**[18F]AV-1451 positron emission tomography in**

**Alzheimer’s disease and progressive supranuclear palsy**

Running title (≤40 characters) (29): ***Tau PET imaging in AD and PSP***

L. Passamonti1,2\*; P. Vázquez Rodríguez1\*; Y.T. Hong1,3; K.S.J. Allinson4; D. Williamson3;

R.J. Borchert1; S. Sami1; T.E. Cope1; W.R. Bevan-Jones5; P.S. Jones1; R. Arnold5; A. Surendranathan5; E. Mak5; L. Su5; T.D. Fryer1,3; F. Aigbirhio1,3; J. T. O’Brien5#; J.B. Rowe1#

Joint \*first and #last authorship

1Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

2Istituto di Bioimmagini e Fisiologia Molecolare, Consiglio Nazionale delle Ricerche, Milano, Italy

3Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, UK

4Department of Histopathology, Cambridge University Hospital, Cambridge, UK

5Department of Psychiatry, University of Cambridge, Cambridge, UK

**Corresponding Author:**

Dr Luca Passamonti,

Department of Clinical Neurosciences

University of Cambridge,

CB2 0SZ, UK

Telephone: +44.01223. 330293

Email: lp337@medschl.cam.ac.uk

**Number of characters in the title including spaces (≤100)**: 99

**Words in the abstract (≤400)**: 399

**Total words excluding title page, abstract, tables, figure legends, and references (≤6000)**: 5131

**Number of figures, tables, and supplementary material**: 4 Figures, 1 Table, and 1 Supplementary file

**Keywords (≤5):** PET, neurodegeneration, tau, Alzheimer’s disease, progressive supranuclear palsy.

**ABSTRACT**

The ability to assess the distribution and extent of tau pathology in Alzheimer’s disease and progressive supranuclear palsy *in vivo* would help to develop bio-markers for these tauopathies and clinical trials of disease-modifying therapies. New radio-ligands for positron emission tomography (PET) have generated considerable interest, and controversy, in their potential as tau bio-markers. We assessed the radiotracer [18F]AV-1451 with PET imaging to compare the distribution and intensity of tau pathology in 15 patients with Alzheimer’s pathology (including amyloid positive mild cognitive impairment), 19 patients with progressive supranuclear palsy, and 13 age- and sex-matched controls. Regional analysis of variance, and a support vector machine, were used to compare and discriminate the clinical groups, respectively. We also examined the [18F]AV-1451 auto-radiographic binding in *post mortem* tissue from patients with Alzheimer’s disease, progressive supranuclear palsy, and a control case to assess the [18F]AV-1451 binding specificity to Alzheimer- and non-Alzheimer tau pathology.

 There was increased [18F]AV-1451 binding in multiple regions in patients with Alzheimer’s disease and progressive supranuclear palsy relative to controls (main effect of group, F2,41=17.5, P<0.0001; ROI x group interaction, F2, 68=7.5, P<0.00001). More specifically, [18F]AV-1451 binding was significantly increased in Alzheimer’s disease patients, relative to both progressive supranuclear palsy patients and controls, in the hippocampus and in occipital, parietal, temporal, and frontal cortices (T’s>2.2, P’s<0.04). Conversely, in progressive supranuclear palsy patients, relative to Alzheimer’s disease patients, [18F]AV-1451 binding was elevated in the midbrain (T=2.1, P<0.04); while progressive supranuclear palsy patients showed, relative to controls, increased [18F]AV-1451 uptake in the putamen, pallidum, thalamus, midbrain, and in the dentate nucleus of the cerebellum (T’s>2.7, P’s<0.02). The support vector machine assigned patients’ diagnoses with 94% accuracy. The *post mortem* auto-radiographic data showed that [18F]AV-1451 strongly bound to Alzheimer-related tau pathology, but less specifically in progressive supranuclear palsy. [18F]AV-1451 binding to the basal ganglia was strong in all groups *in vivo*. *Post mortem* histochemical staining showed absence of neuromelanin-containing cells in the basal ganglia, indicating that off-target binding to neuromelanin is an insufficient explanation of [18F]AV-1451 PET data.

 Overall, we confirm the potential of [18F]AV-1451 as an heuristic biomarker, but caution is indicated in the neuropathological interpretation of its binding. Off-target binding may contribute to disease profiles of [18F]AV-1451 PET. We suggest that [18F]AV-1451 PET is a useful biomarker to assess tau pathology inAlzheimer’s disease and to distinguish it from other tauopathies with distinct clinical and pathological characteristics such as progressive supranuclear palsy.

**INTRODUCTION**

Alzheimer’s disease and progressive supranuclear palsy are both associated with abnormal accumulation of misfolded and aggregated tau protein. In Alzheimer’s disease, oligomeric and aggregated neurofibrillary tau tangles are a major determinant of synaptic / cell dysfunction and death (Goedert et al., 1988; Ballatore et al., 2007; de Calignon et al., 2012), notwithstanding the importance of beta-amyloid in its “toxic alliance” with pathological tau (Bloom, 2014). The intensity and distribution of tau in Alzheimer’s disease also correlates with the clinical syndrome and severity and has been considered as one of the primary factors in the neuropathological staging of Alzheimer’s disease (Braak et al., 2006; Murray et al., 2014; Ossenkoppele et al., 2015).

In patients with progressive supranuclear palsy and in analogous murine models, intra-neuronal and astrocytic aggregates of pathological tau isoforms (in the form of straight filaments) characterize and promote neurodegeneration (Clavaguera et al., 2013). Furthermore, tau pathology is common in other neurological diseases such as fronto-temporal dementia (Hodges et al., 2004), corticobasal degeneration, and may modulate the course of Parkinson’s disease (Spillantini and Goedert, 2001; Irwin et al., 2013), Huntington’s disease (Fernández-Nogales et al., 2014), and multiple sclerosis (Anderson et al., 2008).

Despite the importance of tau pathology in several neurological diseases, it has only recently become possible to assess it using brain imaging in living humans. To be able to measure the burden and distribution of tau pathology in living patients, or those at high risk of developing tau-related disorders, would be a major step forward in the development of disease modifying therapies targeting the tau protein. Specific markers could also enable pathological characterization of syndromes associated with multiple alternate pathologies, such as fronto-temporal dementia and cortico-basal degeneration (Alexander et al., 2014). Such biomarkers would ultimately need to be assessed in longitudinal studies and clinical trials, but cross-sectional studies can assess critical properties such as sensitivity to the presence of different diseases and the expected distribution of pathology.

