

USPIO-enhanced MRI for monitoring neuroinflammation: How many irons in the fire?



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Declaration of Conflict of Interest or Relationship

Speaker Name: Marlène Wiart

I have the following conflict of interest to disclose with regard to the subject matter of this presentation:

✓ **Company name:** Guerbet

Type of relationship: Research grants and stipends (Ferumoxtran-10)

✓ **Company name:** AMAG

Type of relationship: Research contract (Ferumoxytol)

Brain inflammation is a hallmark of many neurological diseases

Chronic diseases

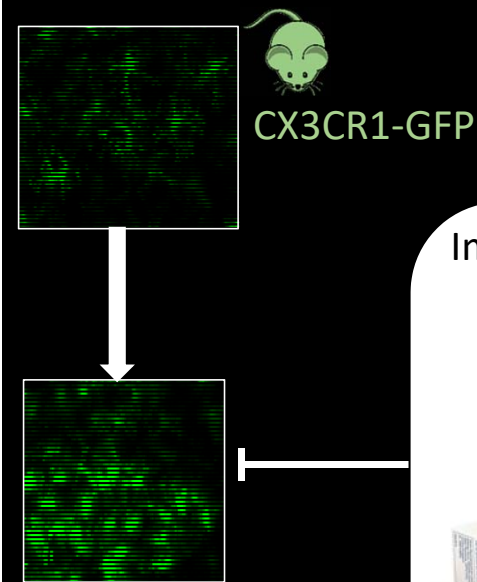
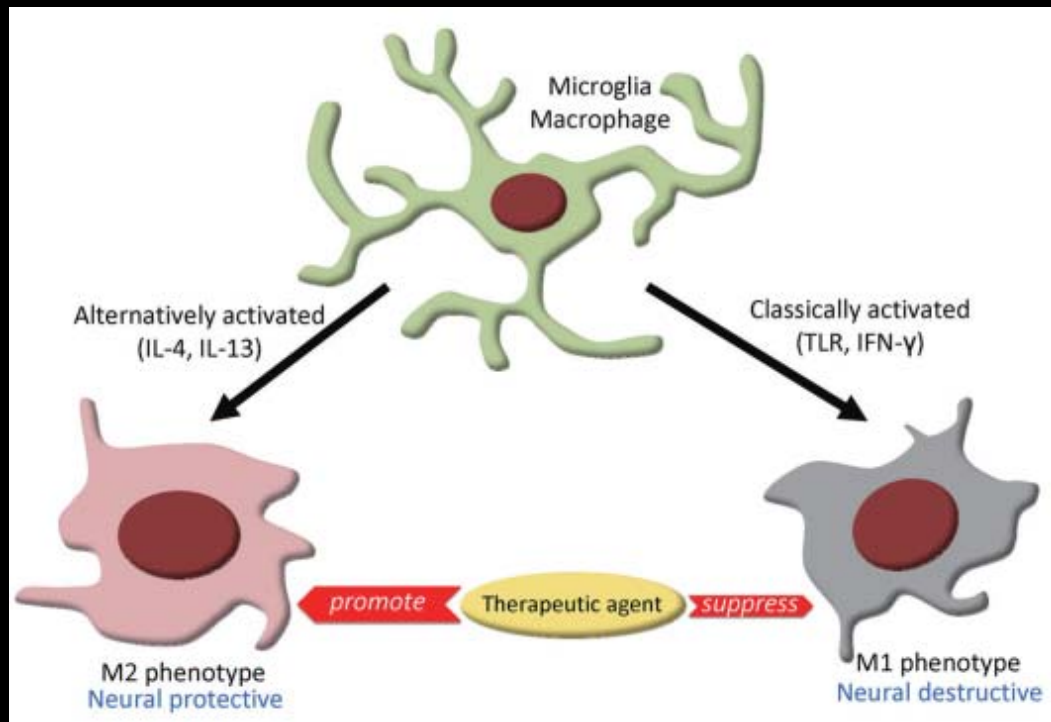
- Multiple sclerosis
- Alzheimer's disease
- Intracranial aneurysms

Acute diseases

- Traumatic brain injury
- Stroke
- Migraine



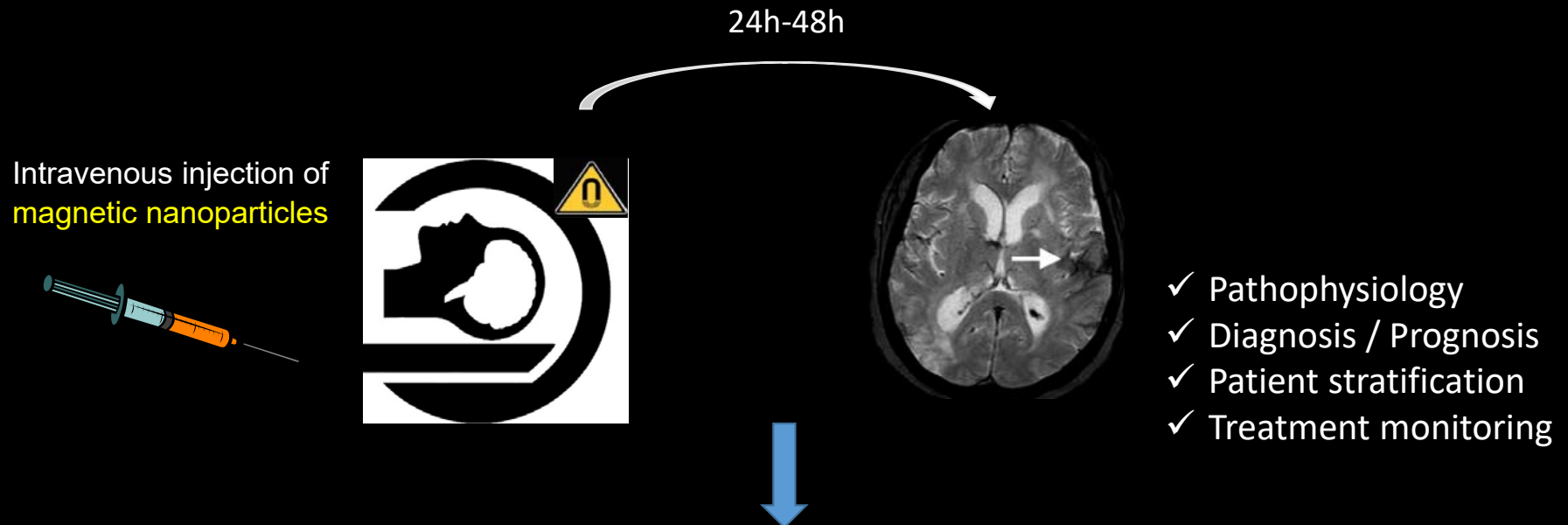
Microglia/Macrophages (M/M) represent a therapeutic target in neuroinflammatory diseases



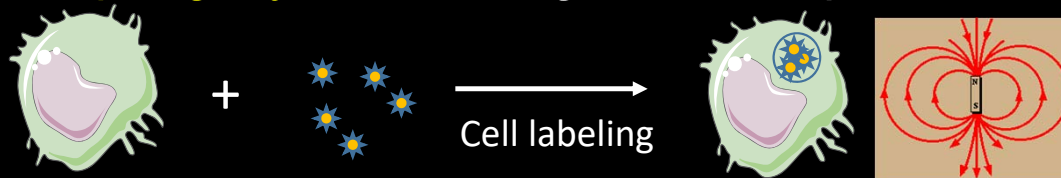
Adapted from Huang YC et al. Acta pharmacologica Sinica 2013

May M/M serve as MRI biomarkers of brain inflammation?

