Azienda Ospedaliera - Università di Perugia
Clinica Neurologica - Prof. P. Calabresi

Le neuroimmagini nella malattia di Parkinson e nei parkinsonismi

Nicola Tambasco
Pietro Chiarini

Perugia, 7 dicembre 2016

Outline

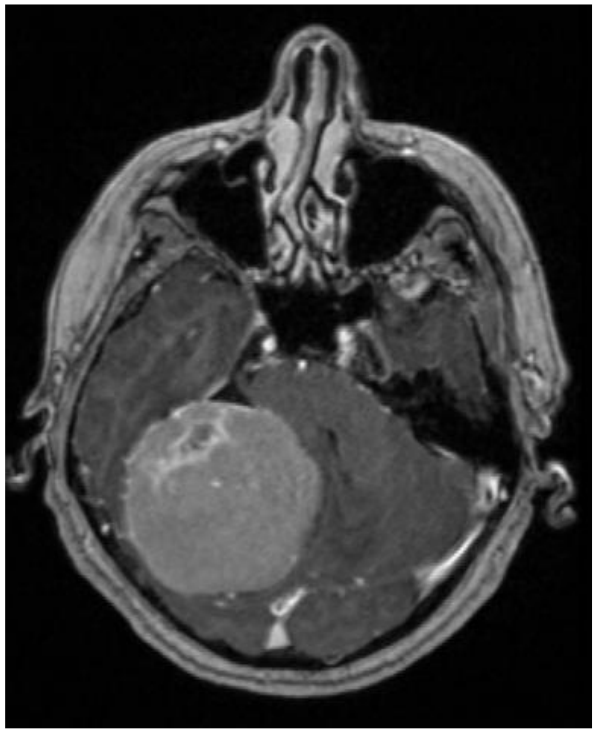
Differential findings across parkinsonisms

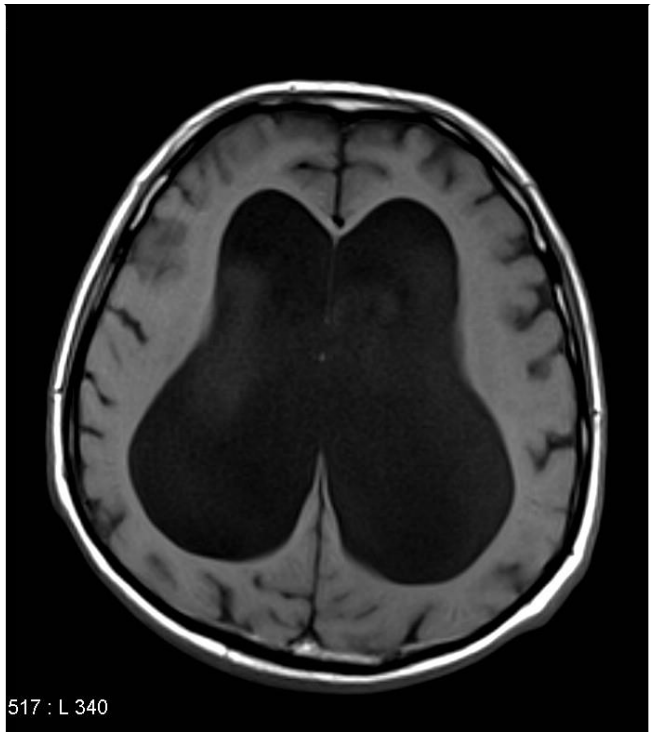
Dopaminergic dysfunction: substantia nigra

