Biomarkers in Prodromal Parkinson's disease

Anat Mirelman, PhD

Laboratory for the study of Early Markers Of Neurodegeneration (LEMON)

Center for the study of Movement, Cognition and Mobility

Neurological Institute, Tel Aviv Medical Center

Sackler School of Medicine, Tel Aviv University

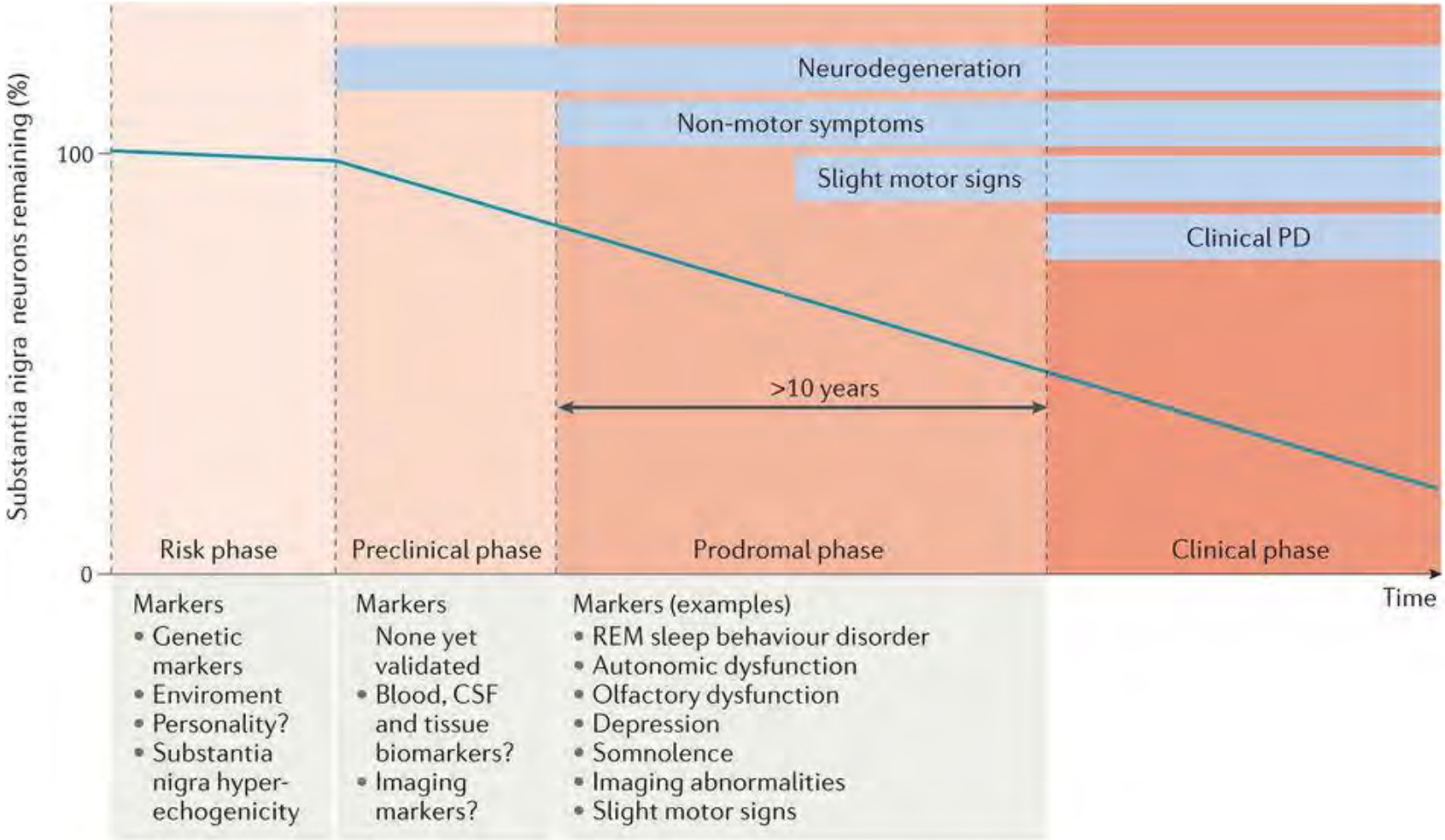

Substantia nigra neurons remaining (%)
100
0
Neurodegeneration
Non-motor symptoms
Slight motor signs
Clinical PD
>10 years
Risk phase
Preclinical phase
Prodromal phase
Clinical phase
Time
Markers
• Genetic markers
• Enviroment
• Personality?
• Substantia nigra hyper-echogenicity
Markers
None yet validated
• Blood, CSF and tissue biomarkers?
• Imaging markers?
Markers (examples)
• REM sleep behaviour disorder
• Autonomic dysfunction
• Olfactory dysfunction
• Depression
• Somnolence
• Imaging abnormalities
• Slight motor signs

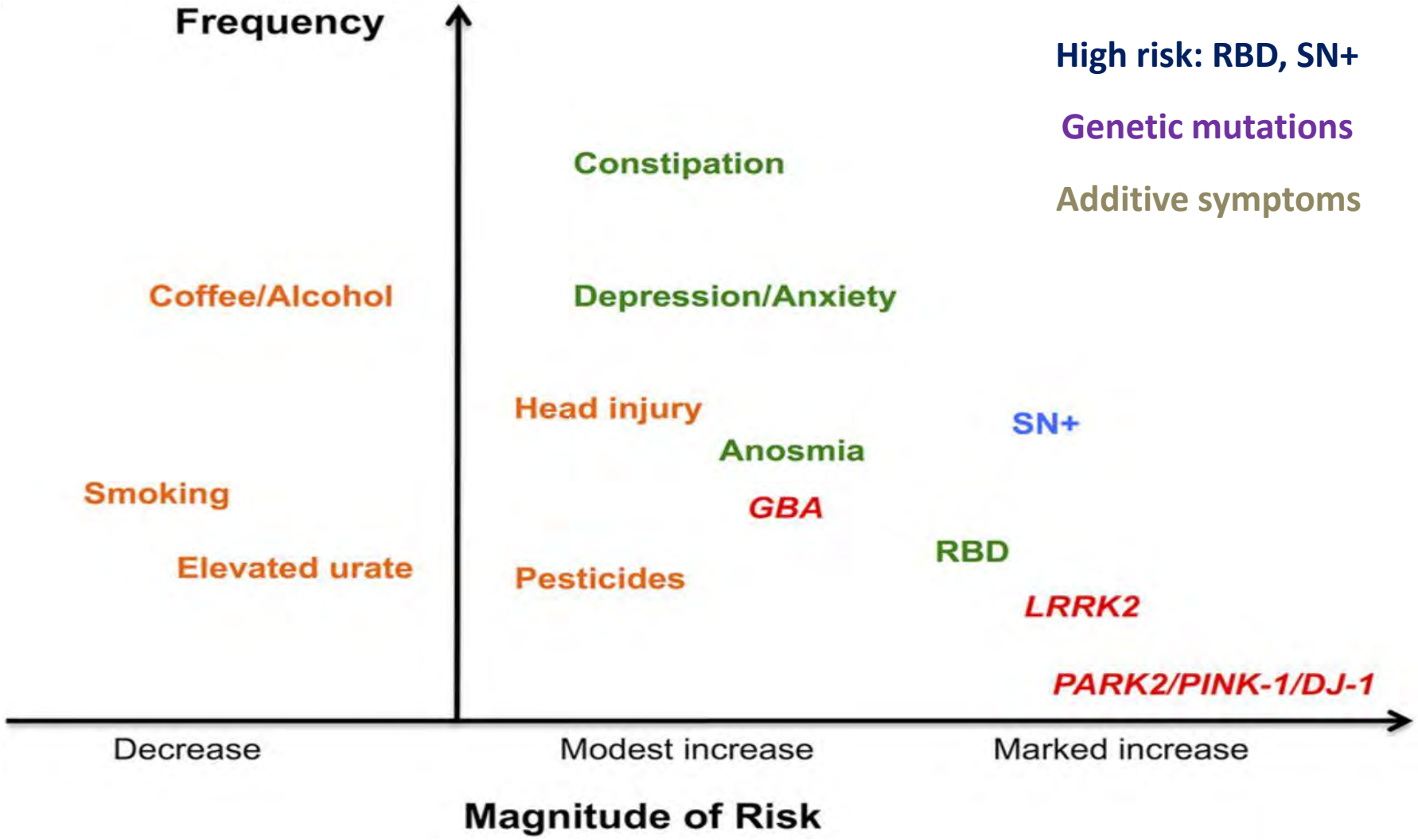
TABLE 1. Summary of Clinical Markers of Premotor PD

