NEUROIMAGING OF DEGENERATIVE DISEASES

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Aim: To understand

Pathophysiology of the disease

Disease progression

Differential diagnosis

Treatment assessment

Parkinson's Disease

belongs to a group of conditions called **motor system disorders**, which are the result of the loss of dopamine-producing brain cells.

https://www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Information-Page
https://www.nia.nih.gov/health/parkinsons-disease

Parkinson's Disease (PD)

PD symptoms

Cardinal symptoms:

- tremor,
- rigidity,
- bra
- stability

atment:

- Dopamine replacement

Over time treatment wears off.
Deep brain stimulation is an alternative

ptoms:

symptoms

oice, speech and swallowing disorders

Gastrointestinal problems

Autonomic dysfunction

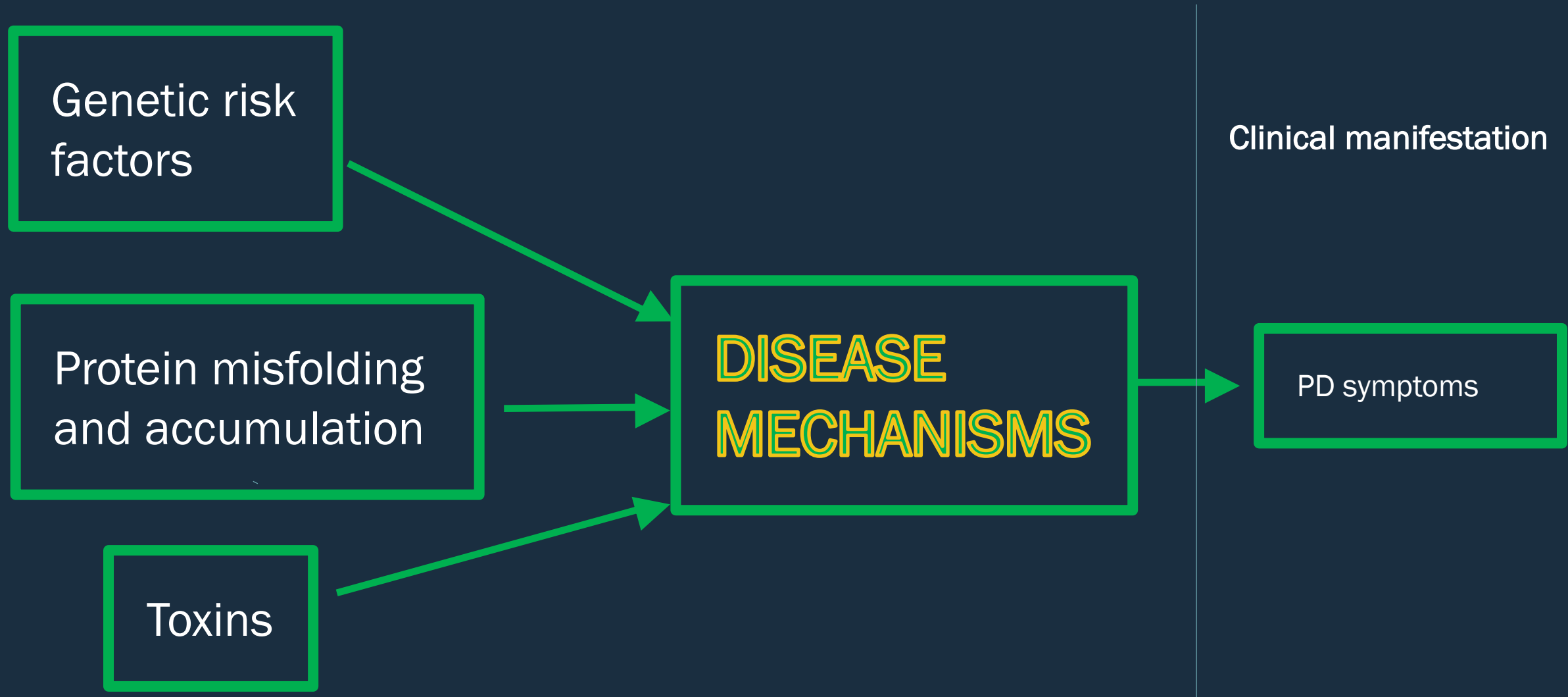
Sleep disorders

Behavioral (apathy, amotivation; impulse control, executive function)

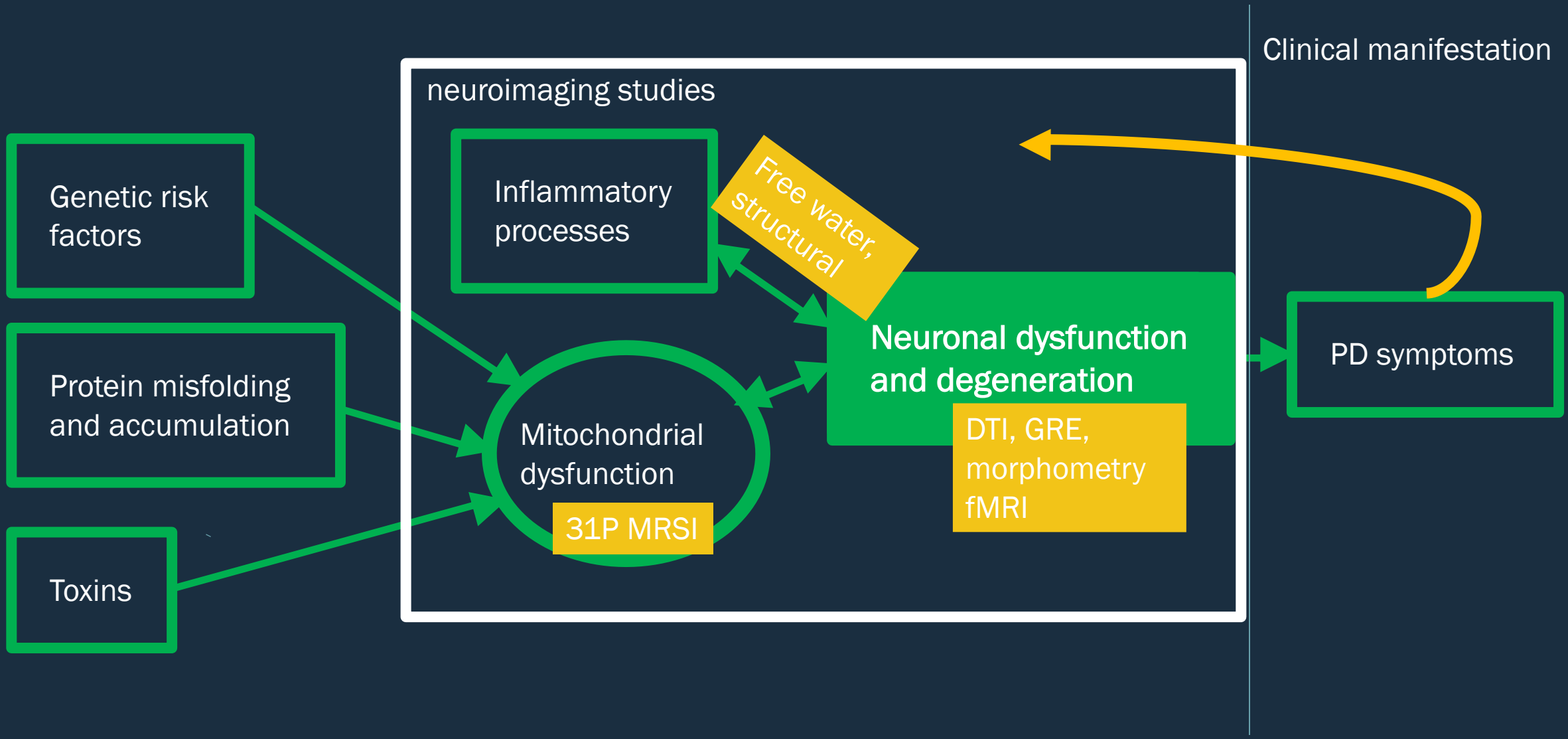
Psychiatric (anxiety and panic, dementia, depression)

Complex disorder

Behind the PD symptoms



Behind the PD symptoms



Multimodal approach:

Structural changes

- High resolution T1 weighted MRI
- Diffusion MRI
- Susceptibility weighted images
- Neuromelanin

Metabolic changes

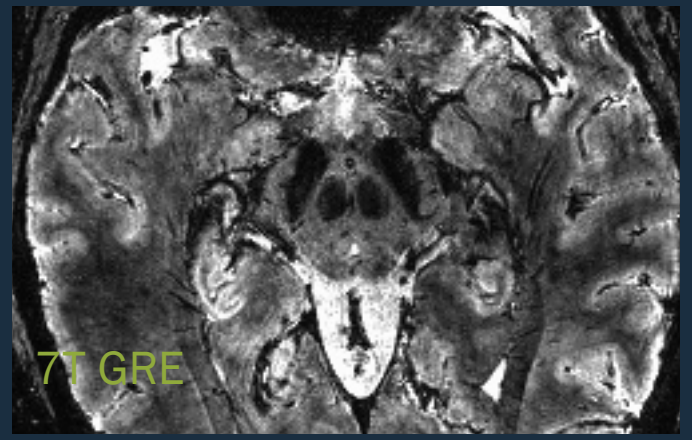
- MR Spectroscopy / PET / SPECT

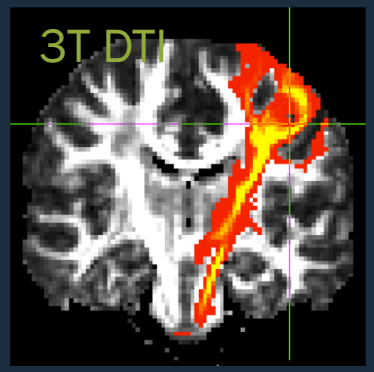
Functional changes

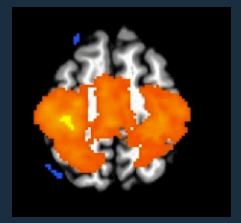
- Functional MRI (task and steady state)

integrated with

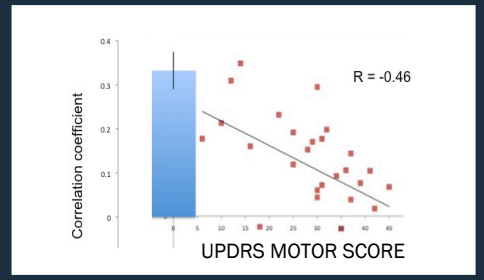
clinical data, electrophysiology, and neuro-stimulation







3T fc-fMRI



Imaging & Clinical manifestation

Uses of neuroimaging to understand disease

- Identify changes
  - *Distinguish whether changes are cause or consequence of the disorder*
- Understand/Predict the onset of a disorder
- Differential diagnosis
- Understand/predict the disease progression
- Assess treatment

Cross-sectional studies

Imaging modality and type of analysis based on the research question

Populations with similar manifestations

Towards imaging biomarkers for PD

- Cross-sectional studies
- Longitudinal studies
- Populations at risk

- Healthy populations
- Differential diagnosis

CASE STUDY:

Parkinson's Disease

"Issues" to be aware when studying this population

- Elderly population
- Brain atrophy
- Neurodegeneration
- Enlarged ventricles
- Vascular issues

- Rigidity (difficult to accommodate head in coil)
- Tremor, dyskinesia (possible extra movement)
- **Heterogeneity of symptoms**

CASE STUDY:

