Michel DOJAT

Research Director Inserm

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kw: Neuroimaging, Neuroinformatics, Image processing, Machine learning, Human Vision, Parkinson

MIAI Grenoble Alpes

GIN

a center dedicated to fundamental and clinical research in the field of neurosciences

OUR MISSION

Understanding the brain
and developing **innovative therapies**
for nervous system diseases

OUR STRATEGY

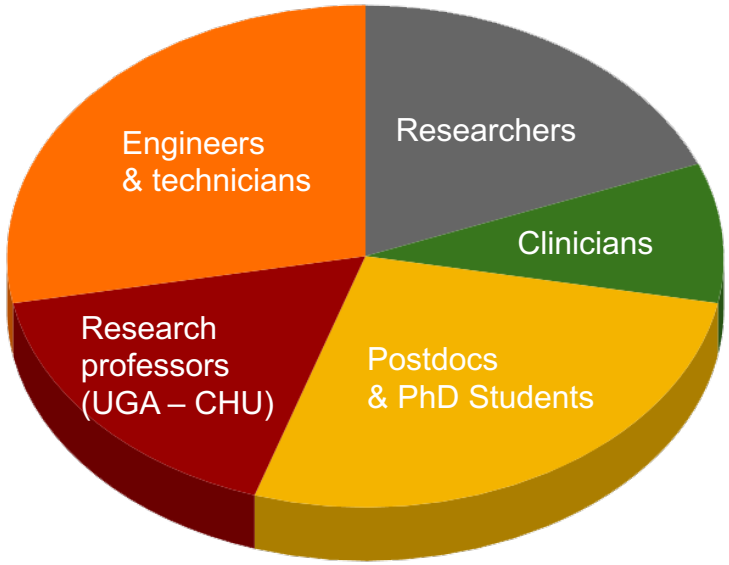
A **research continuum** from molecules, cells to small animals and humans for the study of neurological, neuromuscular and psychiatric pathologies

OUR STRENGTHS

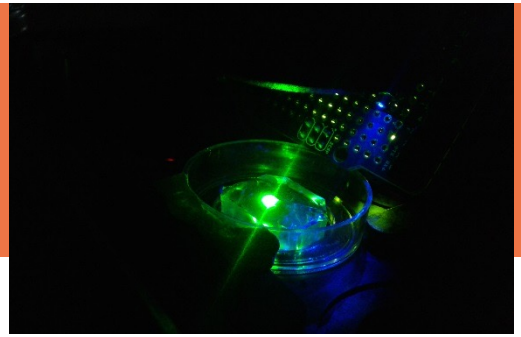
- Molecular and cellular biology of the neuronal cytoskeleton
- Predictive models of cerebral pathologies
- Mapping of neural networks and their alteration in neuropsychiatric disorders
- Functional neurosurgery and deep brain stimulation
- Functional MRI coupled with electrophysiology

UP TO 250 NEUROSCIENTISTS

- 39 Researchers
- 19 Clinicians
- 55 Postdocs and PhD Students
- 34 Research Professors
- 57 engineers and technicians



RESEARCH TOPICS AND EXPERIMENTAL APPROACHES



/ Fundamental neurosciences

Cytoskeleton, Intracellular traffic, Synaptic plasticity, Mechanisms studied in normal and pathological conditions (neurobiological diseases, neurodegenerative diseases, myopathies)

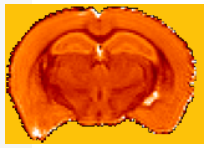
/ Pre-clinical and clinical research

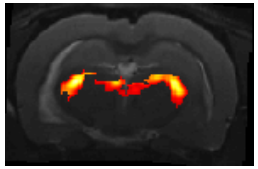
Developing tools and concepts

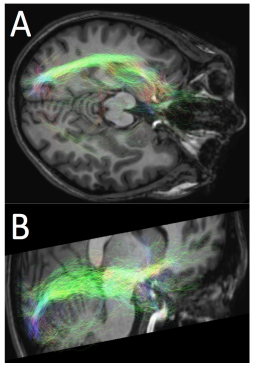
Close links with networks such as GREEN, Neuropsynov, NeuroCoG...

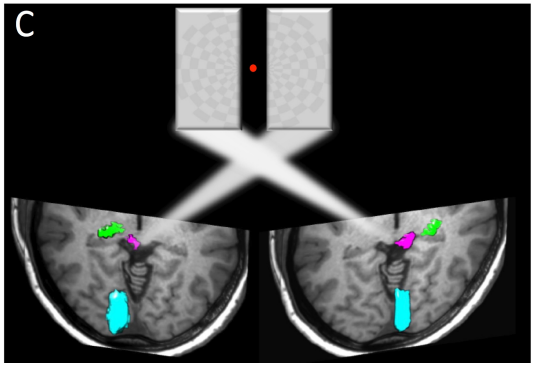
/ Innovative technologies and treatments

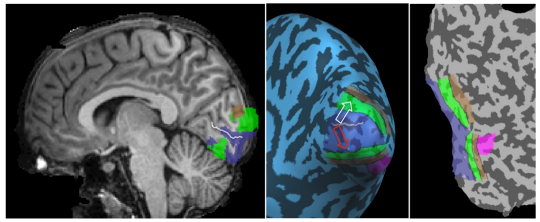
Multidisciplinary approaches including human social sciences, and methodological developments (optogenetics, reconstruction of neural networks, electrophysiology...)

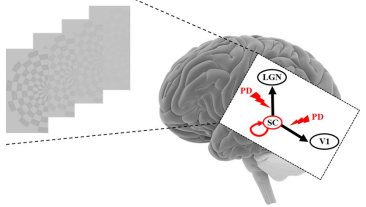












Superior Colliculus Dysfunction as a potential biomarker of Parkinson Disease

Michel Dojat

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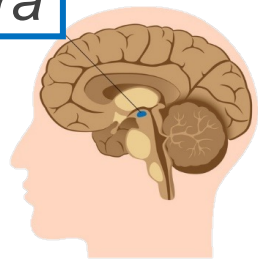
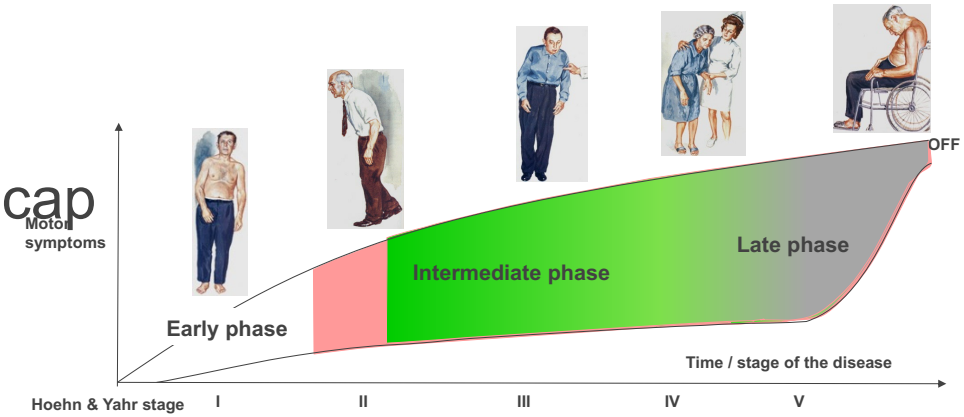
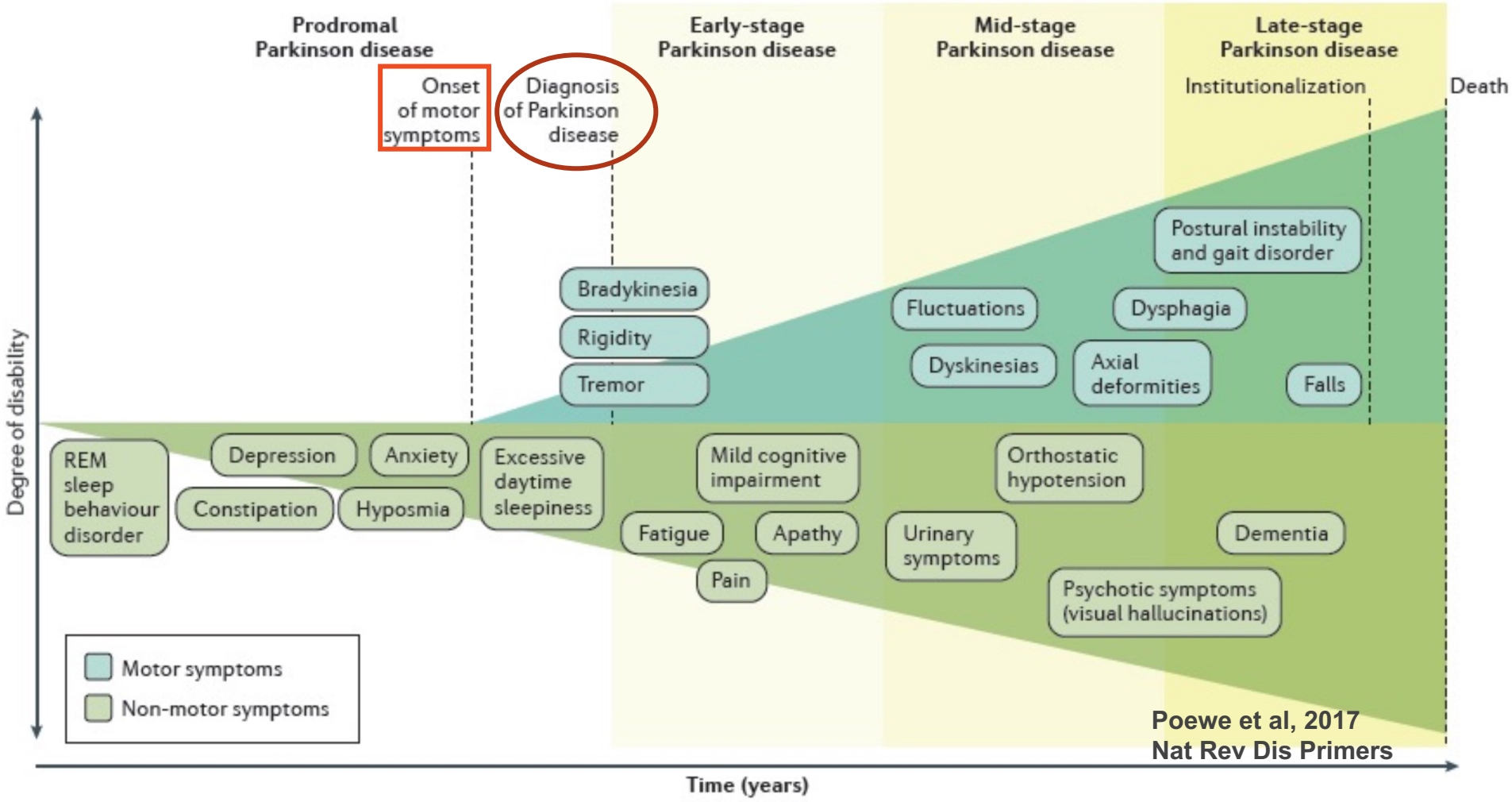
A brief introduction to PD-1

- Degenerative disease
- 10 million cases worldwide
- Loss of dopaminergic neurons in the *substantia nigra*
- Perturbation of other subcortical structures
- Multifactorial: genetics, environment, …
- Pre-motor (silent) phase
- Motor phase leading to handicap
- No cure, but symptom management



