EMISEP
Early spinal cord tissue damage and late disability in RRMS patients

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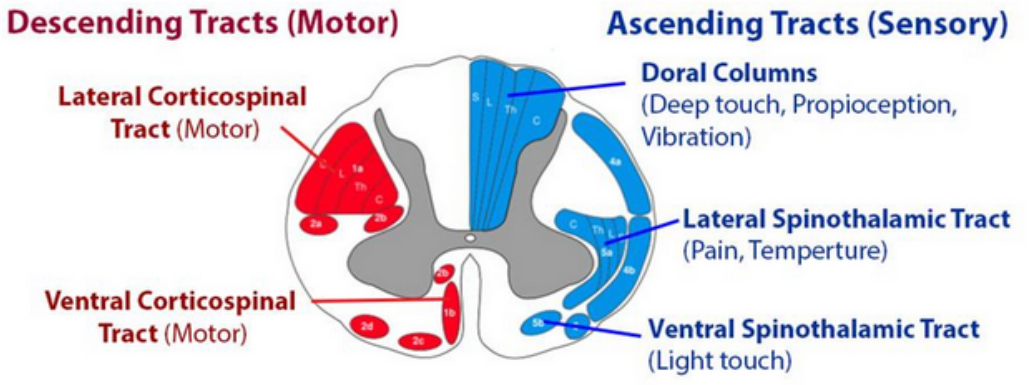
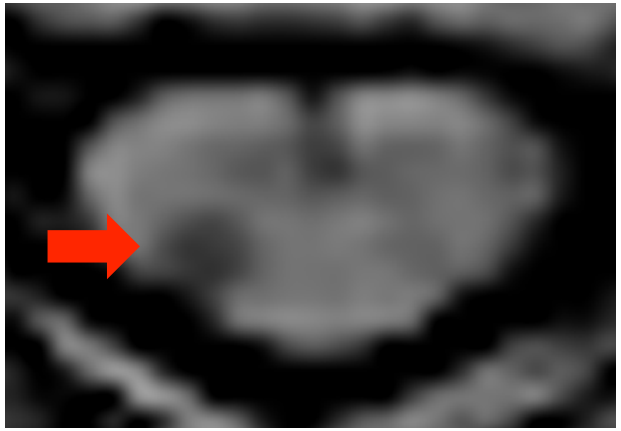
Background

The progressive phenotype of MS usually presents as a worsening pyramidal syndrome of both lower limbs, suggesting a strong spinal cord involvement





MS lesion (MT imaging)

Background

In previous studies:

- Low and inconsistent association between SC lesion load and disability
- Association between quantitative SC MRI measurement and disability

Table 2 | Physical disability in MS and abnormal microstructural and/or metabolic findings in the spinal cord

Disability measure	Cross-section of cervical spinal cord	Lateral column	Posterior column	Spinal cord grey matter
Expanded disability status scale[86,94,95,97,98,100,102–104,108]	FA;[14,95,108] MD;[14,95] RD;[14] MTR[14]	FA;[102] RD;[100,102] m-Ins;[108] Cho;[108] Cre[108]	FA;[102] RD;[100,102] MTCSF[15]	RD;[103] MTR;[88] MTCSF[15]
9-hole peg test[102,108]	Not reported	AD;[102] MD;[102] Cre[108]	FA;[102] RD;[102,108] NAA[108]	Not reported
25-foot timed walk test[86,102]	FA;[104] RD[104]	RD;[102] MTCSF[15]	FA;[102] RD[102,104]	Not reported
Vibration sense[86,97,102]	FA;[14] RD;[14] MTR[14]	Not reported	FA;[102] MD;[102] RD;[102] MTCSF[15]	Not reported
Hip flexion strength[97]	AD;[14] FA;[14] MD;[14] RD[14]	Not reported	Not reported	Not reported
Ankle flexion strength[86]	Not reported	MTCSF[15]	Not reported	Not reported

Abbreviations: AD, axial diffusivity; Cho, choline; Cre, creatine plus phosphocreatine; FA, fractional anisotropy; MD, mean diffusivity; MTR, magnetization transfer ratio; MTSCF, cerebrospinal-fluid-normalized magnetization transfer; Myo-Ins, myo-inositol; NAA, *N*-acetylaspartate; RD, radial diffusivity.

