[^{18}F]AV-1451 tau PET imaging in *MAPT* 10+16 mutation carriers

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Background

Tau pathology underlies about 50% of frontotemporal dementia (FTD) cases, but there are no *in vivo* biomarkers of tau. The [^{18}F]AV-1451 ligand was developed for PET imaging quantification of tau deposition. Few studies have been conducted in FTD so far. Generally studies have reported greater binding in Alzheimer's disease (AD) than FTD except in cases with specific tau mutations which present with paired helical filament (PHF) tau pathology at post-mortem, as seen in AD. However, non-specific binding has been reported in semantic variant FTD which typically has TDP-43 protein inclusions, suggesting this ligand may bind to non-tau pathology associated with neurodegeneration.

Methods

Participants with a specific *MAPT* mutation associated with non-PHF pathology were recruited from the UCL Genetic FTD Initiative (GENFI) study and scanned on a Siemens Biograph 6 PET-CT scanner.

MAPT 10+16 mutation carriers (n=6)		Healthy controls (n=6)	
Age (years) *Mean (SD)*	Gender *Male:Female*	Age (years) *Mean (SD)*	Gender *Male:Female*
42.5 (12.6)	3:3	44.7 (16.7)	3:3

Dynamic PET data were acquired continuously following intravenous bolus injection of [^{18}F]AV-1451 for 120 mins in 3D-mode. Dynamic images were reconstructed using a filtered back projection algorithm (direct inversion Fourier transform), with isotropic voxel size of 2 x 2 x 2 mm^3. Corrections for decay and random counts were performed, and attenuation and scatter were corrected based on a low-dose CT scan acquired preceding PET acquisition. Rigid head motion correction was performed to align the reconstructed dynamic PET frames using image registration for each scan. Frames affected by mismatched attenuation correction were identified by visual inspection and excluded from kinetic analysis.

Results

Standardised uptake value ratios (SUVR) were calculated over 80-100 minutes using the cerebellum as a reference region. Linear regression analyses using log-transformed SUVRs revealed significant differences in uptake between mutation carriers and controls in 3 cortical regions and the putamen subcortically (table).