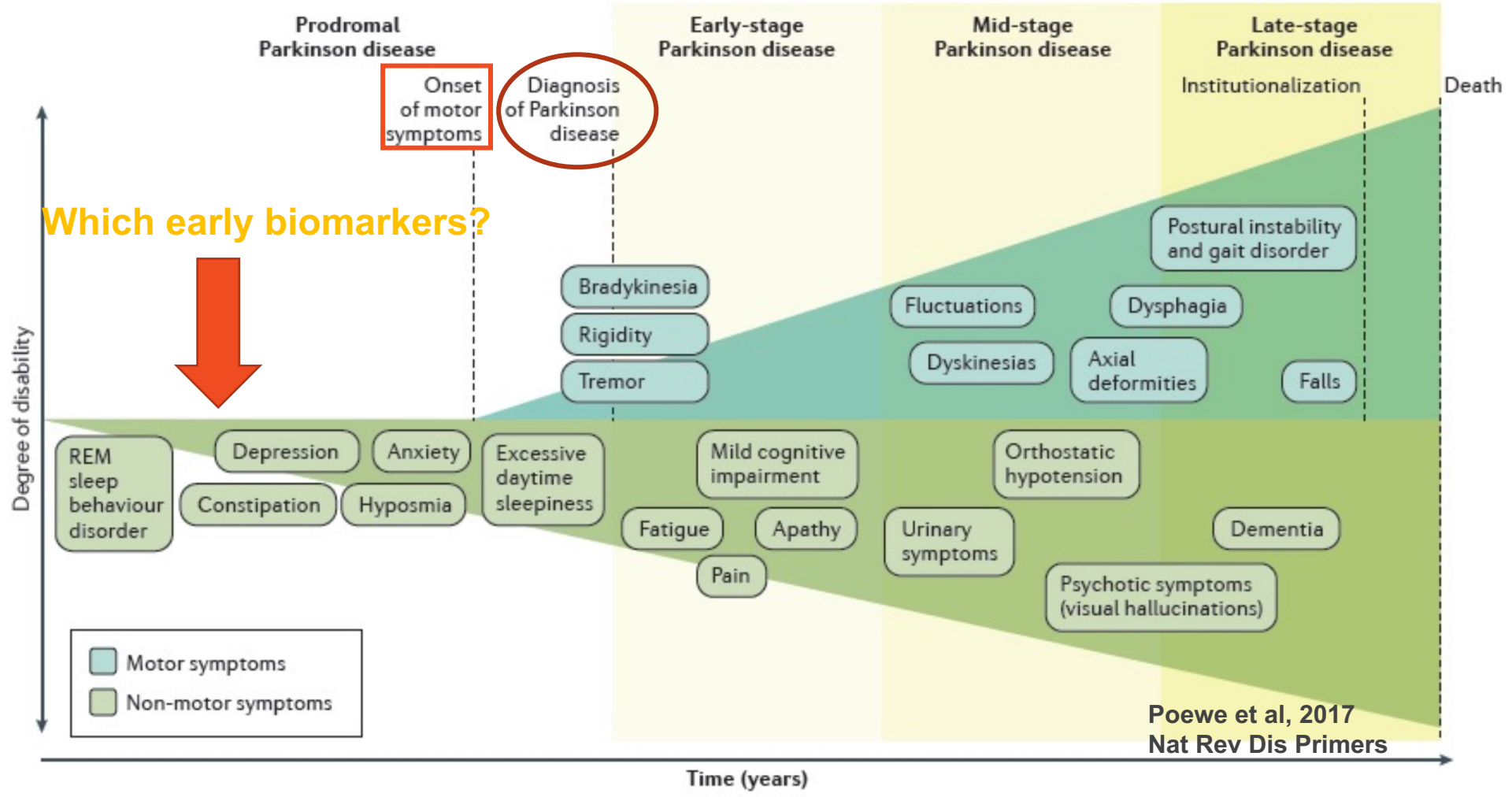


A brief introduction to PD-2



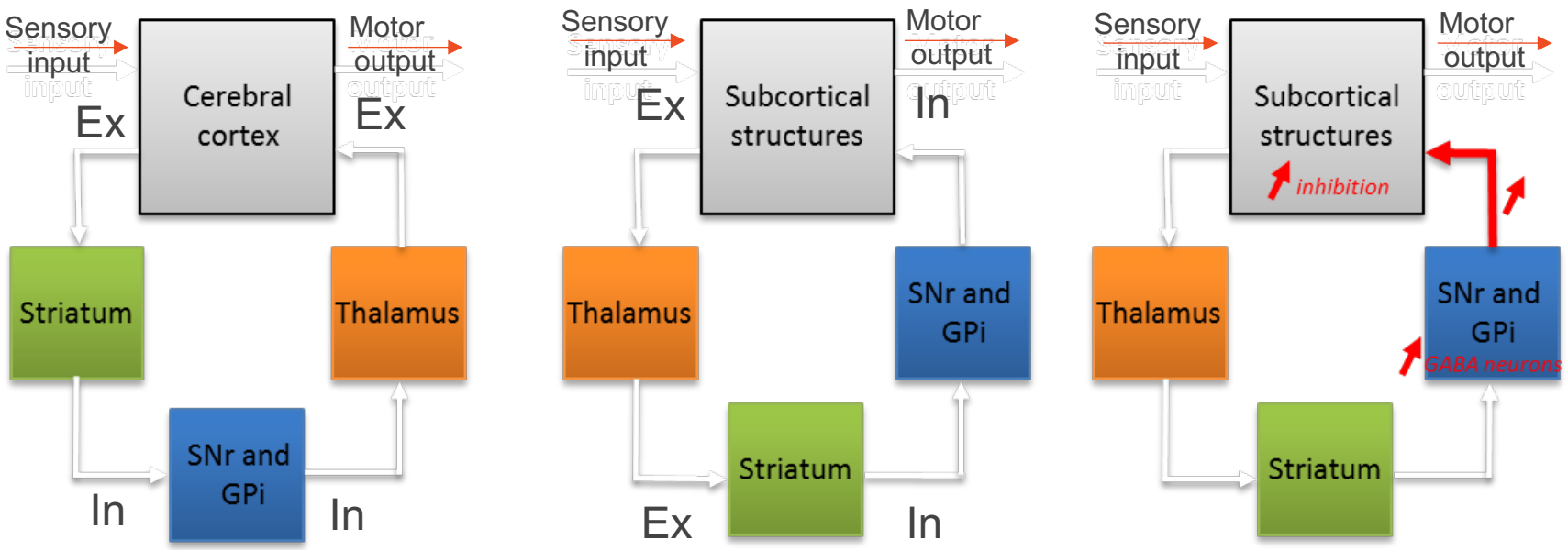
Poewe et al, 2017
Nat Rev Dis Primers

A brief introduction to PD-2



Poewe et al, 2017
Nat Rev Dis Primers

PD: Loop Deregulation



McHaffie et al Trends in Neurosc 2005

Colliculus => multi-sensory structure

Parabrachial complex => nociception

Pedunculopontine nucleus => gait control

Periaqueductal grey nucleus => nociception & avoidance behavior

The Colliculus

Superior Part

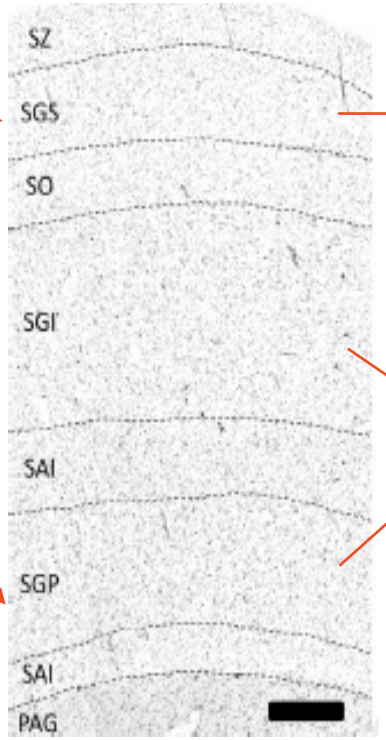
Vision

Retina
Parabigeminal nucl.
V1 et al.
FEF, LIP

Lower Part

Multi-Modalités

Cortical & subcortical regions (SNr, PPN, cerebellum ..)



LGN, Pulvinar ->MT/V5

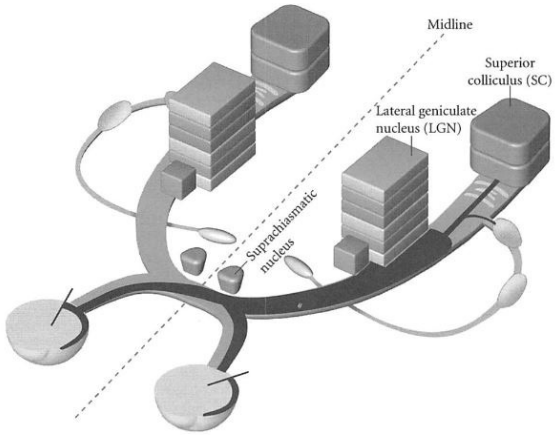
Selection of visual target
Directing attention

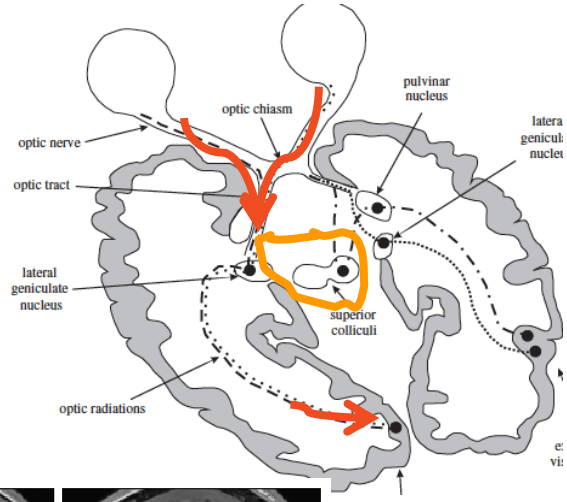
Motor output neurons

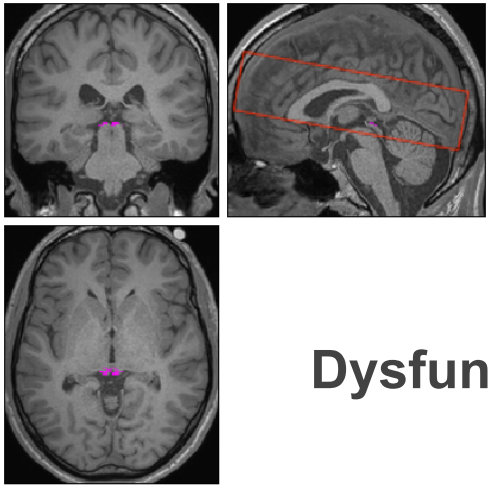
The SC has evolved to provide the brain with the location of targets and threats in the peripherical world.

[May Prog Brain Res 2006]

Superior Colliculus







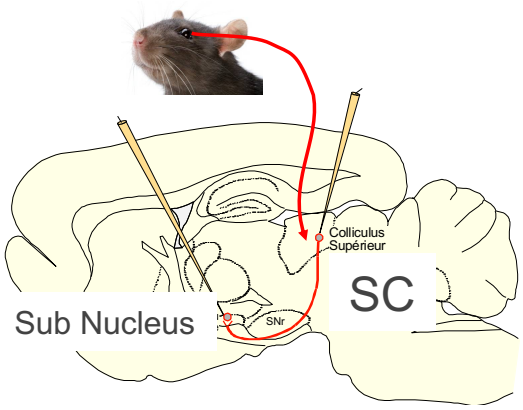
- Receive information directly from the retina
- Occular saccades control
- Attention focalisation
- Novelty detection
- Plannificiation and decision

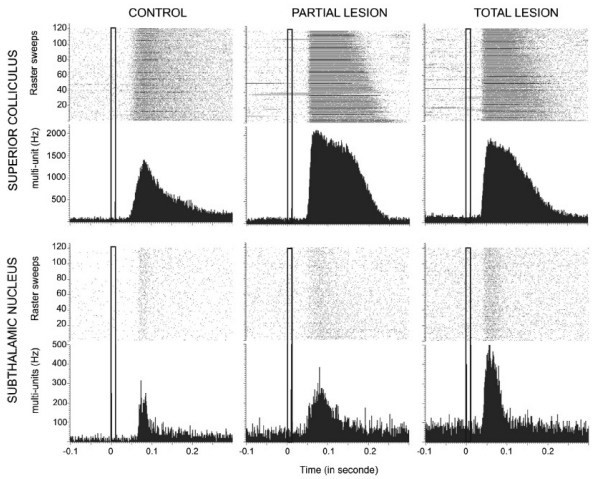
Dysfunction due to PD?

