Riunione annuale SIN
Umbro-Marchigiana

Olfactory tracts: the gates of hell? Towards solving the conundrum

Pasquale Nigro

Key points

- The "prion hypothesis“
- Hyposmia and Parkinson's disease
- Olfactory-tract DTI correlates of hyposmia in Parkinson's disease

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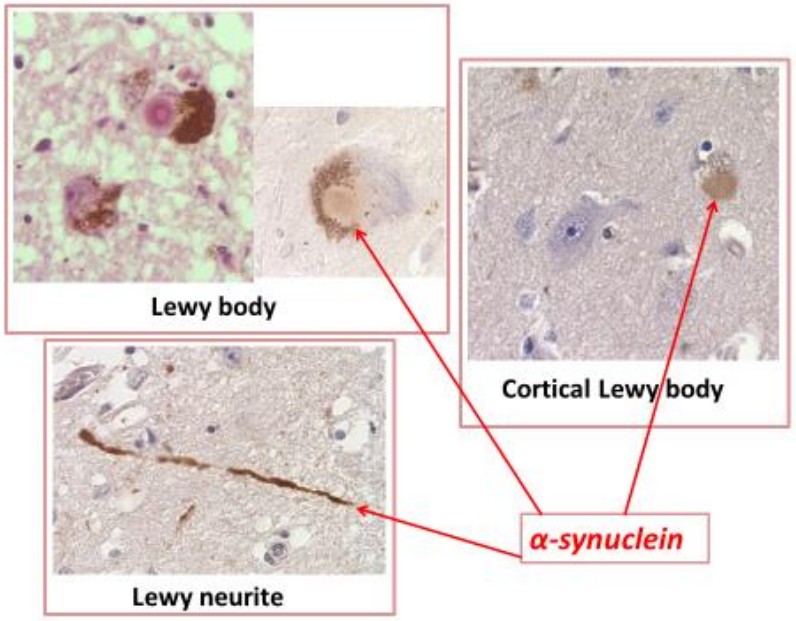
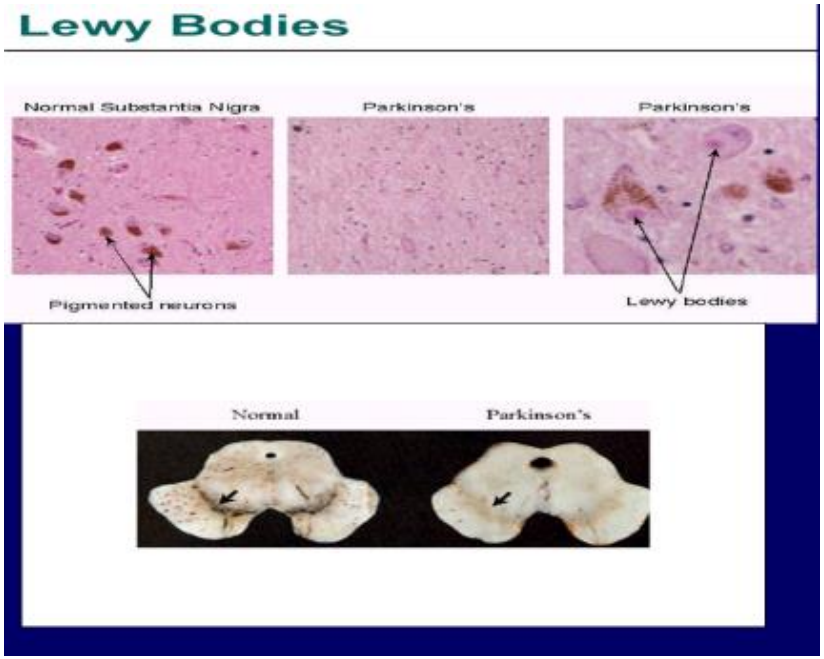
- Hyposmia and Parkinson's disease
- Olfactory-tract DTI correlates of hyposmia in Parkinson's disease

Pathological features

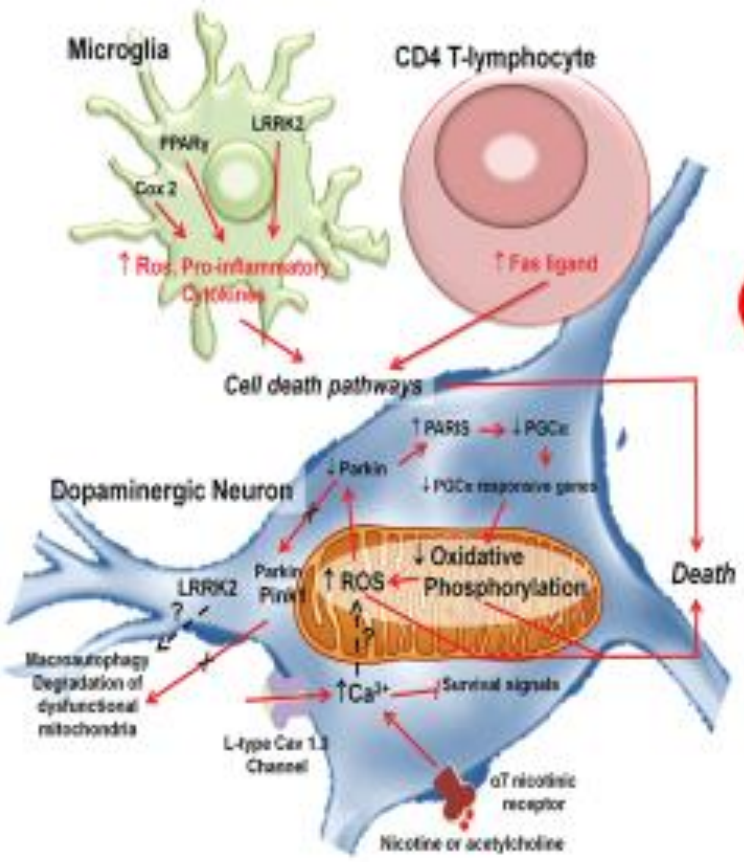
- **Loss of pigmented DA-ergic neurons in the *substantia nigra pc***
- **Presence of α-synuclein positive inclusions (cytoplasm & axons)**

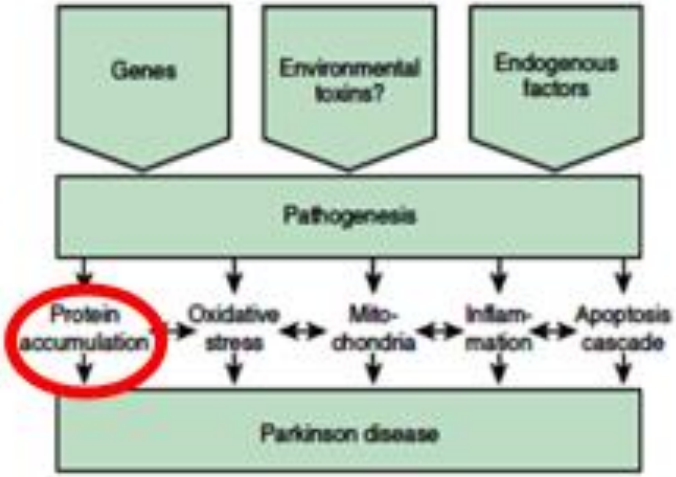
Lewy body (LBs) Lewy neurites (LNs) → LRP **Lewy Related α-synuclein Pathologies**





PD pathogenesis





- Genetic factors
- Enviromental toxins, infections
- Mitochondria dysf. & Oxidative stress
- Neuroinflammation
- Lysosomial & proteasome dysfunction
- Protein accumulation & spreading
- Neuronal death

Hirsch EC. Mov Dis 2013

PD pathogenesis

“Intraneuronal hyaline inclusions in numerous brain regions”

Fritz Heinrich Lewy
1912

“Alpha-synuclein in Lewy bodies”

Spillantini et al., Nature
1997

“Staging of brain pathology related to sporadic Parkinson's disease”