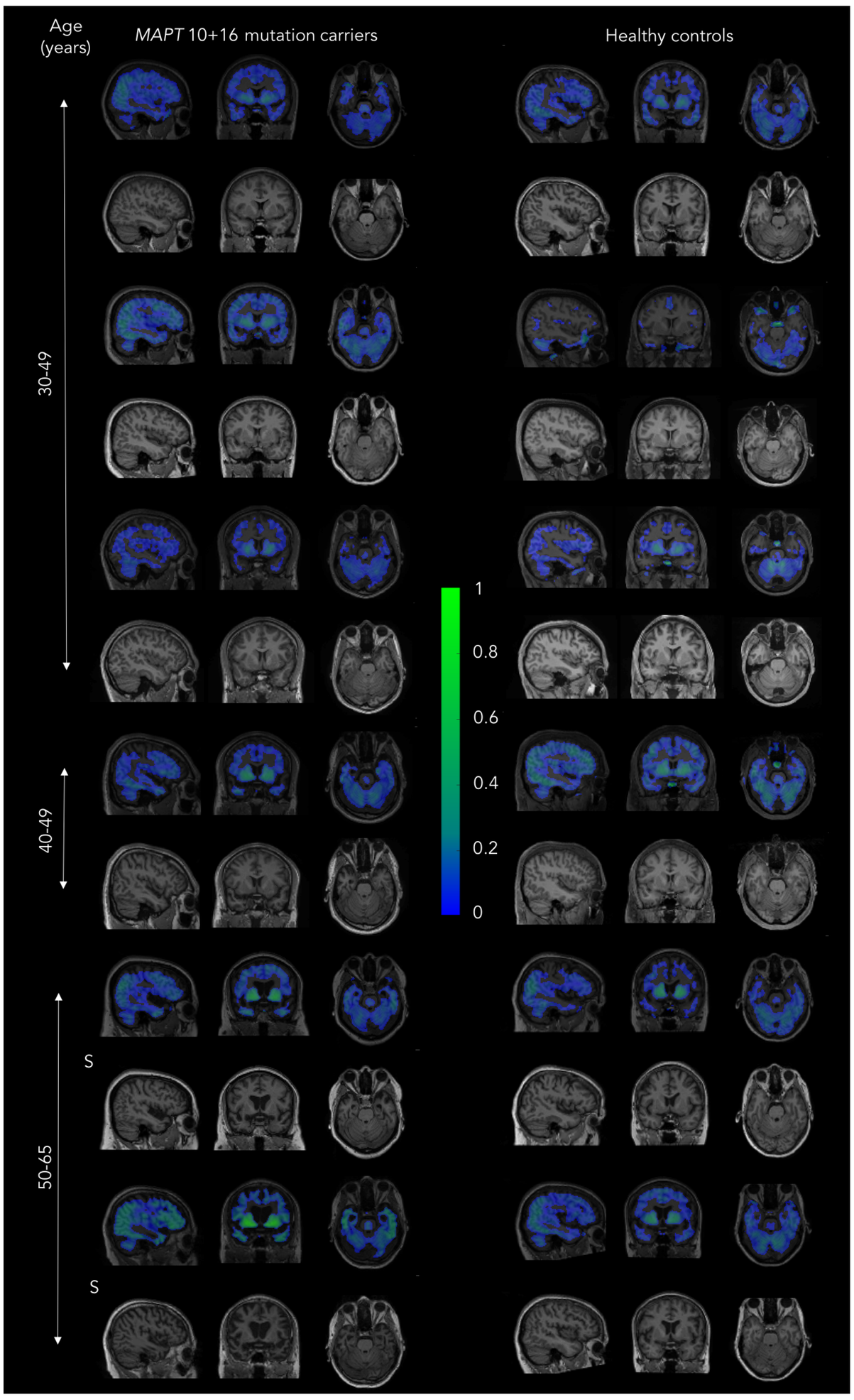
Region		% increase in SUVR in mutation carriers versus controls	*p*-value
Cortical	Frontal	9.2	0.03*
	Temporal	5.4	0.15
	Parietal	8.2	0.03*
	Occipital	3.7	0.11
	Cingulate	10.3	0.02*
	Insula	12.3	0.08
Subcortical	Amygdala/hippocampus	12.3	0.13
	Caudate	14.3	0.11
	Putamen	20.2	0.04*
	Pallidum	20.0	0.09
	Thalamus	11.8	0.13

Table. Percentage increase in SUVR in *MAPT* 10+16 mutation carriers versus controls.

A cortical subregion analysis revealed significant group differences in uptake in multiple areas: ventromedial prefrontal cortex (10.7% increase, p=0.04), motor cortex (9.7, p=0.01), medial (8.0, p=0.01) and lateral parietal cortices (8.9, p=0.03), and anterior (12.0, p=<0.05), middle (10.4, p=<0.01) and posterior (9.5, p=0.02) cingulate cortices.

There was also a significant association between uptake and age, independent of mutation status in: caudate, putamen and pallidum (p=<0.05), thalamus (p=0.02), anterior, middle and posterior cingulate (p=<0.04), medial and lateral parietal (p=<0.04) and occipital cortices (p=<0.05).

Figure. Binding potential (BP) of [^{18}F]AV-1451 in *MAPT* 10+16 mutation carriers (column 1) and healthy controls (column 2). Sagittal, coronal and axial views are displayed for PET images (top) and T1-weighted MR images (below) for each participant. BP was ascertained using the cerebellum as a reference region. S = symptomatic.



Conclusions

Increased uptake was seen in the *MAPT* group despite this mutation being associated with non-PHF pathology, suggesting binding to either other tau species or non-tau pathology. This tracer would benefit from further study in a larger cohort.

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