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

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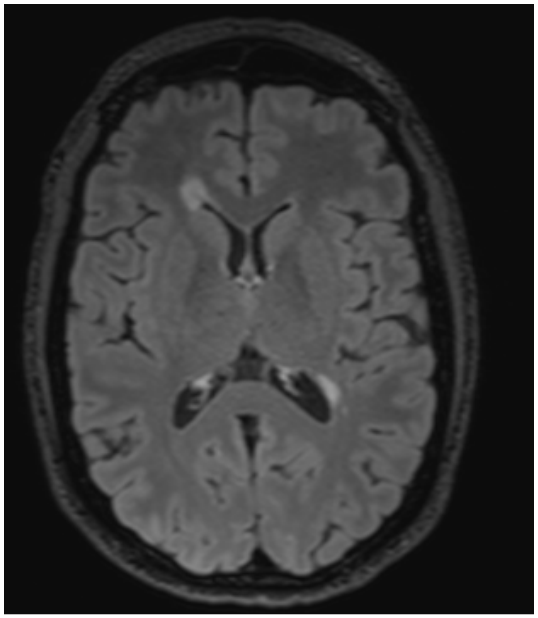
Multiple sclerosis (MS) is an often disabling disease of the central nervous system affecting the brain and the spinal cord.

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.

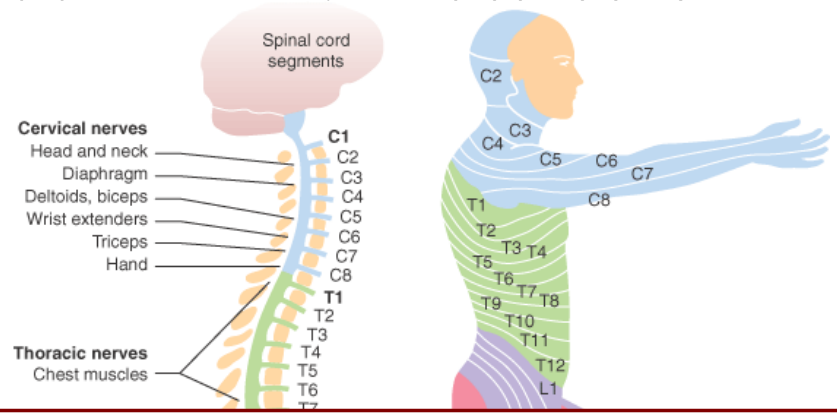
There is a need to identify prognostic factors at the individual level to guide therapeutic decisions.

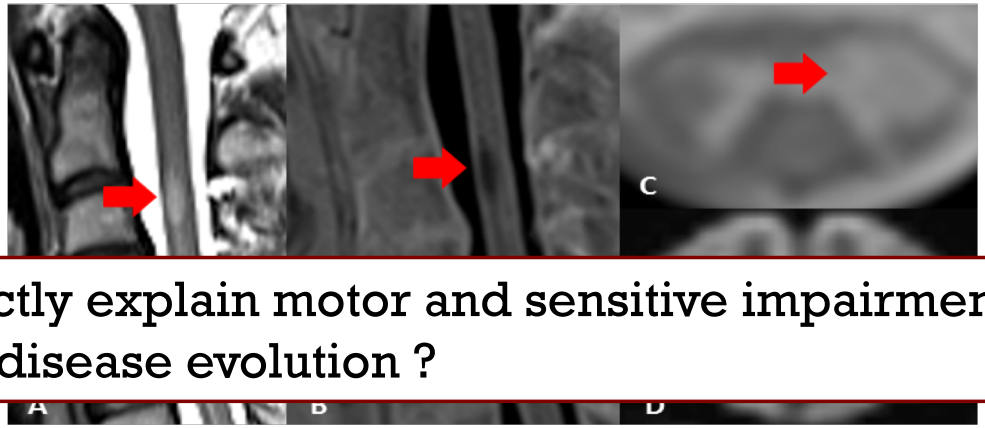


« Clinico-Radiological paradox »

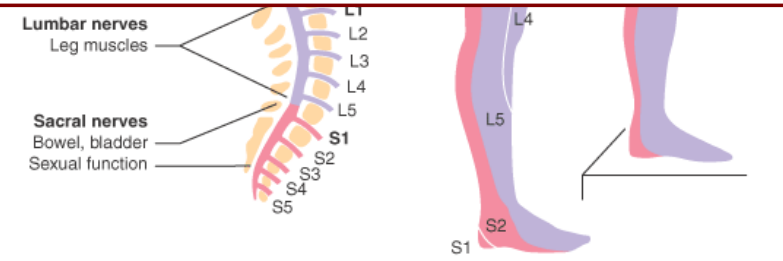
Barkhof et al. 1999

MRI and Multiple Sclerosis – What about Spinal Cord MRI?



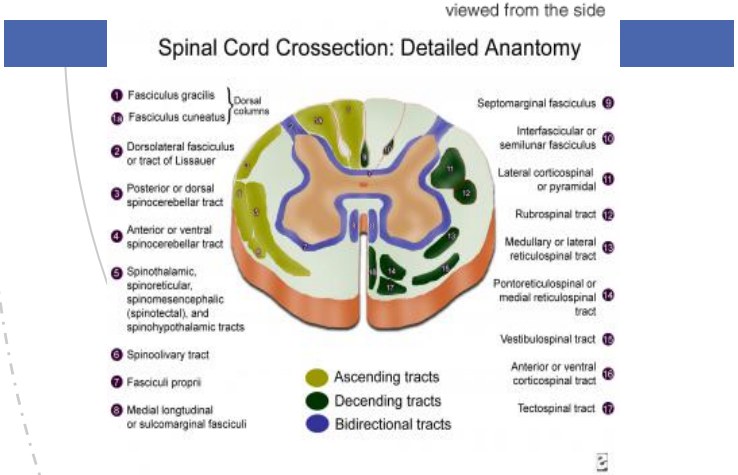


Can spinal cord involment more directly explain motor and sensitive impairment and predict disease evolution ?

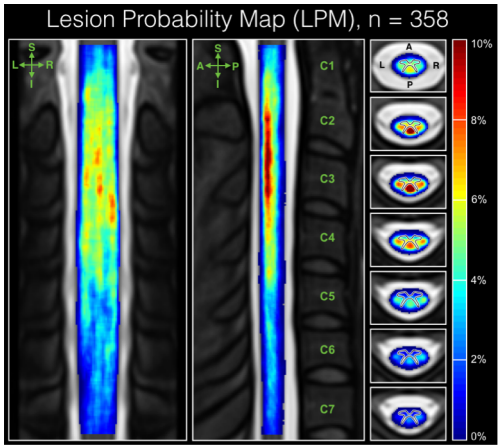


Motor control

Dermatomes
viewed from the side



> 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)*



Eden et al. ISMRM 2018

MRI and Multiple Sclerosis – What about Spinal Cord MRI?

