7MRI in Parkinson and Parkinsonisms

Roberto Ceravolo,

Department of Clinical and Experimental Medicine
University of Pisa

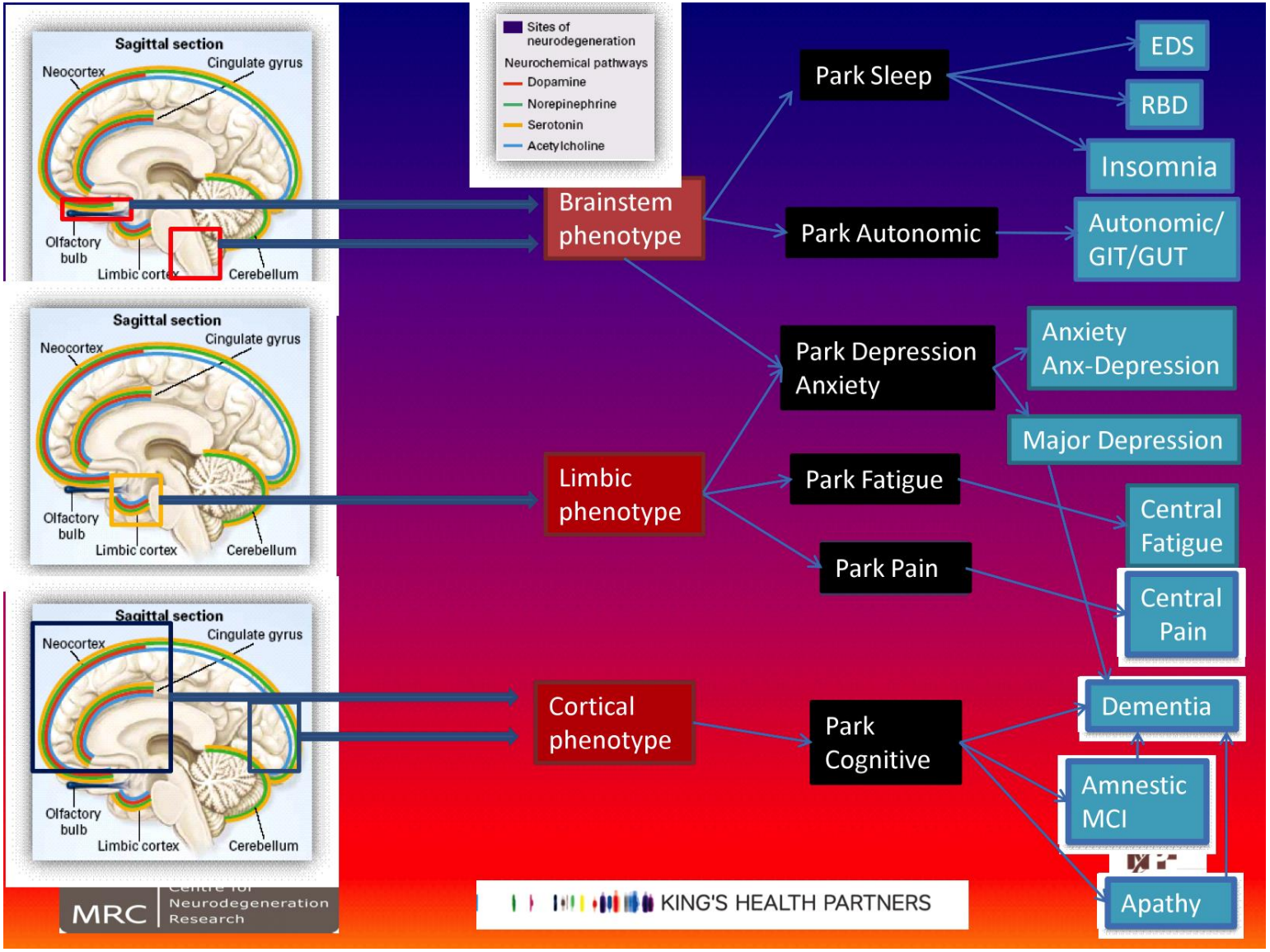
Flor

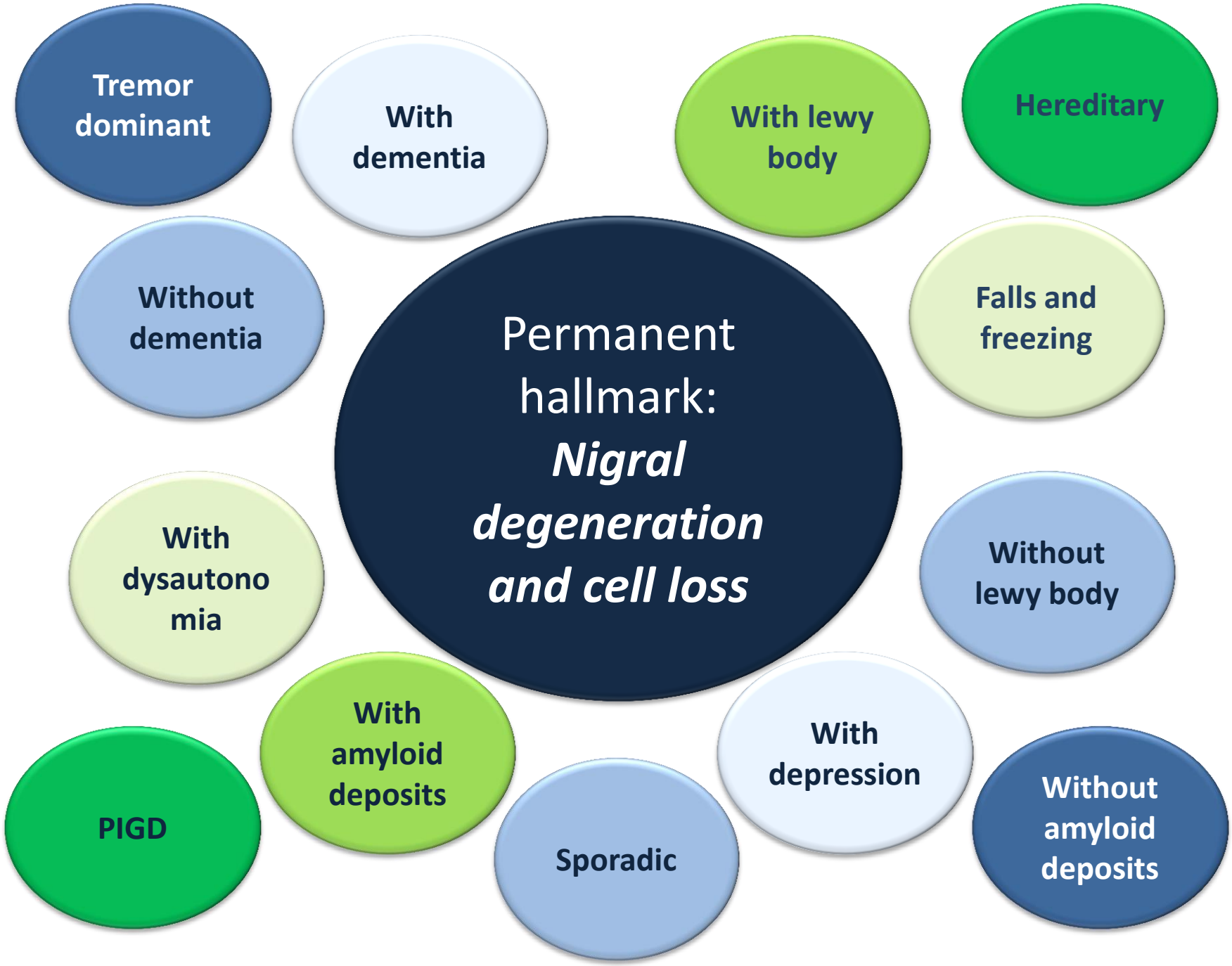
7MRI in Parkinson and Parkinsonisms "exploring substantia nigra"

Roberto Ceravolo,

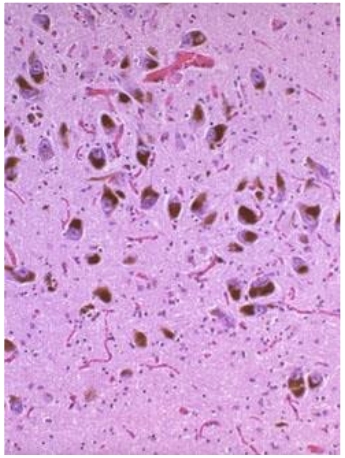
Department of Clinical and Experimental Medicine
University of Pisa

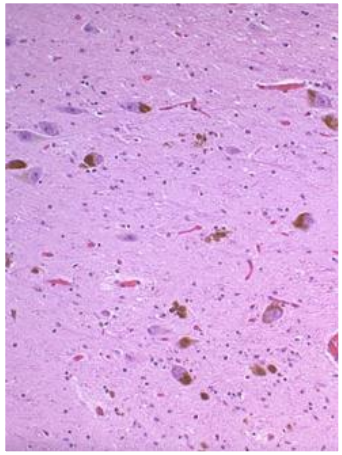
Flor


Sagittal section
Neocortex
Cingulate gyrus
Olfactory bulb
Limbic cortex
Cerebellum
Sites of neurodegeneration
Neurochemical pathways
Dopamine
Norepinephrine
Serotonin
Acetylcholine
Brainstem phenotype
Limbic phenotype
Cortical phenotype
Park Sleep
EDS
RBD
Insomnia
Park Autonomic
Autonomic/ GIT/GUT
Park Depression Anxiety
Anxiety Anx-Depression
Major Depression
Park Fatigue
Central Fatigue
Park Pain
Central Pain
Park Cognitive
Dementia
Amnestic MCI
Apathy
MRC Centre for Neurodegeneration Research
KING'S HEALTH PARTNERS


Tremor dominant
With dementia
With lewy body
Hereditary
Without dementia
Permanent hallmark: *Nigral degeneration and cell loss*
Falls and freezing
With dysautonomia
Without lewy body
With amyloid deposits
With depression
PIGD
Sporadic
Without amyloid deposits

PD: Pathology





HEALTHY SUBJECT

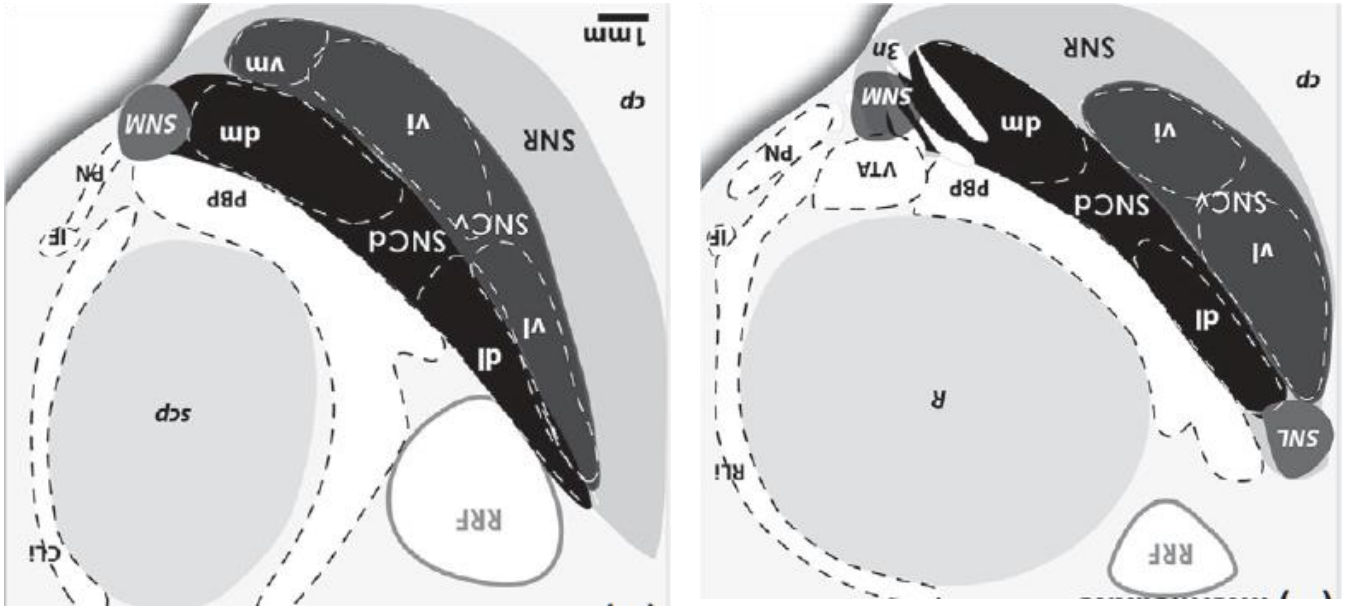
PARKINSON'S DISEASE

Organization of the Substantia Nigra

The human SN is a large structure bordered anteriorly by the cerebral peduncle and posteriorly by the red nucleus and superior cerebellar decussation

The ***pars reticulata (SNr)*** is ventral and composed of g-aminobutyric acid (GABA)ergic neurons that form one of the output nuclei of the basal ganglia along with the internal pallidum.
The ***pars compacta (SNc)*** is dorsal and composed of closely packed dopaminergic neurons which are known to accumulate neuromelanin (nigrosomes)

The SNr contains higher levels of iron than the SNc in normal subjects.



Paxinos and Mai, *The Human Nervous System* 2004

Substantia Nigra of Sommering

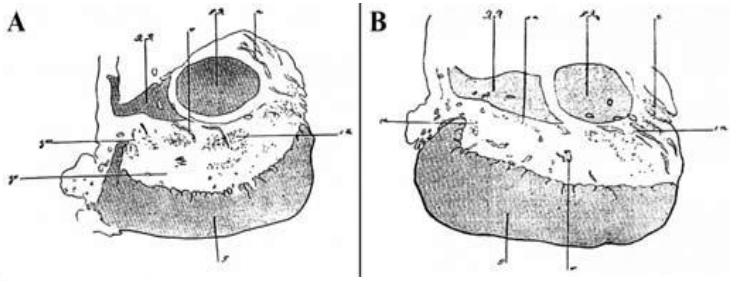
- Discovered in 1786 by the french anatomist Félix Vicq d'Azyr (not Soemmerring);
- More than a century after Paul Blocq , Georges Marinesco and Edouard Brissaud alluded to a possible link between this structure and PD;
- 1919 Constantin Trétiakoff: hypothesized that the substantia nigra is the major pathological site in Parkinson's disease.

Georges Marinesco

Edouard Brissaud

Constantin Trétiakoff

80-year-old healthy patient (A), Parkinson's disease patient(B)

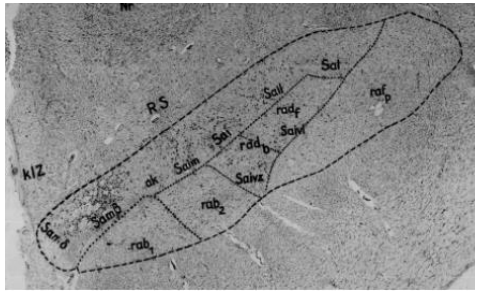


Reviewed by Parent & Parent, 2010

JOURNAL FÜR PSYCHOLOGIE UND NEUROLOGIE
BAND 48, HEFT 1 u. 2, Dezember 1937

[Aus dem Kaiser-Wilhelm-Institut für Hirnforschung, Berlin-Buch. Direktor: Prof. Dr. O. Vogt]

Zur Normalanatomie der Substantia nigra

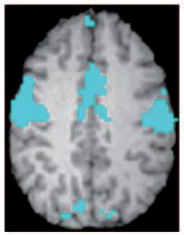


Magnetic Resonance Imaging in Parkinson's Disease

Categories of Substantia Nigra biomarkers

Structural markers	to visualize or segment SN
Diffusion imaging and relaxometry markers	differential and early diagnosis of PD and monitoring PD progression
Functional markers resting state , fMRI-spectroscopy	to investigate functional changes and pathophysiological correlates

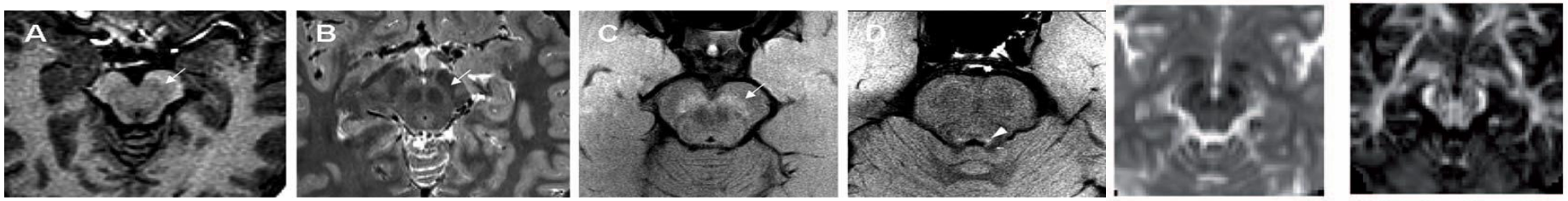
Spectroscopy
brain metabolites



Resting state fMRI

1.5T-3T

functional connectivity



Diffusion imaging

Lehericy S et al., *Mov Disord*. 2012

Study	Cases/controls	Field strength	Technique (b-value/Number of directions)	Primary measure	Findings in SN
Volumetry					
Adachi et al, 1999	25/36	1.5	DWI (825/3)	Volume	Reduced
Oikawa et al, 2002	22/22	1.5	PD/T2/STIR	Volume	No change
Minati et al, 2007	8/8	1.5	IR-T1	Volume	Reduced lateral > medial
Menke et al, 2009	10/10	3	DESPOT1	Volume	Reduced
Peran et al, 2010	30/22	3	T2*	Volume	No change
Magnetization transfer					
Eckert et al. 2004	15/20	1.5		MTR	Reduced
Tambasco et al, 2011	22/10			MTR	Reduced
Relaxometry					
Ordridge et al, 1994	7/7	3		R2′	Increased
Michaeli et al, 2007	8/8	4		T1rho	Increased
				T2rho	Reduced
Martin et al, 2008	26/13	3		R2*	Increased in lateral SNc
Peran et al, 2010	30/22	3		R2*	Increased
Diffusion studies			(*b* value, Nb directions)		
Yoshikawa et al, 2004	41251	1.5	DTI (800, 6)	MD	
				FA	Reduced
Chan et al, 2007	73/78	1.5	DTI (800, 12)	ADC	No change
				FA	Reduced
Vaillancourt et al, 2009	14/14	3	DTI (1000, 27)	FA	Reduced
Menke et al, 2009	10/10	3	DTI (1000, 60)	FA	No change
				Connectivity	Reduced (SN-Tha, SN-Pu)
Menke et al, 2010	10/10	3	DTI (1000, 60)	MD	No change
				FA	No change
				Connectivity	Reduced volume of SN
Peran et al, 2010	30/22	3	DTI (1000, 30)	MD	No change
				FA	Reduced

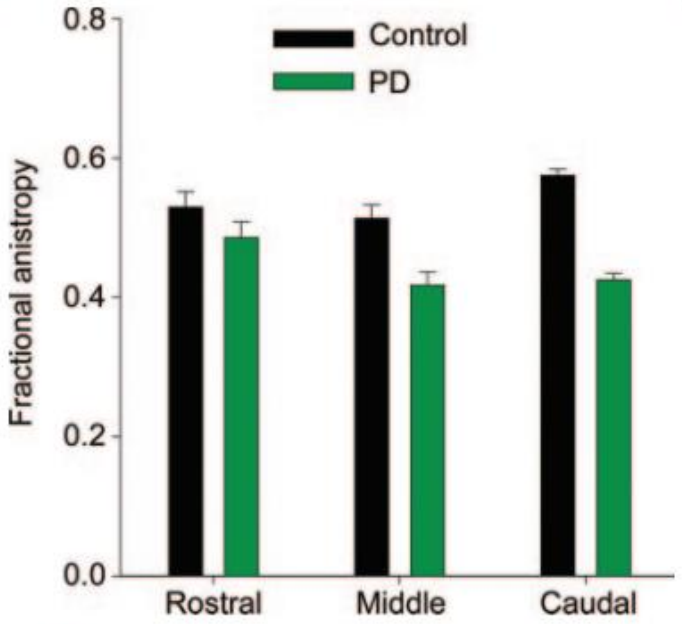
1.5T-3T

Diffusion tension imaging (DTI) in de novo PD

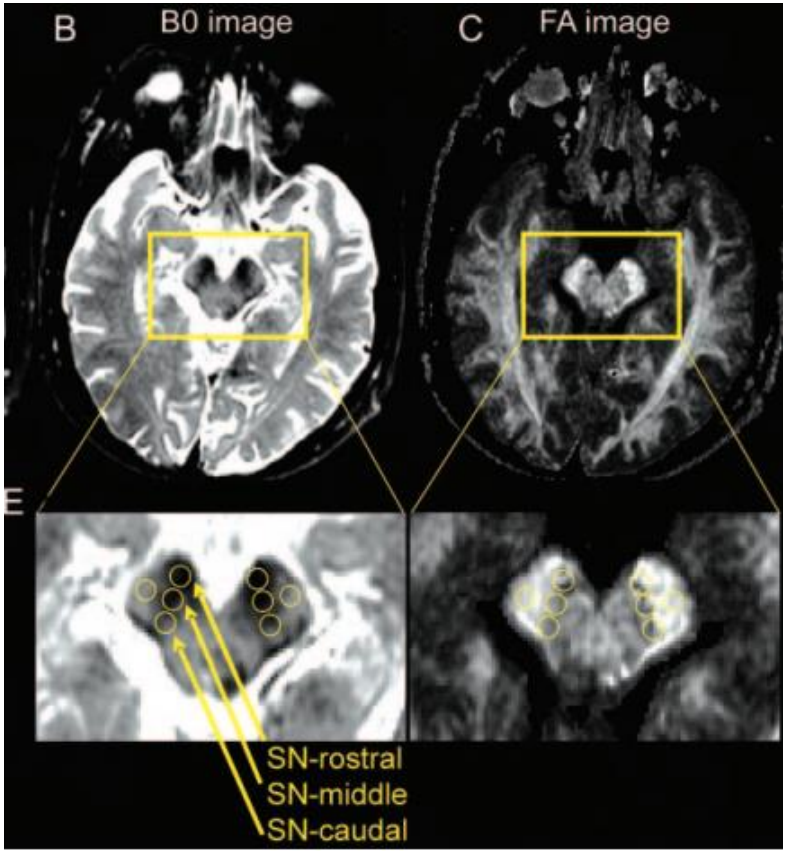
ARTICLES

High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson disease

Figure 2 Differences between groups



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.