Dopaminergic-cholinergic dysfunction: the cognitive impairment

Non – dopaminergic dysfunction: the olfactory system

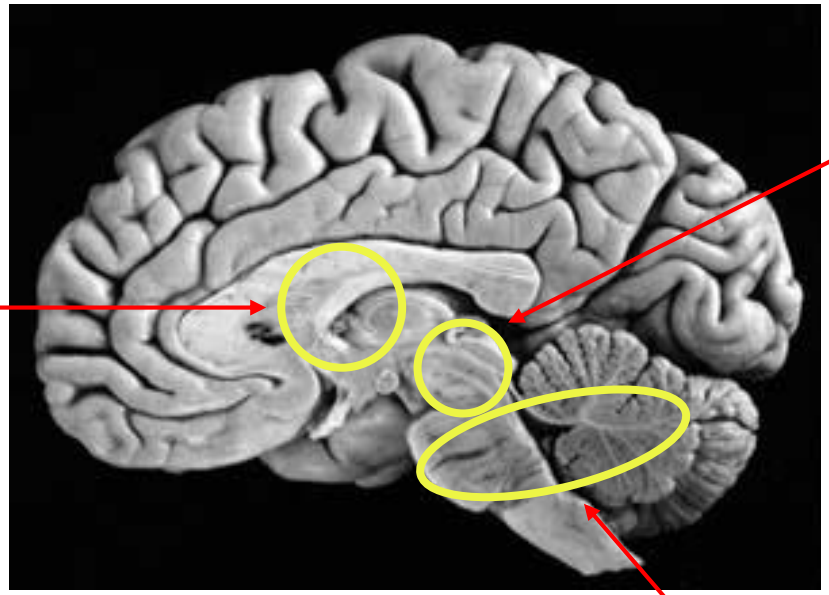
The secondary parkinsonisms

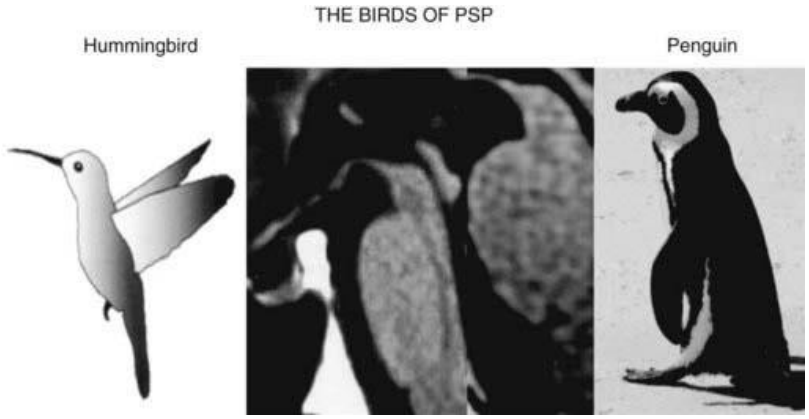




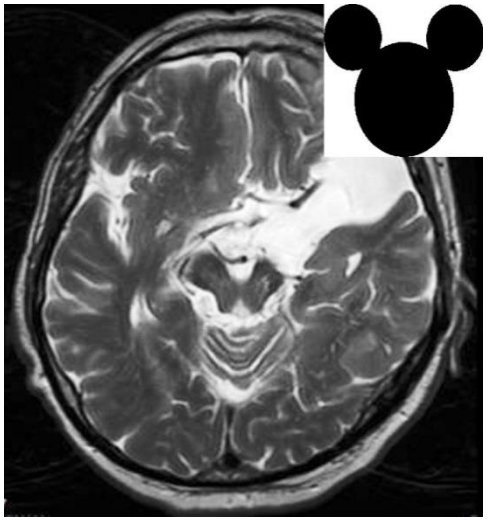
Woitechj L, Park Rel Dis 2012

Conventional MRI

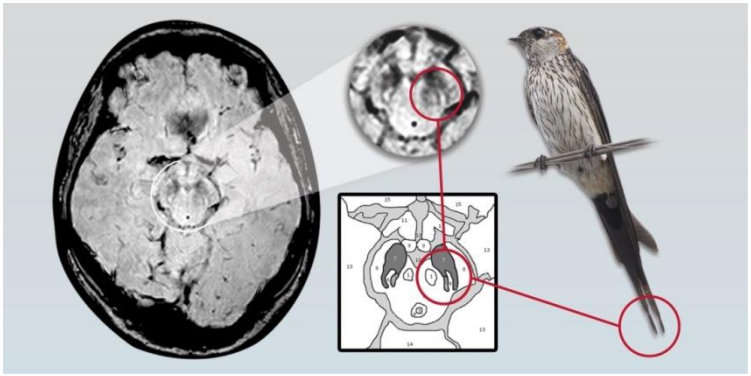


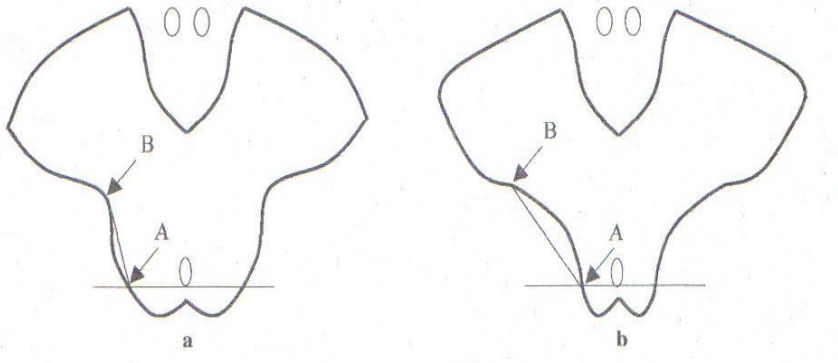


The swallow tail sign



The Morning glory sign



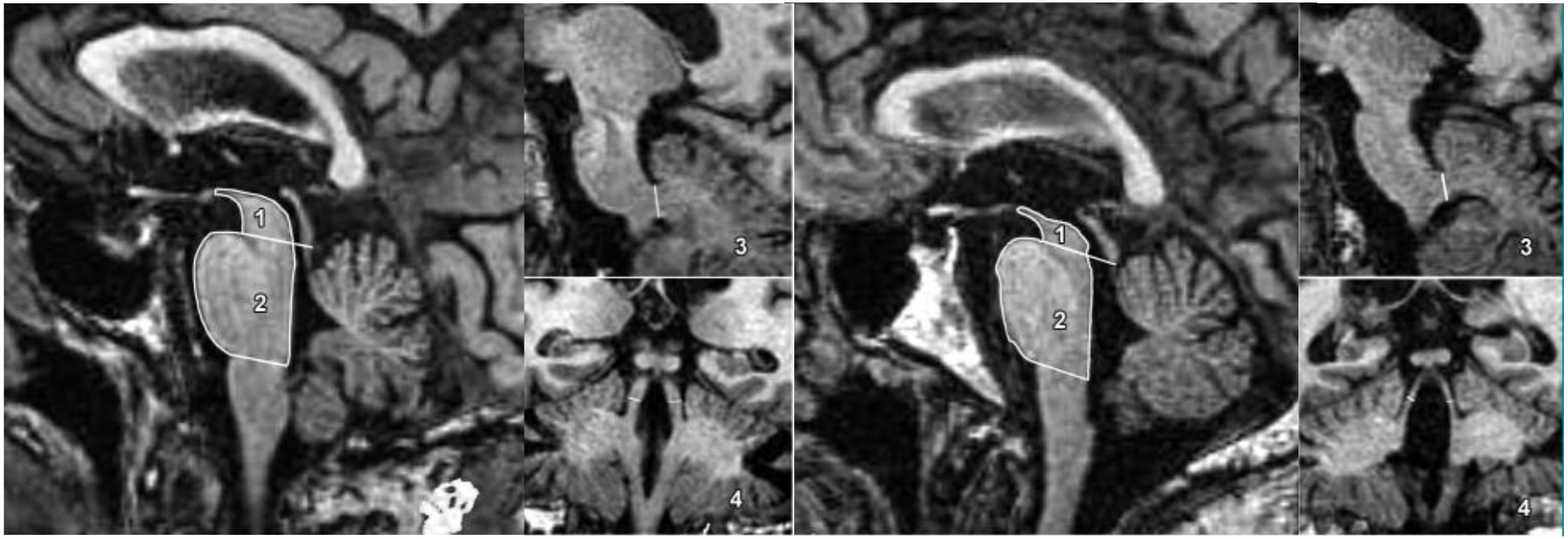


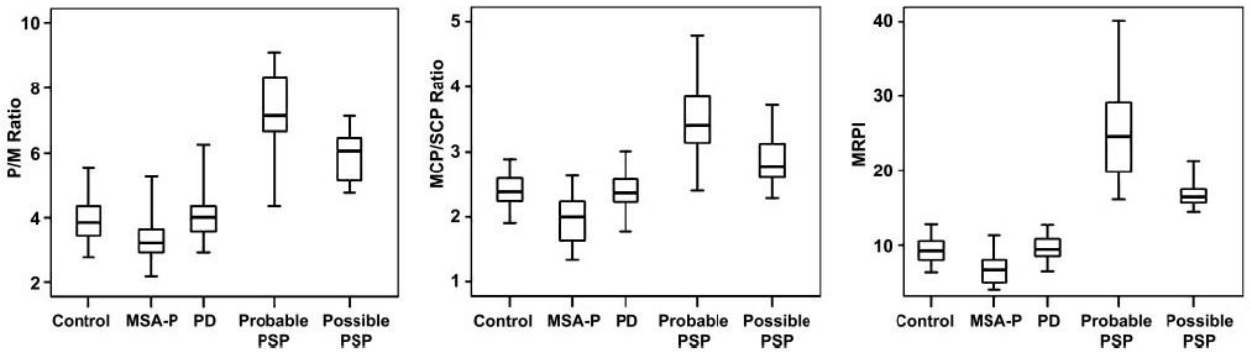
Kato N, Neurol Sci 2003

Oba H, Magn Res Med Sci 2005

Adachi M, Mag Res Imaging Med, 2004

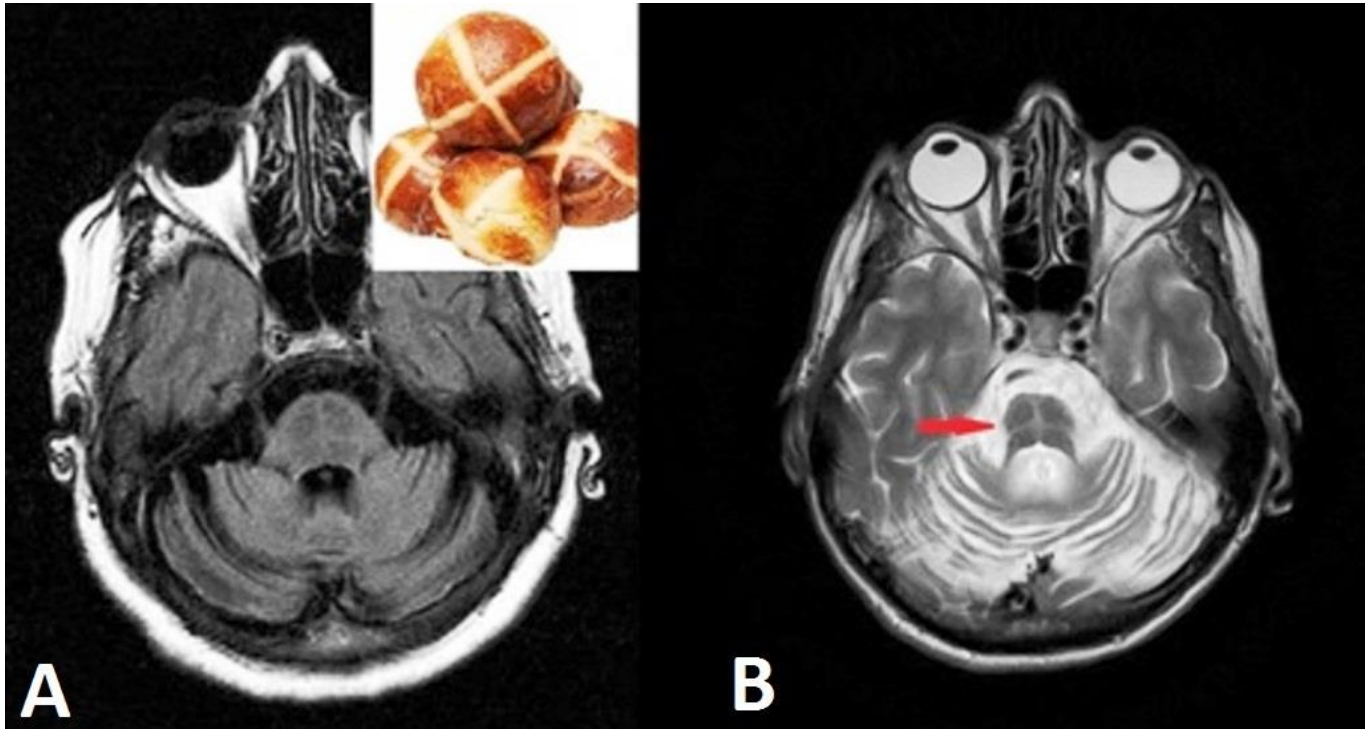
Combined Assessment of Brain Structures



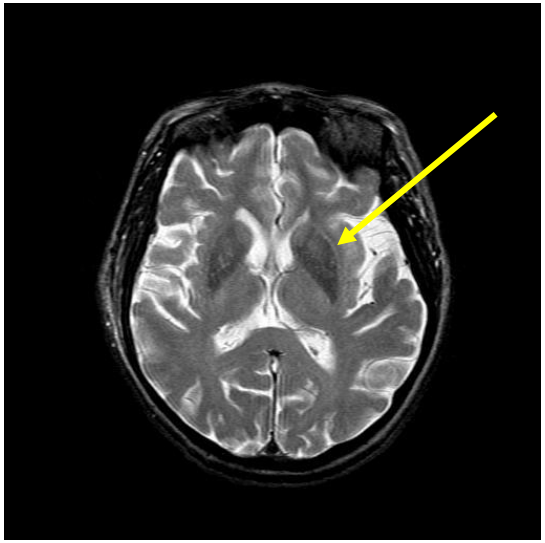


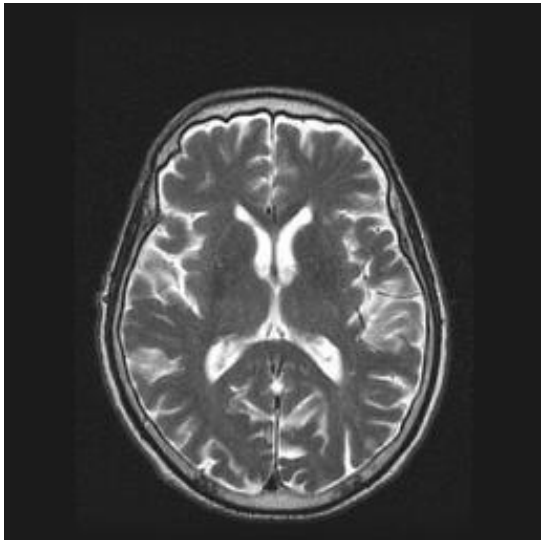
Quattrone A et al, Radiology 2008

The "hot cross bun" sign

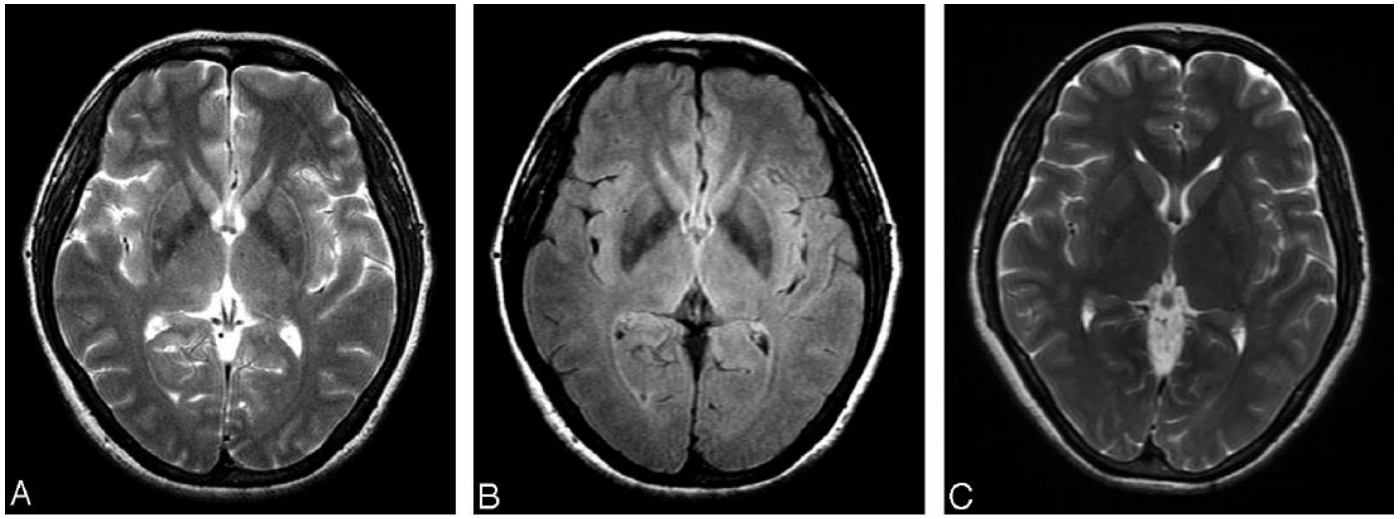


The 'hyperintense Putaminal Rim' Sign





1.5 T



3 T

Lee W-H, AJNR 2005

Movement Disorders
Vol. 24, No. 7, 2009, pp. 949–964

CME

The Dopaminergic System

Review

Proposed Neuroimaging Criteria for the Diagnosis of Multiple System Atrophy

David J. Brooks, MD, Dsc, FRCP[1]* and Klaus Seppi MD[2] for the Neuroimaging Working Group on MSA

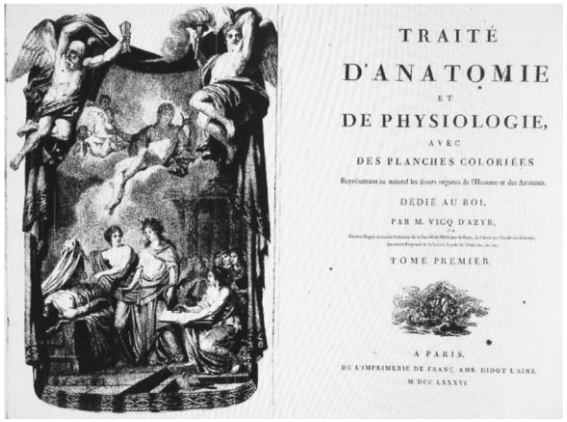
Structural imaging in MSA[a]	
Conventional MRI at 1.5 T	MSA cases may show low putamen, MCP, and brainstem signals and atrophy, and a hyperintense rim on T2 but these features, while supportive (especially versus PD), are not present in all cases and not specific versus other APDs.
MRI-based quantitative assessment of atrophy of different brain structures including MRI-based planimetry and volumetry	Quantitative MR measures of atrophy of different brain structures may help to distinguish MSA from PD (decreased MCP width in MSA; decreased putaminal volume in MSA-P) and PSP (decreased ratio of the area of the midbrain to the area of pons in patients with PSP), but neither of these specific studies have been reproduced.
Diffusion-weighted imaging (DWI)	DWI looks promising for separating atypical from typical PD showing increased diffusivity in the putamen. However, PSP patients can also show increased putaminal diffusivity. The finding of increased diffusivity in the MCP in patients with MSA versus PSP has to be reproduced by others.
Transcranial sonography (TCS)	TCS may be helpful in supporting a diagnosis of MSA as midbrain hyperechogenicity is usually absent, while 90% of PD cases show altered nigral signal. Separation between MSA and PSP patients is suboptimal for both SN and lentiform hyperechogenity. Importantly, at least 10% of the population have a temporal bone window insufficient for an adequate brain parenchyma sonographic analysis.
Functional imaging in MSA	
Presynaptic dopaminergic imaging	Imaging presynaptic dopaminergic function with PET or SPECT reliably separates parkinsonian from nonparkinsonian conditions but does not allow discrimination of MSA from other parkinsonian conditions.
Postsynaptic dopaminergic imaging	MSA cases show reduced putamen dopamine D2 receptor binding, whereas this is normal or elevated in PD. However, the PD and MSA ranges overlap and one-third of MSA cases show normal D2 availability.
FDG PET	FDG PET can be helpful for discriminating typical from atypical PD, particularly when combined with computer-assisted statistical parametric mapping which increases the sensitivity relative to visual analysis from 80 to 95%. MSA cases show striatal, brainstem, and cerebellar hypometabolism while putamen metabolism is elevated and frontotemporal metabolism reduced in PD.
Imaging cardiac sympathetic innervation	Most PD cases show reduced myocardial sympathetic innervation with MIBG SPECT or ^{18}F-dopamine PET, whereas this is not seen in MSA or PSP; however, early PD may show normal cardiac sympathetic innervation and MSA may show reduced cardiac sympathetic innervation.

Brooks DJ and Seppi K, Mov Disord 2009

The Dopaminergic Dysfunction:

Substantia nigra

The Dopaminergic System



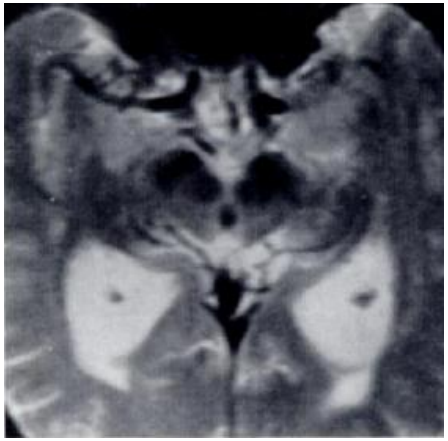
Константин Николаевич Третьяков
1892—1956

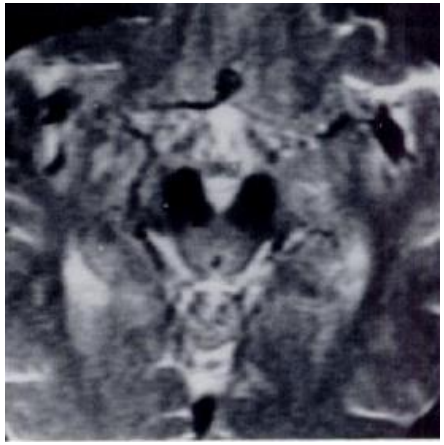
CONTRIBUTION A L'ÉTUDE
DE
l'Anatomie pathologique du Locus Niger
DE SOEMMERING
avec quelques déductions relatives à la pathogénie des troubles
du tonus musculaire
DE LA MALADIE DE PARKINSON

In 1919, Tretiakoff defended his thesis successfully and was awarded his doctorate. His research had involved the examination of the substantia nigra in *54 brains, nine of which had paralysis agitans and three postencephalitic Parkinsonism*. In the six paralysis agitans cases and an additional atypical case he reported *marked loss of the pigmented nigral neurones with swelling of cell bodies, "grumous" degeneration and neurofibrillary alterations.*

In some of the surviving nigral cells he noted inclusion bodies which he called "corps de Lewy" in recognition of Friedrich Lewy's description 7 years earlier of similar inclusions in the dorsal vagal nucleus.

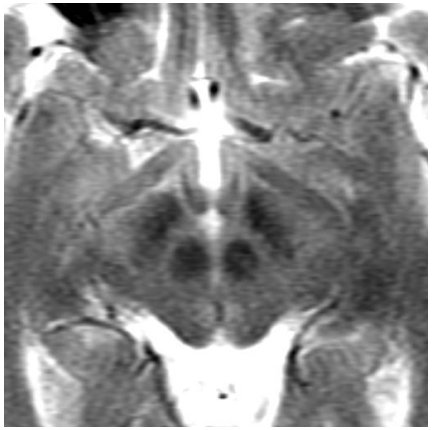
The Dopaminergic System

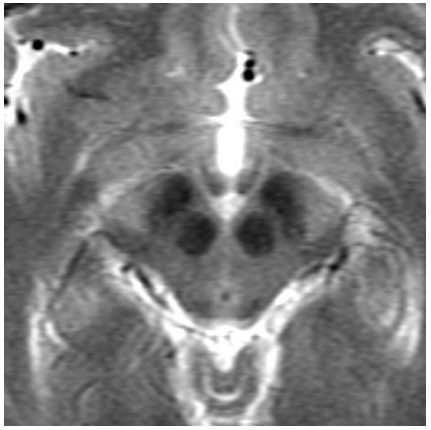


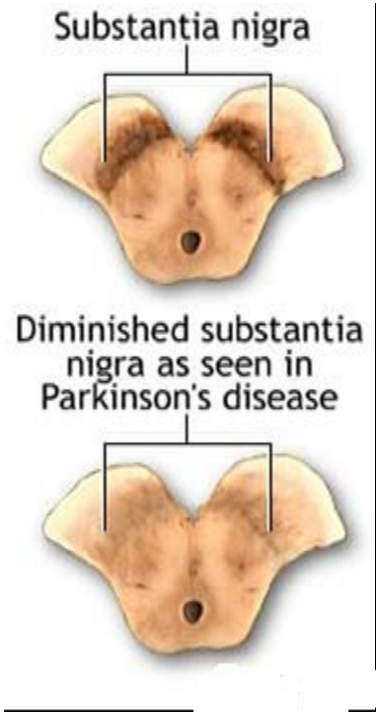


Braffman BH, Grossman RI, Goldberg HI et al. MR imaging of Parkinson disease with spin-echo and gradient-echo sequences. AJR Am J Roentgenol. 1989 Jan;152(1):159-65.

Huber SJ, Chakeres DW, Paulson GW et al. Magnetic resonance imaging in Parkinson's disease. Arch Neurol 1990;47:735-737







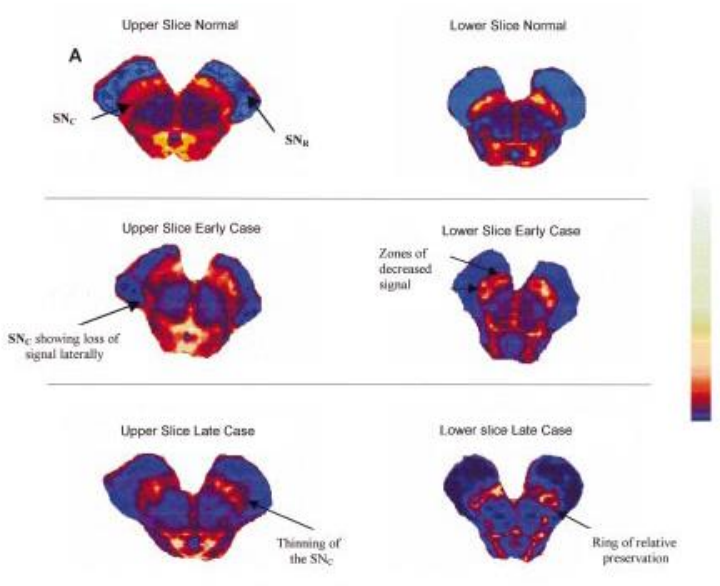
The Dopaminergic System

J Neurol Neurosurg Psychiatry 1999;67:815–818

SHORT REPORT

Parkinson's disease: a novel MRI method for determining structural changes in the substantia nigra

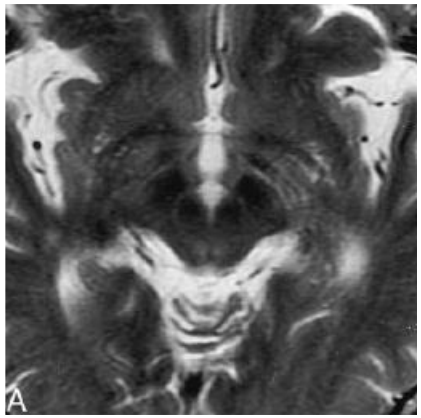
Michael Hutchinson, Ulrich Raff

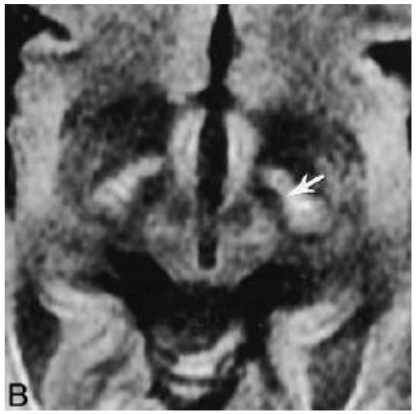


AJNR Am J Neuroradiol 20:1500–1506, September 1999

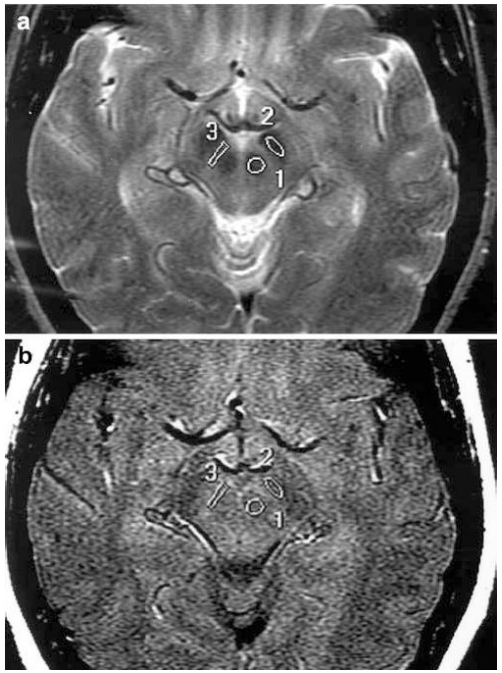
Evaluation of the Substantia Nigra in Patients with Parkinsonian Syndrome Accomplished Using Multishot Diffusion-Weighted MR Imaging

