# Evolving Concepts in the Diagnosis Parkinson‘s Disease: From Street to Bench

NMRC Awards Ceremony & Research Symposium
Singapore, December 6, 2021

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MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

# Conflicts of Interest

*Werner Poewe reports personal fees from:* Alterity, AbbVie, Affiris, AstraZeneca, BIAL, Biogen, Britannia, Lilly, Lundbeck, Neuroderm, Neurocrine, Denali Pharmaceuticals, Novartis, Orion Pharma,Roche, Takeda, Teva, UCB and Zambon (*consultancy and lecture fees in relation to clinical drug development programmes for PD).*

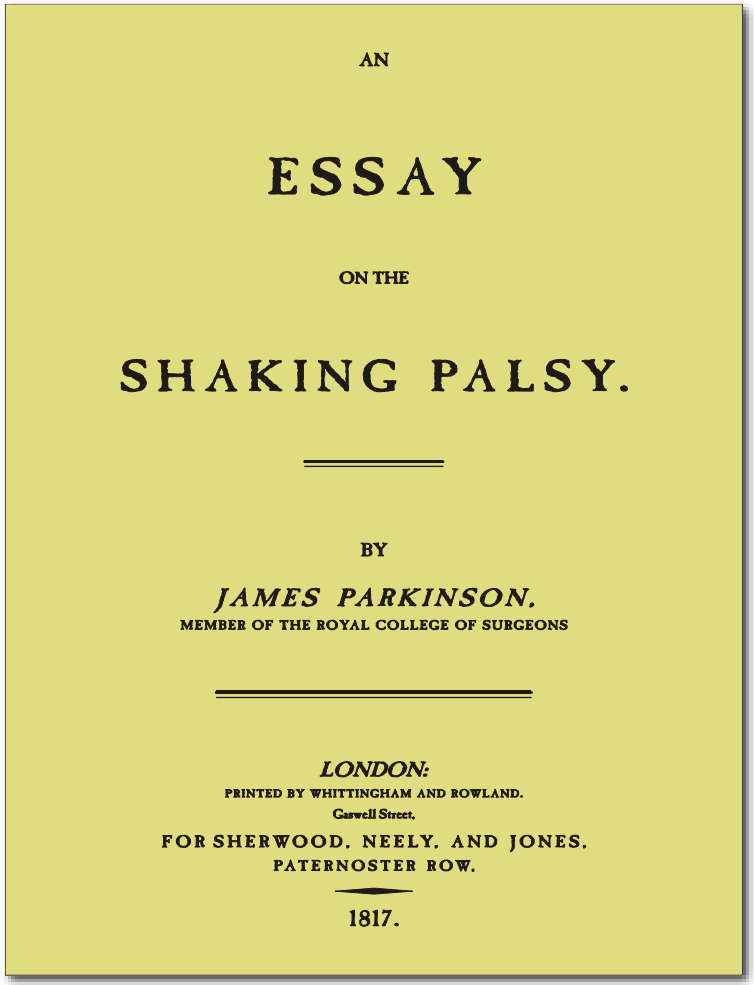
*Royalties: Thieme, Wiley Blackwell, Oxford University Press and Cambridge University Press*

*Grant support: MJFF; EU FP7 & Horizon 2020;*

# OUTLINE

- The 19th Century View
- Current Diagnostic Challenges
- The Promise of Biomarkers

# The “Shaking Palsy” – A Syndrome Observed on the Street



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON.

MEMBER OF THE ROYAL COLLEGE OF SURGEONS

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND.

Gaswell Street.

FOR SHERWOOD. NEELY. AND JONES.

PATERNOSTER ROW.

1817.

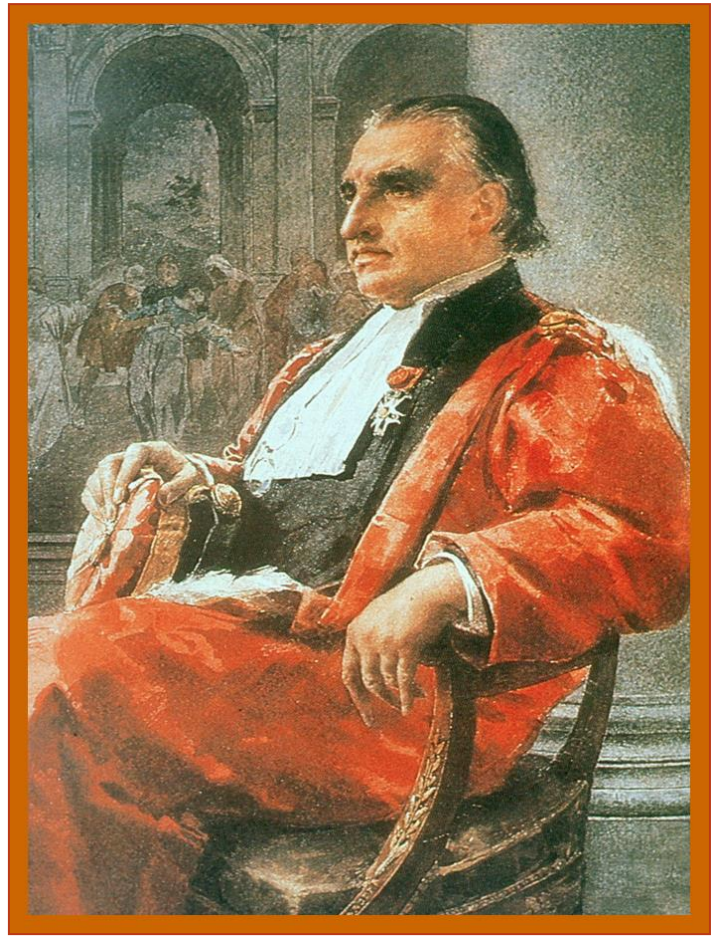
*“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.”*

# Picture of King‘s Bench Prison Yard , Southwark, 1808-1811

Lees A; Brain 2017:40:843-848

# Diagnosing PD on the Street

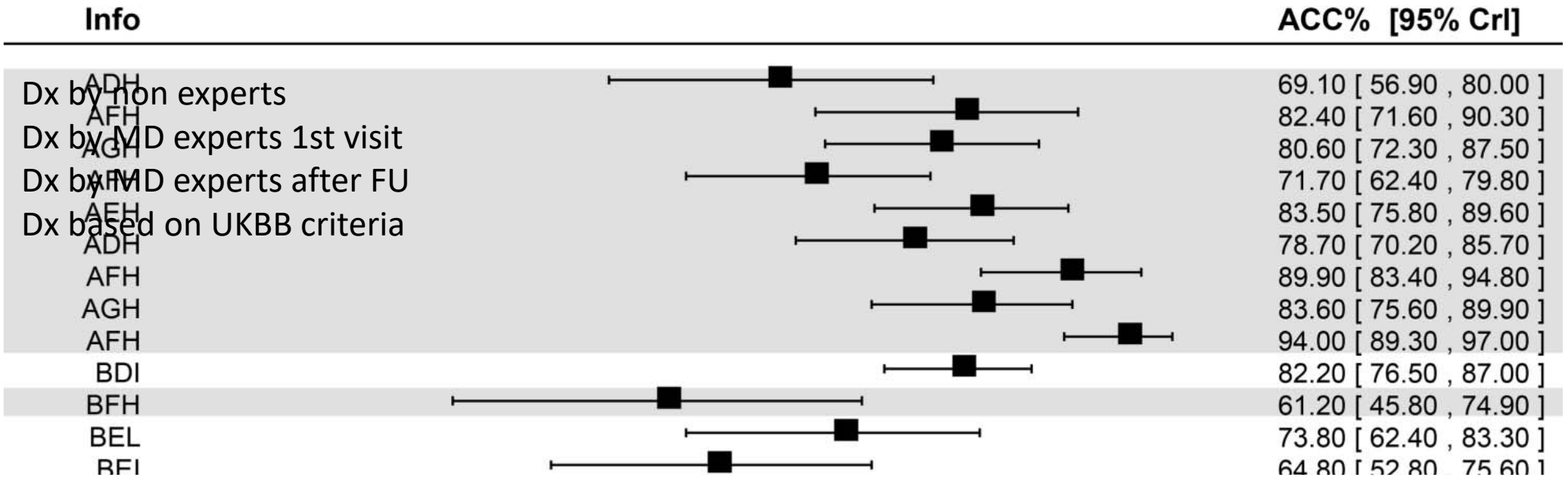
*‚….I have seen such patients everywhere on the streets of Rome, of Amsterdam, in Spain – it is always the same picture. They can be identified from afar, you do not need a medical history….‘*