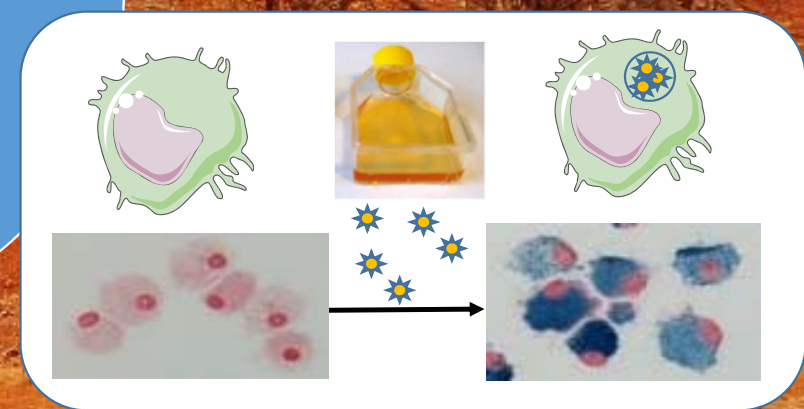
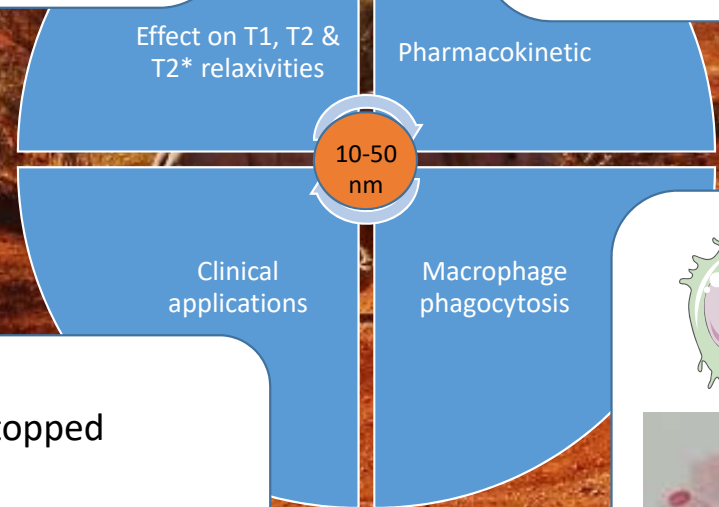
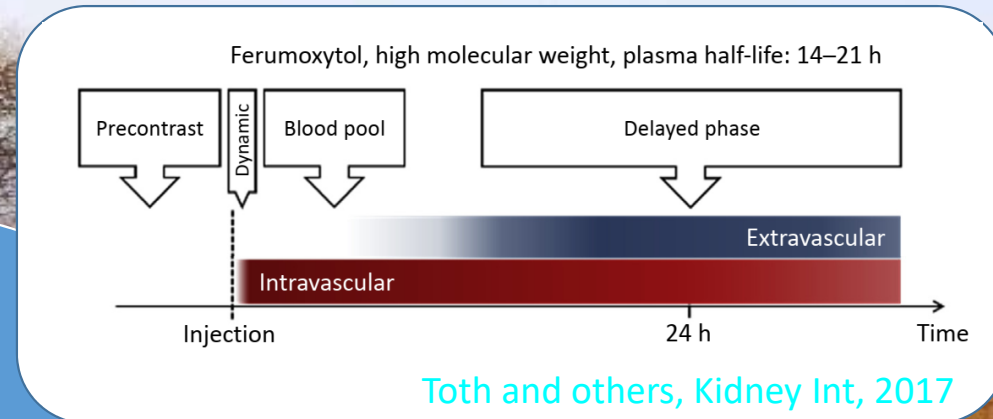
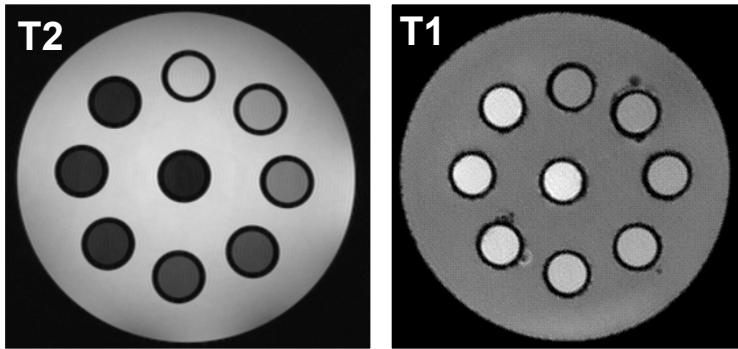
Principle of USPIO-enhanced MRI



In vivo **phagocytosis** of magnetic nanoparticles by **macrophages**



Ultrasmall superparamagnetic particles of iron oxide (USPIO)

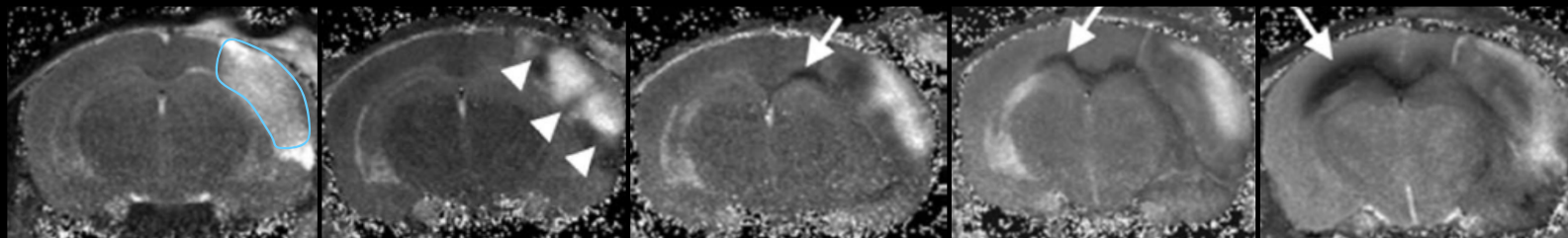
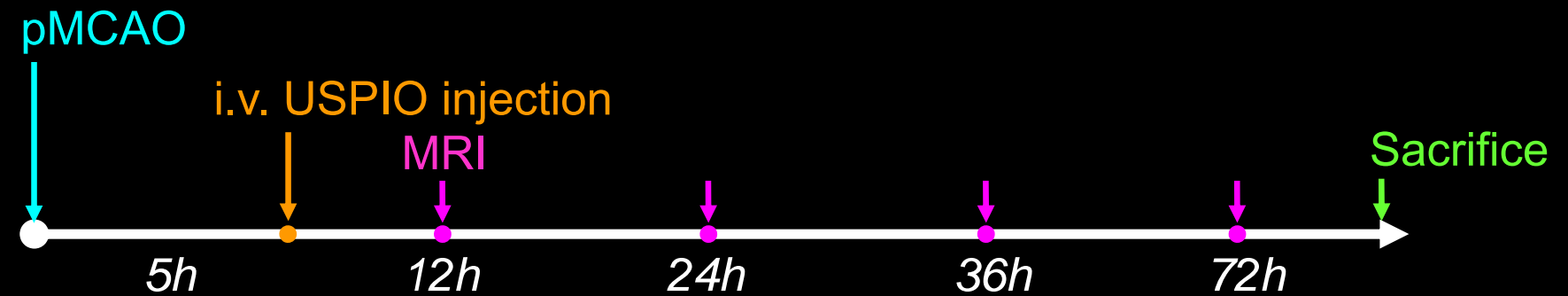


- **Ferumoxtran-10:**
'Historical' USPIOs, now stopped
- **Ferumoxytol:**
Currently the only FDA-approved USPIO
BUT 'off-label' use for radiology