Marker	Level of evidence[a]	Sensitivity	Specificity
Olfaction	High (population-based studies,[38] prospective studies[29])	High (>80% of early PD)	Low (up to one-third of elderly population has olfactory loss)
REM sleep behavior disorder	High (3 cohort studies[48–50])	Low (50% of PD patients have RBD, one-half of these precede disease)	High (up to 65% risk of disease at 10 years)
Autonomic symptoms	High for constipation,[77,78] low/moderate for other symptoms	Moderate-high (most early PD patients have symptoms)	Low (one-third of general population has symptoms)
Cardiac autonomic markers (RR variability, MIBG scintigraphy	Low (no prospective studies, one negative RBD study)	Unknown for RR variability; high for MIBG (most PD patients are abnormal)	Unknown
Depression	Moderate (case-control studies, conflicting cohort studies)	Low (30%–40% of PD patients have depression)	Low (one-third of general population has)
Visual abnormalities: saccadic abnormalities; retinography; optical coherence tomography; color vision	Moderate for color vision (prospective RBD study[29]), low for others	Unknown—most PD patients have abnormalities—unclear if present early in PD	Unknown
Cognitive impairment	Low	Unknown—subtle cognitive changes difficult to detect	Unknown—subtle cognitive changes may be nonspecific

Postuma et al. Movement Disorders 2013

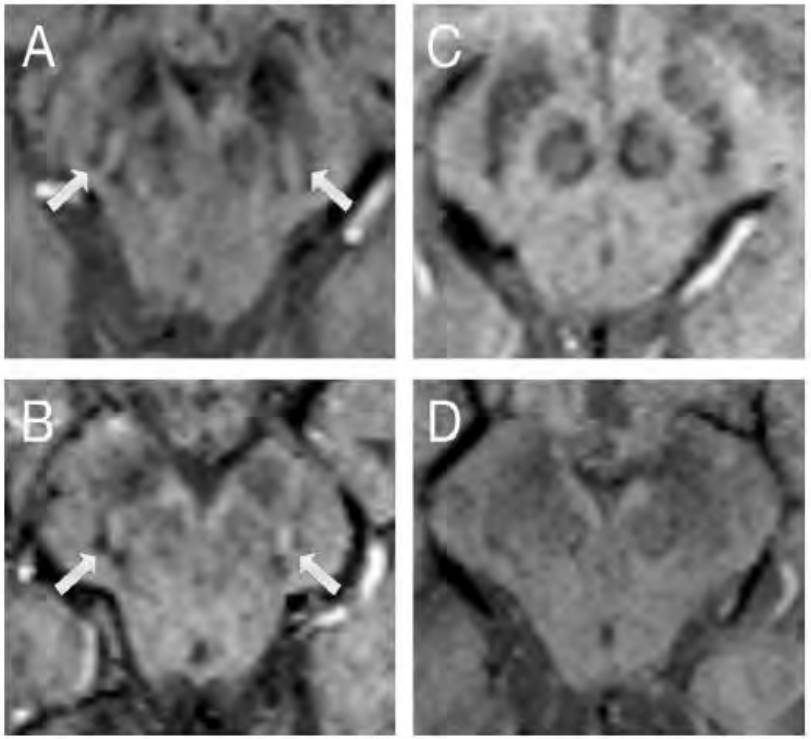
Research aims:
To solve the puzzle

Identifying populations at risk



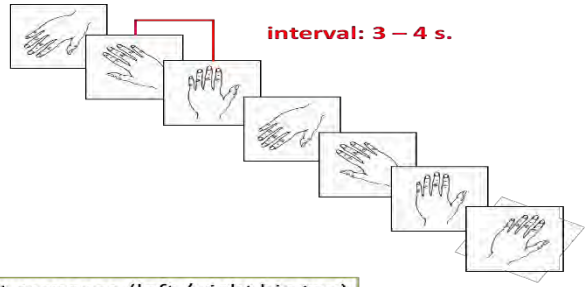
Imaging- Structural

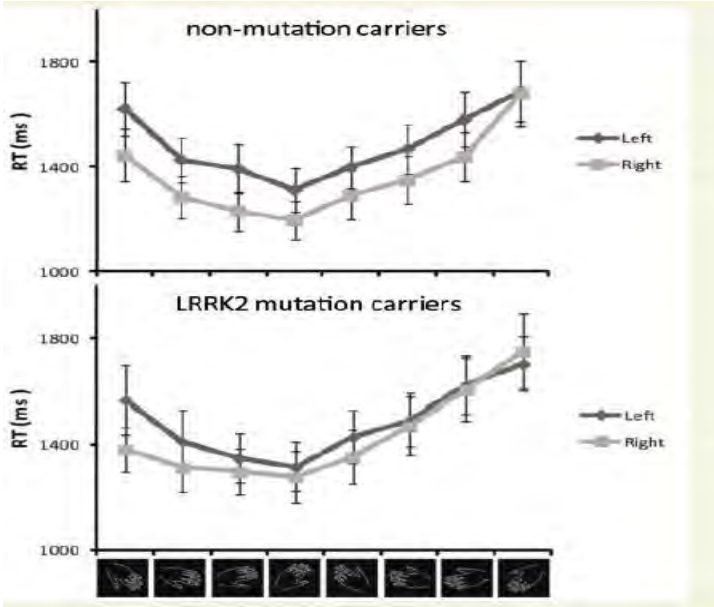
- MRI- “Swallow Tail Sign”
- Lost in 92% of PD
- 1/35 controls
- 10/13 RBD

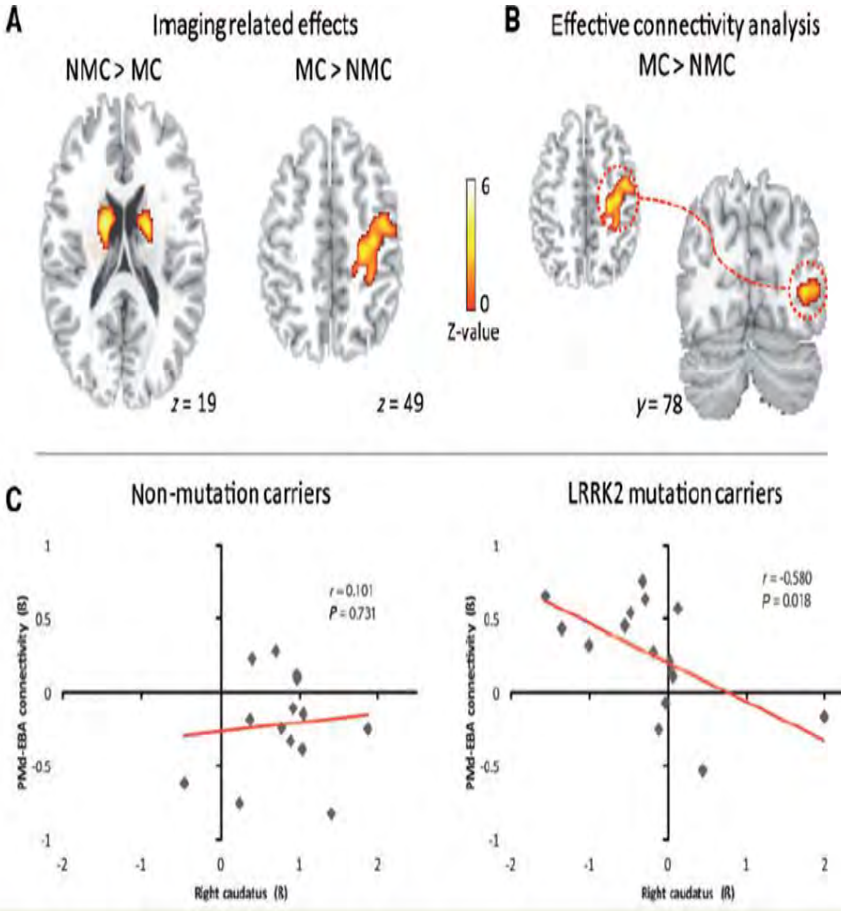


DeMarzi, Ann Neurol, 2016

G2019S mutation carriers use the brain differently to solve motor imagery problems



