PET nella Malattia di Parkinson e Parkinsonismi

Angelo Antonini

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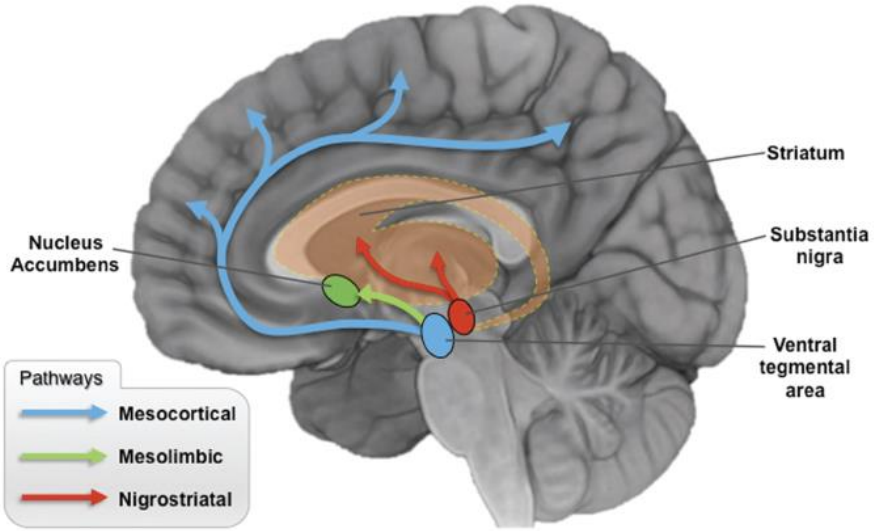
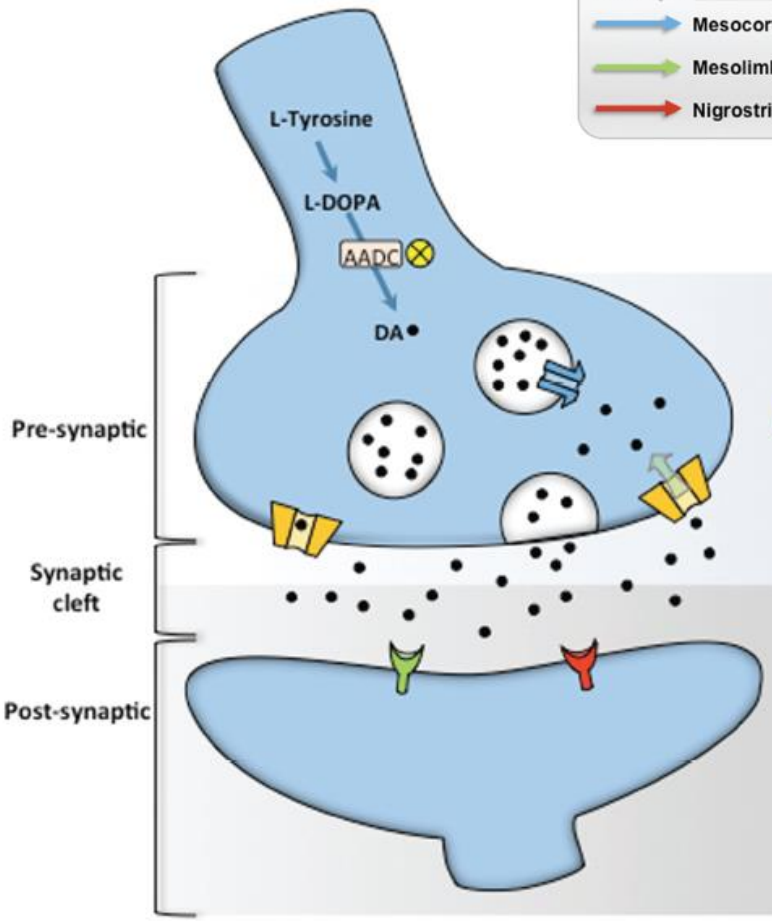
1st Neurology Clinic University Hospital of Padua Italy





PET Target	[^{11}C]	[^{18}F]	[^{123}I]
VMAT2	C-DTBZ	F-DTBZ	
DAT	C-CFT C-RTI 32	F-CFT	I-altropane I-β-CIT I-FP-CIT
DA Synthesis		F-DOPA F-FMT	
D1	C-NNC 112 C-SCH23390	F-Fallypride F-DMFP	
D2/D3	C-Raclopride C-FLB457 C-NMSP C-MNPA C-PHNO C-NPA C-NMB		I-IBZM Epidepride

Strafella A et al. Mov Disorders 2017

Complementary Positron Emission Tomographic Studies of the Striatal Dopaminergic System in Parkinson's Disease

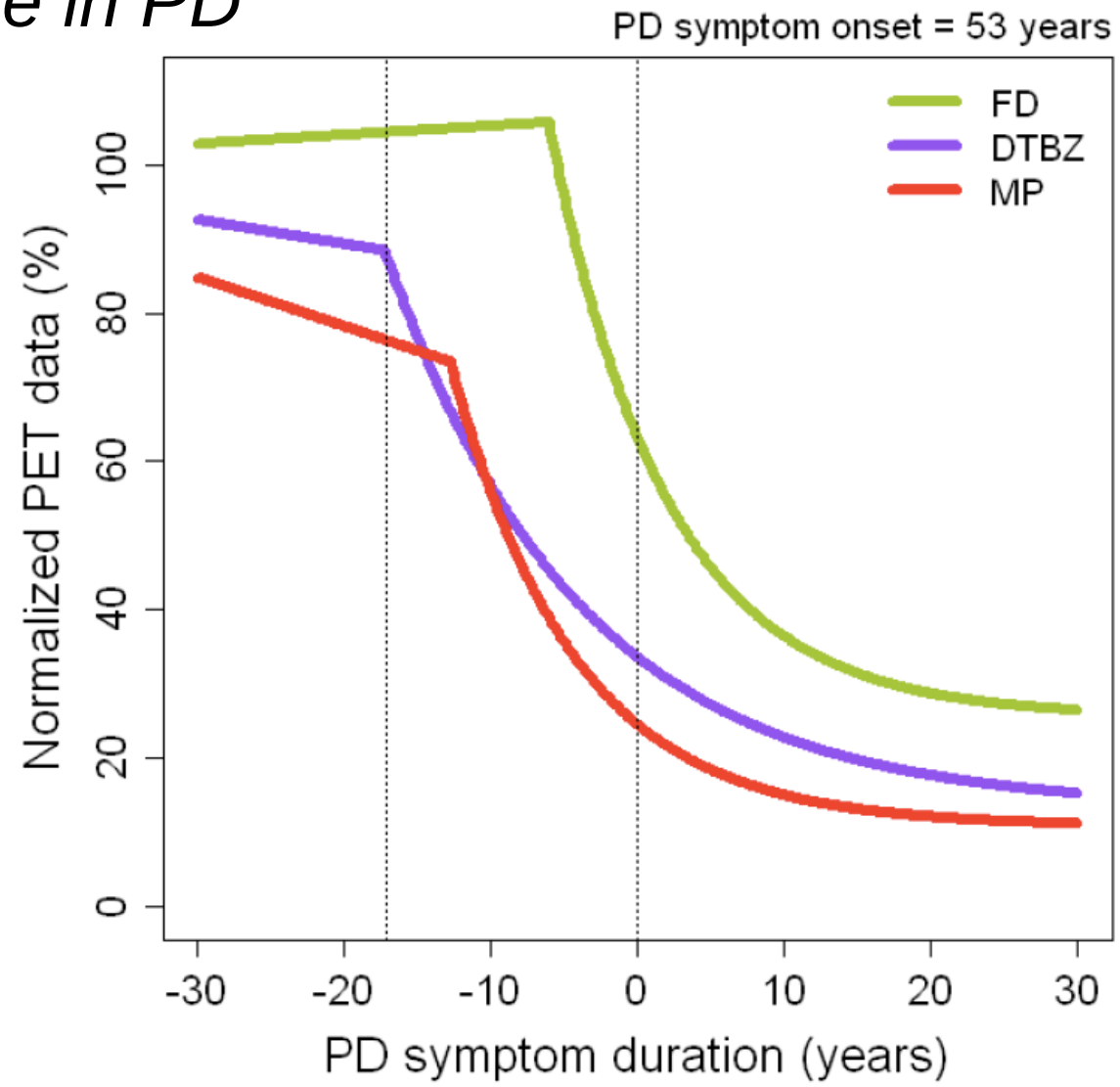
Angelo Antonini, MD; Peter Vontobel; Maria Psylla; Ilonka Günther, PhD; Paul R. Maguire; John Missimer, PhD; Klaus L. Leenders, MD

Table 2. FDOPA, RACLO, and FDG Values in Patients With PD and in Healthy Controls*

Patient No.	FDOPA $K_i \times 10^{-3}$		RACLO Index		FDG GMI	
	Caudate	Putamen	Caudate	Putamen	Caudate	Putamen
			HY–I-II PD			
1	9.58	6.67	2.78	3.43	1.28	1.36
2	8.52	7.54	2.57	2.77	1.19	1.31
3	11.67	7.95	3.03	4.03	1.09	1.10
4	12.97	8.71	2.64	3.28	1.14	1.25
5	11.00	7.56	2.03	2.97	1.22	1.36
6	11.44	5.25	2.21	2.61	1.24	1.33
7	9.61	5.84	2.80	3.41	1.17	1.25
8	5.93	4.61	1.90	2.55	1.16	1.36
9	6.27	4.60	2.92	3.27	1.18	1.40
10	6.67	4.69	2.76	3.45	1.28	1.36
HY–I-II (n=10) mean±SD	9.37±2.47[a]	6.34±1.54[b]	2.56±0.39	3.12±0.52[d]	1.20±0.06	1.31±0.09[e]
Percent of control mean	64	45	112	136	102	105
			HY–III-IV PD			
11	5.23	4.62	1.59	2.32	1.15	1.33
12	7.85	3.90	2.21	2.93	1.11	1.25
13	6.77	5.65	1.95	2.29	1.18	1.27
14	5.76	4.50	2.43	2.95	1.15	1.24
15	9.69	6.32	1.69	1.97	1.09	1.22
16	4.05	3.39	2.10	2.39	1.49	1.43
17	6.17	3.29	1.58	2.35	1.60	1.59
18	7.08	4.41	1.79	2.56	1.15	1.30
19	10.47	5.90	1.78	2.14	1.27	1.38
20	5.44	3.61	2.25	2.96	1.33	1.56
HY–III-IV (n=10) mean±SD	6.85±2.01[c,g]	4.56±1.08[b,f]	1.94±0.30	2.50±0.36	1.25±0.17	1.36±0.13[e]
Precent of control mean	47	33	85	109	107	109
HY–I-IV (n=20) mean±SD	8.11±2.54[a]	5.45±1.59[b]	2.25±0.46	2.81±0.54[d]	1.22±0.13	1.34±0.11[e]
Percent of control mean	55	39	98	123	104	107
Control mean±SD	14.69±3.96	13.99±3.74	2.29±0.34	2.28±0.27	1.17±0.06	1.25±0.06

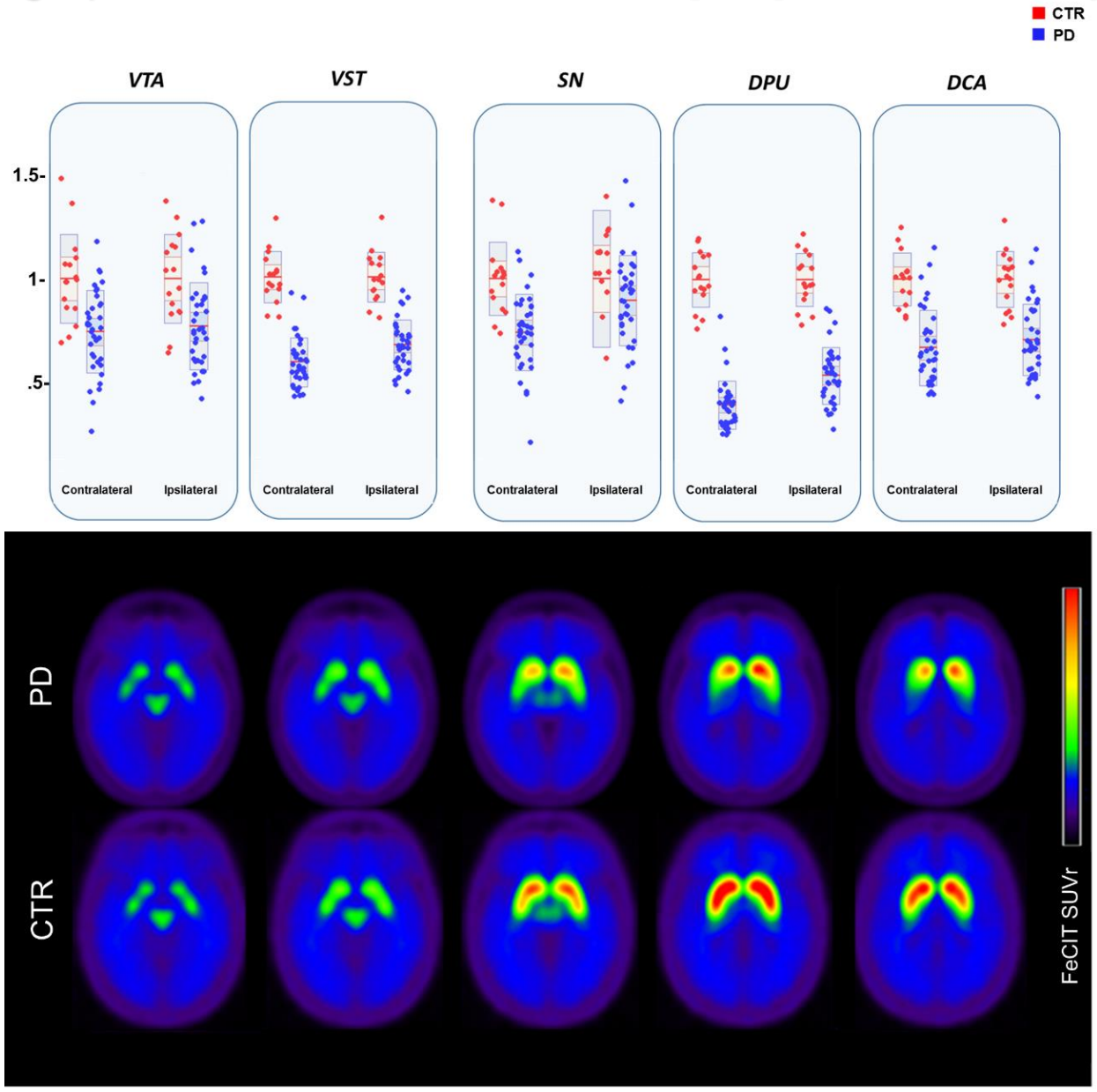
Archives Neurology 1995

The hypothetical course of putamen PET measurements for DTBZ binding, MP binding, and FD uptake in PD



DTBZ = [11C](±)dihydrotetrabenazine; MP = [11C]dthreo-methylphenidate; FD = 6-[18F]-fluoro-L-dopa

α-synuclein-related synaptic dysfunction and consequent axonal damage precede cell death in PD: An [11C]FeCIT PET study



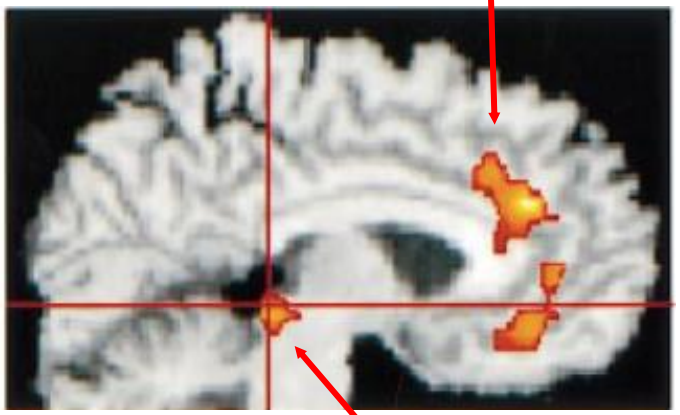
VTA: Ventral Tegmental Area; VST: Ventral Striatum; DPU: Dorsolateral Putamen; DCA: Dorsal Caudate