Villancourt DE et al., *Neurology* 2009

Diffusion tension imaging (DTI) in parkinsonian syndromes

A DTI biomarker for Parkinson's disease?

• Reduction of FA in Substantia Nigra all of 9 studies

• The caudal region of the SN had sensitivity and specificity of 100% for differentiating early, medication naive PD patients from controls – *small number of patients* (Vaillancourt, Neurology 2009)

• No association between disease severity and FA in SN
(Vaillancourt, Neurology 2009; Gattellaro, AJNR AM J Neuroradiol 2009)

Cochrane CJ et al., *Neurology* 2013

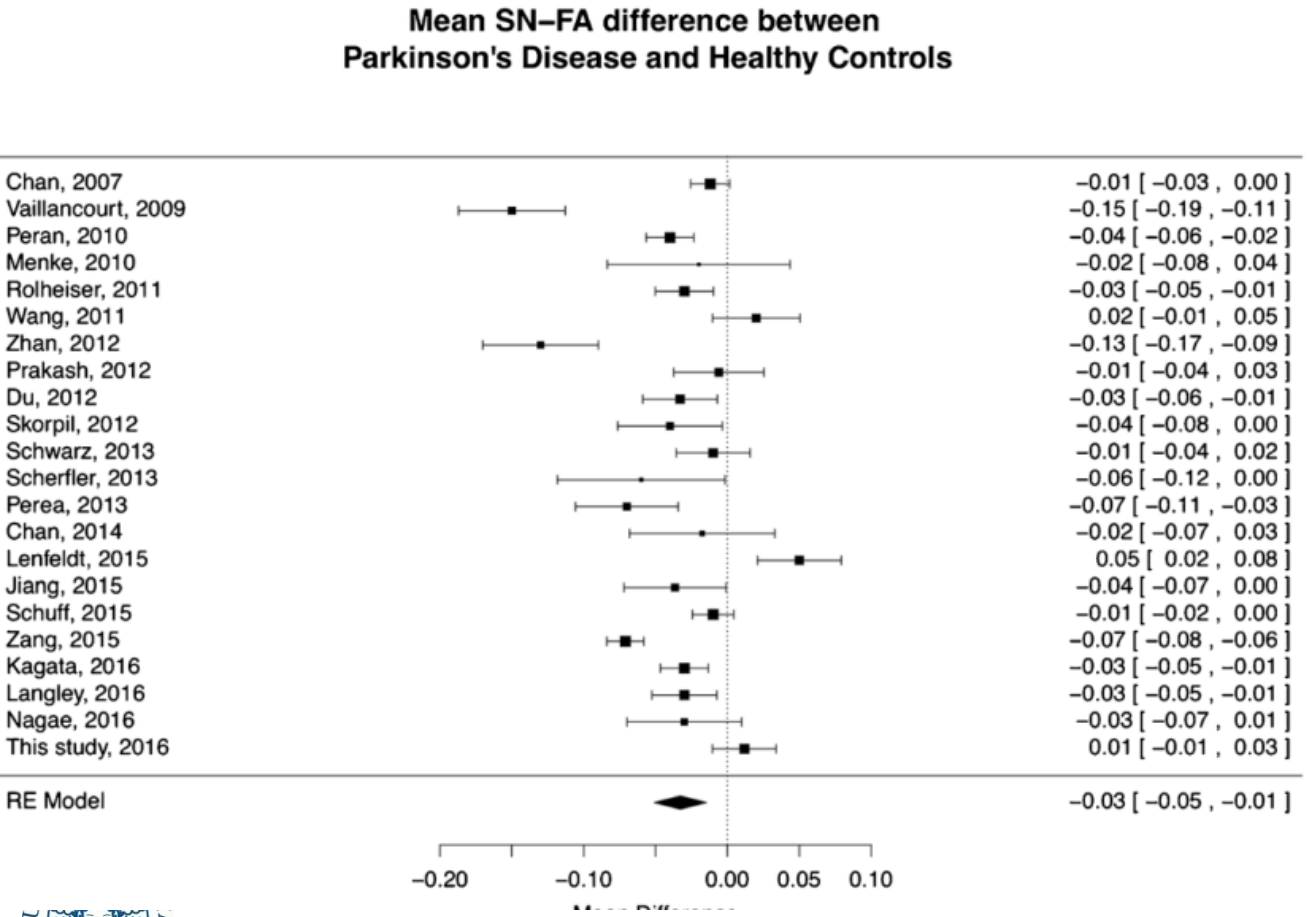
Diffusion tension imaging (DTI) in PD

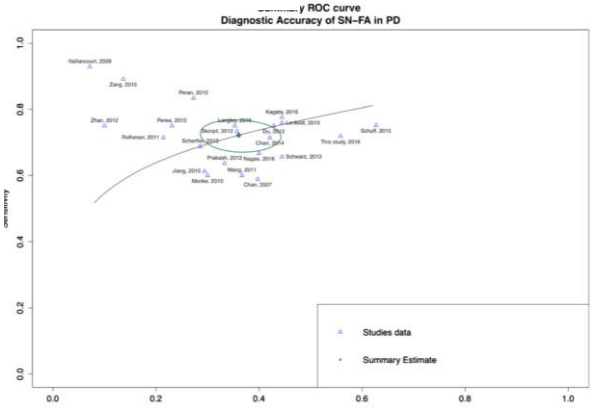
1: regional increase in nigral mean diffusivity in PD
2: no difference using a voxel based approach
3: Meta-analysis of 11 studies on nigral FA changes revealed a significant PD induced FA decrease. There was, however, a very large variation in results. After exclusion of five studies with unusual high values of nigral FA in the control group, an acceptable heterogeneity was reached, but there was non-significant disease effect. The small PD related nigral MD changes in conjunction with the negative findings on VBA and meta-analysis limit the usefulness of nigral MD measures as biomarker of Parkinson's disease. The negative results of nigral FA measurements at regional, sub-regional and voxel level in conjunction with the results of the meta-analysis of nigral FA changes question the stability and validity of this measure as a PD biomarker

Schwarz ST et al., *Neuroimage Clin*. 2013

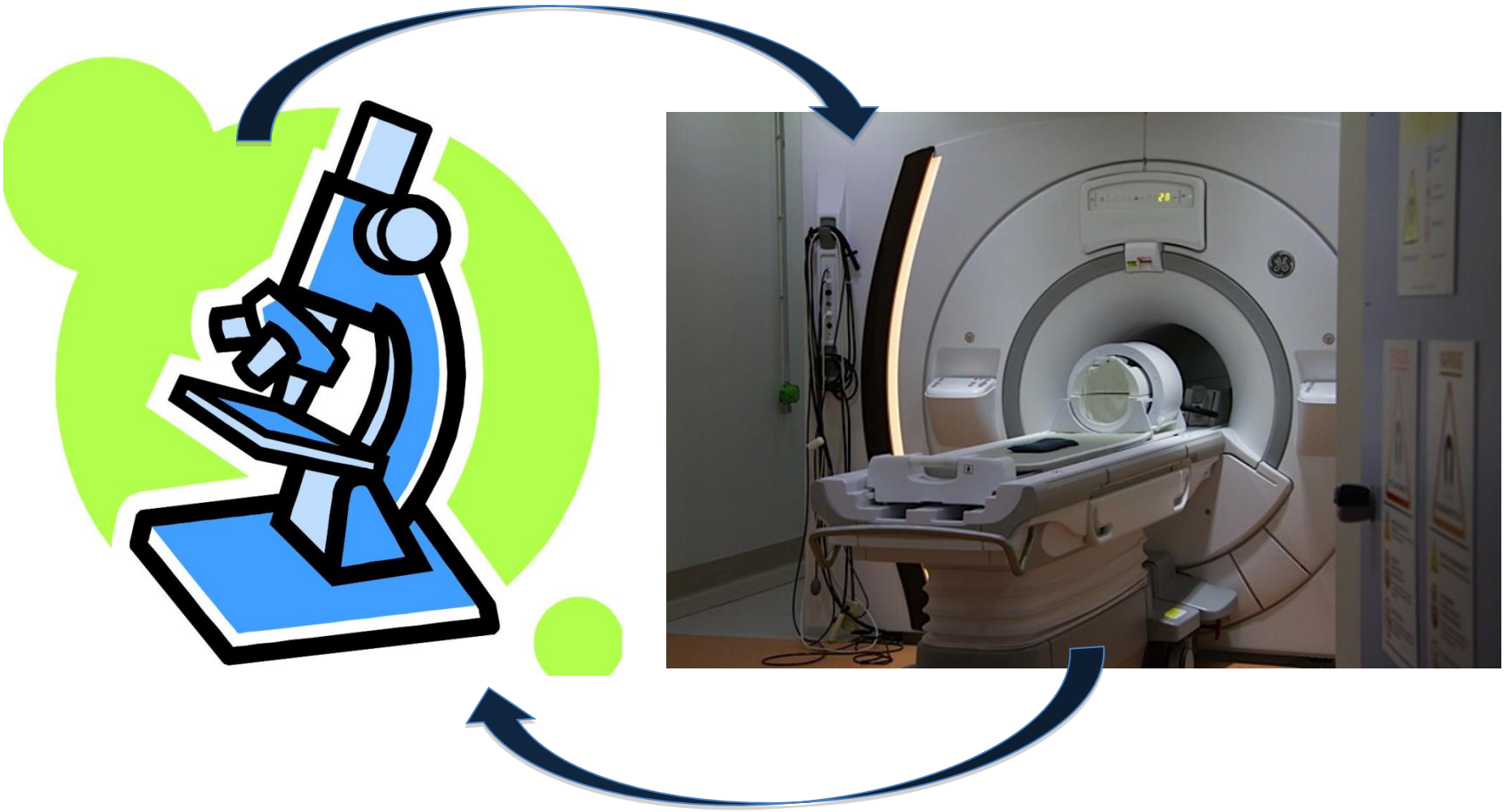
Fractional Anisotropy (FA) in PD

Substantia nigra fractional anisotropy is not a diagnostic biomarker of Parkinson's disease: A diagnostic performance study and meta-analysis



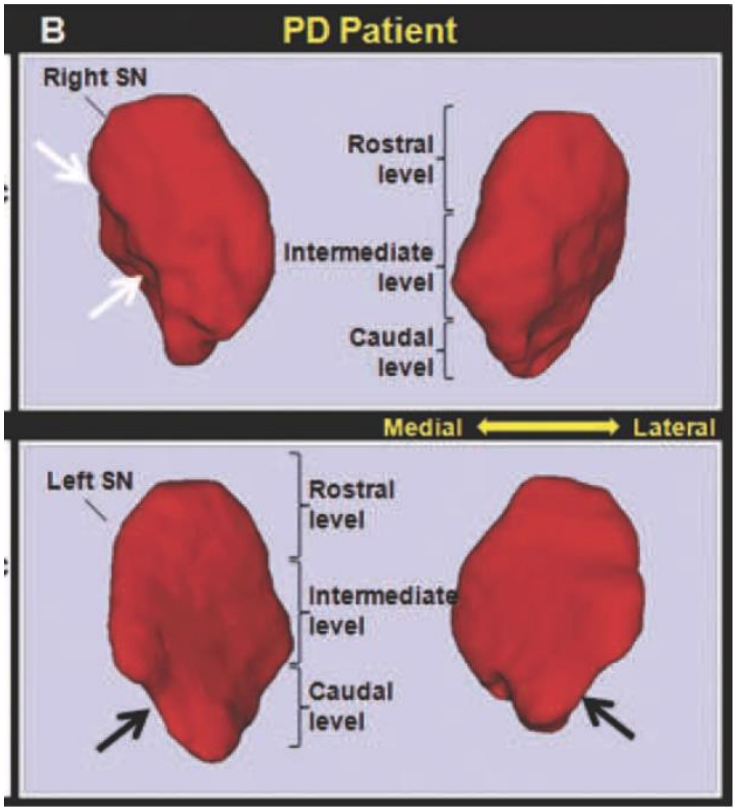


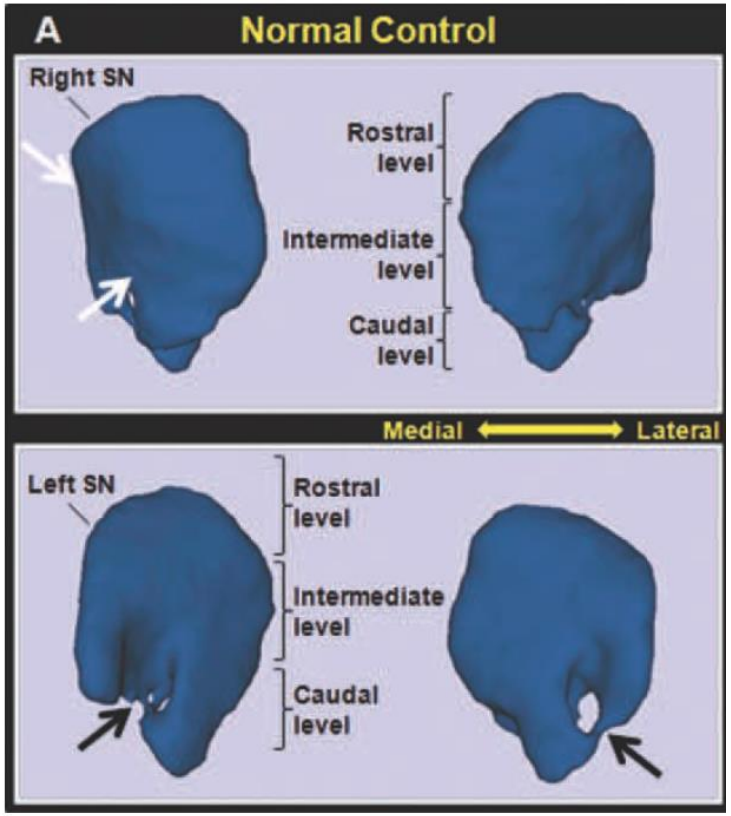
Hirata FC et al., *Eur Radiol*. 2016



7Tesla Magnetic Resonance Imaging of the Substantia Nigra in PD

10 PD e 10 HS; 3D T2*-weighted gradient echo sequence aligned with an oblique coronal plane

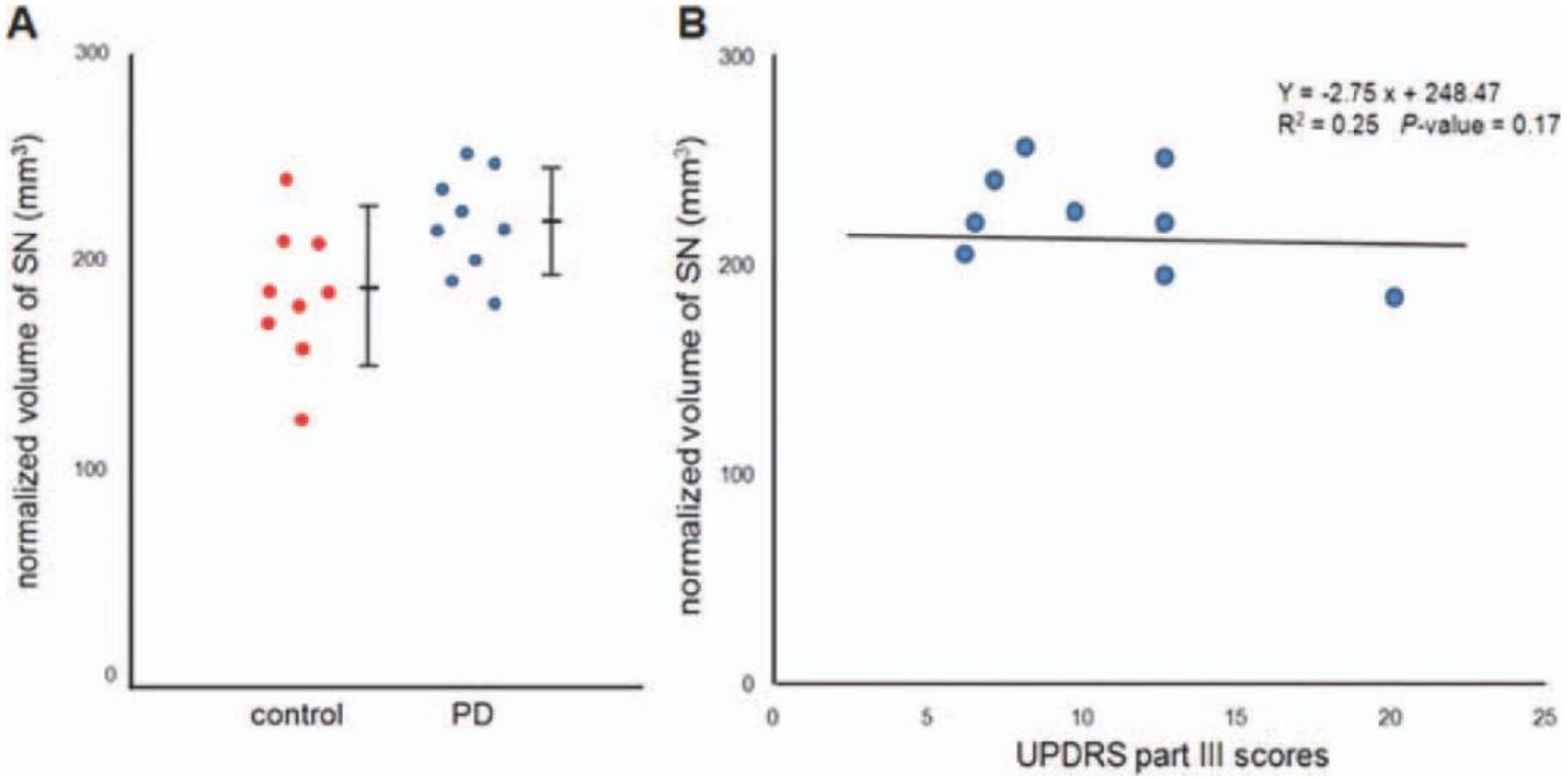




Kwon DH et al., *Ann Neurol.* 2012

7Tesla Magnetic Resonance Imaging of the Substantia Nigra in PD

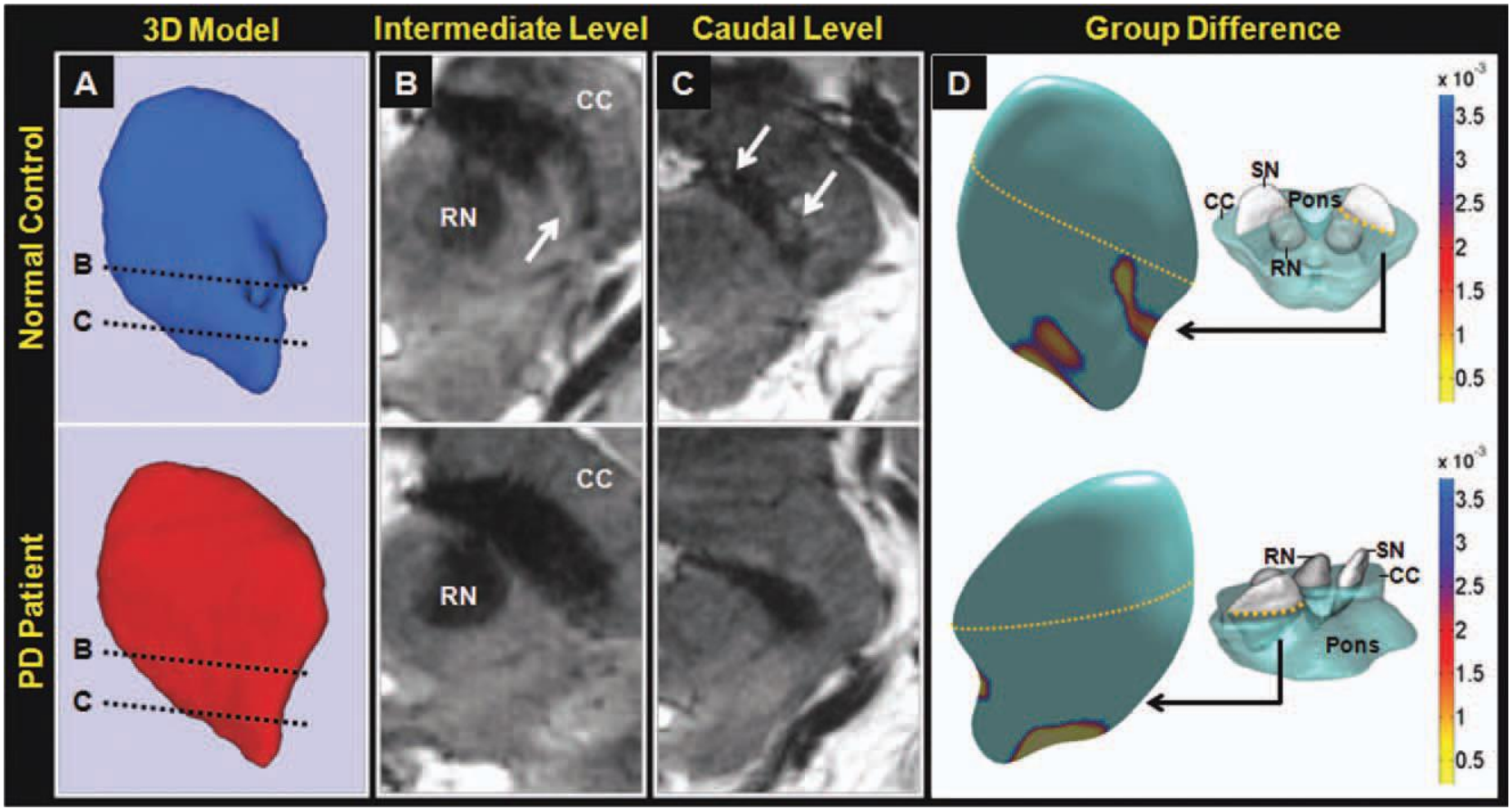
10 PD e 10 HS; 3D T2*-weighted gradient echo sequence aligned with an oblique coronal plane