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

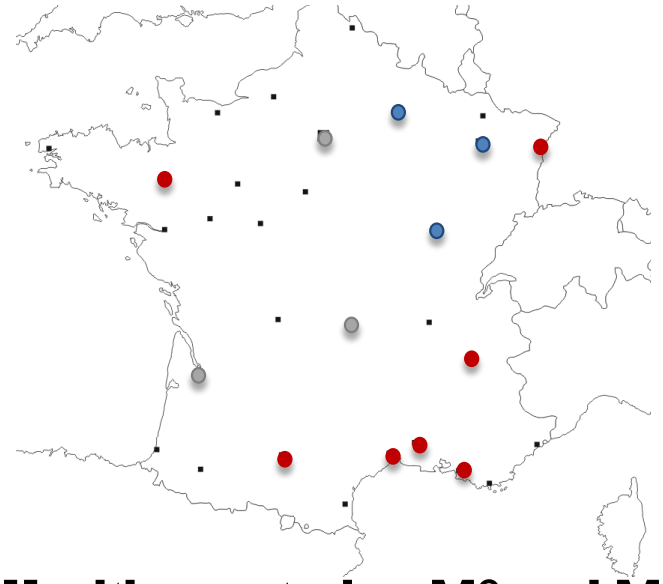
Funding : Ministry of Health 2012
Led by Rennes
Clinical Trials NCT021173375)

PI : Pr. Gilles Edan / Dr. Anne Kerbrat

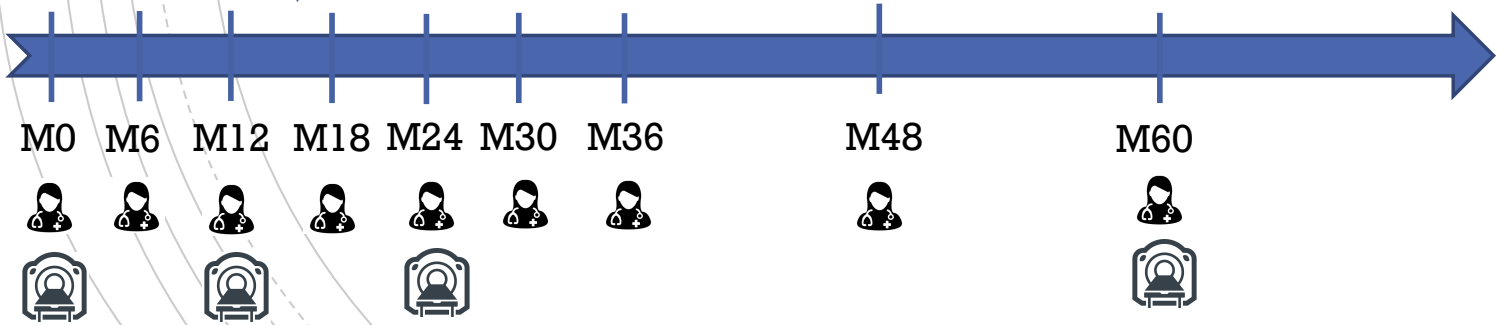
80 patients - 5-year Brain and Spinal Cord MRI and clinical follow up

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



MRI and Multiple Sclerosis – What about Spinal Cord MRI?

EMISEP

Inclusion criteria

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

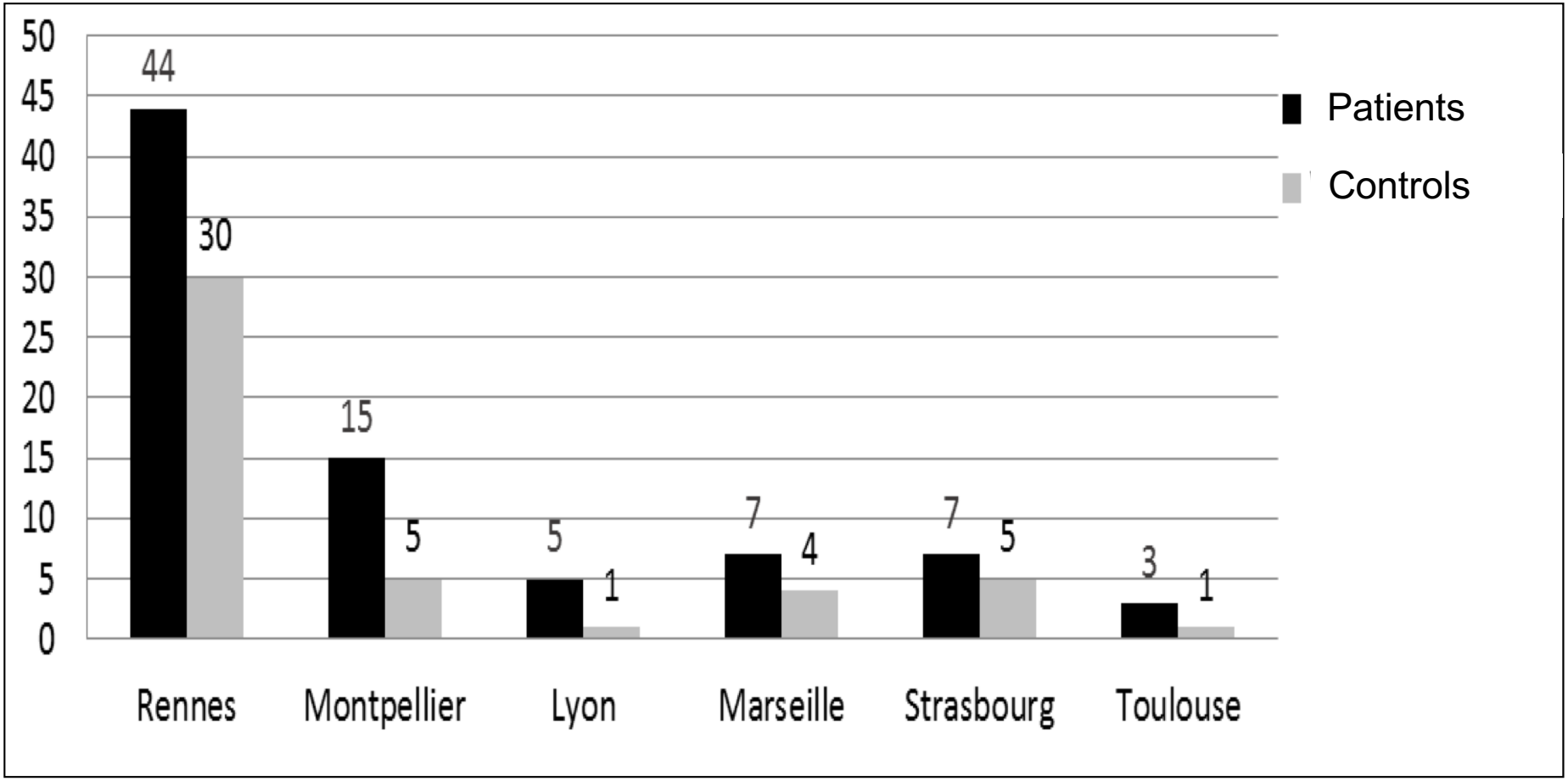
Clinical follow up

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

MRI and Multiple Sclerosis – First results

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

Combes, Monteau, JMRI 2018

MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability

	IRM 1 (Siemens Verio)	IRM 2 (Siemens Verio)	IRM 3 (Siemens Verio)	IRM 4 (Siemens Skyra)	IRM 5 (Siemens 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

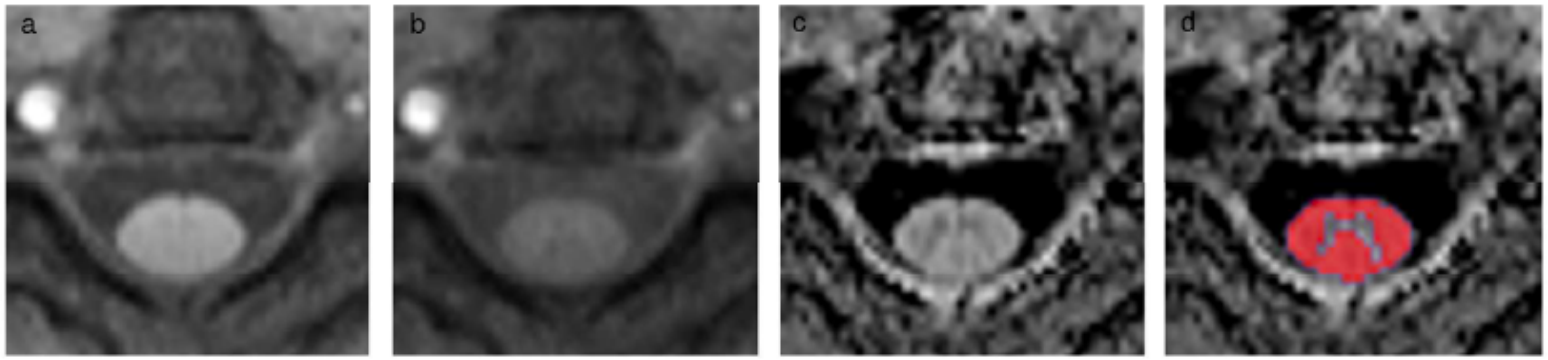
Imaging details

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)