USPIO-enhanced MRI

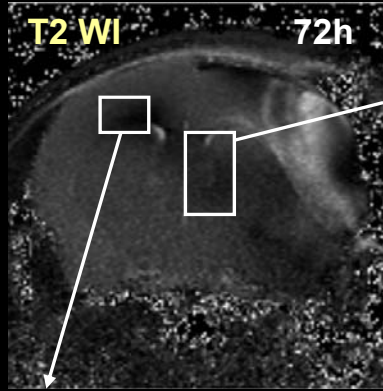
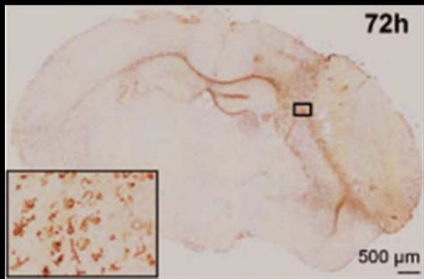
Proof-of-Concept in a mouse model of ischemic stroke



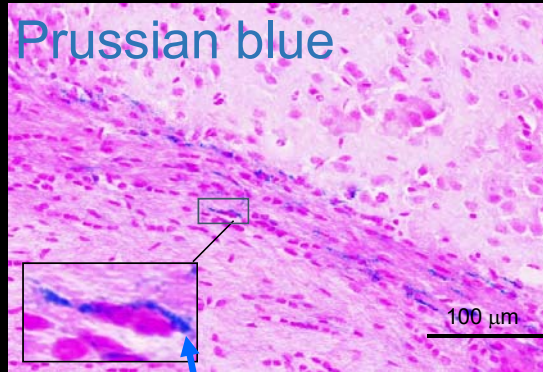
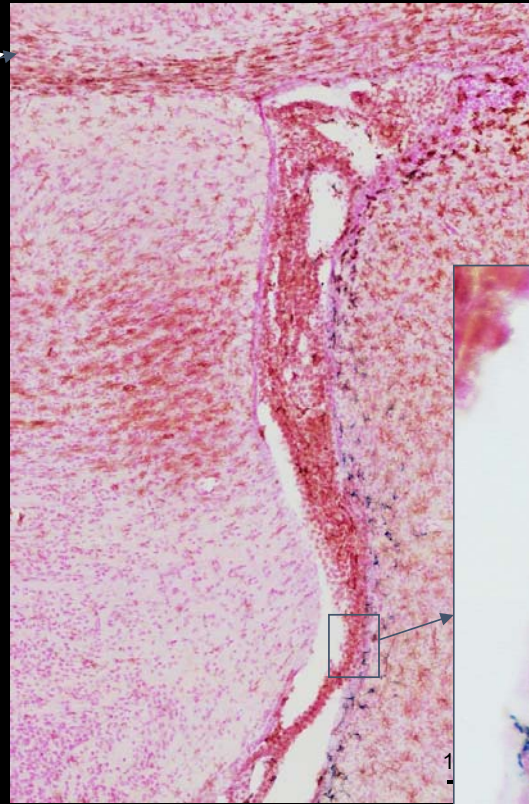
T2-weighted images, spin-echo imaging

USPIOs are taken up by macrophages in vivo after ischemic stroke

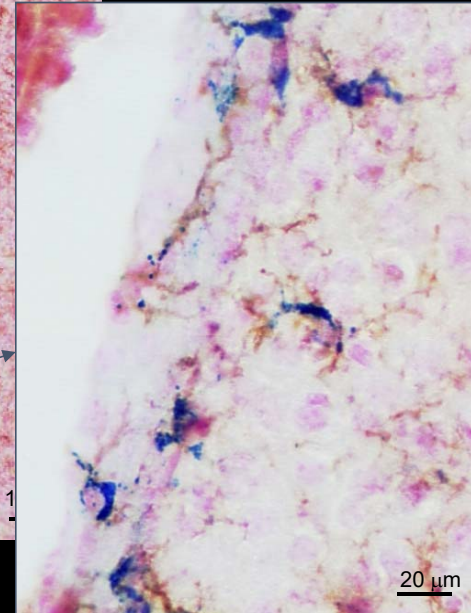
F4/80 (M/M)



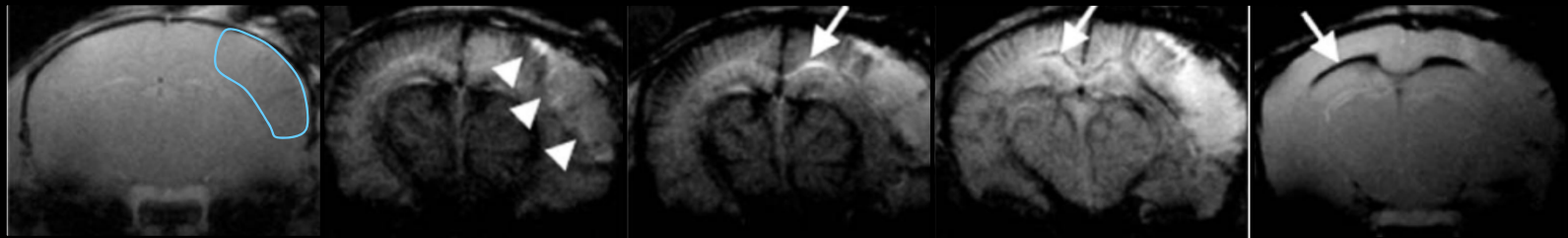
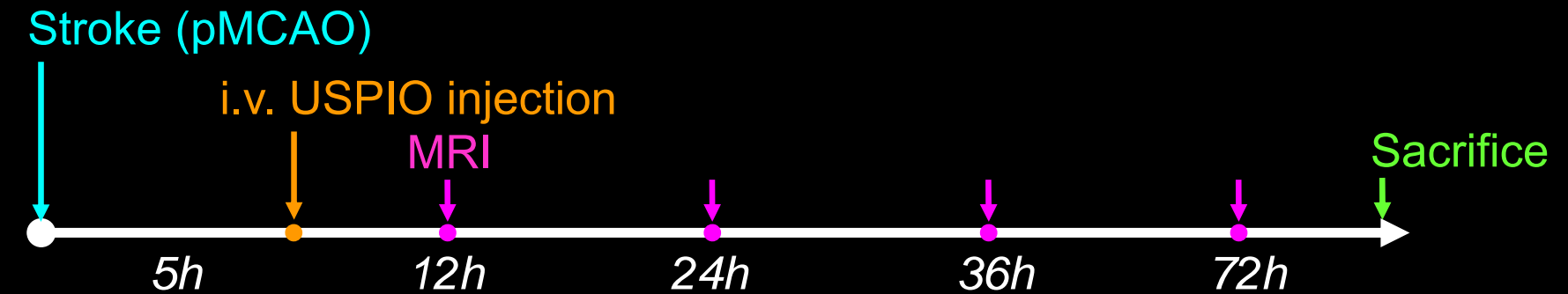
F4/80 + Prussian blue



