

Faculté de médecine

Université 
de Montréal



CANADIAN
OPEN PARKINSON
NETWORK

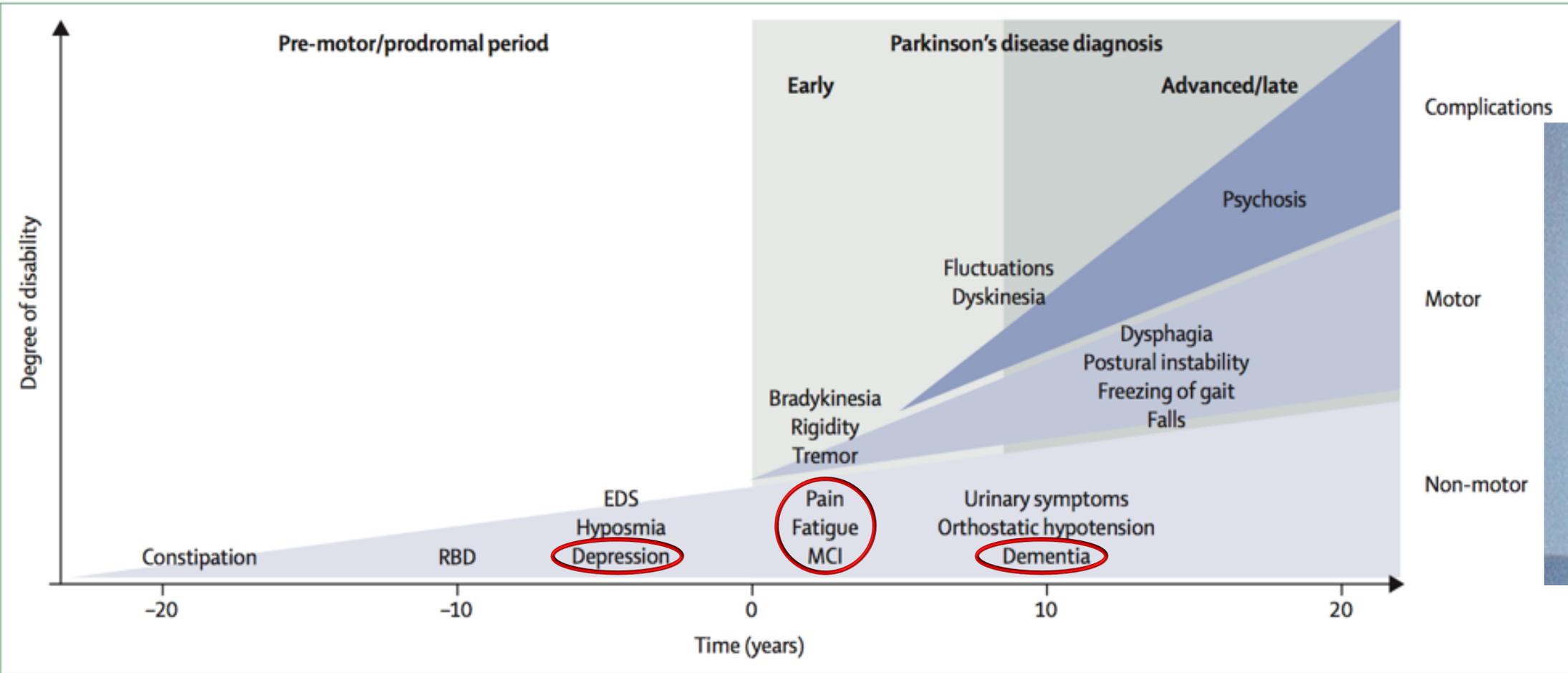
40^e
Anniversaire
1982-2022

Centre de recherche
iugm
Institut universitaire
de gériatrie de Montréal

Non-motor symptoms in Parkinson's disease: Neuroimaging and behavioural studies.

