Advancing from MRI Biomarkers to an Integrative Exploration of the Gut-Brain Axis in Parkinson Disease: Past, Present, and Future Directions

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RÉPUBLIQUE FRANÇAISE
Liberté Égalité Fraternité

INRAE

INRAE objectives

People

- 8200 agents = 2000 scientists / 3000 engineers

National research public institute

- Agriculture, Food and Environment
- Many overlapping themes
- Food / Global health

“The goal is to understand the links between **human health, food, and the environment** to improve the sustainability of food production, food health benefits, and the accessibility of healthy diets”

How do environmental factors intersect with Parkinson's disease (PD) ?

Multifactorial origin with a combination of

- Genetic predisposition factors
- Environmental factors

Increased risk for exposition to

- Pesticides

  PD was recognized as an occupational disease in agriculture professionals in France in 2012
- MPTP analogs

  Contaminant of illicit narcotics
- Metals

  e.g. Manganese intoxication of minors

  See Ball et al. (2019) 10.3389/fneur.2019.00218

How do diet intersect with PD ?

Decreased risk for

- General healthy dietary patterns
- Mediterranean diet
- MIND diet

  Hybrid of the *Dietary Approaches to Stop Hypertension* (DASH) diet and the Mediterranean diet

- Intake of berries

  Beneficial for women but not for men
  … also coffee and tobacco/nicotine !

See Knight et al. (2022) 10.3390/nu14214472

AgroResonance lab

Infrastructure devoted to MRI

- Microscopy
- Pre-clinical on small animals
- Low field magnets

AgroResonance

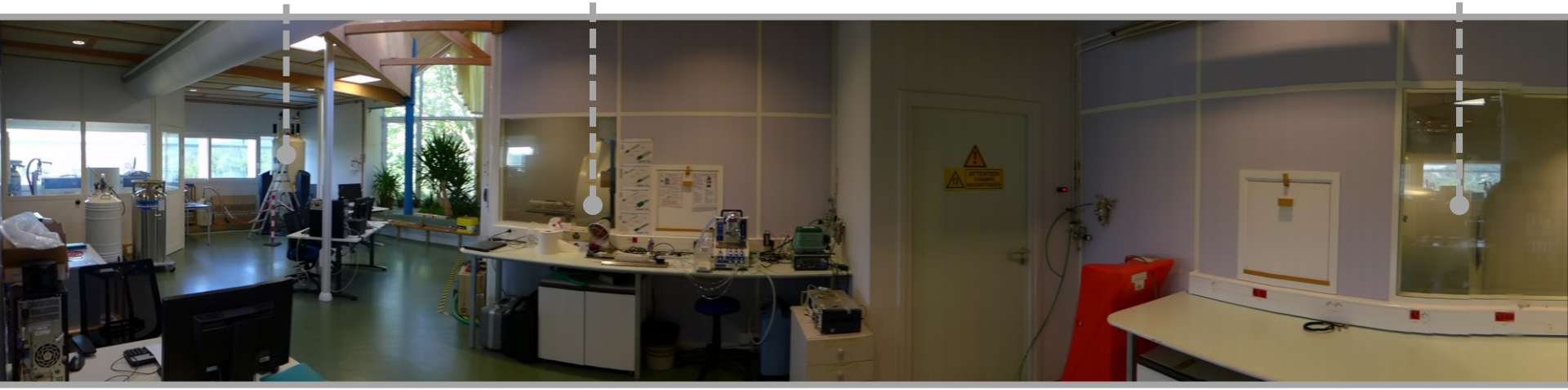
80 volcanoes designated as UNESCO World Heritage sites

Magnetic fields / Targets

in cellulo
9.4T

in vivo rodents
11.7T

in processo
4.7T



In situ
0.3T

in vivo human
3T

Why is MRI highly beneficial for extracting biomarkers of human brain disorders?

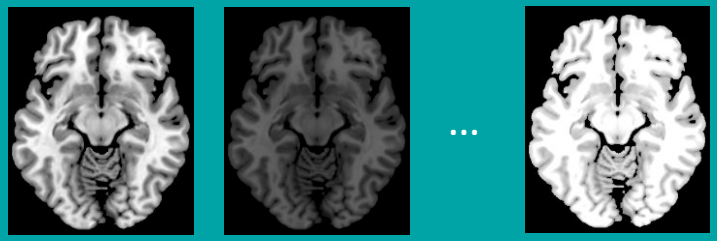
Multi-parametric

- Concentration of spins
- Static spin motions
- Diffusive spin motions
- Chemical exchange
- Nuclei = Mostly 1H but 23Na/19F valuable

MRI signal

- Non linear mixture of several parameters

Classification challenges



p-parameters mapping for each group of subjects

ROI segmentation – size n

Spatial/parameter matrix for each subject
Size n x p

Single parameter (p=1)
Averaging over ROI (n=1)

What we did !

