# PET-MRI in neuroimmunological diseases: the Paris experience with TSPO-PET applied to MS

International OMS workshop

7 October 2022


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# Plan

- Why and how using PET to explore neuroinflammation in MS?
- Exploring neuroinflammation in lesions and normal-appearing tissues in MS
- Regionalization of neuroinflammation in the MS brain
- A dysfunction of the Brain/CSF barrier at the choroid plexus level

# Plan

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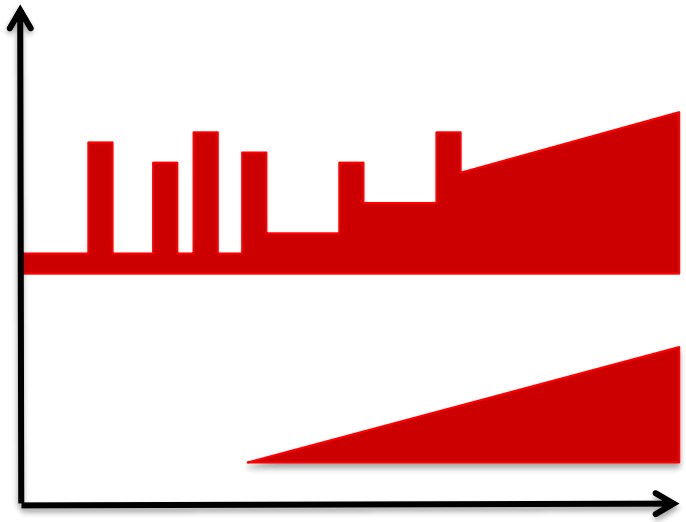
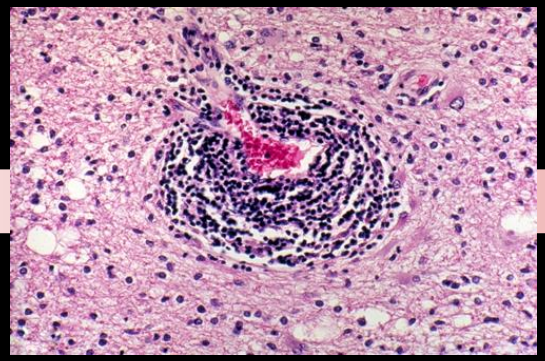
# Adaptive and innate immune systems in the pathophysiology of neurodegeneration

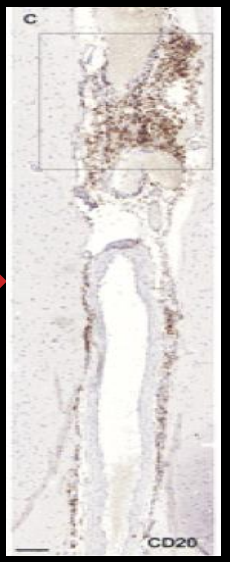
Neurodegeneration

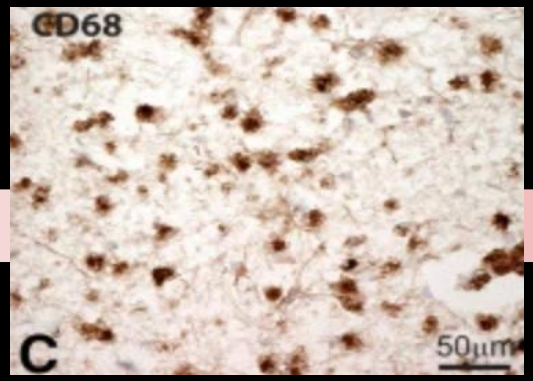




Adaptive immune system

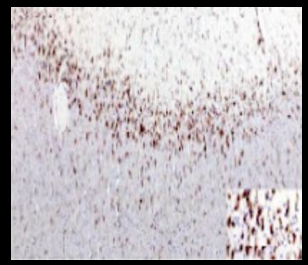
- Acute demyelination
- Axonal transection
- Ectopic lymphocytic inflammation




Innate immune system

- Myelin destruction in acute lesions
- Smouldering plaques
- Diffuse damage in normal-appearing tissues

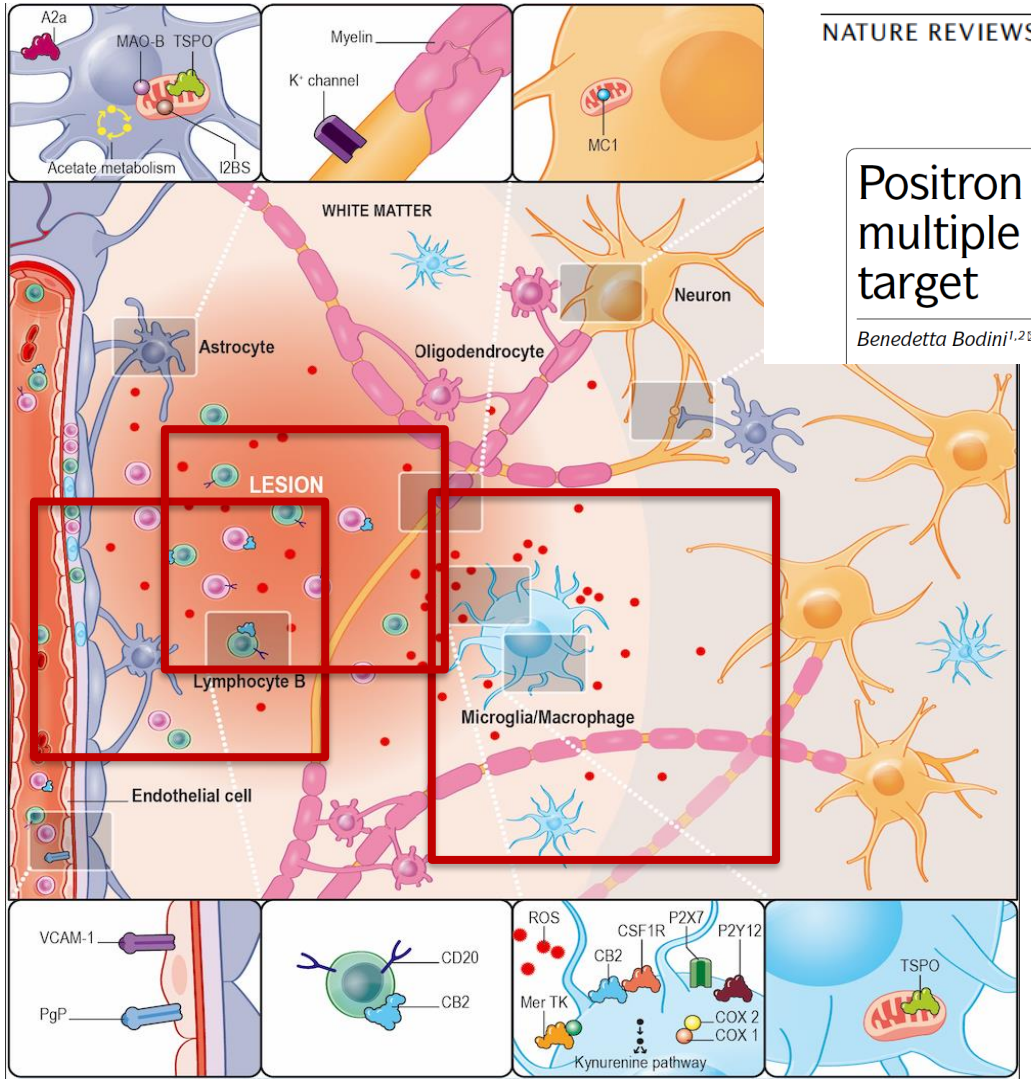


Magliozzi et al, 2007; Howell et al, 2011; Frischer et al, 2015

# Targeting neuroinflammation with PET

PET

- High specificity for cellular/tissular targets
- Generally low resolution



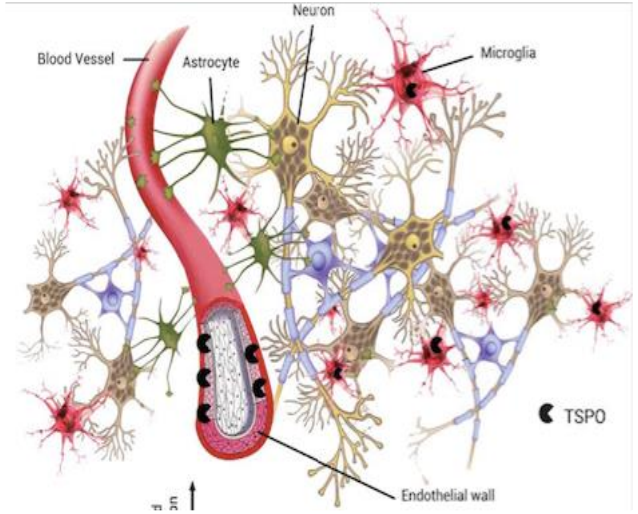

NATURE REVIEWS | NEUROLOGY REVIEWS

Positron emission tomography in multiple sclerosis — straight to the target

*Benedetta Bodini[1,2]✉, Matteo Tonietto[1,3], Laura Airas[4] and Bruno Stankoff[1,2]*

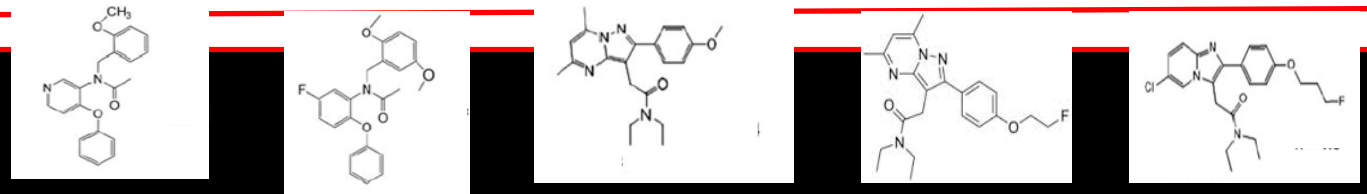
Bodini et al, 2021

# TSPO




- Macromolecular complex localized in the outer mitochondrial membrane
- Expression mainly driven by innate immune cell activation

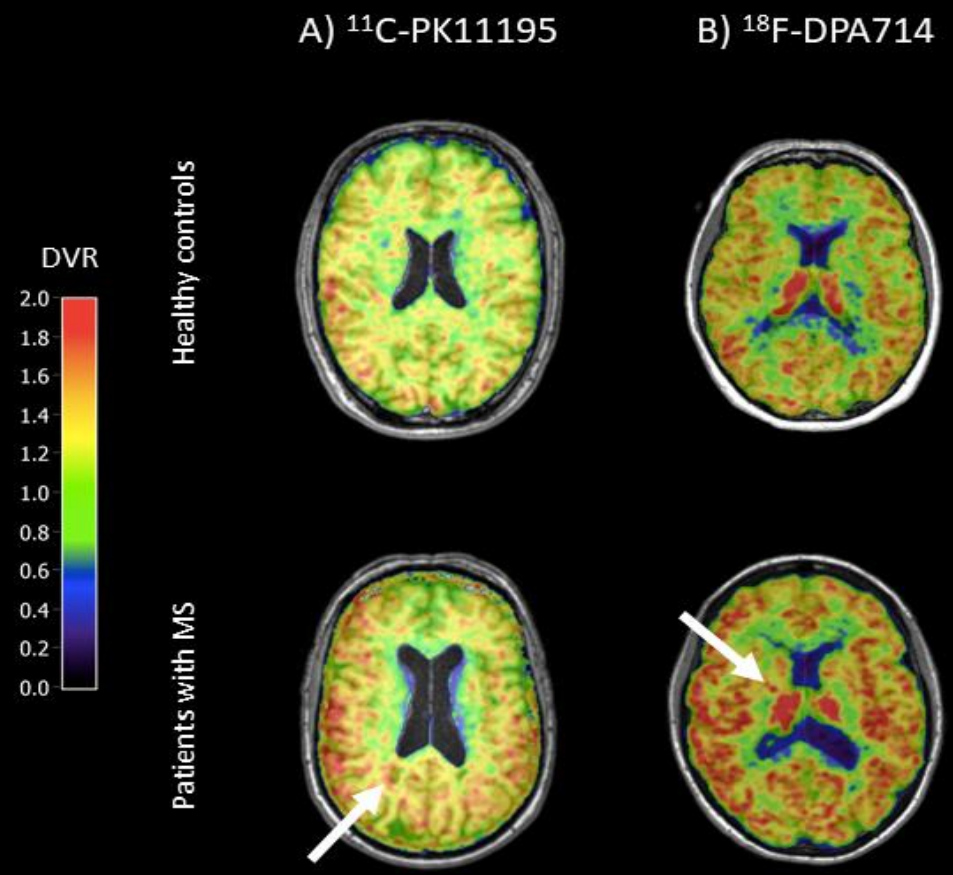
PBR 28 DAA 1106 DPA 713 DPA 714 PBR 111



(Benavides, 1993;1988; Le fur 1988)

# Improving the signal-to-noise ratio using second-generation TSPO tracers

1st generation 2nd generation




- Improved SNR
- Improved affinity

Bodini et al, Nature Reviews Neurology, 2021

# TSPO genetic polymorphism

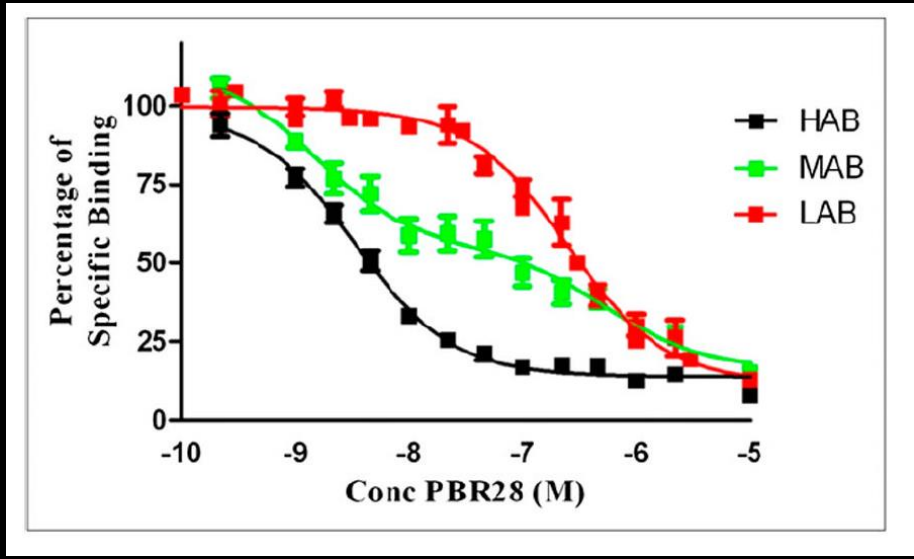
*J Nucl Med.* 2011 January ; 52(1): 24–32. doi:10.2967/jnumed.110.079459.

