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# Multi-center (mono-vendor) longitudinal conventional and quantitative spinal cord MRI in Multiple Sclerosis at 3 Tesla - The EMISEP Study : First results

Elise Banner, Benoit Combès, Anne Kerbrat

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## The EMISEP Study : First results

Multi-center (mono-vendor) longitudinal conventional and quantitative spinal cord MRI in Multiple Sclerosis at 3 Tesla

Funding : French Ministry of Health 2012

Elise Bannier - [elise.bannier@irisa.fr](mailto:elise.bannier@irisa.fr)

CHU Rennes, Unité/Projet Visages

[team.irisa.fr/visages/emisep](http://team.irisa.fr/visages/emisep)

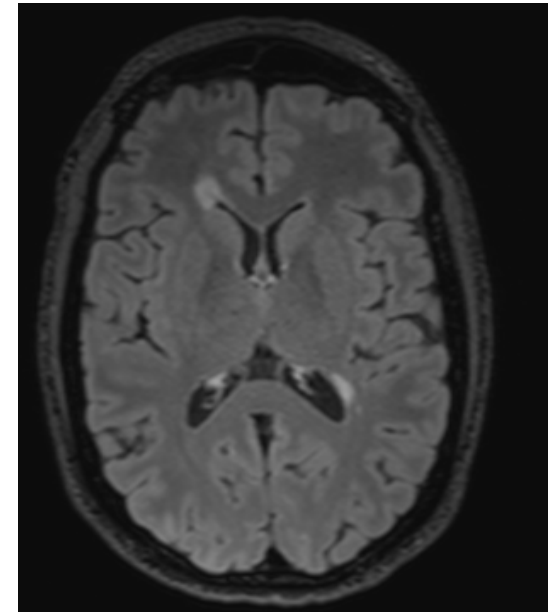


Multiple sclerosis (MS) is an often disabling disease of the central nervous system affecting the brain and the spinal cord.

Especially, walking impairment is considered by the patients as the main cause of disability (Hobart et al., 2003).

However, there is a huge heterogeneity in disability progression between patients.

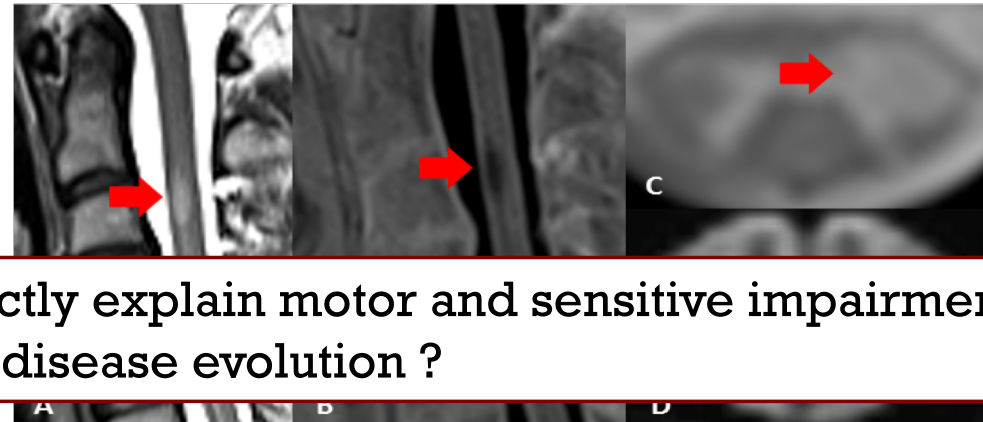
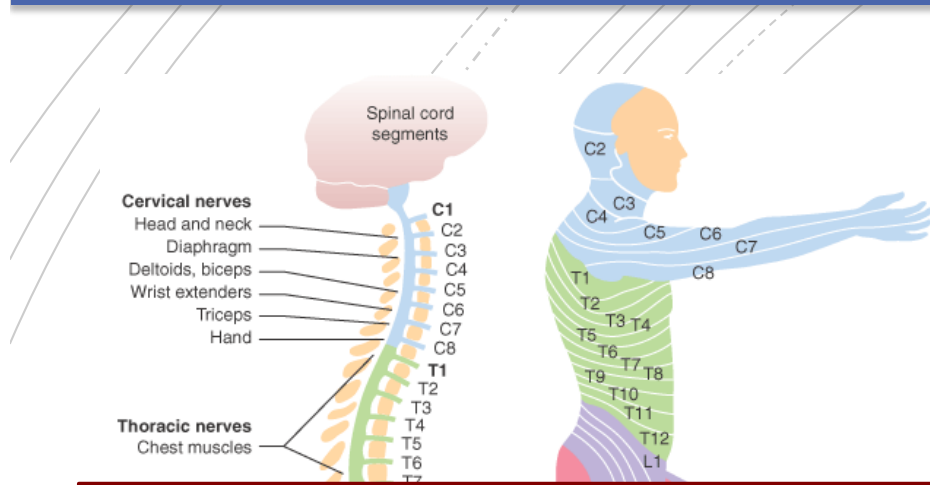
There is a need to identify prognostic factors at the individual level to guide therapeutic decisions.



« Clinico-Radiological paradox »

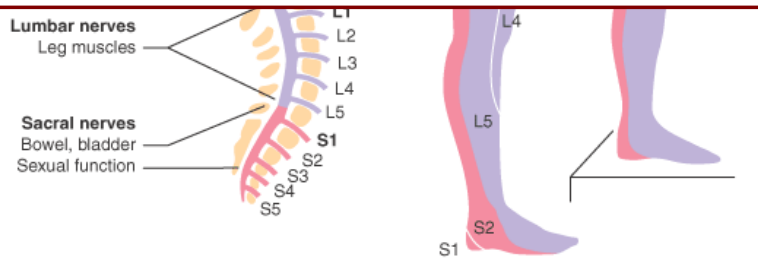
*Barkhof et al. 1999*

# MRI and Multiple Sclerosis – What about Spinal Cord MRI?



Can spinal cord involvement more directly explain motor and sensitive impairment and predict disease evolution ?

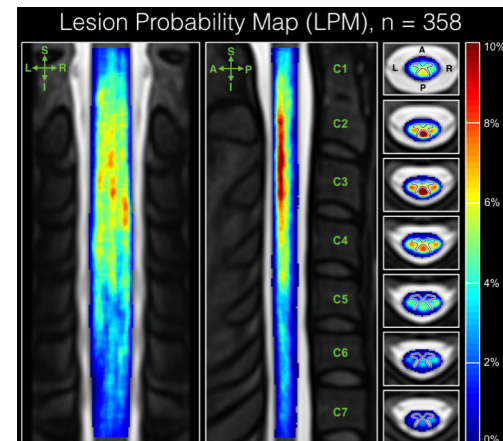
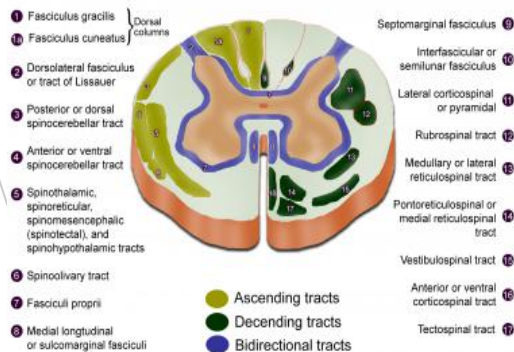
> 75 % of spinal cord images show lesions, more frequently in the cervical than thoracic cord (*Ikuta et al. 1976, Nijeholt et al. 1998, Bot et al. 2002, Eden et al. 2018*)



Motor control

Dermatomes viewed from the side

## Spinal Cord Cross-section: Detailed Anatomy



Eden et al. ISMRM 2018

## Correlation with impairment

- Weak : Focal lesions (Kidd et al. 1993, Nijeholt et al. 1998)
- Stronger with quantitative imaging
  - Atrophy (Daams et al. 2014, Kearney et al. 2014)
  - Diffusion and MT imaging (Zackowski et al. 2009, Oh et al. 2013)

## Prognosis

- Spinal cord focal lesions have an impact on patient prognosis (Brownlee et al, 2016, Arrambide et al. 2018)
- No long term quantitative studies

Relies on improved image quality for lesion and quantitative imaging (Wheeler-Kingshott 2014, Stroman 2014)