Multiple parameters
Averaging over ROI (n=1)

What we have seen yesterday

See e.g. Péran et al. (2018)
10.1002/mds.27307RESEARCH

Multiple parameter
Spatial information

What we would like to do …

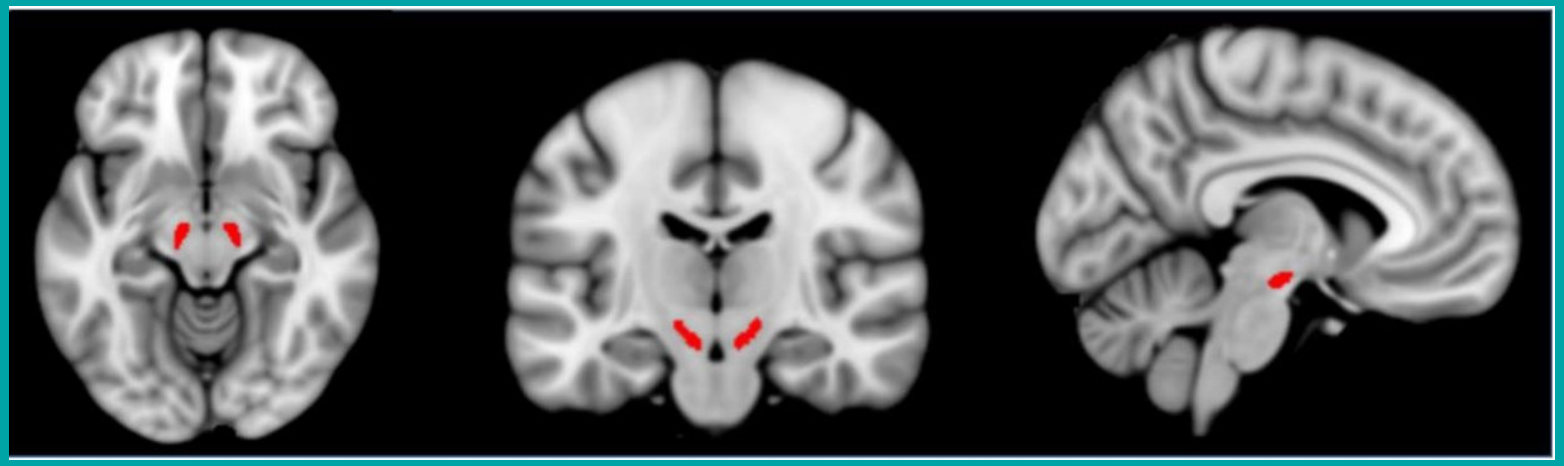
See e.g. Gore et al (2023)
10.1016/j.mex.2023.102359

Iron in the brain

Concentration of iron

- Increase from 30 to 100 % in the substantia nigra (SN) of PD patients
- Iron storage ⇨ oxidative stress / aggregation of alpha-synuclein
- Cause or a consequence of neuronal loss ?

See Foley (2022) 10.1007/s00702-022-02505-5



SN location from Zhang et al. (2017) 10.7554/eLife.26653

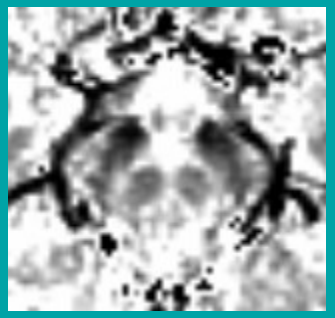
MRI of iron

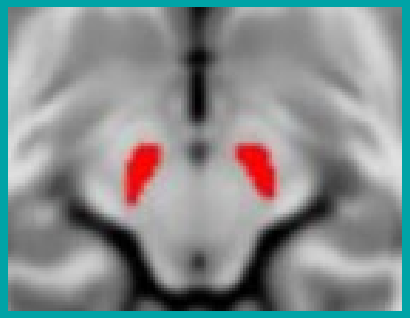
Iron

- Different chemical forms
- Paramagnetic ions

T2* apparent relaxation time

- $R2^* = 1/T2^* = R2^*_b + k[Iron]$
- $R2^*$ can be mapped within all the brain
- k = relaxivity / magnetic field dependent





$R2^*$

OPEN ACCESS Freely available online

PLOS ONE

Is R_2* a New MRI Biomarker for the Progression of Parkinson's Disease? A Longitudinal Follow-Up

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Abstract

Purpose: To study changes of iron content in basal ganglia in Parkinson's disease (PD) through a three-year longitudinal follow-up of the effective transverse relaxation rate R_2*, a validated MRI marker of brain iron content which can be rapidly measured under clinical conditions.

