Dynamic assessment of macrophages infiltration and microstructural damage in MS lesions

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The macrophages

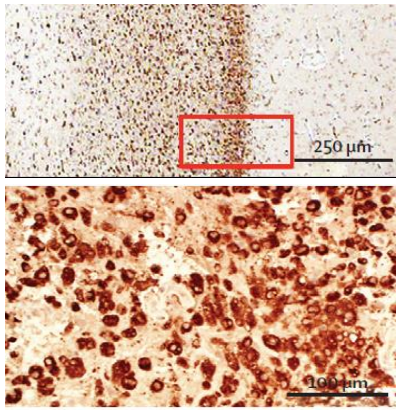
- Components of the innate immune system

  microglia and blood born monocytes

- In animal models of MS :

  1) important effectors of tissue structure loss in the lesions

  2) promote remyelination



(Frischer et al., 2015)

- In pathological studies :

  Active lesions are infiltrated by macrophages with myelin debris

In MS patients ?

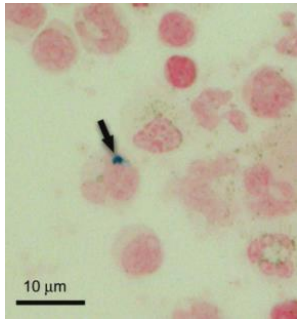
Imaging techniques

Cellular Imaging

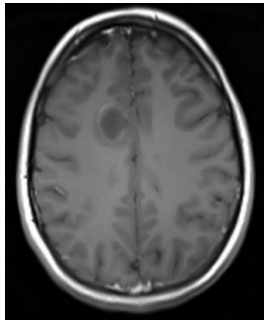
Ultrasmall Superparamagnetic Particles of Iron Oxydes (USPIO)

Marker of blood born monocytes

Decrease T2, T2* and T1



(Vellinga et al., 2008)

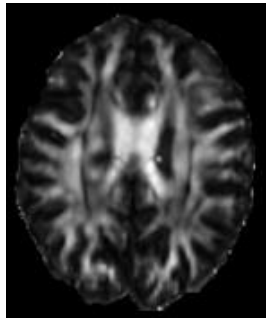


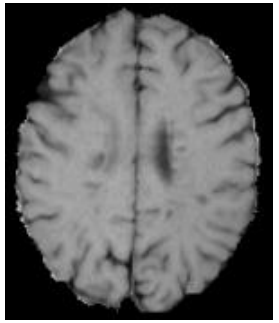
Quantitative Imaging

Marker of tissue structure

MT imaging

Diffusion imaging





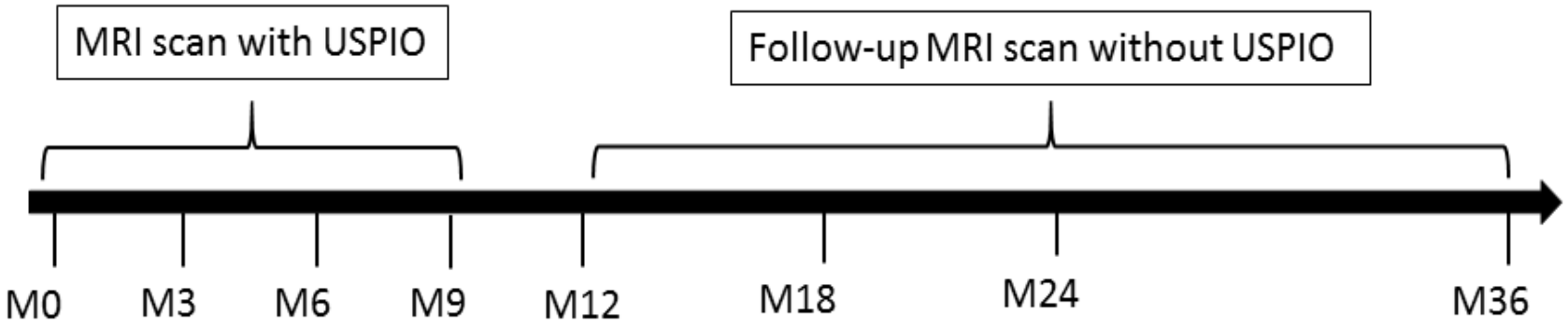
Objectives

To describe the dynamic of macrophages infiltration within MS lesions during the first year of the disease

To describe the link between initial macrophages infiltration and other quantitative MRI metrics reflecting tissue structure for up to 3 years