Parkinson's Disease

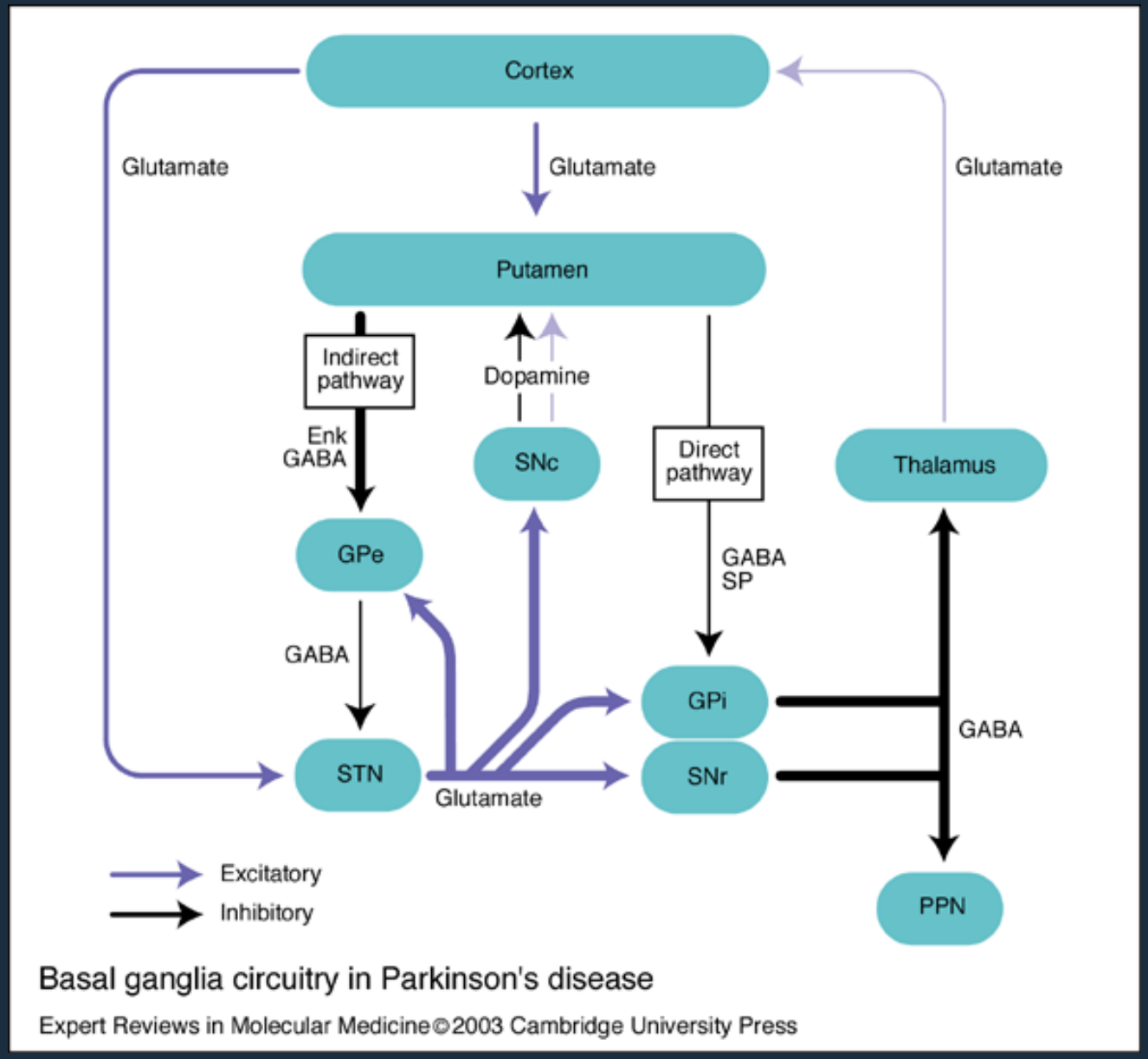
Outline:

- Pathophysiology of the disease
  - fmri
  - morphometry
- Disease progression
  - longitudinal studies
- Differential diagnosis
  - MRS
- Treatment assessment
  - DBS

- Pathophysiology of the disease

(Dys)functional networks in PD

resting state fMRI studies



Basal ganglia circuitry in Parkinson's disease

“sequence effect”

Patients with Parkinson’s disease have difficulties with self-initiating a task and maintaining a steady task performance.

motor deficit?

Network analysis

- Pre-processing AFNI
- Graph theory analysis:
  - *Brain Connectivity Toolbox*
- NETWORK DEFINITION

TABLE 2. Graph metric definitions

Functional segregation of a neural network refers to its ability for specialized processing within clusters of nodes.

Functional integration is related to a neural network's ability to bind information efficiently from distributed regions.

Degree is the number of connections that link a node to the rest of the nodes in the network.

Node strength is computed as the sum of weights of the connections that link a node to the rest of the nodes. It indicates how strongly one node is connected to the rest of the nodes in the network.

Path is the shortest distance (i.e., minimum number of connections) between a node and every other node in the network. Efficiency is inversely related to path length.

Global efficiency is calculated as the inverse of the average shortest path length between all pairs of nodes in the network. It is a measure of functional integration.

Node Betweenness Centrality indicates how central a node is to the communication among other nodes in the network. It is computed as the fraction of all shortest paths in the network that contain a given node. Nodes with high values of betweenness centrality participate in a large number of shortest paths and potentially function as hubs.

Clustering coefficient is computed as the number of connections that exist between the nearest neighbors of a node as a proportion of the maximum number of possible connections. It measures the density of connections between neighboring nodes. High clustering is associated with high local efficiency of information transfer.

Local efficiency is computed as the inverse of the average shortest path connecting all neighbors of a node. It reflects how relevant a node is for the communication among other nodes within a local neighborhood, and is related to the clustering coefficient.

Deficits beyond *motor* network

Sensorimotor network

Execution

(motor output)

Cingulo-opercular network

Task-set maintenance

(maintaining the mental state)

Fronto-parietal network

Adaptive control

(cues and feedback; top-down)

Network: 86 nodes

- FPN: 21 nodes
- CON: 32 nodes
- SMN: 33 nodes

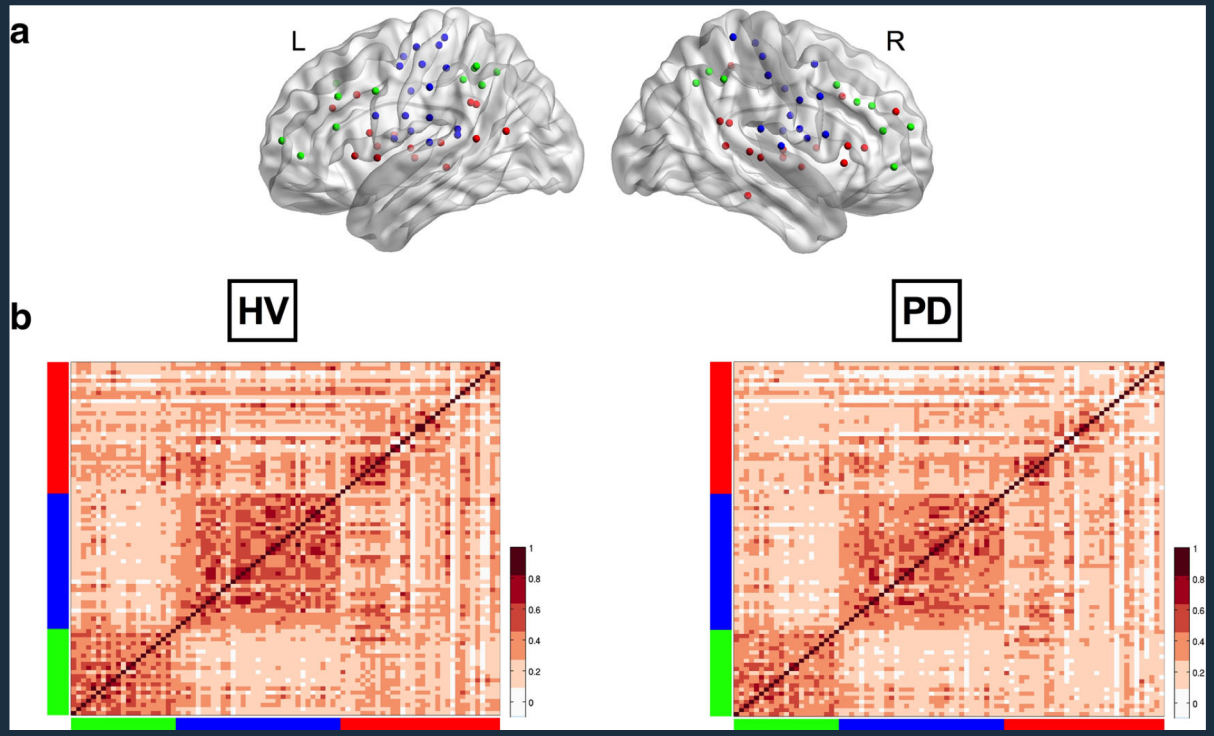
Subjects:

- 30 HV
- 30 PD off medication (H&Y 2-3)

Tinaz, Lauro, Hallett, Horovitz; *Brain Struct Funct 2015*

Deficits in task-set maintenance and execution networks in Parkinson's disease

Sule Tinaz



Network: 86 nodes
FPN: 21 nodes
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Subjects:
30 HV
30 PD off medication

Data pre-processing: AFNI
Network analysis: Matlab and Brain Connectivity Toolbox

Tinaz et al, 2015 Brain Struct Funct

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(motor output)

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Cingulo-opercular network

Task-set maintenance

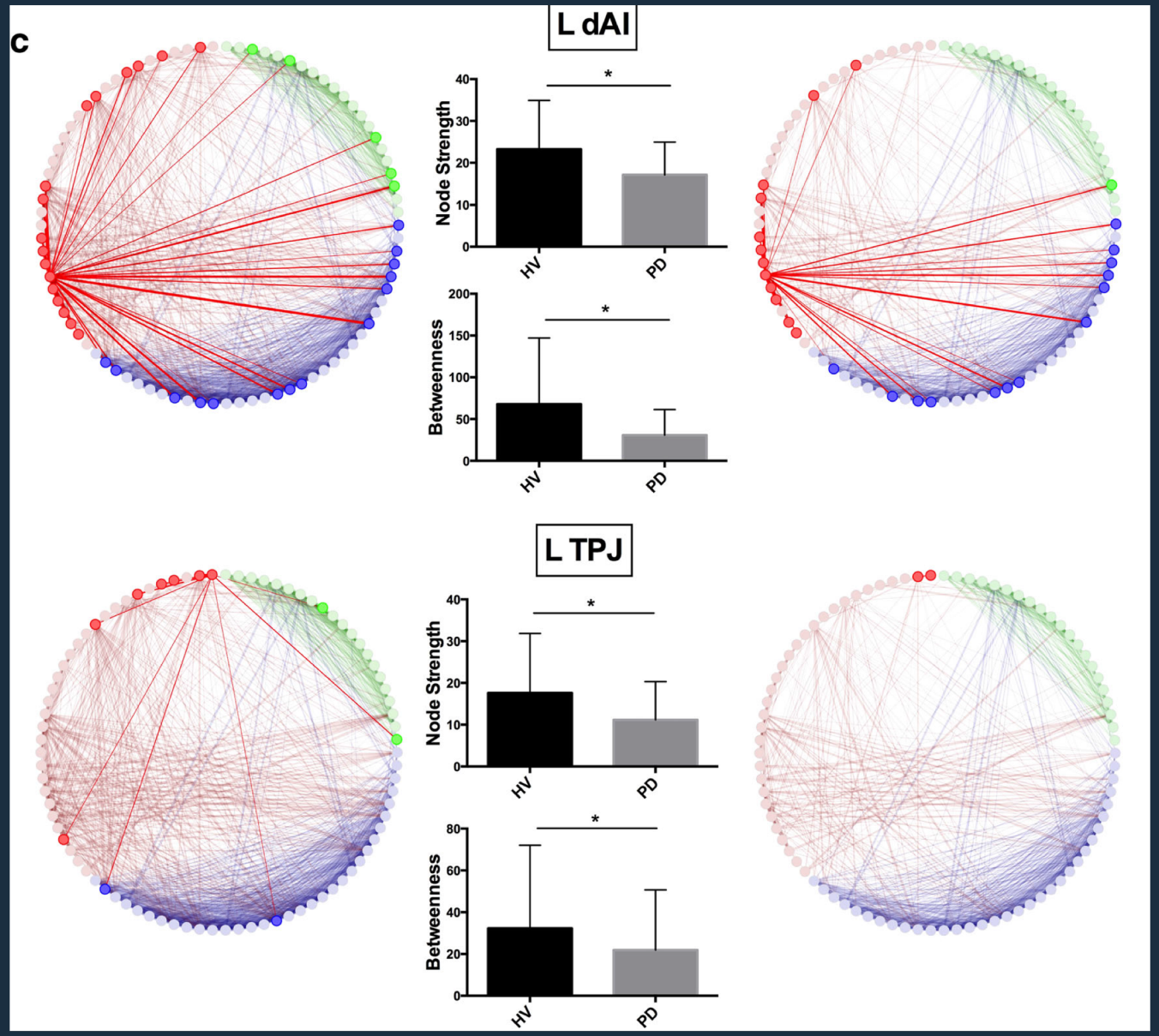
(maintaining the mental state)