## Mixed-Affinity Binding in Humans with 18-kDa Translocator Protein Ligands

**David R.J. Owen[1,2], Roger N. Gunn[2,3], Eugenii A. Rabiner[2,3], Idriss Bennacef[2], Masahiro Fujita[4], William C. Kreisl[4], Robert B. Innis[4], Victor W. Pike[4], Richard Reynolds[5], Paul M. Matthews[2,3], and Christine A. Parker[2]**

## An 18-kDa Translocator Protein (TSPO) polymorphism explains differences in binding affinity of the PET radioligand PBR28

David R Owen[1,2,6], Astrid J Yeo[3,6], Roger N Gunn[2,4,5], Kijoung Song[3], Graham Wadsworth[2], Andrew Lewis[1], Chris Rhodes[1], David J Pulford[3], Idriss Bennacef[2], Christine A Parker[2,4], Pamela L StJean[3], Lon R Cardon[3], Vincent E Mooser[3], Paul M Matthews[2,4], Eugenii A Rabiner[2,4] and Justin P Rubio[3]

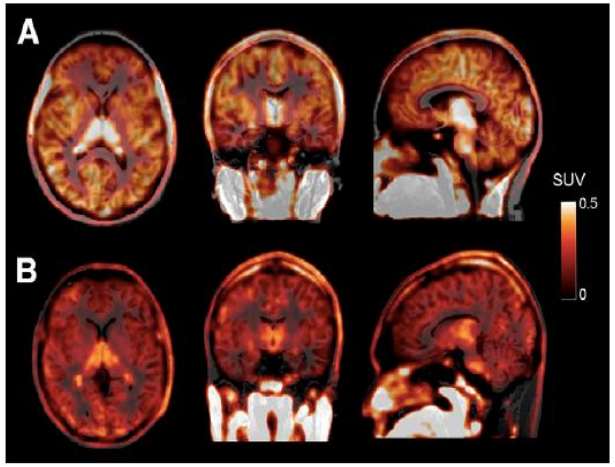



| Ligand | LAB | MAB | HAB |
|---|---|---|---|
| PBR28 | 1 | 28.2 | 55.3 |
| PBR06 | 1 | 9.2 | 17.3 |
| DAA1106 | 1 | 2.9 | 4.7 |
| PBR111 | 1 | 2.5 | 4.0 |
| DPA173 | 1 | 2.7 | 4.4 |
| PK11195 | 1 | 0.9 | 0.8 |

# Quantification of $^{18}$F-DPA-714

**Optimized Quantification of Translocator Protein Radioligand $^{18}$F-DPA-714 Uptake in the Brain of Genotyped Healthy Volunteers**

Sonia Lavisse[1,2], Daniel García-Lorenzo[3,4], Marie-Anne Peyronneau[5], Benedetta Bodini[3–6], Claire Thiriez[1,2,7], Bertrand Kuhnast[5], Claude Comtat[5], Philippe Remy*[1,2,7,8], Bruno Stankoff*[3,4], and Michel Bottlaender[5,9]




**Reliable quantification using the 2-TC model**
**Equilibrium at 60 min**
**Lavisse et al, J Nuc Med 2015**

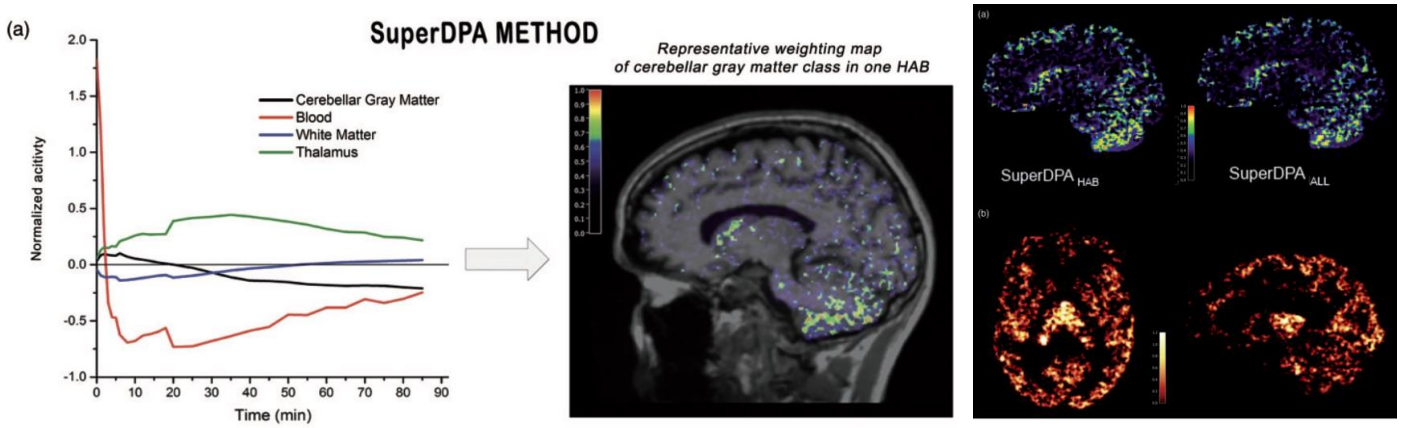
Original Article
JCBFM
Journal of Cerebral Blood Flow & Metabolism
2018, Vol. 38(2) 333–346

DOI: 10.1177/0271678X17693599
journals.sagepub.com/home/jcbfm
SAGE

**Validation of an automatic reference region extraction for the quantification of [$^{18}$F]DPA-714 in dynamic brain PET studies**

Daniel García-Lorenzo[1,*], Sonia Lavisse[2,3,*], Claire Leroy[4,5], Catriona Wimberley[4,5], Benedetta Bodini[1], Philippe Remy[2,3,7], Mattia Veronese[6], Federico Turkheimer[6], Bruno Stankoff[1,8,*] and Michel Bottlaender[4,5,9,*]

- Automatic extraction of a reference region in the cortex using SuperDPA
- Extraction of the binding potential with a Logan reference tissue model



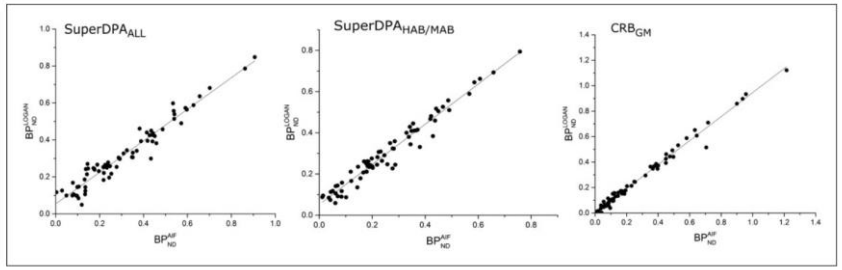
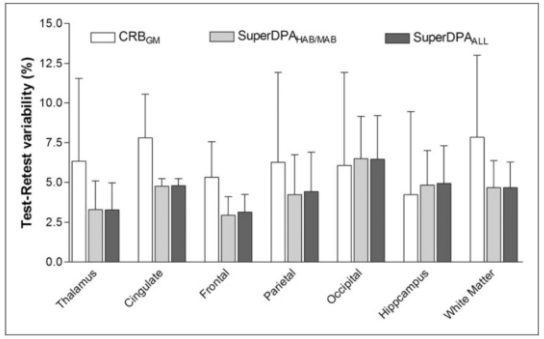




**Figure 4.** Relationship between $BP_{ND}$ estimates with the arterial input function analysis ($BP_{ND}^{AIF}$) and with reference input Logan graphical analysis ($BP_{ND}^{LOGAN}$) using the SuperDPA$_{ALL}$ (left), SuperDPA$_{HAB/MAB}$ (middle) extracted reference region and the CRB$_{GM}$ (right). Regression lines in black lines.




Correlation between
AIF based method and super DPA

Improved reproducibility compared to cerebellar grey matter reference

# Plan

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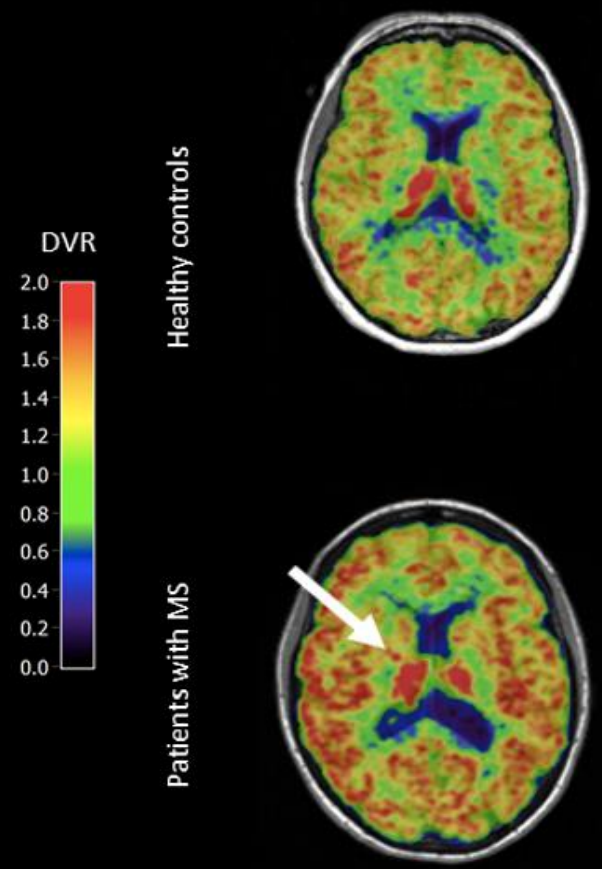
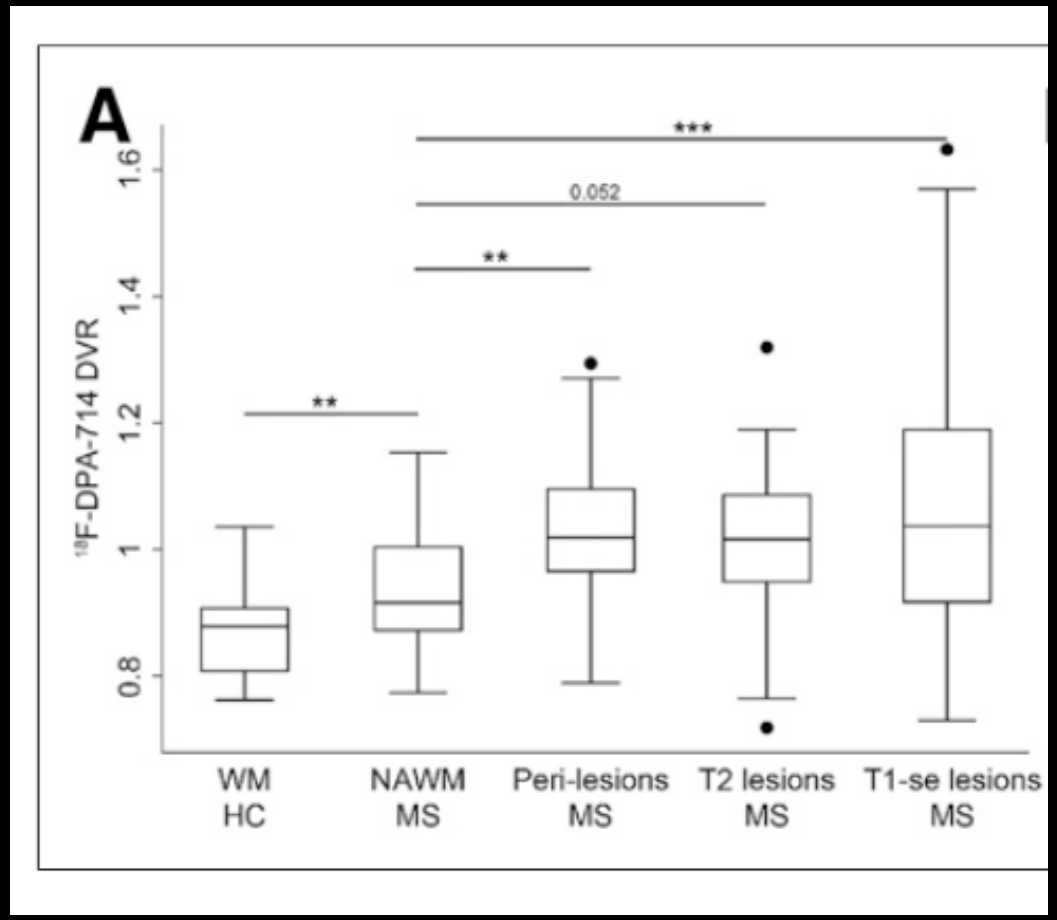
# TSPO binding in the MS brain: region of interest analysis



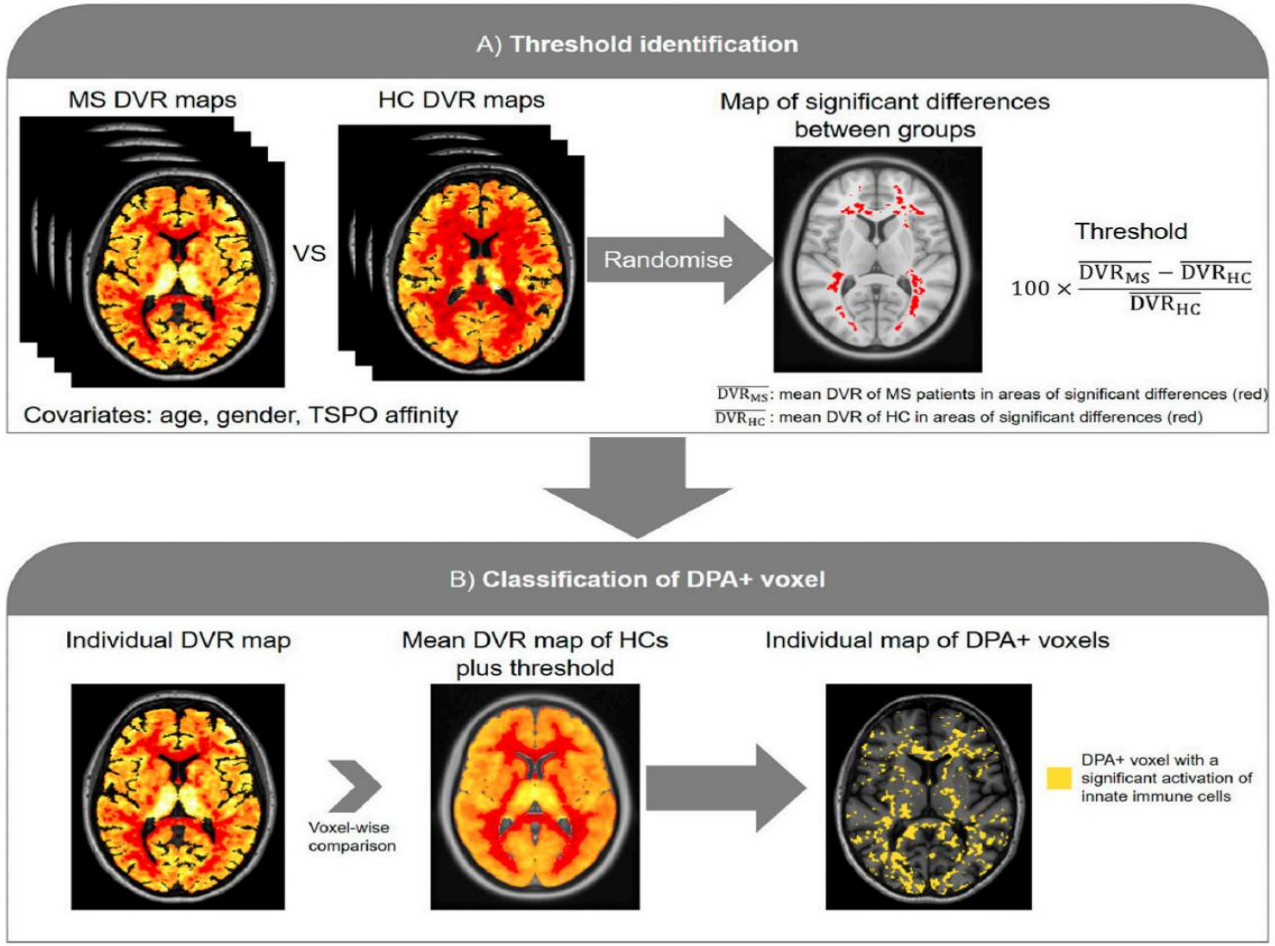




37 MS patients (12 RRMS, 14 SPMS, 11 PPMS) , 19 Healthy controls ; HRRT camera

**Transversal analysis of neuroinflammation in key ROIs**
**Only non enhancing lesions analyzed**

# Individual mapping of innate immune cell activation with TSPO-PET

37 MS patients (12 RRMS, 14 SPMS, 11 PPMS) , 19 Healthy controls




Goals :

