Spinal cord involvement in multiple sclerosis is highly predictive of disability and disease phenotype

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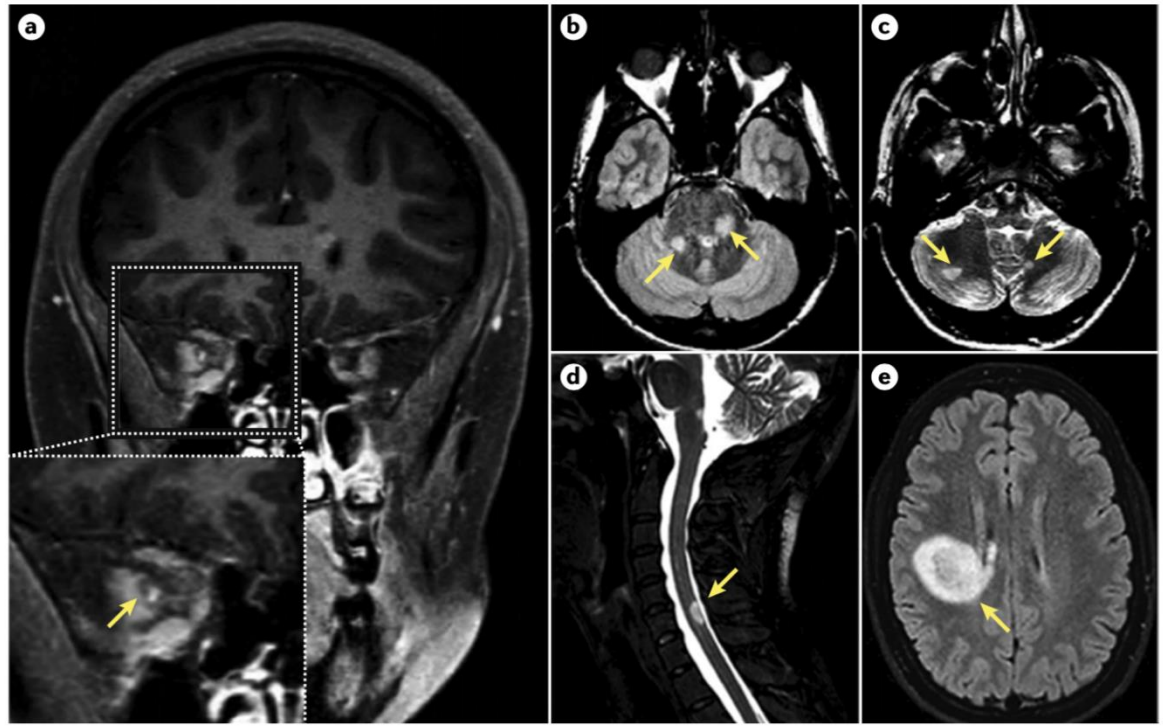
Background

- **Multiple sclerosis** is a chronic, inflammatory, demyelinating and neurodegenerative disease of the central nervous system
- The **pathological hallmark** of MS is the accumulation of **demyelinating lesions** in the white matter (WM) and grey matter (GM) of the brain and spinal cord (SC), but MS pathology is highly complex and heterogenous

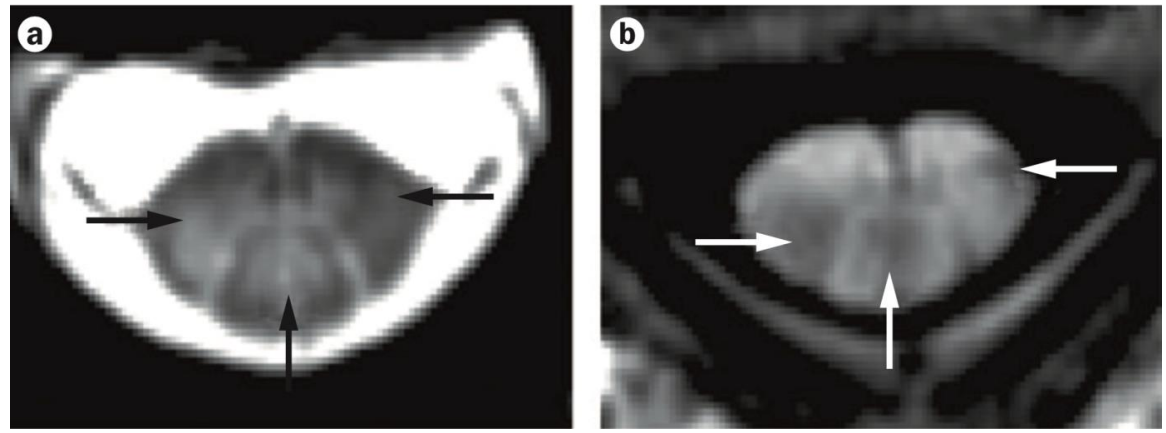
- **Spinal cord (SC) pathology:**
  - Common
  - Likely to be clinically relevant
  - Precise anatomical organization