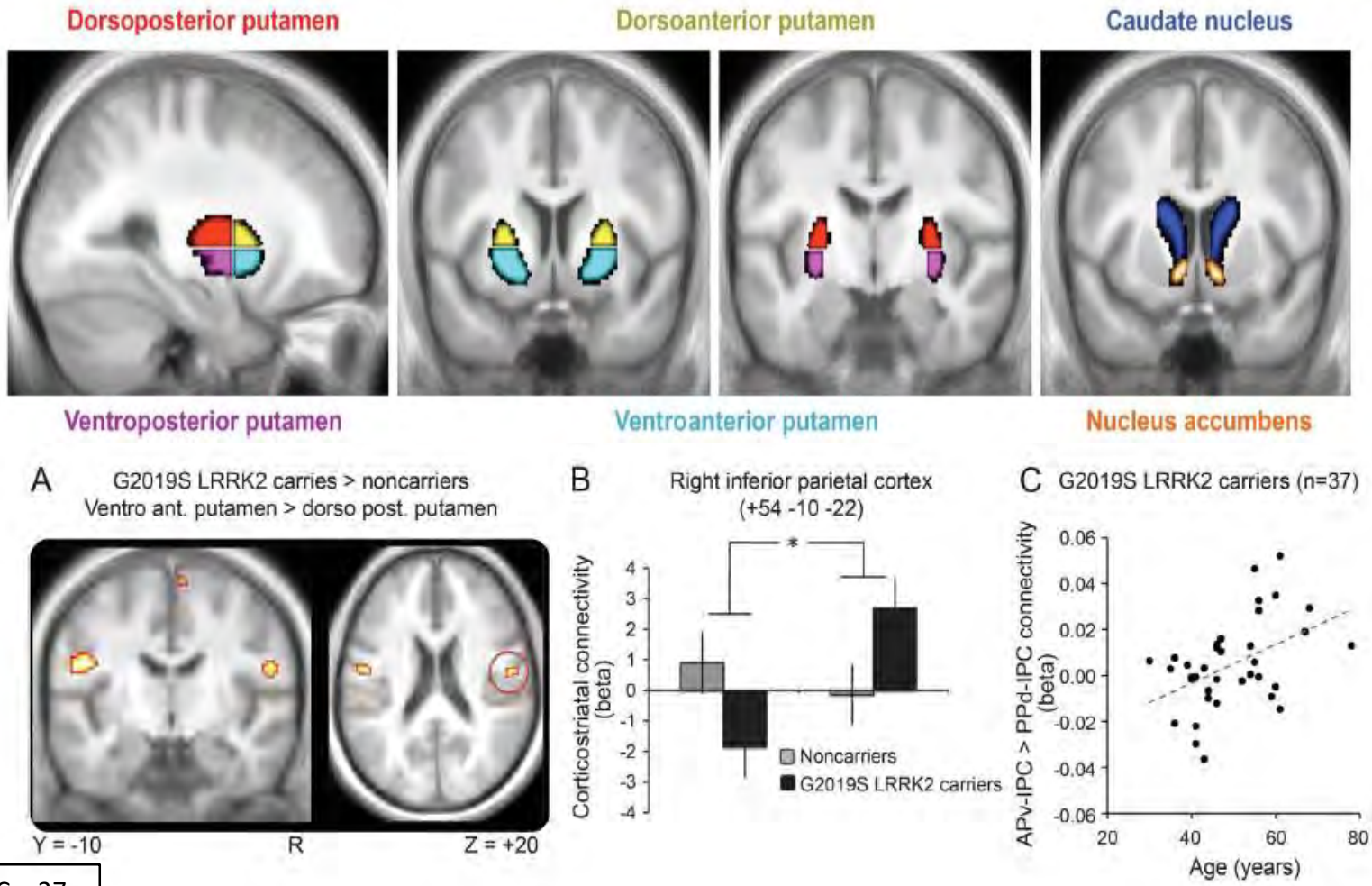




LRRK2 NMC – 21
NMNC - 18

Van Neunen et al. Brain 2013

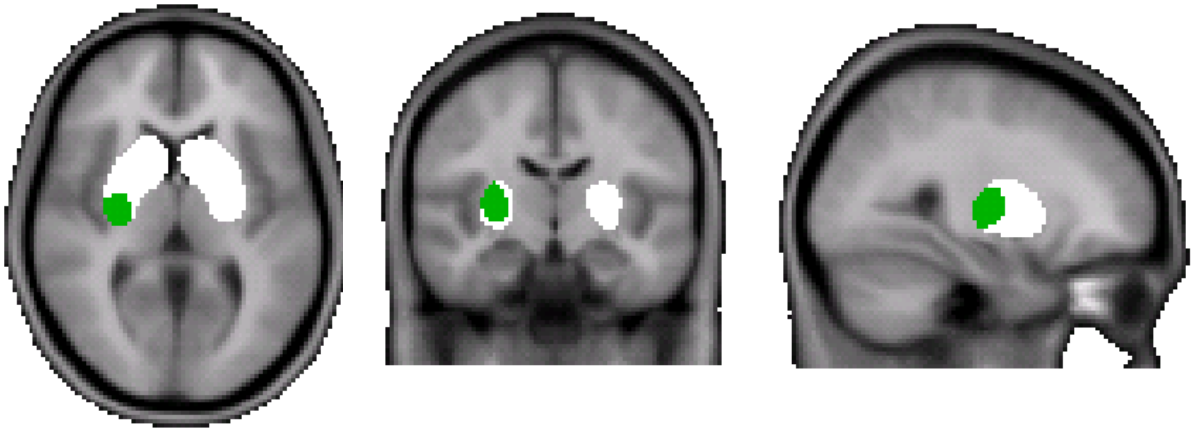
FMRI Resting State functional connectivity



LRRK2 NMC – 37
NMNC - 32

Helmich et al. Neurology 2015

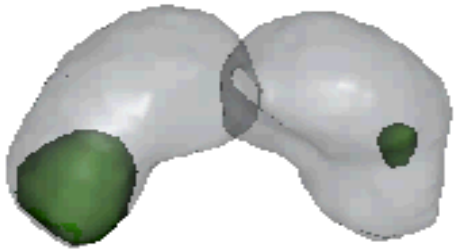
Quantification of DaT uptake using VBM analysis

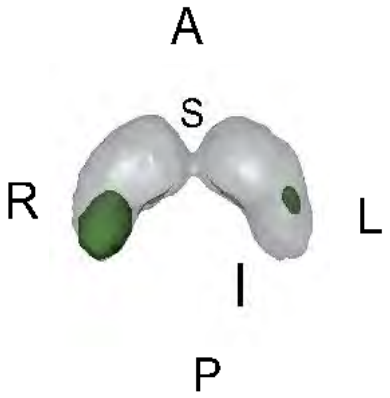


p<0.05; Corrected for multiple comparison

NC>C

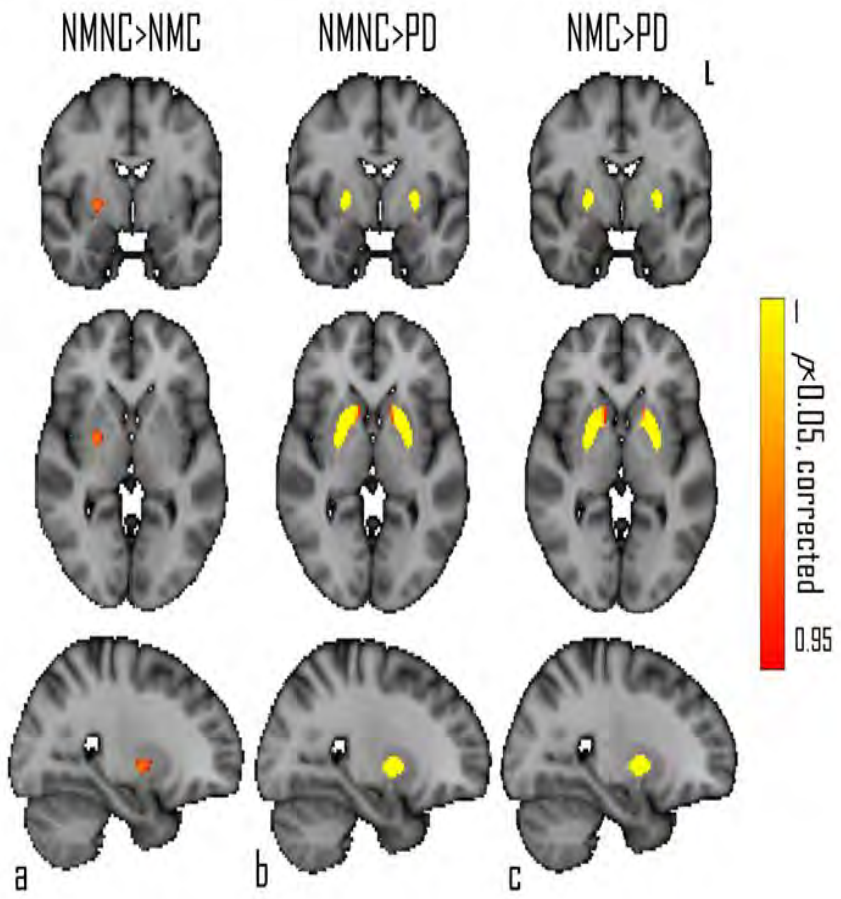
C = First-degree relatives, carriers
NC = First-degree relatives, non carriers

