

The role of tau and neuroinflammation in Progressive Supranuclear Palsy and Alzheimer's Disease

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A mi familia,
y en especial a mis ángeles de la guarda,
Fabio y Abu Socorro.

"I have already lost touch with a couple of people I used to be"
Joan Didion

Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for any other degree, diploma or qualification at the University of Cambridge or any other universities. This thesis is the result of my own work except where specifically indicated in the text, and have been carried out at the University of Cambridge between January 2015 and November 2018 under the supervision of Professor James Rowe.

Due to the collaborative nature of multimodal imaging neuroscience, the work presented here uses the first-person plural (“we”). Below is an overview of contributions to each chapter.

Chapter 2 summarises the relevant parts of the protocol of the NIMROD study. This is a collaboration led by Professors James B. Rowe and John O’Brien, with research assistant support from Dr Richard Bevan-Jones, and Robert Arnold. I undertook the majority of PSP investigation, and contributed to investigation of other groups. This chapter has been published at BMJ Open (Bevan-Jones et al., 2017).

Chapter 3 includes neuropsychological data obtained under the NIMROD research study collected partly by me (mainly PSP cases) with normative and Alzheimer case data by Mr Robert Arnold and Dr Richard Bevan-Jones. The analysis, interpretation and writing represent my own work.

Chapter 4 and chapter 5 draw on data from a large NIMROD study team collaboration, with multiple researchers affiliated with the Wolfson Brain Imaging Centre (WBIC) at Cambridge University, and the departments of PET-CT and Pathology at Addenbrooke’s hospital. The recruitment of patients was by me (PSP cases) and Robert Arnold. PET data pre-processing was carried out by Dr Tim Fryer and Dr Young Hong. Analysis and interpretation was the result of joint work by Dr Luca Passamonti and myself.

Dr Kieren Allison (Cambridge Brain Bank) provided the specific brain tissue needed for these chapters. Dr David Wilkinson and myself performed the phosphor screen autoradiographies using both PET tracers, [¹⁸F]AV1451 and [¹¹C](R)-PK11195. I have also assisted Dr Wilkinson during the immunohistochemistry work for chapter 4, while Oliver Green and Robert Fincham conducted this task for chapter 5. Dr Luca Passamonti contributed to the published manuscript, focusing on PET results. I developed the pathological sections. This work was published with co-first authors, as Passamonti, Vázquez Rodríguez et al., *Brain* 2017 and Passamonti, Vázquez Rodríguez et al., *Neurology* 2018.

The research questions for each of the studies in this thesis were developed by myself in consultation with my supervisor, Professor James Rowe. The length of this thesis does not exceed the 60,000-word limit set by the Degree Committee for the faculties of Clinical Medicine and Clinical Veterinary Medicine.

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Abstract

The ability to assess the distribution and extent of tau pathology and neuroinflammation in Progressive Supranuclear Palsy (PSP) and Alzheimer's disease (AD) 'in vivo' and to validate it using *post mortem* data is critical to develop reliable biomarkers for these disorders, and for tracking the effects of clinical trials using disease-modifying therapies. The main aim of my PhD was therefore to assess the utility of the PET radiotracers [^{18}F]AV1451 and [^{11}C](R)-PK11195 to compare the distribution and intensity of tau pathology and neuroinflammation respectively, in PSP and AD. I use both *in vivo* scanning and *post mortem* tissue from archival cases in the Cambridge Brain Bank. For the *in vivo* studies, I investigated whether tau accumulation and neuroinflammation relate to clinical measures of disease severity and cognitive impairment.

My PhD was undertaken as part of the Neuroimaging of Inflammation in Memory and Other Disorders (NIMROD). Nineteen people with PSP-Richardson's syndrome, 15 patients with amnesic Alzheimer's disease and biomarker-positive mild cognitive impairment (MCI⁺) and 13 age- and sex-matched controls participated. *Post mortem* brain tissue from three subjects (one PSP case, one AD patient, and one control with similar age) were included. Autoradiographic and immunohistochemical analyses were conducted in different cases from those included in the [^{18}F]AV1451 and [^{11}C](R)-PK11195 PET *in vivo* studies.

[^{18}F]AV1451 PET imaging revealed distinct patterns of tau binding in AD and its prodromal state of MCI⁺, in comparison to PSP. The clinical syndromes of AD and MCI⁺ were associated with increased [^{18}F]AV1451 BP_{ND} in widely distributed subcortical and cortical areas that have been consistently implicated in the pathogenesis and progression of AD (e.g. hippocampus, amygdala as well as frontal, parietal, temporal, and occipital cortices). Conversely, PSP was associated with a pattern of increased [^{18}F]AV1451 uptake in the basal ganglia, midbrain, and dentate nucleus of the cerebellum, consistent with the pathophysiology of the disease. Despite this potential of [^{18}F]AV1451 as a tau biomarker, caution in the interpretation of its binding targets is indicated by the neuropathological and autoradiographic data. In particular, while [^{18}F]AV1451 strongly bound to AD-

related tau pathology, non-specific binding of the same tracer can be found in PSP patients and controls. Furthermore, [¹⁸F]AV1451 uptake was not correlated with disease severity in the clinical groups.

[¹¹C](R)-PK11195 PET imaging revealed distinct patterns of inflammation in AD and PSP, and mirrored the pathological distribution for each disease seen by [¹¹C](R)-PK11195 *post mortem* phosphor screen autoradiography and immunohistochemistry. In AD, microglial activation was observed in prefrontal cortex, and medial temporal lobe. In PSP microglial activation was observed in midbrain and basal ganglia. In both clinical cohorts, disease severity correlated with neuroinflammation in the regions most closely associated with principal neuropathological markers including tau aggregates.

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Abbreviations

AA	Alzheimer's Association
A β	Amyloid Beta
ABC	Avidin-Biotin Complex
ACE-R	Addenbrooke's Cognitive Examination – Revised
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ADC	Apparent Diffusion Coefficient
ADL	Activities of Daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRDA	Alzheimer's Disease and Related Disorders Association
AoS	Apraxia of Speech
ApoE	Apolipoprotein E
APP	Amyloid Precursor Protein
arMFC	Anterior Rostral Medial Frontal Cortex
ARSAC	Administration of Radioactive Substances Advisory Committee
BALDS	Bristol Activities of Daily Living Scale
BBD	Brain Bank Donation
BOLD	Blood Oxygen Level Dependent
BPND	Non-displaceable Binding Potential
BRU	Biomedical Research Unit
bvFTD	Behavioural Frontotemporal Dementia
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBI	Cambridge Behavioural Inventory
CBI-R	Cambridge Behavioural Inventory Revised
CBB	Cambridge Brain Bank
CBD	Corticobasal Degeneration
CBS	Corticobasal Syndrome
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer Disease
CGT	Cambridge Gambling Task
CPFT	Cambridgeshire and Peterborough NHS Foundation Trust
CSF	Cerebro-Spinal Fluid

CT	Computed Tomography
CUH	Cambridge University Hospitals
DAB	Diaminobenzidine
DAT	Presynaptic Dopamine Transporters
DeNDRoN	Dementias and Neurodegenerative Diseases Research Networks
DLB	Dementia with Lewy Bodies
DMC	Disorders of Movement and Cognition
DMN	Default Mode Network
DMT	Disease Modifying Therapy
dMT	Dorsal Midbrain Tegmentum
DNA	Deoxyribonucleic Acid
DWI	Diffusion Weighted Imaging
EIF2AK3	Eukaryotic Translation Initiation Factor 2- α Kinase 3
EOAD	Early-Onset Alzheimer's Disease
EOS	End of Synthesis
ESR	Erythrocyte Sedimentation Rate
EIF2a	Eukaryotic Translation Initiation Factor 2A
FAB	Frontal Assessment Battery
FDG	Fludeoxyglucose
FTD	Frontotemporal Dementia
FTLD	Frontotemporal Lobar Dementia
fMRI	Functional Magnetic Resonance Imaging
GDS-15	15-item Geriatric Depression Scale
GLM	General Linear Model
GRF	Gaussian Random Field
GWA	Genome Wide Association
HADS	Hospital Anxiety and Depression Scale
HCS	Healthy Controls
HD	Huntington's Disease
HSB	Herchel Smith Building
IED	Intra/Extra-Dimensional
IFS	INECO Frontal Screening
IWG	International Working Group
IGT	Iowa Gambling Task
JDR	Join Dementia Research

LOAD	Late-Onset Alzheimer's Disease
lvPPA	Logopenic Variant Primary Progressive Aphasia
MAO-A	Monoamine Oxidase-A
MAO-B	Monoamine Oxidase-B
MAPT	Microtubule-Associated Protein Tau
MCI	Mild Cognitive Impairment
MCI ⁺	Mild Cognitive Impairment with positive β -amyloid
MDS	International Parkinson and Movement Disorder Society
MDS-PSP	International Parkinson and Movement Disorder Society-Progressive Supranuclear Palsy
MMSE	Mini Mental Stage Examination
MoCA	Montreal Cognitive Assessment
MOBP	Myelin-associated Oligodendrocyte Basic Protein
MPRAGE	Magnetization-Prepared Rapid Acquisition Gradient-Echo
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSA	Multiple System Atrophy
MTL	Medial Temporal Lobe
NFTs	Neurofibrillary Tangles
NIA	National Institute on Aging
NHS	National Institute Service
NHS	Normal Human Serum
NIA	National Institute on Aging
NIHR	National Institute for Health Research
NIMROD	Neuroimaging of Inflammation in Memory and Other Disorders
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NINDS-SPSP	National Institute of Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy
NNIPPS	Neuroprotection and Natural History in Parkinson Plus Syndromes
NPI	Neuropsychiatry Inventory
NRS	Normal Rabbit Serum
oMFC	Orbital Medial Frontal Cortex
OTS	One Touch Stocking of Cambridge
PBR	Peripheral Benzodiazepine Receptor

PBS	Phosphate Buffered Saline
PCA	Posterior Cortical Atrophy
PD	Parkinson's Disease
PDD	Parkinson's Disease with Dementia
PET	Positron Emission Tomography
PHFs	Paired Helical Filaments
PIB	Pittsburgh Compound-B
PIS	Patient Information Sheet
PPT	Pyramids and Palm Tress
prMFC	Posterior Rostral Medial Frontal Cortex
PSEN1	Presenilin 1
PSEN2	Presenilin 2
PSP	Progressive Supranuclear Palsy
PSPA	Progressive Supranuclear Palsy Association
PSPs	Postsynaptic Potentials
PSP- bvFTD	Progressive Supranuclear Palsy- Behavioural Frontotemporal Dementia
PSP-C	Progressive Supranuclear Palsy-Cerebellar
PSP-CBS	Progressive Supranuclear Palsy-Corticobasal Syndrome
PSP-F	Progressive Supranuclear Palsy-Frontal
PSP-PLS	Progressive Supranuclear Palsy-Primary Lateral Sclerosis
PSP-PGF	Progressive Supranuclear Palsy-Progressive Gait Freezing
PSP-OM	Progressive Supranuclear Palsy-Ocular Motor
PSP-P	Progressive Supranuclear Palsy-Parkinsonism
PSP-RS	Progressive Supranuclear Palsy Rating Scale
PSP-RS	Progressive Supranuclear Palsy-Richardson's Syndrome
PSP-SL	Progressive Supranuclear Palsy-Speech and Language
PSQI	Pittsburgh Sleep Quality Index
RAMB	Biotinylated Rabbit Anti-Mouse Antibody
RAVLT	Rey Auditory Verbal Learning Test
ROIs	Regions of Interest
RNA	Ribonucleic Acid
SD	Standard Deviation
SOC	Stockings of Cambridge
SP	Senile Plaques

SPECT	Single Photon Emission Computerized Tomography
SRT	Simple Reaction Time
SRTM	Simplified Reference Tissue Model
SST	Stop Signal Test
STX6	Syntaxin 6
SUVR	Standardized Uptake Value Ratio
SVM	Support Vector Machine
SWM	Spatial Working Memory
TAC	Time Activity Curve
TMT	Trial Making Test
TREM2	Triggering Receptor Expressed on Myeloid Cells 2
TSPO	Translocator Protein
VBM	Voxel-Based Morphometry
VWM	Verbal Working Memory
WAIS	Wechsler Adult Intelligence Scale
WBC	White Blood Cell
WBIC	Wolfson Brain Imaging Centre

Publications

I have authored or co-authored the following papers during my PhD studies. Sections of these articles' text have been reused in this thesis, and are referenced clearly throughout the text.

Chapter 1:

- Mak, E., Bethlehem, R. A. I., Romero-Garcia, R., Cervenka, S., Rittman, T., Gabel, S., Surendranathan, A., Bevan-Jones, W. R., Passamonti, L., **Vázquez Rodríguez, P.**, Su, L., Arnold, R., Williams, G. B., Hong, Y. T., Fryer, T. D., Aigbirhio, F. I., Rowe, J. B. & O'Brien, J. T. (2018). *In vivo* coupling of tau pathology and cortical thinning in Alzheimer's disease. *Alzheimer's & Dementia*, 10, 678–687. doi: 10.1016/j.dadm.2018.08.005
- Cope, T. E., Borchert, R., Rittman, T., Jones, P. S., Vatansever, D., Allinson, K., Passamonti, L., **Vázquez Rodríguez, P.**, Bevan-Jones, W. R., O'Brien, J. T. & Rowe, J. B. (2018). Tau Burden and the Functional Connectome in Alzheimer's disease and Progressive Supranuclear Palsy. *Brain*, 141(2), 550-567. doi: 10.1093/brain/awx347
- Surendranathan, A., Su, L., Mak, E., Passamonti, L., Hong, Y. T., Arnold, R., **Vázquez Rodríguez, P.**, Bevan-Jones, W. R., Brain, S., Fryer, T. D., Aigbirhio, F., Rowe, J. B. & O'Brien, J. T. (2018). Early Microglial Activation and Peripheral Inflammation in Dementia with Lewy Bodies. *Brain*, 141(12), 3415-3427. doi: 10.1093/brain/awy265

Chapter 2:

- Bevan-Jones, W. R., Surendranathan, A., Passamonti, L., **Vázquez Rodríguez, P.**, Arnold, R., Mak, E., Su, L., Coles, J. P., Fryer, T. D., Hong, Y. T., Williams, G., Aigbirhio, F. I., Rowe, J. B. & O'Brien, J. T. (2017). Neuroimaging of Inflammation in Memory and Related Other Disorders (NIMROD) study protocol: a Study of the Role of Brain Inflammation in Dementia, Depression and Other Neurological Illnesses. *BMJ Open*, 7(1). doi: 10.1136/bmjopen-2016-013187

Chapter 4:

- Passamonti, L.*, **Vázquez Rodríguez, P.***, Hong, Y. T., Allinson, K. S. J., Williamson, D., Borchert, R. J., Sami, S., Bevan-Jones, W. R., Jones, P. S., Arnold, R., Surendranathan, A., Mak, E., Su, L., Fryer, T. D., Aigbirhio, F. I., O'Brien, J. T. & Rowe, J. B. (2017). [¹⁸F]AV-1451 Positron Emission Tomography in Alzheimer's disease (AD) and Progressive Supranuclear Palsy (PSP). *Brain*, 140(3), 781-791. doi: 10.1093/brain/aww340

** These authors contributed equally to the completion of this work.*

Chapter 5:

- Passamonti, L.*, **Vázquez Rodríguez, P.***, Hong, Y. T., Bevan-Jones, W. R., Jones, P. S., Arnold, R., Surendranathan, A., Mak, E., Su, L., Fryer, T. D., Aigbirhio, F. I., O'Brien, J. T. & Rowe, J. B. (2018). [¹¹C](R)-PK11195 PET in Alzheimer's disease and progressive supranuclear palsy. *Neurology*, 90(22), 1989-1996. doi: 10.1212/WNL.0000000000005610

**These authors contributed equally to the completion of this work.*

Chapter 1

Introduction

1.1. Overview

This thesis examines the cognitive and pathological features of tau and microglial activation (neuroinflammation) contrasting two degenerative diseases: progressive supranuclear palsy (PSP) and Alzheimer's disease (AD). Although both of them are distinct in their clinical phenotype, both disorders have in common cognitive and behavioural changes, accumulation of tau aggregates, and chronic neuroinflammation. By contrasting, these two neurodegenerative disorders, we gain better insights into their pathogenesis than examination of either disorder alone. The joint examination of PSP and AD also raises issues regarding the research methods.

In the introduction, I set out the background of clinical, epidemiological, pathological, and genetic aspects of these disorders, in turn. I then highlight the need for a better understanding of PSP pathology *in vivo*. In order to address this, I compare PSP with another better understood tauopathy, AD. I set out why better methods were required to assess the pathology of both disorders *in vivo*, and to understand the link between pathology and functional change. I end with a summary of the objectives of the PhD, and structure of this thesis. Both diseases share important similarities in terms of pathology although there are clearly major differences too. They also raise comparable challenges and issues pertaining to diagnosis, clinical criteria and biomarkers. They are both largely sporadic disorders. There are emerging concepts in both diseases related to spread of pathology, prodromal states, and variation in phenotypes.

The methods used to study PSP and AD *in vivo* and *post mortem* have followed a very similar outline. In the following sections, I pick up on these themes to define and compare PSP and AD, not because they are ever to be confused clinically, but because of the advantage to have disease controls in investigating the new positron emission tomography (PET) and *post mortem* methods, and because of the similar needs of both in biomarker validation.

1.2. Clinical description

1.2.1. History

1.2.1.1. Progressive supranuclear palsy

Dr Steele, along with Dr Richardson and Professor Olszewski (1964), first described progressive supranuclear palsy (PSP). They included the clinical features of nine cases and the neuropathological examinations from seven of them. Though the symptoms quantitatively varied across patients, all of them showed a vertical supranuclear gaze palsy, spasticity of facial musculature, progressive axial rigidity, bulbar palsy symptoms including dysarthria and dysphagia, severe postural instability with early falls (usually backwards), prominent bradykinesia. These features are central to the phenotype of PSP, with the addition of a poor response to dopaminergic drugs (De Bruin and Lees, 1992; Litvan et al., 1996; Riley et al., 1994; Steele et al., 1964).

Cognitive impairment was significant in seven of the original nine cases with PSP, but PSP came to be considered as primarily a "movement disorder" and often managed, and taught, in the broader context of Parkinson's disease (PD). However, cognitive and behavioral changes appear early and often reach the severity of dementia at the late stage of the disease (Brown et al., 2010; Ghosh et al., 2009). Cognitive slowing, impulsive behaviour, difficulty in generating words, and severe apathy are the most common features (Steele et al., 1964; Lansdall et al., 2017). By contrast, other cognitive functions, such as language comprehension, recognition memory, and visuospatial functions remain relatively well preserved (Bak et al., 2005; Bak et al., 2010).

1.2.1.2. Alzheimer's disease

Alzheimer's disease (AD) is named after Dr Alois Alzheimer, who noticed severe changes in the cerebral cortex of a 50 year old woman who had died of a rapid mental illness (Alzheimer, 1906). Her symptoms included memory loss, language problems, sleep disorders, paranoia, and unpredictable behavior such as aggressiveness, confusion, and crying. For several decades, Alzheimer's disease was considered to be a rare, young onset dementia, resembling the case first described by Alzheimer. During this period, late onset cognitive decline and dementia was too often regarded as "senile dementia" or "normal ageing". The

recognition of AD-pathology as the major cause of late life cognitive decline developed in the 1970s and 1980s. At around this time, the concept of “Mild Cognitive Impairment” (MCI) grew, and its link to AD in many cases. In the last 20 years, the concept has developed of a progressive spectrum of impairment, from latent AD-pathology, through MCI to disabling clinical AD. Early criteria for MCI focused on the cognitive profile and severity, with selectively poor function in one cognitive domain (usually memory, but potentially another domain), or in some quarters, multi-domain MCI. However, such cognitively defined MCI left unanswered the questions of aetiology (AD pathology or not), and progression (stable impairments versus progression to clinical AD).

1.2.2. Clinical diagnosis criteria

1.2.2.1. Progressive supranuclear palsy

Early and reliable diagnosis of PSP remains a major clinical challenge, but is justifiably demanded by patients and their carers and is highly important for estimation of prognosis, appropriate allocation to therapeutic trials, and development of new diagnostic tools. Three separate clinical diagnostic criteria dominate the research literature. They differ in their sensitivity and specificity, particularly as the breadth of phenotype of pathologically proven PSP expands.

I. National Institute of Neurological Disorders and Stroke (NINDS) - Society for Progressive Supranuclear Palsy (SPSP) criteria (1996).

A detailed set of criteria for the medical diagnosis of PSP was established during the global workshop funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the Society for PSP (SPSP) (Litvan et al., 1996). The NINDS-SPSP criteria centre on the recognition of a gradual progressive condition beginning after age 40 with two main features: postural instability, and ocular motor dysfunction. The criteria specify three degrees of diagnostic certainty that there are shown in Table 1.

PSP diagnostic certainty	Definition
Possible	Either vertical supranuclear palsy or slowing of vertical saccades. Postural instability with falls within 1 year of disease onset.
Probable	Vertical supranuclear palsy. Postural instability with falls within 1 year of disease onset.
Definite	History of probable or possible PSP. Histopathologic evidence of typical PSP.

Table 1: The National Institute of Neurological Disorders and Stroke (NINDS) – Society for Progressive Supranuclear Palsy (SPSP) criteria (1996).

Abbreviations: PSP, Progressive Supranuclear Palsy.

The NINDS-SPSP criteria have a high specificity, and good sensitivity in contrasting classical PSP with controls and other movement disorders like PD. However, their sensitivity was poor with respect to non-motor phenotypes of PSP (Boeve et al., 2003; Han et al., 2010; Hassan et al., 2012; Josephs et al., 2006; Mochizuki et al., 2003); therefore, in recent years, the classical syndrome of PSP has become increasingly known as Richardson’s syndrome (PSP-RS). However, as shown in Table 2, it is clear that pathological cases of PSP can present with very different phenotypes.

PSP predominance type	Acronym	Reference
Ocular motor	PSP-OM	Litvan et al., 1996; Respondek et al., 2014
Parkinsonism resembling idiopathic Parkinson's disease	PSP-P	Birdi et al., 2002; Williams et al., 2005
Frontal lobe cognitive or behavioural presentations*	PSP-F	Han et al., 2010; Hassan et al., 2012; Litvan et al., 1996
Progressive gait freezing	PSP-PGF	Compta et al., 2007; Facheris et al., 2008; Williams et al., 2007
Corticobasal syndrome	PSP-CBS	Josephs et al., 2006; Ling et al., 2014; Tsuboi et al., 2005
Primary lateral sclerosis	PSP-PLS	Josephs et al., 2006; Nagao et al., 2012
Cerebellar	PSP-C	Iwasaki et al., 2013; Kanazawa et al., 2009
Speech and language disorders**	PSP-SL	Boeve et al., 2003; Josephs et al., 2006; Mochizuki et al., 2003

Table 2: Clinical variants of Progressive Supranuclear Palsy.

*Including behavioral variant Frontotemporal Dementia (bvFTD). **Including non-fluent/agrammatic Primary Progressive Aphasia (nfaPPA) and Apraxia of Speech (AoS). Abbreviations: PSP, Progressive Supranuclear Palsy.

Respondek and colleagues assessed the phenotypic spectrum in a multicentre cohort of 100 autopsy-confirmed PSP patients (Respondek et al., 2014). Their results showed that only 24% of cases were presented as PSP-RS, and more than half of the cases either showed overlapping features of several predescribed phenotypes, or features not fitting proposed classification criteria for PSP phenotypes. As a consequence of this, it emerged the need to review the current criteria.

II. Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) criteria (2005).

The opportunity to revise the clinical diagnostic criteria for PSP arose as a product of a large multicentre trial (Bensimon et al., 2008). The Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) criteria emerged because of the necessity of more sensitive diagnostic criteria for clinical trials of potential disease-modifying therapies in PSP and multiple system atrophy (MSA). The NNIPPS study was designed to assess the efficacy and safety of the drug

Riluzole, and its effect on trying to slow down PSP and MSA progression. The scale of the study and detailed follow-up, with pathology in 27% of cases gave the opportunity to revise the criteria. The principal difference was to relax the criterion of falls within the first year to falls within three years. However, the NNIPPS criteria were not designed to accommodate the rapidly expanding phenotype of PSP.

III. International Parkinson and Movement Disorder Society (MDS) - Progressive Supranuclear Palsy Study Group (PSP) criteria (2017).

The International Parkinson and Movement Disorder Society (MDS) and PSP Study Group criteria (Höglinger et al., 2017) was aiming for use in both clinical and research areas, including the diagnosis of early and alternative PSP syndromes for potential clinical trials. The MDS-PSP criteria are structured and operationalized in detail. The principles are:

- i. Clinical recognition of PSP pathology by keeping high diagnostic sensitivity for PSP-RS (Table 3).
- ii. Sensitivity for early and variant PSP profiles, including cognitive presentations.
- iii. High specificity with regard not only Parkinson’s disease (PD) but also corticobasal syndrome (CBS) attributed to corticobasal degeneration (CBD), and frontotemporal lobar degeneration presenting as behavioural frontotemporal dementia (bvFTD).
- iv. The role of biomarkers (MRI, PET), and genetics in the diagnosis of PSP.

PSP diagnostic certainty	Definition
Suggestive	Suggestive of PSP but not passing the threshold for possible or probable PSP. Suitable for early identification.
Possible	Substantially more sensitive but less specific for PSP. Suitable for descriptive epidemiological studies and clinical care.
Probable	Highly specific but not very sensitive for PSP. Suitable for therapeutic and biological studies.
Definite	Gold standard defining the disease entity.

Table 3: The International Parkinson and Movement Disorder Society (MDS)-Progressive Supranuclear Palsy Study Group (PSP) criteria (2017).
Abbreviations: PSP, Progressive Supranuclear Palsy.

A novel feature in these diagnostic criteria was the inclusion of a new group with cognitive and behavioural presentations, including *PSP-CBS*, *PSP-F* or *PSP-SL*. These share a high probability of underlying PSP or CBD pathology ('*probable 4R-tauopathies*'). Another interesting conclusion of the MDS-PSP was the exclusion of the tau-PET as it was not well enough understood at the time; therefore it was shown to be likely inadequate for diagnosis even if it has a huge potential for understanding mechanisms of the disease in research.

1.2.2.2. Alzheimer's disease

Alzheimer's disease (AD) is also defined clinically, with considerable variation in the criteria used in recent decades. These differences reflect both changing concepts of AD, and new technologies. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) criteria (McKhann et al., 1984) distinguished "probable AD" (with sufficiently severe cognitive deficits for dementia, including memory and at least one other domain) from definite AD (with *post mortem* or rarely biopsy neuropathology).

The International Working Group (IWG; Dubois et al., 2007) recognised three phases of AD identified by combining clinical features with biomarker investigations: *asymptomatic biomarker-positive*, *positive biomarkers and mild cognitive deficits*, and *dementia*. The core features of the new criteria were:

- i. AD diagnosis can be now made *in vivo* rather than depend on autopsy confirmation.
- ii. Greater certainty of AD-pathology (elimination of terminology of 'probable AD'), even prior to the onset of dementia.
- iii. Identification of AD pathology in asymptomatic patients, and symptomatic AD even in the absence of dementia.
- iv. Integration of pathophysiologic (e.g., amyloid- β , tau, and CSF measures) and topographic (e.g., MRI, PET, and FDG) biomarkers.

In parallel to the IWG, the National Institute on Aging (NIA) and Alzheimer's Association (AA) developed a set of criteria (Jack et al., 2011) that also recognised

three distinct stages of AD progression (Table 4). The NIA/AA criteria also incorporate biomarkers.

Stages	Features
Preclinical AD	Before symptoms appear but initial changes are present in the default mode network (DMN; Nobili & Morbelli, 2010).
MCI	Noticeable symptoms begin, and dementia is anticipated in three to four years (Albert et al., 2011).
Dementia due to AD	Daily function is impaired (Thies et al., 2013).

Table 4: The National Institute on Aging (NIA) and Alzheimer's Association (AA) criteria (2011).

Abbreviations: AD, Alzheimer's Disease; MCI, Mild Cognitive Impairment.

The IWG and NIA/AA have many similarities and important differences. The two sets of criteria concur in recognizing the onset of AD prior to dementia. The three phases of AD described in both sets of criteria embrace similar clinical entities but with different terminologies and emphases. IWG criteria emphasize a single clinico-biological approach that includes all symptomatic phases of AD and uses the same diagnostic framework across the spectrum of symptomatic disease, whereas the NIA/AA criteria apply different diagnostic approaches to the three phases. The NIA/AA MCI approach does not establish a continuity with the criteria suggested for preclinical AD in which both types of biomarkers are implied to be positive by the time the patient becomes symptomatic. A notable aspect of the NIA/AA criteria for the pre-dementia symptomatic phase of AD retains the concept of MCI (Albert et al., 2011), which is defined by using the original criteria of Petersen and colleagues (Petersen et al., 1999). Biomarkers are not required for the diagnosis of MCI, although the diagnosis of "MCI due to AD" requires biomarker support given the heterogeneous nature of the MCI syndrome (Ganguli et al., 2011; Jicha et al., 2006).

1.2.2.3. Summary

It is interesting to note the convergence in the current concepts and definitions of PSP and AD. Both research communities now recognise the degree of heterogeneity in terms of phenotype, as well as degrees of certainty and severity. Although early work focused on clinically manifest and disabling disease,

they have introduced operationalized terms for milder or prodromal stages of disease (PSP: suggestive of; AD; MCI).

There is increasing interest in the pre-manifest stages of disease. Dominantly inherited AD makes up less than 5% of the population of patients, but provides an important window into the early development of pathology, with PET and MRI evidence of disease 10-20 years before even MCI onset. In PSP, the lack of frequent autosomal dominant cases has made it harder to study the pre-manifest stage, but it seems likely that a long prodrome exists for PSP, as it also does for PD (Berg et al., 2014; Stern et al., 2012) and FTD (Cash et al., 2018; Rohrer et al., 2013; Rohrer et al., 2015). Currently, PSP criteria refer to PGF and syndromes suggestive of PSP, which although symptomatic not pre-manifest, aim to identify earlier stage disease than the classical descriptions.

In my thesis, I focus on patients with the classical PSP phenotype, also known as PSP-Richardson's syndrome (PSP-RS). They were initially diagnosed under the National Institute of Neurological Disorders and Stroke (NINDS) and the Society for Progressive Supranuclear Palsy (SPSP) criteria (Litvan et al., 1996) but reclassified according to the International Parkinson and Movement Disorder Society (MDS) and the Progressive Supranuclear Palsy Study Group (PSP) criteria (Höglinger et al., 2017).

In the last decade, the concept of AD has changed again, as reflected in the International Working Group (IWG) criteria. These retain the concept of clinical AD with deficits in multiple cognitive domains; but for MCI, they distinguish MCI with evidence of underlying AD pathology (e.g. from amyloid PET or CSF biomarkers), from MCI without biomarker evidence of AD pathology. They also formalize the concept of latent or pre-symptomatic AD. In this thesis, I focus on patients with probable AD pathology as defined by either (i) MCI with biomarker evidence of AD pathology, from amyloid PET; or (ii) clinically probable AD, with deficits in multiple cognitive domains sufficient to impair daily function (Morris, 1993).

1.2.3. Epidemiology

1.2.3.1. Progressive supranuclear palsy

The incidence of progressive supranuclear palsy in developed countries is approximately 1.2 per 100,000 per year, and the prevalence of investigator-diagnosed cases is calculated between 5.8-6.5 per 100,000 (Coyle-Gilchrist et al., 2016; Nath et al., 2001). Earlier studies estimated prevalence from 1.3 to 4.9 per 100,000 (Chiò et al., 1998; Schrag et al., 1999). The apparent increase may be due to methodological differences between studies and the low awareness and common misdiagnosis of PSP (Nath et al., 2001).

Patients with the classic PSP-RS phenotype typically develop clinical features after age 60, with an average of 7 years from symptom onset to death over (Golbe, 2014; Williams et al., 2005). The occurrence of classic PSP-RS rises abruptly with age, from 1.7 at 50 to 59 years to 14.7 at 80 to 99 years (Bower et al., 1997; Coyle-gilchrist et al., 2016). It has also been estimated that 2.9 years is the average time frame from symptoms to diagnosis (Dell'Aquila et al., 2013; Golbe, 1994). The other clinical phenotypes of PSP differ in their clinical course and disease duration (O'Sullivan et al., 2008; Respondek and Höglinger, 2016), but systematic data on differential survival are lacking.

1.2.3.2. Alzheimer's disease

Alzheimer's disease is the most frequent cause of dementia in Western societies corresponding to about 60% of cases (Forette & Boller, 1991; Kalaria et al., 2008). The global prevalence is estimated to be ~24 million, and expected to double by the year 2050 (Alzheimer's Association, 2017). Incidence rates for AD depends on the age of the population, and increases from 1% to 5% in the population over 65 years old, up to 20% to 25% in the population over 80 years old (Brickell et al., 2006; Rao et al., 2014). The rate of progression for Alzheimer's disease varies widely. On average, people with AD live eight to ten years after diagnosis, but there is a very wide range.

With the new 2007 IWG and 2011 NIA criteria, recognizing pre-dementia states of AD, and increased global awareness of dementia, it is likely that prevalence and survival estimates will be revised substantially. With the long asymptomatic prodromal, up to 20 years before symptoms arise (Craig-Schapiro

et al., 2010), future epidemiological studies will need to be clear about which phase of disease they refer to.

1.2.4. Genetics

1.2.4.1. Progressive supranuclear palsy

Progressive supranuclear palsy is largely a sporadic disease. It contrasts with some other forms of frontotemporal lobar dementia (FTLD) that have a high percentage of autosomal dominant disease. However, there are familial cases that resemble PSP in some of their clinical and pathological features. For example, Rojo's confirmed PSP pathology in four family members (Rojo et al., 1999), and likely autosomal dominant transmission. Ros described characteristic PSP features in four family relatives, confirming *post mortem* examination in one case (Ros et al., 2005), and at least 5 ancestors with related diseases. More commonly however, familial PSP-like syndromes are related to mutations in the microtubule-associated protein tau (MAPT) gene (Stanford et al., 2000). These are typically younger in onset than sporadic PSP. Less than 1% of PSP has a recognized autosomal dominant aetiology. However, genome wide associations (GWA) suggest a weak contributory role of several genetic variants to sporadic disease, including syntaxin 6 (STX6); eukaryotic translation initiation factor 2- α kinase 3 (EIF2AK3), and myelin-associated oligodendrocyte basic protein (MOBP) (Höglinger et al., 2011).

1.2.4.2. Alzheimer's disease

The majority of Alzheimer's disease cases are also sporadic (>90%) and present considerable heterogeneity in terms of risk factor profiles and neuropathological features. Around 10% of people with clinical AD are diagnosed before age 65 years (Prince & Jackson, 2009), and about 60% of those early-onset AD (EOAD) have a family history of dementia (Campion et al., 1999; Jarmolowicz et al., 2015; van Duijn et al., 1994), with 13% having a family tree indicative of autosomal dominant transmission (Campion et al., 1999; Jarmolowicz et al., 2015). Single genes causing early-onset AD were identified from linkage studies, including amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) (Sorbi et al., 2001; Tanzi & Bertram, 2005). Although a major breakthrough for understanding and modelling AD in research, these three genes contribute less than 5% of AD cases. In contrast, late-onset AD may be

determined by apolipoprotein E (ApoE ϵ 4), which has consistently been identified as a risk factor for death in the genome-wide association study (GWAS) of longevity (Deelen et al., 2011; Sebastiani et al., 2012). GWAS are used to identify common genetic variants associated with disease susceptibility.

Recent research has also shown a significant etiological role for immune-related processes and inflammation in AD. Triggering receptor expressed on myeloid cells 2 (TREM2) is expressed in microglia. Studies have shown that certain TREM2 variants have an important effect on AD, and that effect is similar to that of APOE (Jonsson et al., 2013; Neumann & Daly, 2013). They are all the risk factors of AD. TREM2 and ApoE ϵ 4 may interact synergistically in the preclinical stage of AD (Casati et al., 2018). GWAS results such as these, even though a huge success and of great importance to the field, still only explain a very small amount of the genetic risk in AD.

None of the cases in my study had familial PSP or familial AD in terms of their family histories, or were known to be positive for mutations in MAPT, APP, PSEN1, PSEN2, TREM2 or ApoE ϵ 4. Cases were not selected or excluded by genetic criteria.

1.3. Pathology

1.3.1. Microtubule associated protein Tau

Tau is a neuronal protein associated to microtubules (Weingarten et al., 1975). Whereas phosphorylation is essential for the normal function of tau protein, hyperphosphorylation has been proposed to play a crucial role of the aggregation of tau isoforms into intraneuronal filamentous inclusions (Buée et al., 2000; Martin, 2011). A growing body of evidence suggests that the generation of toxic tau aggregation represents the leading hallmark of the pathological process in several tauopathies, including PSP and AD (D'Souza and Schellenberg, 2005; Goedert & Jakes, 2005; Kaat et al., 2009; Martin et al., 2011; Spillantini et al., 1998); therefore it is of major interest as an indicator of neurodegenerative mechanisms.

Human tau is encoded by the MAPT gene that is located on chromosome 17q21 (Neve et al., 1986). This is transcribed and yields six different isoforms, lacking or containing exons 2, 3, and 10 by alternative splicing (Andreadis, 2005; Avila et al., 2004). Exon 10 contains a microtubule-binding region similar, but not identical, to other three additional microtubule-binding regions. Thus, isoforms containing exon 10, resulting in tau with four microtubule (tubulin)-binding regions (repeats) are known as tau 4R, whereas alternative spliced isoforms, lacking exon 10, are known as tau 3R. Ultrastructural examinations reveal that neurofibrillary tangles in PSP and AD have a different composition. Pathological tau deposits in PSP are composed of straight filaments with a diameter between 16-18nm of predominantly four repeats tau (Buée and Delacourte, 1999; Dickson et al., 1987). In contrast, AD is characterized by paired helical filaments of tau with a diameter between 10-20 nm of both three (3R) and four (4R) repeats in the microtubule-binding domain (Liu et al., 2001; Sisodia et al., 1990).

1.3.1.1. Progressive supranuclear palsy

Major advances have led PSP to be defined by intracerebral aggregation of the microtubule-associated protein tau, predominantly involving isoforms with four microtubule-binding repeats (4R-tau), in neurofibrillary tangles, oligodendrocytic coils, and, specifically, astrocytic tufts (Dickson et al., 2007; Hauw et al., 1994; Kovacs, 2014). Currently a neuropathological examination is the diagnostic 'gold standard' for PSP (Litvan et al., 1996; Dickson, 1999; Respondek, 2014). 76% of autopsy-confirmed PSP cases were patients with presentations other than PSP-RS (see 1.2.2. for more detailed information).

Macroscopically, the hallmarks of PSP is degeneration of the substantia nigra, the subthalamic nucleus and globus pallidus (Hauw et al., 1994; Kovacs, 2014), the superior cerebellar peduncle, and the dentate nucleus of the cerebellum (Hauw et al., 1994; Kovacs, 2014; Tsuboi et al., 2003). The substantia nigra and locus coeruleus usually displays marked pallor due to the loss of neuromelanin-containing neurons in these regions (Dickson et al., 2010) (Figure 1).

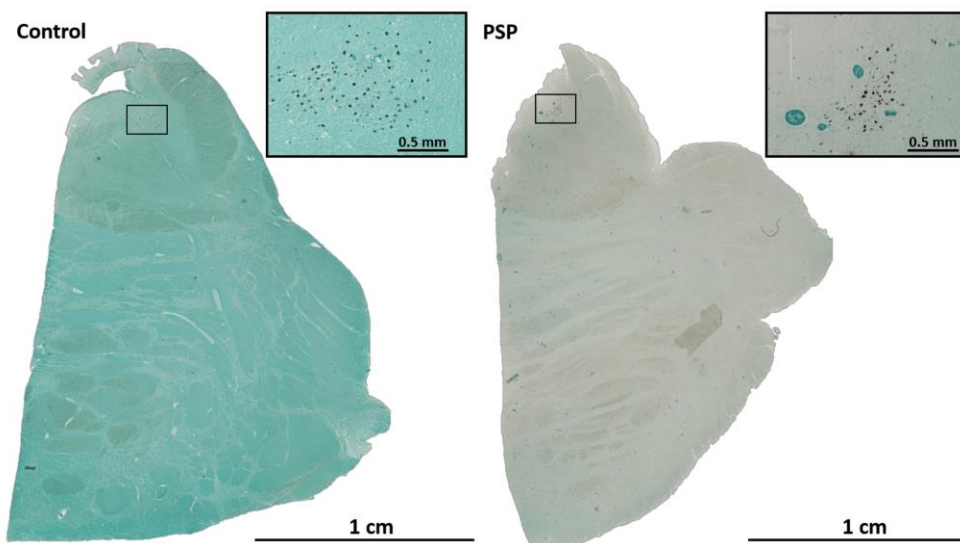


Figure 1: Midbrain of a PSP patient.

This image shows severe degeneration of the locus coeruleus, which reflects loss of neuromelanin and neurons (inset) due to tau pathology. Images provided by Dr Sanne Kaalund.

The overall brain weight (1170 ± 150 grams) can be within normal limits (Dickson et al., 2007) although many PSP cases have mild frontotemporal and precentral gyrus atrophy (Figure 2). The third ventricle and aqueduct of Sylvius may be dilated (Dickson et al., 2007).

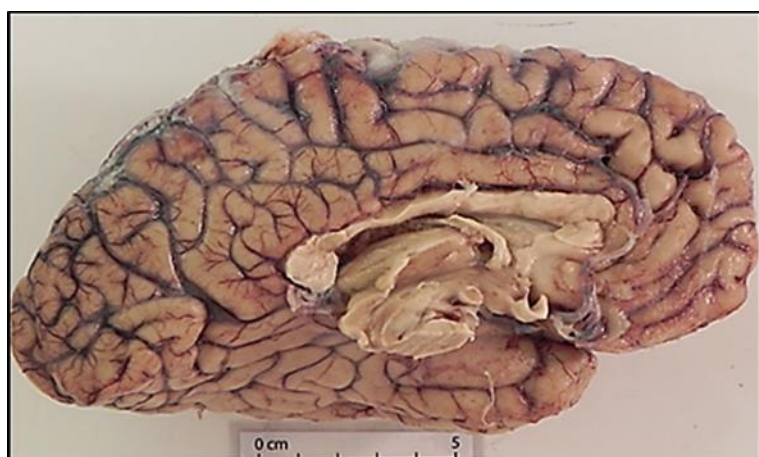


Figure 2: Midsagittal view of a Progressive Supranuclear Palsy brain.

The medial surface of the left hemisphere shows marked atrophy of the precentral gyrus, with lesser degrees of gyral atrophy of frontal and superior parietal areas. Image provided by Dr Kieren Allinson from the Cambridge Brain Bank.

Classical histopathological features comprise neuronal loss, gliosis, and globose neurofibrillary tangles (NFTs) affecting the basal ganglia, cortex and brainstem nuclei. Figure 3 shows the anatomical regions, which are most severely affected; in the basal ganglia these are the subthalamic nucleus, substantia nigra, and globus pallidus, whereas striatum is relatively spared. Affected brainstem regions include the superior colliculus, periaqueductal gray matter, oculomotor nuclei, pontine tegmentum and vestibular nuclei. Hypertrophy of the inferior olivary nucleus in the medulla oblongata may be also noted. The cerebellar dentate nucleus is frequently involved and may show clusters of degenerating presynaptic terminals around dentate neurons (Ishizawa et al., 2000). The cerebral cortex is less affected by neuronal loss and gliosis, although atrophy may be observed in the central fissure (Josephs et al., 2006), frontal cortex and angular gyrus (Schofield et al., 2012).

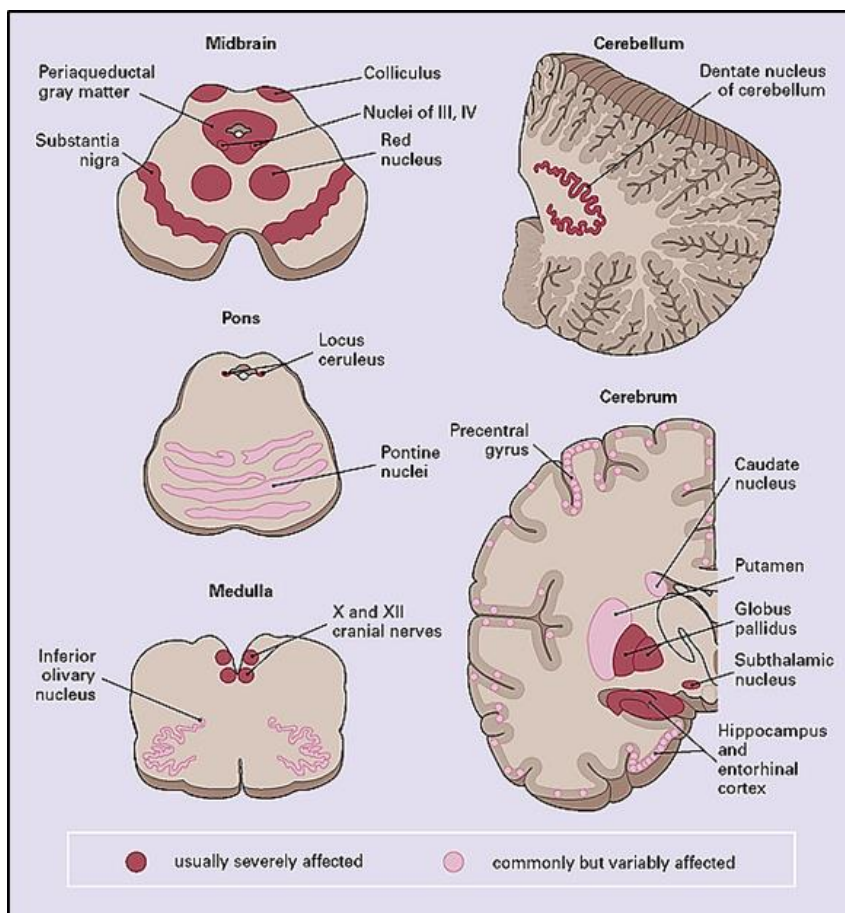


Figure 3: Pathological changes in Progressive Supranuclear Palsy.

This illustration represents the areas affected in Progressive Supranuclear Palsy, which can be divided into those that are consistently and severely affected, and those that are less consistently affected. Figure provided by Ellison & Love 2004, and reprinted with permission.

The neuropathological hallmarks are tau inclusions in glia cells, and neurons. With immunohistochemistry these inclusions can be seen as tufted astrocytes, coiled-bodies in the oligodendrocytes (Nishimura et al., 1992; Yamada et al., 1993), and neurofibrillary tangles in neurons. Glial tau inclusions are primarily localized in the motor cortex, striatum, and superior colliculus in the midbrain (Matsusaka et al., 1998). In addition, the coiled bodies are often found in the white matter, especially in the midbrain and the cerebellum (Braak and Braak, 1989). The neurofibrillary tangles are frequent in basal ganglia, diencephalon, brainstem and spinal cord. The NFTs and glial tau inclusions in PSP are made up of almost entirely 4R tau, which is different from the NFTs of AD, which is made up of 50/50 3R and 4R tau (Hauw et al., 1994). Additional neuronal tau pathology in the form of diffuse granular cytoplasmic immunoreactivity of neurons can be seen in the striatum, globus pallidus, substantia nigra, oculomotor complex, locus coeruleus, pontine base, and dentate nucleus (Figure 4).

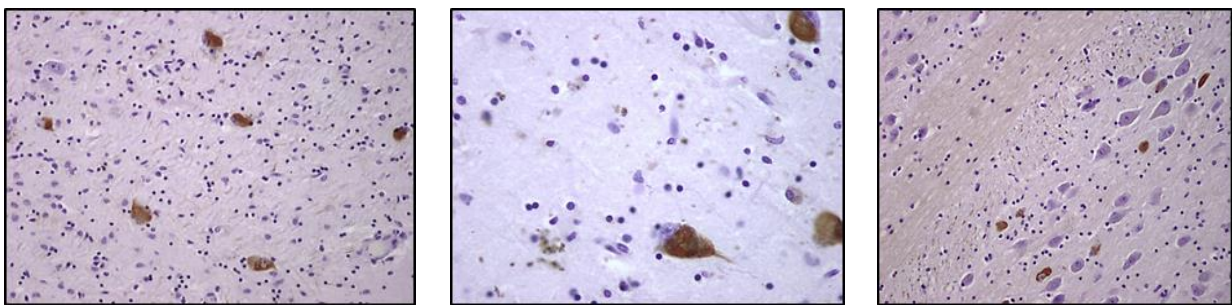


Figure 4: Tau-positive inclusion in Progressive Supranuclear Palsy brain.

Neurofibrillary tangles of tau are shown in brown in the oculomotor (left), substantia nigra (middle) and pontine base (right) brain structures in haematoxylin and eosin staining. Images provided by Dr Kieren Allinson from the Cambridge Brain Bank.

1.3.1.2. Alzheimer's disease

Like PSP, the unquestionable diagnosis of AD is still only possible during a *post mortem* examination. Certain neuropathological changes attributed as hallmark lesions of AD have been specifically associated to AD dementia, while clinical signs of dementia can be caused by several diseases (Albert et al., 2011; McKhann et al., 2011). Autopsy and neuropathological examination are therefore considered the 'gold standard' of AD diagnostics and allow for assessment of AD years to decades before clinical onset (Sperling et al., 2011).

Neuropathologically, AD is defined by the accumulation of two types of insoluble fibrous material: extracellular amyloid- β ($A\beta$) protein in the shape of senile plaques (SP), and NFTs made of abnormally and hyperphosphorylated tau protein. The manner in which NFT formation spreads to various brain areas during the course of AD follows a stereotyped pattern which has been used to define six neuropathological stages, the Braak stages (Braak & Braak, 1991) (Figure 5). Earliest NFTs are observed in the transentorhinal and entorhinal cortex (stages I and II; transentorhinal stages). A more extensive involvement of the entorhinal cortex and the formation of NFTs in sector CA1 of the hippocampus correspond to stages III and IV or to limbic stages. At stages I and II, patients are cognitively unimpaired whereas subjects with limbic stages III and IV may present with mild cognitive impairment. The main feature of stages V and VI is the development of abundant NFTs in neocortical association areas (isocortical stages). Subjects with stages V and VI meet the neuropathological criteria for the diagnosis of AD and are severely demented at the time of death. In contrast to NFTs, the density and distribution of SP follows a different and much more variable pattern. In general, they are first found in isocortical areas of frontal, temporal and occipital lobes (Braak & Braak, 1991; Price et al., 1991). Moreover, abundant amyloid deposits may also found in cognitively normal elderly subjects (Dickson et al., 1992).

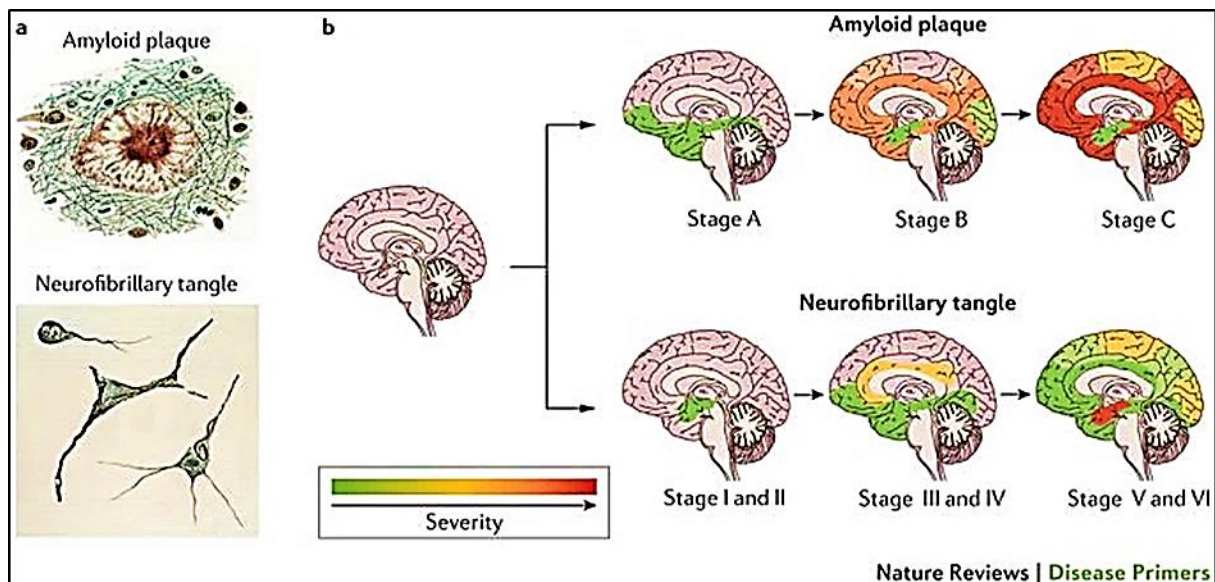


Figure 5: Pathological evolution of Alzheimer's disease.

a) Amyloid plaques and neurofibrillary tangles spread through the brain as the disease progresses b) Typical AD case with amyloid- β deposition (top row) and neurofibrillary tangles degeneration (bottom row). Figure provided by Masters et al., 2015, and reprinted with permission.

Tau has often been suggested as a facilitator of the downstream effects of β -amyloid in AD (Desikan et al., 2012; Jack & Holtzman, 2013). Moreover, it has been shown that tau pathology has a devastating effect on synaptic function (Beharry et al., 2014; Gómez-Isla et al., 1997; Spiess-Jones & Hyman, 2014), and relates more strongly to cognitive functions during life than does β -amyloid (Arriagada et al., 1992; Nelson et al., 2012; Rolstad et al., 2013). In addition, mapping the distribution of tau pathology may further our understanding of disease mechanisms in distinct clinical variants of AD, including posterior cortical atrophy (PCA) and logopenic variant primary progressive aphasia (lvPPA). For instance, in a recent case study of a patient with PCA using tau targeting PET ligand ($[^{18}\text{F}]\text{AV1451}$) was found to be more closely linked to hypometabolism and cognitive deficits than was amyloid- β (Ossenkoppele et al., 2015).

1.3.2. Amyloid

1.3.2.1. Progressive supranuclear palsy

PSP is characterized by the presence of tau isoforms with 4-repeats in the microtubule binding domain (Dickson et al., 2010), and is hence considered a 4R tauopathy (Baker et al., 1999). However, autopsy studies have identified the presence of concomitant amyloid- β proteins in the brains of some subjects with PSP (Dugger et al., 2014; Tsuboi et al., 2003). Whitwell and colleagues (2018) have shown that β -amyloid deposition occurs in a relatively high proportion of PSP subjects as an age-related phenomenon. Unlike in AD, however, there is little evidence that amyloid- β , and PHF-tau, play a significant role in neurodegeneration in PSP (Whitwell et al., 2018). As a consequence, amyloid is not considered further in my thesis as a major contributor to PSP.

1.3.2.2. Alzheimer's disease

The conventional view of AD is that much of the pathology is driven by an increased load of amyloid- β in the brain of AD patients. This view is known as the "amyloid cascade hypothesis", and suggests that the formation of amyloid- β fibrils ($\text{A}\beta$) is directly responsible for triggering tau phosphorylation and neurofibrillary tangle formation leading to neuronal death and dementia (Beyreuther & Masters, 1991; Hardy & Allsop, 1991). Detailed analysis of the amyloid- β hypothesis and its limitations is beyond the scope of my thesis, but, of relevance as it has been the basis of several major trials (as yet unsuccessful), e.g. solanezumab,

bapineuzumab. Their failure may be related to design and stage rather than a refutation of the amyloid- β hypothesis.

Given the correlation between the NFTs depositions in AD patients, with the degree of cognitive impairment, while the burden of amyloid plaque correlates poorly with AD severity (Arriagada et al., 1992; Buchhave et al., 2012), I focus on tau. Ossenkoppele has suggested that AV imaging (Ossenkoppele et al., 2015) alone would be enough for AD differential diagnosis. However, amyloid imaging is important for the AD arm of this thesis, in distinguishing the MCI cases with AD pathology from MCI cases without. This is critical. The literature has clearly indicated that a high proportion of people clinically diagnosed with MCI do not have AD pathology, and amyloid status predicts cognitive change over 2-5 years from MCI diagnosis (Flicker et al., 1993; Gauthier et al., 2006; Reisberg et al., 1982; Wisse et al., 2015). Therefore, my thesis uses amyloid imaging in MCI cases, and my analyses only include cases with positive amyloid scans, PiB has the longest history as a amyloid biomarker for *in vivo* use (Mathis et al., 2002), although [^{18}F] compounds are also now available, e.g. flutemetamol, florbetaben, florbetapir (Martinez et al., 2017; Ong et al., 2013; Thurfjell et al., 2012; Villemagne et al., 2011).

1.3.3. Neuroinflammation

A substantial amount of data supports the idea that inflammation may play a role in many neurodegenerative diseases, with activated microglia being the common denominator (Dheen et al., 2007; Wyss-Coray & Mucke, 2002). Although inflammation in the body is intended to be protective, an excessive inflammatory response can cause or contribute to tissue damage and disease pathology (Lyman et al., 2014). While it is clear that not all activation of microglia results in neuronal cell death, unregulated or overactive microglia are indeed capable of neurotoxic effects (Block & Hong, 2005). Activation of microglia may be induced by infectious agents, injury or chronic accumulation of abnormal protein aggregates (Rivest, 2009). The chronic release of inflammatory mediators, such as pro-inflammatory cytokines, reactive oxygen and nitrogen intermediates and arachidonic acid metabolites may promote the abnormal activation of microglia and astroglia, recruitment of inflammatory cells and destruction of normal neurons and synapses (Frank-Cannon et al., 2009).

1.3.3.1. Progressive supranuclear palsy

Microglial activation and inflammatory cytokine expression have been shown to be pathological features of PSP (Ishizawa & Dickson, 2001; Kreutzberg, 1996). Fernández-Bostrán and colleagues (2011) also showed different patterns of cytokine expression in each group, with significantly higher microglial burdens in the substantia nigra of PSP than in the control group. PET studies have also revealed evidence of activated microglia in relevant structures in the brain of PSP patients involving cortical and subcortical regions such as frontal lobe, caudate nucleus, pallidum, putamen, substantia nigra and midbrain (Gerhard et al., 2006).

1.3.3.2. Alzheimer's disease

Increasing evidence suggests that AD pathogenesis is not restricted to the presence of the two core pathologies, amyloid- β plaques and neurofibrillary tangles. Over the last decade, the presence of a chronic neuroinflammation attributed to activated microglia cells has emerged as a third core pathology in AD (Akiyama et al., 2000; Tuppo et al., 2005; Walters et al., 2016). The inflammatory response has now been observed in multiple studies of *post mortem* tissues of AD patient samples (Sudduth et al., 2013; Itakagi et al., 1989; Knezevic et al., 2018). The sustained activation of the microglia has been demonstrated to exacerbate both β -amyloid and tau pathology and may serve as a link in the pathogenesis of the disorder. It has also been suggested that, in AD, a key factor in the accumulation of β -amyloid throughout the brain is the failure of microglia to remove extracellular amyloid (Hickman et al., 2008; Theriault et al., 2015; Weiner et al., 2006). Indeed, in cortical tissue specimens from patients with AD, the microglia surrounding plaques are impaired at amyloid- β uptake (Frackowiak et al., 1992; Krabbe et al., 2013).

1.4. Imaging biomarkers of PSP and AD/MCI⁺

1.4.1. What does a biomarker mean?

Biomarkers are objective measures reflecting normal biological processes, pathological changes, or pharmaceutical responses to a therapeutic intervention (Atkinson et al., 2001). Biomarkers may have different properties and be relevant at different stages of the disease process. For instance, [¹⁸F]AV1451 radioligand

may be great to localize and quantify tau, but it is less able distinguish Tau from TDP-43 pathology especially in non-Alzheimer's settings such as in FTD (Bevan-Jones et al., 2017). In this way, distinct biomarkers are suited to distinct applications including prediction, diagnosis, phenotyping, prognosis, and stratification for clinical trials.

A full discussion of so-called 'wet' biomarkers (e.g., CSF or blood) is beyond the scope of this thesis. I will concentrate on the role of neuroimaging as a biomarker in neurodegenerative disease.

1.4.2. Neuroimaging of PSP and AD

The differential diagnosis of neurodegenerative disorders is largely based on careful clinical assessment, but imaging techniques may provide useful adjunctive information.

1.4.4.1. Structure

I. Magnetic resonance imaging (MRI)

The use of magnetic resonance imaging (MRI) has become a standard imaging technique in both clinical neurology and research. MRI enables the visualization of degenerative process most readily by showing atrophy in disease-specific patterns. Identifying such patterns not only facilitates the process of clinical diagnosis, but also provides insight into the underlying pathophysiologic mechanisms (Iwata, 2005).

The common MRI features of PSP (Höglinger et al., 2017) are atrophy of the most rostral midbrain, the midbrain tegmentum (MT), the pontine base and third ventricular dilatation with sparing of the cerebellum (Gimenez-Roldan et al., 1994; Savoiardo et al., 1989; Steele et al., 1964). The mid-sagittal T1 MRI sections in PSP patients show atrophy of the midbrain as seen in Figure 6-A. The morphologic features of midbrain atrophy create a specific architecture referred to as the 'Hummingbird' sign (Gröschelet al., 2006). The preserved volume of the pons forms the body of the bird while the atrophied midbrain forms the head and the beak extending towards the optic chiasm (Kato et al., 2003). The 'Hummingbird' sign is sensitive in diagnosing PSP (Kato et al., 2003) because it represents focal atrophy of the rostro-dorsal portion of MT where the neural

centers for vertical gaze specifically affected in PSP are located (Büttner-Ennever and Büttner, 1978). The same pattern of atrophy can be seen on T2-weighted axial sequences with thinning of the cerebral peduncles that result in a concave dorso-lateral midbrain margin (Berg et al., 2011). It is also possible to identify the wide cavity of the deep interpeduncular cistern on the ventral aspect of the pons (Pandey, 2012). These neurological changes combined give the classic radiological sign have become known as the 'Mickey Mouse' sign (Figure 6-B) (Itollikar et al., 2012).

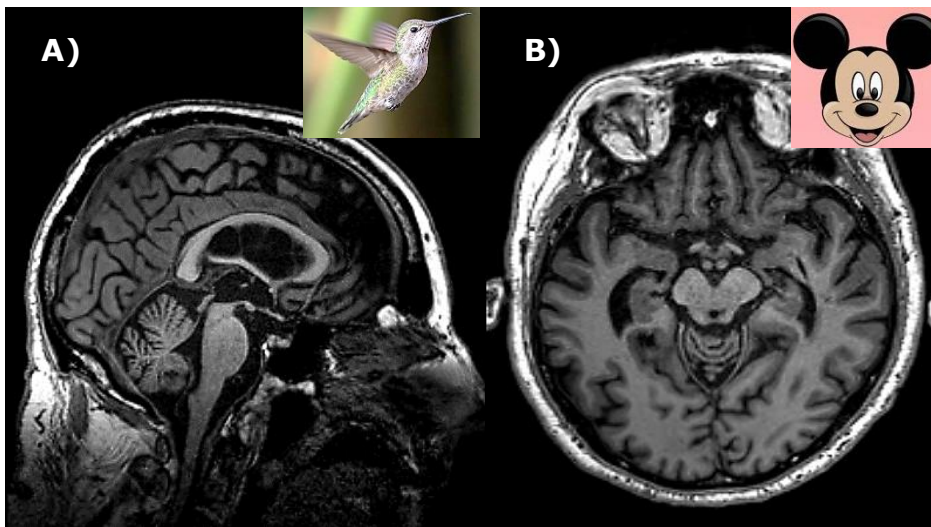


Figure 6: Magnetic resonance imaging of the Progressive Supranuclear Palsy brain.

A) On T1-weighted sagittal MRI image demonstrates abnormal morphology from shortened anteroposterior midbrain diameter, third ventricular dilatation, and flat or concave midbrain in PSP patients corresponding to a shape of a hummingbird (left). B) On T1-weighted axial MR image, the atrophic pattern associated with PSP creates the appearance of 'Mickey mouse' face resulting from concavity of the lateral margin of the midbrain tegmentum (right). Images provided by the NIMROD study.

