[^{11}C]PBR28 inflammatory PET imaging in frontotemporal dementia

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Background

Inflammation as a contributor to disease pathogenesis

- Progranulin involved in inflammatory pathways
- Increased sTREM2 in *GRN* CSF
- sTREM2 enhances microglial activation
- Astrocytic marker YKL-40 increased in FTD CSF

PET imaging of neuroinflammation

- Radiotracers bind TSPO, expressed by active microglia
- [^{11}C]PK11195 binding increased in FTD, consistent with disease topography, but shows non-specific binding and poor sensitivity
- [^{11}C]PBR28 binding is increased in ALS, but has not been previously explored in FTD

Methods

All participants had intravenous bolus injection of [^{11}C]PBR28 before 90 min dynamic PET acquisition in 3D mode. An arterial plasma input function was generated for each participant. All participants also underwent T1-weighted volumetric MRI. A SRTM was used to generate BP_{ND} values (Gunn et al. 1997), using the cerebellum as a reference region. Analyses were performed using MIAKAT™. ROIs were defined on the co-registered MR image. Linear regression analyses with 95% bias-corrected bootstrapped confidence intervals with 1000 repetitions were used to compare BP_{ND} between groups.

Group	*N*	Age at scan [years *M* (SD)]	Gender [*Male:Female*]	TSPO binding [*Medium:High*]
Genetic FTD	7	61.7 (6.4)	6:1	6:1
Healthy controls	4	61.8 (3.3)	3:1	3:1

Results

Region		Genetic FTD [BP_{ND} *M* (SD)]	Healthy controls [BP_{ND} *M* (SD)]
Cortical	Frontal	0.05 (0.09)	-0.03 (0.05)
	Temporal	0.06 (0.05)	-0.01 (0.04)
	Parietal	0.06 (0.18)	-0.07 (0.06)
	Occipital	0.04 (0.07)	-0.05 (0.07)
	Cingulate	0.11 (0.10)	0.03 (0.06)
	Insula	0.09 (0.10)	0.08 (0.06)
Subcortical	Hippocampus	0.13 (0.10)	0.12 (0.04)
	Amygdala	0.24 (0.14)	0.20 (0.13)
	Caudate	-0.31 (0.12)	-0.34 (0.10)
	Putamen	0.14 (0.26)	0.00 (0.09)
	Pallidum	0.24 (0.13)	0.19 (0.12)
	Thalamus	0.11 (0.11)	0.13 (0.10)

Regional BP_{ND} values significantly greater in genetic FTD than healthy controls are in orange.

- BP_{ND} values were significantly higher in genetic FTD than healthy controls in four cortical regions: frontal (mean difference 0.08), temporal (0.07), parietal (0.13) and cingulate (0.08)
- Stratification by genetic mutation revealed highest BP_{ND} in *MAPT* mutation carriers, then *GRN* mutation carriers (see Figure 2)
- BP_{ND} of [^{11}C]PBR28 in *C9orf72* mutation carriers was comparable to that of controls