- Minimise the influence of regional variation in unspecific binding and PVE
- Generate “comparable” maps in HAB and MAB
- Precise regional analysis at the lesional/sublesional level

Benoit et al, ECTRIMS/ACTRIMS 2017
Stankoff, ECTRIMS 2018
Bodini, Poirion et al, J Nuc Med 2020

# Individual mapping of innate immune cell activation with TSPO-PET

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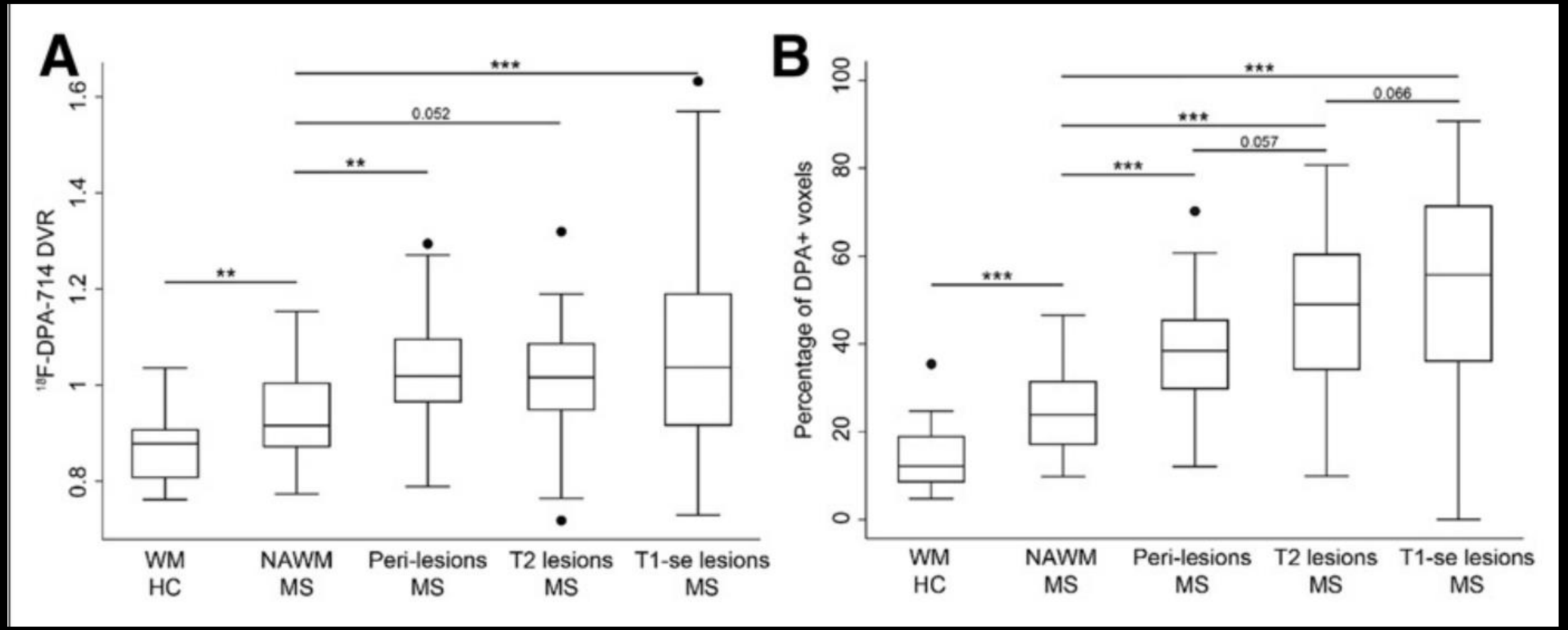


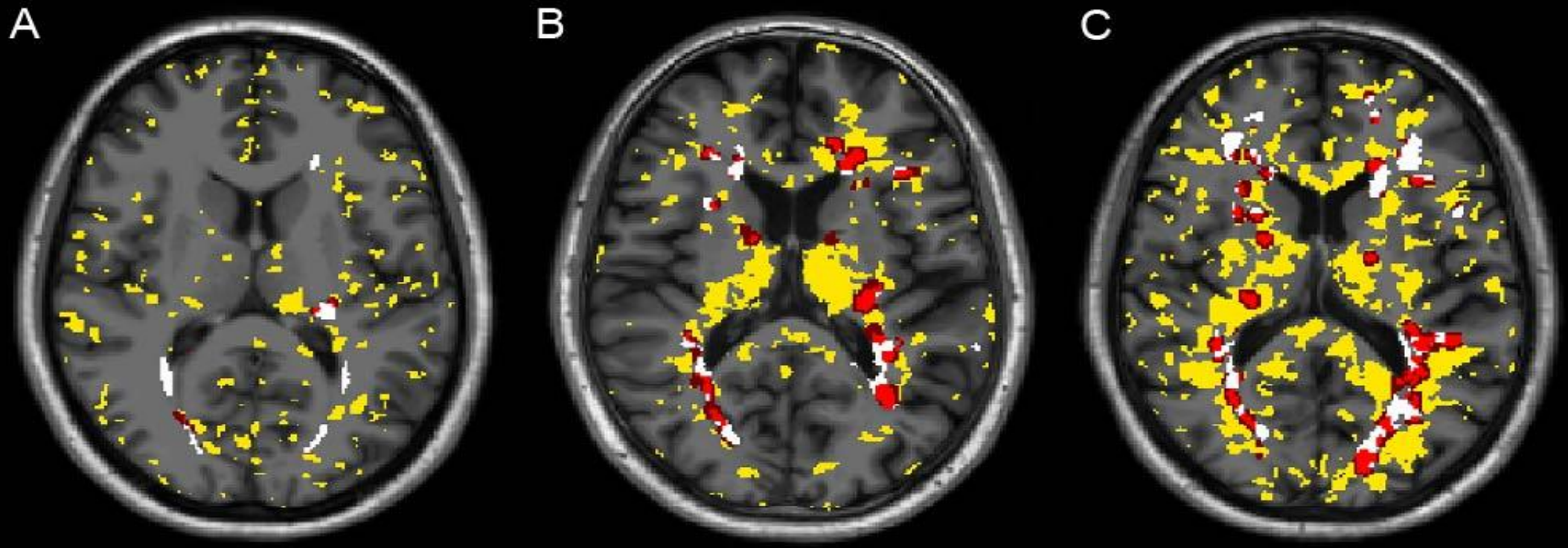

ROI analysis

Mapping of DPA active voxels

Only non enhancing lesions analyzed

Benoit et al, ECTRIMS/ACTRIMS 2017; Stankoff et al, Brain Pathol, 2019; Bodini, Poirion et al, J Nuc Med, 2020

# Individual mapping of innate immune cell activation with TSPO-PET




An innovative post-processing approach to generate individual maps of innate immune cells
Heterogeneous profiles of neuroinflammation depending on subjects
(Bodini, et al, J Nuc Med 2020; Nature Reviews Neurology 2021)

38 MS patients (13 RRMS, 14 SPMS, 11 PPMS) , 19 Healthy controls

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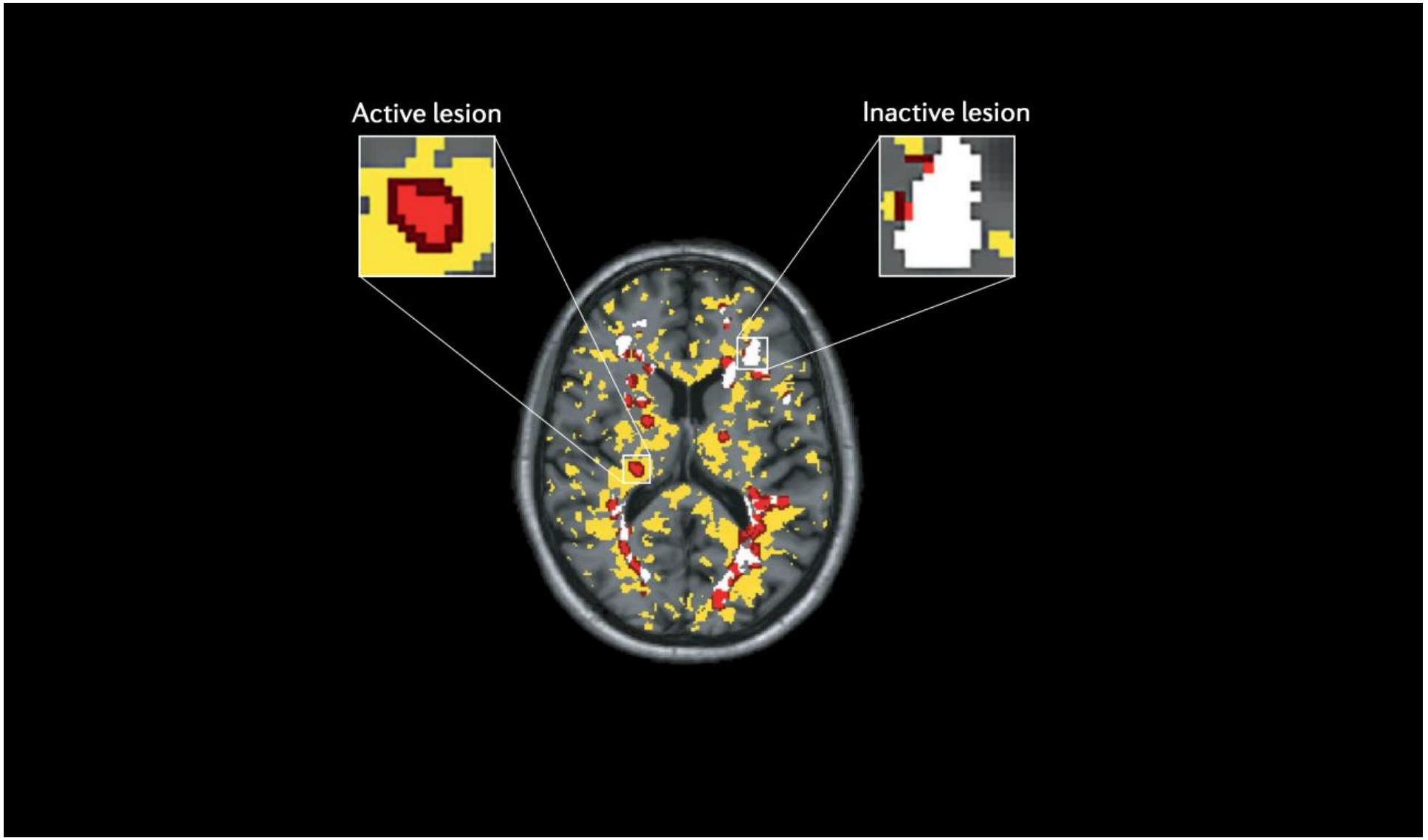
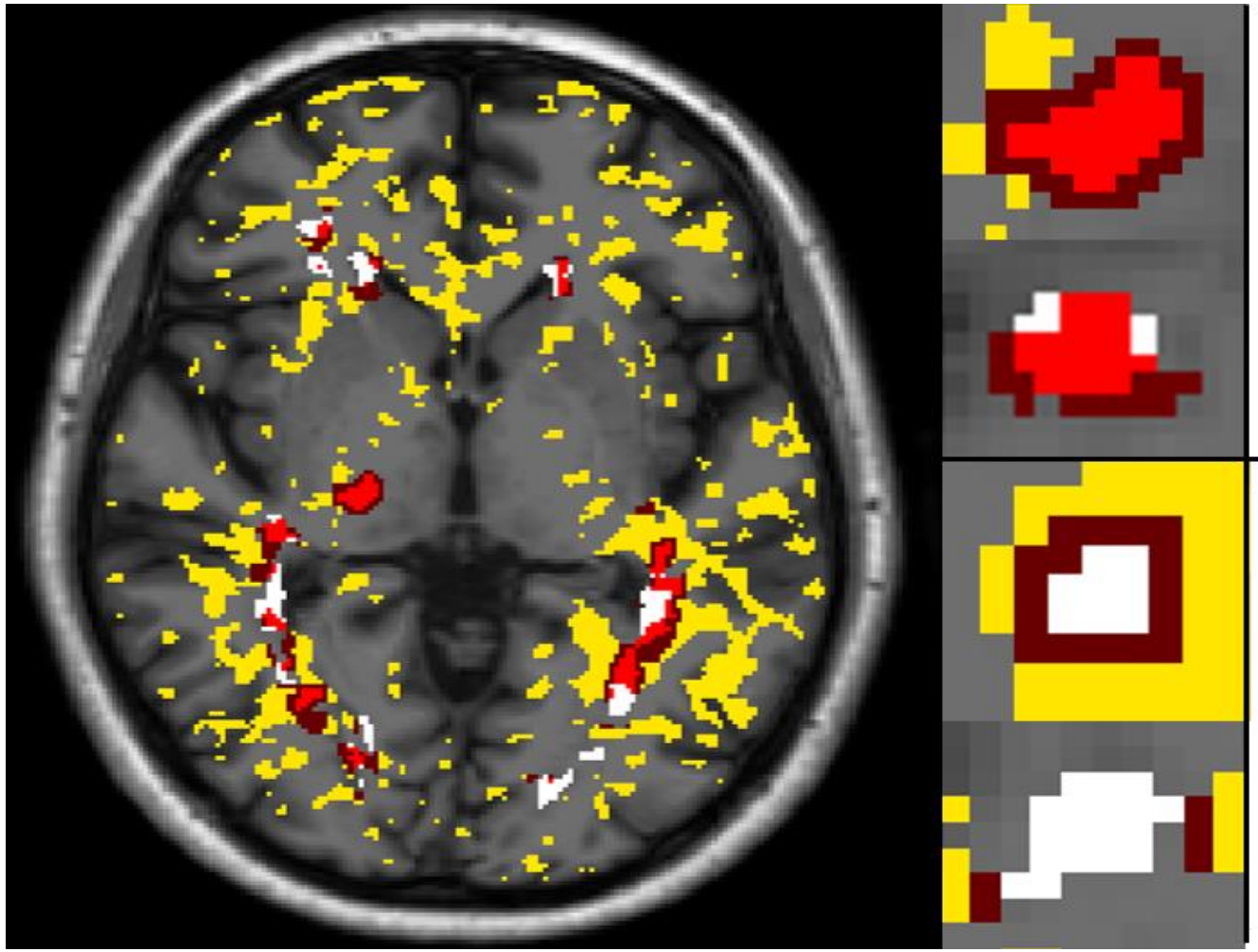