Table 1 Changes in graph metrics in PDs compared with HVs

Node strength	Clustering	Local efficiency	Betweenness
CON			
L dAI↓	R IFG pars Tri↓^	L post MTG/STG↓	L dAI↓
R ITG↓		L TPJ↓	L TPJ↓^
L post MTG/STG↓		R ITG↓*	R MI↓^
L TPJ↓			
FPN			
	–	L IPS↓^	OFG↓^
SMN			
R preCG1↓	R preCG1↓	R preCG1↓	L MI↑
L STG1↓	L preCG1↓	L preCG1↓	L preCG2↑
R PI↓^	L preCG2↓*	R preCG3↓*	
	L STG2↓	L STG1↓^	
	R postCG↓*	L STG3↓^	
	L postCG↓^		
	R preCG2↓^		

Tinaz et al, 2015 Brain Struct Funct

Deficits in task-set maintenance and execution networks in Parkinson's disease



Cingulo-opercular network

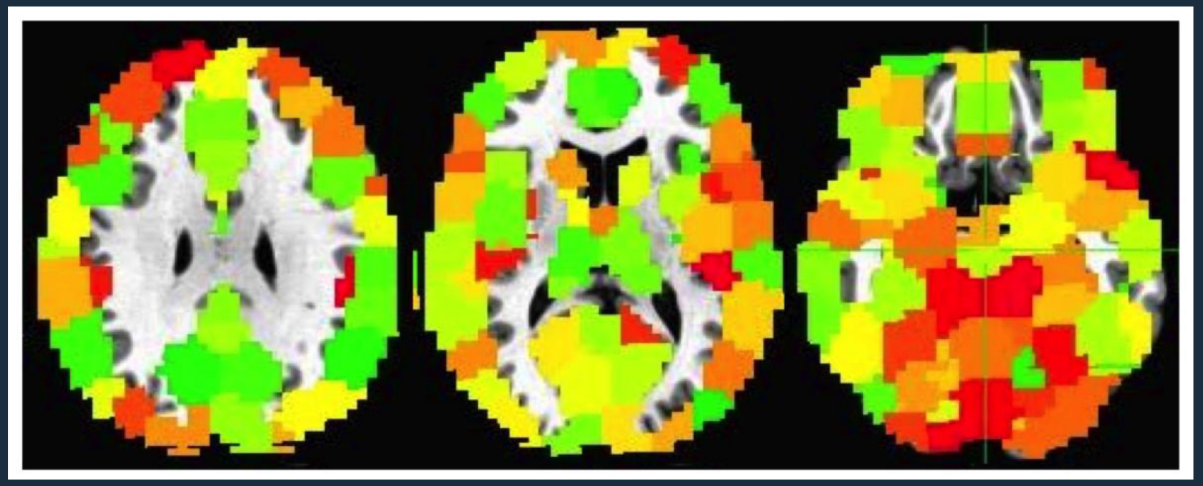
Task-set maintenance

(maintaining the mental state)

Tinaz et al, 2015 Brain Struct Funct

How extensive are the changes in PD?

The connectome (whole brain analysis)



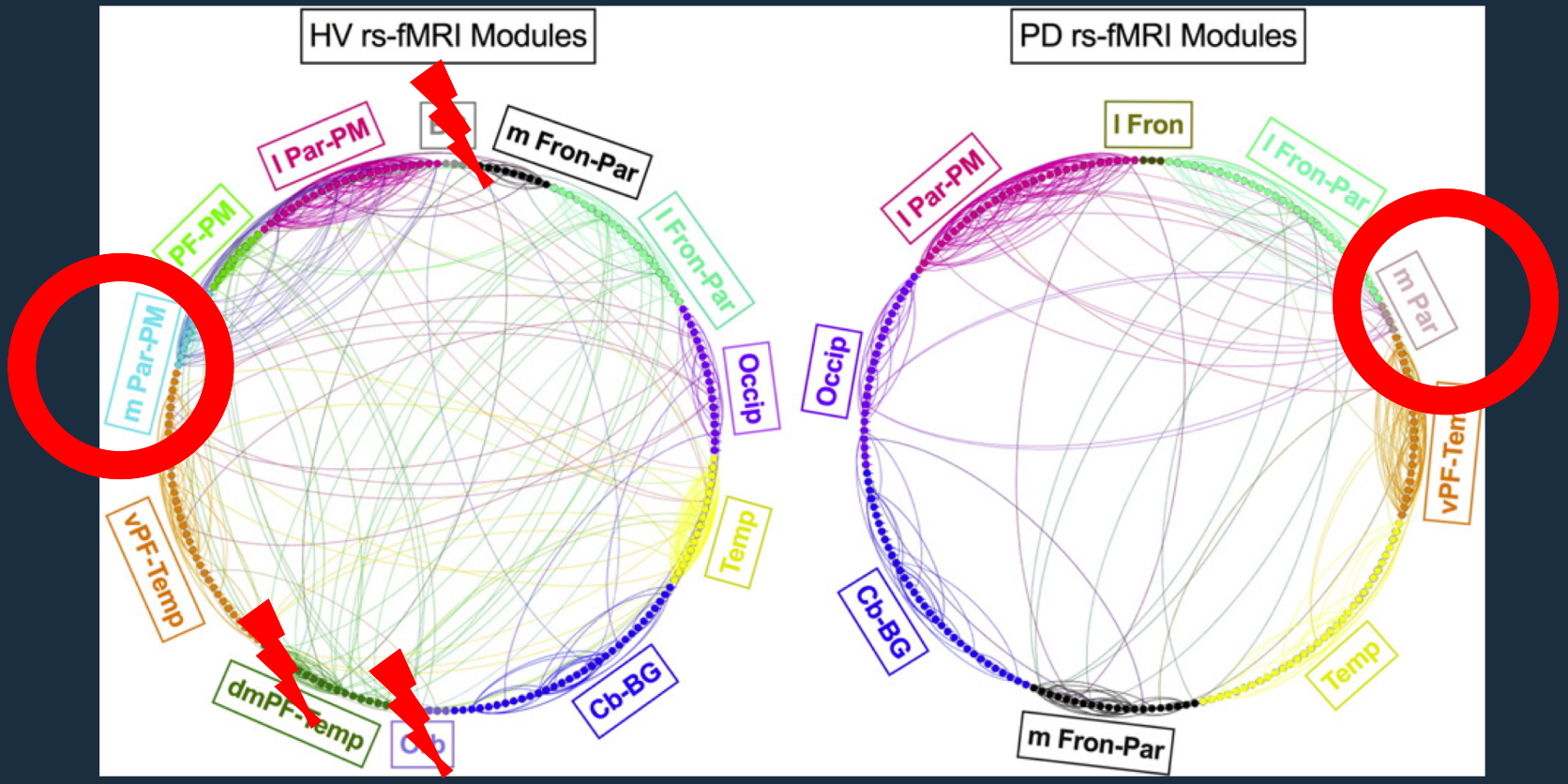
- How to parcel the brain?
  - *Craddock 200*

- Functional and structural analysis
  - *Resting state*
  - *DTI*

Data pre-processing: AFNI; TORTOISE; FATCAT
Network analysis: Matlab and Brain Connectivity Toolbox

Breakdown in the functional modular organization of the PD connectome

Sule Tinaz



Network: 200 nodes

Whole brain

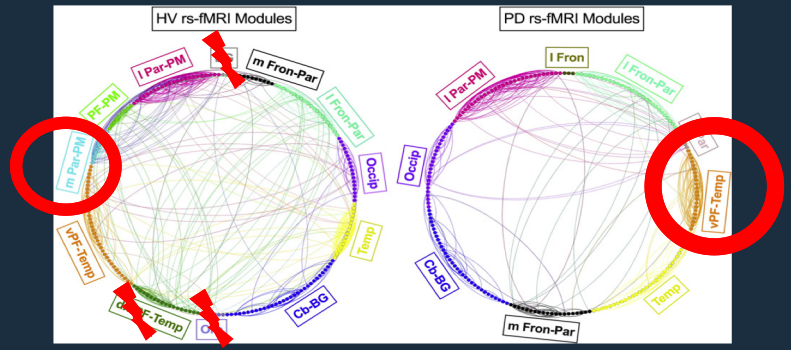
Subjects:
20 HV
20 PD on medication

Tinaz, Lauro, Ghosh, Lungu, Horovitz; *Neuroimage: Clinical, 2017*

Breakdown in the functional modular organization of the PD connectome

Alterations in functional modularity in:
core cognitive networks:
default mode network
dorsal attention networks,
sensorimotor network

lack of modular distinction in the
orbitofrontal and basal ganglia nodes in PD group



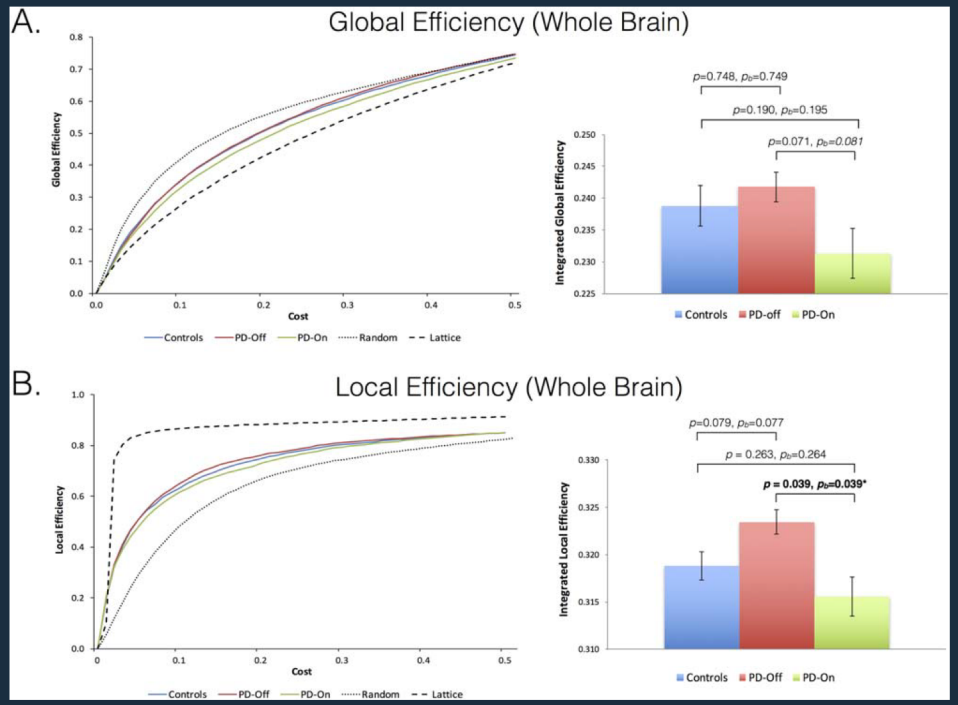
DTI: reduced node strength, clustering coefficient, and local efficiency in a small group of nodes mostly in the frontoparietal regions