The Alzheimer's Disease Neuroimaging Initiative (ADNI; Mueller et al., 2005) is a 5-year consortium study designed to assess the utility of various biomarkers for detecting early changes associated with MCI and AD, and predicting disease course over time, including cross-sectional and longitudinal neuroimaging biomarkers from structural MRI and PET, genetic factors, psychometric scores, and CSF markers. A number of studies utilizing MRI data from this cohort have been published. For instance, using both ROI and three-dimensional mapping techniques differences in structural MRI markers have been found between diagnostic groups (AD, MCI, health control) at baseline assessment, including atrophy in hippocampal and other medial temporal lobe (MTL) regions and enlarged ventricles in patients with AD and MCI (Chou et al.,

2009; Nestor et al., 2008; Risacher et al., 2009; Risacher et al., 2010). Hippocampal volume is sensitive and specific for predicting 1-year conversion from MCI to probable AD (Calvini et al., 2009; Misra et al., 2009). Longitudinal data from the ADNI cohort has been examined to identify change in brain volume using ROI and whole-brain structural change techniques. These studies have detected differences in annual change in whole brain volume, hippocampal volume, and ventricular volume as a function of baseline diagnostic group (Evans et al., 2010; Ho et al., 2010; McEvoy et al., 2009; Morra et al., 2009).

In my thesis, MRI is primarily used for analysis of PET data and has been published separately (Mak et al., 2018). The results showed that compared with the amyloid- β group, tau was increased in widespread regions whereas cortical thinning was restricted to the temporal cortices. Increased tau binding was strongly associated with cortical thinning in each amyloid- β group. Locally, regional tau was associated with temporoparietal atrophy.

II. Voxel-Based Morphometry (VBM)

MRI based measures of atrophy are regarded as valid markers of disease state and progression (Frisoni et al., 2010). The importance of the voxel-based morphometry (VBM) approach (Ashburner & Friston, 2000) is that it is not biased to one particular structure and gives an even-handed and comprehensive assessment of anatomical differences throughout the brain (Ashburner & Friston, 2001).

Since the first VBM based studies in PSP cohorts, many leading research groups have demonstrated subcortical and cortical atrophy (Brenneis et al., 2004; Josephs et al., 2008). Gray matter alterations have been reported in various brain regions, including the frontal/parietal/temporo-occipital lobes, insular cortex, basal ganglia, thalamus, midbrain, pontine, cerebellum, and medial temporal lobe (Agosta et al., 2010; Brenneis et al., 2004; Cordato et al., 2005; Ghosh et al., 2012; Padovani et al., 2006; Price et al., 2004; Saini et al., 2012; Takahashi et al., 2011; Whitwell et al., 2011). Also degeneration of white matter tracts have been identified (Padovani et al., 2006; Whitwell et al., 2011), particularly in the dentatorubrothalamic tract running from the dentate nucleus of the cerebellum, through superior cerebellar peduncles to ventrolateral thalamus.

Progression of atrophy measured by VBM in AD patients matches the stereotypical pattern of an increase in neurofibrillary tangles described by the Braak staging scheme (Braak & Braak, 1995). Atrophy is initially seen in medial temporal structures in early AD/MCI⁺. As AD progresses, atrophy of medial temporal structures becomes more prominent extending into lateral temporal cortex, parietal and frontal association cortex, and posterior cingulate gyrus, and precuneus. Precentral and occipital cortex and cerebellum are spared atrophy (Di Paola et al., 2007; Hirao et al., 2006; Matsuda et al., 2002; Ohnishi et al., 2001; Schmidt-Wilcke et al., 2009).

III. Diffusion Weighted Imaging (DWI)

Diffusion weighted imaging (DWI) is a form of MR imaging based upon measuring the random Brownian motion (Einstein, 1905) of water molecules within an imaging voxel of biological tissue (Hagmann et al., 2006). DWI enables the assessment of the water apparent diffusion coefficient (ADC), a measure of tissue water diffusivity, and may detect changes in the microstructural integrity of nervous tissue earlier than conventional T1- or T2- weighted MRI (Eastwood et al., 2003; Yoshikawa, 2004). Regional ADC (rADC) depends on the interactions between water molecules and the chemical environment as well as the structural barriers at the cellular and subcellular level hindering their motion *in vivo* (Le Bihan et al., 1992). A change of rADC is thought to reflect ultrastructural tissue damage (Paviour et al., 2007).

DWI has been assessed in gray and white matter structures in PSP-RS, showing elevated ADC values in putamen, caudate, globus pallidus, midbrain, SCP and prefrontal and precentral white matter (Nicoletti et al., 2008; Ohshita et al., 2000; Paviour et al., 2007; Tsukamoto et al., 2012). In contrast, previous studies in AD revealed increased diffusivity of water in the temporal stem, posterior cingulate, occipital and parietal white matter pathology compared to controls (Hanyu et al., 1998; Kantarci et al., 2005; Sandson et al., 1999).

1.4.4.2. Metabolic

I. 2-deoxy-2-fluoro-d-glucose (FDG)

The positron emission tomography (PET) tracer [¹⁸F]fluorodeoxyglucose (FDG) allows the measurement of glucose consumption. FDG is a glucose analog

with physiological properties almost identical to glucose, which is transported from the blood to the brain by a carrier-mediated diffusion mechanism. Measurement of glucose consumption with FDG-PET imaging allows us to identify disease-specific cerebral metabolic brain patterns in several neurodegenerative brain diseases at even an early disease stage (Mosconi & McHugh, 2011). Since the first FDG-PET study in man (Reivich et al., 1979), regional differences in cerebral glucose metabolism have been reported in various neurodegenerative brain diseases including parkinsonian syndromes (Teune et al., 2010).

For example, FDG-PET studies have shown hypometabolism in the midbrain, basal ganglia, thalamus and frontal lobes in PSP-RS (Hosaka et al., 2002; Juh et al., 2005; Mishina et al., 2004; Nagahama et al., 1997; Salmon et al., 1997; Yamauchi et al., 1997), with frontal involvement particularly targeting premotor, precentral and prefrontal regions (Garraux et al., 1999), and anterior cingulate (Klein et al., 2005). FDG-PET has been proven to be a promising modality for detecting functional brain changes in AD too, identifying changes in early AD, and helping to differentiate AD from other causes of dementia (Shivamurthy et al., 2015). In patients with early AD, the areas of glucose hypometabolism have been commonly observed in the parieto-temporal association cortices, posterior cingulate cortex, and the precuneus (Fukai et al., 2008; Minoshima et al., 1997).

II. DATscan

This type of imaging uses the radioactive compound, (^{123}I)ioflupane, which has a high binding affinity for presynaptic dopamine transporters (DAT), in particular the striatal brain region associated with parkinsonian syndromes such as PSP, Parkinson's disease (PD), and multiple system atrophy (MSA) (Benamer et al., 2003; Seifert & Wiener, 2013; Tolosa et al., 2007).

Examinations in PSP and MSA versus PD using (^{123}I)ioflupane SPECT have shown reduced striatal binding as a feature of all three disorders, although this was more significant in PSP with no statistical difference between binding in MSA versus PD cases (Antonini et al., 2003). A more recent (^{123}I)ioflupane PET study has reported that PSP cases had more prominent and earlier dopamine transporter loss in the anterior caudate compared with the MSA and PD cases (Oh et al., 2012). Whilst DATscan is not abnormal in AD (Piggott et al., 1999; Suzuki et al.,

2002), a common diagnostic conundrum is to differentiate AD from dementia with Lewy bodies (DLB) (Lopez et al., 2002; Mak et al., 2014) since they share clinical, neuropsychological and pathological features. In this situation a DATscan can be helpful in identify loss of dopaminergic neurons in DLB. As result, an improvement in clinical accuracy when AD is part of the differential diagnosis, DATscan seems to be worthwhile.

1.4.4.3. Neurophysiology

A key challenge to understanding the effects of neurodegeneration is to characterise the changing patterns of brain network connectivity, in response to both the disease and its treatment (Pievani et al., 2011; Seeley et al., 2009; Warren et al., 2012). Many studies examine macroscopic networks using task-free 'resting state' paradigms, in which coactivation of distributed regions, or coherence among spontaneous neural oscillators, is thought to reflect functional networks (Corbetta, 2012). In response to task demands or experimental conditions, these networks are rapidly reconfigured to create a dynamic neuronal workspace for cognitive processing (Kitzbichler et al., 2011).

I. Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) measures brain activity indirectly by detecting changes associated with blood flow (hemodynamic response) related to neuronal energy use (Ogawa & Sung, 2007). The primary form of fMRI uses the blood-oxygen-level dependent (BOLD) contrast. In addition to detecting the BOLD responses from activity due to tasks/stimuli (Huettel et al., 2004), the fMRI paradigm includes also resting-state fMRI (Fox & Raichle, 2007). These networks relate to structurally connected neuroanatomical systems (Greicius et al., 2009; Van Den Heuvel et al., 2009), and it has been shown that these networks are altered in subjects with neurodegenerative disease. For instance, PSP has been proposed as a network-based disorder (Chen et al., 2010; Gardner et al., 2013; Rittman et al., 2016; Salmon et al., 1997). It may be possible to link changes in networks to underlying genetic and molecular process. For example, Rittman and colleagues (2016) measured functional connectivity among gray matter regions during task-free fMRI in subjects with PSP, PD, and healthy controls. They showed that the regional expression of the MAPT gene in

health is associated with regions of high connectivity, which predict the functionally relevant loss of connectivity in PSP.

It may also be possible to investigate potential mechanisms of disease using network analysis and multimodal imaging. For example, Cope et al. assessed the relationship between tau burden and brain connectivity in patients with PSP, AD, and healthy controls (Cope et al., 2018). The results showed strongly connected nodes displayed more tau pathology in AD independent of intrinsic connectivity network. Conversely, in PSP, unlike in AD, those nodes that accrued pathological tau were those that properties associated with increased metabolic demand and a lack of trophic support rather than strong functional connectivity.

1.4.4.4. Electrophysiology

EEG/MEG is a functional neuroimaging technique for mapping brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain, using very sensitive magnetometers (Cohen, 1968). MEG studies have helped to identify neurophysiological network signatures of neurodegenerative diseases leading to dementia, characterized by altered spectral properties of oscillatory brain activity (Hughes et al., 2018; Hughes & Rowe, 2013; Sami et al., 2018). Using MEG it is possible to identify characteristics of altered connectivity that are the result of differential disruption of neuronal microstructure and synaptic physiology by AD versus frontotemporal lobar degeneration, including PSP (Sami et al., 2018).

1.5. Positron emission tomography (PET) and imaging biomarkers

Positron emission tomography (PET) is a non-invasive diagnostic imaging modality utilizing isotope-labelled molecular probes that bind to biomolecules with both high specificity and affinity. This is a technique that may enable longitudinal *in vivo* investigations (Matthews et al., 2012). The development of dedicated PET scanners suitable for imaging animals as small as mice (Bao et al., 2009; Cherry & Gambhir, 2001; Myers & Hume, 2002) has paved the way for researchers to investigate the suitability of PET tracers that could potentially enable visualization

of the density of markers associated with tau (Agosta et al., 2010; Bevan-Jones et al., 2017; Chien et al., 2014; Dickerson et al., 2014; Passamonti et al., 2017), and neuroinflammation (Fan et al., 2015; Gerhard et al., 2006b; Kumar et al., 2012; Venet, et al., 2009).

At the time I started my thesis in 2015, there were only a few studies on tau pathology and neuroinflammation using PET imaging biomarkers *in vivo* in patients with AD, and even less in PSP cohorts. In the last 4 years, the field of tau PET imaging has expanded greatly, which I review in more detail in chapters 4 and 6.

These biomarkers have the capacity to improve our understanding and management of these neurodegenerative diseases. In order to fulfill this potential, several important questions need to be answered. Among these, are the ability of ligands to quantify and localize tau and neuroinflammation *in vivo*, and ultimately track these changes longitudinally. They should also relate to clinical features and severity. In this section, I will start stating the literature of PET biomarkers for tau and inflammation in both PSP and AD at the time of beginning this project. I will then reference some of the research work that has been undertaken in the field since including other PET radioligands.

1.5.1. Tau pathology

The last two decades have been focused on developing novel radioligands for the non-invasive detection of β -amyloid deposition in the brain. While there are a number of PET ligands (Ashford et al., 2011; Herholz & Ebmeier, 2011; Vallabhajosula, 2011) designed to target β -amyloid plaques including [^{18}F]FDDNP (Shin et al., 2011), [^{11}C]PIB (Klunk et al., 2004), Flutemetamol (Vandenberghe et al., 2010), [^{18}F]Florbetaben (Barthel & Sabri, 2011), and [^{18}F]Florbetapir (Clark et al., 2011), there have been very few reports on imaging agents selectively targeting tau aggregates. This has led to a renewed international effort to develop selective tau radiotracers to achieve a more profound understanding of the pathophysiology of PSP, AD, and other neurodegenerative conditions in which tau plays a role. However, given that the ultrastructural form that tau aggregates adopt in AD is PHF, most of the efforts for developing selective tau imaging radiotracers were focused on PHF tau. It was not clear at that stage (and time) if

or how well these tracers will recognize the other conformations of tau aggregates present in non-AD tauopathies, such as PSP. Determining how tau-PET imaging behaves in patients with PSP was one of my main aims in my PhD thesis.

1.5.1.1. [¹⁸F]AV1451 (formerly called [¹⁸F]T807)

Since [¹⁸F]AV1451 (formerly called [¹⁸F]T807) was introduced for AD and MCI populations, many research groups have presented their data with this ligand. Back in 2014, Chien and his collaborators concluded that cortical [¹⁸F]AV1451 retention follows the known distribution of PHF tau in the brain, where higher [¹⁸F]AV1451 cortical uptake was significantly associated with increasing disease severity (Chien et al., 2014), consistent with *post mortem* studies showing the strong association of tau pathology with severity of dementia (Devous et al., 2014). Furthermore, Schöll's recent paper (2017) has concluded that patients with early-onset AD were more prone to tau aggregation in widespread neocortical regions, while the medial temporal lobe showed peak [¹⁸F]AV1451 uptake in late-onset AD (Schöll et al., 2017).

Although predominantly tested in AD and MCI patients, Dickerson and colleagues (2014) reported positive results when they tested [¹⁸F]AV1451 in patients with PSP. There was increased binding of the radiotracer in the brainstem, basal ganglia, subthalamic nucleus, cerebellum, and frontal cortex. This pattern of binding was consistent with the spatial distribution of tau in PSP. However, Smith et al. found higher [¹⁸F]AV1451 binding in the basal ganglia of PSP patients when compared with healthy elderly controls, but also increased with age in both controls and patients (Smith et al., 2017).

Other pathologies such as dementia with Lewy Bodies (DLB), PD and PD with dementia (PPD) have been also investigated using [¹⁸F]AV1451. The results showed that parietal [¹⁸F]AV1451 binding was increased in patients with DLB compared to controls and PD patients, while [¹⁸F]AV1451 uptake was reduced in the substantia nigra in PDD (Smith et al., 2018). The degree to which this reflects off-target binding, or concurrent AD pathology, remains controversial.

1.5.1.2. [¹⁸F]THK523, [¹⁸F]THK5105, and [¹⁸F]THK5117

Preclinical analyses of [¹⁸F]THK523 indicated that this tracer selectively labels tau pathology in the AD brain. For instance, autoradiographic and histofluorescence examinations of THK523 in human AD hippocampal brain sections have demonstrated its high affinity and selectivity for tau pathology (Fodero-Tavoletti et al., 2011). However, the preclinical data suggested that the pharmacokinetics and binding characteristics of [¹⁸F]THK523 did not reach the necessary optimal levels required for PET tracers. Villemagne's paper (2011) concluded that the tracer's uptake pattern in AD patients was not distinguishable from healthy control. Testing in PSP and CBD brain slices revealed no THK523 fluorescence, suggesting that the lack of binding in these straight filament tauopathies may be due to a specificity of THK523 for PHF tau conformation (Fodero-Tavoletti et al., 2014).

Despite [¹⁸F]THK523 compound optimization and [¹⁸F]THK5105 and [¹⁸F]THK5117 were developed (Okamura et al., 2013), it has been shown that the interpretation of [¹⁸F]THK523 PET images, with respect to tau, is confounded by the high monoamine oxidase-B (MAO-B) availability across the entire brain (Gulyás et al., 2011; Hirvonen et al., 2009; Ng et al., 2017).

1.5.1.3. [¹¹C]PBB3

In vitro and animal data indicated that [¹¹C]PBB3 binds reversibly to neurofibrillary tau tangles with high affinity and selectivity in AD (Hashimoto et al., 2014; Maruyama et al., 2013). Moreover, accumulation of [¹¹C]PBB3 was seen in the medial and lateral temporal cortices, and the frontal cortex—consistent with the Braak staging theory of AD (Maruyama et al., 2013).

[¹¹C]PBB3 recently underwent clinical testing in patients with PSP and the highest retention was associated with brain regions responsible for clinical symptoms (Sahara et al., 2017). Another study with PSP patients reported significantly higher binding of [¹¹C]PBB3 in globus pallidus, putamen, thalamus, subthalamus, midbrain, pons, and perirolandic areas compared with healthy controls (Shimada et al., 2016). When tested in a CBD patient, [¹¹C]PBB3 retention was high in the neocortex and subcortical structures. The signal was greater in the right basal ganglia as compared to the left, which was consistent

with the atrophy displayed on the patient's MRI (Maruyama et al., 2013). Another recent studies have reported significantly increased binding in the supplementary motor area, subthalamus, midbrain, and perirolandic areas of CBD patients compared with healthy controls (Sahara et al., 2017; Shimada et al., 2016).

The NIMROD study chose to use [¹⁸F]AV1451, which has most extensive evidence internationally so far. Subsequently, the severity of displacement of THK5351 by selegiline (acting on MAO-B), and lack of large scale data with PBB3, have left [¹⁸F]AV1451 the lead compound despite its controversies, while second generation ligands are developed and validated.

1.5.2. Inflammation

As well as tau pathology, neuroinflammation is increasingly recognized as a key factor in the pathogenesis of neurodegenerative conditions such as PSP and AD (Agostinho et al., 2010; Fernández-Bostrán et al., 2011; Wiley et al., 2009). Deficits in neuronal function and synaptic plasticity in these disorders are believed to be linked to microglial activation. Most of the PET ligands targeting presumed inflammatory targets that have previously been used in animals or humans, have labelled the 18kDa mitochondrial translocator protein (TSPO), formerly known as the peripheral benzodiazepine receptor (PBR) (Chen & Guilarte, 2008; Papadopoulos et al., 2006).

I will next focus on the most studied PET tracers binding to TPSO which are [¹¹C](R)-PK11195 (Roeda et al., 2012), and [¹¹C]PBR28 (Dedeurwaerdere et al., 2012; Hannestad et al., 2012).

1.5.2.1. [¹¹C](R)-PK11195

Using a first-generation TSPO tracer, [¹¹C](R)-PK11195, has been extensively used with PET to evaluate microglial activation in several neurologic disorders, such as stroke (Price et al., 2006), multiple sclerosis (Banati et al., 2000), Alzheimer's disease (Cagnin et al., 2001), Parkinson's disease (Gerhard et al., 2006b), corticobasal degeneration (Gerhard et al., 2004), and Huntington's disease (Pavese et al., 2006). Also, previous *in vivo* [¹¹C](R)-PK11195 PET studies

demonstrated an increased TSPO density accompanying normal aging of the brain (Kumar et al., 2012).

Microglial activation has been detected through *in vivo* studies in very early clinical stages of AD disease showing significant increased [¹¹C](R)-PK11195 binding in the entorhinal, temporoparietal, and cingulate cortex suggesting that neuroinflammation is a first sign in the pathogenesis of the disease (Cagnin et al., 2001; Okello et al., 2009). In addition, *post mortem* data have revealed increase microglia in the frontal cortex, parietal and occipital cortices (Fernández-Bostrán et al., 2011). These results agreed with another study, which combine *post mortem* and animal model. It has been suggested that PK11195 binding in AD *post mortem* tissue and transgenic mice *in vivo* correlates with the extent of TSPO expression in the hippocampus, frontal, temporal, and parietal cortices (Venneti et al., 2009). It has also been reported that TSPO ligand [¹¹C](R)-PK11195 detected neuroinflammation in patients with MCI (Cagnin et al., 2006).

Although the small numbers of PSP patients in the Gerhard's study (2006), their findings show a pattern of increased TSPO expression in PSP patients including cortical and subcortical areas that agrees with the known distribution of neuropathological changes (Dickson, 1999). Previous *post mortem* findings demonstrated that microglial burden in brain tissue were increased in the subthalamic nucleus and substantia nigra of PSP (Fernández-Bostrán et al., 2011) indicated a disease-specific topological relationship with the pathological hallmarks of PSP (Fernández-Bostrán et al., 2011).

1.5.2.2. [¹¹C]PBR28

The field of TSPO radioligands has been quickly extended, with several of so-called 'second-generation' TSPO ligands such as [¹¹C]PBR28 that appeared to be an improved radioligand (Briard et al., 2008). Animal research has concluded that [¹¹C]PBR28 appears to be much better tracer than [¹¹C](R)-PK11195 to image TSPO in monkey brain (Imaizumi et al., 2008). In human studies, Lyoo and his collaborators (2015) reported greater binding in AD patients than controls, particularly in temporal and parietal cortices. In addition, Kreis's group (2013) showed that neuroinflammation, indicated by increased [¹¹C]PBR28 binding, occurs after conversion of MCI to AD and worsens with disease progression.

1.5.3. Limitations of current PET ligands

1.5.3.1. Tau PET tracers

The discrimination of the existing tau-PET tracers for non-AD tauopathies is not well understood. Previous *post mortem* studies using [¹⁸F]AV1451 have shown high affinity for the AD tauopathy (Lowe et al., 2016; Marquié et al., 2015). However, [¹⁸F]AV1451 binding was not observed for the 4R tau aggregates such as PSP, where autoradiographical results indicate less robust staining (Josephs et al., 2006; Lowe et al., 2016). Another area of concern is related to non-specific tau PET binding in subcortical structures in healthy controls, which may suggest that the current tau radioligand could present off-target binding, such as to neuromelanin (Marquié et al., 2015). The possibility that tau PET ligands present non-specific binding is supported by a recent study showing that selegiline, a monoamine oxidase-B (MAO-B) inhibitor, significantly reduces brain AV1451 uptake (Hostetler et al., 2016). Another issue in tau PET quantification is represented by the time window adopted for standardized uptake value ratio (SUVR) semi-quantification. As for [¹⁸F]AV1451, the 80- to 100-minute SUVR, commonly adopted in previous research studies (Saint-Aubert et al., 2017), might be not optimal given the evidence for a further 30% increase of SUVR values up to 180 minutes from injection (Barret et al., 2017).

1.5.3.2. Microglial activation PET tracers

PET imaging with TSPO ligands are potential *in vivo* tools for tracking the progression of neuroinflammation in neurodegenerative disorders such as PSP and AD; however there are several limitations in the first-generation TSPO ligand such as [¹¹C](R)-PK11195, as Zhang and Dupont indicated in their papers. The main concerns are high non-specific binding, low brain penetration, and high plasma protein binding (Zhang, 2015), and such as limited availability of [¹¹C] ligands in clinical settings and low signal-to-noise ratio (Dupont et al., 2017), which may clarify the negative results in others studies using [¹¹C](R)-PK11195 (Schuitemaker et al., 2013; Wiley et al., 2009). Then a second generation of radioligands has been introduced, mainly to overcome some of the [¹¹C](R)-PK11195 limitations, such as [¹¹C]PBR28 that overall displays higher binding affinities (Dupont et al., 2017). However, it was shown that a single-nucleotide polymorphism (that is, rs6971) in the TSPO gene can considerably influence the uptake of the second-generation tracers, making genetic testing mandatory

(Owen et al., 2010, 2012); therefore [¹¹C](R)-PK11195 remains (so far) the best validated and diffusely adopted in human studies, as it does not require TSPO genotype evaluation.

1.6. Aims

My PhD aims to extend the current knowledge on tau pathology and the presence of neuroinflammation in PSP and AD in both *in vivo* and *post mortem*. The first objective was to define the clinical populations focusing on disease phenotype and severity (Chapter 2). Then I examined the cognitive features including the executive function, memory and behaviour, and motor impairments of patients in the NIMROD study, and how they relate to other measures of disease severity in PSP and AD/MCI⁺ (Chapter 3). I assessed the magnitude and patterns of [¹⁸F]AV1451 binding in PSP and AD/MCI⁺, and related them with cognitive impairment and disease severity (Chapter 4). In order to evaluate this *in vivo* work, *post mortem* studies were also completed. Finally, I measured neuroinflammation in terms of microglial activation and linked it with cognitive and motor decline (Chapter 5). *Post mortem* work was undertaken to validate these results (Chapter 4 and 5).

Chapter 2

Neuroimaging of Inflammation in Memory and Related Other Disorders (NIMROD) study protocol

Material in this chapter has been published as part of the full study protocol paper:

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2.1. Introduction

The Neuroimaging of Inflammation in Memory and Related Other Disorders (NIMROD) study was established to test the hypotheses that abnormal tau folding and neuroinflammation play critical roles in the pathogenesis of different forms of dementia and related disorders. For the purpose of my thesis, I will focus on the general research methods related to my study cohorts which were patients with PSP, AD and MCI (amyloid-beta positive, MCI⁺), and healthy control groups.

2.1.1. Contributions

Part of the recruitment of the disease groups (PSP, AD and MCI⁺) was conducted by our medical team during the participant's clinic visits. During the first year of my PhD, I recruited the majority of the PSP cohort while Mr Robert Arnold and Dr Bevan-Jones were in charge of enrolling participants for the AD and MCI⁺ groups through our database and via DeNDRoN and JDR. I also helped them increase the numbers of patients with AD in particular. Control participants were recruited by Mr Robert Arnold and Dr Ajenthan Surendranathan from healthy adults who have indicated a willingness to participate in dementia research via DeNDRoN or JDR. They also recruited healthy friends and non-blood-related family members of patients.

Chapter 3 includes neuropsychological data obtained under the NIMROD research study collected partly by me (mainly PSP cases) with normative and Alzheimer case data by Mr Robert Arnold, and Dr Richard Bevan-Jones. The analysis, interpretation and writing represent my own work.

Chapters 4 and 5 draw on data from a large NIMROD study team collaboration, with multiple researchers affiliated with the Wolfson Brain Imaging Centre (WBIC) at Cambridge University, and the departments of PET-CT and Pathology at Addenbrooke's hospital. The patients were recruited by me (PSP cases), and Mr Robert Arnold. PET data pre-processing was carried out by Dr Tim Fryer and Dr Young Hong. Analysis and interpretation was the result of joint work by Dr Luca Passamonti and myself. Dr Kieren Allison from the Department of Pathology provided specific brain tissue needed for both of my studies, which I took forward with advice and help from Dr David Wilkinson for the phosphor screen

autoradiography and immunohistochemistry in Chapter 4. Dr Robert Finchman and Mr Oliver Green kindly agreed to perform the staining in the *post mortem* tissue in Chapter 5. Dr Allinson also helped with the manual counting of the microglia in Chapter 5.

2.2. General research methods

2.2.1. Ethics statement

NIMROD study has been carried out in accordance with favourable opinions given by the NIHR National Research Ethic Service Committee, East of England - Cambridge Central, under reference 13/EE/0104. Conduct of the study was approved by the Cambridge University Hospital Trusts' Research and Development Departments.

2.2.2. Site and support

The School of Clinical Medicine at the University of Cambridge has led the study in collaboration with Cambridge University Hospitals National Health Service Foundation Trust (CUH). The funding has been provided by the National Institute for Health Research (NIHR) Biomedical Research Unit (BRU) in Dementia, PSP Association, and Wellcome Trust. CUH and University of Cambridge have been collectively acted as the sponsor for this study.

NIMROD has been based at the Addenbrooke's Hospital site in Cambridge. This site includes the Wolfson Brain Imaging Centre (WBIC) where Magnetic Resonance (MR) and Positron Emission Tomography (PET) imaging assessments have taken place, including the production of the PET radiotracers. Cognitive testing has mainly engaged in the CUH premises, in the adjacent Herchel Smith Building (HSB), and department of neurology at University of Cambridge, and/or in participants' own homes. However, as study subjects have been recruited from clinical services within CUH and Cambridgeshire and Peterborough NHS Foundation Trust (CPFT), as well as neighbouring Trusts throughout the region, assessments for some subjects have been undertaken at the location of their local services, or in the participants' homes, if most expedient and convenient to the participant.

2.2.3. Recruitment and selection of study participants

PSP, AD and MCI⁺ participants were recruited from cognitive disorder clinics in neurology, and related services at CUH and other trusts within the region including Cambridgeshire, Lincolnshire, Bedfordshire, Norfolk, Suffolk, Hertfordshire and Essex, where participants are willing to travel to Cambridge for imaging studies. Case registers held by the Dementias and Neurodegeneration specialty of the UK Clinical Research Network (DeNDRoN) and the Join Dementia Research (JDR) platform (www.joindementiaresearch.nihr.ac.uk) were other sources of participants. All participants had mental capacity and provided written informed consent.

2.2.4. Eligibility criteria

Participants were to be included in the study if they were aged over 50 and had sufficient proficiency in English to allow standardised cognitive testing. All participants except controls must have had a reliable informant who was able to complete questionnaires for informant-related scales and provide a background history in order to be included. Further specific inclusion criteria for each cohort are listed below under section 2.2.6. For the cohorts including participants with dementia, we had included only participants with mild-to-moderate dementia, as our experience is that severely impaired participants are highly unlikely to comply with the study protocol. Mild to moderate dementia were defined in this study as mini mental state examination (MMSE) > 12.

2.2.5. Exclusion criteria

Potential participants were excluded if they had a concurrent major psychiatric illness. They were also excluded if they had a contraindication to an MRI scan (e.g., permanent pacemaker), were unable to tolerate an MRI (e.g., claustrophobia) or if they had a comorbidity that limits their ability to take part in the study. Potential participants were also excluded if they had atypical or focal parenchymal appearances on MRI, which were not in keeping with their diagnosis. Systemic inflammatory disease was also an exclusion criterion (e.g. Rheumatoid arthritis, Crohn's disease, active psoriasis), or immunomodulatory medications (e.g., corticosteroids).

2.2.6. Study cohorts

Participants were enrolled into four separate study cohorts (Table 5).

I. Participants with progressive supranuclear palsy (PSP) fulfilled the NINDS-SPSP criteria (Litvan et al., 1996), modified by a relaxation of the falls criterion to falls within 3 years, rather than 1 year, as suggested by the NNIPPS-PSP study group (Bensimon et al., 2008). Our participants were later reclassified according to the MDS-PSP revised clinical diagnostic criteria for the classical PSP phenotype, also known as PSP-Richardson's syndrome (PSP-RS) (Höglinger et al., 2017).

II. Participants with Alzheimer's disease (AD) met the diagnostic criteria for probable AD pathology as defined by National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for AD (McKhann et al., 2011).

III. Participants with biomarker positive mild cognitive impairment (MCI⁺) were defined by MMSE > 24 with a memory impairment at least 1.5 standard deviations below that expected for age and education (Petersen et al., 1999). Amnesic MCI is a condition typically involving a degree of episodic memory deficiency beyond that expected for age and education but without dementia and where no alternative diagnosis may be made (Gross et al., 2017). The condition is recognised as a predictor, though not invariably so, of progression to AD (around 50% of subjects will develop dementia within 3 years). Individuals with MCI who do progress are assumed to have had undetected AD pathology before diagnosis with AD (Li et al., 2013). To select the subgroup with emerging symptoms of AD pathology, we included only people with amnesic MCI who also had biomarker evidence of β -amyloid, in terms of a positive Pittsburgh Compound-B (PiB) PET scan (SUVR > 1.5).

IV. Healthy control (HC) participants are defined as participants with MMSE scores > 26 and without (i) regular memory symptoms, (ii) signs or symptoms suggestive of dementia or (iii) unstable or significant medical illnesses.

	PSP	AD	MCI+	HC
Chapter 3 (Cognition)	20	9	6	13
Chapter 4 (Tau)	19	9	6	13
Chapter 5 (Inflammation)	16	9	7	13

Table 5: Study sample sizes for chapters 3, 4 and 5.

Abbreviations: PSP, Progressive Supranuclear Palsy; AD, Alzheimer’s Disease; MCI+, Mild Cognitive Impairment with positive β -amyloid; HC, Healthy Control.

All, except healthy control subjects, had a reliable informant able to complete questionnaires for informant-rated scales and provide background history. For analysis purposes, we combined patients with clinical diagnostic criteria for AD and MCI+ patients on the grounds that these two groups represent a continuum of disease (Okello et al., 2009).

2.3. Overview of protocol

Participants underwent an initial clinical assessment, including the collection of medical and demographic information (e.g., medication, smoking, alcohol and family history), and disease severity evaluation for PSP and AD/MCI+ group; a neuropsychological assessment battery described in detail below (tailored to each cohort). Participants made between two and four visits for imaging sessions depending on their group.

All participants had an MRI scan. HC participants underwent one PET scan either with [^{18}F]AV1451 or [^{11}C](R)-PK11195. MCI group had three PET scans: [^{18}F]AV1451, [^{11}C](R)-PK11195, and [^{11}C]PiB. For PSP and AD participants completed [^{18}F]AV1451 and [^{11}C](R)-PK11195 PET scanning sessions instead.

2.3.1. NIMROD assessments

NIMROD study used a combination of neuropsychological screening tests focused on global cognition and executive domain-based evaluations. Carer-reported assessments were also completed by the patient’s next of kin. While anxiety was explicitly measured through a questionnaire, mood and sleep disturbances were estimated using indirect measures instead. These evaluations are shown in Table 6, and did not include more than two hours of testing with

additional time for breaks as needed by all participants, and were done at the participant’s home or in our clinic.

Test format	Assessments	Cohort
Global cognitive tests	Addenbrooke's cognitive examination-revised (ACE-R) Mini mental state examination (MMSE)	PSP, AD/MCI+ and HC
Executive domain-based tests	INECO frontal screening (IFS) Trial Making Test (TMT) Stockings Of Cambridge (SOC)	PSP, AD/MCI+ and HC
Carer-reported questionnaires	Cambridge Behavioural Inventory-Revised (CBI-R) Neuropsychiatry Inventory (NPI)	PSP and AD/MCI+
Mood scale	Hospital Anxiety and Depression Scale (HADS)	PSP, AD/MCI+ and HC
Sleep disturbances (indirectly)	Cambridge Behavioural Inventory-Revised (CBI-R) Neuropsychiatry Inventory (NPI)	PSP and AD/MCI+

Table 6: Neuropsychological, carer-reported, mood, and sleep assessments.

Abbreviations: PSP, Progressive Supranuclear Palsy; AD, Alzheimer’s Disease; MCI+, Mild Cognitive Impairment with β -amyloid positive; HC, Healthy Controls.

Disease severity was also gathered in the NIMROD study but only in the patient group by the clinician before the MRI session (Table 7).

Disease severity	Assessments	Cohorts
Clinical	PSP-Rating Scale (PSP-RS)	PSP
Cognition	Clinical Dementia Rating (CDR) Rey Auditory Verbal Learning Test (RAVLT)	AD/MCI+ AD/MCI+

Table 7: Disease severity measures

Abbreviations: PSP, Progressive Supranuclear Palsy; AD, Alzheimer’s Disease; MCI+, Mild Cognitive Impairment with β -amyloid positive; HC, Healthy Controls.

2.3.1.1 Neuropsychology

I. Global cognitive function

Addenbrooke’s Cognitive Examination Revised (ACE-R) & Mini Mental State Examination (MMSE)

The Addenbrooke’s cognitive examination (ACE; Mathuranath et al., 2000) was developed to offer a brief test sensitive to the early stages of dementia, and differentiating subtypes of dementia including PSP, AD, frontotemporal dementia (FTD), and other parkinsonian syndromes (Bier et al., 2004; Dudas et al., 2005;

Galton et al., 2005; Lerner, 2006; Mathuranath et al., 2000). A few years later, Prof Mioshi and colleagues (2006) agreed to review the ACE to include some changes. As a result, ACE revised (ACE-R) was easier to administer, and most importantly, accomplished standards of a valid dementia-screening test, sensitive to early cognitive dysfunction. Like the ACE, the overall ACE-R score is 100 from 5 subscores, each one representing one cognitive domain including attention/orientation, memory, fluency, language and visuospatial (Mathuranath et al., 2000) displayed with more detail in Table 8. This new version introduced cut-off scores for the diagnosis of dementia of 88 (sensitivity = 0.94; specificity = 0.89) and 82 (sensitivity = 0.84; specificity = 1.00) (Mioshi et al., 2006). The ACE-R is relatively quick to administer as it takes approximately 15 minutes to complete in a clinical setting (Mioshi et al., 2006). Like the ACE, the ACE-R also incorporates the Mini mental state examination (MMSE; Folstein et al., 1975), so this score may be also be produced and 30 points is the maximum total.

II. Executive domain-based

INECO Frontal Screening (IFS)

Torralva and colleagues (2009) designed a tool aimed at detecting executive dysfunction: the INECO Frontal Screening (IFS). This specific screening test was designed to determine executive frontal dysfunction in patients with dementia. The executive domain encompasses several subtests that are in turn drawn from well-established clinical tests (Table 9).

Domains	Purpose	Maximum score
Attention and orientation	Orientation in time and space. Registration of three words (i.e., lemon, key, ball). Serial subtraction (i.e., 'could you take seven away from a hundred?' and/or backward spelling (i.e. WORLD)).	18
Memory	Recall of the three items (i.e., lemon, key, ball) after a long delay (10 minutes). Learn the name and address of a fictitious person and recall it at the end of the assessment. If the patient fails to recall one or more items, the recognition part offers three options from which the correct one can be selected. Four general knowledge questions (e.g., 'name of the current Prime Minister').	26
Verbal fluency	Participants are given one minute to produce as many unique words as possible starting with a given letter (i.e., letter 'P') or with a semantic category (i.e., 'animals').	14
Language	Follow an instruction (i.e., 'close your eyes', 'take the paper in your left hand. Fold the paper in half. Put the paper on the floor'). Writing a sentence. *Repetition of single words and/or phrases (e.g., 'statistician', 'no ifs, ands or buts'). **Naming 10 pictures of low frequency items (e.g., 'anchor', 'rhinoceros'). Answering four questions related to these items (e.g., 'point to the item with a nautical connection'). Reading five irregular words (e.g., 'pint', 'height').	26
Visuospatial	***Drawing of overlapping pentagons, and also a cube and a clock. Counting dots (4 arrays). Naming four incomplete letters.	16

Table 8: Addenbrooke's Cognitive Examination-Revised (ACE-R) domains and its testing purposes.

Note that items in bold are asked in the Mini mental state examination (MMSE) being the total score 30 points. *Repetition of 'no ifs, and or buts'. **Naming 'pencil' and 'watch'. ***Drawing of overlapping pentagons.

Test name	Purpose	Maximum score
Motor sequencing	Patient performs the Luria series: "fist, edge, palm" by initially copying the administrator. Repeating the series six times alone	3
Conflicting instructions	Variant of interference sensitivity task from the Frontal Assessment Battery (FAB; Dubois et al., 2000). Subject is asked to hit the table once when the administrator hit it twice, or to hit the table twice when the examiner hits it only once.	3
Go/No-Go	Stop-signal paradigm is most suitable for the study of response inhibition. When the examiner hits the table once, the participant should hit it once as well, but when the examiner hits twice, he/she should do nothing.	3
Backward digit span	Subject is asked to repeat a progressively lengthening string of digits in the reverse order (Wechsler, 1939). Two trials were given at each successive list length, from two to seven digits. If subject passes either trial at a given list length, the next length is administered (maximum six trials).	6
Verbal working memory (VWM)	Evaluates the same function as the previous test but with a slightly different load because the series is highly overlearned for most individuals. Patient is asked to list the months of the year backward, starting with December.	2
Spatial working memory (SWM)	Task is derived from the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1939) but simplified for the screening test. Examiner presents the subject with four cubes and points at them in a given sequence, then the subject is asked to repeat the sequence in reverse order. There are four trials, with sequences of two, three, four, and five cubes.	Number of correct completed sequences
Proverb interpretation	Three similarities (e.g. 'in what way a banana and an orange are alike?') or proverbs (e.g. 'a bird in the hand is worth two in the bush') are read to the subjects and they are asked to explain their meaning.	1
Verbal response inhibition	Task inspired by the Hayling test (Burgess & Shallice, 1997) measuring subject's capacity to inhibit an expected response. Examiner reads aloud six sentences, each missing the last word (e.g., 'it was raining cats and ...'), and participant is constructed to constrain the likely final word. In the first part, subject is read each sentence and ask to complete it correctly while in the second part, subject is asked for a completion word that is syntactically correct but unrelated to the sentence in meaning (e.g., 'apples').	2

Table 9: INECO Frontal Screening (IFS) subtests.

Trail Making Test (TMT)

The Trail Making Test (TMT) is a neuropsychological test of visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning (Arnett & Labovitz, 1995). It consists of two parts (A and B) in which the subject is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. The difference in times to complete the two parts of the test is usually attributed to the increased cognitive demands of Part B.

Stockings of Cambridge (SOC)

The Cambridge neuropsychological test automated battery (CANTAB; Robbins et al., 1994) is a widely used, validated, and reliable neuropsychological battery to assess cognitive dysfunction (Sahakian & Owen, 1992; Bozeat et al., 2000; Egerházi et al., 2007; Robbins et al., 2010; Wild et al., 2008). The CANTAB includes a variety of subtests, such as the Intra/Extra-dimensional (IED) set shift test, stop signal test (SST), stockings of Cambridge (SOC) test, spatial working Memory (SWM) test, and Cambridge gambling task (CGT), that evaluate executive function and measure decision-making ability, response inhibition, and working memory. Each sub-battery employs a touch-sensitive screen and begins with preliminary tests of sensorimotor function.

In this study, SOC task was administered to assess the executive function of the recruited patients. The SOC test examines spatial planning and motor control and is similar to the Tower of London test (Shallice, 1982). The participant is shown two displays. In each of these displays, three stockings - containing three coloured balls - are suspended from a beam. The two displays appear at the top and bottom of the screen. The balls are arranged in different patterns in each display. The participant must move the balls in the bottom display to copy the pattern shown in the top display. The balls are moved one at a time by selecting the required ball, then selecting the position to which it should be moved. The participant is instructed to make as few moves as possible to match the two patterns. Movement time is discounted in a distinct phase of task, in which participants simply copy moves made by the computer. The moves shown by the computer mimic the moves the participant made when originally solving the problem.

2.3.1.2. Carer-reported questionnaires

Carers' reports are also hugely important as they provide a better understanding of the cognitive, behavioural, and emotional symptoms seen often in PSP and AD patients. The role of carers can range from help with everyday tasks such as getting out of bed and personal care such as bathing, to emotional support; therefore their feedback and information are very helpful in describing patient disease progression. The two carer-reported scales used in NIMROD were Cambridge Behavioural Inventory Revised (CBI-R) and NPI that I briefly describe below.

Cambridge Behavioural Inventory - Revised (CBI-R)

The Cambridge Behavioural Inventory (CBI; Bozeat et al., 2000) comprises 81 items aiming to capture cognitive, behavioural and affective symptoms as well as activities of daily living (ADL). It evaluates 13 domains including memory, orientation and attention, everyday skills, self-care, mood, challenging behaviour, disinhibition, eating habits, sleep, stereotypic and motor behaviour, motivation, insight and awareness. The CBI rates the frequency of each particular domain scores from 0 (no impairment) to 4 (severe behavioural deficit). A few years later, Wedderburn and colleagues (2008) derived a shorter version of the CBI that is still detecting behavioural dysfunction as well as its ability to identify disease specific patterns of behaviour. The CBI-R has been reduced to 45 items, minimising administration time and making it more user friendly.

The results of the CBI-R in patients with PSP show the highest prevalence of behavioural symptoms, with high rates of apathy, stereotypic behaviours, disinhibition, and abnormal eating (Aarsland et al., 2001), while in AD, deficits in memory, orientation, everyday skills and self-care are more dominant, reflecting medial temporal and posterior association cortical pathology (Nagahama et al., 2006).

Neuropsychiatric Inventory (NPI)

The Neuropsychiatric Inventory (NPI; Cummings et al., 1994) was mainly designed to detect a range of neuropsychiatric features including delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition,

irritability, and aberrant motor activity. Two more domains have been added later on such as night-time behavioural disturbances and appetite and eating abnormalities (Cummings, 1997). A question is asked about each domain. If the responses to these questions indicate that the patient has problems with a particular domain of behaviour, the caregiver is only then asked all the questions about that domain, rating the frequency of the symptoms (4-point scale), their severity (3-point scale), and the symptom distress (5-point scale).

2.3.1.3. Mood and sleep disturbances

Several cognitive domains may be influenced by affective disorders. Anxiety and depression were assessed in NIMROD by Hospital Anxiety and Depression Scale (HADS), and indirectly measured sleep quality by CBI-R and NPI. Anxiety is uncommon in patients with PSP (Aarsland et al., 2001; Litvan et al., 1996), but the majority of AD patients report anxiety or manifest anxiety (Apostolova & Cummings, 2008; Spalletta et al., 2010) including worried appearance, fear of being left alone, tension, restlessness, and fidgeting.

The relationship between depression and dementia is complex. Depression is also one of the most frequent affective symptoms in subjects with AD. For example, Lyketsos (2002) has estimated in his study that 20% of persons with AD suffered from dysphoria whereas 20% percent suffered from irritability, another likely manifestation of depression. There is inconsistent evidence for depression in PSP, (Menza et al., 1995; Millar et al., 2006; Schrag et al., 2010) in part from the misinterpretation of somatic symptoms as depression.

Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS) was originally developed by Zigmond and Snaith (1983) and is commonly used to determine the levels of anxiety and depression that a patient is experiencing. The HADS is a 14-item scale in which seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0 to 3. Scores for each subscale (anxiety and depression) range from 0 to 21 with scores categorized as follows: 0-7 (normal), 8-10 (mild), 11-14 (moderate), and 15-21 (severe).

2.3.1.4. Disease severity

Disease severity can be described in many ways, e.g. severity of atrophy (MRI) or pathology (PET or *post mortem*). But, here I focus on clinical and cognitive severity scales that are in common use. Disease severity assessments differed between PSP and AD/MCI⁺ due to their different impairment-specific domains.

Progressive Supranuclear Palsy Rating Scale (PSP-RS)

The Progressive Supranuclear Palsy – Rating Scale (PSP-RS; Golbe & Ohman-Strickland, 2007) is a clinician-rated instrument to assess disability and severity of PSP. Administration of the scale takes approximately 15 minutes and it consists of 28 items dividing in six categories: history (daily activities), mentation (behaviour), bulbar, supranuclear ocular motor, limb motor, and gait and midline. The total score is ranging from 0 to 100, and with higher scores indicating more-severe disability or movement abnormality.

Clinical Dementia Rating (CDR)

The Clinical Dementia Rating (CDR) is a clinical global scale to indicate the severity of AD (Hughes et al., 1982), and also to validate the clinical diagnostic criteria for AD (Morris et al., 1988). The assessment consists of semi-structured interviews between the patient and informant to rate the subject's cognitive performance in memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care domains. The level of impairment for each domain scores from 0 (no dementia) to 3 (severe dementia).

Rey's Auditory Verbal Learning Test (RAVLT)

Rey's Auditory Verbal Learning Test (RAVLT; Rey, 1958) is a neuropsychological assessment to evaluate cognitive functions such as attention and concentration, and memory. Several studies have shown that an impairment in RAVLT scores reflects well the underlying pathology caused by AD. For instance, studies lead by Tierney (1994) and Estévez González (2003) have shown that the RAVLT score is an effective early marker to detect AD in individuals with memory complaints.

Briefly, the RAVLT consists of presenting a List A of 15 words that is read aloud to the participant, and then the participant is immediately asked to recall as

many as words from the List A. This procedure is repeated for five consecutive trials. After that, a new List B of 15 new words is read to the participant, who then is immediately asked to recall the words. After the List B trial, the examiner asks participant to recall the words from the first list (List A). After 30-minutes of interpolated testing (timed from the completion of List B recall), the participant is again asked to recall the words from the List A (delayed recall).

2.3.2. Neuroimaging

All participants (PSP, AD/MCI⁺ and healthy controls) were invited to undergo MR and PET imaging procedures, some of which were not conducted the same day. In this methods chapter, I summarise the protocol for acquisition and pre-processing of MRI and PET data. The analysis of methods and statistical inferences are described in detail in chapters 4 and 5, where the procedures necessary differ in relation to tau and neuroinflammation imaging. See sections 4.4.1 and 5.4.1 for details.

2.3.2.1. Magnetic resonance imaging data acquisition

Magnetic resonance imaging (MRI) scanning was carried out at the Wolfson Brain Imaging Centre (WBIC), and all images were examined by a consultant radiologist at Cambridge University Hospitals (CUH) to exclude unexpected brain abnormalities in recruits. Participants with significant abnormalities have been excluded from the study.

All participants underwent an MRI session acquired either on a 3 Tesla (3T) Siemens Magnetom Tim Trio or a Verio scanner (www.medical.siemens.com), using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) T1-weighted sequence (all groups) with TR = 2300ms, TE = 2.98ms, FOV = 240x256mm², 176 slices of 1mm thickness, and flip angle = 9°.

2.3.2.2. Magnetic resonance imaging data pre-processing

The T1-weighted images were used to facilitate tissue class segmentation (grey- and white-matter, together with cerebro-spinal fluid; CSF), and to allow inverse normalisation of template space regions of interest (ROIs) defined by modified Hammers atlas (Hammers et al., 2003) to subject MRI space. The left and right ROIs were combined. The brainstem of the atlas was split into midbrain ($z \geq 22\text{mm}$), pons ($z < -22\text{mm}$) and medulla oblongata ($z = -49\text{mm}$). Each T1

image was non-rigidly registered to the ICBM2009a template brain using ANTS (<http://www.picsl.upenn.edu/ANTS/>) with default settings, and the inverse transform was applied to the modified Hammers atlas (resliced from MNI152 to ICBM2009a space) to bring the ROIs to subject MRI space. For 30% of the study cases, ANTS default settings applied to T1 normalisation did not converge adequately so ANTS parameters were adjusted to normalise the skull stripped T1 to skull stripped template.

2.3.2.3. Positron emission tomography data acquisition

PET scanning was performed either on a GE Advance PET scanner (GE Healthcare, Waukesha, WI) at the WBIC or in the GE Discovery 690 PET/CT scanner at Addenbrooke's hospital. A 15 minutes $^{68}\text{Ge}/^{68}\text{Ga}$ 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.

The radiotracers were produced at the WBIC Radiopharmaceutical Chemistry laboratories with high radiochemical purity (>95%). ^{18}F AV1451, ^{11}C (R)-PK11195 and ^{11}C PiB were produced using the GE PETtrace cyclotron, a 16 MeV proton and 8 MeV deuteron accelerator. The production of ^{18}F AV1451 was based on the synthetic methods developed by Avid Radiopharmaceuticals and modified to use the GE TracerLab FX-FN synthesizer at WBIC. ^{11}C (R)-PK11195 were prepared using the 'Disposable' synthesis system or GE TRACER laboratory FX-C module. ^{11}C PiB was prepared using the GE TRACER laboratory FX-C module. All PET radiotracers information is displayed in Table 10.

^{18}F AV1451

^{18}F AV1451 radioligand was selected to evaluate the density of tau deposits. 370MBq of ^{18}F AV1451 was injected intravenously over 30 seconds at the onset of a 90 minutes scan, with emission data subsequently reconstructed into 58 contiguous time frame (18x5, 6x15, 10x30, 7x60, 4x150 and 13x300 seconds) images for kinetic analysis with the simplified reference tissue model.

[¹¹C](R)-PK11195

[¹¹C](R)-PK11195 radioligand aimed to measure the density of activated microglia as an indication of neuroinflammation. 500MBq [¹¹C](R)-PK11195 was injected intravenously over 30 seconds at the onset of a 75 minutes scan, with emission data subsequently reconstructed into 55 contiguous time frame (18x5, 6x15, 10x30, 7x60, 4x150 and 10x300 seconds) images for kinetic analysis with the blood volume corrected simplified reference tissue model.

[¹¹C]PiB

[¹¹C]PiB PET specifically binds fibrillar amyloid-beta plaques. It indicates the presence of AD pathology, and increases the likelihood that participants with MCI at baseline will clinically convert to AD over time (Okello et al., 2009). 550MBq of [¹¹C]PiB were injected as a bolus followed by PET imaging from 40-70 minutes post-injection, providing imaging data suitable for subsequent standardised uptake value ratio (SUVR) analysis.

PET radiotracer type	[¹⁸F]AV1451	[¹¹C](R)-PK11195	[¹¹C]PiB
Radioligand specific activity at the end of synthesis (GBq/μmol)	> 216	> 85	> 150
PET radioligand injection dose (MBq)	370	500	550
PET duration (minutes)	90	75	45
Frame images	58	55	1
Cohorts	PSP, AD, MCI and healthy control	PSP, AD, MCI and healthy control	MCI
Measurement	Tau pathology	Activated microglia	Amyloid-β deposits

Table 10: NIMROD PET radiotracers and study groups.

Abbreviations: PET, Positron Emission Tomography; GBq, Gigabecquerel; MBq, Megabecquerel; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's disease; MCI, Mild Cognitive Impairment.

More than one PET scan was required in patient groups to allow direct comparison between tau, amyloid, and inflammation. Two healthy control groups were recruited in order for them to prevent excessive radiation exposure; therefore one group took a [¹⁸F]AV1451 PET session and the other healthy cohort attended [¹¹C](R)-PK11195 PET scan instead.

2.3.2.4. Positron emission tomography data pre-processing

Each PET emission frame was reconstructed using the PROMIS 3-dimensional filtered back projection algorithm into a 128 x 128 matrix 157mm 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 random movements, dead time, normalization, scatter, attenuation, and sensitivity.

Each emission image series was realigned using SPM8 to correct for patient motion during data acquisition (www.fil.ion.ucl.ac.uk/spm/software/spm8) and create a mean image. In cases of very large movement (>10mm in translation or >10 degrees of rotation; this applied for 10% of the cases) the SPM co-registration function was used. Every dynamic frame after 1 minute post-injection was co-registered to the first minute frame. This process was repeated until the motion was corrected. The mean aligned PET image was rigidly co-registered to the MRI T1-weighted image using SPM8 and the inverse transformation applied to the modified Hammers atlas to put it in native PET space. Kinetic modelling was then performed on the motion-corrected time series in the cases of [¹⁸F]AV1451 and [¹¹C](R)-PK11195. Reference regions were required for the kinetic modelling analysis.

For [¹⁸F]AV1451, the reference region was 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 PSP or AD/MCI⁺ (Dickson et al., 2010; Okello et al., 2009; Schöll et al., 2016; Schwarz et al., 2016; Williams et al., 2007). This was confirmed in our *post mortem* cases (see section 4.5.2.3.).

It is difficult to identify suitable reference region for [¹¹C](R)-PK11195; therefore, supervised cluster analysis was used to determine the reference tissue time-activity curve (Yaquub et al., 2012). Supervised cluster analysis was designed to extract pure grey matter signal. Yaquub and colleagues (2012) demonstrated that the supervised cluster analysis with 4 kinetic classes (grey, white, blood and high specific binding (HSB)) performs better than 6 kinetic classes (grey, white, bone, soft tissue, blood and HSB). In order to extract the reference time activity curve (TAC), each voxel TAC of the scan was analyzed using the set of predefined kinetic classes to find the scaling coefficient of each kinetic class, so that the total

TAC is equal to the sum of these scaled kinetic classes. A non-negative least squares algorithm (Turkheimer et al, 2007) was used for finding the scaling coefficients. Scaling coefficients of each kinetic class were stored in coefficient maps showing their spatial distribution. Finally, to extract the reference tissue TAC, the coefficient map from the (normal) grey-matter kinetic class was used to calculate the weighted average, as follows:

$$C_t^{ref}(t) = \left(\frac{\sum_{i=1}^N w_i^{grey} \times C_t^{voxel}(t)}{\sum_{i=1}^N w_i^{grey}} \right)$$

where, N is the number of voxels, C_t^{ref} the resulting reference tissue TAC, w_i^{grey} the grey scaling coefficient and C_t^{voxel} the voxel TAC.

[¹⁸F]AV1451 and [¹¹C](R)-PK11195 BP_{ND} 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). CSF partial volumes were calculated by division with the mean ROI probability (normalized to 1) of grey and white matter segments, each smoothed to PET resolution. To test whether correction for CSF affected the main results, we repeated all the [¹⁸F]AV1451 and [¹¹C](R)-PK11195 PET analyses using data not corrected for CSF (see chapter 4, sections 4.4.1.5. and 4.5.1.2., and chapter 5, sections 5.4.1.5. and 5.5.1.2).

[¹¹C]PiB data were quantified using standardized uptake value ratio (SUVR) by dividing the static image by mean radioactivity concentration of the reference tissue region defined by >90% of the superior cerebellum. [¹¹C]PiB data were treated as dichotomous measures (i.e., positive or negative MCI) and considered MCI positive if the average SUVR value across the cortical ROIs was > 1.52 (Hatashita and Yamasaki, 2013).

2.3.3. Neuropathology

2.3.3.1. Human brain tissue samples preparation

Post mortem brain tissue from three subjects (one PSP case, one AD patient and one control with similar age) from the Cambridge Brain Bank (CBB) was included in this study. The phosphor screen autoradiographic and immunohistochemical analyses were conducted in different cases from those included in the [¹⁸F]AV1451 and [¹¹C](R)-PK11195 PET *in vivo* studies. 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 frontal cortex, anterior hippocampus, midbrain and substantia nigra, and basal ganglia (globus pallidus and putamen). 20µm thick sections were cut in a cryostat (Leica CM30505 S Research Cryostat) mounted on Thermo Scientific superfrost plus slides and used for [¹⁸F]AV1451 and [¹¹C](R)-PK11195 PET phosphor screen autoradiographies. In terms of immunohistochemistry work, phosphorylated-tau immunoreactivity (AT8) and tinctorial stain for neuromelanin (Masson-Hamperl stain) were applied in the [¹⁸F]AV1451 project, while microglia immunoreactivity (HLA-DR antibody) was used in [¹¹C](R)-PK11195 PET instead.

Chapter 3

Cognition in progressive supranuclear palsy and Alzheimer's disease/MCI⁺

3.1. Introduction

Progressive supranuclear palsy (PSP) and Alzheimer's disease (AD) are both progressive disorders, in the context of aging. The cognitive profiles of PSP and AD have been reviewed previously, including executive, memory, language, behavioural, and emotional symptoms and signs (Bak et al., 2010; Blennow et al., 2006; Gerstenecker et al., 2013; Ghosh et al., 2009; Hodges et al., 1990; Levy et al., 1996; Litvan et al., 1996; Mathuranath et al., 2000; Milberg & Albert, 1989; Moreira et al., 2017; Perry & Hodges, 1999; Pillon et al., 1986; Radakovic et al., 2017; Reisberg et al., 1987; Robbins et al., 2010; Rosser & Hodges, 1994; Sahakian, 1990; Satler et al., 2017; Spalletta et al., 2010; Steele et al., 1964). In this chapter, I will examine the executive function, memory, and behaviour of patients in the NIMROD study, and how they relate to other measures of disease severity in PSP and AD/MCI⁺, ahead of chapters 4 and 5's analysis of the pathological substrates for cognitive and motor decline.

It is important to point out that some of these cognitive domains may be influenced by mood, anxiety or by sleep disruption. The relationship between depression and dementia is complex. There is substantial evidence supporting that depression is a common symptom in PSP, although rates vary among studies (Menza et al., 1995; Millar et al., 2006; Schrag et al., 2010). Depression is also one of the most frequent affective symptoms in subjects with AD. For example, Lyketsos estimated in his study that 20% of persons with AD suffered from dysphoria whereas 20% percent suffered from irritability, another likely manifestation of depression (Lyketsos et al., 2002). Neuropsychiatric symptoms such as anxiety and irritability are less common in patients with PSP (Aarsland et al., 2001; Litvan et al., 1996). In contrast, the majority of AD patients report anxiety signs (Apostolova & Cummings, 2008; Spalletta et al., 2010) including worried appearance, fear of being left alone, tension, restlessness, and fidgeting.

Disrupted sleep and alertness are increasingly being recognized as common behavioural symptoms in neurodegenerative disorders that negatively affect the quality of life and safety of patient. They may suffer with initiating and maintaining sleep (Di Trapani et al., 1991) or with other disorders such as central apnoea (Walsh et al., 2017) and rapid eye movement (REM) (Lee, 1991). Another sleeping abnormalities include the difficulty with sleep/wake regulation that can lead to

profound sleep deprivation (De Bruine et al., 1996). Abnormalities in sleep architecture and insomnia are more frequently described in PSP than in the other neurodegenerative disorders (Abbott & Videnovic, 2014). Sleep disturbances, in particular, subjective insomnia and daytime sleepiness, have been described in 60% of PSP baseline assessments (Arena et al., 2015). It takes longer for PSP patients to fall asleep, and they wake more frequently during the night, resulting in a shorter time asleep. Nevertheless, patients with AD often have nocturnally disrupted sleep. Bliwise's naturalistic study (1990) showed that sleep patterns might present as agitation during the night-time hours, and excessive daytime napping. His results also suggested decreased REM sleep in proportion to the extent of their dementia (Bliwise et al., 1990).

3.1.1. Executive function

Executive function is a term that covers a range of the cognitive processes including planning, attentional set-shifting, inhibition, and fluency. Executive function is often impaired with PSP (Gerstenecker et al., 2013; O'Keeffe et al., 2007), despite the emphasis on motor deficits in the clinical diagnostic criteria of PSP (Höglinger et al., 2017). Patients who develop PSP may have early and prominent impairments in executive functions. This is commonly attributed to early changes in frontal lobe structure and frontostriatal connections (Gerstenecker et al., 2013; Hodges & Miller, 2001; Sitek et al., 2015). However, Ghosh and his colleagues (2013) found little deterioration over 12 to 18 months after diagnosis, suggesting that executive cognitive decline is an early feature of PSP (Ghosh et al., 2013). In contrast, patients with AD/MCI⁺ present milder executive dysfunction, at least during the early stages (Torralva et al., 2009).

3.1.1.1. Planning

Difficulties in planning tasks and organization occur in 50% to 80% of PSP (Millar et al., 2006). Robbins and colleagues (1994) undertook an early study of executive function in PSP, using the Cambridge Neuropsychological Test Automated Battery (CANTAB), including Stockings of Cambridge Task (SoC), analogous to the Tower of London task (ToL; Shallice, 1982). PSP patients had slowing of cognitive processes, increased initial thinking times and poor ability to solve problems at the first attempt (Robbins et al., 1994). AD patients are also

impaired in planning ahead and executing predetermined plans (Franceschi et al., 2007; Hughes et al., 1982; Satler et al., 2017). The difficulties encountered when taking the ToL test were not restricted to the number of required movements, and in contrast to PSP, reducing the number of moves did not improve AD patient performance.

3.1.1.2. Set-shifting

Set-shifting refers to the ability to shift attention between one aspect of a task or environment and another. Although simple tests of attention and orientation are typically normal in PSP patients, attention set-shifting is considerably reduced (Dubois et al., 2000; Robbins et al., 1994). Set-shifting is impaired in the Trail Making Test (TMT; Arnett & Labovitz, 1995) and Wisconsin Card Sort Test (WCST; Berg, 1948) with fewer categories sorted and more perseverative errors in PSP (Monza et al., 1998; Pillon et al., 1991). Although amnesic deficits are emphasized in AD, attentional control capacities including set-shifting are impaired (Amieva et al., 2004; Belleville et al., 2003; Bondi et al., 2002; Parasuraman & Haxby, 1993; Perry & Hodges, 1999). Amieva's and Bondi's studies have reported that patients with AD are impaired in TMT and WCST tasks. In particular, they found a larger number of perseverative errors in AD subjects than in controls.