Methods: Twenty-seven PD patients and 26 controls were investigated by a first MRI (t_0). Longitudinal analysis was conducted among the 18 controls and 14 PD patients who underwent a second MRI (t_1) 3 years after. The imaging protocol consisted in 6 gradient echo images obtained at different echo-times for mapping R_2*. Quantitative exploration of basal ganglia was performed by measuring the variation of R_2* [R_2*(t_1) – R_2*(t_0)] in several regions of interest.

Results: During the three-year evolution of PD, R_2* increased in Substantia nigra (SN) (by 10.2% in pars compacta, $p = 0.001$, and 8.1% in pars reticulata, $p = 0.013$) and in the caudal putamen (11.4%, $p = 0.011$), without significant change in controls. Furthermore, we showed a positive correlation between the variation of R_2* and the worsening of motor symptoms of PD ($p = 0.028$).

Conclusion: Significant variation of R_2* was longitudinally observed in the SN and caudal putamen of patients with PD evolving over a three-year period, emphasizing its interest as a biomarker of disease progression. Our results suggest that R_2* MRI follow-up could be an interesting tool for individual assessment of neurodegeneration due to PD, and also be useful for testing the efficiency of disease-modifying treatments.

Citation: Ulla M, Bonny JM, Ouchchane L, Rieu I, Claise B, et al. (2013) Is R_2* a New MRI Biomarker for the Progression of Parkinson's Disease? A Longitudinal Follow-Up. PLoS ONE 8(3): e57904. doi:10.1371/journal.pone.0057904

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R2* and neurodegeneration

- Longitudinal study = more specificity
  i.e. Keep the between session variations of $R2^*_b$ small
- $\Delta R2^* = R2^*_1 - R2^*_0 > 0$ in SN of PD patients
- Correlated with the difference of disease rating scales
  i.e. UPDRS$_1$- UPDRS$_0$

For more details see Ulla et al. (2013) 10.1371/journal.pone.0057904

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Intrasubject subcortical quantitative referencing to boost MRI sensitivity to Parkinson's disease