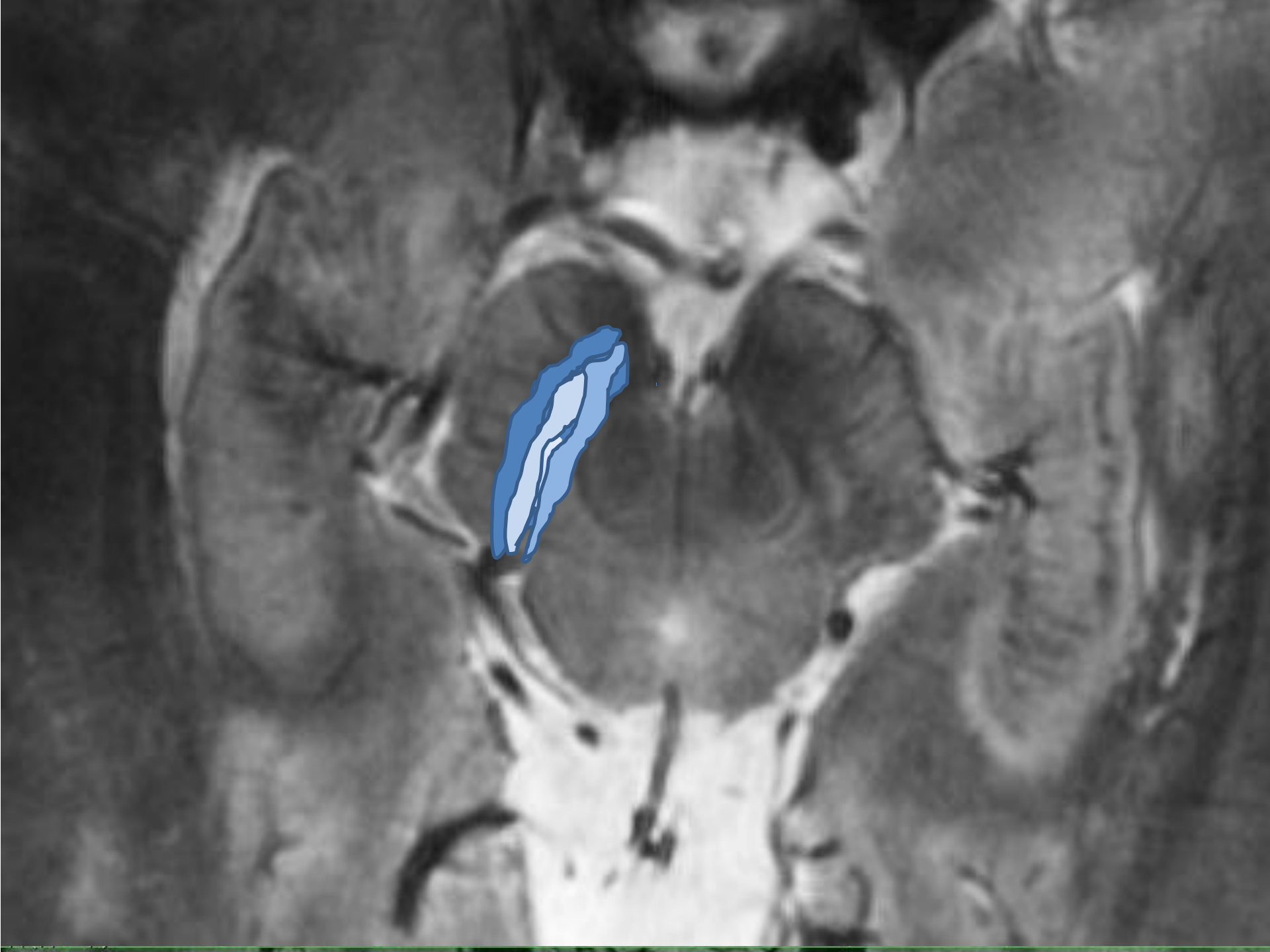
Kwon DH et al., *Ann Neurol.* 2012

7Tesla Magnetic Resonance Imaging of the Substantia Nigra in PD

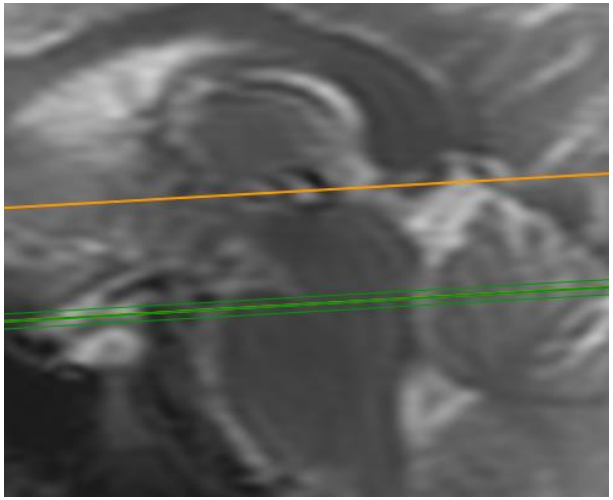
10 PD e 10 HS; 3D T2*-weighted gradient echo sequence aligned with an oblique coronal plane

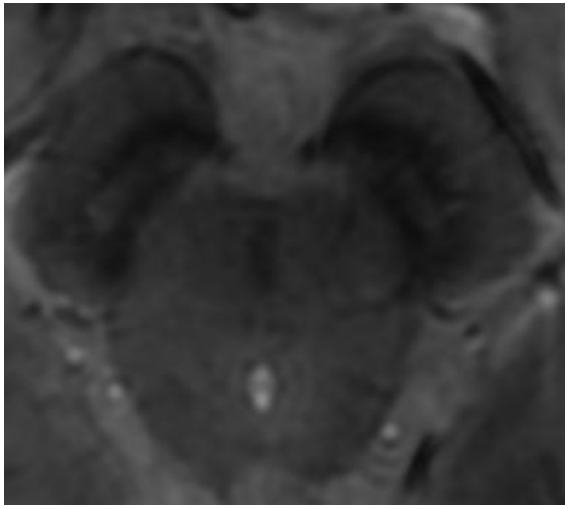


Kwon DH et al., *Ann Neurol.* 2012



Ultra-high field MRI of the SN in Parkinson's Disease

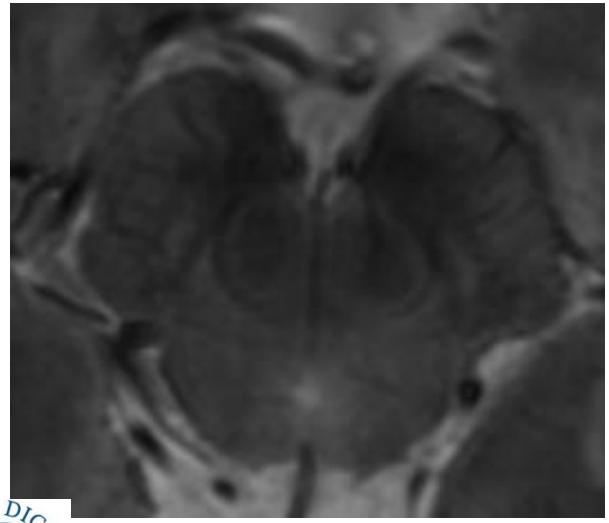




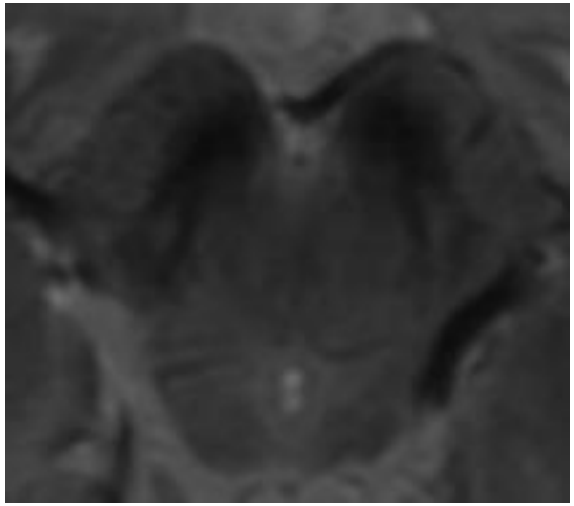
Male, 48 ys

3D SWI

In plane resolution 312µm
Thickness 1.2 mm
Total acquisition time 4' 2''



Male, 48 ys



Female, 68 ys

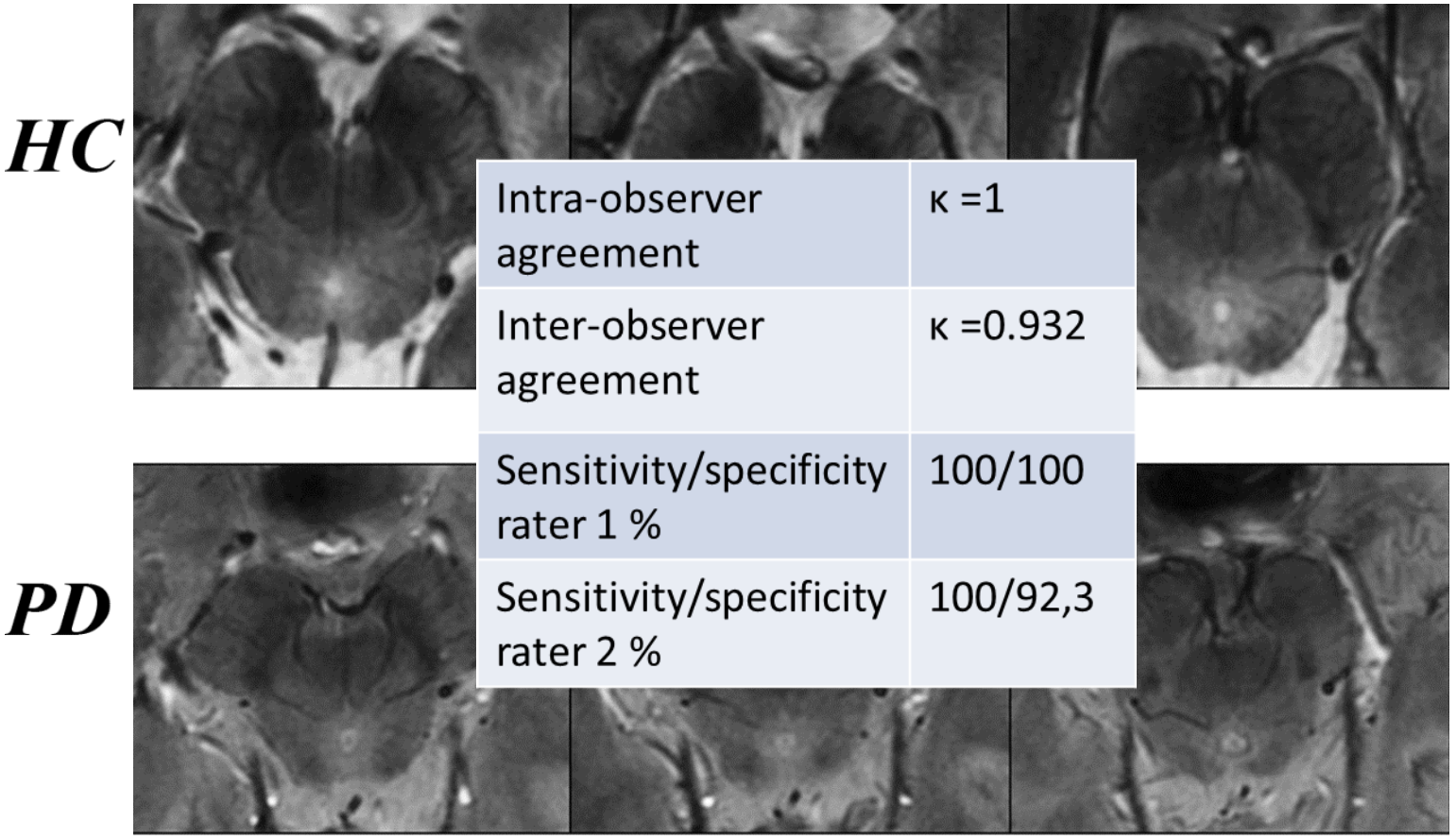
Ultra-high field MRI of the SN in Parkinson's Disease

	HS 13	PD patients 17
Sex M/F	9/4	9/8
Age M(SD) (ys), range *	54.7 (7.9), 40-66	56.0(9.6), 38-70
Disease duration M(SD) (months), range	n.a.	27.2(23.0), 6-96
Hoehn&Yahr M(SD), range	n.a.	1.7(0.4), 1-2
UPDRS II M(SD), range	n.a.	6.9(3.7), 2-13
UPDRS III item M(SD), range	n.a.	17.8(9.0), 9-37
MMSE M(SD), range	30	29.0(0.3), 29-30

*p 0.44

Cosottini M et al., *Radiology* 2014

Ultra-high field MRI of the SN in Parkinson's Disease



Intra-observer agreement	κ =1
Inter-observer agreement	κ =0.932
Sensitivity/specificity rater 1 %	100/100
Sensitivity/specificity rater 2 %	100/92,3