Michito Adachi, Takaaki Hosoya, Tamami Haku, Koichi Yamaguchi, and Toru Kawanami





The Dopaminergic System



Box plot of SNc values

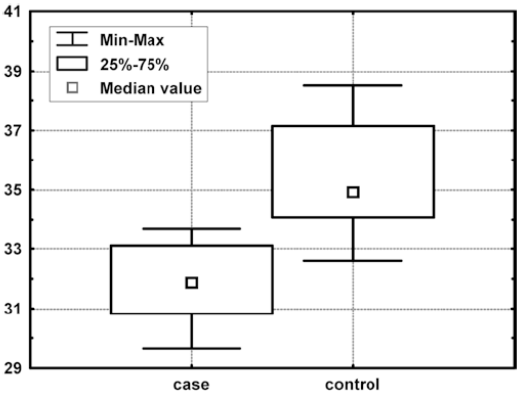


Table 1
Mean MTR Values and *P* Values of Both Groups

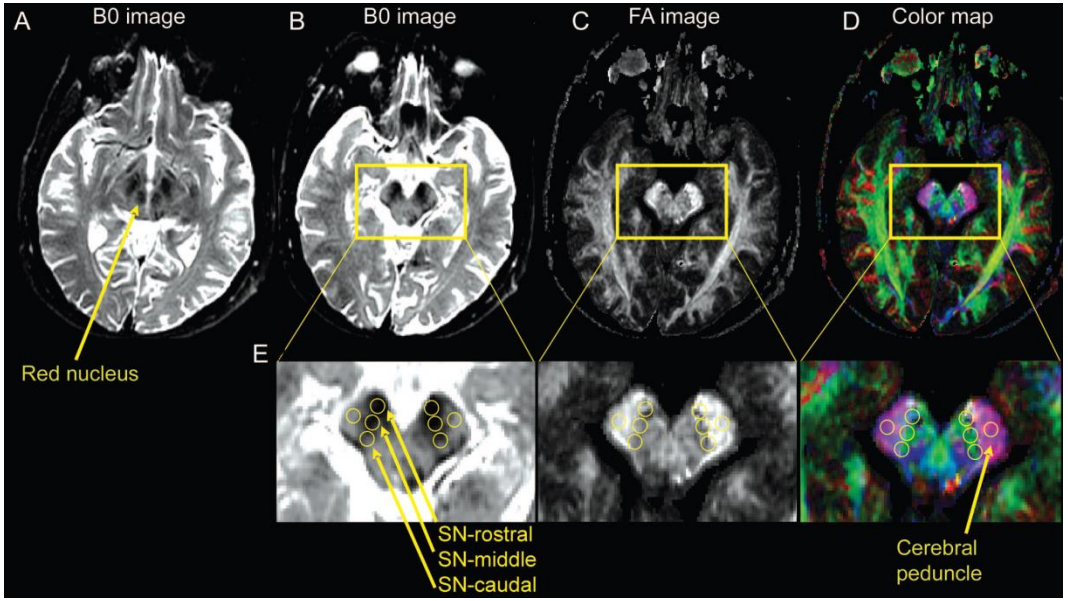
Anatomic Location	Mean MTR		*P* value
	PD Group	Control Group	
SNPC	0.342	0.364	<0.001
SNPR	0.354	0.374	0.006
Red nucleus	0.350	0.362	0.037
Dentate nucleus	0.391	0.395	0.170
Cerebellum	0.339	0.341	0.847
Pons	0.368	0.380	0.046
Globus pallidus	0.393	0.394	0.880
Putamen	0.370	0.379	0.278
Caudat nucleus	0.341	0.351	0.165
Thalamus	0.362	0.365	0.643
Internal capsule posterior horn	0.379	0.380	0.821
Forceps major	0.368	0.375	0.304
Forceps minor	0.374	0.383	0.143
Corpus callosum, genu	0.376	0.391	0.146
Corpus callosum, splenium	0.385	0.394	0.328

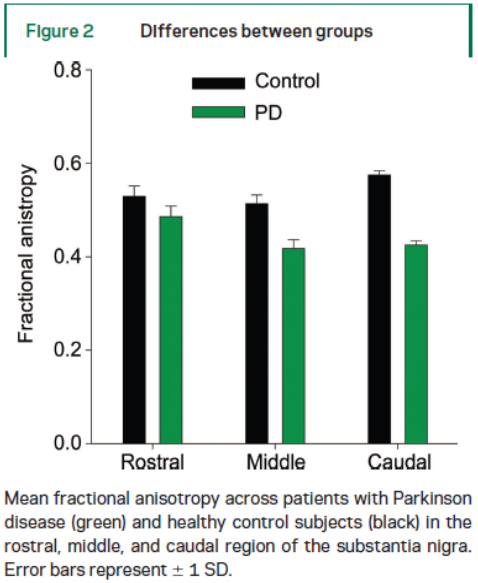
MTR: magnetization transfer ratio; PD: Parkinson disease; SNPC: substantia nigra pars compacta; SNPR: substantia nigra pars reticulate.

Tambasco N et al, Neuroradiology 2003

Anik Y et al, Acad Radiol 2007

The Dopaminergic System





Mean fractional anisotropy across patients with Parkinson disease (green) and healthy control subjects (black) in the rostral, middle, and caudal region of the substantia nigra. Error bars represent ± 1 SD.

The FA values were reduced in the SN of early stage, unmedicated patients with PD.

The difference between de novo patients with PD and healthy control subjects was greatest in the caudal ROI of the SN compared with the middle and rostral SN ROI.

All de novo patients with PD were distinguished from all healthy individuals with 100% sensitivity and specificity.

DTI assessment therefore detected not only group differences, but also accurate individual assignment.

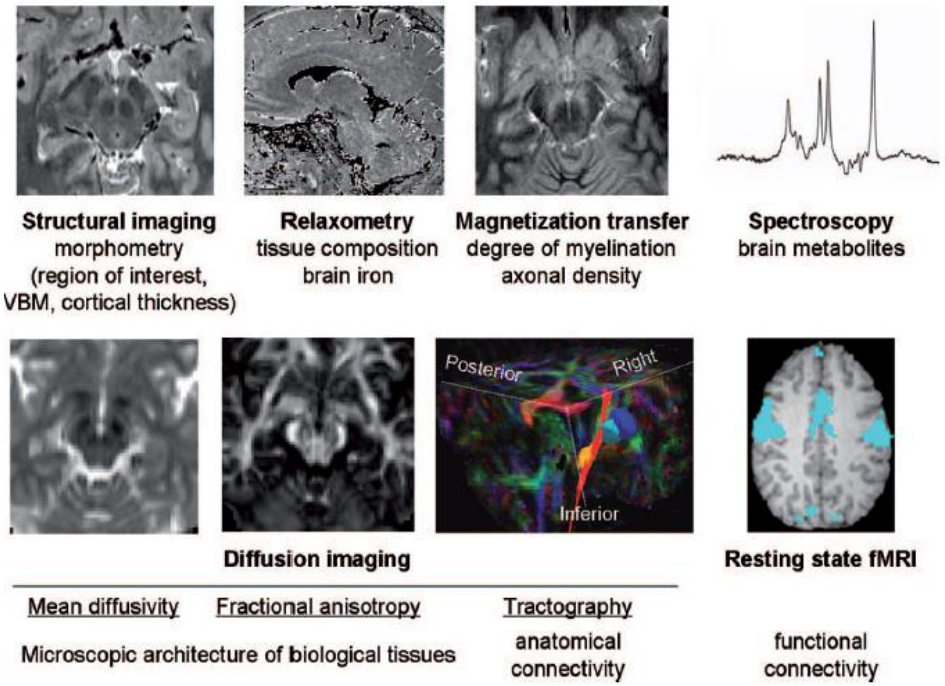
Vaillancourt DE et al, Neurology 2009

The Dopaminergic System

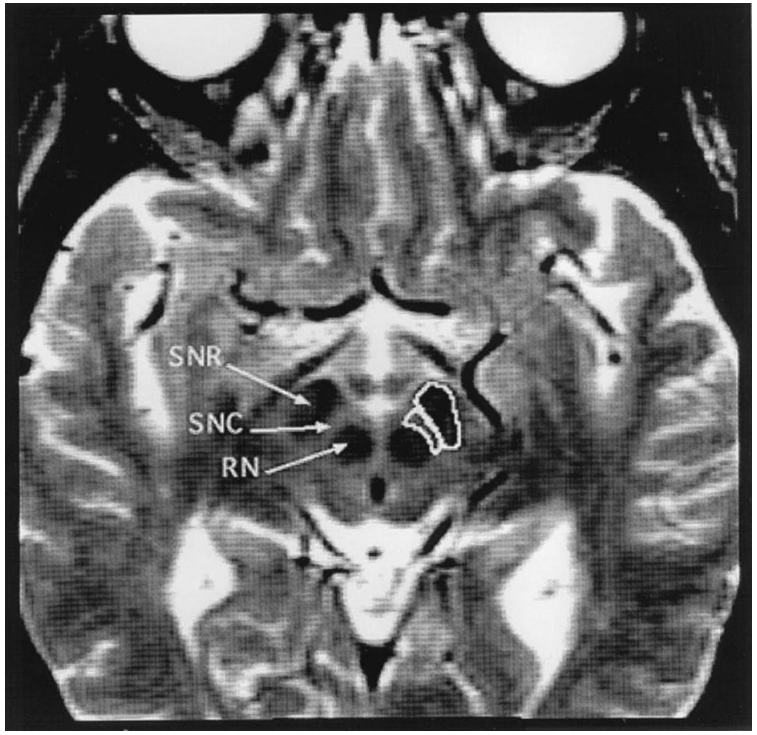
REVIEW

Magnetic Resonance Imaging of the Substantia Nigra in Parkinson's Disease

Stéphane Lehéricy, MD, PhD,[1,2,3,4,5]* Michael A. Sharman, MD,[1,2,3,4,5] Clarisse Longo Dos Santos, PhD,[1,2,3,4,5,6] Raphaël Paquin, PhD,[1,2,3,4,5] and Cecile Gallea, PhD[1,2,3,4,5]



Overview of the techniques and their respective contribution in substantia nigra imaging.



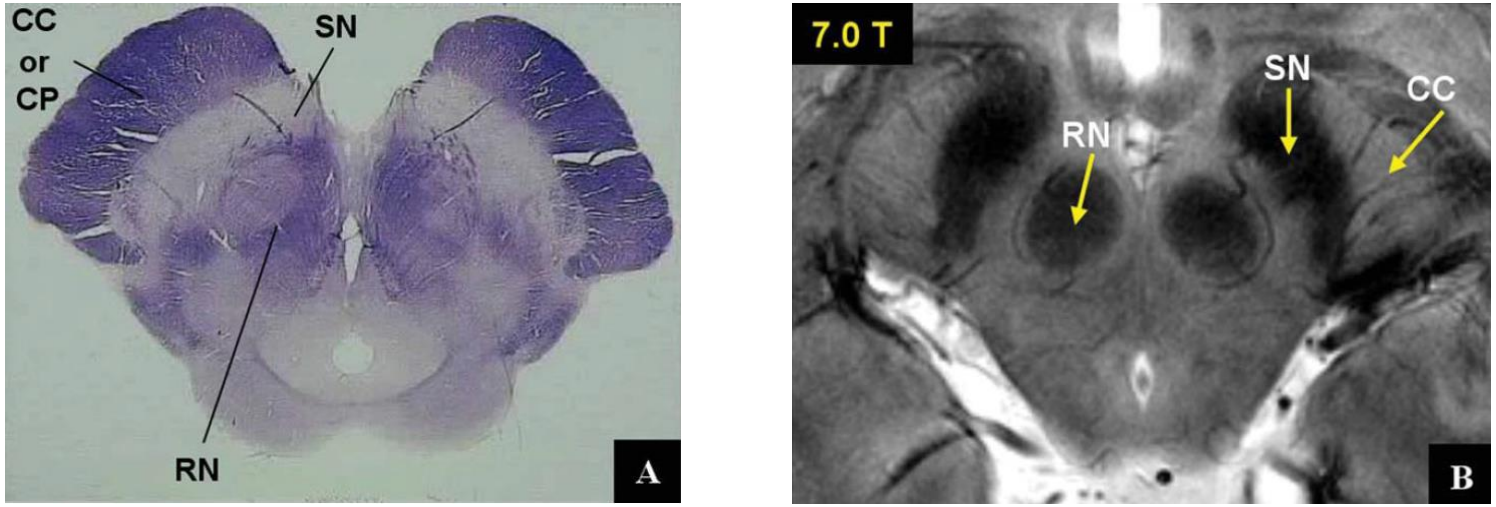
0.5 T and 1.5 T

FDRI

Field dependent R2 increase (FDRI) which is the difference between the R2 measured with the two MRI instruments

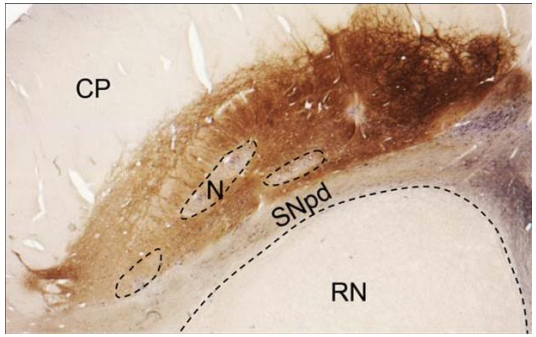
Bartzokis G et al, Magn Res Im 1999

7T magnetic resonance image

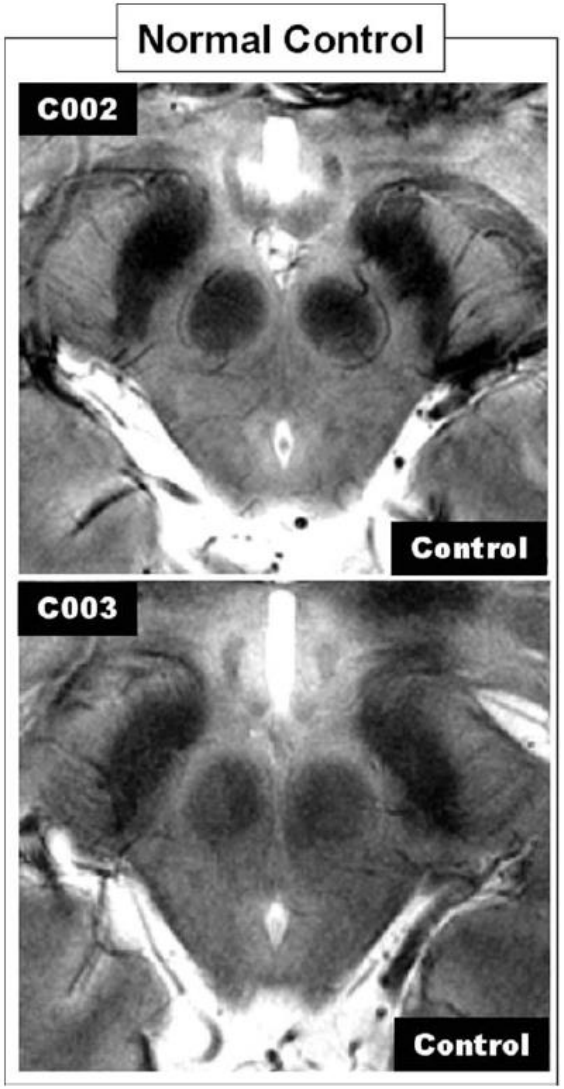


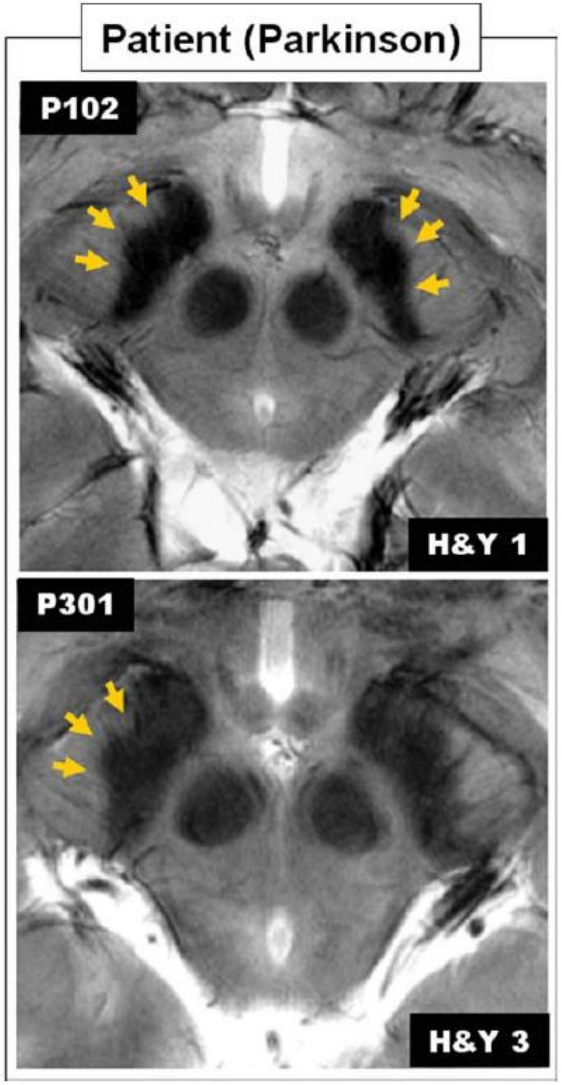
MR images of the midbrain areas in a young normal healthy subject obtained using 7.0T MRI