(Kearney at al., nature review, 2015)

Objectives

➡ Longitudinal studies of quantitative spinal cord MRI are required

The aims of the EMISEP study are:

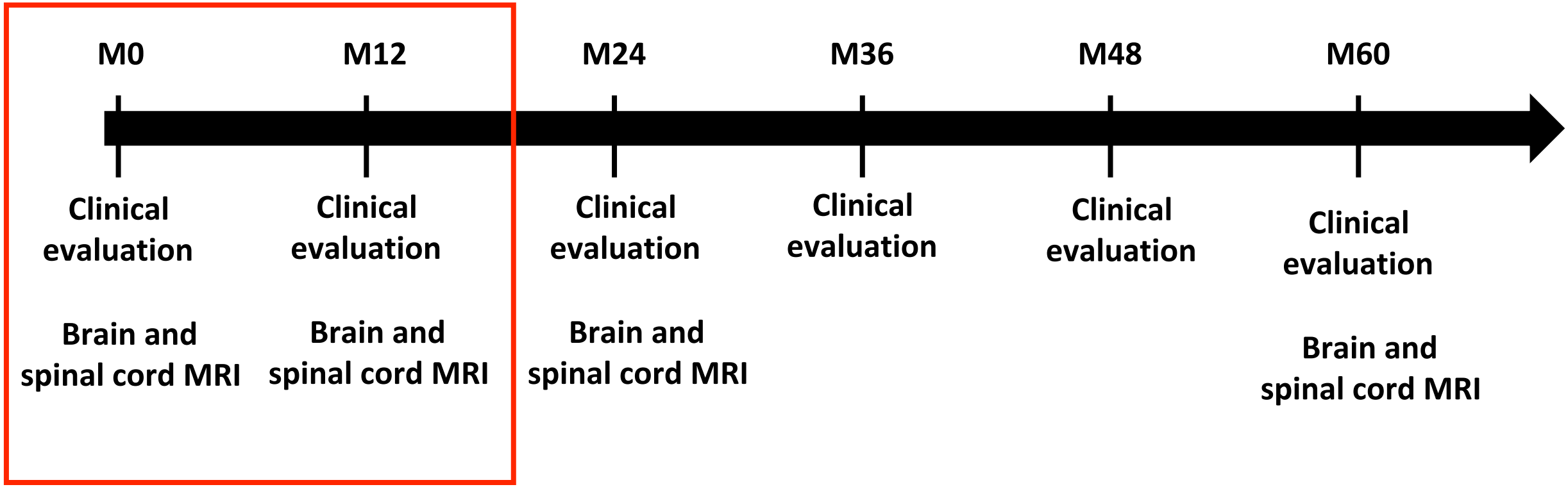
1) To quantify spinal cord microstructural damage in early RRMS patients and its evolution over time
2) To examine the relationship between early SC microstructural damage and clinical metrics 5 years later

Methods

Inclusion criteria:

- RRMS patients according to 2010 criteria
- Disease duration < 12 months
- Age 18-45 years
- Initial MRI criteria of severity with > 9 T2 lesions on brain MRI and/or an initial myelitis documented on spinal cord MRI
- No relapse and no corticosteroids in the month before inclusion.

Study design



Clinical and MRI follow up

Clinical follow up

- EDSS
- Nine-Hole Peg Test
- Time 25-Foot Walk
- the 6-Minutes' Walk Distance Test
- Multiple Sclerosis Walking Scale-12 item questionnaire.
- Qualiveen questionnaire
- Hip strength using dynamometry
- Vibration sensation using a "Vibratron"

Electrophysiological methods (Rennes)

- Conventional Motor evoked potential
- Triple stimulation technique

MRI follow up

Spinal cord:
- Sag T2 TSE
- Sag PSIR
- Axial T2 GRE
- 3D T1 EG
- MT imaging
- DT imaging