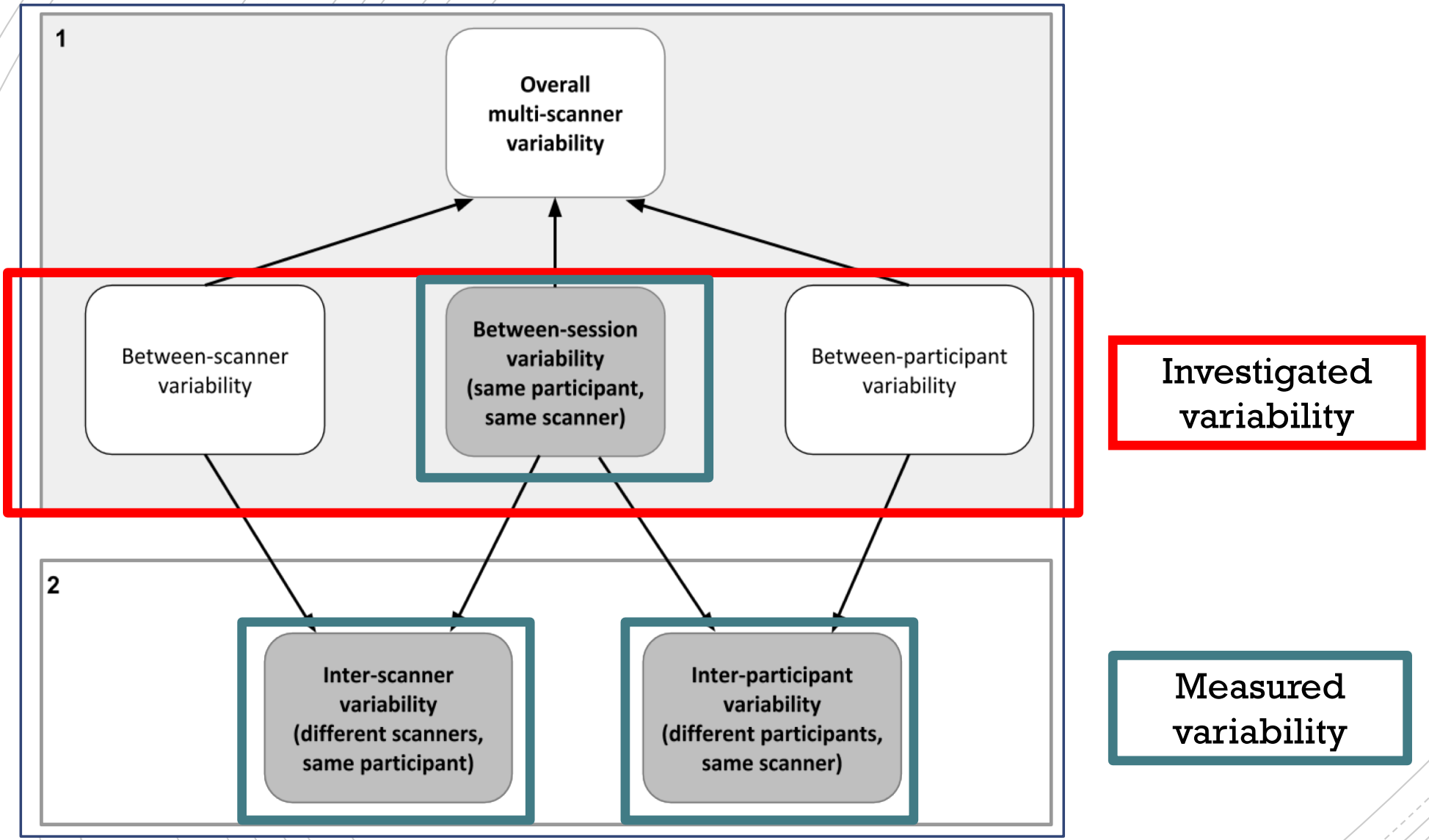
} Spinal Cord toolbox (v3.0)**



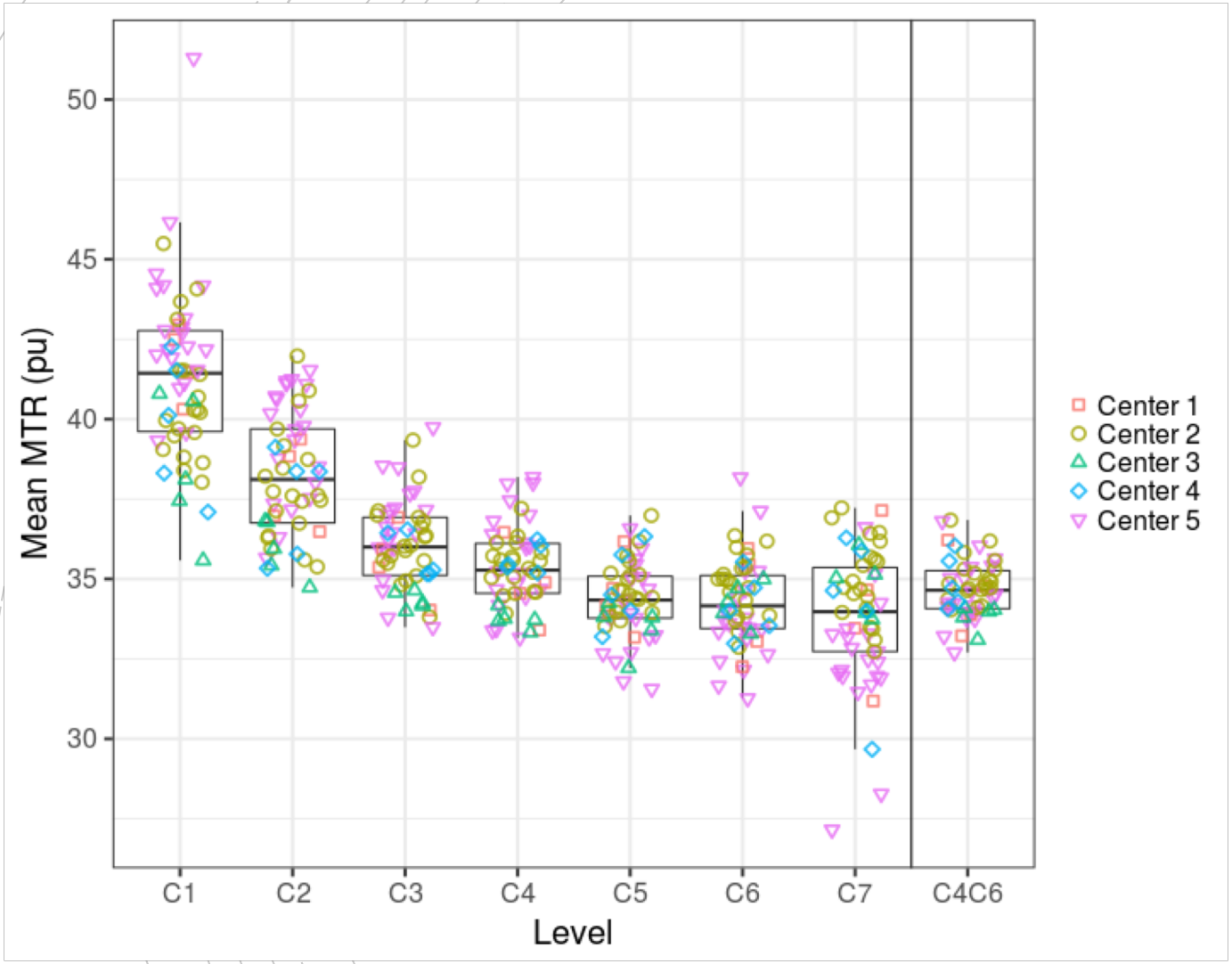
MT0 MT1 MTR Mask

*https://github.com/Inria-Visages/Anima-Public/wiki/ , ** De Leener, Neuroimage 2017

MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability



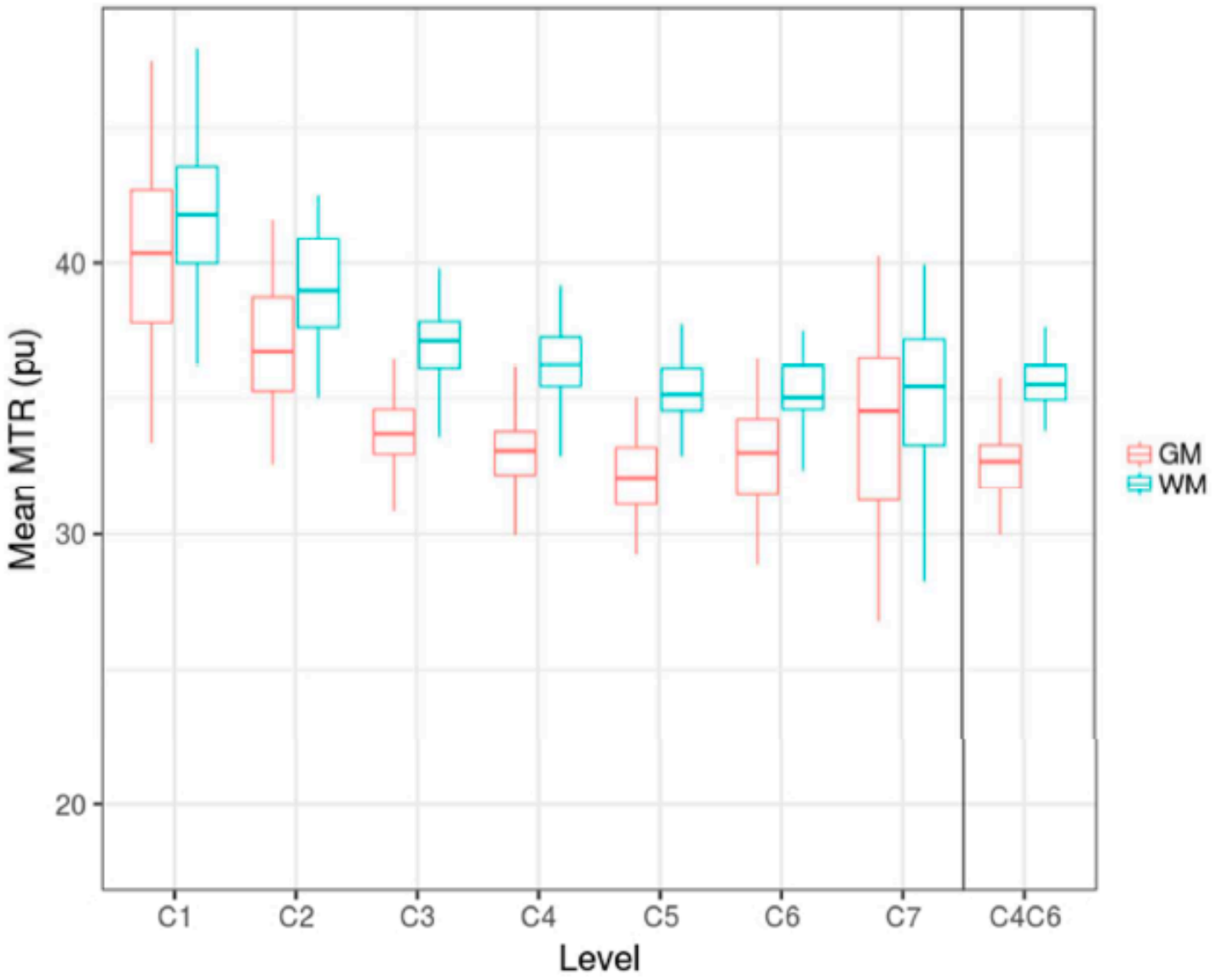
MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability



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

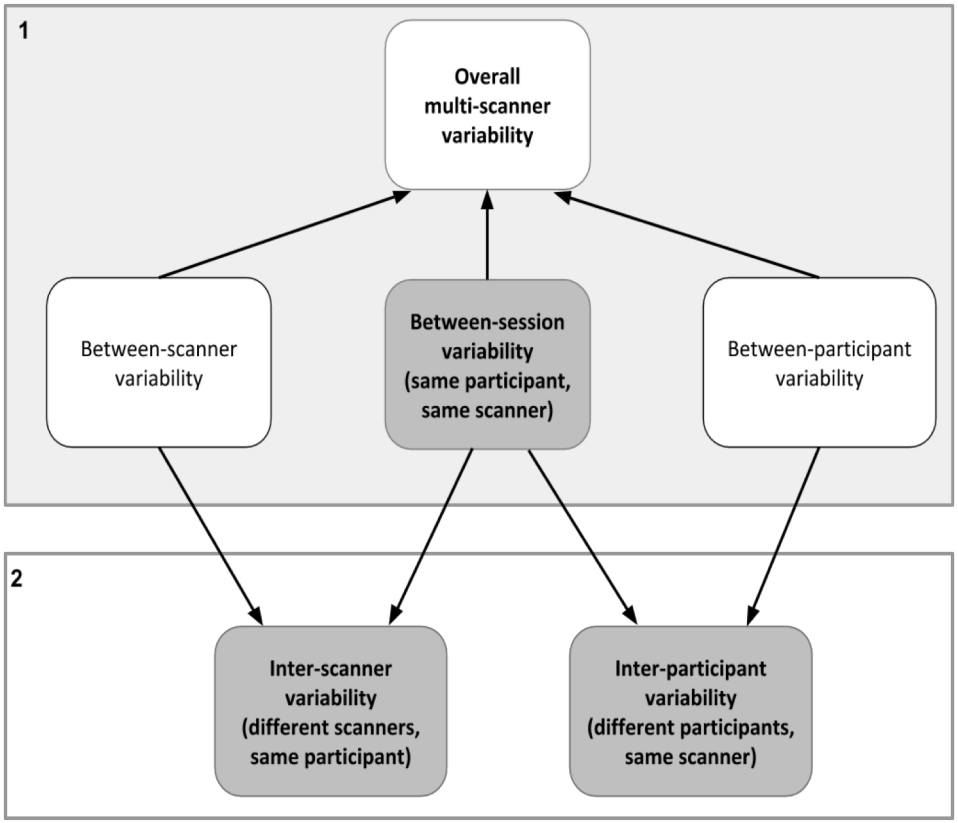
Between-scanner and between-subject variability overlap