Cho Z-H et al, Mov Disord 2011



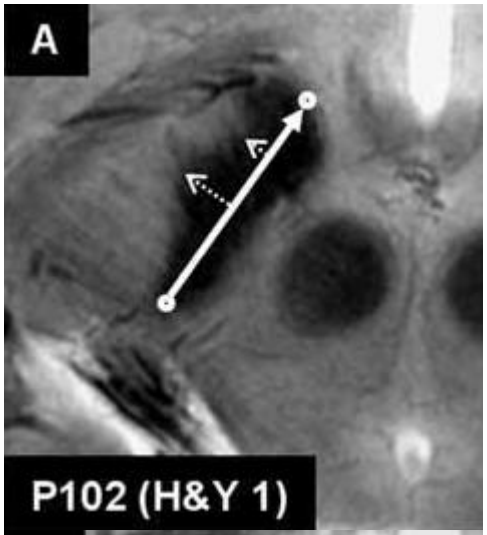
Lehericy S et al, Mov Disord 2014

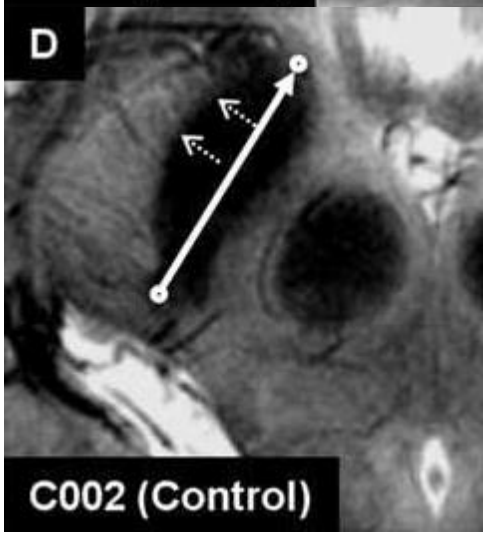


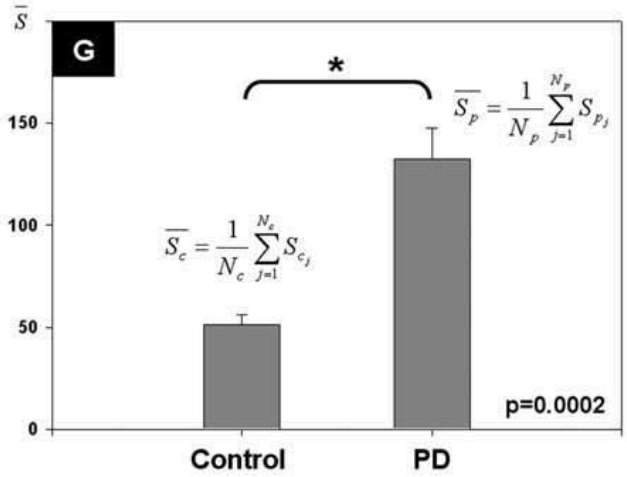


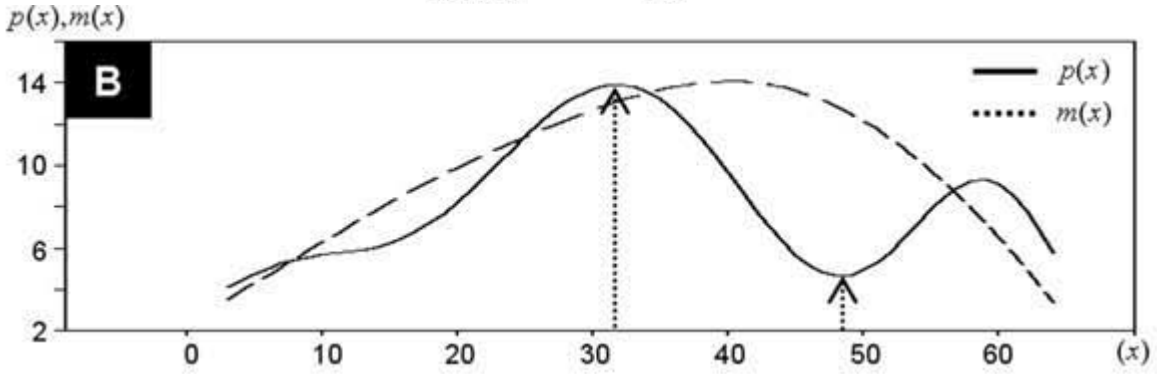
These results suggest that, by using 7.0T MRI, it appears possible to use these visible and distinctive changes in morphology as a diagnostic marker of PD

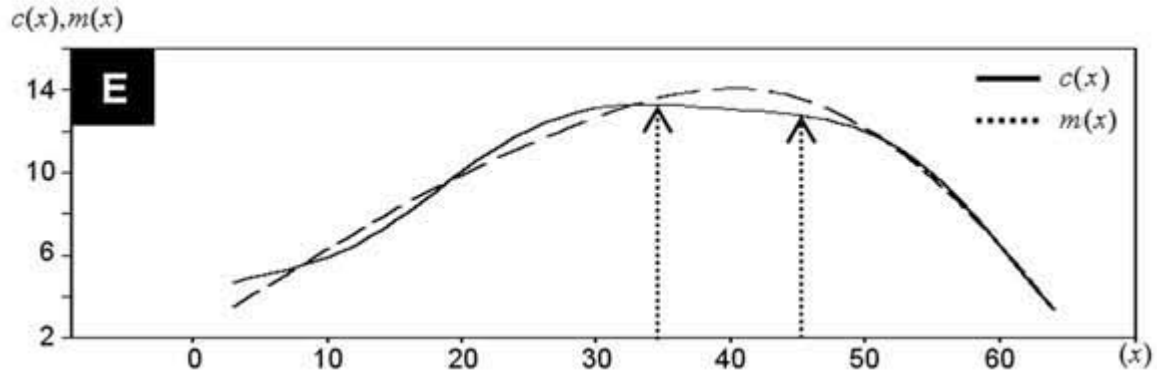
Cho Z-H et al, Mov Disord 2011





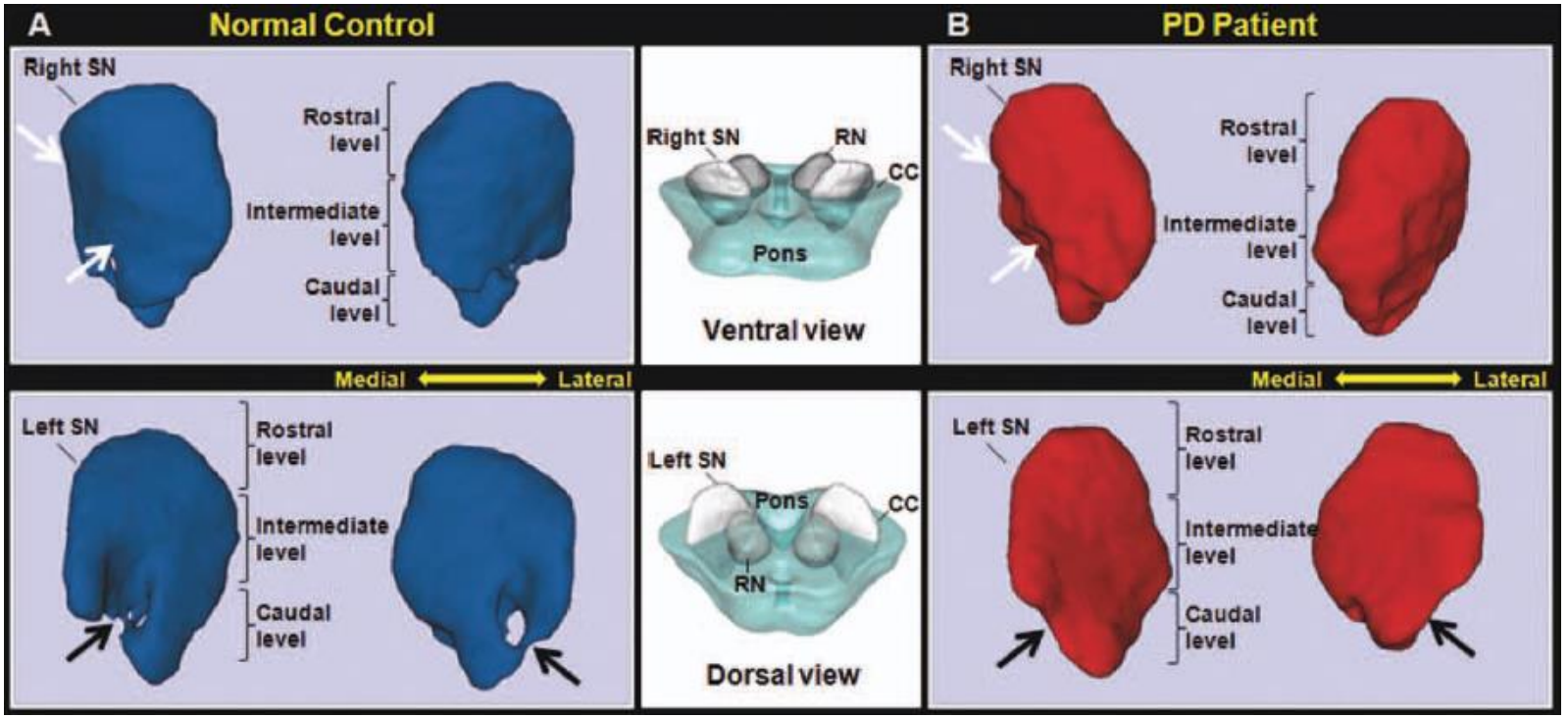






Cho Z-H et al, Mov Disord 2011

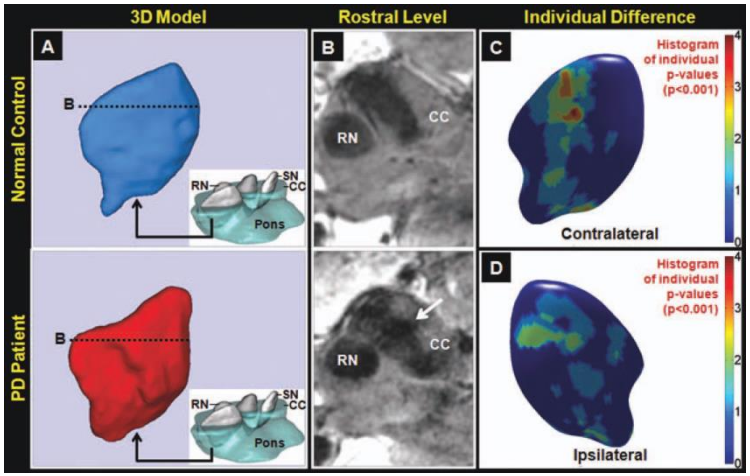
3D 7T magnetic resonance (MR) images

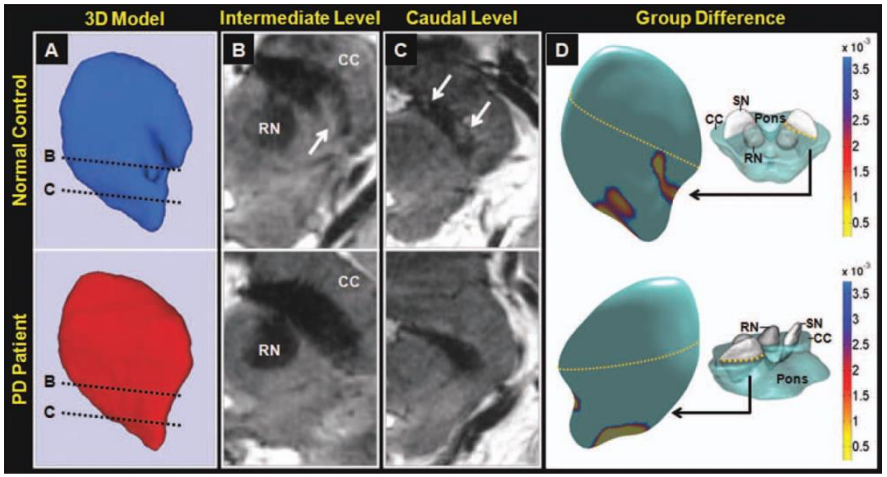


Three-dimensional (3D) models reconstructed from the regions of interest (ROIs). ROI-based 3D models are seen in the ventral and dorsal positions of 2 subjects (control, C06; Parkinson disease [PD], P08). From the ventral view, the lateral aspect of the substantia nigra (SN) in PD (B, upper part) shows an undulating surface compared to that in the normal control (white arrows). Differences in the intermediate and caudal levels between A and B are indicated with black arrows. The entire SN was divided along its longitudinal axis into 3 parts on the basis of the shape differences between control and PD subjects: rostral, intermediate, and caudal levels. CC 5 crus cerebri; RN 5 red nucleus.

Kwon DH et al, Ann Neurol 2012

3D 7T magnetic resonance (MR) images





Kwon DH et al, Ann Neurol 2012

The Dopaminergic System

Dopamine terminal function in the synucleinopathies, PD, DLB, and MSA, can be examined in vivo with both PET and SPECT

presynaptic dopamine transporters (DATs)

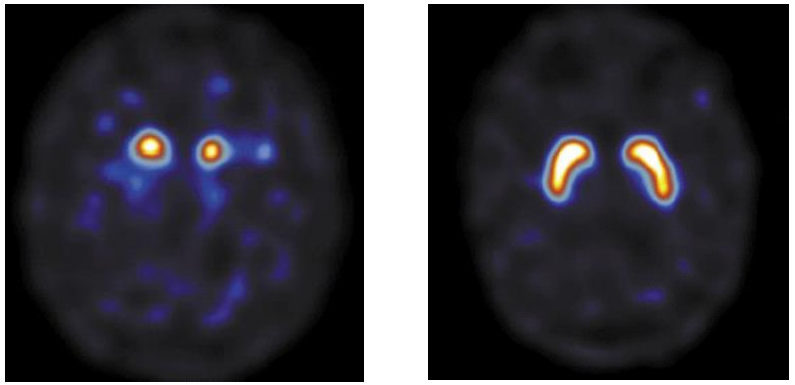
18F-CFT
123I-FP-CIT (DaTscan),
18F-FP-CIT
123I-beta-CIT
123I-altropane
99mTc-TRODAT,
11Cmethylphenidate
11C-nomifensine

aromatic acid decarboxylase (AADC)

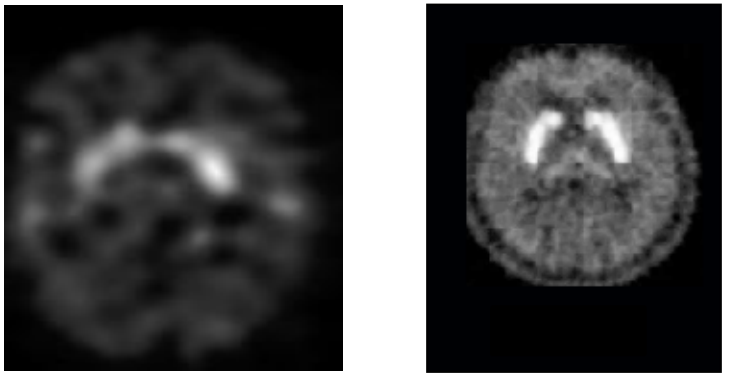
18F-dopa PET

vesicle monoamine transporter

11C-DTBZ
18F-DTBZ



DaTSCAN



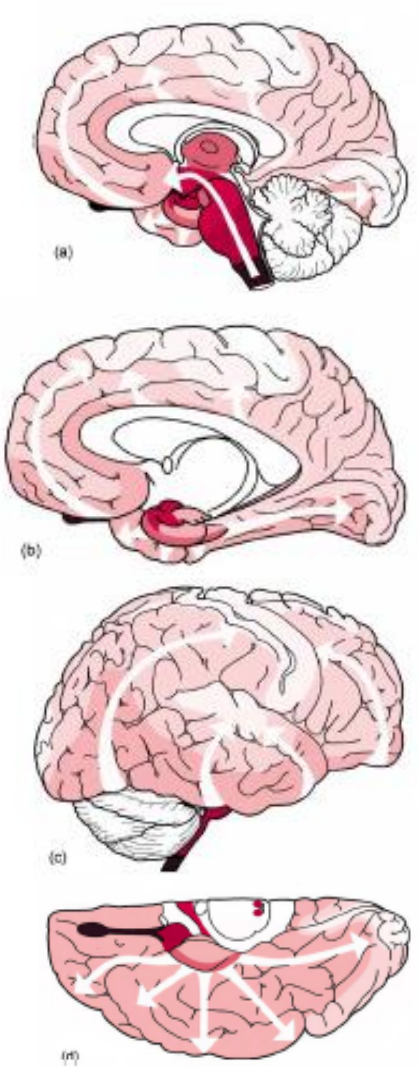
IBZM

D-DOPA

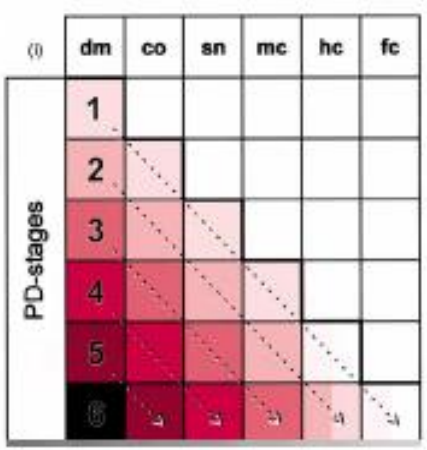
Dopaminergic-cholinergic dysfunction:

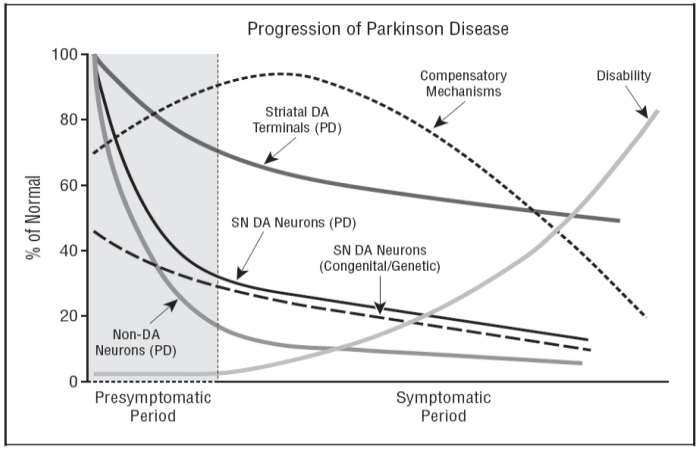
The cognitive impairment

Following Synucleinopathy Progression



Braak' stages

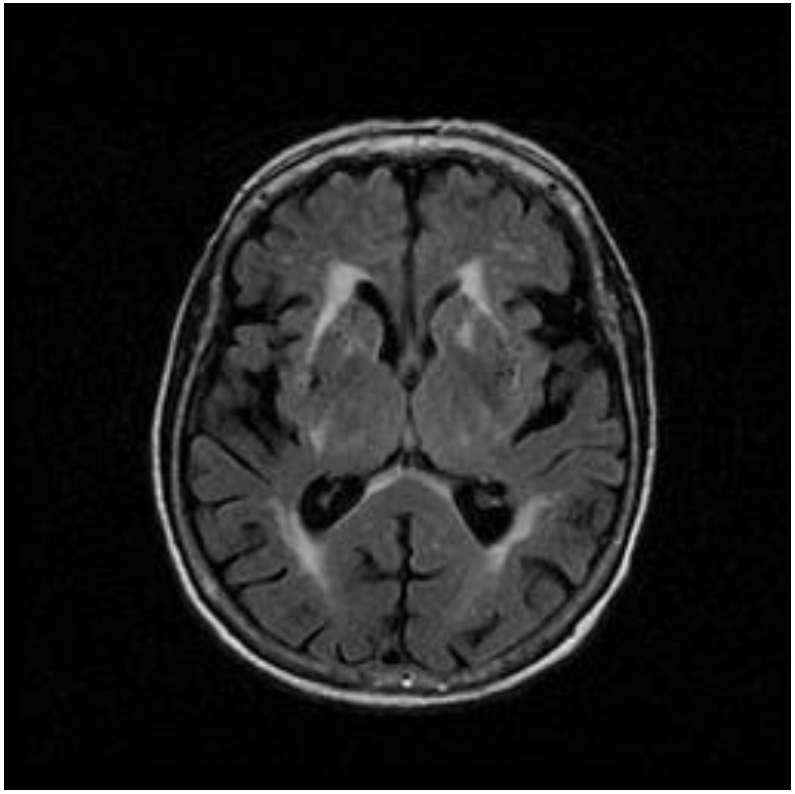




….. the key lesions in PD begin developing—as in other neurodegenerative diseases—a considerable time prior to the appearance of somato-motor dysfunctions.