Carminiti SP et al. Neuroimage 2017

^{18}F-dopa PET cortical changes in PD

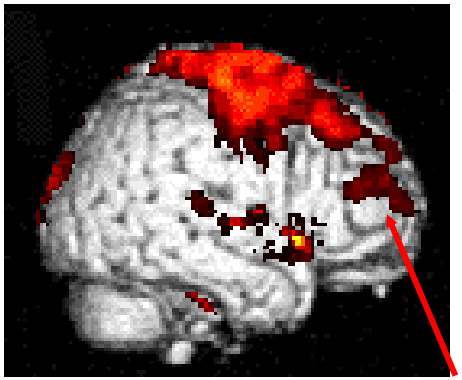
$p < 0.001$

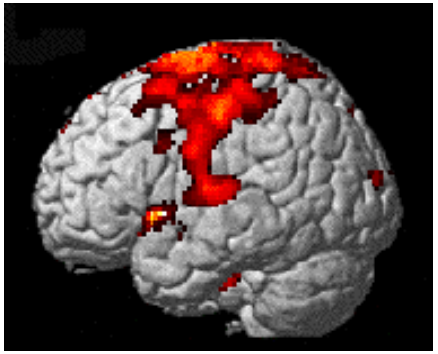
⇧cingulate



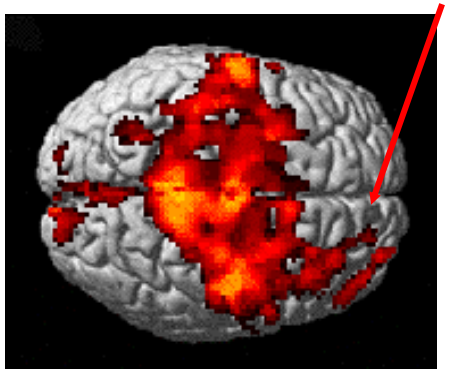
⇧Midbrain

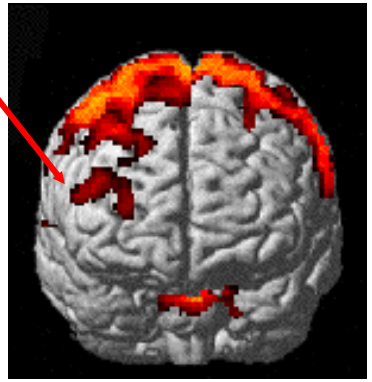
Early PD INCREASES





⇩Prefrontal and motor





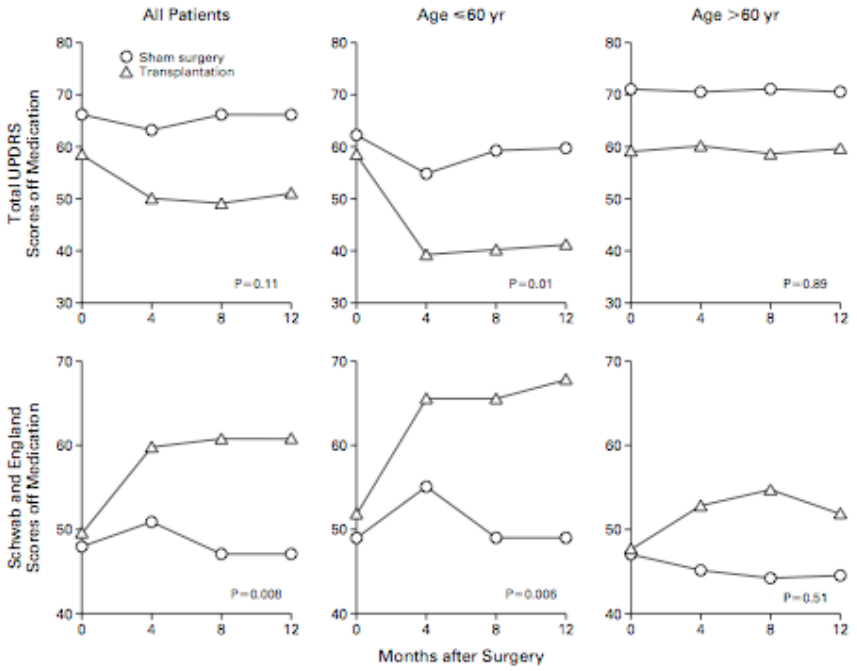
Advanced PD DECREASES

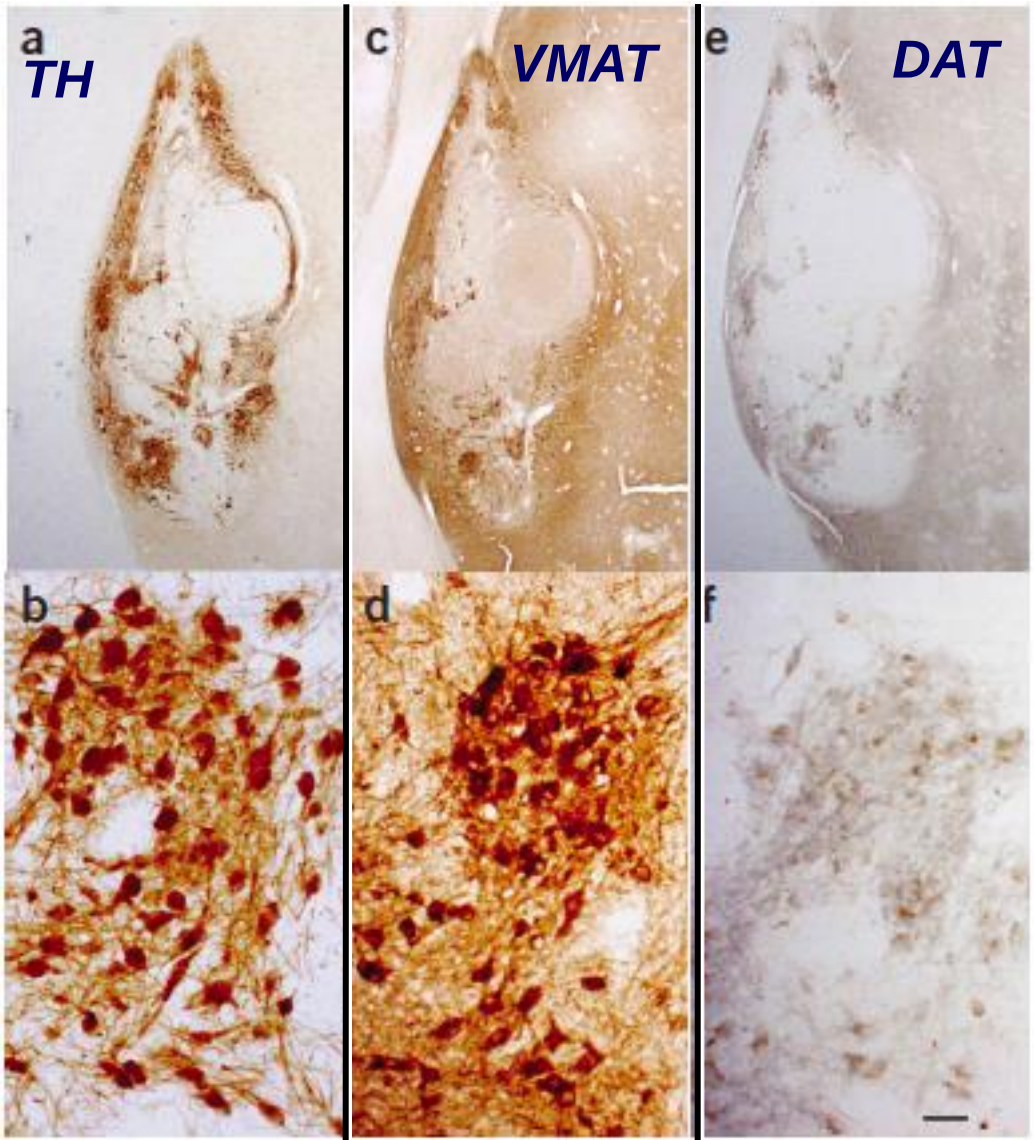
PET, positron emission tomography

Rakshi JS *et al*. *Brain* 1999

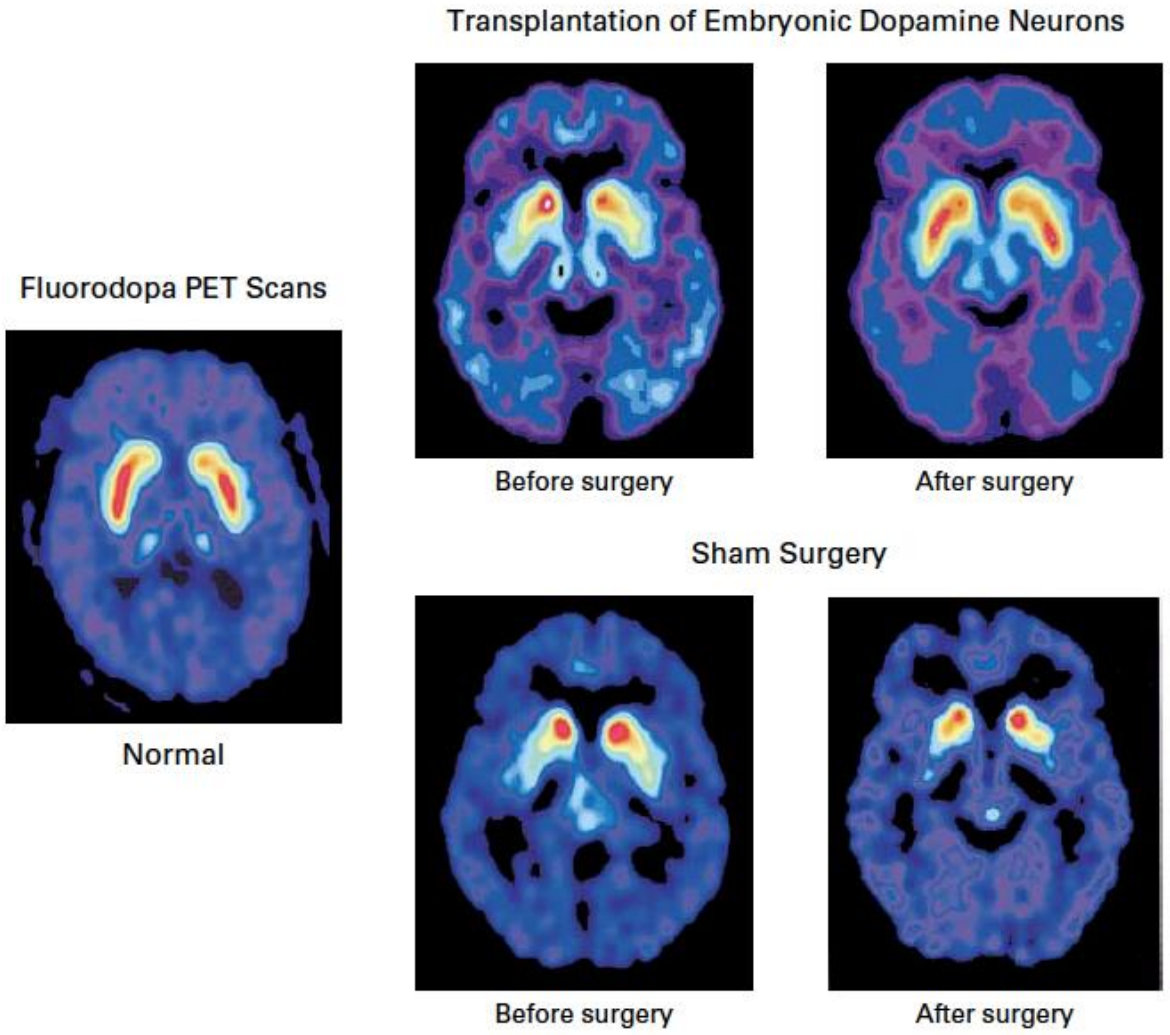
TRANSPLANTATION OF EMBRYONIC DOPAMINE NEURONS FOR SEVERE PARKINSON'S DISEASE

CURT R. FREED, M.D., PAUL E. GREENE, M.D., ROBERT E. BREEZE, M.D., WEI-YANN TSAI, PH.D., WILLIAM DUMOUCHEL, PH.D., RICHARD KAO, SANDRA DILLON, R.N., HOWARD WINFIELD, R.N., SHARON CULVER, N.P., JOHN Q. TROJANOWSKI, M.D., PH.D., DAVID EIDELBERG, M.D., AND STANLEY FAHN, M.D.



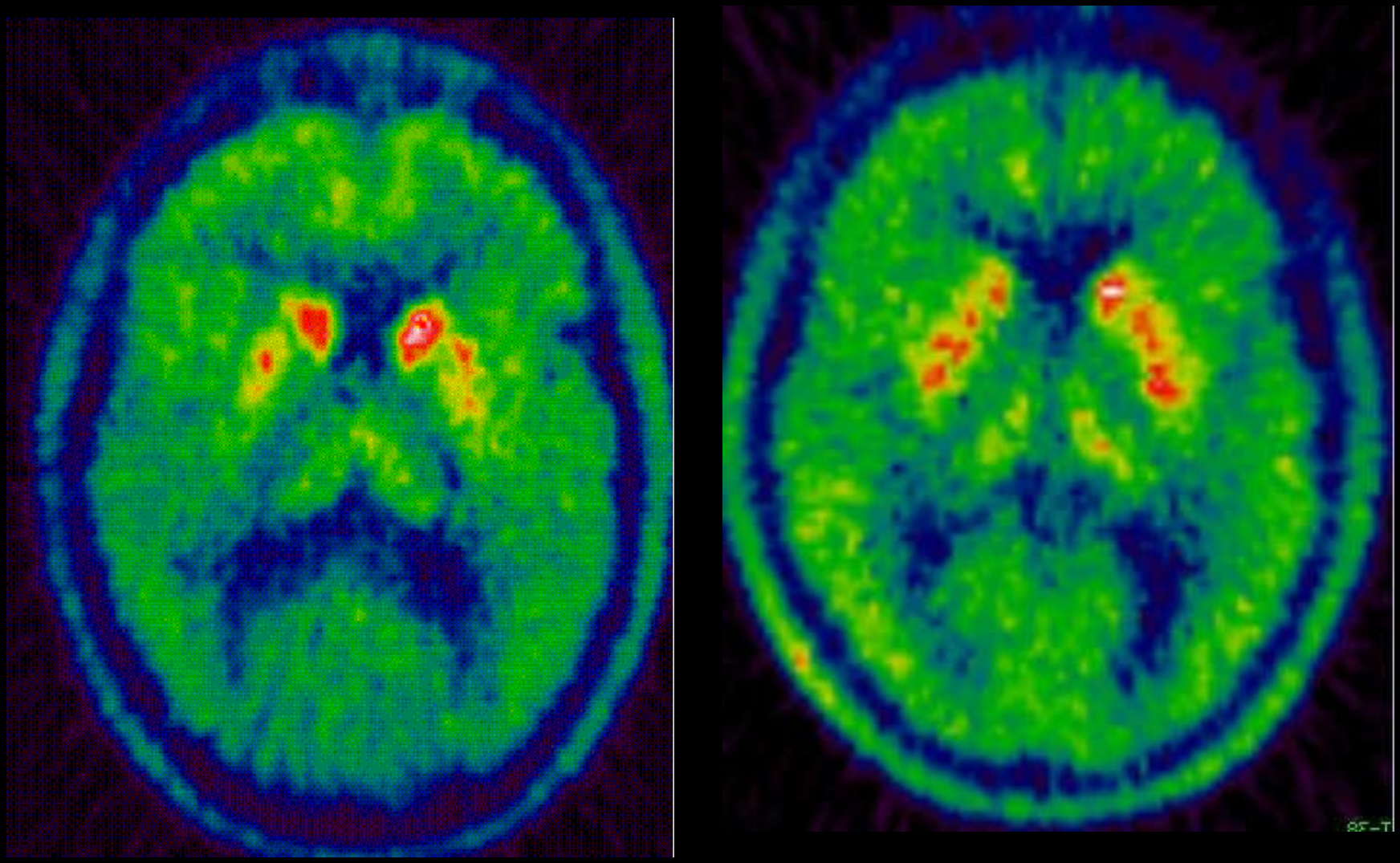


Change in 18F-Fluorodopa Uptake in the Brains of Parkinson Patients after Transplantation, as shown in Fluorodopa PET Scans



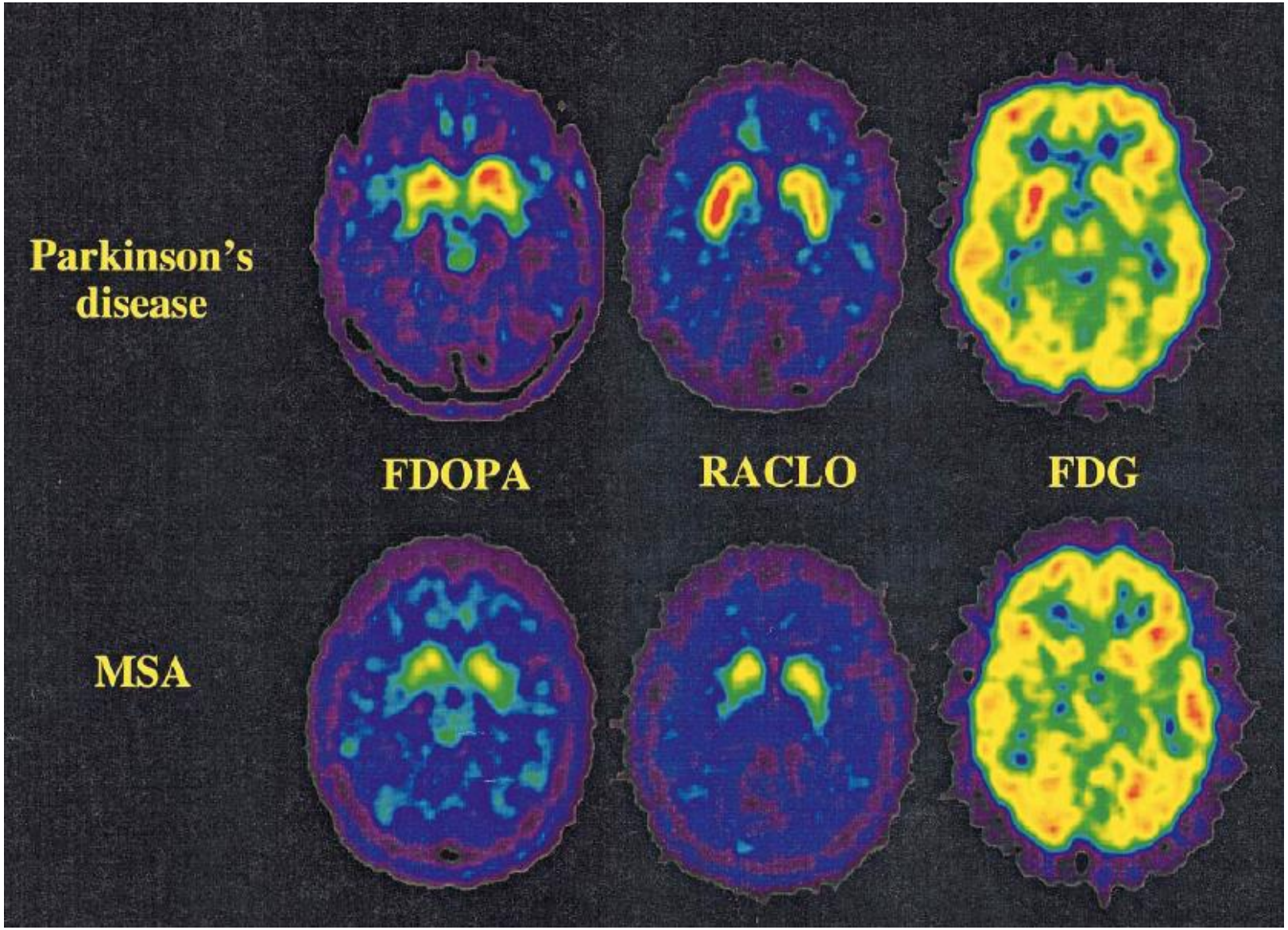
Freed et al. NEJM 2001

FDOPA-PET
2001 Pre-GDNF and 2008 Post-GDNF



Patel N, et al. Neurology (2013)

MSA and PD share similar degree of dopamine cell loss but in MSA there is additional loss of striatal dopamine D2 receptors (RACLO) and reduced striatal metabolism



Antonini A et al. Brain 1997

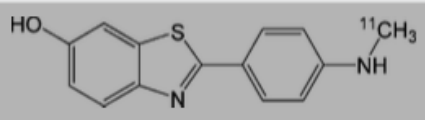
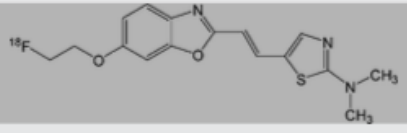
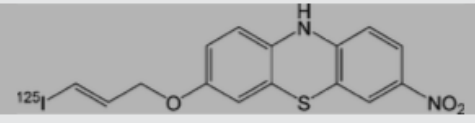
JNM The Journal of NUCLEAR MEDICINE

Foundation Opens $2-Million Competition for Alpha-Synuclein PET Tracer

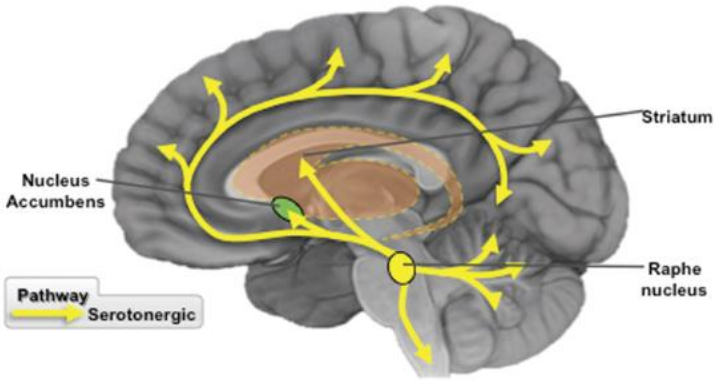
J Nucl Med. 2016;57:10N.

TABLE 1

Summary of Characteristics of PET Radiotracers Relevant to α-Synuclein (Syn) Imaging

Ligand	Structure	Affinity for α-synuclein fibrils (nM)	Affinity for $A\beta_{1-42}$ fibrils (nM)	Binding to α-synuclein–positive human brain homogenates (nM)	Binding to Aβ-positive human brain homogenates (nM)
^{11}C-PIB (*24,25*)		K_d = 4*	K_d = 4.7†	DLB (Aβ+) brain homogenate: K_d = 5*	Binding to AD frontal cortex homogenate (^{11}C-PIB): K_d = 1.4
				DLB (Aβ−), pure DLB: No significant binding*	Binding to AD brain homogenate (^{3}H-PIB): K_d = 3.77*
^{18}F-BF227 (*20*)		K_d = 9.63	K_{d1} = 1.31	Failed to bind to DLB (Aβ−) homogenate	AD brain homogenate: K_d = 25 ± 0.5
			K_{d2} = 80		
^{125}I-SIL23 (*23*)		K_d = 148	K_d (Aβ) = 635	PD dementia brain homogenate: K_d = 119.1–168.3	Not available
			K_d (tau) = 230		

*Values determined for ^{3}H-PIB.
†Fibrils used in assay were $A\beta_{1-40}$.
K_d = dissociation constant.



Cholinergic Neuron

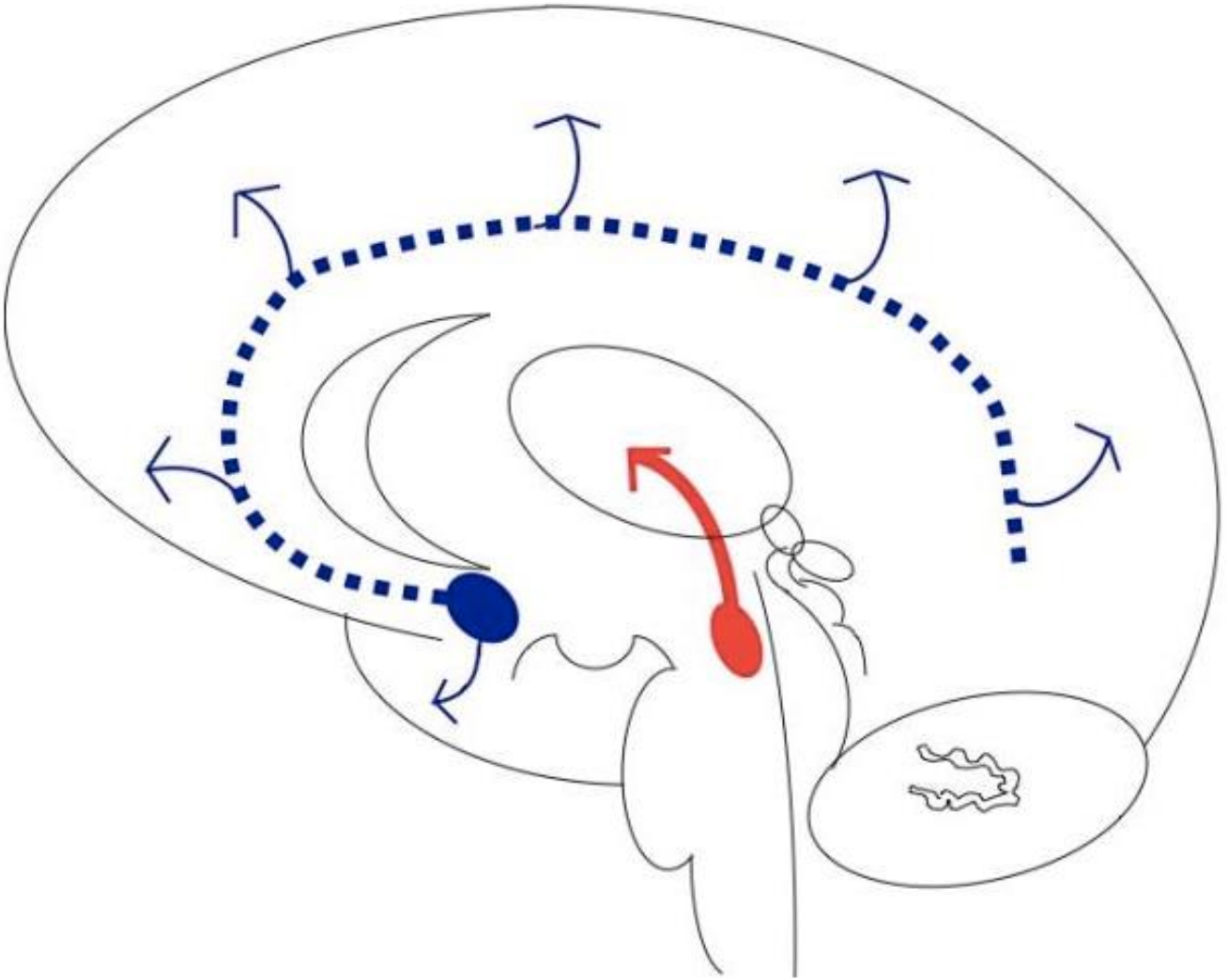
PET Target	[^{11}C]	[^{18}F]
AChE	MP4A PMP	
VAChT		FEOBV VAT
nAChR		Nifene Flubatine 2-FA
mAChR	NMPB	FP-TZTP

Serotonergic Neuron

PET Target	[^{11}C]	[^{18}F]
SERT	DASB	
5-HT$_{2A}$R	RWAY WAY100635 MPT MMT MPPA	MPPF cis-DCWAY
5-HT$_{1A}$R	MDL Altanserin NMSP	Setoperone Altanserin Mefway