Charcot, Lecons du Mardi 1888 (quoted in: Lees A; Brain 2017:40:843-848

# Accuracy of a Clinical Diagnosis of PD

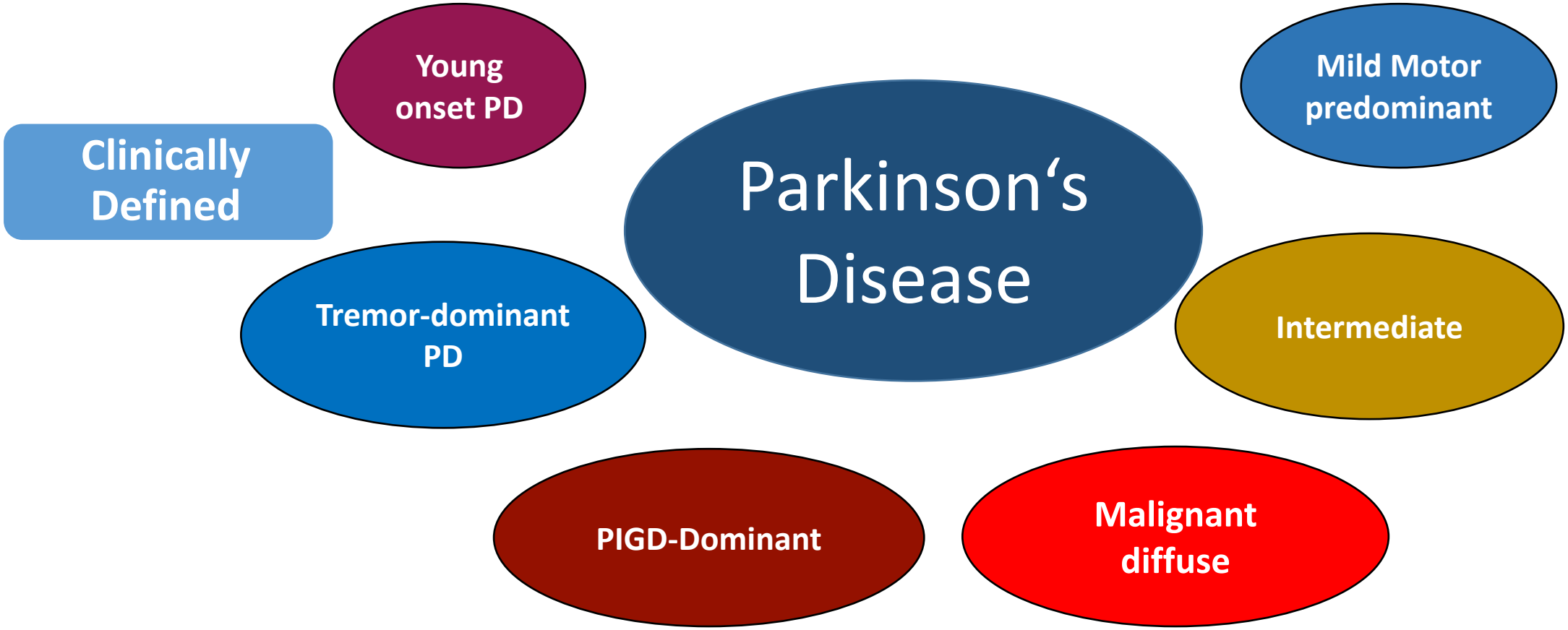
- Meta-Analysis of 11 clinico-pathological studies




- **Pooled diagnostic accuracy of 80.6 %**

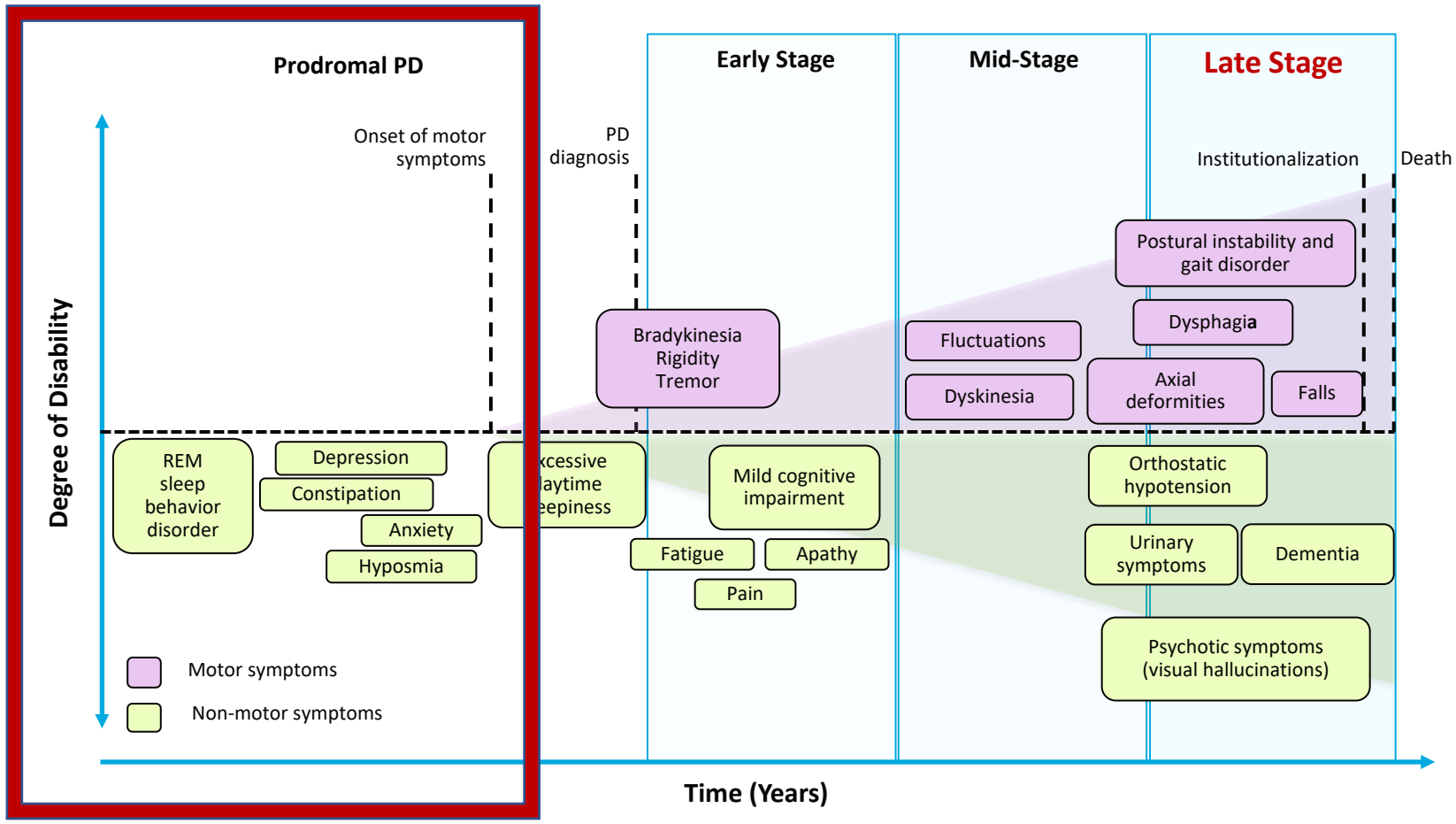
Rizzo & al, Neurology 2016

# Is Parkinson's Disease a Single Entity?




**Biomarker-defined Subtypes: Monogenic, GBA-PD, genetic & non-genetic biomarker signature**

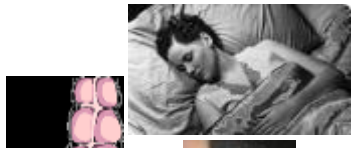
# The Course of Parkinson‘s Disease

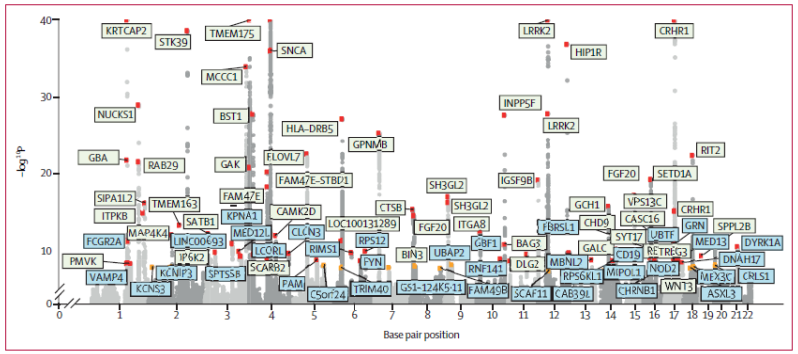


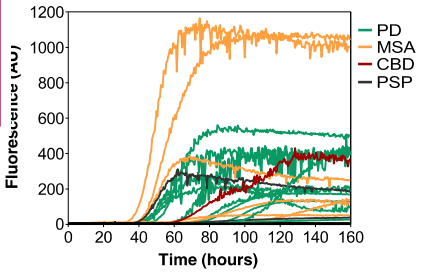

Poewe W, *et al*. (2017) Nat Rev Dis Primers, 3:17013.

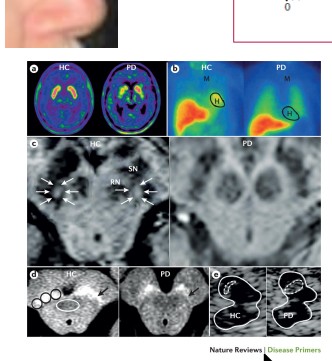
# Diagnosing PD: Role of Biomarkers

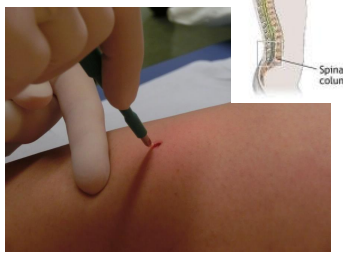
- Clinical Markers
- Imaging
- Genetics
- Biofluids
- Tissues