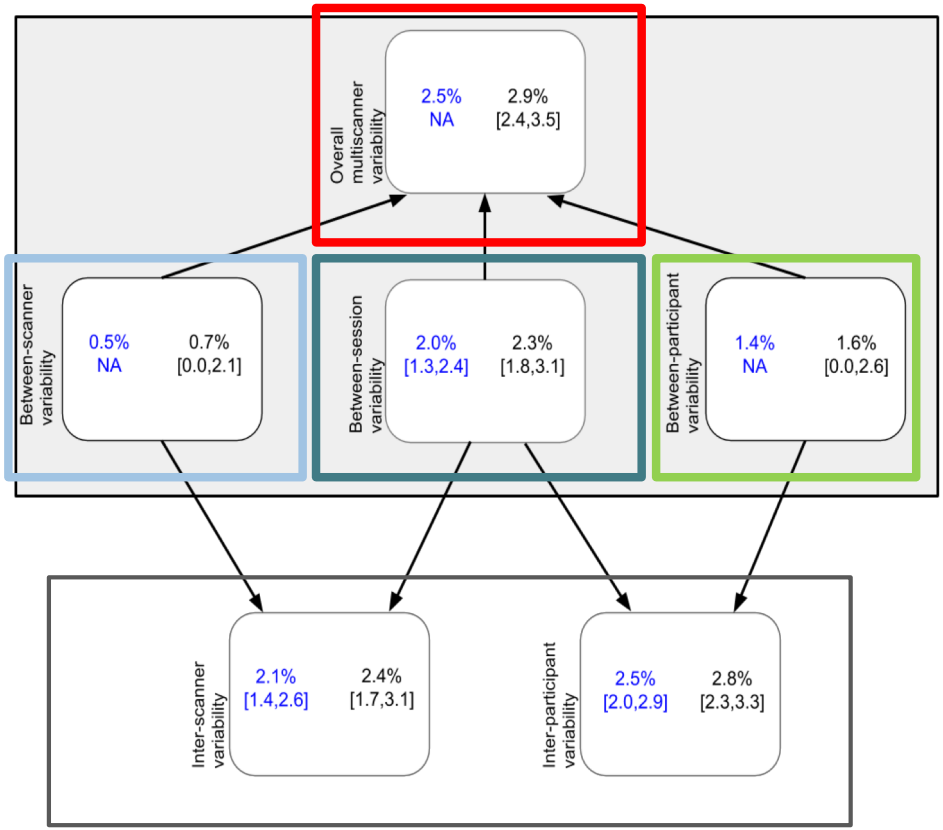
MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability



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

MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability

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

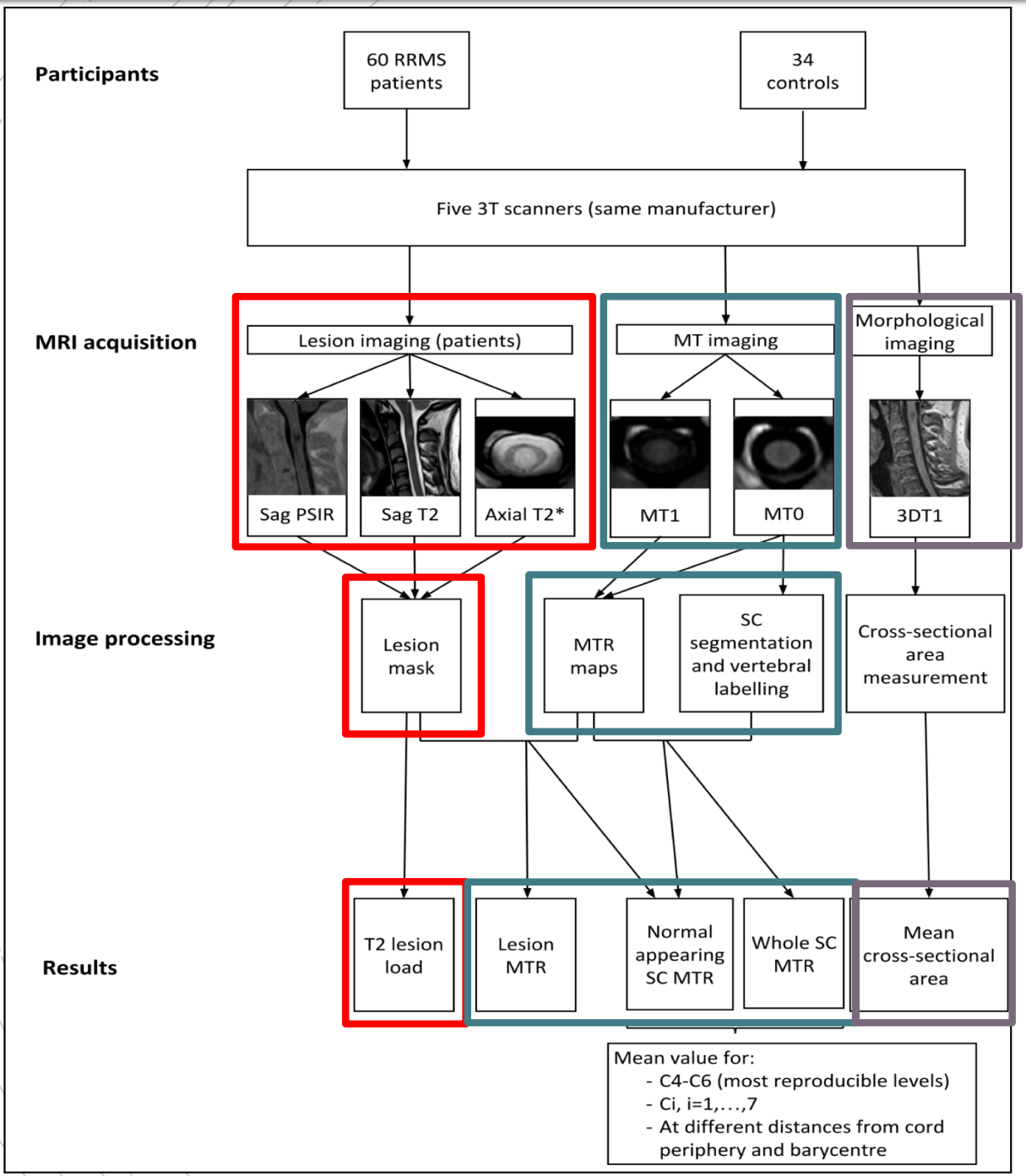
Combes, Kerbrat, Multiple Sclerosis Journal 2018