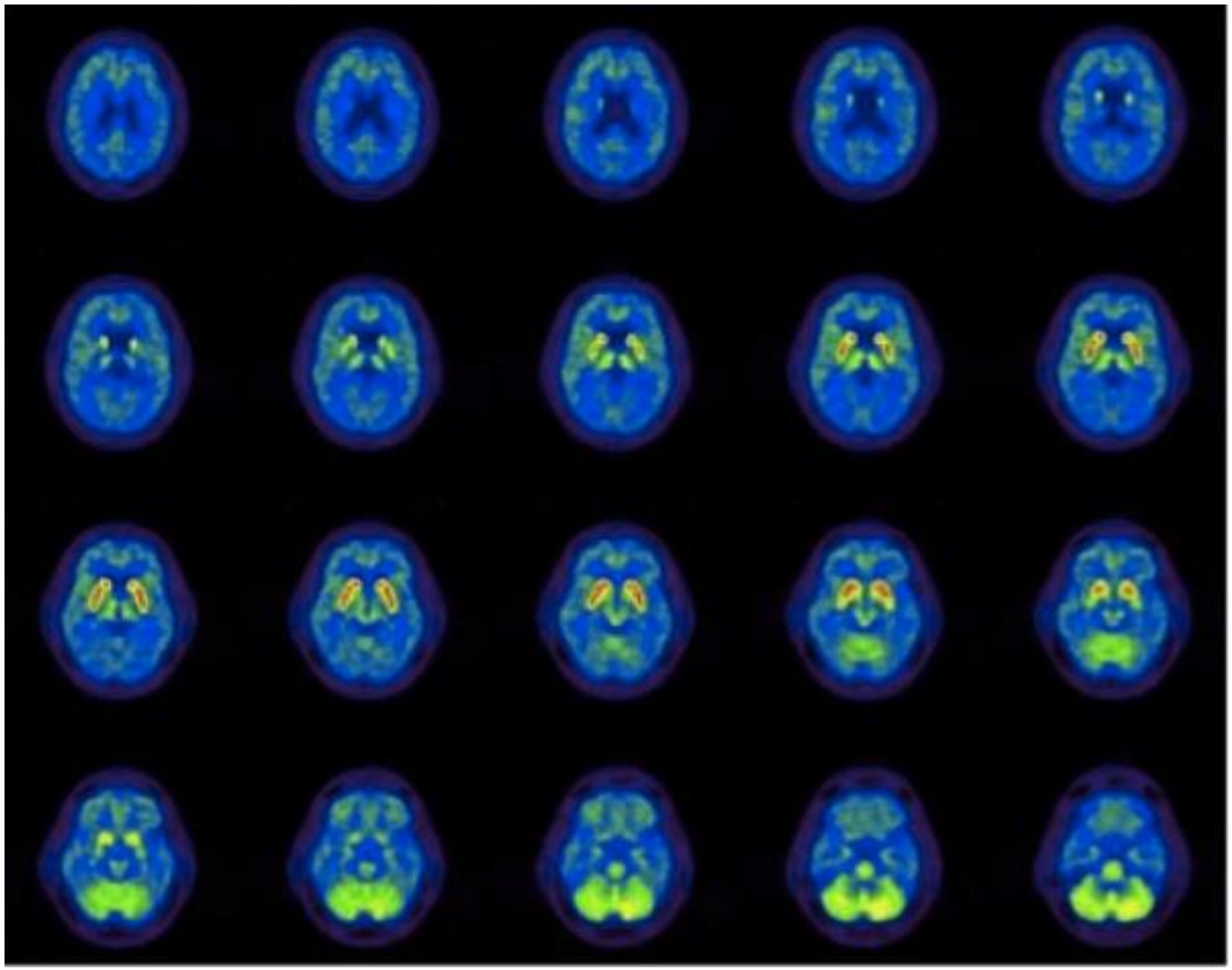
Strafella A et al. Mov Disorders 2017

Schematic overview of the major cholinergic cerebral projections



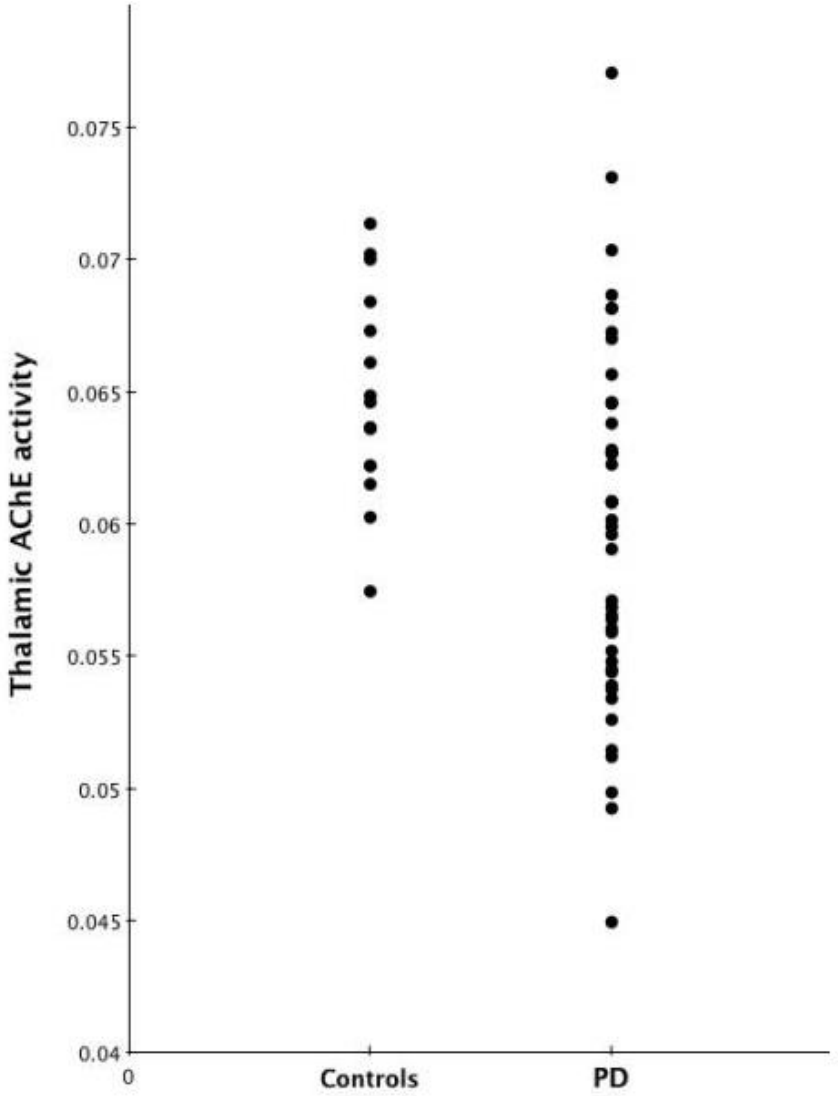
Bohnen & Albin Behav Brain Res 2011

[C-11]PMP AChE PET images showing normal AChE biodistribution with most intense uptake in the basal ganglia, followed by the cerebellum, with lower levels in the cortex



Bohnen & Albin *Behav Brain Res* 2011

Group scatter plot of distribution of thalamic AChE activity (k3 hydrolysis rate, min−1) in control and PD



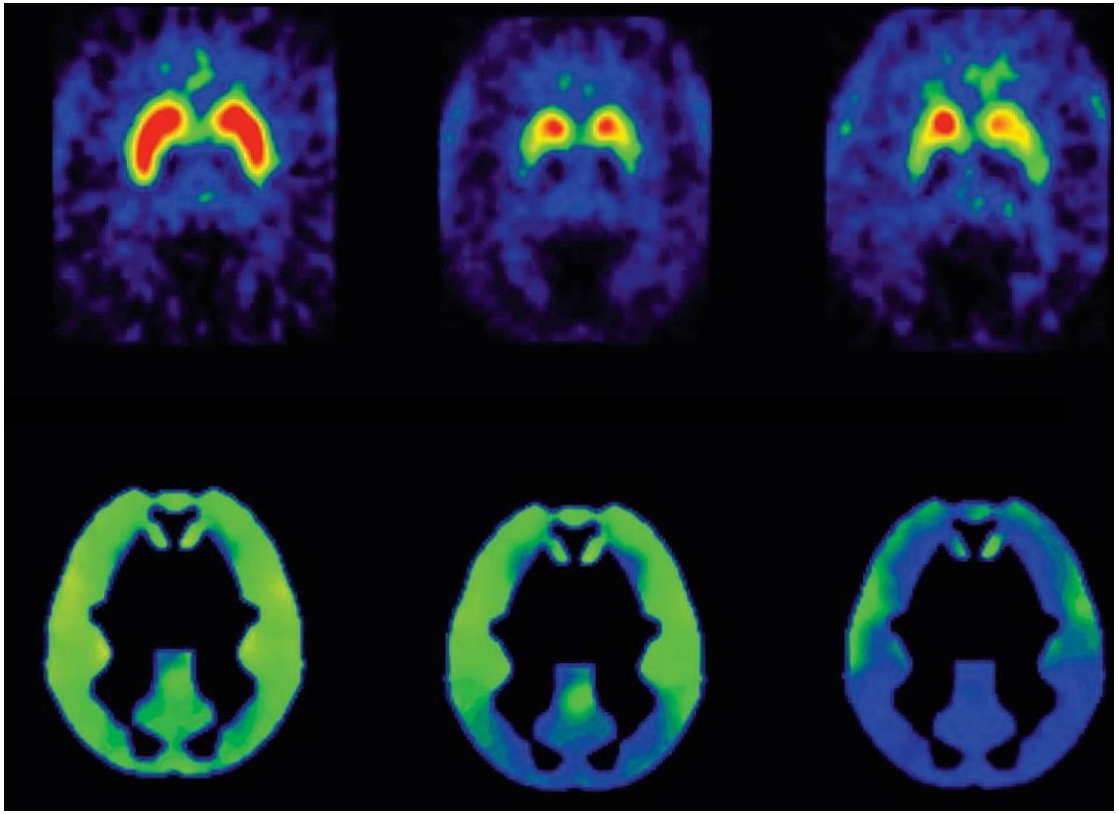
Bohnen & Albin Behav Brain Res 2011

Acetylcholinesterase imaging

^{11}C-NM4PA PET

^{18}F-dopa

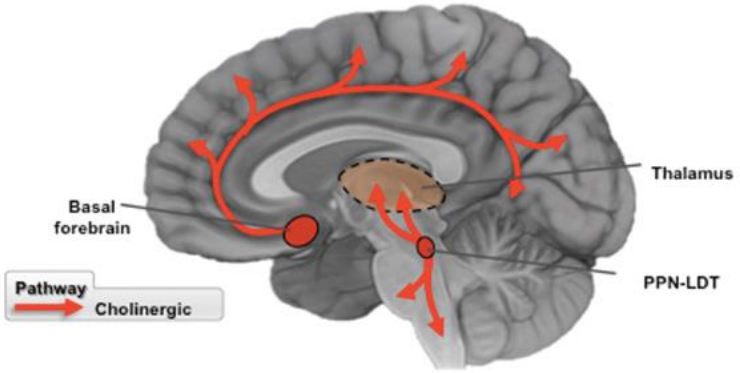
^{11}C-NM4PA



Normal **PD** **PDD**

PDD, PD dementia; PET, positron emission tomography

*Hilker et al. Arch Neurol 2005;**62**:378–82*



Cholinergic Neuron

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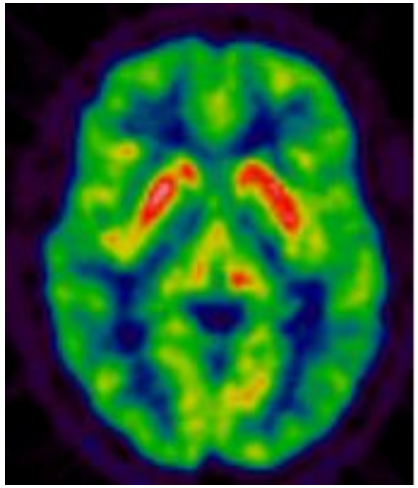
Serotonergic Neuron

PET Target	[11C]	[18F]
SERT	DASB	
5-HT$_{2A}$R	RWAY WAY100635 MPT MMT MPPA	MPPF cis-DCWAY
5-HT$_{1A}$R	MDL Altanserin NMSP	Setoperone Altanserin Mefway