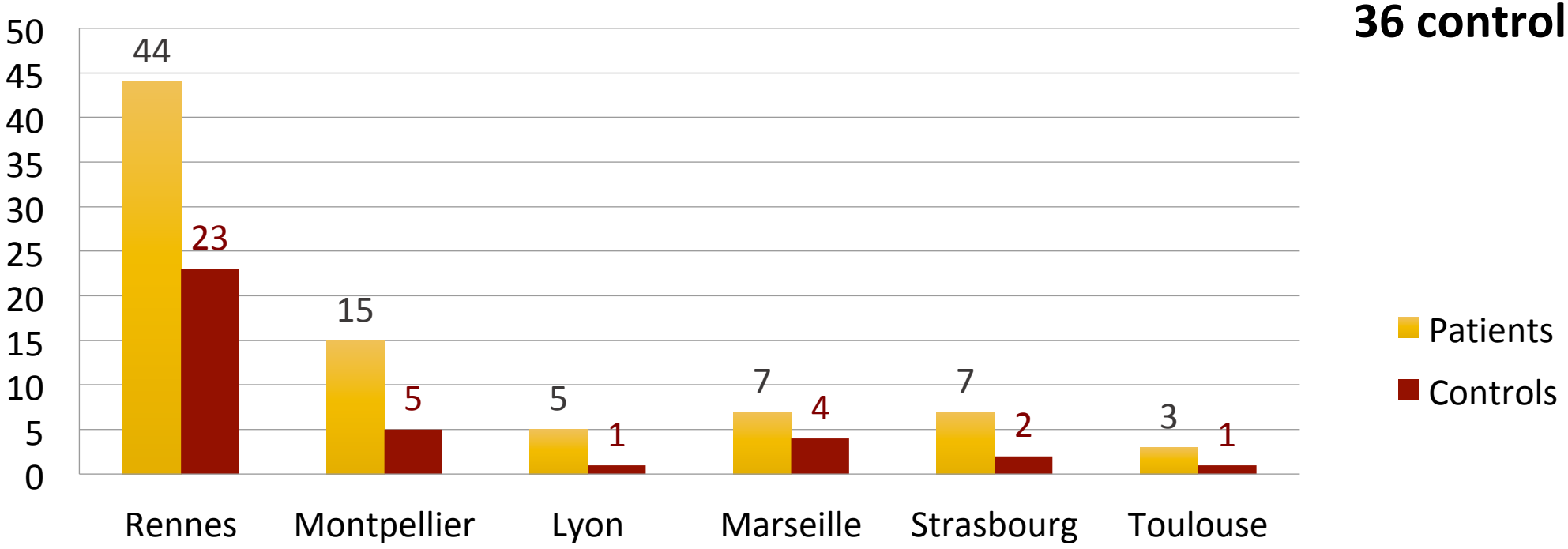
About 50'

Brain:
3DT1, DT imaging, DPT2, 3D FLAIR, 3DT1+Gd

About 20'

Subjects

81 RRMS patients
36 controls



Study 1

Microstructural cervical spinal cord damages in early relapsing remitting MS patients : A multicenter MTR study

Objectives

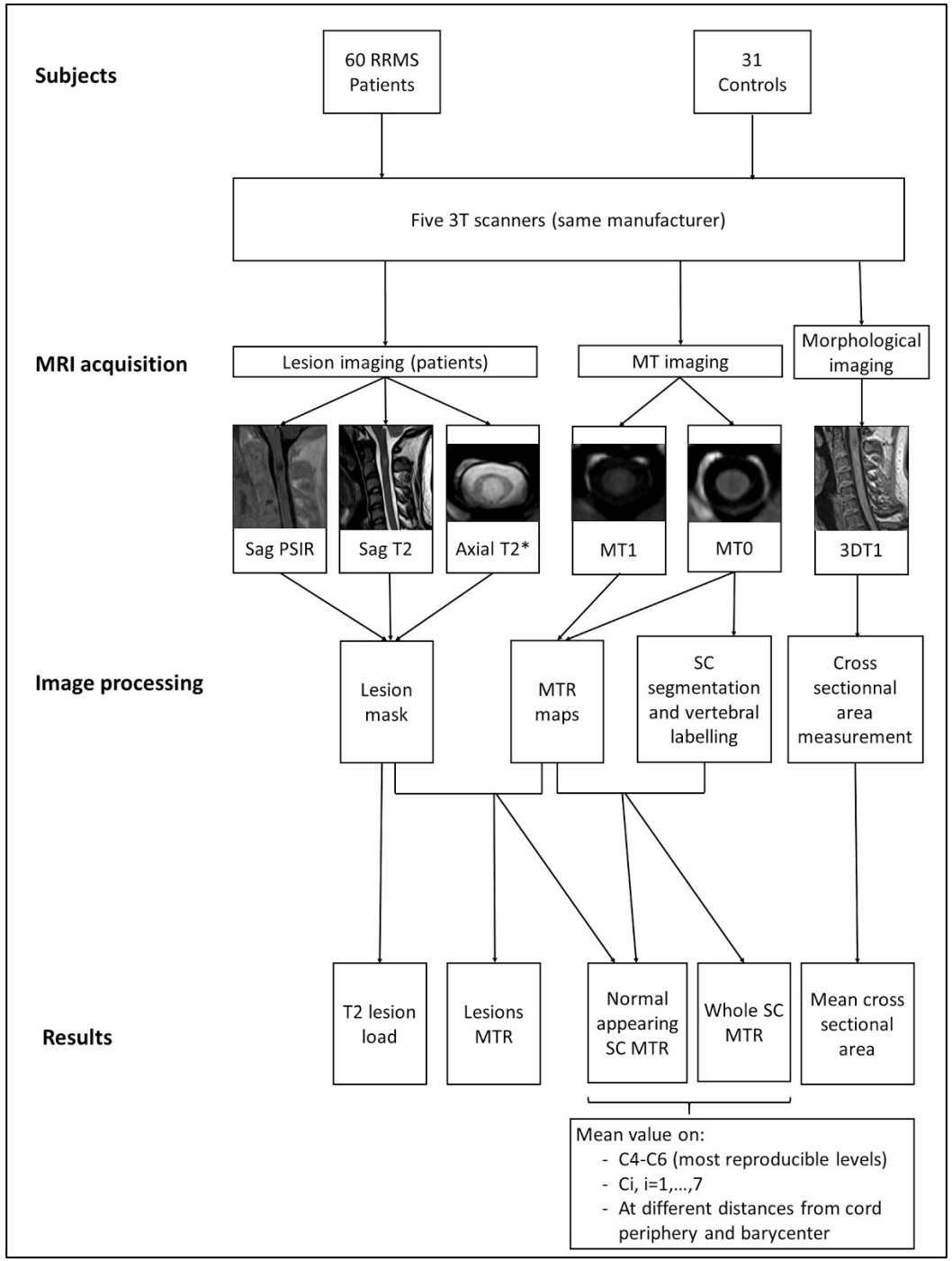
1) To investigate whether changes in cervical cord microstructure quantified using MTR were already measurable in patients with early RRMS