3.1.1.3. Inhibition

Inhibition and inhibitory control are core executive functions. The definitions of inhibition may vary depending on whether the conceptual framework in which inhibitory processes are described such as selective attention (Neill, 1977), visual attention (Posner & Snyder, 1975), working memory (Zacks & Hasher, 1994) or language (Gernsbacher & Faust, 1991), with inhibitory processes acting on thoughts, verbal responses, visual processing, sounds, actions, etc. PSP and AD both impair inhibitory mechanisms. Inhibitory deficits are evident in PSP, with motor recklessness (e.g. inappropriately fast or reactive standing, with high risk of falls), food cramming even during coughing or choking. Their response inhibition is impaired and may lead to impulsivity, which can occur even in the presence of profound akinesia and rigidity (Burrell et al., 2014; Wedderburn et al., 2008). For example, Zhang and colleagues' study (2016) examined the mechanisms of PSP cognitive impairments underlying disinhibition, using saccadic Go/No-Go task.

Their striking results revealed that PSP patients were strongly biased towards making a response and yet were severely impaired at accumulating the necessary evidence to commit to that response. In opposition to this, Amieva's team (2004) investigated the effects of mild AD on the same Go/No-Go task, but no impairment was found.

A clinical bedside test used to elicit a failure of motor inhibition is the 'applause sign': if patients are asked to clap three times, they perseverate and continue clapping (Dubois et al., 2005). This study concluded that this simple test of motor control is able to differentiate PSP from frontal or striatofrontal degenerative diseases such as FTD or PD (Dubois et al., 2005). The current reports using the 'applause sign' in AD are inconclusive. In Luzzi's study (2011), PSP and AD groups presented the 'applause sign' differing significantly from normal subjects. In contrast, Isella and colleagues (2013) concluded that DLB and CBS cohorts had a significantly more frequent 'applause sign', while AD and controls did not show any differences. Another popular screening tests in the differential diagnosis of bradykinetic rigid syndromes is the Frontal Assessment Battery (FAB; Dubois et al., 2000) at the bedside (Brown et al., 2010; Paviour et al., 2005). Paviour's study (2005) demonstrated that letter fluency and motor series best differentiated between the PSP and MSA groups. Additionally, this study showed that lexical fluency and motor series subscores from FAB correctly classified 70% of the PSP, MSA and PD patients. The performance of AD patients in the FAB is better than FTD disorders (Iavarone et al., 2004), but their scores are still lower than healthy controls (Oguro et al., 2006).

The findings of previous studies using Hayling (Ghosh et al., 2013) and Stroop assessments in PSP (Pillon et al., 1995) had lower performance compared with controls. The same results were also found when both verbal inhibitory tasks were administered in AD, as demonstrated being impaired in relation with healthy elderly controls (Belleville et al., 2006).

3.1.1.4. Fluency

Disorders of language are part of the symptomatology of many dementias. Different dementias may differ on tests of language production, such as phonemic and categorical/semantic fluencies (Rosser & Hodges, 1994). The common use of

both phonemic (letter) and semantic (category) fluency tasks in part stems from their face validity as tests of verbal ability and executive control (Ettenhofer et al., 2006). Participants need to retrieve words from their 'mental lexicon', to focus on the task, to select apply certain constraints and avoid repetition. These require executive control (Fisk & Sharp, 2004). Deficits in either verbal ability or executive control may manifest themselves in poor performance in the fluency tasks (Shao et al., 2014). Where other parts of the examination can indicate verbal skills, the fluency tasks can be used as an index of executive function.

Verbal fluency, for both phonological and semantic categories, is severely impaired in PSP (Brown et al., 2010; O'Keeffe et al., 2007; Pillon et al., 1991; Rittman et al., 2013; Soliveri et al., 1999). In controls, phonemic fluency is more difficult than semantic fluency (Rosser & Hodges, 1994). This relative pattern of performance is exaggerated in PSP, although PSP subjects were significantly impaired on both fluency tasks. Phonemic fluency alone provides accurate discrimination between PSP and controls or PD (Rittman et al., 2013), and is severely affected by the time of diagnosis. Patients with PSP may only be able to produce three or four words beginning with 'P' (Ghosh et al., 2013; Rittman et al., 2013). Intriguingly, the few p-words that are produced may not start phonologically with "/p/", and may also be low frequency words with initial sounds "/t/" or "/s/" (e.g. ptarmigan, psychiatrist) in contrast to typically high frequency words produced by controls and AD.

Patients with AD perform poorly on category fluency tasks (e.g. animals), but are less impaired at letter fluency, performing at near normal levels on this task (Cerhan et al., 2002; Henry et al., 2004; Monsch et al., 1992). Traditionally, emphasis has been placed on episodic memory deficits, but recent research indicates that some MCI patients show subtle, non-amnesic cognitive difficulties. Changes in aspects of executive function, such as verbal fluency, have been observed in people years before the clinical diagnosis of AD (Bäckman et al., 2005). For instance, Saxton and her colleagues included verbal fluency tasks in research on neuropsychological performance approximately 1.5 to 5 years prior to the onset of AD. Results indicated that decline in category (semantic) fluency was one of the predictors of subsequent conversion to AD in older adults (Saxton et al., 2004). Another study found that amnesic MCI participants produced

significantly fewer words on category, but not phonemic fluency when compared to healthy controls, though overall performance on both tasks fell within normal limits clinically (Murphy et al., 2006).

3.1.2. Memory

Often memory is understood as an informational processing system in which information is encoded, stored, and retrieved. Although once thought to be a simple concept, memory is now considered to be a collection of mental abilities that use different systems and components within the brain. Therefore, I will explain next these types of memories in brief.

3.1.2.1. Episodic memory

The term episodic memory refers to the capacity to recollect specific events and episodes from our lives. It is a form of mental time travel that is considered to be unique in humans (Tulving, 2002 & 2012). Disturbances to this type of memory system are among the earliest signs and symptoms of AD (Blennow et al., 2006; Cahn et al., 1995; Egerházi et al., 2007; Milberg & Albert, 1989), reflecting the involvement of the hippocampal formation (Fox et al., 1998). It is also one of the key symptoms that is prominent pre-clinically (Bäckman et al., 2004) in the disease, such disruptions may result in difficulty remembering significant past events, such a recent visit to the doctor or trip to the cinema. In contrast, the pattern of episodic memory of PSP patients differs from that of AD patients. While episodic memory is severely affected early in the course of AD, it appears to be relatively spared in PSP (Van der Hurk & Hodges, 1995), although approximately one third patients could manifest impairments of episodic memory (Bak et al., 2005; Brown et al., 2010).

3.1.2.2. Recall vs recognition

Poor delayed recall and recognition memory is a well-established pattern in the AD literature, although recall is considered to become impaired earlier on in the course of the disease (Small et al., 2003). Early studies in AD that used word list learning tasks such as those from the Consortium to Establish a Registry for Alzheimer Disease (CERAD) (Welsh et al., 1992) showed that AD patients rapidly forget information over time and are equally impaired (relative to age-matched controls) on recognition and free recall components of the tasks. This pattern of

performance is considered to reflect deficits in storage caused by deficient consolidation of new memory traces rather than ineffective retrieval of new information (Weintraub et al., 2012). In addition, previous evidence indicates impaired delayed recall scores in word-list learning tasks such as the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958) are perhaps the most accurate measures when used to accurately predict diagnostic conversion from MCI to AD (Estévez-González et al., 2003; Griffith et al., 2006; Maruff et al., 2004).

PSP patients have prominent recall deficits and forgetfulness with relative preservation of short-term and implicit memory processes, in contrast to AD where patients develop aphasia and apraxia (Litvan et al., 1989). Pillon and colleagues (1994) revealed that PSP patients had impaired memory deficits characterized by reduced immediate memory span, consistent with the notion that the cognitive deficits in PSP were due to involvement of frontal-striatal systems.

3.1.2.3. Autobiographical

Autobiographical memory refers to episodic memories of an individual, which are characterized by a sense of subjective time and auto-noetic awareness (Tulving, 1972), and entailed by feelings of emotional re-experience (Markowitsch, 2003). Because of the interaction of episodic and semantic memory and the uniqueness to humans, autobiographical memory is considered to be crucial for the continuity of the self and the development of personal identity (Conway, 2005). Conway described the importance of autobiographical memory to the maintenance of the self: "autobiographical knowledge constrains what the self is, has been, and can be". These processes are typically disturbed in patients with AD (Seidl et al., 2011). Berna's study (2012) revealed that a significant impairment of episodic autobiographical memory performance was associated with MCI, but not with normal aging. Mild autobiographical memory impairment was also observed in PSP, but without a temporal gradient for the recall of autobiographical or personal semantic information (Zarei et al., 2010).

3.1.2.4. Semantic knowledge

Semantic memory refers to memory for words, concepts, rules and abstract ideas which are not specific to time or place. Unlike episodic memories, semantic

memories are independent of ourselves and of time and of our recollective experience (Tulving, 2002; Overman & Becker, 2009).

Patients with AD show mild impairment on a range of semantic memory tests, including word-picture matching, category fluency, picture naming, picture sorting, and generation of verbal definitions (Bentham et al., 1997), which may occur several years prior to diagnosis (Tippett et al., 2007; Verma & Howard, 2012). A loss of semantic knowledge in AD may make it difficult for patients to establish connections to their semantic knowledge base during encoding (Garrard & Carroll, 2006). The loss is however, much milder than in Semantic Dementia (semantic variant primary progressive aphasia). In contrast, patients with PSP perform well on semantic memory tests if they are given sufficient time to complete them (Albert et al., 1974; Podoll et al., 1991).

3.1.2.5. Motor learning

Procedural memory refers to the ability to learn behavioral and cognitive skills and algorithms that are used at an unconscious level (Budson & Price, 2005). For example, patients may lose the ability to perform automatic, skilled movements, such as writing, riding a bike or playing a musical instrument that healthy people take for granted. It is thought that procedural memories are retained in AD for a long time. In fact, it has been proposed that patients with AD could not only acquire, but also retain, long-lasting procedural memories (Kawai et al., 2002) and the retention of this type of memory has been used to help rehabilitate cognitive deficits in patients with AD (Woodberry et al., 2015). In contrast, PSP patients have shown impairments in this type of memory because of a disruption to basal ganglia circuits (Boeve et al., 2003; Magherini & Litvan, 2005).

3.1.3. Behaviour

Behaviour refers to the way that somebody interacts with environment and people around them. Behavioural change is common in PSP and AD, but with different patterns that reflect the underlying cognitive processes. Patients with PSP show the highest prevalence of behavioural symptoms, with high rates of apathy, impulsivity, stereotypic behaviours, disinhibition, and abnormal eating (Bak et al., 2010; Golbe & Ohman-Strickland, 2007; Aarsland et al., 2001). In contrast,

common symptoms in AD include delusions, irritability, agitation, anxiety and depression (Burns et al., 1990; Nagahama et al., 2006).

3.1.3.1. Social and emotional cognition

Social cognition entails a complex set of processes including representation of the self, the perception of social groups (e.g. race and gender stereotypes), and the ability to make inferences about the knowledge, beliefs and desires of the self and of others ('theory of mind') (Fiske & Taylor, 1991). Social cognition tasks engage the anterior rostral medial frontal cortex (arMFC) (Bush et al., 2000; Frith & Frith, 1999). The posterior rostral MFC (prMFC) is involved in action monitoring and the updating of the predicted value of actions, whereas the orbital MFC (oMFC) is involved in monitoring reward and punishment, and in the updating of the predicted value of outcomes (Kahnt et al., 2012; Amodio & Frith, 2006; Perkins et al., 2013). Impaired social and emotion cognition are now recognized to be part of the cognitive syndrome of PSP provoking difficulties with relationships in the family, and communication problems (Ghosh et al., 2009; Ghosh et al., 2013; O'Keefe et al., 2007). Ghosh's studies confirms that patients with PSP have significant impairments in multiple tests of social cognition. They showed, by comparing pictures versus sounds of emotionally distinctive cues, that is not a result of impaired face perception but an integral part of the cognitive dysfunction associated with PSP. Their findings concluded that emotion recognition is affected, preventing them what another person is thinking or feeling.

Deficits in recognizing others' emotions are also reported in AD (Cadieux & Greve, 1997), and in its prodromal stage MCI, (Teng et al., 2007). Martinez and her colleagues (2018) found that patients with AD or PD have a decreased ability to detect emotions compared to their caregivers, although caregivers failed to recognize patients' emotion recognition deficits due to the caregiver burden and depression.

3.1.3.2. Motivation and reward

Motivation refers to the amount of work than an animal or person is willing to commit for a given level of reward. Apathy can be defined as a disorder of motivation, and loss of 'interest' in goal-directed activities (Levy et al., 1998; Robert et al., 2002). Apathy can be profound in PSP, and is a feature in the

diagnostic criteria (Höglinger et al., 2017). It affects over 80% of patients, as indicated by carer ratings of motivation such as Cambridge Behavioural Inventory-Revised (CBI-R) (Bak et al., 2010), and clinical ratings including Dementia Rating Scale (DRS) and Frontal Assessment Battery (FAB) (Brown et al., 2010). It is often one of the earliest features, even if not recognized as such before diagnosis. Indeed, apathy may be misdiagnosed as depression, leading to the delay in diagnosis of PSP. Apathy is also a common neuropsychiatric symptom in patients with AD (Nobis & Husain, 2018; Zhao et al., 2016), with prevalence rates ranging from 55% –80% (Spalletta et al., 2010). It has been reported to cause rapid cognitive and functional decline towards AD dementia in MCI patients (Dujardin et al., 2009; Vicini Chilovi et al., 2009). Recent work in both healthy people and AD confirms the emerging view that apathy is not a single construct but a multidimensional disorder that can also include distinct social as well as emotional deficits (Ang et al., 2017; Radakovic et al., 2017).

PSP is often accompanied by impulsivity, despite paradoxically the presence of apathy. Both apathy and impulsivity are multidimensional concepts (Levy & Dubois, 2006; Nombela et al., 2014), and the processes of motivation, reward and decision-making are some of the cognitive contributory features (Levy & Dubois, 2006; Zhang et al., 2016). Gambling reflects choice impulsivity. It is often assessed using gambling tasks such as the Cambridge Gambling Task (CGT; Zois et al., 2014), and Iowa Gambling Task (IGT; Bechara et al., 1994). Unlike other gambling tasks, the CGT examines decision making, without confounds of learning and working memory, by clearly presenting all information needed to make a decision throughout the task. Patients with frontal lobe lesions place high bets in both ascending and descending conditions, reflecting risky behaviours (Manes et al., 2002). Despite the inclusion of disinhibition in the criteria for PSP and bvFTD, pathological gambling is uncommon in FTLD syndromes (Manes et al., 2002), in contrast to PD (Marques et al., 2018; Voon et al., 2011).

3.2. Aims

The aims of this chapter are:

- I. to determine the behavioural and neuropsychological profiles of patients with PSP and AD/MCI⁺ in the NIMROD study and,

- II. to relate cognitive and behavioural deficits in my cohort to disease severity (PSP-RS and CDR), and functional decline (CBI-R and NPI).

To meet these aims the objectives were:

- I. to summarise the variables and set them in the context of existing literature,
- II. to present group wise summary statistics and,
- III. to describe parametric and non-parametric correlations among key variables.

3.3. NIMROD assessments

The neuropsychological and disease severity evaluations are described in detail in Chapter 2, which are classified in terms of global cognition, executive-domain based tests, carer-reported questionnaires, mood scale measurements, and indirect sleep disturbances rating. See section 2.3.1. for details.

3.4. Material and methods

3.4.1. Participants

The current study was conducted within the context of the 'Neuroimaging of Inflammation in Memory and Other Disorders project (NIMROD, see Chapter 2) (Bevan-Jones et al., 2017).

For the purpose of the substudy present in this chapter, we recruited 20 patients with probable PSP by the 1996 MDS criteria (representing a 'classical phenotype' which is sometimes referred to as Richardson's syndrome, PSP-RS); nine patients meeting diagnostic criteria for probable AD (McKhann et al., 2011), and six patients with MCI⁺ were recruited. All PSP patients also meet 2017 revised criteria for probable PSP-RS (Höglinger et al., 2017; Litvan et al., 1996). Thirteen age- and sex-matched healthy controls with no history of major psychiatric or neurological illnesses, head injury or any other significant medical comorbidity were also included to allow group-wise comparisons with the clinical cohorts.

3.4.2. Statistical analysis

Statistical analyses were performed in SPSS software (V23.0; <https://www.ibm.com/uk-en/marketplace/spss-statistics/purchase>). I compared

the patient groups with the healthy controls, and the performance of PSP versus AD/MCI⁺ patients.

The demographic and neuropsychological data were compared using ANCOVA with Bonferroni correction for *post hoc* tests. Education was considered as covariate in comparisons between patient and controls groups. Continuous rating scales were checked for normality, and subjected to either parametric or nonparametric tests as appropriate. Discrete variables (e.g. sex) were compared by Chi-Square. For neuropsychological measures, I corrected for multiple comparisons within each type of tests (see Tables 14, 15, 16 and 19).

3.5. Results

3.5.1. Demographics

Demographic information is shown in Table 11. There were no significant differences between patient groups and healthy controls in terms of age or sex. Participants with PSP had fewer years of formal education than those with AD/MCI⁺ and HC, but AD/MCI⁺ and HC groups did not differ in years of education.

	PSP (N = 20)	AD/MCI+ (N = 15)	HC (N = 13)	ANOVA (F) or Chi-Square (χ^2) or t-Test (t)	df,df_{error}	p value	Pairwise comparison 1 PSP vs. AD/MCI+	Pairwise comparison 2 PSP vs. HC	Pairwise comparison 3 AD/MCI+ vs. HC
Age mean (SD)	70.40 (±5.84)	72.94 (±8.96)	68.18 (±7.67)	1.44	(2,42)	ns	ns	ns	ns
Gender M/F	12/8	9/6	6/7	0.73	(2,42)	ns	ns	ns	ns
Education mean (SD)	11.95 (±1.82)	14.27 (±3.41)	15.85 (±1.99)	10.35	(2,42)	<0.00001	ns	<0.00001	ns
Symptom Duration* mean (SD)	7.40 (±3.74)	5.69 (±2.19)	na	2.44	(1,33)	ns	na	na	na

Table 11: Demographic profile of patient groups and healthy controls.

p-values indicate significance and state the equivalent threshold for significance after Bonferroni correction for multiple comparisons ($p=0.05/4=0.0125$).

Abbreviations: ns = not significant; SD, Standard Deviation; na, not applicable; df, degrees of freedom; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI+, Mild Cognitive Impairment with amyloid-positive; HC, Healthy Control; M, Male; F, Female.

*As we recognise the 'disease' pathology starts many years before symptoms.

3.5.2. Disease severity

Tables 12 and 13 provide the mean and standard deviation (SD) of the total scores and subscores for each disease severity assessments (Progressive Supranuclear Palsy-Rating Scale in PSP and Clinical Dementia Rating in AD).

	Mean	SD
PSP-RS Max = 100	43.65	±15.44
History Max = 24	9.35	±4.55
Mental Max = 16	3.55	±2.87
Bulbar Max = 8	2.85	±2.11
Supranuclear ocular motor Max = 16	9.75	±3.12
Limb motor Max = 16	4.50	±2.70
Gait and midline Max = 20	13.45	±4.12

Table 12: Progressive Supranuclear Palsy-Rating Scale (PSP-RS) total score and subscores of PSP group.

Abbreviations: PSP-RS, Progressive Supranuclear Palsy-Rating Scale; SD, Standard Deviation.

	Mean	SD
CDR Max = 36	13.53	±4.79
Memory Max = 6	2.60	±0.73
Orientation Max = 6	1.80	±0.67
Judgement and problem solving Max = 6	2.87	±1.45
Community affairs Max = 6	2.27	±0.96
Home and hobbies Max = 6	2.47	±1.18
Personal care Max = 6	1.53	±0.64

Table 13: Clinical Dementia Rating (CDR) total score and subscores of AD/MCI+ group.

Abbreviations: CDR, Clinical Dementia Rating; SD, Standard Deviation.

3.5.3. Neuropsychology

Descriptive data for global cognition, measured by the Addenbrooke's Cognitive Examination-Revised (ACE-R) and Mini-mental State Examination (MMSE) are shown in Table 14. As expected, there was a significant main effect of group for cognitive measures, driven by reduced ACE-R and MMSE scores in PSP and AD/MCI⁺ patients relative to healthy controls. Participants with AD/MCI⁺ had lower score in memory than those with PSP and HC, but PSP and HC groups did not differ in this dimension. PSP group exhibited a poorer performance on verbal fluency including both letter and category fluency assessments in relation with healthy controls. AD/MCI⁺ also performed worse than the control group on verbal fluency, although only in the category fluency task.

The results of the executive domain-based evaluation, using the INECO Frontal Screening (IFS) is presented in Table 15. A between-group comparison showed a significant effect of diagnosis on the total score of the IFS. There were also significant differences for conflicting instructions, Go-No Go, backward digit span, spatial working memory, proverb interpretation, and verbal response inhibition. PSP patients did not show any differences than AD/MCI⁺ on the IFS total score and in any of the eight IFS subtests. However, PSP and AD/MCI⁺ patients revealed a lower performance than healthy controls in terms of the overall IFS score. PSP group executed significantly worst in both backward digit span and proverbs subtests in comparison with the control group. Instead, AD/MCI⁺ group presented lower performance on almost each IFS subtasks such as conflicting instructions, Go-No go, backward digit span, spatial working memory, proverb interpretation, and verbal response inhibition (Table 15).

The results of the Trail Making Test (TMT) are detailed in Tables 16. The TMT results showed a significant effect of diagnosis in the three groups in terms of both time and error scores but only in the Trails A. PSP patients exhibited higher number of errors than healthy controls and AD/MCI⁺ (Table 16). Regrettably, the study sample obtained in the Stockings of Cambridge (SOC) was too little to report any results. This was a consequence of fatigue and long testing sessions. As a matter of fact, only nine patients with PSP, four participants with AD/MCI⁺ and 13 healthy controls were able to complete the full battery of neuropsychological tests.

	PSP = 20 mean (SD)	AD/MCI+ = 15 mean (SD)	HC = 13 mean (SD)	ANOVA (F)	df,df_{error}	p value	Pairwise comparison 1 PSP vs. AD/MCI+	Pairwise comparison 2 PSP vs. HC	Pairwise comparison 3 AD/MCI+ vs. HC
ACE-R Max = 100	79.65 (±16.29)	71.67 (±14.37)	95.54 (±3.15)	9.31	(2,44)	<0.00001	ns	ns	<0.00001
MMSE Max = 30	26.40 (±4.66)	23.87 (±3.96)	29.31 (±0.75)	6.45	(2,44)	0.0002	ns	ns	0.0004
Attention & Orientation Max = 18	16.25 (±2.75)	15.87 (±2.94)	18.00 (±0.00)	1.97	(2,44)	ns	ns	ns	ns
Memory Max = 26	21.05 (±4.46)	12.33 (±4.86)	24.46 (±2.22)	35.36	(2,44)	<0.00001	<0.00001	ns	<0.00001
Fluency Scaled score Max = 14	6.55 (±3.47)	7.67 (±3.67)	12.23 (±1.53)	7.79	(2,44)	0.00009	ns	0.0002	0.0004
Phonemic fluency Words	6.55 (±4.62)	11.40 (±5.77)	15.38 (±4.99)	5.88	(2,44)	0.00045	ns	0.0004	ns
Semantic fluency Words	10.90 (±4.78)	10.40 (±4.62)	22.85 (±4.35)	23.52	(2,44)	<0.00001	ns	<0.00001	<0.00001
Language Max = 26	23.20 (±4.50)	22.53 (±3.27)	25.08 (±0.95)	1.33	(2,44)	ns	ns	ns	ns
Visuospatial Max = 16	12.35 (±4.06)	13.27 (±3.39)	15.69 (±0.48)	2.33	(2,44)	ns	ns	ns	ns
Pentagon copying Max = 1	0.70 (±0.47)	0.67 (±0.48)	1.00 (±0.00)	1.89	(2,44)	ns	ns	ns	ns
Clock drawing Max = 5	3.35 (±1.89)	3.87 (±1.18)	4.92 (±0.27)	2.57	(2,44)	ns	ns	ns	ns

Table 14: Addenbrooke's Cognitive Examination-Revised (ACE-R) and Mini-mental State Examination (MMSE) scores and ACE-R subscores of patient groups and healthy controls.

p-values indicate significance and state the equivalent threshold for significance after Bonferroni correction for multiple comparisons ($p=0.05/11=0.0045$).

Abbreviations: ns = not significant; SD, Standard Deviation; df, degrees of freedom; ACE-R, Addenbrooke's Cognitive Examination-Revised; MMSE, Mini-Mental State Examination; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI+, Mild Cognitive Impairment with amyloid-positive; HC, Healthy Control. Education was included as covariate of no interest in the statistical models.

	PSP = 18 mean (SD)	AD/MCI⁺ = 15 mean (SD)	HC = 13 mean (SD)	ANOVA (F)	df,df_{error}	p value	Pairwise comparison 1 PSP vs. AD/MCI⁺	Pairwise comparison 2 PSP vs. HC	Pairwise comparison 3 AD/MCI⁺ vs. HC
IFS Max = 30	15.63 (±4.45)	13.53 (±6.05)	24.34 (±3.36)	15.10	(2,42)	<0.00001	ns	0.0004	<0.00001
Motor sequencing Max = 3	1.47 (±0.96)	1.33 (±0.89)	2.07 (±0.95)	1.89	(2,42)	ns	ns	ns	ns
Conflicting instructions Max = 3	1.66 (±0.97)	1.53 (±1.45)	2.92 (±0.27)	5.16	(2,42)	0.0011	ns	ns	0.0008
Go-No go Max = 3	1.55 (±0.85)	1.46 (±0.91)	2.53 (±0.66)	4.65	(2,42)	0.0016	ns	ns	0.0014
Backward digit span Max = 6	3.10 (±1.24)	3.13 (±1.12)	4.76 (±1.30)	5.62	(2,42)	0.0007	ns	0.0038	0.0007
VWM Max = 2	1.47 (±0.90)	1.26 (±0.96)	2.00 (±0.00)	2.69	(2,42)	ns	ns	ns	ns
SWM Max = 4	1.83 (±0.78)	1.20 (±0.67)	2.30 (±1.25)	4.88	(2,42)	0.0013	ns	ns	0.0017
Proverb interpretation Max = 3	0.89 (±1.07)	0.93 (±1.01)	2.42 (±0.64)	6.62	(2,42)	0.0003	ns	0.0041	0.0003
Verbal response inhibition Max = 6	3.47 (±2.01)	2.66 (±2.38)	5.30 (±0.75)	5.71	(2,42)	0.0006	ns	ns	0.0005

Table 15: INECO Frontal Screening (IFS) scores and subscores of patient groups and healthy controls.

p-values indicate significance and state the equivalent threshold for significance after Bonferroni correction for multiple comparisons ($p=0.05/9=0.0055$).

Abbreviations: ns = not significant; SD, Standard Deviation; df, degrees of freedom; IFS, INECO Frontal Screening; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with amyloid-positive; HC, Healthy Control; VWM, Verbal Working Memory; SWM, Spatial Working Memory. Education was included as covariate of no interest in the statistical models.

	PSP = 9 mean (SD)	AD/MCI⁺ = 9 mean (SD)	HC = 13 mean (SD)	ANOVA (F)	df,df_{error}	p value	Pairwise comparison 1 PSP vs. AD/MCI⁺	Pairwise comparison 2 PSP vs. HC	Pairwise comparison 3 AD/MCI⁺ vs. HC
Trails A Time	71.67 (±45.06)	47.00 (±20.45)	31.38 (±6.69)	4.17	(2,27)	0.0067	ns	0.0057	ns
Trails A Errors	0.56 (±0.52)	0.00 (±0.00)	0.00 (±0.00)	6.79	(2,27)	0.001	0.003	0.0015	ns
Trails B Time	204.44 (±187.43)	145.67 (±83.47)	64.62 (±13.78)	2.50	(2,27)	ns	ns	ns	ns
Trails B Errors	0.56 (±0.72)	1.00 (±1.50)	0.08 (±0.27)	3.02	(2,27)	ns	ns	ns	ns

Table 16: Trail Making Test (TMT) scores of patient groups and healthy controls.

p-values indicate significance and state the equivalent threshold for significance after Bonferroni correction for multiple comparisons ($p=0.05/4=0.0125$).

Abbreviations: ns = not significant; SD, Standard Deviation; df, degrees of freedom; TMT, Trail Making Test; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with amyloid-positive; HC, Healthy Control. Education was included as covariate of no interest in the statistical models.

3.5.4. Carer-reported impairments

The results of the informant-based questionnaires, Cambridge Behavioural CBI-R (CBI-R) and Neuropsychiatric Inventory (NPI) for each patient group are shown in Tables 17 and 18. There were no significant differences between PSP and AD/MCI⁺ patients in terms of the CBI-R total score; however, AD/MCI⁺ group had higher scores in memory and orientation than those with PSP. In contrast, patients with PSP differed in self-care and eating habits domains.

	PSP = 20 mean (SD)	AD/MCI⁺ = 15 mean (SD)	t - test	df	p value
CBI-R Max = 180	51.40 (±33.24)	43.20 (±26.43)	0.78	33	ns
Memory and orientation Max = 32	8.55 (±6.78)	15.73 (±6.13)	-3.23	33	0.003
Everyday skills Max = 20	8.95 (±6.55)	5.80 (±5.32)	1.52	33	ns
Self-care Max = 16	7.10 (±5.28)	0.80 (±1.26)	5.14	21.84	< 0.0001
Abnormal behaviour Max = 24	4.35 (±5.00)	2.33 (±3.30)	1.35	33	ns
Mood Max = 16	3.80 (±2.76)	2.67 (±2.69)	1.21	33	ns
Beliefs Max = 12	1.10 (±1.94)	0.47 (±1.06)	1.13	33	ns
Eating habits Max = 16	4.35 (±3.76)	1.87 (±2.16)	2.28	33	0.029
Sleep disturbances Max = 8	4.10 (±2.12)	2.87 (±2.47)	1.58	33	ns
Stereotypic and motor behaviour Max = 16	3.00 (±3.32)	3.53 (±3.99)	-0.43	33	ns
Motivation Max = 20	6.10 (±4.56)	6.73 (±6.13)	-0.35	33	ns

Table 17: Cambridge Behavioural CBI-R total score and subscores of patient groups.

Abbreviations: ns = not significant at $p > 0.05$; SD, Standard Deviation; df, degrees of freedom; CBI-R, Cambridge Behavioural Inventory-Revised; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with amyloid-positive. Education was not included as a covariate.

The findings in the NPI assessment between patient groups only differed in the night behaviour feature, being this higher in the PSP cohort in comparison with patients with AD/MCI⁺.

	PSP = 20 mean (SD)	AD/MCI⁺ = 15 mean (SD)	t - test	df	p value
NPI	19.90	13.93	1.16	33	ns
Max = 156	(±15.28)	(±14.63)			
Delusions	0.35	0.53	-0.29	33	ns
Max = 12	(±1.56)	(±2.06)			
Hallucinations	0.65	0.27	0.79	33	ns
Max = 12	(±1.63)	(±1.03)			
Agitation	2.05	1.73	0.31	33	ns
Max = 12	(±2.92)	(±3.03)			
Depression	2.30	1.93	0.38	33	ns
Max = 12	(±2.94)	(±2.54)			
Anxiety	1.55	1.53	0.01	33	ns
Max = 12	(±2.7)	(±2.32)			
Euphoria	0.40	0.33	0.15	33	ns
Max = 12	(±1.27)	(±1.29)			
Apathy	2.15	3.47	-1.03	33	ns
Max = 12	(±3.61)	(±3.85)			
Disinhibition	1.85	0.33	1.95	26.71	ns
Max = 12	(±3.13)	(±1.29)			
Irritation	0.85	1.20	-0.49	33	ns
Max = 12	(±1.78)	(±2.39)			
Abnormal motor behaviour	1.00	0.73	0.28	33	ns
Max = 12	(±3.09)	(±2.15)			
Night behaviour	3.35	0.27	3.33	22.34	0.003
Max = 12	(±3.96)	(±1.03)			
Eating abnormalities	3.53	1.40	1.86	29.70	ns
Max = 12	(±4.15)	(±2.41)			
Stereotype	0.30	0.20	0.29	33	ns
Max = 12	(±1.12)	(±0.77)			

Table 18: Neuropsychiatric Inventory (NPI) total score and subscores of patient groups.

Abbreviations: ns = not significant at $p > 0.05$; SD, Standard Deviation; df, degrees of freedom; NPI, Neuropsychiatry Inventory; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with amyloid-positive.

3.5.5. Mood

Table 19 presents the results of the mood evaluation test, Hospital Anxiety and Depression Scale (HADS). There were no significant differences between patient groups and healthy controls in terms of anxiety. Participants with PSP had greater score in depression than those with AD/MCI⁺ and HC, but AD/MCI⁺ and HC groups did not differ in this variable.

	PSP = 20 mean (SD)	AD/MCI⁺ = 15 mean (SD)	HC = 13 mean (SD)	ANOVA (F)	df,df_{error}	p value	Pairwise comparison 1 PSP vs. AD/MCI⁺	Pairwise comparison 2 PSP vs. HC	Pairwise comparison 3 AD/MCI⁺ vs. HC
Anxiety Max = 21	4.25 (±2.95)	4.53 (±3.29)	4.38 (±3.54)	0.03	(2,45)	ns	ns	ns	ns
Depression Max = 21	5.90 (±2.90)	2.20 (±2.11)	3.31 (±3.96)	6.95	(2,45)	0.001	0.001	ns	ns

Table 19: Hospital Anxiety and Depression Scale (HADS) scores of patient groups and healthy controls.

p-values indicate significance and state the equivalent threshold for significance after Bonferroni correction for multiple comparisons ($p=0.05/2=0.025$).

Abbreviations: ns = not significant; SD, Standard Deviation; df, degrees of freedom; HADS, Hospital Anxiety and Depression Scale; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with amyloid-positive; HC, Healthy Control. Education was not included as a covariate.

3.5.6. Relationships among global cognitive function and age

Figures 7 and 8 present the outcomes whether global cognition related to age in each clinical group. In the PSP group, there was a significant *negative* correlation between global cognitive function, as assessed via the ACE-R total score, and age. In contrast, the AD/MCI⁺ group did not show a significant correlation between the ACE-R score and age.

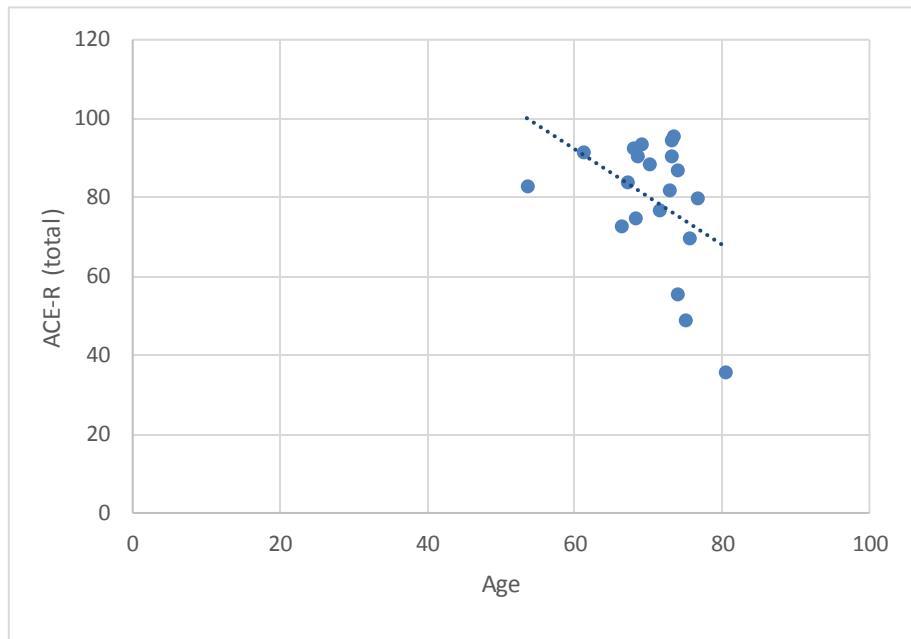


Figure 7: Relationship between global cognitive function (ACE-R) and age in the PSP group.

Scatter-plot with fit line showing significant partial correlation controlling for years of education and HADS depression ($r = -0.471, p = 0.049$) between age (X-axis) and ACE-R score (Y-axis) in the PSP subjects (blue dots). Abbreviations: HADS; Hospital Anxiety and Depression Scale; ACE-R, Addenbrooke's Cognitive Examination-Revised; PSP, Progressive Supranuclear Palsy.

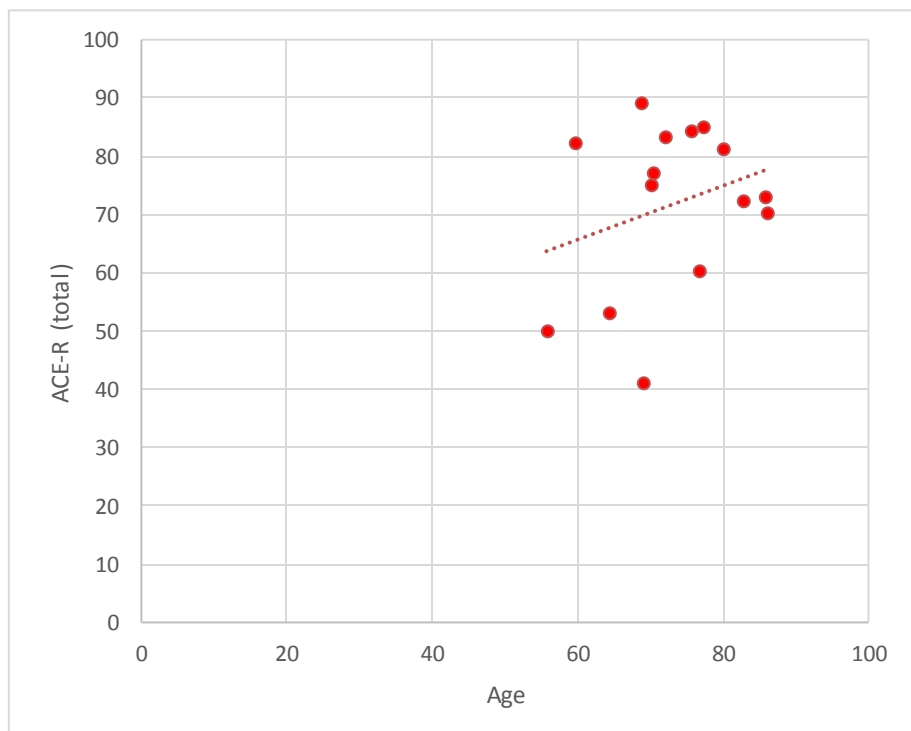


Figure 8: Relationship between global cognitive function (ACE-R) and age in the AD/MCI⁺ group.

Scatter-plot with fit line showing significant partial correlation controlling for years of education and HADS depression ($r = 0.340, p = 0.256$) between age (X-axis) and ACE-R score (Y-axis) in the AD/MCI⁺ subjects (red dots). Abbreviations: HADS; Hospital Anxiety and Depression Scale; ACE-R, Addenbrooke's Cognitive Examination-Revised; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with amyloid-positive.

3.5.7. Relationships between global cognitive function and disease severity

Correlations in terms of global cognition and disease severity, measured by the PSP-RS and CDR in the PSP and AD/MCI⁺, respectively are displayed in Figures 9 and 10. There was a significant *negative* correlation between the ACE-R overall score and PSP-RS. However, not significant correlation was found between ACE-R total score and disease severity (CDR).

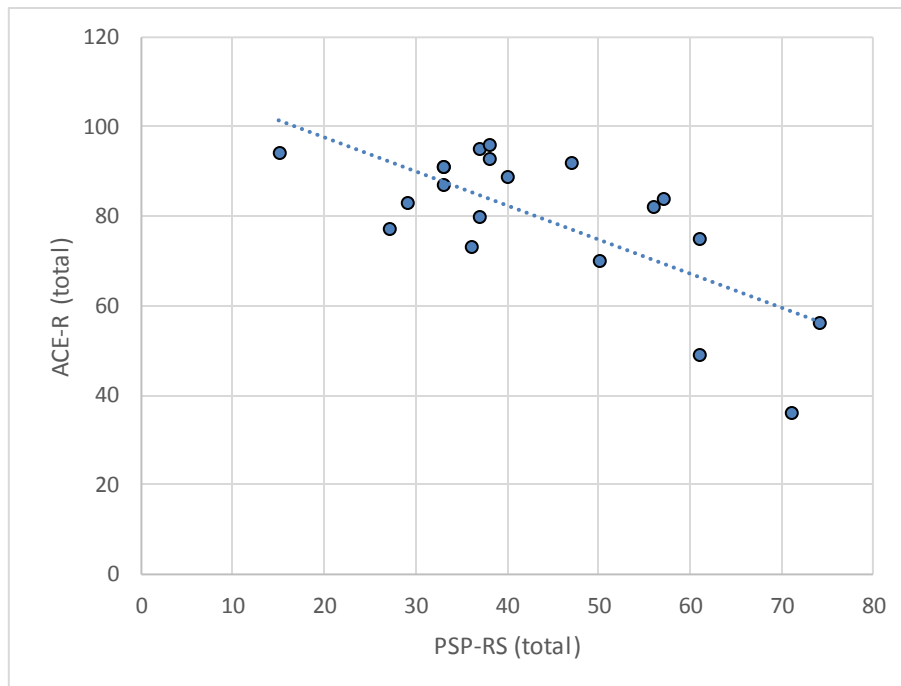


Figure 9: Relationship between global cognitive function (ACE-R) and disease severity (PSP-RS) in the PSP group.

Scatter-plot with fit line showing significant partial correlation controlling for years of education and HADS depression ($r = -0.765, p = 0.000$) between PSP-RS measure (X-axis) and ACE-R score (Y-axis) in the PSP subjects (blue dots). Abbreviations: HADS; Hospital Anxiety and Depression Scale; PSP-RS, Progressive Supranuclear Palsy-Rating Scale; ACE-R, Addenbrooke’s Cognitive Examination-Revised; PSP, Progressive Supranuclear Palsy.

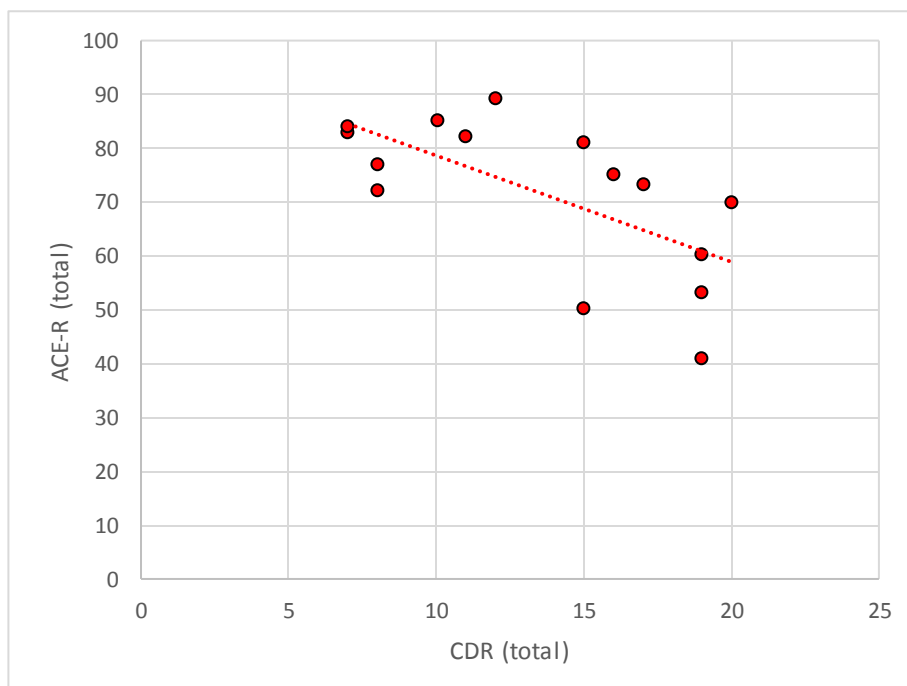


Figure 10: Relationship between global cognitive function (ACE-R) and disease severity (CDR) in the AD/MCI⁺ group.

Scatter-plot with fit line showing significant partial correlation controlling for years of education and HADS depression ($r = 3.40, p = 2.56$) between CDR measure (X-axis) and ACE-R score (Y-axis) in the AD/MCI⁺ subjects (red dots). Abbreviations: HADS; Hospital Anxiety and Depression Scale; CDR, Clinical Dementia Rating; ACE-R, Addenbrooke’s Cognitive Examination-Revised; AD, Alzheimer’s Disease; MCI⁺, Mild Cognitive Impairment with amyloid-positive.

3.5.8. Relationships between executive domain-based function and disease severity

Figures 11 and 12 present the correlations whether executive domain-based function, evaluated by the INECO Frontal Screening (IFS), related to disease severity in each patient group. In the PSP group, there was a significant *negative* correlation between IFS total score and disease severity, as assessed via PSP-RS. AD/MCI⁺ group did also show a significant *negative* correlation between IFS total result and CDR as a disease severity assessment.

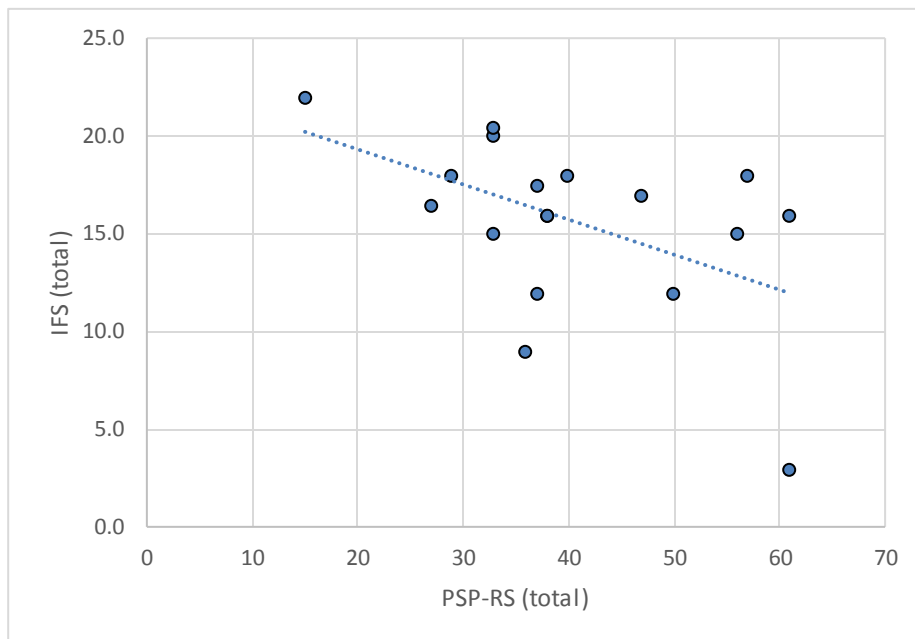


Figure 11: Relationship between the domain-based assessment (IFS) and disease severity scale (PSP-RS) in the PSP group.

Scatter-plot with fit line showing significant partial correlation controlling for years of education and HADS depression ($r = -0.530$, $p = 0.035$) between PSP-RS measure (X-axis) and IFS score (Y-axis) in the PSP subjects (blue dots). Abbreviations: HADS; Hospital Anxiety and Depression Scale; PSP-RS, Progressive Supranuclear Palsy-Rating Scale; IFS, INECO Frontal Screening; PSP, Progressive Supranuclear Palsy.

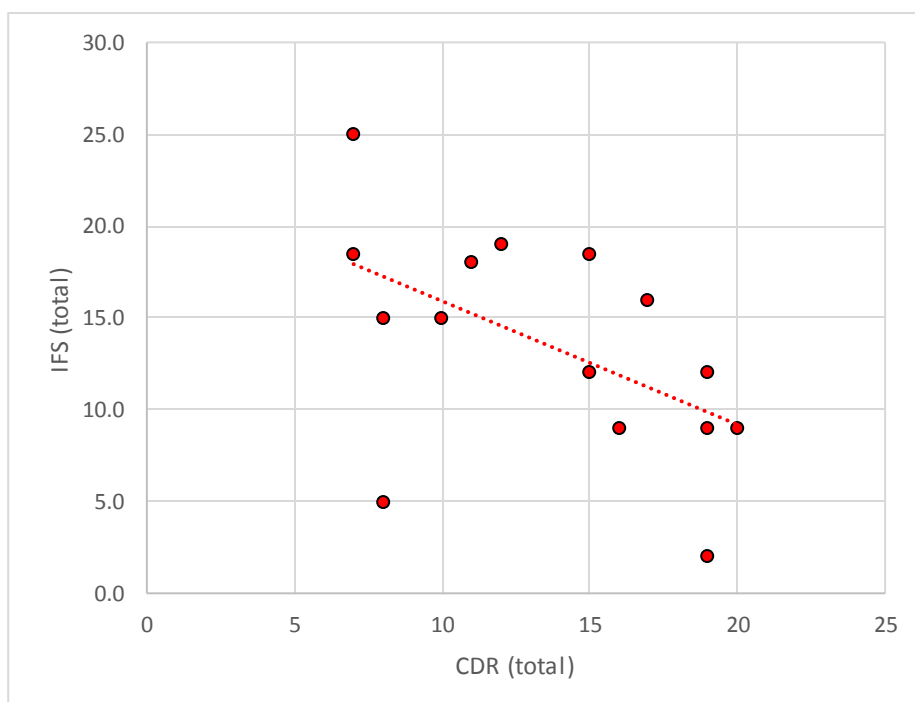


Figure 12: Relationship between the domain-based assessment (IFS) and disease severity scale (CDR) in the AD/MCI⁺ group.

Scatter-plot with fit line showing significant partial correlation controlling for years of education and HADS depression ($r = -0.610$, $p = 0.027$) between CDR measure (X-axis) and IFS score (Y-axis) in the AD/MCI⁺ subjects (red dots). Abbreviations: HADS; Hospital Anxiety and Depression scale; CDR, Clinical Dementia Rating; IFS, INECO Frontal Screening; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with amyloid-positive.

3.5.9. Relationships between carer-reported assessment and disease severity

The results of the relationship in terms of carer-reported assessment measured by the Cambridge Behavioural Inventory-Revised (CBI-R) and disease severity in the clinical groups are displayed in Figures 13 and 14. There was a significant *positive* correlation between the CBI-R overall score and PSP-RS in the PSP cohort. Also, a significant *positive* correlation was found in the AD/MCI⁺ group between the ACE-R total score and disease severity (CDR).

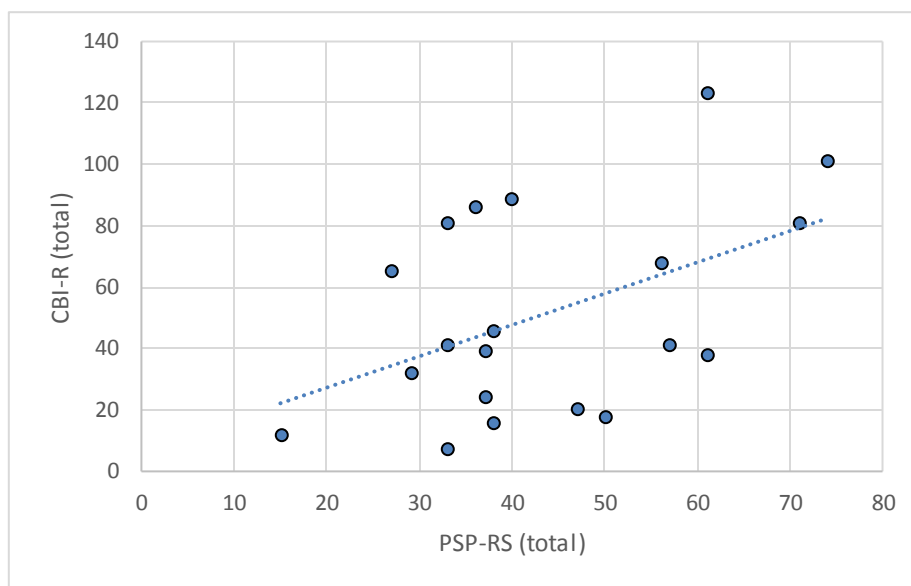


Figure 13: Relationship between the carer-reported assessment (CBI-R) and disease severity scale (PSP-RS) in the PSP group.

Scatter-plot with fit line showing significant Pearson's correlation ($r = 0.474$, $p = 0.035$) between PSP-RS measure (X-axis) and CBI-R score (Y-axis) in the PSP subjects (blue dots). Abbreviations: CBI-R; Cambridge Behavioural Inventory-Revised; PSP-RS, Progressive Supranuclear Palsy-Rating Scale; PSP, Progressive Supranuclear Palsy.

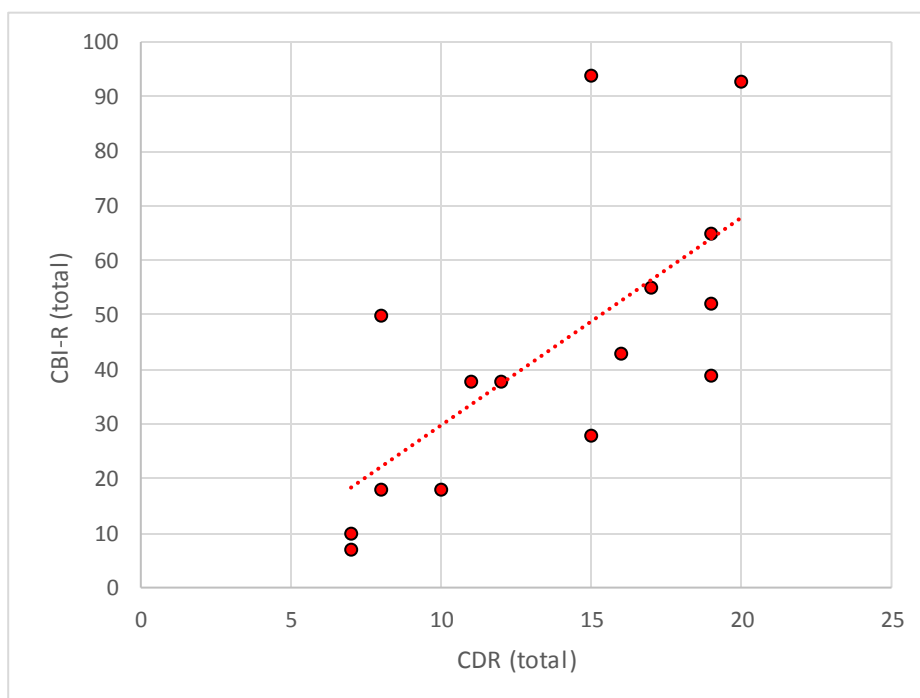


Figure 14: Relationship between carer-reported assessment (CBI-R) and disease severity scale (CDR) in the AD/MCI⁺ group.

Scatter-plot with fit line showing significant Pearson's correlation ($r = 0.690$, $p = 0.004$) between CDR measure (X-axis) and CBI-R score (Y-axis) in the AD/MCI⁺ subjects (red dots). Abbreviations: CDR, Clinical Dementia Rating; CBI-R, Cambridge Behavioural Inventory-Revised; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with amyloid-positive.

3.6. Discussion

Both patient groups had significant levels of cognitive and behavioural deficits, which were broadly in line with the reports from other studies in the literature. In terms of global cognitive screening test scores (ACE-R/MMSE), PSP patients did not differ from AD/MCI⁺. While this suggests that those global scales may not be helpful for discriminating patients, it is an advantage for subsequent analysis that the groups were matched in terms of global cognitive dysfunction.

The differentiation between PSP and AD/MCI⁺ lies in subscales of cognition. For example, in memory subscores: the most pronounced deficit in patients with AD/MCI⁺ was memory, which is typically impaired early in the course of the disease (Blennow et al., 2006; Lindau et al., 2000; Pillon et al., 1991). Memory performance of the PSP patients did not differ from the healthy control group. Burrell and colleagues (2014) have proposed that patients with PSP can perform well on memory tests if they are given sufficient time to complete the test, especially when slow speed of processing (bradyphrenia) is characteristic of PSP. However, memory recall and recognition in ACER are not timed tests, and slow information processing *per se* cannot be assumed to be the cause of impairment.

Healthy controls recalled fewer words on letter fluency than on category fluency, a finding consistent with other studies (Hodges et al., 1990; Monsch et al., 1992). This effect was exaggerated in the PSP group, showing severe impairment on letter fluency. This decline in letter fluency should not be interpreted entirely due to bradykinesia or bradyphrenia, as fluency requires very little motor function and word production tails off long before the end of the 60-second test interval (Rittman et al., 2013). For AD/MCI⁺, the fluency pattern was different. Patients with AD/MCI⁺ performed better on letter fluency than PSP subjects. Thus, AD/MCI⁺ cohort displays a reversal of the normal pattern of performance. Although the letter and category fluency task are superficially similar, they differ in important ways in their task demands. Letter fluency must be performed without reference to meaning, and the spread of activation within the phonological lexicon may proceed less rapidly than at the semantic level (Rosser & Hodges, 1994). By contrast, the category fluency task resembles everyday production tasks, such as making a shopping list, so that healthy participants can exploit existing links between related concepts to retrieve

responses (Shao et al., 2014). In addition, even though it has been recognized that PSP patients have reduced letter fluency (Bak et al., 2005; Pillon et al., 1995), whereas the AD/MCI⁺ deficit is greater for categorical/semantic rather than phonemic (Milberg & Albert, 1989; Rosser & Hodges, 1994), the number of correct exemplars on semantic fluency task produced by both patient groups is similar. In line with my results, clinical studies have found that patients with AD/MCI⁺ has been observed to be relatively more impaired in the category than the letter fluency tasks, consistent with impaired access to semantic information (Laws et al., 2010; Magaud et al., 2010; Meijer et al., 2011). By contrast, PSP patients were significantly more impaired on both types of verbal fluency task compared with controls. PSP can impair both phonological and semantic categories (Bensimon et al., 2008; Brown et al., 2010; O’Keeffe et al., 2007; Pillon et al., 1991; Rittman et al., 2013; Soliveri et al., 1999), but patients with AD/MCI⁺ are most severely impaired in semantic fluency.

It is also necessary to comment on how the differential pattern of both letter and category fluency deficits in PSP and AD might relate to the underlying brain networks involved. Performance on both tasks depends upon frontostriatal circuits that control aspects of executive function and working memory (Rosser & Hodges, 1994). In the case of initial letter fluency, the phonologically based word store is clearly critical, whereas category fluency depends on the intactness of semantic memory (Hodges et al., 1992; Martin & Fedio, 1983; Butters et al., 1987). There is a considerable body of evidence that frontostriatal deficits, of the type found in patients with PSP, result in equally severe impairment on letter and category fluency tasks (Grafman et al., 1990; Soliveri et al., 2000). By contrast, disorders that cause breakdown in the organisation of semantic memory, such as AD, resulted in more pronounced impairment on category fluency due to temporal lobe based deficits (Bak et al., 2005).

Surprisingly, the IFS total score and its executive subdomains did not discriminate between the patient groups. PSP patients showed a significant lower performance than the healthy control group on working memory tests, and proverb interpretation, consistent with the early and prominent impairments in executive function described in PSP (Gerstenecker et al., 2013; Grafman et al., 1990). The IFS total and subscores were reduced in AD/MCI⁺ versus healthy controls groups, even though the differences from PSP were not significant. This suggests an

intermediate deficit in PSP, without statistical significance from either controls of AD/MCI⁺.

The CBI-R *total* score was similar in both patient groups. Nevertheless, the PSP profile encompassed behavioural deficits with impairment in the self-care subsection while AD impaired memory and attention. Self-care difficulties in this group may reflect motor disability, but could also result from organisational and executive impairments that affect instrumental activities of daily living. These results were in keeping with those previously reported (McCrone et al., 2011; Nagahama et al., 2006). Bozeat and collaborators (2000) suggested that eating behaviours distinguished between frontotemporal dementia (FTD) and AD. My results suggest that stereotypical eating habits differentiates also PSP from AD/MCI⁺. AD/MCI⁺ patients were more severely impaired on memory and orientation items than PSP. These findings agree with the general trend found in previous studies that have confirmed that AD/MCI⁺ is characterised by profound impairment in episodic memory (Buckner, 2005; Lindau et al., 2000; Mathuranath et al., 2000; Morris, 1993; Wedderburn et al., 2008).

The feature of neuropsychiatric symptoms, measured by the NPI, showed quite a similar pattern in both disorders. Consistent with previous studies and a priori expectations, sleep disturbances were most pronounced in the PSP group in comparison with patients with AD/MCI⁺. This result confirms Abbot's and Videnovic's views that weaker night time and daytime rhythms may result increased sleep during the day and decreased sleep at night (Abbott & Videnovic, 2014; Videnovic et al., 2014). Interestingly, PSP's carers did not score higher in terms of their relatives eating habits on NPI, however it was significantly different using the CBI-R. This discrepancy may occur as the NPI questions are more towards the exploration of eating changes rather than eating habits. For example, the NPI asks about changes in food preference and features that may result from changes in appetite such as weight gain, whereas the CBI-R is more focused on particular aspects of eating behaviour such as table manners or rigidity of food preferences. Studies using the NPI have found apathy (77% – 91% of cases) and disinhibition (35% – 56% of cases) to be common behavioural features in PSP subjects (Aarsland et al., 2001; Levy et al., 1996; Litvan et al., 1996; Litvan et al., 1998). However, neither behaviour were detected by NPI in the current PSP

group. A potential explanation may be again that NPI, as the CBI-R, are carer-reported assessments; therefore they are susceptible to recall bias. Alternatively, the PSP study group is not typical of PSP: a selection bias towards more motivated patients may have arisen in view of the commitment needed to engage with the demanding multimodal assessment protocol of NIMROD.

The neuropsychiatric profile in patients with PSP differs in some key domains from the AD/MCI⁺ group, but both patients groups have much in common in their differences from controls. The present results confirm that PSP should be considered as not only a movement disorder, but also a disorder with a wide range of neuropsychiatric symptoms.

There were not strong endorsements for depression or anxiety within the study groups. This result agrees with Menza (1995), Livan (1996), and Aarsland (2001), who found that features of depression and anxiety were uncommon in PSP, despite the lack of agreement in the literature about depression in PSP (Millar et al., 2006). In contrast to the literature about depression being one of the most frequent behavioral symptoms in AD (Engedal et al., 2011; Levy et al., 1996; Olin et al., 2002; Shin et al., 2005), depression was not prominent in our AD/MCI⁺ group. This discrepancy may reflect the range of instruments used – and the ease with which physical symptoms of sleep, weight, appetite may move a patient towards the threshold for ‘depression’ in some clinical rating scales (e.g. BDI-II), even though their occurrence in the patient group is not due to depression but other disease specific factors. This confounds the use of thresholded ratings scales in the assessment of depression prevalence. However, we must also acknowledge that our patients may not have been typical, if there was a selection bias to more motivated and engaged patients for such a demanding study protocol.

In this study, we sought to identify the relationships between cognitive deficits, functional decline, and disease severity. Disease severity was judged using the PSP-RS and CDR, respectively. In the present study, the ACE-R total scores showed a positive strong correlation with the PSP-RS and CDR scores. A similar correlation between the ACE-R total scores and the CDR and PSP-RS scores were demonstrated in a previous studies (Mioshi et al., 2006; Passamonti et al., 2018). The domain-based evaluation (IFS) related to disease severity in each clinical group, with a large effect in both disorders. Last but not least, there were

a strong negative correlation between functional decline and disease severity in PSP and AD/MCI⁺.

There are a number of limitations to be considered. First, the current sample was relatively small, and may not be representative of the larger patient populations. Participants needed to agree to participate in several hours of testing including to attend at least to two neuroimaging sessions, score >24 on the MMSE be able to provide informed consent, and not have other central nervous system disorders. This likely yields a select, and perhaps milder, group of patients, and, therefore, results might not generalize to all patients.

Second, as it has been demonstrated by pathological confirmation, PSP can be divided into several phenotypes that are difficult to differentiate during life (Hassan et al., 2012; Williams et al., 2005). Consequently, to provide a more complete description of behavioral abnormalities in PSP, future studies should classify patients according to their subtype as the methodology for distinguishing between subtypes improve. However, our patients were selected as PSP-RS, not other variant phenotypes of PSP.

A further limitation in this chapter is the lack of education matching across the three cohorts. Shorter education was reported by patients with PSP relative to other groups (Table 11). One interpretation of this difference is that healthy 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 PSP (Litvan et al., 2016). Another explanation can be the wider population base for PSP versus more selected Cambridge-based patients with AD and healthy controls.