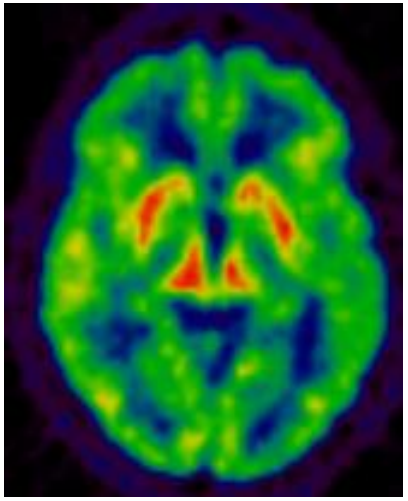
Strafella A et al. Mov Disorders 2017

Serotonin transporter binding in PD

^{11}C-DASB PET

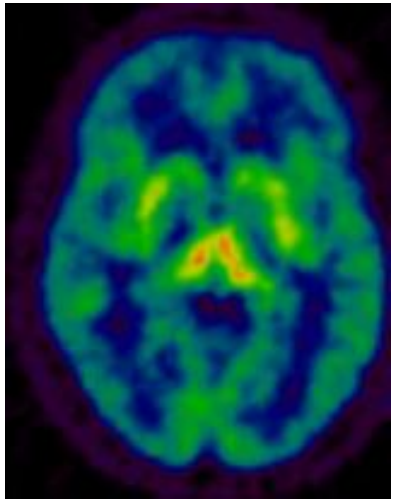


Healthy volunteer



PD without fatigue

PFS-16 = 2



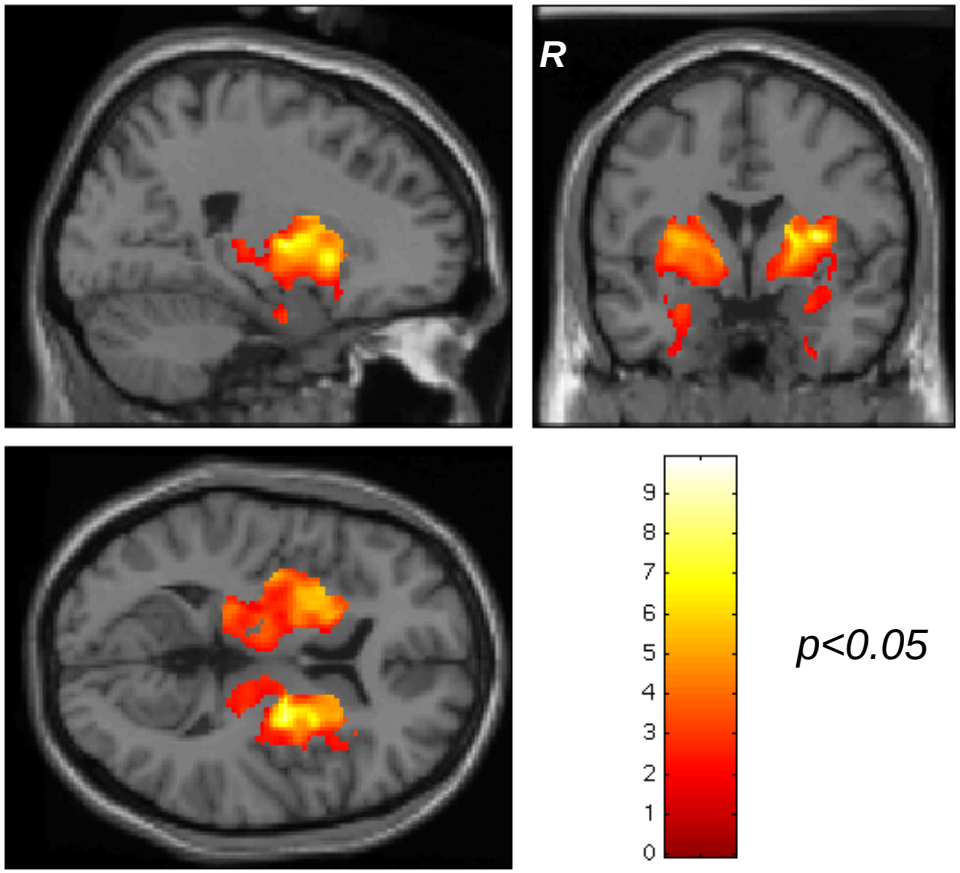
PD with fatigue

PFS-16 = 15

Pavese et al. Brain 2010

SPM analysis

Areas of reduced ^{11}C-DASB binding

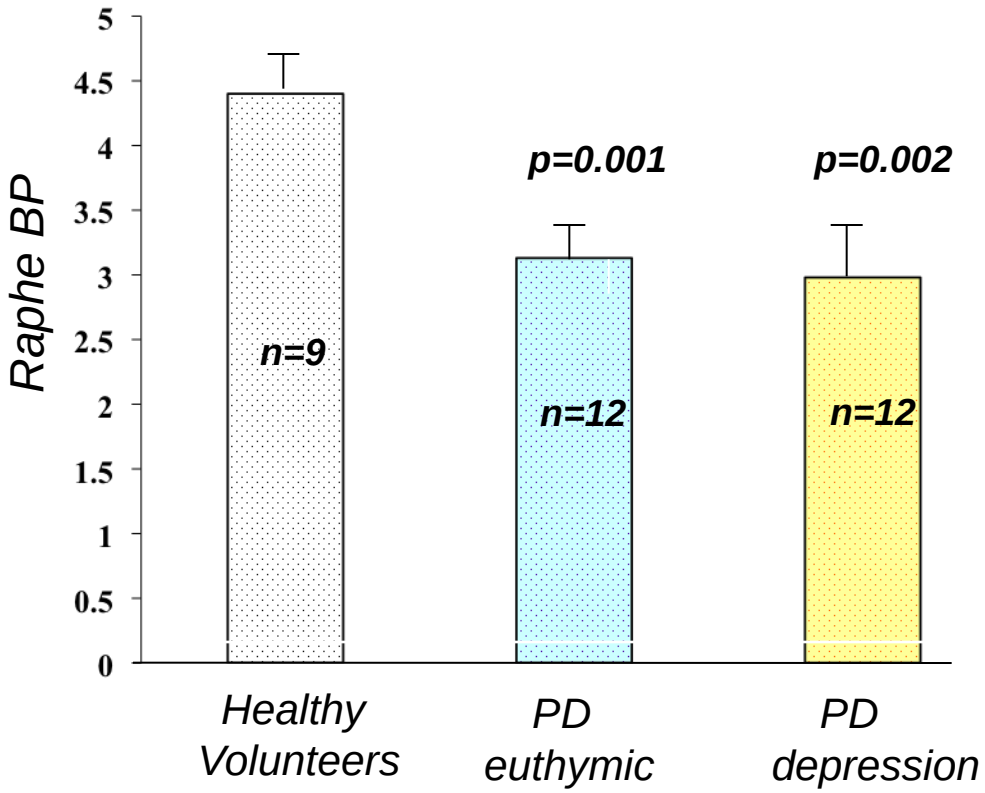


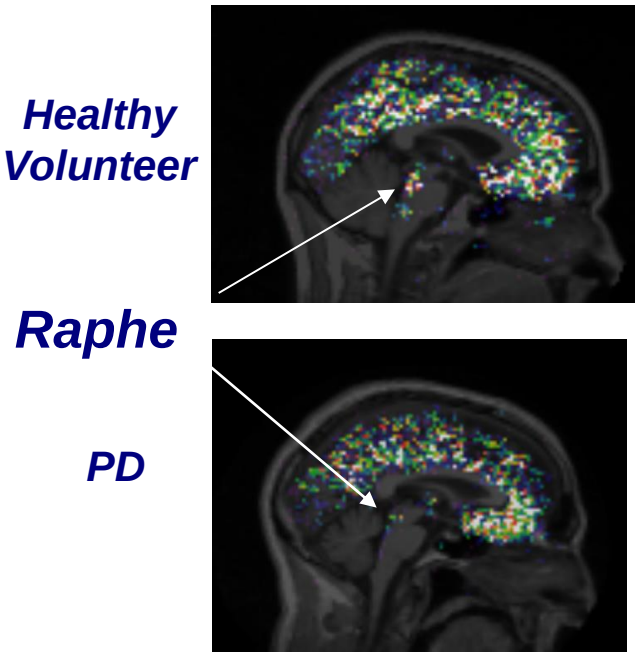
7 PD fatigue < 7 PD without fatigue

Pavese et al. Brain 2010

^{11}C-WAY 100635 PET

HT_{1A} binding in PD depression





Pavese et al. Brain 2010

Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges

David R Williams, Andrew J Lees

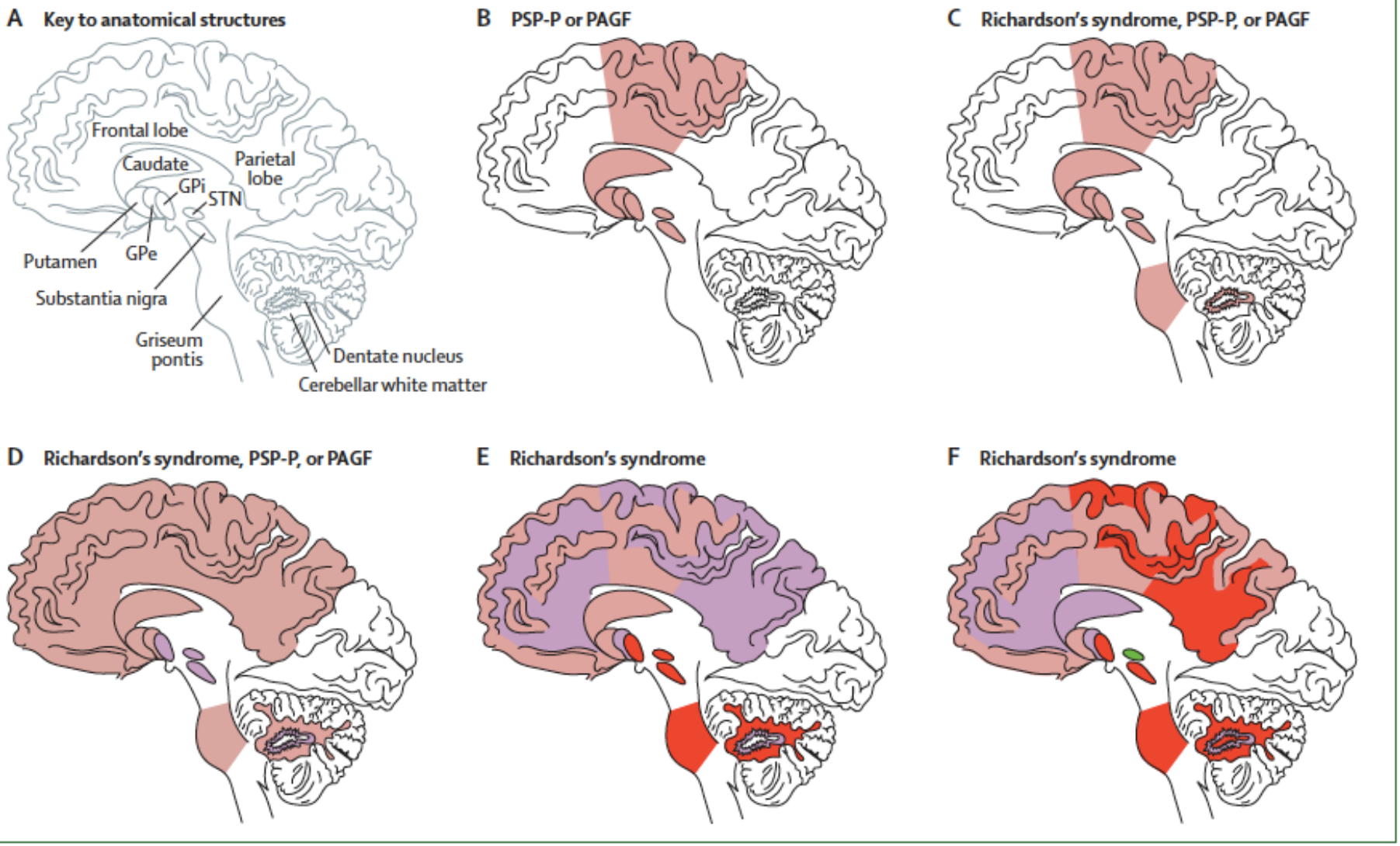
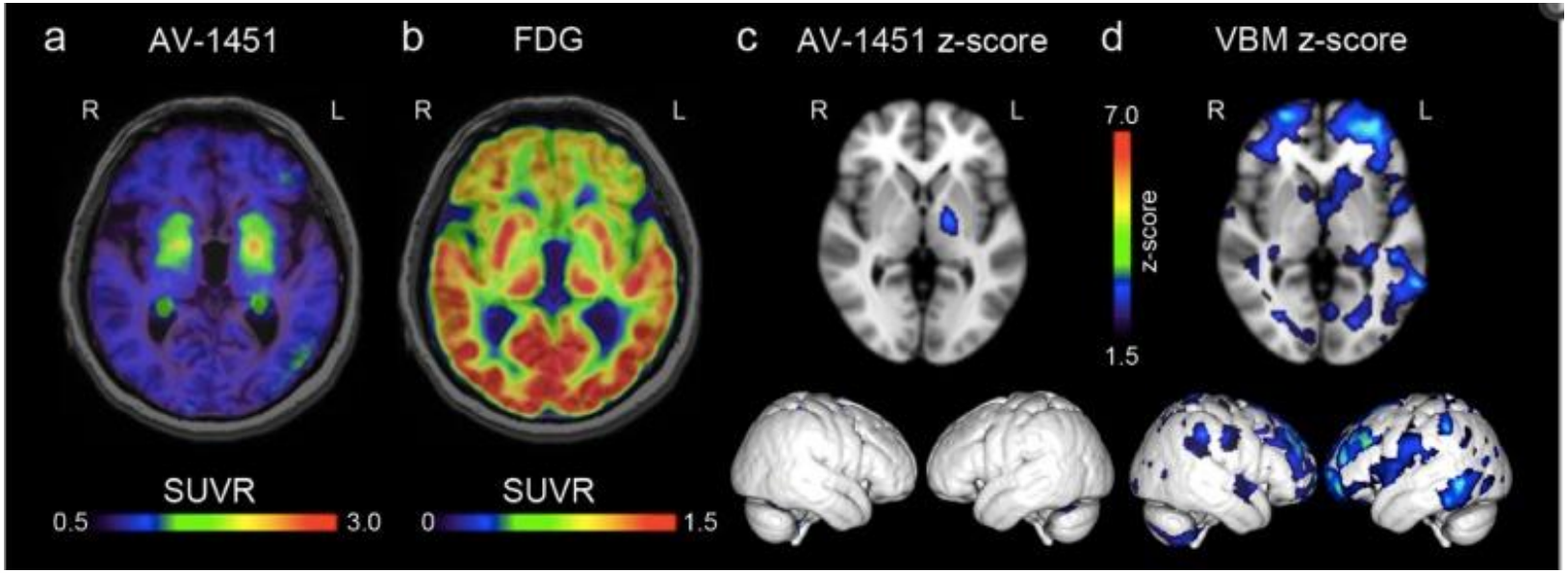
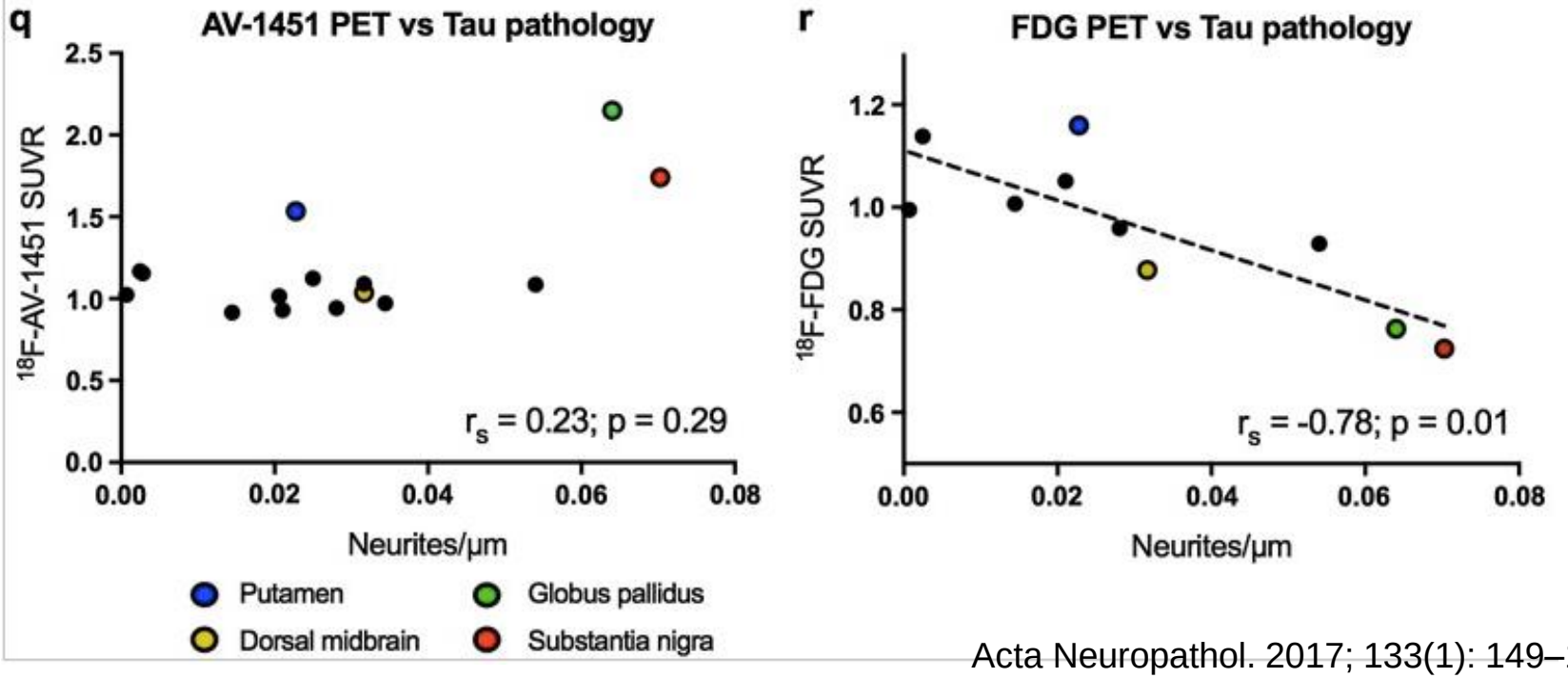


***Figure 2*: Severity of PSP tau pathology varies according to distribution**

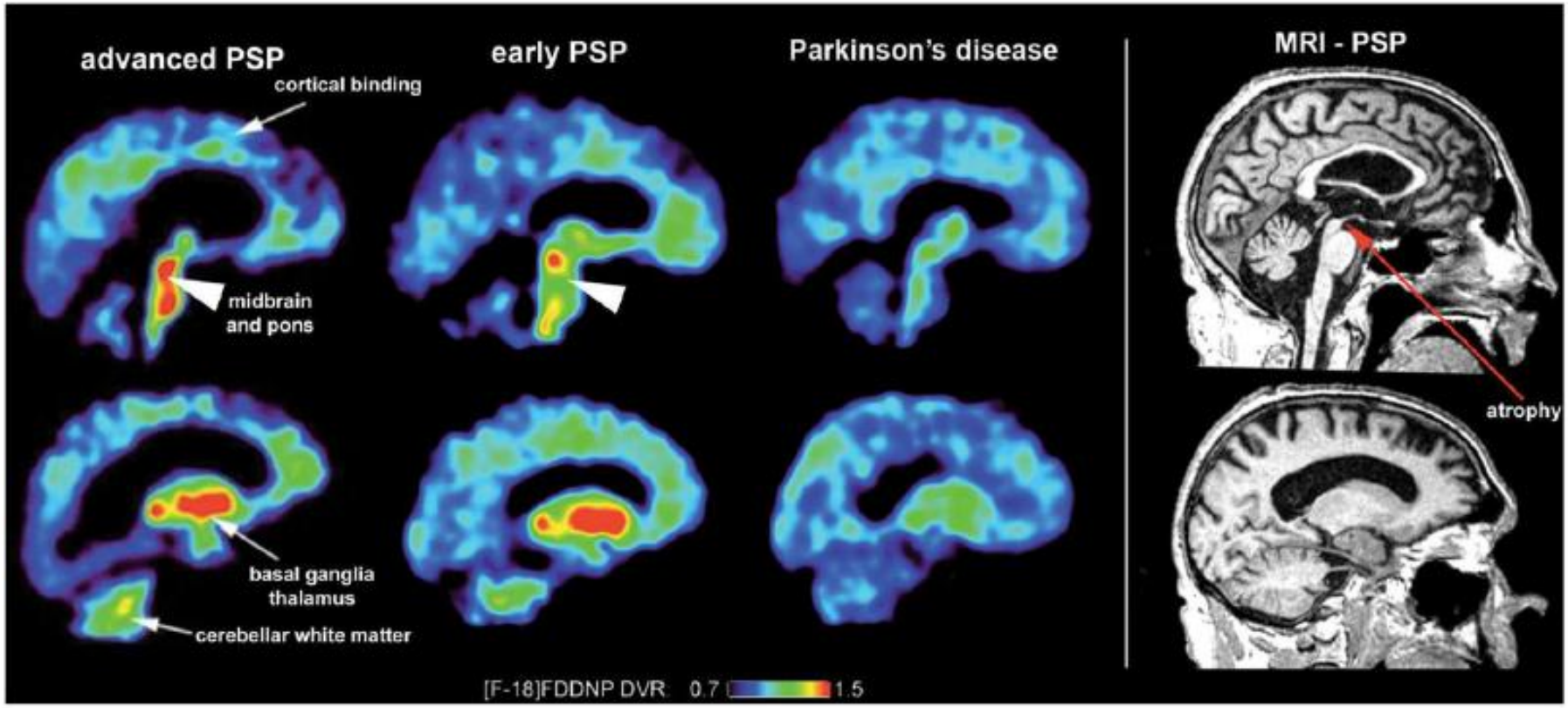
PET retention and neuropathology





Acta Neuropathol. 2017; 133(1): 149–151.

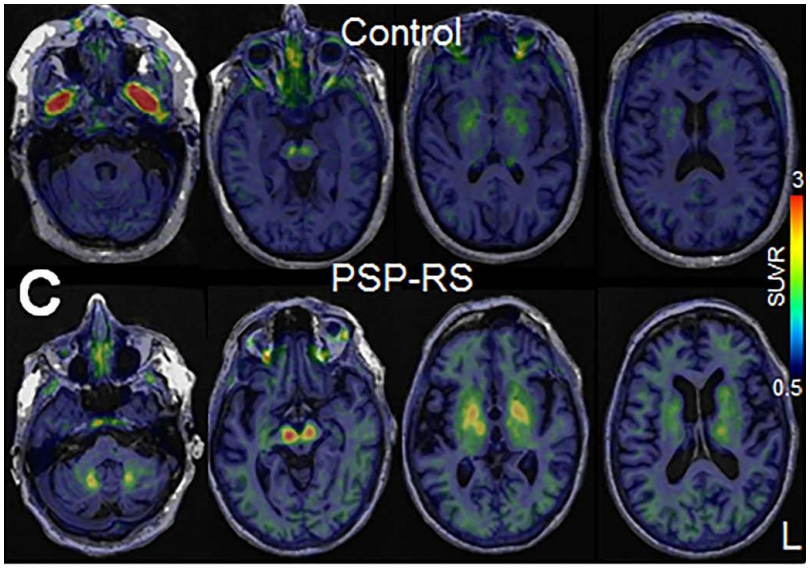
Distribution of [F-18]FDDNP DVR signal in PSP and PD

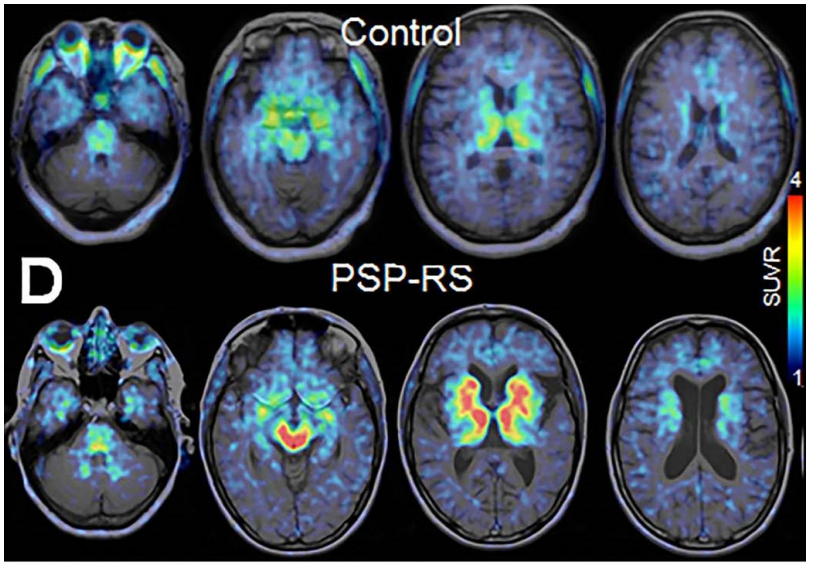


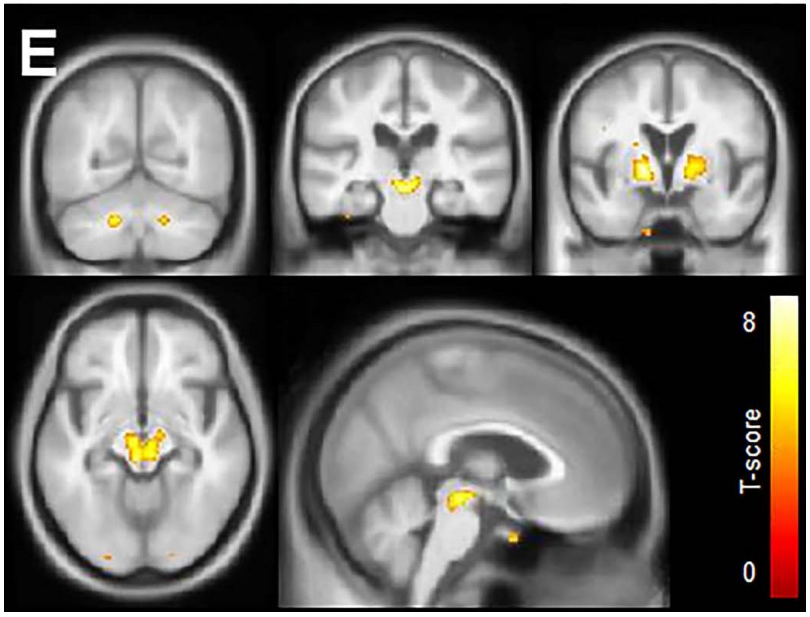
[F-18]FDDNP: (fluoroethyl)(methyl)amino]-2 naphthyl}ethylidene)

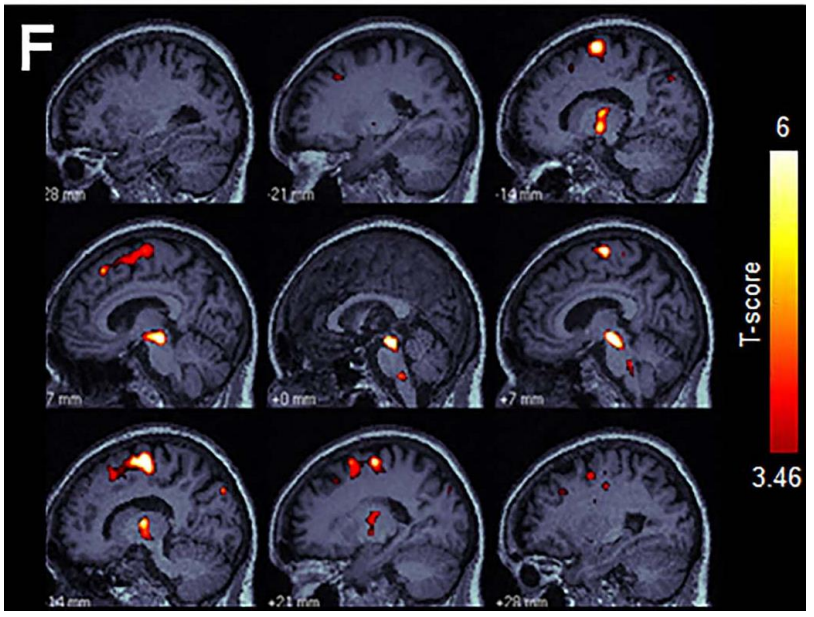
Kepe et al. J Alzheimers Dis. 2013

Different tau-PET ligands bind to tau conformers with differing sensitivity and specificity and show different off-target binding in PSP









[^{18}F]AV-1451

[^{18}F]THK-5351

Withwell J et al. Mov Disorders 2017 (in press)

MCI and dementia in PD

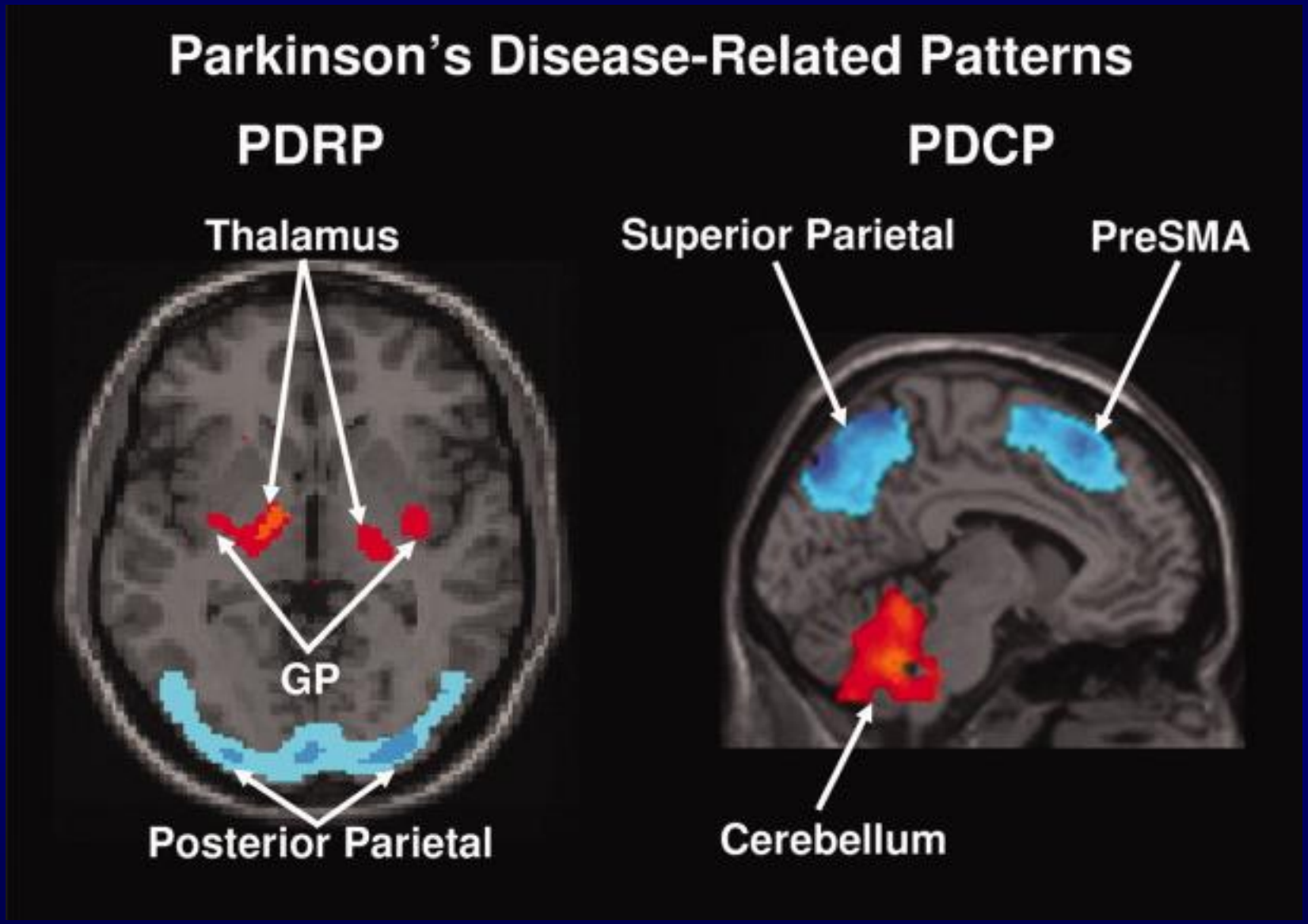
Increased risk in PD of developing cognitive impairment