2) To determine whether or not the MTR reduction is homogeneously distributed in the SC:

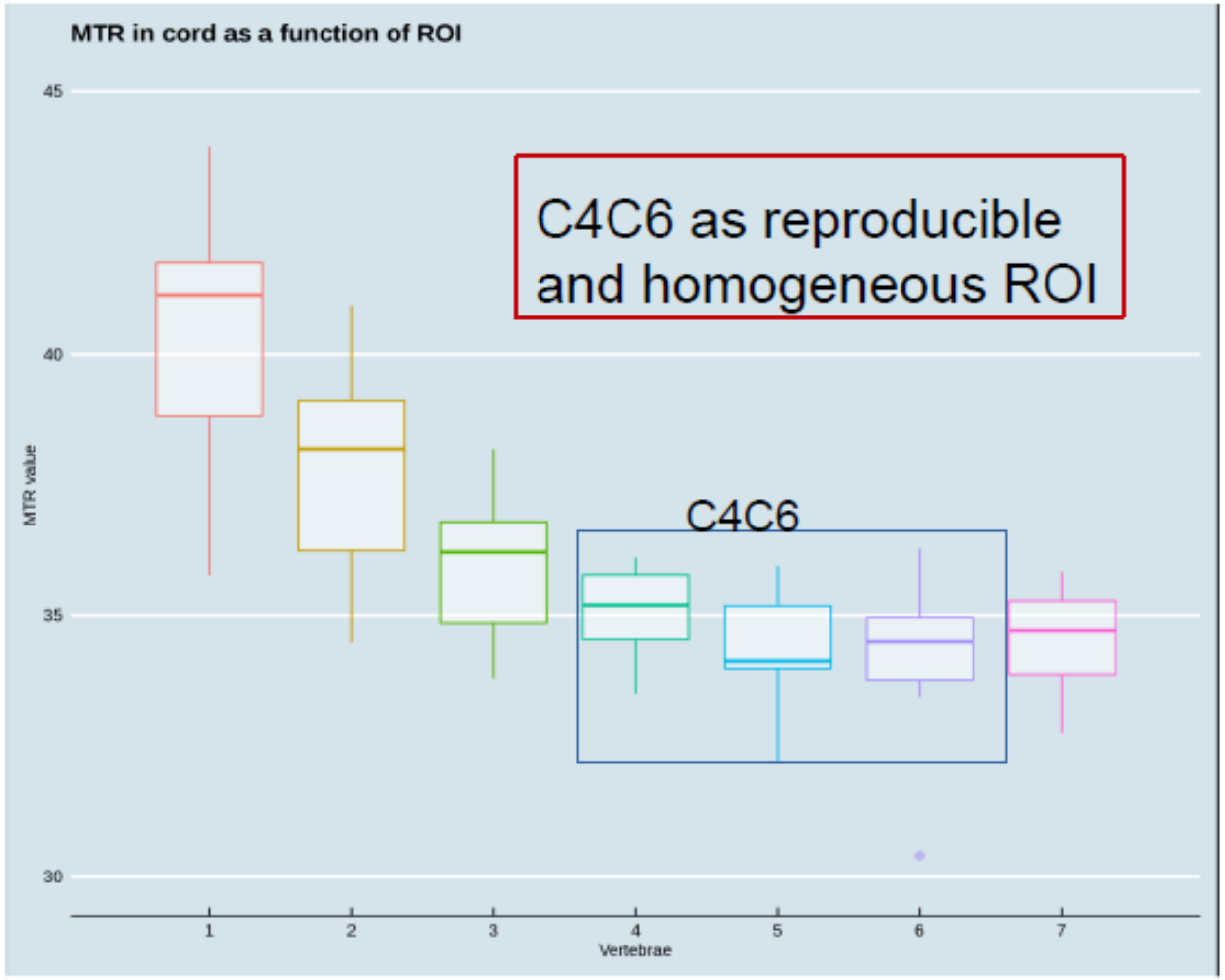
   1. In the sagittal plane: as a function of the vertebral level.
   2. In the axial plane: as a function of the distance from the cord periphery and barycenter