# MRI and Multiple Sclerosis – Study design

## EMISEP

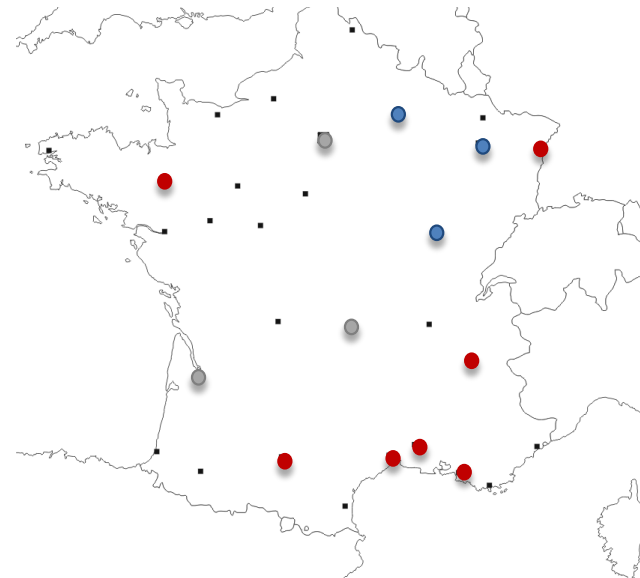
Funding : Ministry of Health 2012  
Led by Rennes  
(Clinical Trials NCT021173375)

PI : Pr. Gilles Edan / Dr. Anne Kerbrat

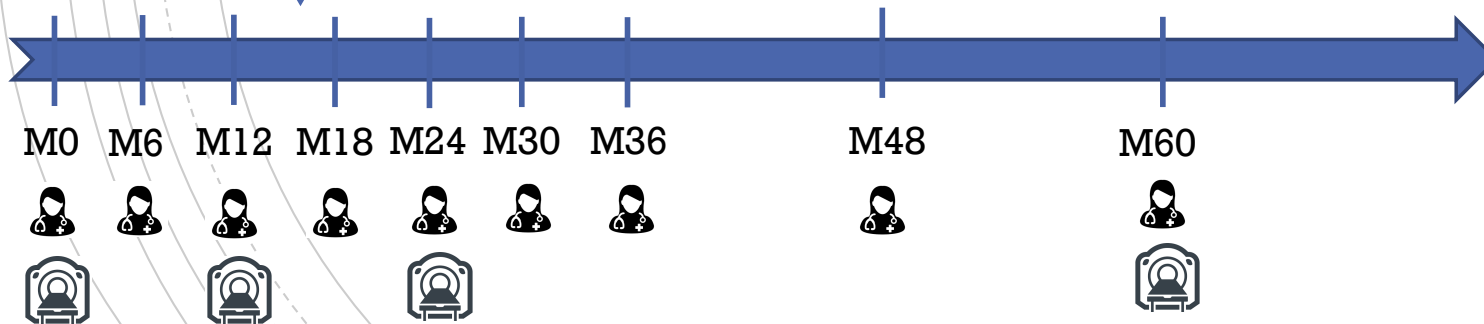
80 patients - 5-year Brain and Spinal  
Cord MRI and clinical follow up

3T Research MR scanners

13 centers initially  
3 scanner change  
<1 inclusion (2 GE scanners)  
→ **7 centers included patients**  
5 Siemens, 1 Philips scanner



+ Healthy controls – M0 and M24



## EMISEP

### Inclusion criteria

RRMS (MacDonald 2010)  
First symptoms < 1 year  
Brain T2 > 9 and/or SC lesion  
EDSS < 3  
18 - 45 years old

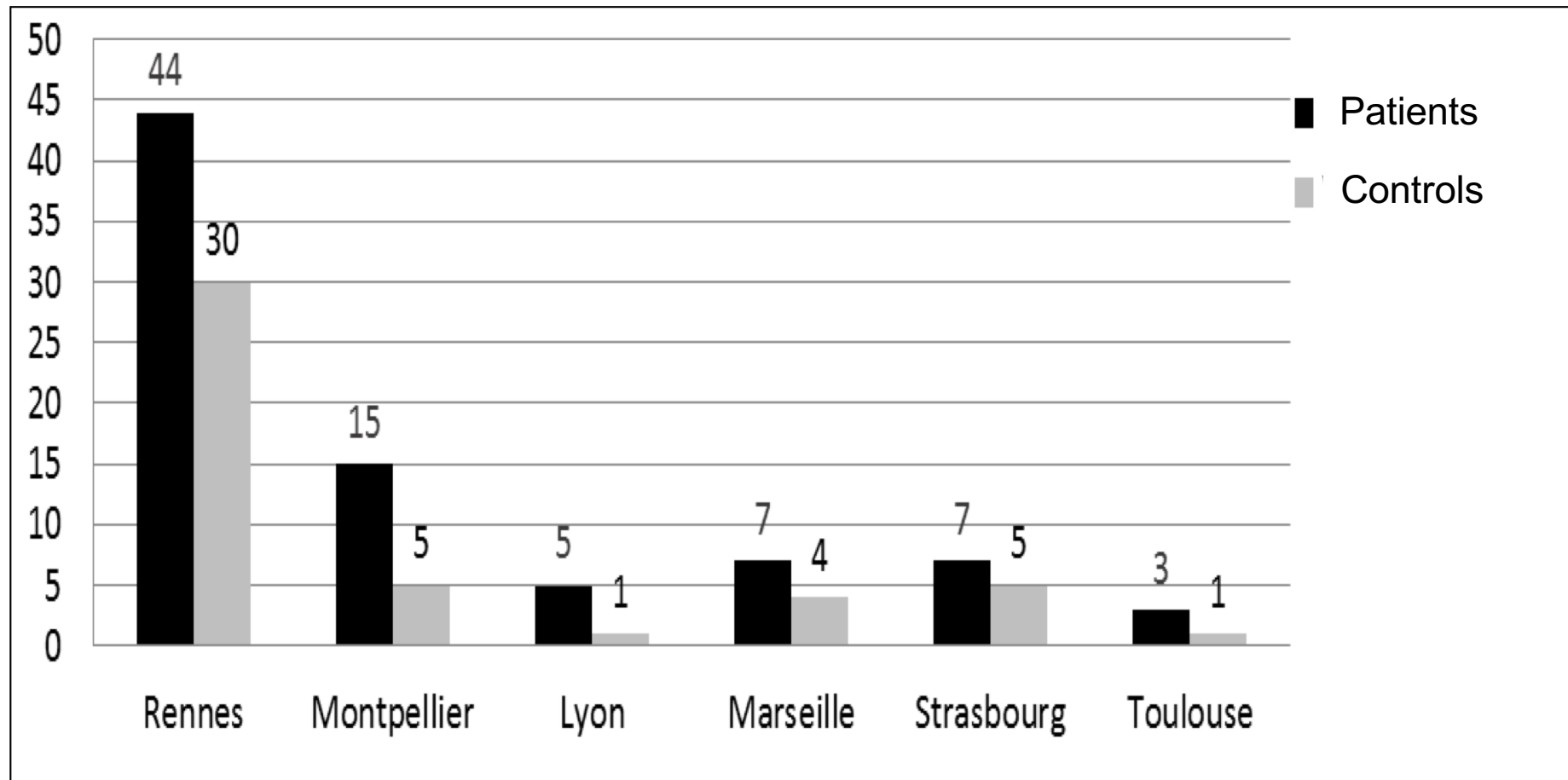
### Clinical follow up

EDSS, 6min, 8 meter, 9 holes peg test  
Auto questionnaires MSWS12, Qualiveen  
Quantitative : Strength and vibration

### Imaging protocol

- Whole cord
  - Sag T2 TSE and PSIR TSE
- Cervical cord
  - Axial 2D T2\* ME GRE C1-C3 and C4-C7 → lesion
  - Sag 3D T1 → atrophy
  - Ax 3D GRE with and without MT → MTR
  - Sag 30 dir Diffusion
- Brain (OFSEP French MS Cohort protocol)
  - Sag 3D T1 pre Gd
  - Sag 3D FLAIR
  - Ax DP/T2 or 3D T2
  - Ax 30 Dir Diffusion
  - Sag 3D T1 post Gd

## MRI and Multiple Sclerosis – Inclusions



**81** patients were included between 2014 and 2017  
**46** healthy controls  
to date **>18 months** follow-up



## Magnetization Transfer Ratio

Healthy Controls reproductibility study  
Intra-subject  
Between-subject  
Between-scanner