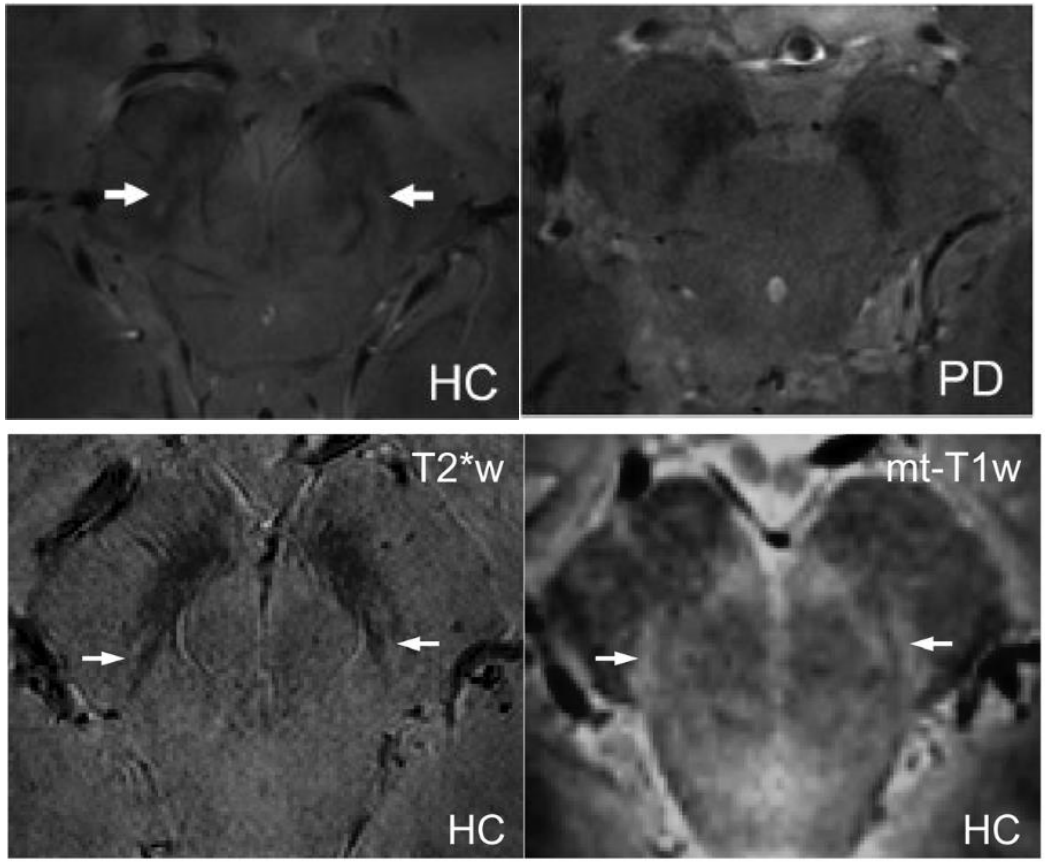
Cosottini M et al., *Radiology* 2014

Ultra-high field MRI of the SN in Parkinson's Disease

Visualization of nigrosome 1 and its loss in PD

Pathoanatomical correlation and in vivo 7 T MRI

(0.35 3 0.35 3 1.00 mm3 voxels

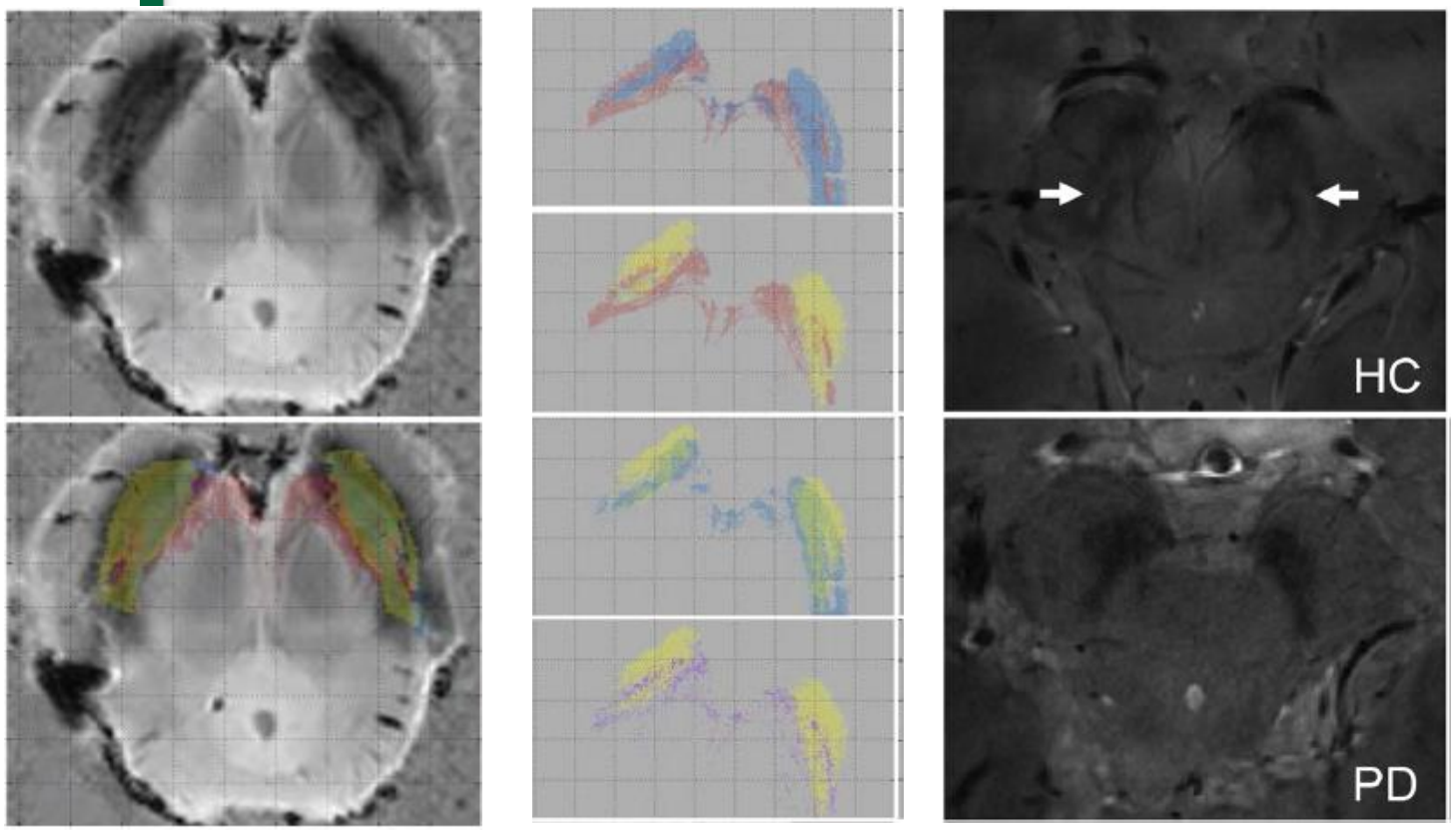


Blazejewska A et al, *Neurology* 2013

Ultra-high field MRI of the SN in Parkinson's Disease

Visualization of nigrosome 1 and its loss in PD

Pathoanatomical correlation and in vivo 7 T MRI



(0.35 3 0.35 3 1.00 mm3 voxels

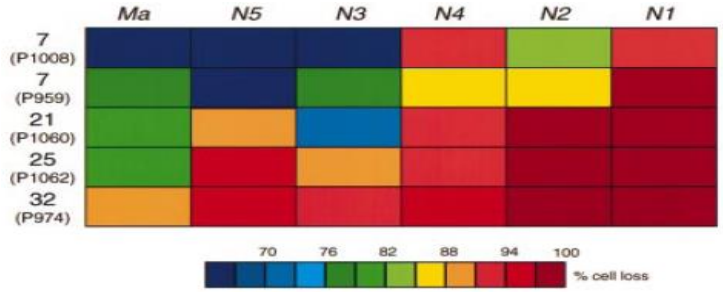
Blazejewska A et al, *Neurology* 2013

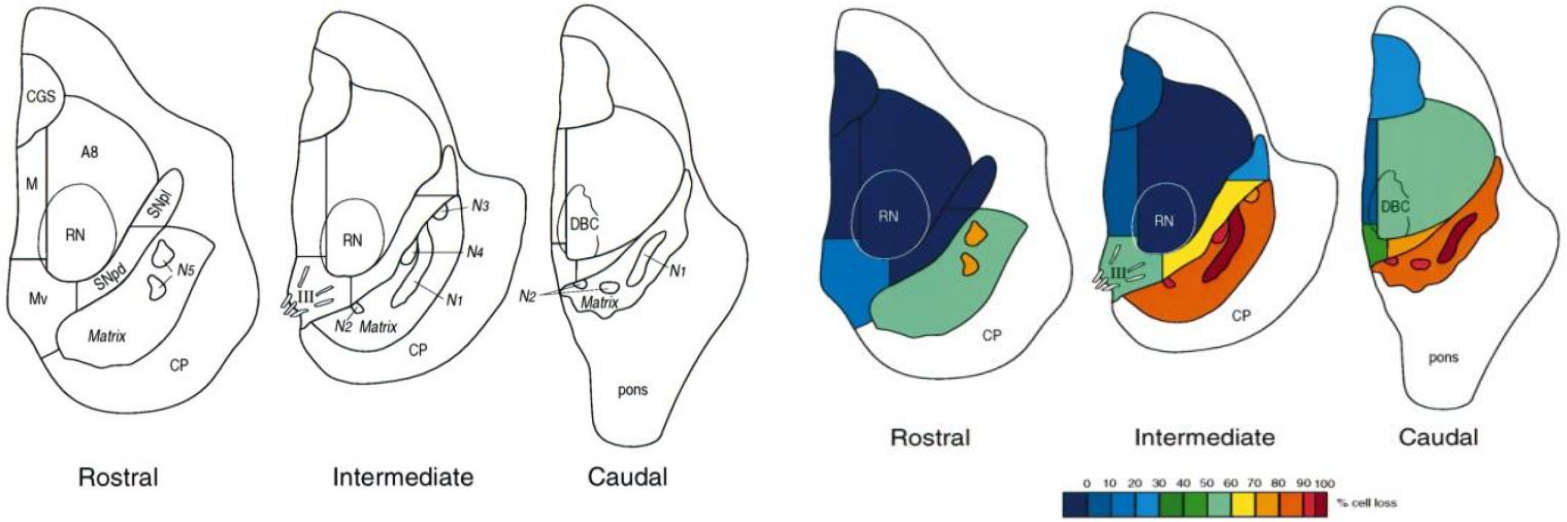
Patterns of loss of dopaminergic neurons in PD

Brain (1999), **122,** 1437–1448

The substantia nigra of the human brain
II. Patterns of loss of dopamine-containing neurons in Parkinson's disease

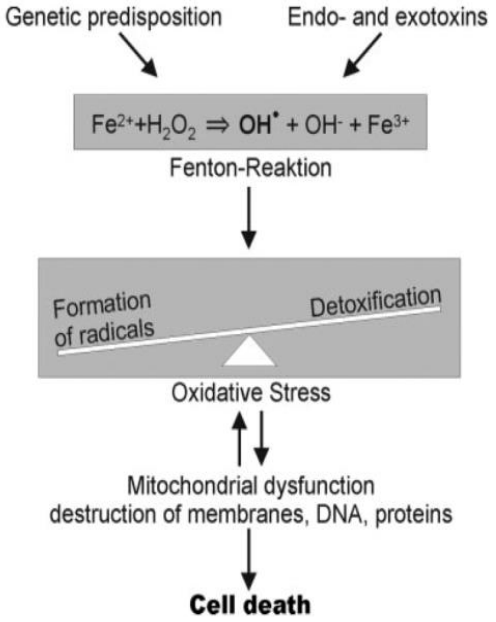
P. Damier,[1,2] E. C. Hirsch, [1] Y. Agid [1] and A. M. Graybiel[2]





Iron in Parkinson's disease: cause or consequence?

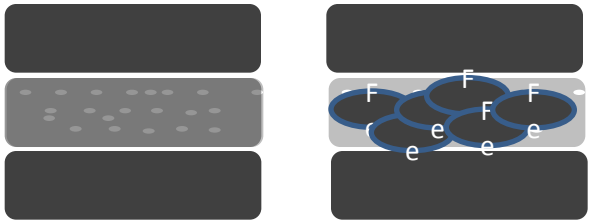
- Several studies have shown that a selective and significant elevation in iron occurs in the substantia nigra (compacta) of patients with PD.
- Animal, toxic, genetic models support this hypotesis
- Conflicting data exist about iron state in pre-clinical stages
- Multiple actors in the scene: fe3+, fe2+, ferritin, melanin, synuclein, microglia
- Neuromelanin could have both a protective and toxic effect: is abundant in highly vulnerable neurons but could also constitute a Fe-chelator



Primary iron increase, saturation of melanin chelator power, increase in F3+, increase in oxidative state, cell death….

or

Cell death due to other factor, decrease in melanin and melaninchelator power, increase in Fe3+, increase in oxidative state, more cell death



The Substantia Nigra in PD at 7 T

- Loss of Nigrosome-1 high signal intensity
- Abnormal contours
- Volume changes
- High diagnostic accuracy

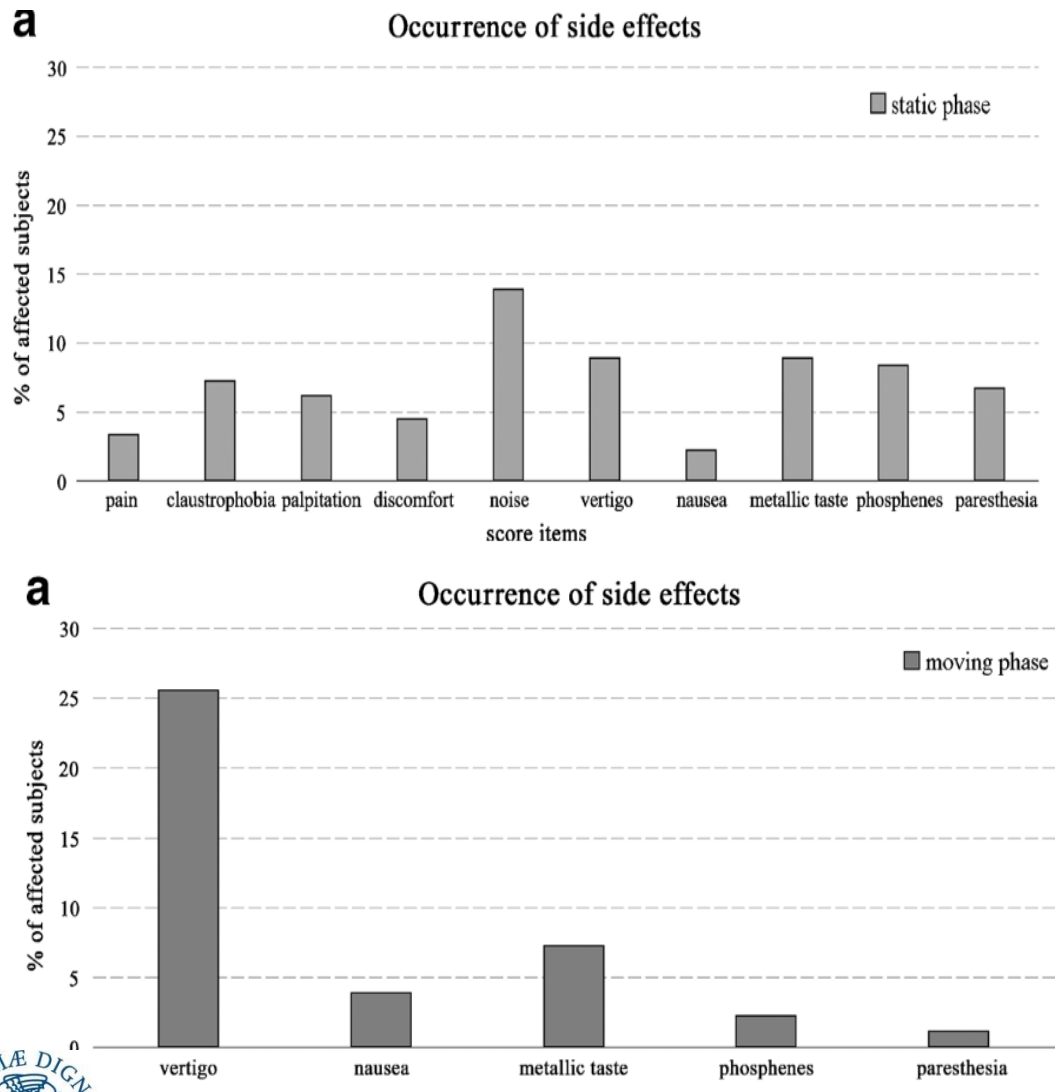
Limitations and future directions

- Safety? Extensive controindications? Higher risk for motion artifacts?
- Comparation 7T vs 3T
- Usefulness in differential diagnosis (atypical parkinsonisms)
- Relationship with functional markers of dopaminergic denervation
- Evaluation in at-risk subjects and dynamics of neurodegeneratve changes

Limitations and future directions

- **Safety? Extensive controindications? Higher risk for motion artifacts?**
- Comparation 7T vs 3T
- Usefulness in differential diagnosis (atypical parkinsonisms)
- Relationship with functional markers of dopaminergic denervation
- Evaluation in at-risk subjects and dynamics of neurodegeneratve changes

Short-term side-effects of 7T MRI: a single-centre experience

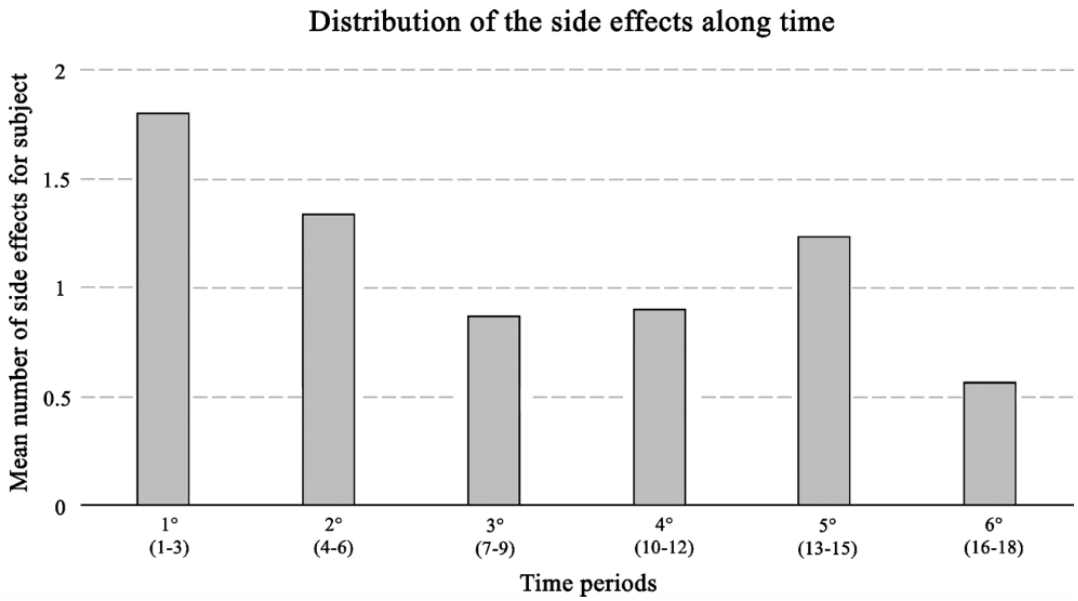


KEY POINTS

- 7T MRI is well tolerated with low incidence of side-effects
- the subjects' discomfort during 7T MRI is reduced as the operators' experience increases
- 7T MRI is practicable in healthy subjects and patients with neurodegenerative diseases

Cosottini M et al., *Eur Radiol* 2014

Short-term side-effects of 7T MRI: a single-centre experience

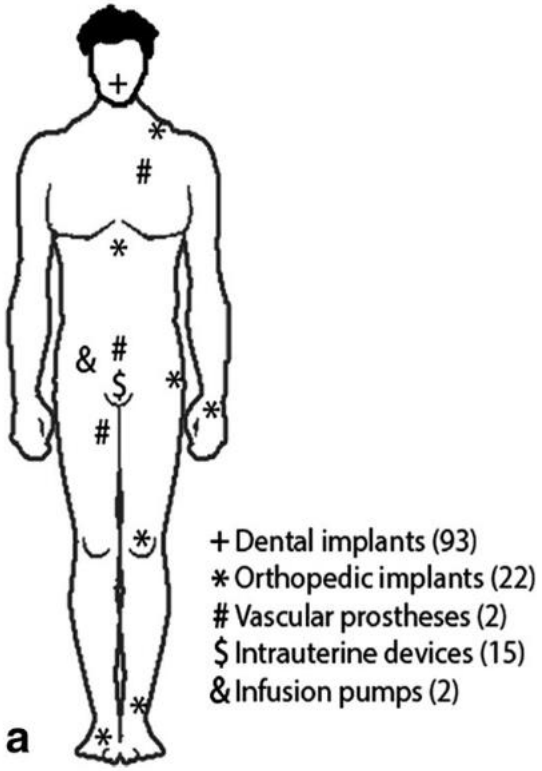


KEY POINTS

- 7T MRI is well tolerated with low incidence of side-effects
- the subjects' discomfort during 7T MRI is reduced as the operators' experience increases
- 7T MRI is practicable in healthy subjects and patients with neurodegenerative diseases

Cosottini M et al., *Eur Radiol* 2014

Experience with magnetic resonance imaging of human subjects with passive implants and tattoos at 7 T: a retrospective study



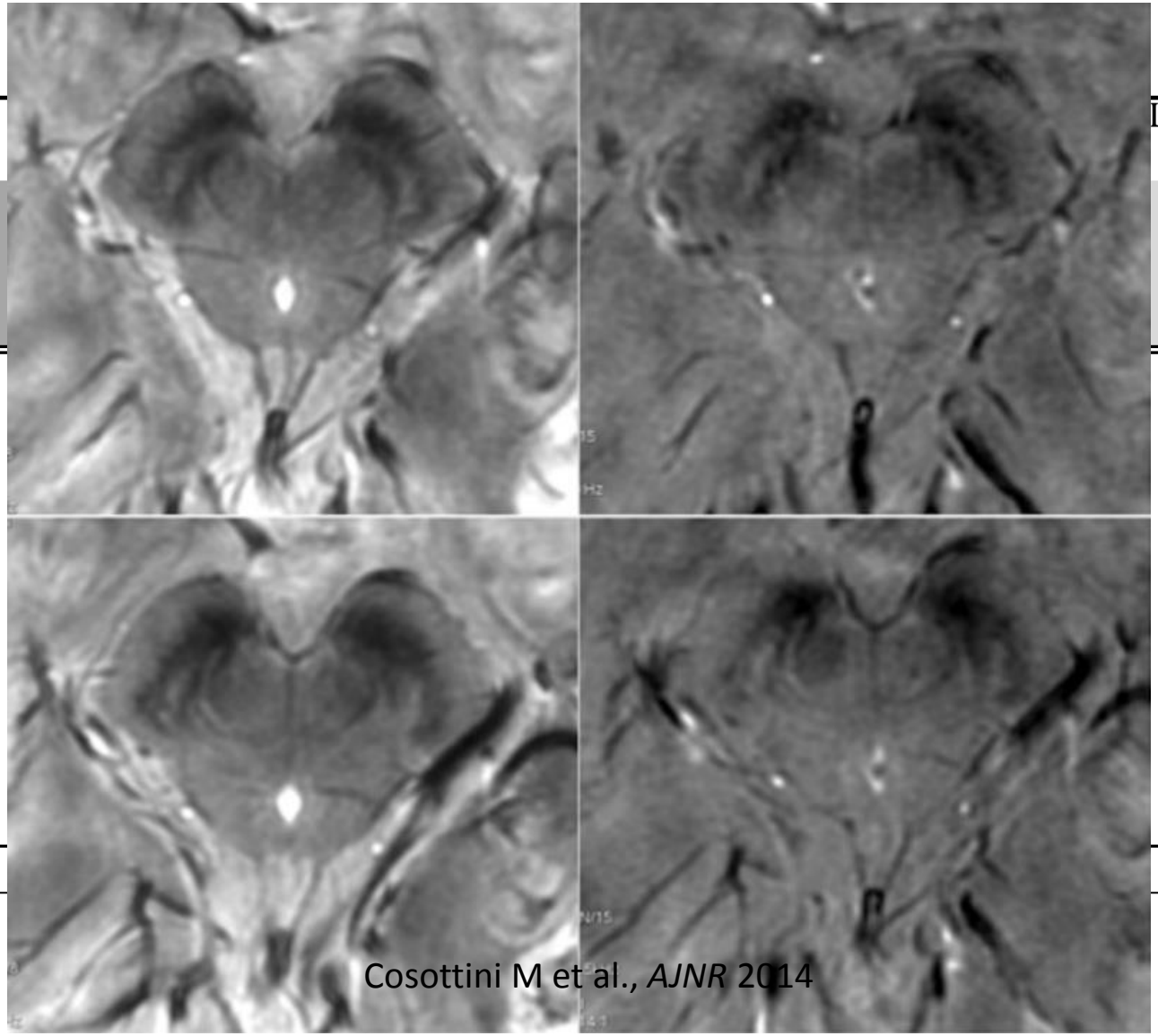
+ Dental implants (93)
* Orthopedic implants (22)
# Vascular prostheses (2)
$ Intrauterine devices (15)
& Infusion pumps (2)

MAGMA 2015

Limitations and future directions

- Safety? Extensive controindications? Higher risk for motion artifacts?
- **Comparation 7T vs 3T**
- Usefulness in differential diagnosis (atypical parkinsonisms)
- Relationship with functional markers of dopaminergic denervation
- Evaluation in at-risk subjects and dynamics of neurodegeneratve changes