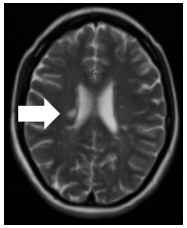
Study design

Monocentric, prospective and longitudinal study
16 CIS patients

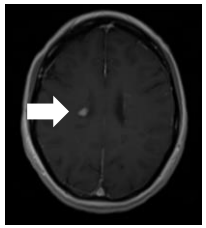


Images acquisition

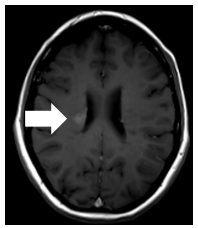
1. Conventional MRI: lesions imaging



T2

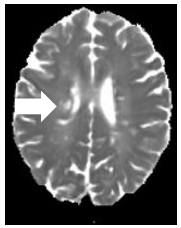


T1+Gd

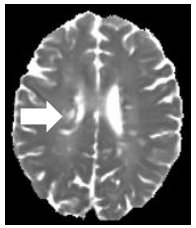


T1+USPIO

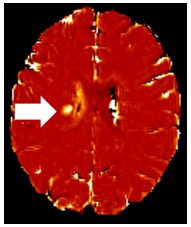
2. Quantitative MRI: macrophage imaging



T2 pre USPIO

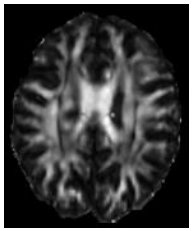


T2 post USPIO

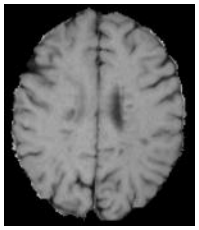


T2 difference

3. Quantitative MRI: tissue structure imaging



Diffusion



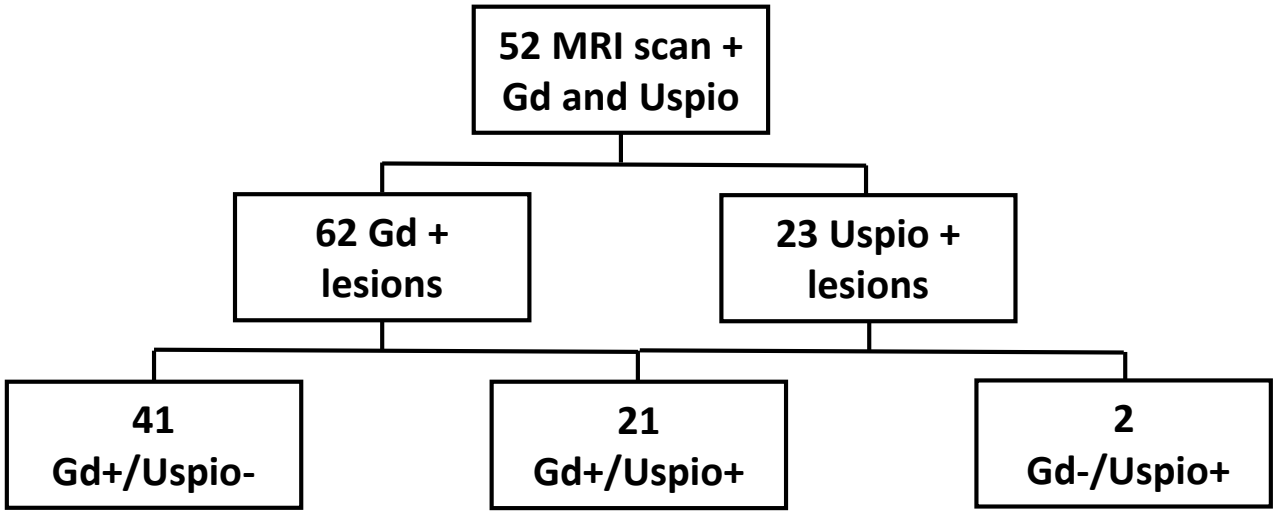
MT

4. Lesions structural and cellular characterization

5. Longitudinal analyses

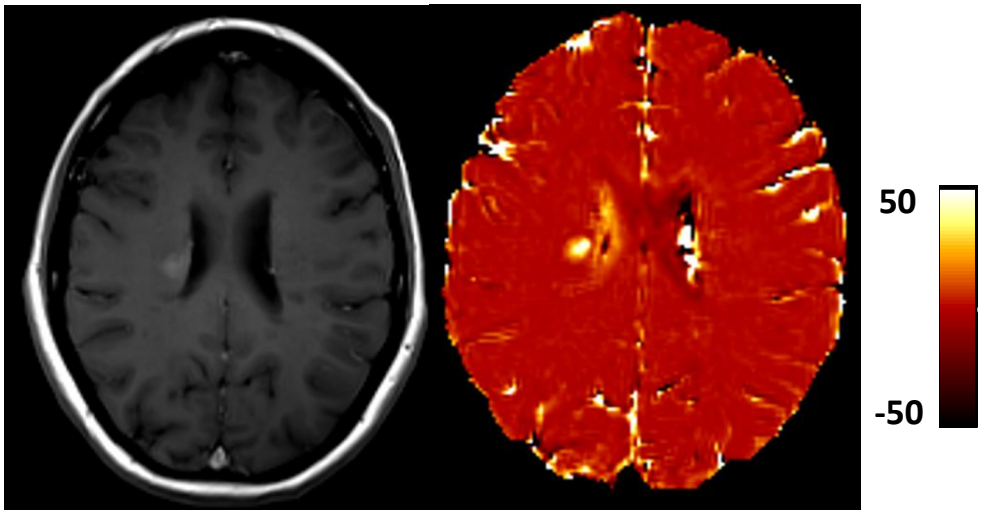
1) What are the occurrences of Gado and Uspio enhancement ?