The vulnerable nerve cell types most likely vary in their proclivities to undergo the pathological changes and, as such, become involved at different times in the course of the disease.

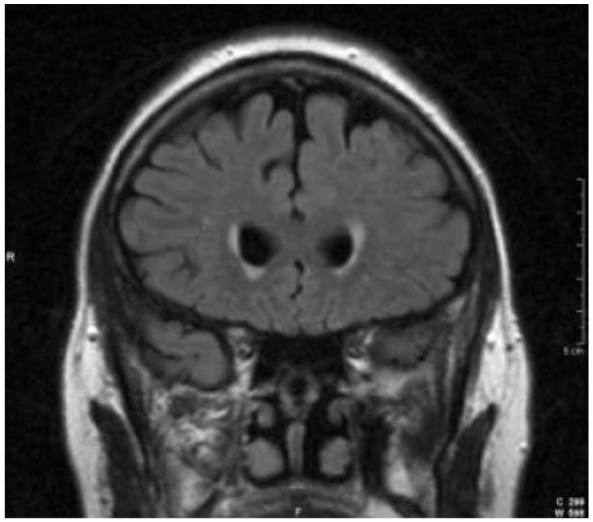
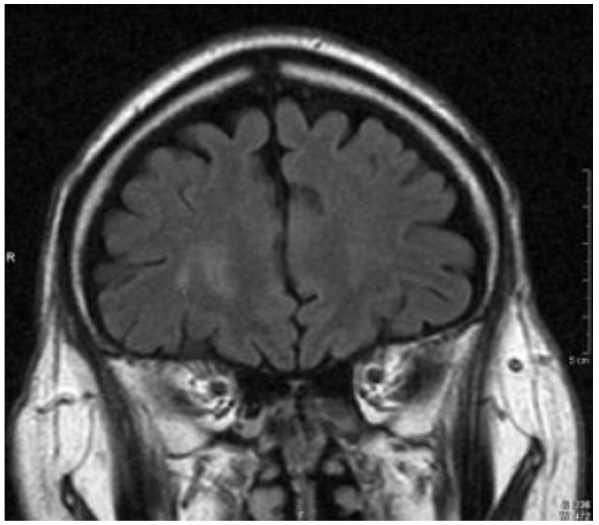
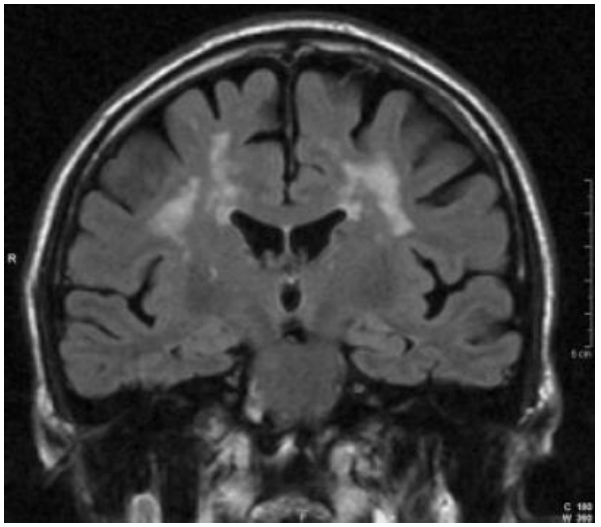
Mechanisms of Dementia in parkinsonisms



"… periventricular hyperintensities may represent a marker for a subclinical type of PD characterized by a more rapid neurodegenerative disease."

Piccini P et al, Arch Neurol 1995

Mechanisms of Dementia in parkinsonisms

White matter hyperintensities in the deep white matter may contribute to dementia in PD.

Score 0 = no abnormalities
Score 1 = lesions less than 3 mm, ≤ 5 lesions
Score 2 = lesions < 3 mm, more than 6 lesions
Score 3 = lesions 4 to 10 mm, ≤ 5 lesions
Score 4 = same as 3, but > 6 lesions
Score 5 = lesions > 11mm, > 1 lesion
Score 6 = confluent lesions

Scheltens P, J Neurol Sci 1993

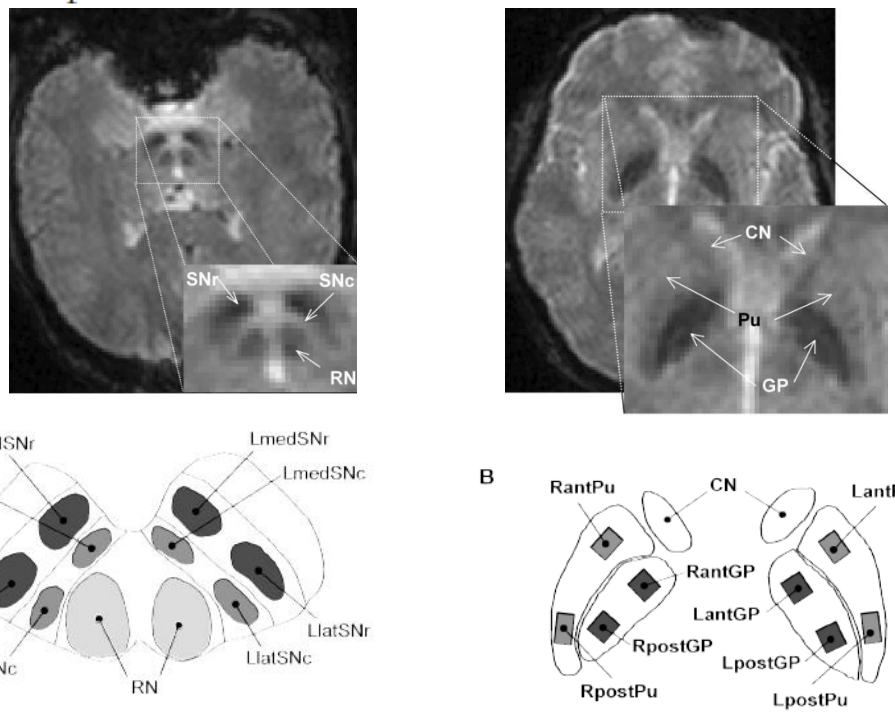
Area	PDND (n = 19)	PDD (n = 16)	Control (n = 20)	*P*
Frontal				
With lesions, n (%)	13 (68)	16 (100)	18 (90)	0.05[d]
Score, mean (SD)[a]	1.6 (1.6)	3.4 (2.0)	2.9 (1.8)	
Temporal				
With lesions, n (%)	0	1 (6)	1 (5)	NS
Score, mean (SD)[a]	—	0.1 (0.25)	0.1 (0.2)	
Parietal				
With lesions, n (%)	15 (79)	14 (87.5)	14 (70)	NS
Score, mean (SD)[a]	1.6 (1.8)	3.3 (2.4)	2.6 (2.3)	
Occipital				
With lesions, n (%)	0	1 (6.25)	0	NS
Score, mean (SD)[a]	—	0.4 (1.5)	—	
Total score, deep white matter				
With lesions, n (%)	17 (89.5)	16 (100)	18 (90.0)	<0.05[e]
Score, mean (SD)[b]	3.3 (2.5)	7.1 (5.0)	5.5 (3.9)	
Basal ganglia				
With lesions, n (%)	4 (21.0)	6 (37.5)	6 (30.0)	NS
Score, mean (SD)[c]	0.9 (2.0)	1.2 (1.8)	1.2 (2.3)	
Periventricular				
With lesions, n (%)	19 (100)	16 (100)	20 (100)	<0.05[f]
Score, mean (SD)[a]	3.0 (1.0)	3.9 (1.4)	3.3 (1.1)	
Infratentorial				
With lesions, n (%)	1 (5.3)	3 (18.8)	3 (15)	NS
Score, mean (SD)[b]	0.3 (1.1)	0.5 (1.2)	0.4 (1.4)	

Beyer MK et al, *Mov Disord* 2006

Mechanisms of Dementia in parkinsonisms

Midbrain iron content in early Parkinson disease

A potential biomarker of disease status



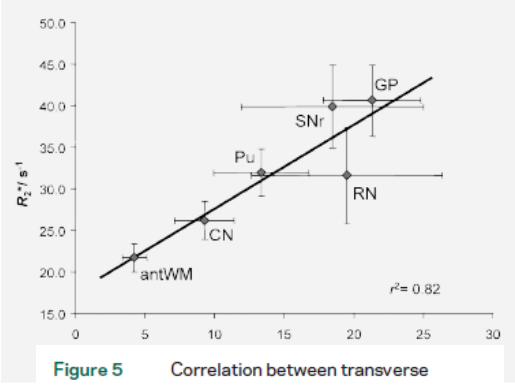
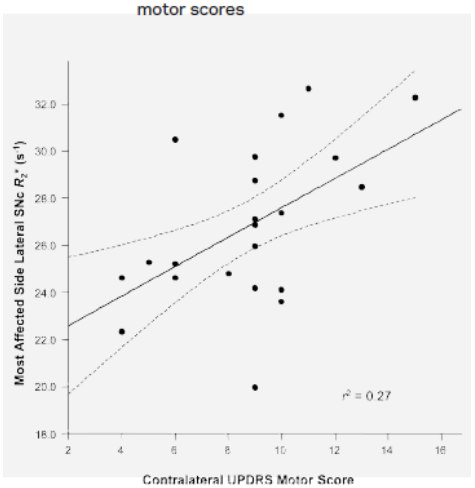


Figure 5 Correlation between transverse relaxation rate (R_2^*) values for the lateral substantia nigra pars compacta (SNc) from the most affected brain side and the contralateral Unified Parkinson's Disease Rating Scale (UPDRS) motor scores



High field strength MRI demonstrates lateral substantia nigra pars compacta abnormalities in early Parkinson disease (PD) consistent with **increased iron content** and corresponding to the known distribution of neuronal loss occurring in this disorder.

Martin WWR et al, Neurology 2008

Mechanisms of Dementia in parkinsonisms

There is evidence that brain iron and other metals are quantitatively different in PD and atypical parkinsonian disorders

Table 2 SWI hypointensity scores (mean ± SD) of the subject groups.

Subject group	Putamen (mean ± SD)	Red nucleus (mean ± SD)	Substantia nigra (mean ± SD)	Dentate nucleus (mean ± SD)
Controls	0.82±0.75	0.64±0.67*	0.64±0.67**	0.64±0.67
PD	0.45±0.69***	0.45±0.82****	0.36±0.81*****	0.73±0.79
MSA-P	0.92±1.08	0.75±0.97******	1±0.95*******	1.42±0.99
PSP	1.75±1.06	1.92±0.99	1.33±1.07	1.50±1

After adjusting the scores for age differences between the groups, significant p values were as follows: *p=0.006 vs. PSP; **p=0.001 vs. PSP; ***p=0.003 vs. PSP; ****p=0.001 vs. PSP; *****p=0.006 vs. PSP; ******p=0.001 vs. PSP; *******p=0.004 vs. PSP

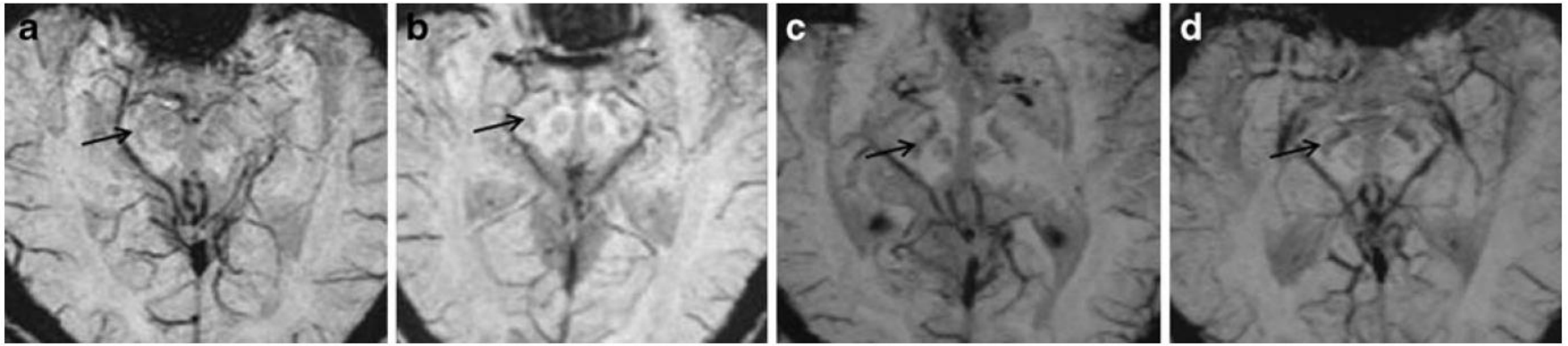


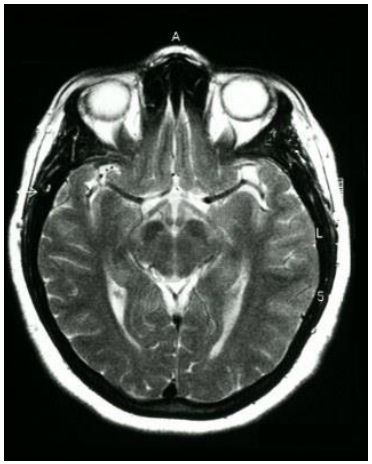
Fig. 3 Increasing grades of substantia nigra (indicated by *black arrow*) hypointensity in SWI: **a** grade 0, **b** grade 1, **c** grade 2, **d** grade 3

SWI shows different patterns of brain mineralization in clinically diagnosed groups of PD, PSP, and MSA-P and may be considered as an additional MR protocol to help differentiate these conditions.