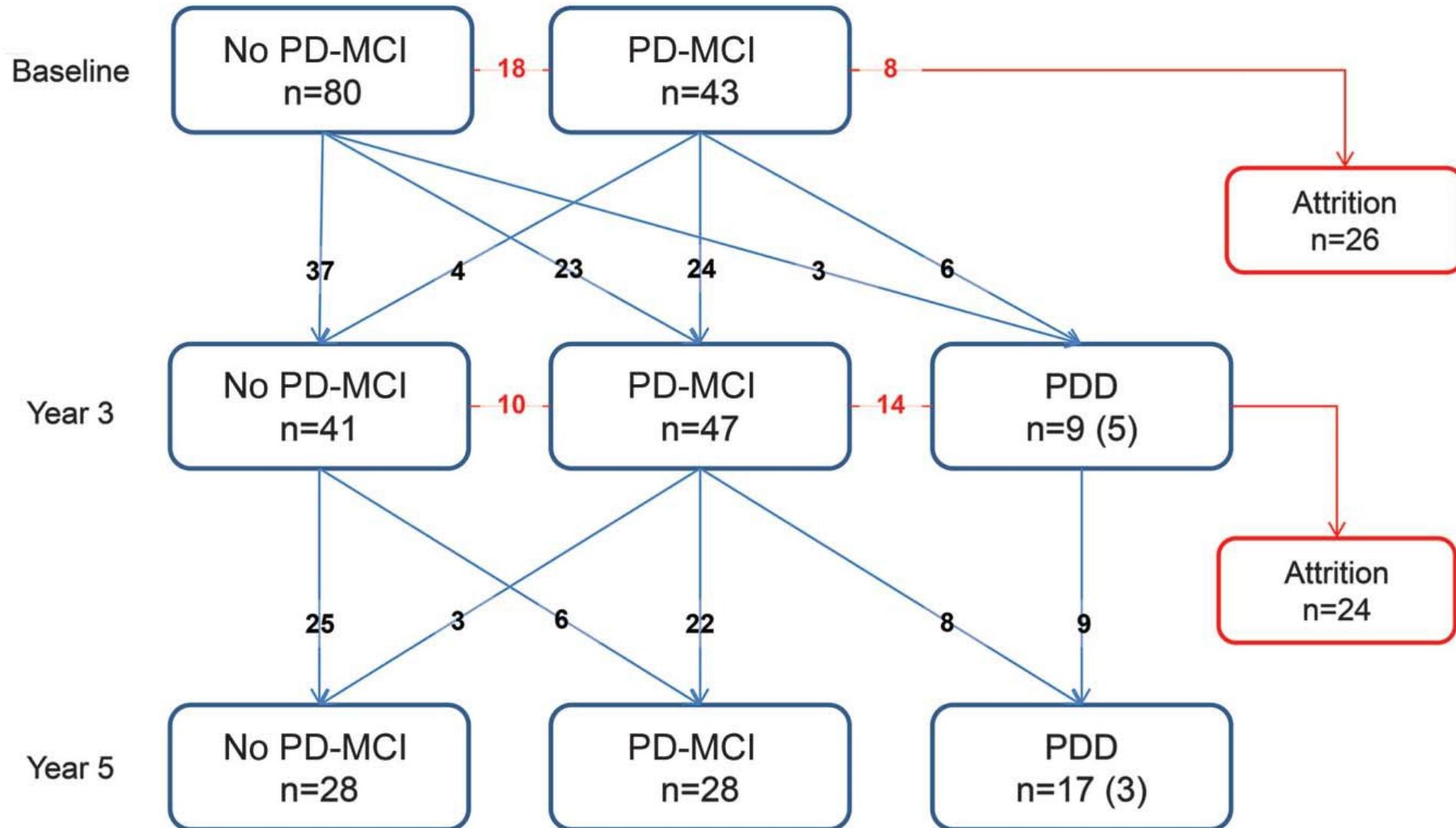
Oury Monchi, PhD

Parkinson's disease is not just a movement disorder

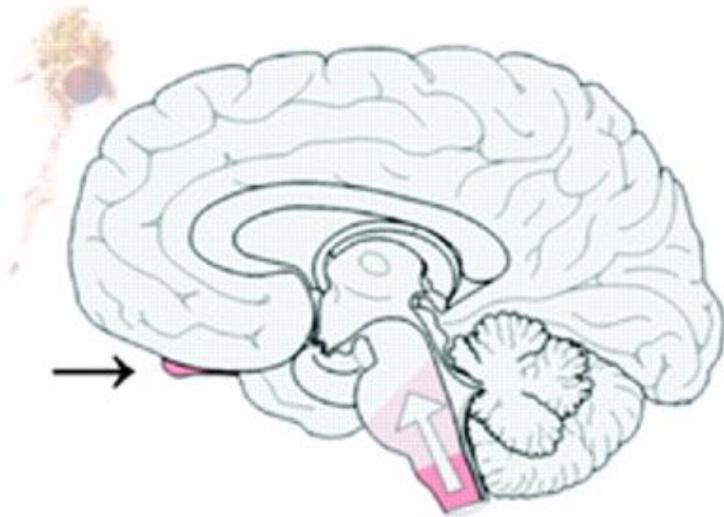


Kalia & Lang
2015, Lancet

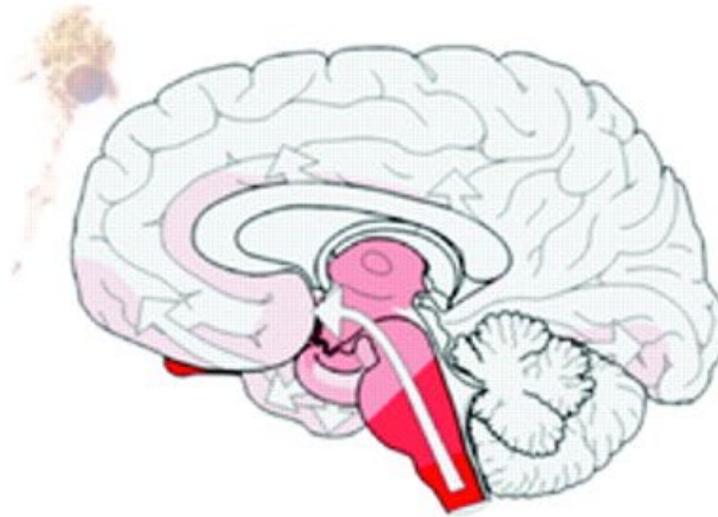
Prevalence longitudinal studies



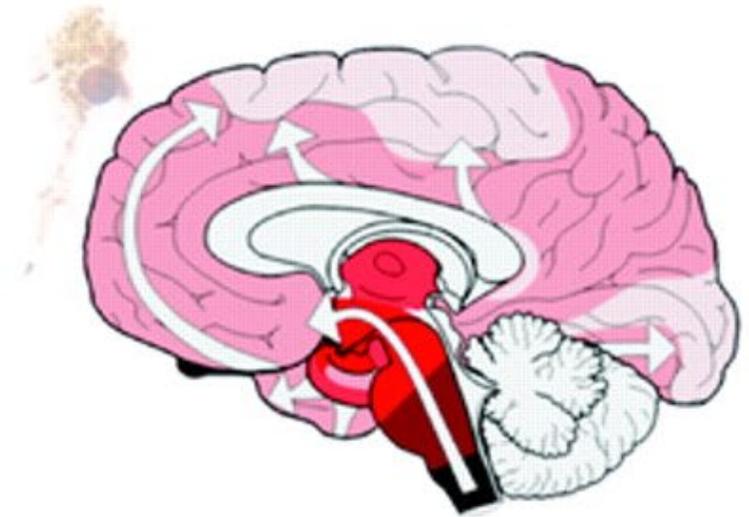
Neuropathology



Braak Parkinson's disease stages 1 & 2
PRECLINICAL



Braak Parkinson's disease stages 3 & 4
CLINICAL PARKINSON'S DISEASE

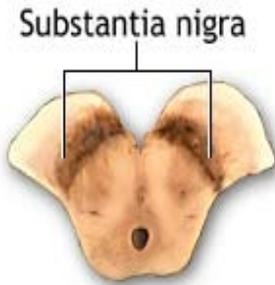


Braak Parkinson's disease stages 5 & 6
COGNITIVE IMPAIRMENT

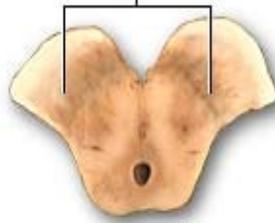
Substantia Nigra and Cortico-striatal loops



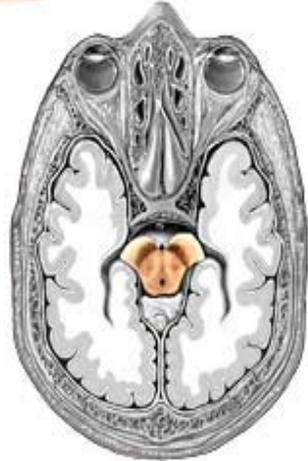
Cut section of the midbrain where a portion of the substantia nigra is visible



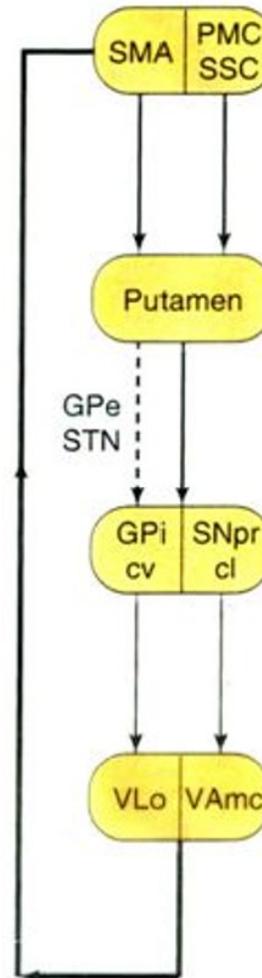
Diminished substantia nigra as seen in Parkinson's disease



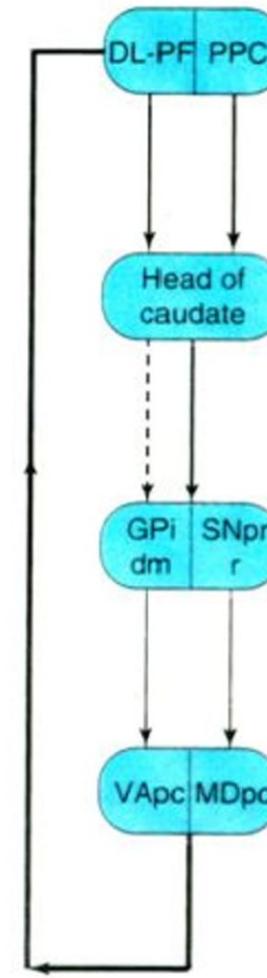
ADAM.



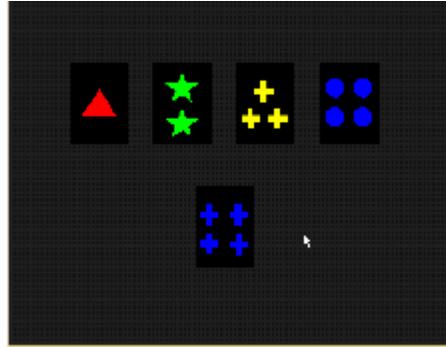
Motor Loop



Cognitive loop

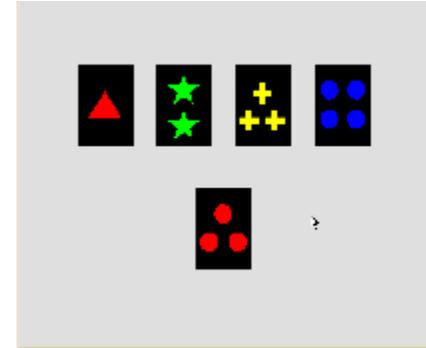


Planing a set-shift: Young healthy adults



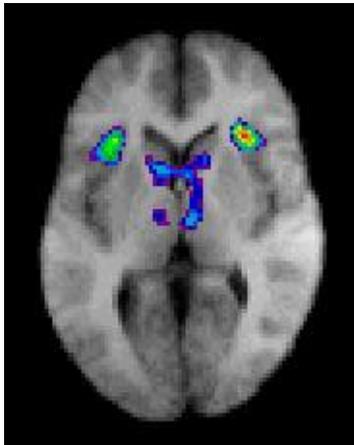
Negative feedback

VS



Positive feedback

Young healthy
adults



Isolation of a cognitive corticostriatal loop that includes ventrolateral PFC, caudate nucleus and thalamus

Monchi et al., 2001: *Journal of Neuroscience*, editor's choice
Science and *Nature Reviews Neuroscience*

fMRI WCST PD-MCI vs. PDnon-MCI OFF

A.

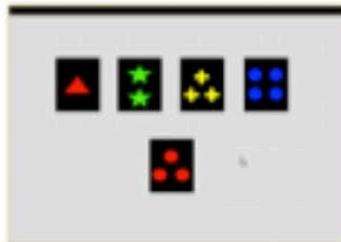
Planning the set-shift

Negative Feedback

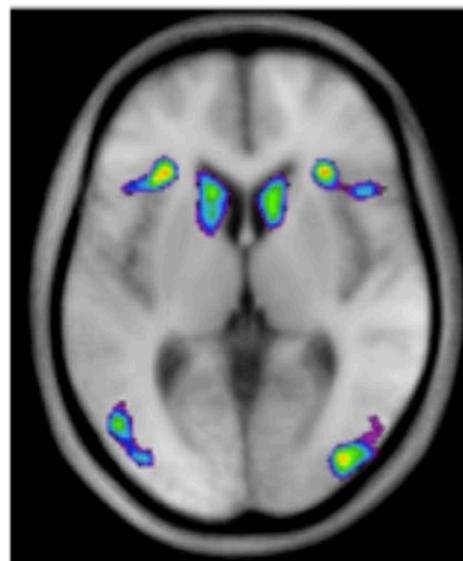


Vs.

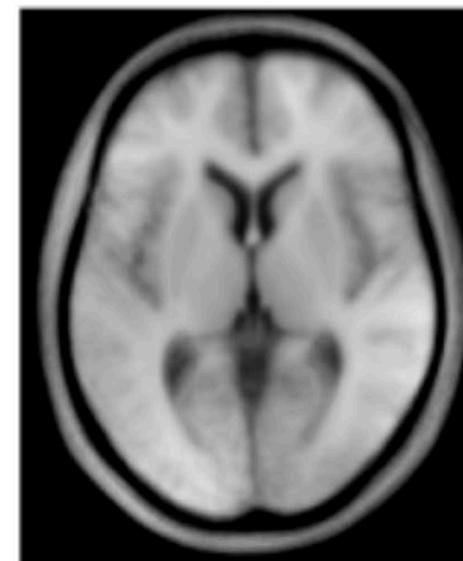
Positive Feedback



Non-MCI



MCI



Z = +4

Nagano-Saito et al. 2014,
Neurobiology of Aging

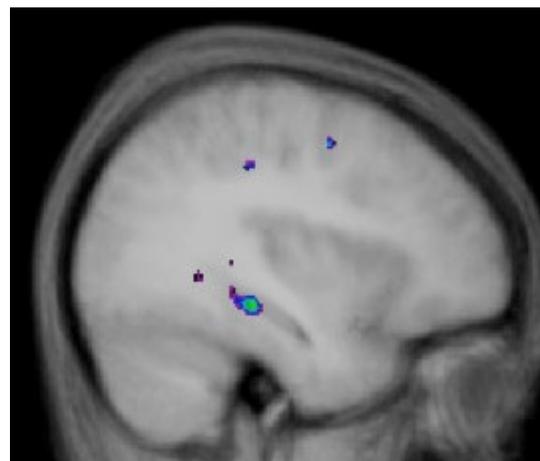
In accordance with Eckman et al., 2012, *Lancet Neurology*