Patient study at M0

## Diffusion imaging

Distortion correction (Snoussi, ISBI 2019)  
Lesion location (Chouteau, ECTRIMS 2018)

## Lesion imaging

PSIR vs T2 TSE (Rojat et al, JFR 2018)

**Article 1**

**Measurement of Magnetization Transfer Ratio (MTR) from Cervical Spinal  
Cord: Multicenter Reproducibility and Variability**

# MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability

|            | IRM 1<br>(Siemens<br>Verio) | IRM 2<br>(Siemens<br>Verio) | IRM 3<br>(Siemens<br>Verio) | IRM 4<br>(Siemens<br>Skyra) | IRM 5<br>(Siemens<br>Prisma) | Total |
|------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|------------------------------|-------|
| # subjects | 4                           | 20                          | 5                           | 5                           | 20                           | 44    |
| # scans    | 4                           | 20                          | 5                           | 5                           | 30                           | 64    |

Between scanner  
Between session

# MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability

## Imaging details

3D GRE, 52 3mm slabs, 0.7mmx0.7mm in-plane resolution,  
TR/TE=38/3.57ms, 23°, water excitation and GRAPPA 2

MT0 : no prepulse

MT1 : with vendor MT prepulse (Gaussian, 1200Hz off-resonance)

## Processing (Benoît Combès, Post-Doc)

Registration of MT1 to MT0 using the Anima toolbox (v2.3)\*

MTR map computation

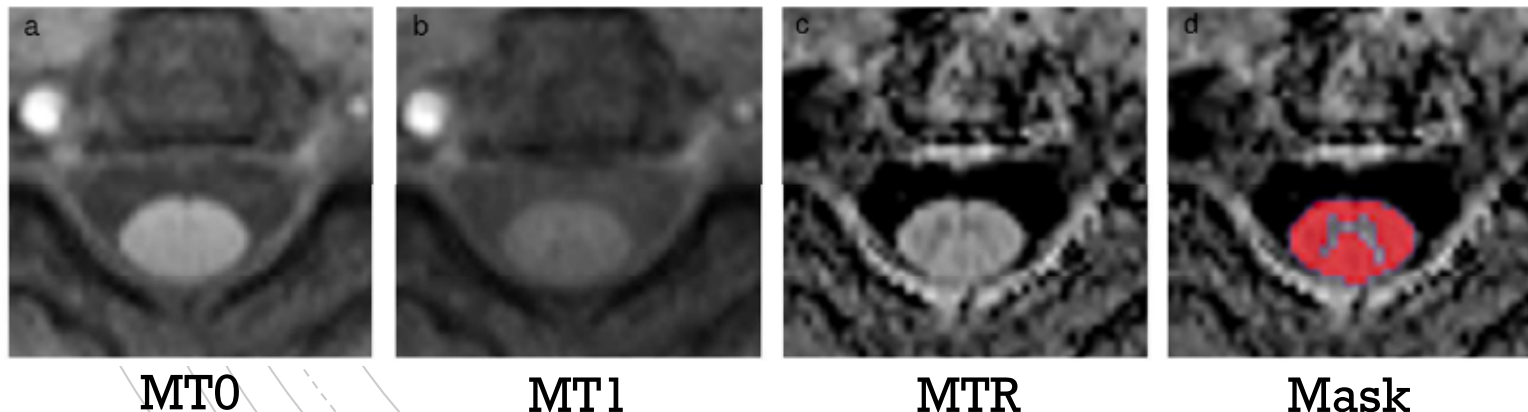
Whole cord segmentation

Vertebra labeling

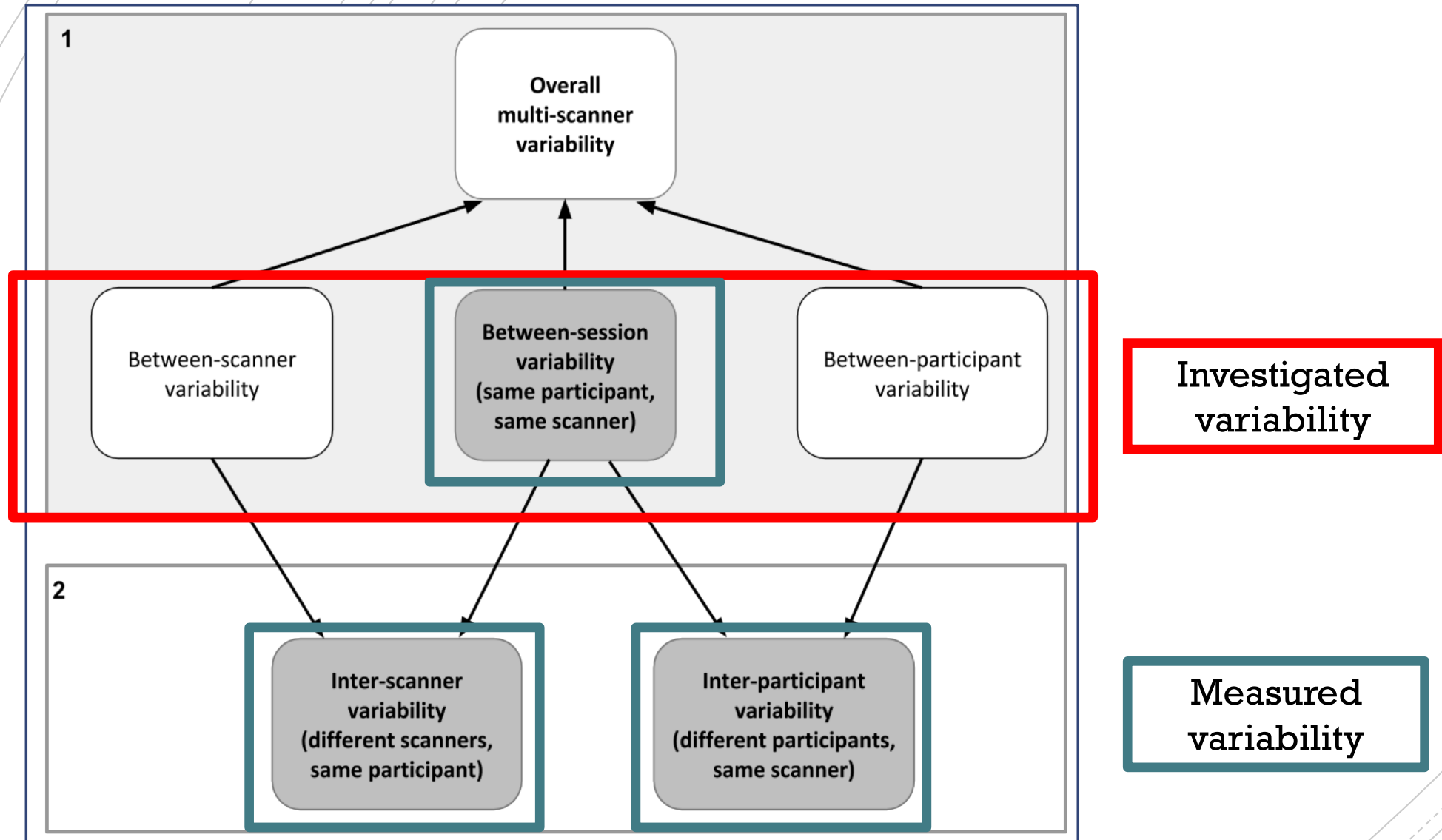
Atlas registration

GW/WM segmentation (>0.8)