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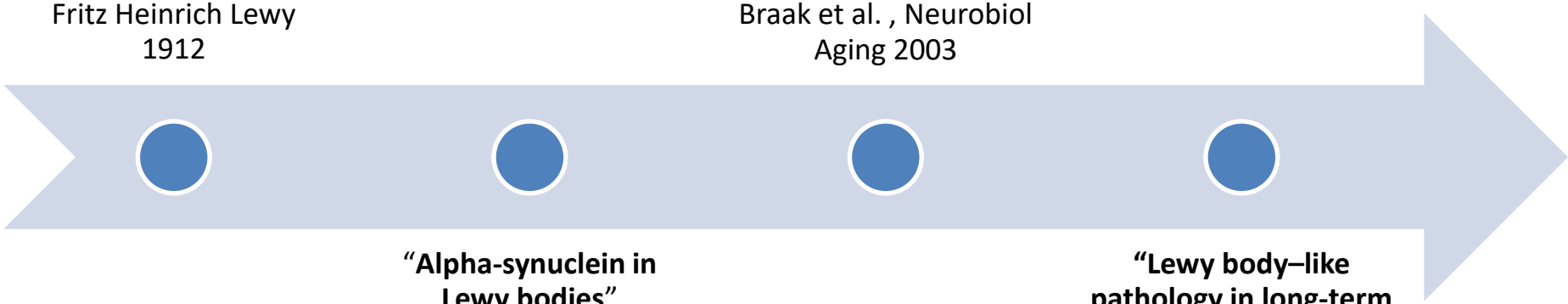
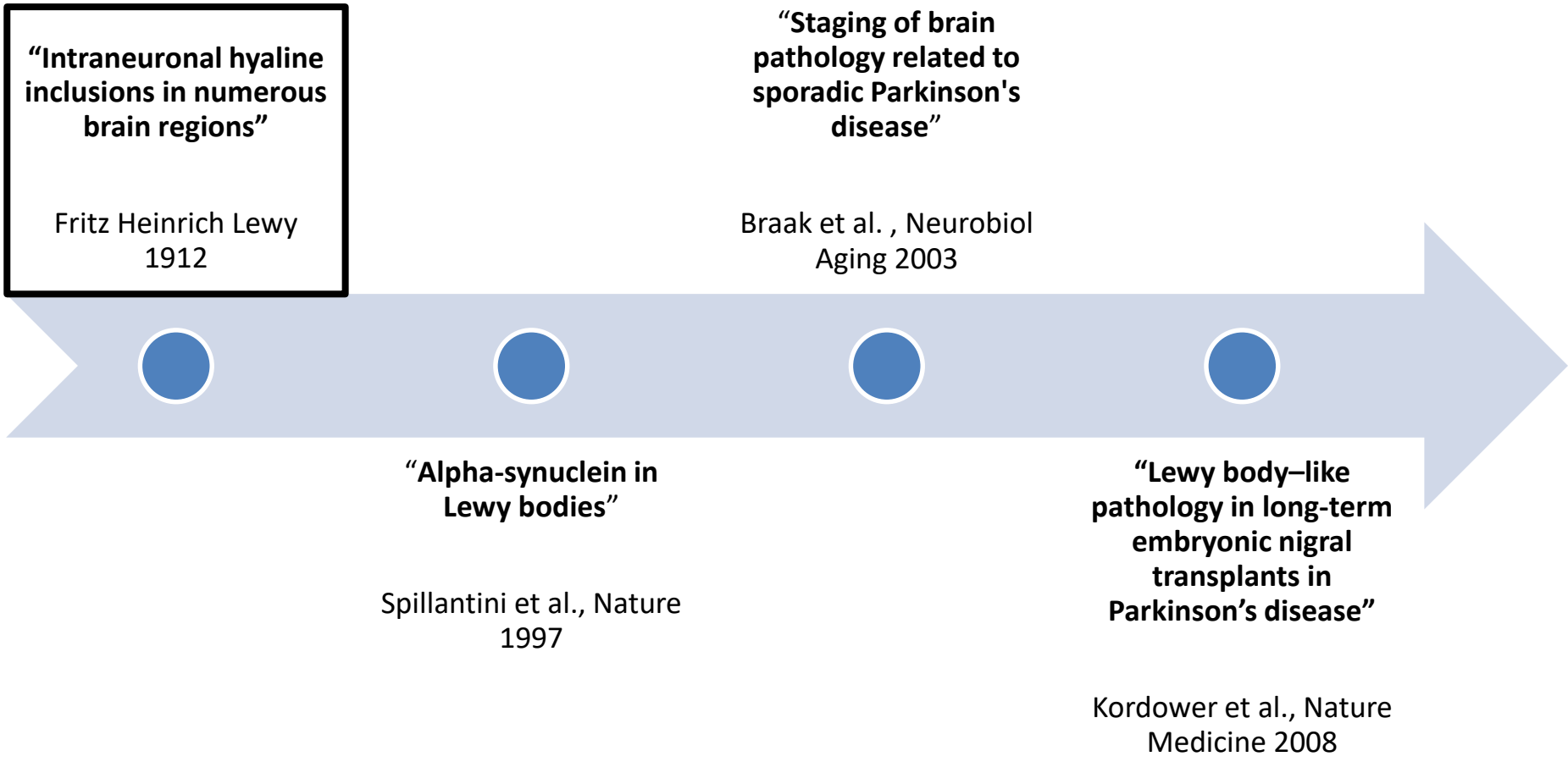


PD pathogenesis



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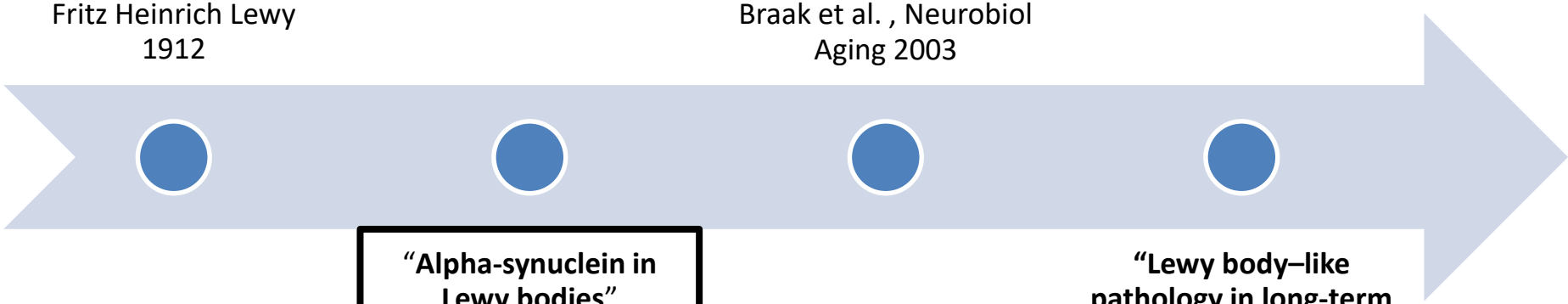
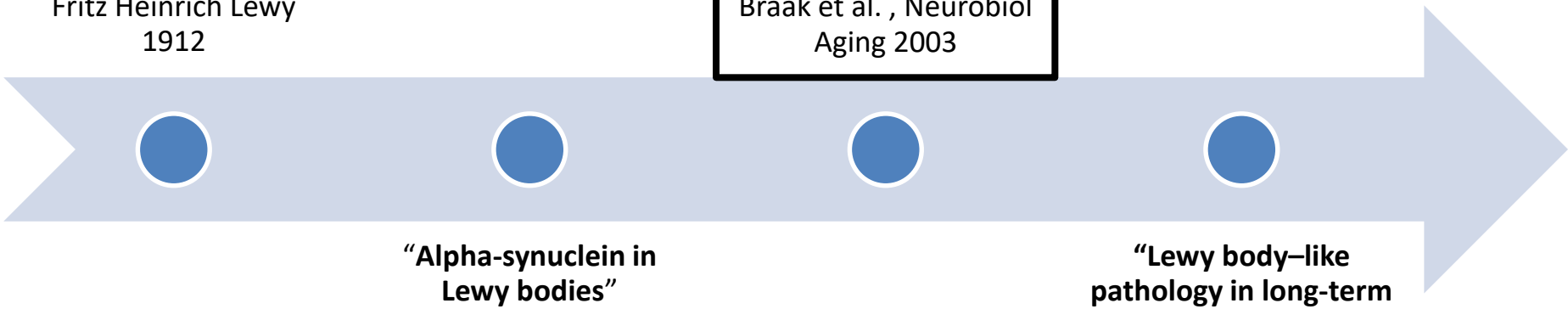