Radio-ligands have recently been developed for positron emission tomography (PET) to measure *in vivo* binding to aggregated tau, including PBB3 (Maruyama et al., 2013), THKcompounds (Okamura et al., 2014), and [18F]AV-1451 (Chien et al., 2013; Xia et al., 2013). In auto-radiographic studies with *post-mortem* human brain tissues, the radiotracer [18F]AV-1451 co-localizes selectively with hyper-phosphorylated tau over amyloid beta plaques (Marquié et al., 2015). In patients with mild cognitive impairment and Alzheimer’s disease, there is higher [18F]AV-1451 binding in frontal, parietal, and temporal cortices relative to age-matched healthy controls (Okello et al., 2009). Progressively increasing regional [18F]AV-1451 binding in Alzheimer’s disease has also been associated with Braak staging of neurofibrillary tau pathology (Schöll et al., 2016; Schwarz et al., 2016), while [18F]AV-1451 PET binding patterns mirror the clinical and neuro-anatomical variability in the Alzheimer’s disease spectrum (Ossenkoppele et al., 2016). Specifically, patients with the amnestic presentation of Alzheimer’s disease showed the highest [18F]AV-1451 uptake in medial temporal lobe regions including the hippocampus, while patients with the logopenic variant of Alzheimer’s disease displayed increased left hemispheric [18F]AV-1451 binding, particularly in posterior temporo-parietal areas implicated in linguistic processes (Ossenkoppele et al., 2016). Performance on domain-specific neuro-psychological tests was also associated with increased [18F]AV-1451 uptake in brain regions involved in episodic memory, visuo-spatial skills, and language production or comprehension (Ossenkoppele et al., 2016).

Nevertheless, critical issues remain unresolved, and in particular the value of [18F]AV-1451 in differentiating distinct tauopathies as well as the specificity of binding to tau as verified through pathological correlation. Neuropathological data with autoradiography have suggested that the [18F]AV-1451 tracer displays strong binding to paired helical filaments characteristic of Alzheimer’s disease (e.g., intra-neuronal and extra-neuronal neurofibrillary tangles and dystrophic neurites), but it does not bind so specifically to the straight tau filaments that are more typical of progressive supranuclear palsy and non-Alzheimer’s disease tauopathies (e.g., cortico-basal degeneration) (Marquié et al., 2015). It has also been proposed that the [18F]AV-145 tracer displays off-target binding, specifically to neuromelanin-containing cells. This was supported by evidence in patients with Parkinson’s disease, *in vivo,* in the midbrain; and *post-mortem,* in retinal and brain tissues in porcine and rodent models (Hansen et al., 2016).

In this study, we sought to evaluate the utility of [18F]AV-1451 PET imaging in Alzheimer’s disease versus non-Alzheimer’s disease tauopathies. We used dynamic imaging with kinetic modelling, rather than standardized uptake value ratios (SUVR), in part to accommodate variations in cerebral perfusion that can reduce reliability of SUVR. We aimed to identify the patterns of [18F]AV-1451 uptake in patients with Alzheimer’s disease and contrast these patterns with those that were expected in patients with progressive supranuclear palsy on the basis of previous studies (Johnson et al., 2016; Ossenkoppele et al., 2016; Schöll et al., 2016; Schwarz et al., 2016).

The value of comparing these two groups lies not in their differential diagnosis, which is clear on clinical grounds alone, but in testing the ligand’s binding against well-established clinico-pathological correlations and distinct distributions of tau pathology. These two disorders represent different kinds of tauopathy, with paired helical *versus* straight filamentous tau. Evidence on [18F]AV-1451’s binding distributions, its off-target binding, and clinical correlations would directly inform the design of forthcoming clinical trials of anti-tau therapies in these diseases.

Overall, we aimed to: (1) identify the patterns of [18F]AV-1451 binding in patients with Alzheimer’s disease, relative to patients with progressive supranuclear palsy as well as sex- and age-matched healthy controls; (2) test whether [18F]AV-1451 binding was associated with disease severity in Alzheimer’s disease and progressive supranuclear palsy, and (3) assess whether regional [18F]AV-1451 binding could distinguish between Alzheimer’s disease and progressive supranuclear palsy groups. We combined patients with clinical diagnostic criteria for Alzheimer’s disease and mild cognitive impairment patients who had biomarker evidence of Alzheimer’s disease pathology (i.e., with a positive scan for amyloid), on the basis that these two groups represent a continuum of disease (Okello et al., 2009). In view of the suggested effect of off-target binding, we also examined [18F]AV-1451 uptake in relation to AT8 immunohistochemistry of hyper-phosphorylated tau protein and tinctorial stain for neuromelanin, in *post mortem* sections from patients with Alzheimer’s disease, progressive supranuclear palsy, and a similarly aged control from the Cambridge Brain Bank.

Our principal hypotheses were that: (1) patients with Alzheimer’s disease and those with mild cognitive impairment and PET scans positive for amyloid would show increased [18F]AV-1451 binding in the cortical and sub-cortical areas associated with Alzheimer’s pathology, including the medial temporal lobe as well as frontal, parietal, and temporal cortices (Serrano-Pozo et al., 2011); (2) patients with progressive supranuclear palsy would display increased [18F]AV-1451 binding especially in the midbrain and basal ganglia, with likely additional binding in frontal cortex (including the motor areas) and supramarginal gyrus (Schofield et al., 2005; Dickson et al., 2007; Smith et al., 2016), and (3) progressive supranuclear palsy and Alzheimer’s disease patients would be distinguishable on the basis of the regional [18F]AV-1451 binding levels, particularly in the hippocampus and midbrain, two key sub-cortical regions that show distinct neuropathological changes in Alzheimer’s disease and progressive supranuclear palsy, respectively.