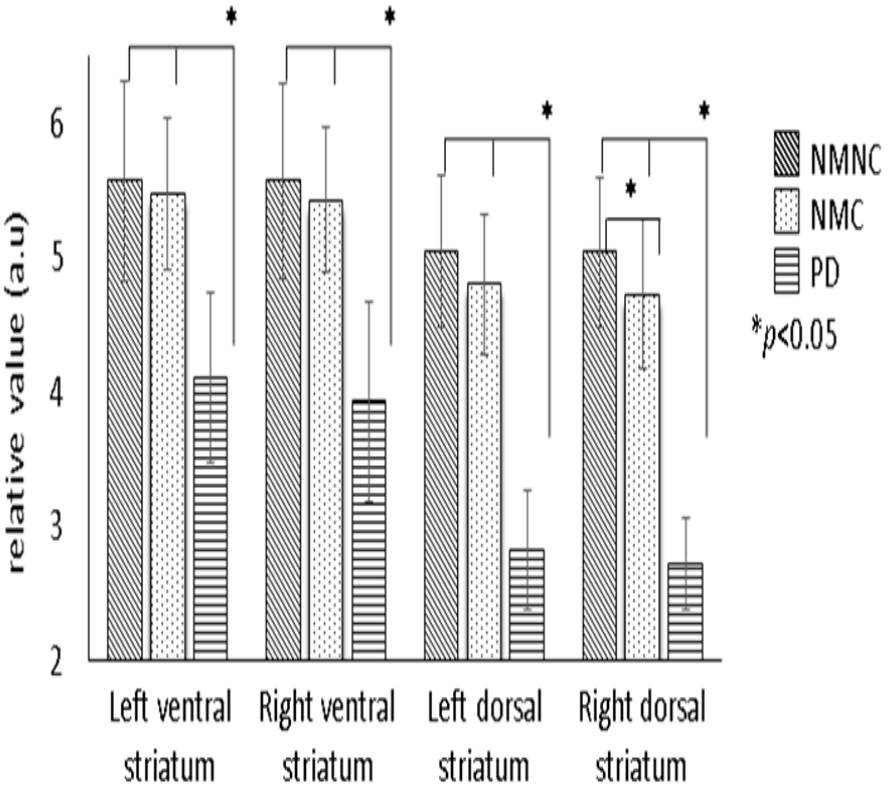




Non Carriers > carriers

Artzi et al. PLOS 2017

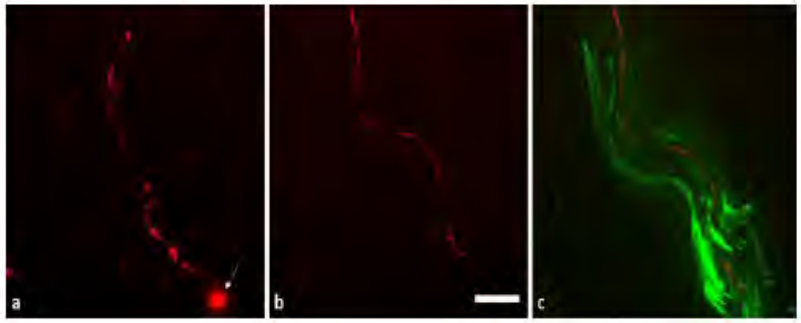




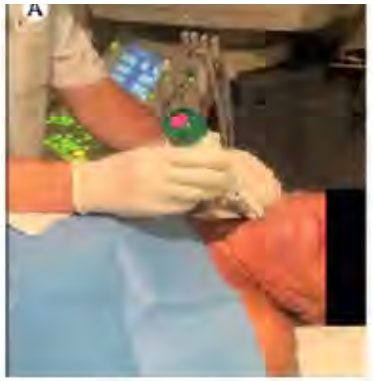
Artzi et al. PLOS 2017

Alpha- synuclein

- Submandibular salivary gland
  - 8/9 idiopathic RBD had positive biopsy
- Skin biopsy
  - 20/25 (80%) early PD were positive
  - 10/18 (56%) iRBD