PD pathogenesis



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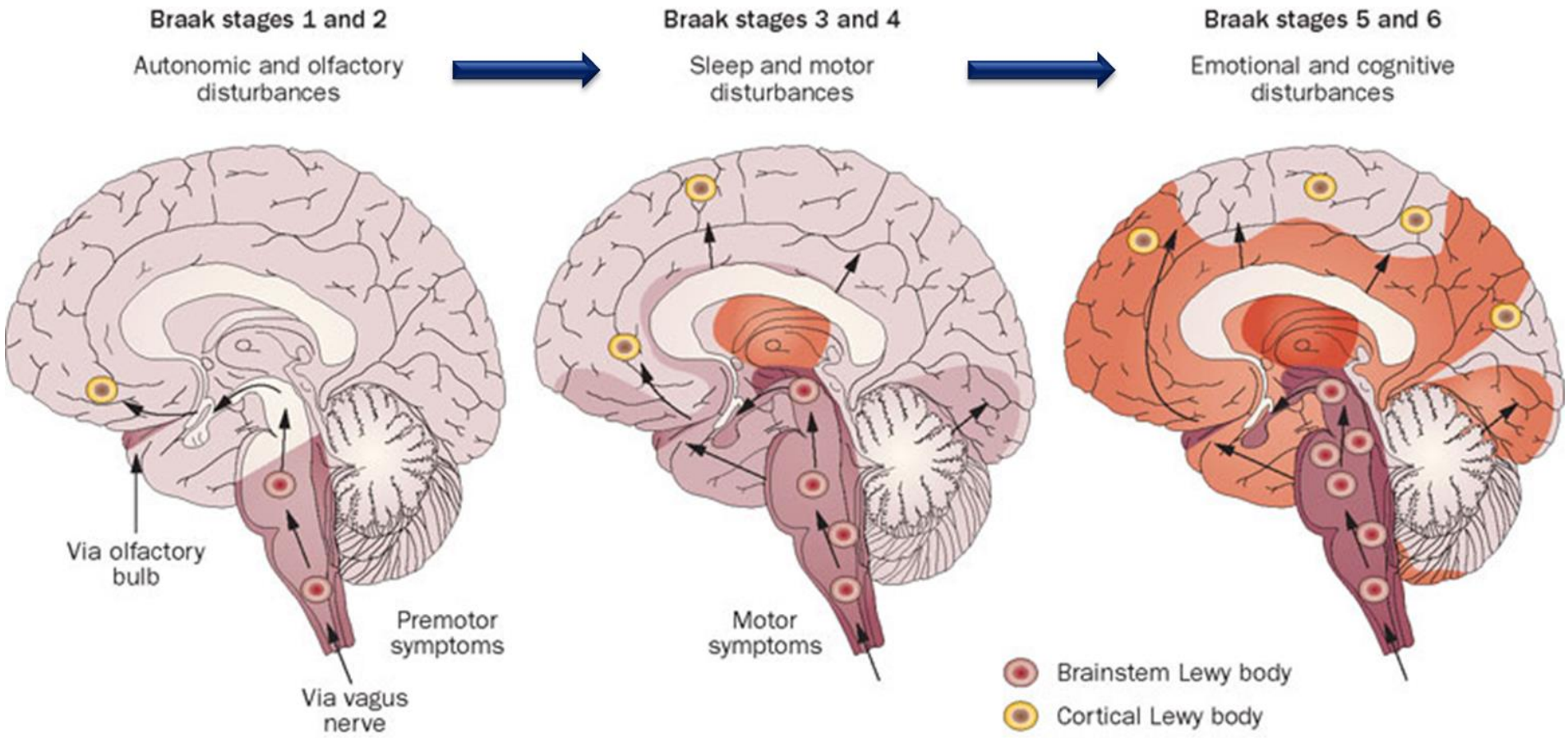