Superior Colliculus

Dysfunction due to PD? Yes in PD Rat's model

V. Coizet (CR, GIN)





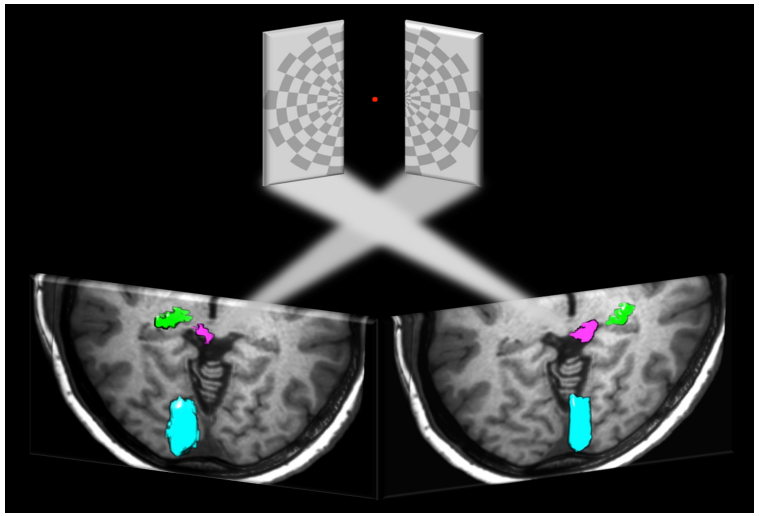
- Fonctionnel (Rolland et al. Neuroscience, 2013)

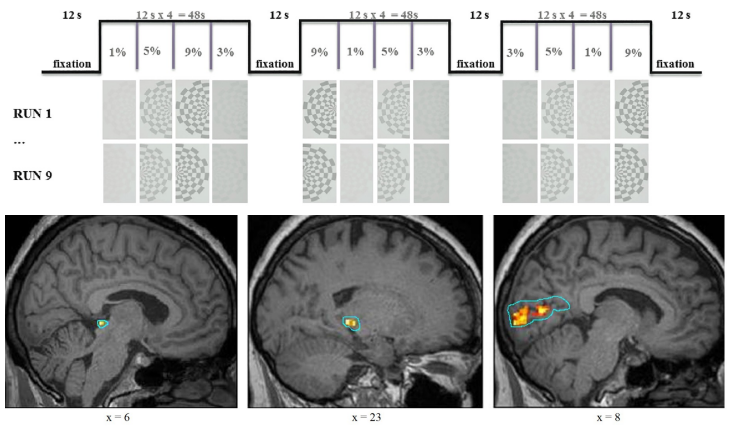
What's happen in Humans?

fMRI in Human - I

Some methodological difficulties

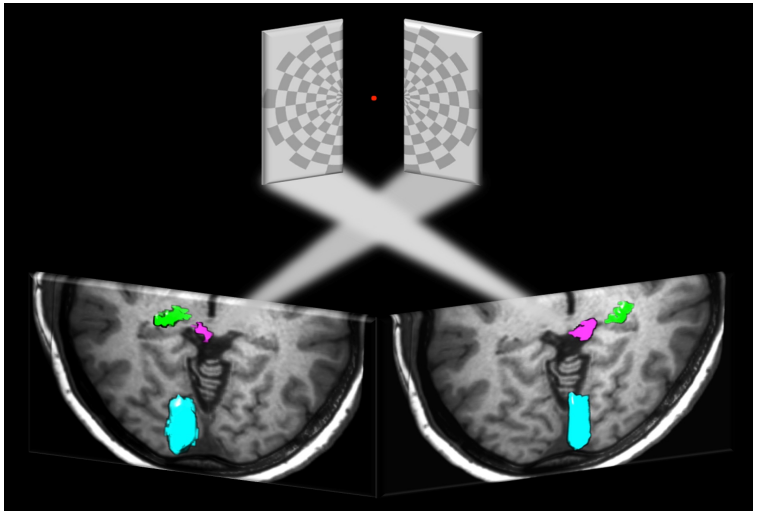
- small structure (≈10 voxels, 3T) => 1.5mm^3
- close to vein => Heart Rate signals as covariate of non-interest
- rapidly saturated