Comparison of 3T and 7T SWAN Imaging of the SN in diagnosing PD



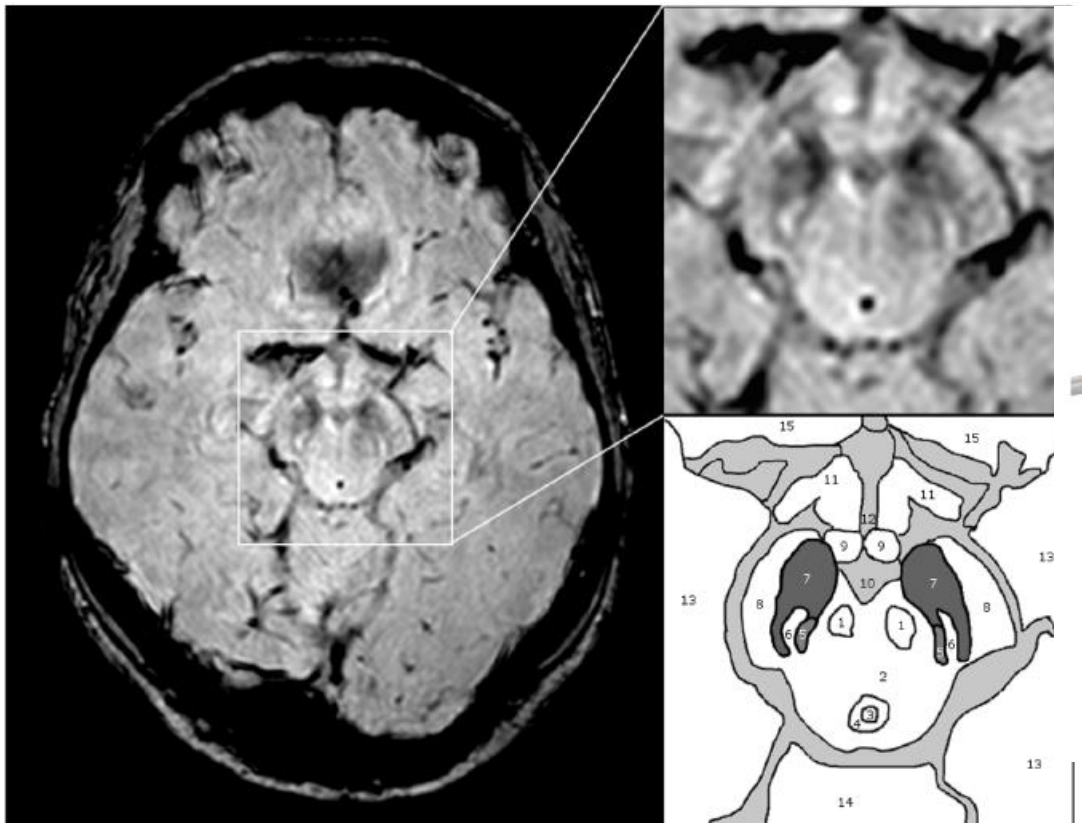
	LA	
	R3	R3
	1th	2nd
SENSITIVITY	79	79
SPECIFICITY	100	100
PPV	100	100
NPV	81	81
ACCURACY	89	89
TP/TN	11/13	11/13

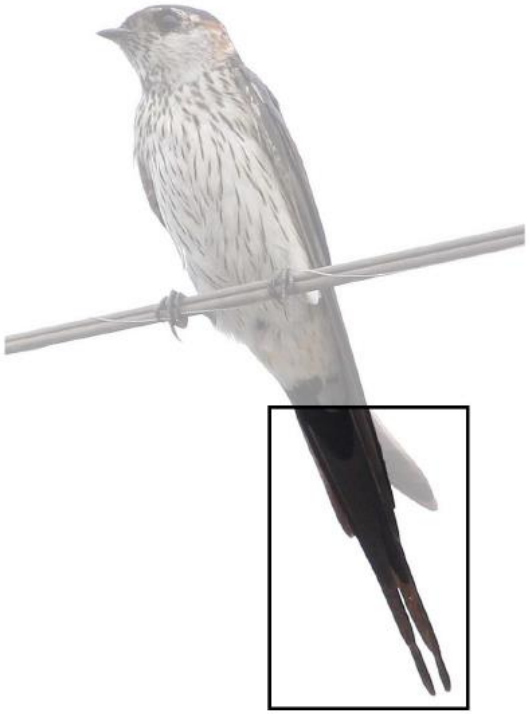
Cosottini M et al., *AJNR* 2014

High field MRI of the SN in Parkinson's Disease

The 'Swallow Tail' Appearance of the Healthy Nigrosome – A New Accurate Test of Parkinson's Disease: A Case-Control and Retrospective Cross-Sectional MRI Study at 3T

Stefan T. Schwarz[1]*, Mohammed Afzal[2], Paul S. Morgan[3], Nin Bajaj[4], Penny A. Gowland[5], Dorothee P. Auer[1]





Schwarz ST et al., *PLOS one* 2014

Routinary approach?

Retrospective evaluation of a consecutive 3-T susceptibility-weighted imaging dataset:
86 examinations: 74 controls (cephalalgia, stroke, epilepsy) and 12 patients with PD

- **SENSITIVITY 91.6%**
- **SPECIFICITY 94.6%**
- **DIAGNOSTIC ACCURACY 94.1%**

Higher values could be obtained in scans of higher quality and specifically obtained to assess the SN state

Cosottini M et al., *Radiology* 2014

Summary of evidences

3T nigrosome MRI evaluation

Both retrospective and prospective approach

Noh et al, 2015
Reiter et al, 2015
Cosottini et al, 2014,2014
Schwartz et al, 2014

175 Patients with PD

True positive 158

False negative 17

232 subjects without PD

True negative 221

False positive 15

Sensitivity	90%
Specificity	94%
PPV	91%
NPV	93%

Loss of dorsolateral nigral hyperintensity as a marker for PD

Meta-Analysis of Dorsolateral Nigral Hyperintensity on Magnetic Resonance Imaging as a Marker for Parkinson's Disease

Philipp Mahlknecht, MD, PhD,[1] Florian Krismer, MD, PhD,[1] Werner Poewe, MD,[1,2] and Klaus Seppi, MD[1,2*]

TABLE 1. Overview of blinded studies included in the analysis

Study	Sequence (scan time in minutes)	PD, n	Disease duration, y[a]	UPDRS-III[a]	Hoehn and Yahr stage[a]	HC, n	APD, n[c]	Non-neuro-degenerative parkinsonism, n[d]	Intrarater kappa	Interrater kappa	Nondiagnostic scans, %
3T											
Schwarz et al 2014[3] (prospective)	HR-SWI (2.4)	10	4.0 ± 3.4	32.5 ± 15.4	1.9 ± 0.9	9			0.82	0.82	0
Schwarz et al 2014[3]	PRESTO (HR-T2*/SWI; 2.6)	9				81[b]					5.3
Reiter et al 2015[6]	SWI (<4.0)	90	5.9 ± 4.3	28.9 ± 11.9	2.3 ± 0.1	35	42		0.869	0.838	12.1
Sung et al 2016[9]	MEDIC (7.3)	29	1.7 (1.0-4.7)	14 (9-25)	2 (2-2)	20		20		0.825	0
Noh et al 2015[10]	MEDIC (4.8)	24	0.8 (0.3-1.0)	13.5 ± 6.2	2 (2-2)	13				0.863	0
Bae et al 2016[8]	SWI (NS)	126	Around 2		2 (1-2)	26	22	36	0.93	0.83	13.2
Oh et al 2016[12]	3D FLAIR (5.8-8.8)	19				0		13		0.625	0
7T											
Blazejewska et al 2013 (prospective)[2]	T2* (10.0)	10	3 ± 2	24 ± 13		8					5.3
Kim et al 2016[7]	T2* (30)	30			1 and 2 (n = 21) 3 and 4 (n = 9)	26	10		1	1	0
Cosottini et al 2014 (prospective)[11]	SWI (4.0)	17	2.3 ± 1.9	17.8 ± 9.0	1.7 ± 0.4	13			1	0.932	6.3

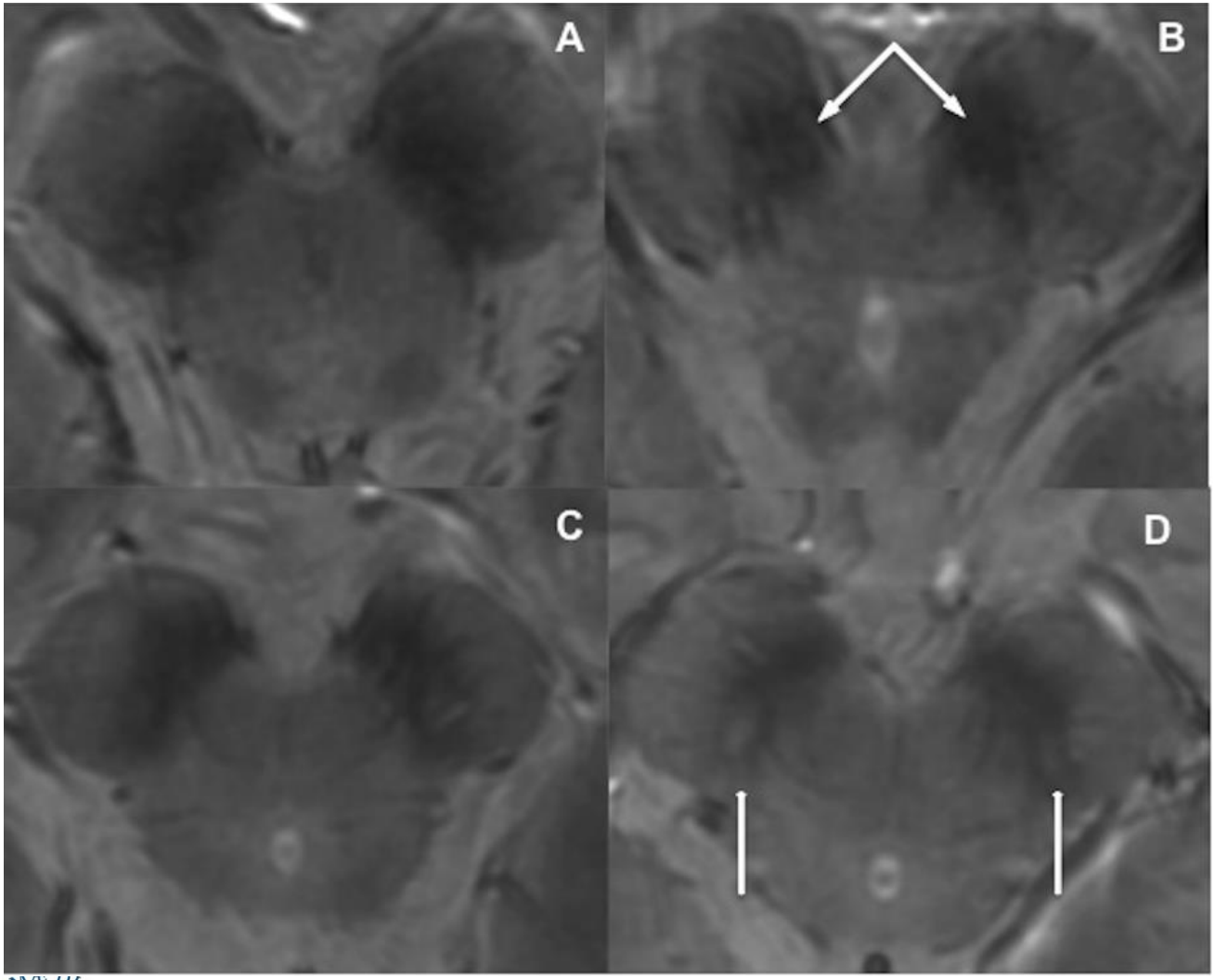
Results: Of the 16 identified studies, 10 were suitable for analysis, including 364 PD and 231 control cases. The meta-analysis showed an overall sensitivity and specificity of the absence of dorsolateral nigral hyperintensity for PD versus controls of 97.7% and 94.6% (3 and 7 Tesla) and of 94.6% and 94.4% (3 Tesla only). Descriptive analysis among the 4 studies including patients with non-PD parkinsonism showed that dorsolateral nigral hyperintensity was absent in 89.4% of cases with atypical parkinsonian disorders (n = 74), but only in 21.7% of cases with non-neurodegenerative parkinsonism (n = 69). Moreover, in 2 of these studies, the absence of dorsolateral nigral hyperintensity predicted ipsilateral dopamine-transporter deficiency with 87.5% sensitivity and 83.6% specificity.

Mahlknecht P et al., *Mov Disord* 2017

Limitations and future directions

- Safety? Extensive controindications? Higher risk for motion artifacts?
- Comparation 7T vs 3T
- **Usefulness in differential diagnosis (atypical parkinsonisms)**
- Relationship with functional markers of dopaminergic denervation
- Evaluation in at-risk subjects and dynamics of neurodegeneratve changes

Ultra-high field MRI of the SN in atypical parkinsonisms



Lack of differential diagnosis between parkinsonisms with qualitative data

Sparing of SN UHF organization in CBD: heterogeneous disease?

Frosini D et al., *J Neural Transm* 2016

Dopamine transporter SPECT in corticobasal degeneration

ELSEVIER

Journal of the Neurological Sciences 216 (2003) 127–134

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Pathological heterogeneity of clinically diagnosed corticobasal degeneration

M. Doran, D.G. du Plessis, T.P. Enevoldson, N.A. Fletcher, E. Ghadiali, A.J. Larner*

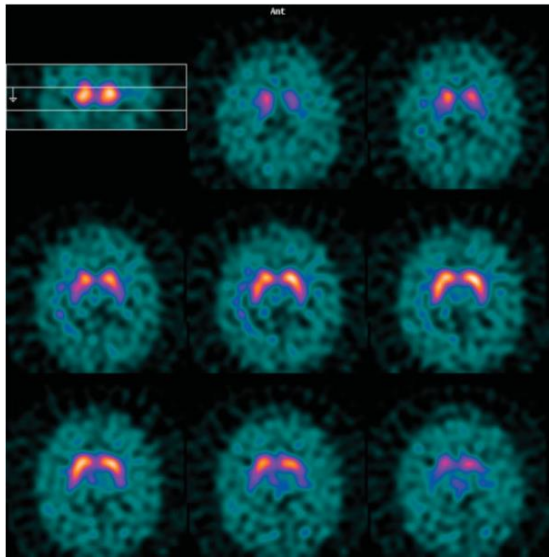
Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Lower Lane, Fazakerley, Liverpool, L9 7LJ, UK

Received 6 September 2002; received in revised form 18 July 2003; accepted 24 July 2003

Abstract

Two patients fulfilling suggested clinical diagnostic criteria for corticobasal degeneration (CBD) are presented, who were found at postmortem to have alternative pathological diagnoses not suspected during life, namely, Alzheimer's disease and Pick's disease, respectively. The nosological position of these cases is considered in light of a literature review of previous reports of clinically diagnosed corticobasal degeneration with atypical (not corticobasal degeneration) pathology. Since such phenocopies may be common, we suggest that all clinically diagnosed cases of corticobasal degeneration should initially be labelled as "corticobasal degeneration syndrome" (CBDS) to emphasize that this is a diagnosis based on clinical phenotype, with the term corticobasal degeneration being reserved for the specific neuropathological phenotype, which itself may have a variety of clinical presentations.

Normal Dopamine Transporter Single Photon-Emission CT Scan in Corticobasal Degeneration

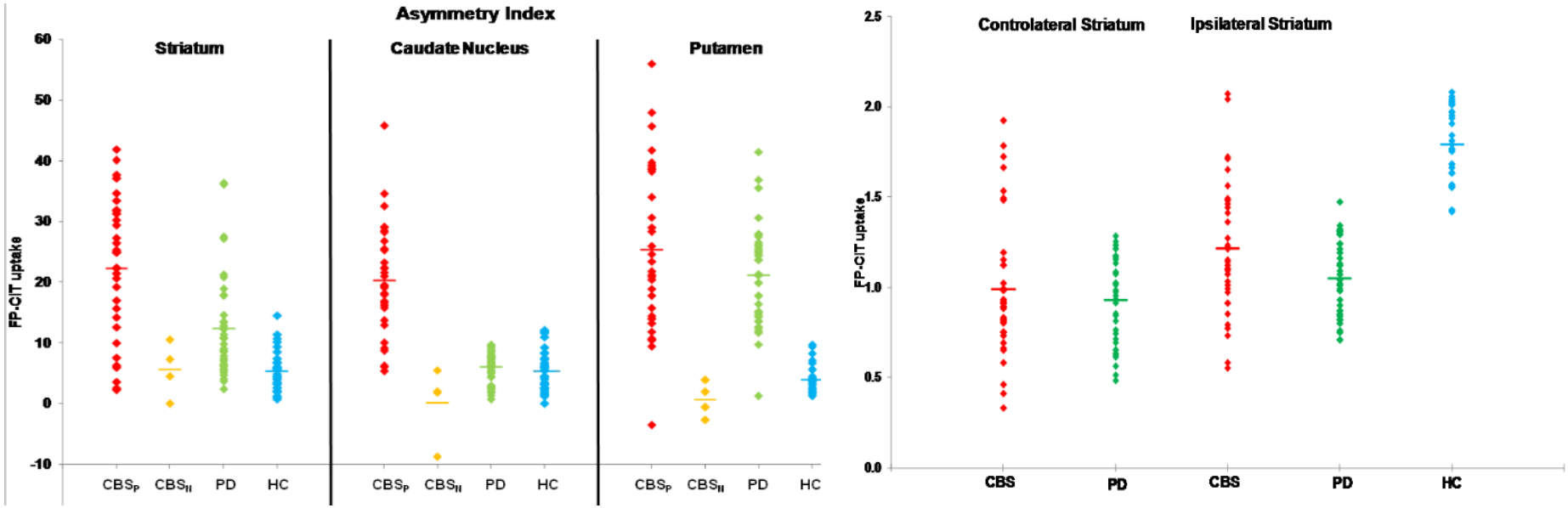


Movement Disorders
Vol. 23, No. 16, 2008, pp. 2420–2431

Dopamine transporter SPECT in corticobasal degeneration

Dopamine Transporter SPECT Imaging in Corticobasal Syndrome

Roberto Cilia[1], Carlo Rossi[2], Daniela Frosini[2], Duccio Volterrani[3], Chiara Siri[1], Cristina Pagni[2], Riccardo Benti[4], Gianni Pezzoli[1], Ubaldo Bonuccelli[2,5], Angelo Antonini[1,6,7], Roberto Ceravolo[2]*



CBS vs healthy controls:

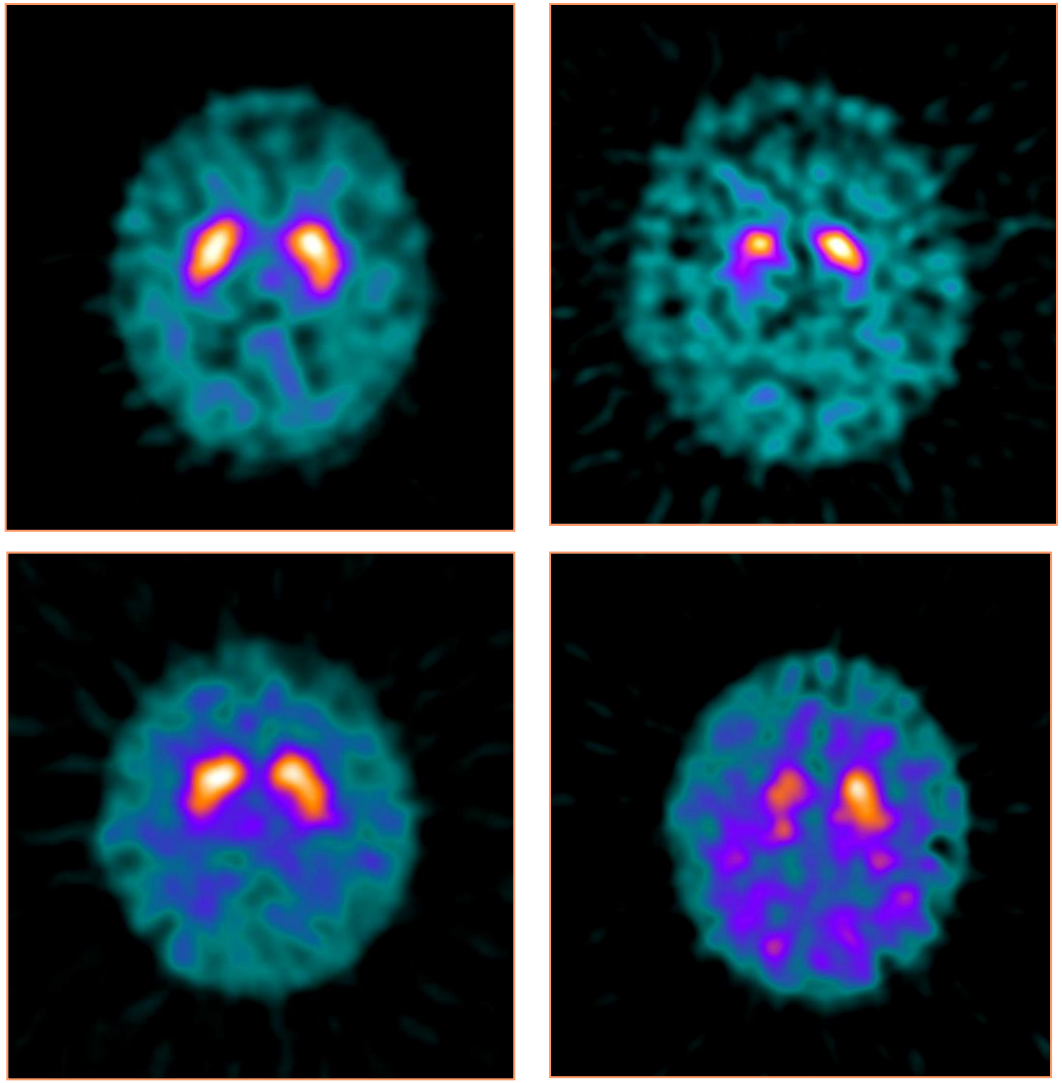
32 pts with pathological SPECT (**CBSp)**

4 pts with normal SPECT (**CBSn**)