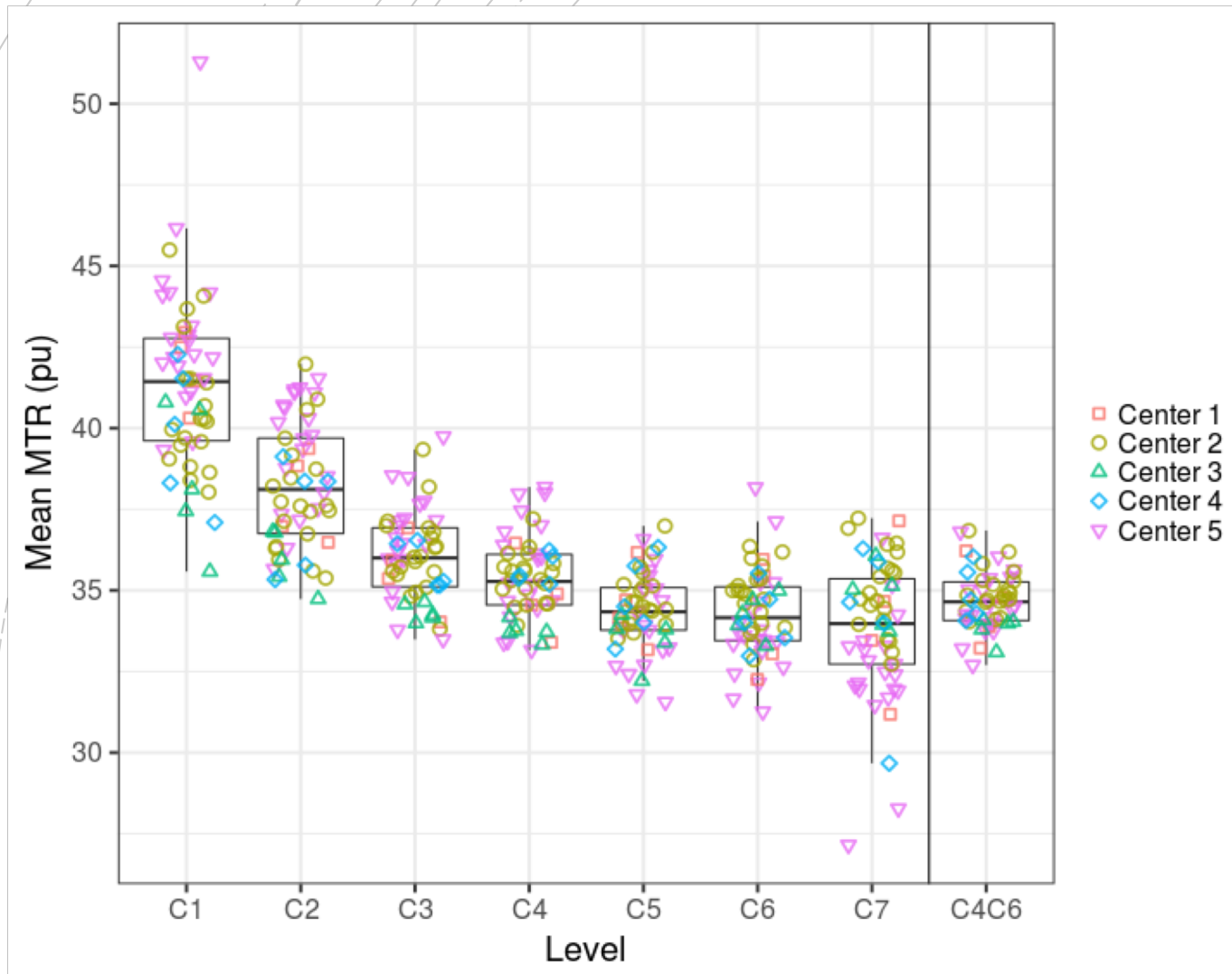
Spinal Cord toolbox (v3.0)\*\*



# MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability



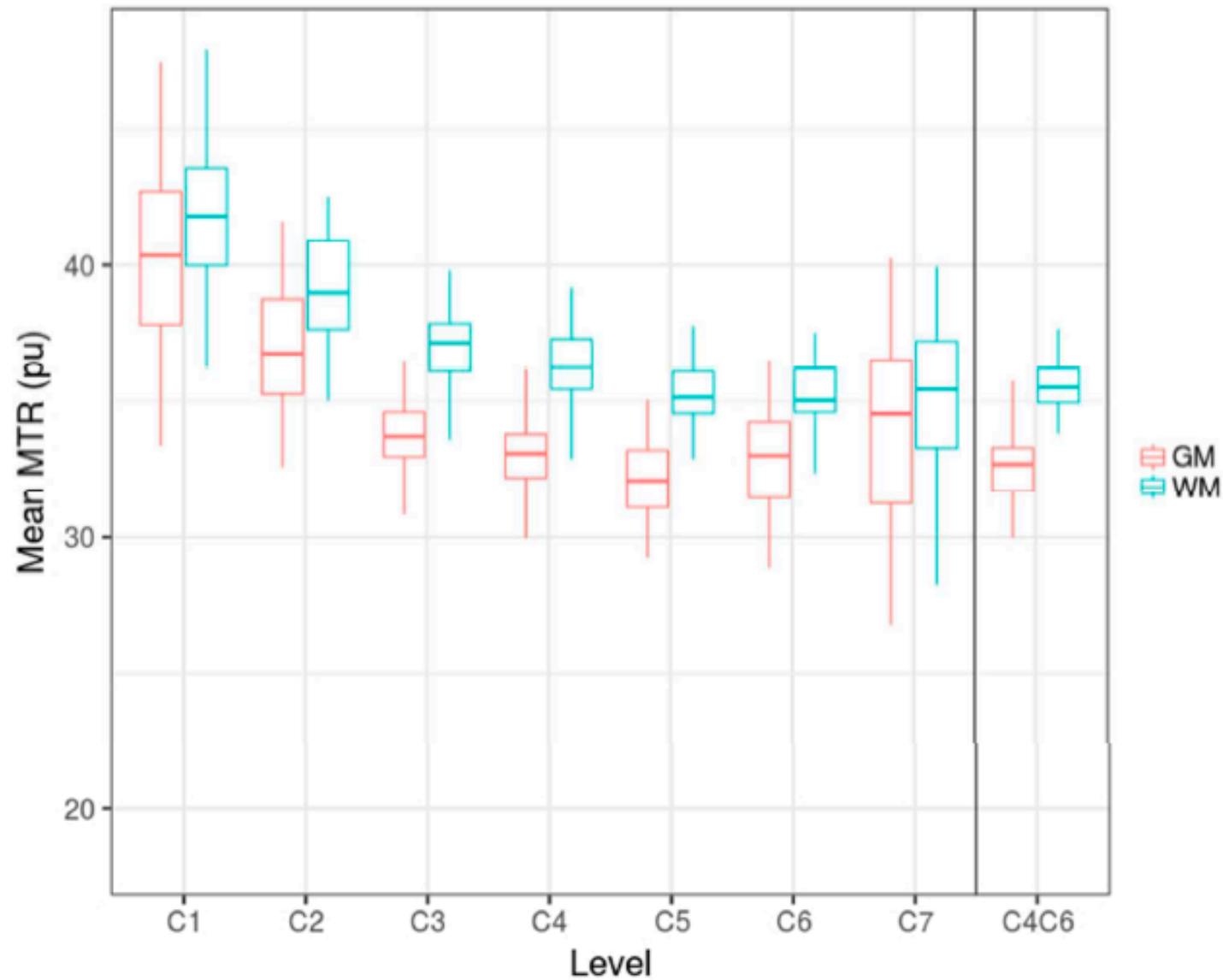
# MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability



Inhomogeneous  
MTR values along  
the cord  
(C4-C6 plateau)