Fourth, cognitive assessment could take several hours to complete. This can be challenging for patients and result in fatigue and loss of concentration. These factors add to measurement error and may be a reason for patients to performance worst or ultimately, abort the testing procedure. We opted to curtail testing where appropriate, resulting in incomplete data on some scales (e.g. TMT and OCS).

Fifth, low scores may arise for different reasons in the patient groups, particularly in the PSP cohort. For example, it is possible that apraxia or other

features of a movement disorder impaired task performance differentially between groups, especially where graphical skills are required for assessment of cognition e.g. ACER visuospatial skills.

Finally, significant differences between the rating of mental measures by individuals with dementia and the reports of their caregivers are well documented (Farias et al., 2005; Leicht et al., 2010; Schulz et al., 2013). Consequently, the CBI-R and NPI scores might be biased and be partially attributed to caregiver burden and stress, and they should not be seen as exclusively objective measures of function (Lansdall et al., 2017).

In summary, I examined the cognitive features including the executive function, memory and behaviour, and motor impairments of patients in the NIMROD study, and how they relate to other measures of disease severity in PSP and AD/MCI⁺. I have then distinguished the typical features of each disease which reflect the classical phenotype.

Chapter 4

Imaging tau in progressive supranuclear palsy and Alzheimer's disease

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** These authors contributed equally to the completion of this work.*

4.1. Introduction

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

Radioligands have recently been developed for positron emission tomography (PET) to measure *in vivo* binding to aggregated tau, including PBB3 (Maruyama et al., 2013), a series of 'THK' compounds (Okamura et al., 2013), and [^{18}F]AV1451 (Chien et al., 2013; Xia et al., 2013). In autoradiographic studies with *post mortem* human brain tissues, the radiotracer [^{18}F]AV1451 colocalizes selectively with hyperphosphorylated tau over β -amyloid plaques (Marquié et al., 2015). NIMROD chose to use [^{18}F]AV1451, which has most extensive evidence internationally so far. Subsequently, the severity of displacement of THK5351 by selegiline (acting on MAO-B), and lack of large scale data with PBB3, have left [^{18}F]AV1451 the lead compound despite its controversies, while second generation ligands are developed and validated.

In patients with MCI and AD, there is higher [^{18}F]AV1451 non-displaceable binding potential (BP_{ND}), a measure of specific binding, in frontal, parietal, and temporal cortices relative to age-matched healthy controls (Okello et al., 2009). Progressively increasing regional [^{18}F]AV1451 binding in AD has also been associated with Braak staging of neurofibrillary tau pathology (Schöll et al., 2016;

Schwarz et al., 2016), while [¹⁸F]AV1451 PET binding patterns mirror the clinical and neuroanatomical variability in the AD spectrum (Ossenkoppele et al., 2016). Specifically, patients with the amnesic presentation of AD showed the highest [¹⁸F]AV1451 uptake in medial temporal lobe regions including the hippocampus, while patients with the logopenic variant of AD displayed increased left hemispheric [¹⁸F]AV1451 binding, particularly in posterior temporoparietal areas implicated in linguistic processes (Ossenkoppele et al., 2016). Performance on domain-specific neuropsychological tests was also associated with increased [¹⁸F]AV1451 uptake in brain regions involved in episodic memory, visuospatial skills, and language production or comprehension (Ossenkoppele et al., 2016).

Nevertheless, critical issues remain unresolved, and in particular the value of [¹⁸F]AV1451 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]AV1451 tracer displays strong binding to paired helical filaments characteristic of AD (e.g., intra- 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 PSP and non-AD disease tauopathies (e.g., CBD) (Marquié et al., 2015). However, it has recently been found that [¹⁸F]AV1451 binds to regions of pathology (i.e., frontal and temporal cortices) in a patient with a *MAPT* gene mutation leading to straight tau filaments and non-AD dementia (Bevan Jones et al., 2016). It has also been proposed that the [¹⁸F]AV1451 tracer displays off-target binding, specifically to neuromelanin-containing cells. This was supported by evidence in patients with PD, *in vivo*, in the midbrain; and *post mortem*, in retinal and brain tissues in porcine and rodent models (Hansen et al., 2016).

4.2. Aims

Here, we assessed the magnitude and patterns of [¹⁸F]AV1451 binding in two very different neurodegenerative diseases, PSP and AD/MCI⁺, characterized by distinct anatomical distributions of pathology and distinct molecular pathologies. The value of comparing these two groups *does not* lie in their differential diagnosis, which is clear on clinical grounds and amyloid-β based biomarkers, but in testing the ligand's binding against well-established

clinicopathological correlations and distinct distributions of tau pathology.

Overall, the aims of the work in this chapter were:

- I. To identify the patterns of [¹⁸F]AV1451 PET binding in patients with PSP, relative to patients with AD/MCI⁺ as well as sex- and age-matched healthy controls.
- II. To assess whether regional [¹⁸F]AV1451 PET binding could distinguish between PSP and AD/MCI⁺ groups.
- III. To test whether [¹⁸F]AV1451 PET binding relates to different measures of clinical severity in PSP and AD/MCI⁺ cohorts.
- IV. In view of the suggested effect of off-target binding, we also examined [¹⁸F]AV1451 uptake in relation to AT8 immunohistochemistry of hyperphosphorylated tau protein and tinctorial stain for neuromelanin, *in post mortem* sections from patients with PSP, AD, and a similarly aged healthy control from the Cambridge Brain Bank (CBB).

4.3. Hypotheses

The principal hypotheses were that:

- I. Patients with PSP would display increased [¹⁸F]AV1451 PET binding especially in the midbrain and basal ganglia, with likely additional binding in frontal cortex (including the motor areas) and supramarginal gyrus, a set of subcortical and cortical regions that have been shown to display tau pathology in PSP (Dickson et al., 2007; Schofield et al., 2005; Smith et al., 2017). Patients with AD and those with MCI and PET scans positive for amyloid-β would show increased [¹⁸F]AV1451 binding in the cortical and subcortical areas associated with AD pathology, including the medial temporal lobe as well as frontal, parietal, and temporal cortices (Serrano-Pozo et al., 2011).
- II. PSP and AD/MCI⁺ patients would be distinguishable on the basis of the regional [¹⁸F]AV1451 PET binding levels, particularly in the hippocampus and midbrain, two key subcortical regions that show distinct neuropathological changes in AD/MCI⁺ and PSP, respectively.
- III. [¹⁸F]AV1451 PET binding would be associated with disease severity in both PSP and AD/MCI⁺ groups, using disease specific measures of severity.

- IV. [¹⁸F]AV1451 binding in PSP and AD *post mortem* brains would mirror the expected brain regions as in the *in vivo* PET study, and not be accounted for by off-target binding to neuromelanin.

4.4. Materials and methods

4.4.1. Neuroimaging

4.4.1.1. Participants

The current study was conducted within the context of the 'Neuroimaging of Inflammation in MemoRY and Other Disorders' project (NIMROD, see also Chapter 2) (Bevan-Jones et al., 2017).

For the purpose of the substudy present in this chapter, we recruited 19 patients with probable PSP by the 1996 MDS criteria (representing a 'classical phenotype' which is sometimes referred to as Richardson's syndrome, PSP-RS); nine patients meeting diagnostic criteria for probable AD (McKhann et al., 2011), and six patients with MCI⁺ were recruited. All PSP patients also meet 2017 revised criteria for probable PSP-RS (Höglinger et al., 2017; Litvan et al., 1996). Thirteen age- and sex-matched healthy controls with no history of major psychiatric or neurological illnesses, head injury or any other significant medical comorbidity were also included to allow group-wise comparisons with the clinical cohorts.

4.4.1.2. Clinical and cognitive assessments

All clinical measures, and cognitive and care-reported assessments that patient groups and healthy controls carry out through the NIMROD study are also explained in chapter 2, section 2.3.1. To test the hypotheses above (section 4.3) we focus on measures set out in Table 20.

Test name	Format	Measured variable	Cohort
PSP-RS	Assessment tool completed by clinician	Disease severity	PSP
ACE-R	Structured test administered by researcher	Disease severity	PSP, AD/MCI ⁺ and HC

Table 20: Clinical and neuropsychological assessments for patient groups and healthy controls.

Abbreviations: PSP-RS, Progressive Supranuclear Palsy-Rating Scale; ACE-R, Addenbrooke's Cognitive Examination-Revised; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with positive β -amyloid; HC, Healthy Control.

4.4.1.3. Magnetic Resonance Imaging data

In brief, all participants underwent an MRI session acquired on a 3 Tesla (3T) using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) T1-weighted sequence. The T1-weighted images were used to facilitate tissue class segmentation and to allow inverse normalisation of template space regions of interest (ROIs) defined by modified 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/>) and the inverse transform was applied to the modified Hammers atlas (resliced from MNI152 to ICBM2009a space) to bring the ROIs to subject MRI space.

For further details of MRI data acquisition and pre-processing, see chapter 2, sections 2.3.2.1. and 2.3.2.2.

4.4.1.4. Positron Emission Tomography data

In summary, all PET scanning was performed either at the WBIC or Addenbrooke's hospital. [^{18}F]AV1451 radioligand was selected to evaluate the density of tau deposits. 370MBq of [^{18}F]AV1451 was injected intravenously over 30 seconds at the onset of a 90 minutes scan.

Each PET emission frame was reconstructed and corrections were applied. Each emission image series was realigned using SPM8 to correct for patient motion during data acquisition and create a mean image. The mean aligned PET image was rigidly co-registered to the MRI T1-weighted image using SPM8 and the inverse transformation applied to the modified Hammers atlas to put it in native PET space. Kinetic modelling was then performed on the motion-corrected time series in the cases of [^{18}F]AV1451. The reference region was 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 dentate nucleus was subtracted from the cerebellar reference region as is a common feature in PSP (Ishizawa et al., 2000). The findings in section 4.5.2.3. corroborated the use of the superior cerebellum as reference region in the PET analyses.

For further details of PET data acquisition and pre-processing, see chapter 2, sections 2.3.2.3. and 2.3.2.4.

4.4.1.5. [¹⁸F]AV1451 BP_{ND} statistical analyses

To compare [¹⁸F]AV1451 binding across groups (PSP, AD/MCI⁺, and healthy controls), individual ROI BP_{ND} values for [¹⁸F]AV1451 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 PSP and AD/MCI⁺ groups, we tested for correlations between regional [¹⁸F]AV1451 BP_{ND} and disease severity using the Progressive Supranuclear Palsy Rating Scale (PSP-RS) for PSP patients and the Addenbrooke's Cognitive Examination-Revised (ACE-R) scores for AD/MCI⁺ patients with Pearson's correlation (with partial correlations accounting for age and education). All analyses were repeated using [¹⁸F]AV1451 BP_{ND} values that were not corrected for CSF partial volume effects.

To assess the ability of [¹⁸F]AV1451 BP_{ND} to distinguish PSP patients from AD/MCI⁺ cases, subject-specific [¹⁸F]AV1451 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 PSP and AD/MCI⁺ was selected (i.e., basal ganglia and midbrain for PSP and superior/inferior temporal cortex, lateral occipital cortex, inferior parietal cortex, and hippocampus for AD/MCI⁺); noting that the ROIs included in the SVM were identical for both groups. This extended the whole-brain hierarchical cluster analysis described in section 4.5.1.4. The accuracy of each ROI to discriminate between the PSP and AD/MCI⁺ 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.

4.4.2. Neuropathology

The human brain tissue preparation is set out in Chapter 2, section 2.3.3.1.

The *post mortem* brain tissue used in this study came from three subjects: one PSP case, one AD case and one control. The PSP patient (NP16-69) was a 79 year old female who died from pneumonia. The AD case (NP16-264) was a 74 year old lady diagnosed with Braak stage VI, and according to her death certificate she died from AD. The control brain tissue (NP16-202) derived from a male of 73 years who died due to rectal colon cancer.

4.4.2.1. [¹⁸F]AV1451 Phosphor screen autoradiography

[¹⁸F]AV1451 phosphor screen autoradiography was performed following a previously published protocol by Marquiè and collaborators (Marquié 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]AV1451 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 AV1451 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 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]AV1451 only) and blocking ([¹⁸F]AV1451 plus 1µm unlabelled AV1451) conditions were compared to estimate total and nonspecific binding of [¹⁸F]AV1451.

4.4.2.2. Immunohistochemistry

I. AT8 immunohistochemistry of hyperphosphorylated tau protein

Sections were incubated in 10mM PBS/0.1% Triton X-100 buffer (Sigma, UK) twice for 5 minutes. Bovine serum albumin (0.7mls 5% w/v dissolved in buffer, Sigma, UK) was applied to each section and left for 1 hour. After washing twice in buffer, 0.7 ml of the primary antibody to tau (mouse monoclonal AT8, 1:1000 dilution) was applied to each section and incubated overnight at 4°C. The following

day, after washing the sections twice in PBS, 0.7ml of the secondary antibody (Alexa Flour 555, 1:1000 dilution) was applied to each section for 1 hour. Samples were washed, dried and coverslipped with Floursave (Calbiochem, UK). Prior to microscopy, sections were stored at 4°C in the dark. Microscopy analysis (Leica DM 6000B) was filtered to detect fluorescence from the antibody (555nm, red) and non-specific fluorescence (488nm, green).

II. Masson Hamperl staining method for the demonstration of neuromelanin

The tinctorial or silver stain for neuromelanin, *in post mortem* sections from patients with PSP, AD, and a similarly aged healthy control was investigated following the Masson Hamperl staining method (Masson, 1923) followed by image analysis. The captured images were processed with a Sigma Scan Pro image analysis software (Jandel Scientific, San Rafael, CA) by conversion to gray-scale images and detection of the immunolabel by its pixel intensity. In brief, frozen sections were dried for 20 minutes (Lamb E18.31), then placed in ultra-pure water for 30 seconds before incubated in silver solution at 60°. After 15 minutes, sections were rinsed in ultra-pure water. Sections were returned to the silver solution for further staining between 3 to 5 minutes as required. After rinsing in ultra-pure water, sections were fixed with 5% sodium thiosulphate. Sections were then counterstained with 0.1% nuclear fast red solution for 5 minutes, rinsed with water, then dehydrated in denatured alcohol (100% IDA) for 15 seconds, twice. After two changes of xylene, 15 seconds each, slides were cover slipped.

4.5. Results

4.5.1. Neuroimaging

4.5.1.1. Demographics and cognitive variables of patients and healthy controls in the [¹⁸F]AV1451 BP_{ND} *in vivo* study

Descriptive data for demographic and cognitive details are shown in Table 21. There were no statistically significant differences between patient and healthy control groups in terms of age or sex. 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 PSP and AD/MCI⁺ patients relative to healthy controls.

	PSP (N=19)	AD/MCI⁺ (N=15)	HC (N=13)	ANOVA (F) or Chi-Square (χ^2)	df	p value
Age mean (SD)	69.5 (± 5.8)	71.6 (± 8.7)	67.2 (± 7.3)	1.2	2	ns
Gender M/F	11/8	9/6	6/7	0.6	2	ns
Education mean (SD)	11.9 (± 1.8)	14.3 (± 3.3)	15.8 (± 1.9)	10.2	2	0.0003
MMSE mean (SD)	26.1 (± 4.5)	25.5 (± 2.8)	29.3 (± 0.7)	4.9	2	0.012
ACE-R mean (SD)	78.7 (± 15.8)	75.9 (± 11.0)	95.5 (± 3.0)	10.3	2	0.0002
PSP-RS mean (SD)	43.6 (± 15.8)	-	-	-	-	-

Table 21: Demographics and cognitive variables of study participants.

Abbreviations: PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with positive β -amyloid; HC, Healthy Control; df, degrees of freedom; SD, Standard Deviation; M, Male; F, Female; MMSE, Mini-Mental State Examination; ACE-R, Addenbrooke's Cognitive Examination-Revised; PSP-RS, Progressive Supranuclear Palsy-Rating Scale; ns = not significant at $p > 0.05$.

4.5.1.2. [¹⁸F]AV1451 BP_{ND} in relation to clinical diagnosis

The mean [¹⁸F]AV1451 BP_{ND} PET map in each group (Figure 15) and quantitative ROI analyses (Figure 16), indicated high [¹⁸F]AV1451 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 ($F_{2,41} = 17.5, p = 0.00001$) and a ROI x group interaction ($F_{2,68} = 7.5, p < 0.00001$), although there was no main effect of ROIs ($F_{2,34} = 0.8, p = 0.8$) (Figure 16). The group and interaction effects were driven in part by greater [¹⁸F]AV1451 BP_{ND} in the AD/MCI⁺ group relative to the PSP and healthy control groups, in cortical and subcortical 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) (Figures 16, 18 and 19). The PSP group, relative to the AD/MCI⁺ group, showed increased [¹⁸F]AV1451 BP_{ND} in the midbrain ($t = 2.1, p < 0.04$); while, relative to healthy controls, PSP patients showed increased [¹⁸F]AV1451 BP_{ND} uptake in the putamen, pallidum, thalamus, midbrain and dentate nucleus of the cerebellum (t 's $> 2.7, p < 0.02$) (Figures 16 and 17).

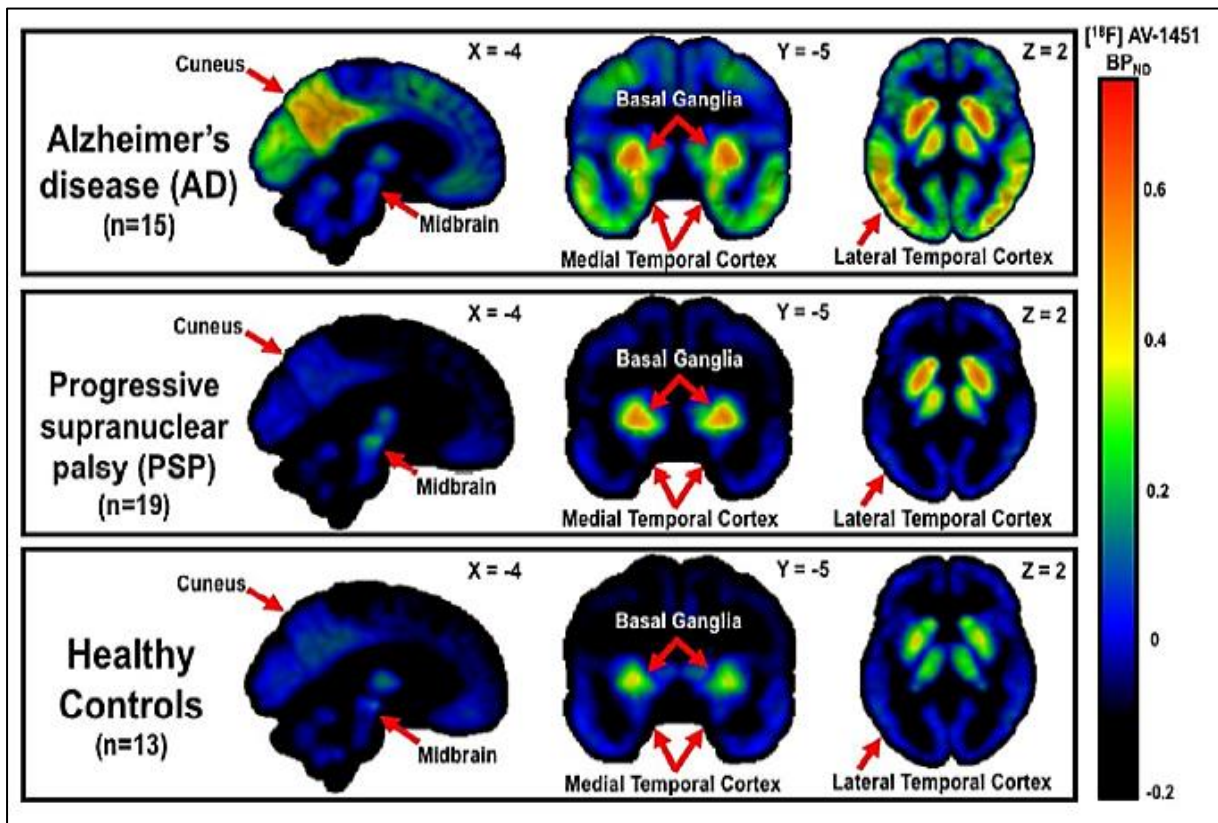


Figure 15: Voxel-wise BP_{ND} maps for $[^{18}F]AV1451$ for patients and healthy controls.

Note the $[^{18}F]AV1451$ binding in the basal ganglia in all groups, albeit higher in AD and PSP patients. Patients with AD also showed increased $[^{18}F]AV1451$ binding in medial temporal lobe regions and widespread neocortical areas, relative to controls and PSP patients, while PSP patients had increased high $[^{18}F]AV1451$ binding to the midbrain, relative to patients with AD and control subjects.

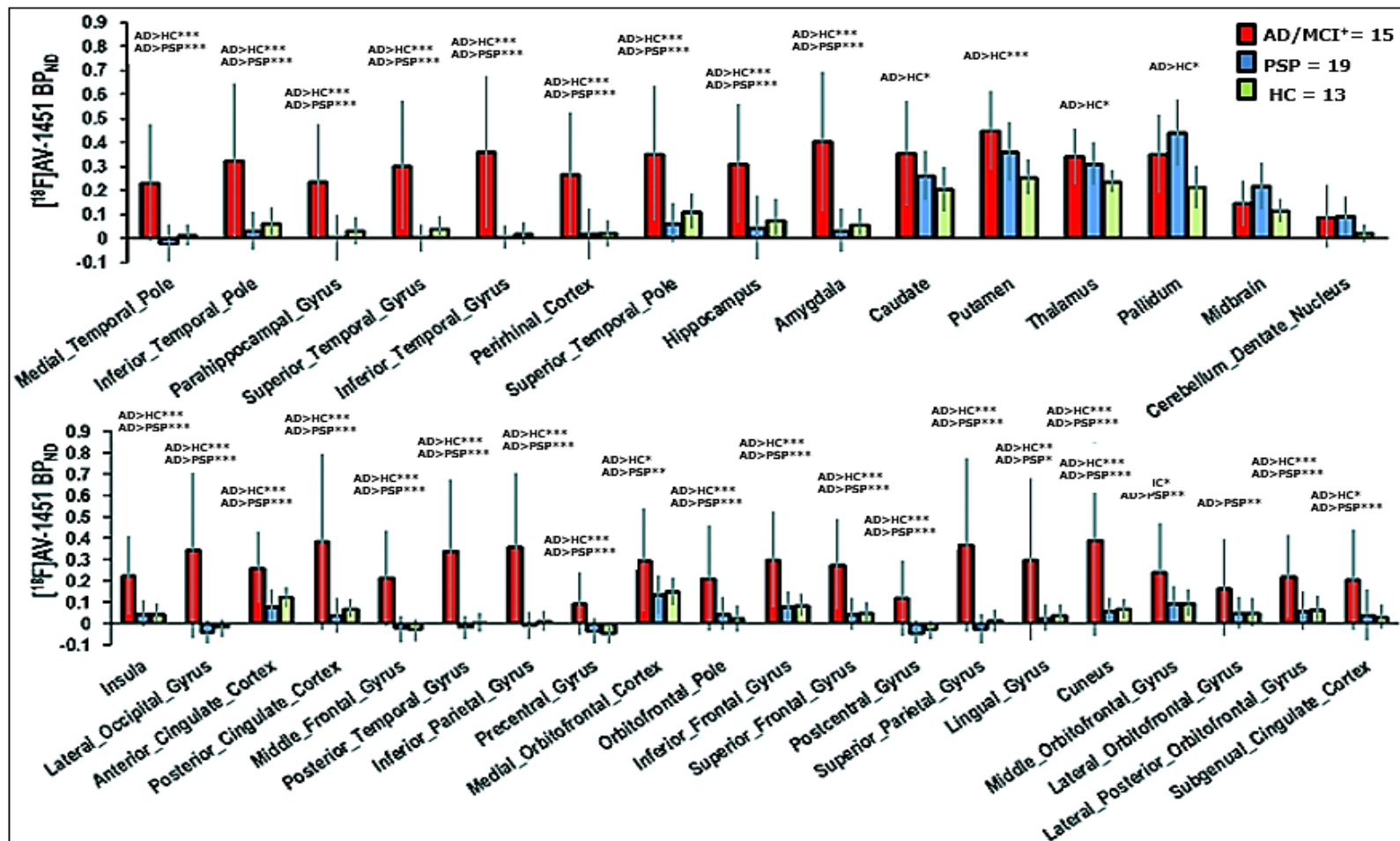


Figure 16: Mean (\pm SD) $[^{18}\text{F}]\text{AV1451 BP}_{\text{ND}}$ in each region of interest for the patient groups and healthy controls. This figure shows the bar plots represent the mean values (\pm SE) of the $[^{18}\text{F}]\text{AV1451 BP}_{\text{ND}}$ in each region of interest for the participant groups: AD/MCI⁺, PSP, and HCs. The $[^{18}\text{F}]\text{AV1451 BP}_{\text{ND}}$ data reported here are corrected for CSF partial volume effects. *Post hoc t* tests: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$. Abbreviations: AD, Alzheimer Disease; MCI⁺, Mild Cognitive Impairment with positive β -amyloid; PSP, Progressive Supranuclear Palsy; HC, Healthy Control; BP_{ND}, Non-displaceable Binding Potential.

Repeating the analyses using [^{18}F]AV1451 BP_{ND} values that were not corrected for CSF partial volume effects yielded similar results ($F_{2,36} = 1.1, p = 0.2$, for the main effect of ROIs; $F_{2,41} = 16.7, p < 0.00001$ for the main effect of group; and $F_{2,72} = 6.3, p < 0.00001$ for the group x ROI interaction).

We then tested whether regional [^{18}F]AV1451 BP_{ND} related to disease severity. In the PSP group, we found no significant correlation between [^{18}F]AV1451 BP_{ND} in any ROI and disease severity, as assessed via the PSP-RS (p 's > 0.16). Similarly, in the AD/MCI⁺ group, there was no significant correlation between ACE-R score and [^{18}F]AV1451 BP_{ND} in any ROI (p 's > 0.14). Repeating the correlation analyses when using the [^{18}F]AV1451 BP_{ND} values that were not corrected for CSF volume yielded similar non-significant results (p 's > 0.1).

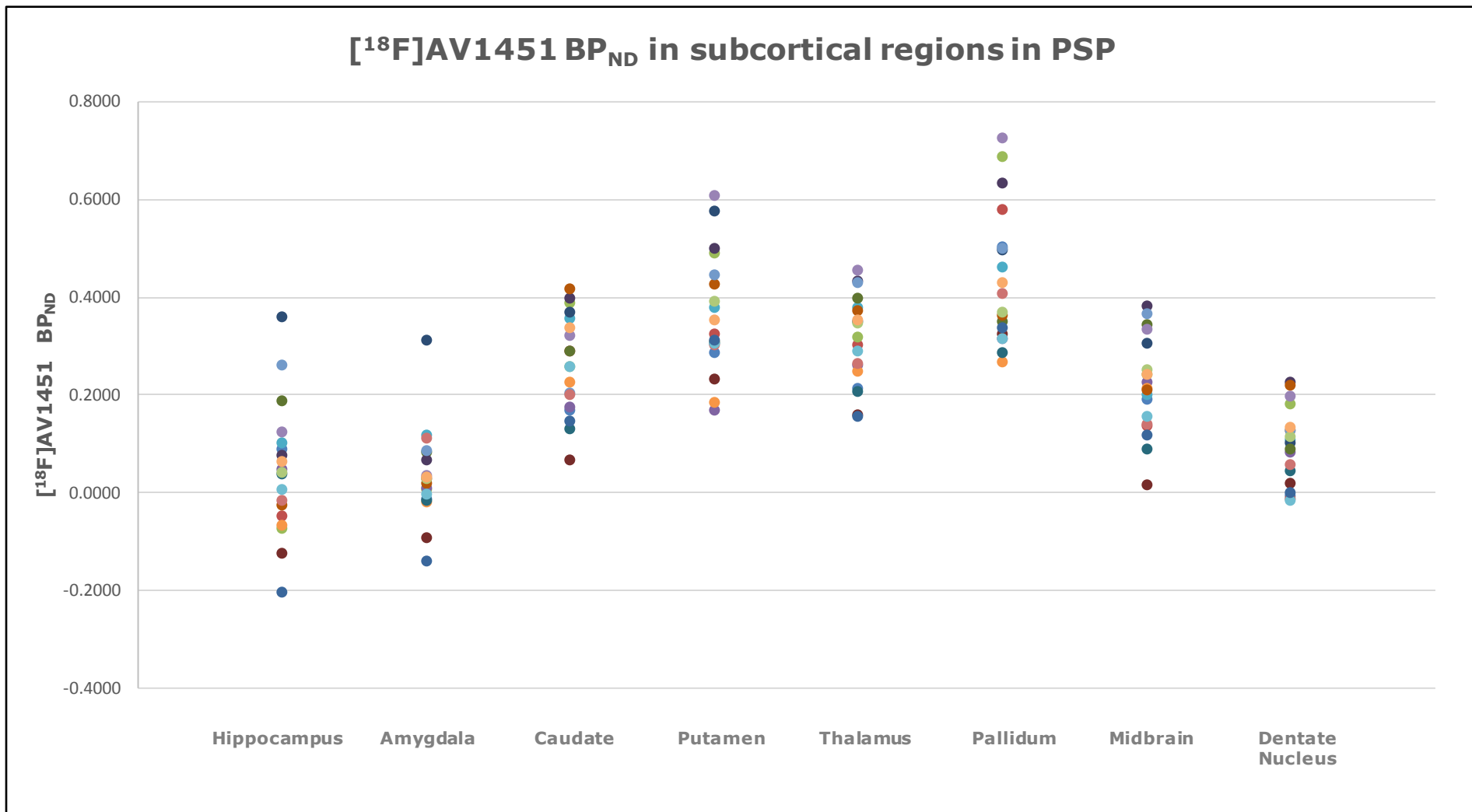


Figure 17: Scatter plot for subcortical regions to show the range of $[^{18}\text{F}]\text{AV1451}$ BP_{ND} values in patients with PSP. Each dot represents one patient, coloured by individual. Abbreviations: BP_{ND} , Non-displaceable Binding Potential; PSP, Progressive Supranuclear Palsy.

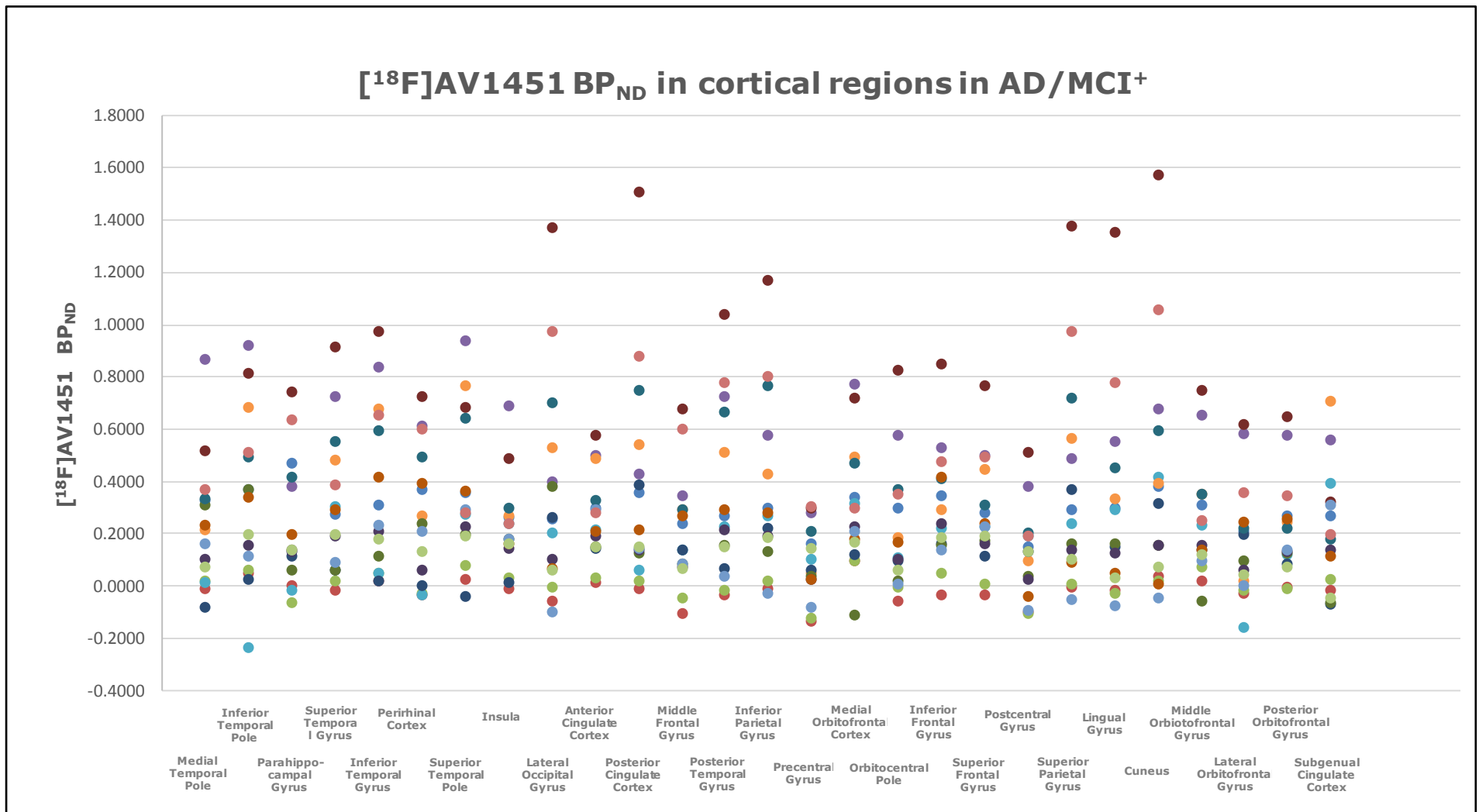


Figure 18: Scatter plot for cortical regions to show the range of [¹⁸F]AV1451 BP_{ND} values in patients with AD/MCI⁺. Each dot represents one patient, coloured by individual. Abbreviations: BP_{ND}, Non-displaceable Binding Potential; AD, Alzheimer’s Disease; MCI⁺, Mild Cognitive Impairment.

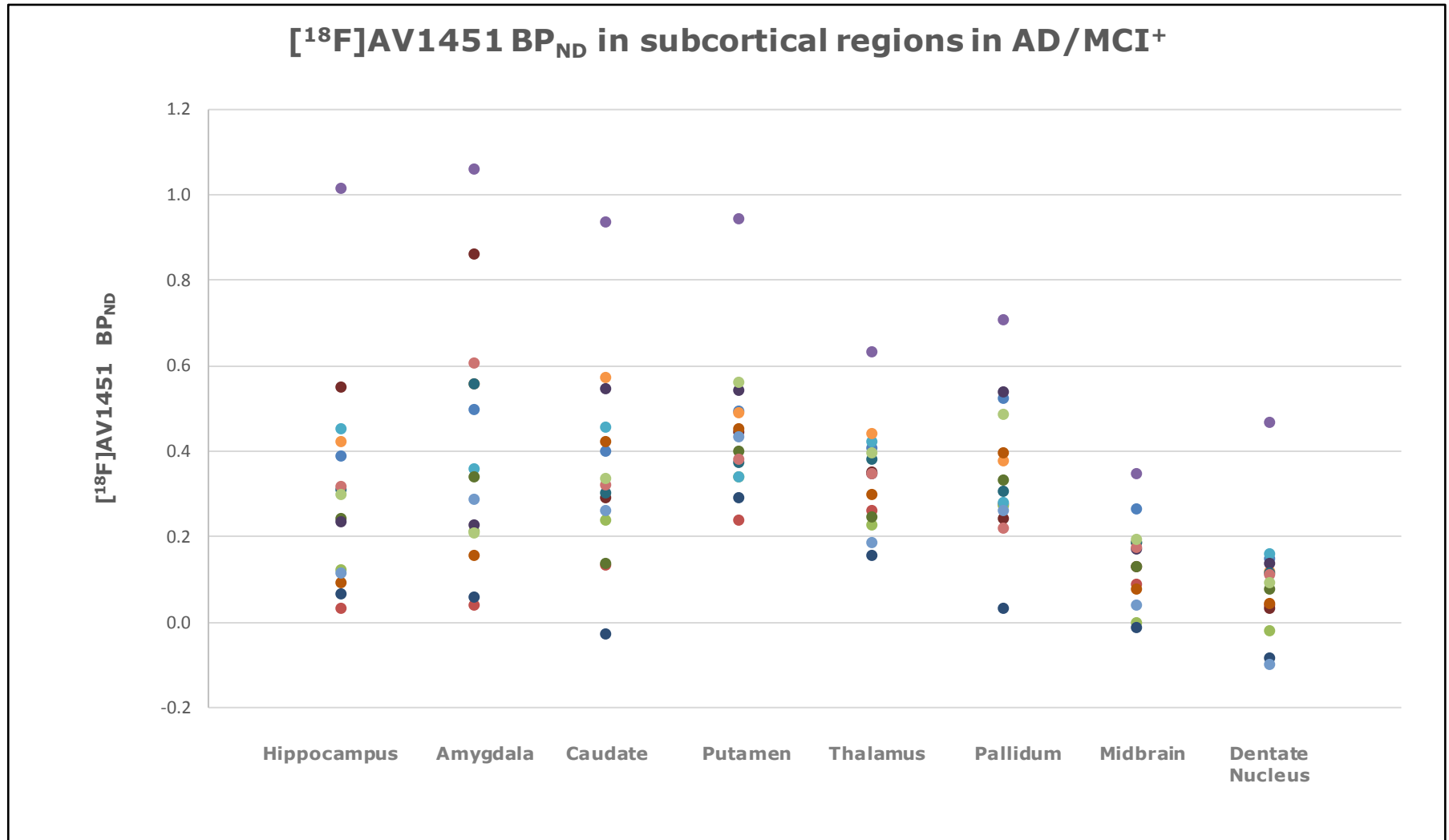


Figure 1918: Scatter plot for subcortical regions to show the range of $[^{18}\text{F}]\text{AV1451 BP}_{\text{ND}}$ values in patients with AD/MCI⁺. Each dot represents one patient, coloured by individual. Abbreviations: BP_{ND}, Non-displaceable Binding Potential; AD, Alzheimer’s Disease; MCI⁺, Mild Cognitive Impairment.

4.5.1.3. Classification of cases by [¹⁸F]AV1451 BP_{ND}

The support vector machine analysis using [¹⁸F]AV1451 BP_{ND} values in a subset of ROIs was able to separate the AD/MCI⁺ patients from PSP cases with a classification accuracy of 94.1%. The accuracy for the other pairwise comparisons is as follows: PSP vs. healthy controls = 90.6%; AD/MCI⁺ vs. healthy controls = 85.7%. The ability of a SVM to separate groups can be readily appreciated from the bivariate plot of hippocampal and midbrain BP_{ND} (Figure 20). Although neither region individually support accurate differentiation of AD from PSP, the combination of data across two regions leads to clear separate on groups.

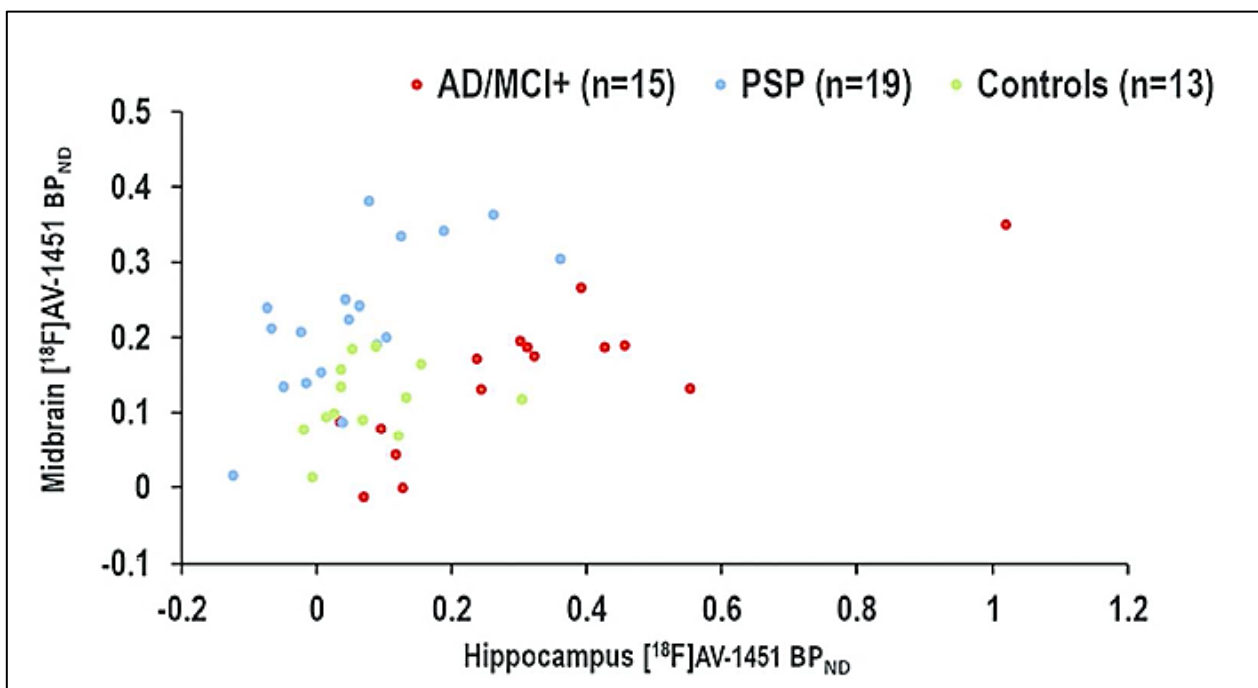


Figure 20: Bivariate plot of [¹⁸F]AV1451 BP_{ND} values in hippocampus and midbrain, in patient groups and healthy controls.

This figure shows the individual [¹⁸F]AV1451 BP_{ND} values in the hippocampus (X-axis) and midbrain (Y-axis) in patients with Alzheimer's Disease/Mild Cognitive Amyloid positive patients (red dots), Progressive Supranuclear Palsy (blue dots) and Healthy controls (green dots). Abbreviations: BP_{ND}, Non-displaceable Binding Potential; AD, Alzheimer's Disease; MCI+, Mild Cognitive Impairment; PSP, Progressive Supranuclear Palsy.

4.5.1.4. Hierarchical clustering analyses

To test whether the distribution of $[^{18}\text{F}]\text{AV1451 BP}_{\text{ND}}$ differed across groups, we used hierarchical clustering according to the similarity of their region-wise $[^{18}\text{F}]\text{AV1451}$ binding, collapsed across hemispheres. The similarities driving this classification can be visualised using multi-dimensional scaling (Figure 21). The accuracy for pair-wise comparisons using hierarchical cluster analyses is as follows: PSP vs. healthy controls = 84.4%; AD/MCI⁺ vs. PSP = 88.2%; AD/MCI⁺ vs. healthy controls = 82%.

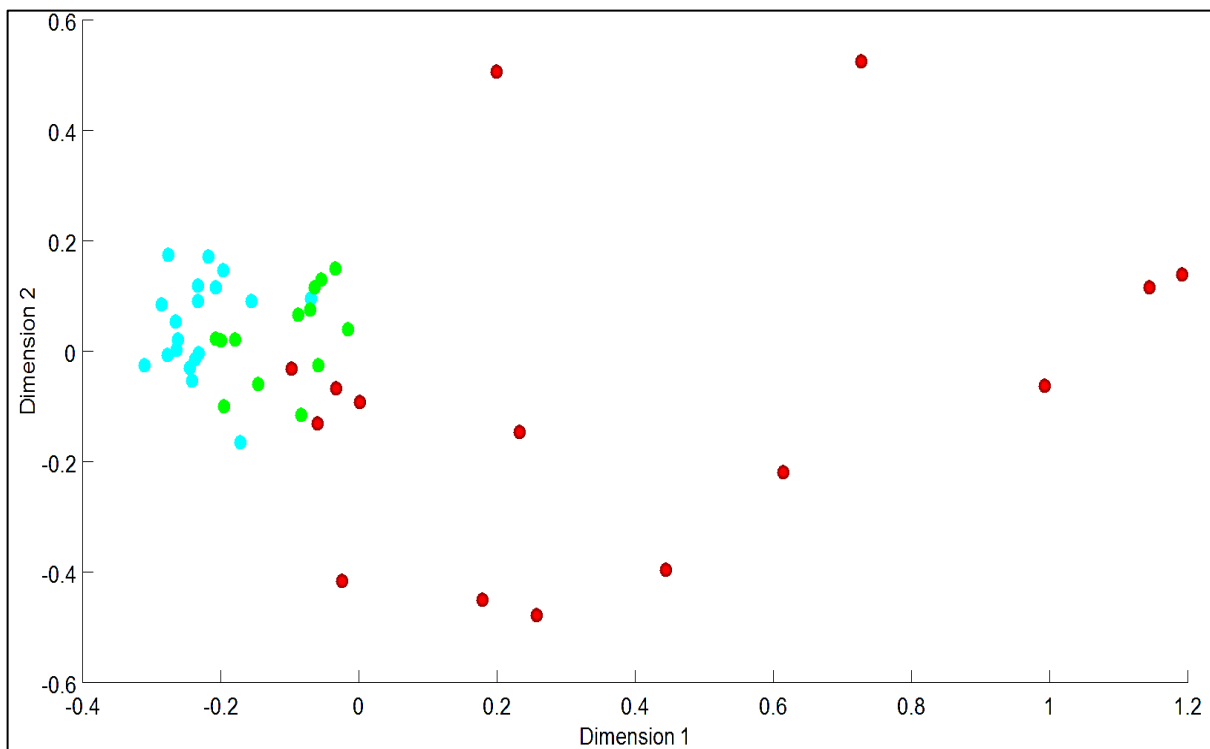


Figure 21: Two dimensional scaling of $[^{18}\text{F}]\text{AV1451 BP}_{\text{ND}}$ distribution across groups. This figure represents the three study groups: Healthy controls (blue dots); Progressive Supranuclear Palsy patients (green dots); Alzheimer's Disease/Mild Cognitive Amyloid Positive patients (red dots).

4.5.2. Neuropathology

A summary of the phosphor screen autoradiography results, AT8 immunohistochemistry data and neuromelanin staining in *post mortem* AD, PSP and healthy control brain cases is shown in Figure 22.

		AD	PSP	Control
Hippocampus	$[^{18}\text{F}]$ AV-1451			
	AT8 (tau)			
	Neuromelanin			
Midbrain	$[^{18}\text{F}]$ AV-1451			
	AT8 (tau)			
	Neuromelanin			
Basal Ganglia	$[^{18}\text{F}]$ AV-1451			
	AT8 (tau)			
	Neuromelanin			
Frontal Cortex	$[^{18}\text{F}]$ AV-1451			
	AT8 (tau)			
	Neuromelanin			

Figure 22:
 $[^{18}\text{F}]$ AV1451 BP_{ND}
**Phosphor screen
 autoradiography and
 immunohistochemistry
 for patient and healthy
 control cases.**

The figure 22 aligns the $[^{18}\text{F}]$ AV1451 autoradiographic binding in key regions of interest in an Alzheimer's disease (AD) case, a patient with progressive supranuclear palsy (PSP), and a control of similar age. Immunohistochemistry data assessing hyperphosphorylated tau (AT8, red) and neuromelanin staining (dark brown) are also shown for the same cases and regions of interest. Note that the yellow stains do not represent antibodies but rather represent non-specific protein immunofluorescence. There is $[^{18}\text{F}]$ AV1451 BP_{ND} in the hippocampus and, to a lesser extent, in the frontal cortex in AD. In contrast, $[^{18}\text{F}]$ AV1451 BP_{ND} to the midbrain slices was not specific to PSP but was also detected in the AD and control cases, who showed little or no tau pathology in the midbrain. Despite the *in vivo* $[^{18}\text{F}]$ AV1451 BP_{ND} to the basal ganglia in all groups (including controls), *post mortem* $[^{18}\text{F}]$ AV1451 BP_{ND} to the basal ganglia was sparse and non-specific in these three cases. Note the absence of neuromelanin-containing cells in the basal ganglia and cortical regions. The magnification of the autoradiography was $\times 1$, while immunohistochemistry pictures (AT8) and neuromelanin staining were taken under a $\times 20$ objective.

4.5.2.1. [¹⁸F]AV1451 Phosphor screen autoradiography

The autoradiography phosphor screen analyses in the AD brain tissue samples revealed that the anterior hippocampus had the highest and most specific binding of the [¹⁸F]AV1451 radiotracer. [¹⁸F]AV1451 binding was also found in the frontal cortex in the AD case, although to a lesser extent than in the hippocampal slice. In contrast, sparse and non-specific [¹⁸F]AV1451 binding was found in the AD basal ganglia tissue. The PSP and healthy control tissues showed overall sparse and nonspecific [¹⁸F]AV1451 binding, including anterior hippocampus, midbrain, basal ganglia and frontal cortex.

4.5.2.2. Immunohistochemistry

Abundant hyperphosphorylated tau protein was detected in the anterior hippocampus of the AD 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 hyperphosphorylated tau was found in the frontal cortex in the AD case, its relatively low density could be due to a slow cortical disease progression in this particular patient. The PSP tissue displayed high concentration of hyperphosphorylated tau in the midbrain and basal ganglia, while the AD brain displayed little AT8 staining in the same ROI. As expected, the healthy 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 AD, PSP or control case, which is in contrast to the strong *in vivo* [¹⁸F]AV1451 BP_{ND} of this radiotracer to the same ROI.

4.5.2.3. Tau immunohistochemistry (AT8) in the superior cerebellum

Only very sparse and punctate tau staining was found in the superior cerebellum of the PSP case (Figure 23-A), while no tau pathology was seen in the AD and control case (see respectively Figures 23-B and 23-C). This is overall consistent with the hypothesis that the superior cerebellum displays little or no tauopathy compared to other brain areas in either PSP and AD (Dickson et al., 2007; Okello et al., 2009; Schöll et al., 2016; Schwarz et al., 2016; Williams et

al., 2007). These findings also corroborated the use of the superior cerebellum as reference regions in the PET analyses (see section 4.4.1.4.).

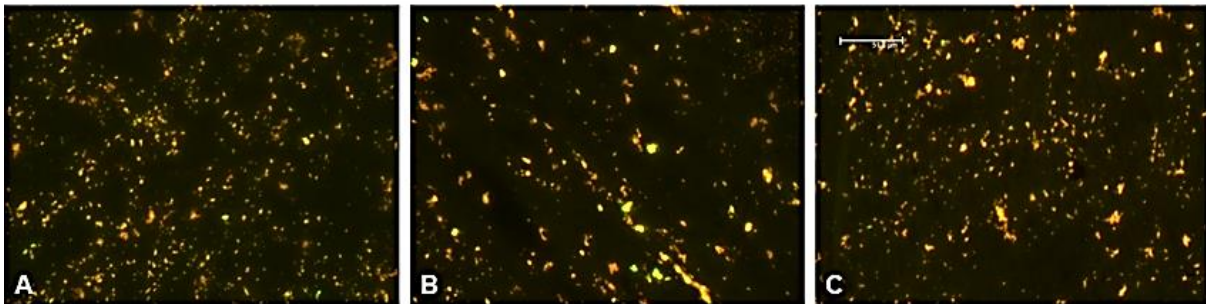


Figure 23: Post mortem immunohistochemistry of hyperphosphorylated tau in the superior cerebellum.

A. Progressive supranuclear palsy. B. Alzheimer's disease. C. No neurodegenerative disorders (healthy control). Note the small and punctate tau staining in the superior cerebellum of the PSP case and the absence of tau pathology in the other cases. The magnification of the immunohistochemistry pictures is x20.

4.6. Discussion

The principal result of our study is that PET imaging with the radiotracer [^{18}F]AV1451 revealed distinct patterns of binding in the primary tauopathy of PSP, in comparison to AD and its prodromal state of MCI⁺. The relatively large size of our PET study confirmed the high accuracy of discrimination between the clinical groups using [^{18}F]AV1451 BP_{ND} data, indeed by visual inspection (see section 4.5.1.2.; Figures 15-19), and with a simple support vector machine (see section 4.5.1.3.; Figure 20). However, despite this heuristic potential of [^{18}F]AV1451 as a tau biomarker, caution in the interpretation of its binding targets is indicated by the neuropathological and autoradiographic data (see section 4.5.2.; Figure 22). In particular, while [^{18}F]AV1451 strongly bound to AD-related tau pathology, non-specific binding of the same tracer can be found in PSP patients and healthy controls (Marquié et al., 2015). Nevertheless, our *post mortem* data suggest that off-target binding to neuromelanin is not a sufficient explanation of the BP_{ND} for [^{18}F]AV1451 at least in the context of PSP, and in some critical regions. For instance, we found *in vivo* significant [^{18}F]AV1451 uptake in the basal ganglia (in all groups including healthy controls) in the absence of *post mortem* neuromelanin-containing cells. This indicates that neuromelanin is not the principal target of off-target binding for [^{18}F]AV1451, 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., 2016).

For [^{18}F]AV1451 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 [^{18}F]AV1451 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 [^{18}F]AV1451 is increased by the demonstration that its binding patterns recapitulate *in vivo* the established *post mortem* distributions of tau pathology in PSP and AD. In addition, [^{18}F]AV1451 PET may have biomarker potential for the differential diagnosis of equivocal cases: whilst the distinction between PSP and AD can be readily made on clinical grounds, patients with PSP-parkinsonism clinically resemble PD (Williams et al., 2005).

In contrast to previous results (Johnson et al., 2016; Ossenkoppele et al., 2016), [^{18}F]AV1451 uptake was not correlated with disease severity in our groups (i.e., PSP-RS in PSP patients and severity of cognitive impairment in AD/MCI+ patients). Although, Smith et al. (2017) only found positive correlation between globus pallidus SUVRs and the PSP-RS values, but not in other regions, including the putamen and thalamus (Smith et al., 2017). 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 PSP and AD. Alternatively, it may be that [^{18}F]AV1451 uptake is inherently limited in staging disease severity in PSP and AD, analogous to the PiB tracer in AD (Hatashita and Yamasaki, 2010).

Technical considerations in assessing the [^{18}F]AV1451 binding *post mortem* and in estimating BP_{ND} *in vivo* must also be considered. First, it is possible that in the autoradiographic protocol (Marquié et al., 2015), ethanol washing and other procedures may have affected the labelling with [^{18}F]AV 1451, especially in the basal ganglia. Second, our PET analyses employed correction of 'partial volume effects', resulting from the CSF volume within each region. This mitigates the potential influence of brain volume loss seen in PSP and AD/MCI+. 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 BP_{ND} values based on cortical and subcortical atrophy, and the consequent inferential error from CSF volume and its correction.

Interestingly, the regions with the most significant group differences in [^{18}F]AV1451 BP_{ND} in PSP and AD *in vivo* were those predicted from prior *post mortem* studies for each disease. More specifically, PSP was associated with a pattern of increased [^{18}F]AV1451 BP_{ND} 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). Conversely, the clinical syndromes of AD and biomarker positive MCI were associated with increased [^{18}F]AV1451 BP_{ND} in widely distributed subcortical and cortical areas that have been consistently implicated in the pathogenesis and progression of AD (e.g., hippocampus, amygdala as well as frontal, parietal, temporal, and occipital cortices) (Braak et al., 2006; Braak and Braak, 1995). Together, these data demonstrated that the [^{18}F]AV1451 ligand recapitulates *in vivo* the typical neuropathological changes seen in PSP and AD, although it cannot be assumed that the cellular and/or molecular targets of [^{18}F]AV1451 binding are the same in both disorders.

[^{18}F]AV1451 BP_{ND} in selected regions of interest also distinguished PSP cases from AD/MCI⁺ patients with an accuracy of 94%, which suggests the potential of this radiotracer to discriminate *in vivo* amongst different tauopathies despite the relatively weak signal. The value of this analysis is not as a diagnostic biomarker, as clinical features readily distinguish the groups, but rather represents an early step in the process of validating [^{18}F]AV1451 PET as a biomarker for tauopathies. Multicentre replication with larger samples and broader diagnostic spectra would nonetheless be necessary, including for example, patients with frontotemporal dementia, corticobasal 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 [^{18}F]AV1451 and do not necessarily generalize to other radioligands. Further work is required to determine the specificity of [^{18}F]AV1451 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: i) PSP pathology

is mainly a 4R isoform tauopathy, while AD is characterized by balanced 3R/4R isoforms (Buée & Delacourte, 1999; Espinoza et al., 2008), and ii) the toxicity of tau aggregates may be driven by oligomers rather than tangles.

In conclusion, we suggest that [^{18}F]AV1451 is a useful PET ligand for *in vivo* studies in clinical populations with non-AD primary tauopathies such as PSP, despite the potential contribution of non-specific or “off-target” binding, and AD pathology. The brain regions with increased [^{18}F]AV1451 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 PSP and AD/MCI⁺ clinical syndromes. Together, our current findings support the further use of [^{18}F]AV1451 PET *in vivo* and *in vitro* to evaluate tau pathology in studies of dementia and neurodegeneration.

Chapter 5

Neuroinflammation in progressive supranuclear palsy and Alzheimer's disease

Material in this chapter has been published as:

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5.1. Introduction

Neurodegenerative disorders are due to long-lasting pathological processes associated with the deposition of abnormal toxic protein aggregates in the brain and the activation of a cascade of aberrant biochemical, metabolic, functional and structural changes (Pievani et al., 2014; Brettschneider et al., 2015). Recent literature has focused on the role of neuroinflammatory processes in neurodegeneration. In particular, it has been intensely investigated whether neuroinflammation occurs as a primary or secondary event in the course of neurodegenerative disorders, possibly exerting either beneficial/regenerative or detrimental effects (Heneka et al., 2014; Du et al., 2017; Pasqualetti et al., 2015). The characteristics of the neuroinflammation response largely depend on the specific features of the trigger insult, including duration and magnitude, which can drive either a neuro-regenerative protective function or a neurotoxic action (Rivest, 2009).

Many studies focusing on the glial cells involved in the inflammatory responses of the brain, namely microglia and astroglia, have over the years pointed out the dynamic and changing behaviour of these cells, accompanied by different morphologies and activation forms. A significant amount of literature points to a key role for activated microglia and astroglia in neurodegenerative disorders. Presence of activated microglia cells has been demonstrated in PSP, AD, PD, and Huntington's disease (HD) (Anderson et al., 2007; Cagnin et al., 2001; Edison et al., 2013; Edison et al., 2008; Fan et al., 2015; Fernández-Bostrán et al., 2011; Gerhard et al., 2006a; Gerhard et al., 2006b; Kropholler et al., 2007; Schuitemaker et al., 2013; Wiley et al., 2009), thus suggesting a biochemical link between the accumulating toxic proteins and microglia activation in neurodegenerative diseases. Comparably, astrocytes play an important role in neurodegenerative disorders with exacerbating effects when they are activated or reactive (Perry et al., 2010). Several approaches have over time revealed different facets of microglial phenotypic diversity, and advanced genetic analyses, in recent years, have added new insights into microglial heterogeneity, opening novel scenarios that researchers have just started to explore.

Clinical studies have shown that microglial activation, a proxy of neuroinflammation, is present even at the early stages not only in AD and PD, but

also in other neurodegenerative conditions such as frontotemporal dementias (FTD) (Stefaniak & O'Brien, 2015; Miyoshi et al., 2010; Lant et al., 2014). Similarly, reactive astrogliosis is an early phenomenon in the progression of AD (Santillo et al., 2011; Carter et al., 2012). The possible detrimental role of microglia activation in neurodegenerative disorders and its influence during the different disease phases remain largely unexplored.

Variations in several genes putatively involved in inflammation and immune responses have been suggested as risk factors of late onset AD on the basis of a genome-wide association study (GWAS) such as *SORL1* (sortilin-related receptor) and *TREM2* (triggering receptor expressed on myeloid cells 2) (Guerreiro et al., 2013; Jonsson et al., 2013; Rogaeva et al., 2007). Conversely, inflammatory genes have not been reported as risk factors of PSP (Sanchez-Contreras et al., 2018).

The currently available PET molecular imaging techniques allow the measurement of neuroinflammation through imaging of both astrocytes and microglia activation (Jacobs et al., 2012). The great majority of research has focused on PET imaging of microglia activation, and many radioligands have been synthesized, the great majority of which target the over-expression of the 18-kDa translocator protein (TSPO). TSPO is an outer mitochondrial membrane protein, expressed mostly by microglia and, to a lesser extent, by astrocytes (Venneti et al., 2006; Liu et al., 2014). Its levels in the central nervous system in healthy conditions are generally low, whereas their over-expression in the disease state has been well documented (Liu et al., 2014). Among the others, [¹¹C](R)-PK11195 is the first PET marker of *in vivo* microglial activation (Chauveau et al., 2008) and has been widely adopted in multiple neurodegenerative conditions, including PSP and AD (Cagnin et al., 2001; Edison et al., 2013; Edison et al., 2008; Fan et al., 2015; Gerhard et al., 2006a; Gerhard et al., 2006b). Understanding whether and how microglia are reacting within a disease course may provide important insights into disease pathogenesis and have remarkable implications for future clinical trials; although one needs to bear in mind that microglial activation represents only part of the complex cascade of events in neuroinflammation (Agostinho et al., 2010).

PET radiotracer development for neuroinflammation beyond TSPO, for imaging neurodegenerative diseases (and other neurological disorders), is an active area of research with several emerging targets and tracers under various stages of preclinical and clinical research studies underway. Today, PET imaging of neuroinflammation is not yet regarded as an *in vivo* biomarker for clinical diagnosis or to evaluate disease progression, but it may help to test novel therapeutic agents targeting glial cells (Hamby & Sofroniew, 2010). A number of novel tracers for microglial activation have already been developed (Tronel et al., 2017) but hardly any PET tracers are used to investigate *in vivo* astrocyte activation.

There is a current interest in developing more astrocyte tracers. For example, Tyancke and colleagues (2018) have recently successfully evaluated [¹¹C]BU99008 as a specific and selective *in vivo* PET radioligand for the imidazoline₂ binding site (I2BS) in humans.

5.2. Aims

I aimed assessed the magnitude and patterns of [¹¹C](R)-PK11195 binding in two very different neurodegenerative entities, PSP and AD/MCI⁺, characterized by distinct anatomical distributions of pathology. The value of this comparison *does not* lie in the differential diagnosis between these clinically diverse entities but rather in establishing the distribution and relevance of neuroinflammation in two distinct tauopathies. Overall, the aims of the work in this chapter were:

- I. To assess neuroinflammation in typical patients with PSP, relative to patients with AD/MCI⁺ and sex- and age-matched healthy controls.
- II. To assess if neuroinflammation relates to clinical severity in PSP and AD/MCI⁺ cohorts, using disease specific measures of severity.
- III. To explore if neuroinflammation is observed *in post mortem* tissue from patients with PSP and AD.

5.3. Hypotheses

The principal hypotheses were that:

- I. PSP patients would show enhanced [^{11}C](R)-PK11195 binding in regions critically implicated in PSP pathogenesis, including the basal ganglia and midbrain (Williams et al., 2007). AD/MCI⁺ patients would display increased [^{11}C](R)-PK11195 binding in cortical and subcortical areas associated with hallmarks of AD pathology, including the medial temporal lobe, parietal, and temporal cortices (Braak et al., 2006).
- II. [^{11}C](R)-PK11195 binding would be associated with disease severity in both PSP and AD/MCI⁺ groups.
- III. [^{11}C](R)-PK11195 binding in PSP and AD *post mortem* brains would mirror the expected brain regions as in the *in vivo* PET study.

5.4. Materials and methods

5.4.1. Neuroimaging

5.4.1.1 Participants

The current project was conducted within the context of the 'Neuroimaging of Inflammation in Memory and Other Disorders' study (NIMROD, see Chapter 2) (Bevan-Jones et al., 2017). The sub-study included 16 PSP patients with probable PSP by the 1996 MDS criteria (representing a 'classical phenotype', which is sometimes referred to as Richardson's syndrome, PSP-RS. All patients also meet 2017 revised criteria for probable PSP-RS (Höglinger et al., 2017; Litvan et al., 1996); nine patients meeting diagnostic criteria for probable AD (McKhann et al., 2011) (typical amnesic phenotype, without biomarkers), and seven amnesic MCI⁺ patients (PiB PET biomarker positive). Thirteen age-, sex-, and education-matched healthy controls with no history of major psychiatric or neurological illnesses, head injury or any other significant medical comorbidity were also recruited. All participants did not have any acute infectious or chronic systemic inflammatory disorder (e.g., lupus, rheumatoid arthritis, Crohn's disease, polymyalgia rheumatica).