Results: USPIO on T1-W images

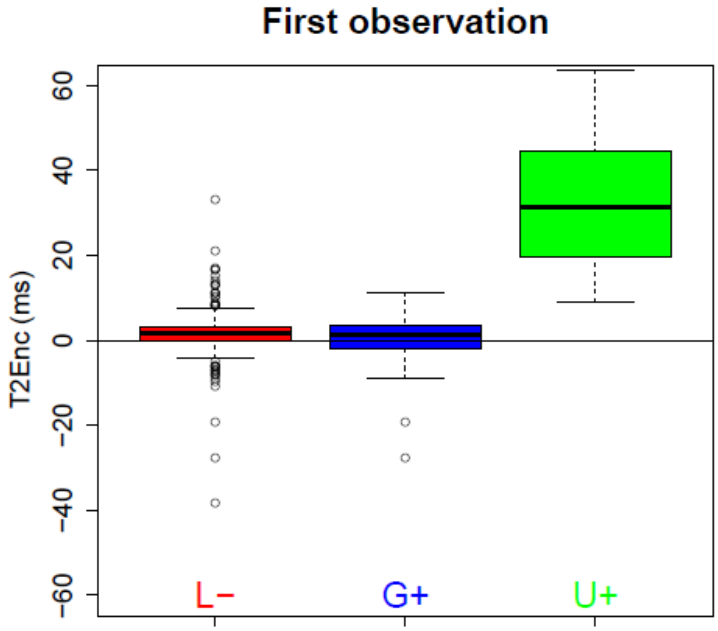


In the present study, USPIO was less sensitive than gadolinium to detect active MS lesions

Results: USPIO on relaxometry maps



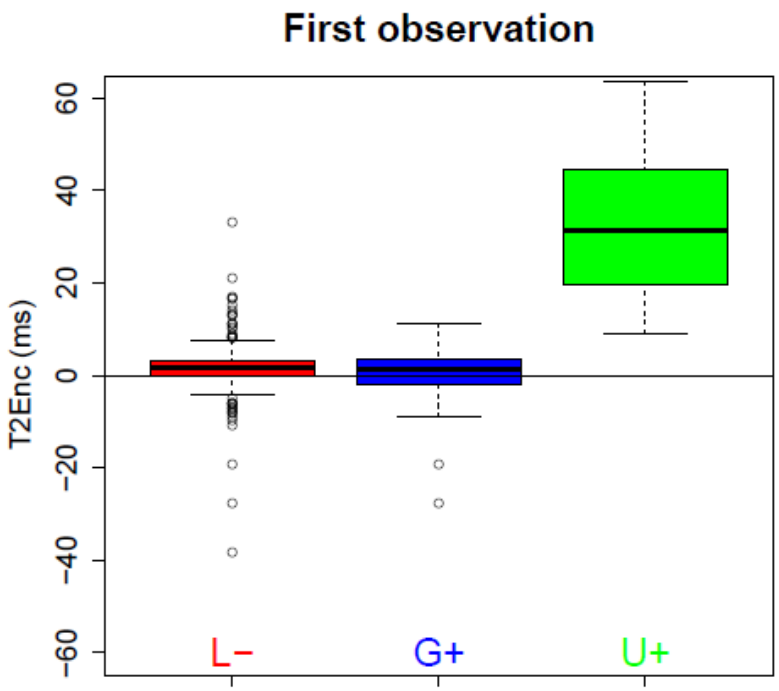
USPIO positive lesions on T1-w images were clearly visible on T2/T2* difference maps