PD-MCI may progress to dementia more frequently and more rapidly than those without cognitive impairment

Approximately 20–30% of PD have mild cognitive changes even at the time of diagnosis

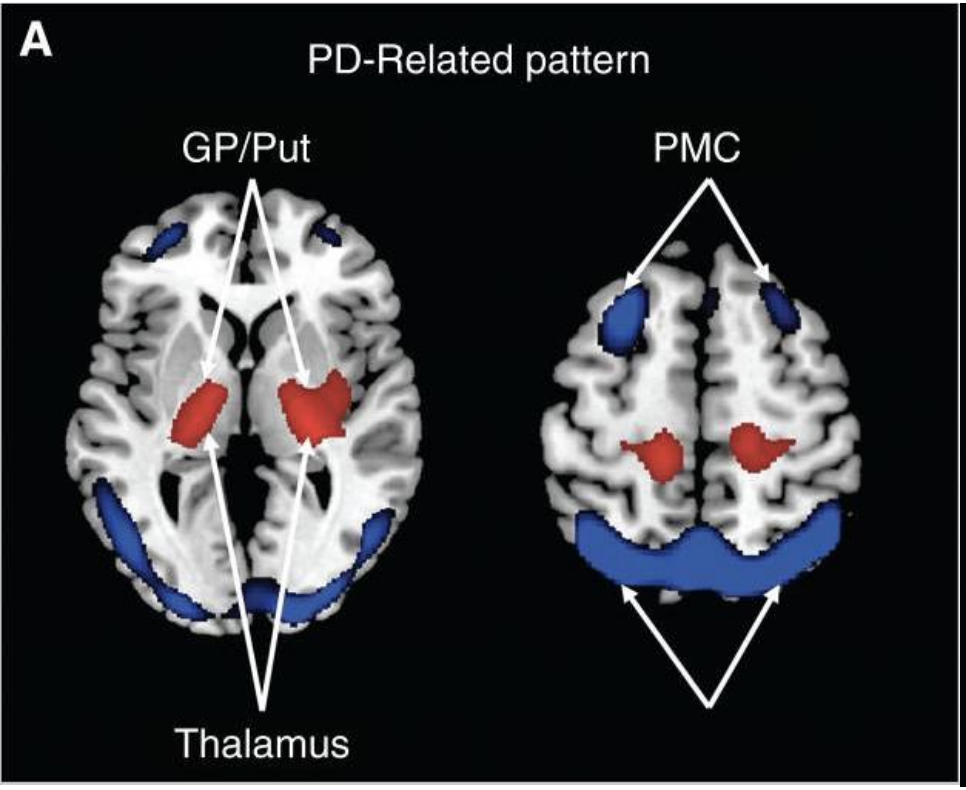
*The point prevalence of dementia is 30**%** and the incidence rate is increased four to six time as compared to age-matched controls*

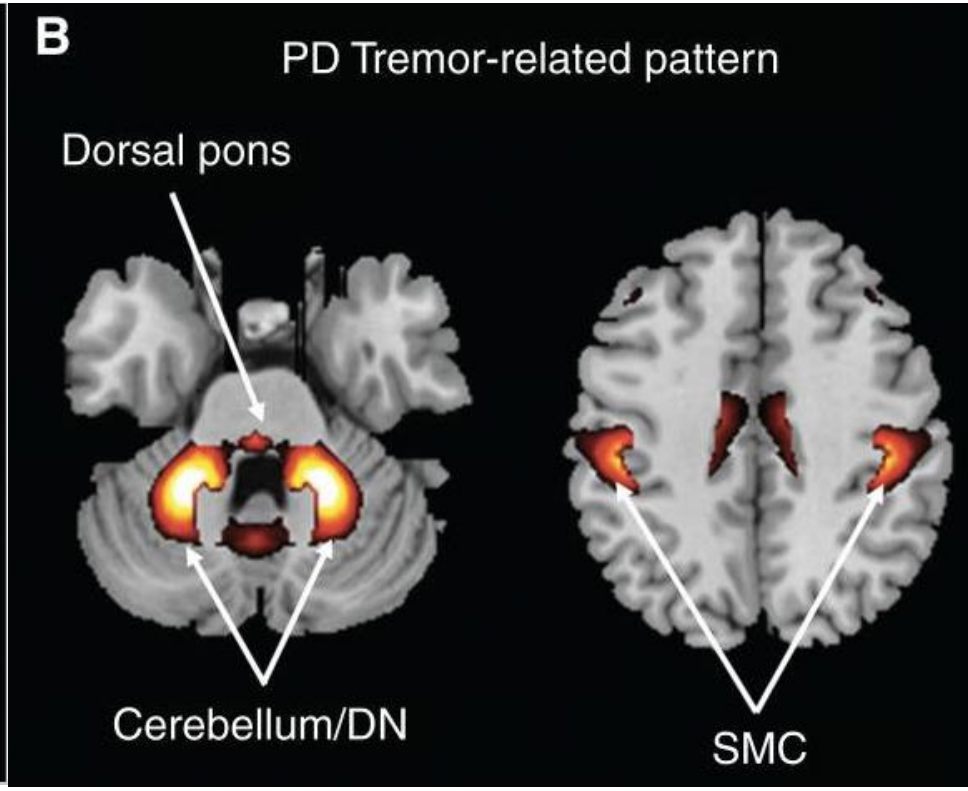
Motor and Cognitive related patterns in PD



Huang et al Neuroimage, 2007

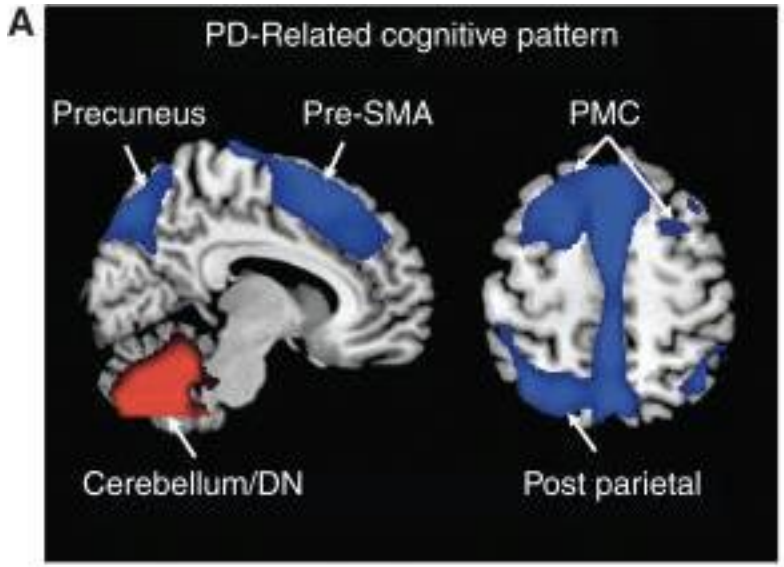
Abnormal metabolic networks in Parkinson's disease (FDG-PET)

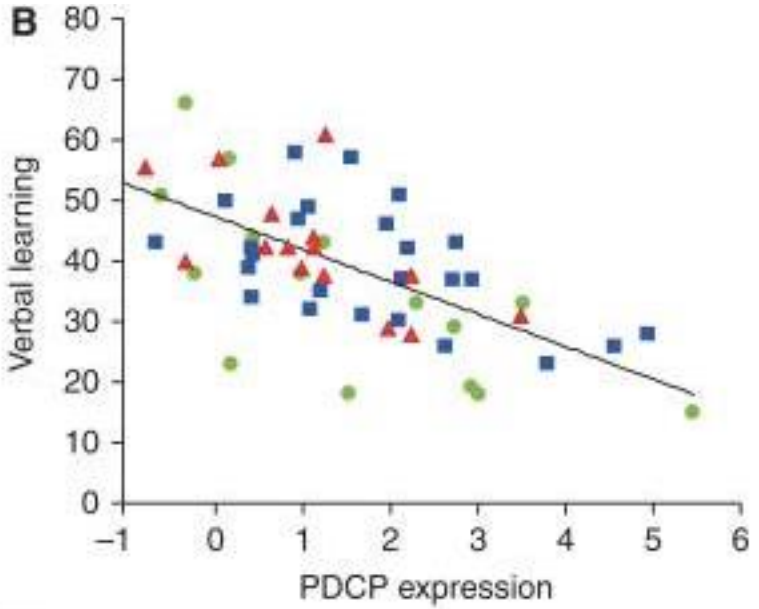


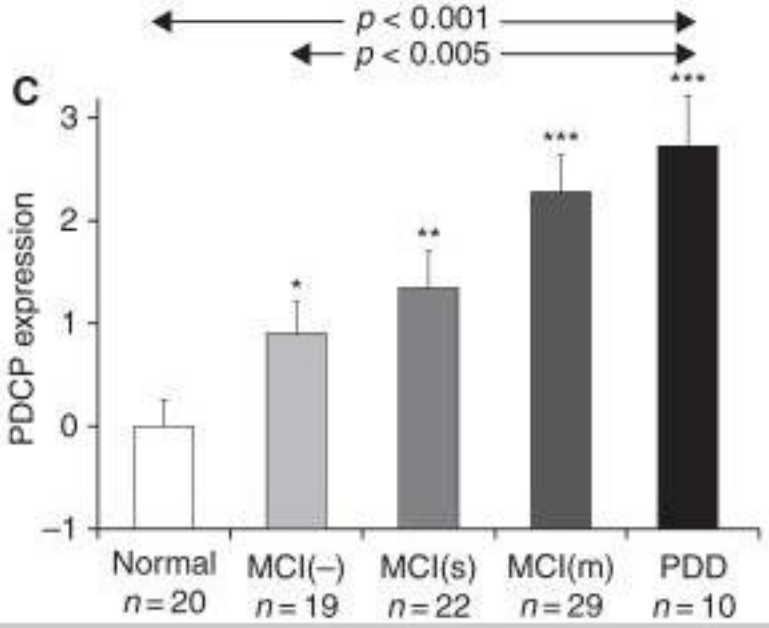


Eidelberg et al. Trends Neuroscience 2009

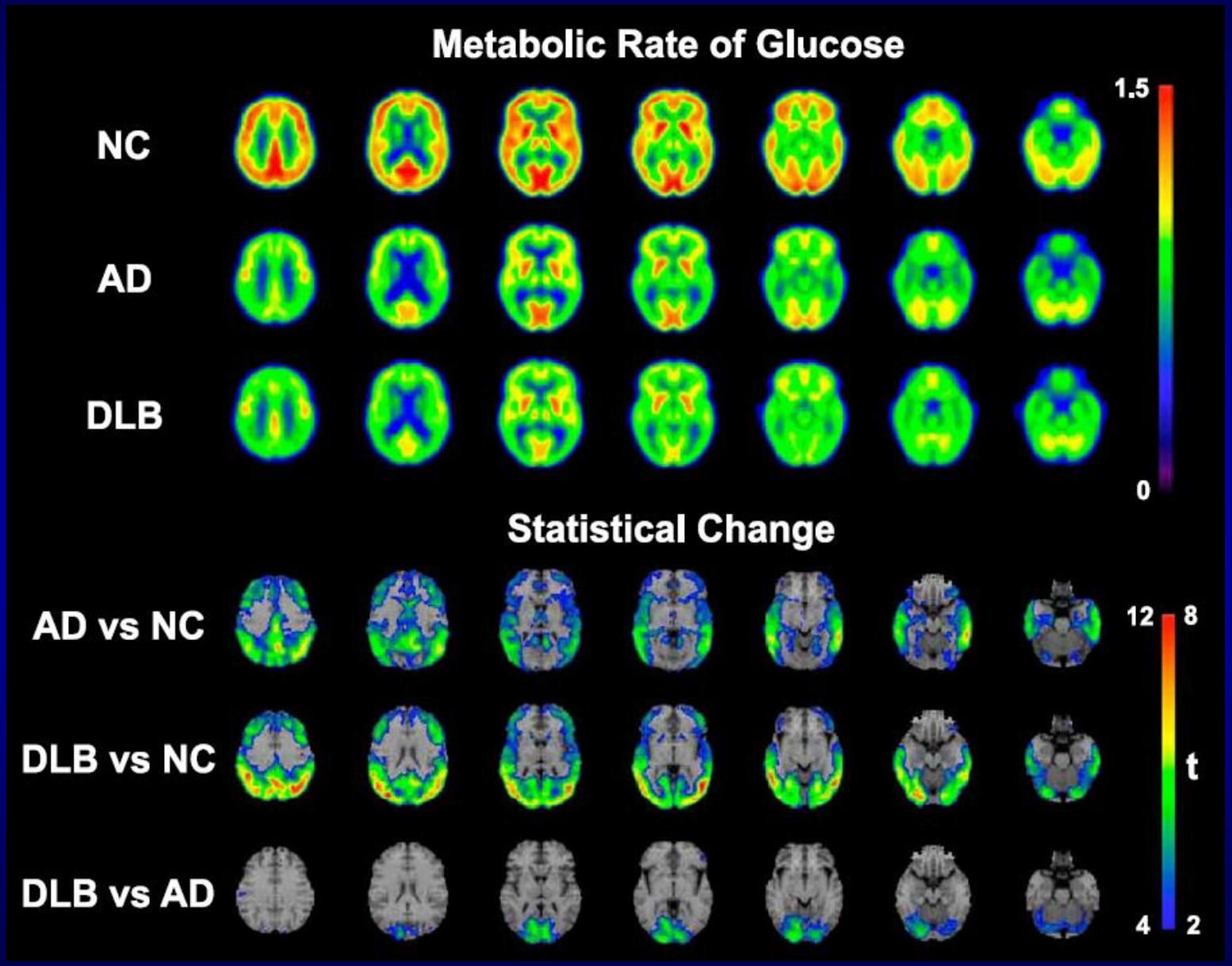
Parkinson's disease-related cognitive pattern: FDG-PET





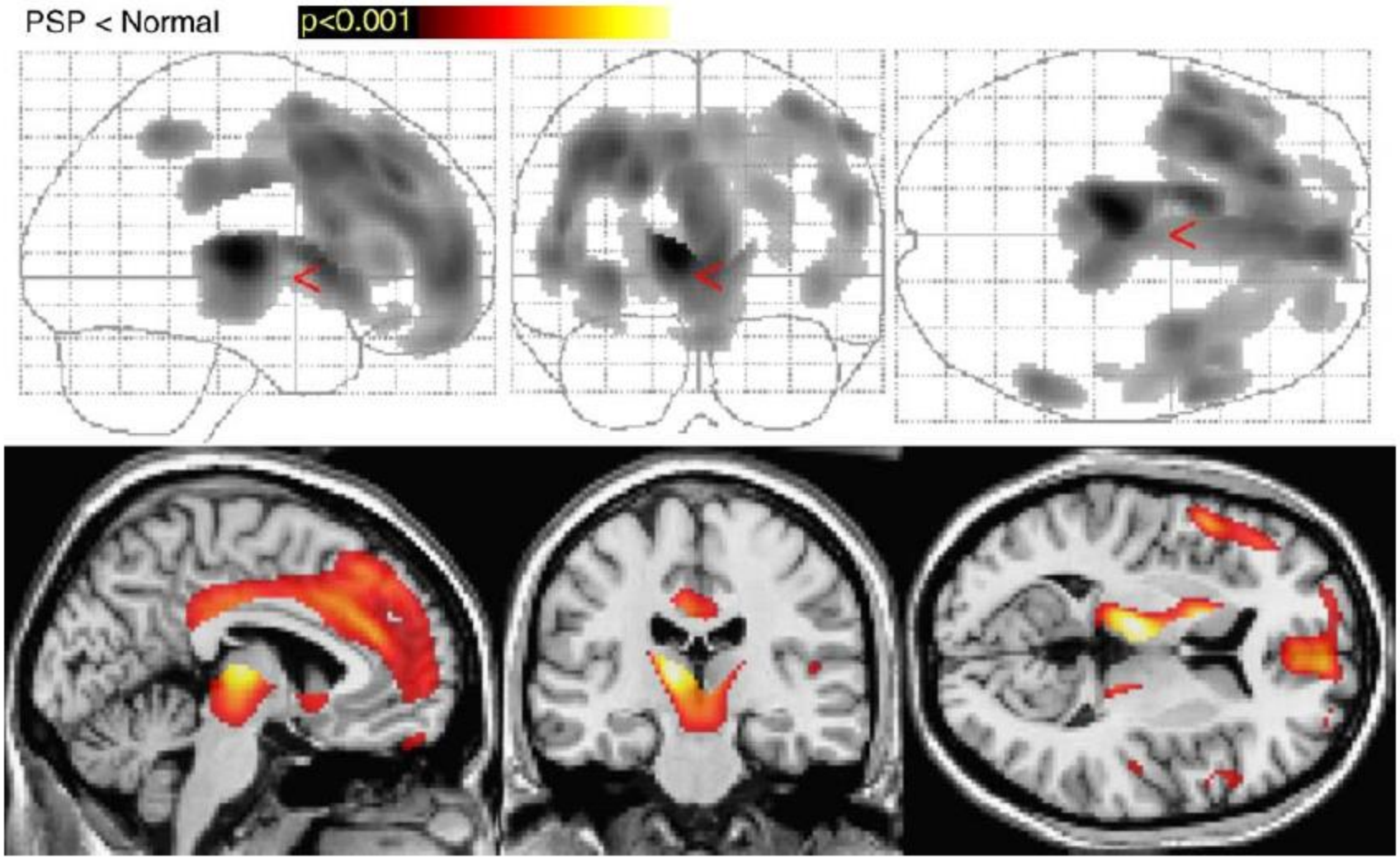


FDG-PET in AD and DLB



Gilman, 2005

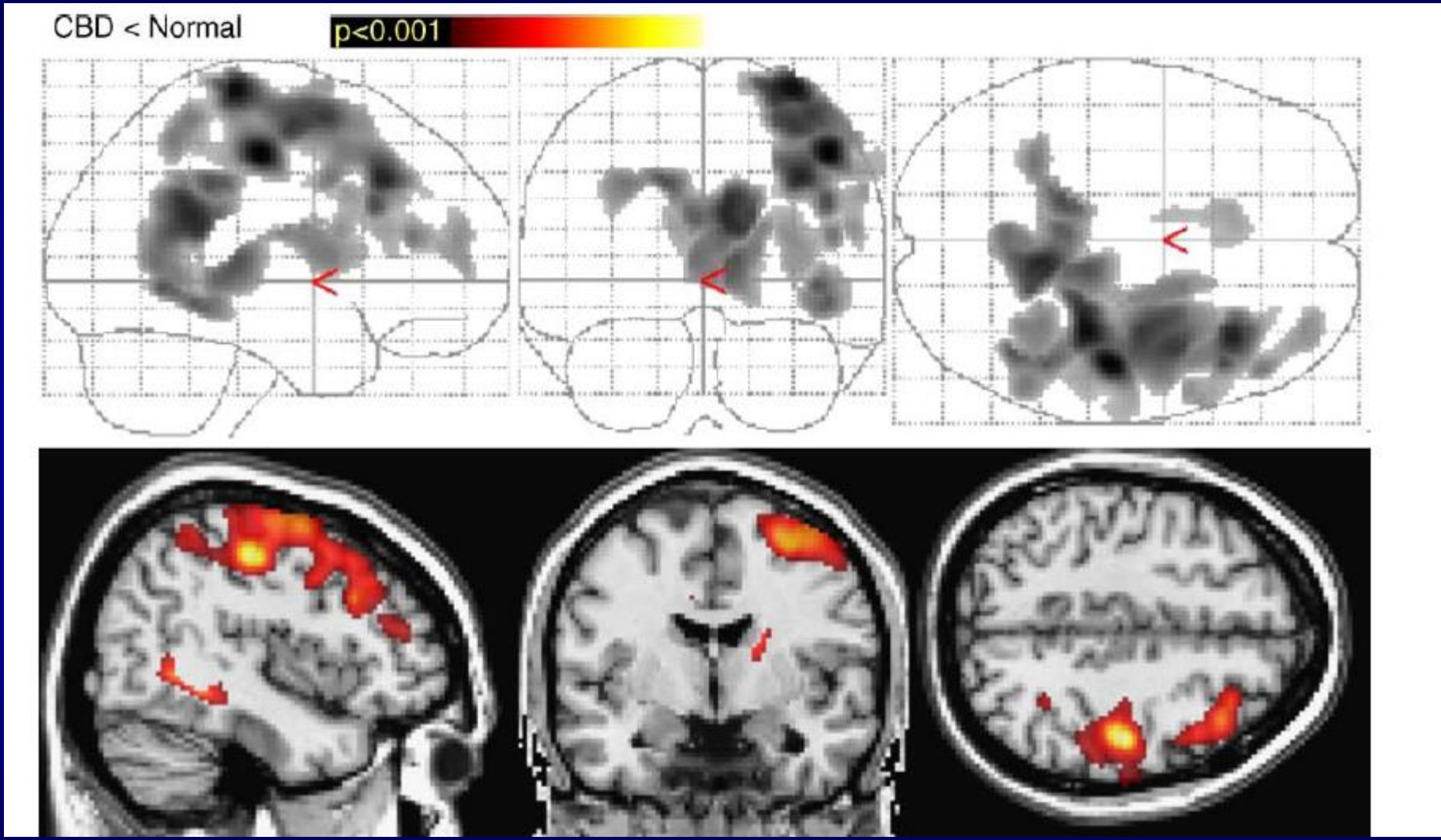
FDG-PET in Progressive Supranuclear Palsy