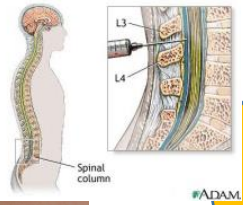


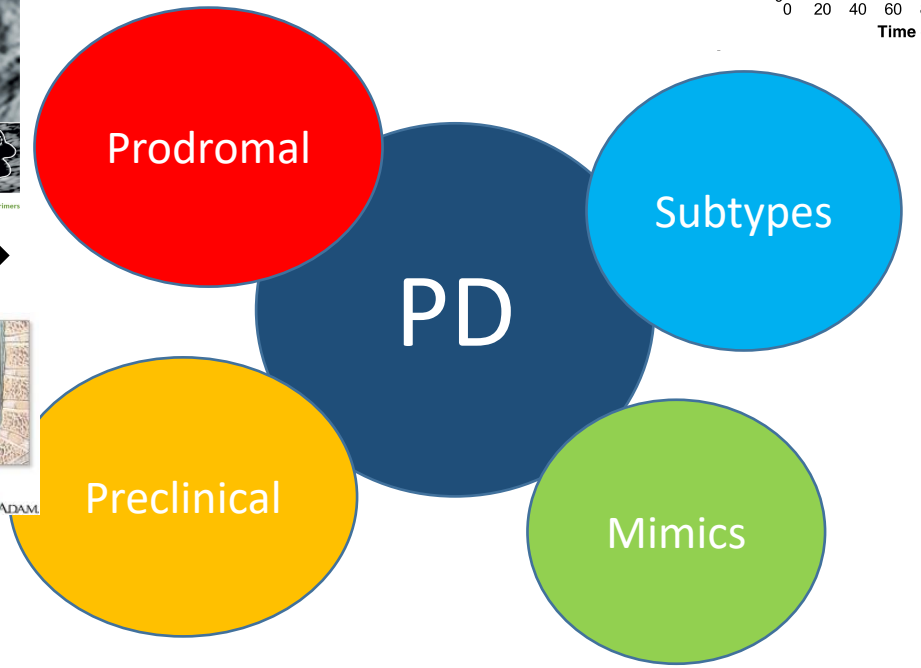


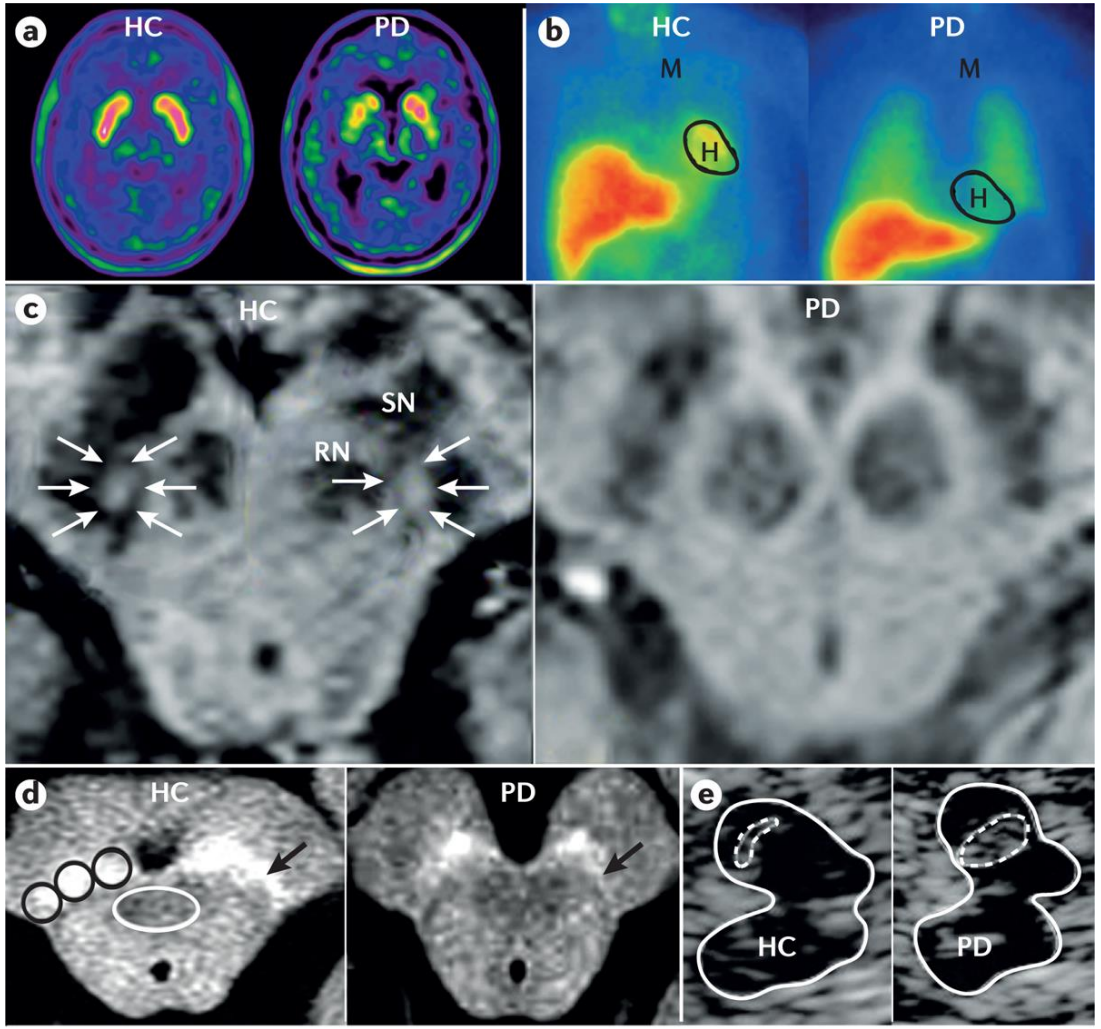


# Imaging Methods used to study Parkinson Disease

**Radiotracer**

**MRI**

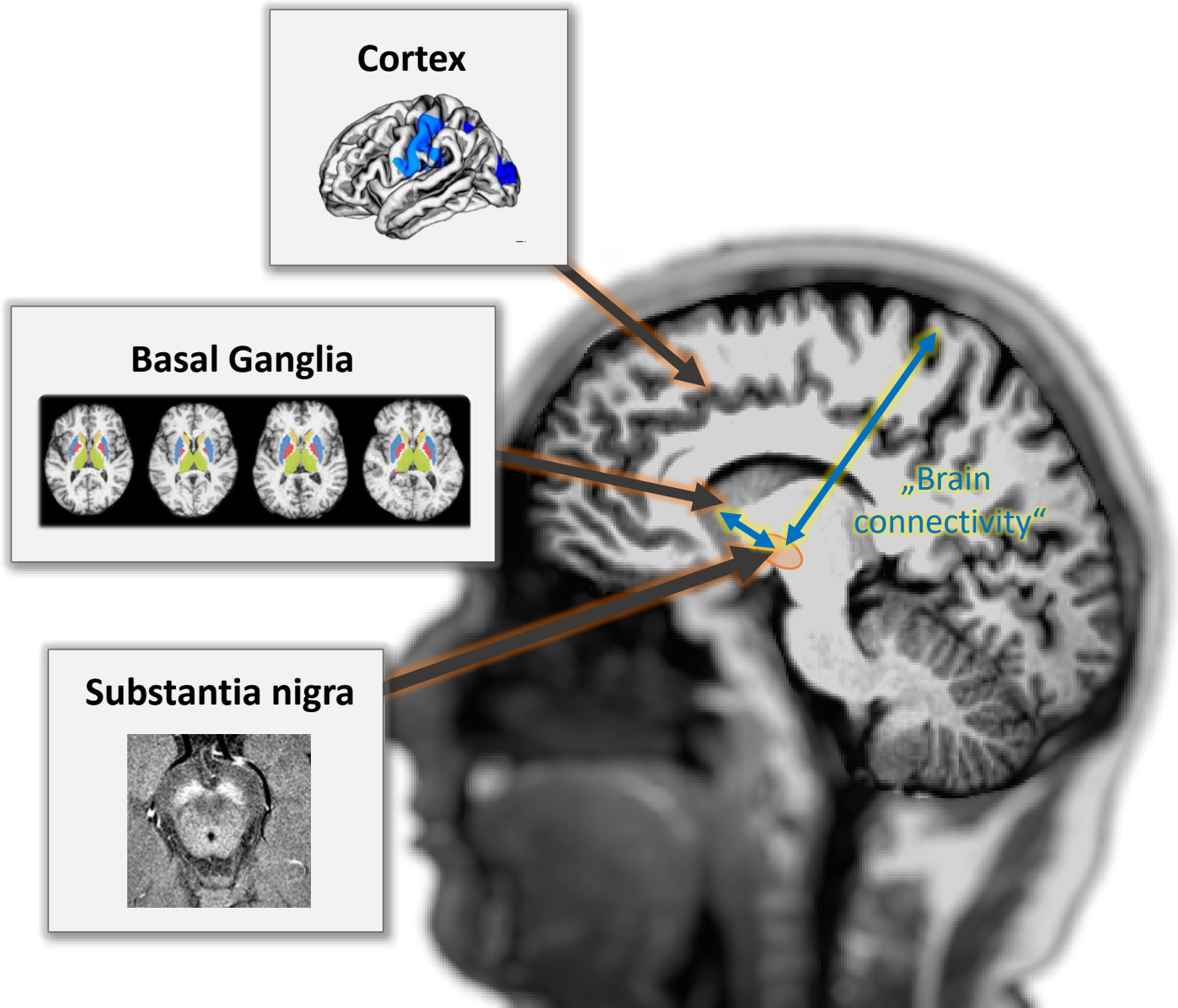



Nature Reviews | Disease Primers

**TCS**

Poewe, W. *et al.* (2017) Parkinson disease
*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2017.13