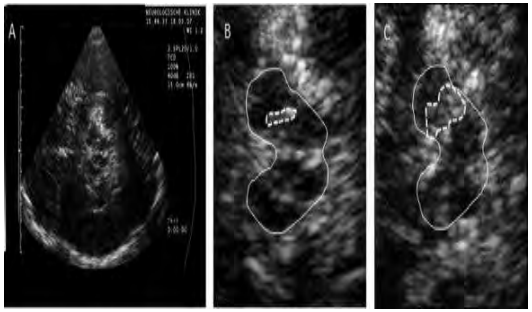


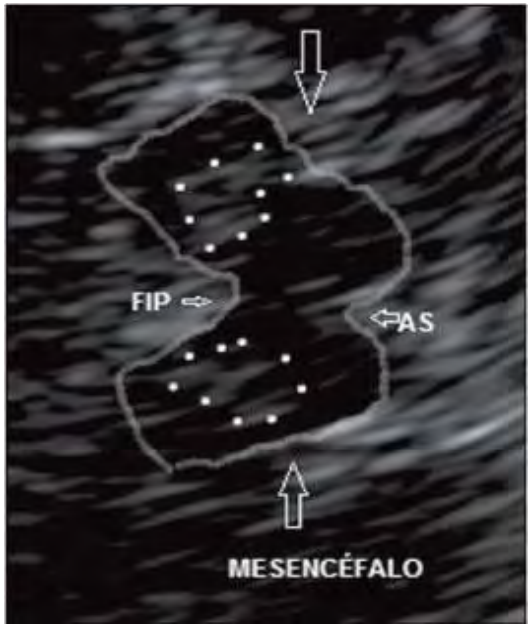
Doppler, et al, Acta Neuropath, 2017

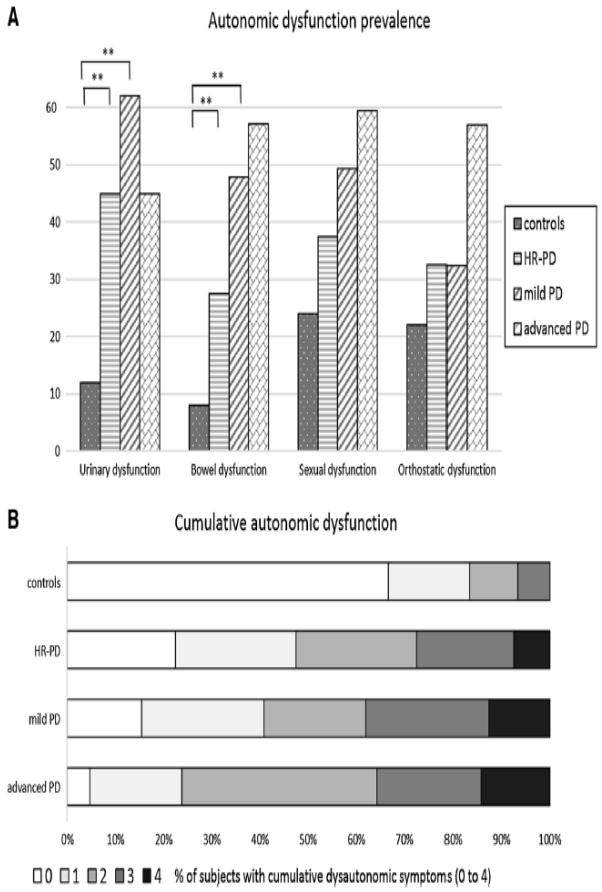


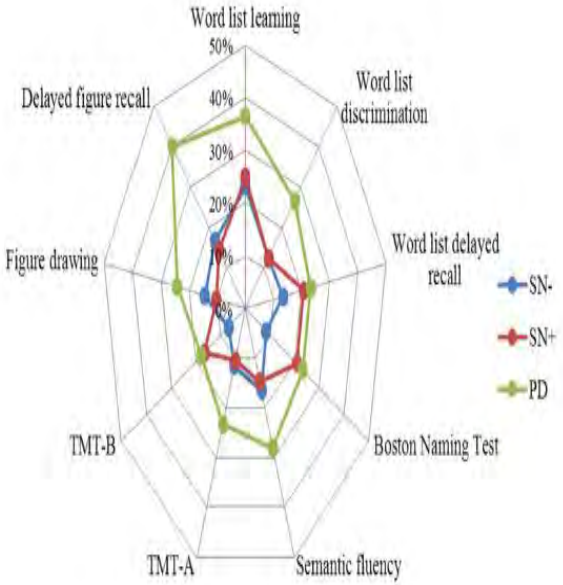
Vilas, Lancet Neurol. 2016

Substansia Nigra hyperechogenicity



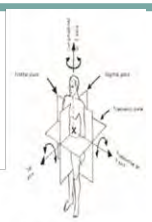


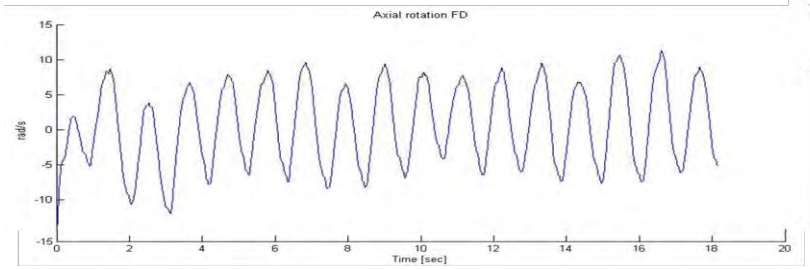


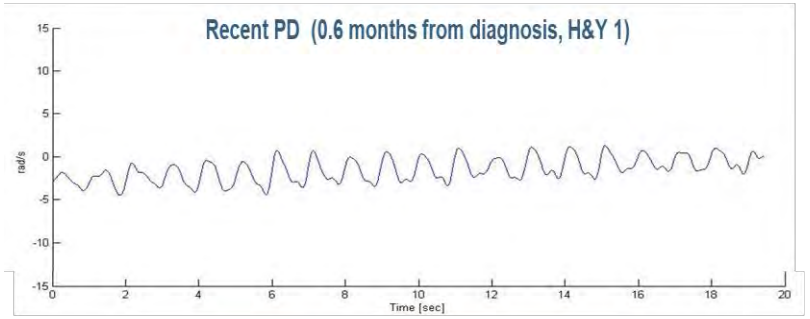


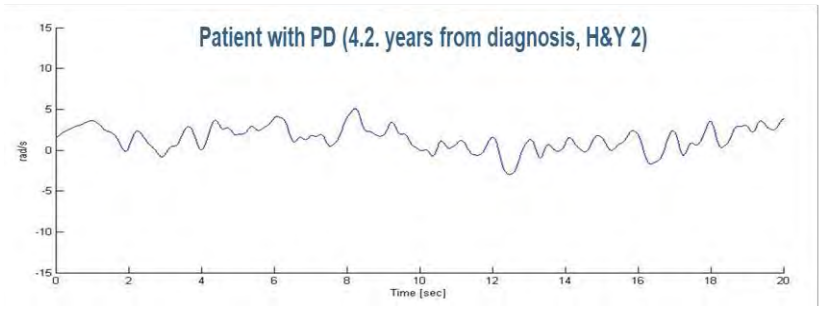
Liepelt-Scarfone et al 2015 ; Yilmaz et al 2016

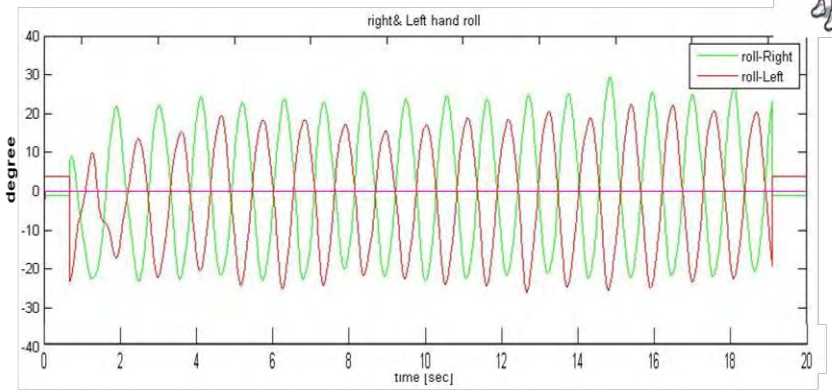
Subtle motor measures in the prodromal stage