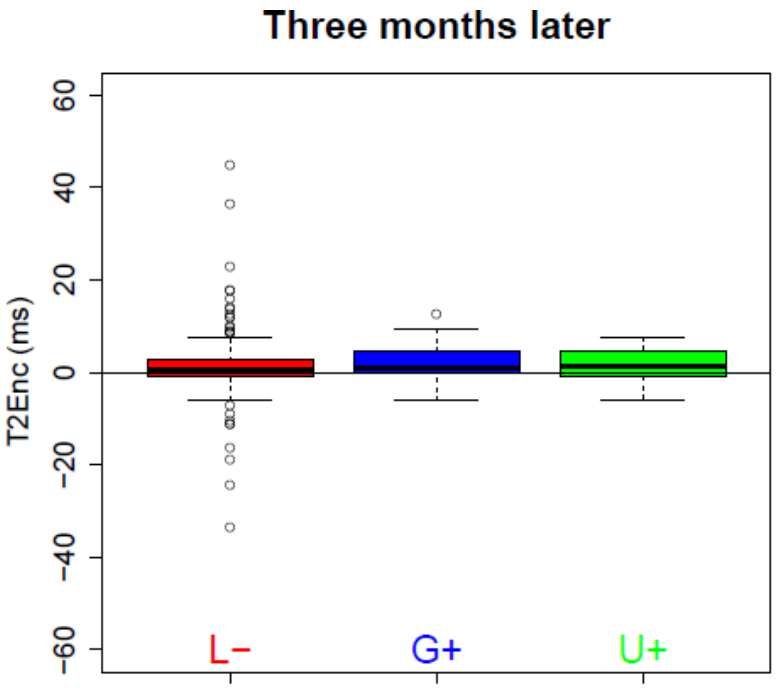


No significant T2/T2* decrease was observed in gadolinium only enhancing lesions

Monocytes infiltration is a phenomenon of various intensity among active lesions

longitudinal analysis of USPIO

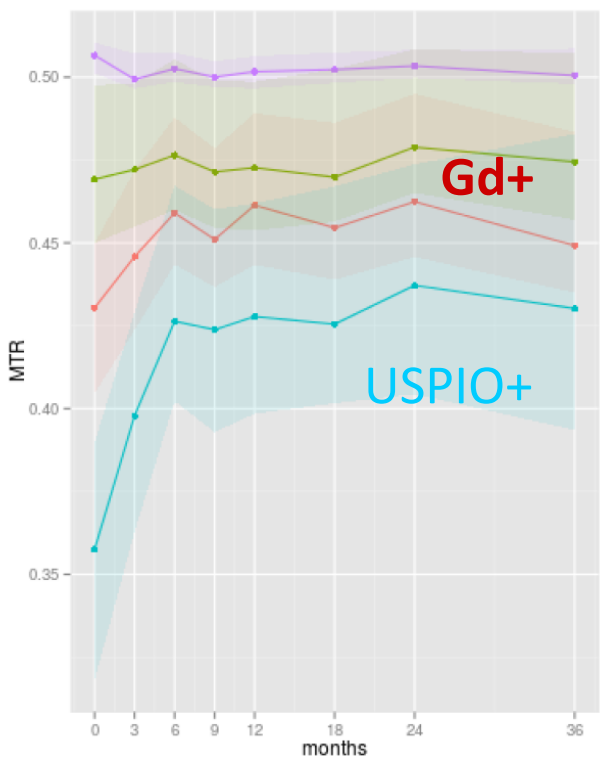


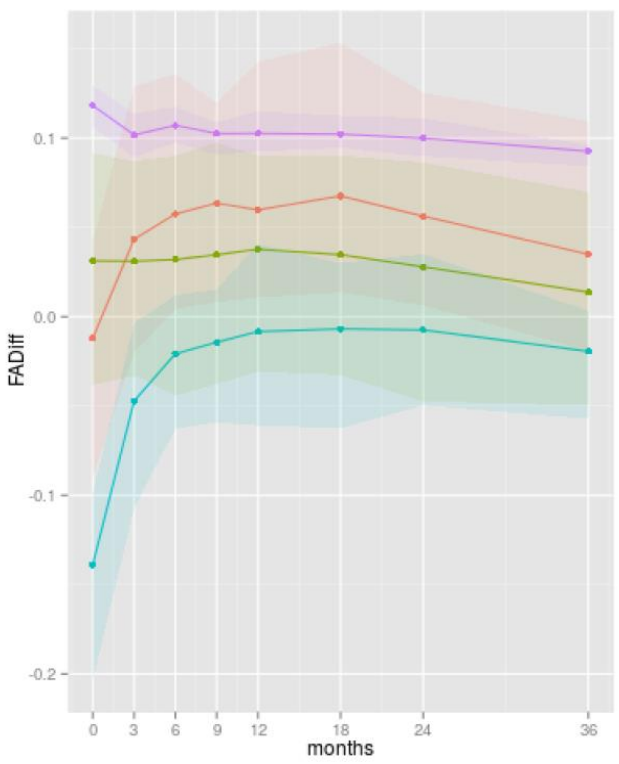


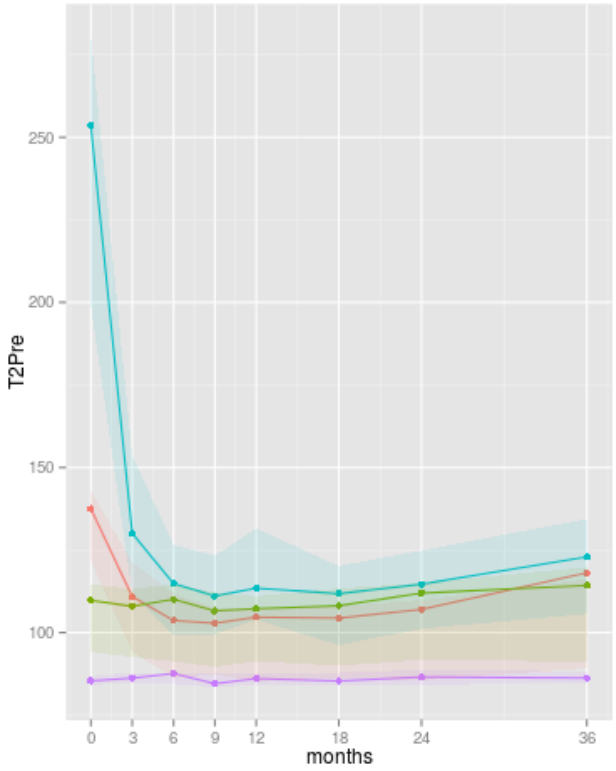
Monocytes infiltration is a transient phenomenon

2) What differentiate Gado and Uspio lesions ?