Longitudinal study fMRI WCST All PD T1 correlated with MOCA evolution

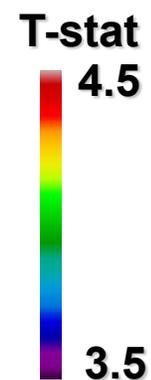
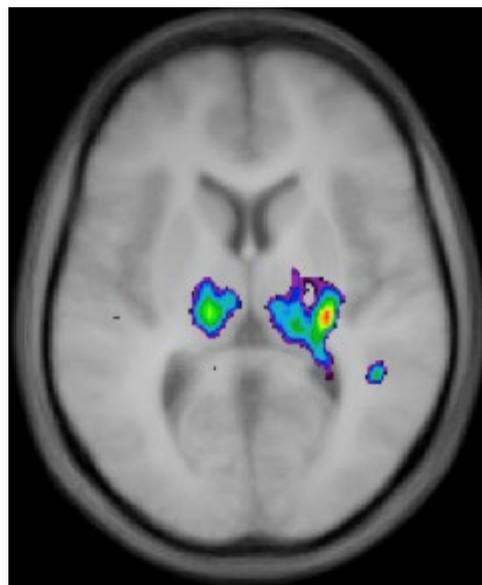
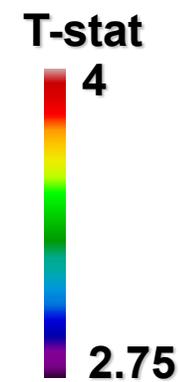
Planning the set-shift



X=-34



X=+36



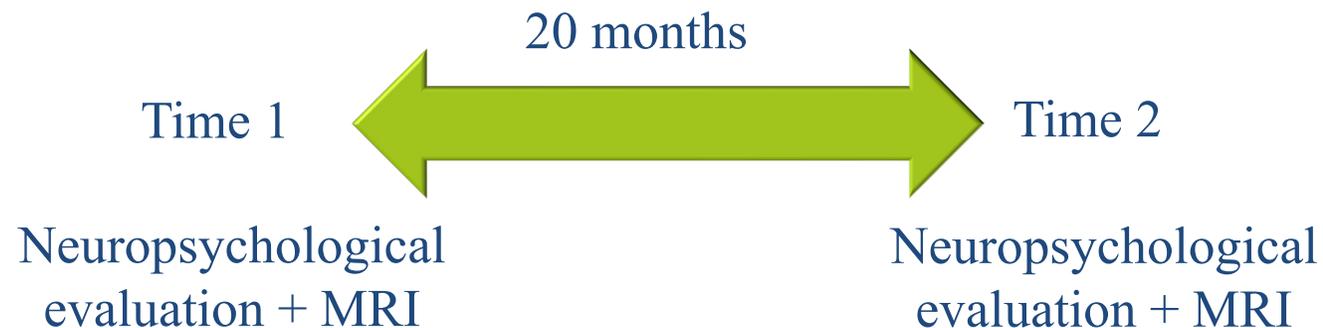
Z=+8

Nagano-Saito et al. Frontiers in Aging Neuroscience, 2016

Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally

- 17 PD patients with MCI
- 15 PD patients without MCI
- 18 Healthy Controls

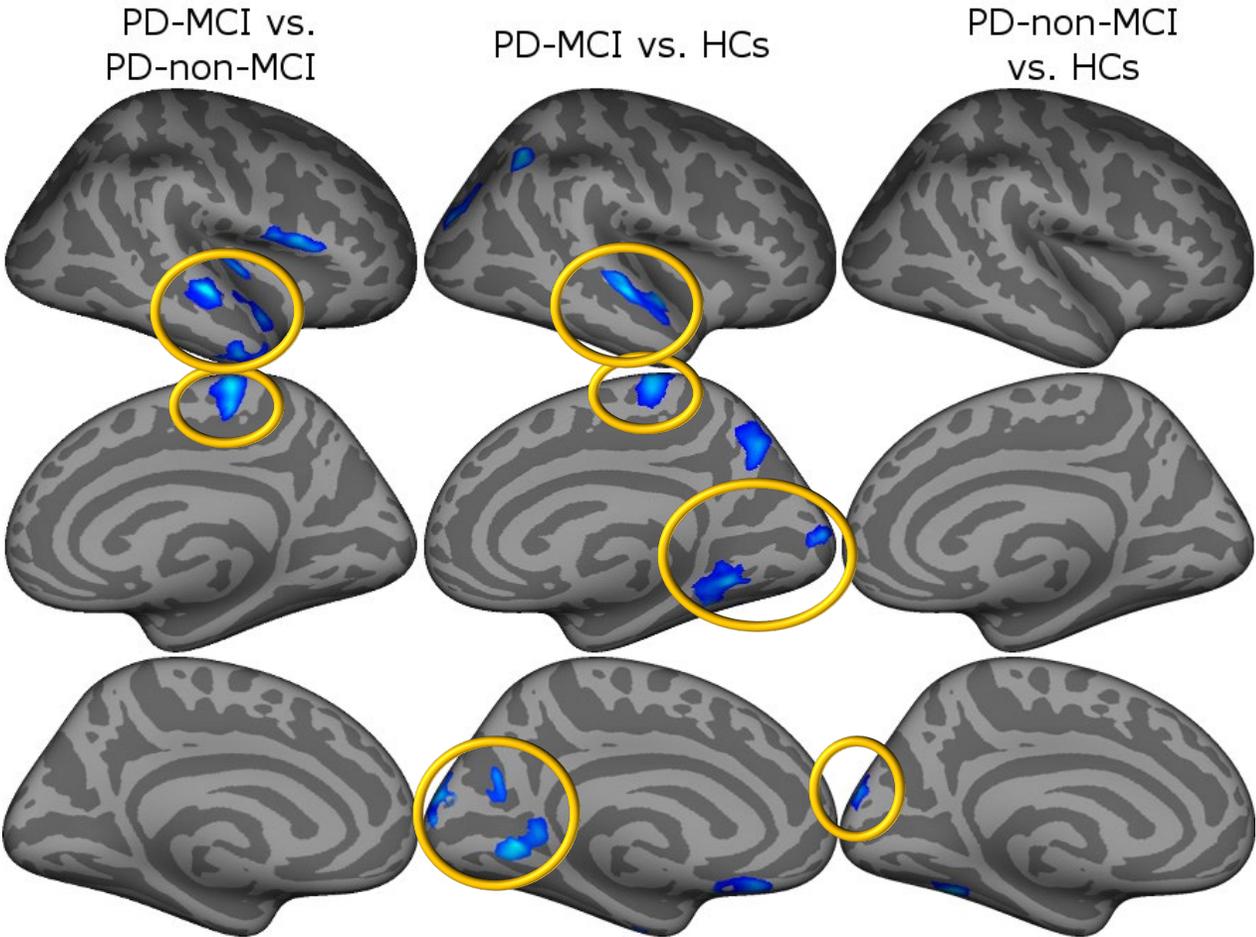
- MRI 3T
- FreeSurfer
 - Cortical thickness
 - Subcortical segmentation



MCI = Mild Cognitive Impairment
PD = Parkinson's disease

FreeSurfer

Results - thickness



PD-MCI	PD-non-MCI	HCs
-1.34%	-0.67%	-0.34%

Results – subcortical

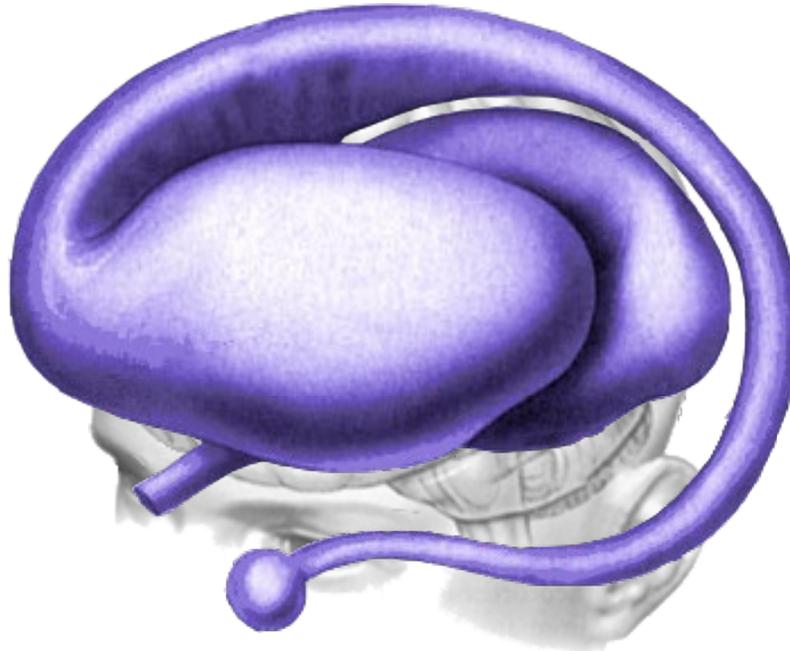
Mean percentage of change over time

	PD-MCI	PD-non-MCI	HCs
Thalamus	-1.51%	-1.80%	-3.71%
Caudate	-1.92%	-2.05	-0.99%
Putamen	-1.64%	-1.41	-0.40%
Hippocampus	-2.07%	-1.96	-3.08%
Amygdala	-6.05%	+0.58	+0.80%
N. Accumbens	-5.98%	-0.91	+2.19%

Ventral striatum has
an increased
degradation

Discussion – subcortical

Cognitively healthy patients



dopamine depletion
in PD progresses
from the dorsal
striatum to the
ventral striatum