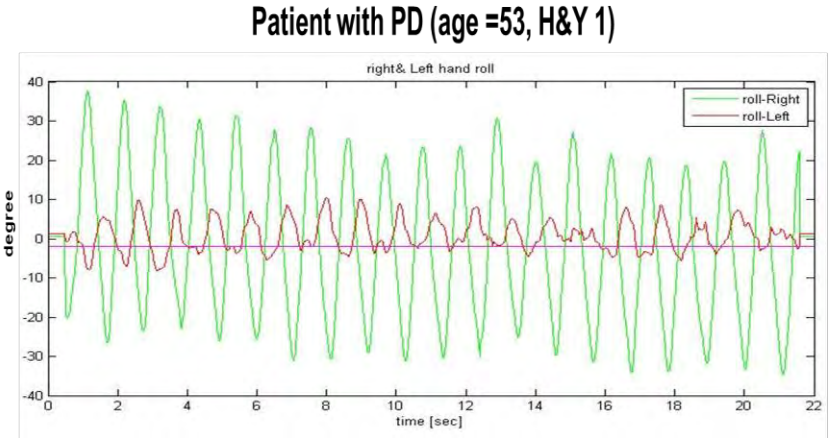






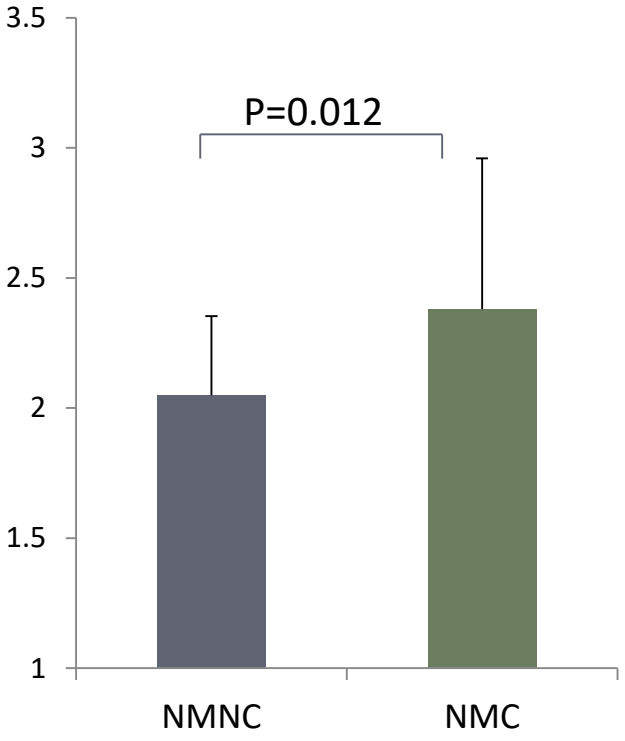




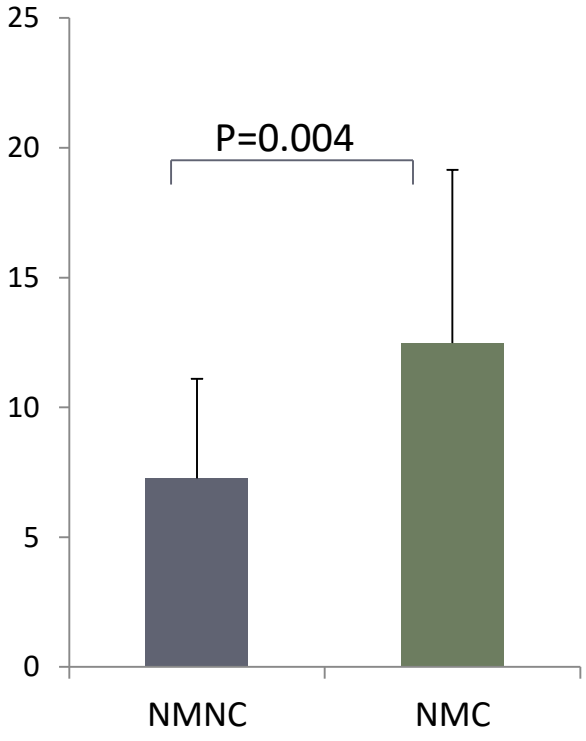


Impaired motor measures in carriers of the G2019S-LRRK2 mutation

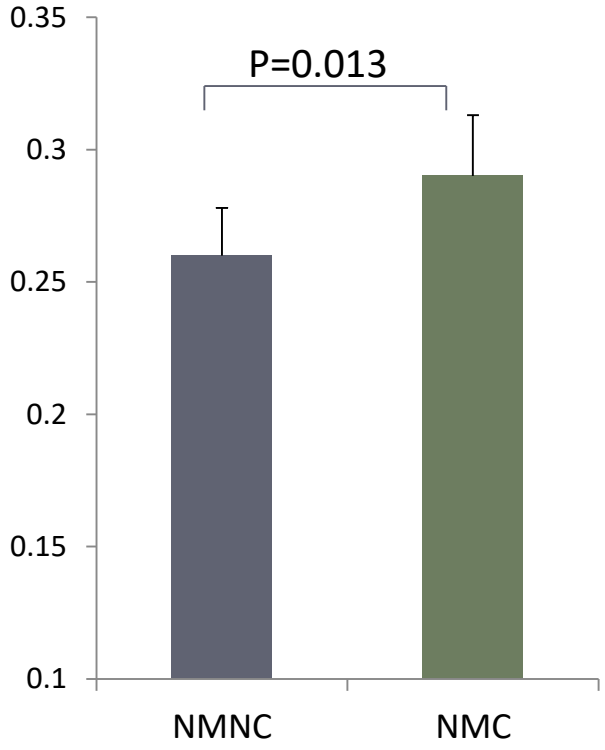
Stride time variabiltiy (CV%)



Arm swing asymmetry (%)



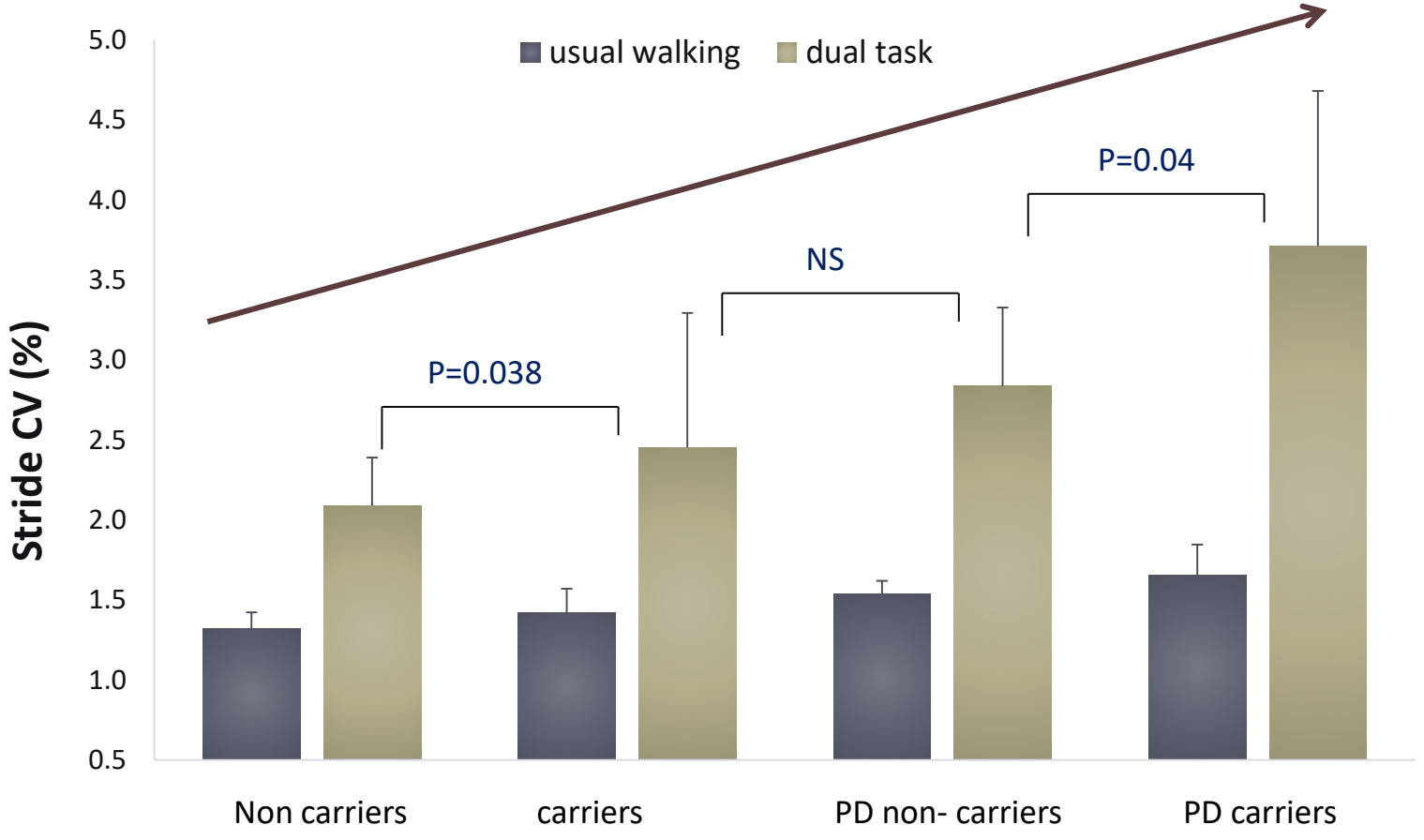
Axial rotation Jerk (deg/s3)



Non manifesting non-carriers (NMNC) =64
Non manifesting carriers (NMC) = 122

Mirelman et al. Movement Disorders 2016

Stride time variability under challenging conditions



Non carriers=61, carriers =62, PD non-carriers= 50, PD carriers =50

Mirelman et al., Movement Disorders 2016

REVIEW

CME

MDS Research Criteria for Prodromal Parkinson's Disease

Daniela Berg, MD,[1*] Ronald B. Postuma, MD, MSc,[2*] Charles H. Adler, MD, PhD,[3] Bastiaan R. Bloem, MD, PhD,[4] Piu Chan, MD, PhD,[5] Bruno Dubois, MD, PhD,[6] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[7] Glenda Halliday, PhD,[8] Lawrence Joseph, PhD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Inga Liepelt-Scarfone, PhD,[1] Irene Litvan, MD,[11] Kenneth Marek, MD,[12] José Obeso, MD, PhD,[13] Wolfgang Oertel, MD,[14] C. Warren Olanow, MD, FRCPC,[15] Werner Poewe, MD,[16] Matthew Stern, MD,[17] and Günther Deuschl, MD[18]

Berg et al Movement Disorders 2015

What about Genetic risk cohorts?