3) To examine the relationship between the MTR loss and clinical metrics

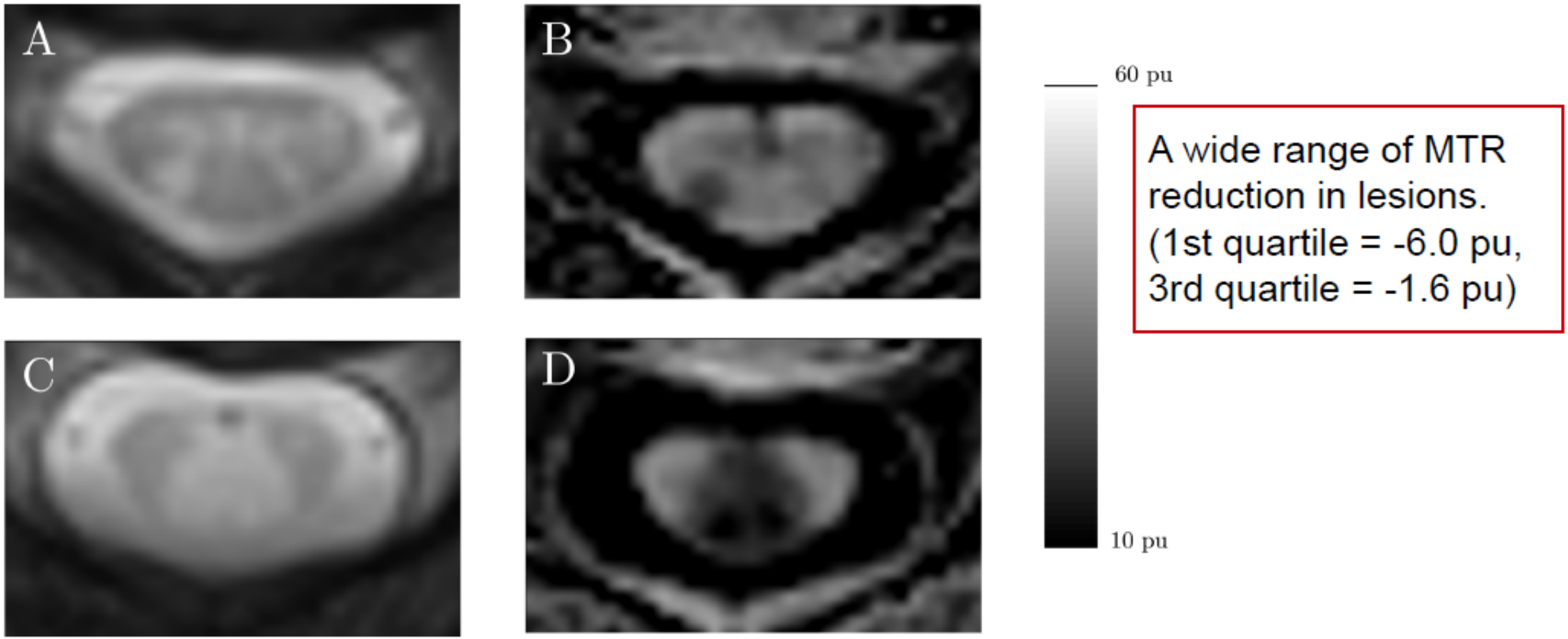
Study design



0) Reproducibity and multicentric settings