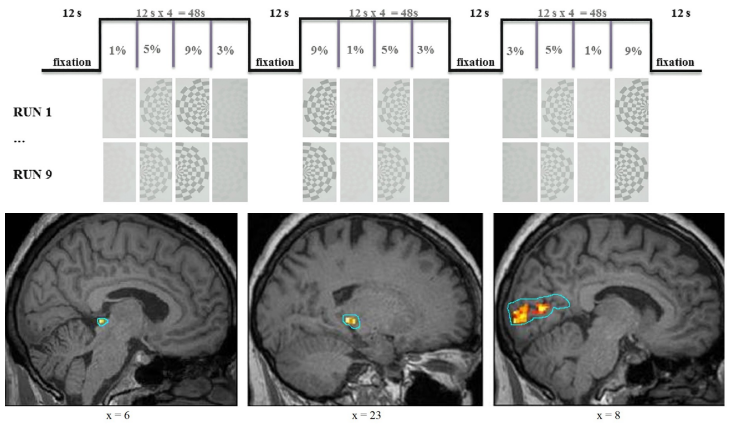




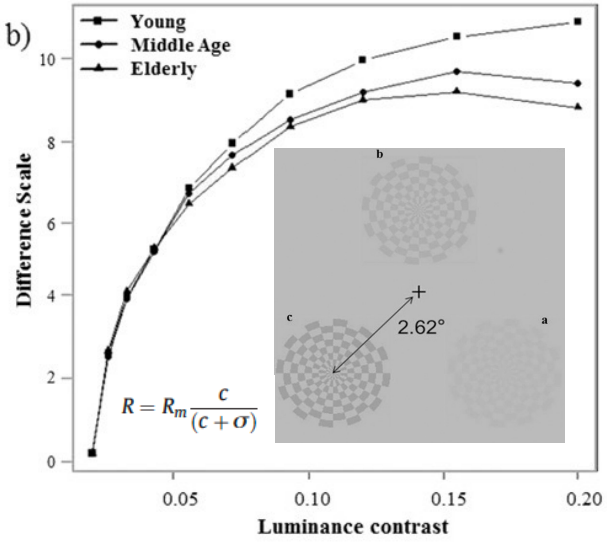
Bellot et al. Neuroimage 2016

fMRI in Healthy Subjects- II



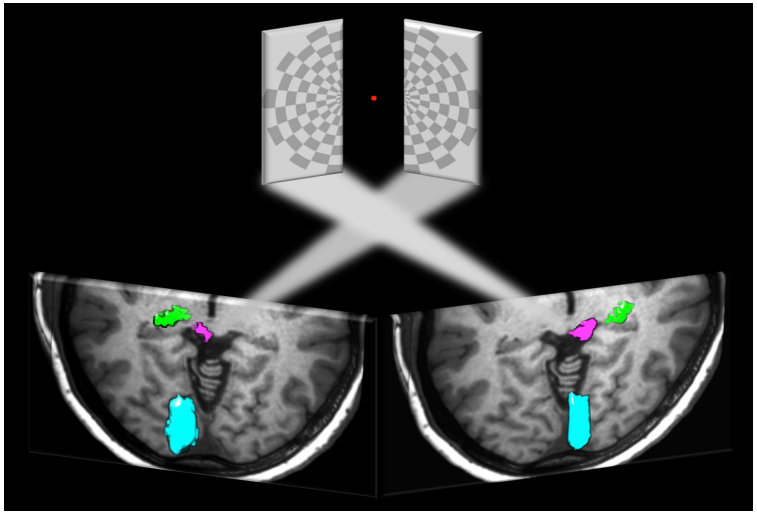


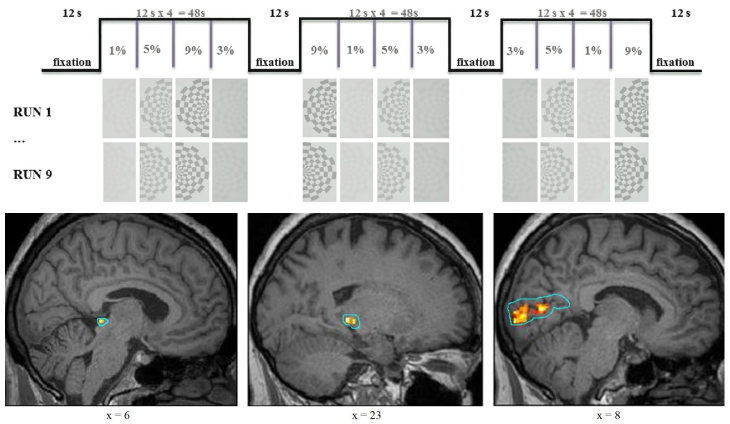
Bellot et al. Neuroimage 2016



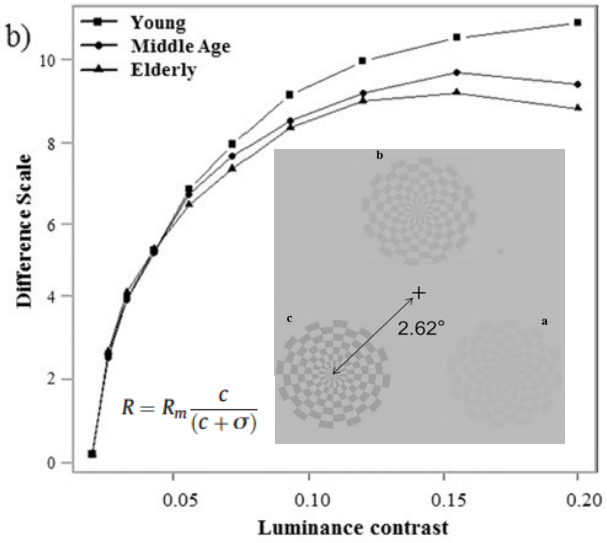
N=30

fMRI in Healthy Subjects- II





Bellot et al. Neuroimage 2016



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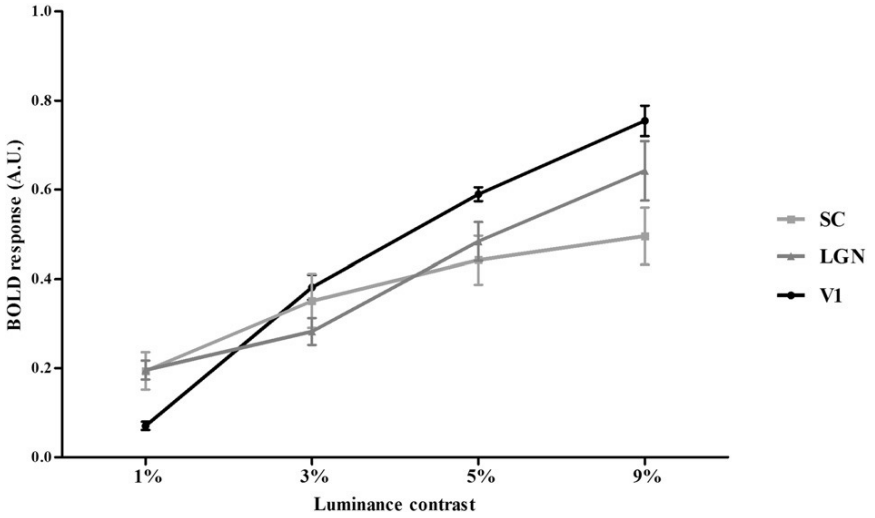
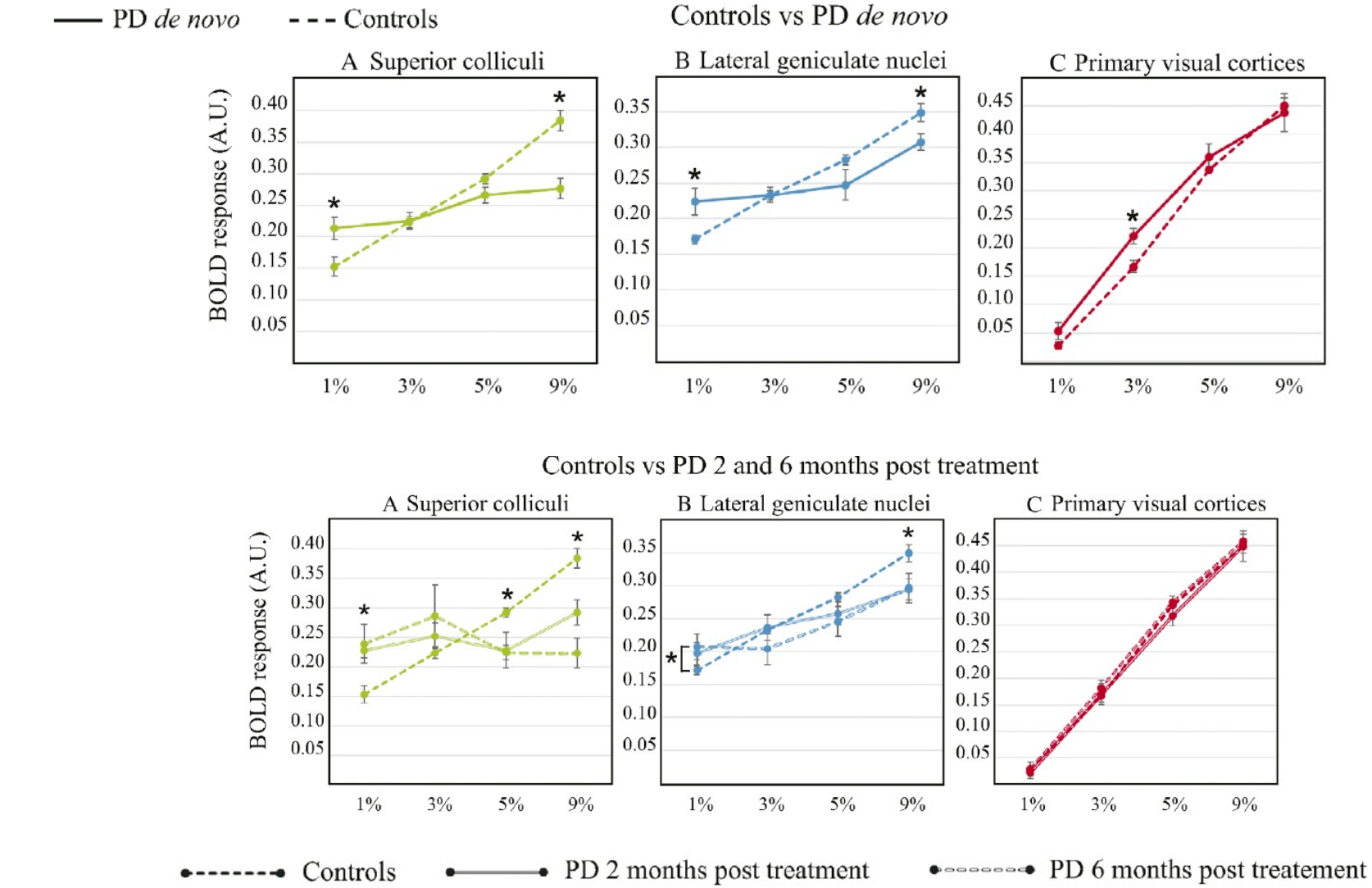


fMRI in PD Subjects

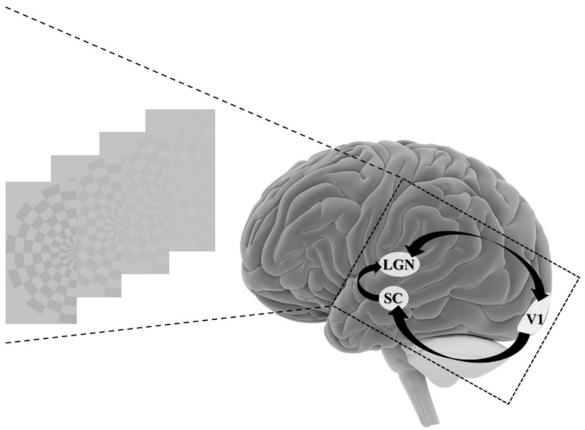
Moro et al. Ann Neuro 2020

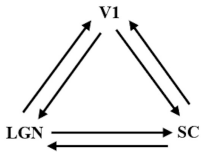
N=22



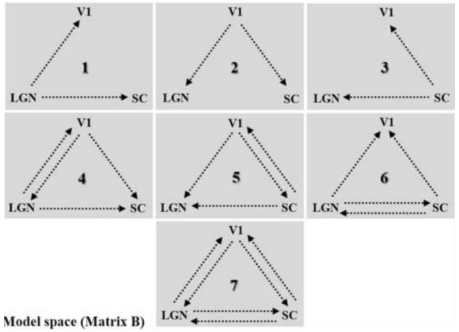
Dynamic Causal Modelling - I

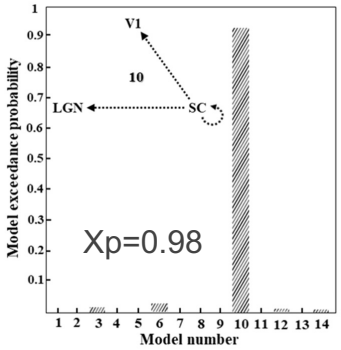
How information is processed?





14 models



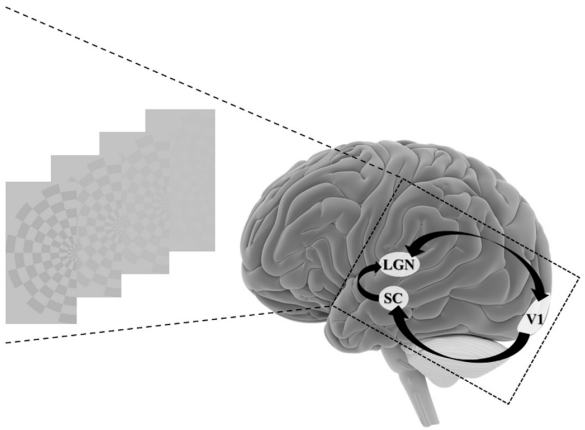


Controls

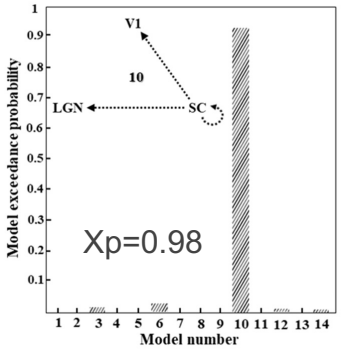
Bellot et al. NeuroImClin 2022

Dynamic Causal Modelling - II

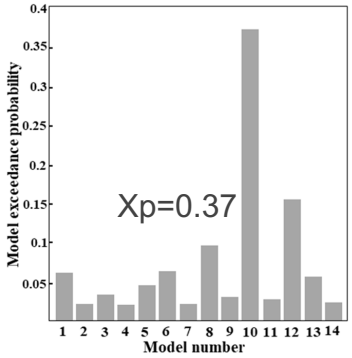
How information is processed?



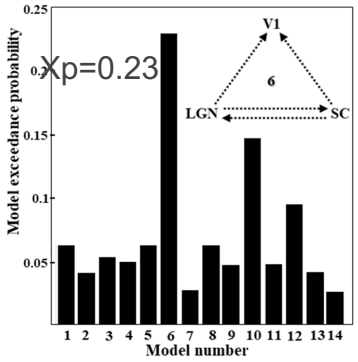
PD effects of functional connectivity?
Effect of L-Dopa treatment?



Controls



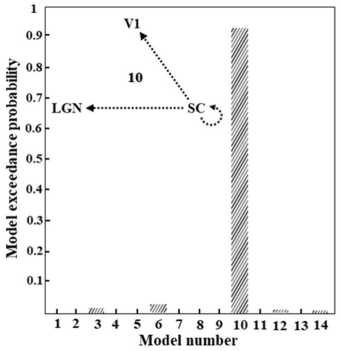
PD & PD+2m Ldopa



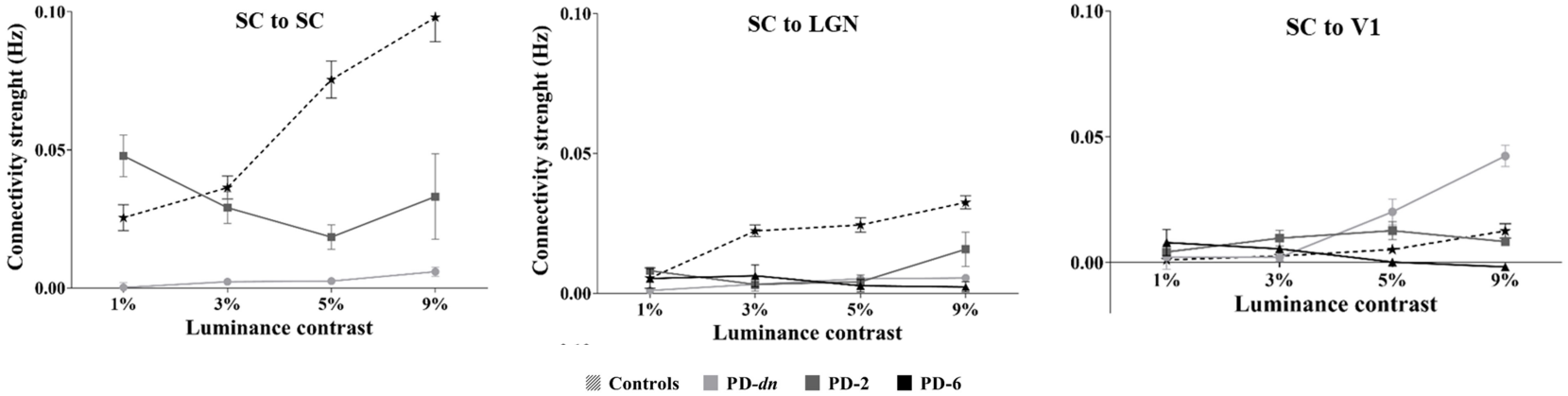
MP+ 6m Ldopa

Bellot et al. NeuroImClin 2022

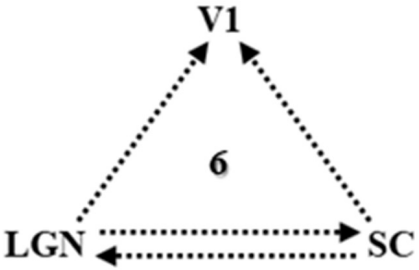
Dynamic Causal Modelling - III



Pivotal role of CS in controls and PD patients
Altered connection modulation except in SC-V1