Intracellular iron



USPIOs internalization may be monitored by MRI



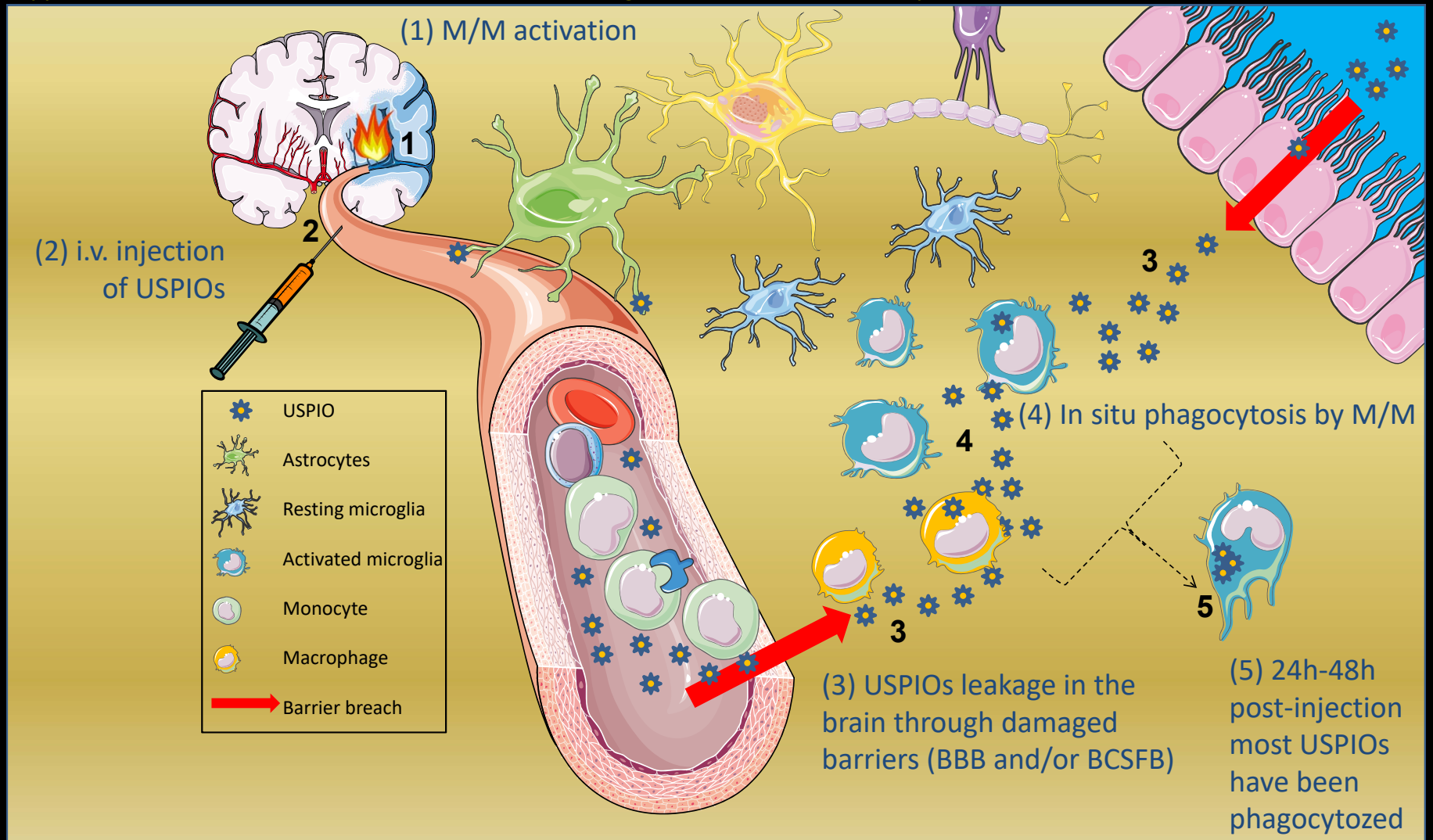
T1-weighted images, gradient-echo imaging

Wiert M, Nighoghossian N, et al, Stroke 2007



Brisset JC, Wiert M, et al. European Radiology 2009

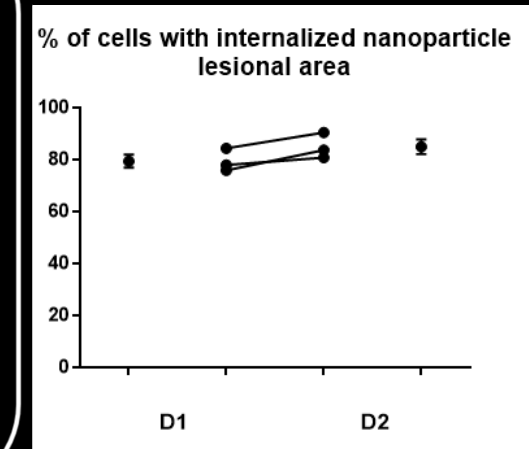
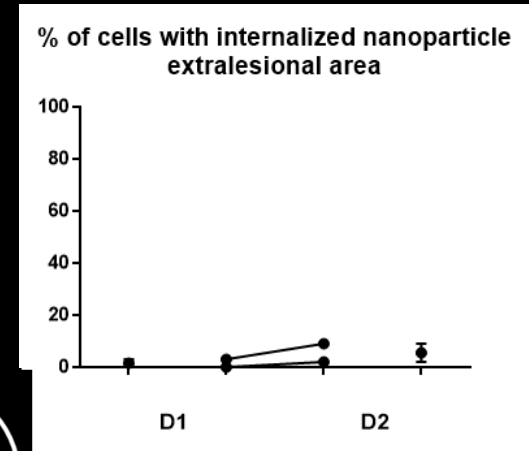
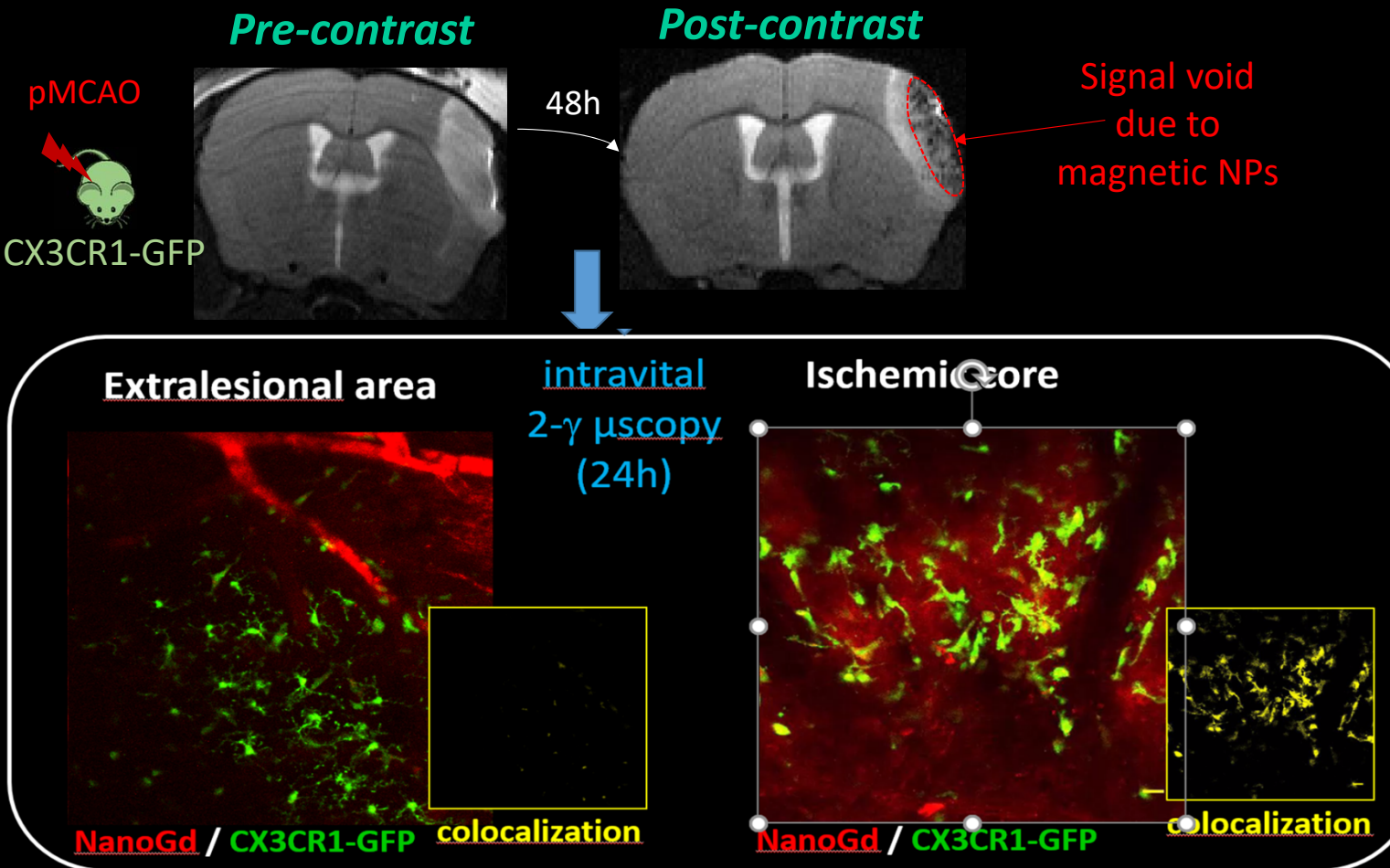
Hypothesis for USPIO-enhanced MRI working mechanisms in the pMCAO model of ischemic stroke