Hyposmia

Constipation

Orthostatic hypotension

Urinary symptoms

Motor Symptom

RBD

MCI

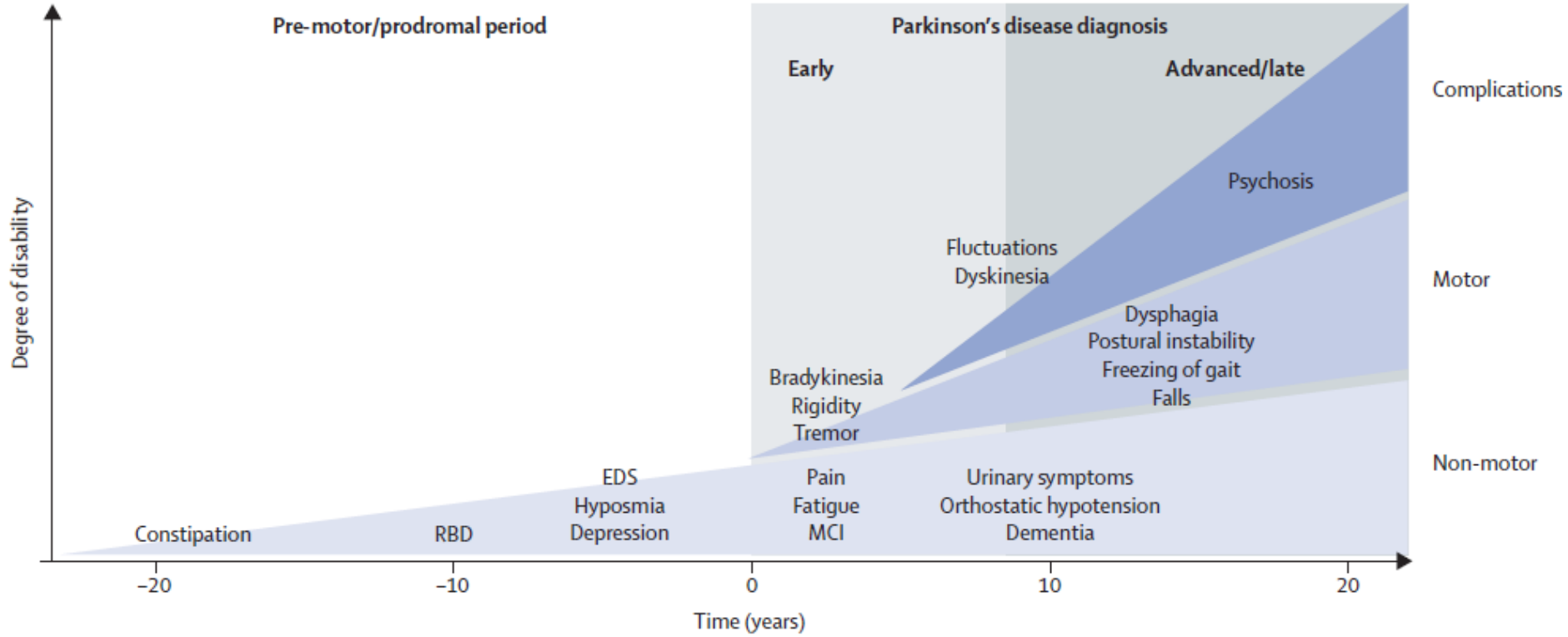
Depression

Dementia

Psychosis

Braak H. et al. Neurobiol Aging 2003

Clinical symptoms and time course of PD progression



Clinical symptoms and time course of Parkinson's disease progression

Lorraine V Kalia, Anthony E Lang. Lancet 2015

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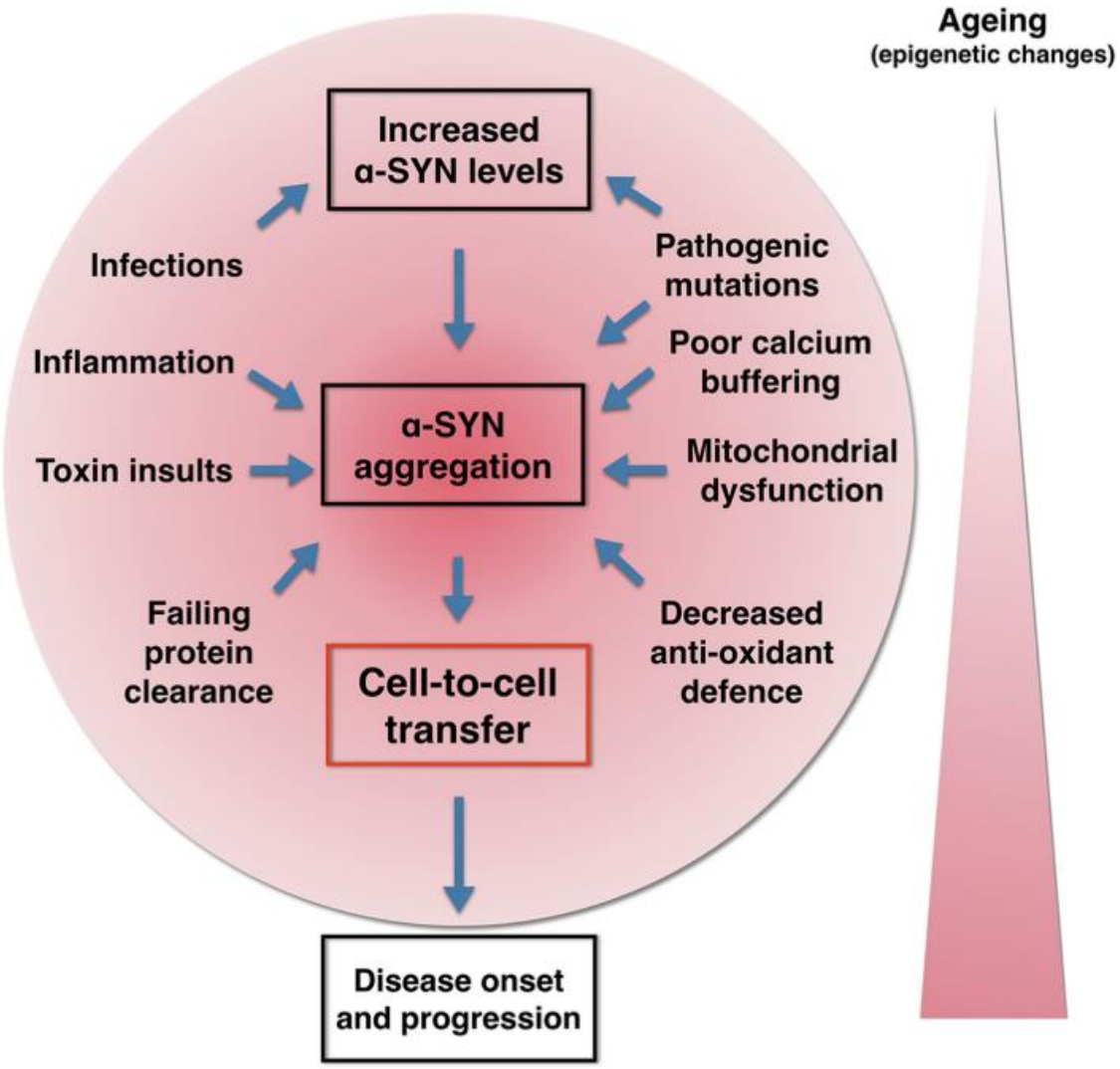
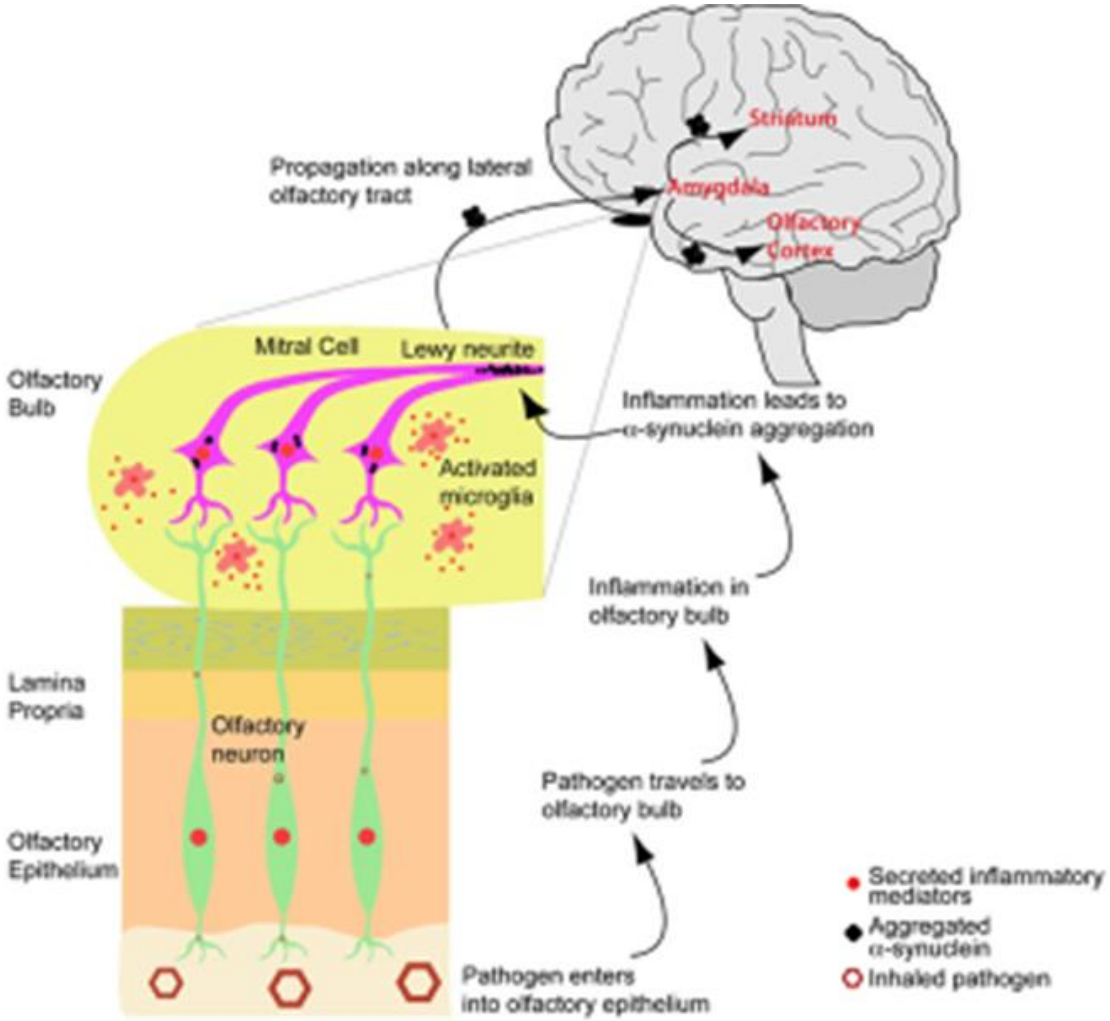
The Prion hypothesis



Patrik Brundin and Ronald Melki. The Journal of Neuroscience, 2017

The Prion hypothesis

synuclein spreading from olfactory bulb

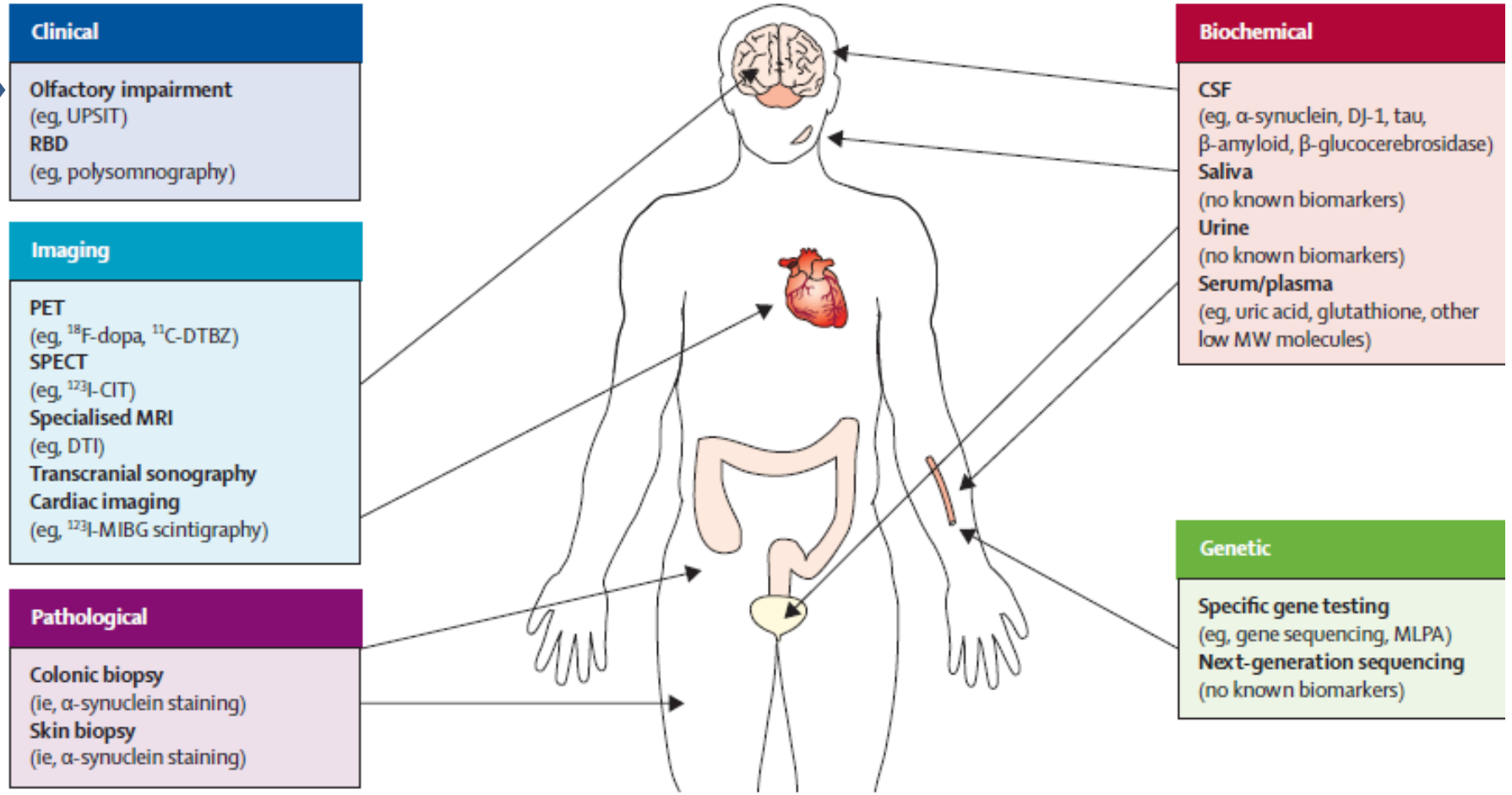


Tomè CML. Molecular Neurobiol 2013

Key points

- The "prion hypothesis“
- Hyposmia and Parkinson's disease
- Olfactory-tract DTI correlates of hyposmia in Parkinson's disease

Potential biomarkers for diagnosis of PD



Lorraine V Kalia, Anthony E Lang. Lancet 2015

MDS Clinical Diagnostic Criteria for PD

Supportive criteria

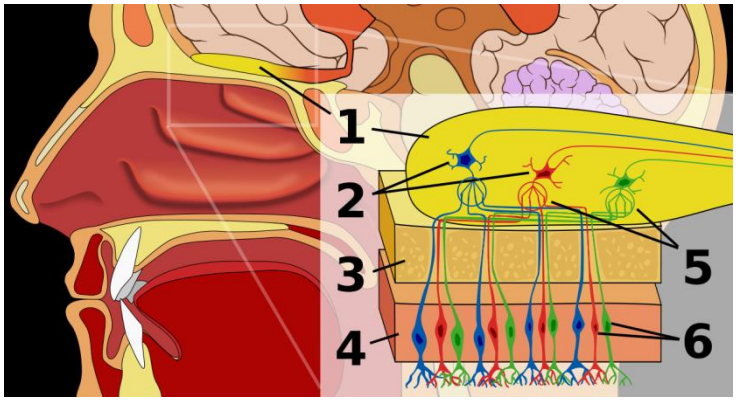
1. Clear and dramatic beneficial response to dopaminergic therapy
2. Presence of levodopa-induced dyskinesia
3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
4. The presence of either **olfactory loss** or cardiac sympathetic denervation on MIBG scintigraphy