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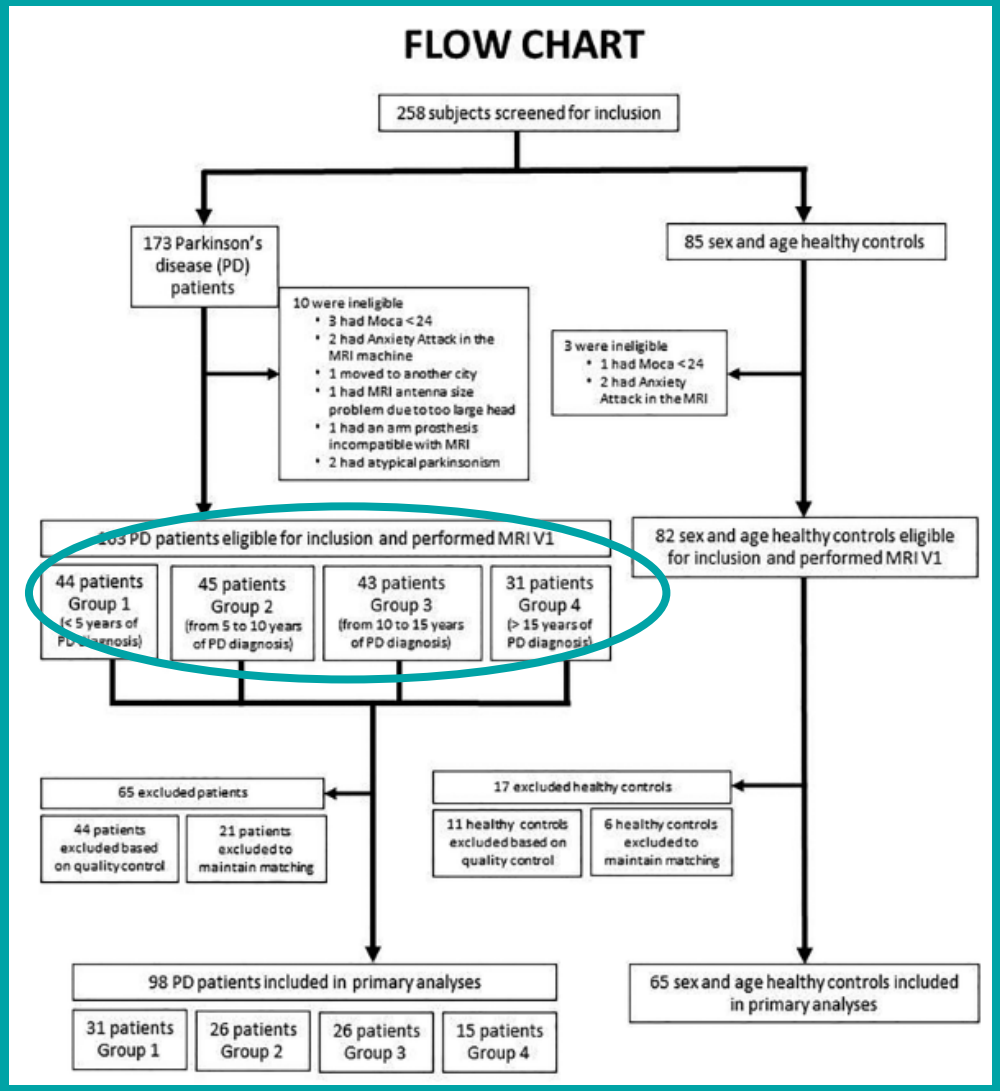
Better data



Longitudinal study

- V2 1 year after

Boosting the R2* sensitivity

- Between-subject SD($R2^*$)~20% in SN mostly independent of the disease

  In the basal ganglia ROIs, between- subject variations are highly correlated !

- Intrasubject quantitative referencing method to reduce these non-specific variations

Disease duration			
PD patients G1	PD patients G2	PD patients G3	PD patients G4
31	26	26	15
$R2^*$	38.3 ± 4.53	39.48 ± 5.24	38.87 ± 7.71	41.96 ± 5.65
	37.29 ± 3.59	39.59 ± 5.63	39.63 ± 7.2	40.09 ± 5.18
ISQR	4.83 ± 4.42	4.91 ± 4.47	6.48 ± 6.63	9.82 ± 4.5
	3.44 ± 3.86	4.97 ± 4.53	7.28 ± 5.75	7.39 ± 5.03

Dominant side

Non-dominant side

Disease duration (years)

1.9 6.7 11.6 17.1

- For more details see Khedder et al. (2022) 10.1016/j.nicl.2022.103231

From biomarkers to the diet

Could dietary supplements potentially enhance the quality of life for individuals with PD ?

Gut-brain axis and PD

Many signs of gastrointestinal (GI) disorders associated with PD

- Dysbiosis = Alteration in the gut microbiota
- Constipation / Highly prevalent ~87 %
- Gut inflammation
- Increased permeability of colon
- α-synuclein (α-syn) aggregates in the GI tract

Two subtypes of PD = “Gut first” or “Brain first”

GI signs, cause or consequences of PD ?

Evidences for bidirectional pathways

Recovery of an healthy microbiota = An exciting therapeutic avenue …

Dietary supplements

Probiotics = living microorganisms

Prebiotics = Non digestible ingredients

Symbiotics = Pro + Pre-biotics

Many studies

- 31 clinical / 207 preclinical studies / 9 meta-analysis on PUBMED
- **Positive tendency for an efficacy**

But more consistency is needed in study design

- Power / number of subject
- Supplement parameters e.g. strains, duration, dosage

MENTAL project / Pre-clinical strategy

Rat model

- Low inter-subject variability in a cohort
- Longitudinal following
- Intra-cerebral injection of adeno-associated viruses to express α-syn in the rat midbrain

see Huntington et al. (2021) 10.14336/AD.2021.0517

Integration of multi-omic/-modal data

- Extensive characterization of gut-brain axis
- Same approach before and after administration of the supplement in the diet
- Integration using explainable AI ⇨ Identification of mechanisms

MENTAL = preclinical strategy

ICM ARAMIS

α-syn PD rat model

① No supp.