5.4.1.2. Clinical and cognitive assessments

The relevant NIMROD tests to test the current hypothesis are displayed in Table 22.

Test name	Format	Measured variable	Cohort
PSP-RS	Assessment tool completed by study clinician	Disease severity	PSP
RAVLT	Researcher administered test of learning, recall and repetition of semantically unrelated words	Disease severity	AD/MCI ⁺
ACE-R	Structured test administered by researcher	Attention and orientation, memory, fluency, language and visuospatial domains	PSP, AD/MCI ⁺ and HC

Table 22: Clinical and neuropsychological assessments for patient groups and healthy controls.

Abbreviations: PSP-RS, Progressive Supranuclear Palsy-Rating Scale; RAVLT, Rey Auditory and Verbal Learning Test; ACE-R, Addenbrooke's Cognitive Examination-Revised; PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with positive β -amyloid; HC, Healthy Control.

5.4.1.3. Magnetic Resonance Imaging data

In brief, all participants underwent an MRI session acquired on a 3 Tesla (3T) using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) T1-weighted sequence. The T1-weighted images were used to facilitate tissue class segmentation and to allow inverse normalisation of template space regions of interest (ROIs) defined by modified 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/>) and the inverse transform was applied to the modified Hammers atlas (resliced from MNI152 to ICBM2009a space) to bring the ROIs to subject MRI space.

For further details of MRI data acquisition and pre-processing, see chapter 2, sections 2.3.2.1. and 2.3.2.2.

5.4.1.4. Positron Emission Tomography data

In summary, all PET scanning was performed at the WBIC or Addenbrooke's hospital. [¹¹C](R)-PK11195 radioligand aimed to measure the density of activated microglia as an indication of neuroinflammation. 500MBq [¹¹C](R)-PK11195 was injected intravenously over 30 seconds at the onset of a 75 minutes scan.

Each PET emission frame was reconstructed and corrections were applied. Each emission image series was realigned using SPM8 to correct for patient motion

during data acquisition and create a mean image. The mean aligned PET image was rigidly co-registered to the MRI T1-weighted image using SPM8 and the inverse transformation applied to the modified Hammers atlas to put it in native PET space. In the absence of a standard reference region for [^{11}C](R)-PK11195; a supervised cluster analysis was used to determine the reference tissue time-activity curve (Yaqub et al., 2012).

In the published paper, we chose not to purpose a voxel-wise approach because the PK signal can be noisy (even with negative values in some voxels, especially in white matter and in ventricles). Smoothing such data would be required for the application of Gaussian Random Field (GRF) theory to voxel-wise statistic maps. But smoothing across grey matter, white matter and ventricles signals might introduce artefacts, making interpretation of the more results difficult. The published data therefore focussed on a ROI analysis that readily permits adjustment of the data for spill-in and spill-out of PET signal. However, in this thesis, I also present the voxel-wise data, to complement the ROI analysis.

The methods are summarised in the next section, but for further details of PET data acquisition and pre-processing, see chapter 2, sections 2.3.2.3 and 2.3.2.4.

5.4.1.5. Regional [^{11}C](R)-PK11195 BP_{ND} statistical analyses

To compare [^{11}C](R)-PK11195 binding across groups (PSP, AD/MCI⁺ and healthy controls), individual ROI BP_{ND} values for [^{11}C](R)-PK11195 were used in a repeated-measures GLM to test for the main effect of ROI, main effect of group, and group \times ROI interaction. Age and sex were included as covariates of no interest. For the AD/MCI⁺ and PSP group, we also tested Pearson's correlations between regional [^{11}C](R)-PK11195 BP_{ND} and disease severity using the PSP-RS for PSP patients and the RAVLT scores for AD/MCI⁺ patients. All analyses were repeated using [^{11}C](R)-PK11195 BP_{ND} values that were not corrected for CSF partial volume effects.

5.4.1.6. Whole brain [^{11}C](R)-PK11195 BP_{ND} statistical analyses

Whole brain voxel-wise analysis was performed on the BP maps. Images were processed in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>)

and in-house scripts. The T1-weighted images were segmented into six tissue classes and matched together using the DARTEL pipeline. The study specific template image was then affine registered to MNI space, so as to present results in standardised stereotactic coordinates, using the combined normalisation transform parameters for each participant's images. The mean images from each PET session were registered to each participant's T1-weighted image. The native space BP map was then transformed into MNI spaces using the DARTEL flow field and template-to-MNI transform. In addition, partial volume corrected BP maps were created using the Meltzer method (Meltzer et al., 1996) to adjust for CSF, and the Muller-Gartner method (Muller-Gartner et al., 1992) to adjust grey matter for white matter fraction. The maps were smoothed by an isotropic Gaussian Kernel of 8mm. Statistical analysis was performed in SPM12, using an ANOVA design with a single factor of three levels, one for each group.

5.4.2. Neuropathology

The human brain tissue preparation is described in Chapter 2, part 2.3.3.1. The *post mortem* brain tissue used in this study came from three subjects: one PSP case, one AD case and one control. The PSP patient (NP16-42) was a 79 year old female who died from sepsis. The AD case (NP16-00151) was an 88 year old male diagnosed with Braak stage VI, and according to his death certificate he died from AD. The control brain tissue (NP16-00258) derived from a female of 49 years who died due to anorexia nervosa.

5.4.2.1. [¹¹C](R)-PK11195 Phosphor screen autoradiography

[¹¹C](R)-PK11195 phosphor screen autoradiography was performed following a previously published protocol by Johnström and colleagues (2012). In brief, frozen brain sections were thawed and immersed in 10mM PBS/0.1% v/v Triton X100 for 2 minutes. After repeating the wash for 2 minutes, 0.2 MBq/ml of [¹¹C](R)-PK11195 was added and sections were incubated for 1 hour. Sections were washed twice in PBS/tween buffer for 2 minutes, rinsed in water and allowed to dry before transfer to a storage phosphor screen (GE healthcare) that had been photo-bleached prior by exposure. The slides and phosphor screen were enclosed in an aluminium film cassette for 3 hours. The slides were mounted on a 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, and images analysed using Aida imaging software.

5.4.2.2. Immunohistochemistry

The microglial burden was investigated in frozen tissue samples provided by the Cambridge Brain Bank. My colleagues Olly Green and Robert Fincham conducted this work using the 3 step Avidin-Biotin Complex (ABC) method (Vector Laboratories Ltd 2017), based on immunohistochemical staining of activated microglia with a monoclonal anti-human HLA-DR (Dako UK, M0775, HLA-DP,DQ,DR Clone CR3/43). Microglial burden is expressed as the LN3 %-area. After fixation of frozen sections in industrial methylated spirits for 10 minutes, sections were incubated with PBS (Oxoid BR001G) for 10 minutes. To reduce nonspecific antibody binding, samples were incubated in 20% normal rabbit serum (NRS) blocker for 20 minutes. Sections were then incubated in primary antibody HLA-DR (Dako UK, M0775) at a dilution of 1:500 in PBS for 1 hour then rinsed in PBS for 10 minutes. Sections were then incubated in biotinylated rabbit anti-mouse secondary antibody (RAMB) (Dako UK, E0345). The secondary antibody was used at a dilution of 1:200 made up in a solution of 10% Normal Human Serum (NHS) (Sigma H4522). Sections were incubated in the secondary antibody for 30 minutes, before being rinsed with PBS for 10 minutes. Sections were then incubated in a tertiary solution of Avidin Biotin Complex solution (Vector Laboratories PK6100) for 30 minutes. Sections were rinsed in PBS, before incubating in 3,3'-Diaminobenzidine (DAB) solution for 4 minutes (Vector Laboratories SK4100). After DAB staining slides were rinsed in water. Slides were then counterstained in Harris' Haematoxylin (Cellpath RBA-4205-009) for 15 seconds, and then rinsed in water for 5 minutes. Sections were differentiated in 1% acid alcohol and then left for 5 minutes to blue in water. The final step was to dehydrate, clear and mount. Microglia were manually counted in selected high magnification fields (x40) fields using an Olympus BX53 light microscope and Lumenera Infinity 2 camera. Regions of interest were selected within each brain region studied (middle frontal gyrus, hippocampus, substantia nigra, basal ganglia, and dentate nucleus). Only amoeboid microglia were counted and not ramified cells (with thanks to Dr Kieren Allinson).

5.5. Results

5.5.1. Neuroimaging

5.5.1.1. Demographics and cognition

Descriptive data for demographic and cognitive details are shown in Table 23. The patient and healthy control groups were matched in terms of age, sex, and education. Nevertheless, to account for any possible residual confounding effect associated with variability in demographic measures, age and sex were included as covariates of no interest in the general linear models of the main effect of ROI, the main effect of group, and the group \times ROI interaction. As expected, there was a significant main effect of group for cognitive measures, driven by reduced MMSE and ACE-R scores in PSP and AD/MCI⁺ patients relative to healthy controls. Episodic memory, as assessed via the RAVLT (delayed recall), was significantly impaired in AD/MCI⁺ patients, relative to controls.

	PSP (N= 16)	AD/MCI⁺ (N=16)	HC (N= 13)	Group difference
Age mean (SD)	68.4 (±5.7)	68.7 (±8.6)	68.0 (±5.3)	ns (per each <i>post hoc</i> t-test group comparison)
Gender M/F	10/6	9/7	5/8	ns (per each <i>post hoc</i> t-test group comparison)
Education mean (SD)	12.2 (±1.9)	13.8 (±3.1)	14.1 (±2.7)	ns (per each <i>post hoc</i> t-test group comparison)
MMSE mean (SD)	27.4 (±1.9)	25.4 (±3.0)	28.7 (±1.0)	F = 7.60, <i>p</i> = 0.002 (HC's > AD***, HC's > PSP*, PSP > AD*)
ACE-R mean (SD)	82.3 (±10.0)	77.5 (±11.0)	91.3 (±5.3)	F = 7.58, <i>p</i> = 0.002 (HC's > AD***, HC's > PSP**)
RAVLT mean (SD)	-	1.3 (±1.4)	9.7 (±3.2)	<i>t</i> = 8.93, <i>p</i> < 0.0001 (HC's > AD***)
PSP-RS mean (SD)	40.8 (±15.0)	-	-	-

Table 23: Demographics and cognitive variables of study participants.

Abbreviations: PSP, Progressive Supranuclear Palsy; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment with positive β -amyloid; HC, Healthy Control; SD, Standard Deviation; M, Male; F, Female; MMSE, Mini-Mental State Examination; ACE-R, Addenbrooke's Cognitive Examination-Revised; RAVLT, Rey Auditory Verbal Learning Test; ns, not significant at *p* < 0.05 (uncorrected) by ANOVA, *post hoc* t-test or chi-squared as appropriate. *Post-hoc* independent samples t-tests (**p* < 0.05, ***p* < 0.01, ****p* < 0.005).

5.5.1.2. Regional [¹¹C](R)-PK11195 BP_{ND} in relation to clinical diagnosis

In the repeated-measures analysis of regional binding, we found a significant main effect of ROI ($F_{2,36} = 3.8, p < 0.001$), main effect of group ($F_{2,36} = 5.7, p < 0.006$), and a group \times ROI interaction ($F_{2,70} = 2.6, p < 0.001$) (Figure 24). The group and interaction effects were driven in part by higher [¹¹C](R)-PK11195 BP_{ND} values in the AD/MCI⁺ group relative to both the PSP and healthy control groups, in cortical and subcortical ROIs including occipital, parietal, and temporal cortices, as well as in the hippocampus, amygdala, and other medial temporal lobe ROIs (Figures 24, 26 and 27). The PSP group, relative to healthy controls, showed increased [¹¹C](R)-PK11195 BP_{ND} in the thalamus, putamen, and pallidum (Figures 24 and 25).

Repeating these analyses using ROI [¹¹C](R)-PK11195 BP_{ND} values that were not corrected for CSF partial volume effects yielded similar results ($F_{2,36} = 2.2, p < 0.0001$, for the main effect of ROIs; $F_{2,36} = 6.1, p < 0.006$ for the main effect of group; and $F_{2,70} = 2.0, p < 0.0001$ for the group \times ROI interaction).

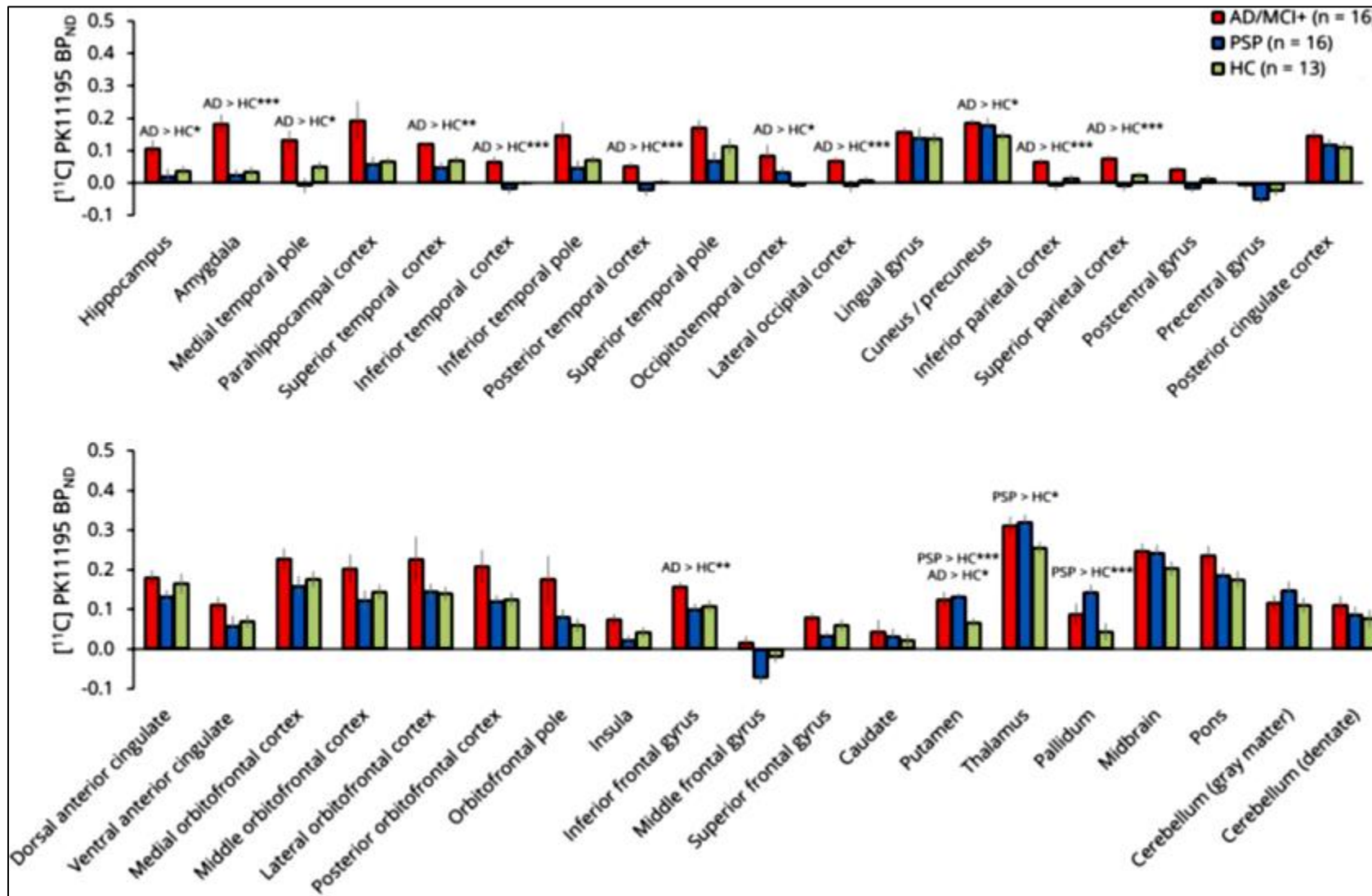


Figure 24: $[^{11}\text{C}](R)\text{-PK11195 BP}_{\text{ND}}$ in each region of interest for the patient groups and healthy controls.

This figure shows the bar plots represent the mean values (\pm SE) of the $[^{11}\text{C}](R)\text{-PK11195 BP}_{\text{ND}}$ in each region of interest for the participant groups: AD/MCI⁺, PSP, and HCs. The $[^{11}\text{C}](R)\text{-PK11195 BP}_{\text{ND}}$ data reported here are corrected for CSF partial volume effects. *Post hoc t* tests: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$. Abbreviations: AD, Alzheimer Disease; MCI⁺, Mild Cognitive impairment with positive β -amyloid; PSP, Progressive Supranuclear Palsy; HC, Healthy Control; BP_{ND}, Non-displaceable Binding Potential.

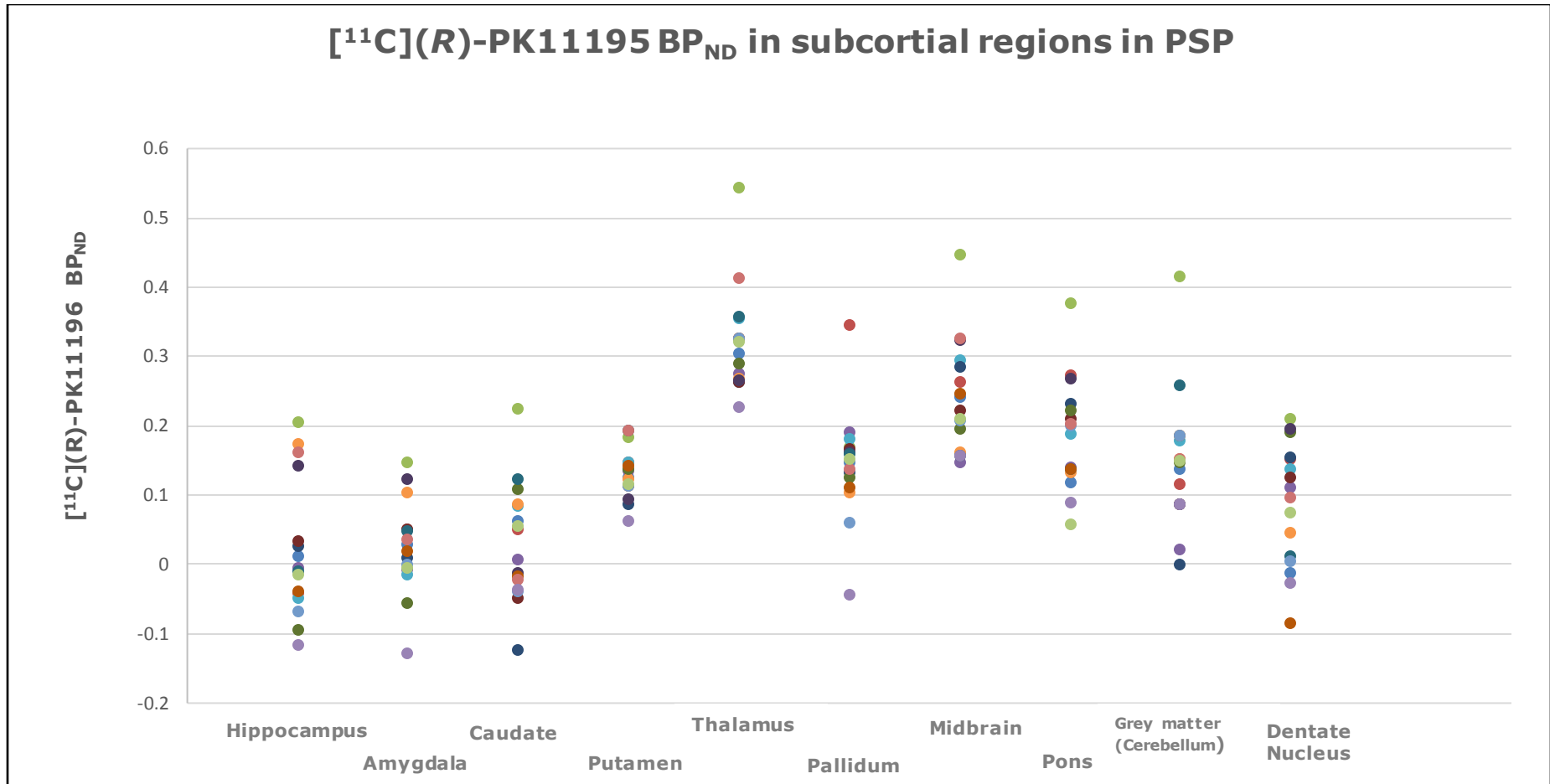


Figure 25: Scatter plot for subcortical regions to show the range of [¹¹C](R)-PK11195 BP_{ND} values in patients with PSP. Each dot represents one patient, coloured by individual. Abbreviations: BP_{ND}, Non-displaceable Binding Potential; PSP, Progressive Supranuclear Palsy.

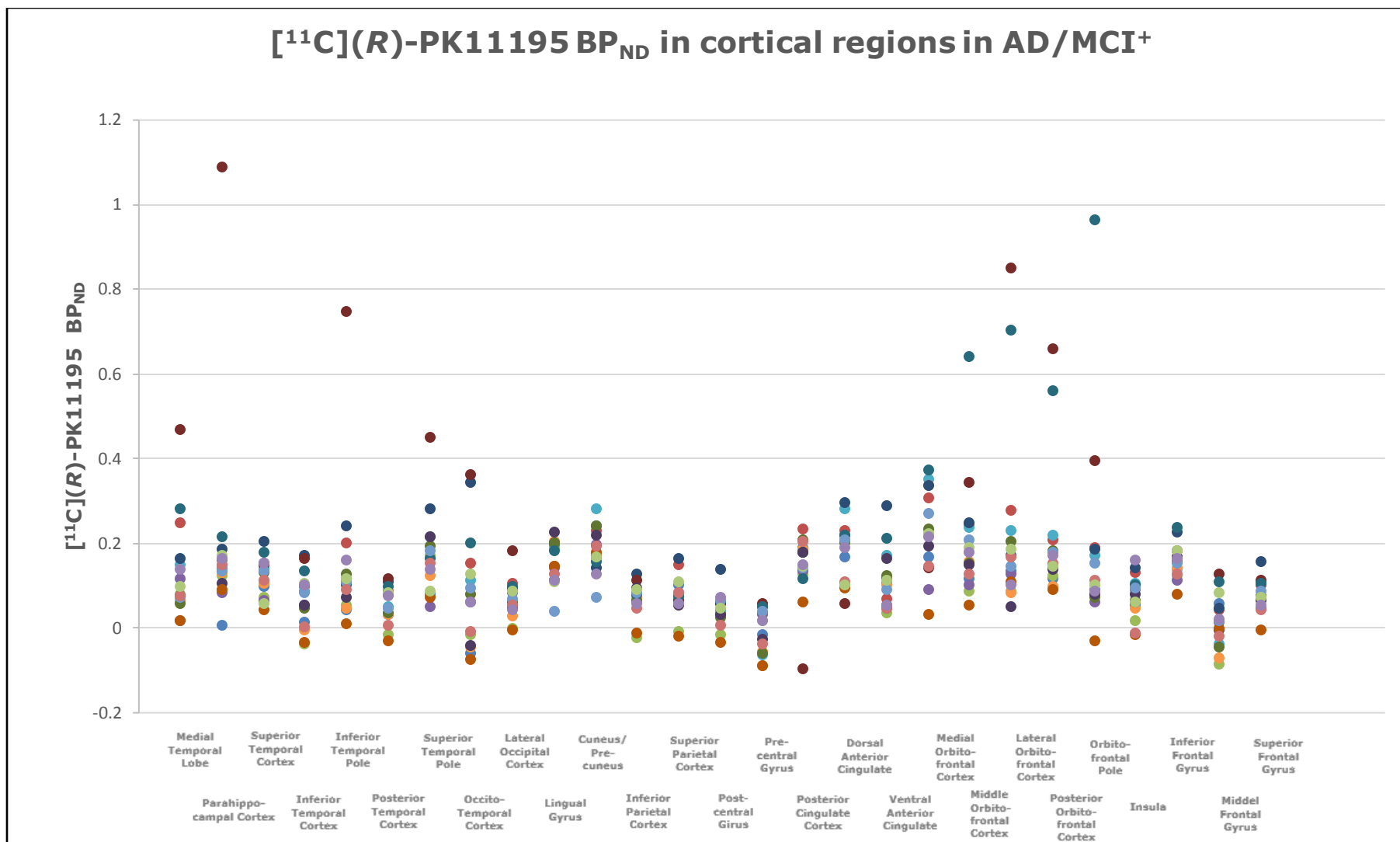


Figure 26: Scatter plot for cortical regions to show the range of $[^{11}\text{C}](R)\text{-PK11195 BP}_{\text{ND}}$ values in patients with AD/MCI⁺. Each dot represents one patient, coloured by individual. Abbreviations: BP_{ND}, Non-displaceable Binding Potential; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment.

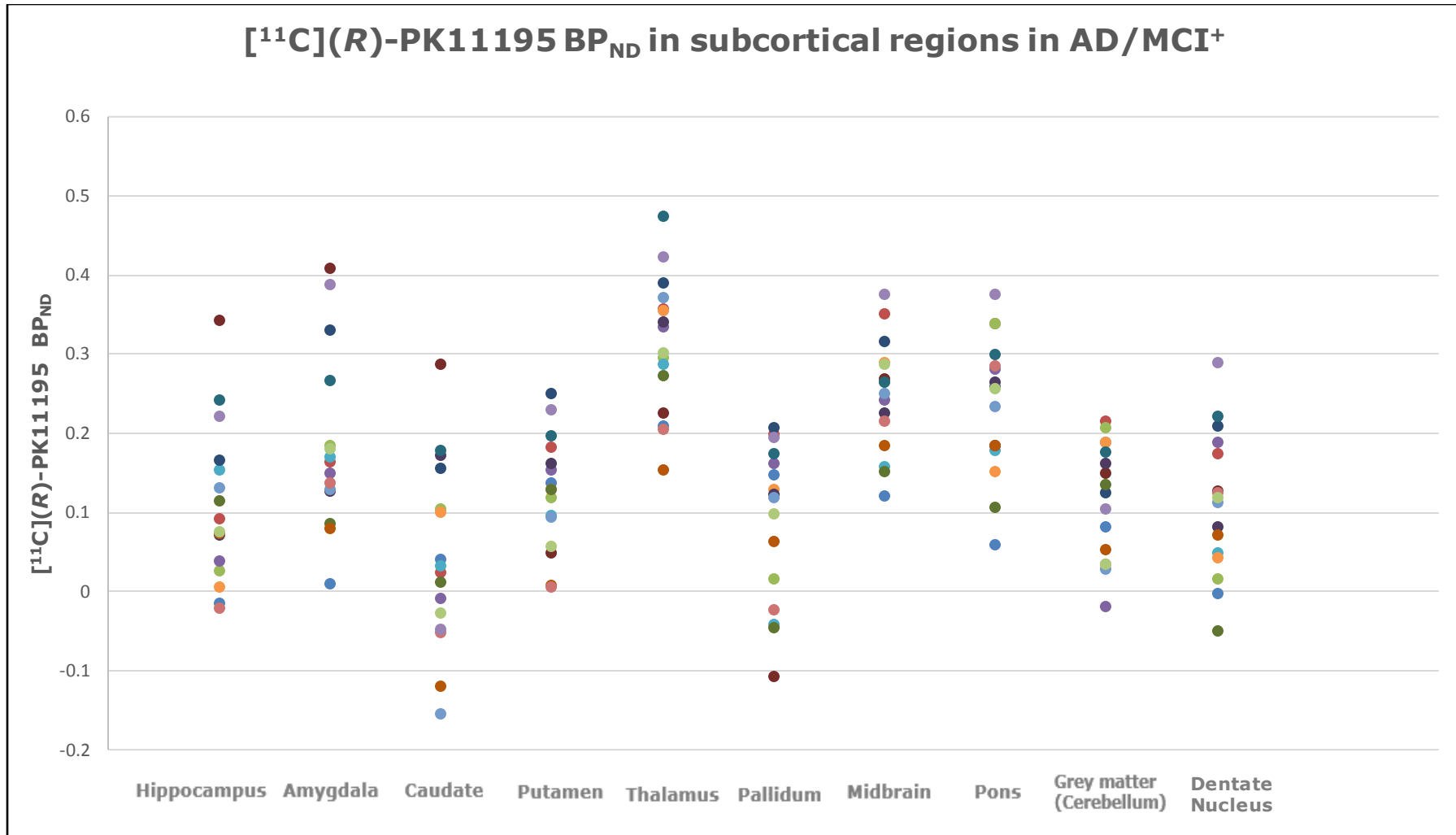


Figure 207: Scatter plot for subcortical regions to show the range of [¹¹C](R)-PK11195 BP_{ND} values in patients with AD/MCI⁺. Each dot represents one patient, coloured by individual. Abbreviations: BP_{ND}, Non-displaceable Binding Potential; AD, Alzheimer's Disease; MCI⁺, Mild Cognitive Impairment.

5.5.1.3. Regional [^{11}C](R)-PK11195 BP_{ND} associated with disease severity

We then tested whether regional [^{11}C](R)-PK11195 BP_{ND} related to disease severity in each clinical group. In the AD/MCI⁺ group, there was a significant *negative* correlation between the RAVLT scores (delayed recall at 30 minutes) and [^{11}C](R)-PK11195 BP_{ND} in the pre-cuneus (Figure 28-A). In the PSP group, we found a significant *positive* correlation between [^{11}C](R)-PK11195 BP_{ND} in the pallidum, midbrain, and pons and disease severity, as assessed via the PSP-RS (Figures 28-B, C and D).

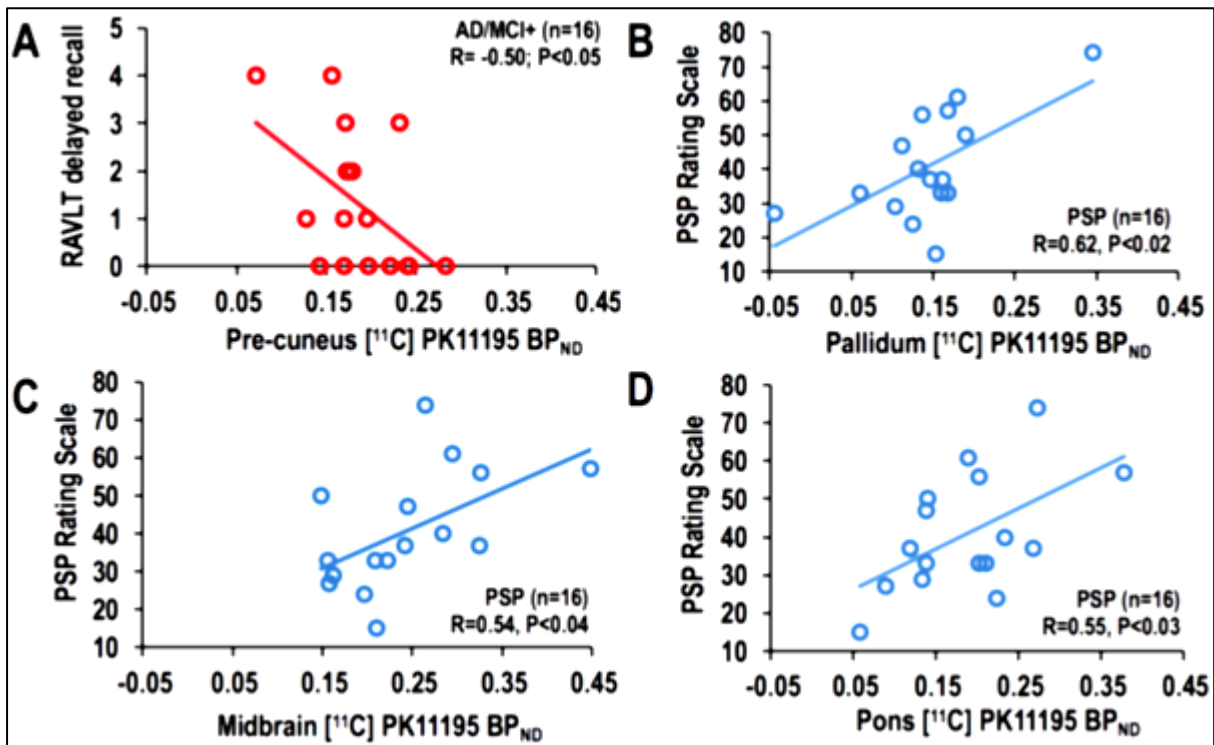


Figure 28: Correlations between disease severity assessments and patient groups.

A. Correlation between [^{11}C](R)-PK11195 BP_{ND} values in the precuneus (X-axis) and RAVLT scores (Y-axis) in patients with AD/MCI⁺ (red dots). B–D. Correlation between [^{11}C](R)-PK11195 BP_{ND} values in the pallidum, midbrain, and pons (x-axes) and PSP-RS (y-axes) in patients with PSP.

Abbreviations: AD, Alzheimer Disease; MCI⁺, Mild Cognitive Impairment with positive β -amyloid; PSP, Progressive Supranuclear Palsy; BP_{ND}, Non-displaceable Binding Potential; RAVLT, Rey Auditory Verbal Learning Test; PSP-RS, Progressive Supranuclear Palsy-Rating Scale.

5.5.1.4. Whole brain voxel-wise [^{11}C](R)-PK11195 BP_{ND}

Figure 29 illustrates the voxel wise maps for [^{11}C](R)-PK11195 BP_{ND} . While broad patterns can be discerned in the distribution of BP_{ND} estimates, the spatial noise can also be seen, as a relatively 'speckled' appearance of the BP_{ND} . For group wise comparisons, the individual data were therefore smoothed, and presented as an array of axial slices in Figures 30 to 32.

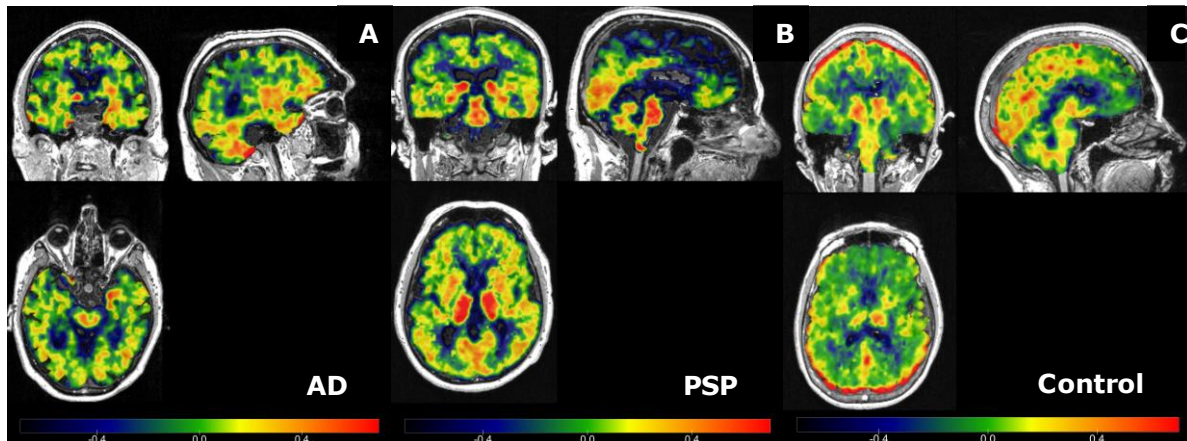


Figure 29: Examples of coronal, transverse and sagittal sections of voxel-wise BP_{ND} maps for [^{11}C](R)-PK11195 co-registered to the individual MRI. Note the [^{11}C](R)-PK11195 binding in the basal ganglia in all groups, albeit higher in the PSP patient (B). Patient with AD (A) also showed increased [^{11}C](R)-PK11195 binding in medial temporal lobe regions and widespread neocortical areas, relative to PSP patient and control (B and C), while in the PSP case (B) had increased high [^{11}C](R)-PK11195 binding to the midbrain, relative to the AD patient and the control subject (A and C). The colour bars denote BP values.

Voxel-wise BP_{ND} contrast for AD/MCI⁺ greater than controls is shown in Figure 30. Two uncorrected peaks were found bilaterally in the anterior medial-temporal lobe which are indicated by the yellow arrows. This result corresponds to the amygdala-hippocampal differences seen in Figure 24, but the group effect appears to be anatomically restricted.

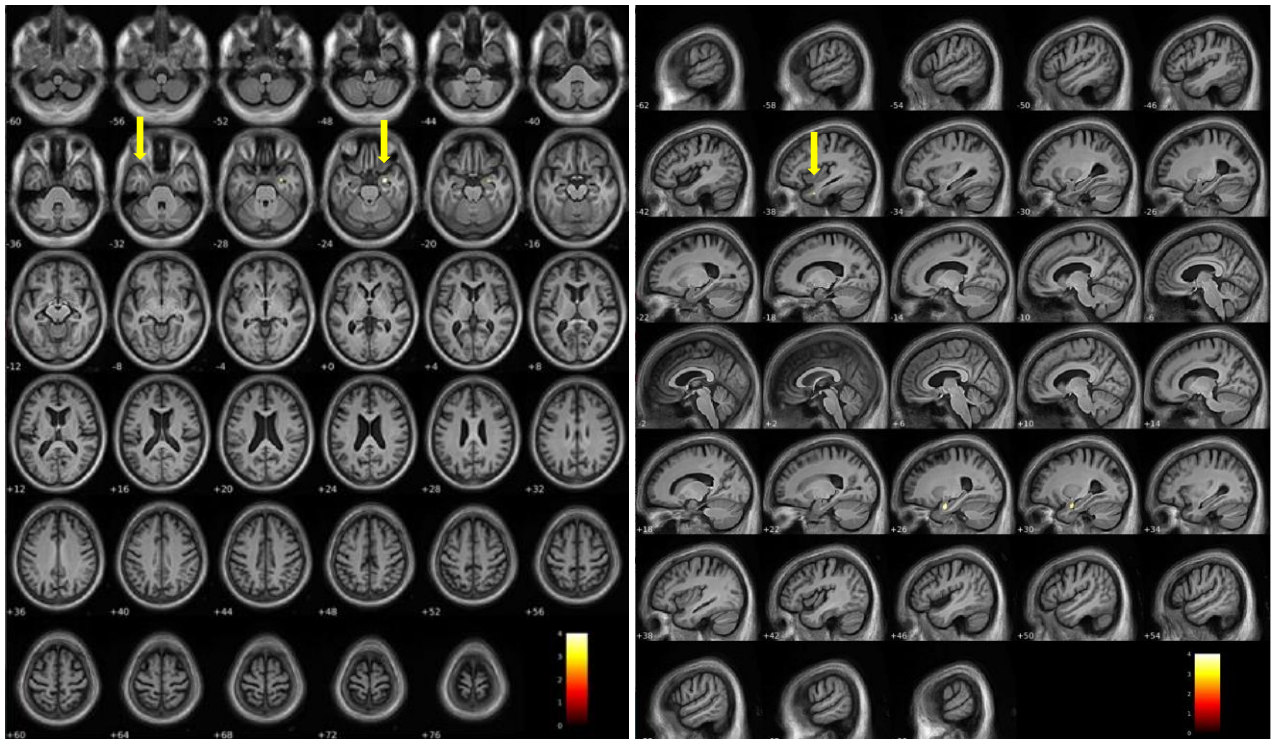


Figure 30: Significant voxels from voxel-wise analysis of $[^{11}\text{C}](R)\text{-PK11195}$ BP_{ND} maps for AD/MCI⁺ greater than controls (uncorrected height threshold $p < 0.001$). Voxels overlaid on axial and sagittal slices of the group-average T1-weighted image in standard MNI space. The colour bars denote t -values. Arrows indicate significant clusters.

Voxel-wise BP_{ND} contrast for PSP greater than controls ($p < 0.05$ FWE cluster-wise) is shown in Figure 31, overlaid on axial and sagittal slices of the group-average T1-weighted image in standard MNI space. This voxel-wise result recapitulates the midbrain differences seen in Figure 24, but at this FWE cluster corrected threshold, the group effect appears to be anatomically restricted and does not identify striatal or thalamic differences. The cerebellar voxel wise effects are also not observed in the cerebellar regional contrast.

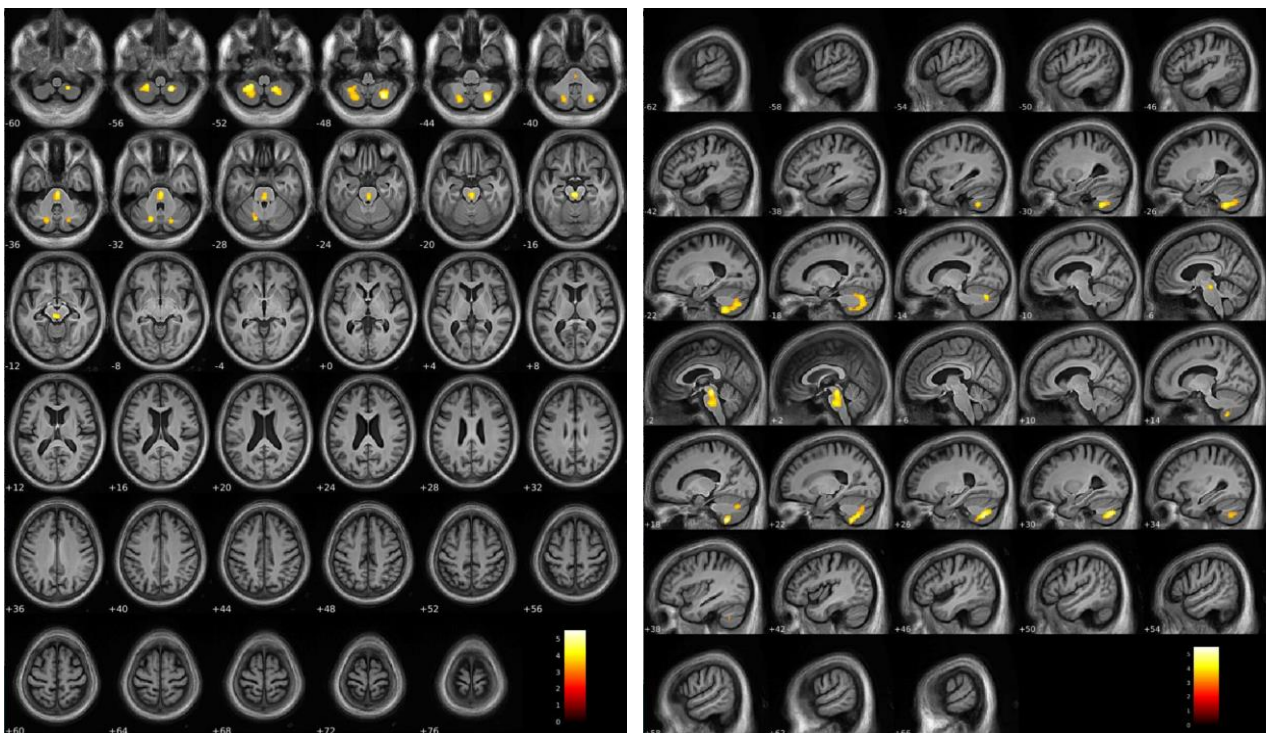


Figure 31: Significant clusters from voxel-wise analysis of $[^{11}\text{C}](R)\text{-PK11195 } BP_{ND}$ maps for PSP greater than controls ($p < 0.05$ FWE, following an initial uncorrected height threshold $p < 0.001$). Clusters overlaid on axial and sagittal slices of the group-average T1-weighted image in standard MNI space. The colour bars denote t -values.

Voxel-wise BP_{ND} contrast for AD/MCI⁺ greater than PSP ($p < 0.05$ FEW cluster-wise) is shown in Figure 32, overlaid on axial and sagittal slices of the group-average T1-weighted image in standard MNI space. This voxel-wise result highlights the regional differences in neuroinflammation in AD/MCI⁺ versus PSP, in the temporal lobe, extending posteriorly to occipital cortex.

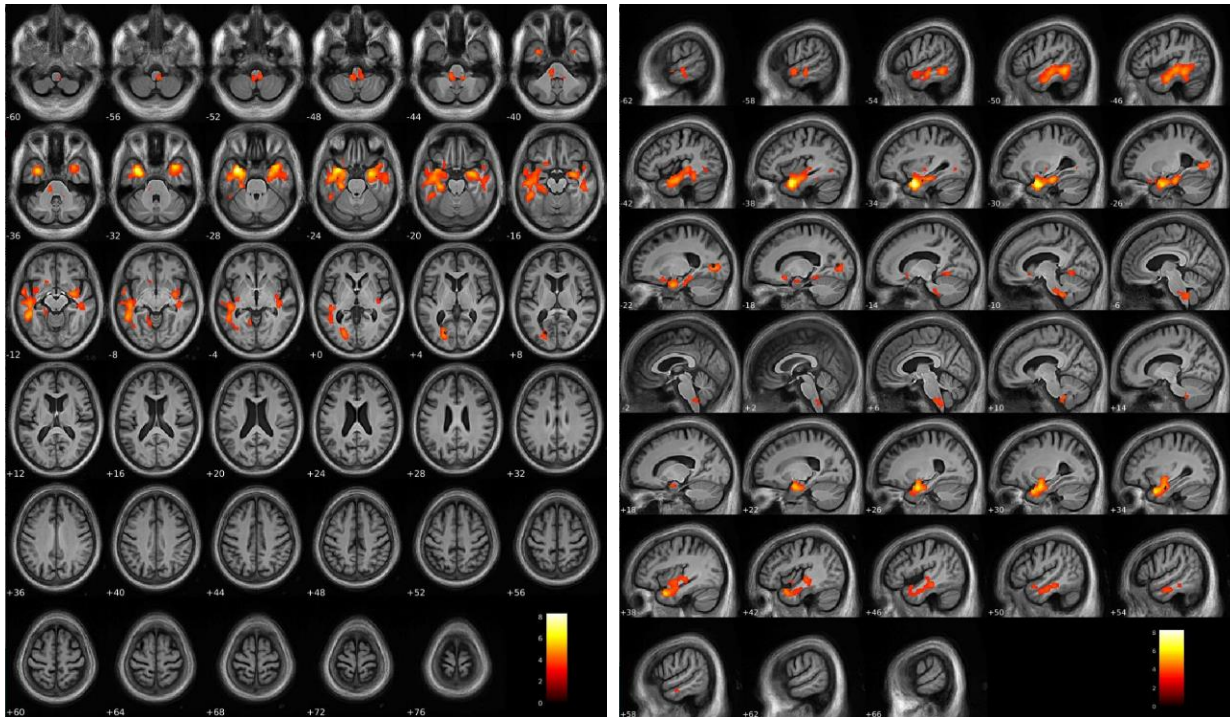


Figure 32: Significant clusters from voxel-wise analysis of $[^{11}\text{C}](R)\text{-PK11195 } BP_{ND}$ maps for AD/MCI⁺ greater than PSP ($p < 0.05$ FEW, following an initial uncorrected height threshold $p < 0.001$). Clusters overlaid on axial and sagittal slices of the group-average T1-weighted image in standard MNI space. The colour bars denote t -values.

5.5.2. Neuropathology

5.5.2.1. $[^{11}\text{C}](R)\text{-PK11195}$ Phosphor screen autoradiography

A summary of the phosphor screen autoradiography results in *post mortem* AD, PSP and control brain cases are shown in Figure 33.

The autoradiography phosphor screen analyses in the AD brain tissue samples revealed that in the white matter of the middle frontal gyrus and cerebellum had the highest and most specific binding of the $[^{11}\text{C}](R)\text{-PK11195}$ in this group. $[^{11}\text{C}](R)\text{-PK11195}$ binding was also found in the hippocampus. In contrast, sparse $[^{11}\text{C}](R)\text{-PK11195}$ binding was found in the AD basal ganglia (globus pallidus and putamen) and midbrain slices.

The highest [^{11}C](R)-PK11195 BP_{ND} in PSP was also detected in the frontal cortex and cerebellum like the AD case, but there was an important [^{11}C](R)-PK11195 uptake in the midbrain. The PSP case showed lower [^{11}C](R)-PK11195 BP_{ND} in the basal ganglia, and non-specific uptake was found in the hippocampus.

The control *post mortem* phosphor autoradiography showed the highest and most specific binding of the [^{11}C](R)-PK11195 uptake in the basal ganglia. [^{11}C](R)-PK11195 binding was also found in the midbrain and the dentate of the cerebellum, although sparse and non-specific [^{11}C](R)-PK11195 uptake was detected in the middle frontal gyrus and hippocampus.

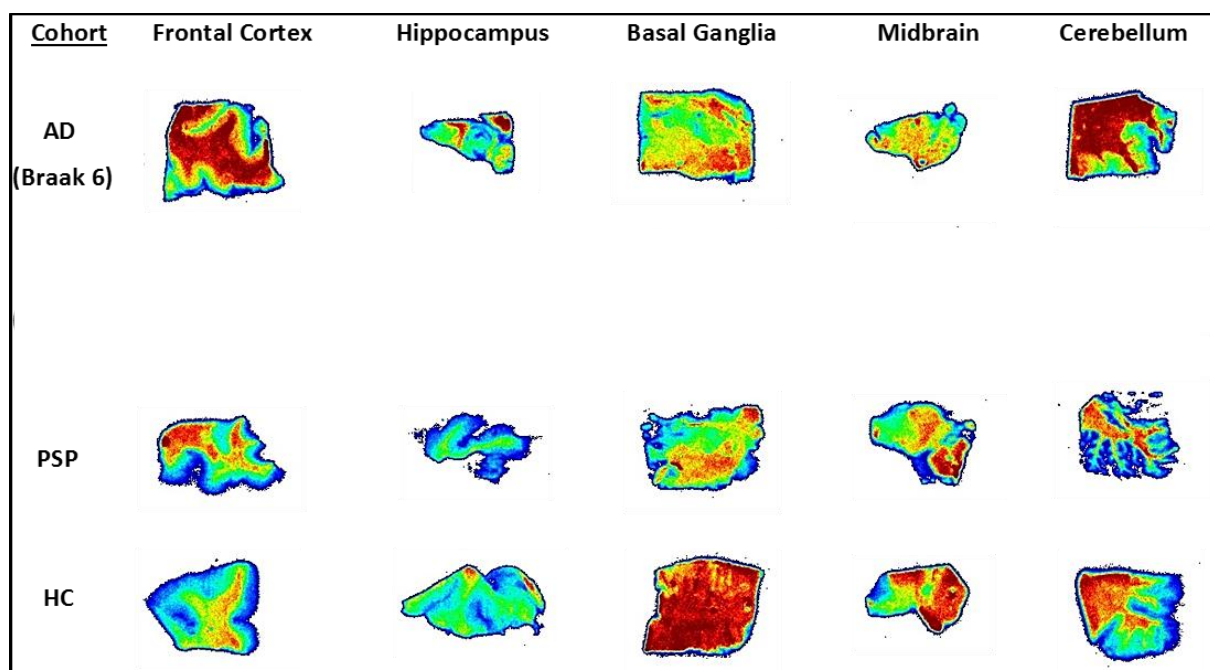


Figure 33: [^{11}C](R)-PK11195 BP_{ND} Phosphor screen autoradiography for patient and healthy control cases.

The Figure 33 aligns the [^{11}C](R)-PK11195 BP_{ND} autoradiographic binding in key regions of interest in an Alzheimer's disease (AD) case, a patient with progressive supranuclear palsy (PSP), and a control of similar age. In the AD case, there was [^{11}C](R)-PK11195 BP_{ND} in the frontal cortex, hippocampus and cerebellum. In contrast, sparse [^{11}C](R)-PK11195 binding was found in the AD basal ganglia (globus pallidus and putamen) and midbrain slices. The PSP tissue showed higher [^{11}C](R)-PK11195 binding in the frontal cortex, midbrain and cerebellum, and in a lower degree in the basal ganglia. In contrast, non-specific [^{11}C](R)-PK11195 uptake was found in the hippocampus in the PSP case. The control case showed substantial [^{11}C](R)-PK11195 uptake within the basal ganglia, midbrain and cerebellum, and to a lesser extent, in the frontal and hippocampus slices. Abbreviations: AD, Alzheimer's Disease; PSP, Progressive Supranuclear Palsy; HC, Healthy Control. The magnification of the autoradiography was x1.

5.5.2.2. Immunohistochemistry

A summary of the HLA-DR immunohistochemistry data in *post mortem* AD, PSP and healthy control brain cases is shown in Figure 34.

Microglia were manually counted in selected high magnification fields (x40)

fields using an Olympus BX53 light microscope and Lumenera Infinity 2 camera. The regions of interest were selected within each brain region studied: middle frontal gyrus, hippocampus, substantia nigra (midbrain), basal ganglia (globus pallidum and putamen), and cerebellar dentate nucleus. Only amoeboid microglia were only counted and not ramified cells (Table 24).

	Alzheimer's Disease	Progressive Supranuclear Palsy	Healthy Control
Middle frontal cortex	11	0	7
Hippocampus	11	0	0
Substantia nigra (Midbrain)	13	15	4
Basal ganglia	0	16	0
Dentate nucleus	4	14	2

Table 24: Number of amoeboid microglial cells.

Abundant activated microglia were identified, particularly in the white matter in the middle frontal gyrus and hippocampus in the AD case, while less activated microglia staining was found in the cerebellar dentate nucleus. The AD brain tissue did not show microglial activation in the globus pallidus and putamen (basal ganglia).

The PSP tissue displayed high concentration of activated microglia in the basal ganglia, substantia nigra in the midbrain, and the cerebellum. In contrast, PSP brain sample did not show HLA-DR immunoreactivity in the middle frontal cortex neither hippocampus, while the AD brain displayed HLA-DR staining in those same ROI's.

The control brain tissue did not show any activation of the microglia in the hippocampus either in the basal ganglia. Instead, amoeboid microglial cells were common in the middle frontal gyrus, and in a lower degree in the substantia nigra and cerebellar dentate nucleus.

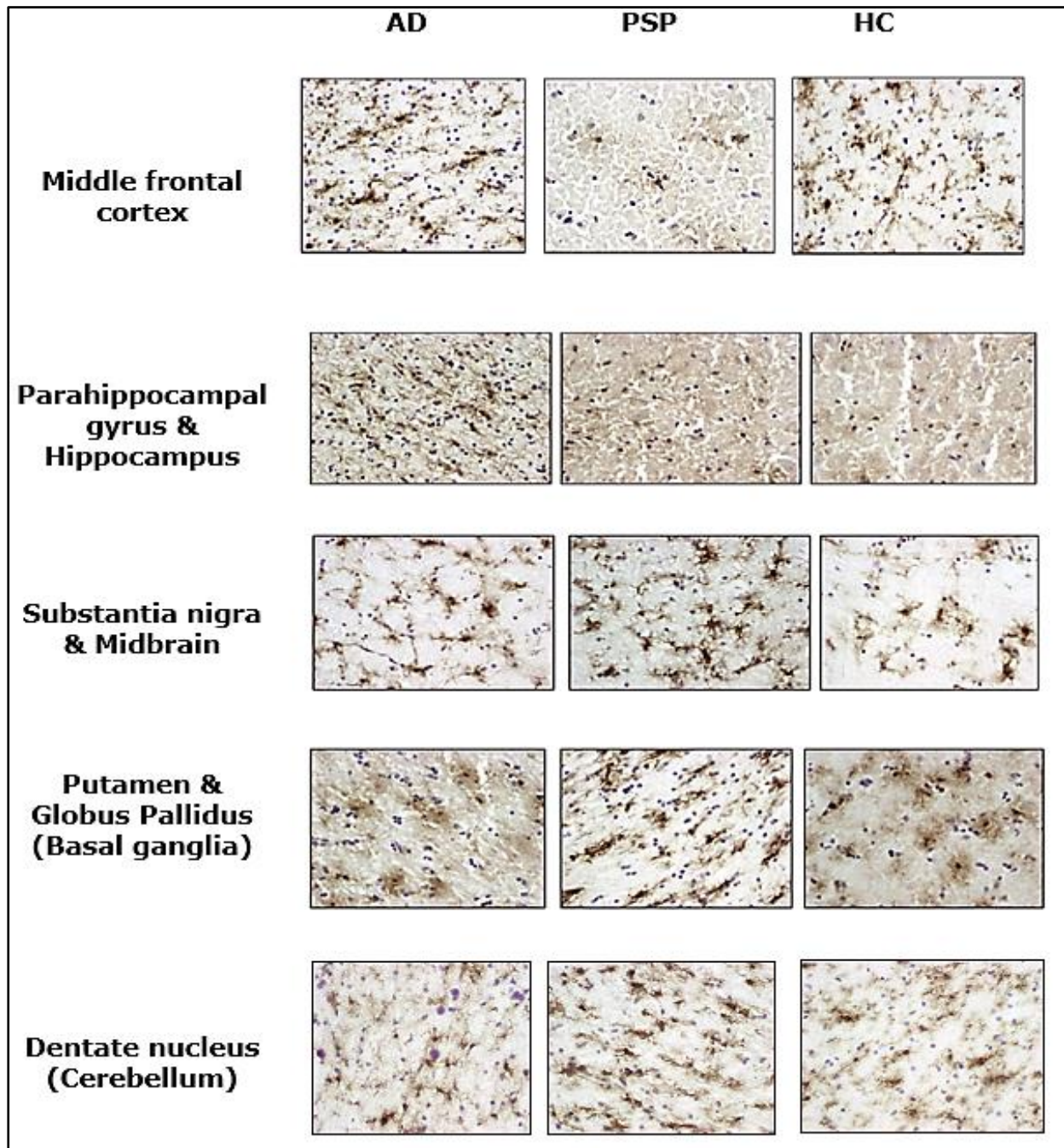


Figure 214: Microglia activation immunohistochemistry (HLA-DR) for patient and healthy control cases.

The Figure 34 aligns the HLA-DR staining in key regions of interest in an Alzheimer's disease (AD) case, a patient with progressive supranuclear palsy (PSP), and a control of similar age. Activated microglia was mainly identified in the middle frontal gyrus, hippocampus and substantia nigra in the AD case. The AD brain tissue did not show microglial activation in the basal ganglia. HLA-DR staining in PSP tissue was detected in the basal ganglia, midbrain and the cerebellar dentate nucleus. In contrast, PSP brain sample did not show HLA-DR immunoreactivity in the middle frontal cortex neither hippocampus. The control case showed activated microglia staining in the middle frontal cortex and to a lesser extent in the midbrain and cerebellar dentate nucleus but did not show any activation of the microglia in the hippocampus either in the basal ganglia. Abbreviations: AD, Alzheimer's Disease; PSP, Progressive Supranuclear Palsy; HC, Healthy Control. Immunohistochemistry pictures (HLA-DR) staining were taken under a $\times 20$ objective.

5.6. Discussion

The brain regions with the most marked abnormalities of [^{11}C](R)-PK11195 PET BP_{ND} in PSP and AD/MCI⁺ were those predicted from the established distribution of neurodegeneration of each disease. Specifically, PSP patients had evidence of enhanced neuroinflammation in the thalamus, pallidum, and putamen, a group of subcortical regions that have been implicated in the pathophysiology of PSP (Hauw et al., 1994; Litvan et al., 1996). The increased [^{11}C](R)-PK11195 binding in the basal ganglia in PSP is also consistent with preliminary findings reported in a study with four PSP patients (Gerhard et al., 2006). Conversely, amnesic AD/MCI⁺ patients had evidence of increased neuroinflammation in the medial temporal lobe as well as parietal and lateral temporal cortices (Braak et al., 2006; Ossenkoppele et al., 2015; Schöll et al., 2016; Schwarz et al., 2016).

Our data demonstrate that the density and distribution of activated microglia in living patients with PSP and AD/MCI⁺ mirror the typical neuropathological changes characteristic of each disorder. This could result from a causal link between neuroinflammation and neurodegeneration, although the association might also derive from the process of neurodegeneration *itself*. A cross-sectional and non-interventional study such as this one cannot alone provide the direction of causality. Nevertheless, the disease-specific anatomical distributions of activated microglia in PSP and AD/MCI⁺ suggest a regional association rather than a side effect of a global increased [^{11}C](R)-PK11195 binding in response to a general inflammatory insult.

Our PET data are also in keeping with previous *post mortem* findings (Fernández-Bostrán et al., 2011) which demonstrated that microglia burden (as assessed via LN3-immuno-staining) showed a disease-specific topological relationship with the pathological hallmarks of PSP and AD (Fernández-Bostrán et al., 2011). More specifically, the previous *post mortem* study (Fernández-Bostrán et al., 2011) found that the microglia density was greater in the substantia nigra of PSP cases relative to AD patients and healthy controls, while AD patients had significantly higher microglia density in the parietal cortices when compared to PSP cases and healthy controls (Fernández-Bostrán et al., 2011). Together with our findings, these data suggest that microglia activation exists with the pathogenic processes underlying PSP and AD could contribute to the process of on-going

neurodegeneration (Fernández-Bostrán et al., 2011). If so, this would warrant the further investigation of immune-therapeutic strategies to modulate neuroinflammation in PSP and AD, although evidence from earlier anti-inflammatory trials in AD remains controversial (Lyketsos et al., 2007; Martin et al., 2008); and no such clinical trials have been conducted in PSP.

In contrast, [^{11}C](R)-PK11195 binding *in post mortem* phosphor screen autoradiography and immunohistochemical analyses were less consistent with [^{11}C](R)-PK11195 PET imaging *in vivo* seen in these diseases and controls.

There are several potential reasons why the thalamic and midbrain [^{11}C](R)-PK11195 binding signal was high across all groups. It may be due to the relatively old age of the donors (Kumar et al., 2012; Cagnin et al., 2001). In a study of normal adults aged 32 to 80 years, Cagnin and colleagues (2001) found that regional [^{11}C](R)-PK11195 did not significantly change with age, except in the thalamus, which showed an age-dependent increase. The thalamus is connected to widespread cortical regions. Similarly, the midbrain is reciprocally connected to several brain regions, primarily the thalamus and basal ganglia, and has one of the highest densities of microglia, particularly in the substantia nigra (Lawson et al., 1990). Therefore, subtle inflammation or injury in other regions may induce amplified microglial responses in the highly connected 'relays' of thalamus and midbrain. Another possible cause is the proximity of the thalamus to several white matter tracts which are highly lipophilic (Catalano et al., 1996). Given the lipophilic nature of [^{11}C](R)-PK11195, there can be high non-specific binding that contributes to the background levels in TSPO-PET imaging in this area (Chen & Guilarte, 2008; Petit-Taboue et al., 1991). This would not explain the high [^{11}C](R)-PK11195 binding in the cerebellum in the AD case, but we do not know the mechanism of death of the AD donor: one might speculate about comorbid sepsis in agonal hours as a contributor to cerebellar inflammation.

Dementia is also a common neurological condition associated with traumatic brain injury (TBI) (Smith et al., 2013), and survivors may deteriorate years after their injury (Whitnall et al., 2006). Neuroinflammation in the form of glial activation triggered by the TBI can persist for many years, and might contribute to the PET signal in some of the patients in the current study. For instance, Ramlackhansingh and collaborators (2011) showed that [^{11}C](R)-PK11195 uptake was detected in the thalamus up to 17 years after TBI. Scott's study (2015)

showed for the first time *in vivo* that the degrees of thalamic microglial activation and thalamo-cortical white matter tract damage are closely related. Glia become activated at sites of injury (Thiel et al., 2010; Maxwell et al., 2006) but also at distant sites (Johnson et al., 2013), including subcortical nuclei like the thalamus (Maxwell et al., 2006).

Our data also confirmed the hypothesis that [¹¹C](R)-PK11195 binding correlates with disease severity in both PSP and AD/MCI⁺; more specifically, with PSP severity as measured via the PSP-RS in PSP and severity of episodic memory impairment as assessed via the RAVLT in AD/MCI⁺. Again, these effects were not global correlations, but adhered to the functional anatomy of cognitive and motor symptoms in PSP and AD (i.e., pallidum, midbrain, and pons in relation to PSP-RS in PSP as well as the cuneus/pre-cuneus in relation to episodic memory deficits in AD).

Overall, the use of [¹¹C](R)-PK11195 PET could provide useful information to stratify patients in future clinical trials or to track the effects of treatments targeting neuroinflammation in neurodegenerative disorders like PSP and AD/MCI⁺. However, to fully meet its potential towards these directions, additional properties are necessary to show for this biomarker of neuroinflammation. Specifically, although recent longitudinal studies in AD have demonstrated that changes in [¹¹C](R)-PK11195 binding may be associated with disease progression (Kreisl et al., 2016; Schuitemaker et al., 2007), such a correlation has not been established in PSP. Neuroinflammation might be stable in symptomatic stages of PSP, as suggested by a pilot study of two PSP patients (Gerhard et al., 2006).