Longitudinal assessment of tissue structure







MTR **FADiff** **T2**

Uspio lesions:

- are associated with an initial major loss of tissue structure

- after improving, remained more severe than gd only lesions

Longitudinal assessment of tissue structure

	m0	m3	m6	m9	m12	m24	m36
MTR							
Corrected p-val	**0.0004**	**0.01**	**0.02**	**0.03**	**0.01**	**0.05**	0.35
CL effect size	**0.84**	**0.78**	**0.74**	**0.72**	**0.76**	**0.70**	0.59
FADiff							
Corrected p-val	**0.0008**	**0.02**	**0.03**	**0.02**	0.06	0.06	0.07
CL effect size	**0.83**	**0.75**	**0.72**	**0.74**	0.69	0.69	0.68
T2							
Corrected p-val	**0.000001**	**0.02**	**0.02**	**0.02**	**0.02**	**0.02**	**0.02**
CL effect size	**0.93**	**0.75**	**0.75**	**0.75**	**0.74**	**0.74**	**0.73**

Uspio lesions:

- are associated with an initial major loss of tissue structure

- after improving, remained more severe than gd only lesions

Discussion

USPIO was less sensitive than gadolinium to detect active MS lesions

	Dousset et al. (2006)	Vellinga et al. (2008)	Tourdias et al. (2012)
Number of patients	10	15	24
USPIO	ferumoxtran-10	SHU-555C	Ferumoxtran-10
Gd positive lesions	55	59	37
USPIO positive lesion	33	188	47

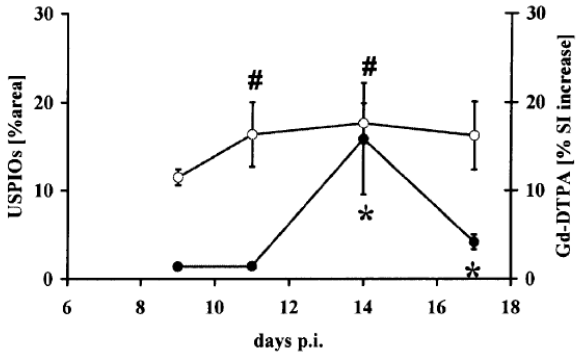
not for clinical practice…

Discussion

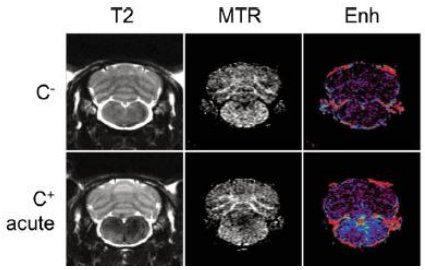
… USPIOs enable dynamic and in-vivo study of the pathogenesis of MS

In our study, blood born monocytes infiltration

- is a transient phenomenon
- is associated with an initial major loss of tissue structure
- the microstructural damage subsequently improved
- USPIO + lesions remained more severe than gd only + lesions

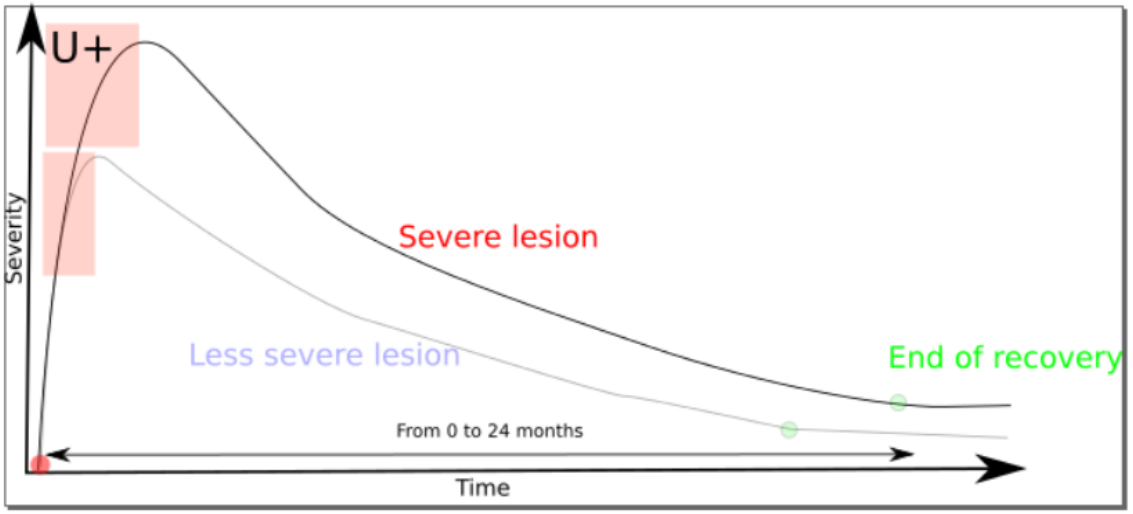


(S Floris et al, 2004)



(M Rausch et al., 2003)