Desestret V, Wiart M, et al. Stroke 2009; Brisset JC, Wiart M et al, IRBM 2018

Seeing is believing...

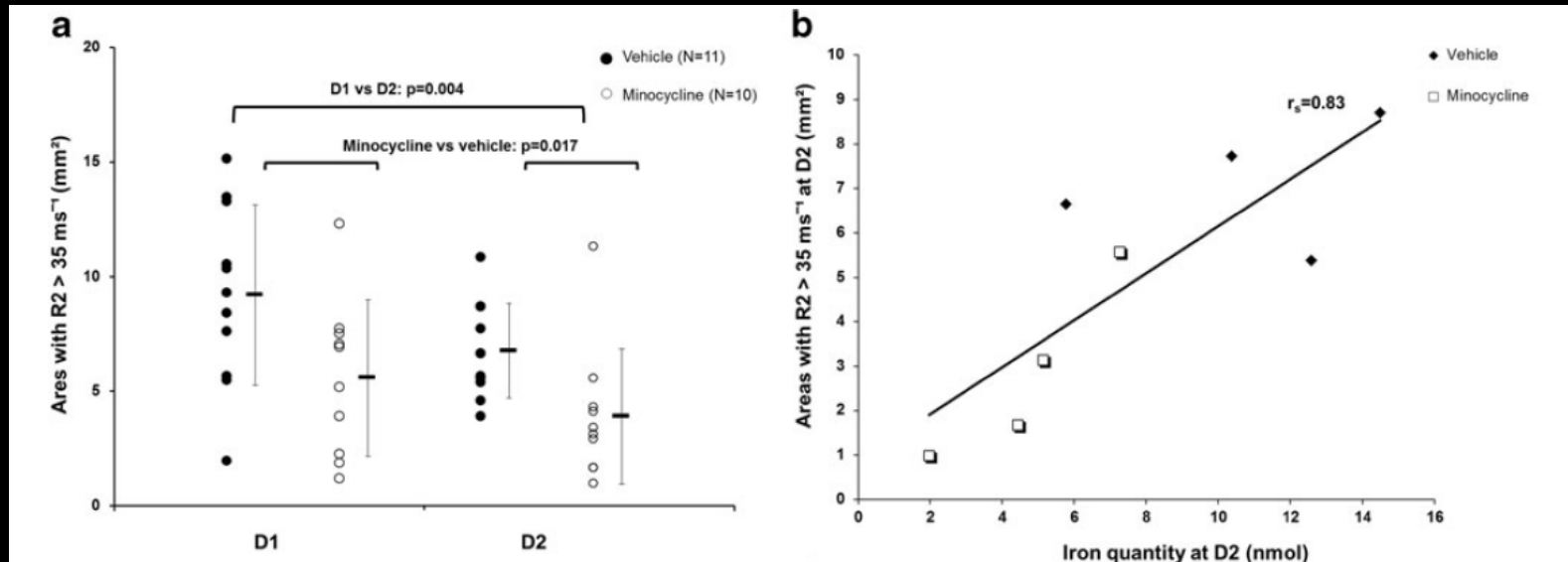
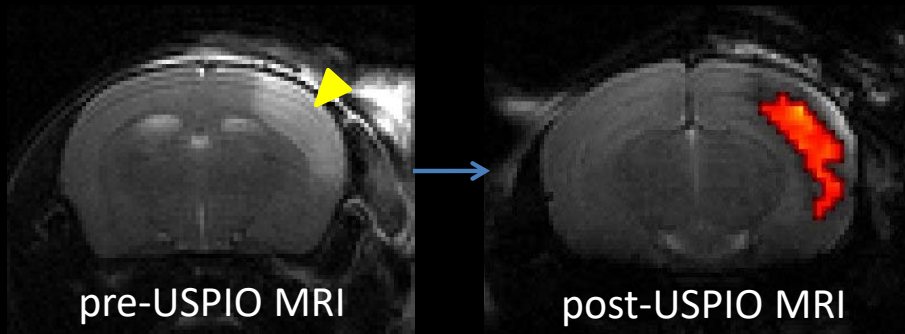
Evidence of nanoparticle (NP) phagocytosis from intravital 2- γ μ scopy in ischemic stroke



/, Wiert M et al, in prep

Can USPIO-enhanced MRI be used for treatment monitoring?

Pre-clinical neuroimaging study: Proof-of-Concept

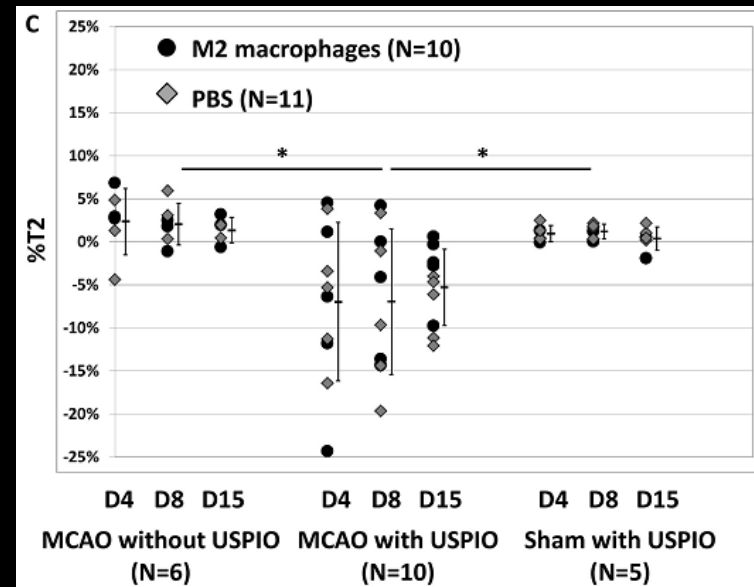
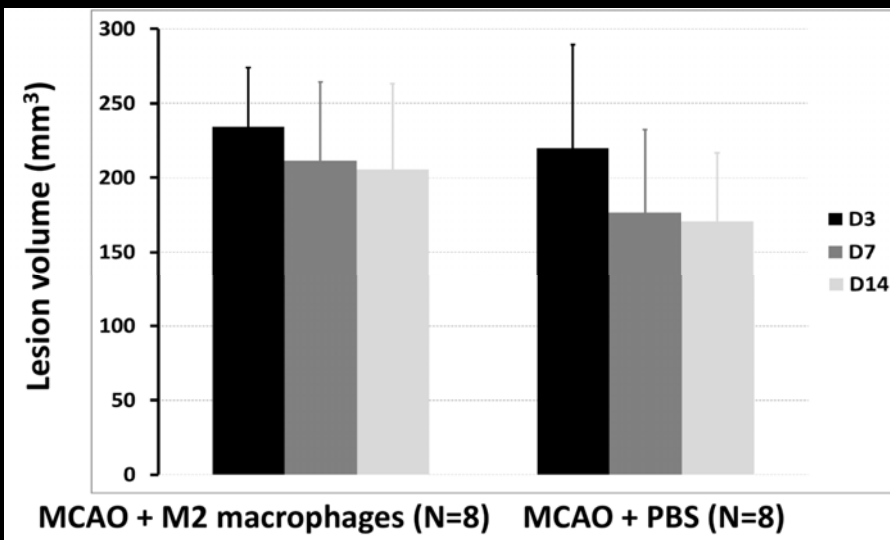
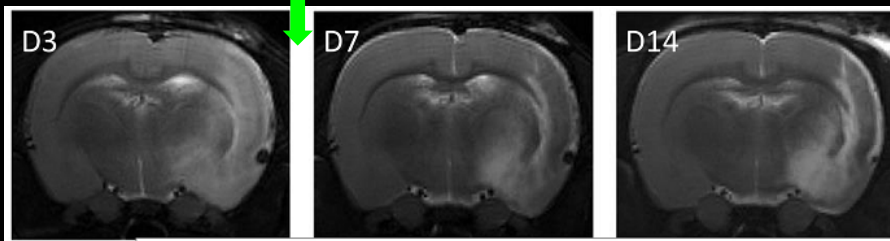