# Detecting PD pathology on MRI

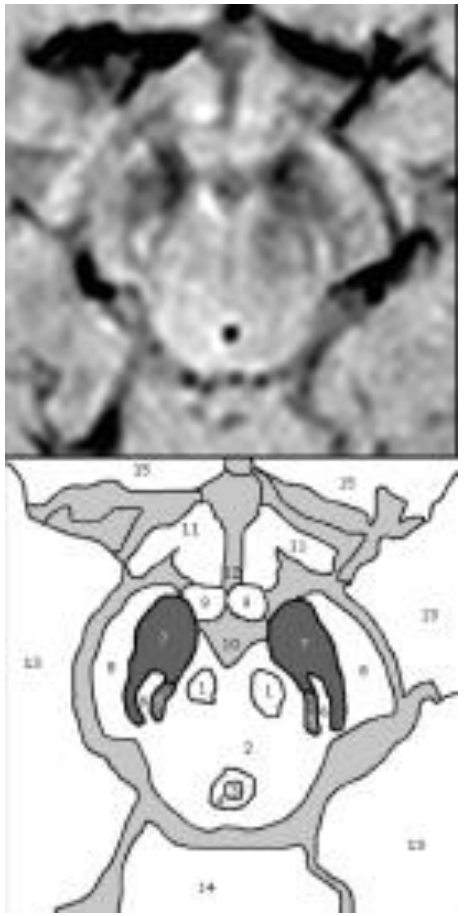



- Volumetry / Planimetry
- Iron-sensitive Imaging
- Neuromelanin-sensitive MRI
- Diffusion-Tensor Imaging
- Tractography
- Magnetization Transfer Imaging
- rs-fMRI

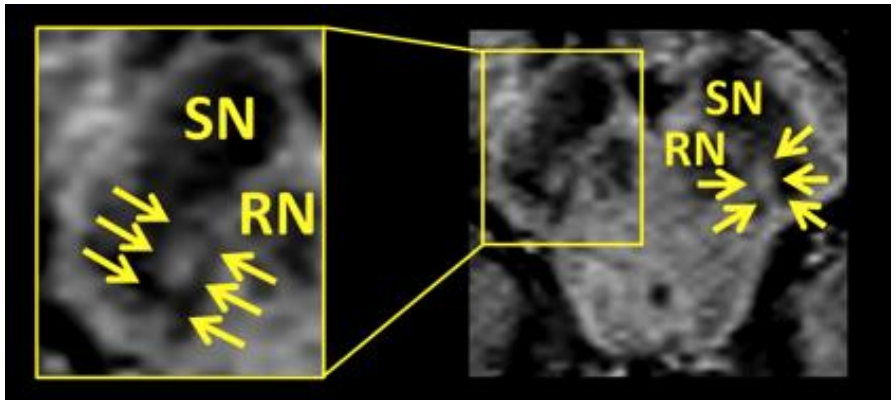
Pathoanatomical (tissue integrity)

Functional (pathophysiology)

# Loss of Dorsolateral Nigral Hyperintensity (DNH) – an Imaging Biomarker for PD?



Schwarz et al. 2014 Plos One



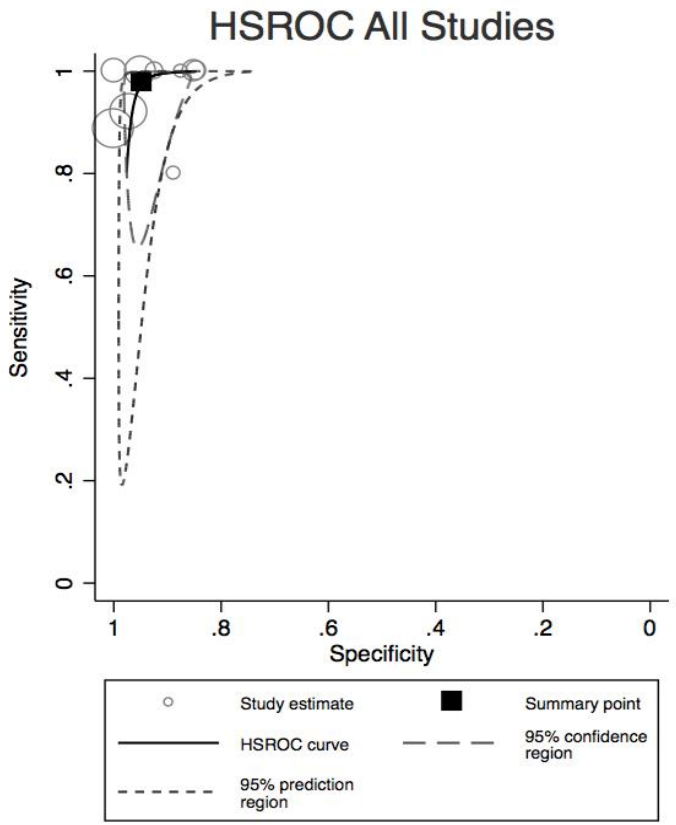

Reiter et al. 2015

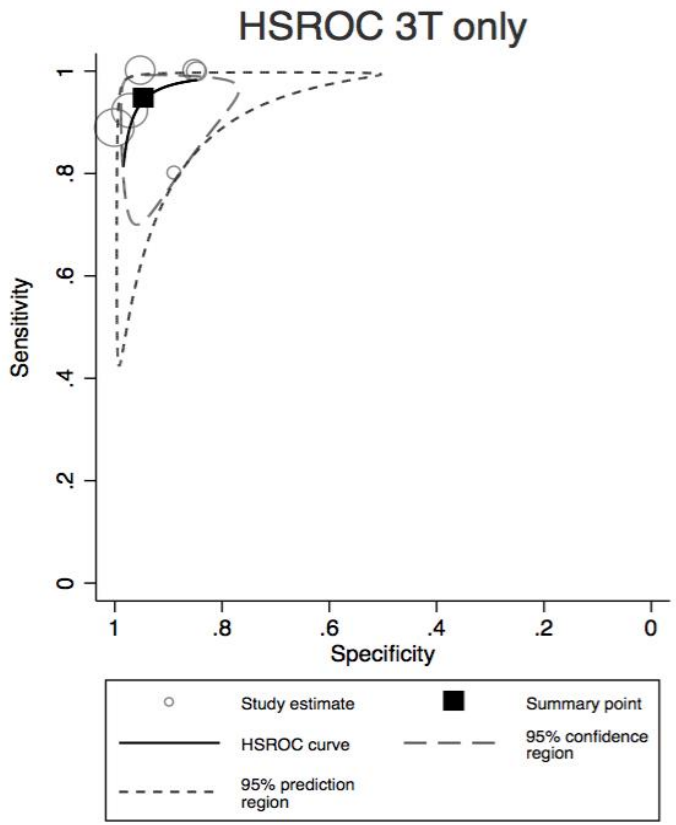
**The „swallow-tail“ sign**

In post-mortem 7T MRI correlates with Nigrosome 1, a histological concept referring to calbindin-poor sub-regions in the SNc

Blazejewska et al. 2013 Neurology

# Performance of DNH in diagnosing PD



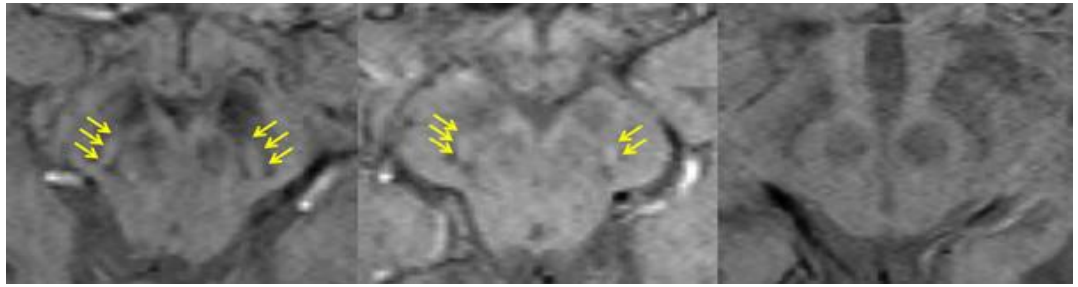

| Meta-Analysis | PD (n) | controls (n) | Pooled Sensitivity (%) | Pooled specificity (%) |
|---|---|---|---|---|
| all studies n=10 | 364 | 231 | 97.7 (95%CI, 85.5–99.7) | 94.6 (95%CI, 89.8–97.2) |
| at 3.0T n=7 | 307 | 184 | 94.6 (95%CI, 85.8–98.0) | 94.4 (95%CI, 87.7–97.5) |

Mahlknecht et al. 2017

# Loss of DNH: an MRI marker of prodromal PD ?

**Loss of Dorsolateral Nigral Hyperintensity on 3.0 Tesla Susceptibility-Weighted Imaging in Idiopathic Rapid Eye Movement Sleep Behavior Disorder**

Roberto De Marzi, MD,[1] Klaus Seppi, MD,[1,2] Birgit Högl, MD,[1] Christoph Müller, MD,[1] Christoph Scherfler, MD,[1,2] Ambra Stefani, MD,[1] Alex Iranzo, MD,[3] Eduardo Tolosa, MD,[3] Joan Santamaria, MD,[3] Elke Gizewski, MD,[2,4] Michael Schocke, MD,[2,4] Elisabeth Skalla, MD,[2,4] Christian Kremser, PhD,[2,4] and Werner Poewe, MD[1,2]



ANN NEUROL 2016;79:1026–1030

- 90 PD, 13 iRBD, 35 HC
- 3T Susceptibility-Weighted images (SWI) assessed by two blinded raters
- **Loss of DNH**
  - **10 of 13 (76.9%) iRBD pts.**
  - **83 of 90 (92.2%) PD pts.**
  - **1 of 35 (2.8%) HC‘s**