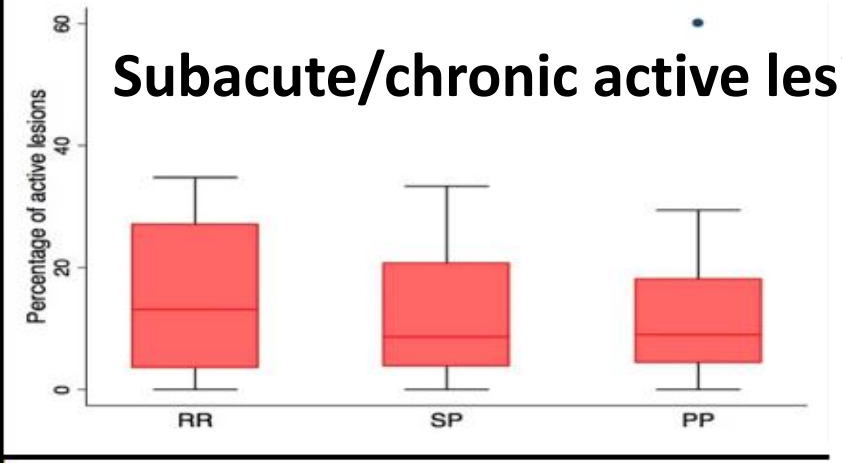

Benoit et al, ECTRIMS/ACTRIMS 2017; Stankoff et al, Brain Pathol, 2019; Bodini, Poirion et al, J Nuc Med, 2020

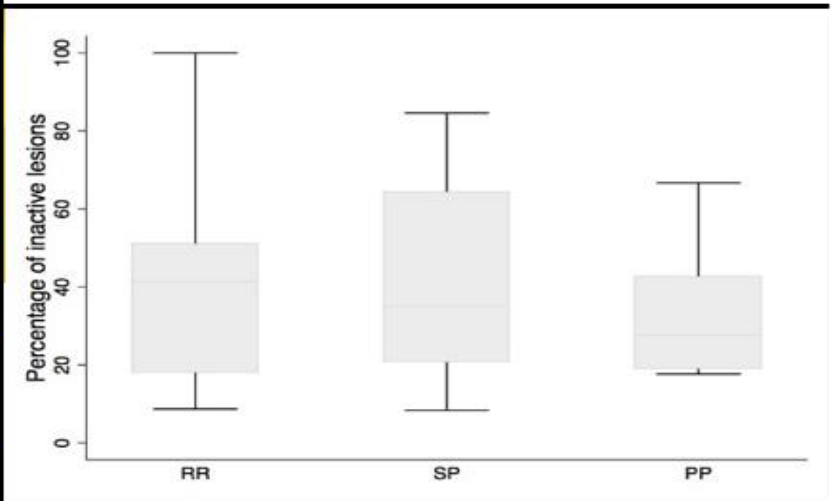
# Active lesions identified using [$^{18}$F]DPA-714 PET



**Classification of each lesion according to the innate immune cells content**

> 50% activated voxels in individual lesions



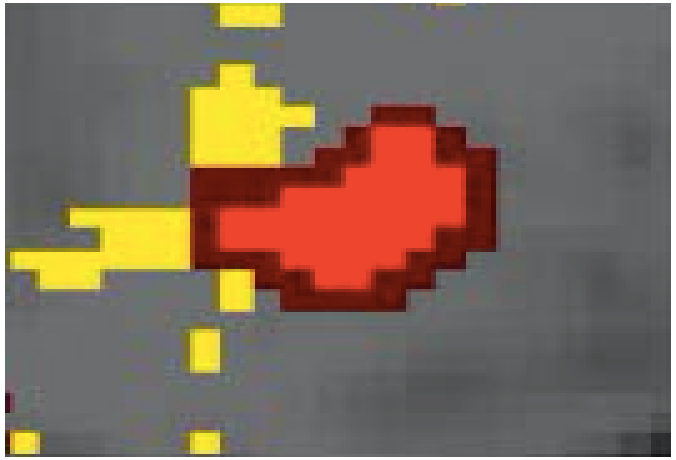




<10% activated voxel in lesions

Benoit et al, ECTRIMS/ACTRIMS 2017; Stankoff et al, Brain Pathol, 2019; Bodini, Poirion et al, J Nuc Med, 2020

# Identifying hidden innate immune cell activation [18F]DPA-714

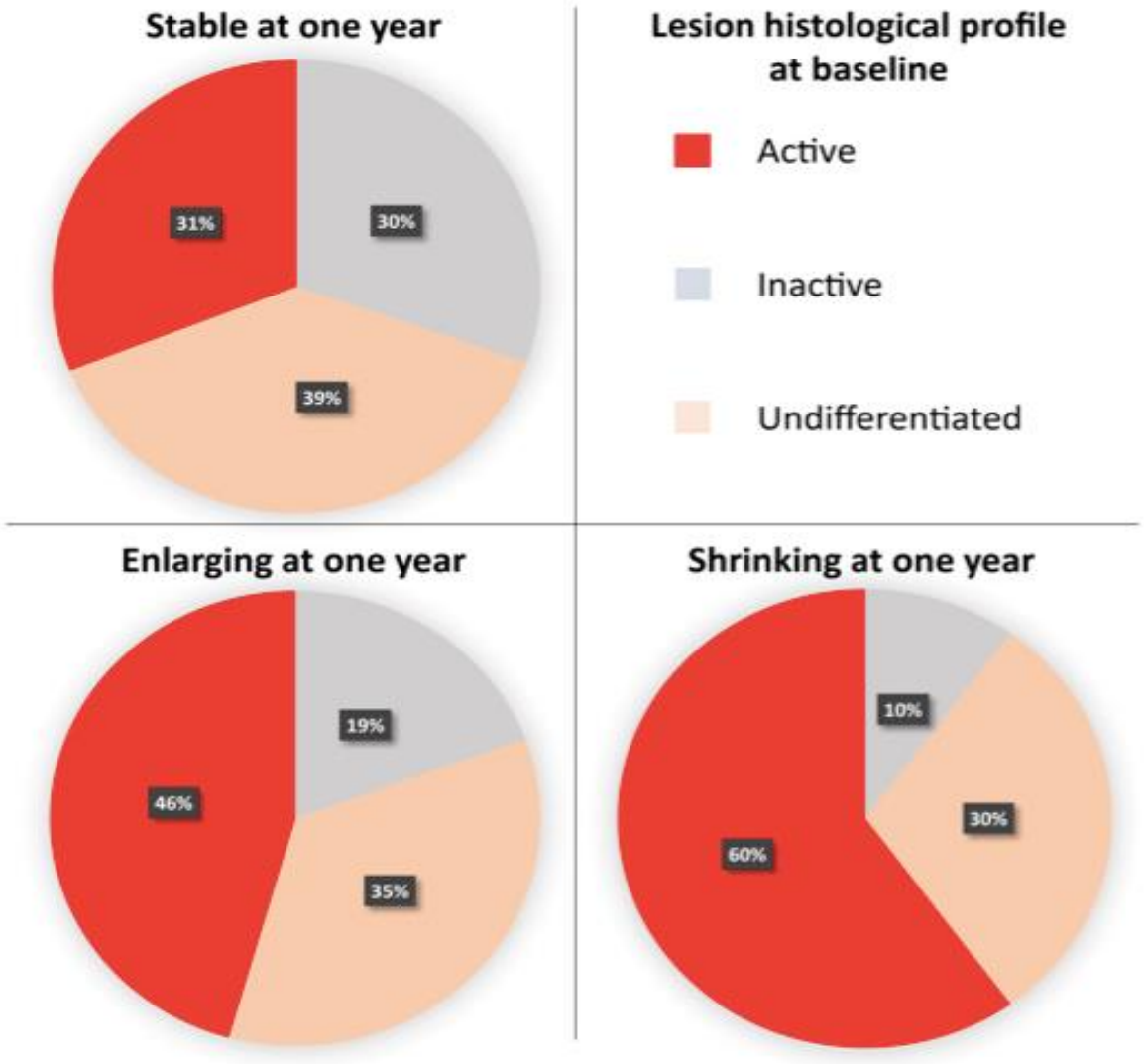
**1.8%** of total lesions classified as *active* based on Gd+ T1 SE sequences