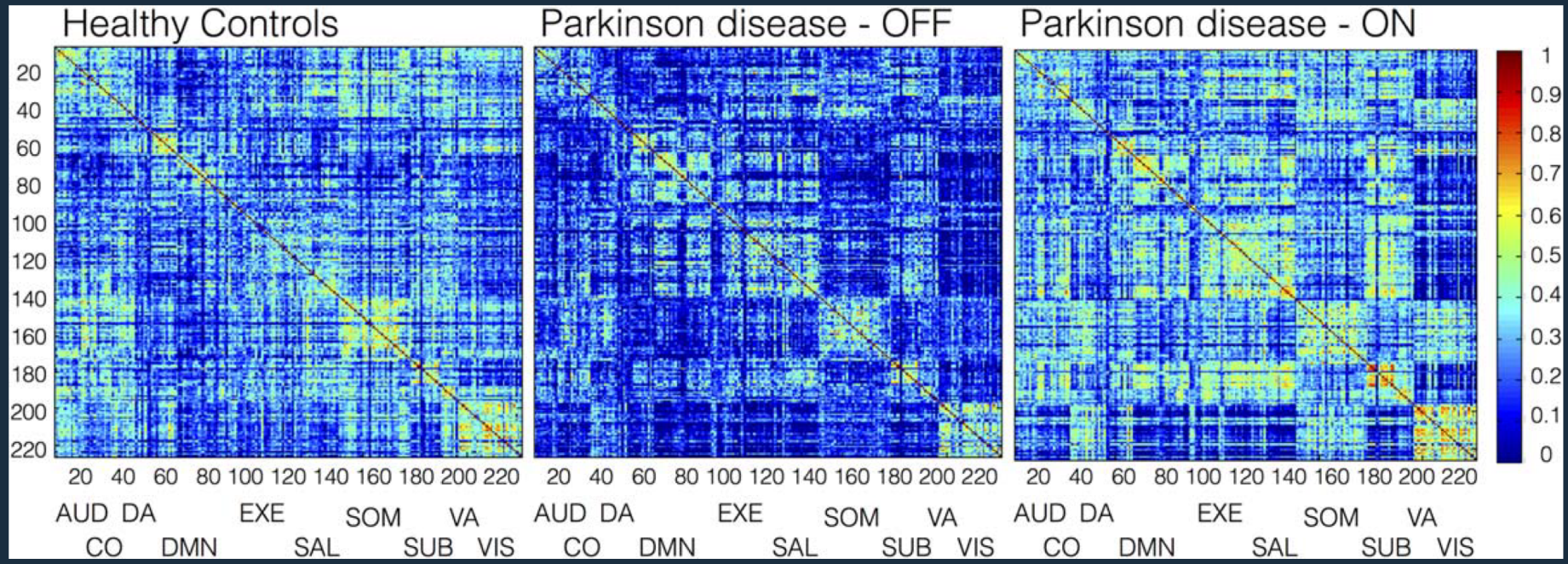
Dopaminergic treatment
does not improve the functional network properties unanimously,
on the contrary, may even be disruptive.

Tinaz, Lauro, Ghosh, Lungu, Horovitz; *Neuroimage: Clinical, 2017*

Effect of medication

Berman et al. Mov Dis 2016





How to parcel the brain?

- Whole brain parcellation (for example Craddock 200)
- Nodes from pre-defined networks

Limitations on ”resting state”

- Comparison of clinical metrics defined on activity with brain at “rest”
- How much “rest” is in “rest”?
- How much motion or active motion suppression is present?

  some control from looking at fluctuations properties of the motor areas.
- How much alertness variability?
  - *State or trait?*

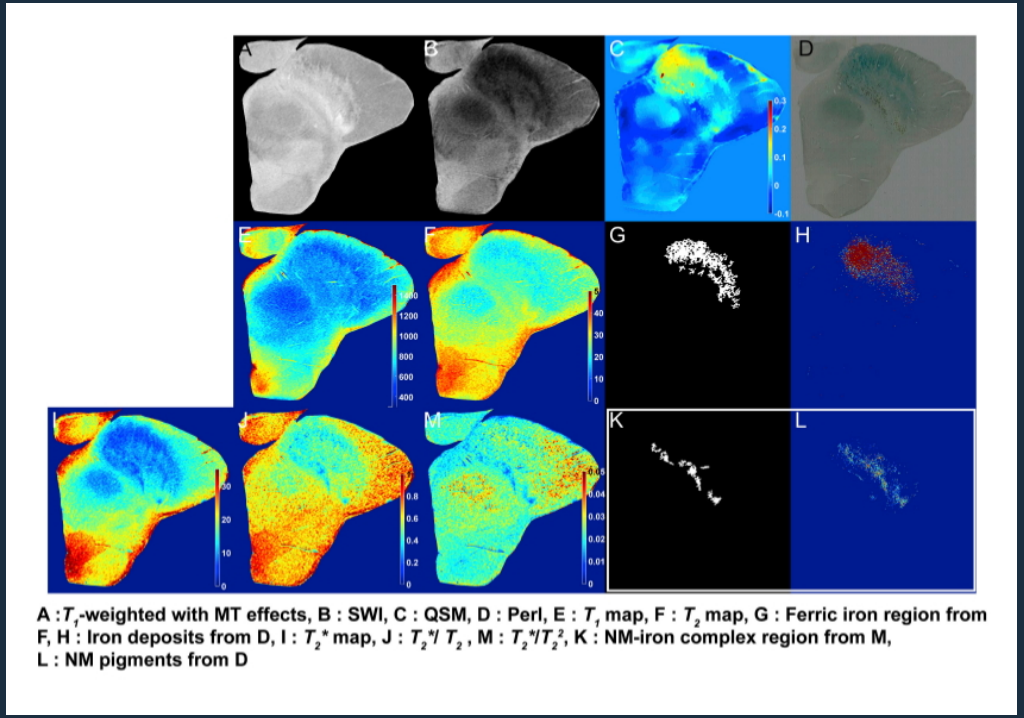
fMRI study remarks

- Parkinson Disease affects brain networks beyond the motor system
  - *Connectivity studies can aid at identifying complexity of the disorder*
- Deficits are related to disease progression and affected by medication
  - *Are these deficits cause or consequence?*
- Functional changes are seen earlier than structural changes observed with tractographic methods
  - *Due to disease course or limitation on methods?*

- Disease progression

Parkinson’s disease (PD) is a progressive neurodegenerative disorder, characterized in histopathologic studies by dopaminergic cell loss in the substantia nigra (SN)

SN degeneration as a landmark



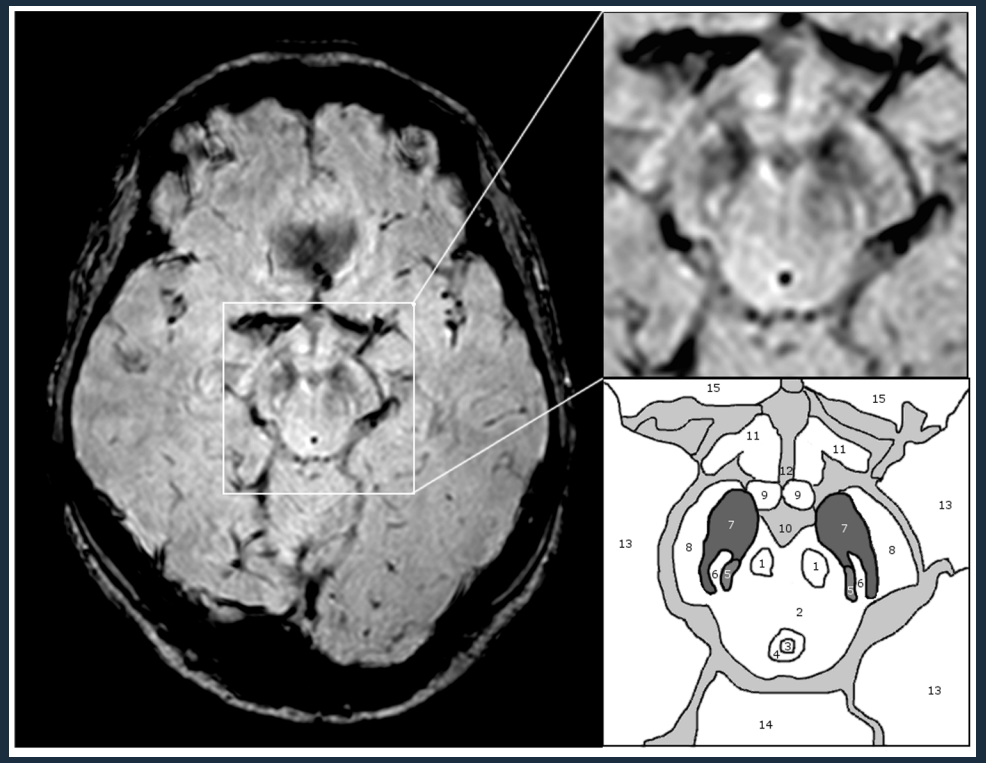
A : T_1-weighted with MT effects, B : SWI, C : QSM, D : Perl, E : T_1 map, F : T_2 map, G : Ferric iron region from F, H : Iron deposits from D, I : T_2^* map, J : T_2^*/T_2, M : T_2^*/T_2^2, K : NM-iron complex region from M, L : NM pigments from D

Lee et al. Neuroimage, 2018

Shapes and contrasts

- Longitudinal studies
- Cross-sectional studies

SN shape ...



n = 105	Physician A		Physician B		Agreement	
	N-PD group	PD group	N-PD group	PD group	N-PD group	PD group
Unilateral or bilateral visible (cases)	47	0	50	1	49	0
Invisible (cases)	4	54	1	53	2	54
Clinical gold standard (cases)	51	54	51	54	51	54
Lack signs of sensitivity in the diagnosis of PD	100%		98.15%		100%	
Lack signs of specific in the diagnosis of PD	92.16%		98.04%		96.08%	

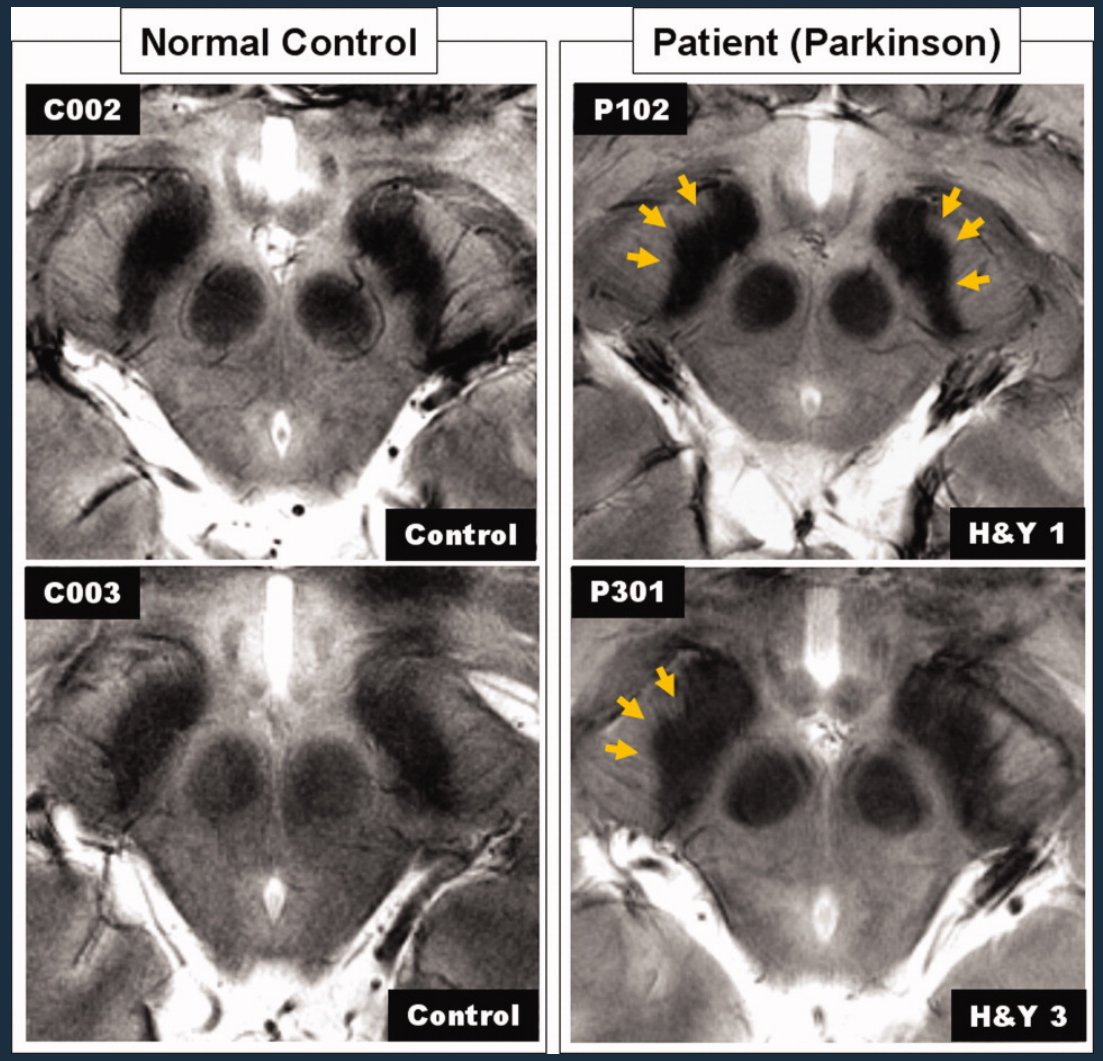
χ^2 test was used according to the signs of "yes", "no" classification. The result was $p = 0.00 < 0.05$ bilateral. The differences were statistically significant.