Perhaps more importantly, it remains to be determined whether the putative effects of anti-inflammatory therapies can reduce the elevated [¹¹C](R)-PK11195 binding in PSP and AD/MCI⁺, consequently, could help slowing the progression of these disorders. This would also enable mediation analysis to test the causality between immune-reactivity and disease progression in dementia and related disorders. Furthermore, we suggest that multi-tracer PET studies will be useful to formally assess how neuroinflammation relates to other important molecular aspects in dementia and related disorders including, for example, studying how neuroinflammation is associated with amyloid load in AD (Fan et al., 2015) as well as with tau burden in AD and PSP. A cross-sectional and single-tracer study like

the present one is not able to address such interesting and open questions, although it represents the necessary first step towards achieving this goal.

Technical considerations regarding the [^{11}C](R)-PK11195 BP_{ND} PET methods should also be considered. In particular, our main regional PET analyses used partial volume correction for CSF, which controlled for differences in CSF signal contamination within each region and across the different diagnostic groups (i.e., PSP, AD/MCI⁺, and healthy control groups). Although this approach is important to reduce the potential influence of brain volume loss seen in PSP and AD/MCI⁺, this MRI-guided method is subject to error due to one imperfect registration of PET and MR images, together with errors in segmentation and point spread function modelling. However, we note that using uncorrected PET data yielded similar results in terms of the main effect of ROI, main effect of group, and group \times ROI interaction, which provides substantiation of the CSF-corrected results. The supervised cluster method for estimating [^{11}C](R)-PK11195 BP_{ND} could also have introduced an under-estimation bias, as the reference tissue may have still included specific binding of the radioligand. In any case, this may have only reduced the effect sizes without altering the risk of reporting false positive results.

We also highlight that our data are specific to [^{11}C](R)-PK11195 and may not generalize to second-generation TSPO ligands (e.g., PBR28) or alternative tracers of neuroinflammation over and above those that bind to TSPO (e.g., COX-1, MPO, macrophage infiltration) (Hamelin et al., 2016; Suridjan et al., 2015; Yokokura et al., 2016). Further studies should assess the utility of such novel markers for *in vivo* imaging of neuroinflammation, bearing in mind that the binding of second-generation TSPO tracers like PBR28 can be affected by genetic variations (i.e., the rs6971 TSPO polymorphism) (Owen et al., 2012).

In conclusion, we have provided clear evidence that [^{11}C](R)-PK11195 is a sensitive PET ligand for *in vivo* and *in post mortem* studies of neuroinflammation in clinical populations with non-AD tauopathy, PSP-Richardson's syndrome, as well as in AD and its prodromal stage of amnesic MCI. The brain regions that showed increased [^{11}C](R)-PK11195 binding were those predicted from the well-established pattern of regional cortical and subcortical neurodegeneration in each disease. Our data support the further use of [^{11}C](R)-PK11195 PET to study

microglial activation in neurodegenerative disorders and in clinical trials that aim to modulate neuroinflammation in neurodegenerative disease.

Chapter 6

General discussion

6.1. Review and interpretation

The aim of this thesis was to advance the understanding of tau pathology and neuroinflammation, in PSP and AD/MCI⁺, through *in vivo* brain imaging and *post mortem* neuropathological investigations. I recruited two distinct patient cohorts and defined them first in terms of their neuropsychological profiles and disease severity. This confirmed the differentiating clinical features, including executive function, memory, behaviour and motor function, and standardized ratings of global disease severity (i.e. Clinical Dementia Rating and PSP Rating Scale). The cognitive profiles were in accord with larger published series. I then tested *in vivo*, whether the classical phenotypes of PSP and AD/MCI⁺ were associated with changes in two neuropathological processes, tau aggregation with tangle formation (AV1451 PET) and inflammation in the form of microglia activation (PK11195 PET). *Post mortem* analyses provided validation of the *in vivo* methods.

The radiotracer [¹⁸F]AV1451 was used as an index of tau aggregation across the whole brain including cortical and subcortical brain regions. The differences in the distribution of tau pathology between PSP and AD/MCI⁺, and the difference in ultrastructure of the tau aggregates, underpinned my predictions of regionally specific binding, for example the midbrain and hippocampus, in patients with PSP and AD/MCI⁺, respectively.

Comparing PSP with controls, there was increased [¹⁸F]AV1451 BP_{ND} in the basal ganglia, midbrain and dentate nucleus of the cerebellum. This approximates the well-characterized distribution of pathology in PSP found *in post mortem* studies (Dickson et al., 2007; Hauw et al., 1994). However, I could not establish any correlation with disease severity. There are several possible explanations for this lack of correlation.

Firstly, it is possible that the ligand is not sensitive enough to the progression or variation in severity of the tauopathy of PSP. In keeping with this it has previously been shown that it has a high affinity for paired helical filaments of tau protein in AD but low or intermediate affinity to straight filaments of tau in various non-AD tauopathies (Marqu   et al., 2015).

Secondly, the progression of pathology in PSP is accompanied by changes in several forms of tau, from oligomeric to filamentous to tangle tau: different stages or severity levels of PSP might be associated with difference in the relative abundance of these different tau species. The relative toxicity of these tau species varies, and there is controversy over their role in cell death. There is direct evidence for NFT toxicity, for example in some mouse models of tauopathy, filaments coincide in the time course of the disease with features such as neuronal death and motor deficits (Ishihara et al., 1999). Similar results were also seen in one *Drosophila* model of tauopathy in which tau filament formation was reported (Wu et al., 2013). However, the target of AV1451 in PSP pathology may not be relevant toxic tau species underlying neurodegeneration (cell death) and thereby relate directly to disease stage or severity. Supporting this evidence from animal models suggests that tau-mediated neuronal death can occur even in the absence of tangle formation. For instance, in most *Drosophila* (Kosmidis et al., 2010; Williams et al., 2000) expressing human tau display behavioural phenotypes indicative of neuronal dysfunction and toxicity without forming tau filaments or larger aggregates. Even in mice, brains may contain some form of insoluble tau but not NFTs or PHFs, while the animals display motor impairment (Spittaels et al., 2000). Such evidence indicates that filaments and NFTs are not necessary for tau-induced toxicity. Indeed, many studies suggest that the tau oligomer, is likely responsible for cell injury and disease progression. The onset of symptoms in animal models following transfection from extracts of human brain tissue (with PSP and AD) correlates with elevated levels of tau oligomer (Gerson et al., 2014; Maeda et al., 2006; Patterson et al., 2011). Importantly this oligomeric tau is not imaged by AV-1451 potentially accounting for the lack of correlation with disease severity.

Thirdly, this study may lack the statistical power (type II error) to test the association between PET and clinical severity. However, our power calculations suggested acceptable power to detect group differences in binding and this was the largest study at the time it was undertaken. Subsequently, larger studies have detected associations between binding and disease severity suggesting a lack of power may have been a contributory factor in the correlational analyses (Ossenkoppele et al., 2016; Schöll et al., 2017).

A further limitation in the identification of the PET correlation with severity is inherent limitation with the clinical measures themselves. These may not be sufficiently sensitive to describe the spectrum of pathological variability in the regions identified by the PET in PSP and AD/MCI⁺, and they will have variability arising from subjective interpretations of the questions.

Finally it is possible that the neurobiology is such that there truly is no cross sectional correlation with severity. This is borne out by the longitudinal AV1451 data. That is to say, there is an increase in binding during earlier phases of disease, but later with massive cell death the tau burden falls again. When averaging over the patients at different phases in a cross sectional study, the linear correlation does not exist.

Taken together, these caveats and the lack of correlation with clinical severity suggest that AV1451 binding cannot be interpreted simplistically as a measure of progressive disease severity. Further work will be required to address these issues if AV1451 is to fulfil a role as a biomarker of tau pathology in PSP.

In my analysis of AD pathology, I considered clinical AD and the prodromal state of biomarker positive MCI as one disease entity, with a continuum in terms of severity. The diagnosis of AD/MCI⁺ was associated with greater [¹⁸F]AV1451 BP_{ND} compared to controls, in the hippocampus, amygdala as well as frontal, parietal, temporal, and occipital cortices. This reflects the regions that are characteristic of the AD pathology *in post mortem* studies. However, once again, no correlation with disease severity was found.

The reasons for a lack of correlation in AD/MCI⁺ may be the same as the reasons in PSP, although the ligand typically shows much higher binding to AD-tau tangles than PSP, suggesting that power and affinity are less likely to be the reasons for a lack of correlation with severity. A biphasic relationship of accumulation of tau in surviving cells and then cell loss, may explain the lack of overall correlation. Others have shown higher binding in clinical AD than MCI (Ossenkoppele et al., 2016) suggesting that there can be an effect of severity, even if not strong enough to be identified on our cohort of patients.

Despite the potential of [^{18}F]AV1451 as a biomarker of disease, caution in the interpretation of its binding targets is suggested by autoradiographic and immunohistochemistry data, and differences in binding between different tauopathies (Sander et al., 2016). While [^{18}F]AV1451 BP_{ND} strongly binds to AD-related cortical tau pathology in other series, and my cohort ($n=15$), non-specific binding has been reported in PSP patients ($n=20$), healthy controls ($n=13$), and disorders that are associated with TDP43 pathology but not tau pathology (e.g. semantic dementia, Bevan-Jones et al., 2017). The concept of off-target binding has overshadowed the use of AV1451 in the last 2 years. The relevant non-tau targets are not definitively known but options include neuromelanin (Marquié et al., 2015) and monoamine oxidase B (MAO-B; Harada et al., 2017; Jang et al., 2018).

The relevance of these off target binding sites may vary between brain region and disease. For example, neuromelanin is expected in the substantia nigra and locus coeruleus, but not cortex (Hansen et al., 2016). Whilst there is no doubt about AV1451 binds avidly to neuromelanin, there is doubt over the relevance of this to cortical and basal ganglia signal in patients. Indeed, my *post mortem* data suggest that off-target binding to neuromelanin is not the explanation for [^{18}F]AV1451 uptake in basal ganglia or cortex (Chapter 4, section 4.5.2.2). I found significant *in vivo* [^{18}F]AV1451 uptake in the basal ganglia (in all groups including healthy controls) in the absence of *post mortem* neuromelanin-containing cells. This indicates that neuromelanin is not the principal target of off-target binding for [^{18}F]AV1451. In the basal ganglia, there is expression of MAO-A and this accounted for most of the signal of an alternative tau PET ligand called THK5351 (Ng et al., 2017). Preclinical studies indicate that AV1451 is also displaced by monoamine oxidase type A agonists (MAO-A; Vermeiren et al., 2018), although a definitive displacement study of human AV1451 binding is awaited. The basal ganglia have high levels of MAO (type A), but MAO (albeit type B) is expressed in activated microglia. This raises the possibility that AV1451 reflects not just tau in PSP and AD, but also the activated microglia, which are the specific target of the TSPO ligand PK11195. Preliminary evidence against this artefactual cross-binding of AV1451 and PK11195 comes from the combination of both ligands in a carrier of a MAPT 10+16 mutation (Bevan-Jones et al., 2016) – in whom there was markedly increased PK11195 binding but no excess of AV151 binding. Further off target

binding sites, including the target in relation to TDP43 disorders (Bevan-Jones et al., 2018; Bevan-Jones et al., 2017) remain to be elucidated.

In Chapter 5, I also reported the assessment of neuroinflammation, providing *in vivo* evidence for microglial activation in both PSP and AD/MCI⁺ using the TSPO ligand [¹¹C](R)-PK11195. In PSP there was greater neuroinflammation in the thalamus, pallidum, and putamen. Conversely, amnesic AD/MCI⁺ patients had evidence of increased neuroinflammation in the medial temporal lobe as well as parietal and lateral temporal cortices.

In contrast to the degree of AV1451 binding, the [¹¹C](R)-PK11195 BP_{ND} correlated with disease severity in both PSP and AD/MCI⁺ groups. I used different disease-specific measures of severity, via the PSP-RS and RAVLT, respectively. Although these effects were not global correlations, they adhered to the respective functional anatomy of cognitive and motor symptoms in PSP and AD/MCI⁺ in published data on tau burden (Ossenkoppele et al., 2018) and atrophy (Frisoni et al., 2010; Mak et al., 2017; Price et al., 2004). Moreover, [¹¹C](R)-PK11195 binding *in post mortem* phosphor screen autoradiography and immunohistochemical analysis of microglial were in agreement in both clinical groups and controls.

6.2. Future directions

I propose four main areas to consider for future research in this area.

(I) My data suggest that despite its limitations, the ligand [¹⁸F]AV1451 has some of the useful properties of a biomarker. It could discriminate two distinct tauopathies by quantifying and localizing 'tau' in regions typically associated with each disease. This may have future applications in terms of developing reliable biomarkers for these disorders, and for tracking the effects of anti-tau clinical trials using disease-modifying therapies. This is already progressing in the setting of AD (Ossenkoppele et al., 2018), where there is greater confidence in the target of the ligand.

I also showed the presence of neuroinflammation in distinctive distributions for both diseases, and a relationship with disease severity. This is consistent with the mechanistic relevance of microglial activation and neuroinflammation to disease progression. Despite the epidemiological (Veld et al., 2001; McGeer et al., 1996), genetic (Malik et al., 2015; Zhang et al., 2015) and PET (Edison et al., 2008; Esposito et al., 2008) evidence for inflammation in AD, the *causal* role of inflammation in pathogenesis is not yet confirmed.

Neuroinflammation may be associated with PSP and AD as independent, causal mediators of disease. But, inflammation might be reactive to pathological protein species such as tau oligomers; or to cell death. Further, interventional, studies will be needed to resolve these uncertainties. The partially protective effect of anti-inflammatories in epidemiological studies hint that inflammation accelerates or aggravates the development of AD. However, randomised placebo-controlled interventional trials are required, to overcome the potential biases in epidemiology – such as the confounding effects of the diseases, or risk factors, which lie behind the use of anti-inflammatories. In PSP, there are fewer studies establishing the presence of *in vivo* neuroinflammation, although Gerhard and colleagues clearly showed the presence of microglial activation in primary tauopathies including PSP in an earlier PET study (Gerhard et al., 2006). Epidemiological data on anti-inflammatory use in PSP is lacking, although it is noteworthy that the genetic associations from genome-wide associations of PSP include loci that are plausible involved in regulating inflammation (Höglinger et al., 2011).

The relationship between inflammation and disease severity seen here motivates further studies focusing on the role of neuroinflammation *in vivo* in PSP, and its relation with tau pathology, cell death and disease progression. This is particularly important because microglia activation may prove to be a modifiable component to PSP pathology, and a target for disease modifying therapies.

(II). Larger cross-sectional studies are required to look at tau and neuroinflammation in PSP and AD/MCI⁺, along with disease severity and clinical features. Studies with increased statistical power from larger cohorts may reveal

significant associations with disease severity, or genetic variation between individuals.

In addition, larger cohorts would benefit from a wider range of clinical phenotypes in both diseases. For example, the clinical spectrum of PSP has expanded in recent years, to include PSP-PGF, PSP-P, PSP-F (Dickson et al., 2007; Höglinger et al., 2017; Ling et al., 2014; Paviour et al., 2007). These other PSP clinical syndromes provide the opportunity to test the association between PET indices of localized pathology and localized functional anatomical deficits across variants. This would mirror advances in AD where the Ossenkoppele study of amnesic-AD, PCA-AD and logopenic aphasia-AD was instrumental in showing the importance of tau over amyloid for phenotypic expression (Ossenkoppele et al., 2016).

It would also be a positive step to compare the PSP clinical spectrum with other tauopathologies (e.g. CBS), and other diseases like PD/DLB which although not primarily tauopathies, are nonetheless modulated by tau haplotype and tau expression (Gomperts et al., 2016; Mak et al., 2017).

Given the problems with AV1451 specificity binding outside of AD the development of second-generation tau tracers that have higher affinity for 4R or straight filamentous tauopathy would be important. PBB3 showed promise in this direction, and data are awaited for 18F-RO-98 and 18F-MK6240 (Betthausen et al., 2018; Pascoalet al., 2018).

(III). Future studies need also to include longitudinal assessment, in order to understand the course of tau and neuroinflammatory changes. I have carried out [¹⁸F]AV1451 follow up on 8 of my 20 PSP patients, analysed in collaboration with Dr Luca Passamonti. Preliminary data are presented in the Appendix 1. In summary, this pilot analysis suggests a negative correlation between the change in [¹⁸F]AV1451 BP_{ND} and change in disease severity, during the mid-stage progression of disease. However, the follow up cases are biased towards mild and slow progressing patients as some of the original cross-sectional patients were too unwell to be re-scanned or were deceased. Clearly, definitive longitudinal studies are required.

In AD longitudinal studies are already underway and there are now several that show increasing tau *in vivo* with disease severity and following Braak staging (Jack et al., 2018; Lowe et al., 2018). The value of using [¹⁸F]AV1451 PET as biomarker of PSP and AD may lie in its ability to track individual differences in disease progression rather than changes at the group level. This is beginning to become clear in AD but not yet in PSP. Similar studies to those coming out of the Alzheimer's Disease Neuroimaging Initiative (ADNI) collaboration, such as those of Lowe and Jack above, will be required in PSP.

(IV). Exploring correlations between [¹⁸F]AV1451, [¹¹C](R)-PK11195 and [¹¹C]PiB binding in this dataset would extend this work. Recent studies have highlighted how the same pathology, PSP, can be associated with diverse functional phenotypes (Respondek et al., 2014; Hoeglinger et al., 2017). Such phenotypic variance may in part arise from the combination of multiple pathogenic processes. I have shown that PET can be used to quantify both neuroinflammation and tau protein aggregation in PSP and AD. But, the relationship between these two processes is not well understood. If highly correlated, one could go on to test the temporal order of inflammation before tau aggregation or vice versa, and the degree to which inflammation and aggregation are synergistic.

(V). Another important application of tau-PET is to inform models of mechanisms of disease. For example, in the past few years, a growing number of studies have provided converging evidence for the cell-to-cell transmissibility of the diverse disease proteins, including tau protein, as a common mechanism for the onset and progression of various neurodegenerative disorders (Frost et al., 2009; Guo & Lee, 2011). The 'transmission hypothesis' for non-prion neurodegenerative diseases provides a viable explanation for the stereotypical pathology spreading patterns that have long been observed in multiple diseases (Brundin et al., 2010; Jucker & Walker, 2011; Lee et al., 2010). Tau-PET allows us to test this hypothesis *in vivo*. For example, areas with high connectivity in AD are most vulnerable to occurring tau pathology (Cope et al., 2018). This may be due to vulnerability to amplification and aggregation of tau intracellularly, but it may also reflect the receipt of pathogenic tau species (Clavaguera et al., 2009, 2014).

6.3. Limitations

There were limitations in this study, with technological, demographic, and neuropathological issues to consider.

In terms of technological limitations, using different PET scanners during the study have due to hardware change and the installations of the new scanner. This introduces another uncontrolled source of variability into the study but was unfortunately unavoidable. This only affected a small number of participants (n=5).

Secondly, there is inevitably some variability in the dose of the radioligand given to each participant. However, more importantly there was also a minimum dose required in order for the scan to proceed. Therefore any variability is above the threshold required for a technically adequate scan and is accounted for in the modelling of the PET data.

Thirdly, there may be limitations with regards the reference region used for modelling the PET data. For AV1451 we chose the superior cerebellum as a region unlike to be affected by PSP or AD pathology making sure to exclude the cerebellar dentate, which is affected in PSP. For PK11195 the reference region was determined in a data driven fashion using supervised cluster analysis.

In terms of demographic and clinical limitations, we included typical PSP-RS and AD participants. This lack of phenotypic spectrum in both PSP and AD reduces the relevance of the study to the real world range of both diseases and also the answers to potential mechanistic questions about the relationship between pathology, symptoms and severity.

A further issue is bias toward to those with early disease as they could complete the study protocol. For example, those with severe motor impairment are likely to be scanned (in particular, MRI session were limited by difficulties with coil closure due to neck rigidity). In addition, even if AD and MCI⁺ belong to the same spectrum, having severe cognitive and functional impairments made enrolment in the study less likely. Although the study aimed to recruit a broad range of severities, the study protocol required a degree of functional and cognitive ability that precluded the enrolment of severely affected participants (i.e. those with a CDR of 3). Consequently, this bias, and a potential pool of cases derived

from a tertiary neurology clinic and inherently missing those with severe disease requiring institutional or nursing care, is unavoidable.

Neuropathological issues include the diversity of tau species and ultrastructure, quantity and affinity in AD versus non-AD tauopathy. The tau pathology of PSP is chemically and morphologically different from AD, and it is perhaps not surprising that [¹⁸F]AV1451, which was developed to bind AD tauopathy, is not optimal to study PSP (see Chapter 4, section 4.5.2). New ligands might address this issue with higher affinity for PSP tau forms, but evidence is awaited for the performance of these new ligands in non-AD pathologies.

Finally, although brain donation contributed to the validation of the NIMROD study, there is a long interval between PET and donation. Additional *post mortem* validation studies from brain tissue that has undergone PET *in vivo* would be a major step forward, but there are few studies that have attempted this (Marquié et al., 2015; Passamonti et al., 2017), in part because of the time lag between being well enough for PET and brain donation, and partly from the limited number of centres with both brain banking and PET programs.


6.4. Conclusion

In conclusion, [¹⁸F]AV1451 and [¹¹C](R)-PK11195 are useful PET ligands for *in vivo* and *in post mortem* studies in clinical populations with Alzheimer's disease and non-AD tauopathy, including PSP-Richardson's syndrome, despite the potential contribution of non-specific or "off-target" binding. The brain regions that showed increased [¹⁸F]AV1451 and [¹¹C](R)-PK11195 binding were those predicted from the well-established pattern of regional cortical and subcortical neurodegeneration in each disease. Together, the current findings support the further use of [¹⁸F]AV1451 and [¹¹C](R)-PK11195 PET to evaluate tau pathology and microglial activation in neurodegenerative disorders and with further validation they could play a role in clinical trials that aim to modulate tau accumulation and neuroinflammation in neurodegenerative disease.



The first International PSP and CBD Symposium, London 2018: It was an honour to have met Dr John Steele at International PSP ad CBD Symposium, who along with Dr Richardson and Professor Olszewski first described progressive supranuclear palsy in 1963.

Appendix



Longitudinal [¹⁸F]AV-1451 PET imaging in Progressive Supranuclear Palsy: The NIMROD study

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Introduction

- Positron emission tomography (PET) biomarkers of pathology in progressive supranuclear palsy (PSP) have the potential to improve early diagnosis and accelerate therapeutic development.
- We previously reported differences in [¹⁸F]AV-1451 binding between patients with PSP, Alzheimer's disease, and healthy controls (1).
- Here we consider the role of [¹⁸F]AV-1451 to understand disease progression, and its potential contribution to clinical trials.

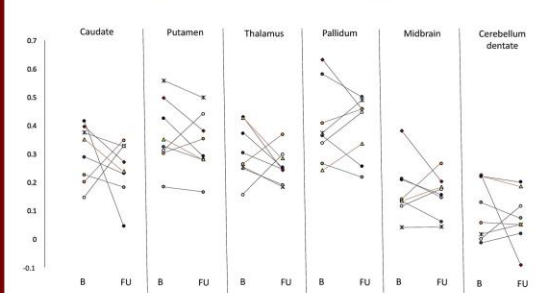
Methods

- Data were acquired at baseline and follow-up (~2 years) in people with PSP, who had taken part in the baseline NIMROD study (1, 2).
- Only 8 out of 19 patients were alive and well enough for re-assessment.
- Non-displaceable binding potential (BP_{ND}) estimates of [¹⁸F]AV-1451 PET were the outcome measures, in a region of interest (ROI) analysis. [¹⁸F]AV-1451 data were corrected for partial volume effects. ANOVA tests were used for group effects and group-by-ROI interactions.
- Person's R statistic were employed to examine correlations between longitudinal changes in disease severity and [¹⁸F]AV-1451 BP_{ND}, adjusted to give annualised rates of change.

Demographic, clinical and cognitive measures

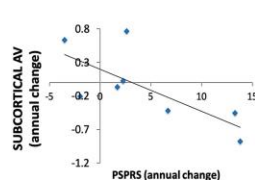
	PSP Baseline	PSP Follow-up	HC
N	8	8	13
Gender (M:F)	4:4	4:4	5:8
Age, years (mean ± SD)	68.0 ± 4.2	69.9 ± 4.2	68.0 ± 5.3
Education (mean ± SD)	11.8 ± 1.0	11.8 ± 1.0	14.1 ± 2.7
PSP-RS (mean ± SD)	39.1 ± 12.7	47.8 ± 17.4	-
ACE-R (mean ± SD)	85.8 ± 9.9	72.9 ± 14.4	91.3 ± 5.3

Longitudinal [¹⁸F]AV-1451 BP_{ND} in PSP

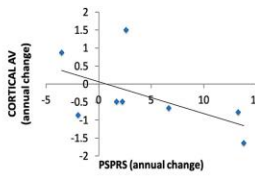


Δ[¹⁸F]AV-1451 BP_{ND} versus Δseverity

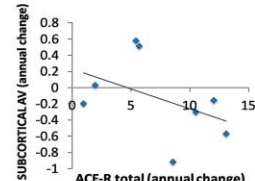
Subcortical*



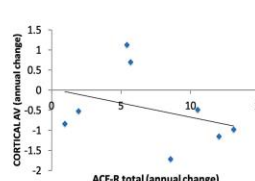
Cortical**



Subcortical AV

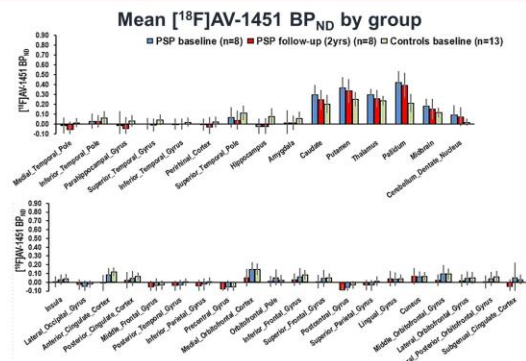


Cortical**



	Subcortical*	Cortical**
Brain regions	Hippocampus, amygdala, insula, caudate nucleus, putamen, thalamus, pallidum, midbrain, pons, medulla, and cerebellum	Temporal cortex, occipital lobe, limbic neo-cortex, parietal lobe, dorsolateral prefrontal cortex, sensorimotor cortex and anterior temporal lobe.

Mean [¹⁸F]AV-1451 BP_{ND} by group



References





1. Passamonti L, Vázquez Rodríguez P, et al. (2017). [¹⁸F]AV-1451 Positron Emission Tomography in Alzheimer's disease (AD) and Progressive Supranuclear Palsy (PSP). Brain.
1. Bevan-Jones W, Surendranathana A, et al. (2017). Neuroimaging of Inflammation in Memory and Related Other Disorders (NIMROD) study protocol: a Study of the Role of Brain Inflammation in Dementia, Depression and Other Neurological Illnesses. BMJ Open; 7(7).

Conclusion

- There is a negative correlation between the change in [¹⁸F]AV-1451 BP_{ND} and change in disease severity. This may reflect the severity of neuronal loss over 2 years.
- All patients from the previous cross-sectional study who were alive and medically safe for further PET imaging volunteered for this study. However, long-term follow-up was biased towards those PSP patients with slower than average disease progression.
- The value of using [¹⁸F]AV-1451 PET as biomarker of PSP may lie in its ability to track individual differences in disease progression rather than changes at the group level. Replication in a larger group is warranted.

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Appendix 1: Provisional analysis of the small longitudinal study of [¹⁸F]AV-1451 PET imaging in Progressive Supranuclear Palsy.

References

- Aarsland, D., Litvan, I., & Larsen, J. P. (2001). Neuropsychiatric symptoms of patients with progressive supranuclear palsy and Parkinson's disease. *J Neuropsychiatry Clin Neurosci*, *13*(1), 42–49. DOI: 10.1176/jnp.13.1.42
- Abbott, S. M., & Videnovic, A. (2014). Sleep Disorders in Atypical Parkinsonism. *Movement Disorders Clinical Practice*. <https://doi.org/10.1002/mdc3.12025>
- Agosta, F., Kostić, V. S., Galantucci, S., Mesaroš, Š., Svetel, M., Pagani, E., ... Filippi, M. (2010). The in vivo distribution of brain tissue loss in Richardson's syndrome and PSP-parkinsonism: A VBM-DARTEL study. *European Journal of Neuroscience*, *32*(4), 640–647. <https://doi.org/10.1111/j.1460-9568.2010.07304.x>
- Agostinho, P., Cunha, R. A., & Oliveira, C. (2010). Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease. *Current Pharmaceutical Design*, *16*(25), 2766–2778.
- Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., ...Wyss-Coray, T. (2000). Inflammation and Alzheimer's disease. *Neurobiology of Aging*, *21*(3), 383–421. [https://doi.org/10.1016/S0197-4580\(00\)00124-X](https://doi.org/10.1016/S0197-4580(00)00124-X)
- Albert, M. L., Feldman, R. G., & Willis, A. L. (1974). The "subcortical dementia" of progressive supranuclear palsy. *Journal of Neurology Neurosurgery and Psychiatry*. <https://doi.org/10.1136/jnnp.37.2.121>
- Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., ... Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. <https://doi.org/10.1016/j.jalz.2011.03.008>

- Alzheimer's Association (2017). 2017 Alzheimer's Disease Facts and Figures. *Alzheimers Dement.* <https://doi.org/10.1016/j.jalz.2017.02.001>
- Alzheimer, A. (1906). Über einen eigenartigen schweren Erkrankungsprozeß der Hirnrinde. *Neurol Central.*
- Amieva, H., Phillips, L. H., Della Sala, S., & Henry, J. D. (2004). Inhibitory functioning in Alzheimer's disease. *Brain.* <https://doi.org/10.1093/brain/awh045>
- Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews Neuroscience.* <https://doi.org/10.1038/nrn1884>
- Anderson, A. N., Pavese, N., Edison, P., Tai, Y. F., Hammers, A., Gerhard, A., ... Turkheimer, F. E. (2007). A systematic comparison of kinetic modelling methods generating parametric maps for [11C]-(R)-PK11195. *NeuroImage*, 36(1), 28–37. <https://doi.org/10.1016/j.neuroimage.2007.02.017>
- Andreadis, A. (2005). Tau gene alternative splicing: Expression patterns, regulation and modulation of function in normal brain and neurodegenerative diseases. *Biochimica et Biophysica Acta - Molecular Basis of Disease.* <https://doi.org/10.1016/j.bbadis.2004.08.010>
- Ang, Y. S., Lockwood, P., Apps, M. A. J., Muhammed, K., & Husain, M. (2017). Distinct subtypes of apathy revealed by the apathy motivation index. *PLoS ONE.* <https://doi.org/10.1371/journal.pone.0169938>
- Antonini, A., Benti, R., De Notaris, R., Tesei, S., Zecchinelli, A., Sacilotto, G., ... Gerundini, P. (2003). 123I-Ioflupane/SPECT binding to striatal dopamine transporter (DAT) uptake in patients with Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Neurological Sciences.* <https://doi.org/10.1007/s10072-003-0103-5>

- Apostolova, L. G., & Cummings, J. L. (2008). Neuropsychiatric manifestations in mild cognitive impairment: A systematic review of the literature. *Dementia and Geriatric Cognitive Disorders*. <https://doi.org/10.1159/000112509>
- Arena, J. E., Weigand, S. D., Whitwell, J. L., Hassan, A., Eggers, S. D., Höglinger, G. U., ... Josephs, K. A. (2015). Progressive supranuclear palsy: progression and survival. *Journal of Neurology*. <https://doi.org/10.1007/s00415-015-7990-2>
- Arnett, J. A., & Labovitz, S. S. (1995). Effect of physical layout in performance of the trail making test. *Psychological Assessment*. <https://doi.org/10.1037/1040-3590.7.2.220>
- Arriagada, P. V., Growdon, J. H., Hedley-Whyte, E. T., & Hyman, B. T. (1992). Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology*. <https://doi.org/10.1212/WNL.42.3.631>
- Ashburner, J., & Friston, K. J. (2000). Voxel-Based Morphometry—The Methods. *NeuroImage*, *11*(6), 805–821. <https://doi.org/10.1006/nimg.2000.0582>
- Ashburner, J., & Friston, K. J. (2001). Why Voxel-based morphometry should be used. *NeuroImage*. <https://doi.org/10.1006/nimg.2001.0961>
- Ashford, J. W., Salehi, A., Furst, A., Bayley, P., Frisoni, G. B., Jack, C. R., ... Perry, G. (2011). Imaging the Alzheimer Brain. *Journal of Alzheimer's Disease*. <https://doi.org/10.3233/JAD-2011-0073>
- Atkinson, A. J., Colburn, W. A., DeGruttola, V. G., DeMets, D. L., Downing, G. J., Hoth, D. F., ... Zeger, S. L. (2001). Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clinical Pharmacology and Therapeutics*. <https://doi.org/10.1067/mcp.2001.113989>
- Avila, J., Lucas, J. J., Perez, M., & Hernandez, F. (2004). Role of tau protein in both physiological and pathological conditions. *Physiological Reviews*.

<https://doi.org/10.1152/physrev.00024.2003>

Bäckman, L., Jones, S., Berger, A. K., Laukka, E. J., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's disease: A meta-analysis. *Neuropsychology*. <https://doi.org/10.1037/0894-4105.19.4.520>

Bäckman, L., Wahlin, Å., Small, B. J., Herlitz, A., Winblad, B., & Fratiglioni, L. (2004). Cognitive functioning in aging and dementia: The Kungsholmen Project. *Aging, Neuropsychology, and Cognition*. <https://doi.org/10.1080/13825580490511099>

Bak, T. H., Crawford, L. M., Berrios, G., & Hodges, J. R. (2010). Behavioural symptoms in progressive supranuclear palsy and frontotemporal dementia. *Journal of Neurology, Neurosurgery & Psychiatry*, *81*(9), 1057–1059. <https://doi.org/10.1136/jnnp.2008.157974>

Bak, T. H., Crawford, L. M., Hearn, V. C., Mathuranath, P. S., & Hodges, J. R. (2005). Subcortical dementia revisited: Similarities and differences in cognitive function between progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). *Neurocase*, *11*(4), 268–273. <https://doi.org/10.1080/13554790590962997>

Baker, M., Litvan, I., Houlden, H., Adamson, J., Dickson, D., Perez-Tur, J., ... Hutton, M. (1999). Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Human Molecular Genetics*. <https://doi.org/10.1093/hmg/8.4.711>

Ballatore, C., Lee, V. M. Y., & Trojanowski, J. Q. (2007). Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nature Reviews. Neuroscience*, *8*(9), 663–672. <https://doi.org/10.1038/nrn2194>

Banati, R. B., Newcombe, J., Gunn, R. N., Cagnin, A., Turkheimer, F., Heppner, F., ... Myers, R. (2000). The peripheral benzodiazepine binding site in the brain in

- multiple sclerosis. Quantitative in vivo imaging of microglia as a measure of disease activity. *Brain*. <https://doi.org/10.1093/brain/123.11.2321>
- Bao, Q., Newport, D., Chen, M., Stout, D. B., & Chatziioannou, A. F. (2009). Performance Evaluation of the Inveon Dedicated PET Preclinical Tomograph Based on the NEMA NU-4 Standards. *Journal of Nuclear Medicine*. <https://doi.org/10.2967/jnumed.108.056374>
- Barret, O., Alagille, D., Sanabria, S., Comley, R. A., Weimer, R. M., Borroni, E., ... Jennings, D. (2017). Kinetic Modeling of the Tau PET Tracer ¹⁸F-AV-1451 in Human Healthy Volunteers and Alzheimer Disease Subjects. *Journal of Nuclear Medicine*. <https://doi.org/10.2967/jnumed.116.182881>
- Barthel, H., & Sabri, O. (2011). Florbetaben to trace Amyloid- β in the Alzheimer brain by means of PET. *Advances in Alzheimer's Disease*. <https://doi.org/10.3233/978-1-60750-793-2-247>
- Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*. [https://doi.org/10.1016/0010-0277\(94\)90018-3](https://doi.org/10.1016/0010-0277(94)90018-3)
- Beharry, C., Cohen, L. S., Di, J., Ibrahim, K., Briffa-Mirabella, S., & Alonso, A. D. C. (2014). Tau-induced neurodegeneration: Mechanisms and targets. *Neuroscience Bulletin*. <https://doi.org/10.1007/s12264-013-1414-z>
- Belleville, S., Rouleau, N., & Van der Linden, M. (2006). Use of the Hayling task to measure inhibition of prepotent responses in normal aging and Alzheimer's disease. *Brain and Cognition*. <https://doi.org/10.1016/j.bandc.2006.04.006>
- Belleville, S., Rouleau, N., Van der Linden, M., & Collette, F. (2003). Effect of manipulation and irrelevant noise on working memory capacity of patients with Alzheimer's dementia. *Neuropsychology*. <https://doi.org/10.1037/0894-4105.17.1.69>

- Benamer, H. T. S., Oertel, W. H., Patterson, J., Hadley, D. M., Pogarell, O., Höffken, H., ... Grosset, D. G. (2003). Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: Part 1. baseline and 3-month observations. *Movement Disorders*. <https://doi.org/10.1002/mds.10482>
- Bensimon, G., Ludolph, A., Agid, Y., Vidailhet, M., Payan, C., & Leigh, P. N. (2008). Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: The NNIPPS Study. *Brain*, *132*(1), 156–171. <https://doi.org/10.1093/brain/awn291>
- Bentham, P. W., Jones, S., & Hodges, J. R. (1997). A comparison of semantic memory in vascular dementia and dementia of Alzheimer's type. *International Journal of Geriatric Psychiatry*. [https://doi.org/10.1002/\(SICI\)1099-1166\(199705\)12:5<575::AID-GPS566>3.0.CO;2-N](https://doi.org/10.1002/(SICI)1099-1166(199705)12:5<575::AID-GPS566>3.0.CO;2-N)
- Berg, D., Postuma, R. B., Bloem, B., Chan, P., Dubois, B., Gasser, T., ... Deuschl, G. (2014). Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. *Movement Disorders*. <https://doi.org/10.1002/mds.25844>
- Berg, D., Steinberger, J. D., Warren Olanow, C., Naidich, T. P., & Yousry, T. A. (2011). Milestones in magnetic resonance imaging and transcranial sonography of movement disorders. *Movement Disorders*. <https://doi.org/10.1002/mds.23766>
- Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *Journal of General Psychology*. <https://doi.org/10.1080/00221309.1948.9918159>
- Berna, F., Schönknecht, P., Seidl, U., Toro, P., & Schröder, J. (2012). Episodic autobiographical memory in normal aging and mild cognitive impairment: A

population-based study. *Psychiatry Research.*

<https://doi.org/10.1016/j.psychres.2012.03.022>

Betthausen, T. J., Cody, K. A., Zammit, M. D., Murali, D., Converse, A. K., Barnhart, T. E., ... Christian, B. T. (2018). In vivo characterization and quantification of neurofibrillary tau PET radioligand [¹⁸F]MK-6240 in humans from Alzheimer's disease dementia to young controls. *Journal of Nuclear Medicine.* <https://doi.org/10.2967/jnumed.118.209650>

Bevan-Jones, R. W., Cope, T. E., Jones, S. P., Passamonti, L., Hong, Y. T., Fryer, T., ... Rowe, J. B. (2018). [18F]AV-1451 binding is increased in frontotemporal dementia due to C9orf72 expansion. *Annals of Clinical and Translational Neurology.* <https://doi.org/10.1002/acn3.631>

Bevan-Jones, W. R., Cope, T. E., Jones, P. S., Passamonti, L., Hong, Y. T., Fryer, T. D., ... Rowe, J. B. (2017). AV-1451 binding in vivo mirrors the expected distribution of TDP-43 pathology in the semantic variant of primary progressive aphasia. *Journal of Neurology, Neurosurgery and Psychiatry.* <https://doi.org/10.1136/jnnp-2017-316402>

Bevan-Jones, W. R., Surendranathan, A., Passamonti, L., Rodríguez, P. V., Arnold, R., Mak, E., ... O'Brien, J. T. (2017). 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*, 7(1). <https://doi.org/10.1136/bmjopen-2016-013187>

Bevan-Jones, W. R., Cope, T. E., Passamonti, L., Fryer, T. D., Hong, Y. T., Aigbirhio, F., ... Rowe, J. B. (2016). [18F]AV-1451 PET in behavioral variant frontotemporal dementia due to MAPT mutation. *Annals of Clinical and Translational Neurology*, 3(12), 940–947. doi: 10.1002/acn3.366

- Beyreuther, K., & Masters, C. L. (1991). Amyloid Precursor Protein (APP) and BZA4 Amyloid in the Etiology of Alzheimer's Disease: Precursor-Product Relationships in the Derangement of Neuronal Function. *Brain Pathology*. <https://doi.org/10.1111/j.1750-3639.1991.tb00667.x>
- Bier, J. C., Ventura, M., Donckels, V., Van Eyll, E., Claes, T., Slama, H., ... Pandolfo, M. (2004). Is the Addenbrooke's Cognitive Examination effective to detect frontotemporal dementia? *Journal of Neurology*, *251*(4), 428–431. <https://doi.org/10.1007/s00415-004-0345-z>
- Birdi, S., Rajput, A. H., Fenton, M., Donat, J. R., Rozdilsky, B., Robinson, C., ... George, D. (2002). Progressive supranuclear palsy diagnosis and confounding features: Report on 16 autopsied cases. *Movement Disorders*. <https://doi.org/10.1002/mds.10211>
- Blennow, K., de Leon, M. J., & Zetterberg, H. (2006). Alzheimer's disease. *Lancet*. [https://doi.org/10.1016/S0140-6736\(06\)69113-7](https://doi.org/10.1016/S0140-6736(06)69113-7)
- Bliwise, D. L., Bevier, W. C., Bliwise, N. G., Edgar, D. M., & Dement, W. C. (1990). Systematic 24-hr behavioral observations of sleep and wakefulness in a skilled-care nursing facility. *Psychology and Aging*. <https://doi.org/10.1037//0882-7974.5.1.16>
- Block, M. L., & Hong, J. S. (2005). Microglia and inflammation-mediated neurodegeneration: Multiple triggers with a common mechanism. *Progress in Neurobiology*. <https://doi.org/10.1016/j.pneurobio.2005.06.004>
- Bloom, G. S. (2014). Amyloid- β and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurology*, *71*(4), 505–508. <https://doi.org/10.1001/jamaneurol.2013.5847>
- Boeve, B., Dickson, D., Duffy, J., Bartleson, J., Trenerry, M., & Petersen, R. (2003). Progressive nonfluent aphasia and subsequent aphasic dementia associated

with atypical progressive supranuclear palsy pathology. *European Neurology*.
<https://doi.org/10.1159/000068502>

Boeve, B. F., Lang, A. E., & Litvan, I. (2003). Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. In *Annals of Neurology*. <https://doi.org/10.1002/ana.10570>

Bondi, M. W., Serody, A. B., Chan, A. S., Ebersone-Shumate, S. C., Delis, D. C., Hansen, L. A., & Salmon, D. P. (2002). Cognitive and neuropathologic correlates of Stroop Color-Word Test performance in Alzheimer's disease. *Neuropsychology*. <https://doi.org/10.1037/0894-4105.16.3.335>

Bower, J. H., Maraganore, D. M., McDonnell, S. K., & Rocca, W. A. (1997). Incidence of progressive supranuclear palsy and multiple system atrophy in Olmsted County, Minnesota, 1976 to 1990. *Neurology*, 49(5), 1284–1288. <https://doi.org/10.1212/WNL.49.5.1284>

Bozeat, S., Gregory, C. A., Lambon Ralph, M. A., & Hodges, J. R. (2000). Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *Journal of Neurology Neurosurgery and Psychiatry*, 69(2), 178–186. <https://doi.org/10.1136/jnnp.69.2.178>

Braak, E., & Braak, H. (1995). Staging of Alzheimer's Disease-Related Neurofibrillary Changes. *Neurobiology of Aging*, 16(3), 271–278. <https://doi.org/10.1007/s00401-006-0127-z>

Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica*, 82(4), 239–259. <https://doi.org/10.1007/BF00308809>

Braak, H., & Braak, E. (1989). Cortical and subcortical argyrophilic grains characterize a disease associated with adult onset dementia. *Neuropathol Appl*

Neurobiol, 15(1), 13–26. <https://doi.org/VBMBraak-Converted#58>

- Braak, H., Alafuzoff, I., Arzberger, T., Kretschmar, H., & Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathologica*, 112(4), 389–404. <https://doi.org/10.1007/s00401-006-0127-z>
- Brenneis, C., Seppi, K., Schocke, M., Benke, T., Wenning, G. K., & Poewe, W. (2004). Voxel based morphometry reveals a distinct pattern of frontal atrophy in progressive supranuclear palsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, 75(2), 246–249. <http://dx.doi.org/10.1136/jnnp.2003.015297>
- Brettschneider, J., Del Tredici, K., Lee, V. M., & Trojanowski, J. Q. (2015). Spreading of pathology in neurodegenerative diseases: a focus on human studies. *Nat Rev Neurosci*, 16(2), 109–120. doi: 10.1038/nrn3887.
- Briard, E., Zoghbi, S. S., Imaizumi, M., Gourley, J. P., Shetty, H. U., Hong, J., ... Pike, V. W. (2008). Synthesis and evaluation in monkey of two sensitive ¹¹C-labeled aryloxyanilide ligands for imaging brain peripheral benzodiazepine receptors in vivo. *Journal of Medicinal Chemistry*. <https://doi.org/10.1021/jm0707370>
- Brickell, K. L., Steinbart, E. J., Rumbaugh, M., Payami, H., Schellenberg, G. D., Van Deerlin, V., ... Bird, T. D. (2006). Early-onset Alzheimer disease in families with late-onset Alzheimer disease: A potential important subtype of familial Alzheimer disease. *Archives of Neurology*. <https://doi.org/10.1001/archneur.63.9.1307>
- Brown, Richard G., Lacomblez, L., Landwehrmeyer, B. G., Bak, T., Uttner, I., Dubois, B., ... Leigh, N. P. (2010). Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy. *Brain*, 133(8), 2382–2393. <https://doi.org/10.1093/brain/awq158>

- Brundin, P., Melki, R., & Kopito, R. (2010). Prion-like transmission of protein aggregates in neurodegenerative diseases. *Nature Reviews Molecular Cell Biology*. <https://doi.org/10.1038/nrm2873>
- Buchhave, P., Minthon, L., Zetterberg, H., Wallin, Å. K., Blennow, K., & Hansson, O. (2012). Cerebrospinal fluid levels of beta amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. *Archives of General Psychiatry*. <https://doi.org/10.1001/archgenpsychiatry.2011.155>
- Buckner, R. L. (2005). Molecular, Structural, and Functional Characterization of Alzheimer's Disease: Evidence for a Relationship between Default Activity, Amyloid, and Memory. *Journal of Neuroscience*. <https://doi.org/10.1523/JNEUROSCI.2177-05.2005>
- Budson, A. E., & Price, B. H. (2005). Memory dysfunction. *The New England Journal of Medicine*. <https://doi.org/10.1056/NEJMra041071>
- Buée, L., Bussière, T., Buée-Scherrer, V., Delacourte, A., & Hof, P. R. (2000). Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Research Reviews*, 33(1), 95–130. [https://doi.org/10.1016/S0165-0173\(00\)00019-9](https://doi.org/10.1016/S0165-0173(00)00019-9)
- Buée, L., & Delacourte, A. (1999). Comparative Biochemistry of Tau in Progressive Supranuclear Palsy, Corticobasal Degeneration, FTDP-17 and Pick's Disease. *Brain Pathology*, 9, 681–693. <https://doi.org/10.1111/j.1750-3639.1999.tb00550.x>
- Burns, A., Jacoby, R., & Levy, R. (1990). Psychiatric phenomena in Alzheimer's disease. I: Disorders of thought content. *British Journal of Psychiatry*. <https://doi.org/10.1192/bjp.157.1.86>
- Burrell, J. R., Hodges, J. R., & Rowe, J. B. (2014). Cognition in corticobasal

- syndrome and progressive supranuclear palsy: A review. *Movement Disorders*.
<https://doi.org/10.1002/mds.25872>
- Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*.
[https://doi.org/10.1016/S1364-6613\(00\)01483-2](https://doi.org/10.1016/S1364-6613(00)01483-2)
- Butters, N., Granholm, E., Salmon, D. P., Grant, I., & Wolfe, J. (1987). Episodic and semantic memory: a comparison of amnesic and demented patients. *J Clin Exp Neuropsychol*, 9(5), 479-497. DOI: 10.1080/01688638708410764
- Büttner-Ennever, J. A., & Büttner, U. (1978). A cell group associated with vertical eye movements in the rostral mesencephalic reticular formation of the monkey. *Brain Research*, 151(1), 31-47. [https://doi.org/10.1016/0006-8993\(78\)90948-4](https://doi.org/10.1016/0006-8993(78)90948-4)
- Cadieux, N. L., & Greve, K. W. (1997). Emotion processing in Alzheimer ' s disease. *Journal of the International Neuropsychological Society*.
<https://doi.org/10.1520/D6724-04R10.1.5>
- Cagnin, A., Kassiou, M., Meikle, S. R., & Banati, R. B. (2006). *In vivo* evidence for microglial activation in neurodegenerative dementia. *Acta Neurologica Scandinavica*. <https://doi.org/10.1111/j.1600-0404.2006.00694.x>
- Cagnin, A., Brooks, D. J., Kennedy, A. M., Gunn, R. N., Myers, R., Turkheimer, F. E., ... Banati, R. B. (2001). *In vivo* measurement of activated microglia in dementia. *Lancet*, 358(9280), 461-467. [https://doi.org/10.1016/S0140-6736\(01\)05625-2](https://doi.org/10.1016/S0140-6736(01)05625-2)
- Cahn, D. A., Salmon, D. P., Butters, N., Wiederholt, W. C., Corey-Bloom, J., Edelstein, S. L., & Barrett-Conner, E. (1995). Detection of dementia of the Alzheimer type in a population-based sample: Neuropsychological test performance. *Journal of the International Neuropsychological Society*.

<https://doi.org/10.1017/S1355617700000242>

- Calvini, P., Chincarini, A., Gemme, G., Penco, M. A., Squarcia, S., Nobili, F., ... Fantacci, M. E. (2009). Automatic analysis of medial temporal lobe atrophy from structural MRIs for the early assessment of Alzheimer disease. *Medical Physics*. <https://doi.org/10.1118/1.3171686>
- Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., ... Frebourg, T. (1999). Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *American Journal of Human Genetics*. <https://doi.org/10.1086/302553>
- Carter, S. F., Scholl, M., Almkvist, O., Wall, A., Engler, H., Langstrom, B., & Nordberg, A. (2012). Evidence for Astrocytosis in Prodromal Alzheimer Disease Provided by 11C-Deuterium-L-Deprenyl: A Multitracer PET Paradigm Combining 11C-Pittsburgh Compound B and 18F-FDG. *Journal of Nuclear Medicine*. <https://doi.org/10.2967/jnumed.110.087031>
- Casati, M., Ferri, E., Gussago, C., Mazzola, P., Abbate, C., Bellelli, G., ... Arosio, B. (2018). Increased expression of TREM2 in peripheral cells from mild cognitive impairment patients who progress into Alzheimer's disease. *European Journal of Neurology*. <https://doi.org/10.1111/ene.13583>
- Cash, D. M., Bocchetta, M., Thomas, D. L., Dick, K. M., van Swieten, J. C., Borroni, B., ... Rohrer, J. D. (2018). Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. *Neurobiology of Aging*. <https://doi.org/10.1016/j.neurobiolaging.2017.10.008>
- Catalano, S. M., Robertson, R. T., & Killackey, H. P. (1996). Individual axon morphology and thalamocortical topography in developing rat somatosensory cortex. *J Comp Neurol*, 367(1), 36–53. DOI: 10.1002/(SICI)1096-9861(19960325)367:1<36::AID-CNE4>3.0.CO;2-K

- Cerhan, J. H., Ivnik, R. J., Smith, G. E., Tangalos, E. C., Petersen, R. C., & Boeve, B. F. (2002). Diagnostic Utility of Letter Fluency, Category Fluency, and Fluency Difference Scores in Alzheimer's Disease. *The Clinical Neuropsychologist*. <https://doi.org/10.1076/clin.16.1.35.8326>
- Chauveau, F., Boutin, H., Van Camp, N., Dollé, F., & Tavitian, B. (2008). Nuclear imaging of neuroinflammation: a comprehensive review of [11C]PK11195 challengers. *Eur J Nucl Med Mol Imaging*, 35(12), 2304-2319. doi: 10.1007/s00259-008-0908-9
- Chen, A. L., Riley, D. E., King, S. A., Joshi, A. C., Serra, A., Liao, K., ... Leigh, R. J. (2010). The disturbance of gaze in progressive supranuclear palsy: Implications for pathogenesis. *Frontiers in Neurology*. <https://doi.org/10.3389/fneur.2010.00147>
- Chen, M. K., & Guilarte, T. R. (2008). Translocator protein 18 kDa (TSPO): Molecular sensor of brain injury and repair. *Pharmacology and Therapeutics*. <https://doi.org/10.1016/j.pharmthera.2007.12.004>
- Cherry, S. R., & Gambhir, S. S. (2001). Use of positron emission tomography in animal research. *ILAR Journal*. <https://doi.org/10.1093/ilar.42.3.219>
- Chien, D. T., Bahri, S., Szardenings, A. K., Walsh, J. C., Mu, F., Su, M. Y., ... Kolb, H. C. (2013). Early Clinical PET Imaging Results with the Novel PHF-Tau Radioligand [F-18]-T807. *Journal of Alzheimer's Disease*, 34(2), 457-468. <https://doi.org/10.3233/JAD-122059>
- Chien, D. T., Szardenings, A. K., Bahri, S., Walsh, J. C., Mu, F., Xia, C., ... Kolb, H. C. (2014). Early clinical PET imaging results with the novel PHF-tau radioligand [F18]-T808. *Journal of Alzheimer's Disease*. <https://doi.org/10.3233/JAD-130098>
- Chiò, A., Magnani, C., & Schiffer, D. (1998). Prevalence of Parkinson's disease in

- Northwestern Italy: Comparison of tracer methodology and clinical ascertainment of cases. *Movement Disorders*, 13(3), 400–405.
<https://doi.org/10.1002/mds.870130305>
- Chou, Y. Y., Leporé, N., Avedissian, C., Madsen, S. K., Parikshak, N., Hua, X., ... Thompson, P. M. (2009). Mapping correlations between ventricular expansion and CSF amyloid and tau biomarkers in 240 subjects with Alzheimer's disease, mild cognitive impairment and elderly controls. *NeuroImage*.
<https://doi.org/10.1016/j.neuroimage.2009.02.015>
- Clark, C. M., Schneider, J. A., Bedell, B. J., Beach, T. G., Bilker, W. B., Mintun, M. A., ... Skovronsky, D. M. (2011). Use of florbetapir-PET for imaging β -amyloid pathology. *JAMA - Journal of the American Medical Association*.
<https://doi.org/10.1001/jama.2010.2008>
- Clavaguera, F., Akatsu, H., Fraser, G., Crowther, R. A., Frank, S., Hench, J., ... Tolnay, M. (2013). Brain homogenates from human tauopathies induce tau inclusions in mouse brain. *Proceedings of the National Academy of Sciences of the United States of America*, 110(23), 9535–9540.
<https://doi.org/10.1073/pnas.1301175110>
- Clavaguera, F., Bolmont, T., Crowther, R. A., Abramowski, D., Frank, S., Probst, A., ... Tolnay, M. (2009). Transmission and spreading of tauopathy in transgenic mouse brain. *Nature Cell Biology*.
<https://doi.org/10.1038/ncb1901>
- Clavaguera, F., Hench, J., Lavenir, I., Schweighauser, G., Frank, S., Goedert, M., & Tolnay, M. (2014). Peripheral administration of tau aggregates triggers intracerebral tauopathy in transgenic mice. *Acta Neuropathologica*.
<https://doi.org/10.1007/s00401-013-1231-5>
- Cohen, D. (1968). Magnetoencephalography: Evidence of magnetic fields

produced by alpha-rhythm currents. *Science*.

<https://doi.org/10.1126/science.161.3843.784>

Compta, Y., Valdeoriola, F., Tolosa, E., Rey, M. J., Martí, M. J., & Valls-Solé, J. (2007). Long lasting pure freezing of gait preceding progressive supranuclear palsy: A clinicopathological study. *Movement Disorders*, *22*(13), 1954–1958. <https://doi.org/10.1002/mds.21612>

Conway, M. A. (2005). Memory and the self. *Journal of Memory and Language*. <https://doi.org/10.1016/j.jml.2005.08.005>

Cope, T. E., Rittman, T., Borchert, R. J., Jones, P. S., Vatansever, D., Allinson, K., ... Rowe, J. B. (2018). Tau burden and the functional connectome in Alzheimer's disease and progressive supranuclear palsy. *Brain*. <https://doi.org/10.1093/brain/awx347>

Corbetta, M. (2012). Functional connectivity and neurological recovery. *Developmental Psychobiology*. <https://doi.org/10.1002/dev.20507>

Cordato, N. J., Duggins, A. J., Halliday, G. M., Morris, J. G. L., & Pantelis, C. (2005). Clinical deficits correlate with regional cerebral atrophy in progressive supranuclear palsy. *Brain*, *128*(6), 1259–1266. <https://doi.org/10.1093/brain/awh508>

Cortes, C., & Vapnik, V. (1995). Support-vector networks. *Machine Learning*, *20*, 273-297. Retrieved from <https://link.springer.com/content/pdf/10.1023%2FA%3A1022627411411.pdf>

Coyle-gilchrist, I. T. S., Dick, K. M., Vázquez, P., Wehmann, E., Wilcox, A., Lansdall, C. J., ... Rowe, J. B. (2016). Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. *Neurology*, *86*, 1736–1743. <https://doi.org/10.1212/WNL.0000000000002638>

- Craig-Schapiro, R., Perrin, R. J., Roe, C. M., Xiong, C., Carter, D., Cairns, N. J., ... Holtzman, D. M. (2010). YKL-40: A novel prognostic fluid biomarker for preclinical Alzheimer's disease. *Biological Psychiatry*.
<https://doi.org/10.1016/j.biopsych.2010.08.025>
- Cummings, J. L. (1997). The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology*.
https://doi.org/10.1212/WNL.48.5_Suppl_6.10S
- Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology*, *44*(12), 2308–2308.
<https://doi.org/10.1212/WNL.44.12.2308>
- D'Souza, I., & Schellenberg, G. D. (2005). Regulation of tau isoform expression and dementia. *Biochimica et Biophysica Acta - Molecular Basis of Disease*.
<https://doi.org/10.1016/j.bbadis.2004.08.009>
- De Bruin, V. M. S., & Lees, A. J. (1992). The clinical features of 67 patients with clinically definite steele-richardson-olszewski syndrome. *Behavioural Neurology*, *5*(4), 229–232. <https://doi.org/10.3233/BEN-1992-5405>
- De Bruin, V. S., Machado, C., Howard, R. S., Hirsch, N. P., & Lees, A. J. (1996). Nocturnal and respiratory disturbances in Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Postgraduate Medical Journal*.
<https://doi.org/10.1136/pgmj.72.847.293>
- De Calignon, A., Polydoro, M., Suárez-Calvet, M., William, C., Adamowicz, D. H., Kopeikina, K. J., ... Hyman, B. T. (2012). Propagation of Tau Pathology in a Model of Early Alzheimer's Disease. *Neuron*, *73*(4), 685–697.
<https://doi.org/10.1016/j.neuron.2011.11.033>
- Dedeurwaerdere, S., Callaghan, P. D., Pham, T., Rahardjo, G. L., Amhaoul, H.,

- Berghofer, P., ... Grégoire, M. C. (2012). PET imaging of brain inflammation during early epileptogenesis in a rat model of temporal lobe epilepsy. *EJNMMI Research*. <https://doi.org/10.1016/j.rx.2012.01.004>
- Deelen, J., Beekman, M., Uh, H. W., Helmer, Q., Kuningas, M., Christiansen, L., ... Slagboom, P. E. (2011). Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. *Aging Cell*. <https://doi.org/10.1111/j.1474-9726.2011.00705.x>
- Dell'Aquila, C., Zoccollella, S., Cardinali, V., de Mari, M., Iliceto, G., Tartaglione, B., ... Logroscino, G. (2013). Predictors of survival in a series of clinically diagnosed progressive supranuclear palsy patients. *Parkinsonism Relat Disord*, 19(11), 980–985. <https://doi.org/10.1016/j.parkreldis.2013.06.014>
- Desikan, R. S., McEvoy, L. K., Thompson, W. K., Holland, D., Brewer, J. B., Aisen, P. S., ... Alzheimer's Disease Neuroimaging Initiative (2012). Amyloid- β -Associated Clinical Decline Occurs Only in the Presence of Elevated P-tau. *Archives of Neurology*. <https://doi.org/10.1001/archneurol.2011.3354>
- Devous, M. D., Joshi, A. D., Navitsky, M. A., Dickson, J., Pontecorvo, M. A., Siderowf, & A., Mintun, M. A. (2014). Test-retest data for the tau PET imaging agent 18F-AV-1451 (previously, 18F-T807). *The journal of Alzheimer's Association*, 10(4), 901. <https://doi.org/10.1016/j.jalz.2014.07.085>
- Dheen, S. T., Kaur, C., & Ling, E. A. Microglial activation and its implications in the brain diseases (2007). *Current Medicinal Chemistry*, 14(11), 1189-1897. DOI: 10.2174/092986707780597961
- Di Paola, M., Macaluso, E., Carlesimo, G. A., Tomaiuolo, F., Worsley, K. J., Fadda, L., & Caltagirone, C. (2007). Episodic memory impairment in patients with Alzheimer's disease is correlated with entorhinal cortex atrophy: A voxel-based morphometry study. *Journal of Neurology*.

<https://doi.org/10.1007/s00415-006-0435-1>

Di Trapani, G., Stampatore, P., La Cara, A., Azzoni, A., & Vaccario, M. L. (1991).

Treatment of progressive supranuclear palsy with methysergide. A clinical study. *Italian Journal of Neurological Sciences*.

Dickerson, B., Domoto-Reilly, K., Daisy, S., Stepanovic, M., Brickhouse, M., &

Johnson, K. (2014). Imaging Tau Pathology in Vivo in FtlD: Initial Experience With [18F] T807 Pet. *Alzheimer's & Dementia*.

<https://doi.org/http://dx.doi.org/10.1016/j.jalz.2014.05.221>

Dickson, D. W. (1999). Neuropathologic differentiation of progressive supranuclear

palsy and corticobasal degeneration. *Journal of Neurology*.

<https://doi.org/10.1007/BF03161076>

Dickson, D. W., Ksiezak-Reding, H., Davies, P., & Yen, S. H. (1987). A monoclonal

antibody that recognizes a phosphorylated epitope in Alzheimer neurofibrillary tangles, neurofilaments and tau proteins immunostains granulovacuolar degeneration. *Acta Neuropathologica*, 73(3), 254–258.

<https://doi.org/10.1007/BF00686619>

Dickson, D. W., Crystal, H. A., Mattiace, L. A., Masur, D. M., Blau, A. D., Davies,

P., ... Aronson, M. K. (1992). Identification of normal and pathological aging in prospectively studied nondemented elderly humans. *Neurobiology of Aging*.

[https://doi.org/10.1016/0197-4580\(92\)90027-U](https://doi.org/10.1016/0197-4580(92)90027-U)

Dickson, D. W., Ahmed, Z., Algom, A. A., Tsuboi, Y., & Josephs, K. A. (2010).

Neuropathology of variants of progressive supranuclear palsy. *Current Opinion in Neurology*, 23(4), 394–400.

<https://doi.org/10.1097/WCO.0b013e32833be924>

Dickson, D. W., Rademakers, R., & Hutton, M. L. (2007). Progressive supranuclear

palsy: pathology and genetics. *Brain Pathology (Zurich, Switzerland)*, 17(1),

74–82. <https://doi.org/10.1111/j.1750-3639.2007.00054.x>

Du, L., Zhang, Y., Chen, Y., Zhu, J., Yang, Y., & Zhang, H. L. (2017). Role of microglia in neurological disorders and their potentials as a therapeutic target.