**METHODS**

**Participants**

The current study was conducted within the context of the “Neuroimaging of Inflammation in MemoRy and Other Disorders (NIMROD)” project (Bevan-Jones et al., In Press). We recruited 19 patients with progressive supranuclear palsy (“probable PSP” by Movement Disorder Society criteria, Litvan et al., 1996, representing the “classical phenotype”, which is sometimes referred to as Richardson’s syndrome), nine patients meeting diagnostic criteria for probable Alzheimer’s disease (McKhann et al., 2011), and six patients with mild cognitive impairment and biomarker evidence of Alzheimer’s disease (i.e., amyloid pathology). Mild cognitive impairment was defined as a mini-mental score examination (MMSE)>24 with a memory impairment at least 1.5 standard deviations below that expected for age and education (Petersen et al., 1999). All participants with mild cognitive impairment had a positive Pittsburgh Compound-B, PiB, PET scan (assessing *in vivo* amyloid pathology). Thirteen age- and sex-matched healthy controls with no history of major psychiatric or neurological illnesses, head injury or any other significant medical co-morbidity were also included to allow group-wise comparisons with the clinical cohorts. All participants were aged over 50 years, had sufficient proficiency in English for cognitive testing and had no contraindications to magnetic resonance imaging (MRI). Patients and healthy controls were identified from the specialist clinics for memory disorders and progressive supranuclear palsy at the Cambridge University Hospitals NHS Trust and from registers held by the “Dementias and Neurodegenerative Diseases Research Network (DeNDRoN)”; part of the NIHR Clinical Research Network. All participants had full mental capacity and provided written informed consent which was approved by the local ethical committee, in accord to the [Declaration of Helsinki](http://brain.oxfordjournals.org/sites/default/files/pdf/Helsinki.pdf). As some of the assessment scales required carers’ input for completion, we also obtained informed written consent from contributory carers.

**Participants’ clinical and neuroimaging assessment**

**Clinical and cognitive assessment (visit 1)**

Participants underwent an initial assessment that included clinical measures of disease severity (e.g., Progressive Supranuclear Palsy Rating Scale) (Golbe and Ohman-Strickland, 2007), demographic questionnaires, and neuropsychological tests (Mini Mental State Examination (MMSE), and Addenbrooke’s Cognitive Examination-Revised (ACE-R)).

**MRI data acquisition (visit 2) and MRI data preprocessing**

Participants underwent an MRI session acquired on a 3 Tesla (Siemens Magnetom Tim Trio and Verio scanner; www.medical.siemens.com) using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) T1-weighted sequence (all groups). The T1-weighted sequence (TR=2300ms, TE=2.98ms, FOV=240x256mm2, 176 slices of 1mm thickness, flip angle=9°) was used to facilitate tissue class segmentation (grey- and white-matter, together with cerebro-spinal fluid (CSF)), and to allow non-rigid registration of standard space regions of interest (ROIs) (Hammers atlas) (Hammers et al., 2003) to subject MRI space. Each T1 image was non-rigidly registered to the ICBM2009a template brain using ANTS ([http://www.picsl.upenn.edu/ANTS](http://www.picsl.upenn.edu/ANTS/)/) and the inverse transform was applied to the Hammers atlas (resliced from MNI152 to ICBM2009a space) to bring the ROIs to subject MRI space.

**PET data acquisition (visit 3 and 4) and PET data preprocessing**

All participants (i.e., Alzheimer’s disease patients, mild cognitive impairment patients, progressive supranuclear palsy patients, and controls) underwent [18F]AV-1451 PET imaging to assess the extent and intensity of brain tau pathology. Subjects with mild cognitive impairment also underwent [11C]PiB PET imaging to assess the density of amyloid β deposits as an indication of Alzheimer’s disease amyloid pathology. All radio-ligands were prepared at the Wolfson Brain Imaging Centre (WBIC), University of Cambridge, with high radiochemical purity (>95%). [11C]PiB was produced with specific activity of >150 GBq/μmol, while [18F]AV-1451 specific activity was of 216±60 GBq/μmol at the end of synthesis. PET scanning was performed on a GE Advance PET scanner (GE Healthcare, Waukesha, WI) and a GE Discovery 690 PET/CT. A 15min 68Ge/68Ga transmission scan was used for attenuation correction on the Advance, which was replaced by a low dose computed tomography (CT) scan on the Discovery 690. The emission protocols were the same on both scanners – 550MBq [11C]PiB injection followed by imaging from 40-70 mins post-injection and 90 mins dynamic imaging (58 frames) following a 370MBq [18F]AV-1451 injection.

Each emission frame was reconstructed using the PROMIS 3-dimensional filtered back projection algorithm into a 128x128 matrix 30cm trans-axial field of view, with a trans-axial Hann filter cut-off at the Nyquist frequency (Kinahan and Rogers, 1989). Corrections were applied for randoms, dead time, normalization, scatter, attenuation, and sensitivity. Each emission image series was aligned using SPM8 to correct for patient motion during data acquisition (www.fil.ion.ucl.ac.uk/spm/software/spm8).

The mean aligned PET image, and hence the corresponding aligned dynamic PET image series, was rigidly registered to the T1-weighted image using SPM8 to extract values from both the Hammers atlas ROIs and those in a reference tissue defined in the superior grey-matter of the cerebellum using a 90% grey-matter threshold on the grey-matter probability map produced by SPM8 smoothed to PET resolution. The superior cerebellum was used as reference region as it is considered to have little or no tau pathology in either progressive supranuclear palsy and Alzheimer’s disease (William 2007; Dickson 2010; Okello et al., 2009; Schöll et al., 2016; Schwarz et al., 2016). This was confirmed in our *post mortem* cases (see **Supplementary material**). All ROI data, including the reference tissue values, were corrected for CSF partial volumes through division with the mean ROI probability (normalized to 1) of grey + white matter segments, each smoothed to PET resolution. To test whether correction for CSF affected the main results, we repeated all the [18F]AV-1451 PET analyses using data not corrected for CSF (see **PET statistical analyses** and **Results** sections).

[11C]PiB data were quantified using SUVR by dividing the mean CSF-corrected radioactivity concentration in each Hammers atlas ROI by the corresponding mean CSF-corrected radioactivity concentration in the reference tissue ROI (whole cerebellum). For [18F]AV-1451 non-displaceable binding potential (BPND), a measure of specific binding, was determined for each Hammers atlas ROI using a basis function implementation of the simplified reference tissue model (SRTM) operating upon the dynamic Hammers atlas and reference tissue ROI data, both with and without CSF correction (Gunn et al., 1997). [11C]PiB data were treated as dichotomous measures (i.e., positive or negative) and considered positive if the ratio of the average SUVR values across the cortical and cerebellar ROIs was > 1.5, as previously described (Hatashita and Yamasaki, 2013).