Gao et al. 2016
European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences

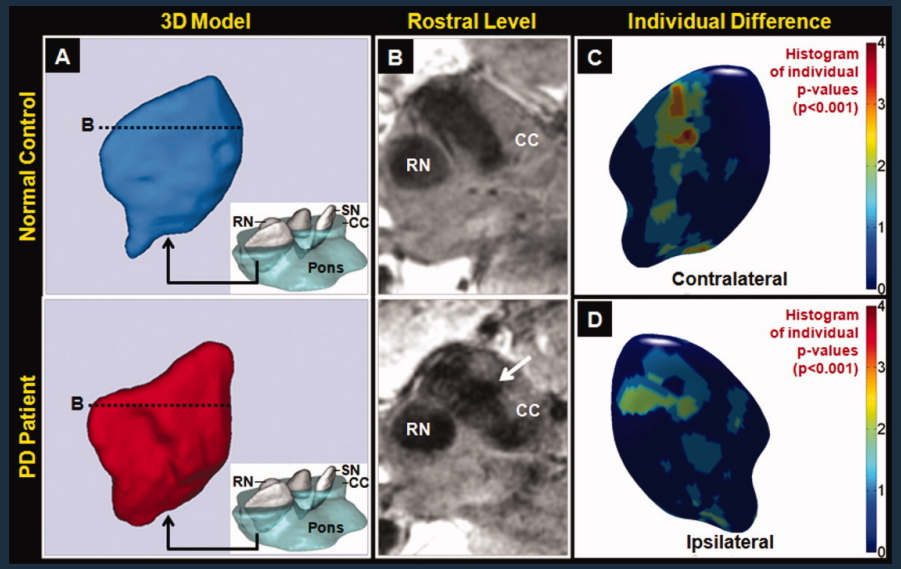
The 'Swallow Tail' Appearance of the Healthy Nigrosome – A New Accurate Test of Parkinson's Disease: A Case-Control and Retrospective Cross-Sectional MRI Study at 3T
Schwarz et al. PLOS One 2014

- https://doi.org/10.1371/journal.pone.0093814

Lateral Boundaries of the SN

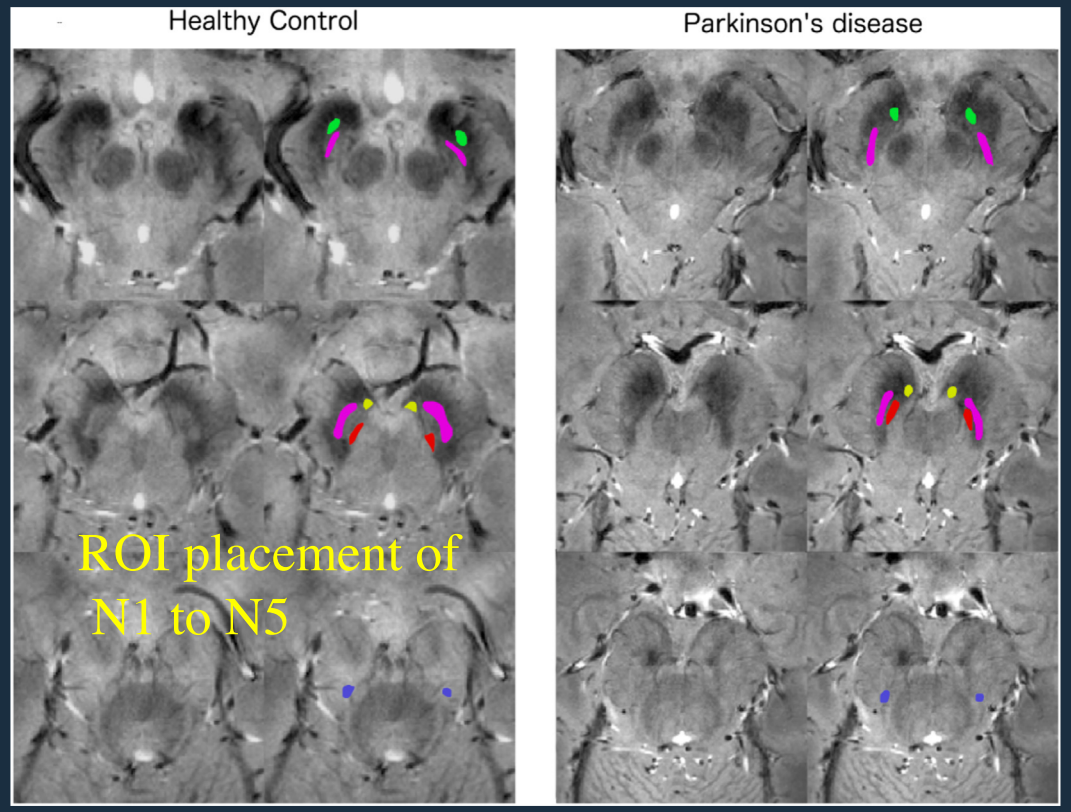


Cho et al. Mov. Disorders 2011

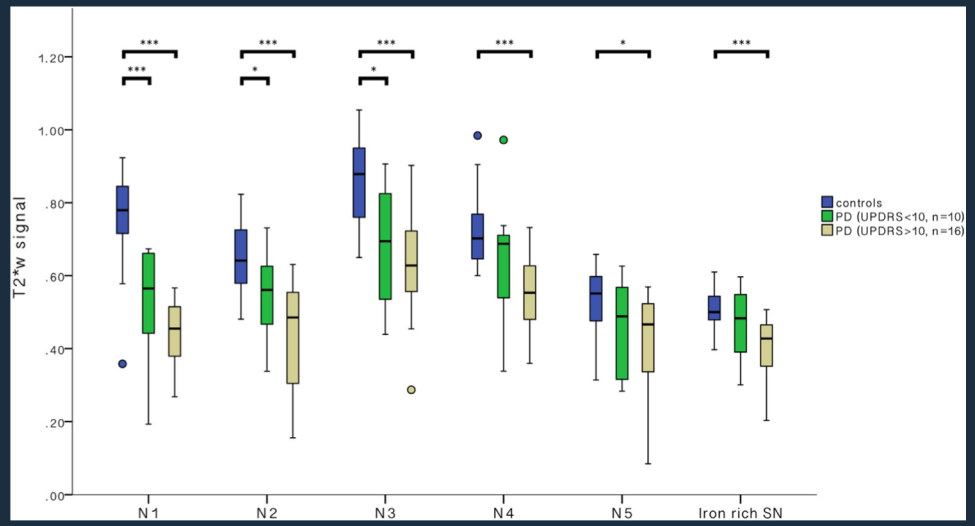


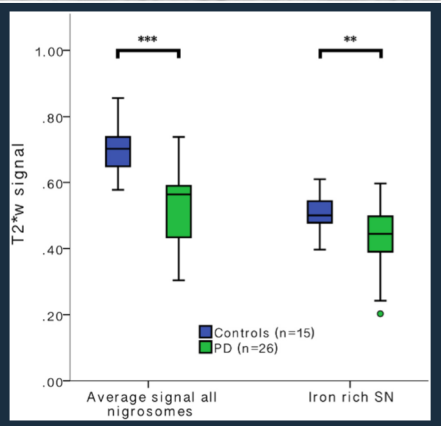
Kwon et al. Annals of Neurology2011 . https://doi.org/10.1002/ana.22592

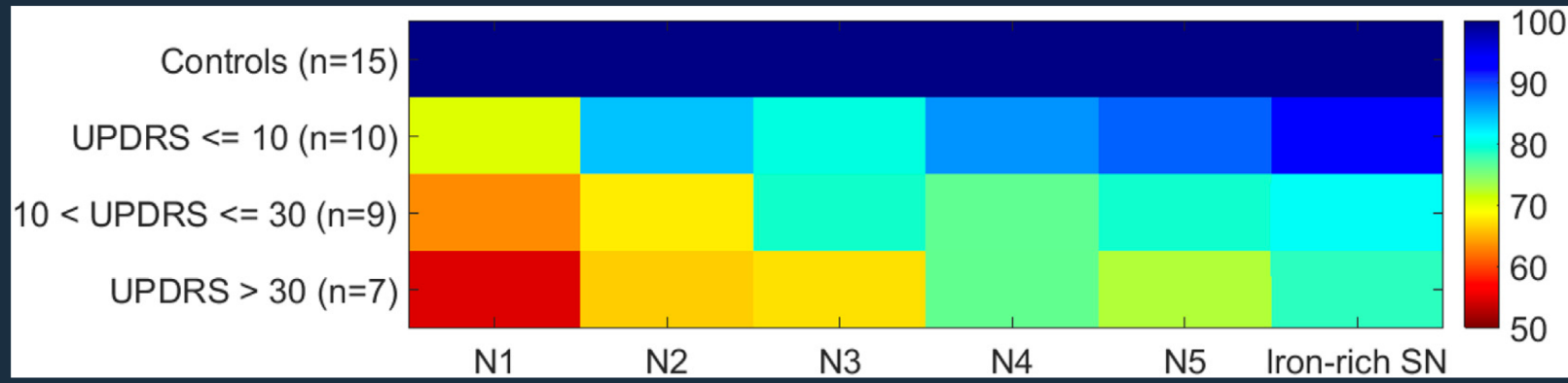
Parkinson's disease related signal change in the nigrosomes 1–5 and the substantia nigra using T2* weighted 7T MRI



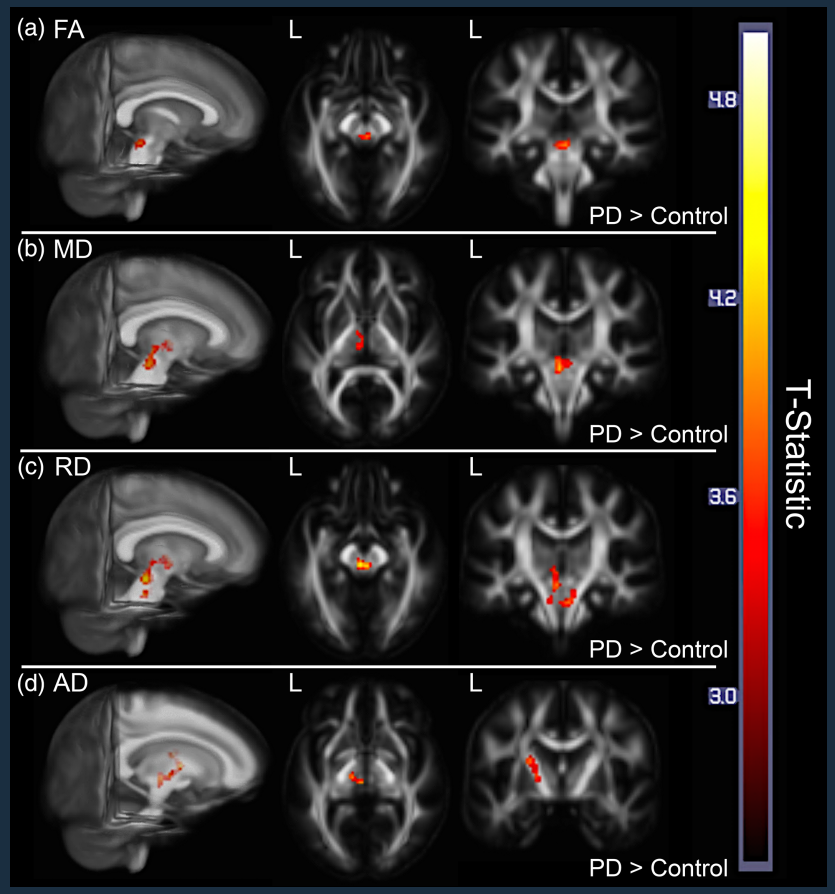
Schwarz et al. NeuroImage: Clinical 19 (2018)