②

Data fusion & analysis

Results of Phase ①

Multi-omic data
- MRI
- Histology
- Metagenomic sequencing
- Transit time in the digestive system
- Behavior

(…)

Preliminary MENTAL data

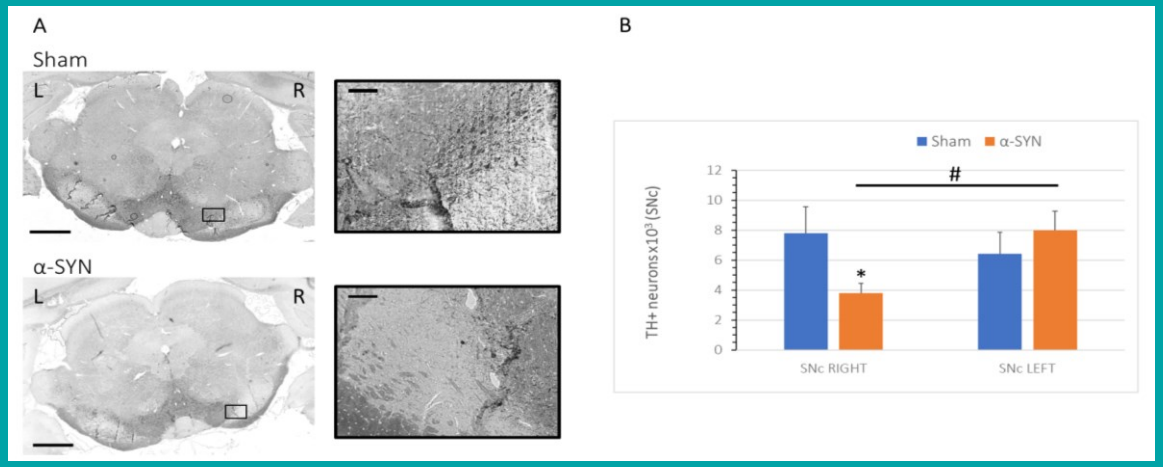
Need for a flexible rat model

- Fischer strain
- Experience on axenic Fisher 344 rats for performing transfer of microbiota

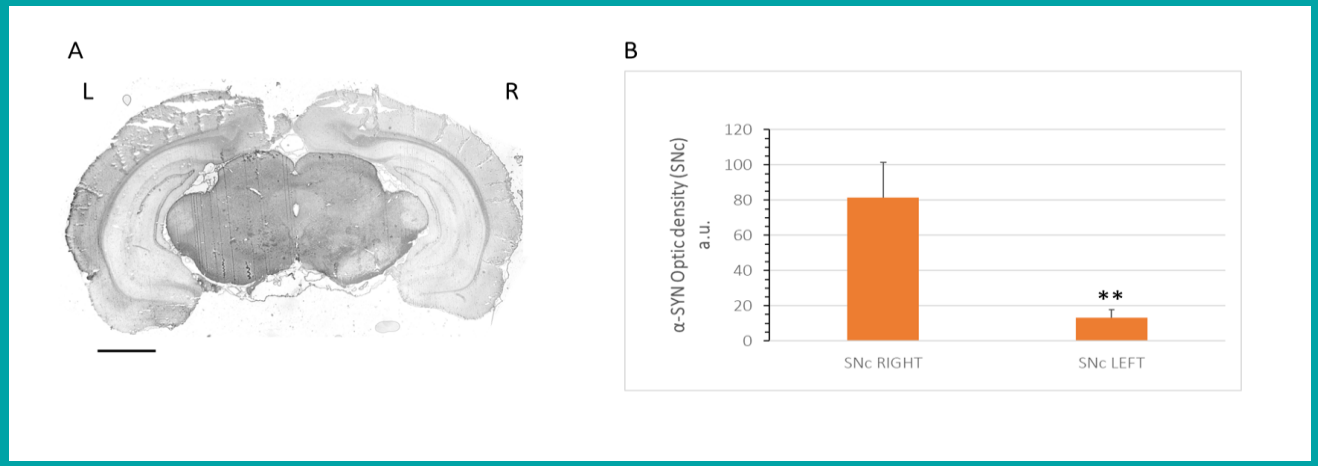
No data of α-syn Fisher 344 rat model of PD

