Background

There is a growing focus on the role of neuroinflammation in frontotemporal dementia (FTD). Microglial burden at post-mortem is significantly increased in all forms of genetic FTD but most extensively in GRN mutation carriers, whose CSF levels of inflammatory biomarkers are also increased.

The $[^{11}C]PBR28$ PET ligand is a putative marker of inflammation which binds to a translocator protein (TSPO) expressed by activated microglia. $[^{11}C]PBR28$ binding is increased in neurodegenerative diseases but has not been investigated in FTD.

Methods

Participants included ten individuals with a diagnosis of genetic behavioural variant FTD (4 GRN, 4 C9orf72, 2 MAPT, mean age 63.4, SD 6.6) and five age-matched healthy controls (mean age 61.8, SD 2.9).

Dynamic PET data were acquired continuously for 90 minutes following injection of $[^{11}C]PBR28$. An arterial plasma input function was generated from arterial blood samples. Participants also underwent volumetric T1-weighted MR imaging.

Non-displaceable binding potential ($BP_{ND}$) values were generated using a simplified reference tissue model with the cerebellum as a reference region. Regions of interest (ROIs) were defined on the co-registered T1-weighted MR image.

Results

$BP_{ND}$ was variable between individuals with genetic FTD (Figure 1). Mann-Whitney group comparisons revealed significantly greater signal in the temporal lobe ($p = 0.04$), posterior cingulate ($p = 0.01$) and putamen ($p = 0.03$) in FTD (Figure 2). ROC curve analyses revealed that posterior cingulate $BP_{ND}$ best discriminated groups (AUC = 0.90, $p = 0.01$).

Separate comparisons in GRN and C9orf72 groups revealed significant increases specifically in GRN mutation carriers vs controls in these three ROIs (temporal lobe $p = 0.03$, posterior cingulate $p = 0.03$ and putamen $p = 0.02$).

Conclusions

There is increased inflammatory PET signal in individuals with genetic FTD, probably led by increased binding in GRN mutation carriers. Regional distribution of $[^{11}C]PBR28$ involved areas known to be affected in GRN-FTD. Microglial activation may be a useful biomarker to better understand GRN-FTD pathogenesis and as a potential outcome measure in future therapeutic trials.