**PET statistical analyses**

To compare [18F]AV-1451 binding across groups (Alzheimer’s disease/mild cognitive impairment PiB+, progressive supranuclear palsy, and controls), individual ROI BPND values for [18F]AV-1451 were used in a repeated-measures general linear model (GLM) to test for the main effect of ROI, main effect of group, and group x ROI interaction. Age and education were included as covariates of no interest. For the Alzheimer’s disease/mild cognitive impairment PiB+ and progressive supranuclear palsy groups, we tested for correlations between regional [18F]AV-1451 BPND and disease severity using the ACE-R scores for Alzheimer’s disease/mild cognitive impairment PiB+ patients and the Progressive Supranuclear Palsy Rating Scale for progressive supranuclear palsy patients with Pearson’s correlation (with partial correlations accounting for age and education). All analyses were repeated using [18F]AV-1451 BPND values that were not corrected for CSF partial volume effects.To assess the ability of [18F]AV-1451 BPND to distinguish Alzheimer’s disease patients from progressive supranuclear palsy cases, subject-specific [18F]AV-1451 data in a set of ROIs were input as key features in a support vector machine (SVM), a multivariate supervised statistical learning method suitable for neuroimaging modalities (Cortes and Vapnik, 1995). A reduced group of ROIs considered as the most characteristic ROIs affected by tau pathology in Alzheimer’s disease and progressive supranuclear palsy was selected (i.e., superior / inferior temporal cortex, lateral occipital cortex, inferior parietal cortex, and hippocampus for Alzheimer’s disease, and basal ganglia and midbrain for progressive supranuclear palsy); noting that the ROIs included in the SVM were identical for both groups. This extended the whole-brain hierarchical cluster analysis described in **Supplementary Materials**. The accuracy of each ROI to discriminate between the Alzheimer’s disease and progressive supranuclear palsy groups was computed using an SVM classifier with a K means cross-validation (K=5) scheme with a linear kernel and standard cost parameter of 1.

**Neuropathological methods**

**Tissue samples preparation**

*Post mortem* brain tissue from three subjects (one Alzheimer’s disease case, one progressive supranuclear palsy patient, and one healthy control with similar age) from the Cambridge Brain Bank was included in this study. The auto-radiographic and immuno-histochemical analyses were conducted in different cases from those included in the PET *in vivo* study. Tissue collection was approved by the local institutional review board. Neuropathological diagnoses were performed according to standardised protocols, on 15 blocked regions of cortex and subcortical regions. For this study, additional blocks of frozen brain tissue were obtained from the anterior hippocampus, midbrain, basal ganglia, and frontal cortex. 20μm thick sections were cut in a cryostat (Leica CM30505 S Research Cryostat) mounted on Thermo Scientific superfrost plus slides and used for [18F]AV-1451 phosphor screen, phosphorylated-tau immunoreactivity (AT8), and tinctorial stain for neuromelanin (Masson-Hamperl stain).

**[18F]AV-1451 phosphor screen auto-radiography**

[18F]AV-1451 for auto-radiographic studies was synthesized in the same way as described above. [18F]AV-1451 phosphor screen auto-radiography was performed following a previously published protocol by Marquiè and collaborators (Marquiè et al., 2015). In brief, 20μm-thick frozen brain sections were fixed in 100% methanol at room temperature for 20 minutes and then transferred to a bath containing high specific activity [18F]AV-1451 in 10mM phosphate-buffered saline (PBS) with a radioactivity concentration of approximately 20μCi/ml. Adjacent brain slices were placed in a bath that was identical in all aspects except that unlabelled AV-1451 was added to yield 1μM chemical concentration, a blocking condition sufficient to saturate essentially all available specific binding sites of tau. After incubation for 60 minutes, racks of slides were removed from the respective radioactive solutions and briefly incubated in a series of wash baths to remove unbound radiotracer. Wash solutions and incubation times were: 10mM PBS for 1 minute, 70% ethanol/30% PBS for 2 minutes, 30% ethanol/70% PBS for 1 minute, and lastly 100% 10mM PBS for 1 minute. Racks were removed from the final wash solution, and slides were allowed to air dry before transfer to a storage phosphor screen (GE healthcare) that had been photo-bleached immediately prior by exposure on a white light box for a minimum of 15 minutes. The slides and phosphor screen were enclosed in an aluminium film cassette and set away from sources of radioactivity for the duration of the overnight exposure period. The cassette was opened and the slides were removed from the exposed screen, which was mounted on the digital imaging system (CR 35 BIO, Durr medical). Scanning of screens was controlled by Aida Image Analyser v.4.27 using 600 dpi resolution (approximately 42μm sampling interval). Digital images were saved at full resolution and pixel depth. Images from adjacent brain slices incubated in the unblocked (high specific activity [18F]AV-1451 only) and blocking ([18F]AV-1451 plus 1μm unlabelled AV-1451) conditions were compared to estimate total and nonspecific binding of [18F]AV-1451.

**RESULTS**

**Demographics and cognitive variables of patients in the PET *in vivo* study**

There were no statistically significant differences between patient and control groups in terms of age or sex (**Table 1**). Shorter education was reported by progressive supranuclear palsy patients relative to other groups (**Table 1**). One interpretation of this difference is that control cohorts over-represent people from higher socio-economic groups and with longer education; however, low education and its effects on health may also be a risk factor for the development of progressive supranuclear palsy (Litvan et al., 2016). Age and education were included as covariates of no interest in the statistical models assessing the main effect of group and group x ROI interaction. As expected, there was a significant main effect of group for cognitive measures, driven by reduced MMSE and ACE-R scores in Alzheimer’s disease/mild cognitive impairment+ and progressive supranuclear palsy patients relative to healthy controls (**Table 1**).