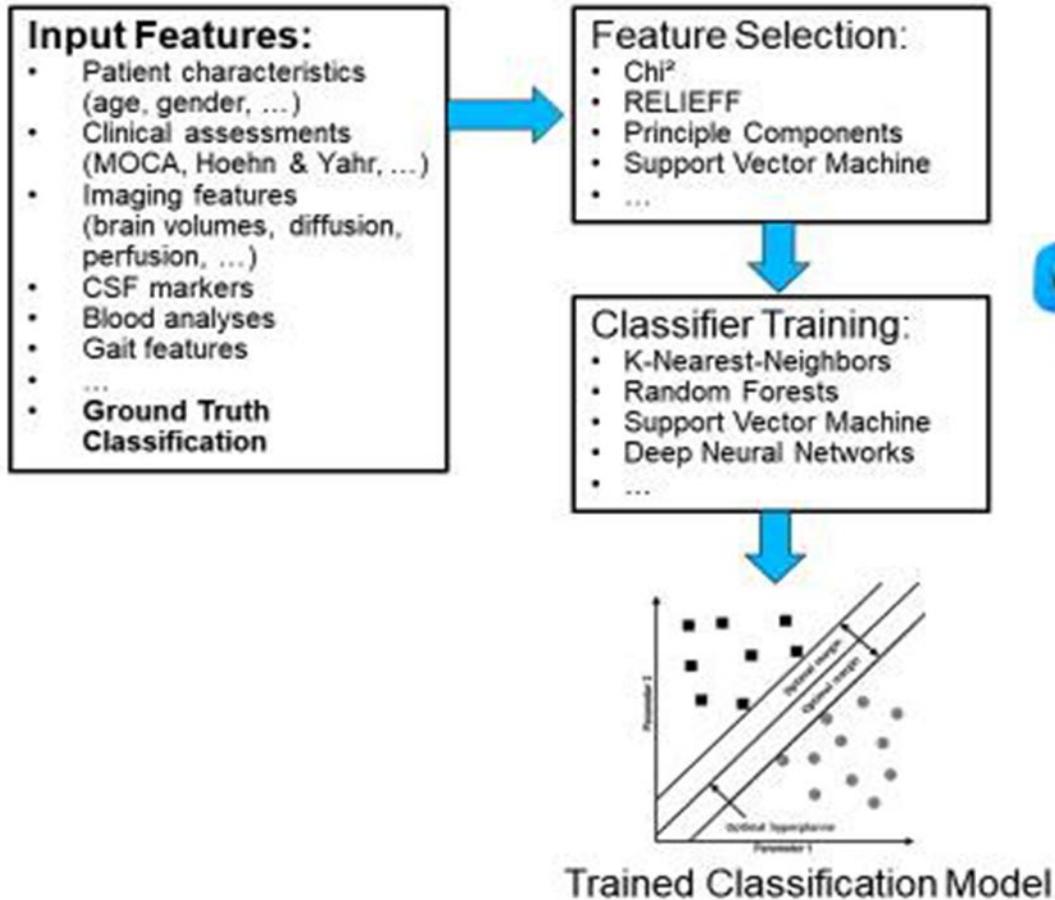
Cognitively impaired patients

Farley I, et. al. Adv Biochem Psychopharmacol 1977
Kish SJ et al., N Engl J Med 1988

Machine learning to predict cognitive decline in PD

Machine Learning for Precision Medicine

Training of Classifiers



To predict a continuous variable such as the evolution of the MoCA, a machine learning regressor is used instead of a classifier

Machine learning to predict cognitive decline longitudinally in early PD

289 de Novo PD patients from the PPMI

Demographic
and
clinical data

Cortical
thickness and
subcortical
volumes

RELIEFF

Support
vector
regression

MoCA
evolution over
4 to 5 years

A total of 87 features
at time 1

Features most predictive of cognitive decline in early PD

Features in final model

Years of education

Baseline MoCA score

Volume of right pallidum

Volume of right fusiform gyrus

Volume of right hippocampus

Accuracy metrics

$R^2 = 0.10$

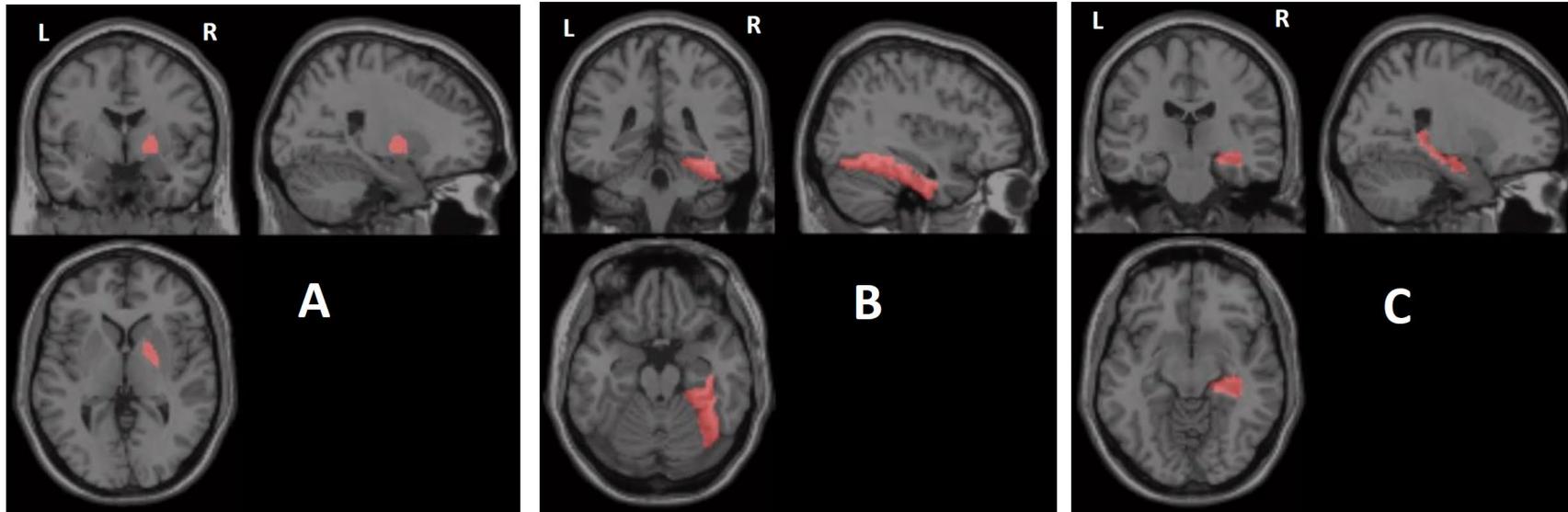
Correlation coefficient = 0.32

Mean absolute error = 2.20

Root mean squared error = 3.16

Table 3. Left column: Features that were part of our final model. Right column: accuracy metrics for this model.

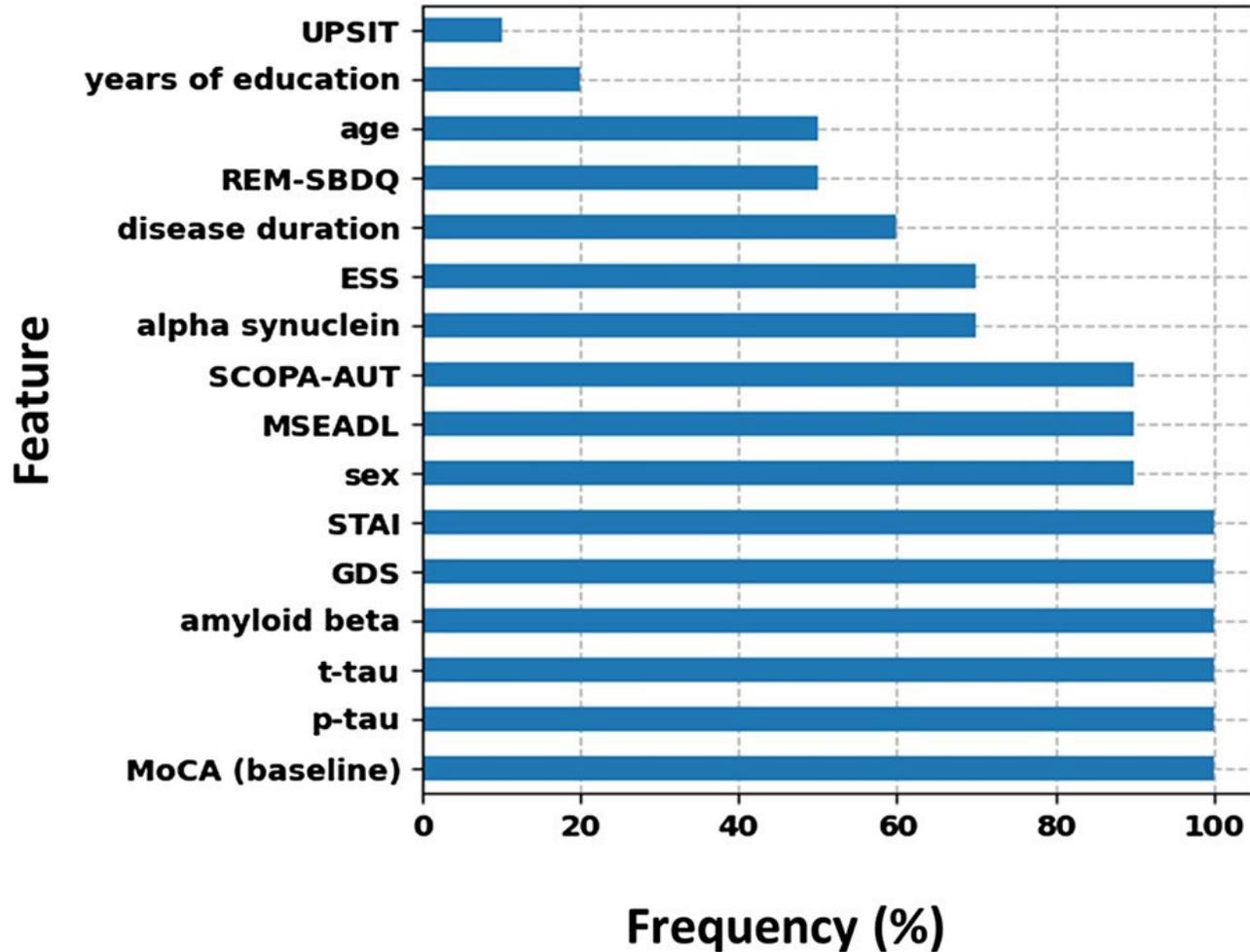
Almgren et al.,
2023, Scientific
Reports



Model with other modalities including CSF biomarkers and common genetic variants

Features	
Demographics	
Age, sex, years of education, handedness, disease duration	
Cognition	
Baseline MoCA score	
Clinical Tests	Cortical regional volumes (all bilateral)
Epworth Sleepiness Scale (ESS)	Frontal: superior frontal gyrus, middle frontal gyrus (rostral, caudal), inferior frontal gyrus (pars opercularis, triangularis, orbitalis), orbitofrontal cortex (lateral, medial), precentral gyrus, paracentral lobule
REM Sleep Behavior Disorder Questionnaire (REM-SBDQ)	Parietal: superior parietal lobule, inferior parietal lobule, precuneus, supramarginal gyrus, postcentral gyrus
University of Pennsylvania Smell Identification Test (UPSIT)	Occipital: cuneus, lateral occipital cortex, pericalcarine cortex, lingual gyrus
MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III	Temporal: entorhinal cortex, parahippocampal gyrus, fusiform gyrus, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, transverse temporal gyrus
Modified Schwab & England Activities of Daily Living Score (MSEADL)	Cingulate: anterior cingulate cortex (caudal and rostral), posterior cingulate cortex, isthmus of cingulate gyrus
Scales for Outcomes in Parkinson's Disease—Autonomic Dysfunction (SCOPA-AUT)	Insula
State-Trait Anxiety Inventory (STAI)	Subcortical volumes^a
Geriatric Depression Scale (GDS)	Amygdala, hippocampus, thalamus, caudate nucleus, putamen, pallidum, accumbens area, medulla, pons, superior cerebellar peduncle (SCP), midbrain
CSF biomarkers	Total brain volume
Amyloid beta ₁₋₄₂	Genetic variants
Total tau	APOE ε4
Phosphorylated tau	MAPT (rs17649553)
Alpha-synuclein	GBA (N370S)
	BDNF (rs6265)
	COMT (val158met)
	LRRK2 (G2019S)
	SNCA (rs356181)
	SNCA (rs3910105)