**37.1%** of total lesions were defined as *active* based on DPA-PET

Bodini, Poirion et al, 2020

# Dynamic evolution of [18F]DPA-714 subacute-chronic active lesions




**10% of all lesions changed volume after one year** (7% enlarged, 3% shrank).

**Active lesions were more likely to enlarge or shrink over time**

Benoit et al, ECTRIMS/ACTRIMS 2017;
Stankoff et al, Brain Pathol, 2019

# Subacute and chronic active lesions and rajectories of clinical disability

EDSS step change

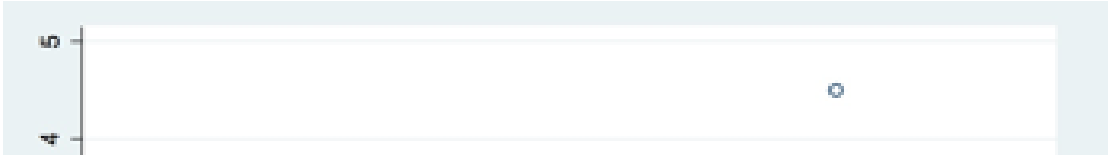
**N. OF ACTIVE LESIONS**

Beta-coeff=0.76
p=0.001

EDSS step change

**% ACTIVATION in the Perilesions**

Beta-coeff=0.50
p=0.01

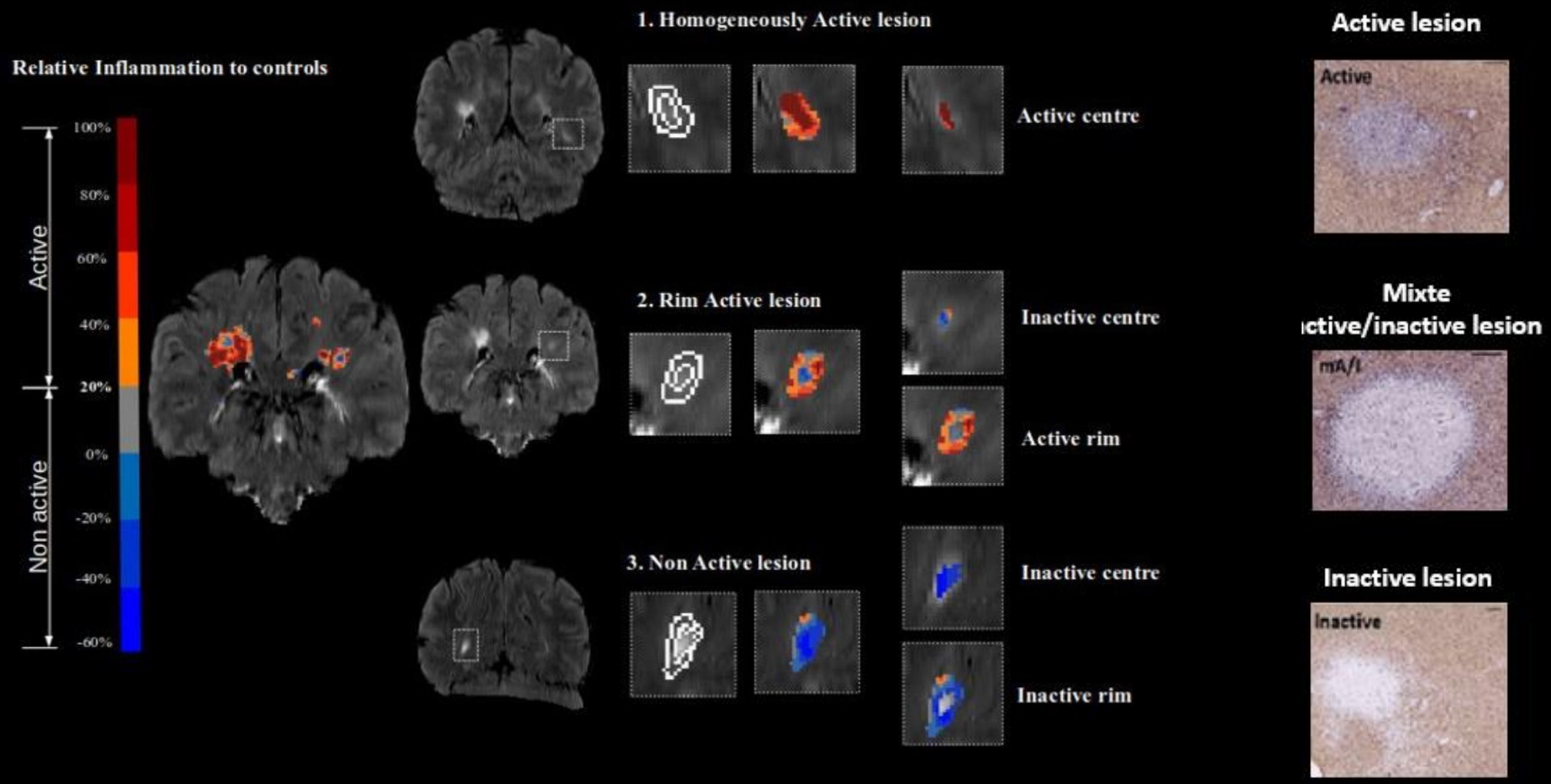


**EDSS step change during the 2 years preceeding study entry**

**Innate immune cells activation: a marker of individual trajectory of disability worsening**

Bodini, Poirion et al, J Nuc Med 2020

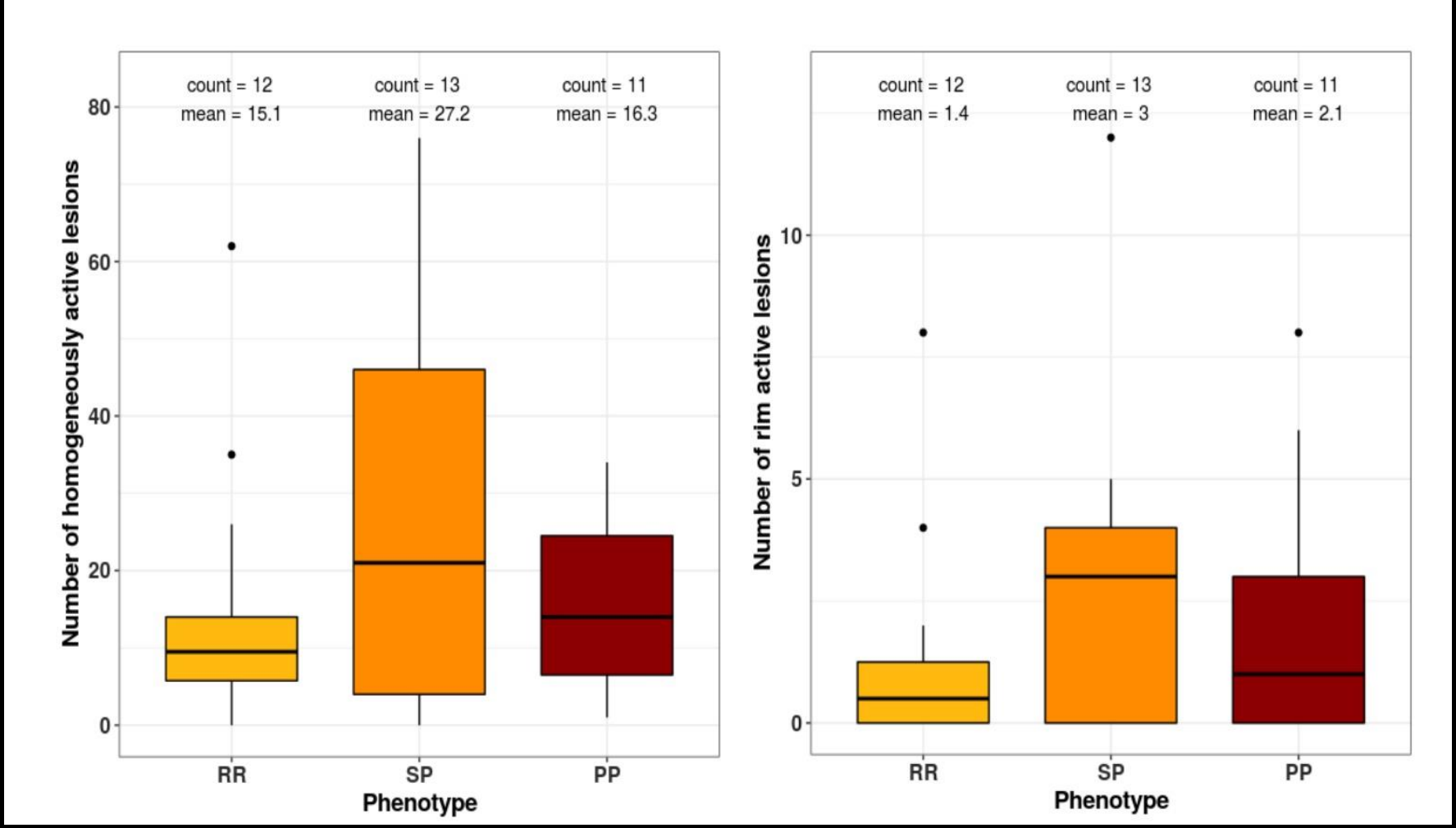
# Exploring the smouldering component of MS lesions: a new PET-based classification




Homogeneously active (53%) and mixte active/inactive lesions (6%)

Hamzaoui, Garcia et al 2022

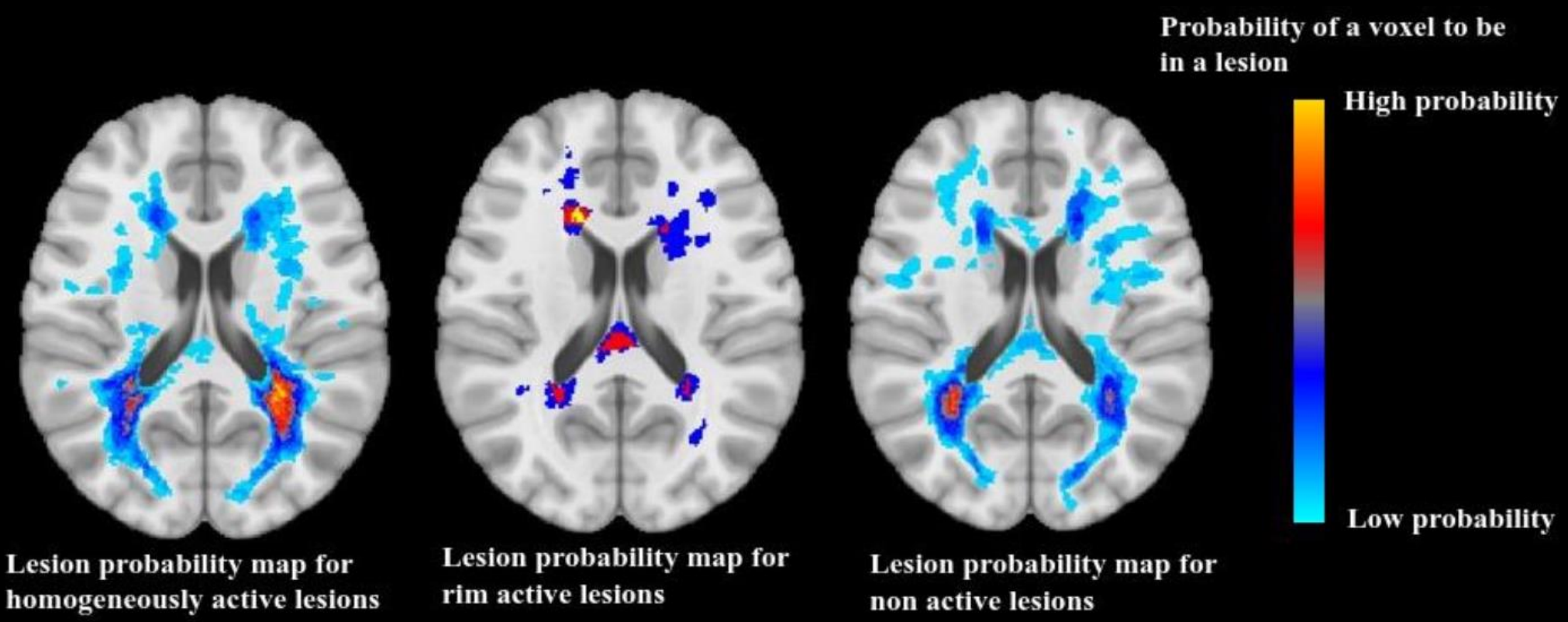
# Exploring the smouldering component of MS lesions: a new PET-based classification



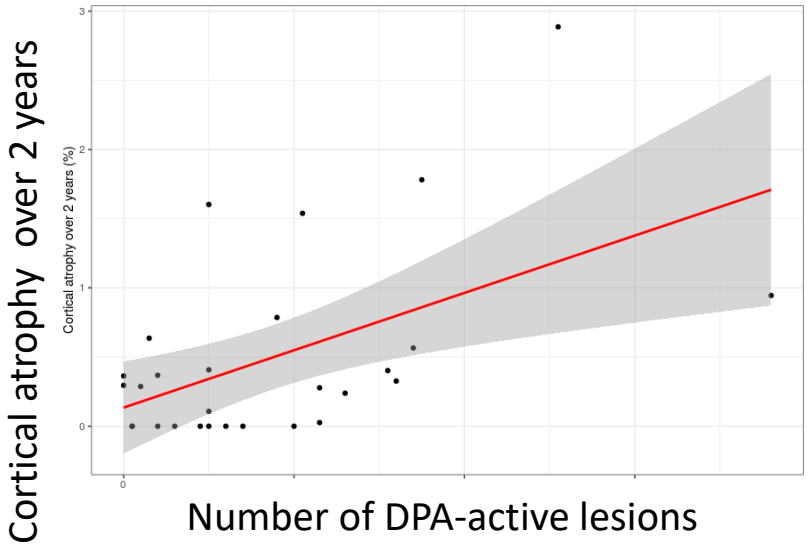

Homogeneously active and rim-active lesions at all MS stages

Bodini, Poirion et al, 2020; Hamzaoui, Garcia et al 2022

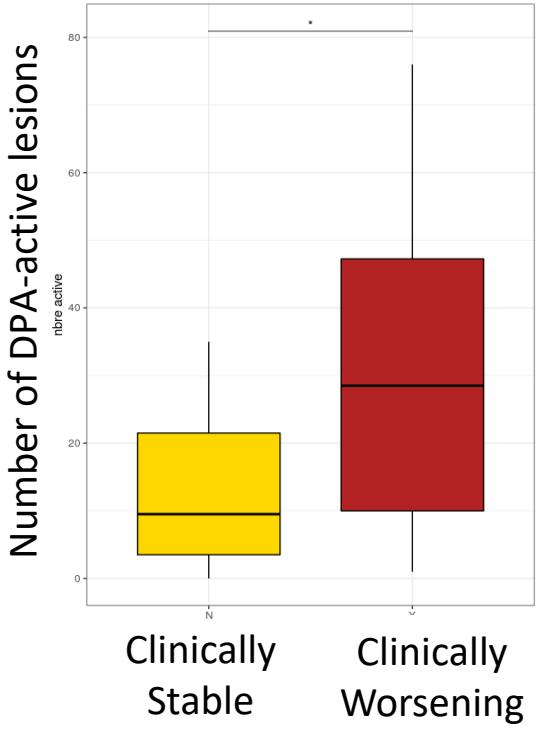
# The regional distribution of lesions according to their neuroinflammatory profiles

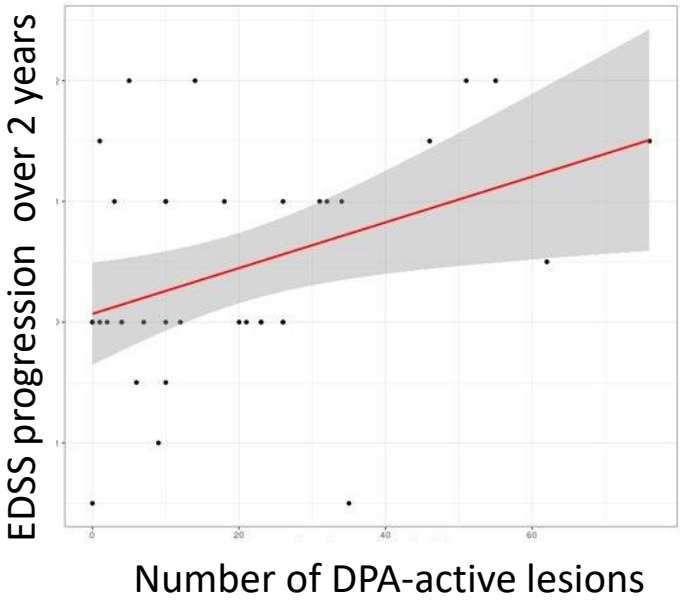


# Homogeneously active lesions predict cortical atrophy and clinical progresison




P =0.024
Rho=0.43




P =0.024
Rho=0.37

Hamazoui, Garcia et al, *2022*

# Plan

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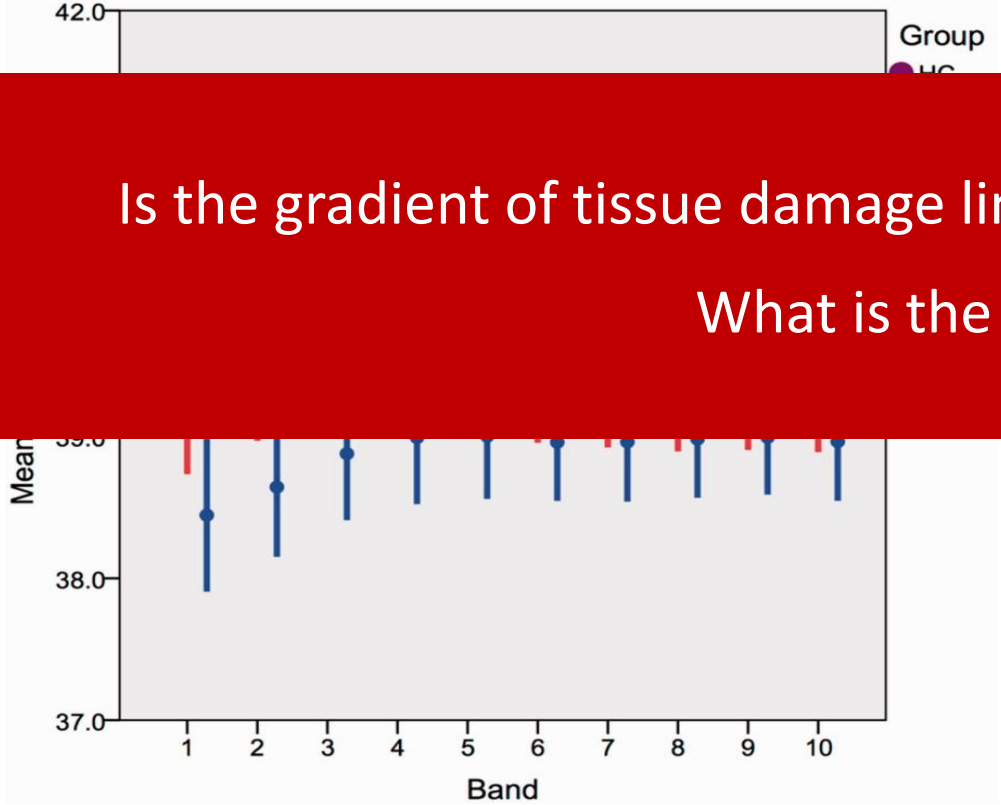
- Exploring neuroinflammation in lesions and normal-appearing tissues in MS
- **Regionalization of neuroinflammation in the MS brain**
- A dysfunction of the Brain/CSF barrier at the choroid plexus level

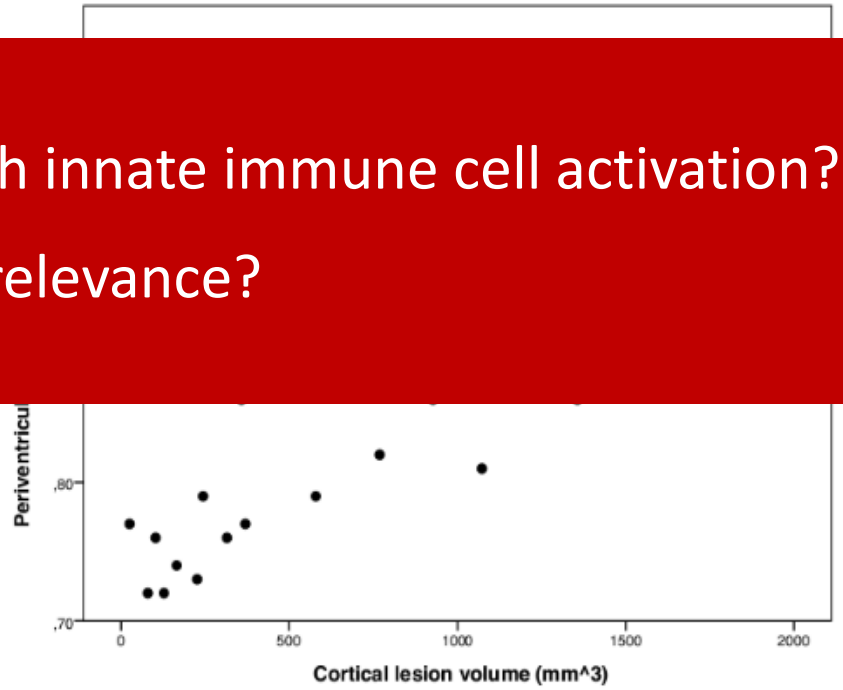
# Is chronic neuroinflammation the result of CSF/meningeal-derived factors?