Importance of LGN at 6m under Ldopa



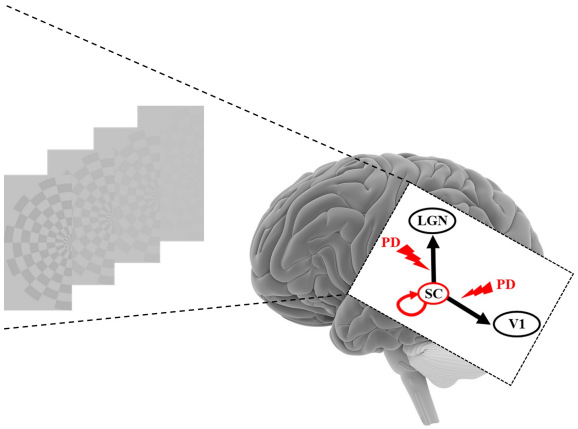
Bellot et al. NeuroImClin 2022

Conclusion

- In *de novo* Patients
  - Function role of V1 is preserved
  - Functional deficit of CS
  - Functional deficit of LGN
  - No functional restoration with 6-months L-dopa treatment

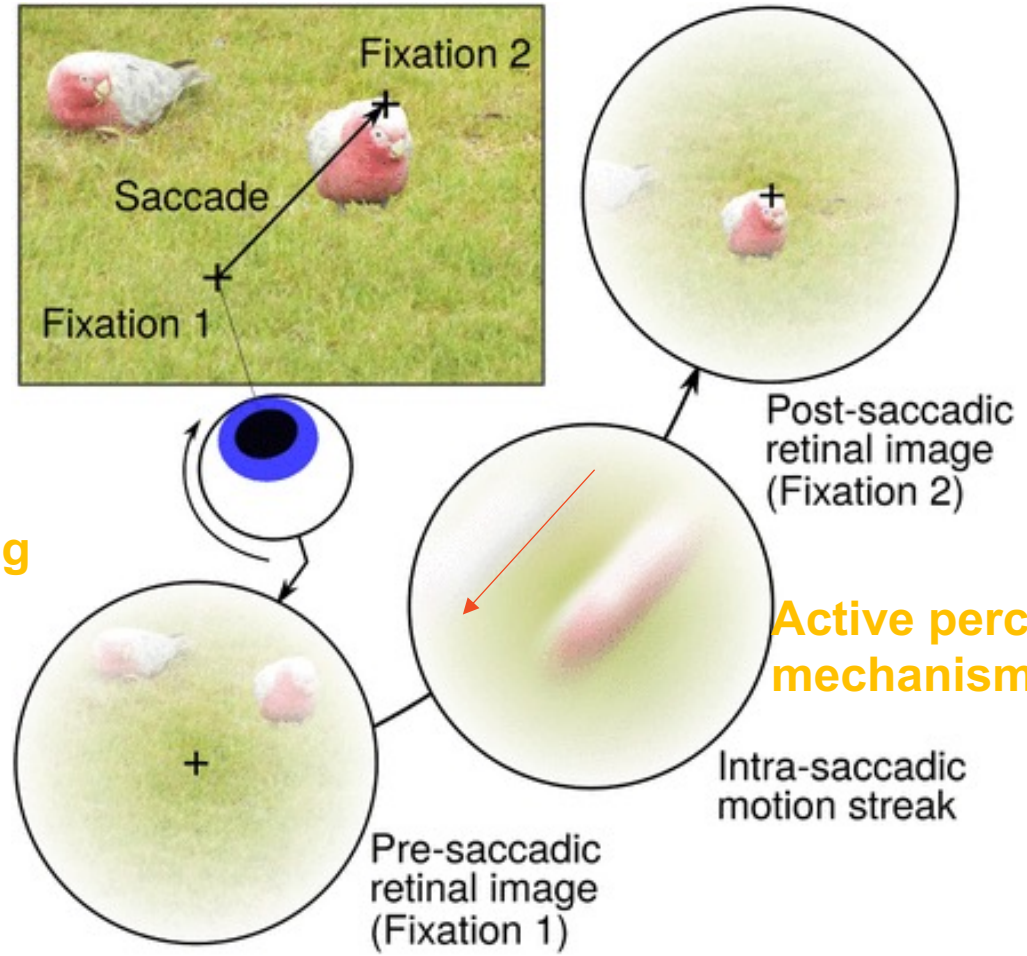
Non conscious deficit

Which Psychophysical tests for the diagnosis of such a deficit?



Scene perception

Brain construction of stable vision of the world



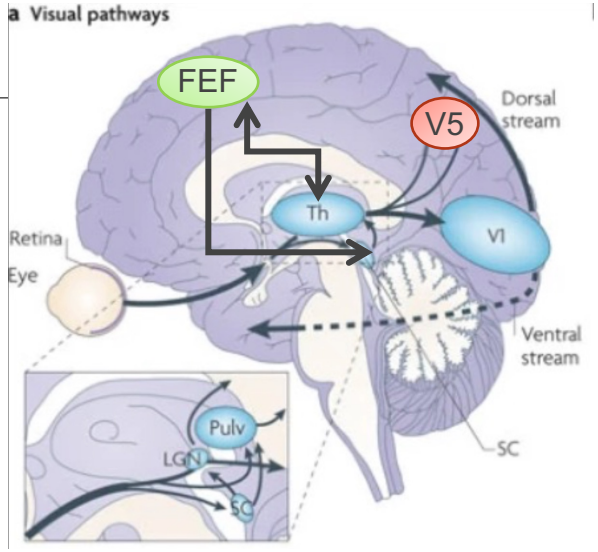
What's happen during Saccades?

Active perception mechanism suppression?

Motion perception during saccadic eye movements

Eric Castet and Guillaume S. Masson

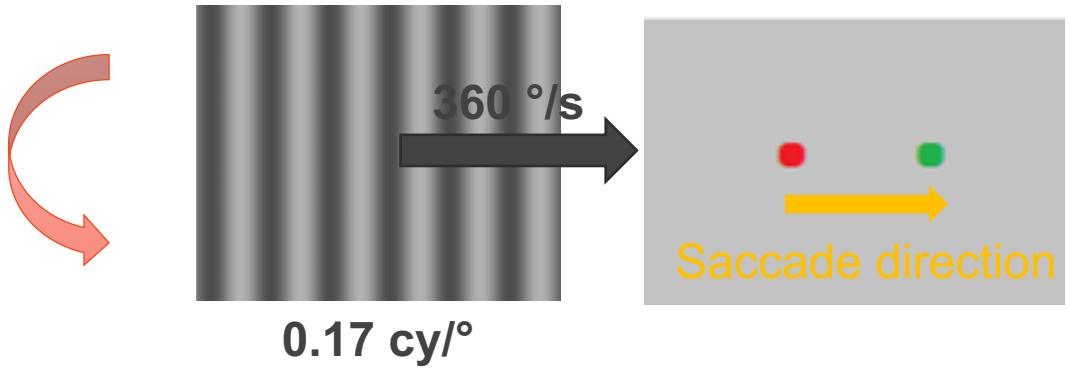
© 2000 Nature



Is effective when

✓ stimulus optimized to preferentially activated the magnocellular pathway
(motion detectors sensitive to a restricted range of spatio-temporal frequencies)

Stimulus : spatio-temporal progressive wave of **low spatial frequency** (0.17 cy/°) and **high velocity** (360 °/s) moving in the same direction as the saccade



Psycho-physique experiment

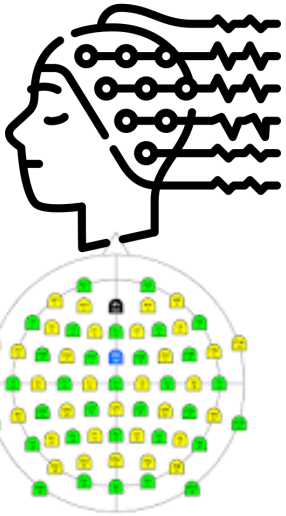
Cortical support of this perception?

PhD G. Nicolas

Coll. A. Guérin-Dugué – PhD: G. Nicolas

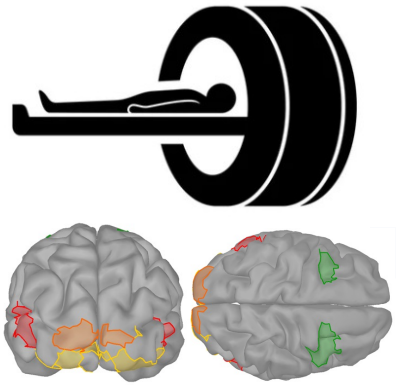
- Hypothesis H1:
  - Implication of V1-V2, MT-V5 when subjects see the motion of the stimulus during the saccade.
- Methods:
  - 49 participants
  - EEG, ET, MRI