Mol. Neurobiol, *54*(10), 7567–7584. doi: 10.1007/s12035-016-0245-0

Dubois, B., Slachevsky, A., Pillon, B., Beato, R., Villalpona, J. M., & Litvan, I. (2005). “Applause sign” helps to discriminate PSP from FTD and PD.

Neurology. <https://doi.org/10.1212/01.WNL.0000165977.38272.15>

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., ... Scheltens, P. (2007). Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology*.

[https://doi.org/10.1016/S1474-4422\(07\)70178-3](https://doi.org/10.1016/S1474-4422(07)70178-3)

Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000). The FAB: A frontal assessment battery at bedside. *Neurology*, *55*(11), 1621–1626.

<https://doi.org/10.1212/WNL.55.11.1621>

Dudas, R. B., Berrios, G. E., & Hodges, J. R. (2005). The Addenbrooke’s Cognitive Examination (ACE) in the differential diagnosis of early dementias versus affective disorder. *American Journal of Geriatric Psychiatry*, *13*(3), 218–226.

<https://doi.org/10.1097/00019442-200503000-00007>

Dugger, B. N., Adler, C. H., Shill, H. A., Caviness, J., Jacobson, S., Driver-Dunckley, E., & Beach, T. G. (2014). Concomitant pathologies among a spectrum of parkinsonian disorders. *Parkinsonism and Related Disorders*.

<https://doi.org/10.1016/j.parkreldis.2014.02.012>

Dujardin, K., Sockeel, P., Delliaux, M., Destée, A., & Defebvre, L. (2009). Apathy may herald cognitive decline and dementia in Parkinson’s disease. *Movement Disorders*.

<https://doi.org/10.1002/mds.22843>

Dupont, A. C., Largeau, B., Ribeiro, M. J. S., Guilloteau, D., Tronel, C., & Arlicot,

- N. (2017). Translocator protein-18 kDa (TSPO) positron emission tomography (PET) imaging and its clinical impact in neurodegenerative diseases. *International Journal of Molecular Sciences*. <https://doi.org/10.3390/ijms18040785>
- Eastwood, J. D., Lev, M. H., Wintermark, M., Fitzek, C., Barboriak, D. P., DeLong, D. M., ... Provenzale, J. M. (2003). Correlation of early dynamic CT perfusion imaging with whole-brain MR diffusion and perfusion imaging in acute hemispheric stroke. *AJNR American Journal of Neuroradiology*, 24(9), 1869–1875.
- Edison, P., Archer, H. A., Gerhard, A., Hinz, R., Pavese, N., Turkheimer, F. E., Hammers, A., Tai, Y. F., Fox, N., Kennedy, A., & Rossor, M. B. D. (2008). Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study. *Neurobiology of Disease*, 32(3), 412–419. <https://doi.org/10.1016/j.nbd.2008.08.001>
- Edison, P., Ahmed, I., Fan, Z., Hinz, R., Gelosa, G., Ray Chaudhuri, K., ... Brooks, D. J. (2013). Microglia, amyloid, and glucose metabolism in Parkinson's disease with and without dementia. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 38(6), 938–949. <https://doi.org/10.1038/npp.2012.255>
- Egerházi, A., Berecz, R., Bartók, E., & Degrell, I. (2007). Automated Neuropsychological Test Battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. <https://doi.org/10.1016/j.pnpbp.2007.01.011>
- Einstein, A. (1905). Investigations on the Theory of the Brownian Movement. *Annalen Der Physik*. <https://doi.org/10.1002/andp.19053220806>
- Engedal, K., Barca, M. L., Laks, J., & Selbaek, G. (2011). Depression in Alzheimer's

- disease: Specificity of depressive symptoms using three different clinical criteria. *International Journal of Geriatric Psychiatry*.
<https://doi.org/10.1002/gps.2631>
- Espinoza, M., de Silva, R., Dickson, D. W., & Davies, P. (2008). Differential incorporation of tau isoforms in Alzheimer's disease. *Journal of Alzheimer's Disease*, *14*(1), 1–16. <https://doi.org/10.1016/j.biotechadv.2011.08.021>
- Esposito, G., Giovacchini, G., Liow, J. S., Bhattacharjee, A. K., Greenstein, D., Schapiro, M., ... Rapoport, S. I. (2008). Imaging Neuroinflammation in Alzheimer's Disease with Radiolabeled Arachidonic Acid and PET. *Journal of Nuclear Medicine*. <https://doi.org/10.2967/jnumed.107.049619>
- Estévez-González, A., Kulisevsky, J., Boltes, A., Otermín, P., & García-Sánchez, C. (2003). Rey verbal learning test is a useful tool for differential diagnosis in the preclinical phase of Alzheimer's disease: Comparison with mild cognitive impairment and normal aging. *International Journal of Geriatric Psychiatry*.
<https://doi.org/10.1002/gps.1010>
- Ettenhofer, M. L., Hambrick, D. Z., & Abeles, N. (2006). Reliability and stability of executive functioning in older adults. *Neuropsychology*.
<https://doi.org/10.1037/0894-4105.20.5.607>
- Evans, M. C., Barnes, J., Nielsen, C., Kim, L. G., Clegg, S. L., Blair, M., ... Fox, N. C. (2010). Volume changes in Alzheimer's disease and mild cognitive impairment: Cognitive associations. *European Radiology*.
<https://doi.org/10.1007/s00330-009-1581-5>
- Facheris, M. F., Maniak, S., Scaravilli, F., Schüle, B., Klein, C., & Pramstaller, P. P. (2008). Pure akinesia as initial presentation of PSP: A clinicopathological study. *Parkinsonism and Related Disorders*, *14*(6), 517–519.
<https://doi.org/10.1016/j.parkreldis.2007.11.004>

- Fan, Z., Aman, Y., Ahmed, I., Chetelat, G., Landeau, B., Ray Chaudhuri, K., ... Edison, P. (2015). Influence of microglial activation on neuronal function in Alzheimer's and Parkinson's disease dementia. *Alzheimer's and Dementia*, *11*(6), 608-621. <https://doi.org/10.1016/j.jalz.2014.06.016>
- Fan, Z., Okello, A. A., Brooks, D. J., & Edison, P. (2015). Longitudinal influence of microglial activation and amyloid on neuronal function in Alzheimer's disease. *Brain*, *138*(12), 3685–3698. <https://doi.org/10.1093/brain/awv288>
- Farias, S. T., Mungas, D., & Jagust, W. (2005). Degree of discrepancy between self and other-reported everyday functioning by cognitive status: Dementia, mild cognitive impairment, and healthy elders. *International Journal of Geriatric Psychiatry*. <https://doi.org/10.1002/gps.1367>
- Fernández-Bostrán, R., Ahmed, Z., Crespo, F. A., Gatenbee, C., Gonzalez, J., Dickson, D. W., & Litvan, I. (2011). Cytokine expression and microglial activation in progressive supranuclear palsy. *Parkinsonism & Related Disorders*, *17*(9), 683–688. <https://doi.org/10.1016/j.parkreldis.2011.06.007>
- Fisk, J. E., & Sharp, C. A. (2004). Age-related impairment in executive functioning: Updating, inhibition, shifting, and access. *Journal of Clinical and Experimental Neuropsychology*, *26*(7), 874–890. <https://doi.org/10.1080/13803390490510680>
- Fiske, S. T., & Taylor, S. E. (1991). *Social cognition (2nd ed.)*. McGraw-Hill series in social psychology. <https://doi.org/10.1007/s00440-015-0632-x>
- Flicker, C., Ferris, S. H., & Reisberg, B. (1993). A Two-Year Longitudinal Study of Cognitive Function in Normal Aging and Alzheimer's Disease. *Journal of Geriatric Psychiatry and Neurology*. <https://doi.org/10.1177/089198879300600205>
- Fodero-Tavoletti, M. T., Furumoto, S., Taylor, L., McLean, C. A., Mulligan, R. S.,

- Birchall, I., ... Villemagne, V. L. (2014). Assessing THK523 selectivity for tau deposits in Alzheimer's disease and non-Alzheimer's disease tauopathies. *Alzheimer's Research and Therapy*. <https://doi.org/10.1186/alzrt240>
- Fodero-Tavoletti, M. T., Okamura, N., Furumoto, S., Mulligan, R. S., Connor, A. R., McLean, C. A., ... Villemagne, V. L. (2011). 18F-THK523: A novel in vivo tau imaging ligand for Alzheimer's disease. *Brain*. <https://doi.org/10.1093/brain/awr038>
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189–198. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
- Forette, F., & Boller, F. (1991). Hypertension and the risk of dementia in the elderly. *The American Journal of Medicine*. [https://doi.org/10.1016/0002-9343\(91\)90430-6](https://doi.org/10.1016/0002-9343(91)90430-6)
- Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*. <https://doi.org/10.1038/nrn2201>
- Fox, N. C., Warrington, E. K., Seiffer, A. L., Agnew, S. K., & Rossor, M. N. (1998). Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease. A longitudinal prospective study. *Brain*. <https://doi.org/10.1093/brain/121.9.1631>
- Frackowiak, J., Wisniewski, H. M., Wegiel, J., Merz, G. S., Iqbal, K. & Wang, K. C. (1992). Ultrastructure of the microglia that phagocytose amyloid and the microglia that produce β -amyloid fibrils. *Acta Neuropathologica*, 84(3), 225–233.
- Franceschi, M., Caffarra, P., De Vreese, L., Pelati, O., Pradelli, S., Savarè, R., ...

- Neri, M. (2007). Visuospatial planning and problem solving in Alzheimer's disease patients: A study with the tower of London test. *Dementia and Geriatric Cognitive Disorders*. <https://doi.org/10.1159/000109827>
- Frank-Cannon, T. C., Alto, L. T., McAlpine, F. E., & Tansey, M. G. (2009). Does neuroinflammation fan the flame in neurodegenerative diseases? *Molecular Neurodegeneration*. <https://doi.org/10.1186/1750-1326-4-47>
- Frisoni, G. B., Fox, N. C., Jack Jr, C. R., Scheltens, P., & Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nature Reviews Neurology*. <https://doi.org/10.1016/j.neurobiolaging.2008.06.016>;
- Frith, C. D., & Frith, U. (1999). Interacting minds - A biological basis. *Science*. <https://doi.org/10.1126/science.286.5445.1692>
- Frost, B., Jacks, R. L., & Diamond, M. I. (2009). Propagation of Tau misfolding from the outside to the inside of a cell. *Journal of Biological Chemistry*. <https://doi.org/10.1074/jbc.M808759200>
- Fukai, M., Hirosawa, T., Kikuchi, M., Hino, S., Kitamura, T., Ouchi, Y., ... Minabe, Y. (2008). Different Patterns of Glucose Hypometabolism Underlie Functional Decline in Frontotemporal Dementia and Alzheimer's Disease: FDG-PET Study. *Neuropsychiatry*. <https://doi.org/10.4172/Neuropsychiatry.1000365>
- Galton, C. J., Erzinçlioglu, S., Sahakian, B. J., Antoun, N., & Hodges, J. R. (2005). A comparison of the Addenbrooke's Cognitive Examination (ACE), conventional neuropsychological assessment, and simple MRI-based medial temporal lobe evaluation in the early diagnosis of Alzheimer's Disease. *Cognitive and Behavioral Neurology*, *18*(3), 144–150. <https://doi.org/10.1097/01.wnn.0000182831.47073.e9>
- Ganguli, M., Snitz, B. E., Saxton, J. A., Chang, C. C. H., Lee, C. W., Vander Bilt, J., ... Petersen, R. C. (2011). Outcomes of mild cognitive impairment by

- definition: A population study. *Archives of Neurology*.
<https://doi.org/10.1001/archneurol.2011.101>
- Gardner, R. C., Boxer, A. L., Trujillo, A., Mirsky, J. B., Guo, C. C., Gennatas, E. D., ... Seeley, W. W. (2013). Intrinsic connectivity network disruption in progressive supranuclear palsy. *Annals of Neurology*.
<https://doi.org/10.1002/ana.23844>
- Garrard, P. & Carroll, E. (2006). Lost in semantic space: a multi-modal, non-verbal assessment of feature knowledge in semantic dementia. *Brain*, *129*, 1152–1163. doi:10.1093/brain/awl069
- Garraux, G., Salmon, E., Degueldre, C., Lemaire, C., Laureys, S., & Franck, G. (1999). Comparison of impaired subcortico-frontal metabolic networks in normal aging, subcortico-frontal dementia, and cortical frontal dementia. *NeuroImage*. <https://doi.org/10.1006/nimg.1999.0463>
- Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., ... Winblad, B. (2006). Mild cognitive impairment. *Lancet*.
[https://doi.org/10.1016/s0140-6736\(06\)68542-5](https://doi.org/10.1016/s0140-6736(06)68542-5)
- Gerhard, A., Trender-Gerhard, I., Turkheimer, F., Quinn, N. P., Bhatia, K. P., Brooks, D. (2006a). *In vivo* imaging of microglial activation with [11C](R)-PK11195 PET in progressive supranuclear palsy. *Movement Disorders*, *21*, 89–93.
- Gerhard, A., Pavese, N., Hotton, G., Turkheimer, F., Es, M., Hammers, A., ... Brooks, D. J. (2006b). *In vivo* imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. *Neurobiology of Disease*.
<https://doi.org/10.1016/j.nbd.2005.08.002>
- Gerhard, A., Watts, J., Trender-Gerhard, I., Turkheimer, F., Banati, R. B., Bhatia, K., & Brooks, D. J. (2004). *In vivo* imaging of microglial activation with

- [11C](R -PK11195 PET in corticobasal degeneration. *Movement Disorders*.
<https://doi.org/10.1002/mds.20162>
- Gernsbacher, M. A., & Faust, M. E. (1991). The Mechanism of Suppression: A Component of General Comprehension Skill. *Journal of Experimental Psychology: Learning, Memory, and Cognition*. <https://doi.org/10.1037/0278-7393.17.2.245>
- Gerson, J. E., Sengupta, U., Lasagna-Reeves, C. A., Guerrero-Muñoz, M. J., Troncoso, J., & Kaye, R. (2014). Characterization of tau oligomeric seeds in progressive supranuclear palsy. *Acta Neuropathologica Communications*. <https://doi.org/10.1186/2051-5960-2-73>
- Gerstenecker, A., Mast, B., Duff, K., Ferman, T. J., & Litvan, I. (2013). Executive dysfunction is the primary cognitive impairment in progressive supranuclear palsy. *Archives of Clinical Neuropsychology*, 28(2). <https://doi.org/10.1093/arclin/acs098>
- Ghosh, B. C. P., Rowe, J. B., Calder, A. J., Hodges, J. R., & Bak, T. H. (2009). Emotion Recognition in Progressive Supranuclear Palsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, 80(10), 1143–1145. <https://doi.org/10.1136/jnnp.2008.155846>
- Ghosh, B. C. P., Calder, A. J., Peers, P. V., Lawrence, A. D., Acosta-Cabronero, J., Pereira, J. M., ... Rowe, J. B. (2012). Social cognitive deficits and their neural correlates in progressive supranuclear palsy. *Brain: A Journal of Neurology*, 135(7), 2089–2102. <https://doi.org/10.1093/brain/aws128>
- Ghosh, B. C. P., Carpenter, R. H. S., & Rowe, J. B. (2013). A Longitudinal Study of Motor, Oculomotor and Cognitive Function in Progressive Supranuclear Palsy. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0074486>
- Gimenez-Roldan, S., Mateo, D., Benito, C., Grandas, F., & Perez-Gilabert, Y.

- (1994). Progressive supranuclear palsy and corticobasal ganglionic degeneration: differentiation by clinical features and neuroimaging techniques. *J Neural Transm Suppl*, 4295053989, 79–90. <https://doi.org/10.1016/j.neuroimage.2005.02.013>
- Goedert, M, Wischik, C., Crowther, R., Walker, J., & Klug, A. (1988). 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. *Proceedings of the National Academy of Sciences of the United States of America*, 85, 4051–4055. Retrieved from papers2://publication/uuid/7D6CE7EA-87C4-4C6A-9BB6-13969F8150F9
- Goedert, M., & Jakes, R. (2005). Mutations causing neurodegenerative tauopathies. *Biochimica et Biophysica Acta - Molecular Basis of Disease*. <https://doi.org/10.1016/j.bbadis.2004.08.007>
- Golbe, L. I. (1994). The epidemiology of PSP. *J. Neural Transm. Suppl*, 42(1), 263–273. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7964691>
- Golbe, L. I. (2014). Progressive supranuclear palsy. *Seminars in Neurology*, 34(2), 151–159. <https://doi.org/10.1055/s-0034-1381736>
- Golbe, L. I. & Ohman-Strickland, P. A. (2007). A clinical rating scale for progressive supranuclear palsy. *Brain: A Journal of Neurology*, 130(6), 1552–1565. <https://doi.org/10.1093/brain/awm032>
- Gómez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J. H., Petersen, R. C., ... Hyman, B. T. (1997). Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Annals of Neurology*. <https://doi.org/10.1002/ana.410410106>
- Gomperts, S. N., Locascio, J. J., Makaretz, S. J., Schultz, A., Caso, C., Vasdev, N., ... Johnson, K. (2016). Tau positron emission tomographic imaging in the lewy

body diseases. *JAMA Neurology*.

<https://doi.org/10.1001/jamaneurol.2016.3338>

Grafman, J., Litvan, I., Gomez, C., & Chase, T. N. (1990). Frontal lobe function in progressive supranuclear palsy. *Arch Neurol*, 47(590240957), 553–558.

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*. <https://doi.org/10.1093/cercor/bhn059>

Griffith, H. R., Netson, K. L., Harrell, L. E., Zamrini, E. Y., Brockington, J. C., & Marson, D. C. (2006). Amnesic mild cognitive impairment: Diagnostic outcomes and clinical prediction over a two-year time period. *Journal of the International Neuropsychological Society*. <https://doi.org/10.1017/S1355617706060267>

Gröschel, K., Kastrup, A., Litvan, I., & Schulz, J. B. (2006). Penguins and hummingbirds: Midbrain atrophy in progressive supranuclear palsy. *Neurology*, 66(6), 949–950. <https://doi.org/10.1212/01.wnl.0000203342.77115.bf>

Gross, A. L., Hassenstab, J. J., Johnson, S. C., Clark, L. R., Resnick, S. M., Kitner-Triolo, M., ... Albert, M. S. (2017). A classification algorithm for predicting progression from normal cognition to mild cognitive impairment across five cohorts: The preclinical AD consortium. *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, 8, 147–155. <https://doi.org/10.1016/j.dadm.2017.05.003>

Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., Rogaevea, E., Majounie, E., ... Hardy, J. (2013). *TREM2* Variants in Alzheimer's Disease. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa1211851>

Gulyás, B., Pavlova, E., Kása, P., Gulya, K., Bakota, L., Várszegi, S., ... Halldin, C.

- (2011). Activated MAO-B in the brain of alzheimer patients, demonstrated by [11C]-l-deprenyl using whole hemisphere autoradiography. *Neurochemistry International*. <https://doi.org/10.1016/j.neuint.2010.10.013>
- Gunn, R. N., Lammertsma, A. A., Hume, S. P., & Cunningham, V. J. (1997). Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage*, 6(4), 279–287. <https://doi.org/10.1006/nimg.1997.0303>
- Guo, J. L., & Lee, V. M. Y. (2011). Seeding of normal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles. *Journal of Biological Chemistry*. <https://doi.org/10.1074/jbc.M110.209296>
- Hagmann, P., Jonasson, L., Maeder, P., Thiran, J.-P., Wedeen, V. J., & Meuli, R. (2006). Understanding Diffusion MR Imaging Techniques: From Scalar Diffusion-weighted Imaging to Diffusion Tensor Imaging and Beyond. *RadioGraphics*, 26(1), 205–223. <https://doi.org/10.1148/rg.26si065510>
- Hamby, M. E., & Sofroniew, M. V. (2010). Reactive astrocytes as therapeutic targets for CNS disorders. *Neurotherapeutics*, 7(4), 494-506. doi: 10.1016/j.nurt.2010.07.003
- Hamelin, L., Lagarde, J., Dorothee, G., Leroy, C., Labit, M., Comley, R. A., ... Sarazin, M. (2016). Early and protective microglial activation in Alzheimer's disease: A prospective study using 18F-DPA-714 PET imaging. *Brain*, 139(4), 1252–1264. <https://doi.org/10.1093/brain/aww017>
- Hammers, A., Allom, R., Koepp, M. J., Free, S. L., Myers, R., Lemieux, L., ... Duncan, J. S. (2003). Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Human Brain Mapping*, 19(4), 224–247. <https://doi.org/10.1002/hbm.10123>
- Han, H. J., Kim, H., Park, J.-H., Shin, H.-W., Kim, G. U., Kim, D. S., ... Kim, Y. J.

- (2010). Behavioral changes as the earliest clinical manifestation of progressive supranuclear palsy. *Journal of Clinical Neurology (Seoul, Korea)*, 6(3), 148–151. <https://doi.org/10.3988/jcn.2010.6.3.148>
- Hannestad, J., Gallezot, J. D., Schafbauer, T., Lim, K., Kloczynski, T., Morris, E. D., ... Cosgrove, K. P. (2012). Endotoxin-induced systemic inflammation activates microglia: [11C]PBR28 positron emission tomography in nonhuman primates. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2012.06.055>
- Hansen, A. K., Knudsen, K., Lillethorup, T. P., Landau, A. M., Parbo, P., Fedorova, T., ... Borghammer, P. (2016). In vivo imaging of neuromelanin in Parkinson's disease using 18F-AV-1451 PET. *Brain*, 139(7), 2039-2049. doi: 10.1093/brain/aww098
- Hanyu, H., Sakurai, H., Iwamoto, T., Takasaki, M., Shindo, H., & Abe, K. (1998). Diffusion-weighted MR imaging of the hippocampus and temporal white matter in alzheimer's disease. *Journal of the Neurological Sciences*. [https://doi.org/10.1016/S0022-510X\(98\)00043-4](https://doi.org/10.1016/S0022-510X(98)00043-4)
- Harada, R., Ishiki, A., Kai, H., Sato, N., Furukawa, K., Furumoto, S., ... Okamura, N. (2017). Correlations of ¹⁸F-THK5351 PET with post-mortem burden of tau and astrogliosis in Alzheimer's disease. *Journal of Nuclear Medicine*. <https://doi.org/10.2967/jnumed.117.197426>
- Hardy, J., & Allsop, D. (1991). Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends in Pharmacological Sciences*. [https://doi.org/10.1016/0165-6147\(91\)90609-V](https://doi.org/10.1016/0165-6147(91)90609-V)
- Hashimoto, H., Kawamura, K., Igarashi, N., Takeji, M., Fujishiro, T., Aihara, Y., ... Zhang, M. R. (2014). Radiosynthesis, Photoisomerization, Biodistribution, and Metabolite Analysis of 11C-PBB3 as a Clinically Useful PET Probe for Imaging of Tau Pathology. *Journal of Nuclear Medicine*.

<https://doi.org/10.2967/jnumed.114.139550>

- Hassan, A., Parisi, J. E., & Josephs, K. A. (2012). Autopsy-proven progressive supranuclear palsy presenting as behavioral variant frontotemporal dementia. *Neurocase*. <https://doi.org/10.1080/13554794.2011.627345>
- Hatashita, S., & Yamasaki, H. (2013). Diagnosed Mild Cognitive Impairment Due to Alzheimer's Disease with PET Biomarkers of Beta Amyloid and Neuronal Dysfunction. *PLoS ONE*, *8*(6). <https://doi.org/10.1371/journal.pone.0066877>
- Hatashita, S., & Yamasaki, H. (2010). Clinically different stages of Alzheimer's disease associated by amyloid deposition with [11C]-PIB PET imaging. *Journal of Alzheimer's Disease*, *21*(3), 995–1003. doi: 10.3233/JAD-2010-100222
- Hauw, J. J., Daniel, S. E., Dickson, D., Horoupian, D. S., Jellinger, K., Lantos, P. L., ... Litvan, I. (1994). Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Neurology*, *44*(11), 2015–2019. <https://doi.org/10.1212/WNL.44.11.2015>
- Heneka, M. T., Kummer, M. P., & Latz, E. Innate immune activation in neurodegenerative disease. *Nat Rev Immunol*, *14*(7), 463-477. doi: 10.1038/nri3705.
- Henry, J. D., Crawford, J. R., & Phillips, L. H. (2004). Verbal fluency performance in dementia of the Alzheimer's type: A meta-analysis. *Neuropsychologia*. <https://doi.org/10.1016/j.neuropsychologia.2004.02.001>
- Herholz, K., & Ebmeier, K. (2011). Clinical amyloid imaging in Alzheimer's disease. *The Lancet Neurology*. [https://doi.org/10.1016/S1474-4422\(11\)70123-5](https://doi.org/10.1016/S1474-4422(11)70123-5)
- Hickman, S. E, Allison, E. K., & Khoury, J. E. (2008). Microglial Dysfunction and Defective β -Amyloid Clearance Pathways in Aging Alzheimer's Disease Mice. *Journal of Neurosciences*, *28*(33). 8354-8360. <https://doi.org/10.1523/JNEUROSCI.0616-08.2008>

- Hirao, K., Ohnishi, T., Matsuda, H., Nemoto, K., Hirata, Y., Yamashita, F., ... Iwamoto, T. (2006). Functional interactions between entorhinal cortex and posterior cingulate cortex at the very early stage of Alzheimer's disease using brain perfusion single-photon emission computed tomography. *Nucl Med Commun*. <https://doi.org/00006231-200602000-00008> [pii]
- Hirvonen, J., Kailajärvi, M., Haltia, T., Koskimies, S., Ngren, K., Virsu, P., ... Rinne, J. O. (2009). Assessment of MAO-B occupancy in the brain with PET and 11 C-L-deprenyl-D 2: A dose-finding study with a novel MAO-B inhibitor, EVT 301. *Clinical Pharmacology and Therapeutics*. <https://doi.org/10.1038/clpt.2008.241>
- Ho, A. J., Hua, X., Lee, S., Leow, A. D., Yanovsky, I., Gutman, B., ... Thompson, P. M. (2010). Comparing 3 T and 1.5 T MRI for tracking Alzheimer's disease progression with tensor-based morphometry. *Human Brain Mapping*. <https://doi.org/10.1002/hbm.20882>
- Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy (1992). *Brain*, *115*, 1783-1806.
- Hodges, J. R., & Miller, B. (2001). The neuropsychology of frontal variant frontotemporal dementia and semantic dementia. Introduction to the special topic papers: Part II. *Neurocase*, *7*(2), 113-121. <https://doi.org/10.1093/neucas/7.2.113>
- Hodges, J. R., Salmon, D. P., & Butters, N. (1990). Differential impairment of semantic and episodic memory in Alzheimer's and Huntington's diseases: A controlled prospective study. *Journal of Neurology, Neurosurgery and Psychiatry*. <https://doi.org/10.1136/jnnp.53.12.1089>
- Höglinger, G. U., Melhem, N. M., Dickson, D. W., Sleiman, P. M. A., Wang, L. S.,

- Klei, L., ... Zecchinelli, A. L. (2011). Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. In *Nature Genetics*. <https://doi.org/10.1038/ng.859>
- Höglinger, G. U., Respondek, G., Stamelou, M., Kurz, C., Josephs, K. A., Lang, A. E., ... Bordelon, Y. (2017). Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Movement Disorders*, 32(6), 853–864. <https://doi.org/10.1002/mds.26987>
- Hosaka, K., Ishii, K., Sakamoto, S., Mori, T., Sasaki, M., Hirono, N., & Mori, E. (2002). Voxel-based comparison of regional cerebral glucose metabolism between PSP and corticobasal degeneration. *Journal of the Neurological Sciences*. [https://doi.org/10.1016/S0022-510X\(02\)00102-8](https://doi.org/10.1016/S0022-510X(02)00102-8)
- Hostetler, E. D., Walji, A. M., Zeng, Z., Miller, P., Bennacef, I., Salinas, C., ... Evelhoch, J. L. (2016). Preclinical Characterization of 18F-MK-6240, a Promising PET Tracer for In Vivo Quantification of Human Neurofibrillary Tangles. *Journal of Nuclear Medicine*. <https://doi.org/10.2967/jnumed.115.171678>
- Huettel, S. A., Song, A. W. & McCarthy, G. (2004). Functional Magnetic Resonance Imaging. Massachusetts, MA: Sunderland. Retrieved from <https://www.sinauer.com/media/wysiwyg/tocs/FMRI.pdf>
- Hughes, L. E., Rittman, T., Robbins, T. W., & Rowe, J. B. (2018). Reorganisation of cortical oscillatory dynamics underlying disinhibition in frontotemporal dementia. *Brain*, 141, 2486–2499.
- Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *British Journal of Psychiatry*. <https://doi.org/10.1192/bjp.140.6.566>
- Hughes, L. E., & Rowe, J. B. (2013). The impact of neurodegeneration on network

- connectivity: A study of change detection in frontotemporal dementia. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn_a_00356
- Iavarone, A., Ronga, B., Pellegrino, L., Loré, E., Vitaliano, S., Galeone, F., & Carlomagno, S. (2004). The Frontal Assessment Battery (FAB): Normative data from an Italian sample and performances of patients with Alzheimer's disease and frontotemporal dementia. *Functional Neurology*. <https://doi.org/15595714>
- Imaizumi, M., Briard, E., Zoghbi, S. S., Gourley, J. P., Hong, J., Fujimura, Y., ... Fujita, M. (2008). Brain and whole-body imaging in nonhuman primates of [11C]PBR28, a promising PET radioligand for peripheral benzodiazepine receptors. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2007.09.063>
- Isella, V., Rucci, F., Traficante, D., Mapelli, C., Ferri, F. & Appollonio, I. M. (2013). The applause sign in cortical and cortical-subcortical dementia. *J Neurol*, 260(4), 1099-1103. doi: 10.1007/s00415-012-6767-0.
- Ishihara, T., Hong, M., Zhang, B., Nakagawa, Y., Lee, M. K., Trojanowski, J. Q., & Lee, V. M. Y. (1999). Age-dependent emergence and progression of a tauopathy in transgenic mice overexpressing the shortest human tau isoform. *Neuron*. [https://doi.org/10.1016/S0896-6273\(00\)81127-7](https://doi.org/10.1016/S0896-6273(00)81127-7)
- Ishizawa, K., Lin, W. L., Tiseo, P., Honer, W. G., Davies, P., & Dickson, D. W. (2000). A qualitative and quantitative study of glumose degeneration in progressive supranuclear palsy. *Journal of Neuropathology and Experimental Neurology*, 59(6), 513–524. Retrieved from <papers2://publication/uuid/461974EF-449D-4A52-A9A6-BC0ECF26E018>
- Ishizawa, K. & Dickson, D. W. (2001). Microglial activation parallels system degeneration in progressive supranuclear palsy and corticobasal degeneration. *J Neuropathol Exp Neurol*, 60(6), 647-657. DOI:

10.1093/jnen/60.6.647

- Itagaki, S., McGeer, P., Akiyama, H., Zhu, S. & Selkoe, D. (1989). Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. *J. Neuroimmunol.*, 24(3), 173-182. [https://doi.org/10.1016/0165-5728\(89\)90115-X](https://doi.org/10.1016/0165-5728(89)90115-X)
- Itoikar, S. M., Salagre, S. B., & Kalal, C. R. (2012). "Hummingbird sign", 'penguin sign' and "mickey mouse sign" in progressive supranuclear palsy. *Journal of Association of Physicians of India*.
- Iwasaki, Y., Mori, K., Ito, M., Tatsumi, S., Mimuro, M., & Yoshida, M. (2013). An autopsied case of progressive supranuclear palsy presenting with cerebellar ataxia and severe cerebellar involvement. *Neuropathology*. <https://doi.org/10.1111/neup.12012>
- Iwata, M. (2005). [MRI diagnosis of neurodegenerative disorders]. *Rinshō Shinkeigaku = Clinical Neurology*, 45(11), 947-951. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16447770>
- Jack, C. R., Albert, M. S., Knopman, D. S., McKhann, G. M., Sperling, R. A., Carrillo, M. C., ... Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*. <https://doi.org/10.1016/j.jalz.2011.03.004>
- Jack, C. R., & Holtzman, D. M. (2013). Biomarker modeling of Alzheimer's disease. *Neuron*. <https://doi.org/10.1016/j.neuron.2013.12.003>
- Jack, C. R., Wiste, H. J., Schwarz, C. G., Lowe, V. J., Senjem, M. L., Vemuri, P., ... Petersen, R. C. (2018). Longitudinal tau PET in ageing and Alzheimer's disease. *Brain*. <https://doi.org/10.1093/brain/awy059>
- Jacobs, A. H., Tavitian, B., & INMiND consortium (2012). Noninvasive molecular

- imaging of neuroinflammation. *Journal of cerebral blood flow and metabolism*, 32(7), 1393–1415. doi:10.1038/jcbfm.2012.53
- Jang, Y. K., Lyoo, C. H., Park, S., Oh, S. J., Cho, H., Oh, M., ... Seo, S. W. (2018). Head to head comparison of [18F] AV-1451 and [18F] THK5351 for tau imaging in Alzheimer's disease and frontotemporal dementia. *European Journal of Nuclear Medicine and Molecular Imaging*. <https://doi.org/10.1007/s00259-017-3876-0>
- Jarmolowicz, A. I., Chen, H.-Y., & Panegyres, P. K. (2015). The Patterns of Inheritance in Early-Onset Dementia: Alzheimer's Disease and Frontotemporal Dementia. *American Journal of Alzheimer's Disease and Other Dementias*. <https://doi.org/10.1177/1533317514545825>
- Jicha, G. A., Parisi, J. E., Dickson, D. W., Johnson, K., Cha, R., Ivnik, R. J., ... Petersen, R. C. (2006). Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Archives of Neurology*. <https://doi.org/10.1001/archneur.63.5.674>
- Johnson, K. A., Schultz, A., Betensky, R. A., Becker, J. A., Sepulcre, J., Rentz, D., ... Sperling, R. (2016). Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Annals of Neurology*, 79(1), 110–119. <https://doi.org/10.1002/ana.24546>
- Johnström, P., Bird, J. L., & Davenport, A. P. (2012). Quantitative phosphor imaging autoradiography of radioligands for positron emission tomography. *Methods Mol Biol*, 897, 205–20. doi: 10.1007/978-1-61779-909-9_10
- Johnson, V. E., Stewart, J. E., Begbie, F. D., Trojanowski, J. Q., Smith, D. H., & Stewart, W. (2013). Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain*, 136(1), 28–42. doi: 10.1093/brain/aws322

- Jonsson, T., Stefansson, H., Steinberg, S., Jonsdottir, I., Jonsson, P. V., Snaedal, J., ... Stefansson, K. (2013). Variant of TREM2 associated with the risk of AD. *N. Engl. J. Med.*, *368*(2), 107-116. doi: 10.1056/NEJMoa1211103
- Josephs, K. A., Petersen, R. C., Knopman, D. S., Boeve, B. F., Whitwell, J. L., Duffy, J. R., ... Dickson, D. W. (2006). Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. *Neurology*, *66*(1), 41-48. <https://doi.org/10.1212/01.wnl.0000191307.69661.c3>
- Josephs, K. A., Duffy, J. R., Strand, E. A., Whitwell, J. L., Layton, K. F., Parisi, J. E., ... Jr, C. R. J. (2006). Clinicopathologic and imaging correlates of progressive aphasia and apraxia of speech. *Brain*, *129*(6), 1385-1398. <https://doi.org/10.1093/brain/awl078>.Clinicopathologic
- Josephs, K. A., Katsuse, O., Beccano-Kelly, D. A., Lin, W. L., Uitti, R. J., Fujino, Y., ... Dickson, D. W. (2006). Atypical progressive supranuclear palsy with corticospinal tract degeneration. *Journal of Neuropathology and Experimental Neurology*. <https://doi.org/10.1097/01.jnen.0000218446.38158.61>
- Josephs, K. A., Whitwell, J. L., Dickson, D. W., Boeve, B. F., Knopman, D. S., Petersen, R. C., ... Jack, C. R. (2008). Voxel-based morphometry in autopsy proven PSP and CBD. *Neurobiology of Aging*. <https://doi.org/10.1016/j.neurobiolaging.2006.09.019>
- Jucker, M., & Walker, L. C. (2011). Pathogenic protein seeding in Alzheimer disease and other neurodegenerative disorders. *Annals of Neurology*. <https://doi.org/10.1002/ana.22615>
- Juh, R., Pae, C. U., Kim, T. S., Lee, C. U., Choe, B., & Suh, T. (2005). Cerebral glucose metabolism in corticobasal degeneration comparison with progressive supranuclear palsy using statistical mapping analysis. *Neuroscience Letters*. <https://doi.org/10.1016/j.neulet.2005.03.057>

- Kaat, L. D., Boon, A. J. W., Azmani, A., Kamphorst, W., Breteler, M. M. B., Anar, B., ... Van Swieten, J. C. (2009). Familial aggregation of parkinsonism in progressive supranuclear palsy. *Neurology*, *73*(2), 98–105. <https://doi.org/10.1212/WNL.0b013e3181a92bcc>
- Kahnt, T., Chang, L. J., Park, S. Q., Heinzle, J., & Haynes, J. D. (2012). Connectivity-based parcellation of the human orbitofrontal cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*. <https://doi.org/10.1523/JNEUROSCI.0257-12.2012>
- Kalaria, R. N., Maestre, G. E., Arizaga, R., Friedland, R. P., Galasko, D., Hall, K., ... Antuono, P. (2008). Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol*. [https://doi.org/S1474-4422\(08\)70169-8](https://doi.org/S1474-4422(08)70169-8) [pii]\r10.1016/S1474-4422(08)70169-8
- Kanazawa, M., Shimohata, T., Toyoshima, Y., Tada, M., Kakita, A., Morita, T., ... Nishizawa, M. (2009). Cerebellar involvement in progressive supranuclear palsy: A clinicopathological study. *Movement Disorders*. <https://doi.org/10.1002/mds.22583>
- Kantarci, K., Petersen, R., Boeve, B., Knopman, D., Weigand, S., O'Brien, P., ... Jack, C. (2005). DWI predicts future progression to Alzheimer disease in amnesic mild cognitive impairment. *Neurology*.
- Kato, N., Arai, K., & Hattori, T. (2003). Study of the rostral midbrain atrophy in progressive supranuclear palsy. *Journal of the Neurological Sciences*, *210*(1–2), 57–60. [https://doi.org/10.1016/S0022-510X\(03\)00014-5](https://doi.org/10.1016/S0022-510X(03)00014-5)
- Kawai, H., Kawamura, M., Mochizuki, S., Yamanaka, K., Arakaki, H., Tanaka, K., & Kawachi, J. (2002). [Longitudinal study of procedural memory in patients with Alzheimer-type dementia]. *N{\=}{o} to Shinkei = Brain and Nerve*.

<https://doi.org/11993158>

Kinahan, P. E., & Rogers, J. G. (1989). Analytic 3D image reconstruction using all detected events. *IEEE Transactions on Nuclear Science*, 36(1 pt 1), 964–968.

<https://doi.org/10.1109/23.34585>

Kitzbichler, M. G., Henson, R. N. A., Smith, M. L., Nathan, P. J., & Bullmore, E. T. (2011). Cognitive Effort Drives Workspace Configuration of Human Brain Functional Networks. *Journal of Neuroscience*.

<https://doi.org/10.1523/JNEUROSCI.0440-11.2011>

Klein, R. C., de Jong, B. M., de Vries, J. J., & Leenders, K. L. (2005). Direct comparison between regional cerebral metabolism in progressive supranuclear palsy and Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*. <https://doi.org/10.1002/mds.20493>

Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., ... Långström, B. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. *Ann Neurol*. <https://doi.org/10.1002/ana.20009>

Knezevic, D. & Mizrahi, R. (2018). Molecular imaging of neuroinflammation in Alzheimer's disease and mild cognitive impairment. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 80, 123-131. <https://doi.org/10.1016/j.pnpbp.2017.05.007>

Kosmidis, S., Grammenoudi, S., Papanikolopoulou, K., & Skoulakis, E. M. C. (2010). Differential Effects of Tau on the Integrity and Function of Neurons Essential for Learning in *Drosophila*. *Journal of Neuroscience*. <https://doi.org/10.1523/JNEUROSCI.1490-09.2010>

Kovacs, G. G. (2014). Introduction: classification of neurodegenerative diseases. *Neuropathology of Neurodegenerative Diseases A Practical Guide*, 1–7. <https://doi.org/10.1017/CBO9781107588660>

- Krabbe, G., Halle, A., Matyash, V., Rinnenthal, J. L., Eom, G. D., Bernhardt, U., Miller, K. R., Prokop, S., Kettenmann, H. & Heppner, F. L. (2013). Functional Impairment of Microglia Coincides with Beta-Amyloid Deposition in Mice with Alzheimer-Like Pathology. *PLoS ONE* 8(4): e60921. <https://doi.org/10.1371/journal.pone.0060921>
- Kreisl, W. C., Lyoo, C. H., Liow, J.-S., Wei, M., Snow, J., Page, E., ... Innis, R. B. (2016). 11 C-PBR28 binding to translocator protein increases with progression of Alzheimer's disease. *Neurobiology of Aging*, 44, 53–61. <https://doi.org/10.1016/j.neurobiolaging.2016.04.011>
- Kreisl, W. C., Lyoo, C. H., McGwier, M., Snow, J., Jenko, K. J., Kimura, N., ... Innis, R. B. (2013). In vivo radioligand binding to translocator protein correlates with severity of Alzheimer's disease. *Brain*. <https://doi.org/10.1093/brain/awt145>
- Kreutzberg, G. W. (1996). Microglia: a sensor for pathological events in the CNS. *Trends in Neurosciences*, 19(8), 312-318.
- Kropholler, M. A., Boellaard, R., van Berckel, B. N. M., Schuitmaker, A., Kloet, R. W., Lubberink, M. J., ... Lammertsma, A. A. (2007). Evaluation of reference regions for (R)-[11C] (R)-PK11195 studies in Alzheimer's disease and Mild Cognitive Impairment. *Journal of Cerebral Blood Flow & Metabolism*, 27(12), 1965–1974. <https://doi.org/10.1038/sj.jcbfm.9600488>
- Kumar, A., Muzik, O., Shandal, V., Chugani, D., Chakraborty, P., & Chugani, H. T. (2012). Evaluation of age-related changes in translocator protein (TSPO) in human brain using 11C-[R]-PK11195 PET. *Journal of Neuroinflammation*. <https://doi.org/10.1186/1742-2094-9-232>
- Lansdall, C. J., Coyle-Gilchrist, I. T. S., Jones, P. S., Rodríguez, P. V., Wilcox, A., Wehmann, E., ... Rowe, J. B. (2017). Apathy and impulsivity in frontotemporal lobar degeneration syndromes. *Brain*, 140(6), 1792–1807.

<https://doi.org/10.1093/brain/awx101>

Lant, S. B., Robinson, A. C., Thompson, J. C., Rollinson, S., Pickering-Brown, S., Snowden, J. S., Davidson, Y. S., Gerhard, A., & Mann, D. M. A. (2014). Patterns of microglial cell activation in frontotemporal lobar degeneration. *Neuropathology and Applied Neurobiology*, 40(6), 686-696. <https://doi.org/10.1111/nan.12092>

Larner, A. J. (2006). Audit of the Addenbrooke's Cognitive Examination (ACE) in clinical practice. *International Journal of Geriatric Psychiatry*, 20(6), 593-594. DOI: 10.1002/gps.1336

Laws, K. R., Duncan, A., & Gale, T. M. (2010). "Normal" semantic-phonemic fluency discrepancy in Alzheimer's disease? A meta-analytic study. *Cortex*. <https://doi.org/10.1016/j.cortex.2009.04.009>

Lawson, L. J., Perry, V. H., Dri, P., & Gordon, S. (1990). Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience*, 39(1), 151-170. DOI: 10.1016/0306-4522(90)90229-w

Le Bihan, D., Turner, R., Douek, P., & Patronas, N. (1992). Diffusion MR imaging: clinical applications. *AJR Am J Roentgenol*, 159(3), 591-599. <https://doi.org/10.2214/ajr.159.3.1503032>

Lee, S. (1991). The neuropsychiatric evolution of a case of progressive supranuclear palsy. *The British Journal of Psychiatry*.

Lee, S. J., Desplats, P., & Sigurdson, C. (2010). Cell-to-cell transmission of non-prion protein aggregates. *Nature Reviews. Neurology*. <https://doi.org/10.1038/nrneurol.2010.191>

Leicht, H., Berwig, M., & Gertz, H. J. (2010). Anosognosia in Alzheimers disease: The role of impairment levels in assessment of insight across domains. *Journal of the International Neuropsychological Society*.

<https://doi.org/10.1017/S1355617710000056>

- Levy, M. L., Miller, B. L., Cummings, J. L., Fairbanks, L. A., & Craig, A. (1996). Alzheimer disease and frontotemporal dementias. Behavioral distinctions. *Arch Neurol*, *53*(7), 687–690. <https://doi.org/10.1001/archneur.1996.00550070129021>
- Levy, M. L., Cummings, J. L., Fairbanks, L. A., Masterman, D., Miller, B. L., Craig, A. H., ... Litvan, I. (1998). Apathy Is Not Depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(3), 314–319. <https://doi.org/10.1176/jnp.10.3.314>
- Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral Cortex*. <https://doi.org/10.1093/cercor/bhj043>
- Li, S., Okonkwo, O., Albert, M., & Wang, M. C. (2013). Variation in Variables that Predict Progression from MCI to AD Dementia over Duration of Follow-up. *American Journal of Alzheimer's Disease*, *2*(1), 12–28. <https://doi.org/10.7726/ajad.2013.1002>
- Lindau, M., Almkvist, O., Kushi, J., Boone, K., Johansson, S. E., Wahlund, L. O., ... Miller, B. L. (2000). First symptoms--frontotemporal dementia versus Alzheimer's disease. *Dement Geriatr Cogn Disord*. <https://doi.org/17251>
- Ling, H., de Silva, R., Massey, L. A., Courtney, R., Hondhamuni, G., Bajaj, N., ... Revesz, T. (2014). Characteristics of progressive supranuclear palsy presenting with corticobasal syndrome: A cortical variant. *Neuropathology and Applied Neurobiology*, *40*(2), 149–163. <https://doi.org/10.1111/nan.12037>
- Litvan, I., Agid, Y., Calne, D., Campbell, G., Dubois, B., Duvoisin, R. C., ... Zee, D. S. (1996). Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the

- NINDS-SPSP international workshop. [Review] [88 refs]. *Neurology*, 47(1), 1–9.
- Litvan, I., Agid, Y., Jankovic, J., Goetz, C., Brandel, J. P., Lai, E. C., ... Pearce, R. K. (1996). Accuracy of clinical criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). *Neurology*, 46(4), 922–930. <https://doi.org/10.1212/WNL.46.4.922>
- Litvan, I., Hauw, J., Bartko, J., Lantos, P., Daniel, S., Horoupian, D., ... Anderson, D. (1996). Validity and Reliability of the Preliminary NINDS Neuropathologic Criteria for PSP and Related Disorders. *Journal of Neuropathology and Experimental Neurology*. <https://doi.org/10.1097/00005072-199601000-00010>
- Litvan, I., Mangone, C. A., McKee, A., Verny, M., Parsa, A., Jellinger, K., ... Pearce, R. K. (1996). Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. *J Neurol Neurosurg Psychiatry*.
- Litvan, I., Mega, M. S., Cummings, J. L., & Fairbanks, L. (1996). Neuropsychiatric aspects of progressive supranuclear palsy. *Neurology*, 47, 1184–1189. <https://doi.org/10.1212/WNL.47.5.1184>
- Litvan, I., Grafman, J., Gomez, C., & Chase, T. N. (1989). Memory impairment in patients with progressive supranuclear palsy. *Archives of Neurology*. <https://doi.org/10.1001/archneur.1989.00520430059018>
- Litvan, I., Paulsen, J. S., Mega, M. S., & Cummings, J. L. (1998). Neuropsychiatric assessment of patients with hyperkinetic and hypokinetic movement disorders. *Archives of Neurology*, 55(10), 1313–1319. <https://doi.org/10.1001/archneur.55.10.1313>
- Litvan, I., Lees, P. S., Cunningham, C. R., Rai, S. N., Cambon, A. C., Standaert,

- D. G., ... for ENGENE-PSP (2016). Environmental and occupational risk factors for progressive supranuclear palsy: Case-control study. *Movement disorders*, 31(5), 644–652. doi:10.1002/mds.26512
- Liu, W. K., Le, T. V., Adamson, J., Baker, M., Cookson, N., Hardy, J., ... Dickson, D. W. (2001). Relationship of the extended tau haplotype to tau biochemistry and neuropathology in progressive supranuclear palsy. *Annals of Neurology*. <https://doi.org/10.1002/ana.1159>
- Liu, G. J., Middleton, R. J., Hatty, C. R., Wai-Ying, W., Chan, K. R., Pham, T., Harrison-Brown, M., Dodson, E., Veale, K. & Banati, R. B. (2014). The 18 kDa Translocator Protein, Microglia and Neuroinflammation. *Brain Pathology*, 24(6), 631-653. <https://doi.org/10.1111/bpa.12196>.
- Lopez, O. L., Becker, J. T., Kaufer, D. I., Hamilton, R. L., Sweet, R. A., Klunk, W., & DeKosky, S. T. (2002). Research evaluation and prospective diagnosis of dementia with Lewy bodies. *Archives of Neurology*. <https://doi.org/10.1001/archneur.59.1.43>
- Lowe, V. J., Curran, G., Fang, P., Liesinger, A. M., Josephs, K. A., Parisi, J. E., ... Murray, M. E. (2016). An autoradiographic evaluation of AV-1451 Tau PET in dementia. *Acta Neuropathologica Communications*, 4(1), 58. <https://doi.org/10.1186/s40478-016-0315-6>
- Lowe, V. J., Wiste, H. J., Senjem, M. L., Weigand, S. D., Therneau, T. M., Boeve, B. F., ... Jack, C. R. (2018). Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. *Brain*. <https://doi.org/10.1093/brain/awx320>
- Luzzi, S., Fabi, K., Pesallaccia, M., Silvestrini, M., & Provinciali, L. (2011). Applause sign: is it really specific for Parkinsonian disorders? Evidence from cortical dementias. *J Neurol Neurosurg Psychiatry*, 82(8), 830-833. doi:

10.1136/jnnp.2010.224394.

- Lyketsos, C. G., Breitner, J. C. S., Green, R. C., Martin, B. K., Meinert, C., Piantadosi, S., & Sabbagh, M. (2007). Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. *Neurology*, *68*(21), 1800–1808. <https://doi.org/10.1212/01.wnl.0000260269.93245.d2>
- Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & Dekosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *Journal of the American Medical Association*. <https://doi.org/10.1001/jama.288.12.1475>
- Lyman, M., Lloyd, D. G., Ji, X., Vizcaychipi, M. P., & Ma, D. Neuroinflammation: The role and consequences (2014). *Neuroscience Research*, *79*, 1-12. <https://doi.org/10.1016/j.neures.2013.10.004>
- Lyoo, C. H., Ikawa, M., Liow, J.-S., Zoghbi, S. S., Morse, C. L., Pike, V. W., ... Kreisl, W. C. (2015). Cerebellum Can Serve As a Pseudo-Reference Region in Alzheimer Disease to Detect Neuroinflammation Measured with PET Radioligand Binding to Translocator Protein. *Journal of Nuclear Medicine*. <https://doi.org/10.2967/jnumed.114.146027>
- Maeda, S., Sahara, N., Saito, Y., Murayama, S., Ikai, A., & Takashima, A. (2006). Increased levels of granular tau oligomers: An early sign of brain aging and Alzheimer's disease. *Neuroscience Research*. <https://doi.org/10.1016/j.neures.2005.11.009>
- Magaud, E., Kebir, O., Gut, A., Willard, D., Chauchot, F., Olie, J. P., ... Krebs, M. O. (2010). Altered semantic but not phonological verbal fluency in young help-seeking individuals with ultra high risk of psychosis. *Schizophrenia Research*. <https://doi.org/10.1016/j.schres.2010.05.005>

- Magherini, A., & Litvan, I. (2005). Cognitive and behavioral aspects of PSP since Steele, Richardson and Olszewski's description of PSP 40 years ago and Albert's delineation of the subcortical dementia 30 years ago. *Neurocase*. <https://doi.org/10.1080/13554790590962979>
- Mak, E., Bethlehem, R. A. I., Romero-Garcia, R., Cervenka, S., Rittman, T., Gabel, S., ... O'Brien, J. T. (2018). In vivo coupling of tau pathology and cortical thinning in Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. <https://doi.org/10.1016/j.dadm.2018.08.005>
- Mak, E., Gabel, S., Su, L., Williams, G. B., Arnold, R., Passamonti, L., ... O'Brien, J. T. (2017). Multi-modal MRI investigation of volumetric and microstructural changes in the hippocampus and its subfields in mild cognitive impairment, Alzheimer's disease, and dementia with Lewy bodies. *International Psychogeriatrics*. <https://doi.org/10.1017/S1041610216002143>
- Mak, E., Su, L., Williams, G. B., & O'Brien, J. T. (2014). Neuroimaging characteristics of dementia with Lewy bodies. *Alzheimer's Research and Therapy*. <https://doi.org/10.1186/alzrt248>
- Malik, M., Parikh, I., Vasquez, J. B., Smith, C., Tai, L., Bu, G., ... Estus, S. (2015). Genetics ignite focus on microglial inflammation in Alzheimer's disease. *Molecular Neurodegeneration*. <https://doi.org/10.1186/s13024-015-0048-1>
- Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., & Robbins, T. (2002). Decision-making processes following damage to the prefrontal cortex. *Brain*. <https://doi.org/10.1093/brain/awf049>
- Markowitsch, H. J. (2003). Memory. Disturbances and Therapy. In *Neurological Disorders: Course and Treatment: Second Edition*. <https://doi.org/10.1016/B978-012125831-3/50222-7>

- Marques, A., Durif, F., & Fernagut, P. O. (2018). Impulse control disorders in Parkinson's disease. *Journal of Neural Transmission*.
<https://doi.org/10.1007/s00702-018-1870-8>
- Marquié, M., Normandin, M. D., Vanderburg, C. R., Costantino, I. M., Bien, E. A., Rycyna, L. G., ... Gómez-Isla, T. (2015). Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. *Annals of Neurology*, *78*(5), 787–800. <https://doi.org/10.1002/ana.24517>
- Martin, A., & Fedio, P. (1983). Word production and comprehension in Alzheimer's disease: The breakdown of semantic knowledge. *Brain and Language*, *19*(1), 124-141. [http://dx.doi.org/10.1016/0093-934X\(83\)90059-7](http://dx.doi.org/10.1016/0093-934X(83)90059-7)
- Martin, B. K., Szekely, C., Brandt, J., Piantadosi, S., Breitner, J. C. S., Craft, S., ... Mullan, M. (2008). Cognitive function over time in the Alzheimer's disease anti-inflammatory prevention trial (ADAPT): Results of a randomized, controlled trial of naproxen and celecoxib. *Archives of Neurology*, *65*(7), 896–905. <https://doi.org/10.1001/archneur.2008.65.7.nct70006>
- Martin, L., Latypova, X., & Terro, F. (2011). Post-translational modifications of tau protein: Implications for Alzheimer's disease. *Neurochemistry International*, *58*(4), 458–471. <https://doi.org/10.1016/j.neuint.2010.12.023>
- Martinez, G., Vernooij, R. W., Fuentes Padilla, P., Zamora, J., Bonfill Cosp, X., & Flicker, L. (2017). 18F PET with florbetapir for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *The Cochrane Database of Systematic Reviews*.
<https://doi.org/10.1002/14651858.CD012216.pub2>
- Martinez, M., Multani, N., Anor, C. J., Misquitta, K., Tang-Wai, D. F., Keren, R., ... Tartaglia, M. C. (2018). Emotion detection deficits and decreased empathy in patients with Alzheimer's disease and Parkinson's disease affect caregiver

- mood and burden. *Frontiers in Aging Neuroscience*.
<https://doi.org/10.3389/fnagi.2018.00120>
- Maruff, P., Collie, A., Darby, D., Weaver-Cargin, J., Masters, C., & Currie, J. (2004). Subtle memory decline over 12 months in mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*.
<https://doi.org/10.1159/000080229>
- Maruyama, M., Shimada, H., Suhara, T., Shinotoh, H., Ji, B., Maeda, J., ... Higuchi, M. (2013). Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron*, 79(6), 1094–1108.
<https://doi.org/10.1016/j.neuron.2013.07.037>
- Masson, P. (1923). *Diagnostics de Laboratoire*. Paris: A. Maloine et Fils
- Mathis, C. A., Bacskai, B. J., Kajdasz, S. T., McLellan, M. E., Frosch, M. P., Hyman, B. T., ... Klunk, W. E. (2002). A lipophilic thioflavin-T derivative for positron emission tomography (PET) imaging of amyloid in brain. *Bioorganic & Medicinal Chemistry Letters*. [https://doi.org/10.1016/S0960-894X\(01\)00734-X](https://doi.org/10.1016/S0960-894X(01)00734-X)
- Mathuranath, P. S., Nestor, P. J., Berrios, G. E., Rakowicz, W., & Hodges, J. R. (2000). A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*, 55(11), 1613–1620.
<https://doi.org/10.1212/WNL.55.11.1613>
- Matsuda, H., Kitayama, N., Ohnishi, T., Asada, T., Nakano, S., Sakamoto, S., ... Katoh, A. (2002). Longitudinal evaluation of both morphologic and functional changes in the same individuals with Alzheimer's disease. *J Nucl Med*.
<https://doi.org/VBMBraak-Converted #22; VBMprediction-Converted #14>
- Matsusaka, H., Ikeda, K., Akiyama, H., Arai, T., Inoue, M., & Yagishita, S. (1998). Astrocytic pathology in progressive supranuclear palsy: Significance for

- neuropathological diagnosis. *Acta Neuropathologica*, 96(3), 248–252.
<https://doi.org/10.1007/s004010050891>
- Matthews, P. M., Rabiner, E. A., Passchier, J., & Gunn, R. N. (2012). Positron emission tomography molecular imaging for drug development. *British Journal of Clinical Pharmacology*. <https://doi.org/10.1111/j.1365-2125.2011.04085.x>
- Maxwell, W. L., MacKinnon, M. A., Smith, D. H., McIntosh, T. K., & Graham, D. I. (2006). Thalamic Nuclei After Human Blunt Head Injury. *J Neuropathol Exp Neurol*, 65(5), 478-488.
- McCrone, P., Payan, C. A., Knapp, M., Ludolph, A., Agid, Y., Leigh, P. N., & Bensimon, G. (2011). The economic costs of progressive supranuclear palsy and multiple system atrophy in France, Germany and the United Kingdom. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0024369>
- McEvoy, L. K., Fennema-Notestine, C., Roddey, J. C., Hagler, D. J., Holland, D., Karow, D. S., ... Dale, A. M. (2009). Alzheimer Disease: Quantitative Structural Neuroimaging for Detection and Prediction of Clinical and Structural Changes in Mild Cognitive Impairment. *Radiology*.
<https://doi.org/10.1148/radiol.2511080924>
- McGeer, P. L., Schulzer, M., & McGeer, E. G. (1996). Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. *Neurology*.
<https://doi.org/10.1212/WNL.47.2.425>
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*.
<https://doi.org/10.1212/WNL.34.7.939>

- McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., ... Phelps, C. H. (2011). 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. *Alzheimer's and Dementia*. <https://doi.org/10.1016/j.jalz.2011.03.005>
- Meijer, J. H., Schmitz, N., Nieman, D. H., Becker, H. E., van Amelsvoort, T. A. M. J., Dingemans, P. M., ... de Haan, L. (2011). Semantic fluency deficits and reduced grey matter before transition to psychosis: A voxelwise correlational analysis. *Psychiatry Research - Neuroimaging*. <https://doi.org/10.1016/j.psychresns.2011.01.004>
- Meltzer, C. C., Leal, J. P., Mayberg, H. S., Wagner, H. N., & Frost, J. J. (1990). Correction of PET data for partial volume effects in human cerebral cortex by MR imaging. *J Comput Assist Tomogr*, 14 (4), 561–570. DOI: 10.1097/00004728-199007000-00011
- Menza, M. A., Cocchiola, J., & Golbe, L. I. (1995). Psychiatric symptoms in progressive supranuclear palsy. *Psychosomatics*. [https://doi.org/10.1016/S0033-3182\(95\)71610-3](https://doi.org/10.1016/S0033-3182(95)71610-3)
- Milberg, W., & Albert, M. (1989). Cognitive differences between patients with progressive supranuclear palsy and Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*. <https://doi.org/10.1080/01688638908400919>
- Millar, D., Griffiths, P., Zermansky, A. J., & Burn, D. J. (2006). Characterizing behavioral and cognitive dysexecutive changes in progressive supranuclear palsy. *Movement Disorders*, 21(2), 199–207. <https://doi.org/10.1002/mds.20707>
- Minoshima, S., Giordani, B., Berent, S., Frey, K. A., Foster, N. L., & Kuhl, D. E.

- (1997). Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol*. <https://doi.org/10.1002/ana.410420114>
- Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, *21*(11), 1078–1085. <https://doi.org/10.1002/gps.1610>
- Mishina, M., Ishii, K., Mitani, K., Ohyama, M., Yamazaki, M., Ishiwata, K., ... Katayama, Y. (2004). Midbrain hypometabolism as early diagnostic sign for progressive supranuclear palsy. *Acta Neurologica Scandinavica*. <https://doi.org/10.1111/j.1600-0404.2004.00293.x>
- Misra, C., Fan, Y., & Davatzikos, C. (2009). Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: Results from ADNI. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2008.10.031>
- Miyoshi, M., Shinotoh, H., Wszolek, Z. K., Strongosky, A. J., Shimada, H., Arakawa, R., Higuchi, M., Ikoma, Y., Yasuno, F., Fukushi, K., Irie, T., Ito, H., & Suhara, T. (2010). In vivo detection of neuropathologic changes in presymptomatic MAPT mutation carriers: a PET and MRI study. *Parkinsonism Relat Disord*, *16*(6), 404–408. doi: 10.1016/j.parkreldis.2010.04.004
- Mochizuki, A., Ueda, Y., Komatsuzaki, Y., Tsuchiya, K., Arai, T., & Shoji, S. (2003). Progressive supranuclear palsy presenting with primary progressive aphasia—-clinicopathological report of an autopsy case. *Acta Neuropathologica*, *105*(6), 610–614. <https://doi.org/10.1007/s00401-003-0682-5>
- Monsch, A. U., Bondi, M. W., Butters, N., Thal, L. J., Salmon, D. P., & Katzman, R. (1992). Comparisons of Verbal Fluency Tasks in the Detection of Dementia of the Alzheimer Type. *Archives of Neurology*.