Gupta D, Neuroradiology 2010

Mechanisms of Dementia in parkinsonisms

Susceptibility-Weighted Imaging technique



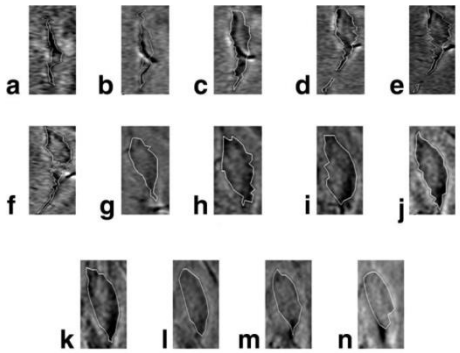
pre e post-processing

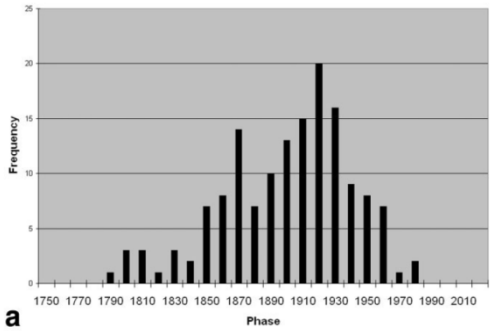
Selezione sequenze

Selezione ROIs

Analisi valori

$$\varphi(phase) = -\gamma \Delta B T_E$$





Mechanisms of Dementia in parkinsonisms

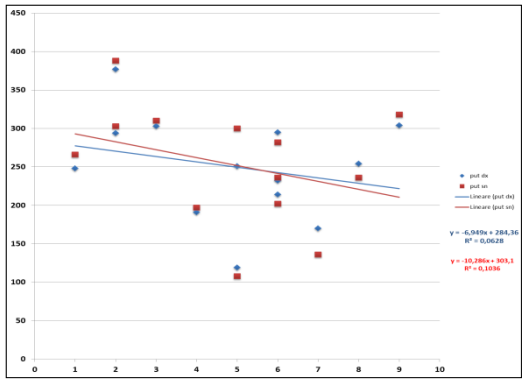
First step:
Global cognitive functioning was measured using the Montreal Cognitive Assessment (MoCA);
Second step:

1. *attention and working memory: digits forwards/backwards,*
2. *executive functions: verbal fluency test and semantic fluency,*
3. *language: WAIS-IV similarities (McKhann et al, 1984),*
4. *memory: Wechsler Memory Scale-IV Logical Memory subtest,*
5. *Visuospatial function: Clock drawing test.cognitive tests,*

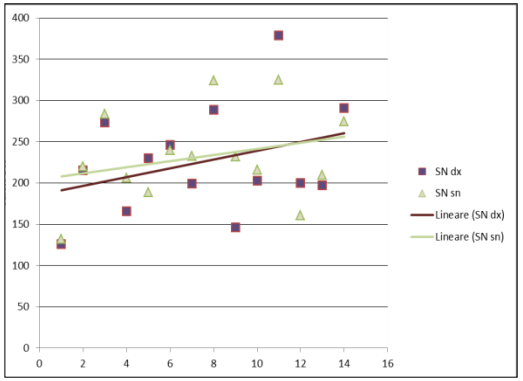
according to the Movement Disorder Society Task Force - MDS-TF (Litvan, I. et al. 2012)

1. *Neuropsychiatric Inventory (NPI) to assess neuropsychiatric symptoms (Cummings et al 1994, Assal et al 2002)*
2. *Instrumental Activities of Daily Living (Lawton and Brody, 1969)*
3. *Activities of Daily Living scales (Katz, 1983).*

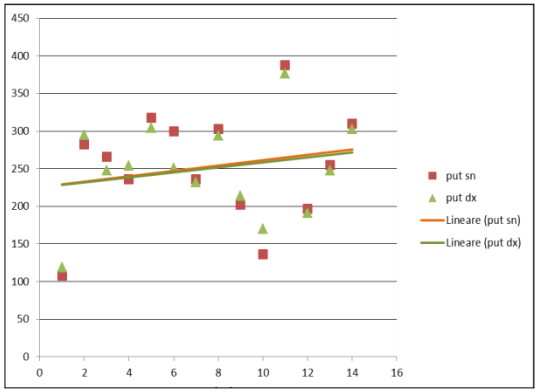
Valori SWI



Durata di malattia



Analogie WAIS-R/SN



Analogie WAIS-R/Put

Mechanisms of Dementia in parkinsonisms

Susceptibility weighted MRI correlate with motor and cognitive dysfunction in Parkinson's disease

	Putamen	GP	Caudate nucleus	RN	SN	Dentate	Frontal WM
Disease years	0.01	-0.16	-0.20	-0.11	**-0.48***	-0.23	-0.17
H&Y	-0.04	-0.22	-0.06	-0.11	-0.45	-0.07	-0.04
ADL	0.32	0.14	0.17	0.22	**0.49****	0.29	**0.36***
IADL	0.32	0.14	0.17	0.22	**0.49****	0.29	**0.36***
UPDRS-on	-0.08	**-0.42***	0.12	0.08	-0.22	0.04	0.10
UPDRS-off	-0.15	**-0.45***	-0.11	-0.07	-0.40*	-0.01	-0.07

	Mean ± SD	Putamen	Globus pallidus	Caudate nucleus	Red nucleus	Substantia nigra	Dentate nucleus	Frontal white matter
MMSE	28.2 ± 2.3	0.28	**0.40***	0.16	0.09	0.35	0.19	-0.04
Analogie	15.7 ± 5.3	**0.59*****	**0.48****	**0.45***	**0.48****	**0.38***	**0.47****	**0.35***
Racco	11.8 ± 3.3	-0.10	-0.08	-0.20	-0.22	-0.22	-0.10	-0.19
Flufon	29.2 ± 7.7	0.03	0.20	0.00	0.11	0.22	0.05	-0.03
Flusem	29.3 ± 14.4	0.02	0.04	-0.08	0.06	0.29	-0.02	-0.13
Digit a	5.9 ± 1.0	0.12	0.06	0.14	0.04	0.02	0.12	-0.01
Digit	3.8 ± 1.0	0.13	0.08	0.03	0.00	0.06	-0.28	-0.11
MoCA	25.0 ± 3.6	0.28	**0.36***	0.17	0.01	**0.41***	0.18	0.15
SRT	535.6 ± 289.7	0.04	-0.06	-0.06	-0.07	-0.31	0.03	-0.11
GNT	-0.3 ± 1.3	0.14	0.25	0.21	0.04	**0.44***	0.13	0.22
PRM	-0.4 ± 1.1	0.13	0.36	0.10	0.05	0.14	-0.13	0.02
SSP	-0.1 ± 1.0	0.33	0.32	0.33	0.21	**0.38***	0.16	0.20
SOCITT	0.6 ± 0.6	0.13	0.05	0.03	0.16	0.03	-0.12	-0.07
SOCPS	-0.4 ± 1.0	-0.09	0.06	0.07	-0.06	0.14	0.09	-0.07

Mechanisms of Dementia in parkinsonisms

Susceptibility weighted MRI correlate with motor and cognitive dysfunction in Parkinson's disease

	MOCA ≥26	MOCA <26	p-value	
Putamen	266.5 ± 43.3	223.6 ± 55.9	**0.027**	*
Globus pallidus	222.6 ± 46.4	185.8 ± 44.5	**0.033**	*
Caudate nucleus	292.7 ± 43.9	263.8 ± 50.8	0.159	
Red nucleus	247.0 ± 35.7	232.6 ± 42.8	0.327	
Substantia nigra	247.9 ± 37.8	221.3 ± 50.4	**0.020**	*
Dentate nucleus	252.7 ± 38.3	228.4 ± 36.2	0.147	
Frontal white matter	289.6 ± 40.9	272.1 ± 38.3	0.197	

A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance

Paolo Calabresi, Barbara Picconi, Lucilla Parnetti, Massimiliano Di Filippo

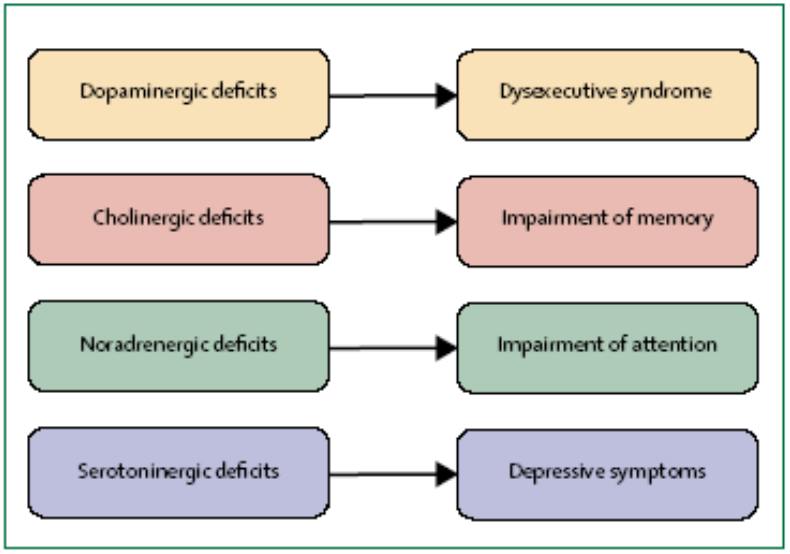
Lancet Neurol 2006; 5: 974–83

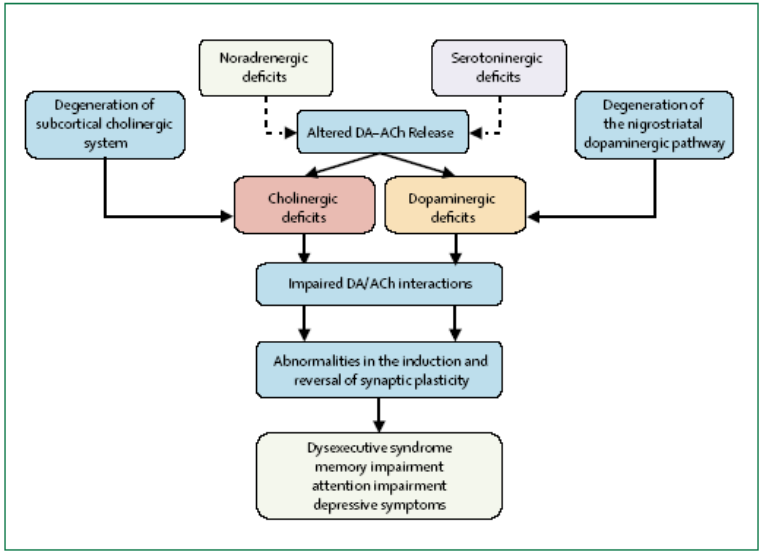
Clinica Neurologica, Dip. Specialità Medico-Chirurgiche, Università di Perugia, Italy (P Calabresi MD, L Parnetti MD, M Di Filippo MD); Fondazione Santa Lucia, IRCCS Rome, Italy (P Calabresi, B Picconi PhD, M Di Filippo)

Correspondence to:

Professor Paolo Calabresi, Clinica Neurologica, Facoltà di Medicina

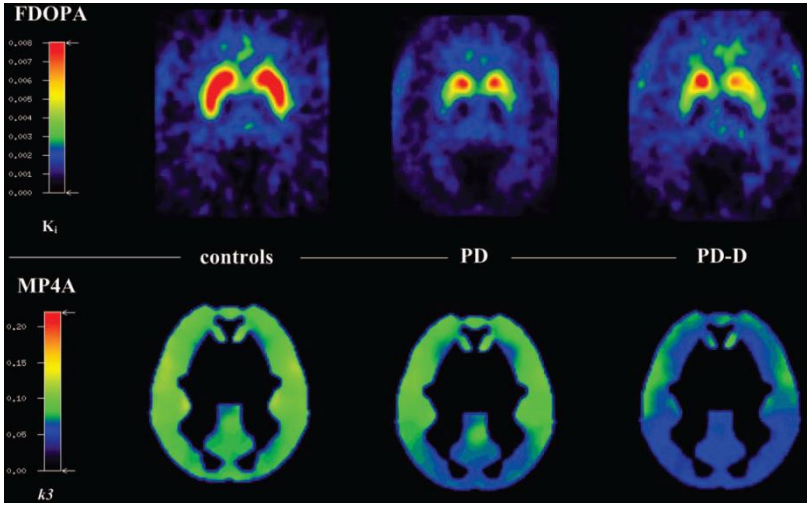
Parkinson's disease is classically characterised as a motor neurodegenerative disorder. Motor symptoms in the disorder are secondary to an altered dopamine–acetylcholine balance due to reduced striatal dopaminergic tone and subsequent cholinergic overactivity. In the past, anticholinergic drugs were given to improve motor aspects of the disease. There is now an increasing interest in the cognitive and non-motor symptoms of Parkinson's disease and in cholinesterase-inhibitor therapy for dementia associated with Parkinson's disease. In this Personal View, we reconsider the dopamine–acetylcholine balance theory and look at recent clinical findings and the possible cooperative role of dopamine and acetylcholine in the induction and maintenance of the long-lasting changes of striatal and cortical synaptic plasticity. We also discuss a convergent versus parallel model to explain cognitive dysfunctions in Parkinson's disease according to dopamine–acetylcholine dependent alterations in synaptic plasticity.





Mechanisms of Dementia in parkinsonisms

18fluorodopa (FDOPA)



N-[11C]-methyl-4-piperidyl actetate (MP4A)

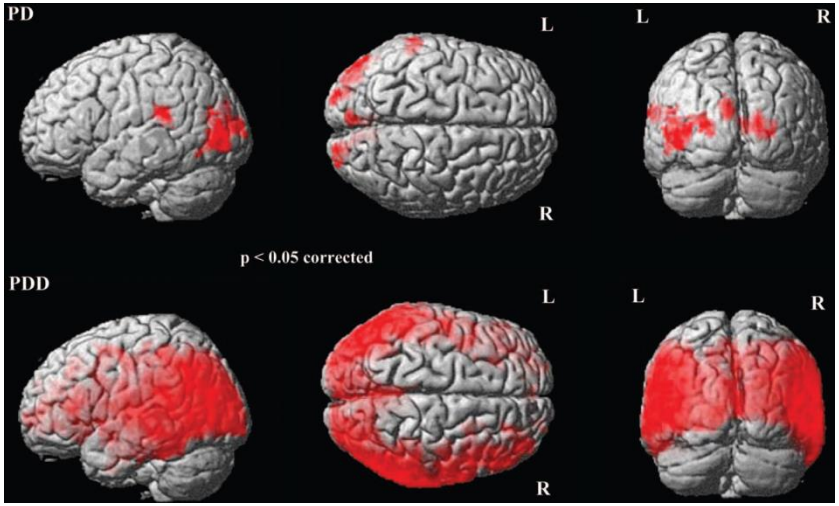


Table 5 *Regions with significant covariance of cortical MP4A k_3 reduction and right-to-left averaged caudate and putaminal FDOPA K_i values in PD and PDD patients*

	Talairach coordinates					
	x	y	z	z_{max}	Voxels pc	*p*
PD						
Putamen						
R middle frontal gyrus	32	52	-2	4.58	125	0.001
Caudate						
R middle frontal gyrus	30	44	22	4.61	102	<0.001
PDD						
Putamen						
L postcentral gyrus	−42	−22	60	4.60	381	<0.001
R precuneus	24	−76	42	5.32	247	<0.001
L superior temporal gyrus	−46	−28	16	4.74	559	<0.001
R middle frontal gyrus	36	28	42	4.28	126	<0.011

While nondemented patients with Parkinson disease had a **moderate cholinergic dysfunction**, subjects with Parkinson disease associated dementia (PDD) presented with a **severe cholinergic deficit in various cortical regions**. The finding of a closely associated striatal FDOPA and cortical MP4A binding reduction suggests a common disease process leading to a complex transmitter deficiency syndrome in PDD.

Hilker R, Neurology 2005

Non dopaminergic dysfunction:

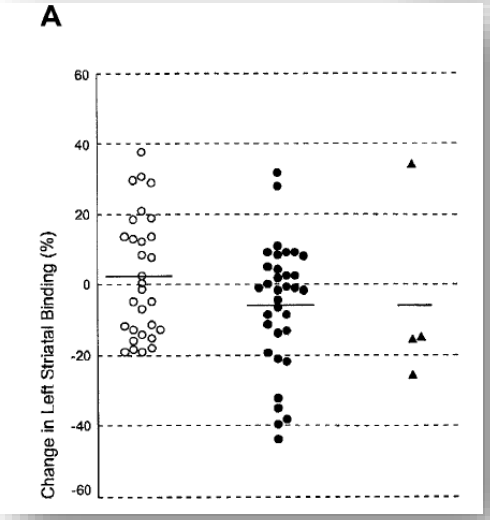
The olfactory system

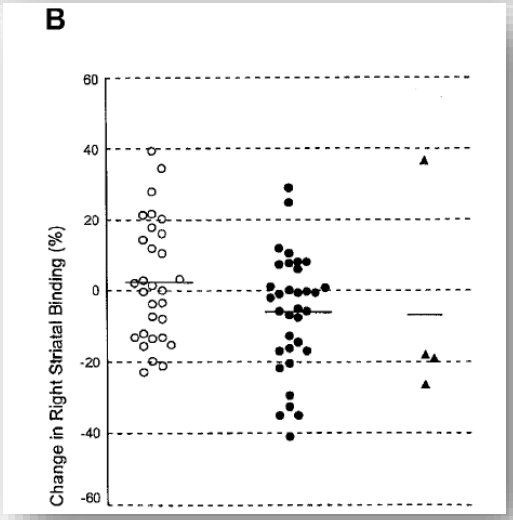
The olfactory system

ORIGINAL ARTICLES

Idiopathic Hyposmia As a Preclinical Sign of Parkinson's Disease

Mirthe M. Ponsen, MD,[1] Diederick Stoffers, MA,[1,2] Jan Booij, MD, PhD,[3]
Berthe L. F. van Eck-Smit, MD, PhD,[3] Erik Ch. Wolters, MD, PhD,[1] and Henk W. Berendse, MD, PhD[1]





Two years from baseline, 10% of the individuals with idiopathic hyposmia, who also had strongly reduced [123I]-CIT binding at baseline, had developed clinical PD as opposed to none of the other relatives in the cohort.