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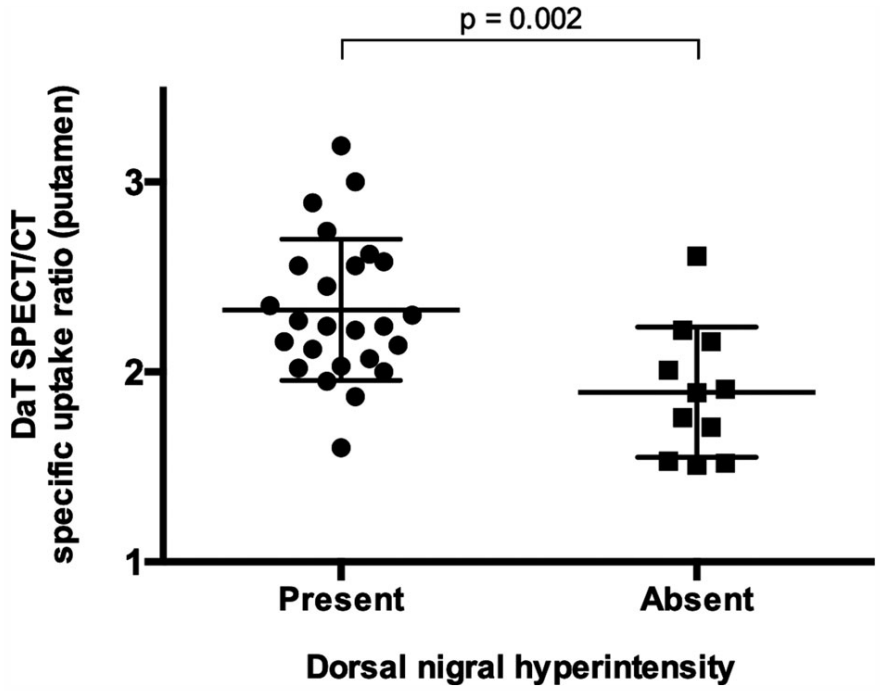
RESEARCH ARTICLE

# Nigrosome 1 imaging in REM sleep behavior disorder and its association with dopaminergic decline

Thomas R. Barber[1,2,3], Ludovica Griffanti[1,2,4], Kevin M. Bradley[5], Daniel R. McGowan[6], Christine Lo[1,2], Clare E. Mackay[1,3], Michele T. Hu[1,2] & Johannes C. Klein[1,2,3,4]

*Annals of Clinical and Translational Neurology* 2020; 7(1): 26–35

- SWI of SN in 46 RBD vs 27 PD vs 32 Ctrls.
- Loss of DNH
  - 96% of PD
  - 27% of RBD
  - 8% of Ctrls
- Putamenal DAT-Spect signal lower in RBD/DNH- vs RBD/DNH+



# Diagnosing PD: Role of Biomarkers

- Clinical Markers
- Imaging
- Genetics
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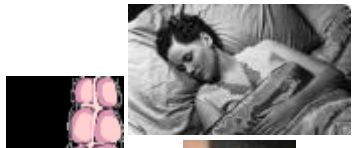
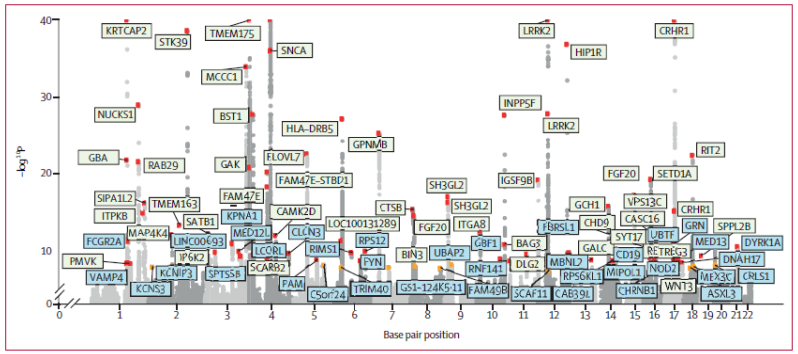
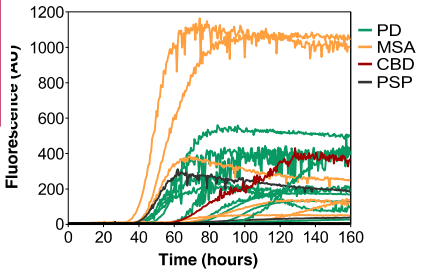
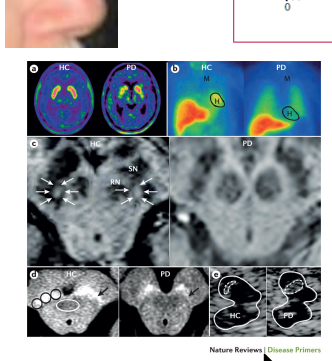
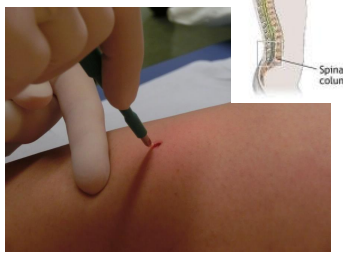
- Tissues

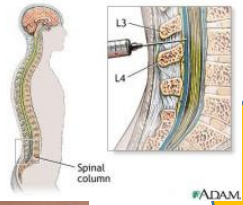


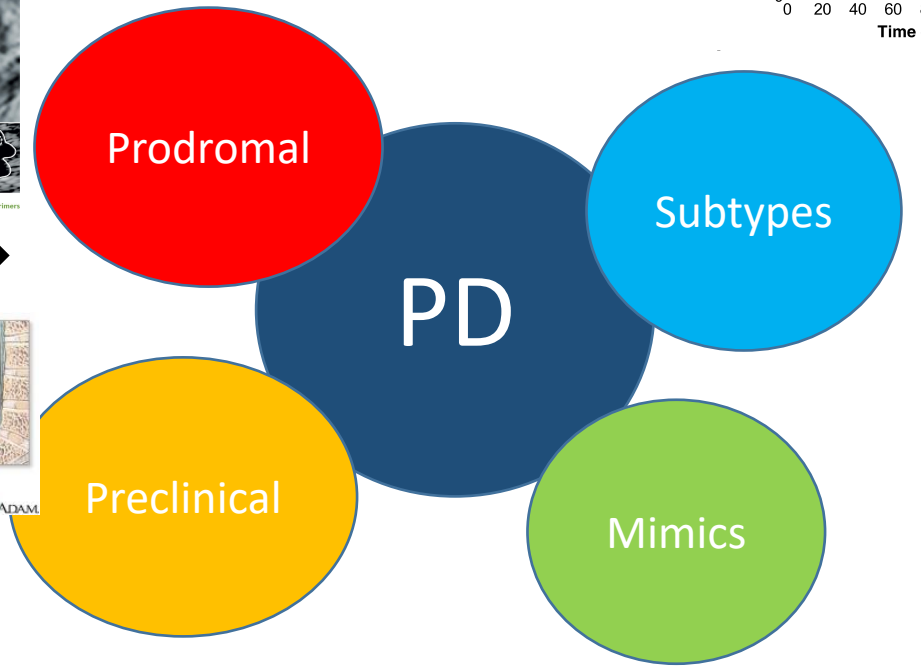




# Diagnosing PD via α-Synuclein seeding activity in CSF?

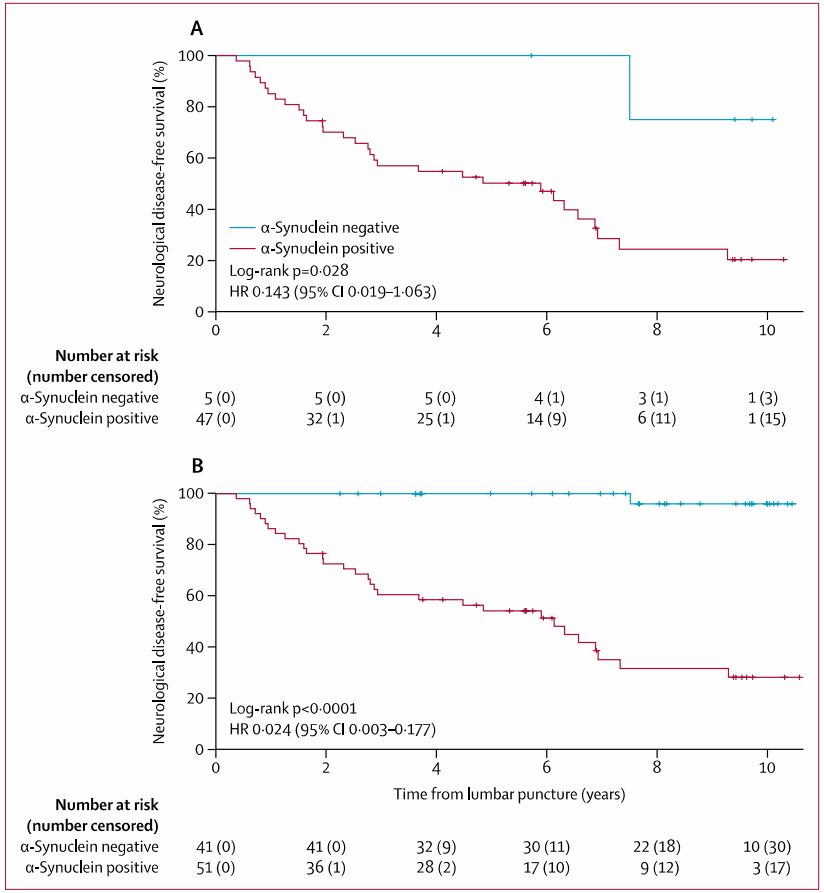
| Diagnostic Groups | Sensitivity | Specificity | Authors |
|---|---|---|---|
| PD (20) vs Ctrls (15) | 95 % | 100 % | *Fairfoul & al., 2016* |
| PD (76) vs Ctrls (83) | 88 % | 94 % | *Shahwanaz & al., 2017** |
| PD (53) vs Ctrls (52) | 84 % | 98 % | *Van Rumund & al., 2019* |
| PD (10) vs Ctrls (10) | 90 % | 80 % | *Garrido & al., 2019* |
| PD (105) vs Ctrls (79) | 96 % | 82 % | *Kang & al., 2019* |
| PD (71) vs Ctrls (62) | 94 % | 98 % | *Rossi & al., 2020* |
| PD (94) vs Ctrls (56) | 94 % | 100 % | *Shahwanaz & al., 2020** |
| | | | |
| PD (53) vs non-a-syn parkinsonism (26) | 84 % | 89 % | *Van Rumund & al., 2019* |
| PD (71) vs PSP/CBS (30) | 94 % | 100 % | *Rossi & al., 2020* |
| PD (88) vs MSA (65) | 95% | - | *Shahwanaz & al., 2020** |