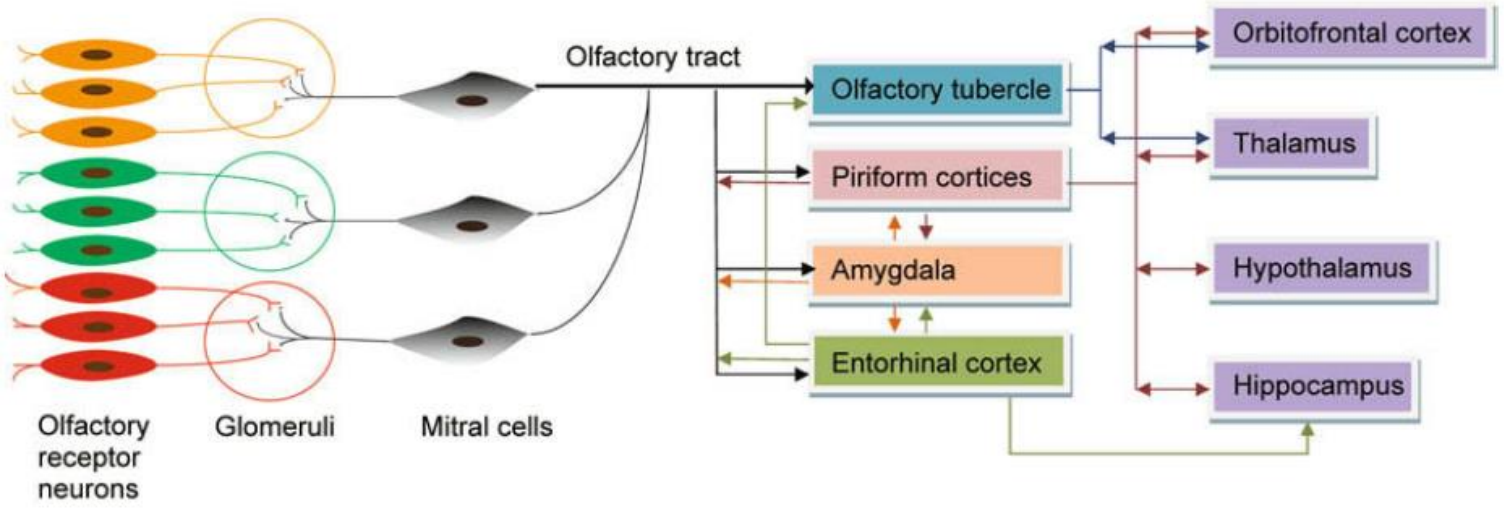
Red flags

1.Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
3. Early bulbar dysfunction: severe dysphonia or dysarthria or severe dysphagia
4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5. Severe autonomic failure in the first 5 y of disease. This can include:
   a) Orthostatic hypotension or
   b) Severe urinary retention or urinary incontinence in the first 5 y of disease associated with erectile dysfunction
6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include: sleep dysfunction, autonomic dysfunction, hyposmia, or psychiatric dysfunction
9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia
10. Bilateral symmetric parkinsonism

Postuma et al. Movement Disorders, 2015

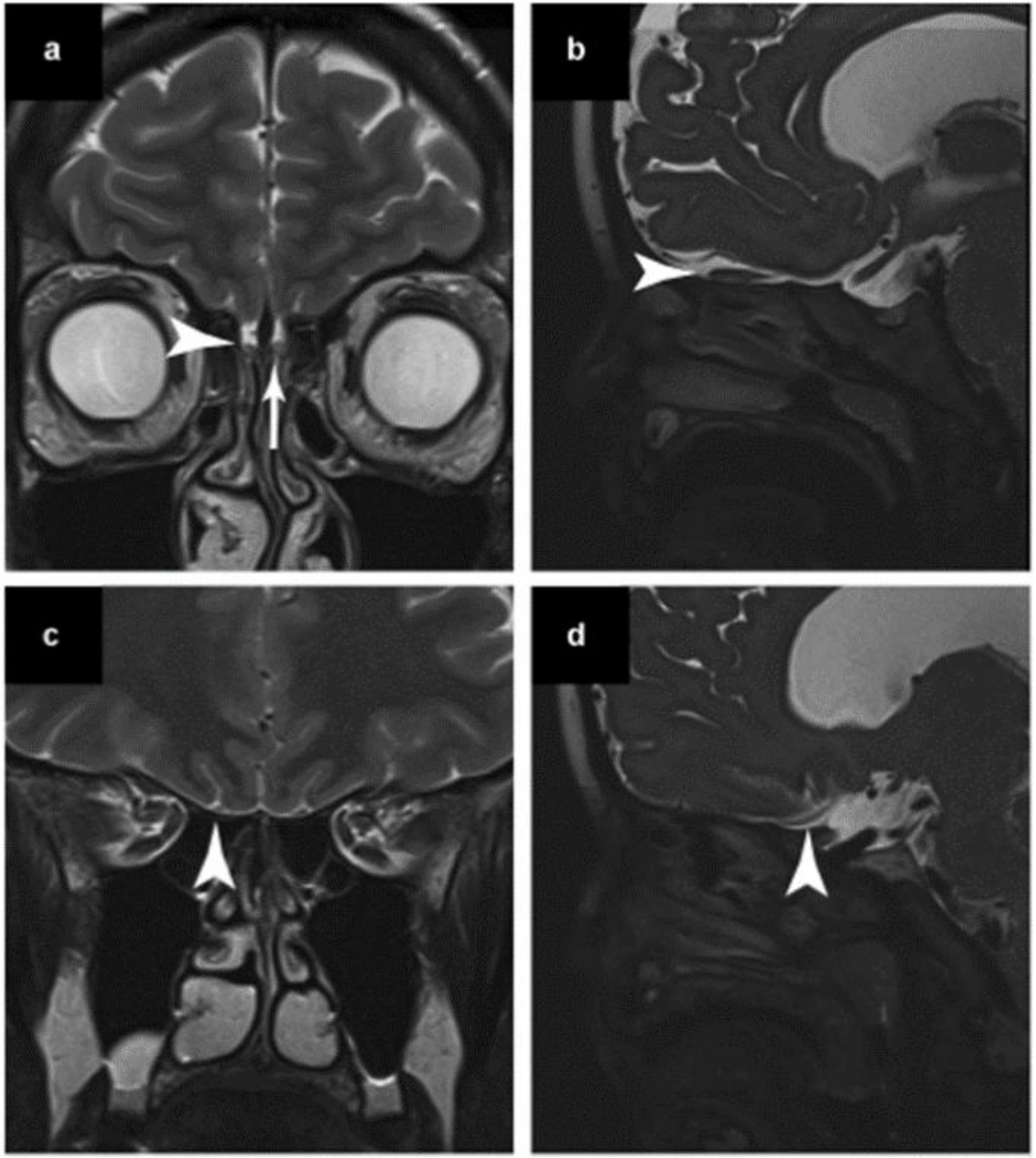
Olfactory System





Qian Xiao, et al. Neurosci Bull 2014

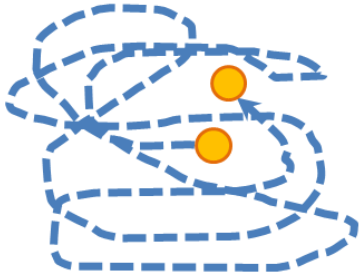
MRI

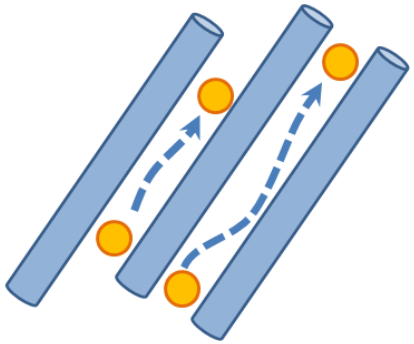


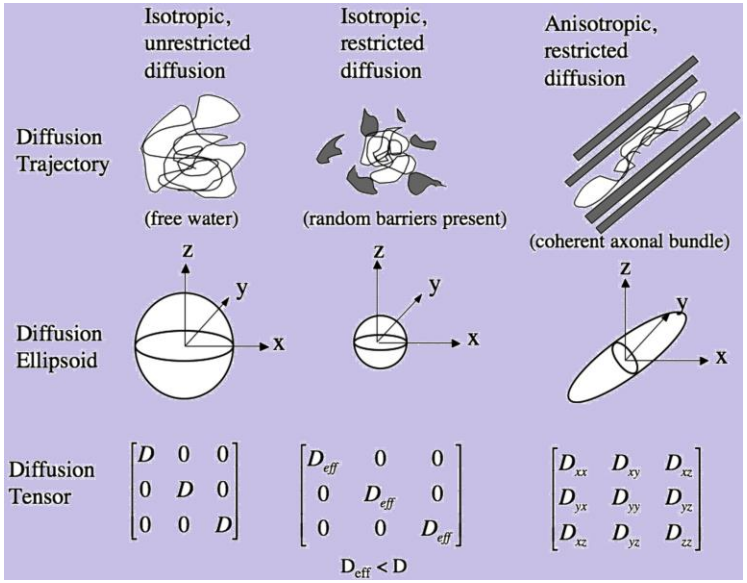
Ponsen M et al. Ann Neurol 2004

DIFFUSION MRI

Diffusion Tensor Imaging (DTI)