Marinescu M, Wiart M, et al, Eur Radiol 2013

Can USPIO-enhanced MRI be used for treatment monitoring?

Pre-clinical neuroimaging study: Example of application

Administration of M2-polarized macrophages i.v.



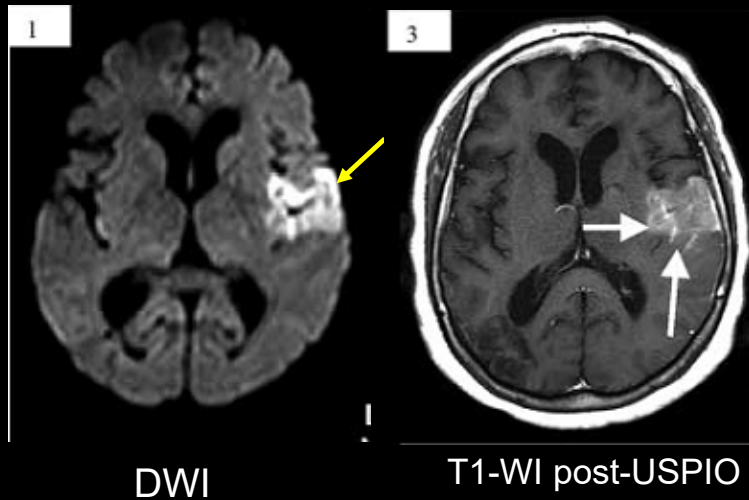
Desestret V, Wiart M, et al, Plos One 2013

Clinical applications of USPIO-enhanced MRI in neurology

Seminal works



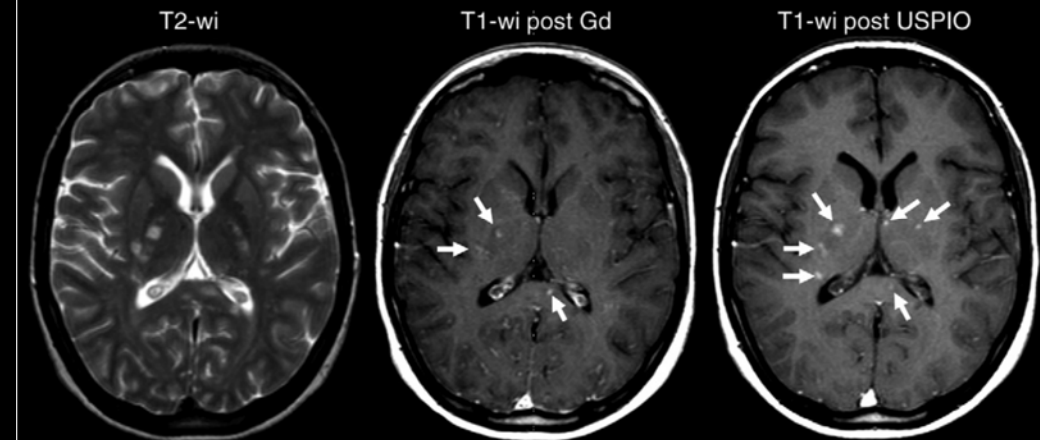
Ischemic stroke



Nighoghossian N, Wiart M et al, Stroke 2007



Multiple Sclerosis

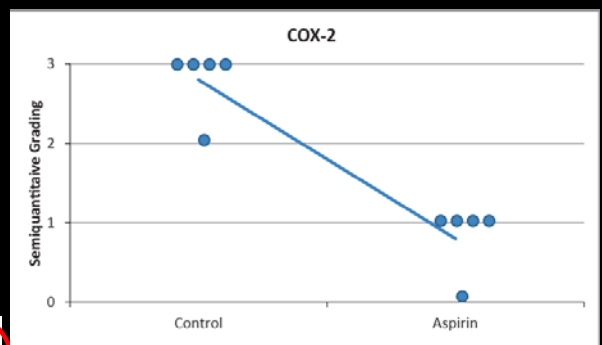
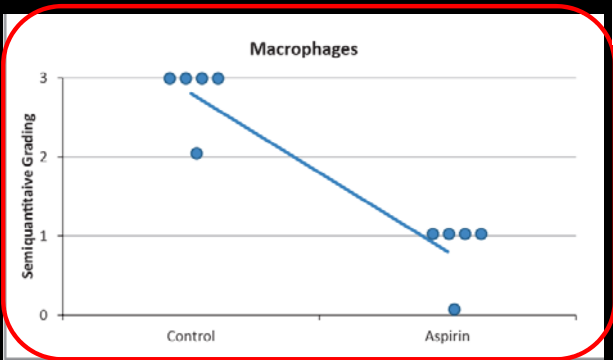
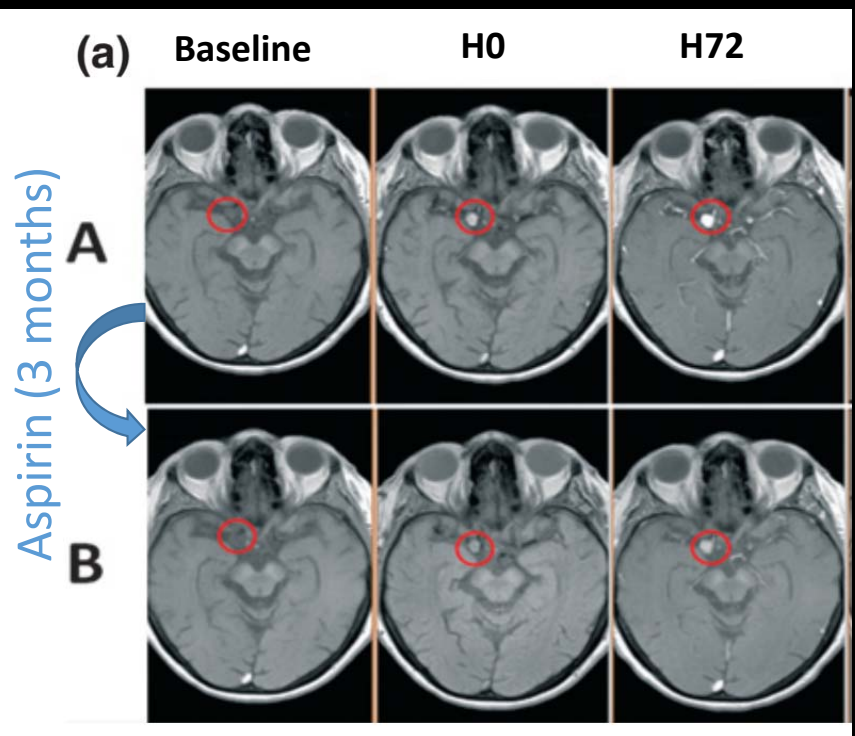


Tourdias T et al, Radiology 2012

Can USPIO-enhanced MRI be used for treatment monitoring?