Among the most salient non-motor features of PD is smell dysfunction, which occurs in at least 90% of cases and often appears years prior to the motor disturbance

Doty et al, 1988

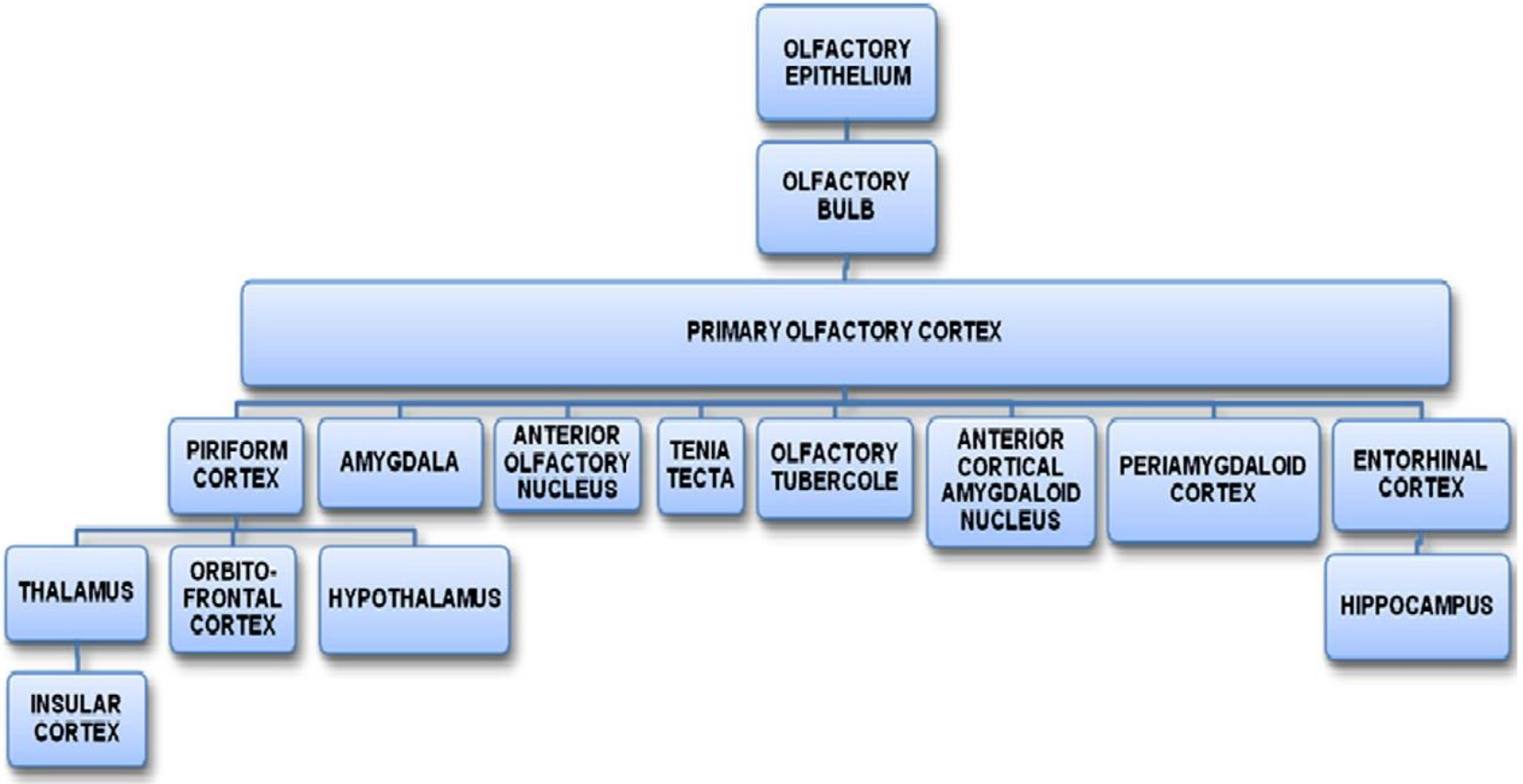
The olfactory system

Monogenic PD

PARK1/PARK4 locus mutations (α-synuclein):	*anosmic*
PARK2 locus mutations (Parkin gene):	*normal*
PARK6 locus mutations (Pink-1 gene):	*hyposmic*
PARK 8 locus mutations (LRRK2 gene):	*hyposmic*
GBA:	*hyposmic*

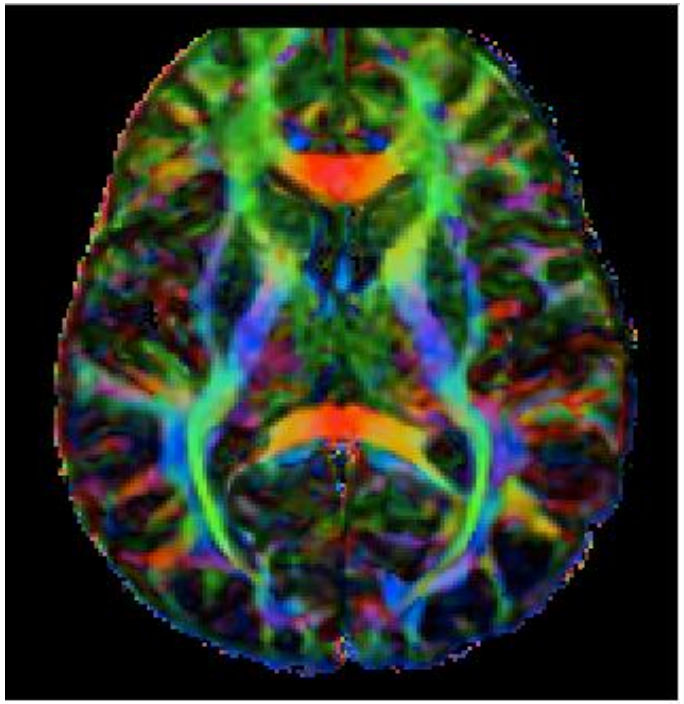
Hyposmic	***propably hyposmic***	***Normal***
PD	*Drug induced parkinsonism*	*CBD*
LUBAG		*Essential tremor*
Pure Autonomic failure		*Vascular parkinsonism*
PDC-Guam		*PSP*
MSA (lieve)		*MPTP*
LBD		

The olfactory system



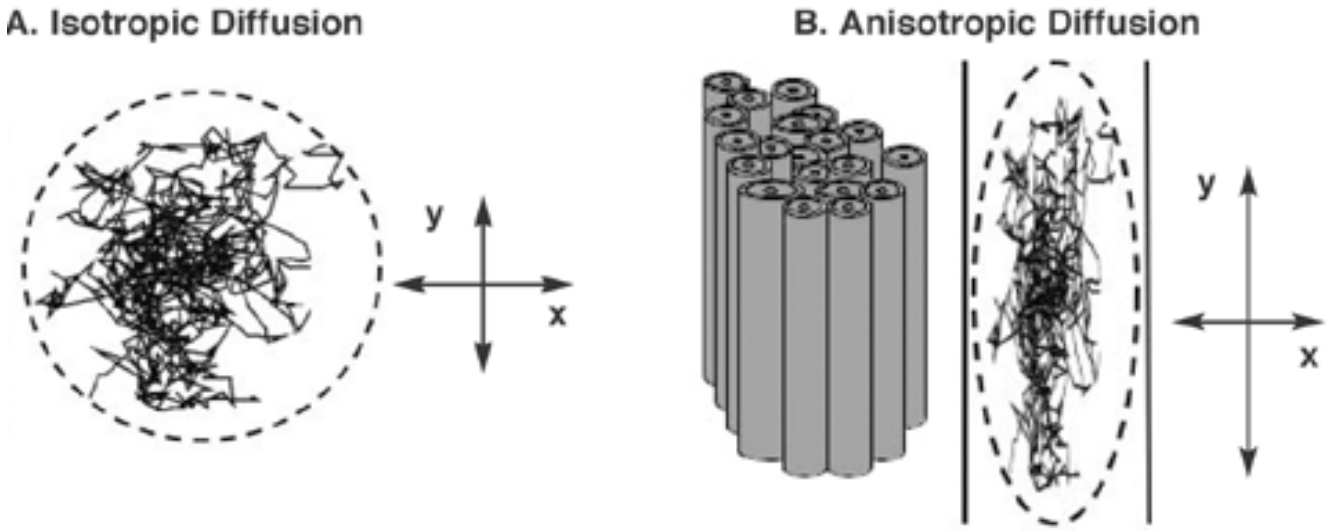
Barresi M et al, J Neurol Sci 2012

DIFFUSION TENSOR IMAGING (DTI)



Anisotropia

La diffusione in un bicchiere d'acqua è uguale in tutte le direzioni → ***isotropica***
*La diffusione misurata in un tessuto dipende dalla direzione →****anisotropica***



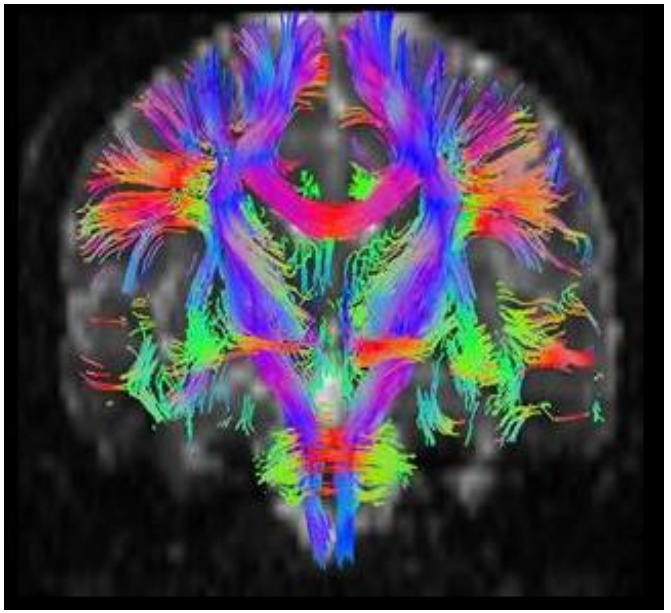
Nella sostanza bianca cerebrale l'anisotropia riflette l'organizzazione nei fasci di fibre.
La ***fractional anisotropy (FA)*** *è la misura del grado di anisotropia in un dato voxel. Un'alterazione della FA è indice della perdita dell'integrità microstutturale delle fibre nervose*

Trattografia

Tecnica basata sulla dipendenza direzionale delle molecole d'acqua nella sostanza bianca (anisotropia)

consente di ricostruire i percorsi delle fibre nervose

- Rosso -> direzione sagittale
- Verde -> direzione coronale
- Blu -> direzione assiale



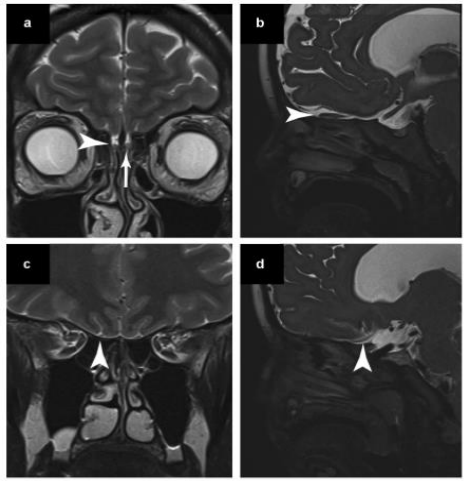
DTI-MRI e IOIT

5 pazienti parkinsoniani e 6 controlli sani

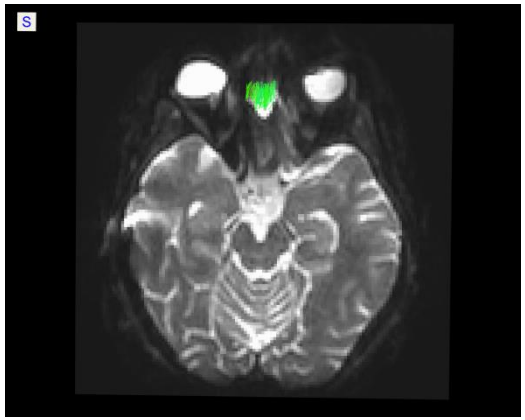
Valutazione sistema olfattivo (IOIT)

Acquisizione

Sequenze



Post-processing



- RM 3 Tesla
- Sequenze DTI in assiale
- ROI per tratto olfattivo

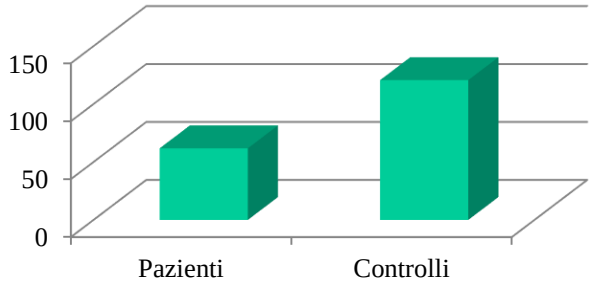
Ricostruzione dei tratti di fibre con la trattografia

Parametri DTI

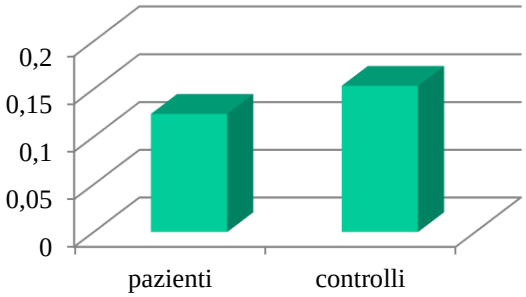
Controllo	N° dei tratti	Volume	Fractional anisotropy	DS
1	44	0,28	0,19	0,12
2	129	0,94	0,16	0,04
3	125	0,86	0,14	0,05
4	137	0,73	0,17	0,07
5	198	1,04	0,13	0,05
6	91	0,51	0,13	0,06

Paziente	N° dei tratti	Volume	Fractional anisotropy	DS
1	103	0,77	0,15	0.06
2	82	0,87	0,12	0,08
3	51	0,46	0,11	0,03
4	24	0,21	0,11	0,04
5	49	0,48	0,13	0,06