<https://doi.org/10.1001/archneur.1992.00530360051017>

- Monza, D., Soliveri, P., Radice, D., Fetoni, V., Testa, D., Caffarra, P., ... Girotti, F. (1998). Cognitive dysfunction and impaired organization of complex motility in degenerative Parkinsonian syndromes. *Archives of Neurology*, 55(3), 372–378. <https://doi.org/10.1001/archneur.55.3.372>
- Moreira, H. S., Costa, A. S., Castro, S. L., Lima, C. F., & Vicente, S. G. (2017). Assessing executive dysfunction in neurodegenerative disorders: A critical review of brief neuropsychological tools. *Frontiers in Aging Neuroscience*. <https://doi.org/10.3389/fnagi.2017.00369>
- Morra, J. H., Tu, Z., Apostolova, L. G., Green, A. E., Avedissian, C., Madsen, S. K., ... Thompson, P. M. (2009). Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. *Human Brain Mapping*. <https://doi.org/10.1002/hbm.20708>
- Morris, J. C. (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology*. <https://doi.org/10.1212/WNL.43.11.2412-a>
- Morris, J. C., McKeel, D. W., Fulling, K., Torack, R. M., & Berg, L. (1988). Validation of clinical diagnostic criteria for Alzheimer's disease. *Annals of Neurology*. <https://doi.org/10.1002/ana.410240105>
- Mosconi, L., & McHugh, P. F. (2011). FDG- and amyloid-PET in Alzheimer's disease: Is the whole greater than the sum of the parts? *Quarterly Journal of Nuclear Medicine and Molecular Imaging*. <https://doi.org/R39112332> [pii]
- Mueller, S. G., Weiner, M. W., Thal, L. J., Petersen, R. C., Jack, C., Jagust, W., ... Beckett, L. (2005). The Alzheimer's disease neuroimaging initiative. *Neuroimaging Clinics of North America*. <https://doi.org/10.1016/j.nic.2005.09.008>

- Muller-Gartner, H. W., Links, J. M., Prince, J. L., Bryan, R. N., McVeigh, E., Leal, J. P., Davatzikos, C., & Frost, J. J. (1992). Measurement of radiotracer concentration in brain gray matter using positron emission tomography: MRI-based correction for partial volume effects. *J Cereb Blood Flow Metab*, *12*(4), 571–583. DOI: 10.1038/jcbfm.1992.81
- Murphy, K. J., Rich, J. B., & Troyer, A. K. (2006). Verbal fluency patterns in amnesic mild cognitive impairment are characteristic of Alzheimer's type dementia. *Journal of the International Neuropsychological Society*. <https://doi.org/10.1017/S1355617706060590>
- Murray, M. E., Kouri, N., Lin, W. L., Jack, C. R., Dickson, D. W., & Vemuri, P. (2014). Clinicopathologic assessment and imaging of tauopathies in neurodegenerative dementias. *Alzheimer's Research and Therapy*. <https://doi.org/10.1186/alzrt231>
- Myers, R., & Hume, S. (2002). Small animal {PET}. *Eur Neuropsychopharmacol*.
- Nagahama, Y., Fukuyama, H., Turjanski, N., Kennedy, A., Yamauchi, H., Ouchi, Y., ... Shibasaki, H. (1997). Cerebral glucose metabolism in corticobasal degeneration: comparison with progressive supranuclear palsy and normal controls. *Movement Disorders: Official Journal of the Movement Disorder Society*. <https://doi.org/10.1002/mds.870120510>
- Nagahama, Y., Okina, T., Suzuki, N., & Matsuda, M. (2006). The Cambridge behavioral inventory: Validation and application in a memory clinic. *Journal of Geriatric Psychiatry and Neurology*, *19*(4), 220–225. <https://doi.org/10.1177/0891988706286545>
- Nagao, S., Yokota, O., Nanba, R., Takata, H., Haraguchi, T., Ishizu, H., ... Uchitomi, Y. (2012). Progressive supranuclear palsy presenting as primary lateral sclerosis but lacking parkinsonism, gaze palsy, aphasia, or dementia. *Journal*

- of the Neurological Sciences*. <https://doi.org/10.1016/j.jns.2012.09.005>
- Nath, U., Ben-Shlomo, Y., Thomson, R. G., Morris, H. R., Wood, N. W., Lees, A. J., & Burn, D. J. (2001). The prevalence of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) in the UK. *Brain*, *124*(Part 7), 1438–1449. <https://doi.org/10.1093/brain/124.7.1438>
- Neill, W. T. (1977). Inhibitory and facilitatory processes in selective attention. *Journal of Experimental Psychology: Human Perception and Performance*. <https://doi.org/10.1037/0096-1523.3.3.444>
- Nelson, P. T., Alafuzoff, I., Bigio, E. H., Bouras, C., Braak, H., Cairns, N. J., ... Beach, T. G. (2012). Correlation of alzheimer disease neuropathologic changes with cognitive status: A review of the literature. *Journal of Neuropathology and Experimental Neurology*. <https://doi.org/10.1097/NEN.0b013e31825018f7>
- Nestor, S. M., Rupsingh, R., Borrie, M., Smith, M., Accomazzi, V., Wells, J. L., ... Bartha, R. (2008). Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. *Brain*. <https://doi.org/10.1093/brain/awn146>
- Neumann, H., & Daly, M. J. (2013). Variant *TREM2* as Risk Factor for Alzheimer's Disease. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMe1213157>
- Neve, R. L., Harris, P., Kosik, K. S., Kurnit, D. M., & Donlon, T. A. (1986). Identification of cDNA clones for the human microtubule-associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein 2. *Molecular Brain Research*. [https://doi.org/10.1016/0169-328X\(86\)90033-1](https://doi.org/10.1016/0169-328X(86)90033-1)

- Ng, K. P., Pascoal, T. A., Mathotaarachchi, S., Therriault, J., Kang, M. S., Shin, M., ... Rosa-Neto, P. (2017). Monoamine oxidase B inhibitor, selegiline, reduces 18F-THK5351 uptake in the human brain. *Alzheimer's Research & Therapy*. <https://doi.org/10.1186/s13195-017-0253-y>
- Nicoletti, G., Tonon, C., Lodi, R., Condino, F., Manners, D., Malucelli, E., ... Quattrone, A. (2008). Apparent diffusion coefficient of the superior cerebellar peduncle differentiates progressive supranuclear palsy from Parkinson's disease. *Movement Disorders*. <https://doi.org/10.1002/mds.22279>
- Nishimura, M., Namba, Y., Ikeda, K., & Oda, M. (1992). Glial fibrillary tangles with straight tubules in the brains of patients with progressive supranuclear palsy. *Neuroscience Letters*, 143(1-2), 35-38. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/1436679>
- Nobili, F., & Morbelli, S. (2010). [18F] FDG-PET as a Biomarker for Early Alzheimer's Disease. *The Open Nuclear Medicine Journal*. <https://doi.org/10.2174/1876388X01002010046>
- Nobis, L., & Husain, M. (2018). Apathy in Alzheimer's disease. *Current Opinion in Behavioral Sciences*. <https://doi.org/10.1016/j.cobeha.2017.12.007>
- Nombela, C., Rittman, T., Robbins, T. W., & Rowe, J. B. (2014). Multiple modes of impulsivity in parkinson's disease. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0085747>
- O'Keefe, F. M., Murray, B., Coen, R. F., Dockree, P. M., Bellgrove, M. A., Garavan, H., ... Robertson, I. H. (2007). Loss of insight in frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy. *Brain*. <https://doi.org/10.1093/brain/awl367>
- O'Sullivan, S. S., Massey, L. A., Williams, D. R., Silveira-Moriyama, L., Kempster, P. A., Holton, J. L., ... Lees, A. J. (2008). Clinical outcomes of progressive

- supranuclear palsy and multiple system atrophy. *Brain: A Journal of Neurology*, 131(Pt 5), 1362–1372. <https://doi.org/10.1093/brain/awn065>
- Ogawa, S., & Sung, Y. W. (2007). Functional magnetic resonance imaging. *Scholarpedia*. <https://doi.org/10.4249/scholarpedia.3105>
- Oguro, H., Yamaguchi, S., Abe, S., Ishida, Y., Bokura, H., & Kobayashi, S. (2006). Differentiating Alzheimer's disease from subcortical vascular dementia with the FAB test. *Journal of Neurology*. <https://doi.org/10.1007/s00415-006-0251-7>
- Oh, M., Kim, J. S., Kim, J. Y., Shin, K. H., Park, S. H., Kim, H. O., ... Lee, C. S. (2012). Subregional Patterns of Preferential Striatal Dopamine Transporter Loss Differ in Parkinson Disease, Progressive Supranuclear Palsy, and Multiple-System Atrophy. *Journal of Nuclear Medicine*. <https://doi.org/10.2967/jnumed.111.095224>
- Ohnishi, T., Matsuda, H., Tabira, T., Asada, T., & Uno, M. (2001). Changes in brain morphology in Alzheimer disease and normal aging: is Alzheimer disease an exaggerated aging process? *AJNR. American Journal of Neuroradiology*. <https://doi.org/10.1146/annurev.pharmtox.39.1.19>
- Ohshita, T., Oka, M., Imon, Y., Yamaguchi, S., Mimori, Y., & Nakamura, S. (2000). Apparent diffusion coefficient measurements in progressive supranuclear palsy. *Neuroradiology*. <https://doi.org/10.1007/s002340000372>
- Okamura, N., Furumoto, S., Harada, R., Tago, T., Yoshikawa, T., Fodero-Tavoletti, M., ... Kudo, Y. (2013). Novel 18F-Labeled Arylquinoline Derivatives for Noninvasive Imaging of Tau Pathology in Alzheimer Disease. *Journal of Nuclear Medicine*, 54(8), 1420–1427. <https://doi.org/10.2967/jnumed.112.117341>
- Okello, A., Koivunen, J., Edison, P., Archer, H. A., Turkheimer, F. E., Nägren, K.,

- ... Brooks, D. J. (2009). Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. *Neurology*, 73(10), 754–760. <https://doi.org/10.1212/WNL.0b013e3181b23564>
- Olin, J. T., Katz, I. R., Meyers, B. S., Schneider, L. S., & Lebowitz, B. D. (2002). Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*. <https://doi.org/10.1097/00019442-200203000-00004>
- Ong, K., Villemagne, V. L., Bahar-Fuchs, A., Lamb, F., Chételat, G., Raniga, P., ... Rowe, C. C. (2013). 18F-florbetaben A β imaging in mild cognitive impairment. *Alzheimer's Research & Therapy*. <https://doi.org/10.1186/alzrt158>
- Ossenkoppele, R., Rabinovici, G. D., Smith, R., Cho, H., Scholl, M., Strandberg, O., ... Hansson, O. (2018). Discriminative accuracy of [18F]flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. *JAMA - Journal of the American Medical Association*. <https://doi.org/10.1001/jama.2018.12917>
- Ossenkoppele, R., Schonhaut, D. R., Baker, S. L., O'Neil, J. P., Janabi, M., Ghosh, P. M., ... Rabinovici, G. D. (2015). Tau, amyloid, and hypometabolism in a patient with posterior cortical atrophy. *Annals of Neurology*, 77(2), 338–342. <https://doi.org/10.1002/ana.24321>
- Ossenkoppele, R., Schonhaut, D. R., Schöll, M., Lockhart, S. N., Ayakta, N., Baker, S. L., ... Rabinovici, G. D. (2016). Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain*, 139(5), 1551–1567. <https://doi.org/10.1093/brain/aww027>
- Overman, A. A. & Becker, J. T. (2009). The Associative Deficit in Older Adult Memory: Recognition of Pairs Is Not Improved by Repetition. *Psychol Aging*,

24(2), 501–506. doi: 10.1037/a0015086

Owen, D. R., Howell, O. W., Tang, S. P., Wells, L. A., Bennacef, I., Bergstrom, M., ... Parker, C. A. (2010). Two binding sites for 3HPBR28 in human brain: Implications for TSPO PET imaging of neuroinflammation. *Journal of Cerebral Blood Flow and Metabolism*. <https://doi.org/10.1038/jcbfm.2010.63>

Owen, D. R., Yeo, A. J., Gunn, R. N., Song, K., Wadsworth, G., Lewis, A., ... Rubio, J. P. (2012). An 18-kDa Translocator Protein (TSPO) polymorphism explains differences in binding affinity of the PET radioligand PBR28. *Journal of Cerebral Blood Flow and Metabolism*, 32(1), 1–5. <https://doi.org/10.1038/jcbfm.2011.147>

Padovani, A., Borroni, B., Brambati, S. M., Agosti, C., Broli, M., Alonso, R., ... Perani, D. (2006). Diffusion tensor imaging and voxel based morphometry study in early progressive supranuclear palsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, 77(4), 457–463. <https://doi.org/10.1136/jnnp.2005.075713>

Pandey, S. (2012). Hummingbird sign in progressive supranuclear palsy disease. *Journal of Research in Medical Sciences*, 17(2): 197-198

Papadopoulos, V., Baraldi, M., Guilarte, T. R., Knudsen, T. B., Lacapère, J. J., Lindemann, P., ... Gavish, M. (2006). Translocator protein (18 kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function. *Trends in Pharmacological Sciences*. <https://doi.org/10.1016/j.tips.2006.06.005>

Parasuraman, R., & Haxby, J. V. (1993). Attention and Brain Function in Alzheimer's Disease: A Review. *Neuropsychology*. <https://doi.org/10.1037/0894-4105.7.3.242>

Pascoal, T. A., Shin, M., Kang, M. S., Chamoun, M., Chartrand, D.,

- Mathotaarachchi, S., ... Rosa-Neto, P. (2018). In vivo quantification of neurofibrillary tangles with [18F]MK-6240. *Alzheimer's Research and Therapy*. <https://doi.org/10.1186/s13195-018-0402-y>
- Pasqualetti, G., Brooks, D. J., & Edison, P. (2015). The role of neuroinflammation in dementias. *Curr. Neurol. Neurosci*, 15(4), 17. doi: 10.1007/s11910-015-0531-7
- Passamonti, L., Vázquez Rodríguez, P., Hong, Y. T., Allinson, K., Bevan-Jones, R., Williamson, D., Jones, P. S., Arnold, R., Borchert, R. J., Surendranathan, A. J., O'Brien, J. & Rowe, J. B. (2018). [11C](R)-PK11195 binding in Alzheimer disease and progressive supranuclear palsy. *Neurology*, 90(22), 1989–1996.
- Passamonti, L., Vázquez Rodríguez, P., Hong, Y. T., Allinson, K. S. J., Williamson, D., Borchert, R. J., ... Rowe, J. B. (2017). 18F-AV-1451 positron emission tomography in Alzheimer's disease and progressive supranuclear palsy. *Brain*. <https://doi.org/10.1093/brain/aww340>
- Patterson, K. R., Remmers, C., Fu, Y., Brooker, S., Kanaan, N. M., Vana, L., ... Binder, L. I. (2011). Characterization of prefibrillar tau oligomers in vitro and in Alzheimer disease. *Journal of Biological Chemistry*. <https://doi.org/10.1074/jbc.M111.237974>
- Pavese, N., Gerhard, A., Tai, Y. F., Ho, A. K., Turkheimer, F., Barker, R. A., ... Piccini, P. (2006). Microglial activation correlates with severity in Huntington disease: A clinical and PET study. *Neurology*. <https://doi.org/10.1212/01.wnl.0000222734.56412.17>
- Paviour, D. C., Thornton, J. S., Lees, A. J., & Jäger, H. R. (2007). Diffusion-weighted magnetic resonance imaging differentiates parkinsonian variant of multiple-system atrophy from progressive supranuclear palsy. *Movement Disorders*. <https://doi.org/10.1002/mds.21204>

- Pavouir, D. C., Winterburn, D., Simmonds, S., Burgess, G., Wilkinson, L., Fox, N. C., ... Jahanshahi, M. (2005). Can the frontal assessment battery (FAB) differentiate bradykinetic rigid syndromes? Relation of the FAB to formal neuropsychological testing. *Neurocase*. <https://doi.org/10.1080/13554790590962933>
- Pearson Clinical, Burgess, P. W., & Shallice, T. (1997). The Hayling and Brixton tests. *Bury St Edmunds, UK: Thames Valley Test Company Limited.*, 2–4.
- Perkins, S. C., Welsh, R. C., Stern, E. R., Taylor, S. F., & Fitzgerald, K. D. (2013). Topographic analysis of the development of individual activation patterns during performance monitoring in medial frontal cortex. *Developmental Cognitive Neuroscience*. <https://doi.org/10.1016/j.dcn.2013.09.001>
- Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. A critical review. *Brain*. <https://doi.org/10.1093/brain/122.3.383>
- Perry, V. H., Nicoll, J. A., & Holmes, C. (2010). Microglia in neurodegenerative disease. *Nat Rev Neurol*, 6(4), 193-201. doi: 10.1038/nrneurol.2010.17.
- Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology*, 56(3), 303–308. <https://doi.org/10.1001/archneur.56.3.303>
- Petit-Taboué, M. C., Baron, J. C., Barré, L., Travère, J. M., Speckel, D., Camsonne, R., & MacKenzie, E. T. (1991). Brain kinetics and specific binding of [¹¹C]PK 11195 to omega 3 sites in baboons: positron emission tomography study. *Eur J Pharmacol*, 200(2-3), 347-351. DOI: 10.1016/0014-2999(91)90594-g
- Pievani, M., de Haan, W., Wu, T., Seeley, W. W., & Frisoni, G. B. (2011). Functional network disruption in the degenerative dementias. *The Lancet Neurology*. [https://doi.org/10.1016/S1474-4422\(11\)70158-2](https://doi.org/10.1016/S1474-4422(11)70158-2)

- Pievani, M., Filippini, N., van den Heuvel, M. P., Cappa, S. F., Frisoni, G. B. (2014). Brain connectivity in neurodegenerative diseases-from phenotype to proteinopathy. *Nat Rev Neurol*, 10(11), 620-633. doi: 10.1038/nrneurol.2014.178.
- Piggott, M. A., Marshall, E. F., Thomas, N., Lloyd, S., Court, J. A., Jaros, E., ... Perry, E. K. (1999). Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: Rostrocaudal distribution. *Brain*. <https://doi.org/10.1093/brain/122.8.1449>
- Pillon, B., Dubois, B., Lhermitte, F., & Agid, Y. (1986). Heterogeneity of cognitive impairment in progressive supranuclear palsy, Parkinson's disease, and Alzheimer's disease. *Neurology*, 36(0028-3878), 1179-1185. <https://doi.org/10.1212/WNL.36.9.1179>
- Pillon, B., Dubois, B., & Agid, Y. (1991). Severity and specificity of cognitive impairment in Alzheimer's, Huntington's, and Parkinson's diseases and progressive supranuclear palsy. *Annals of the New York Academy of Sciences*. <https://doi.org/10.1212/WNL.41.5.634>
- Pillon, B., Deweer, B., Michon, A., Malapani, C., Agid, Y., & Dubois, B. (1994). Are explicit memory disorders of progressive supranuclear palsy related to damage to striatofrontal circuits? Comparison with Alzheimer's, Parkinson's, and Huntington's diseases. *Neurology*, 44(7), 1264-1270.
- Pillon, B., Gouider-Khouja, N., Deweer, B., Vidailhet, M., Malapani, C., Dubois, B., & Agid, Y. (1995). Neuropsychological pattern of striatonigral degeneration: Comparison with Parkinson's disease and progressive supranuclear palsy. *Journal of Neurology Neurosurgery and Psychiatry*. <https://doi.org/10.1136/jnnp.58.2.174>
- Podoll, K., Schwarz, M., & Noth, J. (1991). Language functions in progressive

- supranuclear palsy. *Brain*. <https://doi.org/10.1093/brain/114.3.1457>
- Posner, M. I., & Snyder, C. R. R. (1975). Facilitation and inhibition in the processing of signals. *Attention and Performance V*.
- Price, C. J. S., Wang, D., Menon, D. K., Guadagno, J. V., Cleij, M., Fryer, T., ... Warburton, E. A. (2006). Intrinsic activated microglia map to the peri-infarct zone in the subacute phase of ischemic stroke. *Stroke*. <https://doi.org/10.1161/01.STR.0000226980.95389.0b>
- Price, J. L., Davis, P. B., Morris, J. C., & White, D. L. (1991). The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. *Neurobiology of Aging*. [https://doi.org/10.1016/0197-4580\(91\)90006-6](https://doi.org/10.1016/0197-4580(91)90006-6)
- Price, S., Paviour, D., Scahill, R., Stevens, J., Rossor, M., Lees, A., & Fox, N. (2004). Voxel-based morphometry detects patterns of atrophy that help differentiate progressive supranuclear palsy and Parkinson's disease. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2004.06.013>
- Prince, M., & Jackson, J. (2009). World Alzheimer Report 2009. *Alzheimer's Disease International*. <https://doi.org/10.1111/j.0963-7214.2004.00293.x>
- Radakovic, R., Starr, J. M., & Abrahams, S. (2017). A novel assessment and profiling of multidimensional apathy in Alzheimer's disease. *Journal of Alzheimer's Disease*. <https://doi.org/10.3233/JAD-170292>
- Ramlackhansingh, A. F., Brooks, D. J., Greenwood, R. J., Bose, S. K., Turkheimer, F. E., Kinnunen, K. M., Gentleman, S., Heckemann, R. A., Gunanayagam, K., Gelsa, G., & Sharp, D. J. (2011). Inflammation after trauma: Microglial activation and traumatic brain injury. *Annals of Neurology*, *70*(3), 374-383. <https://doi.org/10.1002/ana.22455>
- Rao, A. T., Degnan, A. J., & Levy, L. M. (2014). Genetics of Alzheimer disease.

- American Journal of Neuroradiology*. <https://doi.org/10.3174/ajnr.A3545>
- Reisberg, B., Borenstein, J., Salob, S. P., Ferris, S. H., Franssen, E., & Georgotas, A. (1987). Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J Clin Psychiatry, 48 Suppl*, 9–15.
- Reisberg, B., Ferris, S. H., De Leon, M. J., & Crook, T. (1982). The global deterioration scale for assessment of primary degenerative dementia. *American Journal of Psychiatry*. <https://doi.org/10.1176/ajp.139.9.1136>
- Reivich, M., Kuhl, D., Wolf, a, Greenberg, J., Phelps, M., Ido, T., ... Sokoloff, L. (1979). The [18F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circulation Research, 44(1)*, 127–137. <https://doi.org/10.1161/01.RES.44.1.127>
- Respondek, G., & Höglinger, G. U. (2016). The phenotypic spectrum of progressive supranuclear palsy. *Parkinsonism & Related Disorders, 22 Suppl 1*, S34-6. <https://doi.org/10.1016/j.parkreldis.2015.09.041>
- Respondek, G., Stamelou, M., Kurz, C., Ferguson, L. W., Rajput, A., Chiu, W. Z., ... Höglinger, G. U. (2014). The phenotypic spectrum of progressive supranuclear palsy: A retrospective multicenter study of 100 definite cases. *Movement Disorders, 29(14)*, 1758–1766. <https://doi.org/10.1002/mds.26054>
- Rey, A. (1958). *L'examen clinique en psychologie. [The clinical examination in psychology.]*. *L'examen clinique en psychologie*.
- Riley, D. E., Fogt, N., & Leigh, R. J. (1994). The syndrome of "pure akinesia" and its relationship to progressive supranuclear palsy. *Neurology, 44(6)*, 1025–1029. <https://doi.org/10.1212/WNL.44.6.1025>
- Risacher, S. L., Shen, L., West, J. D., Kim, S., McDonald, B. C., Beckett, L. A., ... Saykin, A. J. (2010). Longitudinal MRI atrophy biomarkers: Relationship to

- conversion in the ADNI cohort. *Neurobiology of Aging*.
<https://doi.org/10.1016/j.neurobiolaging.2010.04.029>
- Risacher, S., Saykin, A., Wes, J., Shen, L., Firpi, H., & McDonald, B. (2009). Baseline MRI Predictors of Conversion from MCI to Probable AD in the ADNI Cohort. *Current Alzheimer Research*.
<https://doi.org/10.2174/156720509788929273>
- Rittman, T., Ghosh, B. C., McColgan, P., Breen, D. P., Evans, J., Williams-Gray, C. H., ... Rowe, J. B. (2013). The Addenbrooke's Cognitive Examination for the differential diagnosis and longitudinal assessment of patients with parkinsonian disorders. *Journal of Neurology, Neurosurgery and Psychiatry*.
<https://doi.org/10.1136/jnnp-2012-303618>
- Rittman, T., Rubinov, M., Vértes, P. E., Patel, A. X., Ginestet, C. E., Ghosh, B. C. P., ... Rowe, J. B. (2016). Regional expression of the MAPT gene is associated with loss of hubs in brain networks and cognitive impairment in Parkinson disease and progressive supranuclear palsy. *Neurobiology of Aging*.
<https://doi.org/10.1016/j.neurobiolaging.2016.09.001>
- Rivest, S. (2009). Regulation of innate immune responses in the brain. *Nature Reviews Immunology*. <https://doi.org/10.1038/nri2565>
- Robbins, T. W., James, M., Owen, A. M., Lange, K. W., Lees, A. J., Leigh, P. N., ... Summers, B. A. (1994). Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. *J Neurol Neurosurg Psychiatry*, 57(1), 79–88. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8301310%5Cnhttp://jnnp.bmj.com.ezp.lib.unimelb.edu.au/content/57/1/79.full.pdf
- Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., McInnes, L., & Rabbitt,

- P. (2010). Cambridge Neuropsychological Test Automated Battery (CANTAB): A Factor Analytic Study of a Large Sample of Normal Elderly Volunteers. *Dementia and Geriatric Cognitive Disorders*.
<https://doi.org/10.1159/000106735>
- Robert, P. H., Clairet, S., Benoit, M., Koutaich, J., Bertogliati, C., Tible, O., ... Bedoucha, P. (2002). The Apathy Inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *International Journal of Geriatric Psychiatry*.
<https://doi.org/10.1002/gps.755>
- Roeda, D., Kuhnast, B., Damont, A., & Dollé, F. (2012). Synthesis of fluorine-18-labelled TSPO ligands for imaging neuroinflammation with Positron Emission Tomography. *Journal of Fluorine Chemistry*.
<https://doi.org/10.1016/j.jfluchem.2011.03.020>
- Rogaeva, E., Meng, Y., Lee, J. H., Gu, Y., Kawarai, T., Zou, F., ... St. George-Hyslop, P. (2007). The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nature Genetics*.
<https://doi.org/10.1038/ng1943>
- Rohrer, J. D., Warren, J. D., Fox, N. C., & Rossor, M. N. (2013). Presymptomatic studies in genetic frontotemporal dementia. In *Revue Neurologique*.
<https://doi.org/10.1016/j.neurol.2013.07.010>
- Rohrer, J. D., Nicholas, J. M., Cash, D. M., van Swieten, J., Dopper, E., Jiskoot, L., ... Rossor, M. N. (2015). Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: A cross-sectional analysis. *The Lancet Neurology*. [https://doi.org/10.1016/S1474-4422\(14\)70324-2](https://doi.org/10.1016/S1474-4422(14)70324-2)
- Rojo, A., Pernaute, R. S., Fontán, A., Ruíz, P. G., Honnorat, J., Lynch, T., ... De

- Yébenes, J. G. (1999). Clinical genetics of familial progressive supranuclear palsy. *Brain*. <https://doi.org/10.1093/brain/122.7.1233>
- Rolstad, S., Berg, A. I., Bjerke, M., Johansson, B., Zetterberg, H., & Wallin, A. (2013). Cerebrospinal fluid biomarkers mirror rate of cognitive decline. *Journal of Alzheimer's Disease*. <https://doi.org/10.3233/JAD-121960>
- Ros, R., Garre, P. G., Hirano, M., Tai, Y. F., Ampuero, I., Vidal, L., ... De Yébenes, J. G. (2005). Genetic linkage of autosomal dominant progressive supranuclear palsy to 1q31.1. *Annals of Neurology*. <https://doi.org/10.1002/ana.20449>
- Rosser, A., & Hodges, J. R. (1994). Initial letter and semantic category fluency in Alzheimer's disease, Huntington's disease, and progressive supranuclear palsy. *Journal of Neurology, Neurosurgery and Psychiatry*. <https://doi.org/10.1136/jnnp.57.11.1389>
- Sahakian, B. J. (1990). Computerized assessment of neuropsychological function in Alzheimer's disease and Parkinson's disease. *Geriatric Psychiatry, 5*, 211–213.
- Sahakian, B. J. & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *Journal of Royal Society of Medicine, 85*(7), 399–402.
- Sahara, N., Shimojo, M., Ono, M., Takuwa, H., Febo, M., Higuchi, M., & Suhara, T. (2017). In vivo tau imaging for a diagnostic platform of tauopathy using the rTg4510 mouse line. *Frontiers in Neurology*. <https://doi.org/10.3389/fneur.2017.00663>
- Saini, J., Bagepally, B. S., Sandhya, M., Pasha, S. A., Yadav, R., & Pal, P. K. (2012). In vivo evaluation of white matter pathology in patients of progressive supranuclear palsy using TBSS. *Neuroradiology, 54*(7), 771–780. <https://doi.org/10.1007/s00234-011-0983-7>

- Saint-Aubert, L., Lemoine, L., Chiotis, K., Leuzy, A., Rodriguez-Vieitez, E., & Nordberg, A. (2017). Tau PET imaging: present and future directions. *Molecular Neurodegeneration*. <https://doi.org/10.1186/s13024-017-0162-3>
- Salmon, E., Van Der Linden, M., & Franck, G. (1997). Anterior cingulate and motor network metabolic impairment in progressive supranuclear palsy. *NeuroImage*. <https://doi.org/10.1006/nimg.1997.0262>
- Sami, S., Williams, N., Hughes, L. E., Cope, T. E., Rittman, T., Coyle-Gilchrist, I. T., Rowe, J. B. (2018). Neurophysiological signature of Alzheimer's disease and frontotemporal lobar degeneration: pathology versus phenotype. *Brain*, *141*, 2500–2510. <https://doi.org/10.1093/brain/awy180>
- Sanchez-Contreras, M. Y., Kouri, N., Cook, C. N., Serie, D. J., Heckman, M. G., Finch, N. A., ... Ross, O. A. (2018). Replication of progressive supranuclear palsy genome-wide association study identifies *SLCO1A2* and *DUSP10* as new susceptibility loci. *Molecular Neurodegeneration*. <https://doi.org/10.1186/s13024-018-0267-3>
- Sander, K., Lashley, T., Gami, P., Gendron, T., Lythgoe, M. F., Rohrer, J. D., ... Årstad, E. (2016). Characterization of tau positron emission tomography tracer [18F]AV-1451 binding to postmortem tissue in Alzheimer's disease, primary tauopathies, and other dementias. *Alzheimer's and Dementia*. <https://doi.org/10.1016/j.jalz.2016.01.003>
- Sandson, T. A., Felician, O., Edelman, R. R., & Warach, S. (1999). Diffusion-weighted magnetic resonance imaging in Alzheimer's disease. *Dement Geriatr Cogn Disord*, *10*(2), 166-171. DOI: 10.1159/000017099
- Santillo, A. F., Gambini, J. P., Lannfelt, L., Långström, B., Ulla-Marja, L., Kilander, L., & Engler, H. (2011). In vivo imaging of astrocytosis in Alzheimer's disease: an (1)(1)C-L-deuteriodesprenyl and PIB PET study. *Eur J Nucl Med Mol*

Imaging, 38(12), 2202–2208. DOI: 10.1007/s00259-011-1895-9

Satler, C., Guimarães, L., & Tomaz, C. (2017). Planning ability impairments in probable Alzheimer's disease patients: Evidence from the Tower of London test. *Dementia & Neuropsychologia*. <https://doi.org/10.1590/1980-57642016dn11-020006>

Savoiaro, M., Strada, L., Girotti, F., D'Incerti, L., Sberna, M., Soliveri, P., & Balzarini, L. (1989). MR imaging in progressive supranuclear palsy and Shy-Drager syndrome. *J. Comput. Assist. Tomogr*, 13(4), 555–560. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2745772>

Saxton, J., Lopez, O. L., Ratcliff, G., Dulberg, C., Fried, L. P., Carlson, M. C., ... Kuller, L. (2004). Preclinical Alzheimer disease: Neuropsychological test performance 1.5 to 8 years prior to onset. *Neurology*. <https://doi.org/10.1212/01.WNL.0000147470.58328.50>

Schmidt-Wilcke, T., Poljansky, S., Hierlmeier, S., Hausner, J., & Ibach, B. (2009). Memory performance correlates with gray matter density in the entorhinal/perirhinal cortex and posterior hippocampus in patients with mild cognitive impairment and healthy controls - A voxel based morphometry study. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2009.04.092>

Schofield, E. C., Caine, D., Kril, J. J., Cordato, N. J., & Halliday, G. M. (2005). Staging disease severity in movement disorder tauopathies: Brain atrophy separates progressive supranuclear palsy from corticobasal degeneration. *Movement Disorders*, 20(1), 34–39. <https://doi.org/10.1002/mds.20286>

Schofield, E. C., Hodges, J. R., Bak, T. H., Xuereb, J. H., & Halliday, G. M. (2012). The relationship between clinical and pathological variables in Richardson's syndrome. *Journal of Neurology*. [https://doi.org/10.1007/s00415-011-6205-](https://doi.org/10.1007/s00415-011-6205-8)

- Schöll, M., Lockhart, S. N., Schonhaut, D. R., O'Neil, J. P., Janabi, M., Ossenkoppele, R., ... Jagust, W. J. (2016). PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron*, 89(5), 971–982. <https://doi.org/10.1016/j.neuron.2016.01.028>
- Schöll, M., Ossenkoppele, R., Strandberg, O., Palmqvist, S., Jögi, J., Ohlsson, T., ... Hansson, O. (2017). Distinct 18F-AV-1451 tau PET retention patterns in early- and late-onset Alzheimer's disease. *Brain*. <https://doi.org/10.1093/brain/awx171>
- Schrag, A., Ben-Shlomo, Y., & Quinn, N. P. (1999). Prevalence of progressive supranuclear palsy and multiple system atrophy: A cross-sectional study. *Lancet*, 354(9192), 1771–1775. [https://doi.org/10.1016/S0140-6736\(99\)04137-9](https://doi.org/10.1016/S0140-6736(99)04137-9)
- Schrag, A., Sheikh, S., Quinn, N. P., Lees, A. J., Selai, C., Mathias, C., ... Jahanshahi, M. (2010). A comparison of depression, anxiety, and health status in patients with progressive supranuclear palsy and multiple system atrophy. *Movement Disorders: Official Journal of the Movement Disorder Society*. <https://doi.org/10.1002/mds.22794>
- Schuitmaker, A., van Berckel, B. N., Kropholler, M. A., Veltman, D. J., Scheltens, P., Jonker, C., Lammertsma, A. A., & Boellaard, R. (2007). SPM analysis of parametric (R)-[11C] (R)-PK11195 binding images: plasma input versus reference tissue parametric methods. *NeuroImage*, 35(4), 1473–1479. DOI: 10.1016/j.neuroimage.2007.02.013
- Schuitmaker, A., Kropholler, M. A., Boellaard, R., van der Flier, W. M., Kloet, R. W., van der Doef, T. F., ... van Berckel, B. N. M. (2013). Microglial activation in Alzheimer's disease: An (R)-[11C] (R)-PK11195 positron emission tomography study. *Neurobiology of Aging*, 34(1), 128–136.

<https://doi.org/10.1016/j.neurobiolaging.2012.04.021>

- Schulz, R., Cook, T. B., Beach, S. R., Lingler, J. H., Martire, L. M., Monin, J. K., & Czaja, S. J. (2013). Magnitude and causes of bias among family caregivers rating Alzheimer disease patients. *American Journal of Geriatric Psychiatry*. <https://doi.org/10.1016/j.jagp.2012.10.002>
- Schwarz, A. J., Yu, P., Miller, B. B., Shcherbinin, S., Dickson, J., Navitsky, M., ... Mintun, M. S. (2016). Regional profiles of the candidate tau PET ligand 18F-AV-1451 recapitulate key features of Braak histopathological stages. *Brain*, *139*(5), 1539–1550. <https://doi.org/10.1093/brain/aww023>
- Scott, G., Hellyer, P. J., Ramackhansingh, A. F., Brooks, D. J., Matthews, P. M., & Sharp, D. J. (2015). Thalamic inflammation after brain trauma is associated with thalamo-cortical white matter damage. *Journal of neuroinflammation*, *12*, 224. doi:10.1186/s12974-015-0445-y
- Sebastiani, P., Solovieff, N., DeWan, A. T., Walsh, K. M., Puca, A., Hartley, S. W., ... Perls, T. T. (2012). Genetic signatures of exceptional longevity in humans. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0029848>
- Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative Diseases Target Large-Scale Human Brain Networks. *Neuron*. <https://doi.org/10.1016/j.neuron.2009.03.024>
- Seidl, U., Lueken, U., Thomann, P. A., Geider, J., & Schröder, J. (2011). Autobiographical memory deficits in Alzheimer's disease. *Journal of Alzheimer's Disease*. <https://doi.org/10.3233/JAD-2011-110014>
- Seifert, K. D., & Wiener, J. I. (2013). The impact of DaTscan on the diagnosis and management of movement disorders: A retrospective study. *American Journal of Neurodegenerative Disease*.
- Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011).

- Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*. <https://doi.org/10.1101/cshperspect.a006189>
- Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*. <https://doi.org/10.1098/rstb.1982.0082>
- Shao, Z., Janse, E., Visser, K., & Meyer, A. S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Frontiers in Psychology*, 5(JUL). <https://doi.org/10.3389/fpsyg.2014.00772>
- Shimada, H., Sahara, T., Shinotoh, H., Hirano, S., Yamada, M., Kimura, Y., ... Higuchi, M. (2016). Clinical significance of tau accumulation assessed by [¹¹C]PBB3 PET in diverse tauopathies. *Molecular Imaging and Biology*. <https://doi.org/http://dx.doi.org/10.1007/s11307-016-0969-2>
- Shin, I. S., Carter, M., Masterman, D., Fairbanks, L., & Cummings, J. L. (2005). Neuropsychiatric symptoms and quality of life in Alzheimer disease. *Am J Geriatr Psychiatry*, 13(6), 469–474. <https://doi.org/10.1176/appi.ajgp.13.6.469>
- Shin, J., Kepe, V., Barrio, J. R., & Small, G. W. (2011). The merits of FDDNP-PET imaging in Alzheimer's disease. *Advances in Alzheimer's Disease*. <https://doi.org/10.3233/978-1-60750-793-2-265>
- Shivamurthy, V. K. N., Tahari, A. K., Marcus, C., & Subramaniam, R. M. (2015). Brain FDG PET and the diagnosis of dementia. *AJR. American Journal of Roentgenology*. <https://doi.org/10.2214/AJR.13.12363>
- Sisodia, S. S., Koo, E. H., Beyreuther, K., Unterbeck, A., & Price, D. L. (1990). Evidence that β -amyloid protein in Alzheimer's disease is not derived by normal processing. *Science*. <https://doi.org/10.1126/science.1691865>
- Sitek, E. J., Konkeli, A., Dąbrowska, M., & Sławek, J. (2015). Utility of frontal

assessment battery in detection of neuropsychological dysfunction in richardson variant of progressive supranuclear palsy. *Neurologia i Neurochirurgia Polska*, 49(1), 36–40.
<https://doi.org/10.1016/j.pjnns.2014.12.002>

Small, B. J., Fratiglioni, L., & Bäckman, L. (2003). Stability of preclinical memory deficit in Alzheimer's disease. *Research and Practice in Alzheimer's Disease*.
<https://doi.org/10.1093/brain/124.1.96>

Smith, D. H., Johnson, V. E., & Stewart, W. (2013). Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat Rev Neurol*, 9(4), 211–21. doi: 10.1038/nrneurol.2013.29

Smith, R., Schain, M., Nilsson, C., Strandberg, O., Olsson, T., Hägerström, D., ... Hansson, O. (2017). Increased basal ganglia binding of 18F-AV-1451 in patients with progressive supranuclear palsy. *Movement Disorders*.
<https://doi.org/10.1002/mds.26813>

Smith, R., Schöll, M., Londos, E., Ohlsson, T., & Hansson, O. (2018). 18F-AV-1451 in Parkinson's Disease with and without dementia and in Dementia with Lewy Bodies. *Scientific Reports*. <https://doi.org/10.1038/s41598-018-23041-x>

Soliveri, P., Monza, D., Paridi, D., Radice, D., Grisoli, M., Testa, D., ... Girotti, F. (1999). Cognitive and magnetic resonance imaging aspects of corticobasal degeneration and progressive supranuclear palsy. *Neurology*, 53(3), 502–507.
<https://doi.org/10.1212/WNL.53.3.502>

Soliveri, P., Monza, D., Paridi, D., Carella, F., Genitrini, S., Testa, D., & Girotti, F. (2000). Neuropsychological follow up in patients with Parkinson's disease, striatonigral degeneration-type multisystem atrophy, and progressive supranuclear palsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, 69, 313–318. <http://dx.doi.org/10.1136/jnnp.69.3.313>

- Sorbi, S., Forleo, P., Tedde, a, Cellini, E., Ciantelli, M., Bagnoli, S., & Nacmias, B. (2001). Genetic risk factors in familial Alzheimer's disease. *Mech Ageing Dev.* [https://doi.org/10.1016/S0047-6374\(01\)00308-6](https://doi.org/10.1016/S0047-6374(01)00308-6)
- Spalletta, G., Musicco, M., Padovani, A., Rozzini, L., Perri, R., Fadda, L., ... Palmer, K. (2010). Neuropsychiatric symptoms and syndromes in a large cohort of newly diagnosed, untreated patients with Alzheimer disease. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry.* <https://doi.org/10.1097/JGP.0b013e3181d6b68d>
- Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R., Kaye, J., Montine, T. J., Park, D. C.,.... Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7(3), 280-292. <https://doi.org/10.1016/j.jalz.2011.03.003>
- Spillantini, M. G., Bird, T. D., & Ghetti, B. (1998). Frontotemporal dementia and Parkinsonism linked to chromosome 17: a new group of tauopathies. *Brain Pathology (Zurich, Switzerland)*, 8(2), 387-402. <https://doi.org/10.1111/j.1750-3639.1998.tb00162.x>
- Spires-Jones, T. L., & Hyman, B. T. (2014). The Intersection of Amyloid Beta and Tau at Synapses in Alzheimer's Disease. *Neuron.* <https://doi.org/10.1016/j.neuron.2014.05.004>
- Spittaels, K., Van Den Haute, C., Van Dorpe, J., Geerts, H., Mercken, M., Bruynseels, K., ... Van Leuven, F. (2000). Glycogen synthase kinase-3 β phosphorylates protein tau and rescues the axonopathy in the central nervous system of human four-repeat tau transgenic mice. *Journal of Biological*

- Chemistry*. <https://doi.org/10.1074/jbc.M006219200>
- taStanford, P. M., Halliday, G. M., Brooks, W. S., Kwok, J. B. J., Storey, C. E., Creasey, H., ... Schofield, P. R. (2000). Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of the tau gene. Expansion of the disease phenotype caused by tau gene mutations. *Brain*. <https://doi.org/10.1093/brain/123.5.880>
- Steele, J., Richardson, J. C., & Olszewski, J. (1964). Progressive Supranuclear Palsy. *Annals of Neurology*, 10.
- Stefaniak, J., & O'Brien, J. (2015). Imaging of neuroinflammation in dementia: a review. *Journal of Neurology, Neurosurgery & Psychiatry*, 21–28. <https://doi.org/10.1136/jnnp-2015-311336>
- Stern, M. B., Lang, A., & Poewe, W. (2012). Toward a redefinition of Parkinson's disease. *Movement Disorders*. <https://doi.org/10.1002/mds.24051>
- Sudduth, T. F., Schmitt, F. A., Nelson, P. T., & Wilcock, D. M. (2013). Neuroinflammatory phenotype in early Alzheimer's disease. *Neurobiol Aging*, 34(4), 1051–1059. doi: 10.1016/j.neurobiolaging.2012.09.012
- Suridjan, I., Pollock, B. G., Verhoeff, N. P. L. G., Voineskos, A. N., Chow, T., Rusjan, P. M., ... Mizrahi, R. (2015). In-vivo imaging of grey and white matter neuroinflammation in Alzheimer's disease: a positron emission tomography study with a novel radioligand, [18F]-FEPPA. *Molecular Psychiatry*, 20(12), 1579–1587. <https://doi.org/10.1038/mp.2015.1>
- Suzuki, M., Desmond, T. J., Albin, R. L., & Frey, K. A. (2002). Striatal monoaminergic terminals in lewy body and Alzheimer's dementias. *Annals of Neurology*. <https://doi.org/10.1002/ana.10186>
- Takahashi, R., Ishii, K., Kakigi, T., Yokoyama, K., Mori, E., & Murakami, T. (2011). Brain alterations and mini-mental state examination in patients with

progressive supranuclear palsy: voxel-based investigations using f-fluorodeoxyglucose positron emission tomography and magnetic resonance imaging. *Dementia and Geriatric Cognitive Disorders Extra*, 1(1), 381–392.
<https://doi.org/10.1159/000333368>

Tanzi, R. E., & Bertram, L. (2005). Twenty years of the Alzheimer's disease amyloid hypothesis: A genetic perspective. *Cell*.
<https://doi.org/10.1016/j.cell.2005.02.008>

Teng, E., Lu, P. H., & Cummings, J. L. (2007). Deficits in facial emotion processing in mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*.
<https://doi.org/10.1159/000100829>

Teune, L. K., Bartels, A. L., De Jong, B. M., Willemsen, A. T. M., Eshuis, S. A., De Vries, J. J., ... Leenders, K. L. (2010). Typical cerebral metabolic patterns in neurodegenerative brain diseases. *Movement Disorders*, 25(14), 2395–2404.
<https://doi.org/10.1002/mds.23291>

Thériault, P., ElAli, A. & Rivest, S. (2015). The dynamics of monocytes and microglia in Alzheimer's disease. *Alzheimer's Research & Therapy*, 7(41).

Thiel, E., Korfel, A., Martus, P., Kanz, L., Griesinger, F., Rauch, M., Röth, A., Hertenstein, B., von Toll, T., Hundsberger, T., Mergenthaler, H. G., Leithäuser, M., Birnbaum, T., Fischer, L., Jahnke, K., Herrlinger, U., Plasswilm, L., Nägele, T., Pietsch, T., Bamberg, M., & Weller, M. (2010). High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol*, 11(11), 1036-1047. doi: 10.1016/S1470-2045(10)70229-1

Thies, W., Bleiler, L., & Alzheimer's Association. (2013). Alzheimer's disease facts and figures. *Alzheimer's & Dementia*.
<https://doi.org/10.1016/j.jalz.2013.02.003>

- Thurfjell, L., Lötöjnen, J., Lundqvist, R., Koikkalainen, J., Soininen, H., Waldemar, G., ... Vandenberghe, R. (2012). Combination of biomarkers: PET [¹⁸F]flutemetamol imaging and structural MRI in dementia and mild cognitive impairment. *Neurodegenerative Diseases*.
<https://doi.org/10.1159/000335381>
- Tierney, M. C. (1994). Use of the Rey Auditory Verbal Learning Test in Differentiating Normal Aging from Alzheimer Parkinson's Dementia. *Psychological Assessment*, 6(2), 129-134.
- Tippett, L. J., Meier, S. L., Blackwood, K., & Diaz-Asper, C. (2007). Category specific deficits in Alzheimer's disease: Fact or artefact? *Cortex*.
[https://doi.org/10.1016/S0010-9452\(08\)70690-7](https://doi.org/10.1016/S0010-9452(08)70690-7)
- Tolosa, E., Borgh, T. V., & Moreno, E. (2007). Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-Year follow-up of an open-label study. *Movement Disorders*.
<https://doi.org/10.1002/mds.21710>
- Torralva, T., Roca, M., Gleichgerrcht, E., López, P., & Manes, F. (2009). INECO Frontal Screening (IFS): A brief, sensitive, and specific tool to assess executive functions in dementia. *Journal of the International Neuropsychological Society*, 15(5), 777–786. <https://doi.org/10.1017/S1355617709990415>
- Tsuboi, Y., Slowinski, J., Josephs, K. A., Honer, W. G., Wszolek, Z. K., & Dickson, D. W. (2003). Atrophy of superior cerebellar peduncle in progressive supranuclear palsy. *Neurology*, 60(11), 1766–1769.
<https://doi.org/10.1212/01.WNL.0000068011.21396.F4>
- Tsuboi, Y., Josephs, K. A., Boeve, B. F., Litvan, I., Caselli, R. J., Caviness, J. N., ... Dickson, D. W. (2005). Increased tau burden in the cortices of progressive supranuclear palsy presenting with corticobasal syndrome. *Movement*

- Disorders*, 20(8), 982–988. <https://doi.org/10.1002/mds.20478>
- Tsuboi, Y., Josephs, K. A., Cookson, N., & Dickson, D. W. (2003). APOE E4 is a determinant for Alzheimer type pathology in progressive supranuclear palsy. *Neurology*. <https://doi.org/10.1212/01.WNL.0000044340.37138.A9>
- Tsukamoto, K., Matsusue, E., Kanasaki, Y., Kakite, S., Fujii, S., Kaminou, T., & Ogawa, T. (2012). Significance of apparent diffusion coefficient measurement for the differential diagnosis of multiple system atrophy, progressive supranuclear palsy, and Parkinson's disease: Evaluation by 3.0-T MR imaging. *Neuroradiology*. <https://doi.org/10.1007/s00234-012-1009-9>
- Tronel, C., Largeau, B., Santiago Ribeiro, M. J., Guilloteau, D., Dupont, A. C. & Arlicot, N. (2017). Molecular Targets for PET Imaging of Activated Microglia: The Current Situation and Future Expectations. *Int J Mol Sci*, 18(4). doi: 10.3390/ijms18040802
- Tulving, E. (1972). Episodic and semantic memory systems. In *Organization of Memory*. <https://doi.org/10.1017/S0140525X00047257>
- Tulving, E. (2002). Episodic Memory: From Mind to Brain. *Annual Review of Psychology*. <https://doi.org/10.1146/annurev.psych.53.100901.135114>
- Tulving, E. (2012). Episodic Memory and Autonoesis: Uniquely Human? In *The Missing Link in Cognition: Origins of self-reflective consciousness*. <https://doi.org/10.1093/acprof:oso/9780195161564.003.0001>
- Tuppo, E. E., & Arias, H. R. (2005). The role of inflammation in Alzheimer's disease. *Int J Biochem Cell*, 37(2), 289-305. DOI: 10.1016/j.biocel.2004.07.009
- Turkheimer, F. E., Edison, P., Pavese, N., Roncaroli, F., Anderson, A. N., Hammers, A., Gerhard, A., Hinz, R., Tai, Y. F. & Brooks, D. J. (2007). Reference and target region modeling of [11C]-(R)-PK11195 brain studies. *J Nucl Med.*, 48, 158–167.

- Tyacke, R. J., Myers, J. F. M., Venkataraman, A., Mick, I., Turton, S., Passchier, J., Husbands, S. M., Rabiner, E. A., Gunn, R. N., Murphy, P. S., Parker, C. A., & Nutt, D. J. (2018). Evaluation of 11C-BU99008, a PET Ligand for the Imidazoline2 Binding Site in Human Brain. *J Nucl Med*, 59(10), 1597-1602. doi: 10.2967/jnumed.118.208009
- Vallabhajosula, S. (2011). Positron emission tomography radiopharmaceuticals for imaging brain beta-amyloid. *Seminars in Nuclear Medicine*. <https://doi.org/10.1053/j.semnuclmed.2011.02.005>
- Van Den Heuvel, M. P., Mandl, R. C. W., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Human Brain Mapping*. <https://doi.org/10.1002/hbm.20737>
- van der Hurk, P. R., & Hodges, J. R. (1995). Episodic and Semantic Memory in Alzheimer's Disease and Progressive Supranuclear Palsy: A Comparative Study. *Journal of Clinical and Experimental Neuropsychology*. <https://doi.org/10.1080/01688639508405137>
- van Duijn, C. M., de Knijff, P., Cruts, M., Wehnert, A., Havekes, L. M., Hofman, A., & Van Broeckhoven, C. (1994). Apolipoprotein E4 allele in a population-based study of early-onset Alzheimer's disease. *Nature Genetics*. <https://doi.org/10.1038/ng0594-74>
- Vandenberghe, R., Van Laere, K., Ivanoiu, A., Salmon, E., Bastin, C., Triau, E., ... Brooks, D. J. (2010). 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment a phase 2 trial. *Annals of Neurology*. <https://doi.org/10.1002/ana.22068>
- Veld, B. A, Ruitenber, A., Hofman, A., Launer, L. J., van Duijn, C. M., Stijnen, T., Breteler, M. M., & Stricker, B. H. (2001) Nonsteroidal anti-inflammatory drugs

- and the risk of Alzheimer's disease. *N Engl J Med*, 345(21), 1515-1521. DOI: 10.1056/NEJMoa010178
- Venneti, S., Lopresti, B. J., and Wiley, C. A. (2006). The peripheral benzodiazepine receptor (Translocator protein 18kDa) in microglia: from pathology to imaging. *Progress in Neurobiology*, 80(6), 308–322. doi: 10.1016/j.pneurobio.2006.10.002
- Venneti, S., Lopresti, B. J., Wang, G., Hamilton, R. L., Mathis, C. A., Klunk, W. E., ... Wiley, C. A. (2009). PK11195 labels activated microglia in Alzheimer's disease and in vivo in a mouse model using PET. *Neurobiology of Aging*. <https://doi.org/10.1016/j.neurobiolaging.2007.11.005>
- Venneti, S., Wiley, C. A., & Kofler, J. (2009). Imaging microglial activation during neuroinflammation and Alzheimer's disease. *Journal of Neuroimmune Pharmacology*. <https://doi.org/10.1007/s11481-008-9142-2>
- Verma, M., & Howard, R. J. (2012). Semantic memory and language dysfunction in early Alzheimer's disease: A review. *International Journal of Geriatric Psychiatry*. <https://doi.org/10.1002/gps.3766>
- Vermeiren, C., Motte, P., Viot, D., Mairet-Coello, G., Courade, J. P., Citron, M., ... Gillard, M. (2018). The tau positron-emission tomography tracer AV-1451 binds with similar affinities to tau fibrils and monoamine oxidases. *Movement Disorders*. <https://doi.org/10.1002/mds.27271>
- Vicini Chilovi, B., Conti, M., Zanetti, M., Mazzù, I., Rozzini, L., & Padovani, A. (2009). Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dementia and Geriatric Cognitive Disorders*. <https://doi.org/10.1159/000210045>
- Videnovic, A., Lazar, A. S., Barker, R. A., & Overeem, S. (2014). "The clocks that time us" - Circadian rhythms in neurodegenerative disorders. *Nature Reviews*

- Neurology*. <https://doi.org/10.1038/nrneuro.2014.206>
- Villemagne, V. L., Ong, K., Mulligan, R. S., Holl, G., Pejoska, S., Jones, G., ... Rowe, C. C. (2011). Amyloid Imaging with 18F-Florbetaben in Alzheimer Disease and Other Dementias. *Journal of Nuclear Medicine*. <https://doi.org/10.2967/jnumed.111.089730>
- Voon, V., Sohr, M., Lang, A. E., Potenza, M. N., Siderowf, A. D., Whetteckey, J., ... Stacy, M. (2011). Impulse control disorders in parkinson disease: A multicenter case-control study. *Annals of Neurology*. <https://doi.org/10.1002/ana.22356>
- Walsh, C. M., Ruoff, L., Walker, K., Emery, A., Varbel, J., Karageorgiou, E., ... Neylan, T. C. (2017). Sleepless Night and Day, the Plight of Progressive Supranuclear Palsy. *Sleep*. <https://doi.org/10.1093/sleep/zsx154>
- Walters, A., Phillips, E., Zheng, R., Biju, M. & Kuruvilla, T. (2016). Evidence for neuroinflammation in Alzheimer's disease. *Progress in Neurology and Psychiatry*, 20(5), 25-31. <https://doi.org/10.1002/pnp.444>
- Warren, J. D., Rohrer, J. D., & Hardy, J. (2012). Disintegrating Brain Networks: From Syndromes to Molecular Nexopathies. *Neuron*. <https://doi.org/10.1016/j.neuron.2012.03.006>
- Wechsler, D. (1939). The measurement and appraisal of adult intelligence. Baltimore, MD: Williams & Wilkins <https://doi.org/http://dx.doi.org/10.1037/11167-000>
- Wedderburn, C., Wear, H., Brown, J., Mason, S. J., Barker, R. A., Hodges, J., & Williams-Gray, C. (2008). The utility of the Cambridge Behavioural Inventory in neurodegenerative disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 79(5), 500–503. <https://doi.org/10.1136/jnnp.2007.122028>
- Weingarten, M. D., Lockwood, A. H., Hwo, S. Y., & Kirschner, M. W. (1975). A

- protein factor essential for microtubule assembly. *Proceedings of the National Academy of Sciences of the United States of America*.
<https://doi.org/10.1073/pnas.72.5.1858>
- Weiner, H. L. & Frenkel, D. (2006). Immunology and immunotherapy of Alzheimer's disease. *Nature Reviews Immunology*, 6, 404–416.
- Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*.
<https://doi.org/10.1101/cshperspect.a006171>
- Welsh, K. A., Butters, N., Hughes, J. P., Mohs, R. C., & Heyman, A. (1992). Detection and Staging of Dementia in Alzheimer's Disease: Use of the Neuropsychological Measures Developed for the Consortium to Establish a Registry for Alzheimer's Disease. *Archives of Neurology*.
<https://doi.org/10.1001/archneur.1992.00530290030008>
- Whitnall, L., McMillan, T. M., Murray, G. D., & Teasdale, G. M. (2006). Disability in young people and adults after head injury: 5–7 year follow up of a prospective cohort study. *Neurology, Neurosurgery & Psychiatry*, 77(5), 640-645.
- Whitwell, J. L., Ahlskog, J. E., Tosakulwong, N., Senjem, M. L., Sychalla, A. J., Petersen, R. C., ... Josephs, K. A. (2018). Pittsburgh Compound B and AV-1451 positron emission tomography assessment of molecular pathologies of Alzheimer's disease in progressive supranuclear palsy. *Parkinsonism & Related Disorders*. <https://doi.org/10.1016/j.parkreldis.2017.12.016>
- Whitwell, J. L., Avula, R., Master, A., Vemuri, P., Senjem, M. L., Jones, D. T., ... Josephs, K. A. (2011). Disrupted thalamocortical connectivity in PSP: A resting-state fMRI, DTI, and VBM study. *Parkinsonism and Related Disorders*, 17(8), 599–605. <https://doi.org/10.1016/j.parkreldis.2011.05.013>
- Whitwell, J. L., Master, A. V., Avula, R., Kantarci, K., Eggers, S. D., Edmonson, H.

- A., ... Josephs, K. A. (2011). Clinical Correlates of White Matter Tract Degeneration in Progressive Supranuclear Palsy. *Archives of Neurology*, 68(6).
<https://doi.org/10.1001/archneurol.2011.107>
- Wild, K., Howieson, D., Webbe, F., Seelye, A., & Kaye, J. (2008). Status of computerized cognitive testing in aging: A systematic review. *Alzheimer's and Dementia*. <https://doi.org/10.1016/j.jalz.2008.07.003>
- Wiley, C. A., Lopresti, B. J., Venetis, S., Price, J., Klunk, W. E., DeKosky, S. T., & Mathis, C. A. (2009). Carbon 11-labeled Pittsburgh Compound B and carbon 11-labeled (R)-PK11195 positron emission tomographic imaging in Alzheimer disease. *Archives of Neurology*, 66(1), 60–67.
<https://doi.org/10.1001/archneurol.2008.511>
- Williams, D. R., De Silva, R., Paviour, D. C., Pittman, A., Watt, H. C., Kilford, L., ... Lees, A. J. (2005). Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain*, 128(6), 1247–1258.
<https://doi.org/10.1093/brain/awh488>
- Williams, D. R., Holton, J. L., Strand, C., Pittman, A., De Silva, R., Lees, A. J., & Revesz, T. (2007). Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. *Brain*, 130(6), 1566–1576. <https://doi.org/10.1093/brain/awm104>
- Williams, D. R., Holton, J. L., Strand, K., Revesz, T., & Lees, A. J. (2007). Pure akinesia with gait freezing: A third clinical phenotype of progressive supranuclear palsy. *Movement Disorders*, 22(15), 2235–2241.
<https://doi.org/10.1002/mds.21698>
- Williams, D. W., Tyrer, M., & Shepherd, D. (2000). Tau and tau reporters disrupt central projections of sensory neurons in *Drosophila*. *Journal of Comparative*

Neurology. [https://doi.org/10.1002/1096-9861\(20001225\)428:4<630::AID-CNE4>3.0.CO;2-X](https://doi.org/10.1002/1096-9861(20001225)428:4<630::AID-CNE4>3.0.CO;2-X)

Wisse, L. E. M., Butala, N., Das, S. R., Davatzikos, C., Dickerson, B. C., Vaishnavi, S. N., ... Wolk, D. A. (2015). Suspected non-AD pathology in mild cognitive impairment. *Neurobiology of Aging*. <https://doi.org/10.1016/j.neurobiolaging.2015.08.029>

Woodberry, E., Browne, G., Hodges, S., Watson, P., Kapur, N., & Woodberry, K. (2015). The use of a wearable camera improves autobiographical memory in patients with Alzheimer's disease. *Memory*. <https://doi.org/10.1080/09658211.2014.886703>

Wu, T. H., Lu, Y. N., Chuang, C. L., Wu, C. L., Chiang, A. S., Krantz, D. E., & Chang, H. Y. (2013). Loss of vesicular dopamine release precedes tauopathy in degenerative dopaminergic neurons in a *Drosophila* model expressing human tau. *Acta Neuropathologica*. <https://doi.org/10.1007/s00401-013-1105-x>

Wyss-Coray, T., & Mucke, L. (2002). Inflammation in neurodegenerative disease - a double-edged sword. *Neuron*.

Xia, C. F., Arteaga, J., Chen, G., Gangadharmath, U., Gomez, L. F., Kasi, D., ... Kolb, H. C. (2013). [(18)F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, 9(6), 666-676. <https://doi.org/10.1016/j.jalz.2012.11.008>

Yamada, T., Calne, D. B., Akiyama, H., McGeer, E. G., & McGeer, P. L. (1993). Further observations on Tau-positive glia in the brains with progressive supranuclear palsy. *Acta Neuropathologica*. <https://doi.org/10.1007/BF00227727>

- Yamauchi, H., Fukuyama, H., Nagahama, Y., Katsumi, Y., Dong, Y., Konishi, J., & Kimura, J. (1997). Atrophy of the corpus callosum, cognitive impairment, and cortical hypometabolism in progressive supranuclear palsy. *Annals of Neurology*. <https://doi.org/10.1002/ana.410410509>
- Yaqub, M., Van Berckel, B. N. M., Schuitemaker, A., Hinz, R., Turkheimer, F. E., Tomasi, G., ... Boellaard, R. (2012). Optimization of supervised cluster analysis for extracting reference tissue input curves in (R)-[11C]PK11195 brain PET studies. *Journal of Cerebral Blood Flow and Metabolism*, 32(8), 1600–1608. <https://doi.org/10.1038/jcbfm.2012.59>
- Yokokura, M., Terada, T., Bunai, T., Nakaizumi, K., Takebayashi, K., Iwata, Y., ... Ouchi, Y. (2016). Depiction of microglial activation in aging and dementia: Positron emission tomography with [11C]DPA713 versus [11C](R)PK11195. *J Cereb Blood Flow Metab*. <https://doi.org/10.1177/0271678x16646788>
- Yoshikawa, K. (2004). Early pathological changes in the parkinsonian brain demonstrated by diffusion tensor MRI. *Journal of Neurology, Neurosurgery & Psychiatry*, 75(3), 481–484. <https://doi.org/10.1136/jnnp.2003.021873>
- Zacks, R. T., & Hasher, L. (1994). Directed ignoring Inhibitory regulation of working memory. *Inhibitory Processes in Attention, Memory and Language* .
- Zarei, M., Pouretmad, H. R., Bak, T., & Hodges, J. R. (2010). Autobiographical memory in progressive supranuclear palsy. *European Journal of Neurology*. <https://doi.org/10.1111/j.1468-1331.2009.02777.x>
- Zhang, J. (2015). Mapping neuroinflammation in frontotemporal dementia with molecular PET imaging. *J Neuroinflammation*, 12, 108. <https://doi.org/10.1186/s12974-015-0236-5>
- Zhang, J., Rittman, T., Nombela, C., Fois, A., Coyle-Gilchrist, I., Barker, R. A., ... Rowe, J. B. (2016). Different decision deficits impair response inhibition in

progressive supranuclear palsy and Parkinson's disease. *Brain*.
<https://doi.org/10.1093/brain/awv331>

Zhang, Z. G., Li, Y., Ng, C. T., & Song, Y. Q. (2015). Inflammation in Alzheimer's Disease and Molecular Genetics: Recent Update. *Archivum Immunologiae et Therapiae Experimentalis*. <https://doi.org/10.1007/s00005-015-0351-0>

Zhao, Q. F., Tan, L., Wang, H. F., Jiang, T., Tan, M. S., Tan, L., ... Yu, J. T. (2016). The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *Journal of Affective Disorders*.
<https://doi.org/10.1016/j.jad.2015.09.069>

Zigmond, A. S. & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, 67(6), 361-370.

Zois, E., Kortlang, N., Vollstädt-Klein, S., Lemenager, T., Beutel, M., Mann, K., & Fauth-Bühler, M. (2014). Decision-making deficits in patients diagnosed with disordered gambling using the Cambridge Gambling task: The effects of substance use disorder comorbidity. *Brain and Behavior*.
<https://doi.org/10.1002/brb3.231>