To conclude

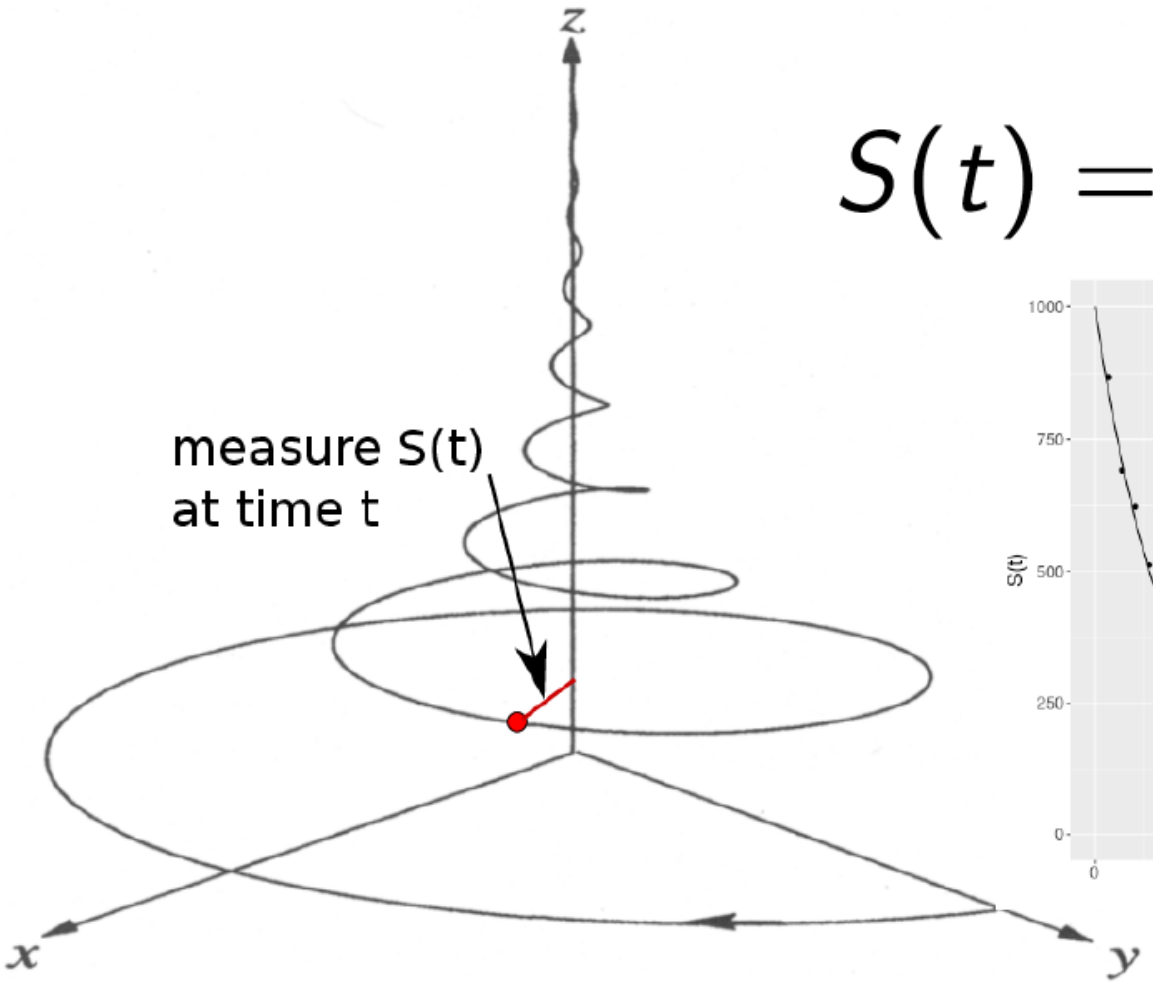


Limits

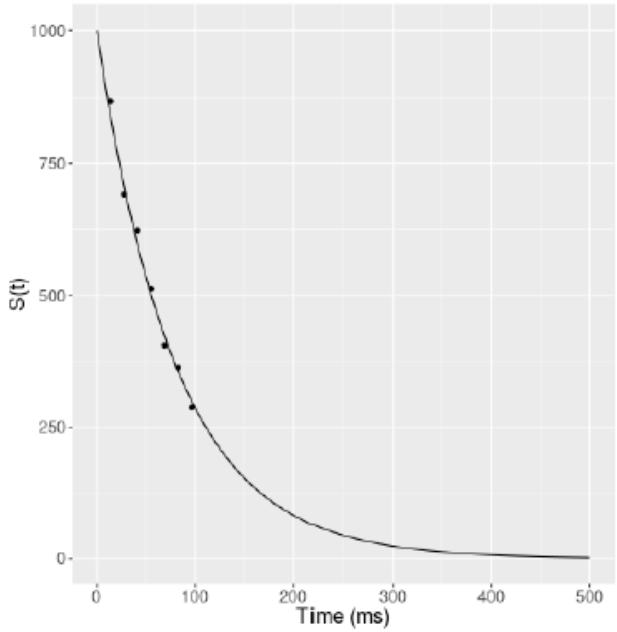
Time resolution
Sensitivity
Specificity

A few words about comparing T2 Relaxometry values

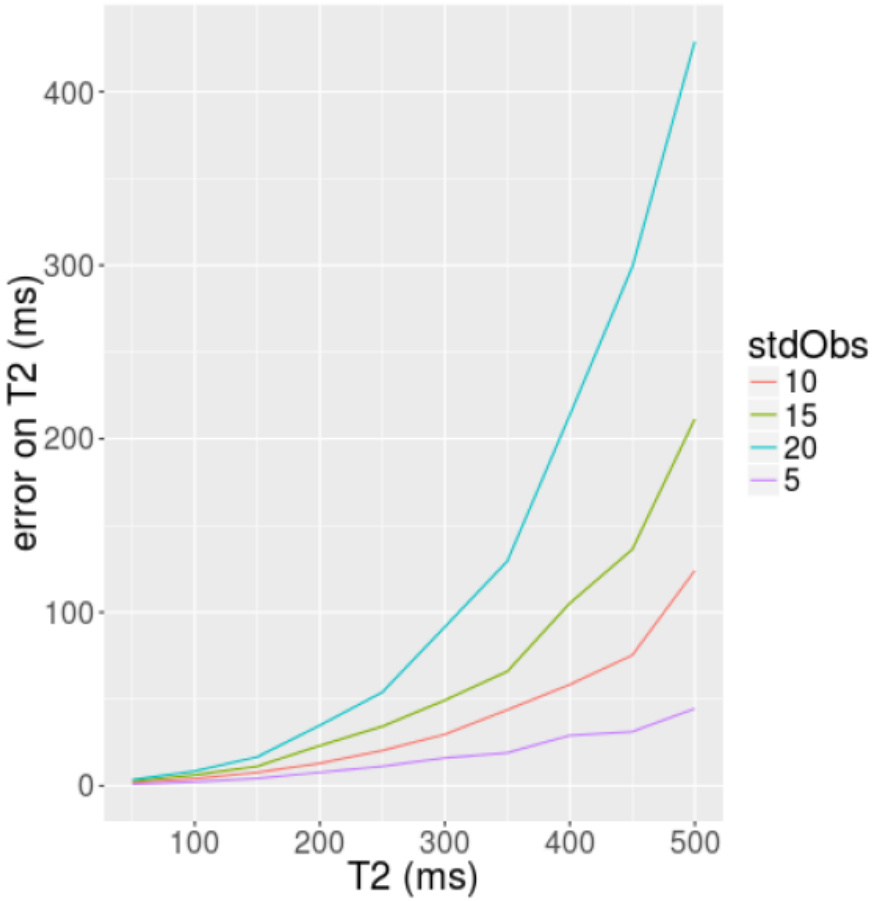