Longitudinal white matter microstructural change in Parkinson's disease

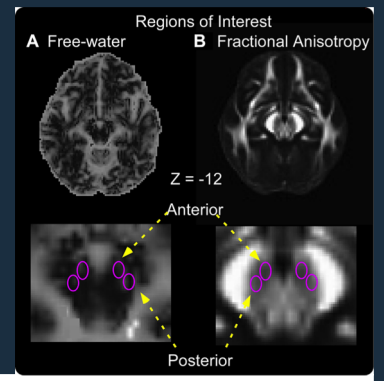


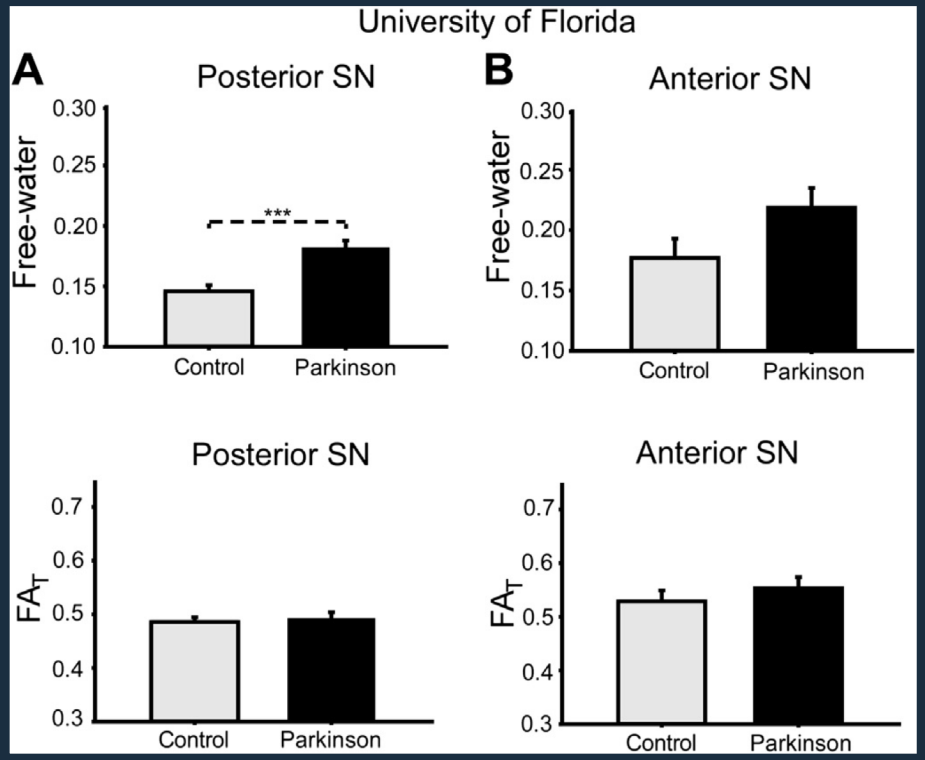
Measure	Contrast direction	T-statistic	Location(s)	Cluster extent (mm^3)
FA	PD decrease > control	3.94	B. midbrain tegmentum, periaqueductal gray matter	344
MD	PD increase > control	4.14	B. midbrain tegmentum, L. thalamus	896
RD	PD increase > control	4.39	B. midbrain tegmentum, B. pontine crossing tract, L. thalamus	1,624
AD	PD increase > control	4.29	L. post. limb of internal capsule, L. thalamus, L. midbrain tegmentum	1,240

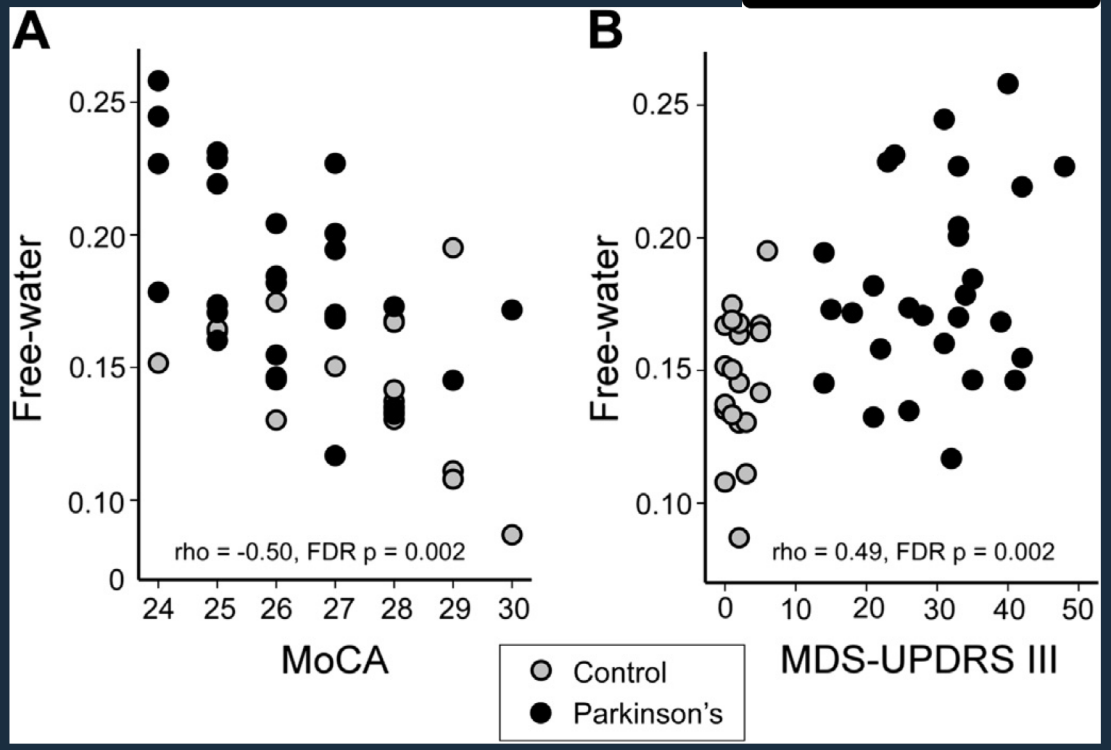
Pozorski et al. **Longitudinal white matter microstructural change in Parkinson's disease, HBM First published: 27 June 2018, DOI: (10.1002/hbm.24239)**

Increased free water in the substantia nigra of Parkinson's disease

Ofori et al. Neurobiology of Aging 2015

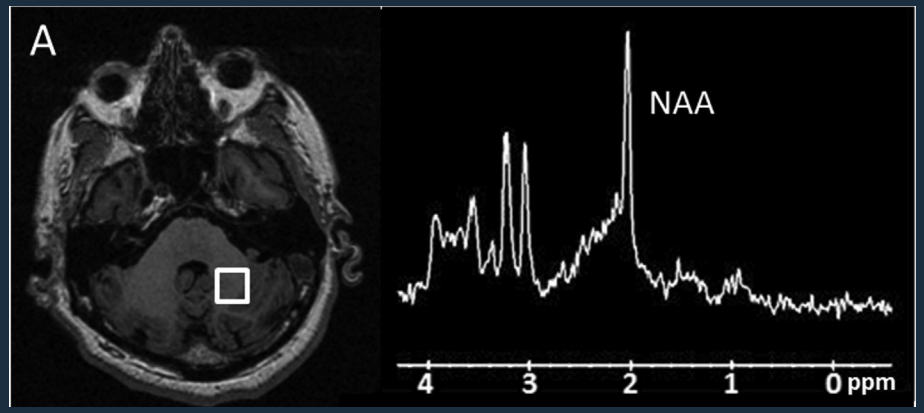




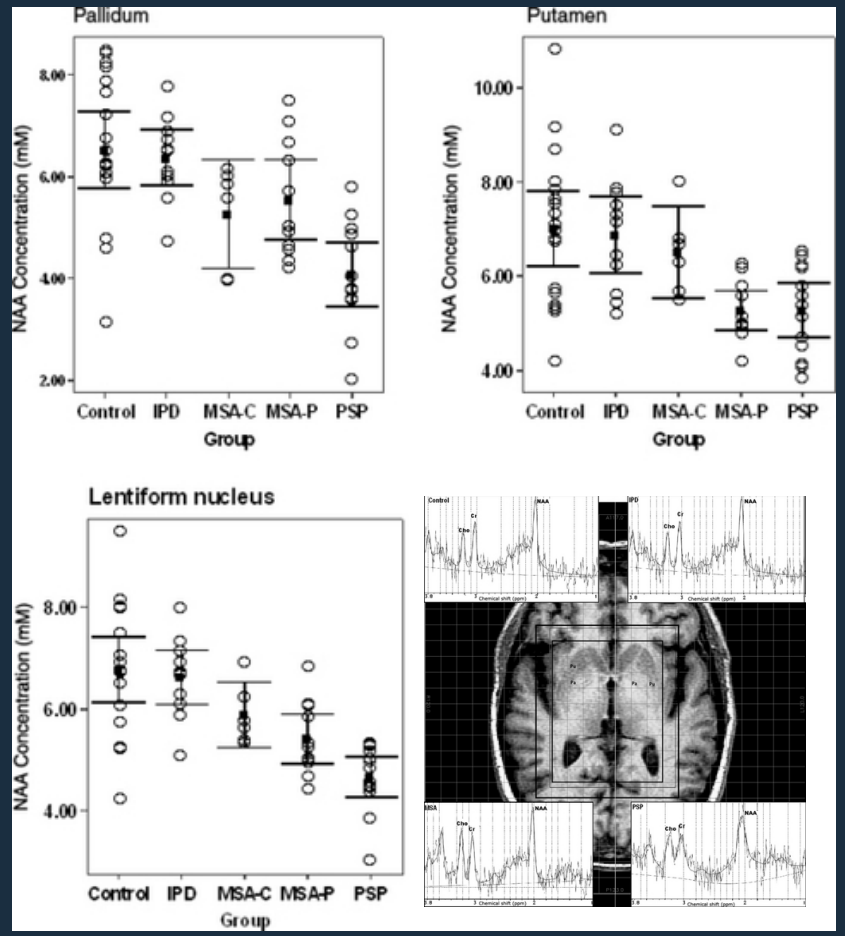


- Differential diagnosis

MRS to differentiate Parkinsonian syndromes



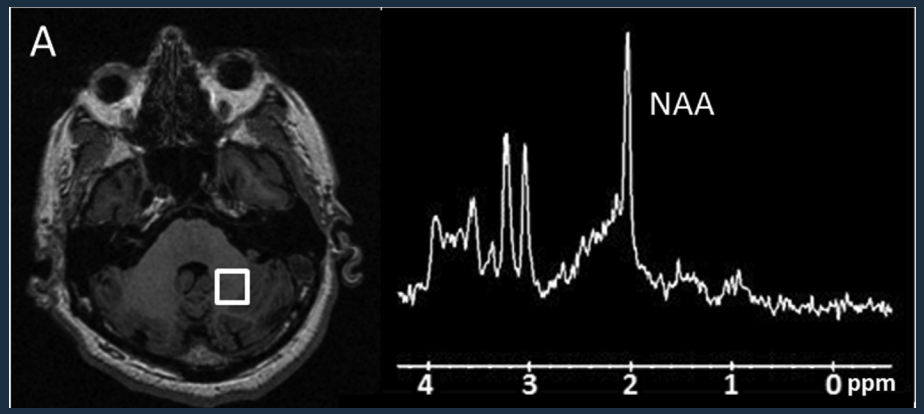
S. Zanigni et al.
Parkinsonism and Related Disorders 21 (2015) 929e937