CBSn follow-up

Case 1

Case 2



Ceravolo R et al., *Parkinsonism Relat Disord.* 2013

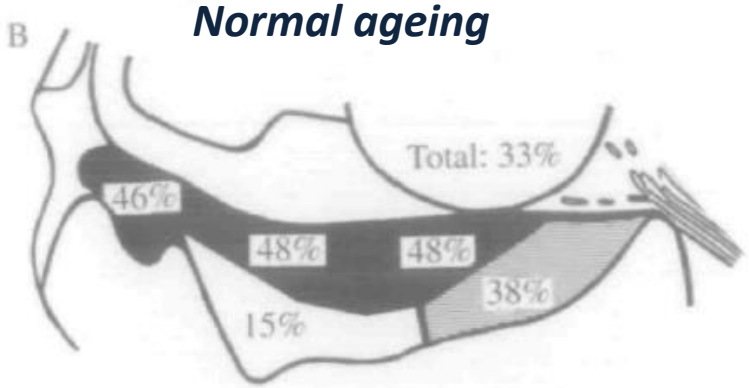
Substantia Nigra changes in normal ageing, PD and PSP

AGEING AND PARKINSON'S DISEASE: SUBSTANTIA NIGRA REGIONAL SELECTIVITY

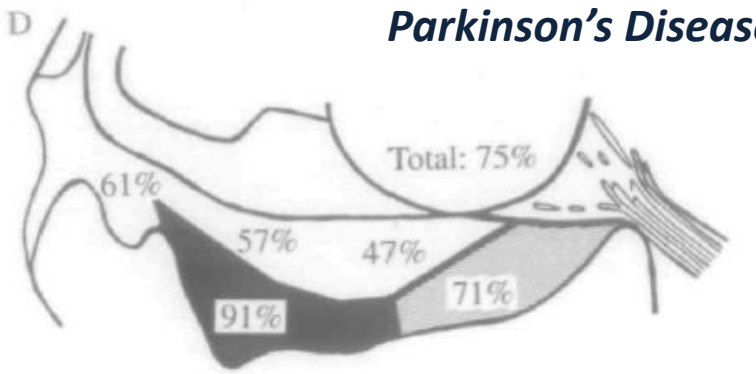
by JULIAN M. FEARNLEY *and* ANDREW J. LEES

(From the National Hospital, Queen Square, London, UK)

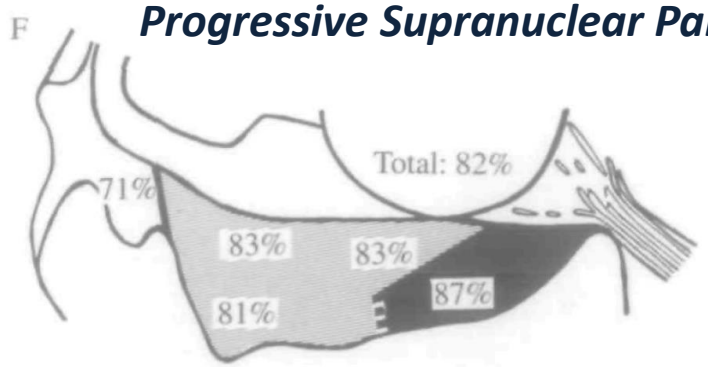
Normal ageing



Parkinson's Disease



Progressive Supranuclear Palsy



9.4 T MR microscopy of the substantia nigra with pathological validation in controls and disease

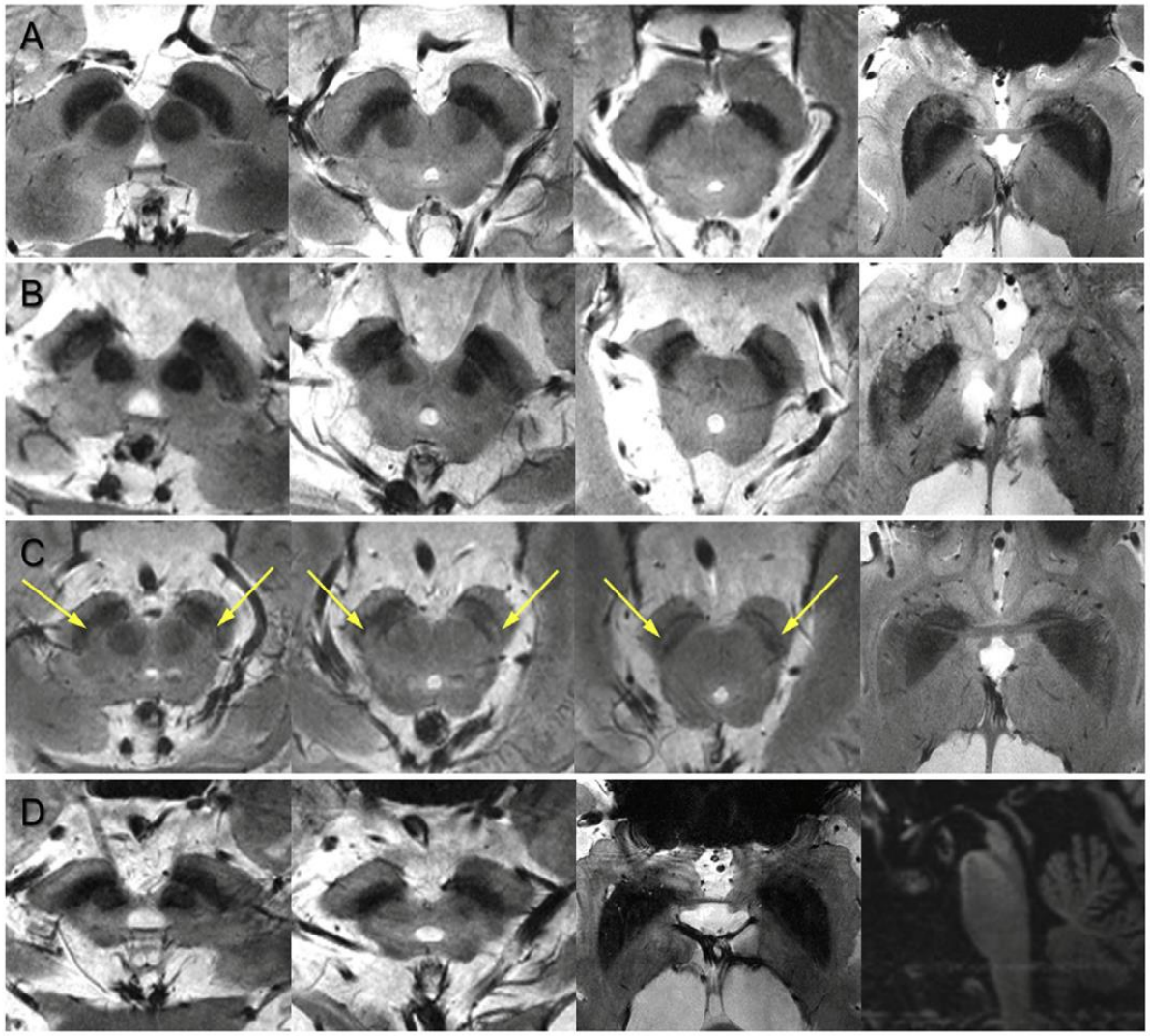
LA Massey[a,b,*], MA Miranda[c], O Al-Helli[a,e], HG Parkes[e], JS Thornton[f], P-W So[g], MJ White[f], L Mancini[f], C Strand[b], J Holton[b], AJ Lees[a,b,d], T Revesz[b], TA Yousry[e,f]

A B S T R A C T

Background: The anatomy of the substantia nigra on conventional MRI is controversial. Even using histological techniques it is difficult to delineate with certainty from surrounding structures. We sought to define the anatomy of the SN using high field spin-echo MRI of pathological material in which we could study the anatomy in detail to corroborate our MRI findings in controls and Parkinson's disease and progressive supranuclear palsy.
Methods: 23 brains were selected from the Queen Square Brain Bank (10 controls, 8 progressive supranuclear palsy, 5 Parkinson's disease) and imaged using high field 9.4 Tesla spin-echo MRI. Subsequently brains were cut and stained with Luxol fast blue, Perls stain, and immunohistochemistry for substance P and calbindin. Once the anatomy was defined on histology the dimensions and volume of the substantia nigra were determined on high field magnetic resonance images.
Results: The anterior border of the substantia nigra was defined by the crus cerebri. In the medial half it was less distinct due to the deposition of iron and the interdigitation of white matter and the substantia nigra. The posterior border was flanked by white matter bridging the red nucleus and substantia nigra and seen as hypointense on spin-echo magnetic resonance images. Within the substantia nigra high signal structures corresponded to confirmed nigrosomes. These were still evident in Parkinson's disease but not in progressive supranuclear palsy. The volume and dimensions of the substantia nigra were similar in Parkinson's disease and controls, but reduced in progressive supranuclear palsy.
Conclusions: We present a histologically validated anatomical description of the substantia nigra on high field spin-echo high resolution magnetic resonance images and were able to delineate all five nigrosomes. In accordance with the pathological literature we did not observe changes in the nigrosome structure as manifest by volume or signal characteristics within the substantia nigra in Parkinson's disease whereas in progressive supranuclear palsy there was microarchitectural destruction.

Massey LA et al., *Neuroimage* 2017

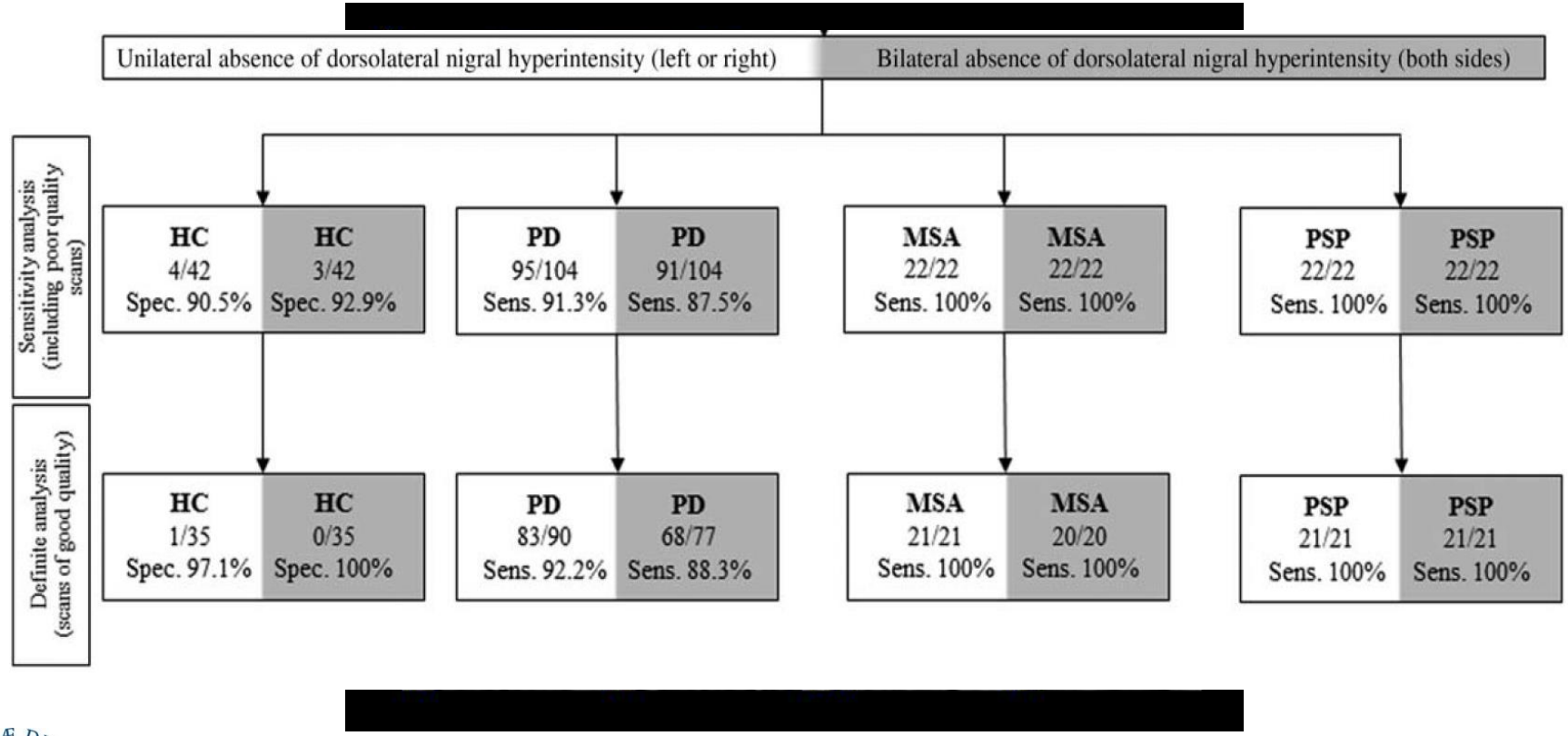
Loss of dorsolateral nigral hyperintensity in PD, MSA and PSP on 7T MRI



Kim JM et al., *Parkinsonism Relat Disord.* 2016

High field MRI of the SN in atypical parkinsonisms

42 Healthy controls
104 Parkinson's Disease
22 Multiple System Atrophy
22 Progressive Supranuclear Palsy



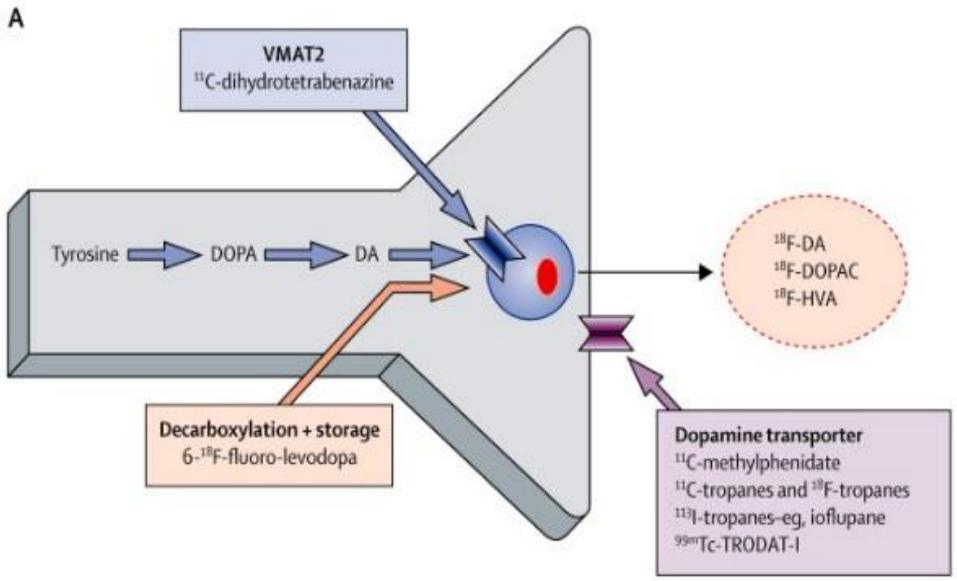
Reiter E et al, *Mov Disord* 2015

Limitations and future directions

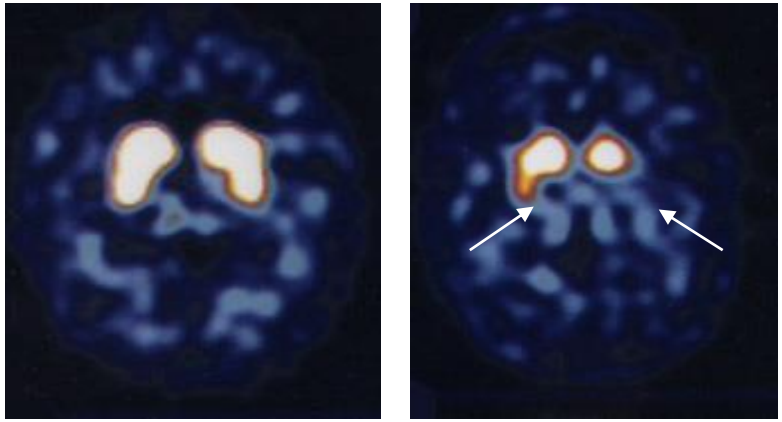
- Safety? Extensive controindications? Higher risk for motion artifacts?
- Comparation 7T vs 3T
- Usefulness in differential diagnosis (atypical parkinsonisms)
- **Relationship with functional markers of dopaminergic denervation**
- Evaluation in at-risk subjects and dynamics of neurodegeneratve changes

Imaging dopamine terminal function

DAT TRACER BINDING = Density of DAergic terminals



^{123}I-ioflupane SPECT images



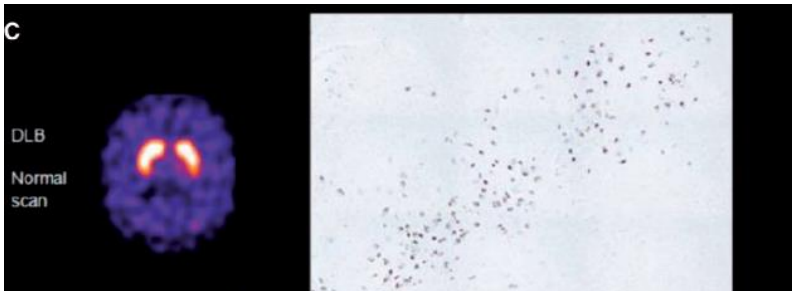
Healthy Control

Parkinson's disease

Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias

Colloby et al.

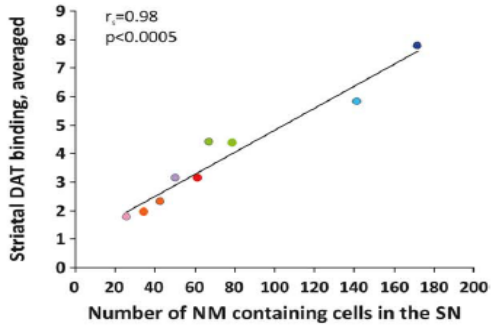
Brain 2012

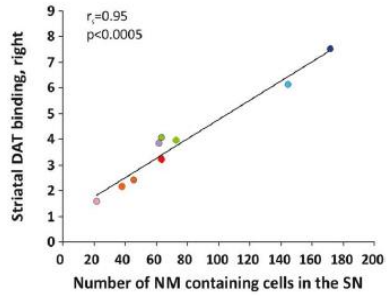


Tracer uptake was associated with nigral dopaminergic neuronal density, but not with a-synuclein , tau or amyloid b burden

Correlation of Striatal Dopamine Transporter Imaging With Post Mortem Substantia Nigra Cell Counts

Julia Kraemmer, MD,[1] Gabor G. Kovacs, MD,[2] Laura Perju-Dumbrava, MD,[1] Susanne Pirker, MD,[1] Tatiana Traub-Weidinger, MD,[3] and Walter Pirker, MD[1]*





Movement Disorders, 2014

AJNR 2015

Nigrosome 1 Detection at 3T MRI for the Diagnosis of Early-Stage Idiopathic Parkinson Disease: Assessment of Diagnostic Accuracy and Agreement on Imaging Asymmetry and Clinical Laterality

Y. Noh, Y.H. Sung, J. Lee, and E.Y. Kim

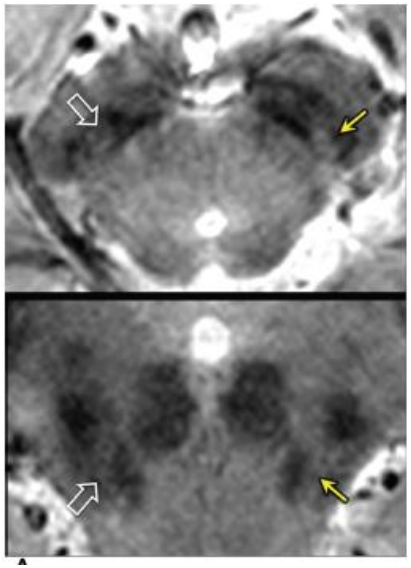
18F-FP-CIT & 3T MRI

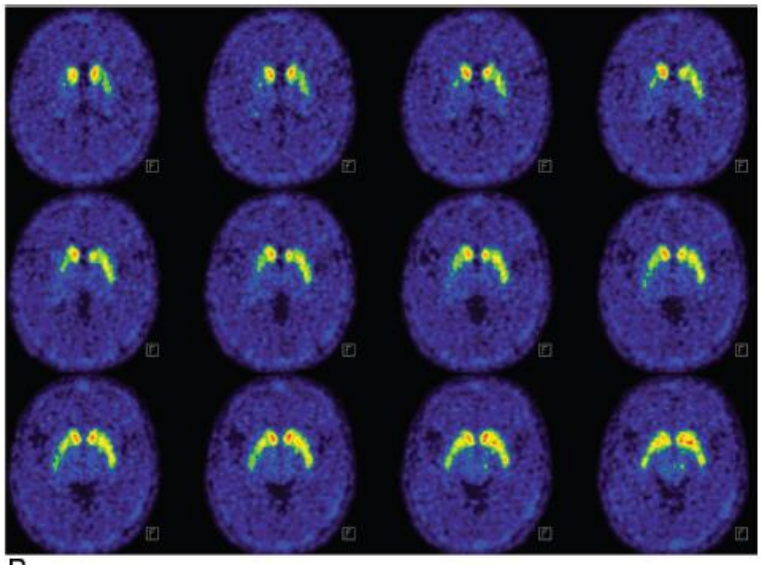
24 PD

13 HC

Sensitivity, specificity, and accuracy of the nigrosome 1 detection at 3T MR imaging were 100%, 84.6%, and 94.6%, respectively.