EEG



64 sensors

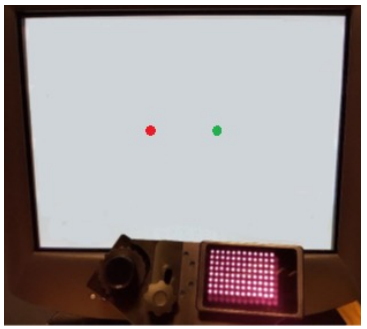
MRI



Nicolas et al
HBM 2022

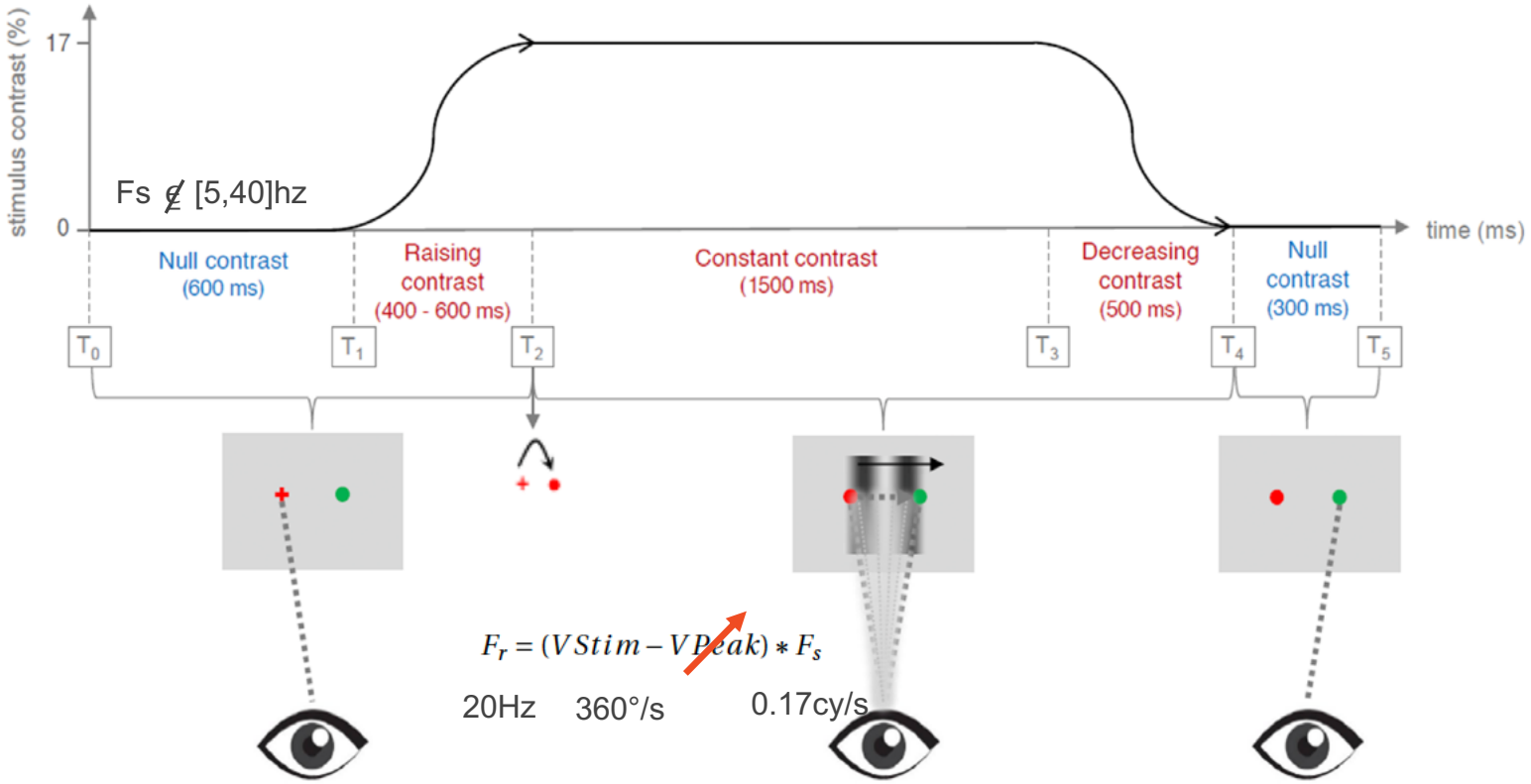
Eye-tracking

Distance to the screen
= 68 cm

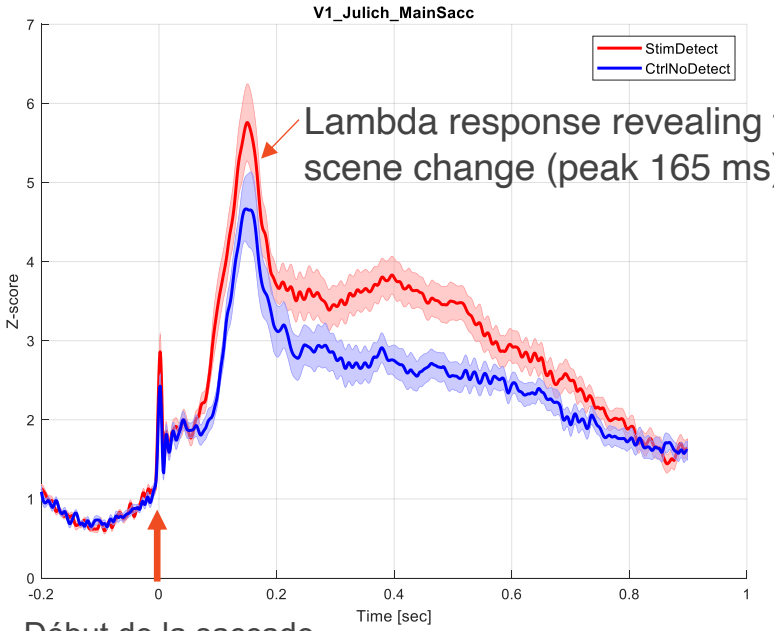


Protocol

- **Condition of interest** : perception of the stimulus motion with stimulus moving from left to right
- **Control condition** : no perception of the stimulus motion with stimulus moving from bottom to top

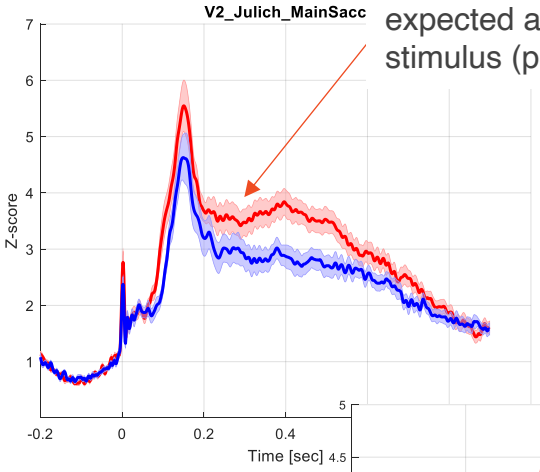


Magnocellular pathway involvement

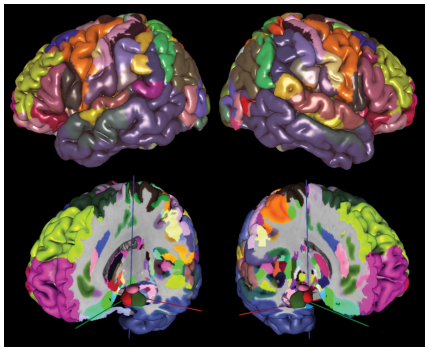


Lambda response revealing this visual scene change (peak 165 ms)

Début de la saccade

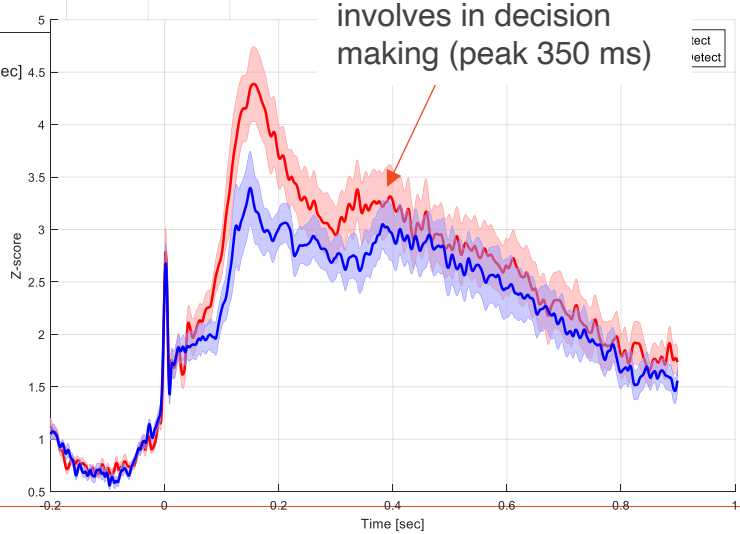


reveals discrimination processes between an expected and an unexpected stimulus (peak 240 ms)



Amunts et al., (2020)

Nicolas et al JOV 2021



involves in decision making (peak 350 ms)

Conclusion

- These findings could provide an additional argument in favor of the perception of motion during saccades.
- Magnocellular pathway activativation.
- In normal condition, what's happen in PD?
  - Hypothesis H2: Intra-Saccadic Motion perception is altered in PD patients
  - Two students A Deverin (June-Sept 2021) & P. Perelle Avr-July 2022 have improved the Stimulus presentation
  - Master 2023:
    - Intra-saccadique motion perception; Acquisition and analysis of oculometric signals

PD & Hallucinations

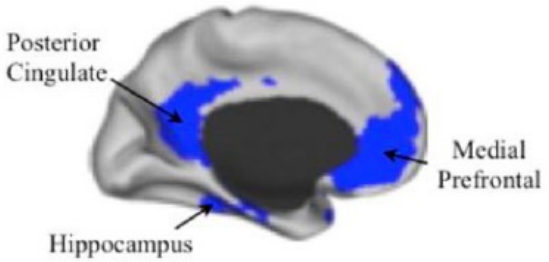
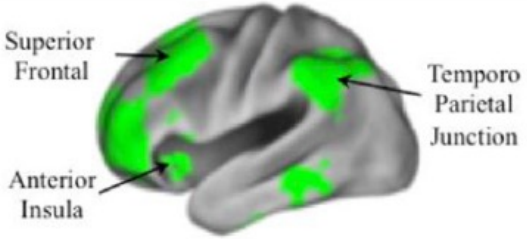
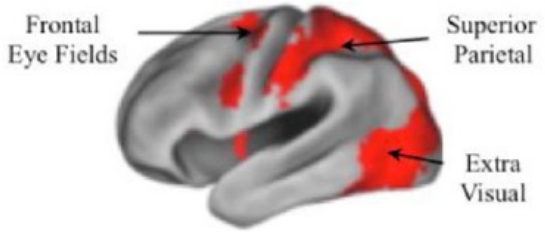
What we know

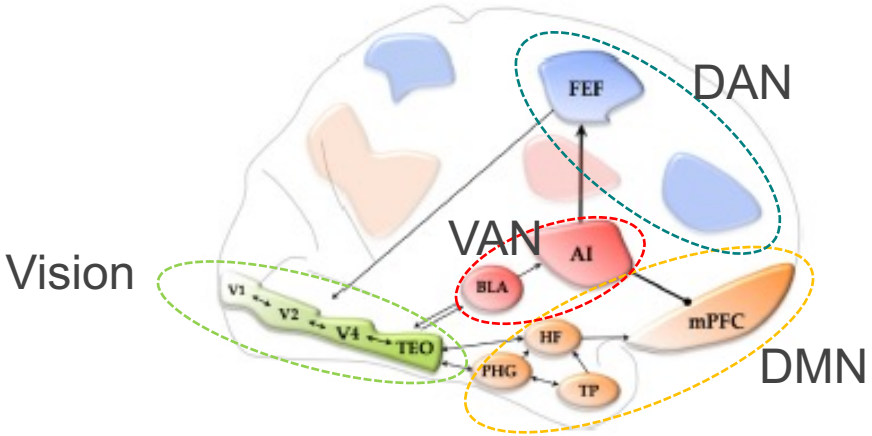
- Frequent: 20– 40 % (Diederich et al Nat Rev Neurol 2009)
- No fully due to adversariel effect of L-Dopa (Fénelon et al Neuro 2006, Fénelon et Alves J Nerol Sci 2010)
- Associated to dementia risk
- Associated to sleep disorders (cf I. Arnuff)
- Visual, Presence feeling, Multi-modal