- Imaging method that uses the diffusion of water molecules to generate contrast in MR images
- Molecular diffusion in tissues is not free, but reflects interactions with many obstacles, such as macromolecules, fibers and membranes
- DTI scans derive neural tract directional information from the data using 3D or multidimensional vector algorithms based on six or more gradient directions, sufficient to compute the diffusion tensor

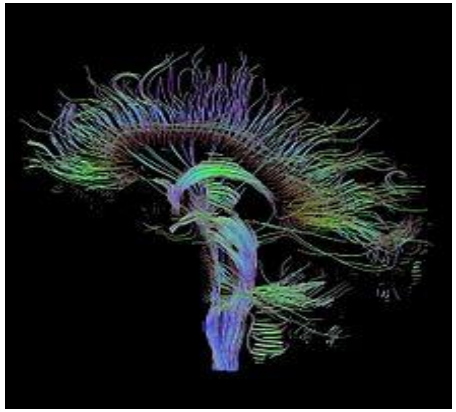
DIFFUSION MRI

Diffusion Tensor Imaging (DTI)

Fractional anisotropy (FA): measure that reflects the degree of diffusivity in the different directions.

Mean diffusivity (MD) represents the overall movement of water molecules within the brain.

Structurally intact white matter has high FA and low MD, whereas structurally compromised white matter has low FA and high MD.



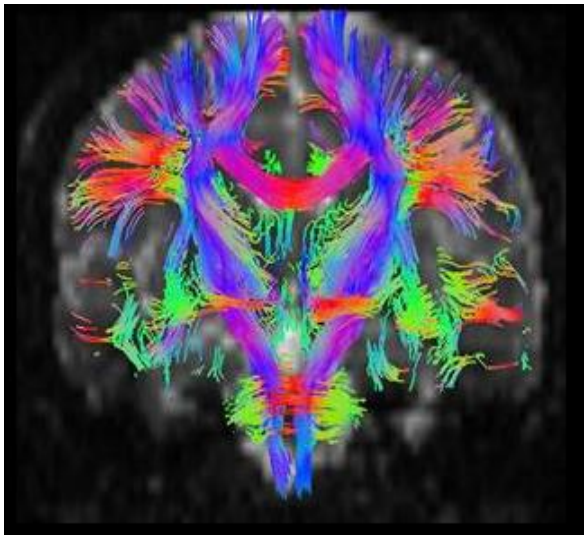
Measurements can either be extracted locally in predefined regions using region of interest (ROI) analysis or tractography or, alternatively, globally using voxel-based analysis (VBA) or tract-based spatial statistics (TBSS).

DIFFUSION MRI

Diffusion Tensor Imaging (DTI)
Tractography

- Diffusion tensor imaging data can be used to perform tractography within white matter.

- Fiber tracking algorithms can be used to track a fiber along its whole length.



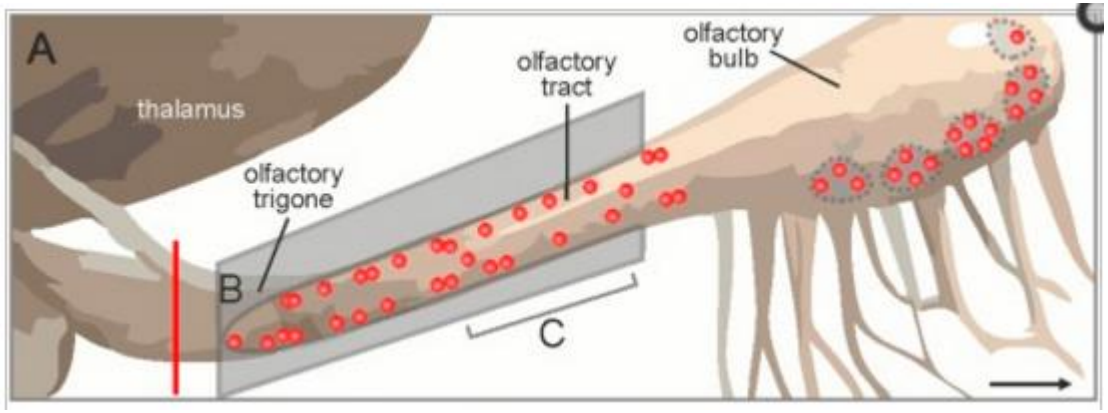
- **Red** indicates directions in the X axis: right to left or left to right
- **Green** indicates directions in the Y axis: posterior to anterior or from anterior to posterior.
- **Blue** indicates directions in the Z axis: foot-to-head direction or vice versa.

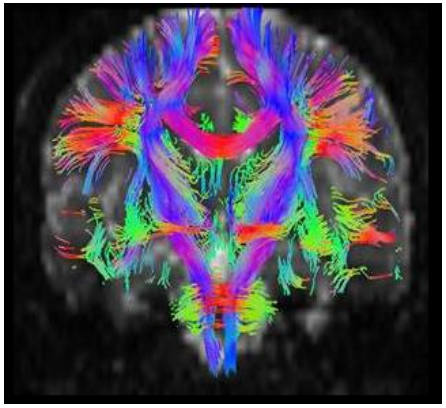
Key points

- The "prion hypothesis“
- Hyposmia and Parkinson's disease
- Olfactory-tract DTI correlates of hyposmia in Parkinson's disease

Aim of the study

To investigate the olfactory-tract DTI correlates of hyposmia in patients with PD, using fiber tracking and comparing with a matched control group





Methods

Exclusion criteria for all subjects:

- history of head trauma
- nasal fracture or diagnosis of rhinitis and/or nasal polyps
- detection of expansive lesions in the anterior cranial fossa
- ear, nose, and throat (ENT) diseases

HC →

Neurological exam

PD →

UPDRS III, H&Y, IOIT

MRI

Methods

Olfactory assessment IOIT

Tester Number	Smell
1	CLOVES
2	ROSE
3	LAVENDER
4	BANANA
5	PINE-TREE – FIR-TREE
6	MUSHROOM
7	TALC
8	MINT
9	COCONUT
10	STRAWBERRY CANDY
11	APPLE
12	CHEESE
13	**WATERMELON**
14	FRESH-CUT GRASS
15	VIOLET FLOWERS
16	SAGE
17	LIQUORICE
18	LAUNDRY SOAP
19	WOOD-LIKE SMELL
20	**COFFEE – COFFEE LIQUEUR**
21	CHOCOLATE - COCOA
22	OREGANO
23	**BASIL**
24	ROSEMARY
25	GARLIC
26	LEMON
27	PEACH
28	INCENSE
29	ORANGE
30	ANISE – SANBUCA
31	PINEAPPLE – PINEAPPLE JUICE
32	EUCALIPTOLUS CANDY
33	UNPLEASANT SMELL

(A) started with the tester n°1

(B) read the suggested answer for the Tester in exam

(C) rub lightly the Tester with a little piece of paper.

(D) sniff the tester while looking at the answers suggested (bring the smelling area of the tester near your nose at a distance of about 1 cm. If the Tester thouches the nose, simply rub your nose with a tissue slightly dampened with water. After this operation the test can be restarted and finished).

(E) choose one of the answers among the four suggested, crossing or circling it. Once chosen, the answer can not be changed. In the case that you are unable to perceive an odour it is highly suggested to respond nonetheless. At the conclusion of the test dispose of the tester and tissues utilised. Without hesitation go on until no. 33.

Hyposmia was identified, according to the age, using the following cut-off:

4/33 (30-49 yr)
5/33 (50-59 yr)
6/33 (60-69 yr)
7/33 (70-79 yr)

Methods

MRI protocol and data processing

Image acquisition: DTI 32 directions (TE=55 ms, TR=9350 ms)

Voxel: 1,8x1,8x1,8 mm3

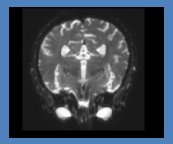
Matrix 128x128x45

Preprocessing, software DTIPrep

- quality control of images, correction for eddy current
- Control and correction of artifacts caused by motion and magnetic susceptibility
- Extraction of final DTI image