Features included in the best model for Moca decline in PD



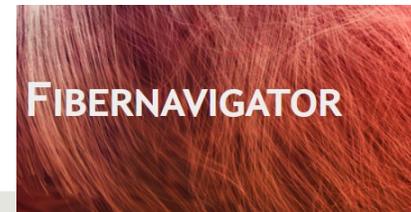
- The present study confirms that clinical test scores and CSF biomarkers are essential for the prediction of cognitive decline in PD.
- In contrast, brain volumes and genetics were not part of the best performing model in our study.
- Questionnaire on RBD was a selected feature in accordance with studies by Gagnon, Postuma et al.
- Many of the CSF biomarker selected by the model are associated with Alzheimer's disease pathology.

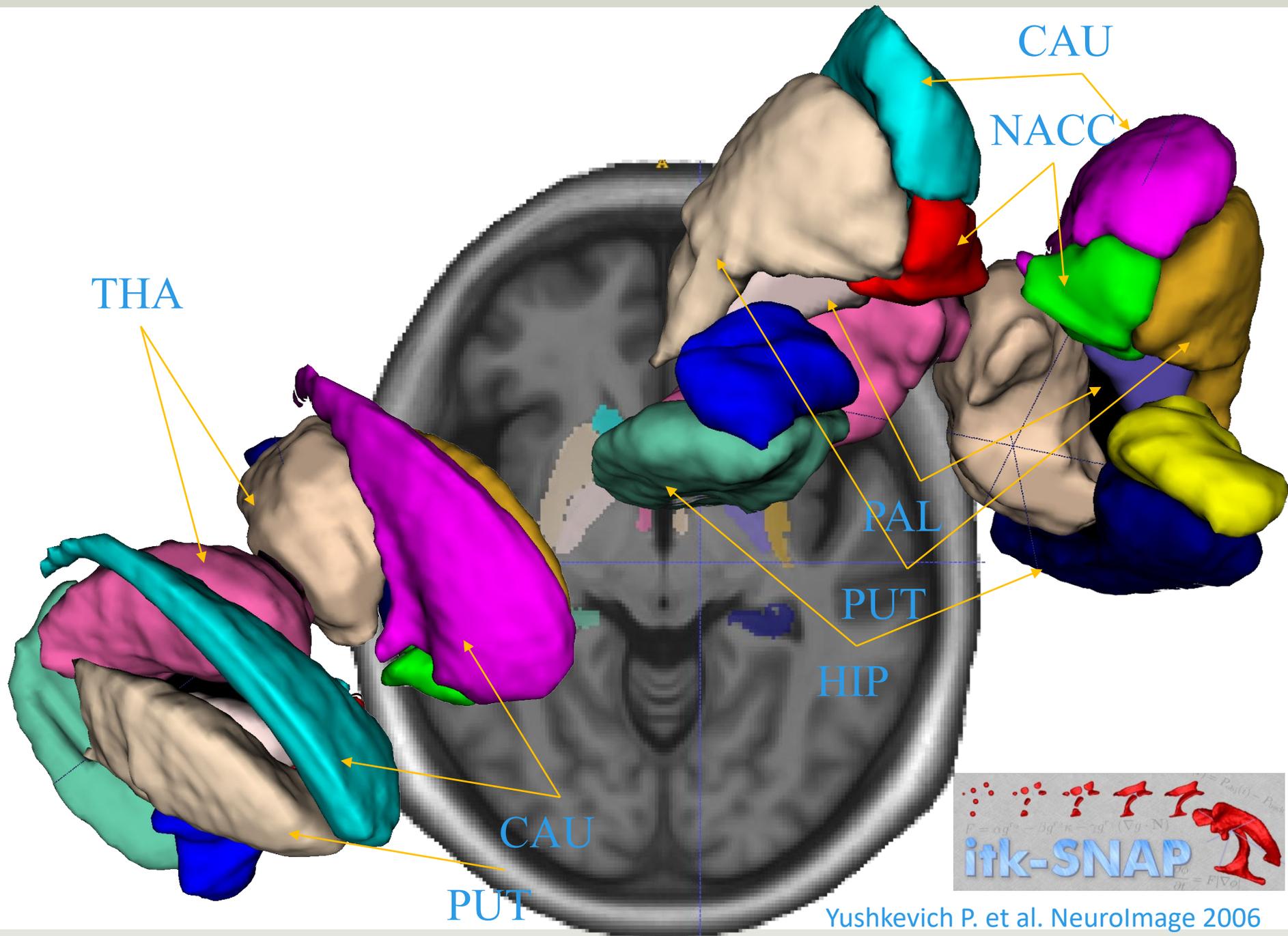
High -angular-resolution diffusion imaging for tractography

- 19 PD-MCI (patients with MCI)
- 20 PD-NC (patients with normal cognition)
- 16 Healthy Controls

- MRI 3T
- Neuropsychological evaluation

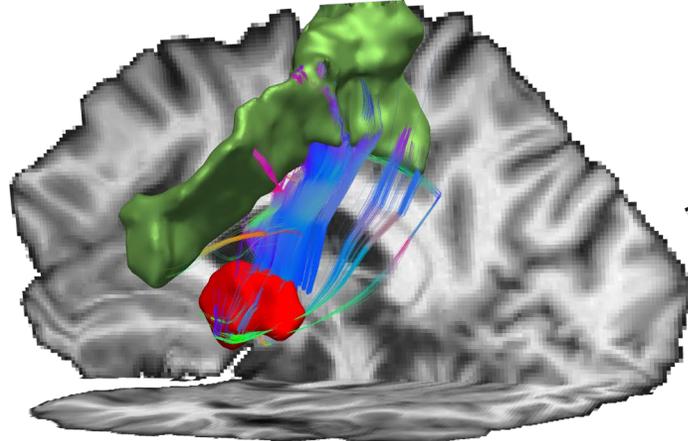
- ITKsnap
 - Cortical regions
 - Subcortical volumes
- Fibernavigator/ MRtrix
 - Tract count (RS)
 - Tract volume
 - FA (fractional anisotropy)
 - AD (axial diffusivity)
 - RD (radial diffusivity)
 - MD (mean diffusivity)
 - AFD (Apparent Fiber Density)



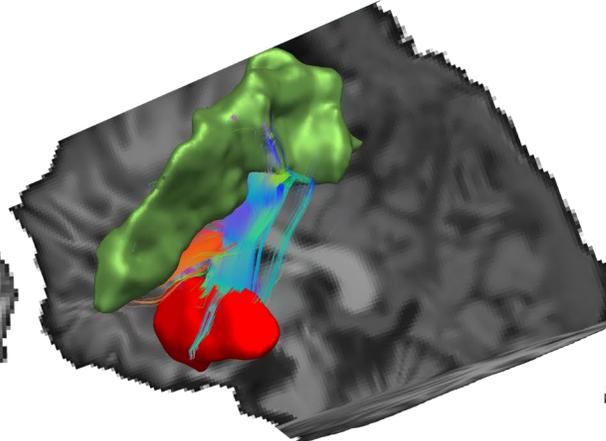


Tractography Illustration Example (RS/number of tracts)