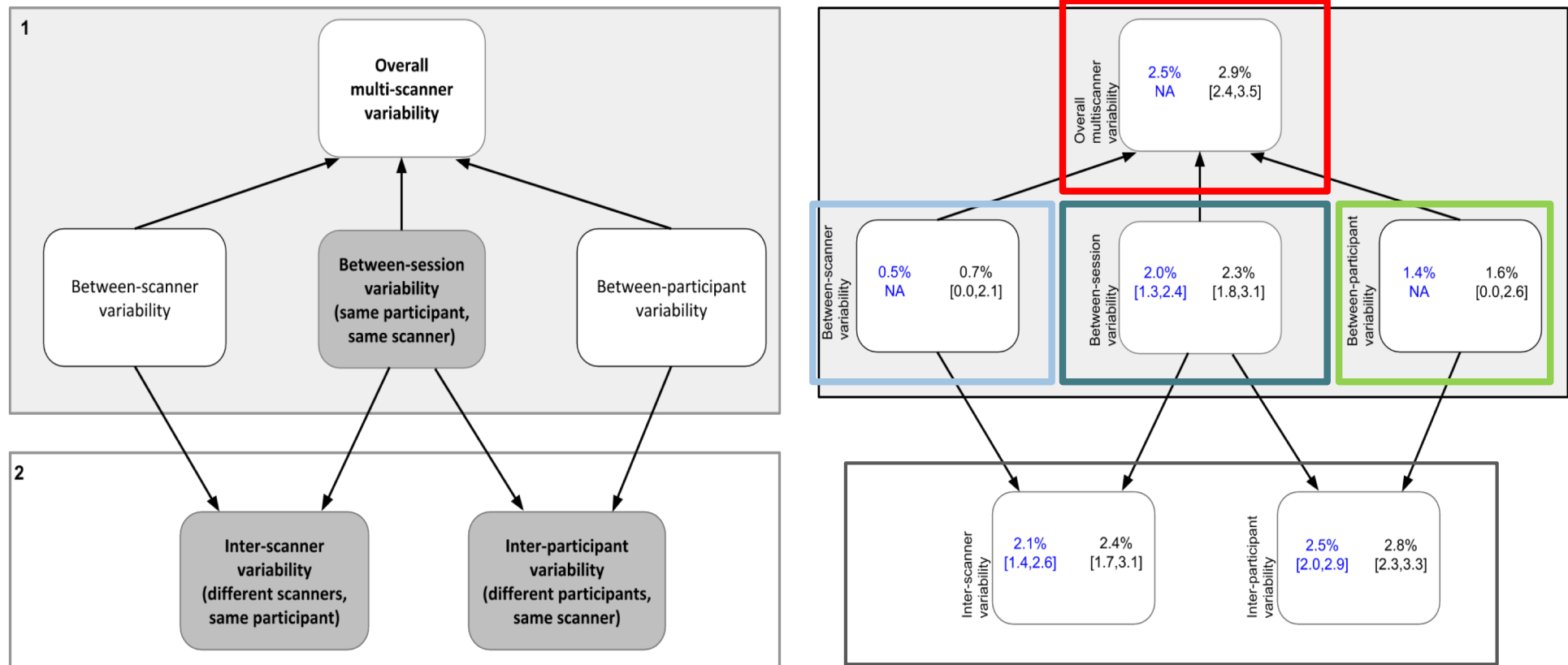
Between-scanner  
and  
between-subject  
variability  
overlap

# MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability



Boxplots of mean MTR measurements in gray matter (GM) and white matter (WM) for each level between C1 and C7 and for C4-C6.

# MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability



**Variation coefficient** = (standard deviation / mean) x 100



Global variation coefficient of 3% (0.9 pu) is compatible with the detection of 1pu MTR Variations between 2 groups (45 per group, type I error= 0.05 and type II error= 0.10)

**These results show that it is possible to use cervical cord MTR in multicenter studies**

**Yet**

**This was evaluated on a single vendor  
Inhomogenous MTR along the cord**

**The investigation in longitudinal studies remains challenging**

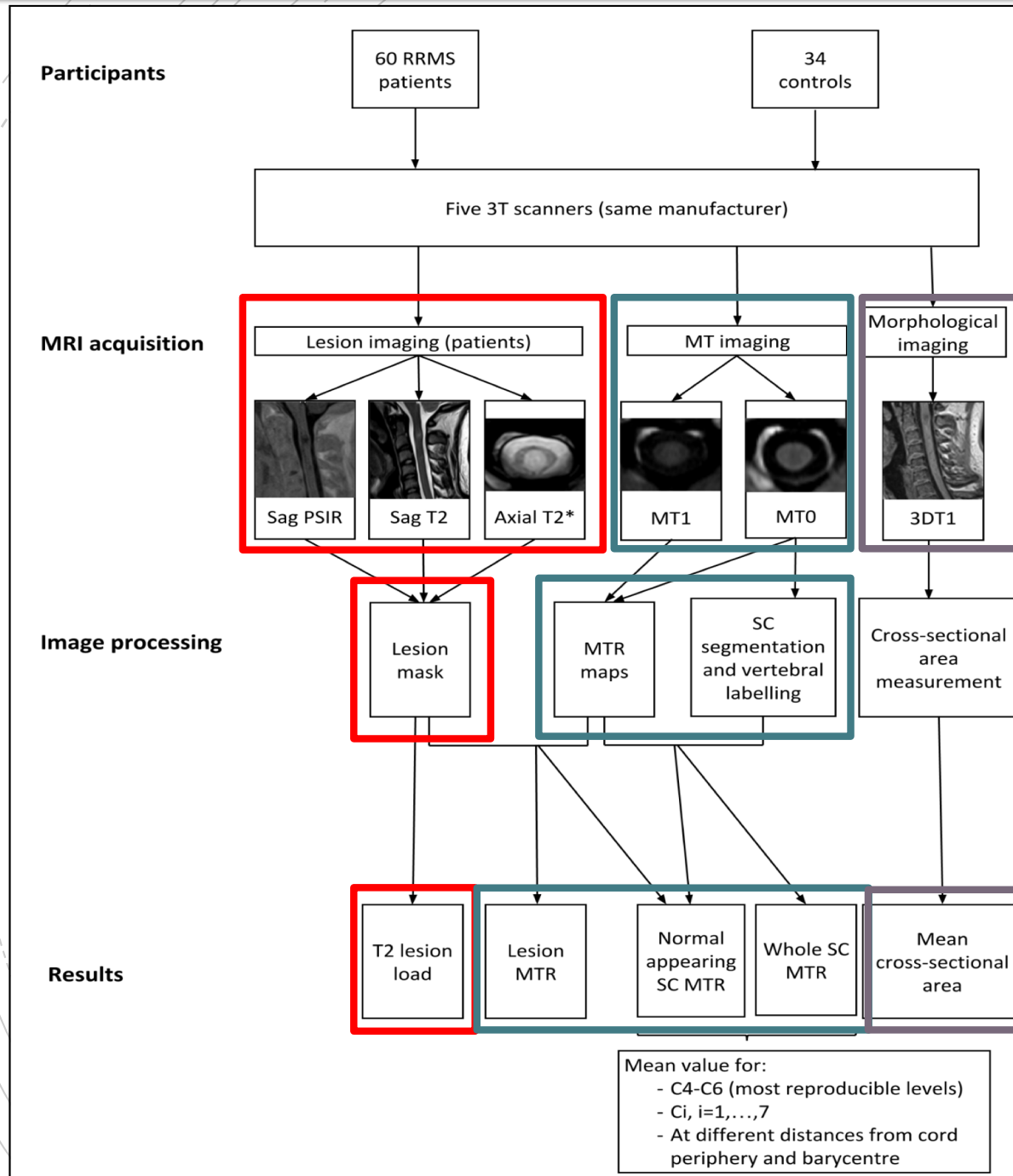
**Article 2**

**Focal and diffuse cervical spinal cord damage in patients with early relapsing-remitting MS: A multicentre magnetization transfer ratio study**