A periventricular gradient of MTR




Liu et al, Brain 2015

Relationship between cortical and periventricular NAWM damage



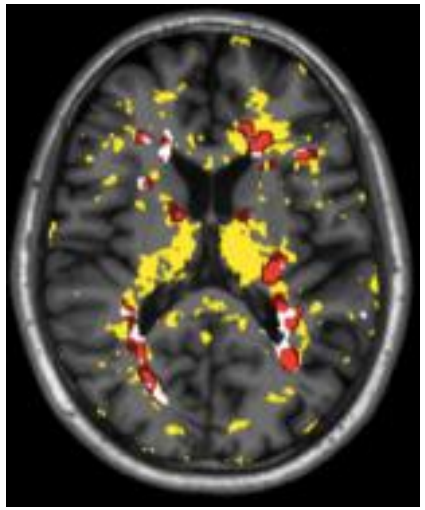

Pardini et al, NeuroImage Clin 2017

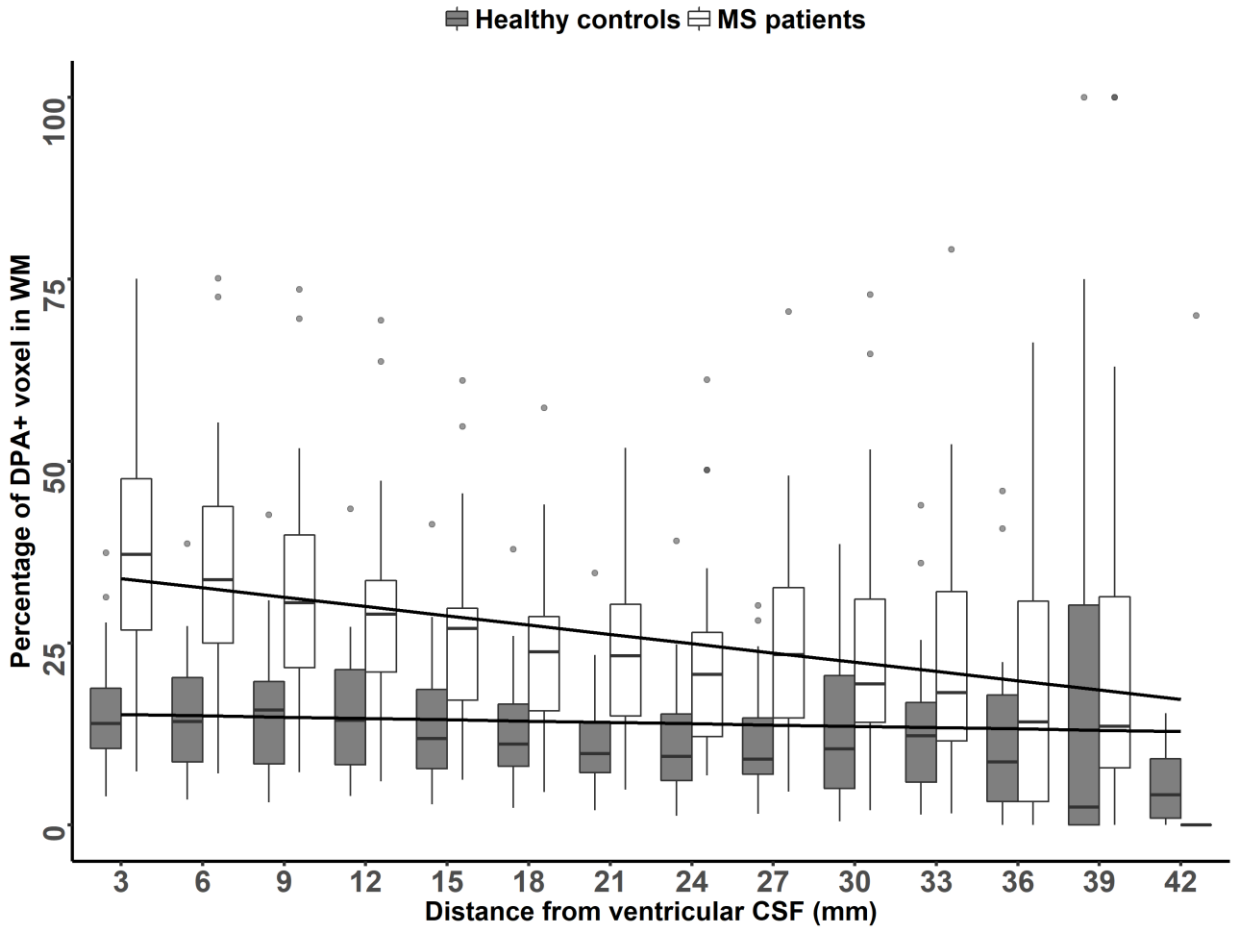
Is the gradient of tissue damage linked with innate immune cell activation?

What is the clinical relevance?

# A periventricular gradient of innate immune cell activation measured with PET

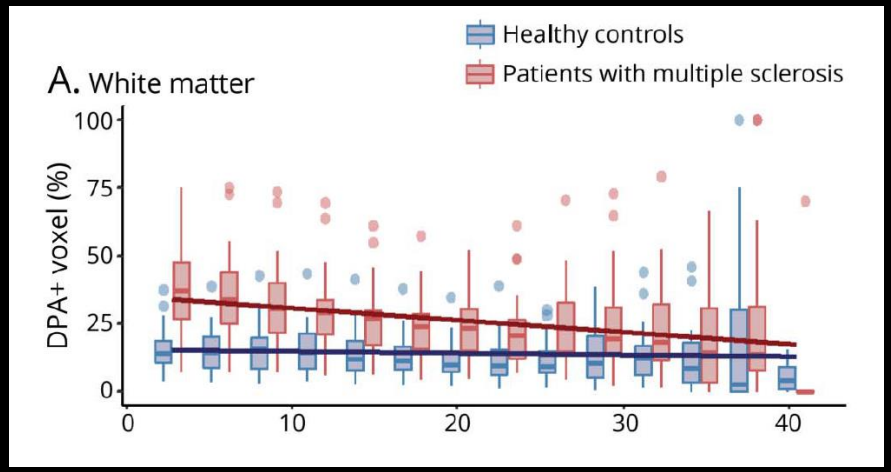
## White matter

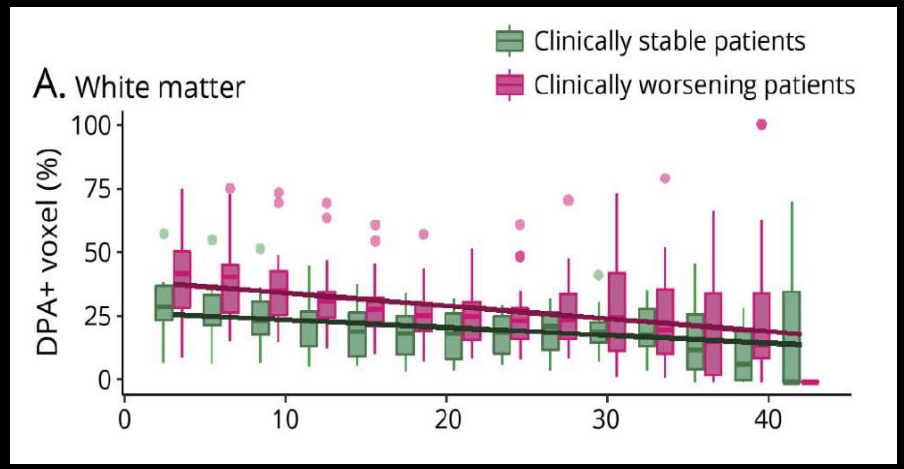




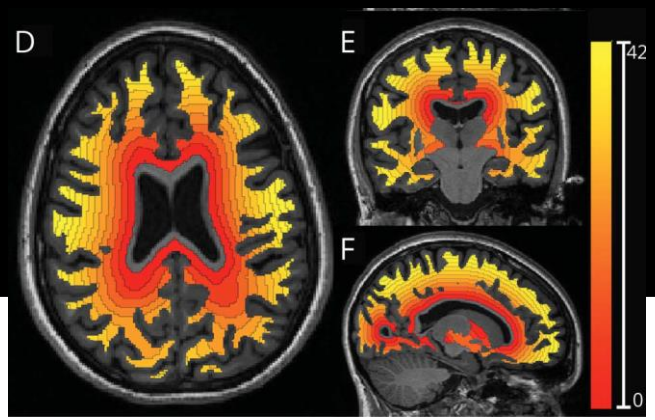

Poirion et al, Neurology, 2021

# Periventricular innate immune cell activation correlates with disability progression



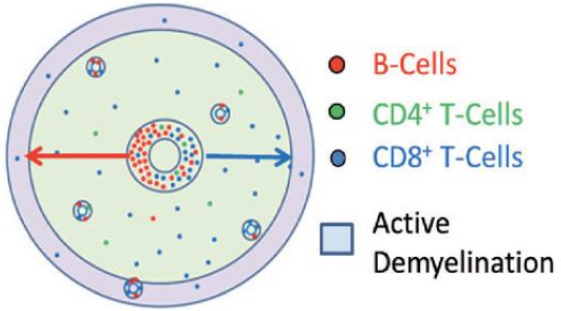

- Innate immune cell activation in MS predominates in periventricular regions
- Activation of microglia and macrophages in periventricular normal-appearing white matter is associated with microstructural damage and disability worsening




Poirion et al, 2021

# A periventricular gradient of innate immune cell activation: the hypotheses

- Compartmentalized inflammation in the perivenular space predominates around ventricles?

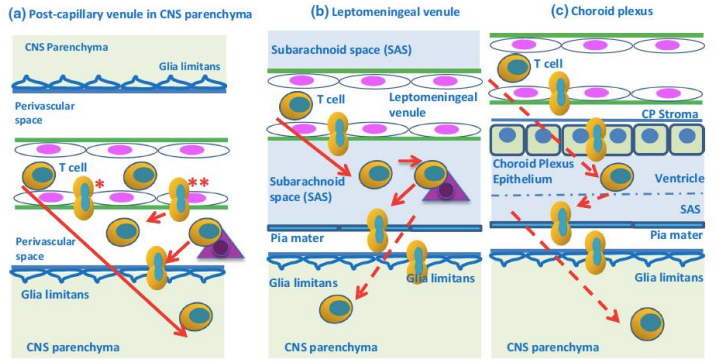



Machado-Santos, Brain, 2018

- CSF derived pro-inflammatory factors?

Cytokines, chemokines (Magliozzi, Ann Neurol 2018);
Fibrinogen (Peterson et al, Nat Rev 2018);
Ceramide (Wentling, PNAS, 2019) …

- The blood-CSF barrier (choroid plexus) ?




Engelhardt et al, Acta Neuropathol, 2016

# Plan

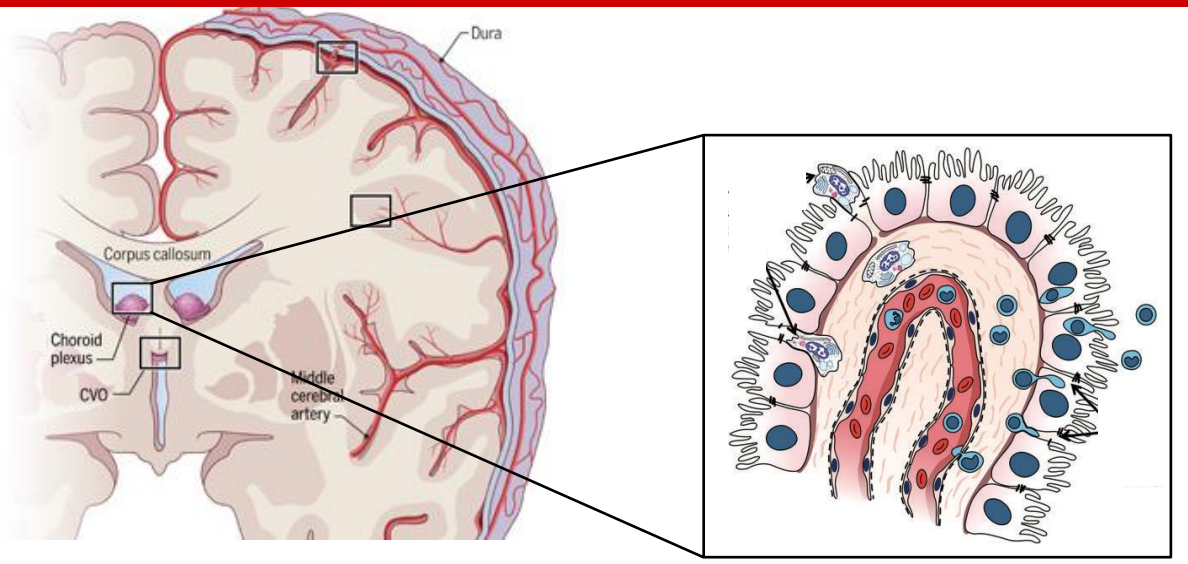
- Why using PET to explore neuroinflammation in MS?
- Exploring neuroinflammation in lesions and normal-appearing tissues in MS
- Regionalization of neuroinflammation in the MS brain
- **A dysfunction of the Brain/CSF barrier at the choroid plexus level**

# Choroid plexuses in animal models of MS and in post-mortem brains

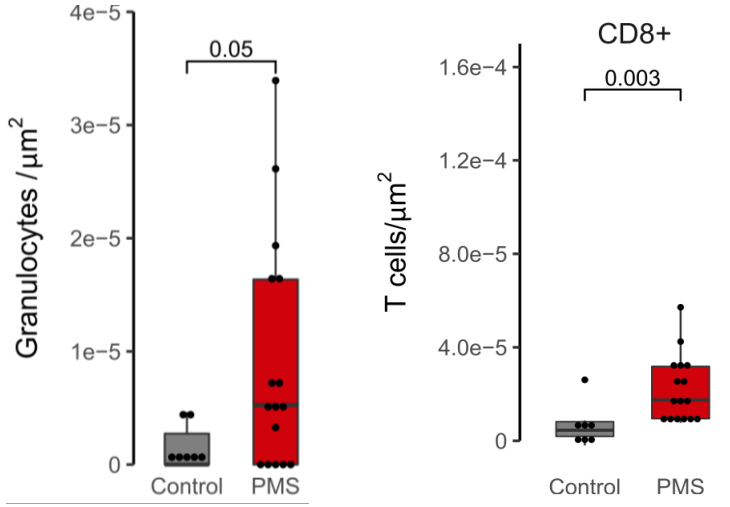
The CPs act as a **unique neuro-immunological interface** integrating CNS signals with those from circulating immune cells.

In the EAE model of MS, the CPs allow the initial entry of encephalitogenic T-Helper cells into the CNS.

Post-mortem studies have shown **infiltrating innate cells, granulocytes** and **CD8+ T cells** in the CPs of MS.