MTR from Cervical Spinal Cord: Patient vs Controls at M0

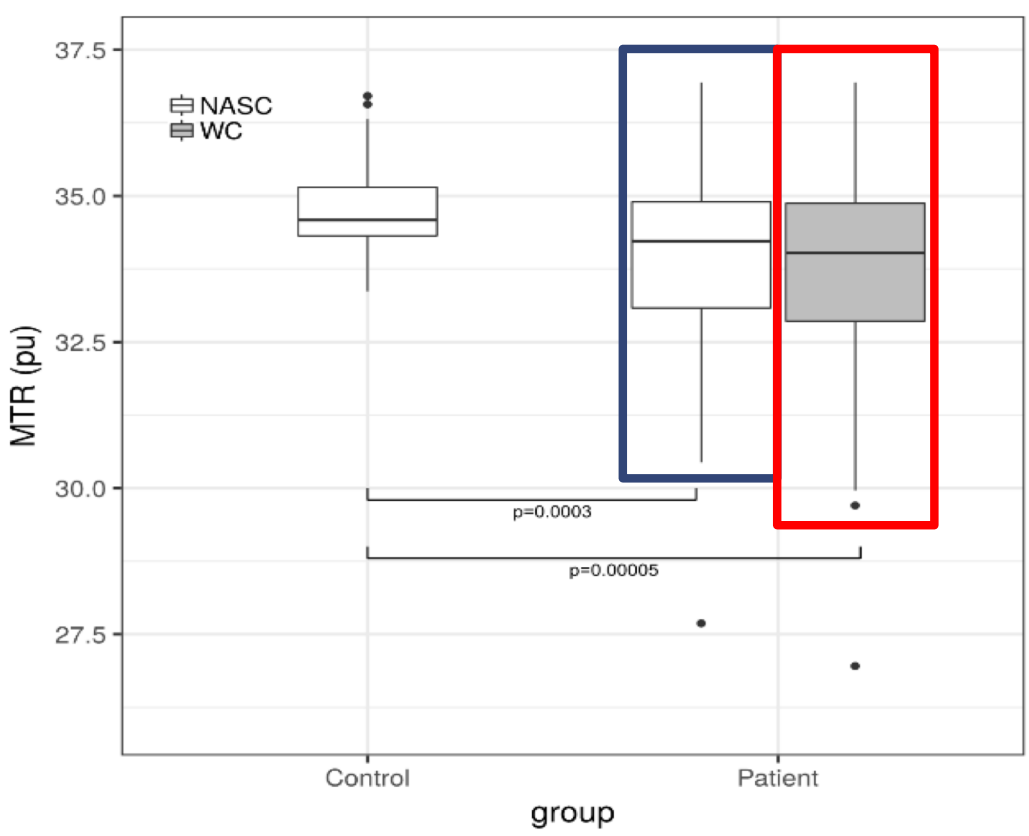
Goals

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



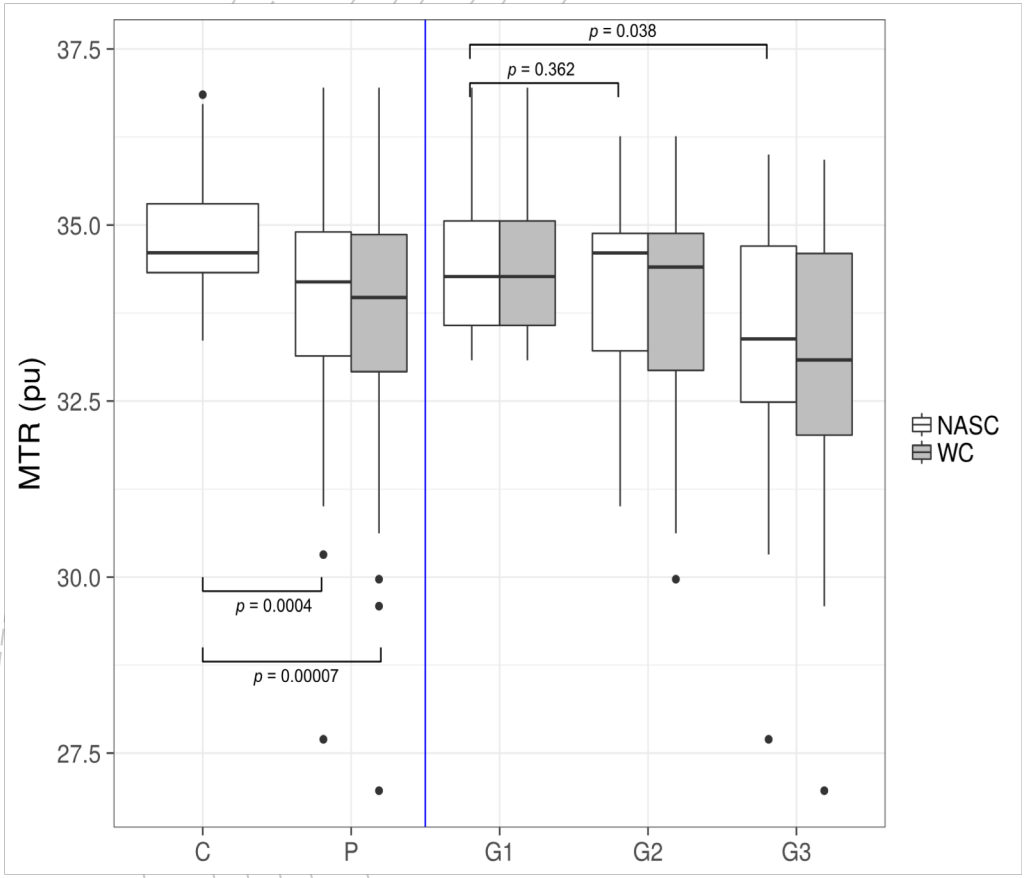
MTR from Cervical Spinal Cord: Patient vs Controls at M0