Clinical neuroimaging study (1/2)

Patients with intracranial aneurysms



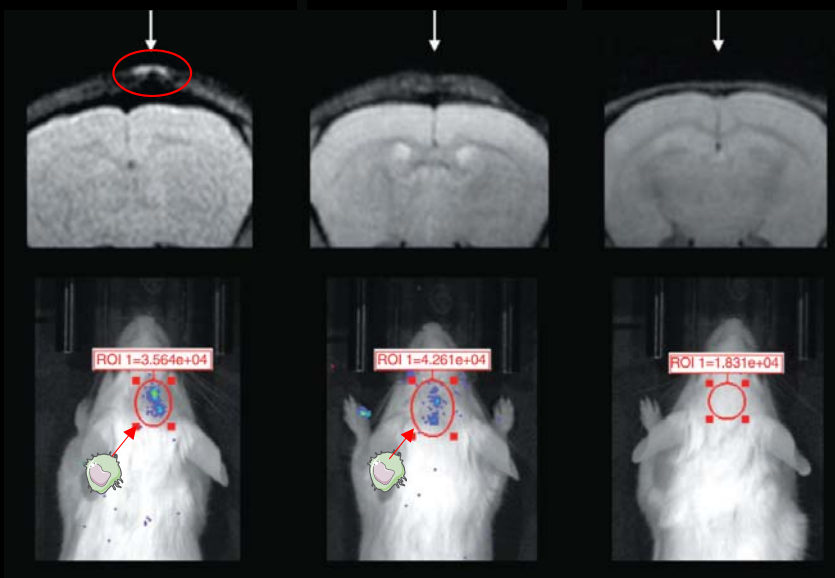
Adapted from Hasan D et al, J Am Heart Assoc 2013

Can USPIO-enhanced MRI be used for treatment monitoring?

Clinical neuroimaging study (2/2)