Processing, software Diffusion Toolkit

- Fiber tracking
- Extraction of MD and FA images

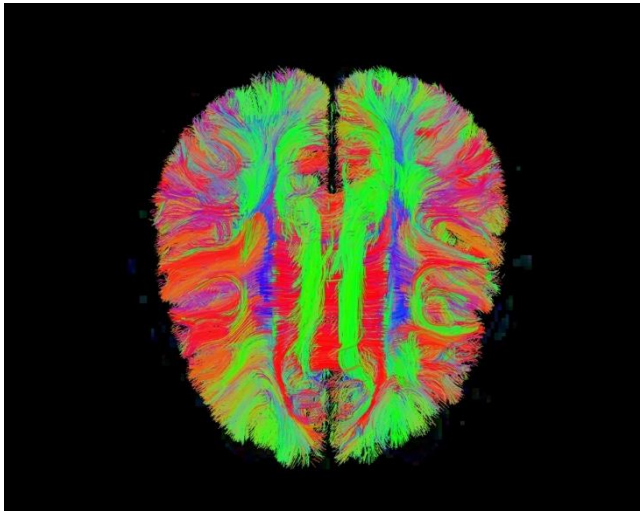


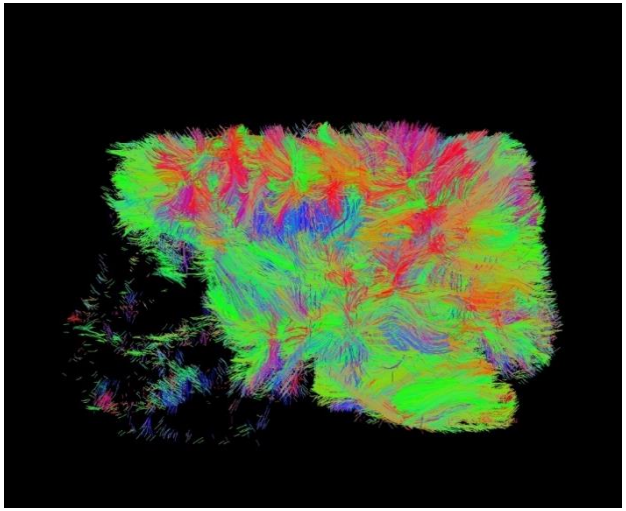
Post-processing, software TrackVis

- Analysis of fiber track data
- ROI delineation
- MD, FA, RD, volume, lenght

Methods

Post-processing, software TrackVis





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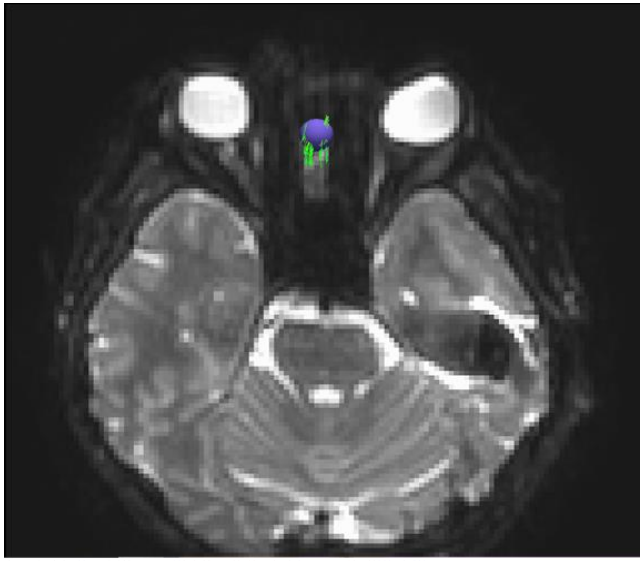
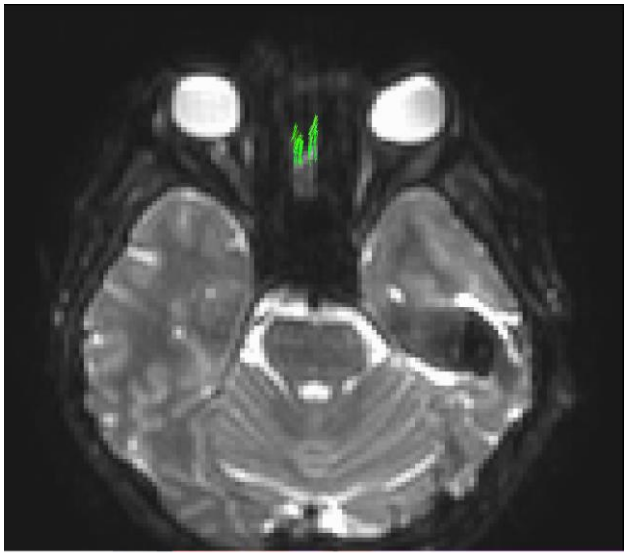




- ROI delineation

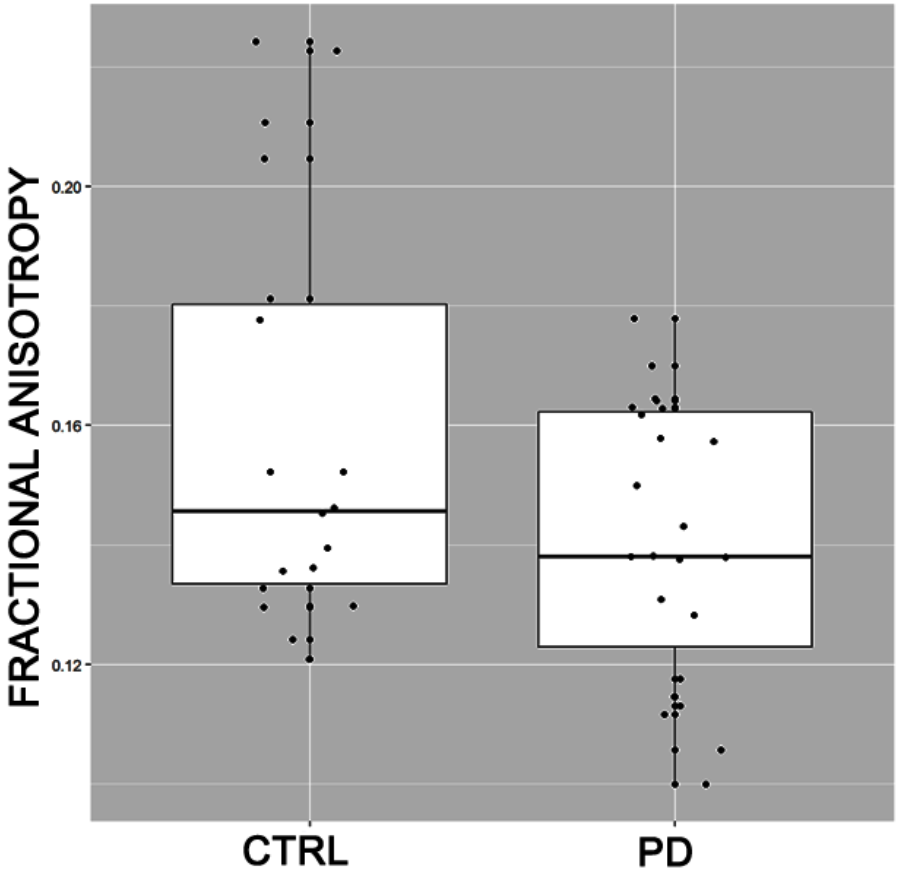
Results

Clinical variables

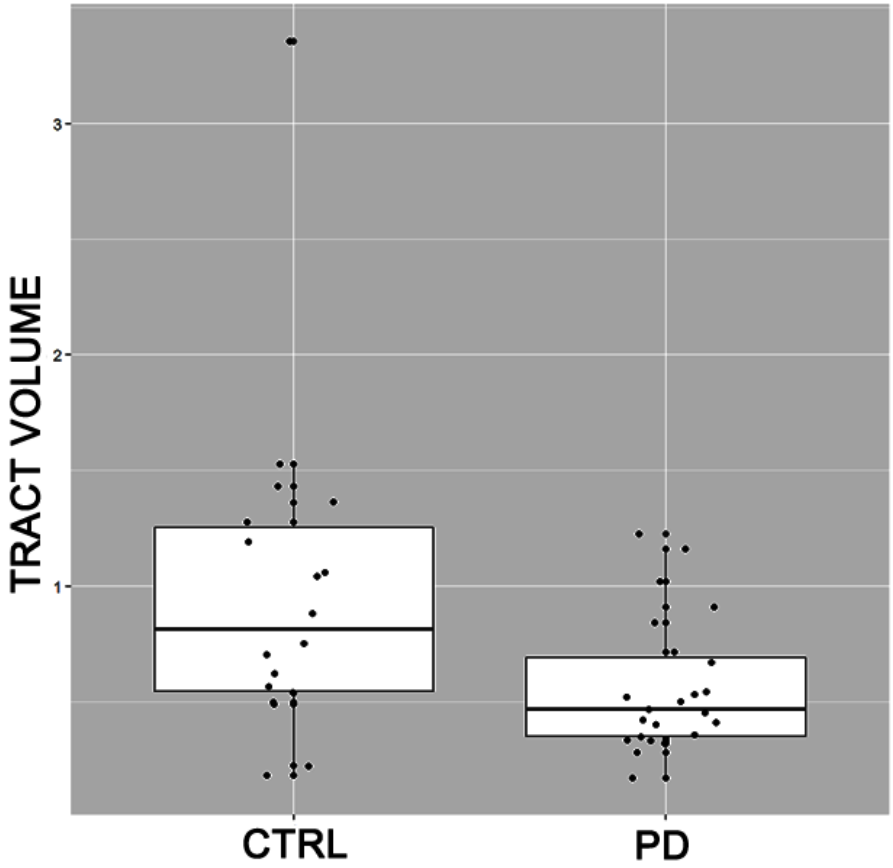
Controls (n=18)	
M/F	12/6
Age (yr)	59.6±13.7
Patients (n=23)	
M/F	15/8
Age (yr)	63.6±9.3
Duration of disease (yr)	2.7±2.3
H&Y	1.9±0.5
UPDRS III - ON	24.5±12.3
IOIT	13.7±4.9