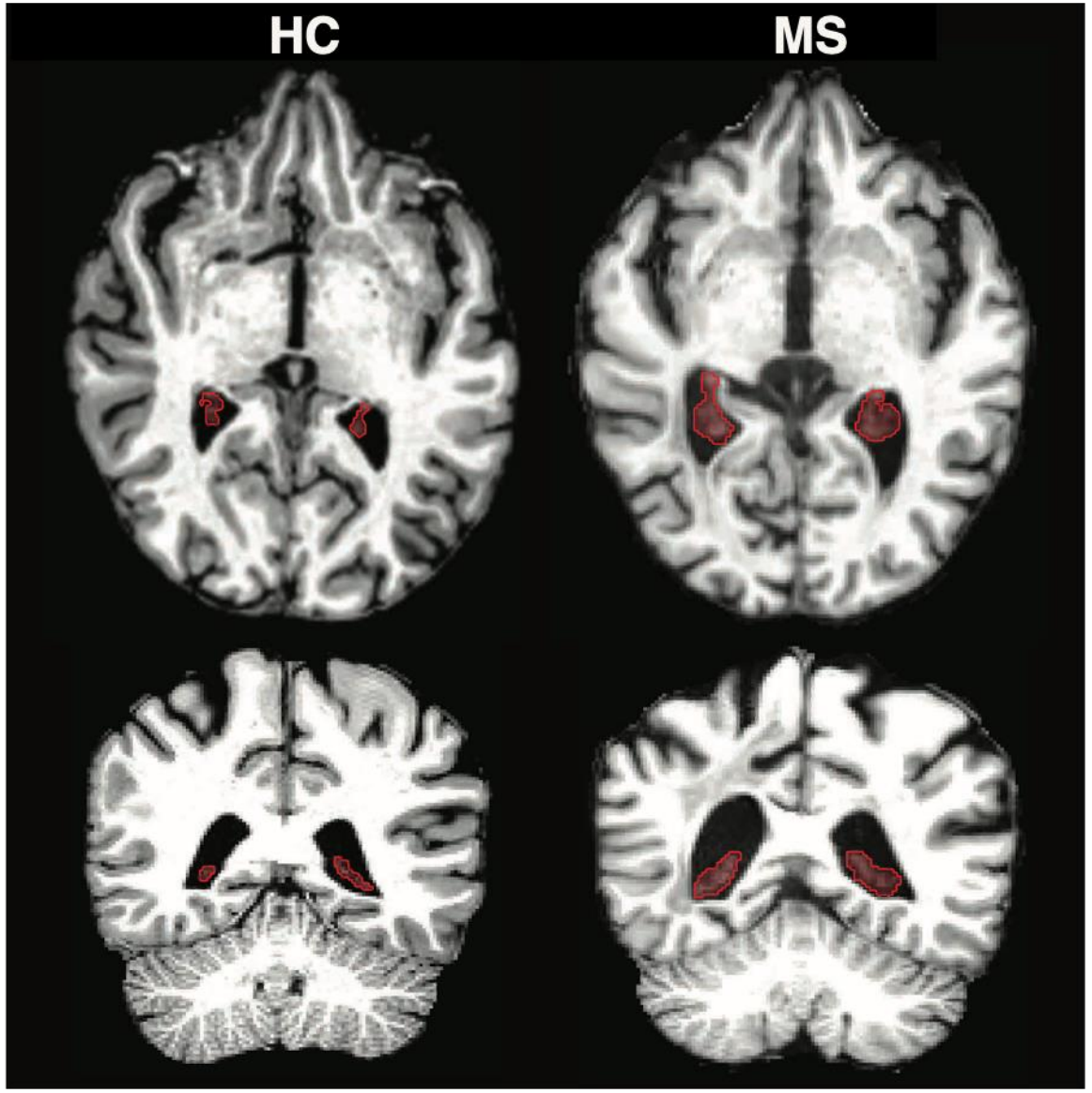



Kaur C et al, 2016



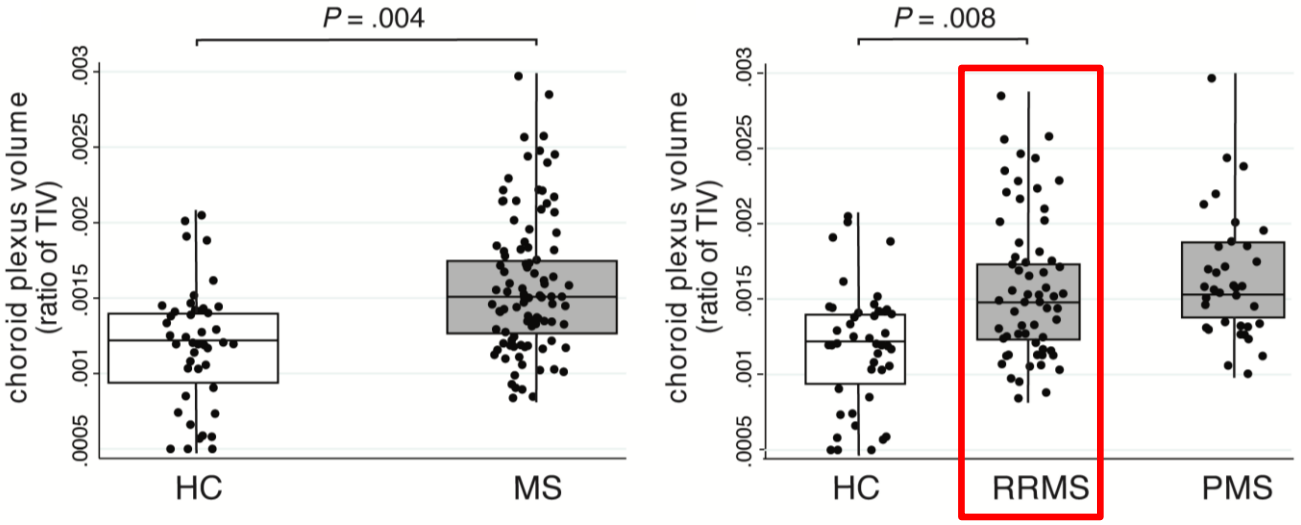

Reboldi et al, 2009; Schwartz et al, 2014; Rodríguez-Lorenzo et al, 2020

# Choroid plexuses in people with MS are larger than in healthy controls



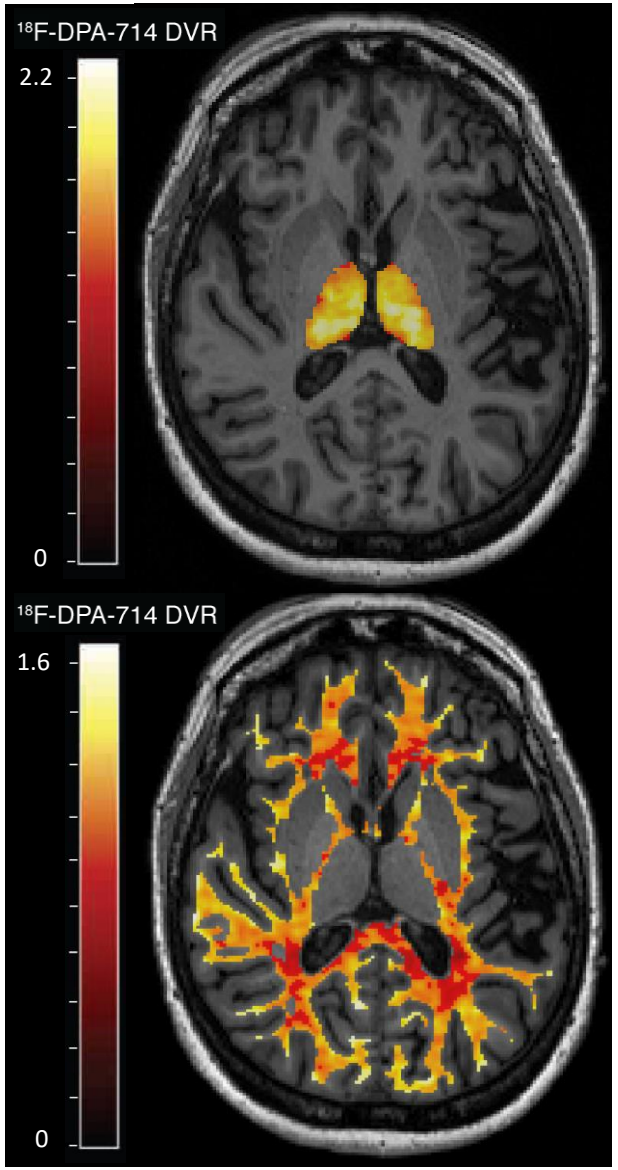

Choroid plexus volume is **35% greater**

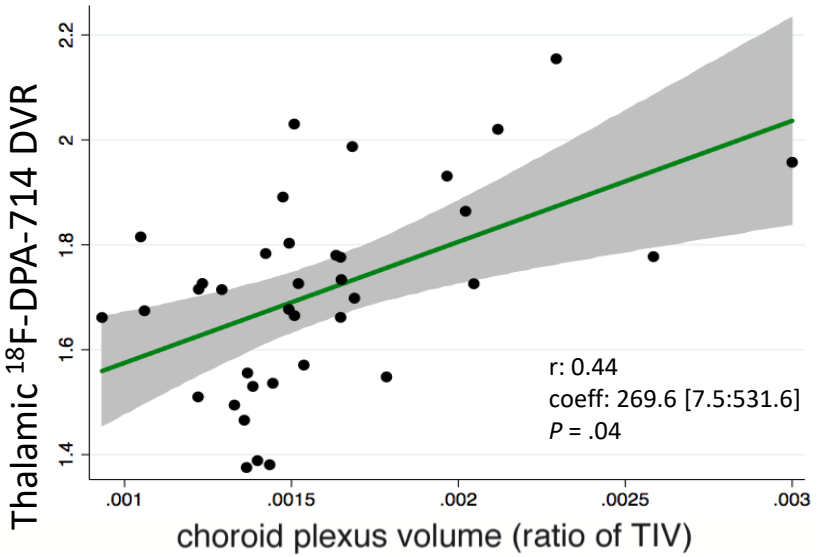
in patients with MS compared with HC

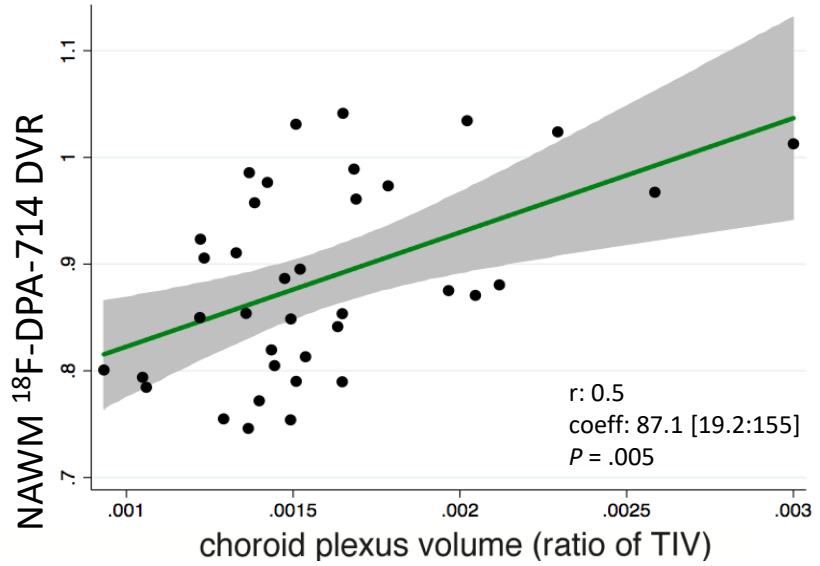



Ricigliano et al, Radiology 2021

# CP volume correlates with parenchimal neuroinflammation



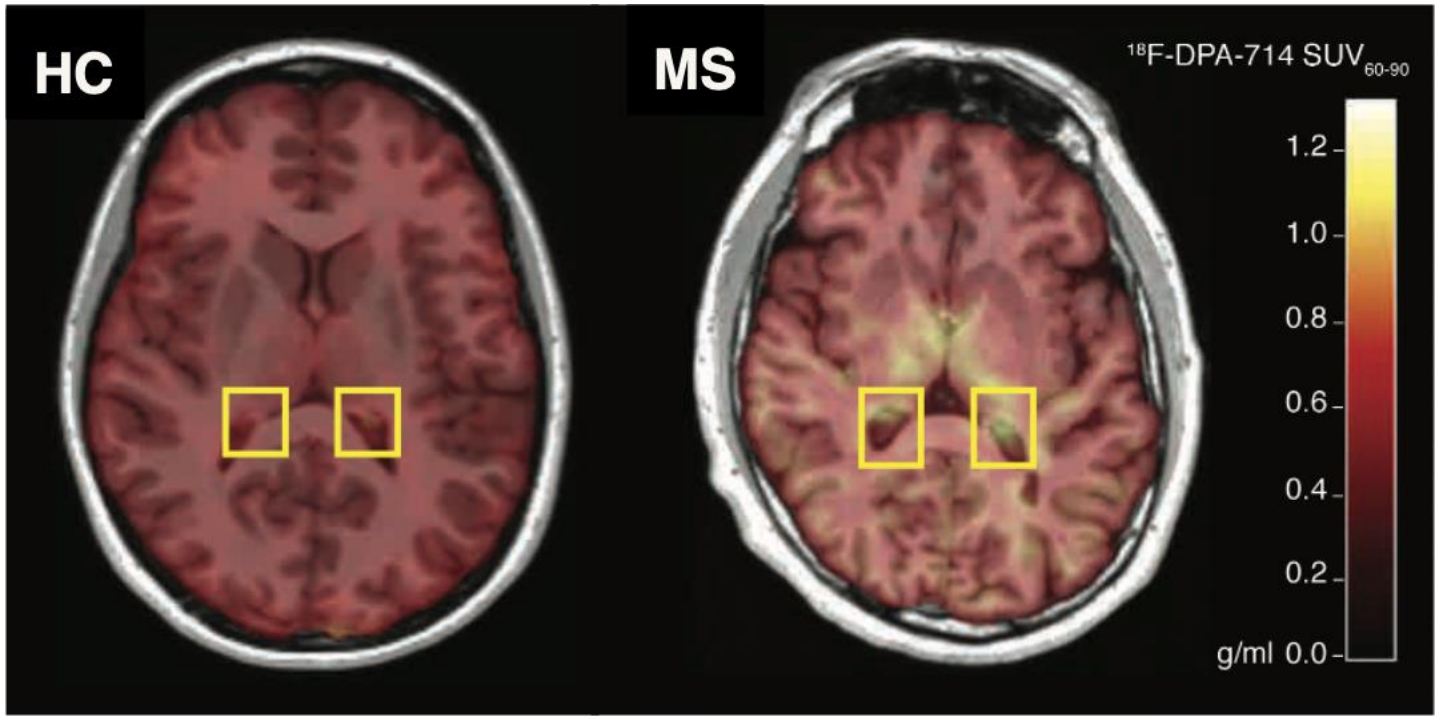

Larger CPs are associated with

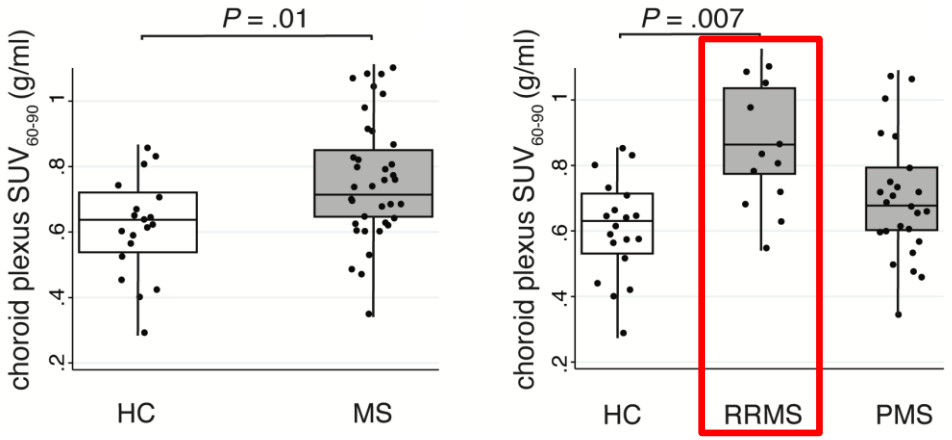
**greater innate immune cell activation in the thalami and the NAWM**