T2 relaxation time estimation



$$S(t) = M_z^0 \cdot e^{\frac{-t}{T_2}}$$

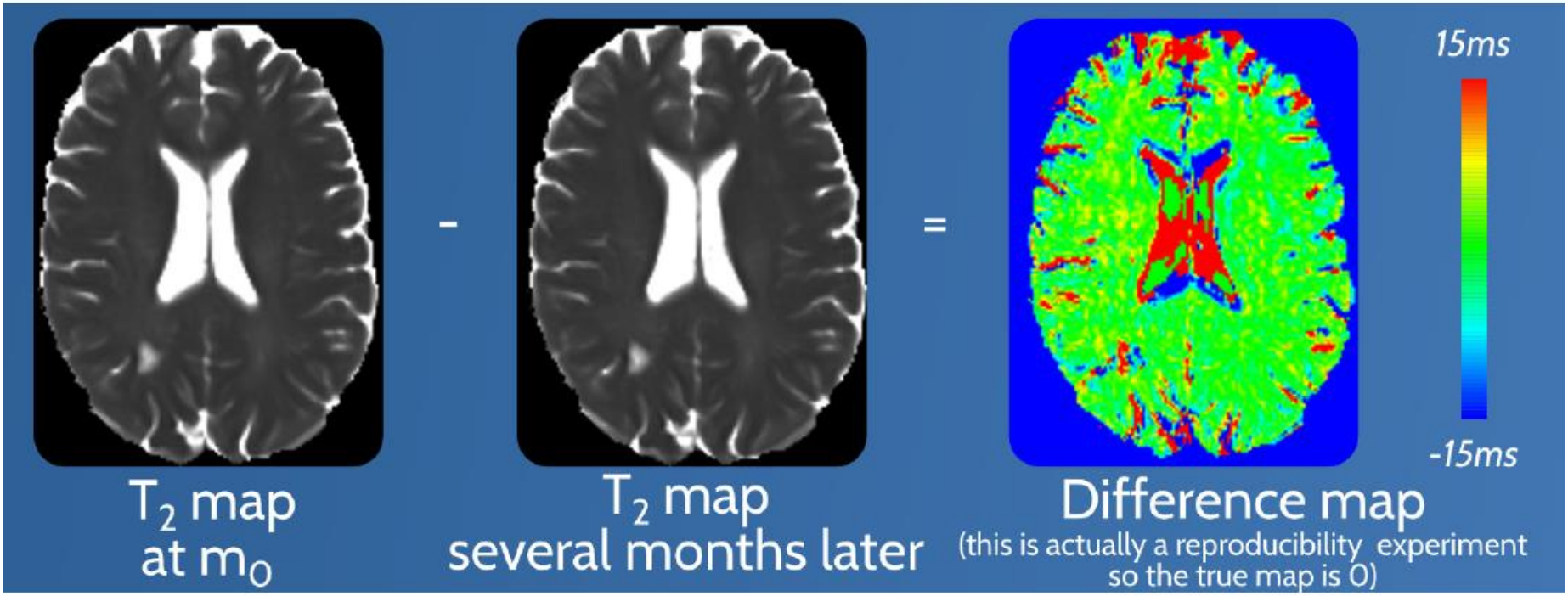


Beware of uncertainty



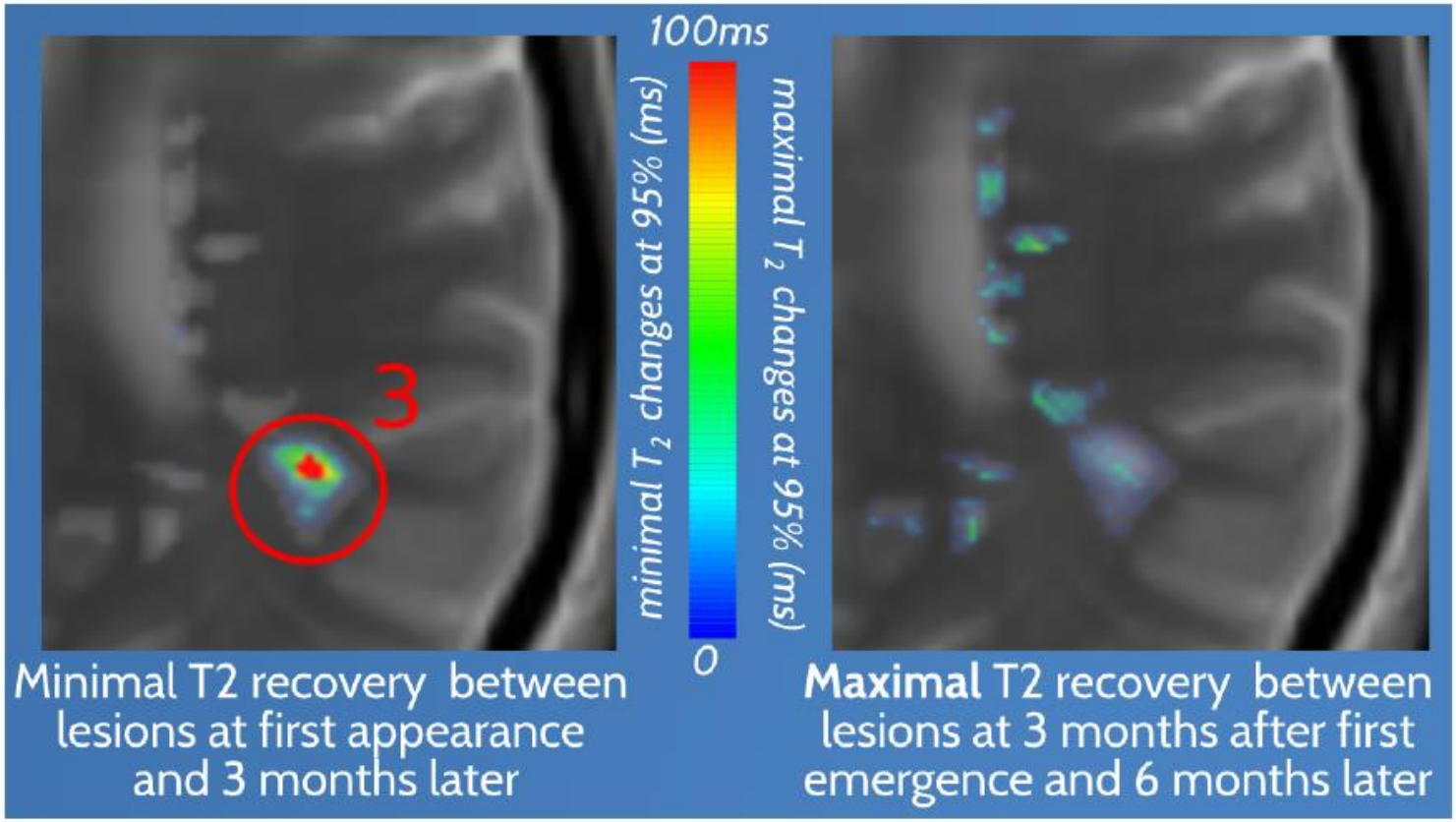
For 7 equally-spaced (13.8 ms) echoes

Beware of uncertainty



For 7 equally-spaced (13.8 ms) echoes

A Bayesian model to assess relaxometry changes



A Bayesian Model to Assess T2 Values and their Changes Over Time in qMRI, miccai 16. Combès et al.