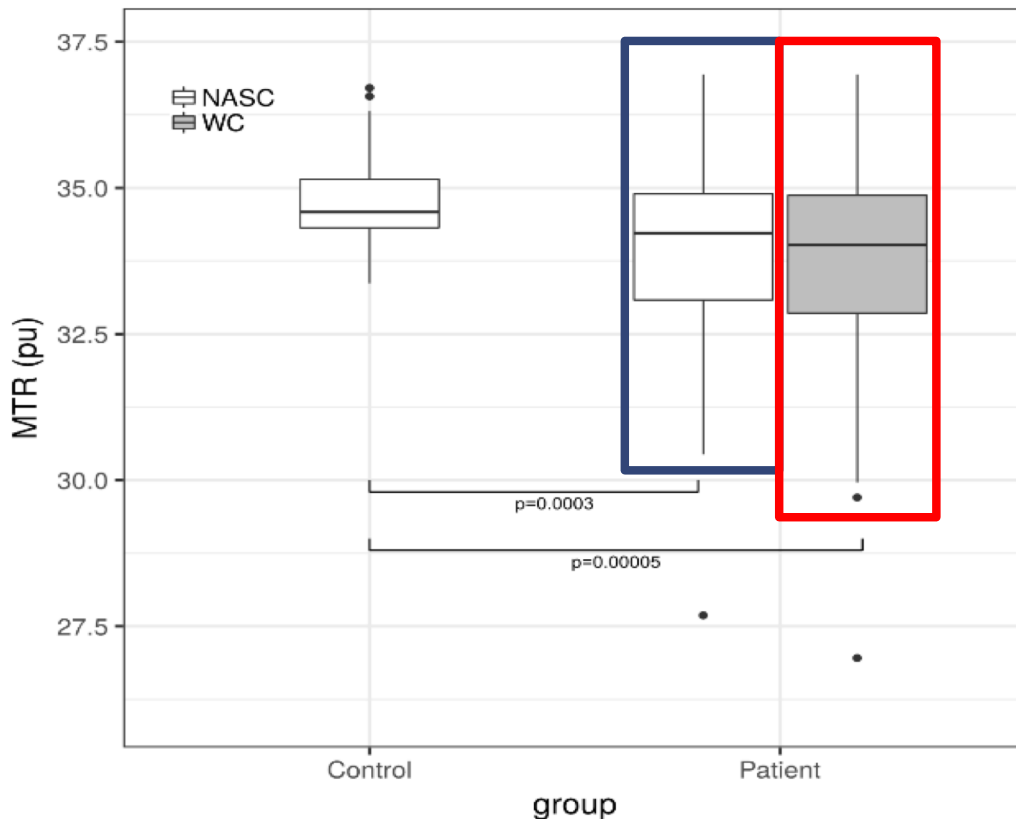
## Goals

- Quantify MTR changes in early RRMS patients in comparison with healthy controls
- Describe spatial distribution within and outside lesions
- Correlate MTR measurements with clinical scores

# MTR from Cervical Spinal Cord: Patient vs Controls at M0



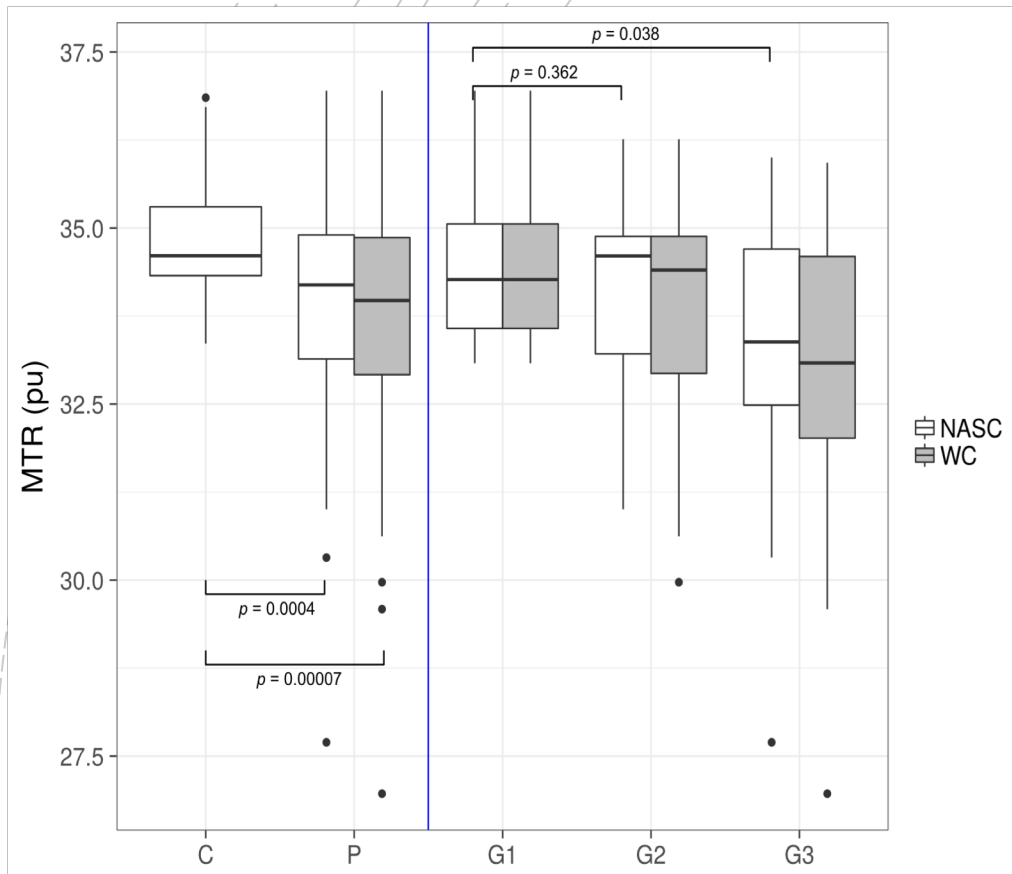
# MTR from Cervical Spinal Cord: Patient vs Controls at M0



| MTR values       |                    | Controls       | Patients       |
|------------------|--------------------|----------------|----------------|
| WC               | Mean (SD) pu       | 34.85 (0.85)   | 33.74 (1.78)   |
|                  | 95% CI for mean pu | [34.53, 35.16] | [33.28, 34.20] |
|                  |                    |                |                |
| NASC             | Mean (SD) pu       | NA             | 33.95 (1.60)   |
|                  | 95% CI for mean pu | NA             | [33.53, 34.36] |
|                  |                    |                |                |
| T2 focal lesions | Mean (SD) pu       | NA             | 27.98 (3.85)   |
|                  | 95% CI for mean pu | NA             | [26.65, 29.30] |
|                  |                    |                |                |

MTR (C4-C6) is significantly lower in patients versus controls considering the normal appearing spinal cord (lesion excluded) and the whole spine

# MTR from Cervical Spinal Cord: Patient vs Controls at M0



The more focal lesions the lower the MTR, also in the normal appearing spinal cord