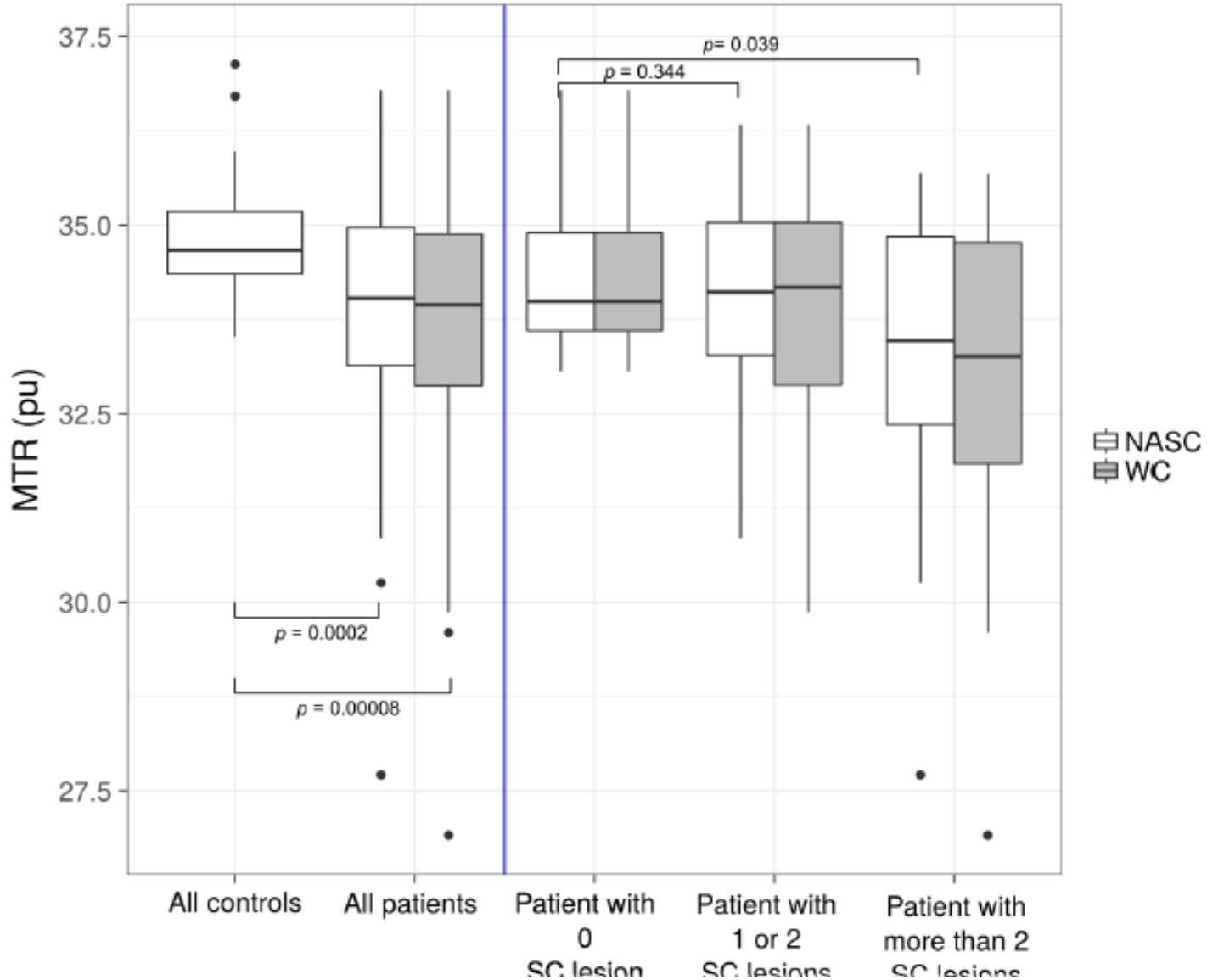


1) MTR reduction in lesions

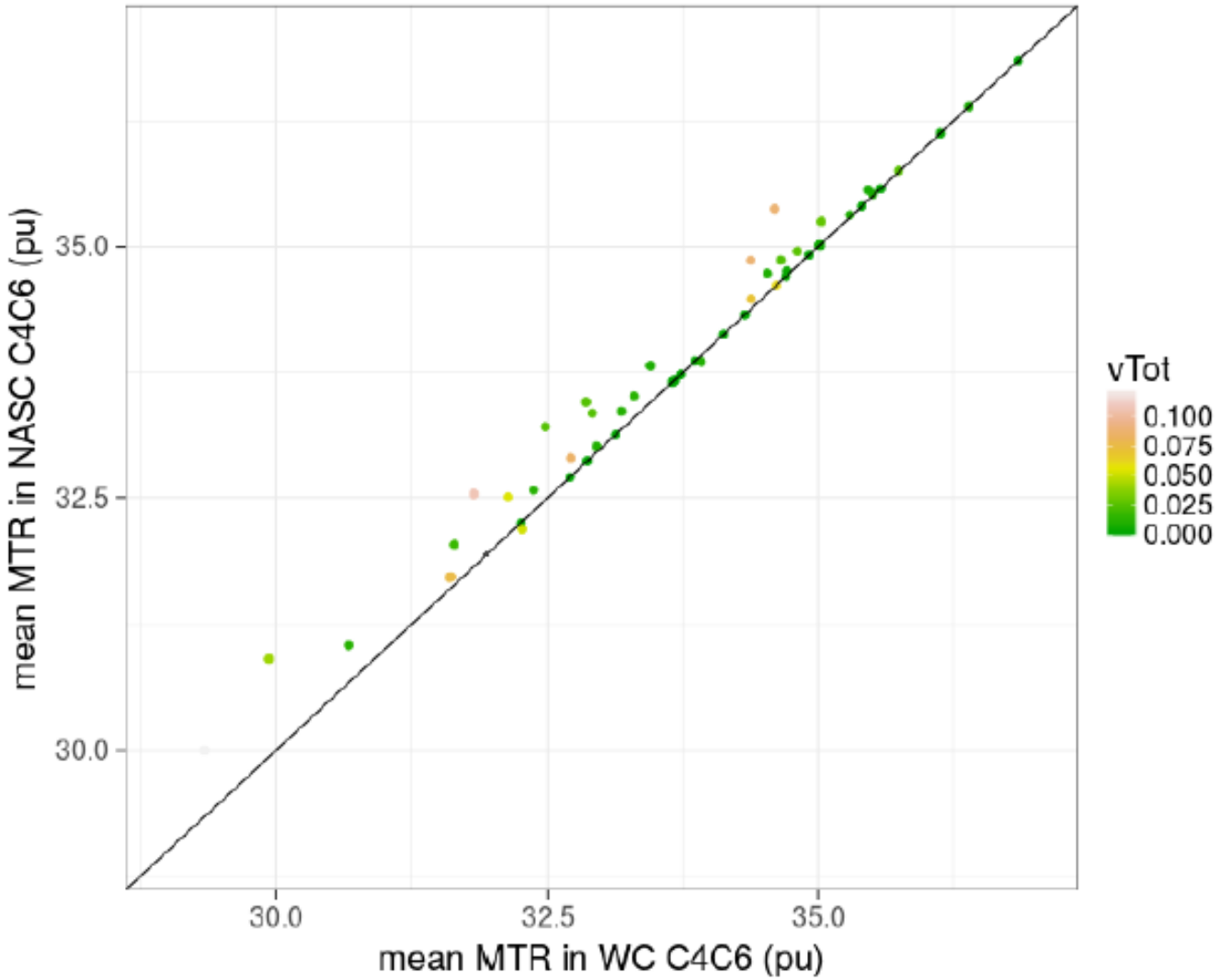


A wide range of MTR reduction in lesions. (1st quartile = -6.0 pu, 3rd quartile = -1.6 pu)

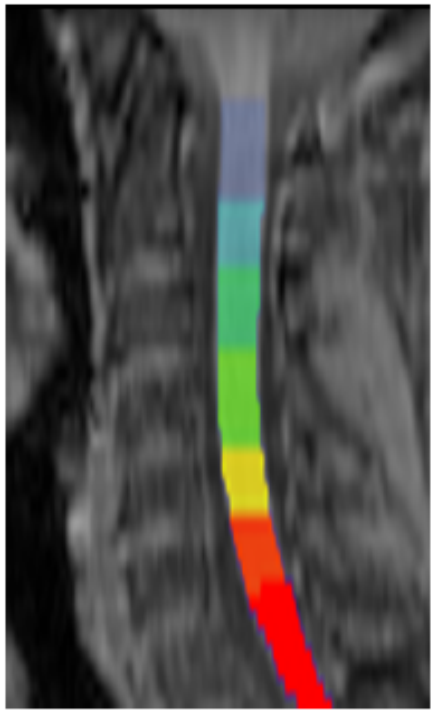
2) Mean MTR reduction in patient-to-control