*** PMCA**

## Detection of α-synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: a longitudinal observational study

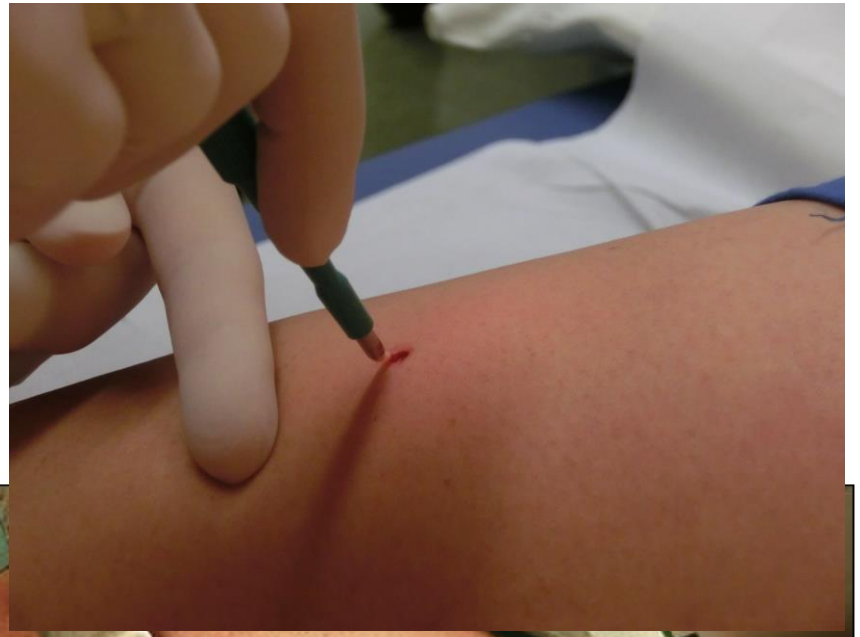
*Alex Iranzo, Graham Fairfoul, Anutra Chumbala Na Ayudhaya, Monica Serradell, Ellen Gelpi, Isabel Vilaseca, Raquel Sanchez-Valle, Carles Gaig, Joan Santamaria, Eduard Tolosa, Renata L Riha, Alison J E Green*

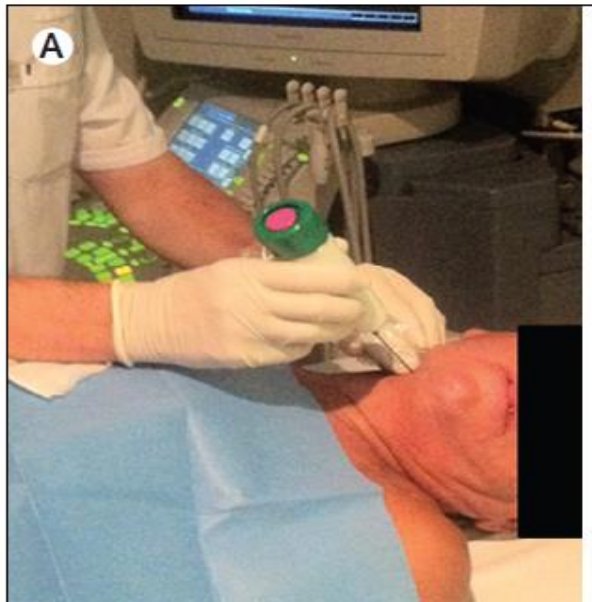
- 52 iRBD vs 40 matched HC‘s
- Baseline CSF a-syn RT-QuIC
- Long term follow-up (mean 7-8 yrs)
- 90% of iRBD vs 10% of HC‘s RT-QuIC pos
- Sensitivity and specificity of 90%
- 62% vs 0 HC‘s of iRBD converted  to PD/DLB
- 97% of converters RT-QuIC positive at baseline

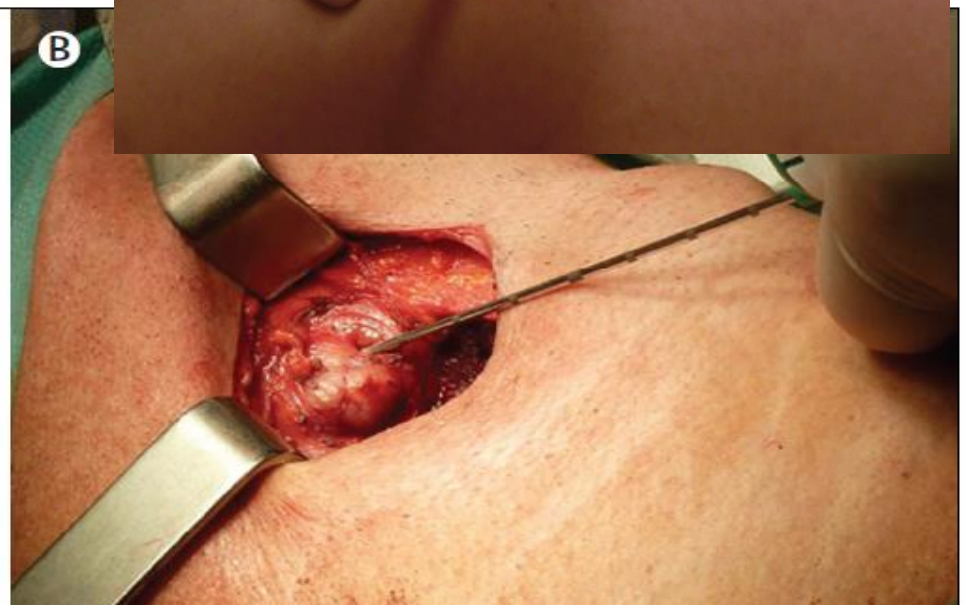



*Lancet Neurol* 2021; 20: 203–12

# Tissue Biopsies for α-synuclein



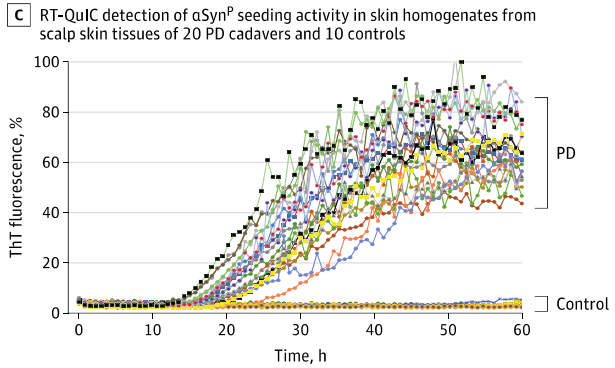


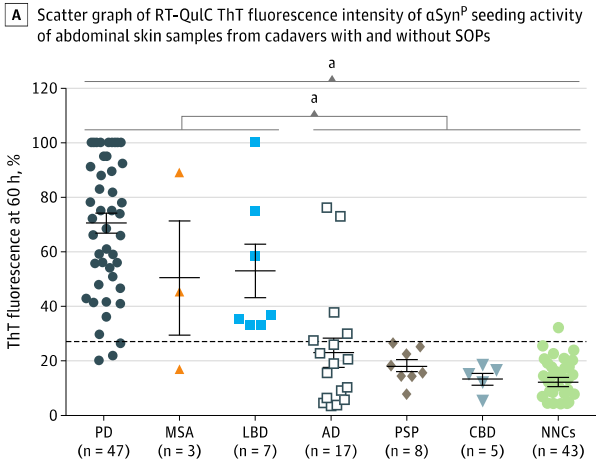



JAMA Neurology | Original Investigation

# Skin α-Synuclein Aggregation Seeding Activity as a Novel Biomarker for Parkinson Disease

Zerui Wang, MD, PhD; Katelyn Becker, MS; Vincenzo Donadio, MD, PhD; Sandra Siedlak, MS; Jue Yuan, MS; Masih Rezaee, MD; Alex Incensi, MSc; Anastasia Kuzkina, MD; Christina D. Orrú, PhD; Curtis Tatsuoka, PhD; Rocco Liguori, MD; Steven A. Gunzler, MD; Byron Caughey, PhD; Maria E. Jimenez-Capdeville, PhD; Xiongwei Zhu, PhD; Kathrin Doppler, MD; Li Cui, MD, PhD; Shu G. Chen, PhD; Jiyan Ma, MD, PhD; Wen-Quan Zou, MD, PhD



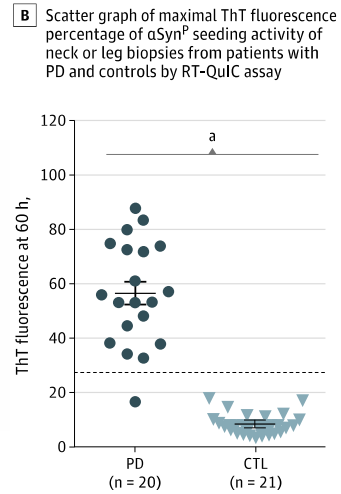




## Autopsied skin sample homogenates

- 57 with synucleinopathies
- 30 with tauopathies
- 41 NNC's
- *93% sensitivity & specificity for a-syn RT-QuIC*