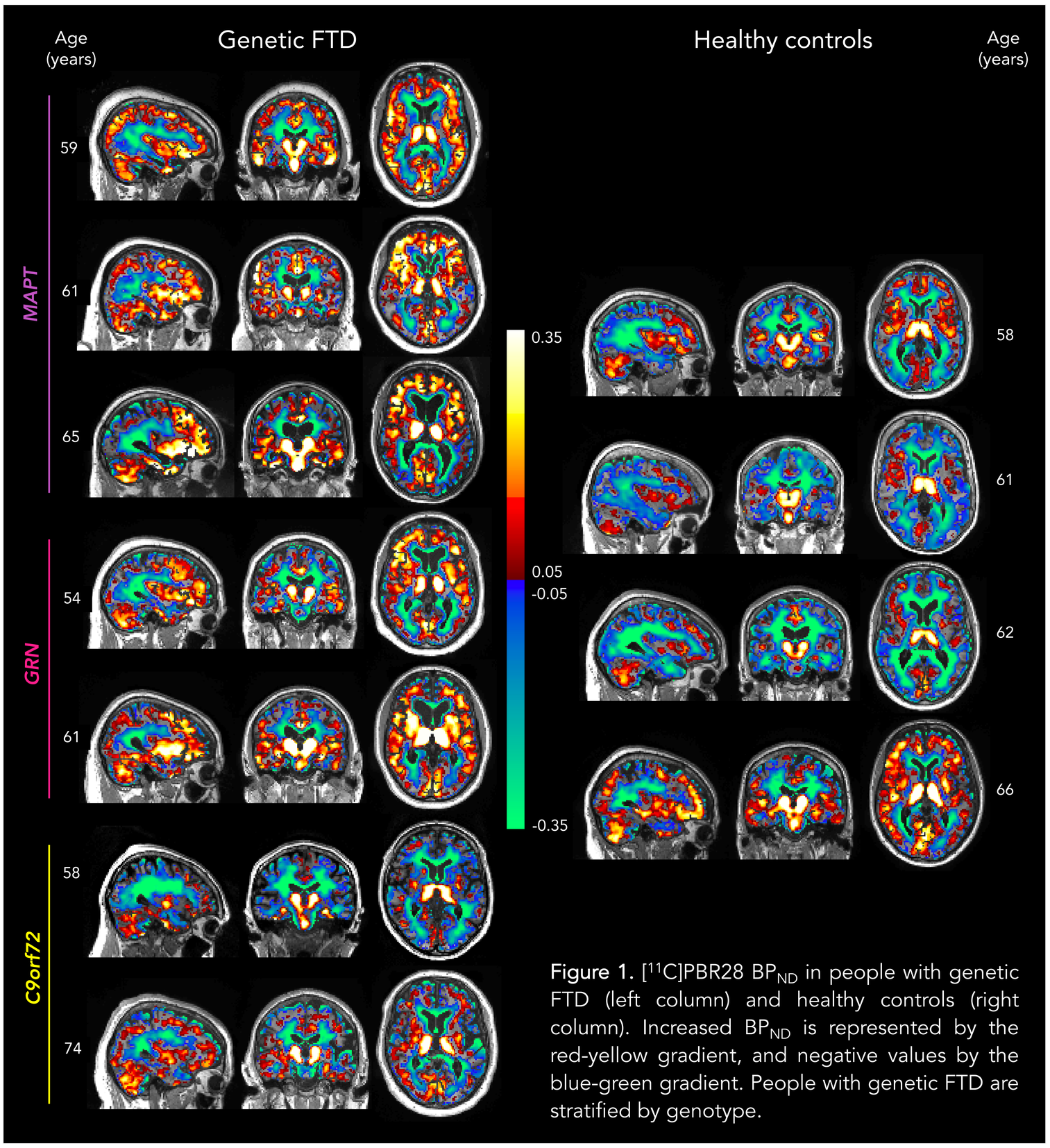

Figure 1. [^{11}C]PBR28 BP_{ND} in people with genetic FTD (left column) and healthy controls (right column). Increased BP_{ND} is represented by the red-yellow gradient, and negative values by the blue-green gradient. People with genetic FTD are stratified by genotype.