What we hypothesis

- Due to perceptual and attentional deficits

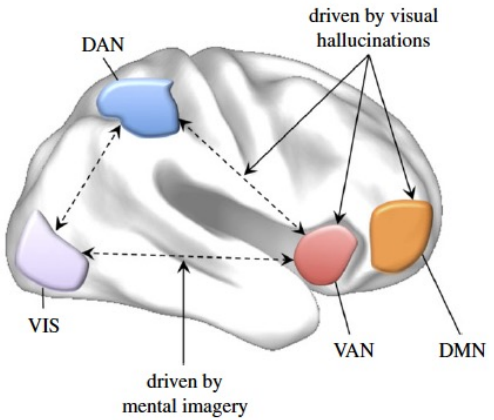
DMN, VAN & DAN & Vision

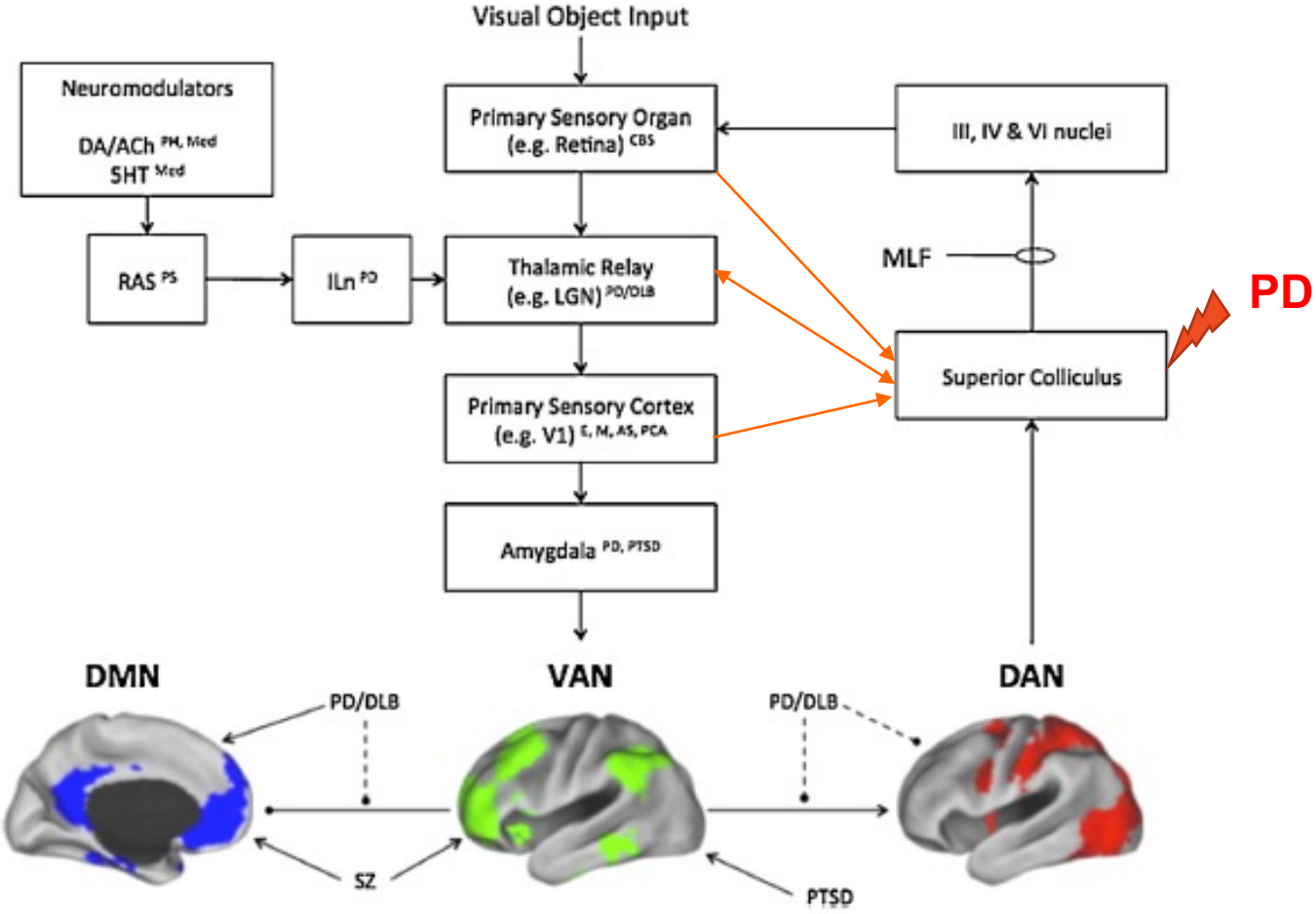
Default Mode Network	Ventral Attention Network	Dorsal Attention Network
		
Task-independent thought **Mind wandering**	**Mediate activation of other networks** **Engages attention to salient stimuli**	**Voluntary orienting** **Cognitive information processing**



Neural mechanisms for Visual Hallucinations

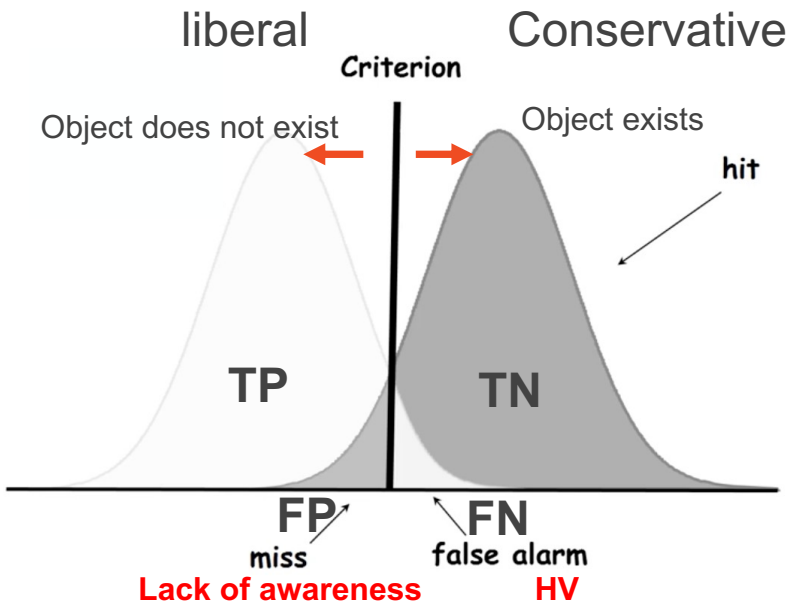
Impairement communications between DMN, DAN & VAN





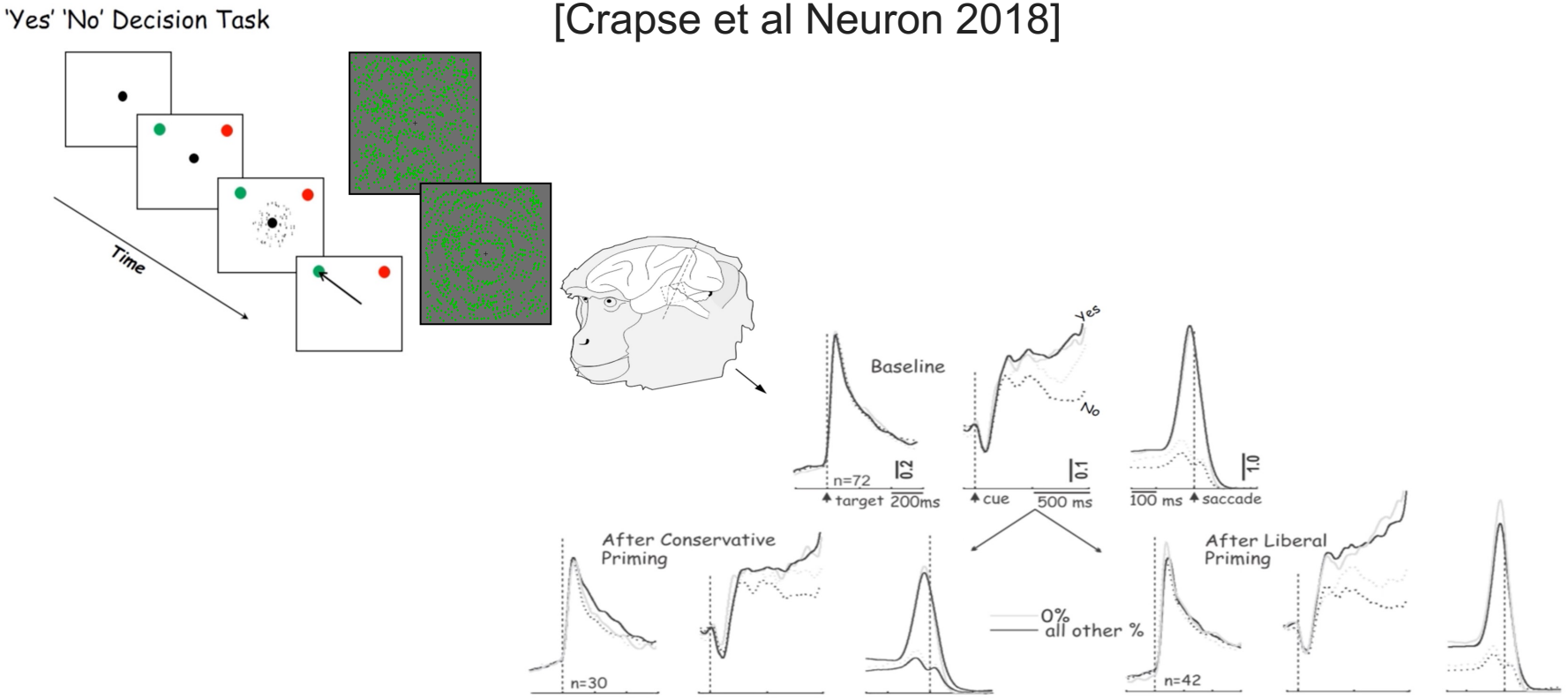
[Shine et al Prog NeuroBio 2015]

Decision criteria



Role of SC in Decision Criteria

[Crapse et al Neuron 2018]



Activity difference decreases

Activity difference increases

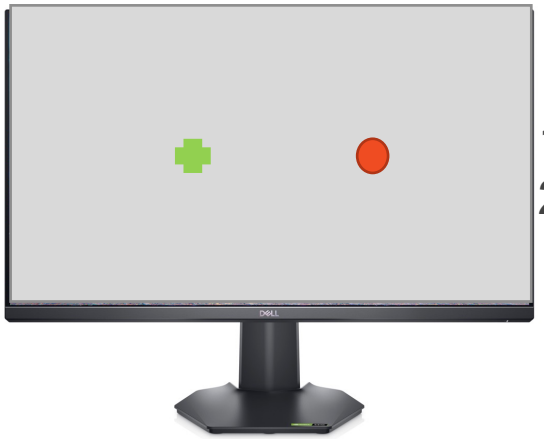
Manipulation of SC activity alters the decision criteria

Hallucinations in PD

- H3: More Alteration of SC => More Hallucinations
  [Dolgov & McBeath, Behav Brain 2005]

Future study

- Test PD w. and wo. HV
- Compare to HC age paired



1920x1080
27”

Anna Castrioto
Eugénie Lhommée

Other early biomakers –I - Structural

No Structural Differences Are Revealed by VBM in 'De Novo' Parkinsonian Patients

Verónica Muñoz Ramírez[a,b], Florence Forbes[b], Pierrick Coupé[c], Michel Dojat[a]

MEDINFO 2019 © 2019 International Medical Informatics Association (IMIA) and IOS Press.

Structural T1-w MRI of:

- 144 de novo PD patients (age: 61.30 ± 9.06; sex: 53 F, 91 M)
- 66 healthy controls (age: 60.12 ± 11.39; sex: 23 F, 43 M)

acquired with a 3T Siemens Trio Tim scanner

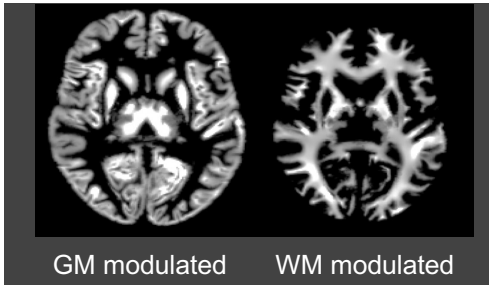
PARKINSON'S PROGRESSION MARKERS INITIATIVE

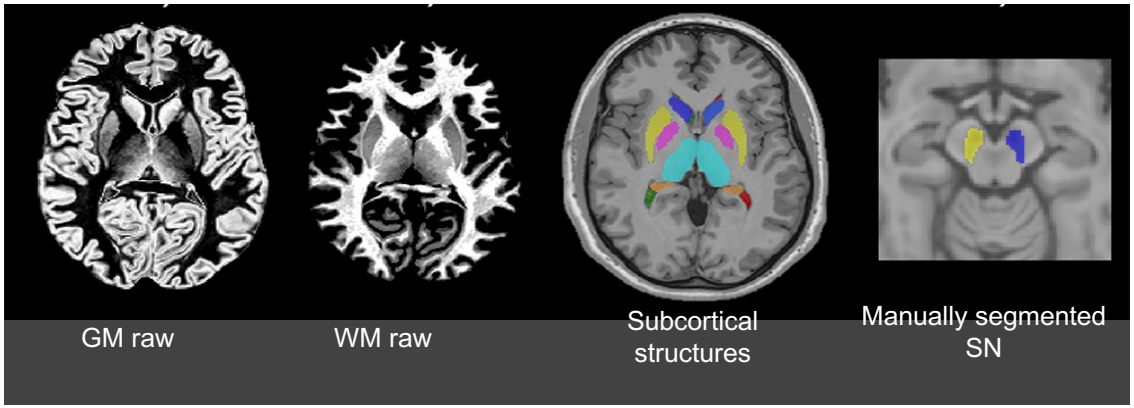
cat Computational Anatomy Toolbox

Jena University

volBrain

IBIME, UPV, Spain
LaBRI, Univ. de Bordeaux, France





Other early biomakers –II - Structural

Image modality	Region	Preclinical and prodromal PD	Early-stage PD	Moderate to late-stage PD
T1-weighted structural MRI	NA	+	++	++
Dopaminergic PET/SPECT	Striatum	+	+++	+++
Non-dopaminergic PET	NA	++	++	++
Metabolic and network imaging	NA	+++	+++	+++
Iron-sensitive MRI	SN	+	++	+++
Free-water imaging	aSN	–	–	++
	pSN	++	+++	+++
Neuromelanin-sensitive MRI	aSN	–	–	++
	pSN	++	+++	+++