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

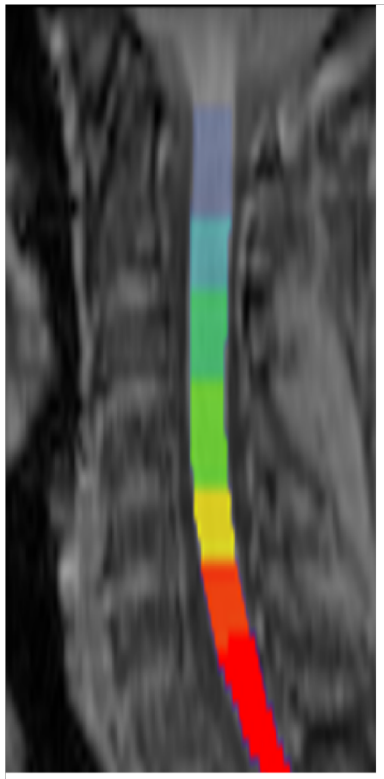
no lesion

1-2 lesions

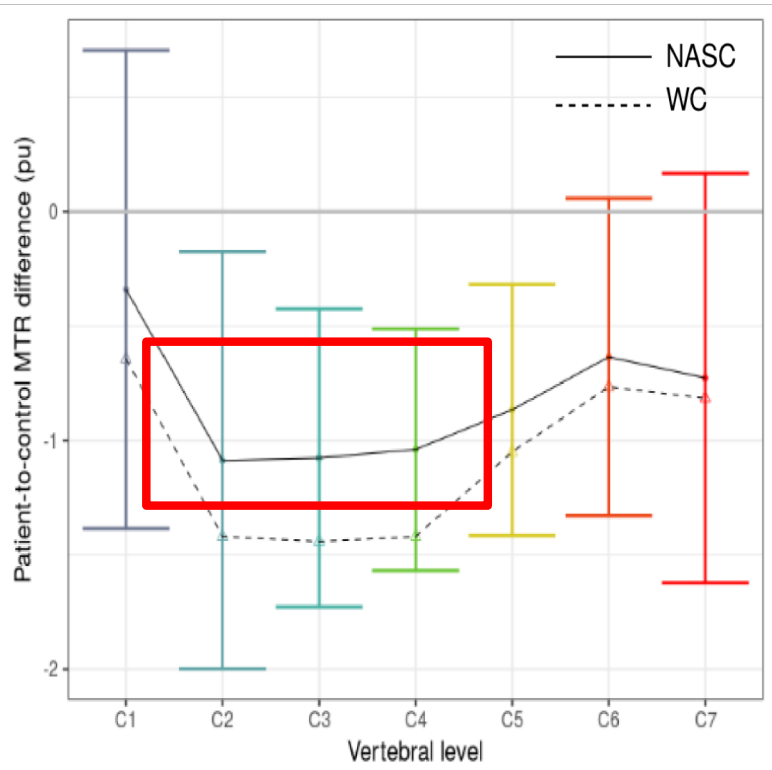
3 lesions or more

MTR from Cervical Spinal Cord: Patient vs Controls at M0

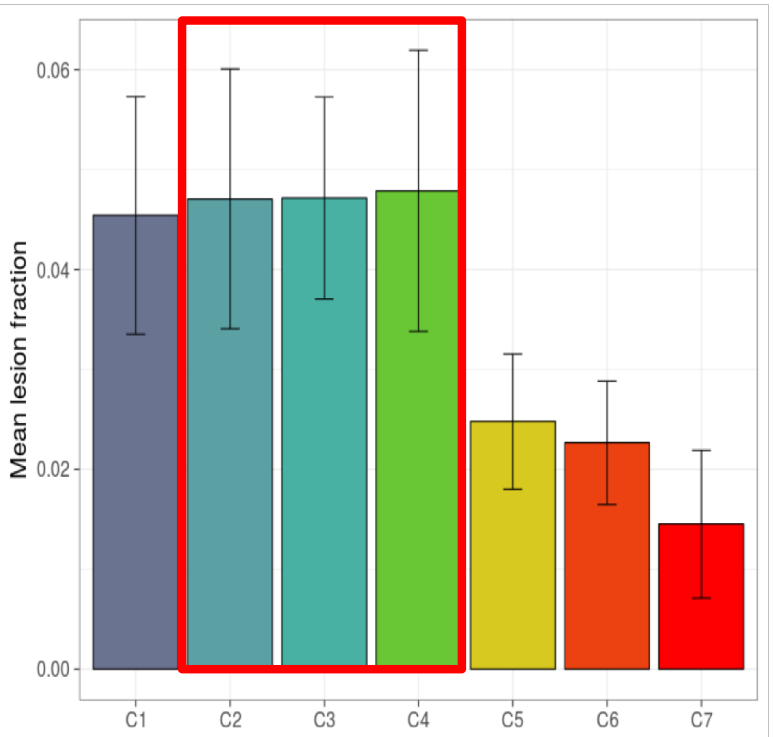
In the sagittal plane



A



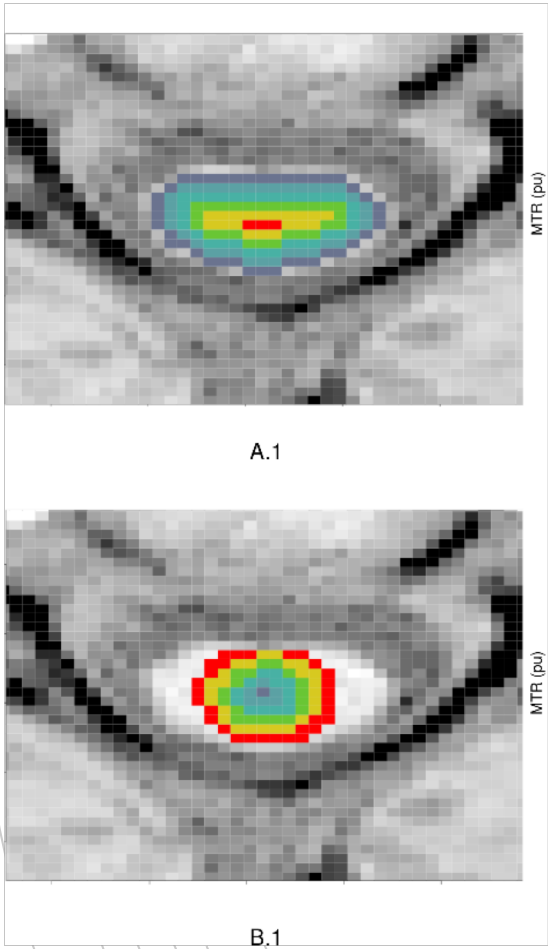
B

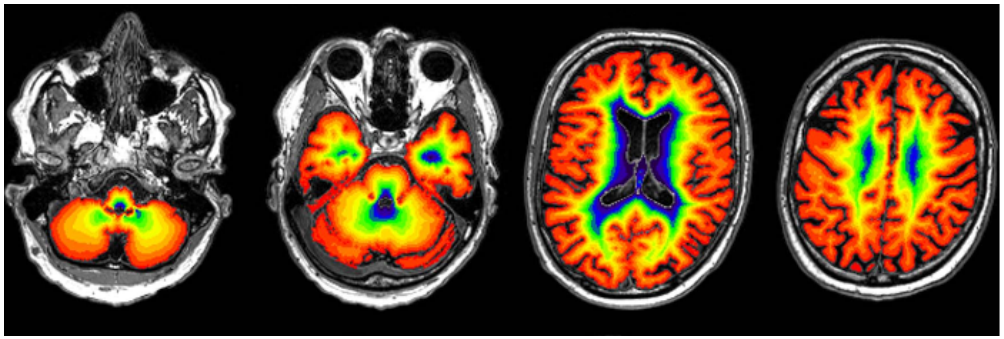


C

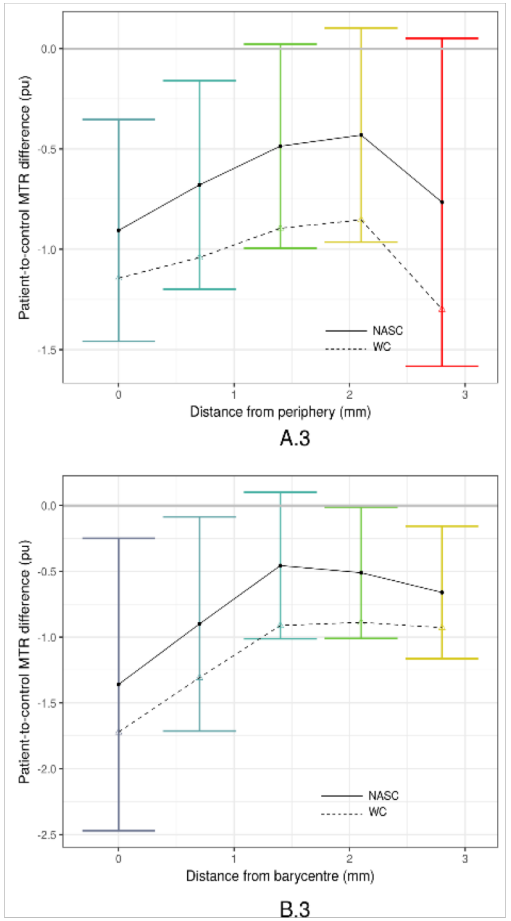
MTR from Cervical Spinal Cord: Patient vs Controls at M0

In the axial plane





(Pardini et al. 2016)