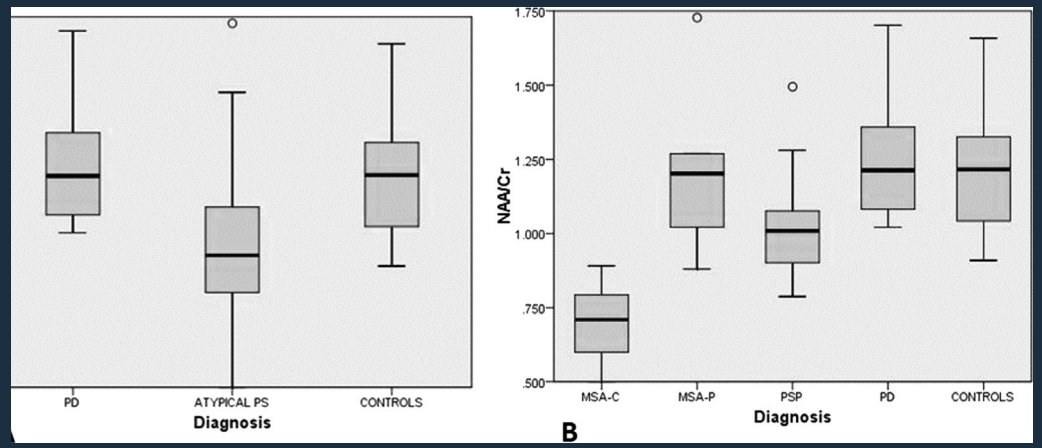


Quantitative magnetic resonance spectroscopic imaging in Parkinson's disease, progressive supranuclear palsy and multiple system atrophy
Guevara et al. 2010 European Journal of Neurology V17,I9

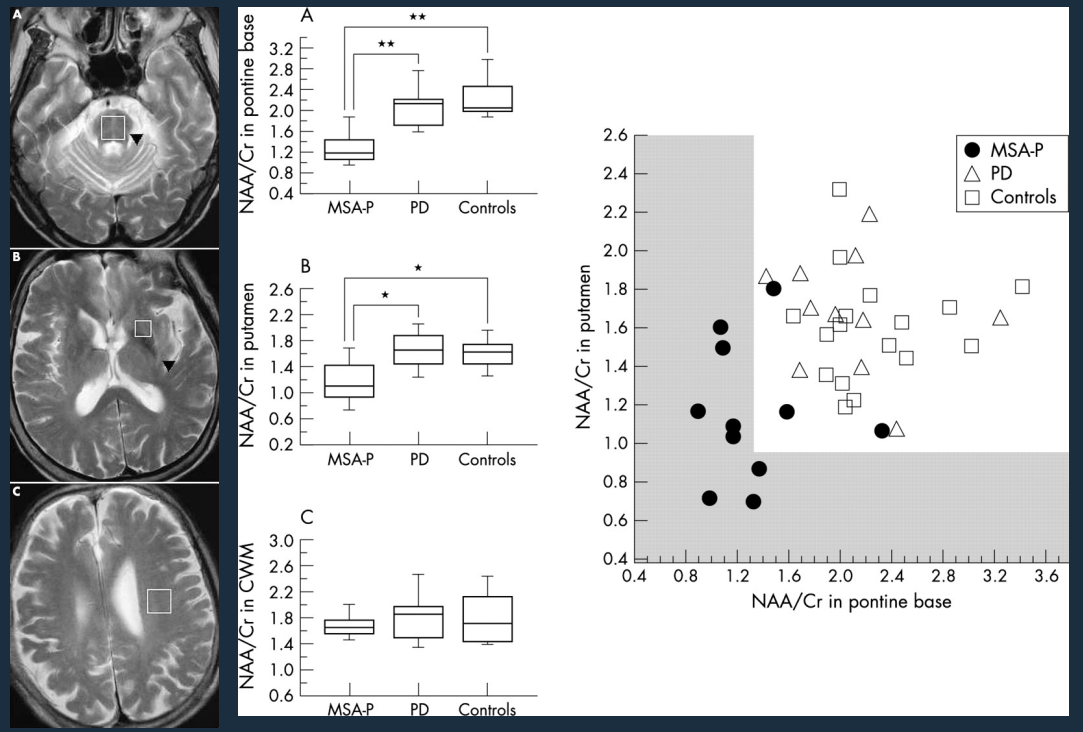
MRS to differentiate Parkinsonian syndromes

- Differential diagnosis





S. Zanigni et al.
Parkinsonism and Related Disorders 21 (2015) 929e937



Watanabe, Fukatsu, Katsuno, et al
J Neurol Neurosurg Psychiatry 2004;75:103–109

- Treatment assessment

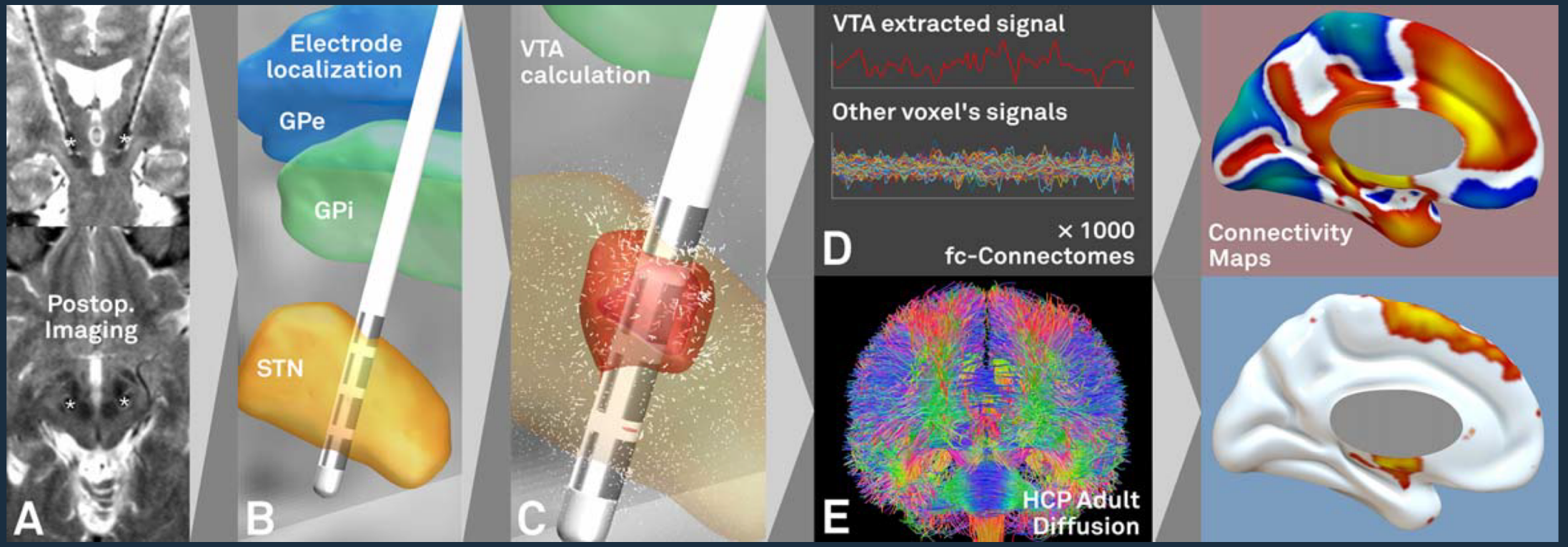
Treatment assessment

- On-off medication studies (as mentioned before)
  - *DBS (our approach individual ; M Fox: database)*
  -

- tremor dominant (TD) and postural instability/gait difficulty (PIGD) subtype

Connectivity from databases to predicts DBS Outcome in Parkinson Disease

Horn et al. ANN NEUROL 2017;82:67–78



Big data

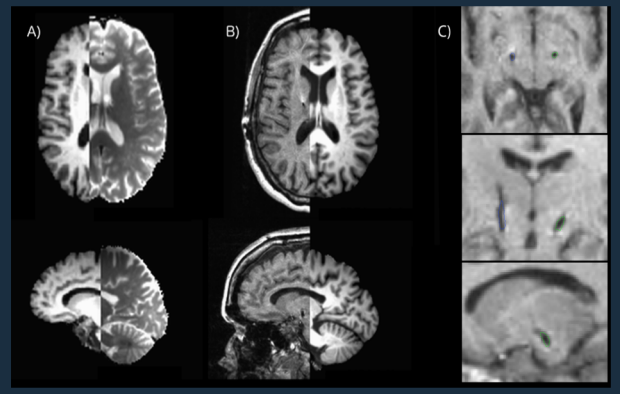
- PPMI (Parkinson's progression markers initiative)
  - *http://www.ppmi-info.org/study-design/research-documents-and-sops/l*

- Human connectome project
  - *https://www.humanconnectome.org/study/hcp-young-adult/document/1200-subjects-data-release*

Connectivity from individual subject to predicts DBS Outcome in Parkinson Disease

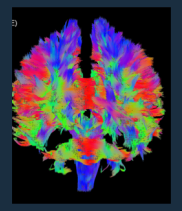
Lauro et al. Human Brain Mapping 2016.

Images Registration (target: T2w pre- AC-PC aligned)
pre-op: T1w, T2w, DWI 33dir
post-op: T1w, CT
within AFNI



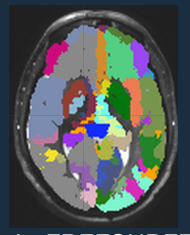
DBSproc1

tractography



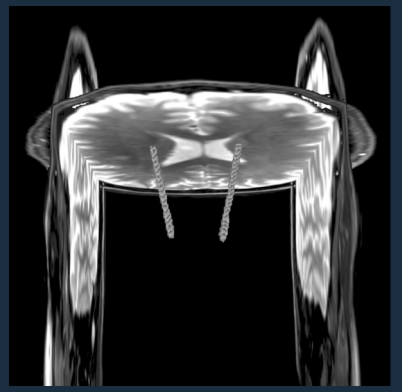
In FATCAT;
preprocessing in TORTOISE;

segmentation

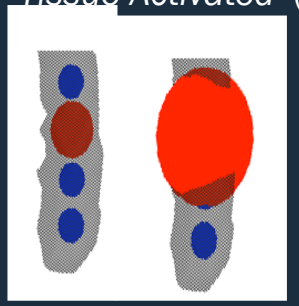


In FREESURFER;

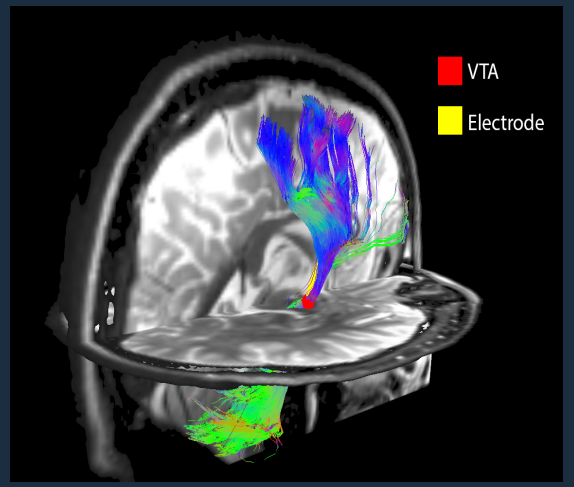
Identify contacts from the CT scan



Estimate *Volume of Tissue Activated* (VTA)



