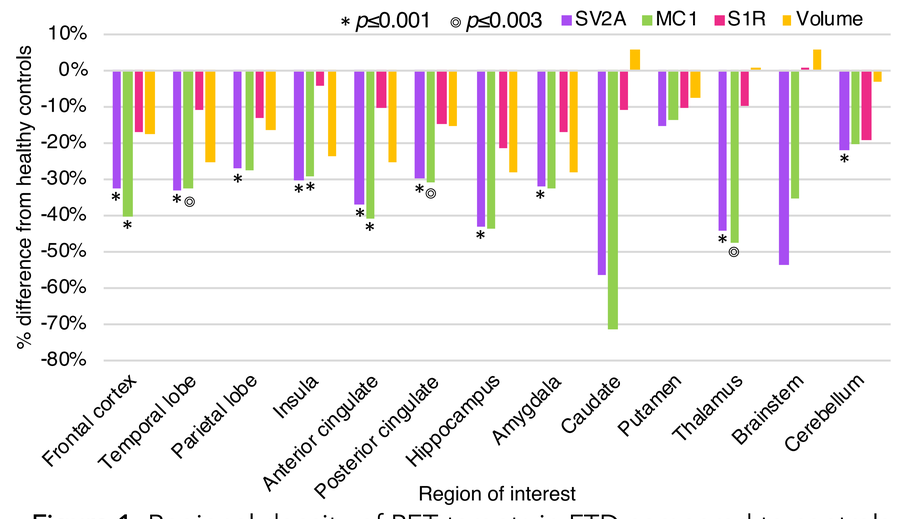
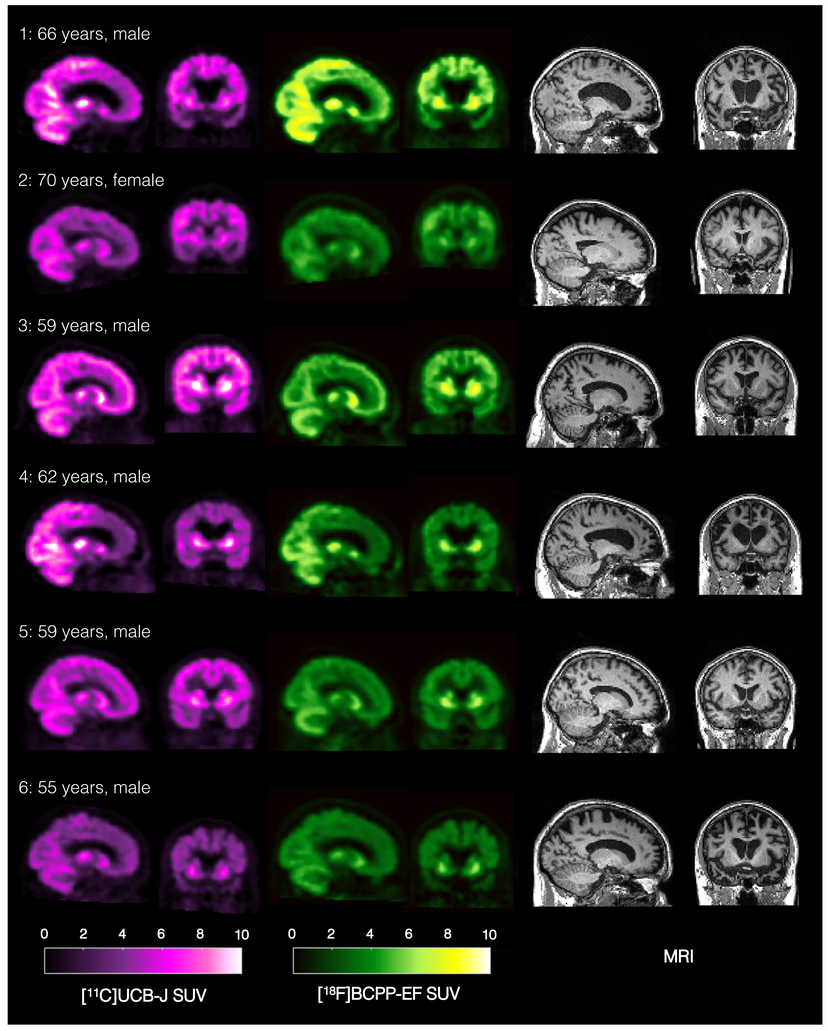


Figure 1. Regional density of PET targets in FTD compared to controls

Figure 2. The distribution of tracer retention in the FTD group



4. Conclusions

Significant reductions in binding of [^{11}C]UCB-J and [^{18}F]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.

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