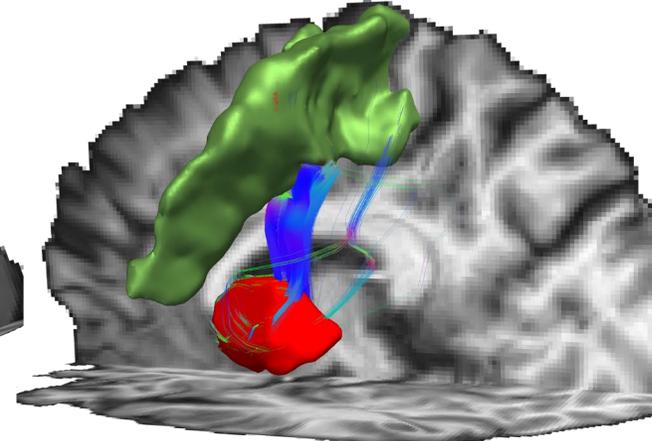
M1- Putamen right



HC

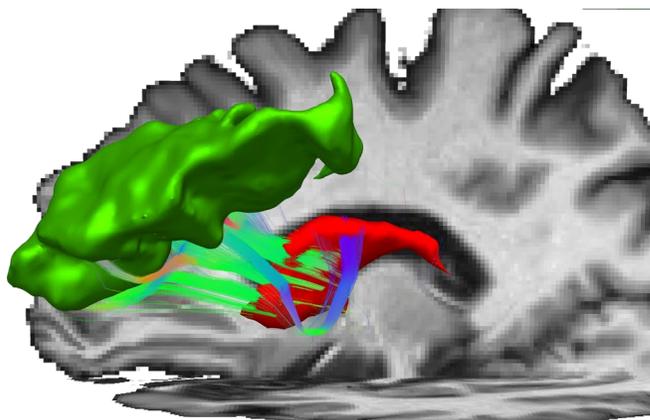


PDN

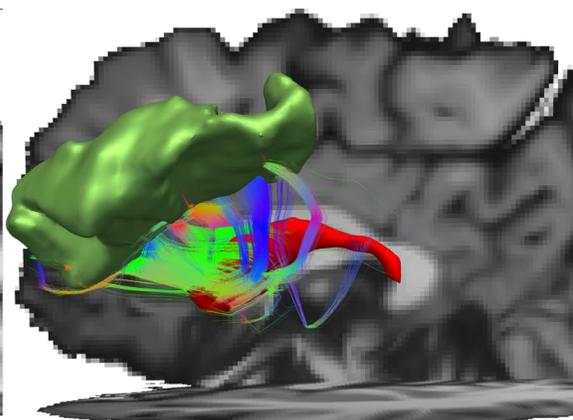


PD-MCI

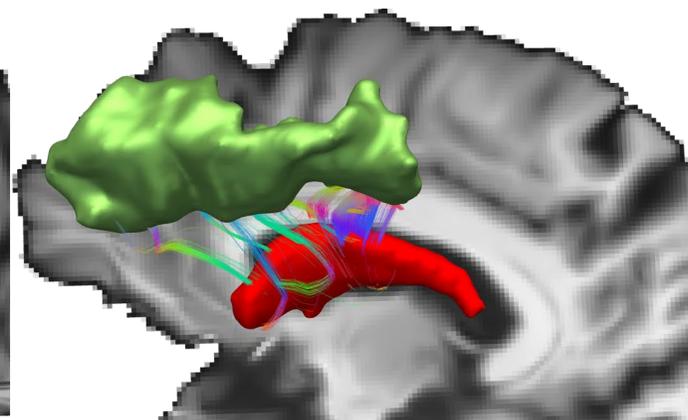
DLPFC-Caudate right



HC



PDN



PD-MCI

Effect of MBI on cognitive deficits in PD

➤ **Mild Behavioral Impairment (MBI):**

A neurobehavioural syndrome to identify patients with increased risk of developing dementia (Ismail Z et al. 2017, Alz & Dem)

Characterized by later life emergence of sustained NPS behavioural and personality changes lasting more than 6 months

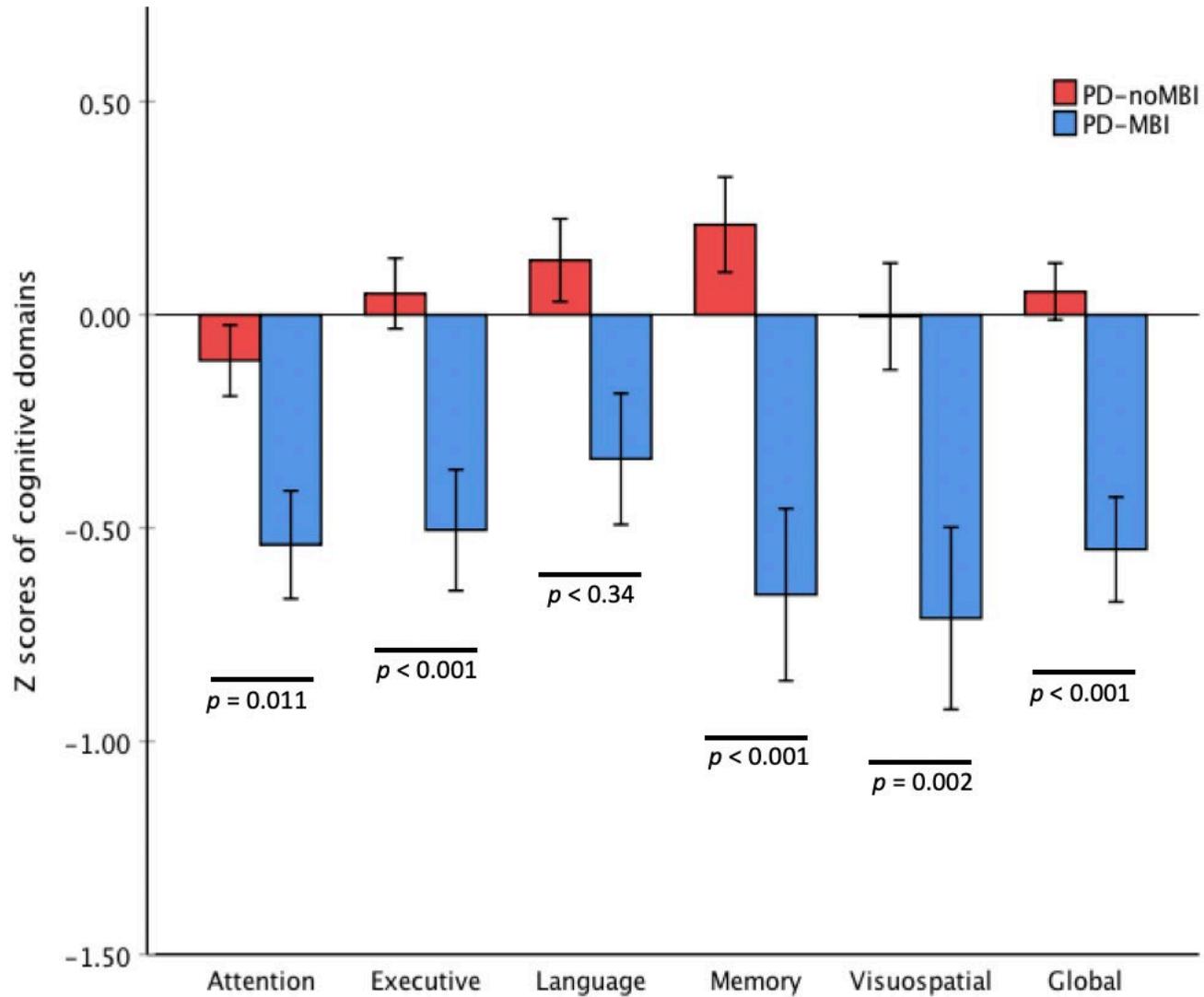
Cannot be explained by the presence of late life psychiatric often pre-existing general psychiatric illness such as depression, anxiety

➤ **Non-PD patients with MBI** higher conversion rate to dementia than a comparator group consisting of late life psychiatric disorders or than patients with no NPS

Effect of MBI on cognitive deficits in PD

- **MBI-checklist (MBI-C)**, takes only 5-7 minutes to complete. Filled by the caregiver/partner
- **The MBI-C** evaluates 5 domains: apathy, mood/anxiety, impulse dyscontrol/agitation, social cognition, and psychosis
- No research evaluated the association between MBI and cognitive deficits in PD
- 60 idiopathic PD patients at Hoehn & Yahr stages II-III
- Based on MBI-C scores, participants were divided into two groups: High MBI-C and low MBI-C

Effect of MBI on cognitive deficits in PD



Effect of MBI on cognitive deficits in PD

Table 1 Correlation with MBI-C total score in 60 PD patients (Spearman's rho, p-value)

	Attention	Executive	Language	Memory	Visuospatial	Global	MoCA
UPDRS-III	-0.260,	-0.304,	-0.236,	-0.358,	-0.354,	-0.385,	-0.396,
controlled	0.047	0.019	0.071	0.005	0.006	0.003	0.002

Table 2 Correlation with MBI-C total score in all PD when controlling for MCI status (Spearman's rho, p-value)

	Attention	Executive	Language	Memory	Visuospatial	Global	MoCA
UPDRS-III	-0.178,	-0.173,	-0.144,	-0.269,	-0.280,	-0.275,	-0.328,
controlled	0.182	0.194	0.281	0.045	0.033	0.037	0.012

Effect of MBI on cortical thickness and volumetry in PD

PD-noMBI vs. PD-MBI

A. Thickness

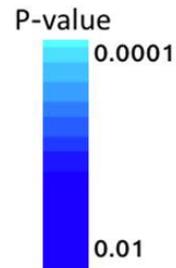


B. Volume



Correlation with MBI-C total in PD

C. Volume



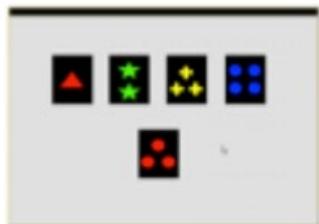
Previous studies:
Thinning of the anterior temporal lobe is associated with significant cognitive decline over time

Negative Feedback



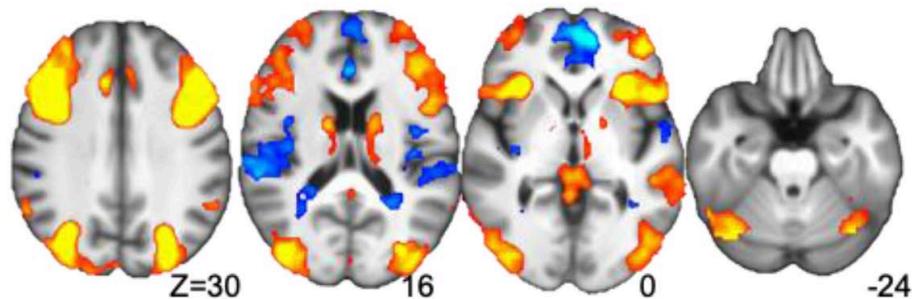
Vs.