Hypometabolism of the frontal lobe, mid-brain, thalamus, midbrain

Juh et al 2005

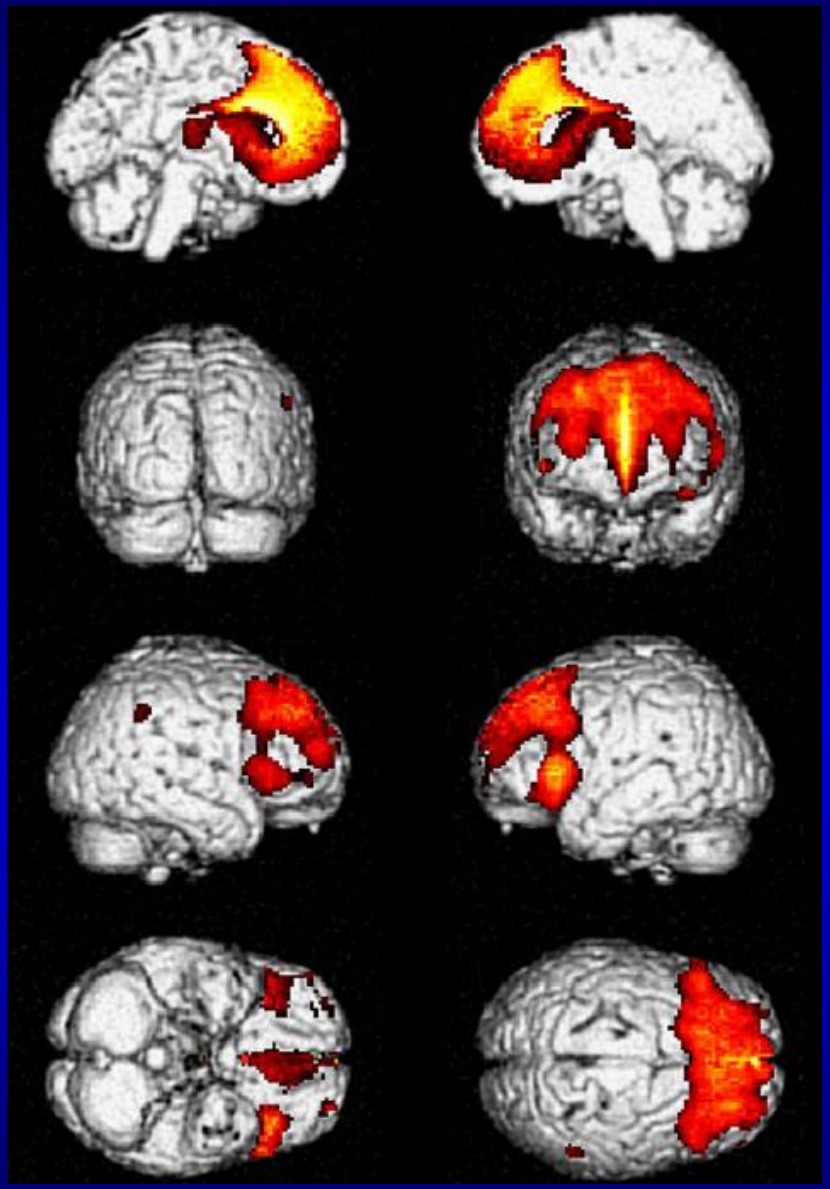
FDG-PET in Cortico-Basal-Degeneration



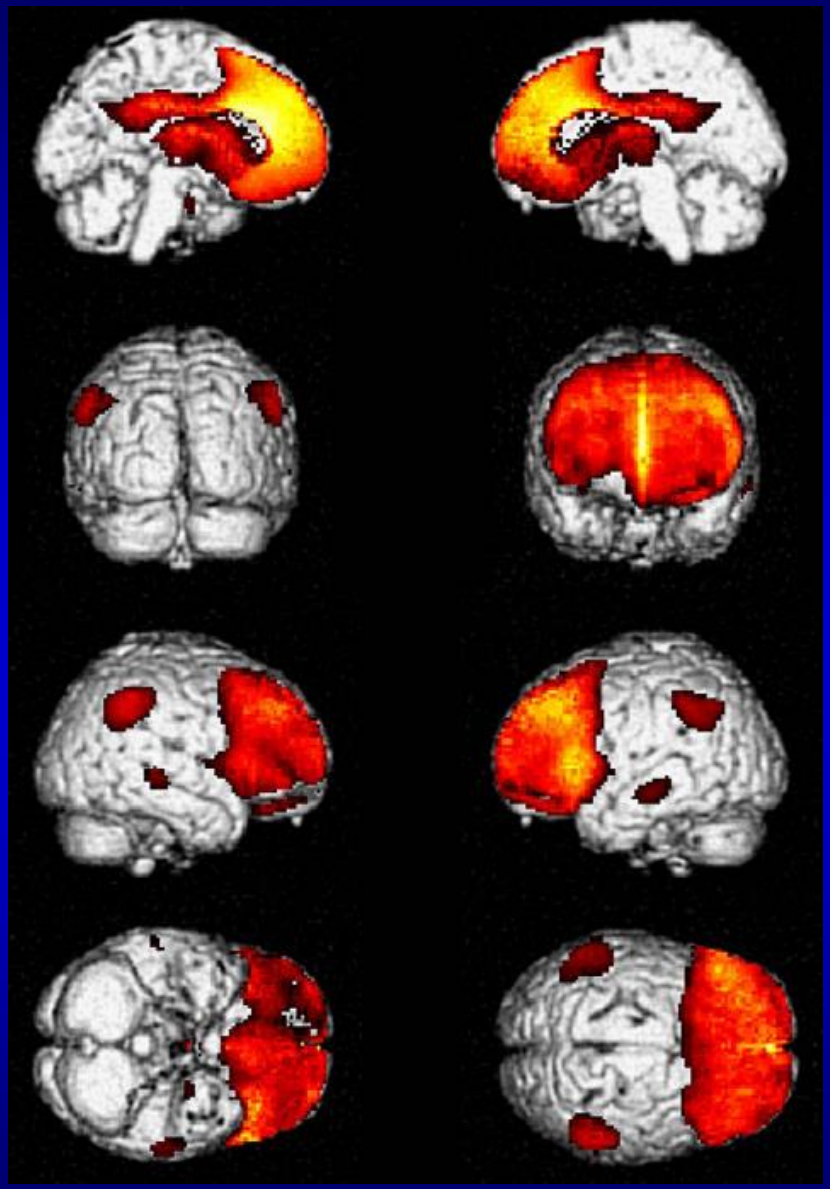
Hypometabolism of the parietal lobe, medial frontal gyrus and cinglate

Juh et al 2005

Progressive Decline of brain glucose metabolism in FTD



22 FTD vs. 15 healthy subjects



FTD vs. HS 20 months later

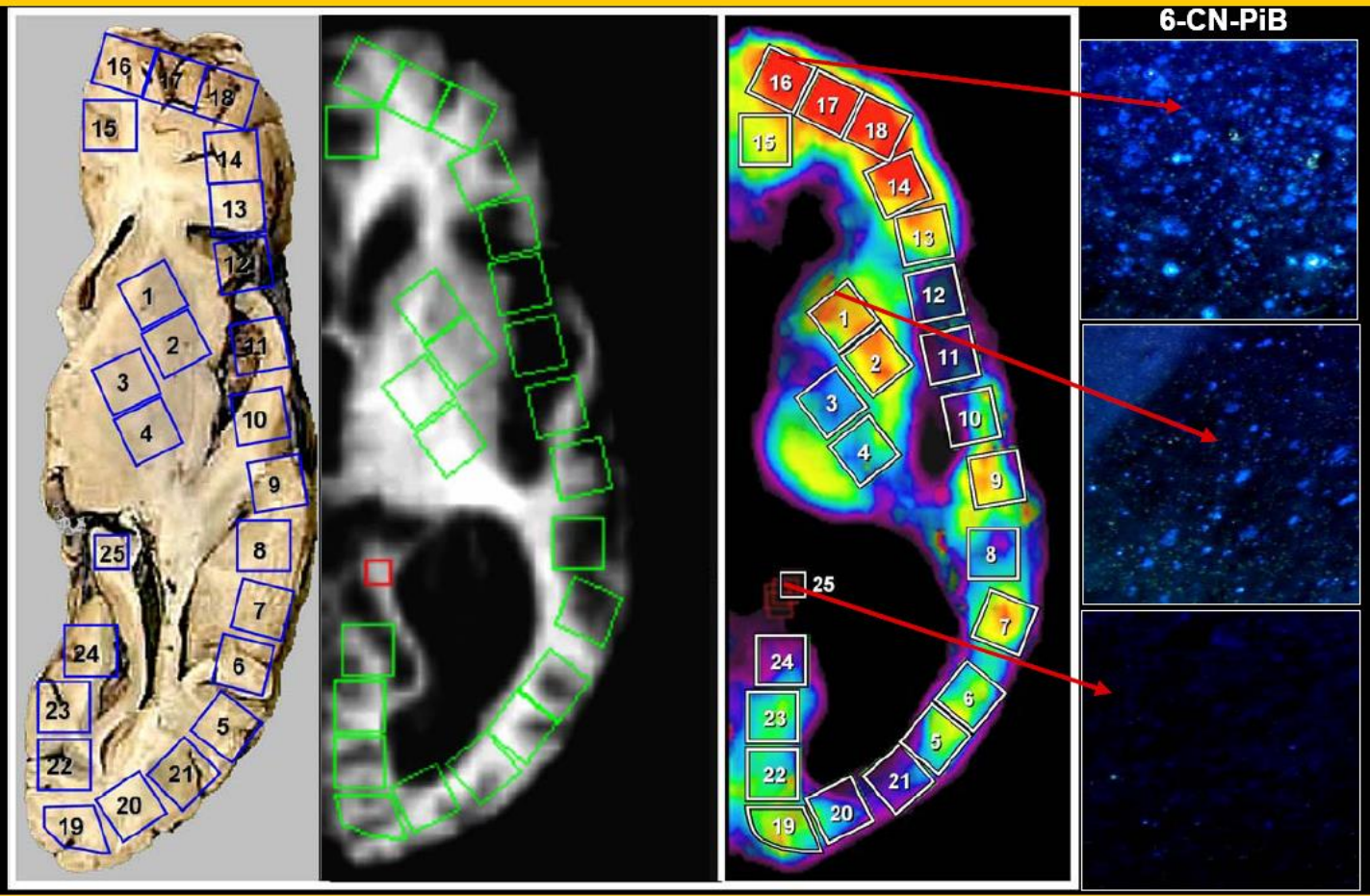
Diehl-Schmid et al 2006

Aβ imaging

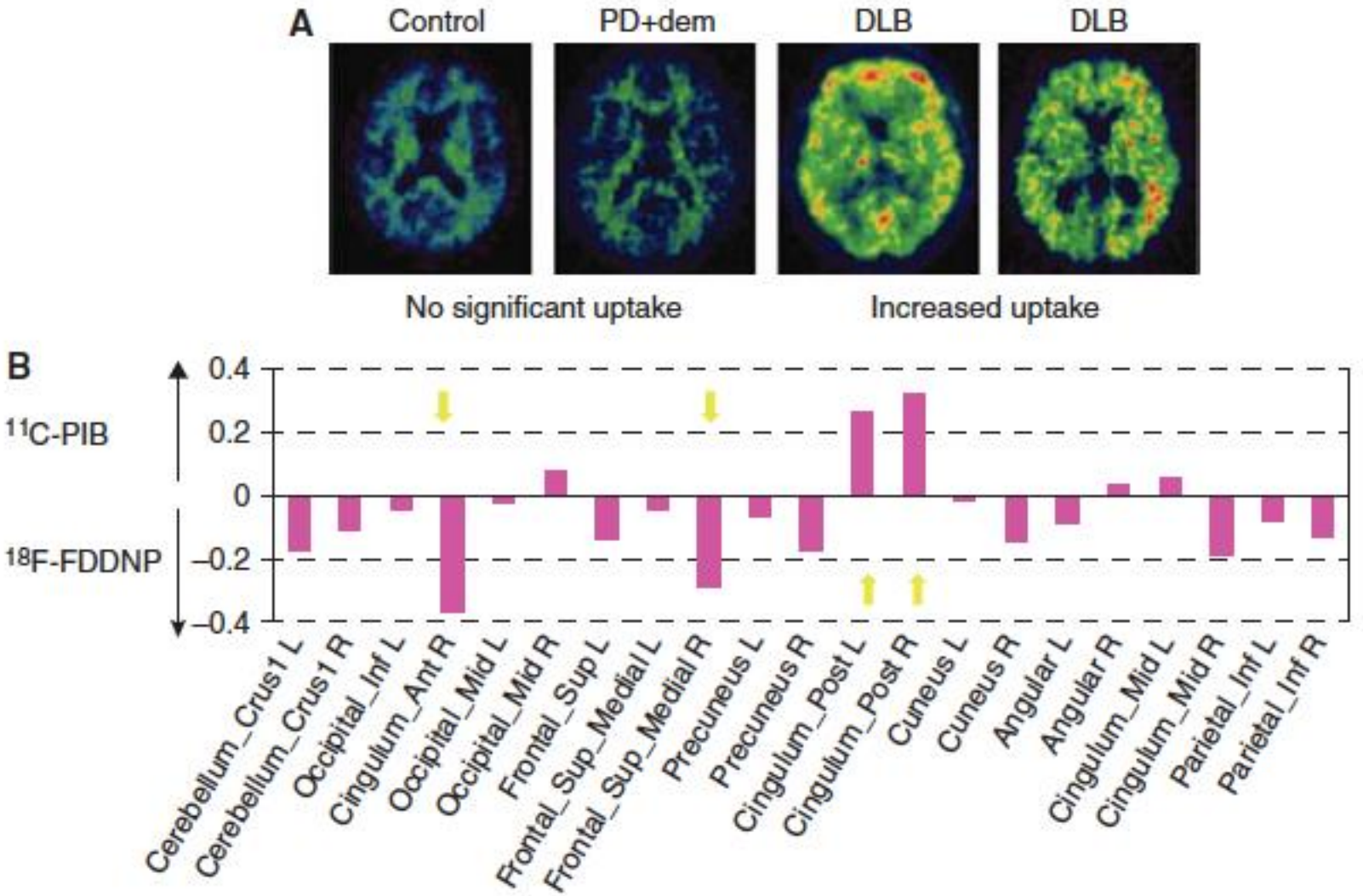
- The most extensively studied and best validated tracer with positron emission tomography (PET) is the ^{11}carbon-labelled Pittsburgh Compound-B (^{11}C-PIB)
- PIB binds specifically to fibrillar beta-amyloid (Aβ) deposits, and is a sensitive marker for Aβ pathology

Ikonomovic et al. Brain 2008;131:1630-1645

[^{11}C]PiB Retention *In Vivo* Correlates Well with Aβ Levels Determined Post-Mortem

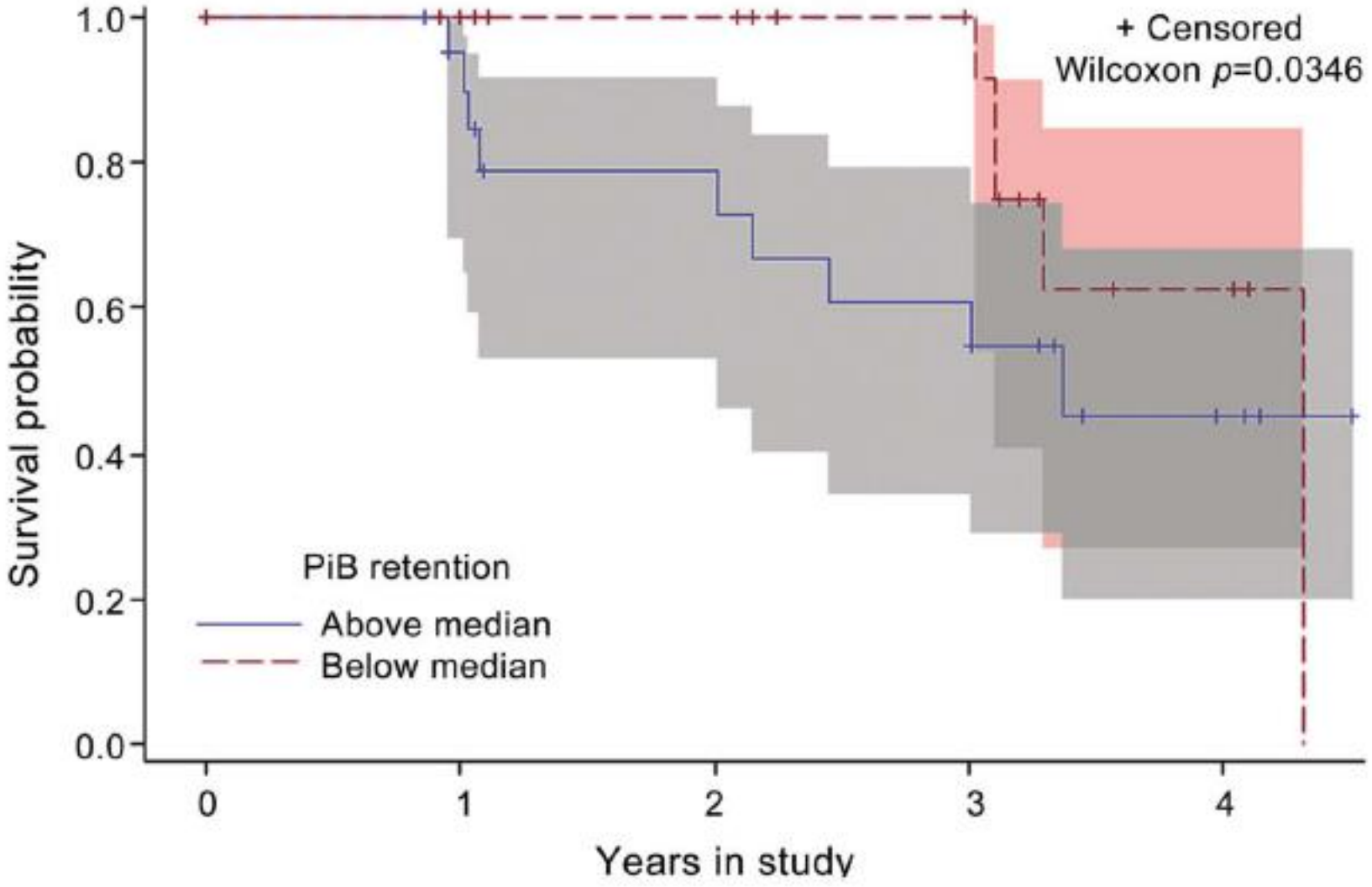


Imaging amyloid deposition in Lewy body diseases



Gomperts SN et al Neurology, 2008

Subjects with Pittsburgh compound B (PiB) retention above the median for the sample converted to a more severe cognitive state sooner than those with values below the median