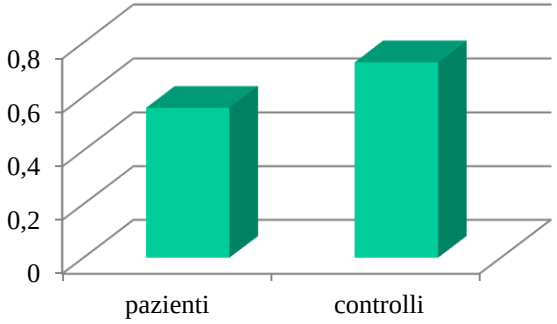
Track count

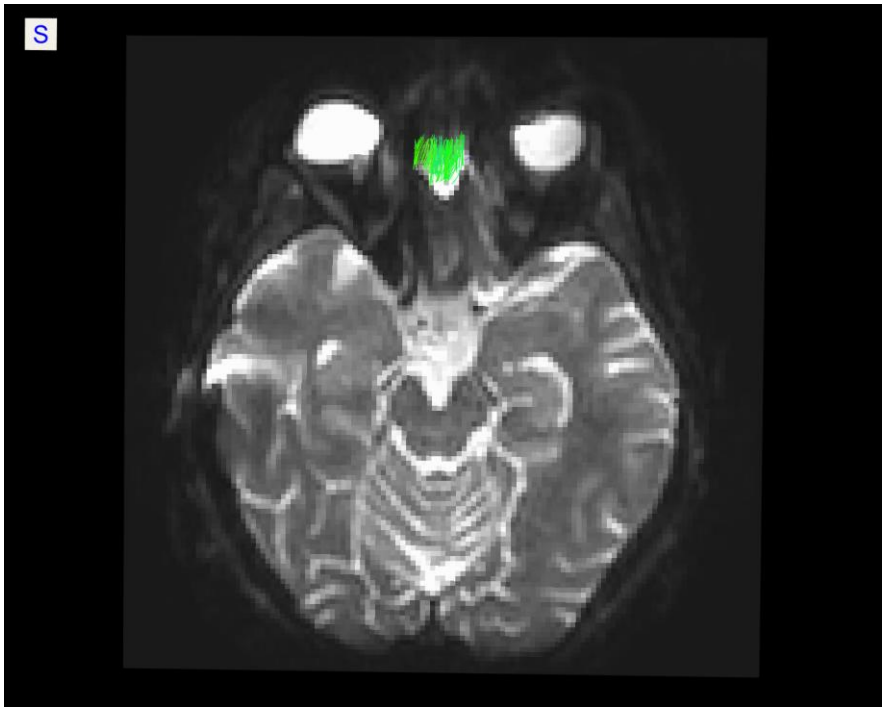


FA

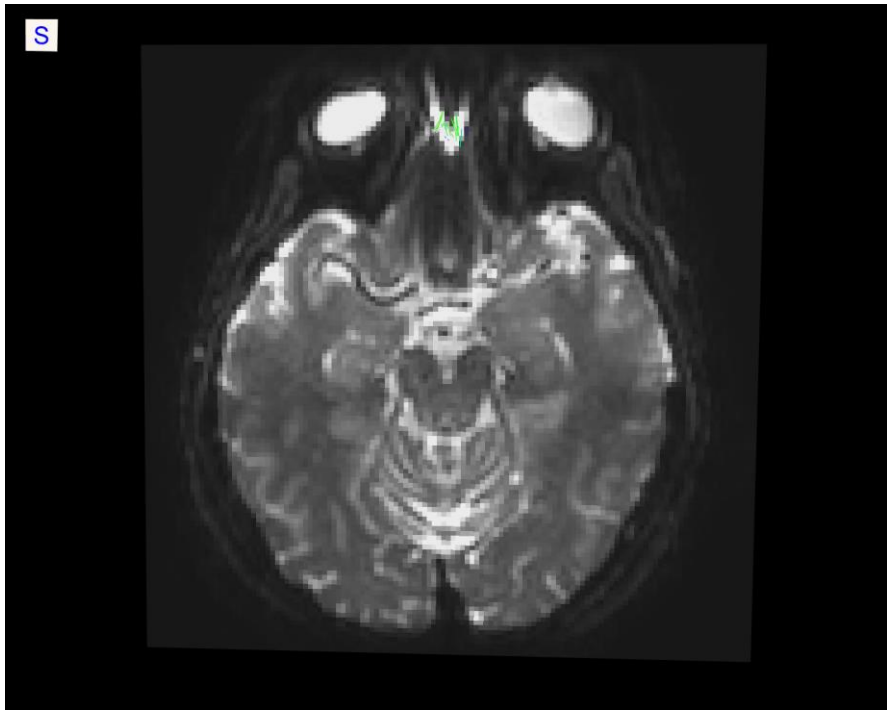


Volume



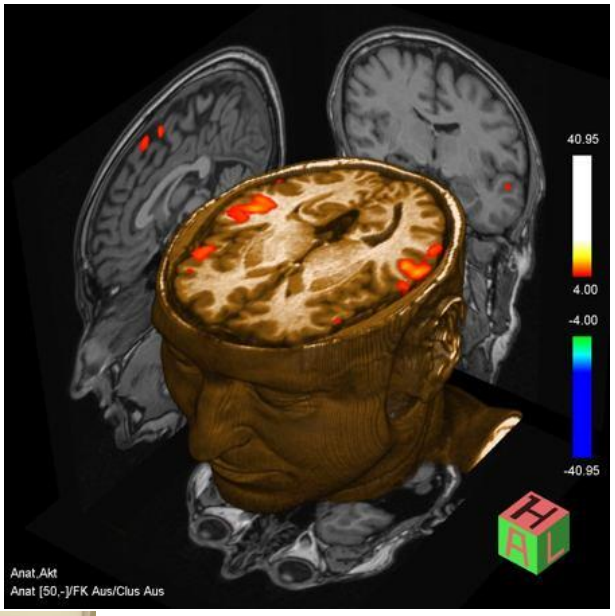


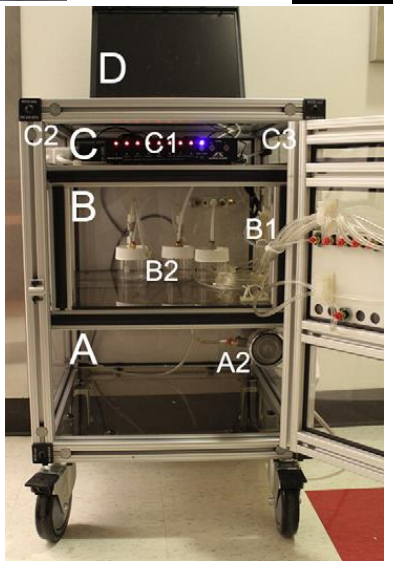
Olfactory tract of a normal subject

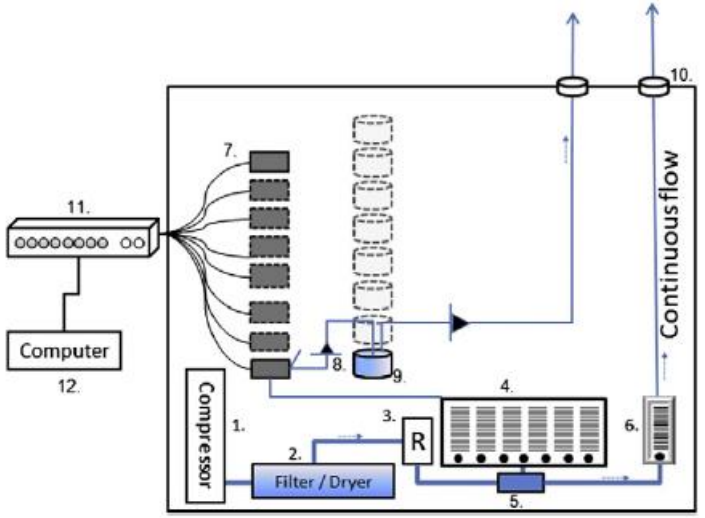


Olfactory tract of a Parkinson's disease patient

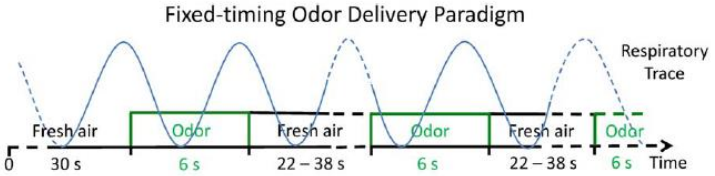
The olfactory system

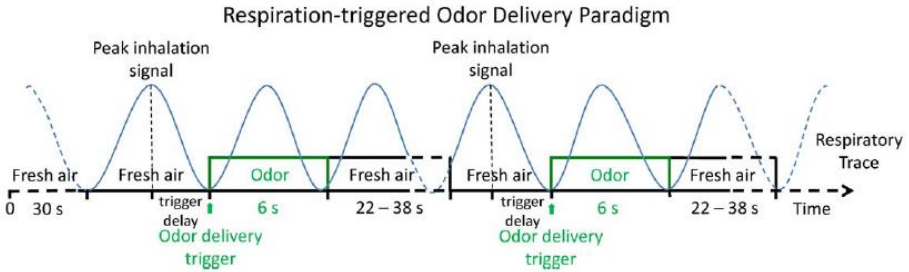


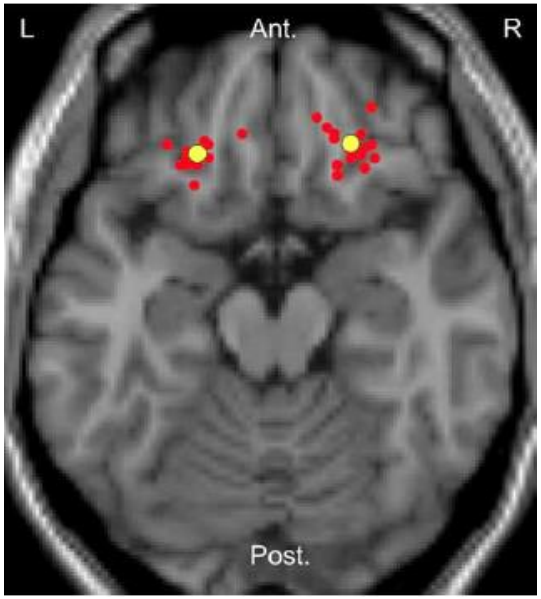


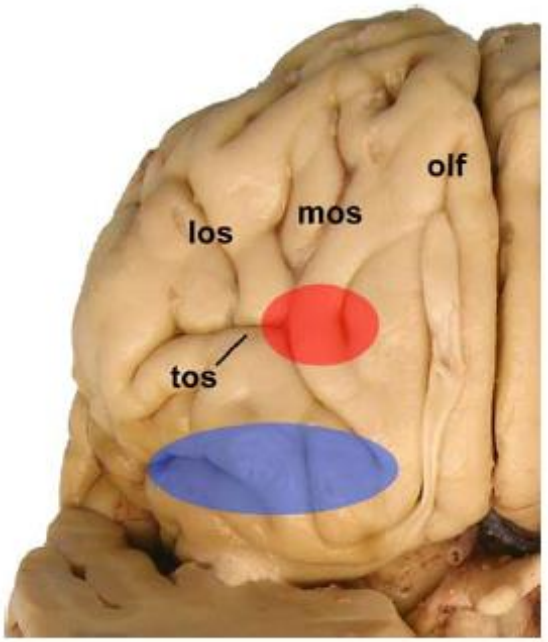


The olfactory system

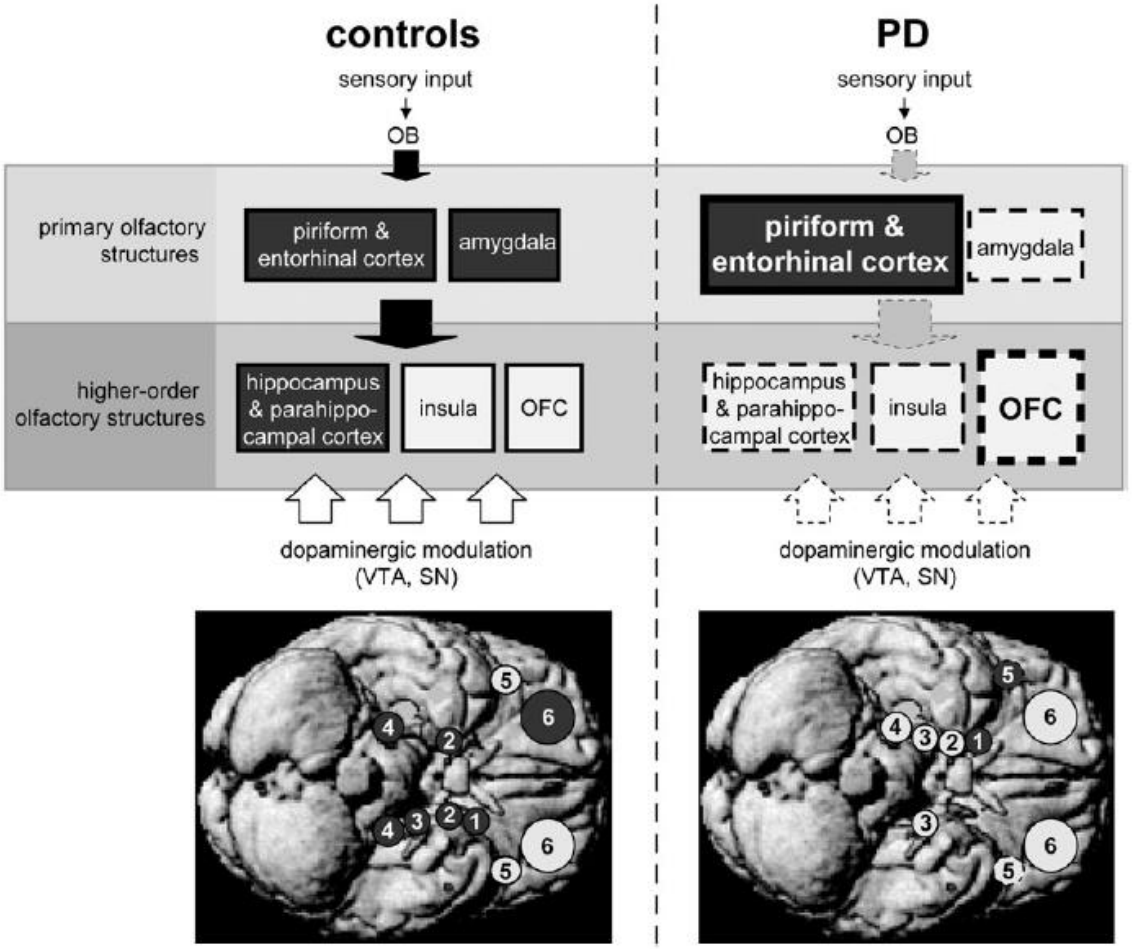






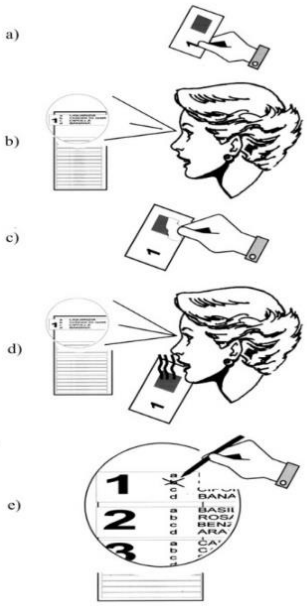


The olfactory system

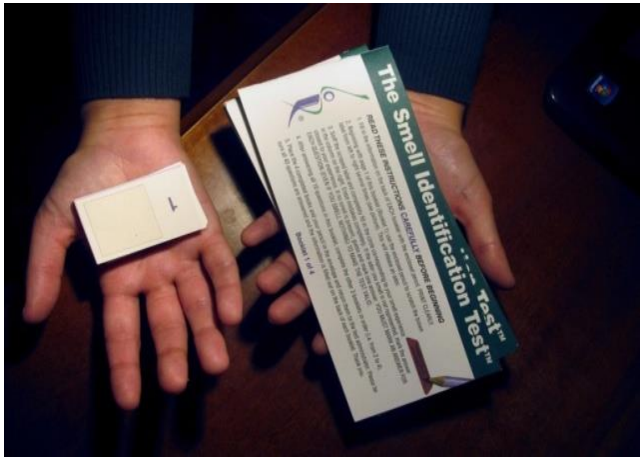


1: Piriform and entorhinal cortex, 2: amygdala, 3: parahippocampal cortex, 4: hippocampus, 5: insula, and 6: OFC. OB: olfactory bulb,VTA: ventral tegmental area, SN: substantia nigra.

The olfactory system



Test olfattivo Ioit



Selezione di due odoranti fra 33 testati

Massimamente individuato (>70%)

Marsiglia 0,01%

Minimamente individuato (<30%)

Basilico 0,001%

The olfactory system

Immagini ottenute con MRI 3 T in due fasi:

1. Acquisizione d'immagini morfologiche T1 pesate
2. Acquisizione di sequenze EPI-T2 pesate per la valutazione dell'attivazione cerebrale

rest	**basilico**	**rest**	**basilico**	**rest**	**basilico**	**rest**	**basilico**	**rest**
rest	**marsiglia**	**rest**	**marsiglia**	**rest**	**marsiglia**	**rest**	**marsiglia**	**rest**
rest	**basilico**	**rest**	**basilico**	**rest**	**basilico**	**rest**	**basilico**	**rest**
rest	**marsiglia**	**rest**	**marsiglia**	**rest**	**marsiglia**	**rest**	**marsiglia**	**rest**

- ***4 prove***
- ***Ogni prova ha una durata complessiva di 4 ½ min***
- ***In ogni prova si alternano fasi di riposo e fasi di task (basilico, marsiglia) da 30 secondi l'una***

The olfactory system

Marsiglia
Ipoattivazione

➢ ***STRUTTURE OLFATTIVE PRIMARIE***

- **area paraippocampale bilaterale**
- **amigdala bilaterale**

➢ ***STRUTTURE OLFATTIVE SECONDARIE***

- **talamo bilaterale**
- **ippocampo**
- **cervelletto bilaterale**
- **cingolo anteriore bilaterale**
- **area temporale media e superiore bilaterale**
- **insula bilaterale**
- **area occipitale media dx**

Basilico
Ipoattivazione

- **area paraippocampale sin**
- **amigdala sin**

- **area temporale superiore dx**
- **ampie aree parietali/occipitali**

The olfactory system

Massimamente individuato (>70%)

Marsiglia 0,01%

Maggior *stimolazione network olfattivo*

Minimamente individuato (<30%)

Basilico 0,001%

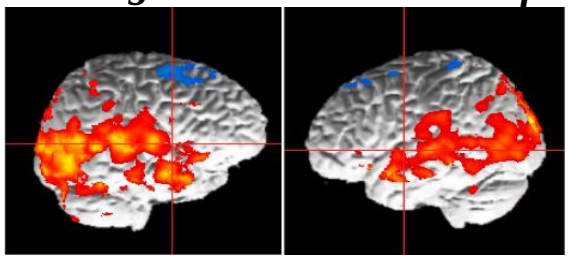
Minor *stimolazione network olfattivo*

Attivazione aree

Maggior *numero di aree funzionali ipoattive*

Minor *numero di aree funzionali ipoattive*

C-Pz right ***C-Pz left***



REVIEW

Imaging Synucleinopathies

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ABSTRACT: In this review the structural and functional imaging changes associated with the synucleinopathies PD, MSA, and dementias associated with Lewy bodies are reviewed. The role of imaging for supporting differential diagnosis, detecting subclinical disease, and following disease progression is discussed and its potential use for monitoring disease progression is debated. © 2016 International Parkinson and Movement Disorder Society

Key Words: Parkinson's; MRI; PET; SPECT; MSA; DLB

In both late-onset, idiopathic Parkinson's disease (PD) and the genetic forms associated with alpha-synuclein (α-Syn) mutations and multiplications or leucine-rich repeat kinase 2 (LRRK2) and glucocerebrosidase (GBA) gene mutations, cell loss occurs in association with abnormal α-Syn aggregation. α-Syn fibrils are found in intraneuronal Lewy inclusion bodies and Lewy neuritis, and this pathology targets the dopamine cells in the SNc and midbrain tegmentum, noradrenergic cells in the locus ceruleus, serotonergic cells in the median raphe, and cholinergic projections from the pedunculopontine nucleus and nucleus basalis. The pathology is first thought to arise in the dorsal motor nucleus of the vagus and olfactory bulbs.[1] It then ascends through the brainstem to limbic and association cortex, and 80% of PD cases will eventually develop dementia (PDD) if they survive 20 years with their disease.[2] When dementia is present before or within 1 year of parkinsonism, the condition is labeled dementia with Lewy bodies (DLB).[3] The distribution of aggregated α-Syn as Lewy bodies (LBs) in DLB and PDD is similar, though there is a higher prevalence of concommitant Alzheimer's pathology in DLB.[4]

MSA is another synucleinopathy associated with parkinsonism, but, unlike PD, early autonomic failure, falls and postural instability, and ataxia are clinical features of this disorder. Its pathology differs from PD and is characterized by argyrophilic cytoplasmic glial inclusions containing aggregated α-Syn and ubiquitin found in central white matter (WM), the SN and the striatum, and also pontine and medullary nuclei, the cerebellum, and the intermediolateral columns of the spinal cord.[5,6] Nearly all cases to date have been sporadic.

Ideally, one would wish to directly image the aggregated α-Syn load in the synucleinopathies, but this has proved problematic. Given this, imaging studies have relied on demonstrating the structural and functional changes associated with α-Syn pathology.

MRI is able to examine water proton relaxation and the amplitude and direction of water diffusion along nerve fibers enabling alterations in structural connectivity to be detected. It can also detect nigral and striatal iron deposition and loss of nigral melanin as altered susceptibility. Using blood-oxygen-level–dependent (BOLD) sequences, MRI can monitor the slow oscillatory changes in venular oxygenation in brain regions at rest and during actions. Detection of synchronized oscillations of venous oxygenation in different brain regions at rest provides evidence of their functional connectivity, and independent attentional,

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Così da quella imagine divina,
per farmi chiara la mia corta vista,
data mi fu soave medicina

Dante (XX canto)

Grazie per l'attenzione