- **Risk markers**
- Male sex
- Regular pesticide exposure
- Occupational solvent exposure
- Nonuse of caffeine
- Smoking
- First-degree relative with PD
- Known gene mutation
- SN hyperechogenicity

Prodromal markers

PSG-proven RBD or Positive RBDQ

Dopaminergic PET/SPECT

Possible sub threshold parkinsonism (UPDRS >3 exc. tremor)

Olfactory loss

Constipation

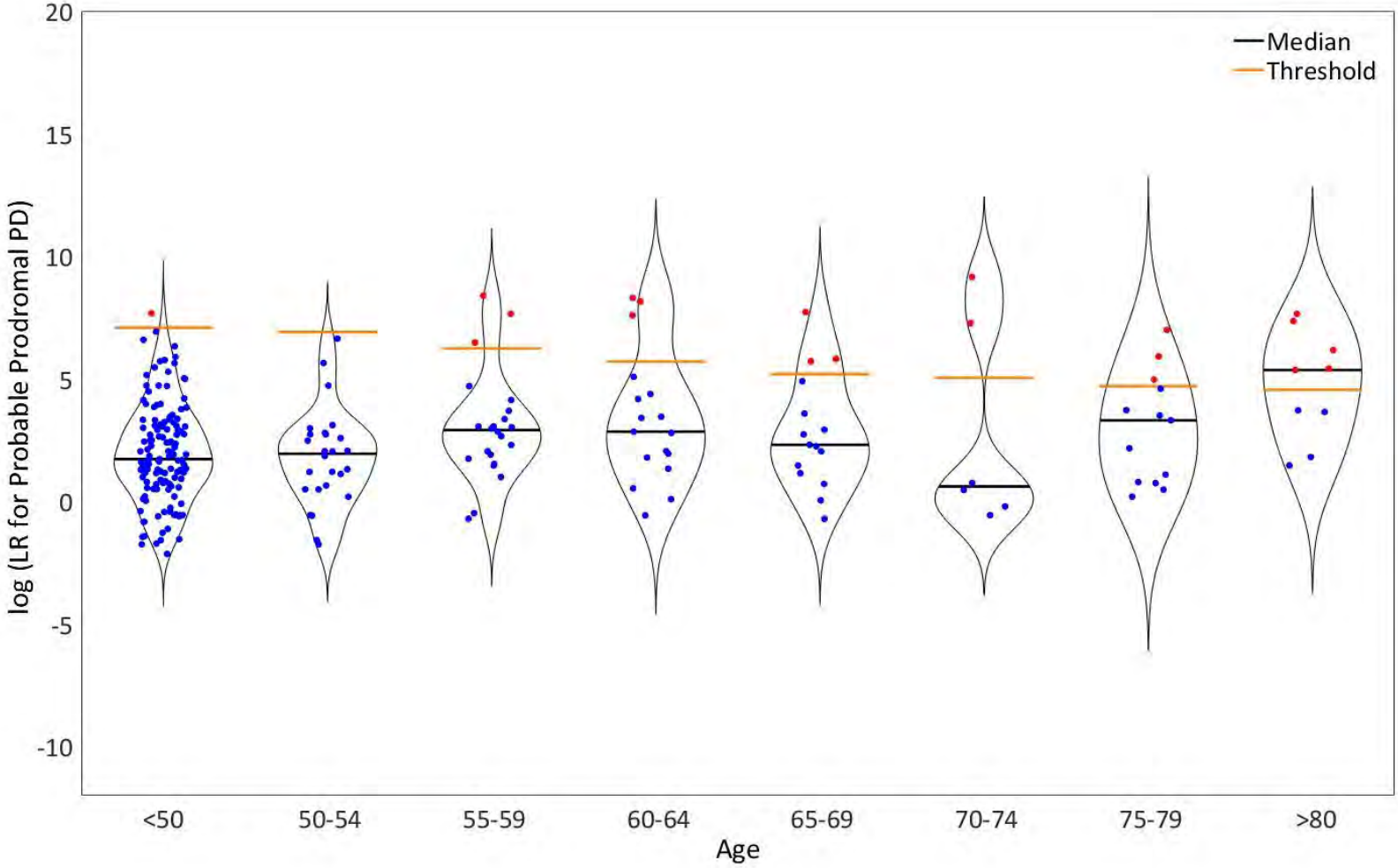
Excessive daytime somnolence

Symptomatic hypotension

Severe erectile dysfunction

Urinary dysfunction

Depression



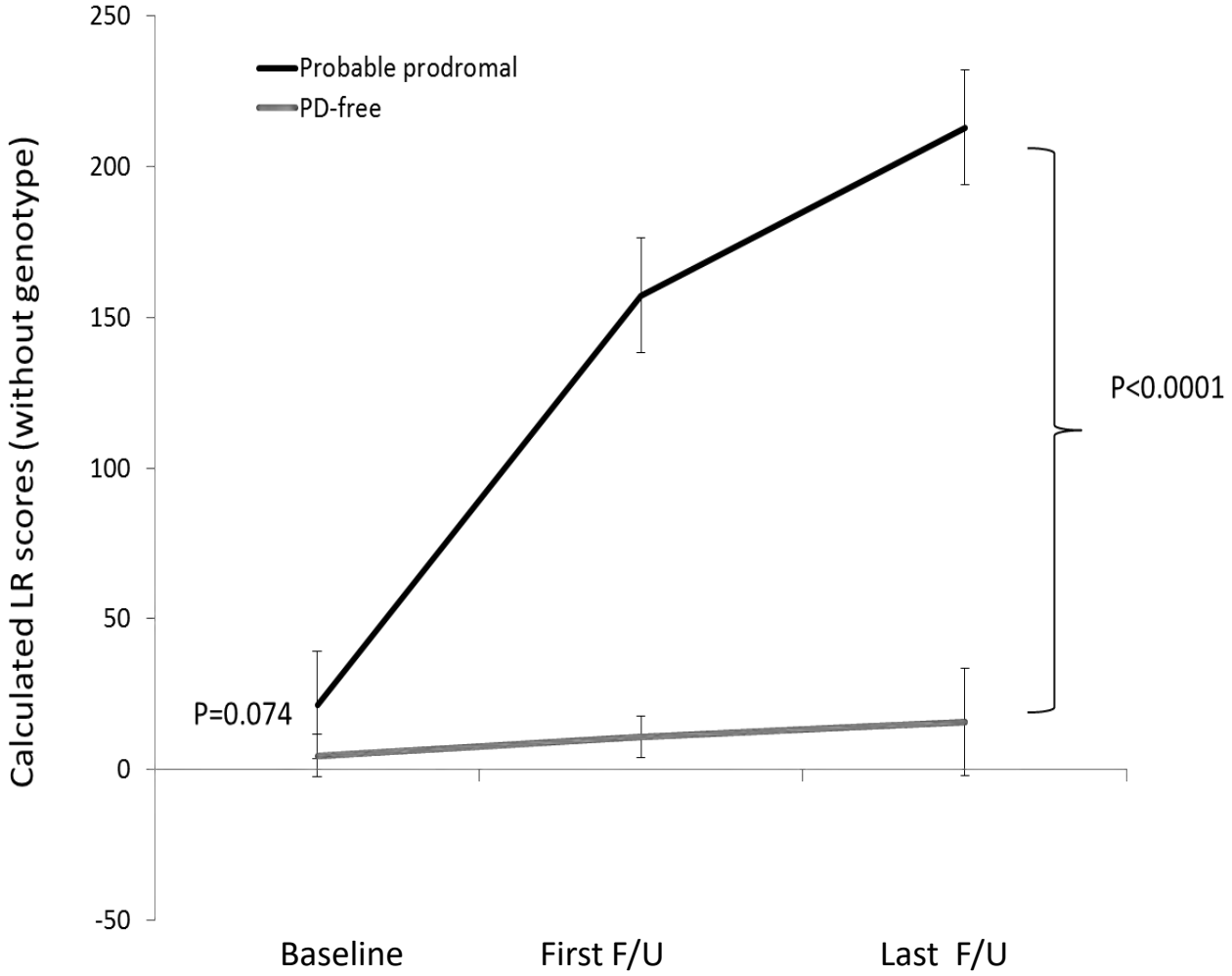
Mirelman et al Movement Disorders 2018

Phenoconversion

- 10 / 231 participants were diagnosed with incident PD during follow- up (4 after 3 years and another 6 after 5 years).
- 6 were children of patients with PD and 4 were siblings of patients.
- All 10 phenoconvertors were carriers of the G2019S-*LRRK2* mutation
- 8 out of these 10 subjects had reached the 80%