Mitchell et al. Jama Neuro 2021

Imaging modality	Disease-state biomarker	Progression biomarker	Clinical application and potential limitations
T1-weighted structural MRI	Potential disease-state biomarker in preclinical, prodromal, early-stage, and moderate to late-stage PD	Potential progression biomarker in early-stage and moderate to late-stage PD (detected >18 mo)	PD-specific progression effects require long follow-up periods

Other early biomakers –III - Structural

- Subtle differences
- Few-shot learning

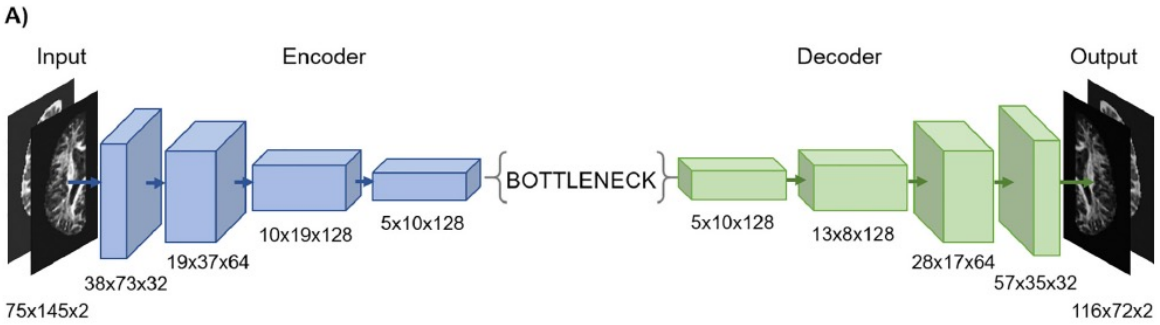
Other early biomakers –III - Structural

Subtle differences
Few-shot learning

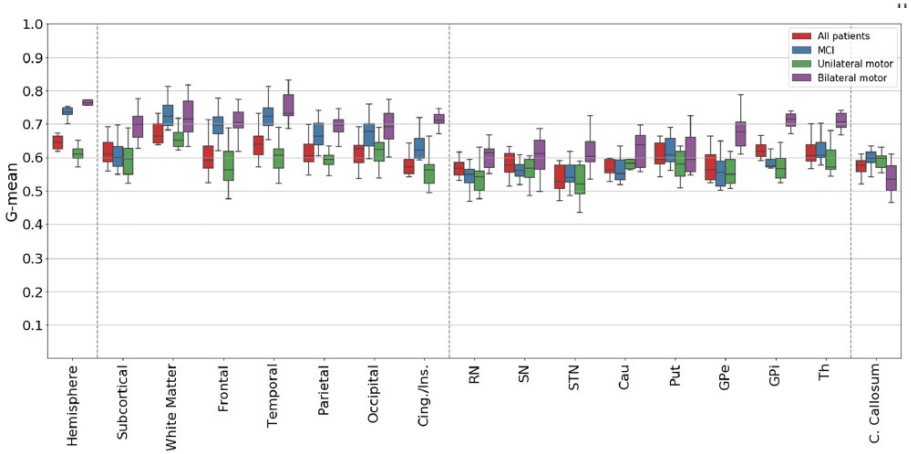
DTI (MD, FA)

Training on healthy subjects (Tr: 41; Te: 15)

Variational Auto-Encoder

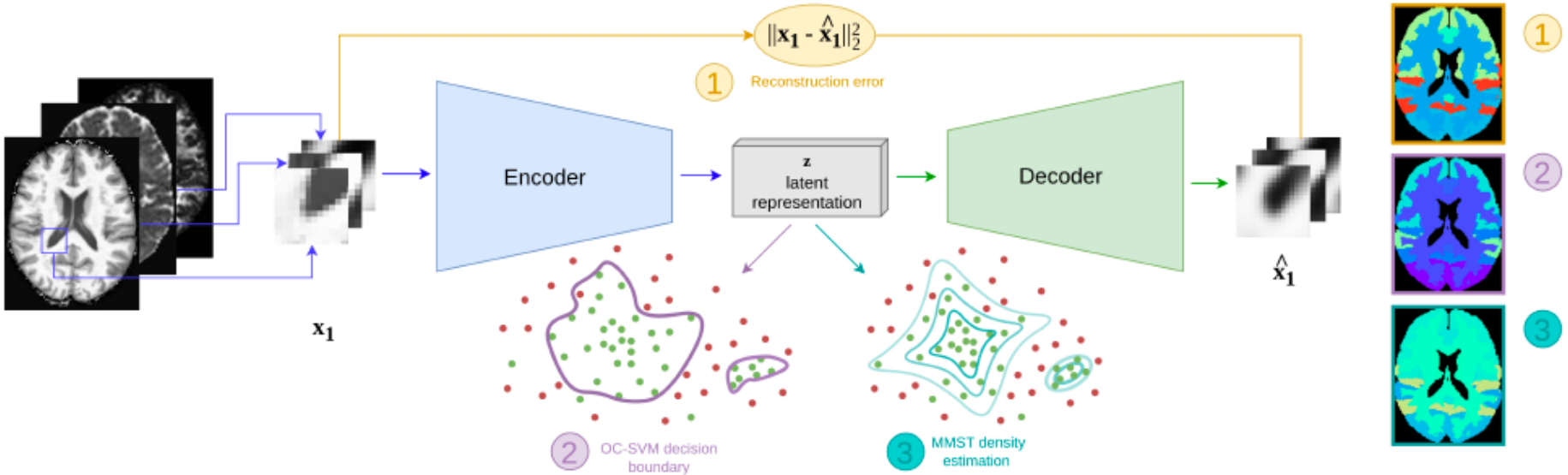


Reconstruction PD patients
Anomalies detection

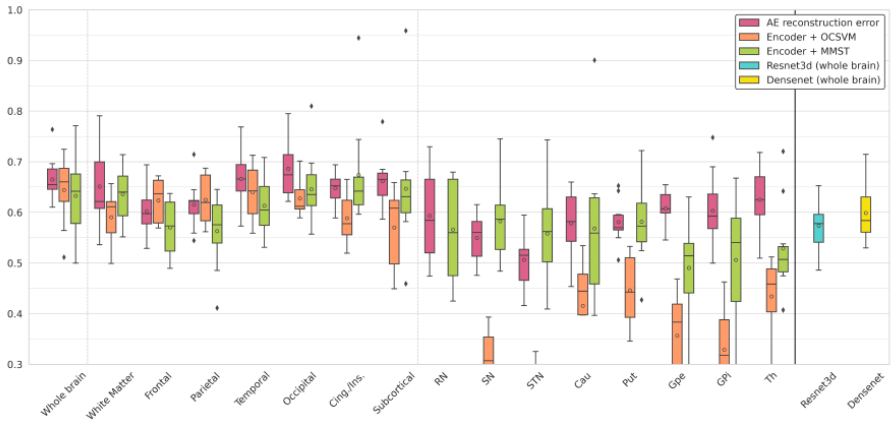


Munoz-Ramirez et al. Art Int Med 2022

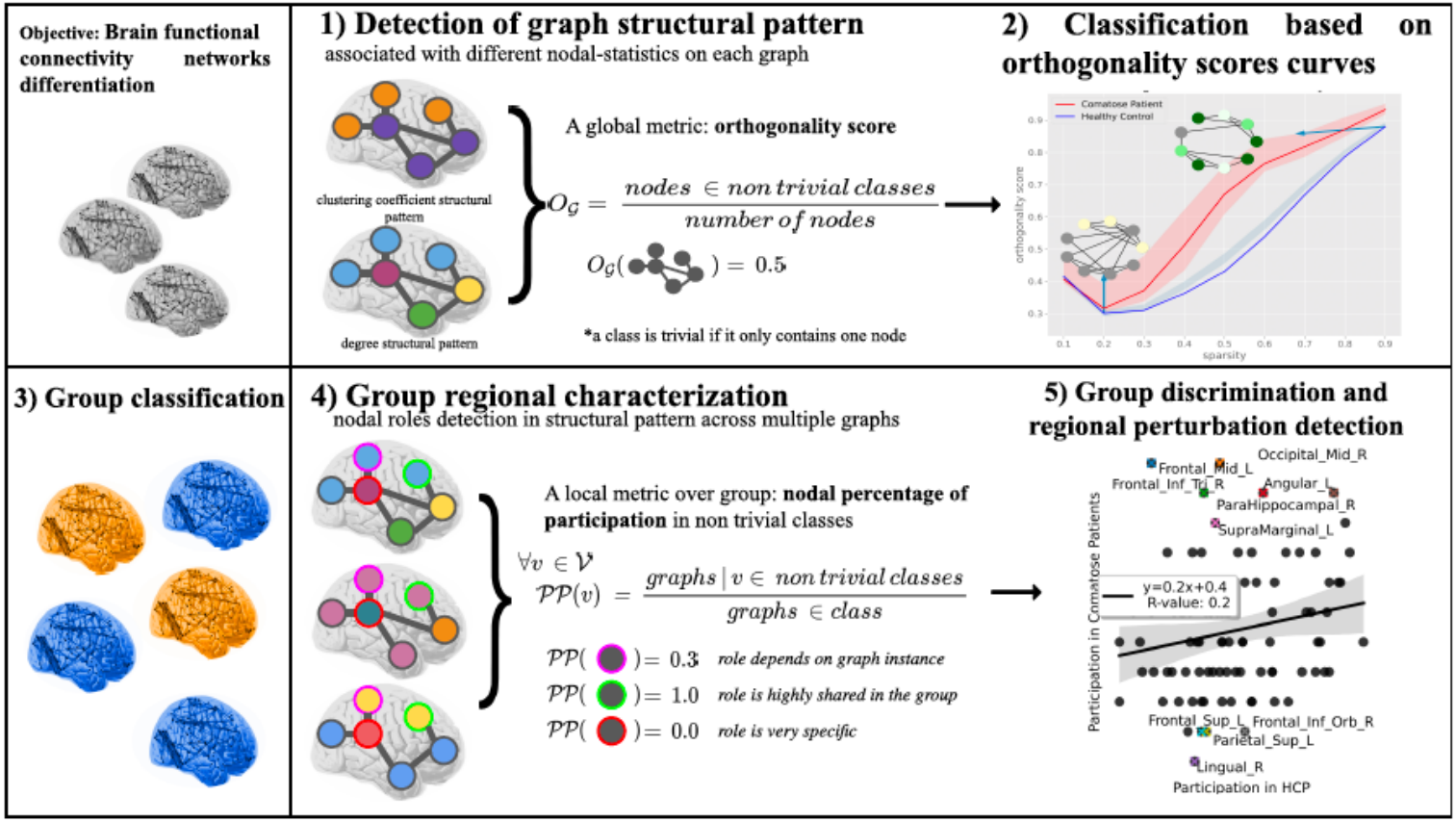
Other early biomakers –IV - Structural



Pinon et al. Isbi 2022



Other early biomakers –IV – Resting State & Functional Connectivity Graph



Carboni et al Phy Lett E 2013

PD patients w. wo HV

Marques Ana P Park Dis 2020

Sponsors

Fondation de l'Avenir
Accélérateur de progrès médical

France Parkinson

financé par
IDEX Université Grenoble Alpes

NeuroCoG
Univ. Grenoble Alpes

MIAI
Grenoble Alpes

FLI
France Life Imaging

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CREATIS

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