In PD the agreement of asymmetry between clinical laterality and nigrosome 1 detection was good (0.724). The degree of the 18F-FP-CIT PET binding showed fair agreement (0.235) with clinical laterality.

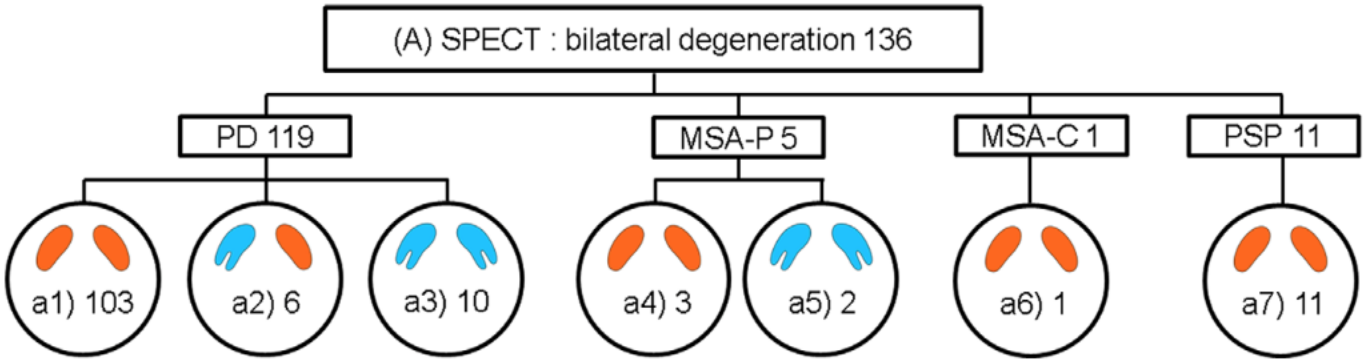


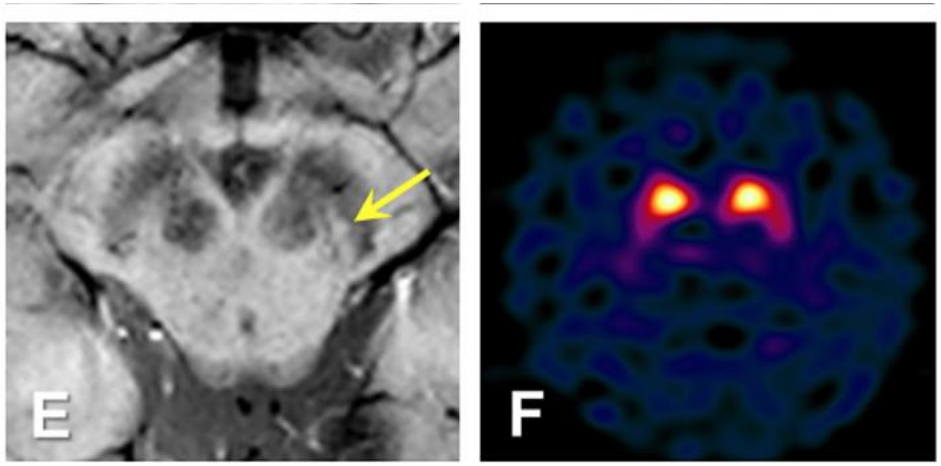


-18F-FP-CIT PET shows nigrostriatal functional changes that are earlier than structural changes observed in the nigrosome 1 detection ????

-support the dying-back phenomenon ????

Loss of Nigral Hyperintensity on 3 Tesla MRI of Parkinsonism: Comparison With ^{123}I-FP-CIT SPECT





Bae et al, Mov Dis 2016

Limitations and future directions

- Safety? Extensive controindications? Higher risk for motion artifacts?
- Comparation 7T vs 3T
- Usefulness in differential diagnosis (atypical parkinsonisms)
- Relationship with functional markers of dopaminergic denervation
- **Evaluation in at-risk subjects and dynamics of neurodegeneratve changes**

MDS Research Criteria for prodromal PD

PREMOTOR PHASE

PRECLINICAL PARKINSONISM	Neurodegenerative process has begun but no sign or symptoms are present.
PRODROMAL PARKINSONISM	Early symptoms or signs of neurodegeneration are present, but classic clinical diagnosis based on motor features is not yet possible.

MOTOR PHASE

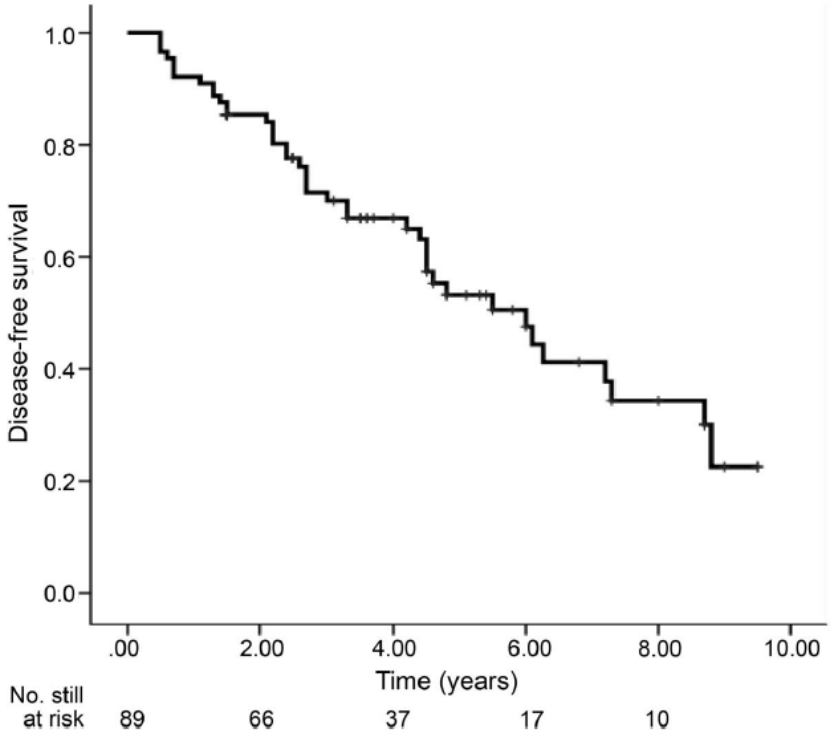
CLINICAL PARKINSONISM	Full parkinsonism is present (as defined in accordance to current MDS diagnostic criteria)

Berg D et al, *Mov Disord*. 2015

Biomarkers of parkinsonism: CLINICAL MARKERS

iRBD

REM sleep behaviour disorder (RBD) is a parasomnia characterized by the loss of normal skeletal muscle atonia during REM sleep with prominent motor activity accompanying dreaming (BOEVE BF, *Brain 2007; ICSD2)*.



iRBD as a prodromal marker

- ***HIGH SPECIFICITY***

80% of PSG-proven RBD individuals develop a neurodegenerative outcome (synucleinopathies);

-MODEST SENSITIVITY

Only one-third to one-half of patients with early PD have RBD

-Lead Time relatively long

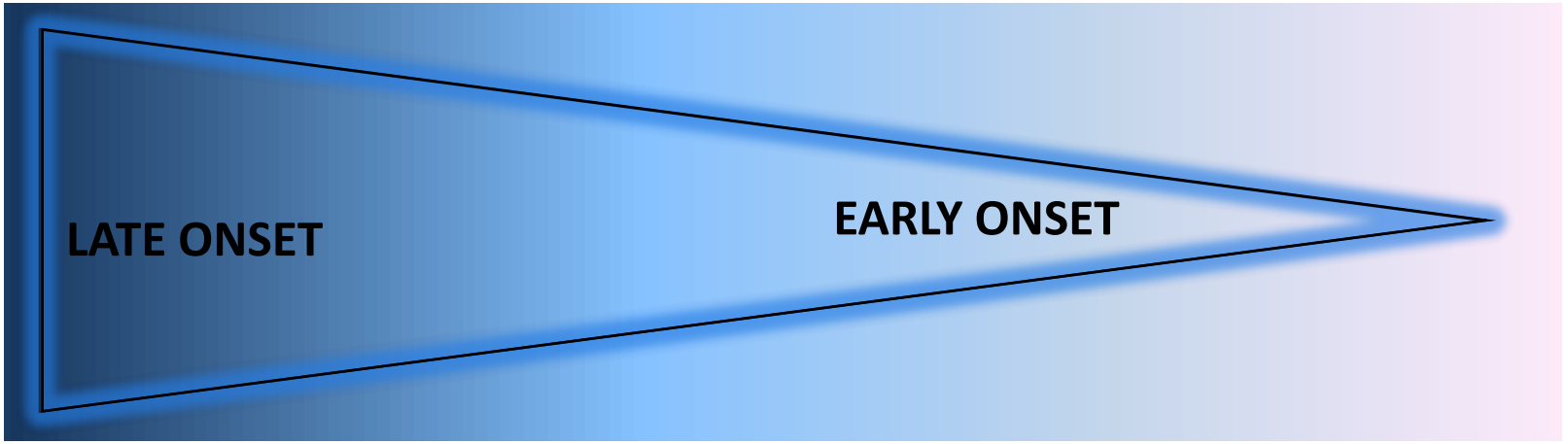
The median estimate of time between RBD and neurodegenerative disease onset is 13 years

Autosomal dominant PD genes

Polymorphisms
(++ in dominant PD genes: RR 1.1-1.4)

Mutations in dominant PD genes: reduced penetrance: RR 5-20

Sporadic ***Familial***



Multifactorial ***Mendelian***

Autosomal dominant PD genes

PARK8 - LRRK2 - Dardarin

Only 6 mutations with confirmed pathogenicity and familial recurrence (high risk)

1-2% of sporadic PD ⟸ *G2019S mutation* ⟹ ***5-8% of familial PD***

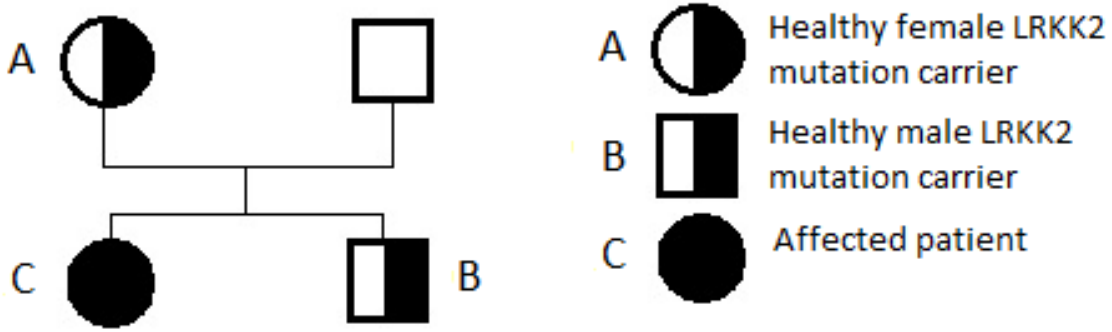
Founder effect among Ashkenazi Jews and North African Arabs

- variable presentation, onset 3rd-8th decade
- indistinguishable from idiopathic PD also for non-motor signs, but:
  - less hyposmia
  - less cognitive impairment and dementia
  - less frequent occurrence of lewy body pathology
- same prevalence for men and women (no sex effect)
- reduced penetrance: 25-30% by age 80 years
- The risk of PD for LRRK2 mutation carriers varies with the age: 28% at age 59 years, 51% at 69 years, and 74% at 79 years;

Gaig, PLoS one 2014; Saunders-Pullmann, Ann Clin Trans Neurol 2014; Srivatsal, Mov Disord 2015; Marder, Neurology 2015; Kalia Jama Neurol 2015; Gan Or, Park Relat Disord 2015; Infante et al, Neurobiol Ag 2015

Nigral and nigrostriatal imaging in high-risk individuals

LRKK2 mutation carriers: a family report



All G2019SLRKK2 mutation carriers (symptomatic and asymptomatic) underwent:

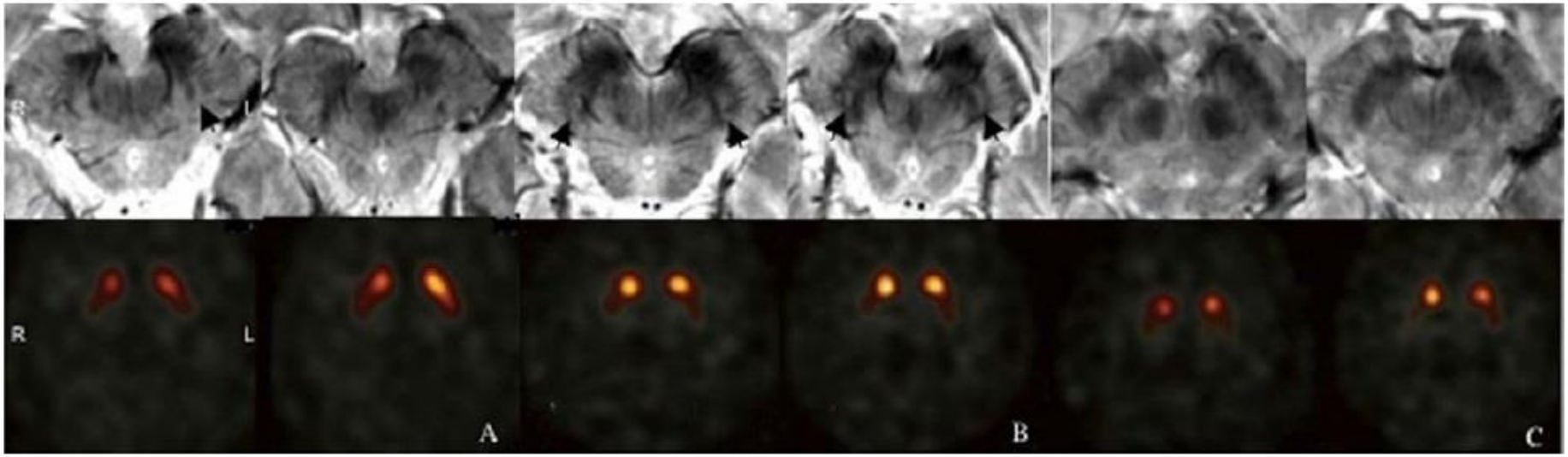
123I-FP-CIT SPECT imaging;
7T MRI (SWAN sequences).

Ceravolo R et al, *Mov Disord* 2015

Nigral and nigrostriatal imaging in high-risk individuals

LRKK2 mutation carriers: a family report

	Right nigrosome	*Left nigrosome*	*Right ^{123}I-FP-CIT uptake*	*Left ^{123}I-FP-CIT uptake*
A) Asymptomatic LRRK2 mutation carrier	Abnormal	Normal	Abnormal	Abnormal
B) Asymptomatic LRRK2 mutation carrier	Normal	Normal	Abnormal	Abnormal
C) Symptomatic LRRK2 carrier	Abnormal	Abnormal	Abnormal	Abnormal



Ceravolo R et al, *Mov Disord* 2015

Nigral and nigrostriatal imaging in high-risk individuals

PSG-proven iRBD individuals: study protocol

14 iRBD patients	28 PD patients	15 healthy controls
Inclusion criteria: - PSG-proven RBD; - DaTSCAN within the last 3 months.	*Inclusion criteria:* - MDS diagnostic criteria for PD are fulfilled; - DaTSCAN compatible with nigro-striatal degeneration.	*Inclusion criteria:* - healthy subjects with no parkinsonian or dementia signs and without sleep disorders.

⇩

Clinical examination in order to:
- Verify the fulfilment of inclusion/exclusion criteria;
- Rule out the presence of contraindications to ultra-high field MRI;
- Administer standardised rating scales (UPDRS III, MMSE, NMSS, RBDSS).

Ultra-high field MRI (SWAN sequences)

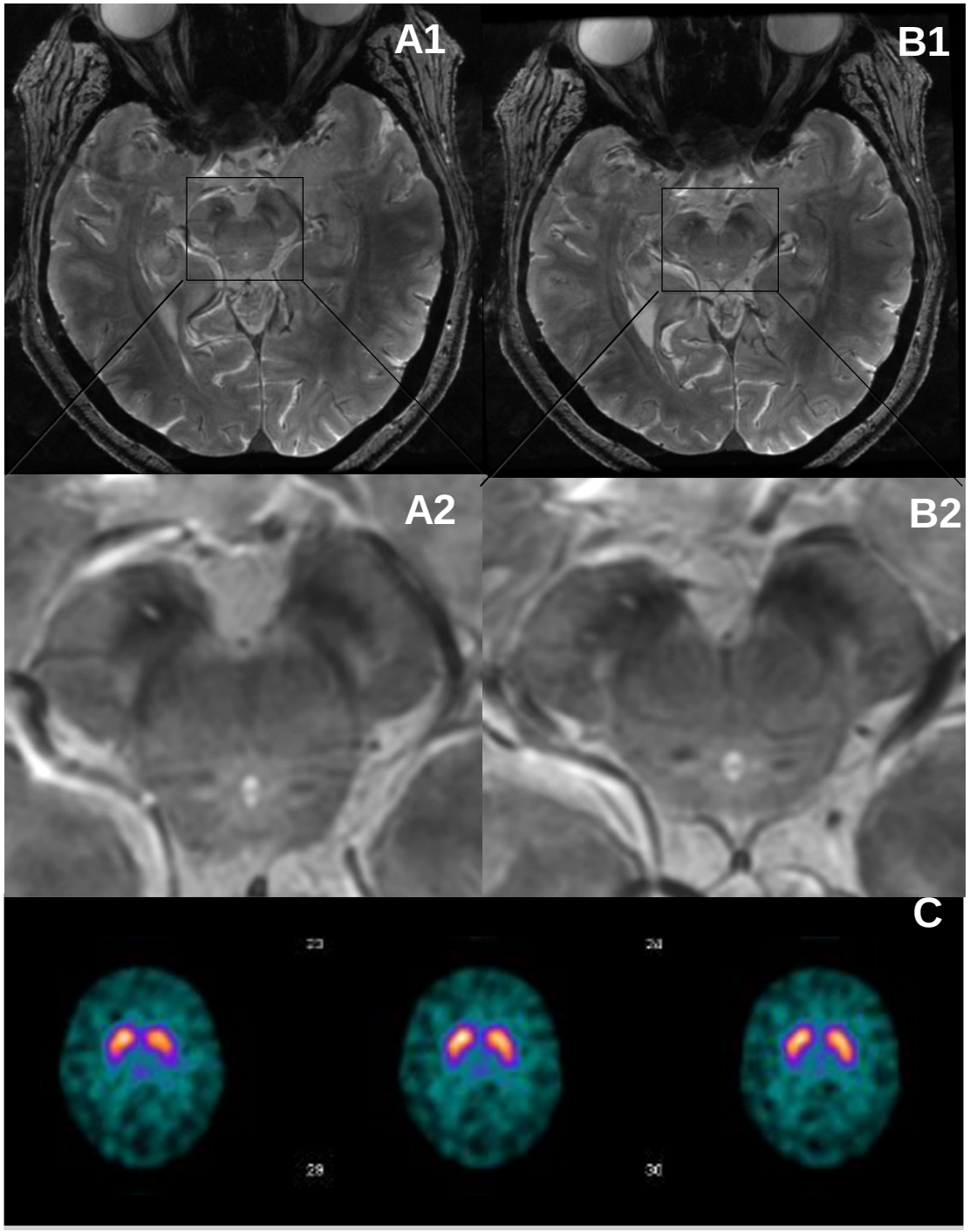
Unpublished data

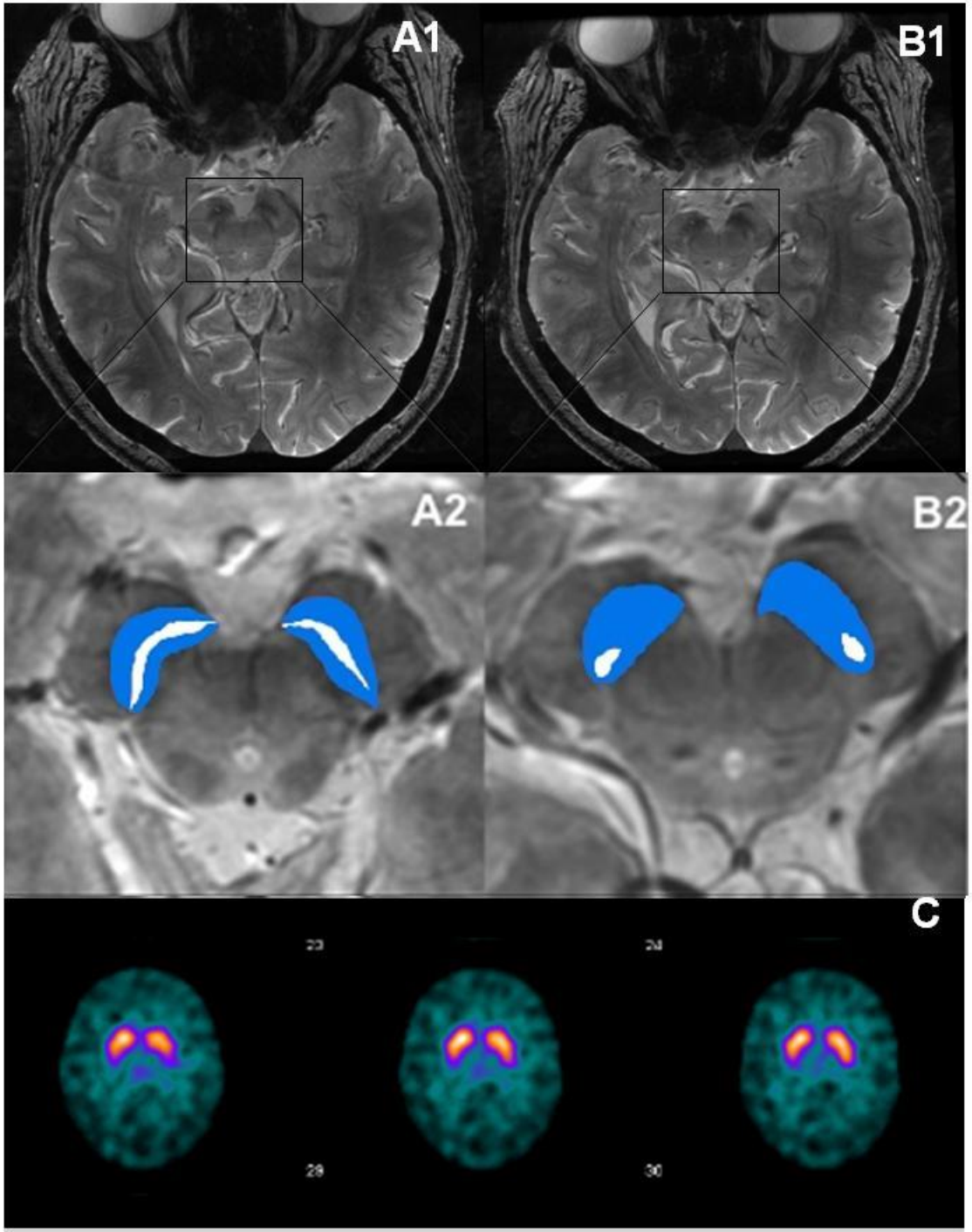
Nigral and nigrostriatal imaging in high-risk individuals