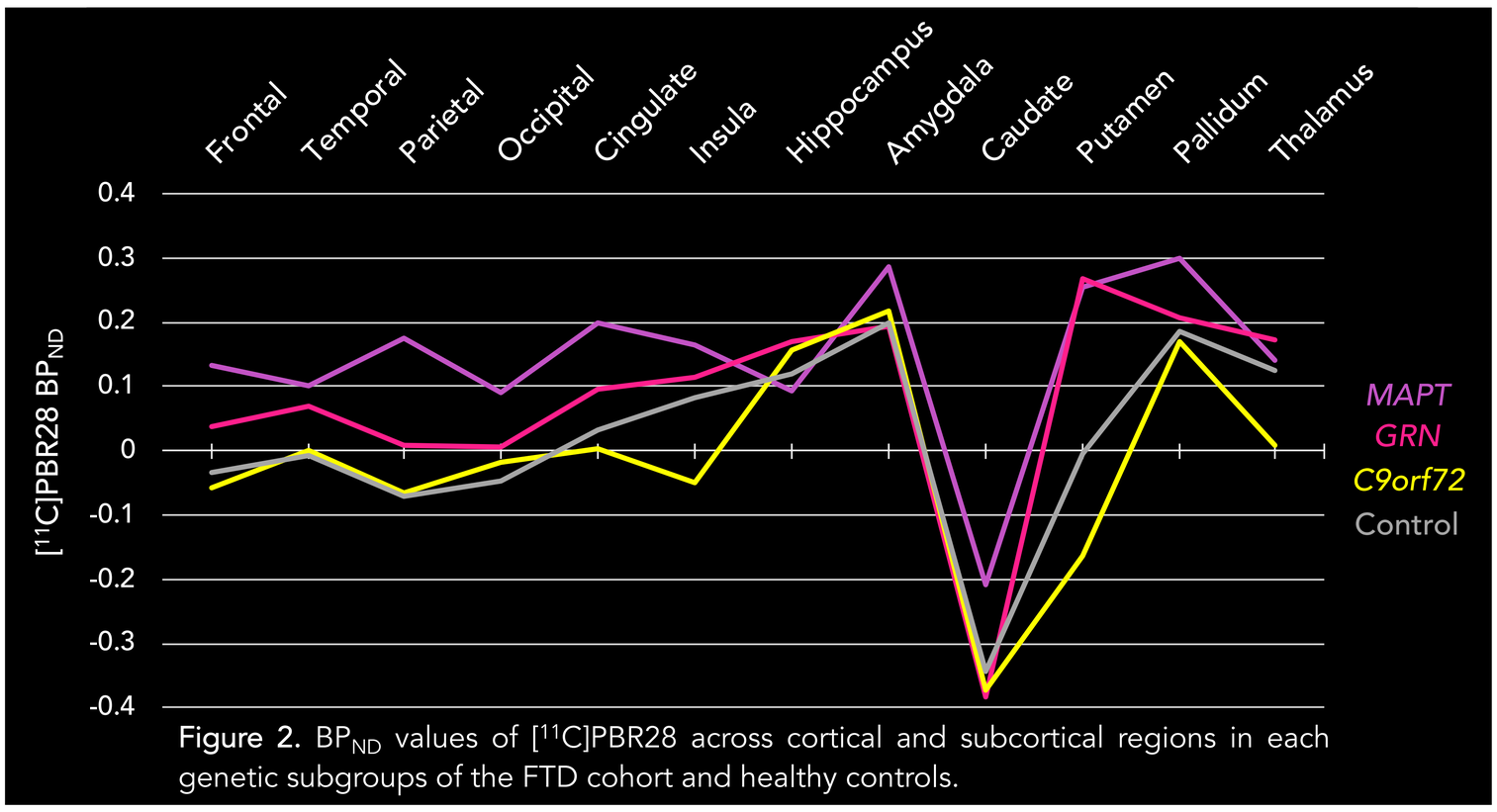

Figure 2. BP_{ND} values of [^{11}C]PBR28 across cortical and subcortical regions in each genetic subgroups of the FTD cohort and healthy controls.

Conclusions

This data demonstrates increased binding of [^{11}C]PBR28 in a cohort of individuals with genetic FTD compared with age- and gender-matched healthy controls. The distribution of increased binding reflects the pattern of atrophy associated with bvFTD. *MAPT* mutation carriers exhibited the greatest binding, consistent with pathological findings. Analyses with an increased sample size will explore differential genetic binding patterns and associated measures.

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