**\*\*\*\*\*\*\* Table 1 about here \*\*\*\*\*\*\***

**[18F]AV-1451 binding in relation to clinical diagnosis**

The mean [18F]AV-1451 BPND PET map in each group (**Figure 1**) and quantitative ROI analyses (**Figure 2**), indicated high [18F]AV-1451 uptake in the basal ganglia in all groups including controls. In the repeated-measures ANOVA of regional binding, we found a significant main effect of group (F2,41=17.5, P=0.00001) and a ROI x group interaction (F2, 68=7.5, P<0.00001), although there was no main effect of ROIs (F2,34=0.8, P=0.8) (**Figure 2**). The group and interaction effects were driven in part by greater [18F]AV-1451 BPND in the Alzheimer’s disease/mild cognitive impairment+ group relative to the progressive supranuclear palsy and control groups, in cortical and sub-cortical ROIs including frontal, parietal, lateral temporal, and occipital cortices as well as the hippocampus and other medial temporal lobe ROIs (post-hoc t-tests, T’s>2.2, P’s<0.04) (**Figure 2**). The progressive supranuclear palsy group, relative to the Alzheimer’s disease group, showed increased [18F]AV-1451 BPND in the midbrain (T=2.1, P’s<0.04); while, relative to controls, progressive supranuclear palsy patients showed increased [18F]AV-1451 BPND uptake in the putamen, pallidum, thalamus, midbrain, and dentate nucleus of the cerebellum (T’s>2.7, P<0.02) (**Figure 2**). There was no correlation between age and [18F]AV-1451 in any of the ROIs (all R’s<0.2; P’s>0.1).

**\*\*\*\*\*\*\* Figure 1 about here \*\*\*\*\*\*\***

**\*\*\*\*\*\*\* Figure 2 about here \*\*\*\*\*\*\***

Repeating the analyses using [18F]AV-1451 BPND values that were not corrected for CSF partial volume effects yielded similar results (F2,36=1.1, P=0.2, for the main effect of ROIs; F2,41=16.7, P<0.00001 for the main effect of group; and F2, 72=6.3, P<0.00001 for the group x ROI interaction). We then tested whether regional [18F]AV-1451 BPND related to disease severity. In the Alzheimer’s disease/mild cognitive impairment+ group, there was no significant correlation between ACE-R score and [18F]AV-1451 BPND in any ROI (P’s>0.14). Similarly, in the progressive supranuclear palsy group, we found no significant correlation between [18F]AV-1451 BPND in any ROI and disease severity, as assessed via the Progressive Supranuclear Palsy Rating Scale (P’s>0.16). Repeating the correlation analyses when using the [18F]AV-1451 BPND values that were not corrected for CSF volume yielded similar non-significant results (P’s>0.1).

**Classification of cases by [18F]AV-1451** **BPND**

The SVM analysis using [18F]AV-1451 BPND values in a subset of ROIs was able to separate the Alzheimer’s disease/mild cognitive impairment+ patients from progressive supranuclear palsy cases with a classification accuracy of 94.1%. The accuracy for the other pair-wise comparisons is as follows: Alzheimer’s disease/mild cognitive impairment+ vs. controls=85.7%; progressive supranuclear palsy vs. controls=90.6% (**Figure 3** for data plot from two characteristic ROIs). In **Supplementary Material** we also report the high accuracy of pair-wise comparisons between groups using hierarchical cluster analyses, based on the regional distribution of [18F]AV-1451 BPND across the whole brain (Bevan Jones, et al., 2016a).

**\*\*\*\*\*\*\* Figure 3 about here \*\*\*\*\*\*\***

**Phosphor screen auto-radiography and immune-histochemistry *post mortem***

A summary of the auto-radiography results, AT8 immuno-histochemistry data, and neuromelanin staining in *post mortem* Alzheimer’s disease, progressive supranuclear palsy, and a control case is shown in **Figure 4**.

The autoradiography phosphor screen analyses in the Alzheimer’s disease brain tissue samples revealed that the anterior hippocampus had the highest and most specific binding of the [18F]AV-1451 radiotracer. [18F]AV-1451 binding was also found in the frontal cortex in the Alzheimer’s disease case, although to a lesser extent than in the hippocampal slice. In contrast, sparse and nonspecific [18F]AV-1451 binding was found in the Alzheimer’s disease basal ganglia tissue.

The progressive supranuclear palsy and control tissues showed overall sparse and nonspecific [18F]AV-1451 binding, including anterior hippocampus, midbrain, basal ganglia, and frontal cortex.

 Abundant hyper-phosphorylated tau protein was detected in the anterior hippocampus of the Alzheimer’s disease case, while small and punctate tau staining was found in the midbrain and frontal cortex of the same patient, which is overall consistent with the results of the phosphor screen autoradiography. Although hyper-phosphorylated tau protein was found in the frontal cortex in the Alzheimer’s disease case, its relatively low density could be due to a slow cortical disease progression in this particular patient.

The progressive supranuclear palsy tissue displayed high concentration of hyper-phosphorylated tau in the midbrain and basal ganglia, while the Alzheimer’s disease brain displayed little AT8 staining in the same ROI.

As expected, the control brain did not show AT8 immunoreactivity in any of the ROIs examined.

 Neuromelanin-containing cells were only observed in the midbrain in all post-mortem cases. Of note, no neuromelanin-containing cells were found in the basal ganglia in either the Alzheimer’s disease, progressive supranuclear palsy or control case, which is in contrast to the strong *in vivo* [18F]AV-1451 binding of this radiotracer to the same ROI.

**\*\*\*\*\*\*\* Figure 4 about here \*\*\*\*\*\*\***

**DISCUSSION**

The principal result of our study is that PET imaging with the radiotracer [18F]AV-1451 revealed distinct patterns of binding in Alzheimer’s disease and its prodromal state of mild cognitive impairment, in comparison to the primary tauopathy of progressive supranuclear palsy. The relatively large size of our PET study confirmed the high accuracy of discrimination between the clinical groups using [18F]AV-1451 BPND data, with a simple support vector machine and indeed by visual inspection (**Figure 1** and **2**). However, despite this heuristic potential of [18F]AV-1451 as a tau biomarker, caution in the interpretation of its binding targets is indicated by the neuropathological and autoradiographic data (Marquiè et al., 2015). In particular, while [18F]AV-1451 strongly bound to Alzheimer’s disease-related tau pathology, non-specific binding of the same tracer can be found in progressive supranuclear palsy patients and controls (Marquiè et al., 2015). Nevertheless, our *post mortem* data suggest that off-target binding to neuromelanin is not a sufficient explanation of the BPND for [18F]AV-1451 at least in the context of progressive supranuclear palsy, and in some critical regions. For instance, we found *in vivo* significant [18F]AV-1451 uptake in the basal ganglia (in all groups including controls) in the absence of *post mortem* neuromelanin-containing cells. This indicates that neuromelanin is not the principal target of off-target binding for [18F]AV-1451, but there may be other off-target binding sites which have as yet not been identified, including non-tau targets in disorders associated with predominantly TDP43 pathology (Bevan-Jones et al., 2016b).