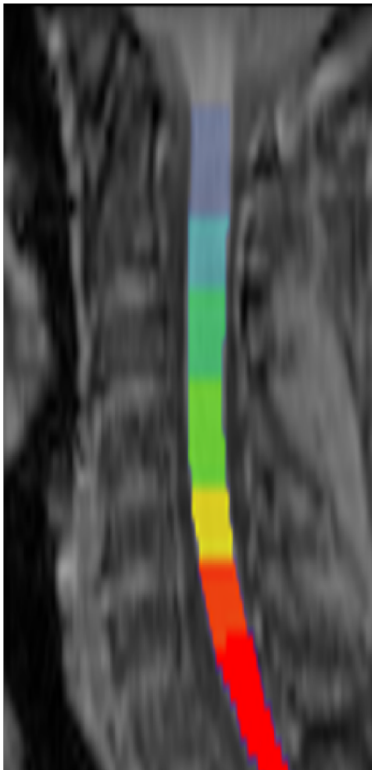
no lesion

1-2 lesions

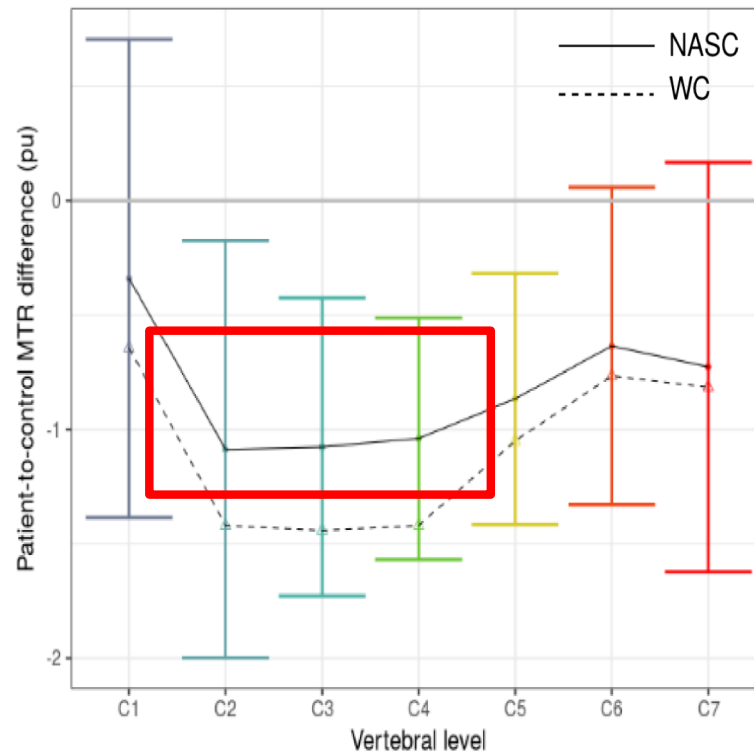
3 lesions or more

# MTR from Cervical Spinal Cord: Patient vs Controls at M0

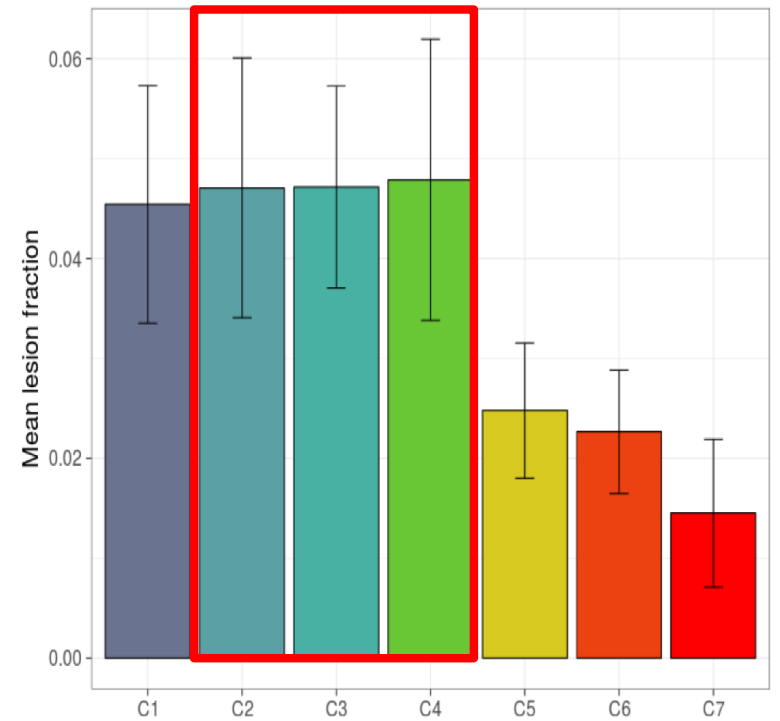
In the sagittal plane



A



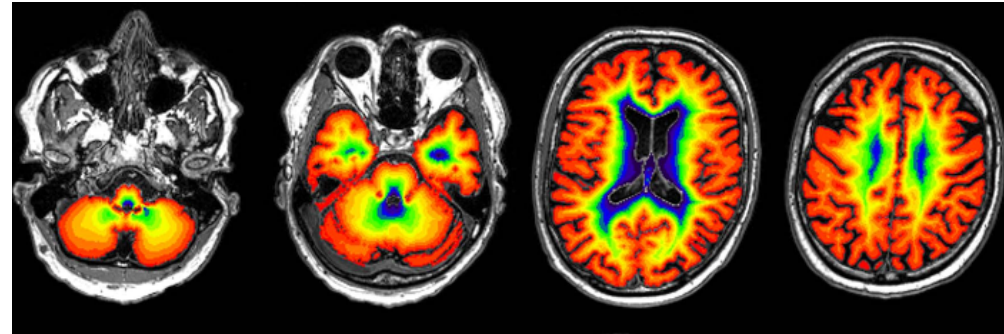
B



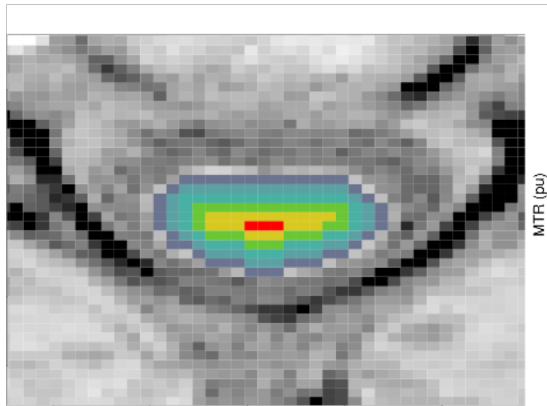
C

# MTR from Cervical Spinal Cord: Patient vs Controls at M0

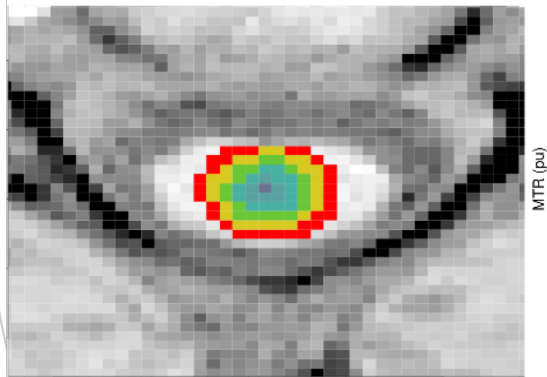
In the axial plane



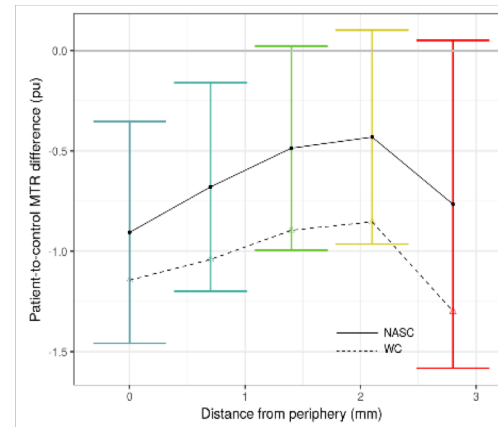
(Pardini et al. 2016)