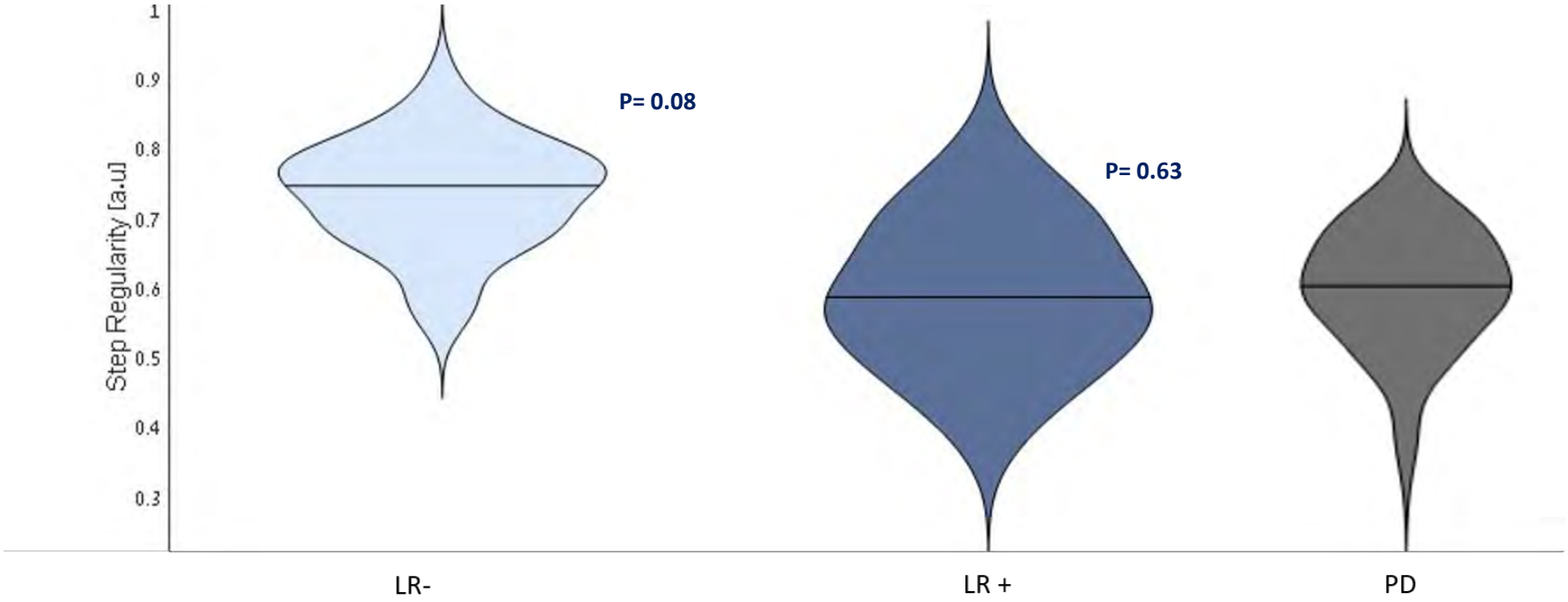
Mirelman et al Movement Disorders 2018

Change over time

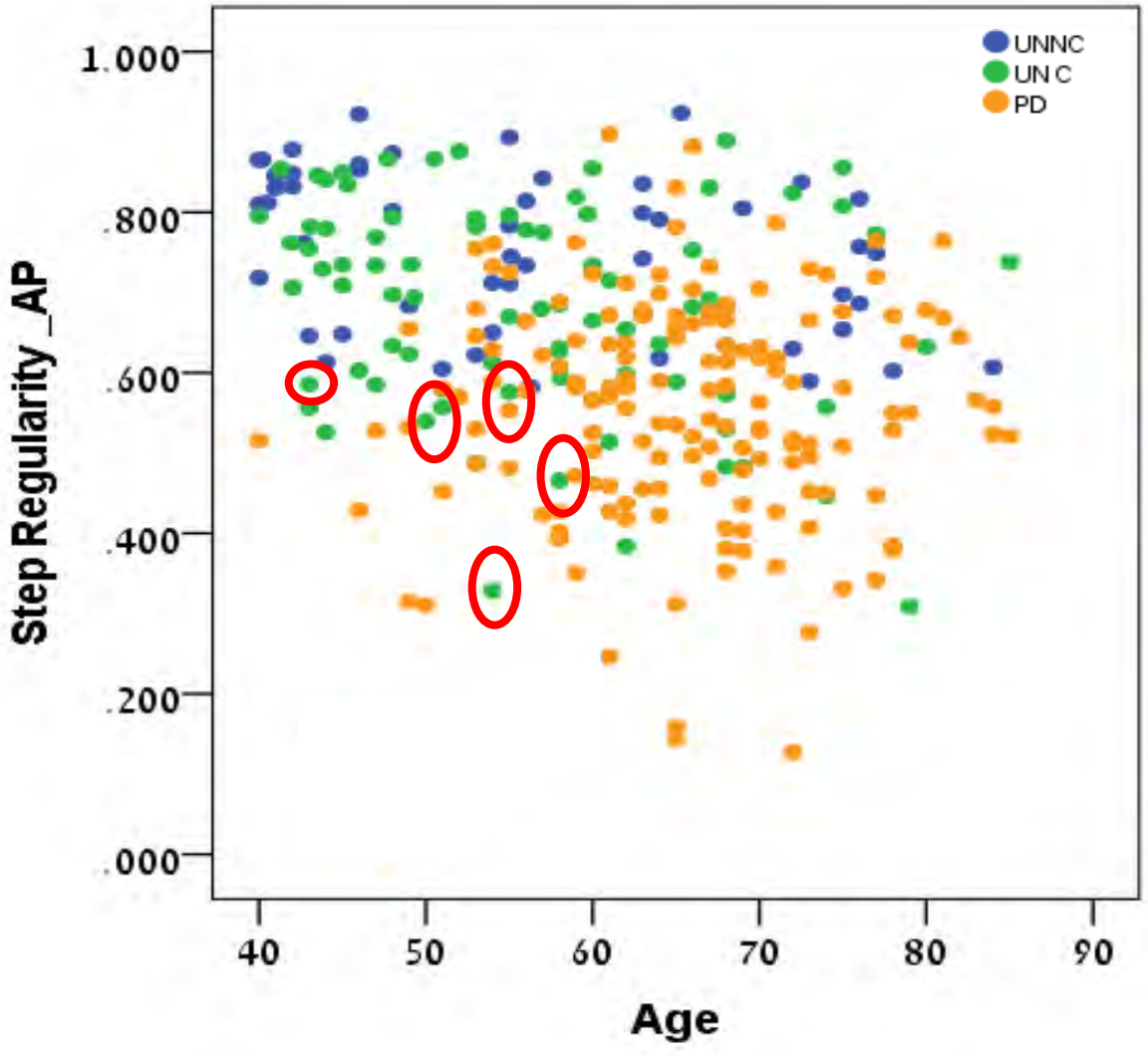


Mirelman et al Movement Disorders 2018

Free-living Measures from Wearables



Stride regularity a potential marker of disease



Summary and take home message

Differences on a group level can be found in many clinical and motor measures

Differences are more pronounced when subjects are challenged, unmasking compensatory function

Need to investigate specific thresholds with the highest predictive validity

Explore the comparability of studies in specific populations to iPD

Thank you for your attention

Collaborators
Prof. Nir Giladi
Prof. Jeff Hausdorff
Prof Avi Orr-Urtreger
Prof. Tanya Gurevich
Dr. Avner Thaler
Dr. Mali Gana Weiss
Dr. Anat Bar Shira
Dr. Inbal Maidan
Dr. Talia Herman
Dr. Amgad Droby
Marina Brozgol
Eran Gazit
Shirley Shema
Pablo Cornejo Thumm
Hagar Bernad-Elazari
Shiran Shustak
Inbar Hillel
Ora Asaias
Lee Goldstein
Marina Sela
Batsheva Cohen
Liat Yechimoivh

Tel-Aviv Sourasky Medical Center

CMCM
Center for Study of Movement, Cognition and Mobility

TEL AVIV UNIVERSITY אוניברסיטת תל אביב

National Parkinson Foundation

NNE Neuroscience
Global Research & Development

National Institutes of Health

Israel Science Foundation

Seventh Framework Programme

European Commission

Biogen

The Michael J. Fox Foundation for Parkinson's Research