DBSproc2

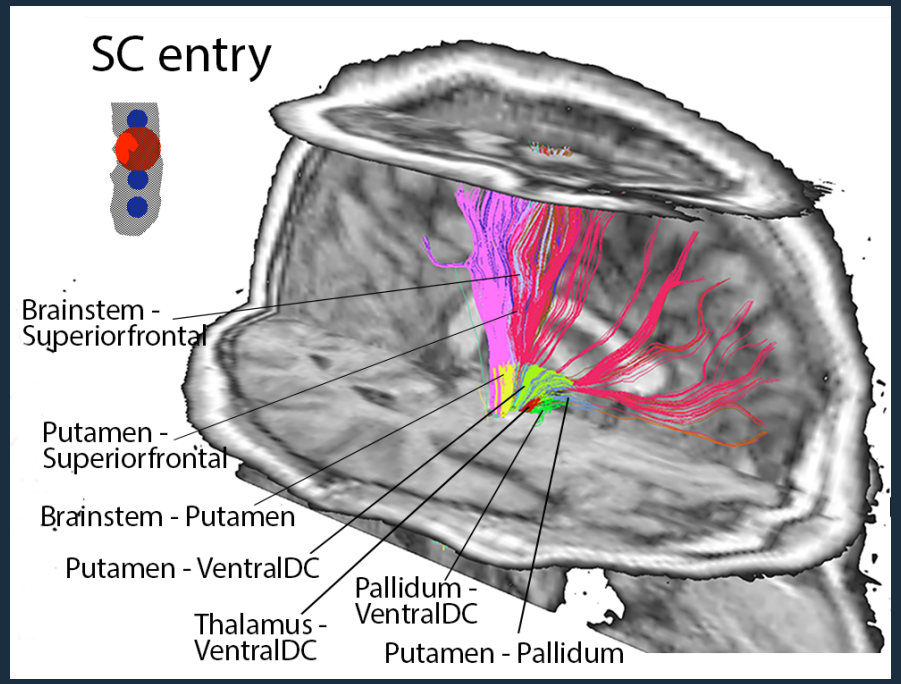


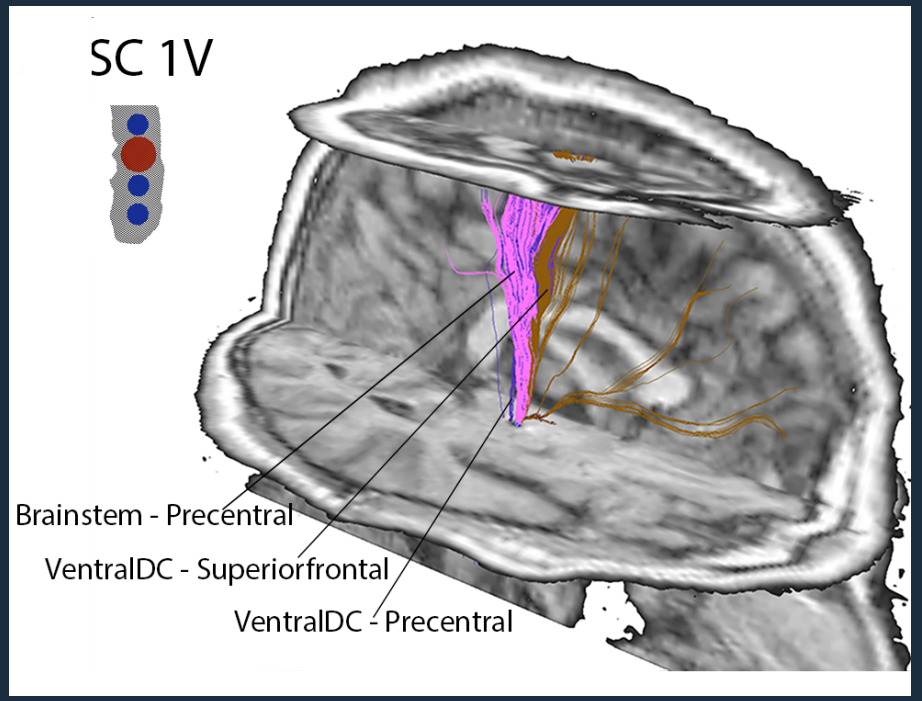
Methods: DBSproc

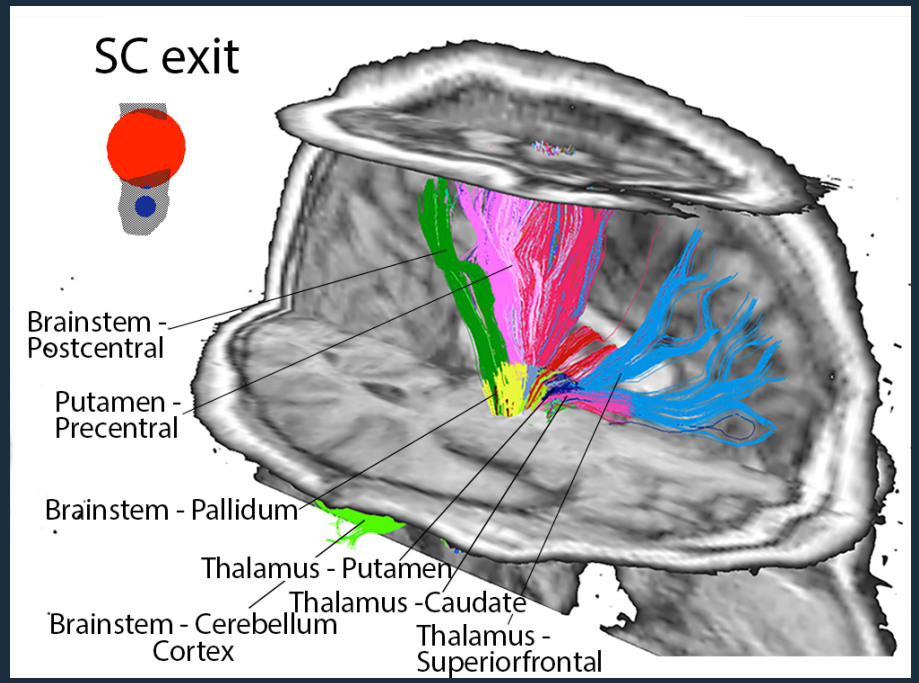
explore the data

Individual subject
Single contact Tractography

Lauro et al. Human Brain Mapping 2016.

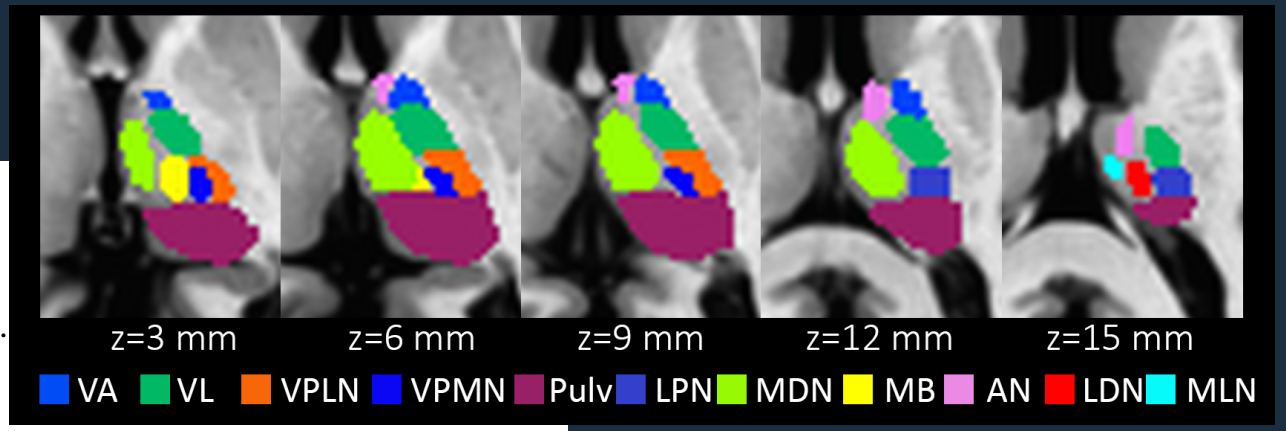


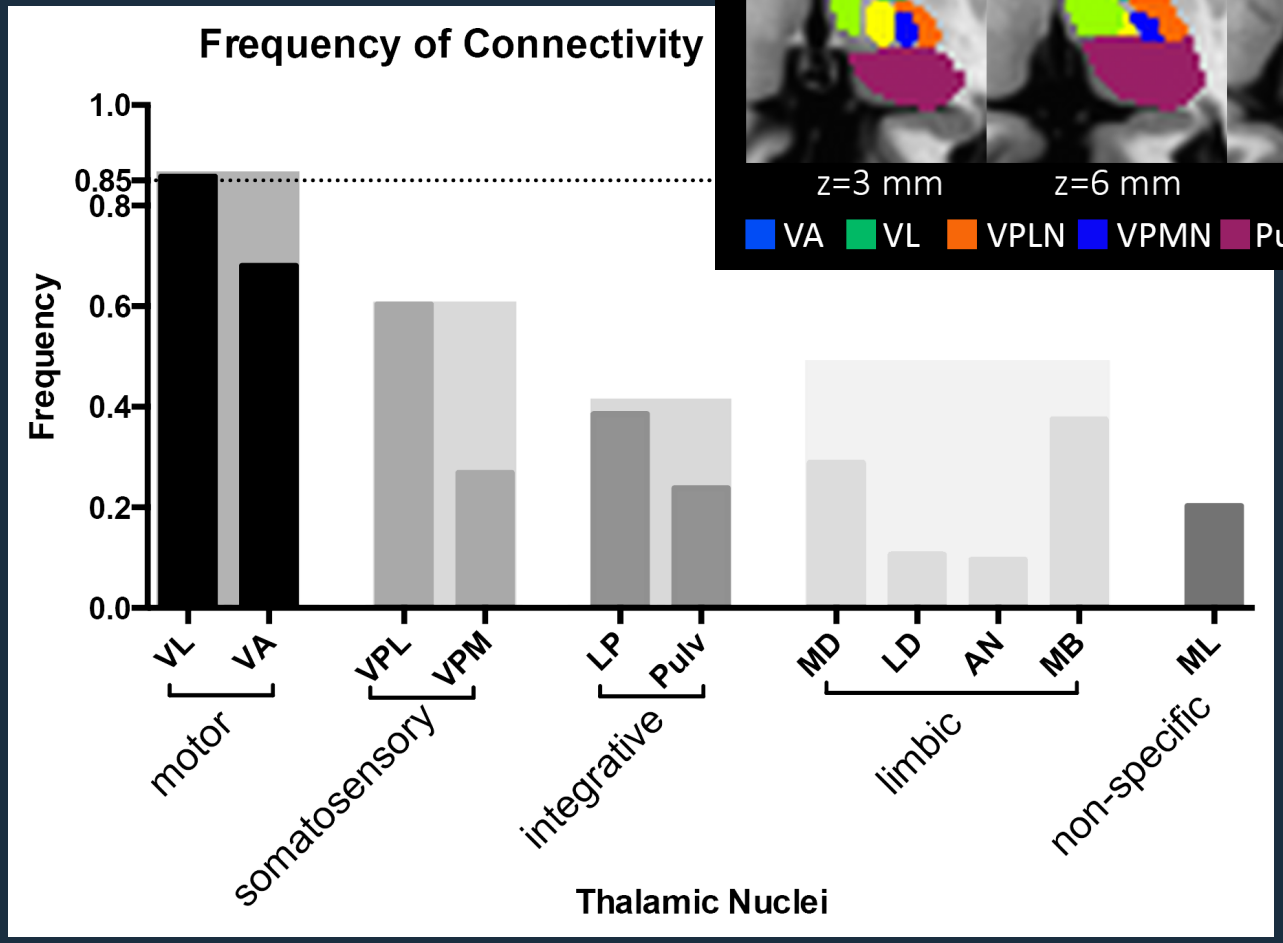




VTA - Thalamic Nuclei connectivity

Horovitz et al. ISMRM 2016





Binary analysis (195 EC)
Threshold: 105 streamlines