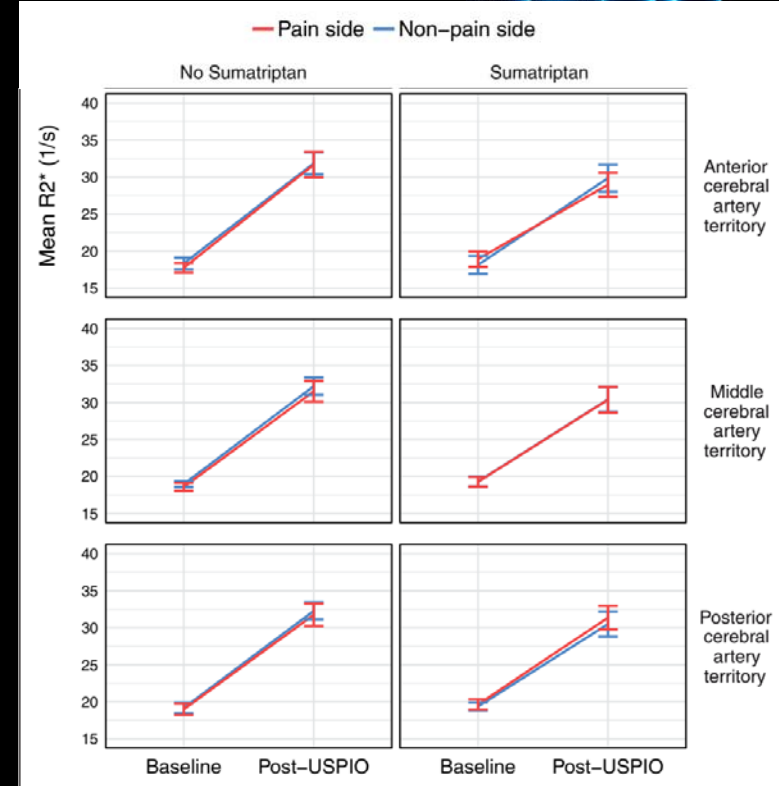
Mouse model of migraine attack

Migraine + USPIO Migraine only Healthy control

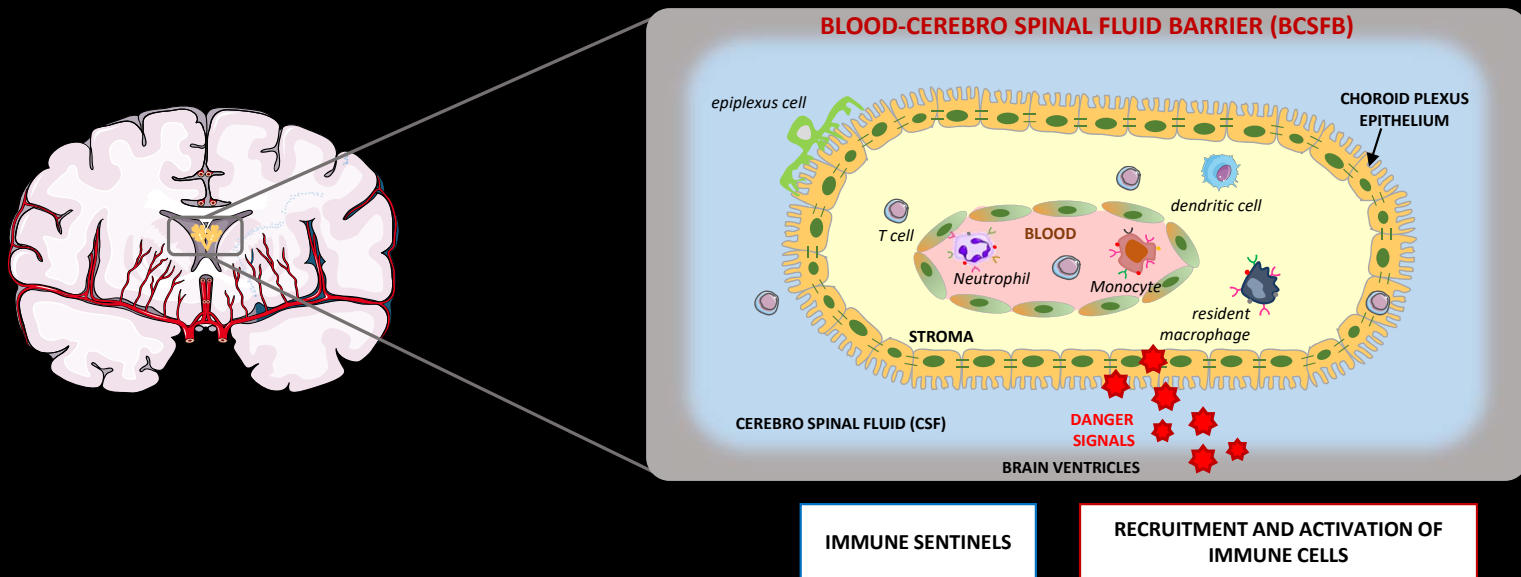


Khan S et al, Cephalgia 2019

Patients with migraine attack



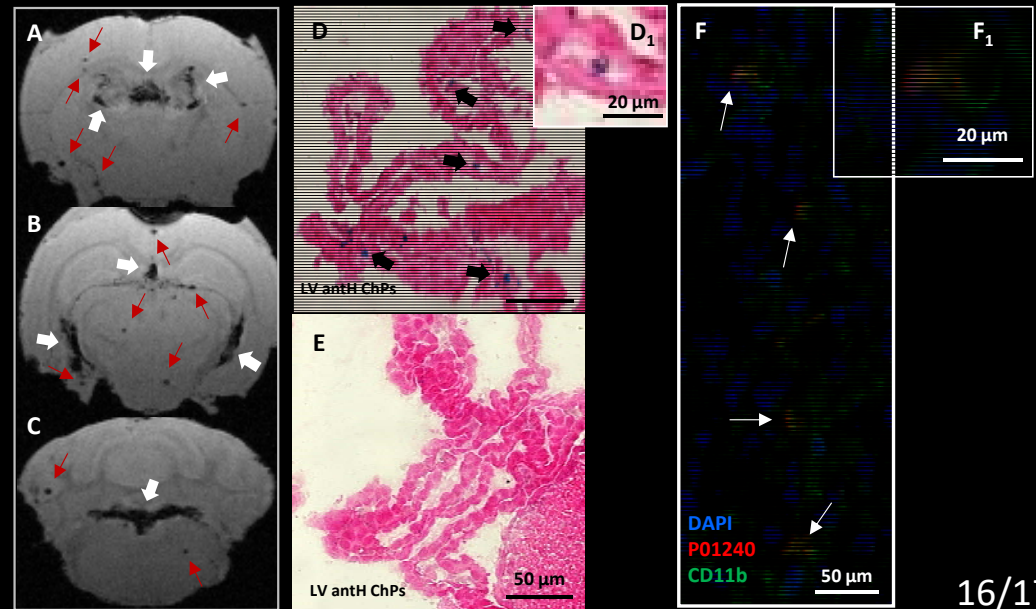
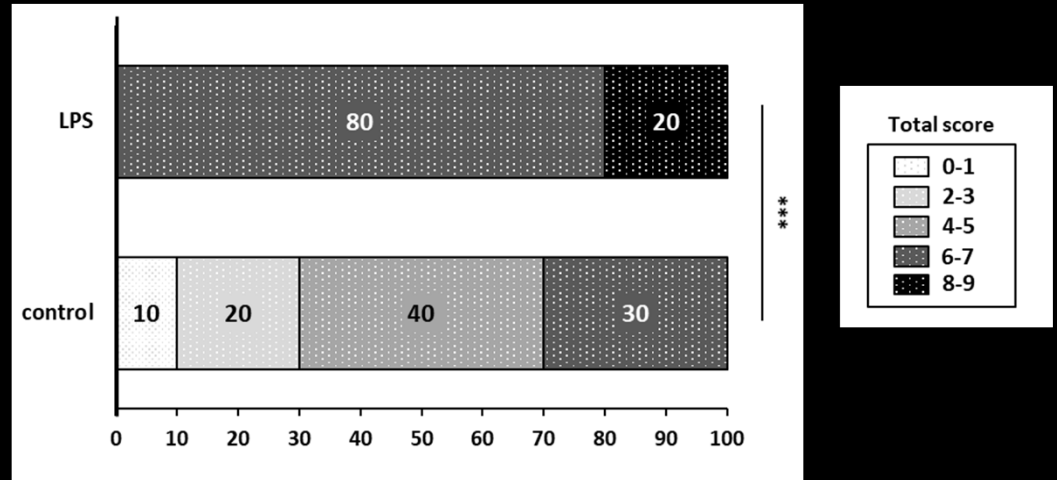
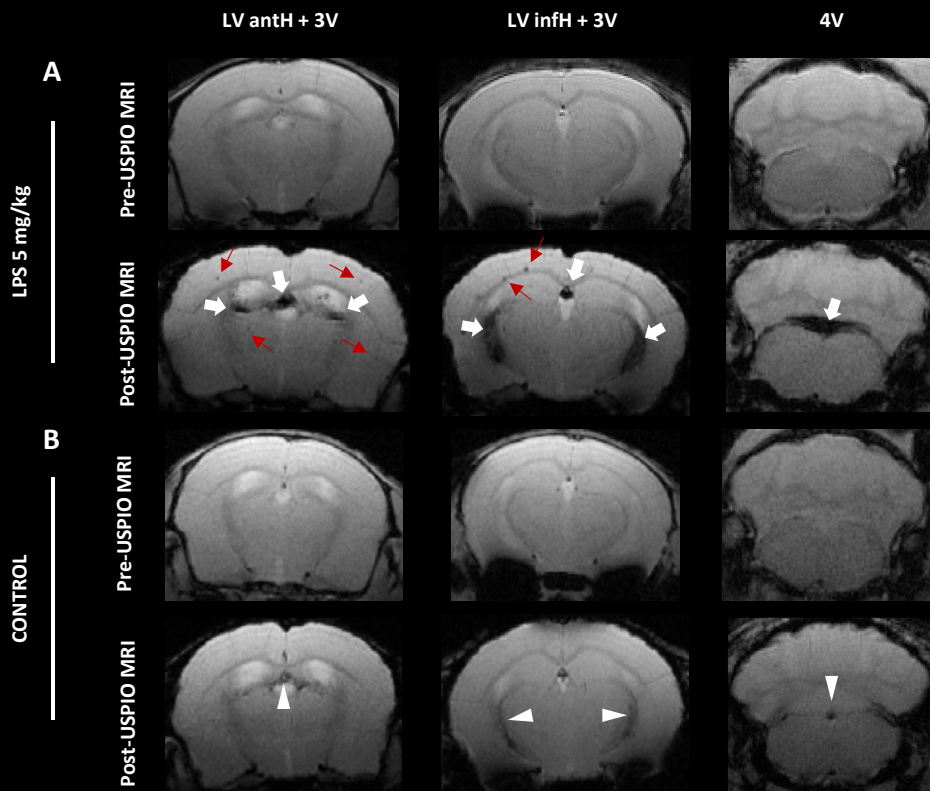
Can USPIO-enhanced MRI be used to detect neuroinflammation w/o USPIOs accumulating in the brain parenchyma?



- Choroid plexus are “gates to the brain” [Schwartz et al, Nat Rev Immunol 2013](#)
- ChPs are involved in the early pathophysiology of neuroinflammatory disorders
- ✓ multiple sclerosis, Alzheimer’s disease, stroke, SIRS ...

USPIO-enhanced MRI of the choroid plexus is an early marker of neuroinflammation

Mouse model of neuroinflammation (LPS i.p.)



Take home messages

- Microglia/Macrophages may serve as imaging biomarkers of neuroinflammation thanks to USPIO-enhanced MRI
- Some USPIOs may be used in patients (although 'off-label'): USPIO-enhanced MRI has already been used for investigating a range of neurological diseases in the clinical field
- USPIO-enhanced MRI has the potential to monitor the effects of drug treatment in neurological diseases
 - But difficulty to quantify the MR signal

Acknowledgments



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Hasan Al Said
Quyen Do



<http://www.nanobrain.fr/>

ANR-15-CE18-0026-01



<http://www.rhu-marvelous.fr>

ANR-16-RHUS-0009



<https://www.cermep.fr/>