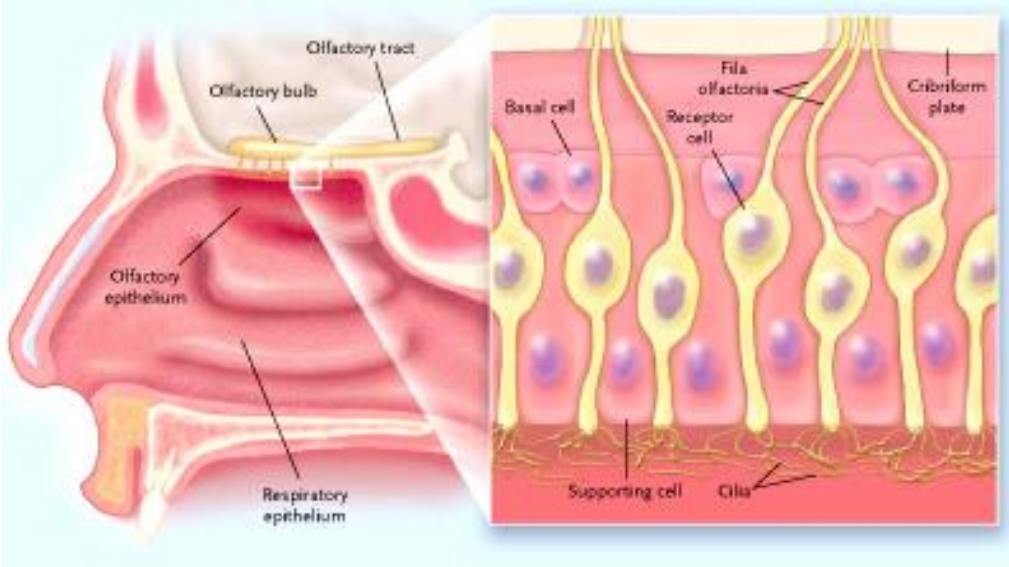
## In vivo Skin biopsy homogenates

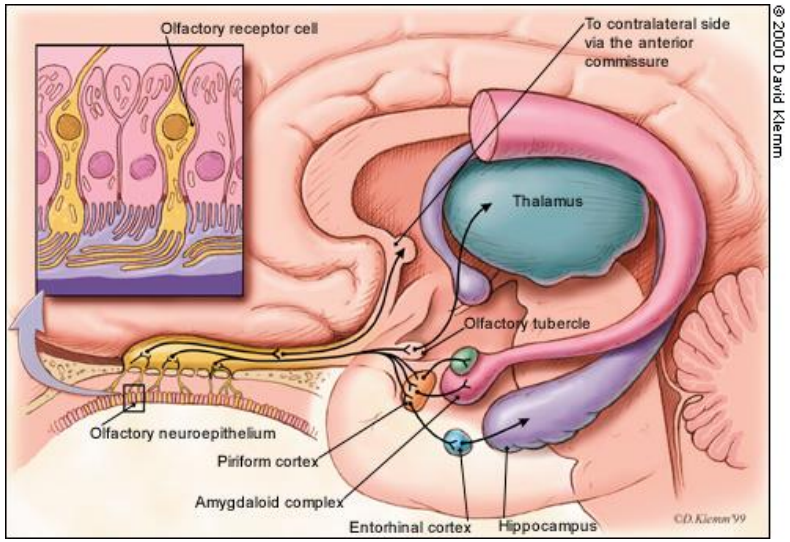
- 20 PD
- 21 HC's
- *95% sensitivity & 100% specificity for PD vs controls*

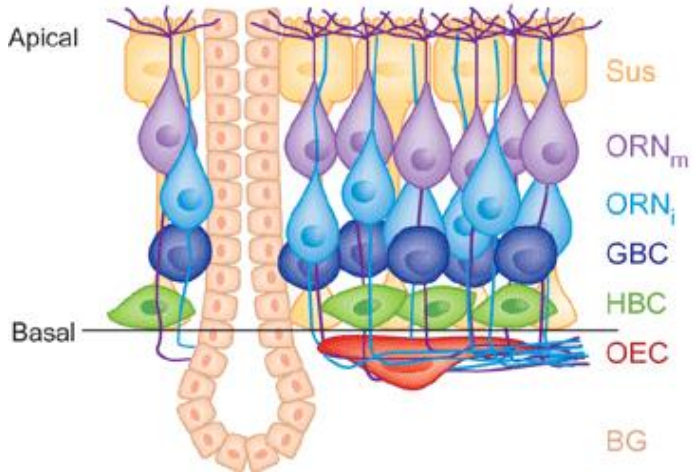


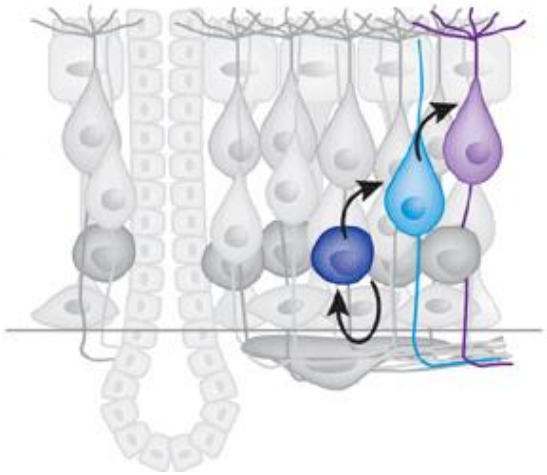

*JAMA Neurol.* 2021;78(1):30-40. doi:10.1001/jamaneurol.2020.3311

# Olfactory Neurons and Neural Pathway



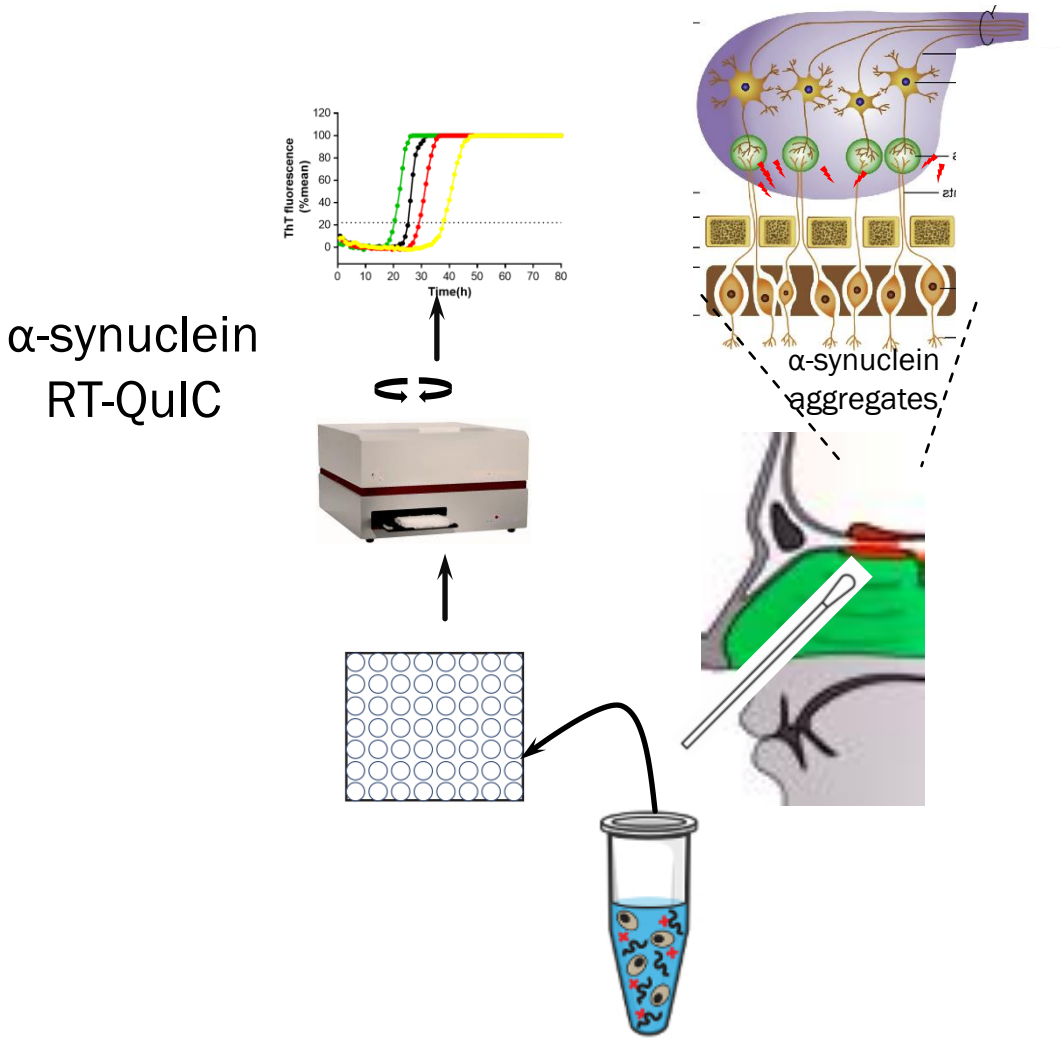



**Olfactory Neurons**

- **Ongoing replication**
- **Half life of 60 days**
- **From Stem cells**

# α-SYNUCLEIN SEEDS IN THE OLFACTORY MUCOSA IN PD AND IRBD




- α-synuclein RT-QuIC in olfactory mucosa samples
  - 63 iRBD
  - 41 PD
  - 59 controls