For [18F]AV-1451 PET to meet its full potential as a biomarker to stratify or monitor the effect of disease modifying drugs in future clinical trials, additional properties would therefore need to be established. In particular, further work is needed to demonstrate changes in [18F]AV-1451 PET over time, or in response to treatment. A cross-sectional study as this one cannot be used to infer longitudinal change, but it can be employed to inform and model a biomarker’s potential. More specifically, the relevance of [18F]AV-1451 is increased by the demonstration that its binding patterns recapitulate *in vivo* the established *post mortem* distributions of tau pathology in Alzheimer’s disease and progressive supranuclear palsy. In addition, [18F]AV-1451 PET may have biomarker potential for the differential diagnosis of equivocal cases: whilst the distinction between Alzheimer’s disease and progressive supranuclear palsy can be readily made on clinical grounds, patients with progressive supranuclear palsy-parkinsonism clinically resemble Parkinson’s disease (Williams et al., 2005).

In contrast to previous results (Johnson et al., 2016; Ossenkoppele et al., 2016), [18F]AV-1451 uptake was not correlated with disease severity in our groups (i.e., severity of cognitive impairment in Alzheimer’s disease patients and Progressive Supranuclear Palsy Rating scale in progressive supranuclear palsy patients). There are several possible explanations for the lack of a correlation in our study, including lack of statistical power (type II error) or the use of clinical measures that were not sufficiently sensitive to describe the full spectrum of clinical variability in Alzheimer’s disease and progressive supranuclear palsy. Alternatively, it may be that [18F]AV-1451 uptake is inherently limited in staging disease severity in Alzheimer’s disease and progressive supranuclear palsy, analogous to the PiB tracer in Alzheimer’s disease (Hatashita and Yamasaki, 2010).

Technical considerations in assessing the [18F]AV-1451 binding *post mortem* and in estimating BPND *in vivo* must also be considered. First, it is possible that in the auto-radiographic protocol19, ethanol washing, and other procedures may have affected the labelling with [18F]AV-1451, especially in the basal ganglia. Second, our PET analyses employed correction of ‘partial volume effects’, resulting from the cerebro-spinal fluid (CSF) volume within each region. This mitigates the potential influence of brain volume loss seen in Alzheimer’s disease and progressive supranuclear palsy. Nevertheless, using uncorrected PET data yielded qualitatively similar results in terms of the main effect of group and group x ROI interaction, which suggests that we avoided “over-correcting” the BPND values based on cortical and sub-cortical atrophy, and the consequent inferential error from CSF volume and its correction.

Interestingly, the regions with the most significant group differences in [18F]AV-1451 BPND in Alzheimer’s disease and progressive supranuclear palsy *in vivo* were those predicted from prior *post mortem* studies for each disease. More specifically, the clinical syndromes of Alzheimer’s disease and biomarker positive mild cognitive impairment were associated with increased [18F]AV-1451 BPND in widely distributed sub-cortical and cortical areas that have been consistently implicated in the pathogenesis and progression of Alzheimer’s disease (e.g., hippocampus, amygdala as well as frontal, parietal, temporal, and occipital cortices) (Braak and Braak, 1995; Braak et al., 2007). Conversely, progressive supranuclear palsy was associated with a pattern of increased [18F]AV-1451 BPND in the basal ganglia, midbrain, and dentate nucleus of the cerebellum, consistent with the pathophysiology of the disease (Hauw et al., 1994; Litvan et al., 1996). Together, these data demonstrated that the [18F]AV-1451 ligand recapitulates *in vivo* the typical neuropathological changes seen in Alzheimer’s disease and progressive supranuclear palsy, although it cannot be assumed that the cellular and/or molecular targets of [18F]AV-1451 binding are the same in both disorders.

[18F]AV-1451 BPND in selected regions of interest also distinguished Alzheimer’s disease cases from progressive supranuclear palsy patients with an accuracy of 94% which suggests the potential of this radio-tracer to discriminate *in vivo* amongst different tauopathies. The value of this analysis is obviously not as a diagnostic biomarker, as clinical features readily distinguish the groups, but rather represents an early step in the process of validating [18F]AV-1451 PET as a biomarker for tauopathies. Multicentre replication with larger samples and broader diagnostic spectra would nonetheless be necessary, including for example, patients with fronto-temporal dementia, cortico-basal syndrome, or pre-symptomatic individuals with high risk of developing tau-related neurodegenerative disorders (e.g., carrying specific gene mutations).

Finally, we note that our data are specific to [18F]AV-1451, and do not necessarily generalize to other radio-ligands. Further work is required to determine the specificity of [18F]AV-1451 and other candidate ligands’ binding to the different isoforms of tau protein, their differential modes of modification (e.g., phosphorylation, acetylation) and aggregation (e.g., oligomeric states). These issues are of high relevance for this and other studies because: (1) Alzheimer’s disease is characterized by balanced 3R/4R isoforms, while progressive supranuclear palsy pathology is mainly a 4R isoform tauopathy (Buée and Delacourte, 1999; Espinoza et al., 2008), and (2) the toxicity of tau aggregates may be driven by oligomers rather than tangles.

In conclusion, we suggest that [18F]AV-1451 is a useful PET ligand for *in vivo* studies in clinical populations with Alzheimer’s disease pathology and non-Alzheimer’s disease primary tauopathies such as progressive supranuclear palsy, despite the potential contribution of non-specific or “off-target” binding. The brain regions with increased [18F]AV-1451 binding were those predicted from the well-established patterns of neurodegeneration in both diseases, and are in keeping with the cognitive and motor features classically seen in Alzheimer’s disease and progressive supranuclear palsy clinical syndromes. Together, our current findings support the further use of [18F]AV-1451 PET *in vivo* and *in vitro* to evaluate tau pathology in studies of dementia and neurodegeneration.