Gomperts SN et al Neurology, 2013

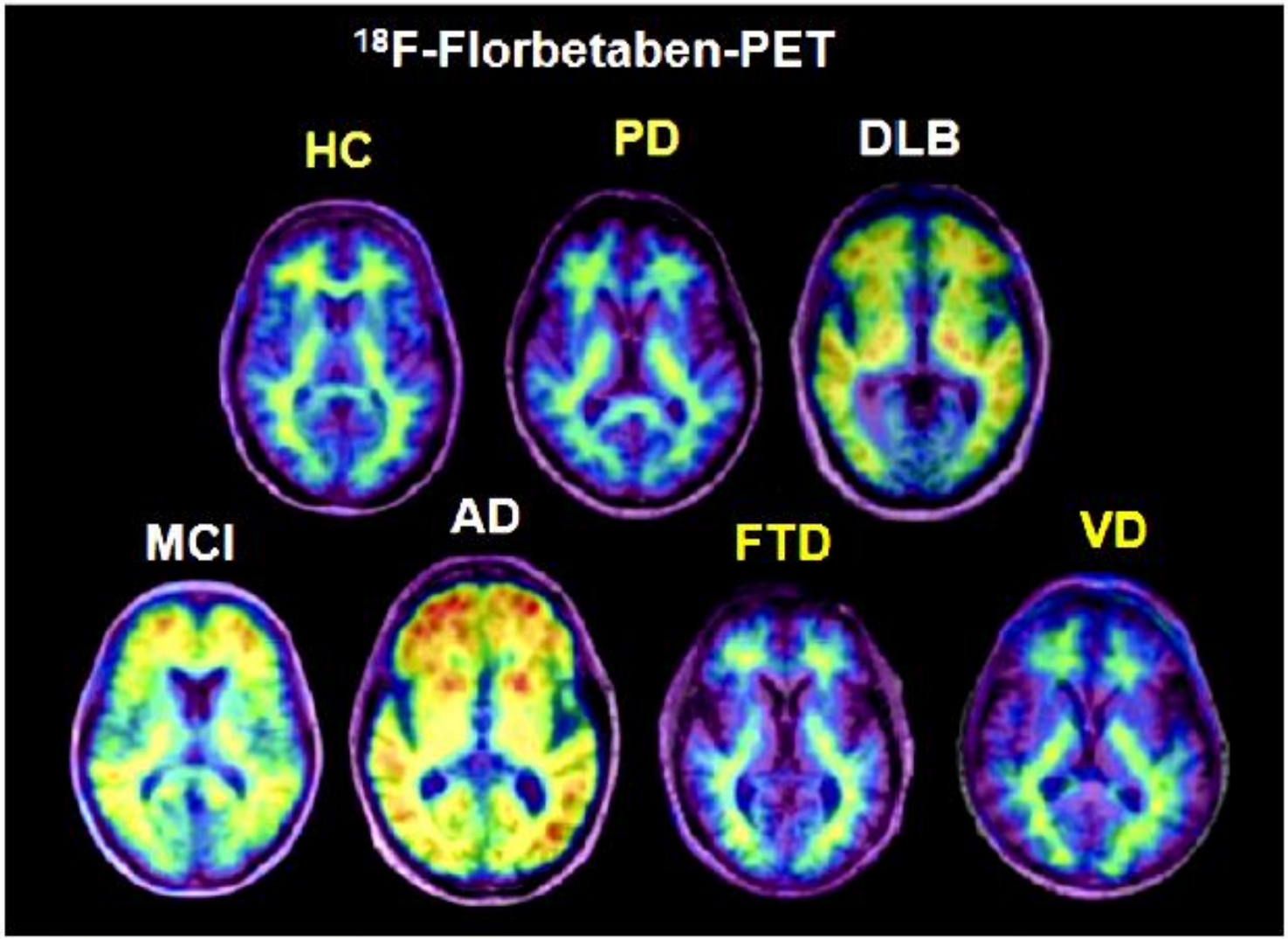
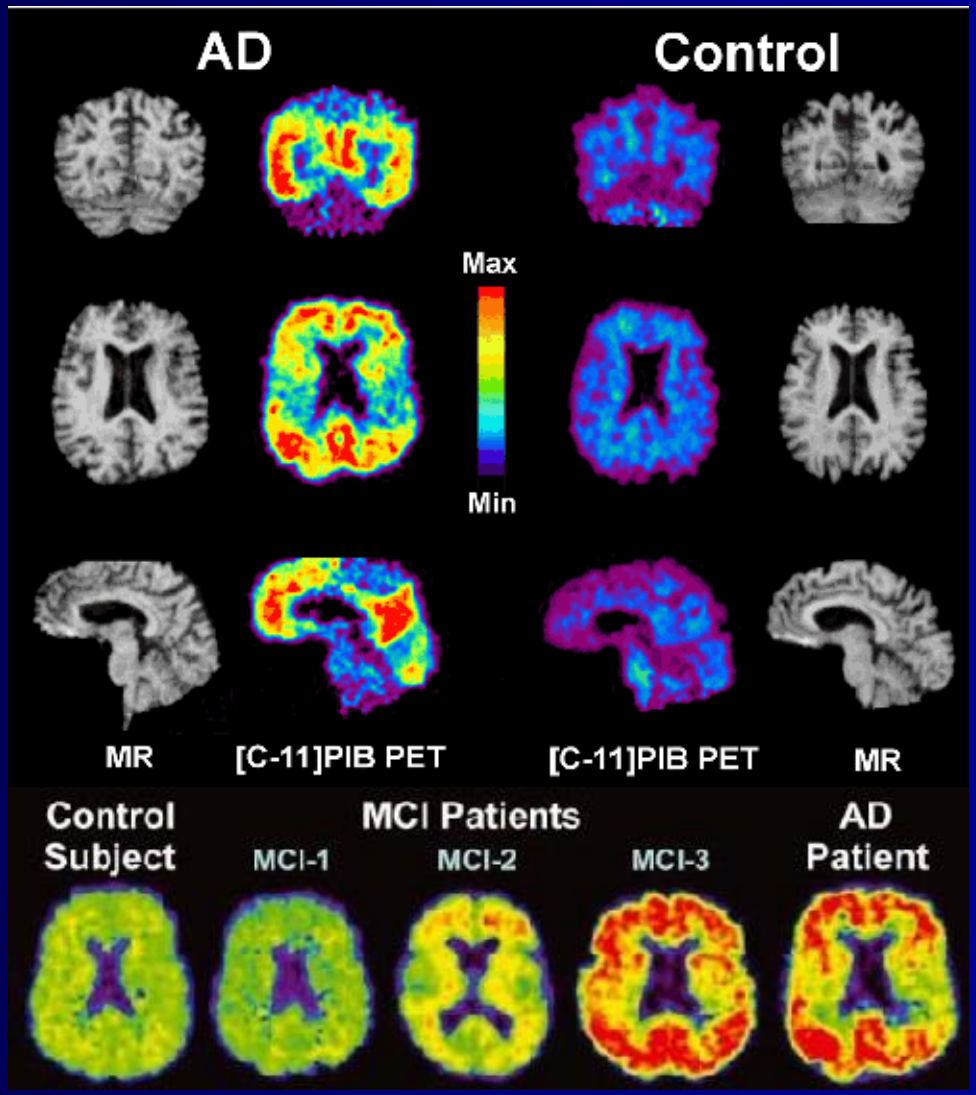


Figure 14 ^{18}F-Florbetaben-PET in differential diagnosis of dementia. VD, pure vascular dementia. (Reprinted by permission of the Society of Nuclear Medicine from Rowe.[106])

In vivo imaging of β amyloid with PIB -PET



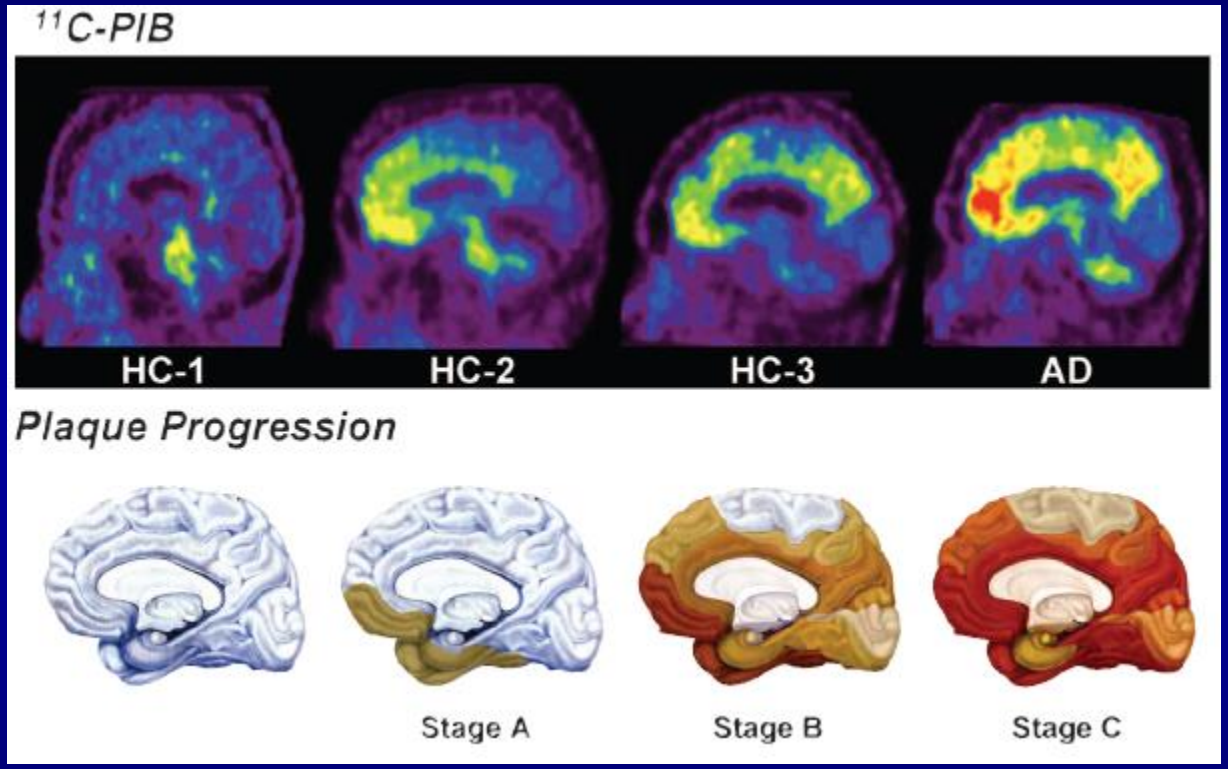
Klunk et al, 2004

Imaging β-amyloid burden in aging and dementia

NEUROLOGY 2007;68:1718-1725

Healthy controls:

- *21 no binding*
- *6 (22%) increased binding*
  - *pattern similar to AD*
  - *resembling the stages of Aβ deposition according to Braak pathological studies*



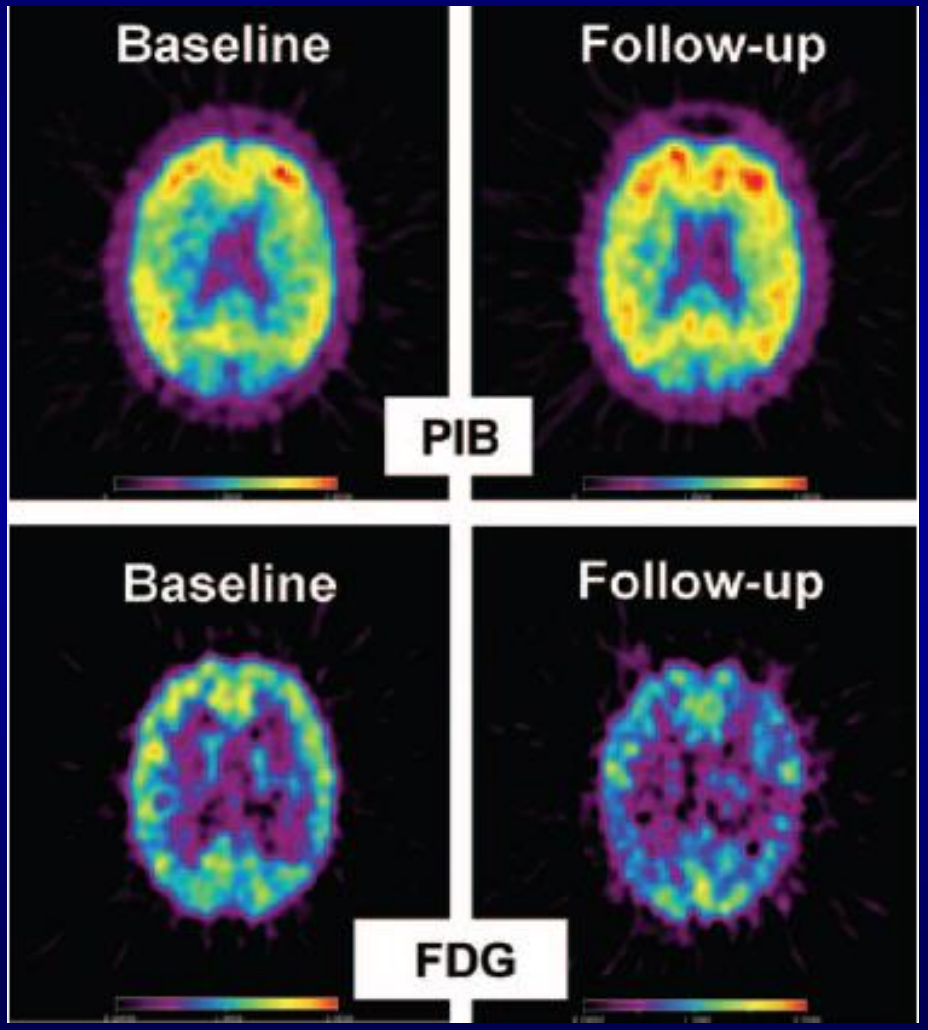
Prevalence of AD at age 85 from15 to 25%, but…
30% of non-demented >75 ys with moderate Aβ deposition at post-mortem

Rowe CC et al, 2007

doi:10.1093/brain/awl178 *Brain* (2006), **129**, 2856–2866

Two-year follow-up of amyloid deposition in patients with Alzheimer's disease

- *16 patients with mild AD*
- *Aβ deposition stable over two years of follow-up*
- *20% decrease in glucose metabolism in posterior cingulate cortex and temporo-parietal cortex*
- *Significant clinical deterioration in a subgroup of patients*

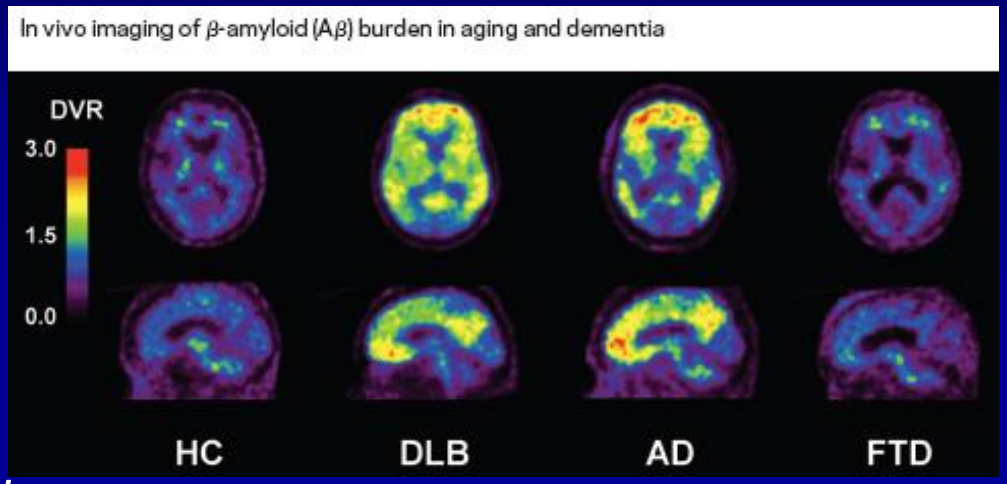


Engler H et al, 2007

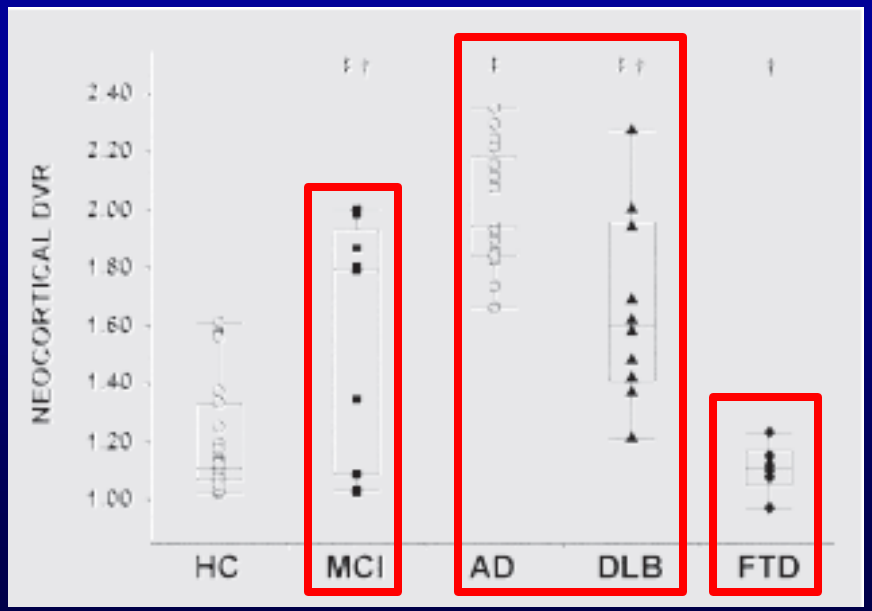
Imaging β-amyloid burden in aging and dementia

NEUROLOGY 2007;68:1718-1725

Patients
- *17 AD*
- *10 DLB*
- *6 FTD*
- *9 MCI*
- *27 age-matched controls*



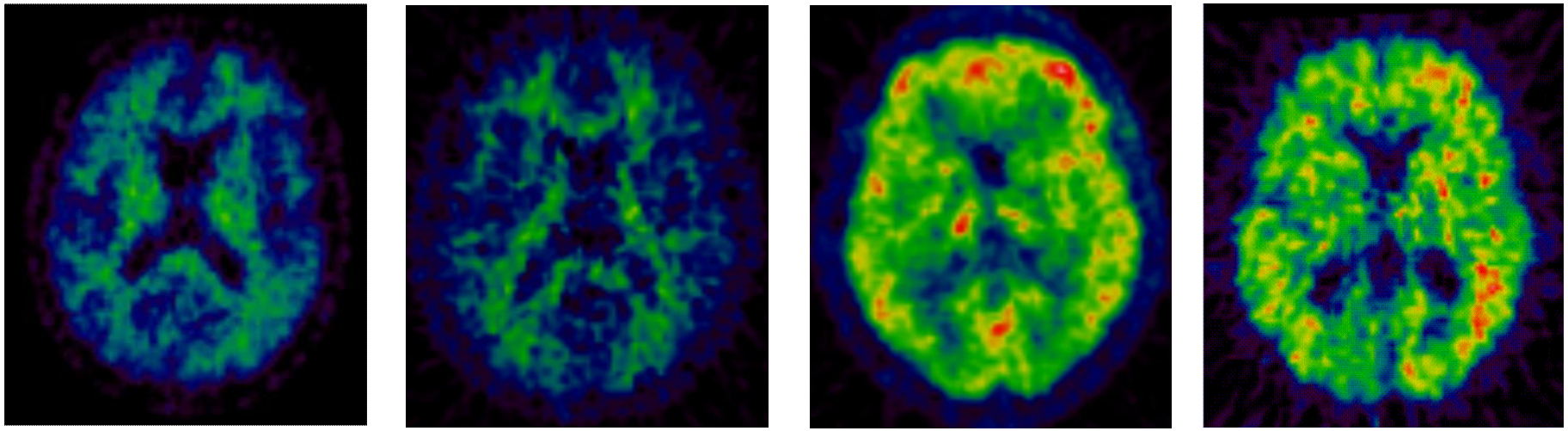
- ***AD:*** *markedly increased binding (PCC/precuneus, temporal and parietal cortex, frontal cortex and striatum)*
- ***DLB:*** *increased binding, generally lower and variable.*



- ***FTD:*** *normal values*
- ***MCI:*** *from normal to AD*

^{11}C-PIB uptake in a healthy volunteer, PDD subject without significant amyloid, and two DLB patients with a significant amyloid load

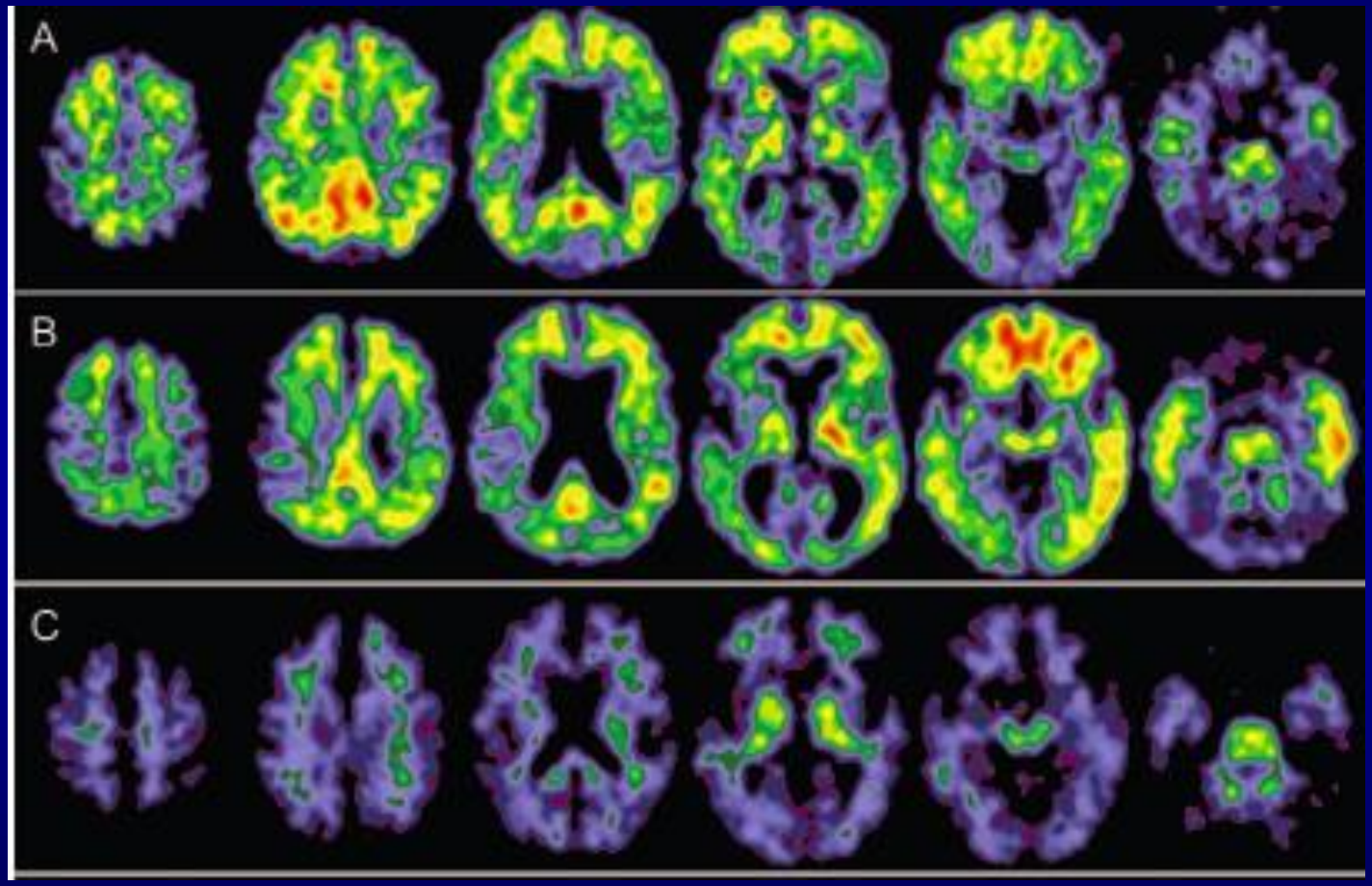
Control ***PD with late dementia*** ***PD with early dementia (DLB)***



No significant uptake ***Increased uptake in 70%***

Edison P et al JNNP, 2008

PIB maybe increased in PDD with visuospatial and memory deficits



Burack et al Neurology 2010

Amyloid Deposition in Parkinson's Disease and Cognitive Impairment: A Systematic Review