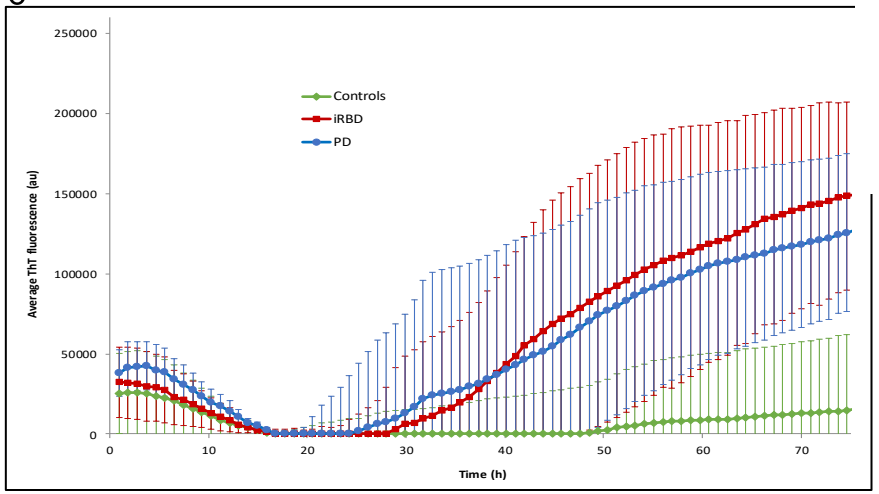
Stefani & al, Brain 2021

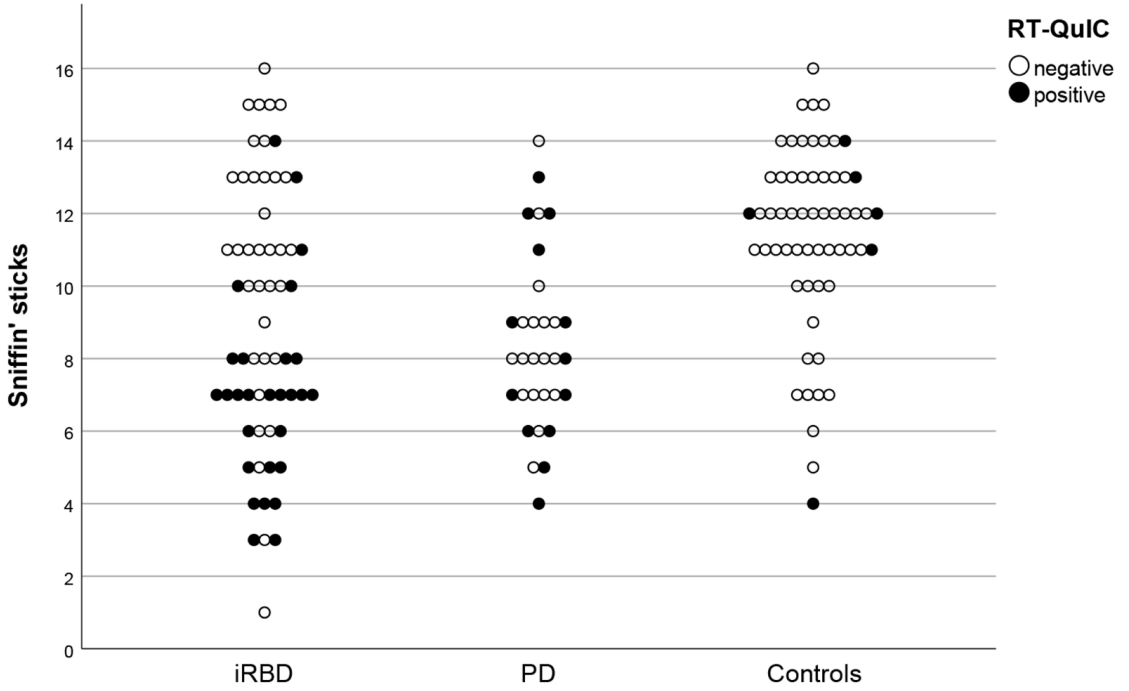
# α-Synuclein Seeds in the OM in PD and iRBD

**RT-QuIC positve:**

- 44.4% of IRBD
- 46.3% of PD
- 10.2% of HC's

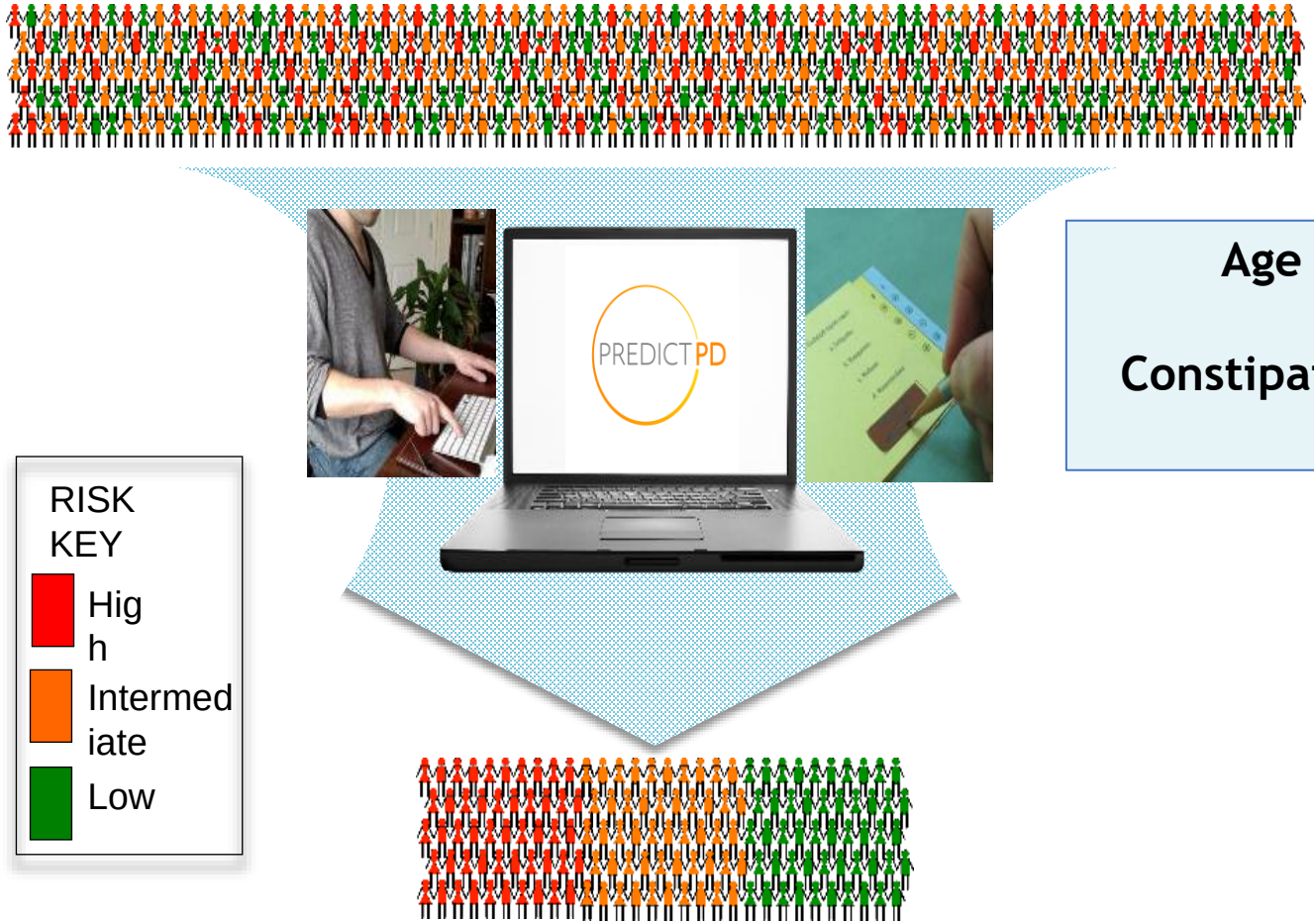
- **Sensitivity** (iRBD+PD vs ctrls): 45.2%
- **Specificity** (iRBD+PD vs ctrls): 89.8%




In iRBD, RT-QuIC correlated with olfactory dysfunction

Stefani & al, Brain 2021




Age ,Gender,Family history of PD, Head injury
Medications ,Hypertension
Constipation,Depression/anxiety, Erectile dysfunction
Alcohol Coffee Smoking

REM-sleep Behaviour Disorder
Smell loss
Tapping speed
Genetic variation

Parkinson's disease

RESEARCH ARTICLE

PREDICT-PD: An Online Approach to Prospectively Identify Risk Indicators of Parkinson's Disease

Alastair J. Noyce, MRCP, PhD,[1,2] Lea R'Bibo, MSc, MRes,[1] Luisa Peress, BSc,[2] Jonathan P. Bestwick, MSc,[3] Kerala L. Adams-Carr, MB, BS, BA,[1,4] Niccolo E. Mencacci, MD,[1] Christopher H. Hawkes, FRCP, MD,[2] Joseph M. Masters, BSc,[2] Nicholas Wood, FRCP, PhD,[1] John Hardy, PhD,[1] Gavin Giovannoni, FRCP, PhD,[5] Andrew J. Lees, FRCP, MD,[1] and Anette Schrag, FRCP, PhD[1]*

Movement disorders

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RESEARCH PAPER

PREDICT-PD: Identifying risk of Parkinson's disease in the community: methods and baseline results

Alastair J Noyce,[1,2] Jonathan P Bestwick,[3] Laura Silveira-Moriyama,[1,4] Christopher H Hawkes,[2] Charles H Knowles,[2] John Hardy,[1] Gavin Giovannoni,[2] Saiji Nageshwaran,[5] Curtis Osborne,[2] Andrew J Lees,[1] Anette Schrag[5]

# CONCLUSIONS

- Dignosing PD still anchored on careful clinical examinatiom
- Imaging, genetic and molecular biomarkers help identify
  - PD-mimics
  - disease subtypes
  - Prodromal PD
- Identifying Prodromal PD is key for future disease-modifying therapies
- Population-based screening for PD risk is becoming a realistic scenario