**ACKNOWLEDGMENTS**

Thanks to our volunteers for participating in this study and to the radiographers/technologists at the Wolfson Brain Imaging Centre and PET/CT Unit, Addenbrooke’s Hospital for their invaluable support in data acquisition. We thank the NIHR Dementias and Neurodegenerative Diseases Research Network for help with subject recruitment. We also thank Avid (Lilly) for supplying the precursor for the manufacturing of AV-1451 for use in this study. This study was funded by the National Institute for Health Research (NIHR, RG64473) Cambridge Biomedical Research Centre and Biomedical Research Unit in Dementia, PSP Association, and the Wellcome Trust (JBR 103838); the Medical Research Council of Cognition and Brain Sciences Unit, Cambridge (MC-A060-5PQ30). None of the authors have conflicts of interest to report.

**LEGEND TO FIGURES**

**Figure 1.** Non-displaceable binding potential maps (BPND) for [18F]AV-1451 for Alzheimer’s disease (AD), including PiB positive mild cognitive impairment, progressive supranuclear palsy (PSP), and healthy controls. Note the [18F]AV-1451 uptake in the basal ganglia in all groups, albeit higher in AD and PSP patients. AD patients also showed increased [18F]AV-1451 uptake in medial temporal lobe regions and widespread neocortical areas, relative to controls and PSP patients, while PSP patients had increased high [18F]AV-1451 binding to the midbrain, relative to AD patients and controls (see Figure 2 and Results section in the main text for quantitative analyses).

**Figure 2.** Mean (± standard deviation) [18F]AV-1451 non-displaceable binding potential (BPND) in each region of interest forthe participant groups: Alzheimer’s disease (AD) and amyloid positive mild cognitive impairment (MCI+); progressive supranuclear palsy (PSP); healthy controls (HC). The [18F]AV-1451 BPND data reported here are corrected for cerebro-spinal fluid (CSF) volume. See the Results section for statistics related to CSF corrected and uncorrected data.

**Figure 3.** Individual [18F]AV-1451 non-displaceable binding potential (BPND) values in the hippocampus (X axis) andmidbrain (Y axis) in patients with Alzheimer’s disease (AD) and amyloid positive mild cognitive impairment (MCI+) (red dots), progressive supranuclear palsy (PSP) (cyan dots), and healthy controls (HCs) (green dots).

**Figure 4.** *Post-mortem* data. The figure aligns the [18F]AV-1451 auto-radiographic binding in key regions of interest (ROIs) in an Alzheimer’s disease (AD) case, a progressive supranuclear palsy (PSP) patient, and a control of similar age. Immuno-histochemistry data assessing hyper-phosphorylated tau (AT8, red), and neuromelanin staining (dark brown) are also shown for the same cases and ROIs. There is [18F]AV-1451 binding in the anterior hippocampus and, to a lesser extent, in the frontal cortex in AD. In contrast, [18F]AV-1451 binding to the mibrain slices was not specific to PSP but was also detected in the AD and control cases, who respectively showed little or no tau pathology in the midbrain. Despite the *in vivo* [18F]AV-1451 binding to the basal ganglia in all groups (including controls, see **Figure 1** and **2**), *post mortem* [18F]AV-1451 binding to the basal ganglia was sparse in these three cases. Note the absence of neuromelanin-containing cells in the basal ganglia and cortical regions. The magnification of the immunohistochemistry pictures (AT8) and neuromelanin staining is x20.

**REFERENCES**

Alexander SK, Rittman T, Xuereb JH, Bak TH, Hodges JR, Rowe JB. Validation of the new consensus criteria for the diagnosis of corticobasal degeneration. J Neurol Neurosurg Psychiatry 2014: jnnp–2013–307035.

Anderson JM, Hampton DW, Patani R, Pryce G, Crowther RA, Reynolds R, et al. Abnormally phosphorylated tau is associated with neuronal and axonal loss in experimental autoimmune encephalomyelitis and multiple sclerosis. Brain 2008; 131: 1736–1748.

Ballatore C, Lee VM-Y, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer’s disease and related disorders. Nat Rev Neurosci 2007; 8: 663–672.

Bevan-Jones RW, Surendranathan A, Passamonti L, Vázquez-Rodríguez P, Arnold R, Mak E, Su L, Coles JP, Fryer TD, Hong YT, Williams G, Aigbirhio F, Rowe JB, O’Brien JT. Neuroimaging of inflammation in memory and related other disorders (NIMROD) study protocol: a deep phenotyping cohort study of the role of brain inflammation in dementia, depression and other neurological illnesses. BMJ Open, (In Press).

Bevan Jones, W. R., Cope, T. E., Passamonti, L., Fryer, T. D., Hong, Y. T., Aigbirhio, F., Kril, J. J., Forrest, S. L., Allinson, K., Coles, J. P., Simon Jones, P., Spillantini, M. G., Hodges, J. R., O'Brien, J. T. and Rowe, J. B. (2016a), [18F]AV-1451 PET in behavioral variant frontotemporal dementia due to MAPT mutation. Ann Clin Transl Neurol. doi:10.1002/acn3.366.

Bevan-Jones RW, Cope TE, Passamonti L, Fryer TD, Hong YT, Aigbirhio F, Coles JP, Simon Jones P, O'Brien JT, Rowe JB. [18F] AV1451 PET imaging in semantic dementia. Journal of Neurochemistry 2016b; (Poster presentation).

Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol 2014; 71: 505–508.

Braak H, Braak E. Staging of alzheimer’s disease-related neurofibrillary changes. Neurobiology of Aging 1995; 16: 271–278.

Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol. 2006; 112: 389–404.

Buée L, Delacourte A. Comparative biochemistry of tau in progressive supranuclear palsy, corticobasal degeneration, FTDP-17 and Pick’s disease. Brain Pathol. 1999; 9: 681–693.

Chien DT, Bahri S, Szardenings AK, Walsh JC, Mu F, Su M-Y, et al. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. J. Alzheimers Dis. 2013; 34: 457–468.

Clavaguera F, Akatsu H, Fraser G, Crowther RA, Frank S, Hench J, et al. Brain homogenates from human tauopathies induce tau inclusions in mouse brain. Proc Natl Acad Sci U S A 2013; 110: 9535–9540.

Cortes C, Vapnik V. Support-Vector Networks. Machine Learning 1995; 20: 273–297.

de Calignon A, Polydoro M, Suárez-Calvet M, William C, Adamowicz DH, Kopeikina KJ, et al. Propagation of Tau Pathology in a Model of Early Alzheimer’s Disease. Neuron 2012; 73: 685–697.