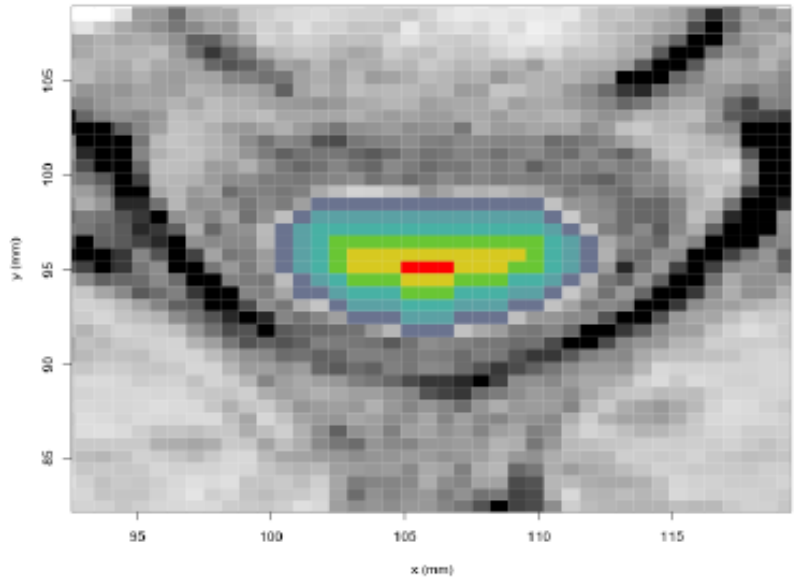
2) MTR in patient-to-control MTR reduction

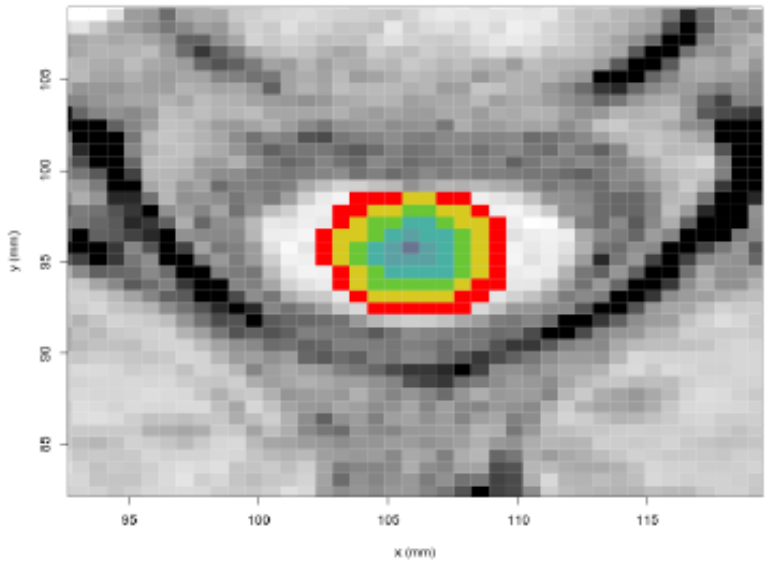


3) MTR in patient-to-control MTR reduction in vertebral levels



4) MTR in patient-to-control MTR reduction in the axial plane





5) Correlation to clinics

Low but significant correlation to clinical scores at M0.

	EDSS	Motor EDSS
MTR WC	-0.21 ($p = 0.11$)	**-0.35 ($p = 0.01$)**
MTR NASC	-0.14 ($p = 0.27$)	**-0.31 ($p = 0.02$)**
SC lesion load	**0.27 ($p = 0.04$)**	**0.31 ($p = 0.02$)**
CSA	0.08 ($p = 0.58$)	0.07 ($p = 0.61$)
Brain lesion load	0.09 ($p = 0.60$)	0.27 ($p = 0.12$)

Conclusions

Cervical SC tissue damage:

- Is not restricted to macroscopic lesions in patients with early RRMS
- Is measurable using MTR in a multicentre context
- Is not homogeneously distributed with a greater damage in NASC at the cervical levels with more focal lesions and near the barycenter and the periphery of the SC

Longitudinal studies are ongoing…