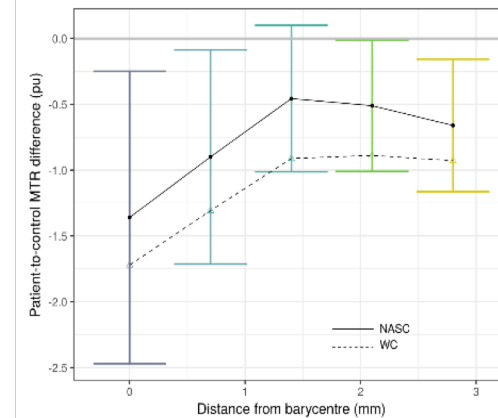
A.1



B.1



A.3



B.3



# MTR from Cervical Spinal Cord: Patient vs Controls at M0

## Correlation with clinical scores

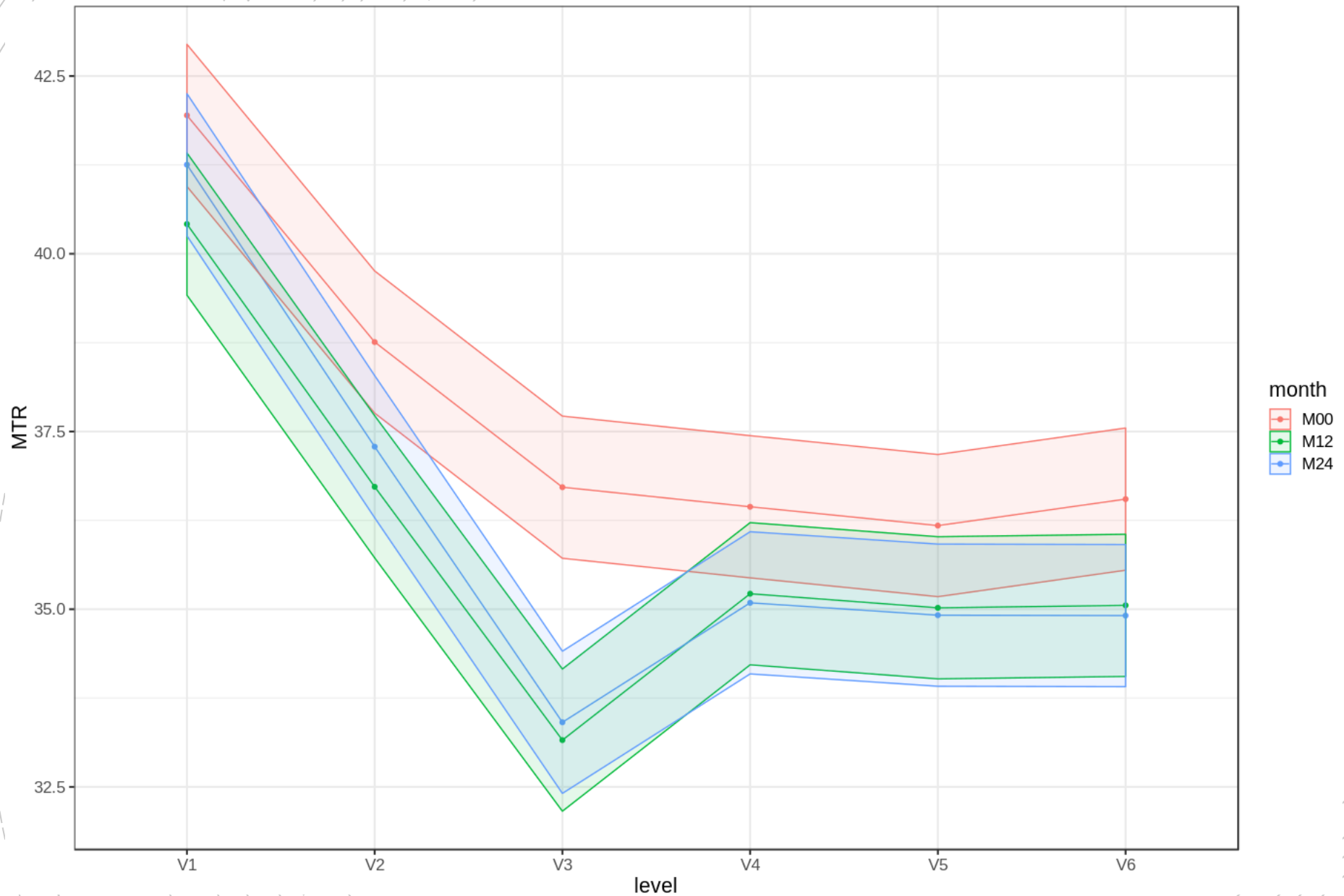
|                                | <b>EDSS</b>         | <b>Pyramidal<br/>EDSS</b>         | <b>8m</b>           | <b>6 minutes</b>                  | <b>12 MSWS</b>                   |
|--------------------------------|---------------------|-----------------------------------|---------------------|-----------------------------------|----------------------------------|
| <b>MTR</b>                     | -0.21<br>(p = 0.14) | <b>-0.27</b><br><b>(p = 0.05)</b> | -0.08<br>(p = 0.57) | 0.13<br>(p = 0.36)                | -0.12<br>(p = 0.39)              |
| <b>Cord Lesion<br/>volume</b>  | 0.26<br>(p = 0.06)  | <b>0.28</b><br><b>(p = 0.03)</b>  | 0.00<br>(p = 1.00)  | <b>-0.26</b><br><b>(p = 0.05)</b> | <b>0.30</b><br><b>(p = 0.03)</b> |
| <b>CSA</b>                     | 0.08<br>(p = 0.58)  | 0.01<br>(p = 0.92)                | 0.04<br>(p = 0.75)  | -0.04<br>(p = 0.79)               | -0.06<br>(p = 0.67)              |
| <b>Brain lesion<br/>volume</b> | 0.15<br>(p = 0.27)  | 0.12<br>(p = 0.38)                | -0.12<br>(p = 0.37) | -0.11<br>(p = 0.43)               | 0.07<br>(p = 0.63)               |

Diffuse and focal spinal cord burden can be measured at the beginning of the disease, and is correlated with lesion load

Longitudinal data needs to be processed to investigate whether initial burden can predict disability at 1, 2, 3 and 5 years.

# MTR from Cervical Spinal Cord: Longitudinal data – Ongoing work

## A particular case



# MTR from Cervical Spinal Cord: Longitudinal data

A particular case



**M0**

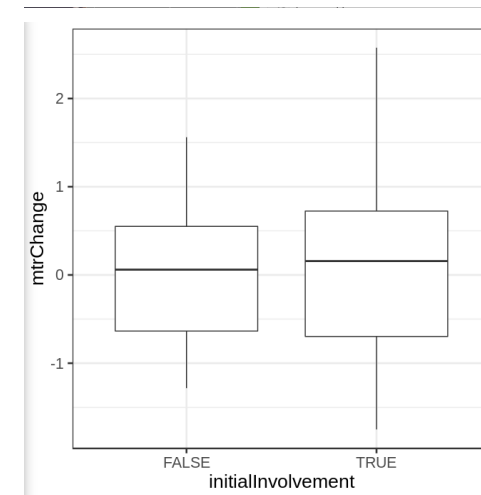
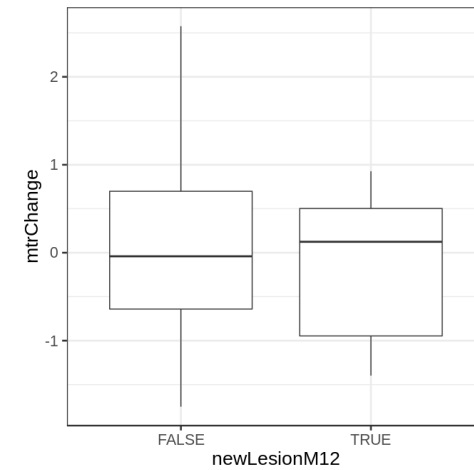
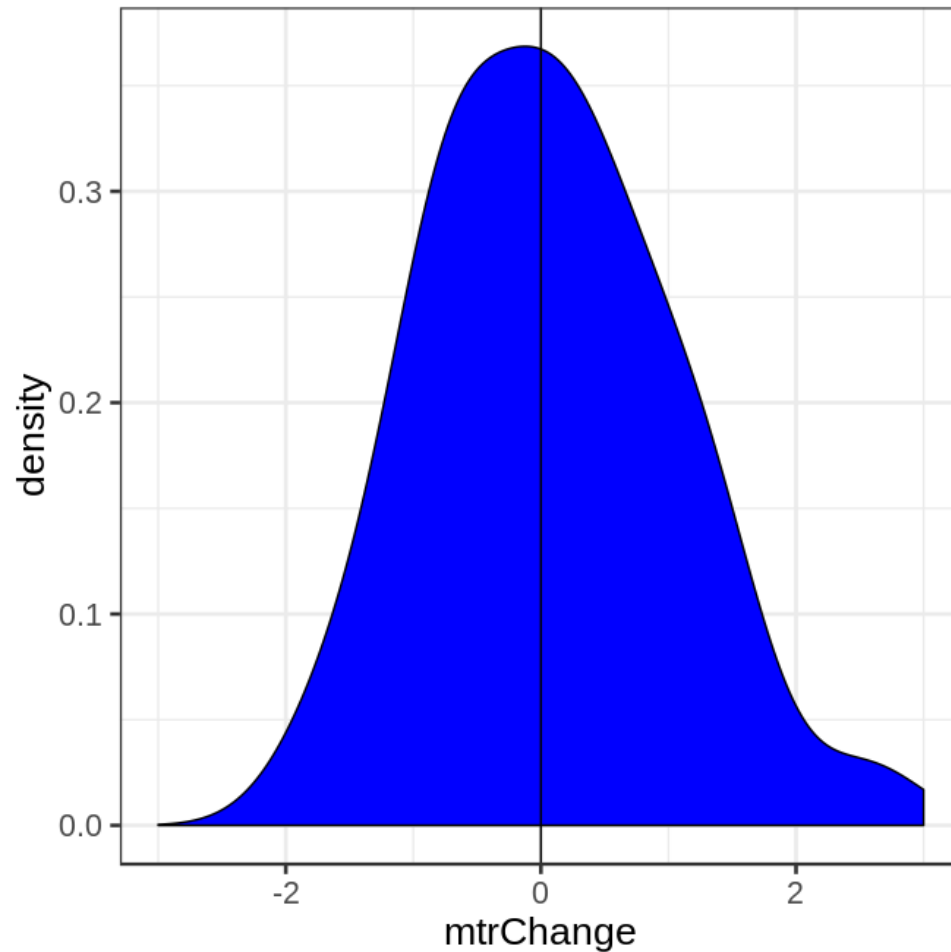


**M12**



**M24**

## Whole cord MTR change between M12 and M0 in a group of 39 patients



...ongoing work

# Acknowledgments

- Gilles Edan, Anne Kerbrat and Benoit Combès
- EMISEP study group : Neurologists, radiologists, MR Techs, MR Physicists, Research assistants from Montpellier, Strasbourg, Marseille, Lyon, Clermont-Ferrand, Nîmes and Rennes (list @ [team.irisa.fr/visages/emisep](https://team.irisa.fr/visages/emisep))
- Research group Visages (Empenn) Univ Rennes, CNRS, Inria, Inserm, IRISA UMR 6074, Empenn - ERL U 1228
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