Dickson DW, Rademakers R, Hutton ML. progressive supranuclear palsy: pathology and genetics. Brain Pathol. 2007; 17: 74–82.

Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephs KA. Neuropathology of variants of progressive supranuclear palsy. Curr. Opin. Neurol. 2010; 23: 394–400.

Espinoza M, de Silva R, Dickson DW, Davies P. Differential Incorporation of Tau Isoforms in Alzheimer’s Disease. J Alzheimers Dis 2008; 14: 1–16.

Fernández-Nogales M, Cabrera JR, Santos-Galindo M, Hoozemans JJM, Ferrer I, Rozemuller AJM, et al. Huntington’s disease is a four-repeat tauopathy with tau nuclear rods. Nat Med 2014; 20: 881–885.

Goedert M, Wischik CM, Crowther RA, Walker JE, Klug A. Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau. PNAS 1988; 85: 4051–4055.

Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain 2007; 130: 1552–1565.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. Neuroimage 1997; 6: 279-287.

Hammers A, Allom R, Koepp MJ, Free SL, Myers R, Lemieux L, et al. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. Hum Brain Mapp 2003; 19: 224–247.

Hansen AK, Knudsen K, Lillethorup TP, Landau AM, Parbo P, Fedorova T, et al. In vivo imaging of neuromelanin in Parkinson’s disease using 18F-AV-1451 PET. Brain 2016; 139: 2039–2049.

Hatashita S, Yamasaki H. Clinically different stages of Alzheimer’s disease associated by amyloid deposition with [11C]-PIB PET imaging. J. Alzheimers Dis. 2010; 21: 995–1003.

Hatashita S, Yamasaki H. Diagnosed Mild Cognitive Impairment Due to Alzheimer’s Disease with PET Biomarkers of Beta Amyloid and Neuronal Dysfunction. PLoS One 2013; 8: e66877

Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 1994; 44: 2015–2019.

Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, et al. Clinicopathological correlates in frontotemporal dementia. Ann Neurol. 2004; 56: 399–406.

Irwin DJ, Lee VM-Y, Trojanowski JQ. Parkinson’s disease dementia: convergence of α-synuclein, tau and amyloid-β pathologies. Nat Rev Neurosci 2013; 14: 626–636.

Johnson KA, Schultz A, Betensky RA, Becker JA, Sepulcre J, Rentz D, et al. Tau PET imaging in aging and early Alzheimer’s disease. Ann Neurol. 2016; 79: 110-119.

Kinahan PE, Rogers JG. Analytic 3D image reconstruction using all detected events. IEEE Transactions on Nuclear Science 1989; 36: 964–968.

Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996; 47: 1–9.

Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J. Neuropathol. Exp. Neurol. 1996; 55: 97–105.

Litvan I, Lees PSJ, Cunningham CR, Rai SN, Cambon AC, Standaert DG, et al. Environmental and occupational risk factors for progressive supranuclear palsy: Case-control study. Mov. Disord. 2016; 31: 644–652.

Marquié M, Normandin MD, Vanderburg CR, Costantino IM, Bien EA, Rycyna LG, et al. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. Ann. Neurol. 2015; 78: 787–800.

Maruyama M, Shimada H, Suhara T, Shinotoh H, Ji B, Maeda J, et al. Imaging of Tau Pathology in a Tauopathy Mouse Model and in Alzheimer Patients Compared to Normal Controls. Neuron 2013; 79: 1094–1108.

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011; 7: 263–269.

Murray ME, Kouri N, Lin W-L, Jack CR, Dickson DW, Vemuri P. Clinicopathologic assessment and imaging of tauopathies in neurodegenerative dementias. Alzheimers Res Ther 2014; 6: 1.

Okamura N, Furumoto S, Fodero-Tavoletti MT, Mulligan RS, Harada R, Yates P, et al. Non-invasive assessment of Alzheimer’s disease neurofibrillary pathology using 18F-THK5105 PET. Brain 2014; 137: 1762–1771.

Okello A, Koivunen J, Edison P, Archer HA, Turkheimer FE, Någren K, et al. Conversion of amyloid positive and negative MCI to AD over 3 years. Neurology 2009; 73: 754–760.

Ossenkoppele R, Schonhaut DR, Baker SL, O’Neil JP, Janabi M, Ghosh PM, et al. Tau, Amyloid, and Hypometabolism in a Patient with Posterior Cortical Atrophy. Ann Neurol 2015; 77: 338–342.

Ossenkoppele R, Schonhaut DR, Schöll M, Lockhart SN, Ayakta N, Baker SL, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer’s disease. Brain 2016; 139: 1551–1567.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 1999; 56: 303–308.

Schofield EC, Caine D, Kril JJ, Cordato NJ, Halliday GM. Staging disease severity in movement disorder tauopathies: brain atrophy separates progressive supranuclear palsy from corticobasal degeneration. Mov. Disord. 2005; 20: 34–39.

Schöll M, Lockhart SN, Schonhaut DR, O’Neil JP, Janabi M, Ossenkoppele R, et al. PET Imaging of Tau Deposition in the Aging Human Brain. Neuron 2016; 89: 971–982.

Schwarz AJ, Yu P, Miller BB, Shcherbinin S, Dickson J, Navitsky M, et al. Regional profiles of the candidate tau PET ligand 18F-AV-1451 recapitulate key features of Braak histopathological stages. Brain 2016; 139: 1539–1550.

Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011; 1: a006189.

Smith R, Schain M, Nilsson C, Strandberg O, Olsson T, Hägerström D, et al. Increased basal ganglia binding of (18) F-AV-1451 in patients with progressive supranuclear palsy. Mov. Disord. 2016

Spillantini M, Goedert M. TAu and parkinson disease. JAMA 2001; 286: 2324–2326.

Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson’s syndrome and PSP-parkinsonism. Brain 2005; 128: 1247–1258.

Williams DR, Holton JL, Strand C, Pittman A, de Silva R, Lees AJ, et al. Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson’s syndrome. Brain 2007; 130: 1566–1576.

Xia C-F, Arteaga J, Chen G, Gangadharmath U, Gomez LF, Kasi D, et al. [(18)F]T807, a novel tau positron emission tomography imaging agent for Alzheimer’s disease. Alzheimers Dement 2013; 9: 666–676.