as measured by $^{18}$F-DPA-714 DVR

Ricigliano et al, Radiology 2021

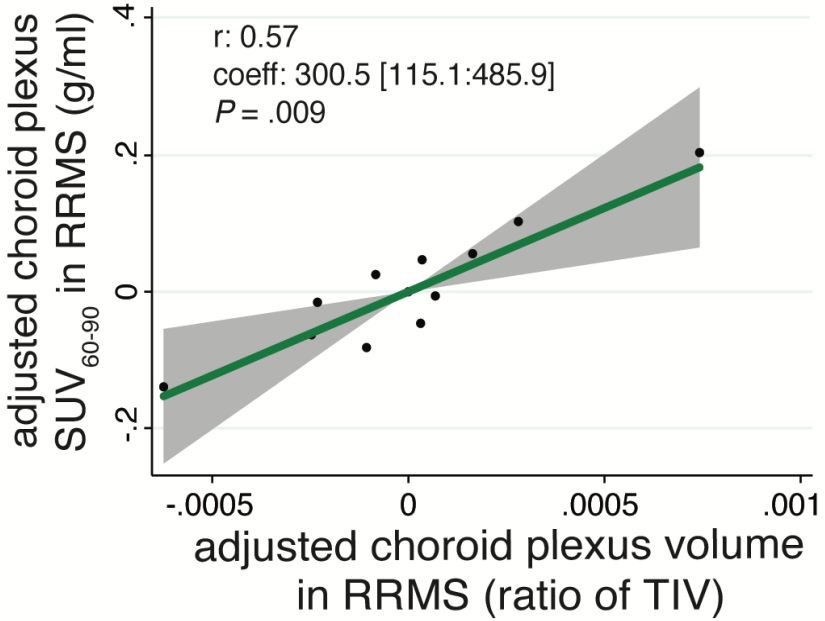
# TSPO PET reveals inflamed choroid plexuses in MS



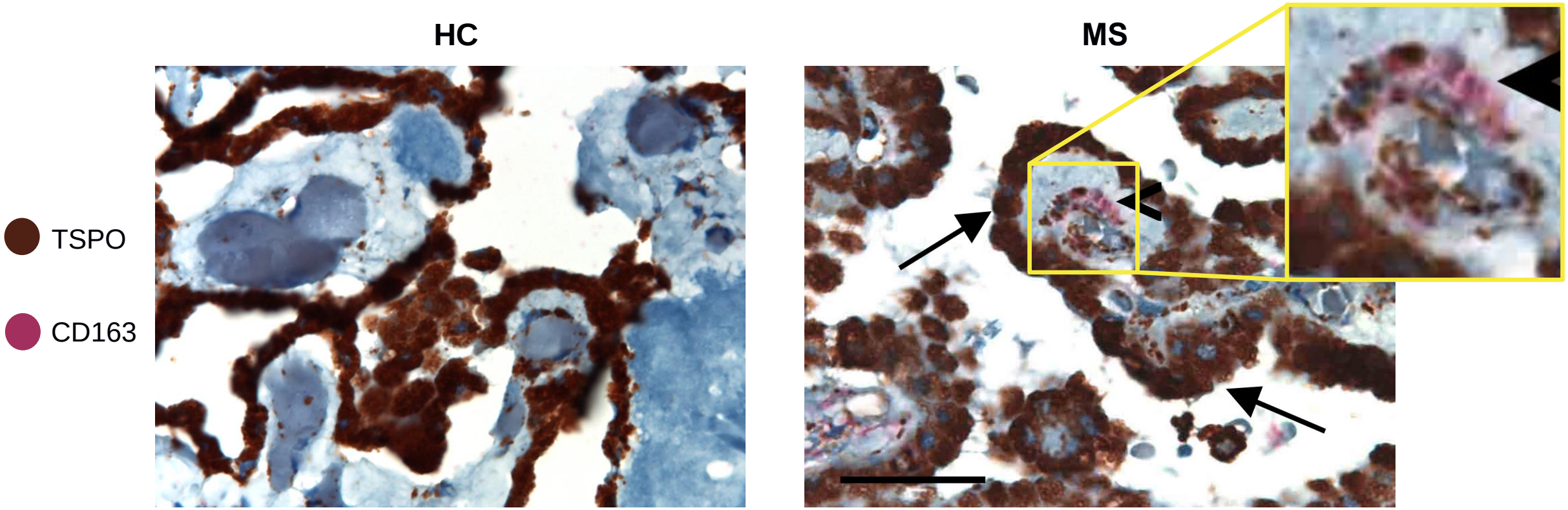

Choroid plexuses in MS have a **18.5%**

**higher DPA uptake** compared with HC




Ricigliano et al, Radiology 2021

# [18F]DPA-714 uptake in MS Choroid plexuses

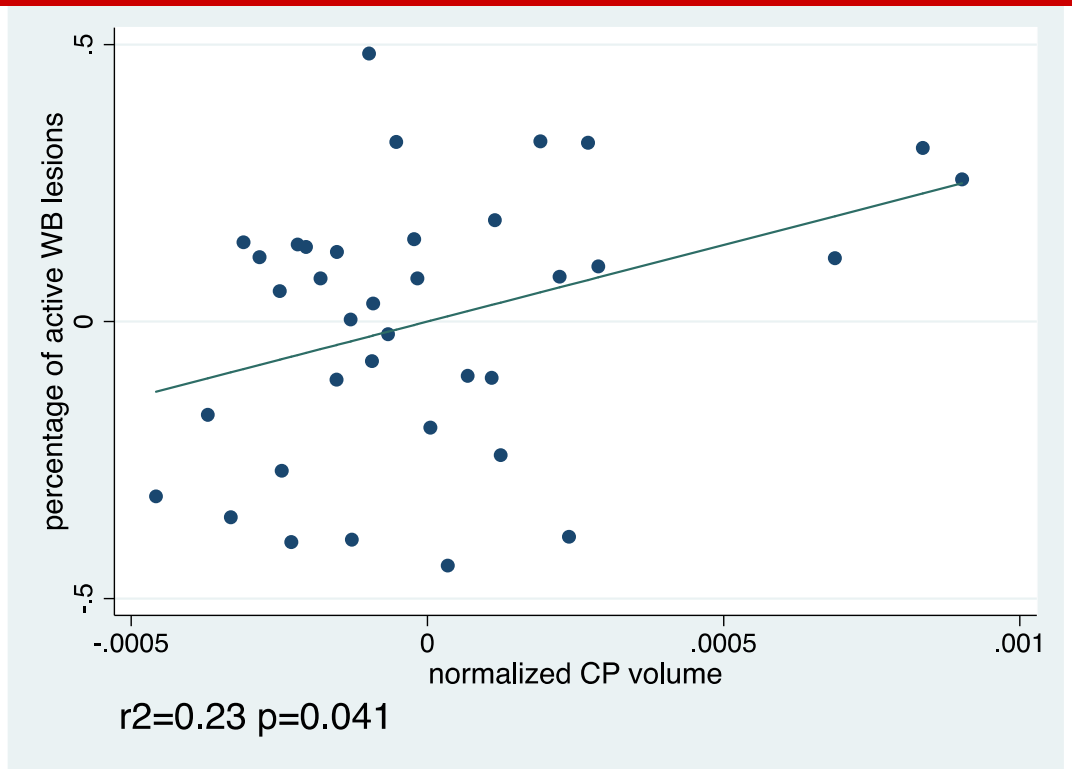



Infiltrating **CD163+ macrophages contribute to the higher TSPO expression in MS CPs**,

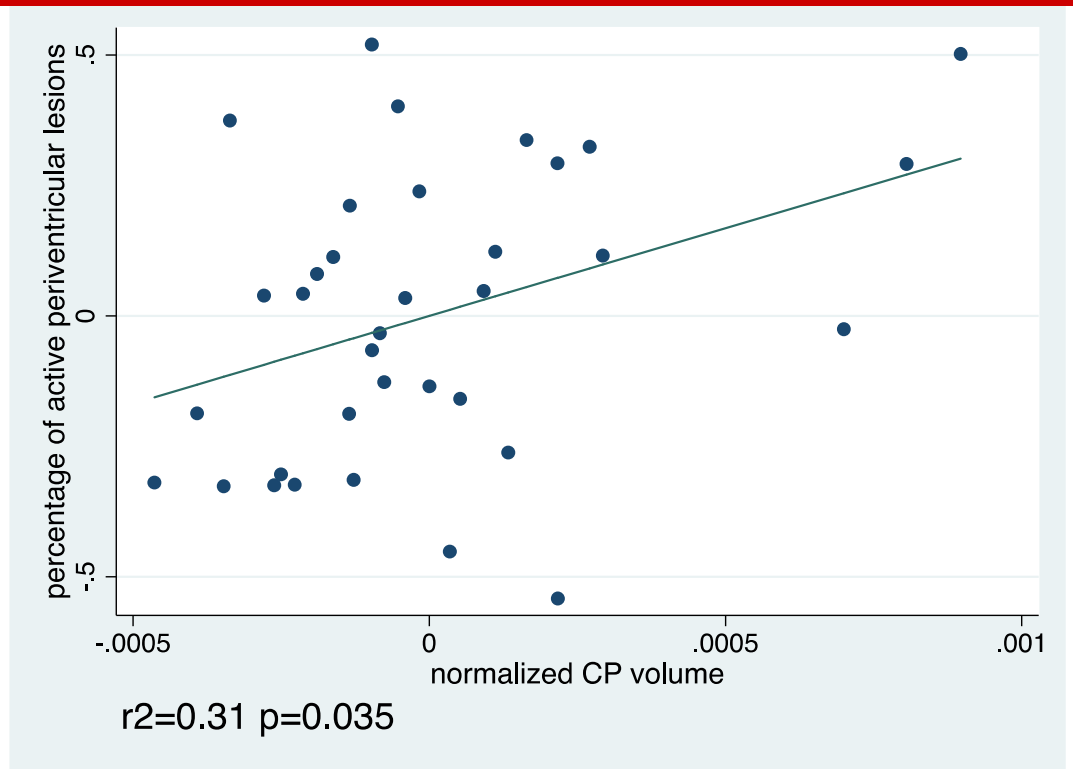
in addition to TSPO expression in the CP epithelium of both MS and HC

Ricigliano et al, 2022

# Relationship between choroid plexus volume and DPA-active lesions




RRMS: $r^2$=0.52 p=0.011




RRMS: $r^2$=0.74 p<0.001

larger CPs → higher percentage of active lesions in the whole brain, particularly in the periventricular region

Multivariable linear regressions adjusted for age, sex and verticular volume

# Conclusions

- TSPO PET is applicable in clinical studies without arterial sampling
- TSPO PET allows to generate regional individual mapping of neuroinflammation, reflecting innate immune cells density, in the MS brain
- Molecular imaging reveals smouldering component in the majority of lesions, that may start at the relapsing stage, and is linked to disability progression
- The smouldering component is regionalized in the brain and may involve a BCSFB dysfunction at the choroid plexus level

# Acknowledgements

**B Stankoff/ C Lubetzki ICM team**

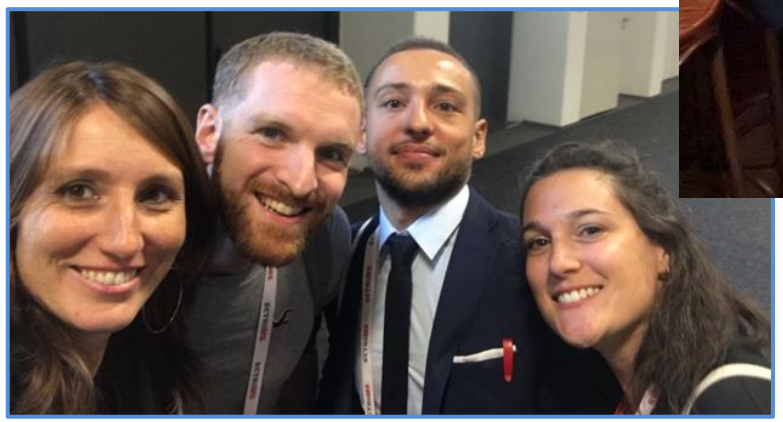
Repair in MS: from biology to cllinical translation

Bruno Stankoff
Matteo Tonietto
Emilie Poirion
Andrea Lazzarotto
Mariem Hamzaoui
Giacomo Boffa
Arya Yazdan Panah
Annalisa Colombi
Emanuele Morena
Jeanne Garcia
Emeline Chaugne
Milena Pitombeira
Théodore Soulier
Erika Portera
Natalia Shor

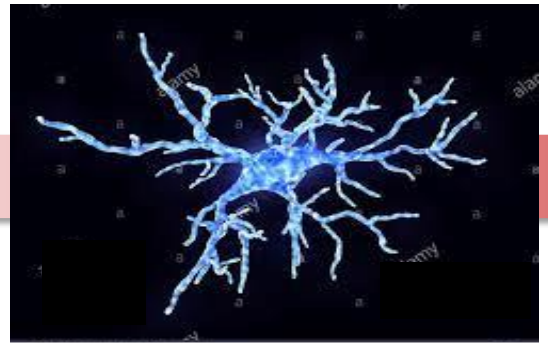
Catherine Lubetzki
Céline Louapre
B Zalc

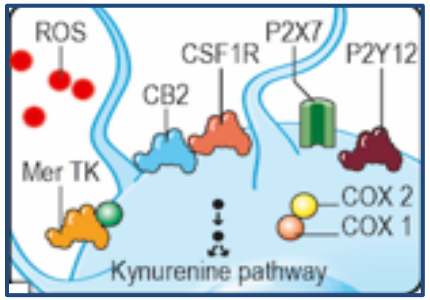
Vincent Lebon
Michel Bottlaender
Bertrand Kuhnast
Philippe Gervais

Danielle Seilhean
Elodie Martin



# Novel perspectives in innate immune cell imaging






## FUTURE TARGETS FOR MICROGLIA AND MACROPHAGES

Macrophage colony stimulating factor 1 receptor

P2Y12R
P2X7R

PNAS

**PET imaging of microglia by targeting macrophage colony-stimulating factor 1 receptor (CSF1R)**

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**The $P2X_7$ receptor tracer [$^{11}$C]SMW139 as an *in vivo* marker of neuroinflammation in multiple sclerosis: a first-in man study**

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Beaino et al, 2017; Horti et al, 2019; Hagens et al, 2020; Bodini et al, *Nat Rev Neurol*, 2021; Zhou et al, 2021