Preliminary results / Histology

Nigral sections



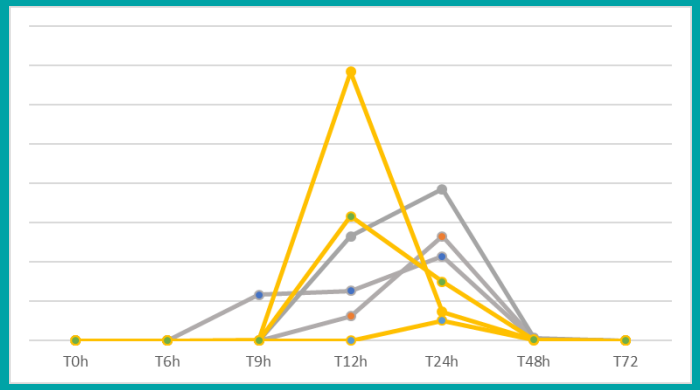
Loss of dopaminergic neurons



α-synucleinopathy

Preliminary results / Transit time

Number of spores



Controls

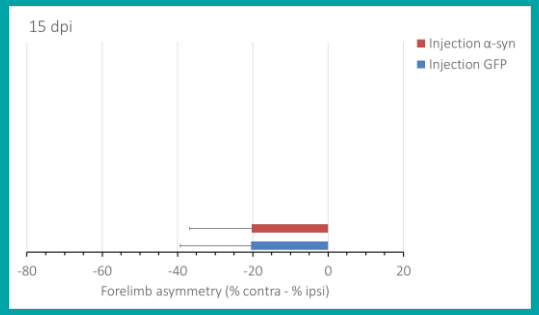
PD

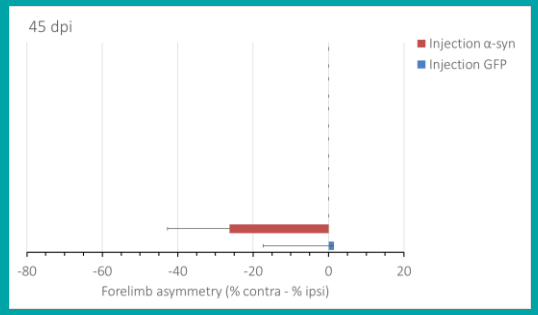
Longer transit time in the digestive system

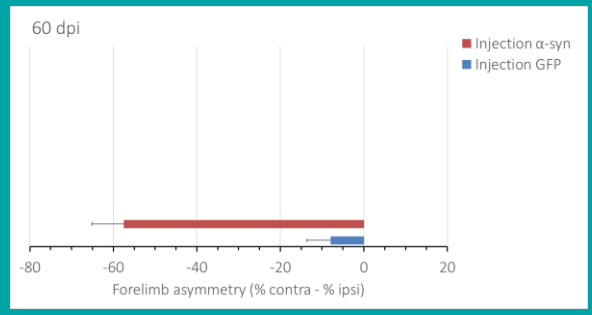
⇨ Constipation

Preliminary results / Behavior

Time after intra-cerebral injection







Motor symptoms appearance at 45 DPI

Early conclusions

Fisher 344 rat model

- Consistent symptoms of PD at 90 DPI
- Multimodal characterization in the gut-brain axis

Metagenomic sequencing and MRI analysis in course

Future work

- Integration with explainable IA
- Development of a “personalized” multi-target supplement for promoting healthy microbiota

MENTAL project / Clinical strategy

Microbial imbalances

- Inconsistent and sometimes contradictory findings
- Many confounding variables

  e.g. Geographic background, age, sex, diet, medication, GI symptoms

see Boertien et al. (2019) 10.3233/JPD-191711

Good quality data needed

Clinical WPs

Eating disorders

NS PARK network

- Clinical and genetic data

NutiNet-Santé

- Diet

French-Gut

- Microbiota

Controls included

Data fusion & analysis

ICM ARAMIS

Conclusions

Animal models

- Valuable tools for elucidating physiopathological mechanisms
- AND establishing proof-of-principle for potential dietary supplement therapies

BUT

- Preclinical tools often lag behind those available for human investigation,
- Models merely serve as proxies for human diseases

Human data

- Efforts must be made to minimize the impact of confounding variables
- Increased degrees of freedom necessitate extensive databases that adhere to the FAIR principles

Contact

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High field MRI — AgroResonance
http://www6.inra.fr/agroresonance

In vivo multimodal imaging — IVIA IBiSA infrastructure
https://www.ibisa.net/plateformes/detail.php?tri=&srch=&q=495