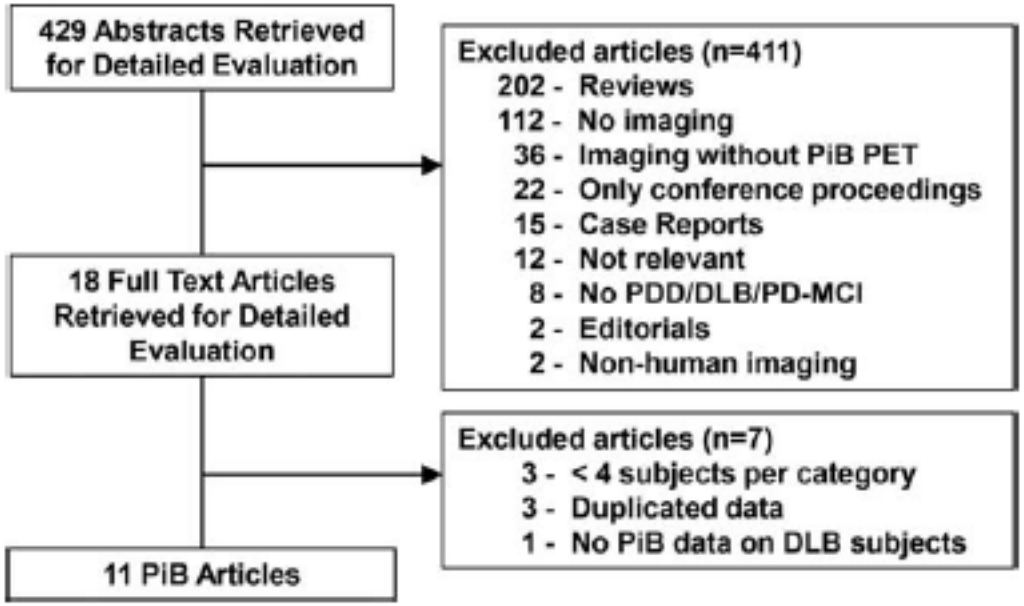
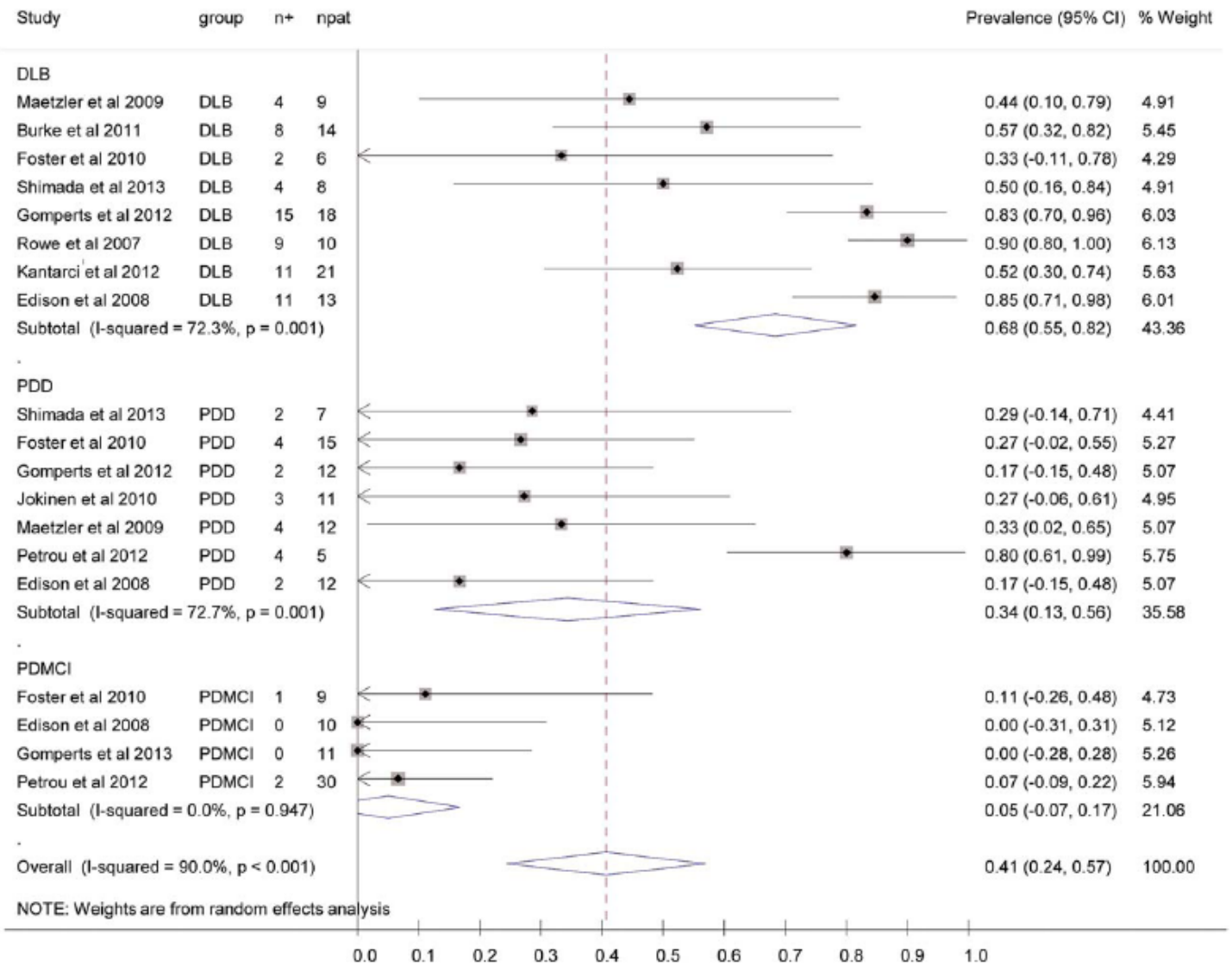


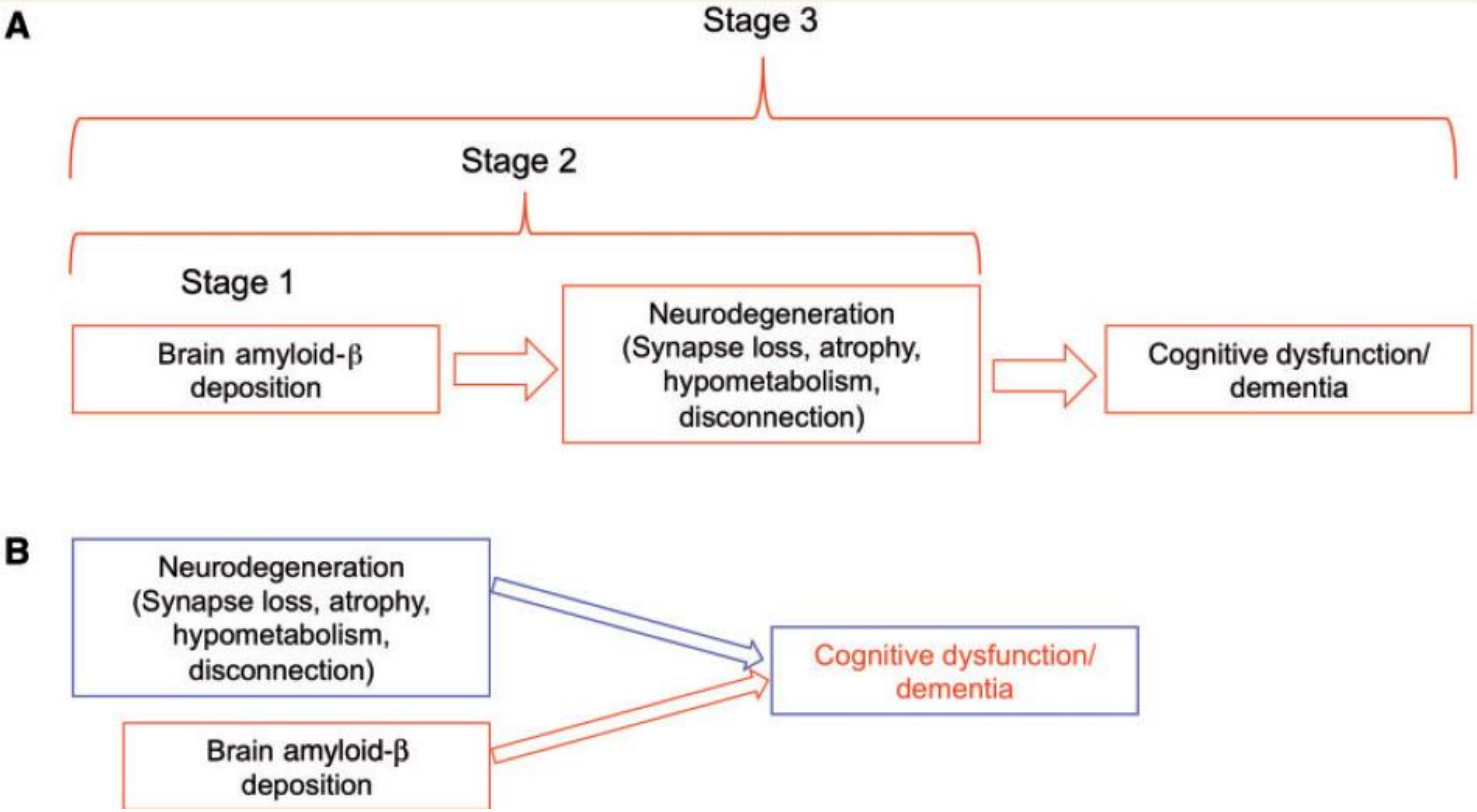
FIG. 1. Flowchart illustrates the selection of studies. PiB, Pittsburgh compound B; PET, positron emission tomography; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies; PD-MCI, Parkinson's disease with mild cognitive impairment.

Petrou M et al. Mov Disord 2015

Forest plot of point prevalence of PiB-positive studies among the entities encompassed by parkinsonism and cognitive impairment



Petrou M et al. Mov Disord 2015

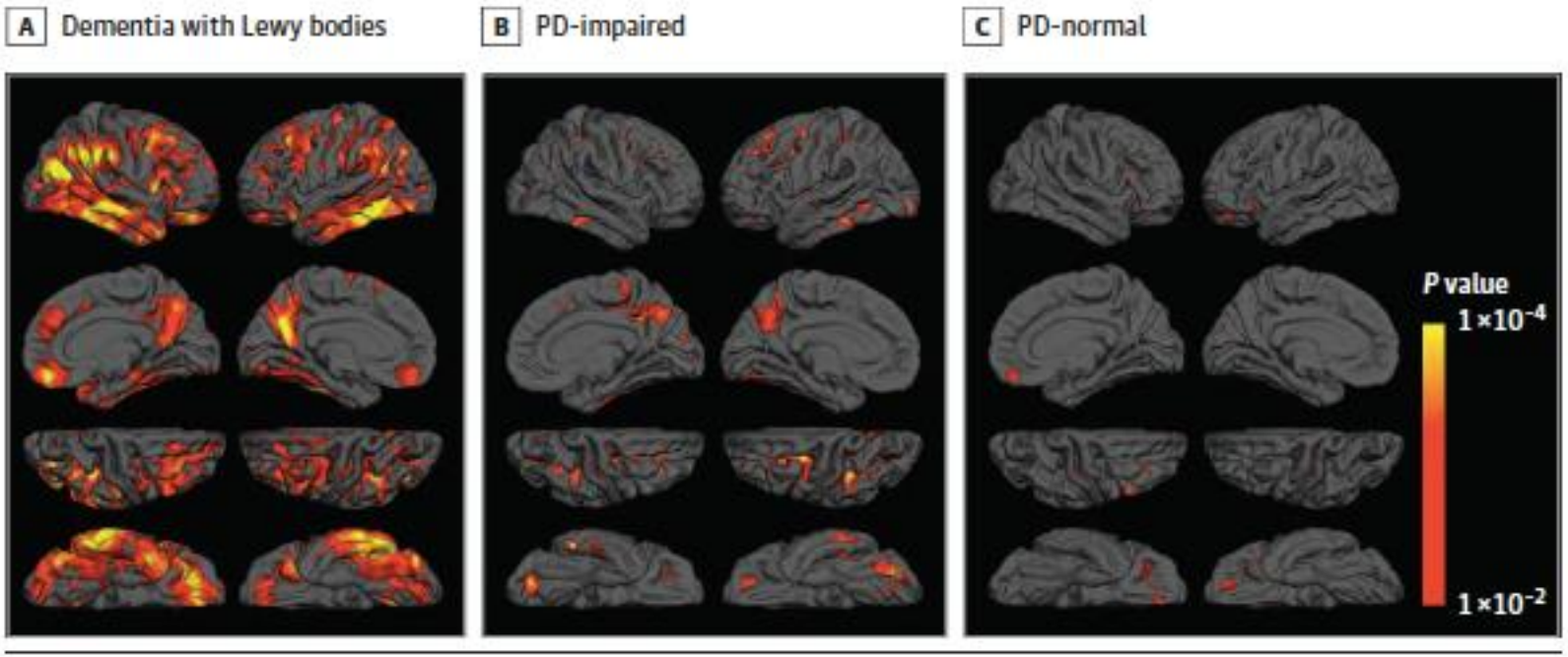


Jagust et al. Brain 2016

JAMA Neurology | Original Investigation

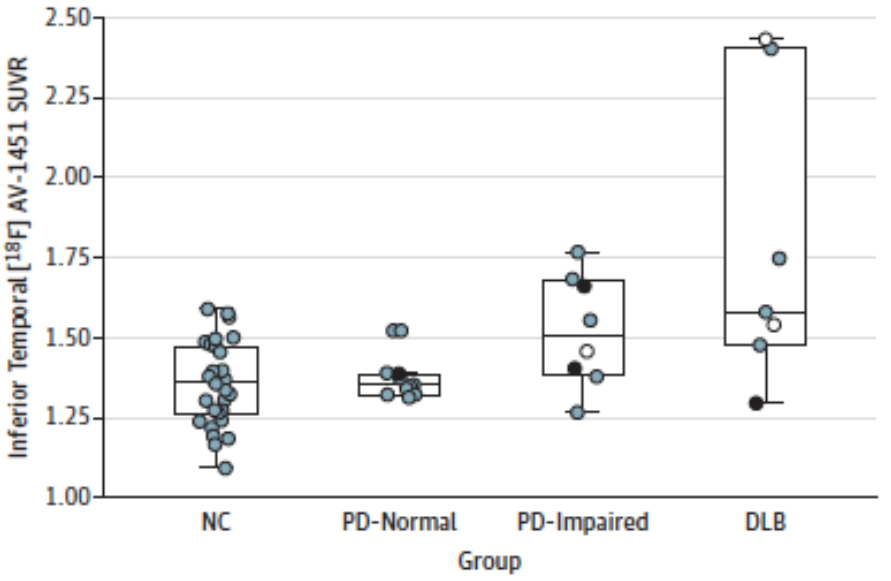
Tau Positron Emission Tomographic Imaging in the Lewy Body Diseases

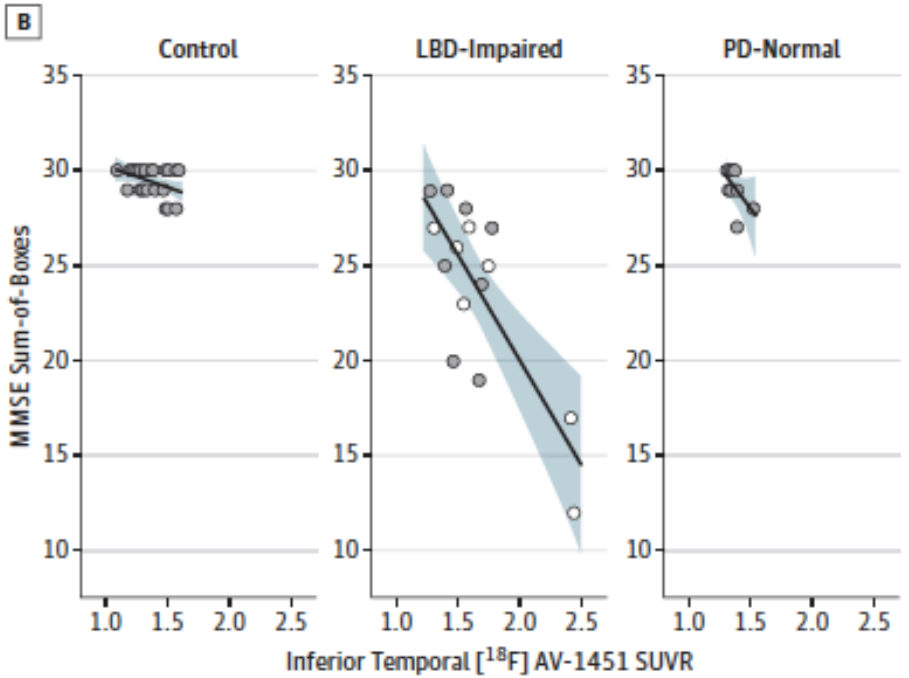
Stephen N. Gomperts, MD, PhD; Joseph J. Locascio, PhD; Sara J. Makaretz, BS; Aaron Schultz, PhD; Christina Caso, BS; Neil Vasdev, PhD; Reisa Sperling, MD; John H. Growdon, MD; Bradford C. Dickerson, MD; Keith Johnson, MD



Gomperts SN et al. JAMA Neurology 2016

Figure 3. Tau Deposition and Its Relation to Amyloid Burden Across the Diagnostic Groups



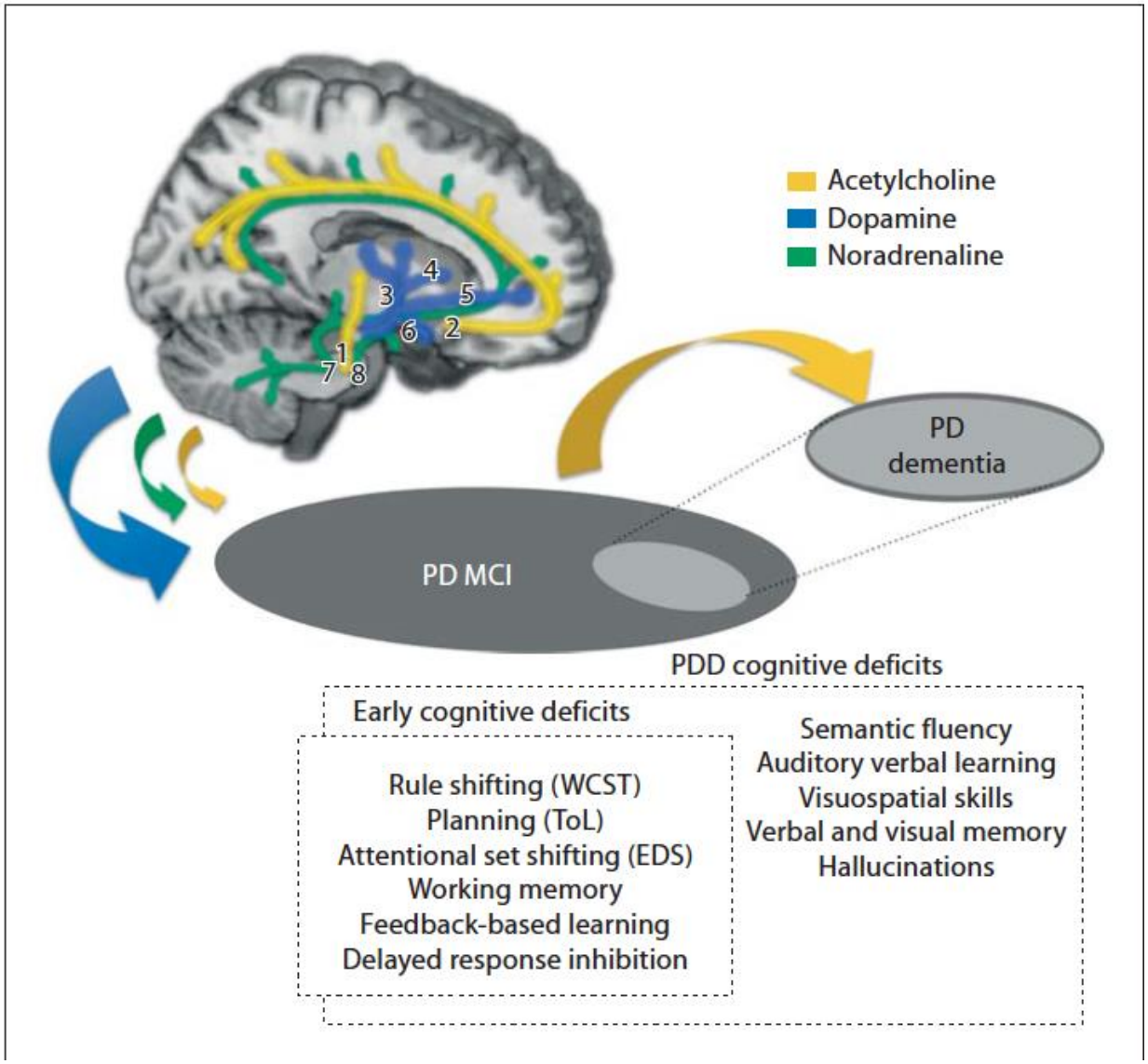


Gomperts SN et al. JAMA Neurology 2016

Cognitive Impairment in Parkinson's Disease: The Dual Syndrome Hypothesis

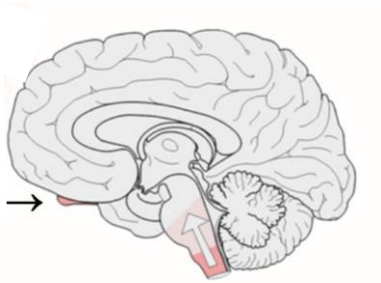
Angie A. Kehagia[a] Roger A. Barker[b] Trevor W. Robbins[c, d]

Neurodegener Dis 2013;11:79–92

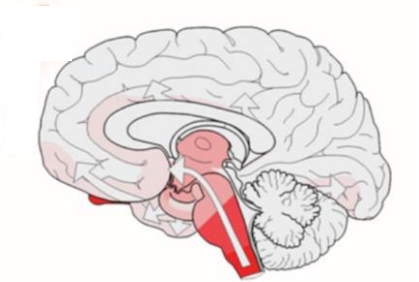


Parkinson's disease

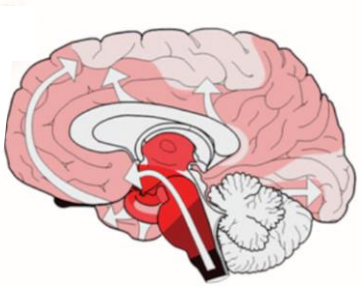
Normal Cognition



Mild Cognitive Impairment



Dementia



Premotor stage

Early stage

Advanced stage