Positive Feedback

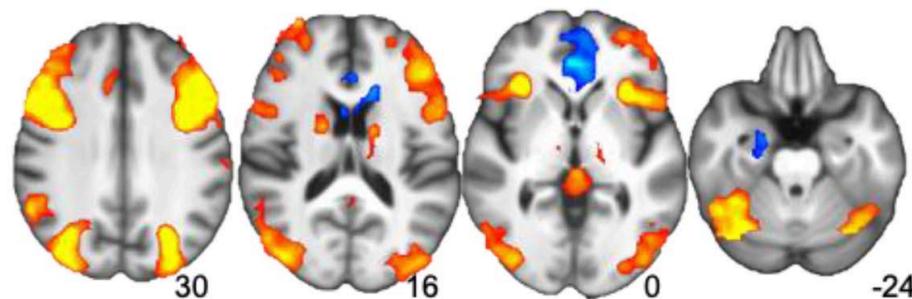


A. Planning the set-shift

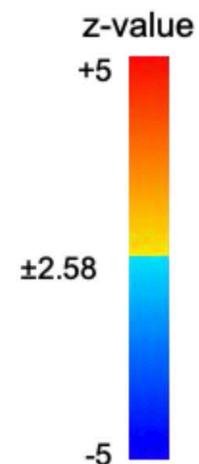
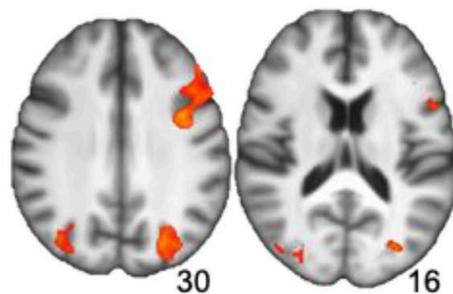
HC



PD-noMBI



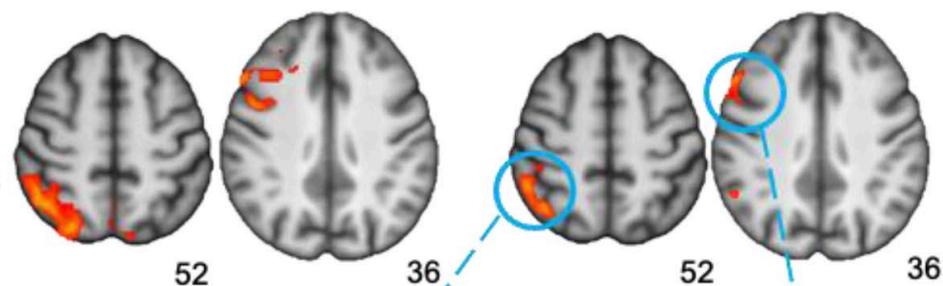
PD-MBI



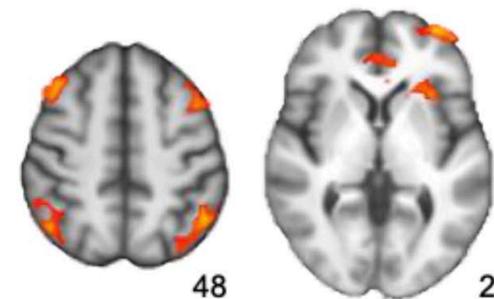
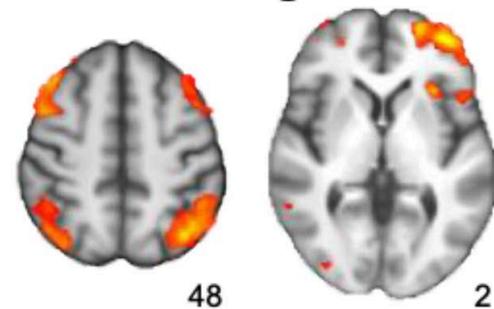
HC > PD-MBI

PD-noMBI > PD-MBI

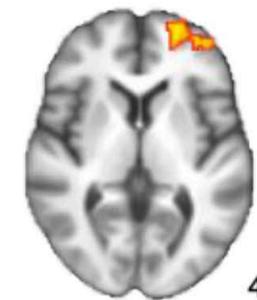
Group comparisons



B. Executing the set-shift

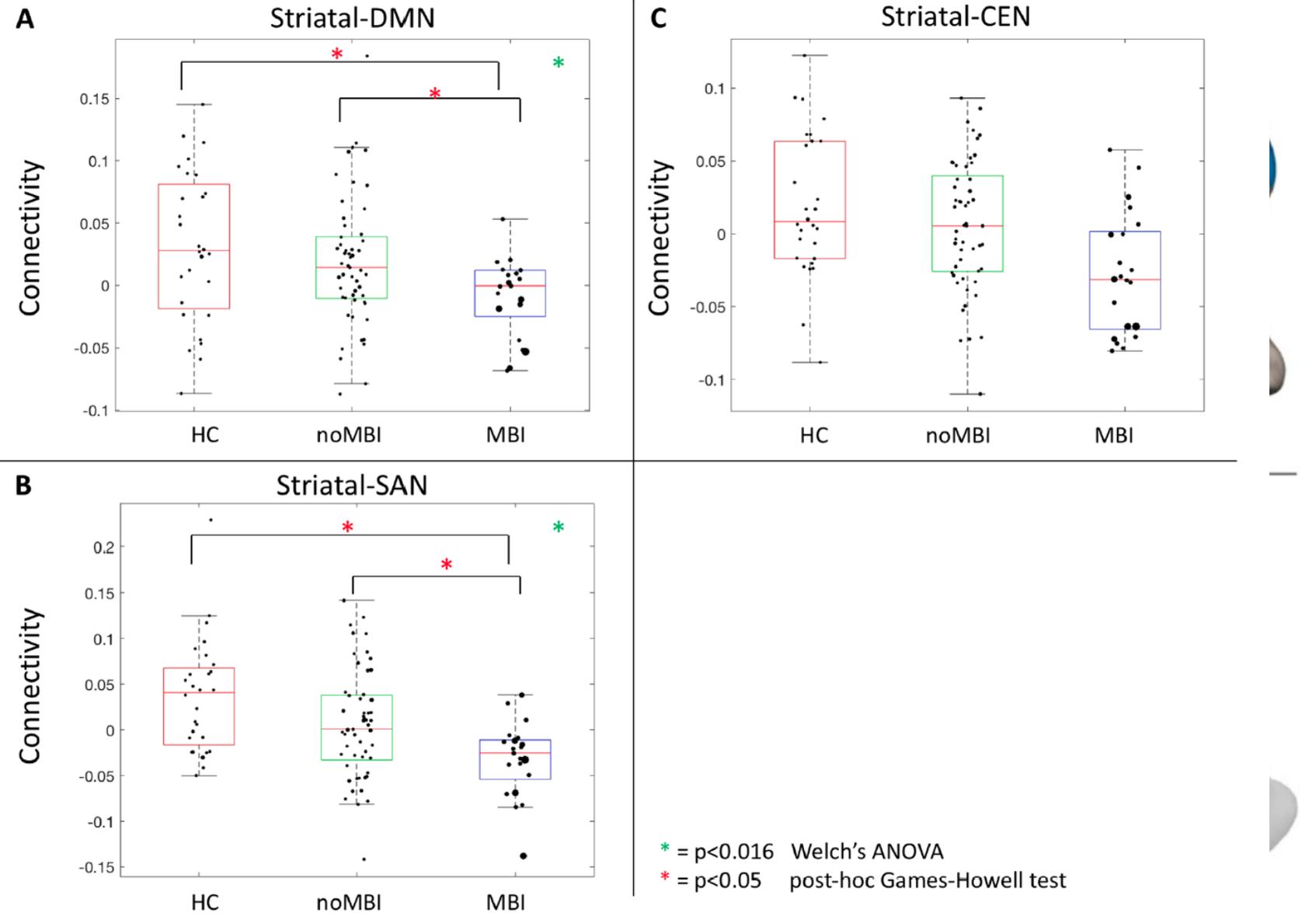


HC > PD-MBI



Yoon et al. 2021,
Neuroimage
Clinical

MBI in PD is associated with decreased cortico-striatal connectivity



Lang et al., 2020,
Neuroimage Clinical

Interim summary

- Mild behavioural Impairment (MBI) could be a practical marker for early detection of cognitive decline in PD. We have an ongoing longitudinal study funded by CIHR to determine that.
- In the future, we will evaluate in collaboration with Jean-Francois Gagnon whether MBI affects the trajectory of progression towards synucleopathy in RBD patients.

Prevalence of Pain in PD

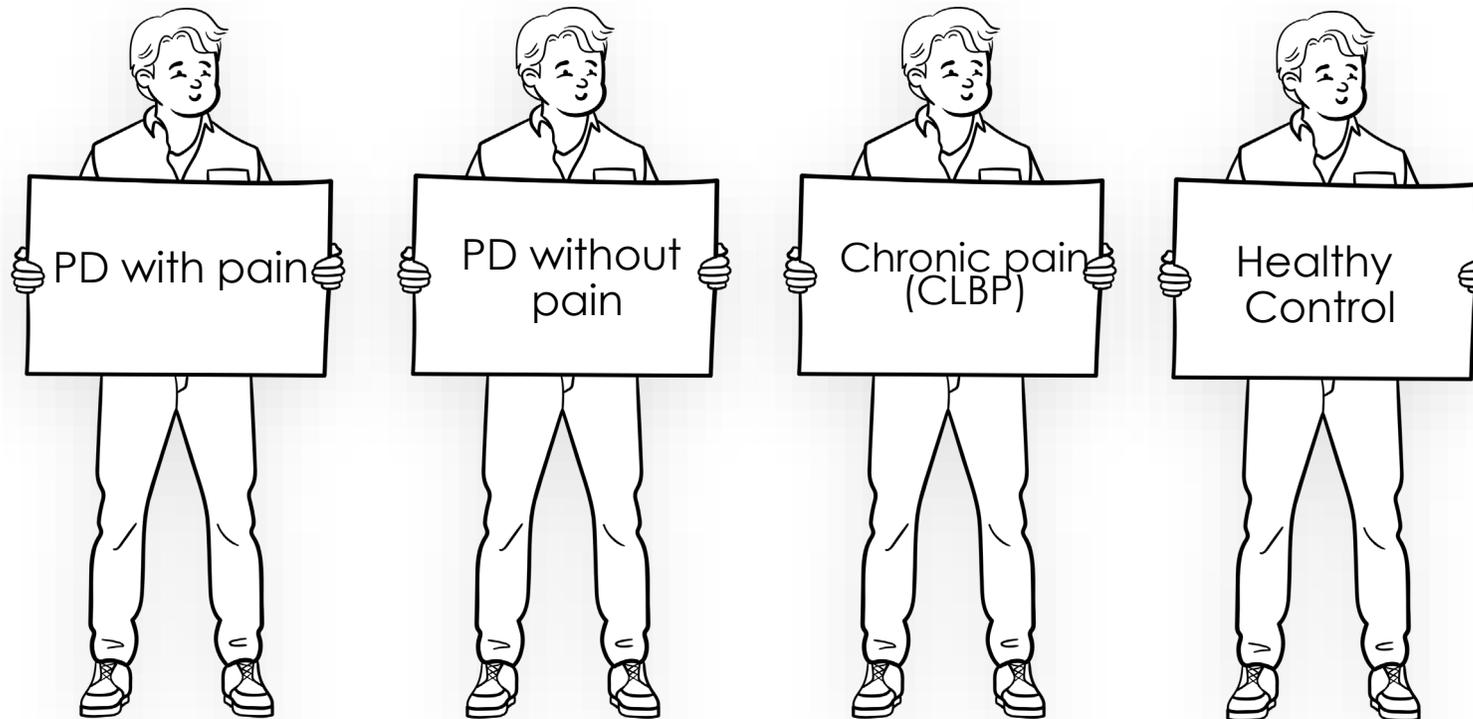
- 40 to 85% of patients experience chronic pain (Ford, 2010; Silverdale et coll., 2018) However it is not known why this is the case
- Painful symptoms often appear in the initial stages of the disease (Fil et al, 2013; Pont-Sunyer et al, 2015)
- Gradual changes as the disease progresses (Forkmann et al, 2017)
- Greater impact on quality of life than motor symptoms (Gallagher et al, 2010)
- Often undiagnosed or misdiagnosed (Shulman et al, 2002)

Research aims

- I. Could alterations in the sensory profiles and/or pain modulation mechanisms be at the origin of the high prevalence of chronic pain in PD patients?
- II. Are sensory profiles and pain modulation mechanisms similar in PD with pain and PD without pain, and how do they compare with those of chronic pain patients without PD?
- III. Does L-Dopa modify pain profiles in PD?
- IV. What are the neural and functional signatures of nociceptive processes in PD. Differences in activation patterns during painful experience and painful expectations will be explored using fMRI

Objectives of the 1st study

- ▣ Characterize sensory profiles (pain thresholds) by comparing ON and OFF in PD patients
- ▣ Discover the differences in the effectiveness of pain modulation (sensory, cognitive, affective)



Impaired pain perception in PD?