MTR from Cervical Spinal Cord: Patient vs Controls at M0

Correlation with clinical scores

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

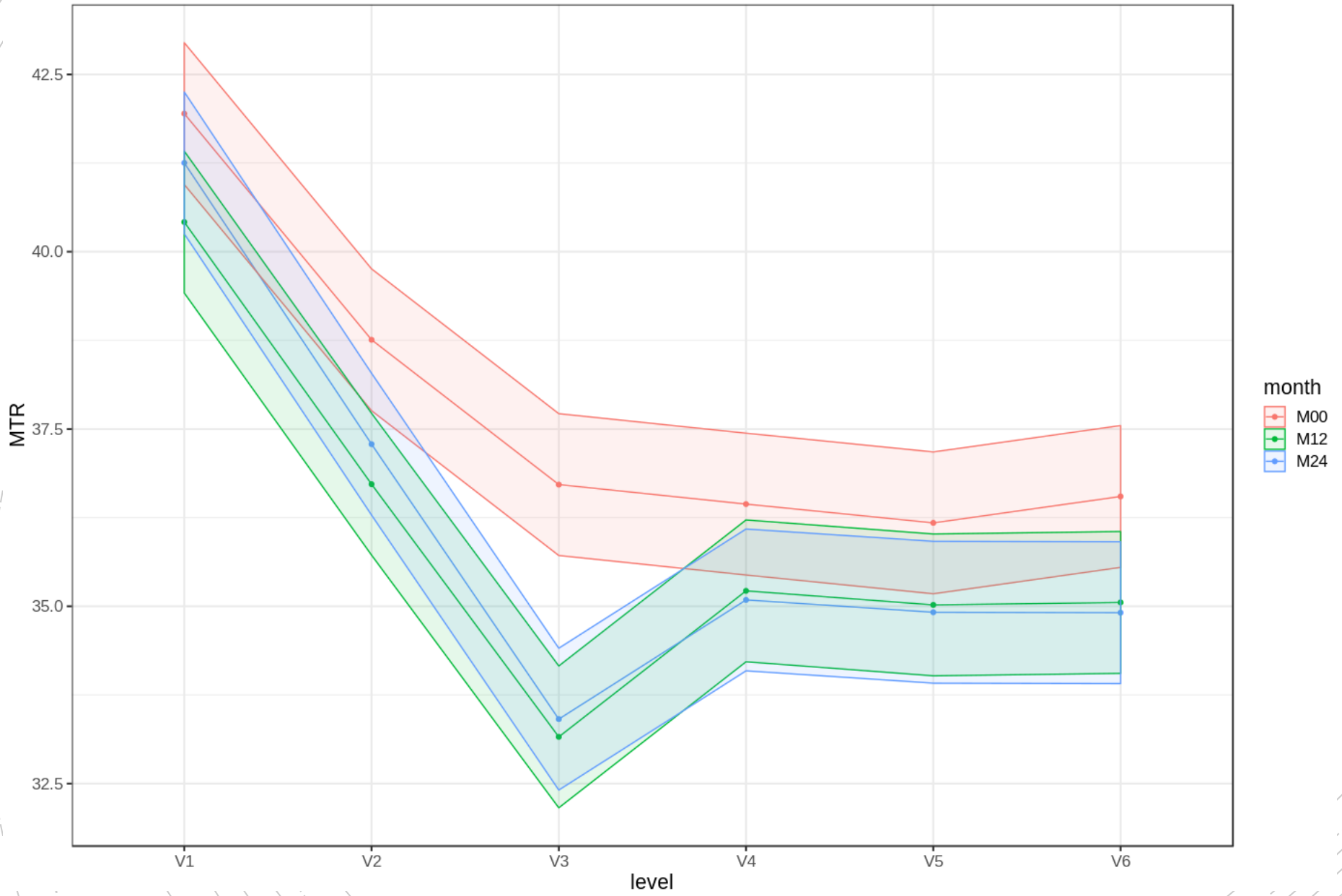
MTR from Cervical Spinal Cord: Patient vs Controls at M0

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



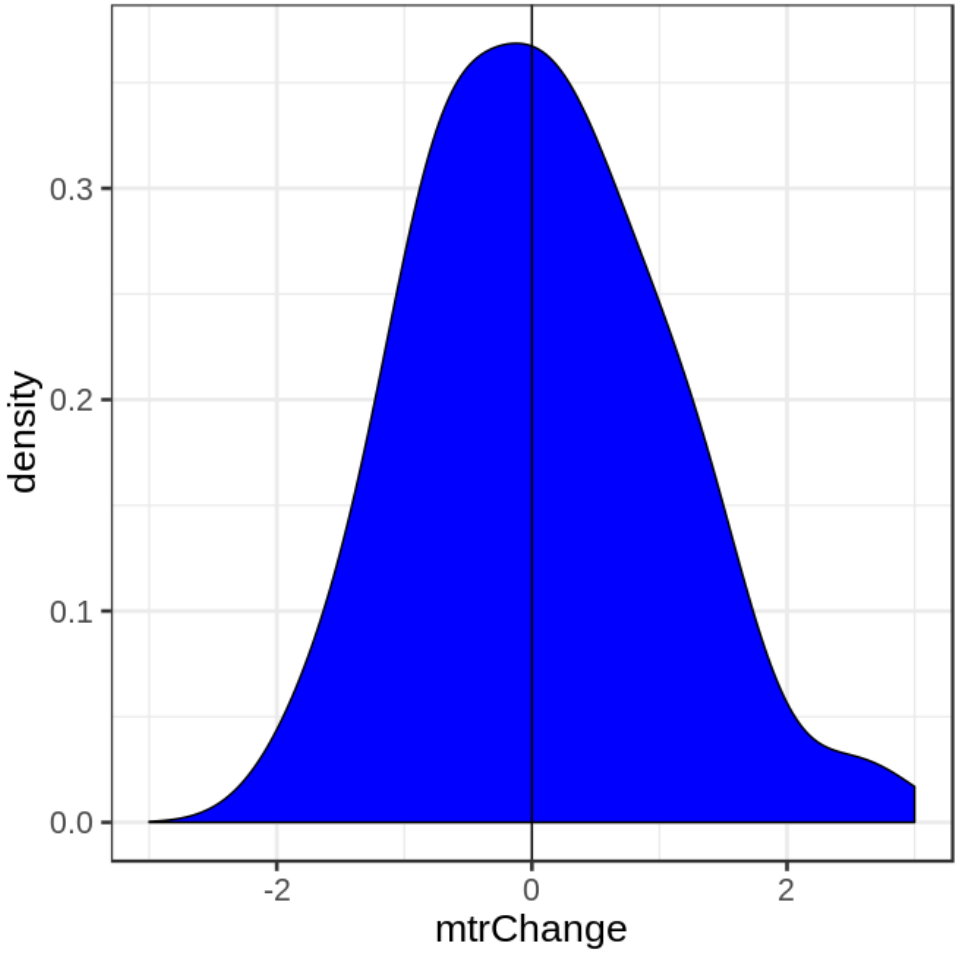
MTR from Cervical Spinal Cord: Longitudinal data

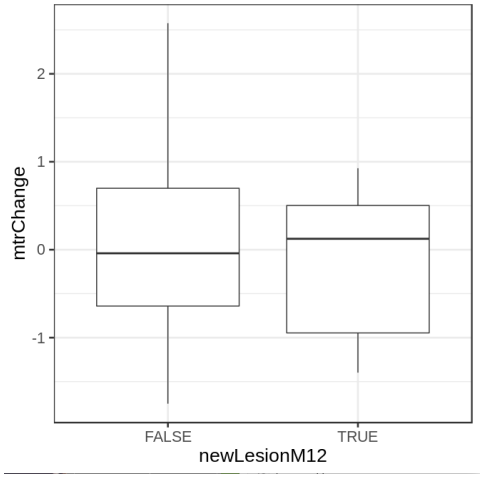
A particular case

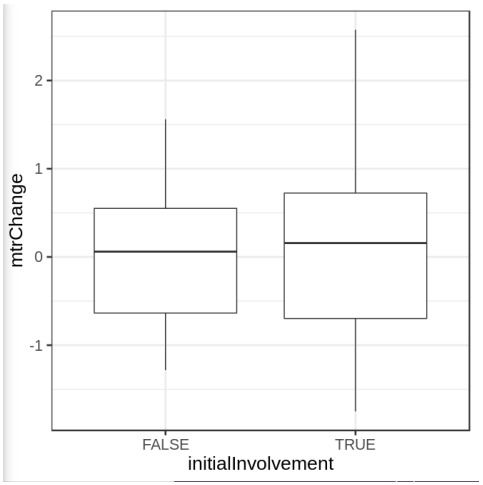
		
M0	**M12**	**M24**

MTR from Cervical Spinal Cord: Longitudinal data

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







…ongoing work

Acknowledgments

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