Results

Analysis of processed DTI data



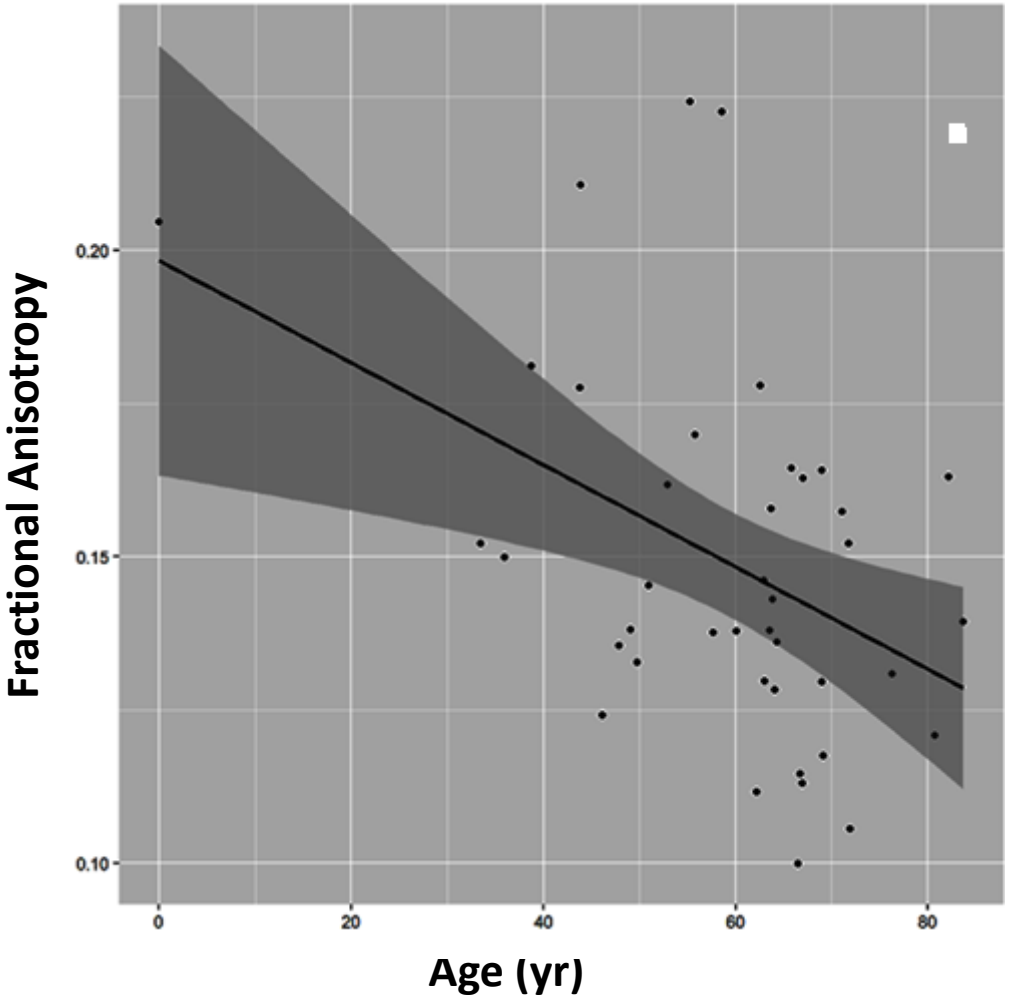
$p = 0.028$



$p < 0.0001$

Results

Analysis of processed DTI data

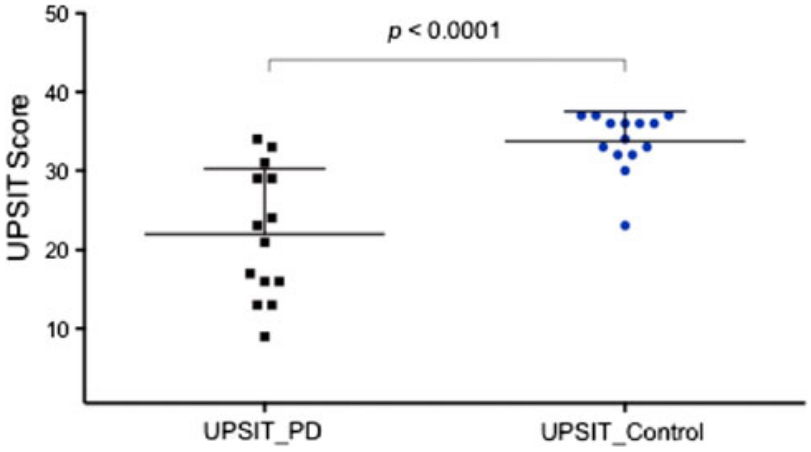


In PD patients significant correlation was found between FA and age ($r = -0.37$, $P<0.05$, Spearman's rank correlation).

Diffusion imaging and hyposmia in PD

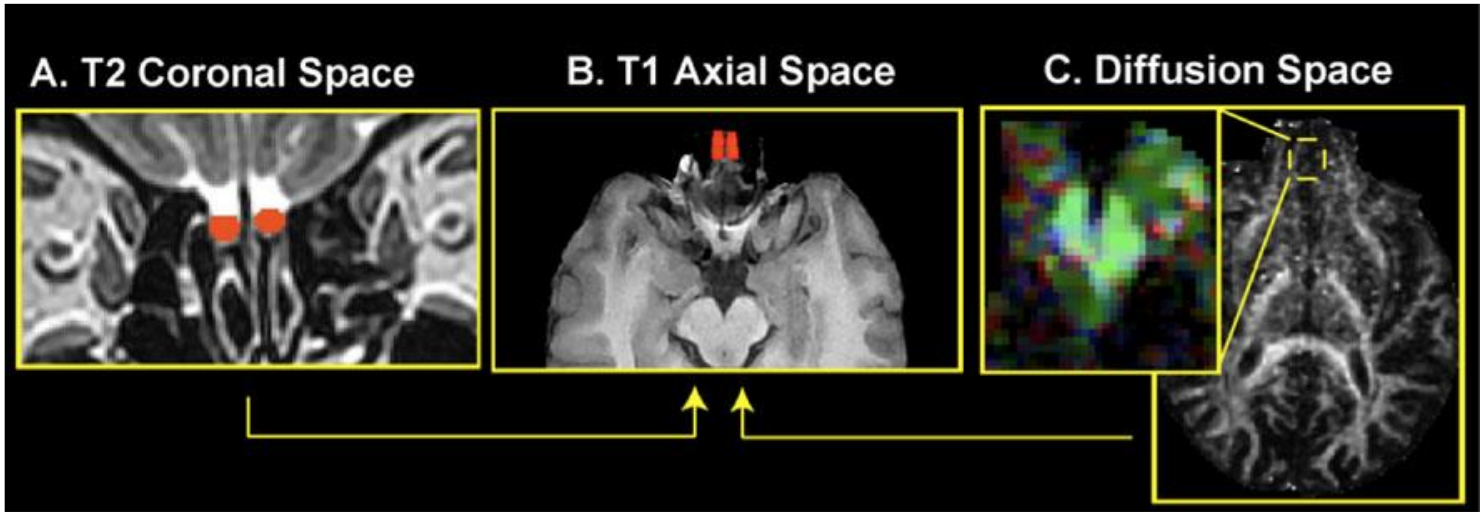
		Technique
Scherfler et al. (2006)	12 PD- 12 HC	DWI
Zhang et al. (2009)	25 PD- 25 HC	DTI (VBA)
Ibarretxe-Bilbao et al. (2010)	24 PD- 24 HC	DTI (TBSS and ROI)
Rolheiser et al. (2011)	14 PD- 14 HC	DTI (TBSS and ROI)
Skorpil et al. (2012)	14 PD- 15 HC	DTI (ROI)
Scherfler et al. (2013)	16 PD- 14 HC	DTI (ROI)
Nigro et al. (2016)	21 PD- 30 HC	DTI (NBS)
Georgiopoulos et al. (2017)	22 PD- 13 HC	DTI (TBSS and ROI)

Discussion



Olfactory region of interest statistics

	Control mean (SD)	PD subject mean (SD)	*p*
FA	**0.207 (0.0079)**	**0.166 (0.0193)**	**<0.0001**
MD	0.00163 (0.000323)	0.00191 (0.000389)	0.0487
AD	0.00185 (0.000380)	0.00221 (0.000448)	0.029
RD	0.00147 (0.000303)	0.00176 (0.000360)	0.0309
Voxels in ROI	776 (101)	777 (118)	0.989



Rolheiser et al. J Neurol 2011

Conclusions

Significantly decreased olfactory identification function in all PD patients

↓

Fiber tracking DTI analysis of olfactory-tract is feasible in PD

↓

Group differences in DTI parameters

↓

Significant correlation FA-age

Take Home Message

A screening approach that initially involves olfactory function testing followed by fiber tracking DTI analysis of olfactory-tract may be viable as a means of establishing cohorts of subjects with probable pre-motor PD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