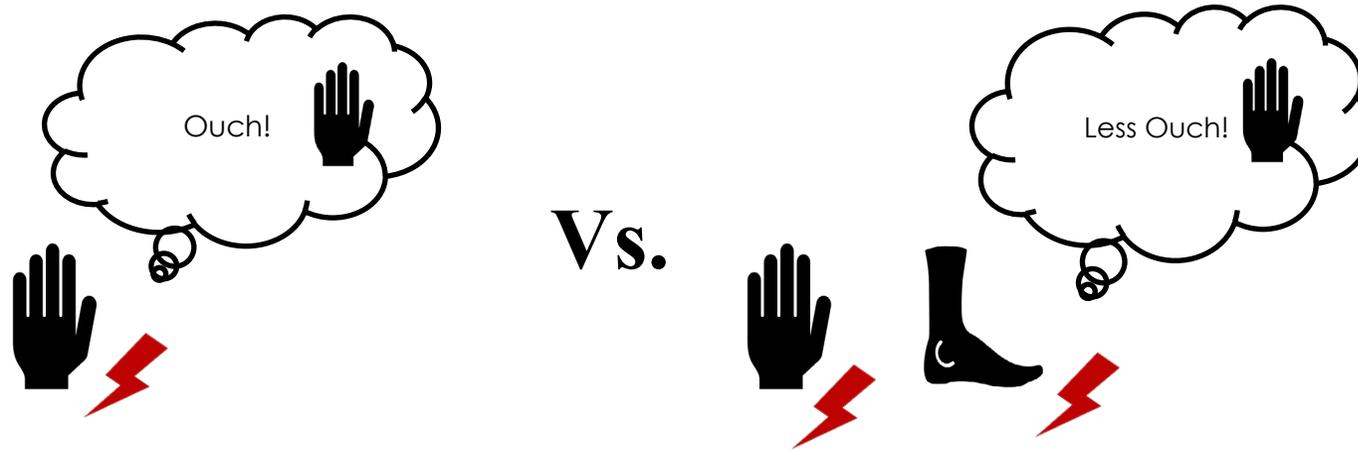
We will explore using Quantitative Sensory Testing

- Decreased pain threshold and tolerance in PD (Marsala et al, 2010)
- Pain thresholds are lower in PD with pain (Djaldetti et al, 2004)
- Levodopa Improves Pain Awareness (Lim et al, 2008)



Is Sensory Pain Modulation altered in PD?

Sensory : conditioned pain modulation (CPM)



De novo PD patients (Grashorn et al, 2019):
No significant difference between PD patients and control
BUT the counter-irritation effect is weaker in PD!

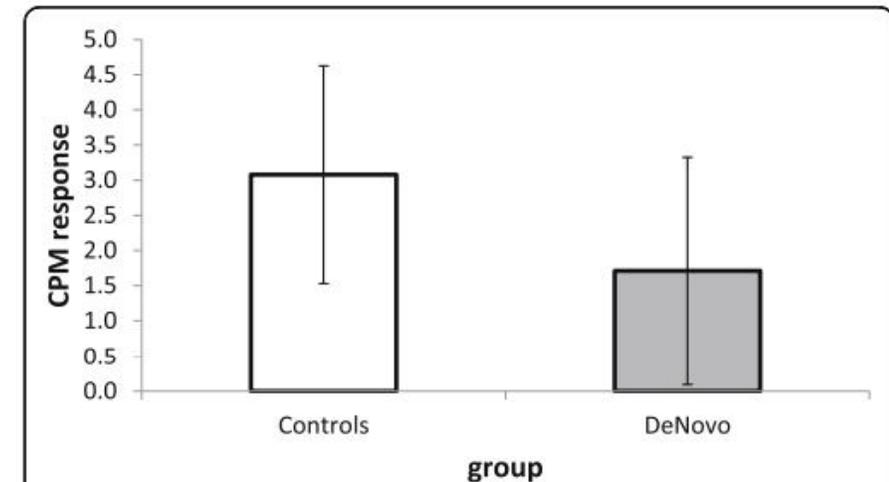
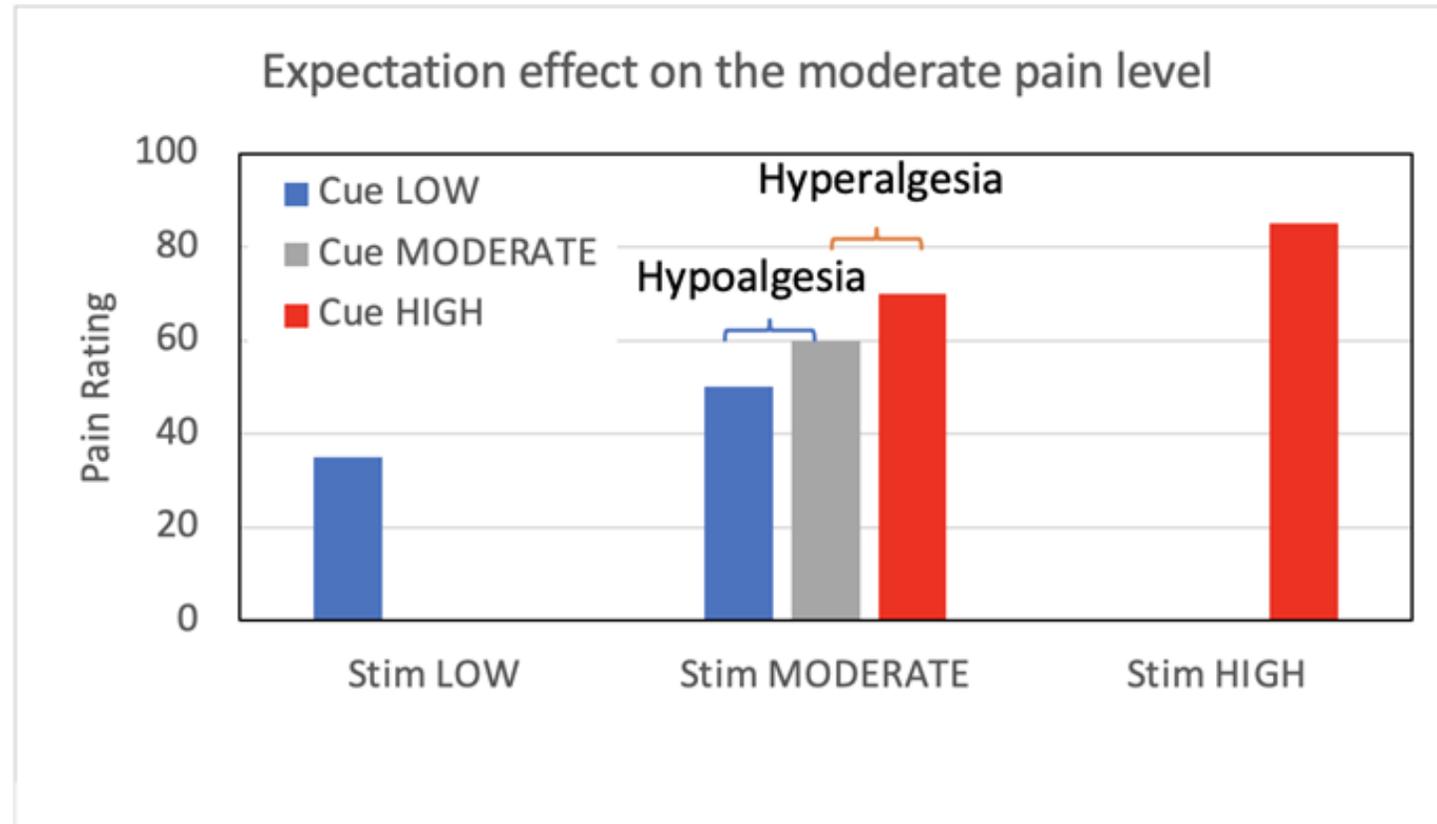


Fig. 2 Conditioned pain modulation magnitudes are shown for healthy controls and de novo PD patients. Means and standard error of means are presented. There were no group differences between de novo patients (gray bar) and controls (white bar)

Is Cognitive Modulation of Pain Altered in PD?

Cognitive : pain expectations effect



A priori expectations can have an analgesic effect on pain perception (dopamine, endogenous opioid system) (Scott et al, 2008)

Collaborators/Funding

PCAN lab

- Iris Kathol, PhD
- Stefan Lang, MD, PhD
- Eunjin Yoon, PhD
- Mekale Kibreab, BSc
- Hannes Almgren, PhD
- Imola Mihalecz, MSc
- Gabriel Pinilla-Monsalve MD, MSc
- Bérengère Houzé, PhD
- Sandra Masoud, BSc

Université de Montréal

- Alexandru Hanganu, MD, PhD
- Pierre Rainville, PhD
- Pierre Bellec, PhD

Université 
de Montréal



University of Calgary

- Justyna Sarna, MD, PhD
- Bruce Pike, PhD
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