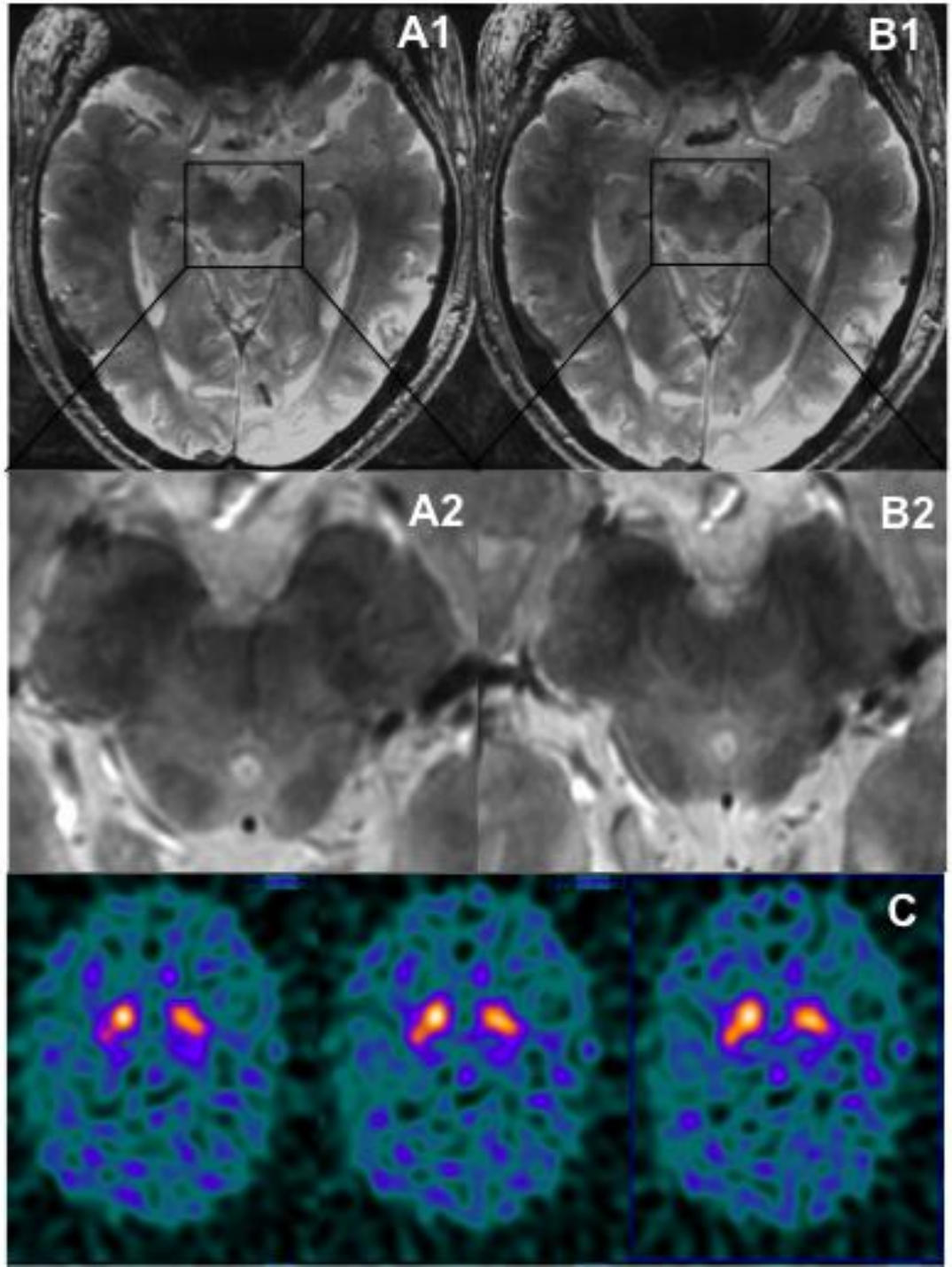
PSG-proven iRBD individuals: results

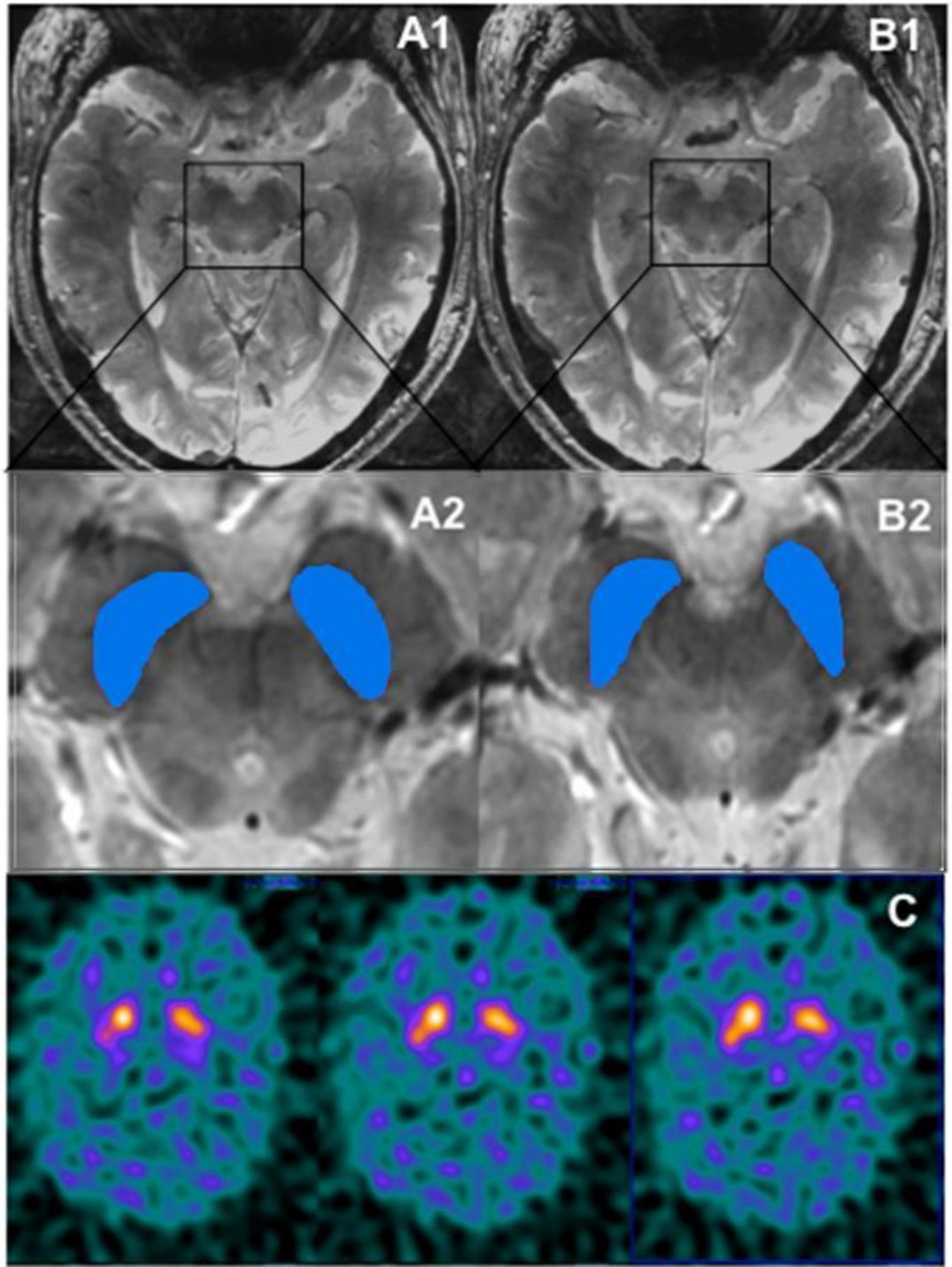
iRBD patients	PD patients	Healthy controls
60% reduction in dopamine tracer uptake (DaTSCAN)	100% reduction in dopamine tracer uptake (DaTSCAN)	DaTSCAN not performed
60% loss of dorsolateral nigral hyperintensity (MRI)	96,43% loss of dorsolateral nigral hyperintensity (MRI)	7,14% loss of dorsolateral nigral hyperintensity (MRI)
66% loss at least one abnormal marker (DaTSCAN, MRI or both)		

Unpublished data


A1
B1
A2
B2
C


A1
B1
A2
B2
C


A1
B1
A2
B2
C


A1
B1
A2
B2
C

In summary

Open questions and issues

1) The MRI SN change is highly specific for degenerative parkinsonism and it is present in about 2/3 of high-risk subjects (LRRK2 carriers, RBD)

2) Key points to be done:

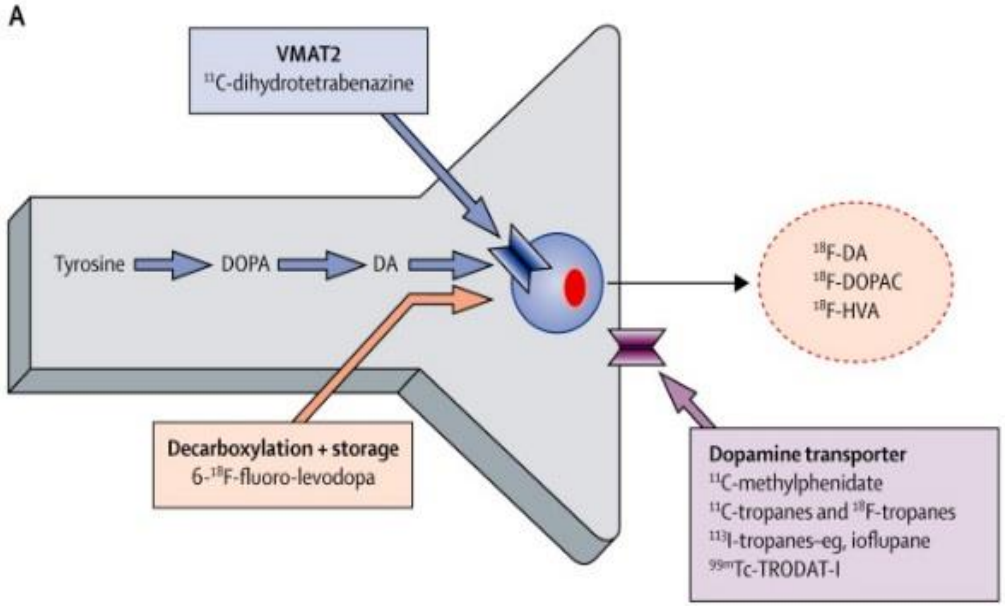
- to complete the follow-up to assess the clinical conversion in such subjects
- to increase the population study and replicate the results

3) The discrepancy between the SN MRI change and DAT imaging is worth to be furtherly investigated

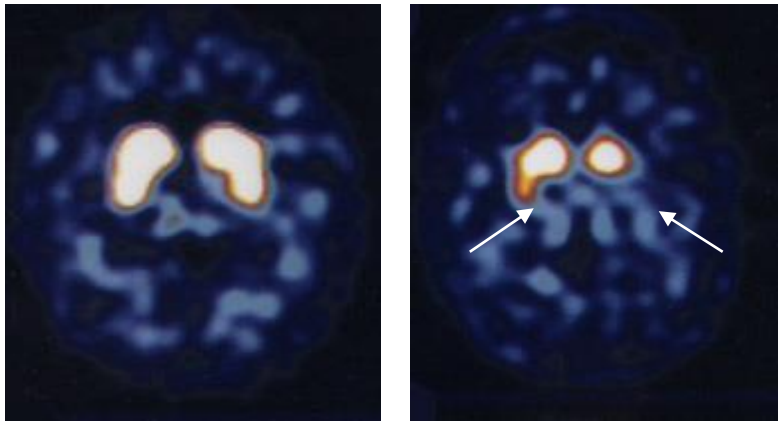
- is DAT imaging more sensitive by showing compensatory mechanisms?
- is MRI change not sensitive enough, depending on the iron deposition?

DAT early compensatory mechanism

DAT TRACER BINDING = Density of DAergic terminals



^{123}I-ioflupane SPECT images



Healthy Control | Parkinson's disease

In early compensatory mechanism:
↓*DAT-* ↑*DA turnover-* ↑*synaptic DA*

When disease progresses:
↓*DAT-* ↑*DA turnover-greater oscillations in synaptic DA-motor complications*

Is PD a synaptopathy?

Retrograde Axonal Degeneration in Parkinson Disease

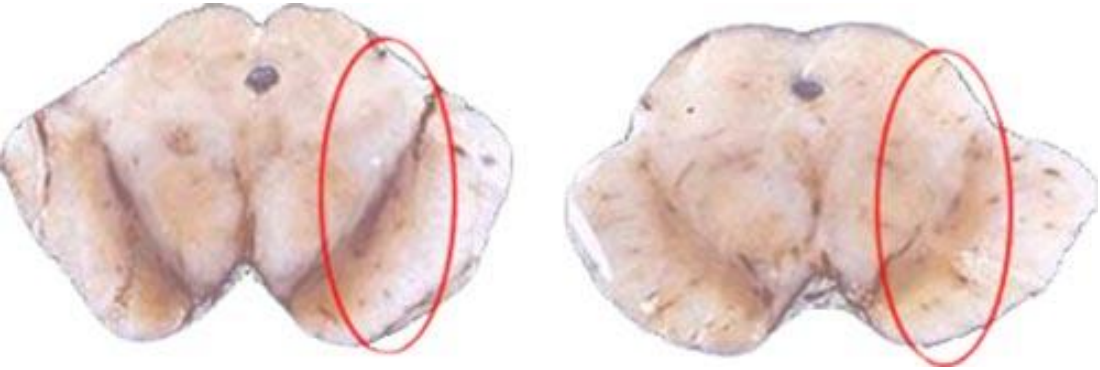
Patricia Tagliaferro[a] and Robert E. Burke[a,b,*]

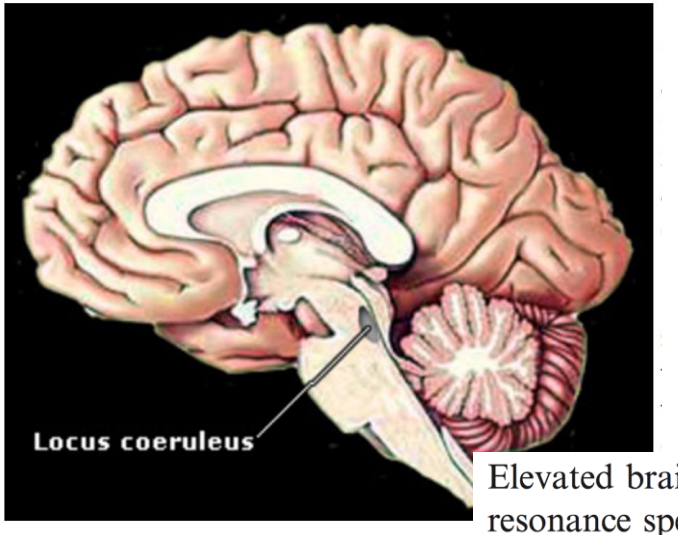
Journal of Parkinson's Disease 6 (2016) 1–15

Early Synaptic Dysfunction in Parkinson's Disease: Insights From Animal Models

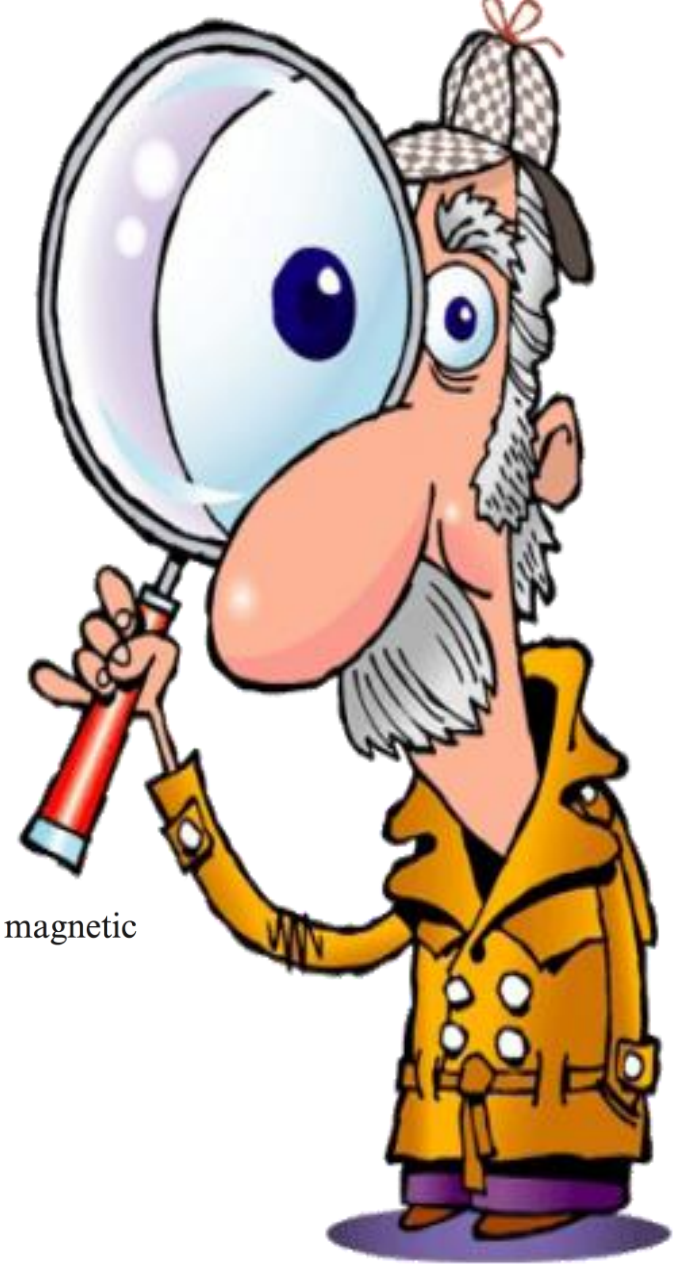
Tommaso Schirinzi, MD,[1] Graziella Madeo, MD,[1] Giuseppina Martella, PhD,[1,2] Marta Maltese, PhD,[1] Barbara Picconi, PhD,[2] Paolo Calabresi, MD,[2,3] and Antonio Pisani, MD, PhD[1,2*]

Movement Disorders, Vol. 31, No. 6, 2016





Elevated brain lactate in schizophrenia: a 7T magnetic resonance spectroscopy study



Reproducibility Measurement of Glutathione, GABA, and Glutamate: Towards In Vivo Neurochemical Profiling of Multiple Sclerosis With MR Spectroscopy at 7T

Brain glutamate in anorexia nervosa: a magnetic resonance spectroscopy case control study at 7 Tesla

ACKNOWLEDGMENTS

Università di Pisa
Ubaldo Bonuccelli
Daniela Frosini
Valentina Nicoletti
Elisa Unti
Martina Giuntini

Fondazione IMAGO 7
Mirco Cosottini
Mauro Costagli
Michela Tosetti

Medicina Nucleare Università di Pisa
Duccio Volterrani