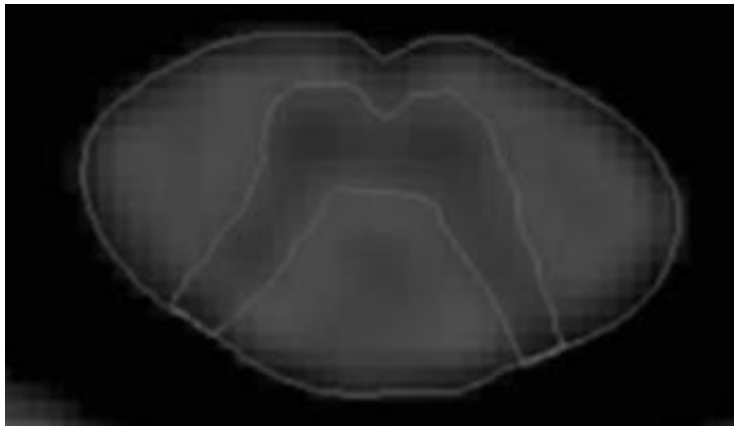


Background

Cervical SC lesion load:

- Correlated with EDSS score on single 2D slices at C2-C3 vertebral level
- Axial 3D T_2-weighted superior accuracy compared to sagittal
- No study with SC axial 3D lesion volumes (LV) in MS performed yet





Cervical cord atrophy:

- Correlated with EDSS score
- **GM atrophy:** strongest predictor of EDSS in multivariate models including brain lesion load and atrophy measures

Aims

- To investigate **cervical SC damage in MS** by combining several well-established MRI measures

- To assess the role of **SC involvement** in explaining the severity of **clinical disability** in MS

- To investigate the contribution of **SC involvement** in explaining the **heterogeneity of disease clinical phenotypes** in MS

Methods

- **Subjects:** 57 relapsing-remitting (RR) MS, 54 progressive MS (PMS) patients and 32 healthy controls (HC)

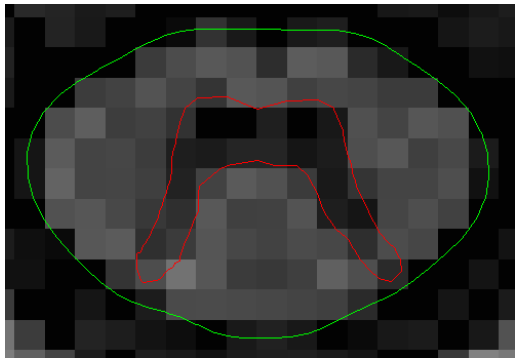
- **Neurologic assessment:** rating of the **EDSS score** + general & clinical Hx

- **MRI acquisition (3.0 T scanner):**
  - Brain 3D T_1–weighted, T_2–weighted and FLAIR images
  - Cervical SC 3D T_1–weighted, T_2–weighted, diffusion-weighted and sagittal 2D STIR images
  - Cervical SC axial PSIR at C2-C3 vertebral level

MRI analysis

Spinal cord

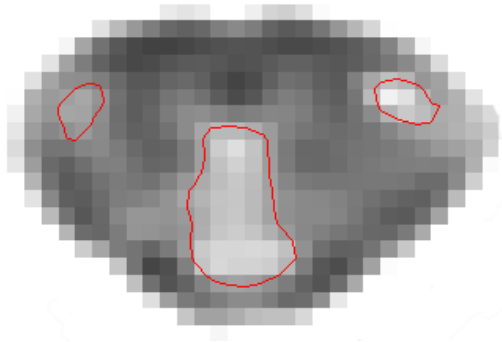
PSIR C2-C3 level



Green – global SC cross-sectional area

Red – GM cross-sectional area

3D T_2



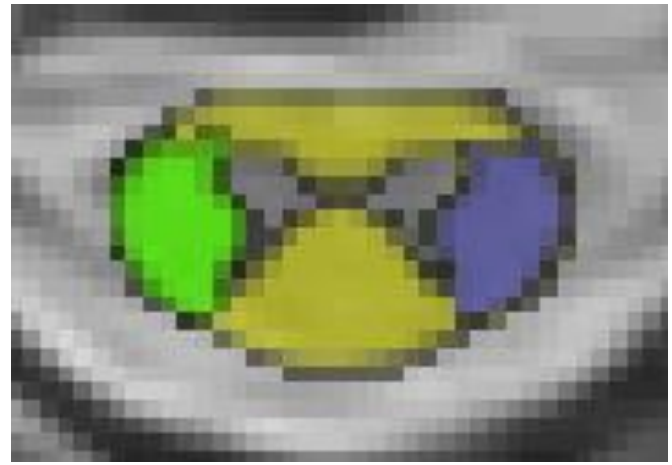
DTI

Brain

- **T_2-hyperintense LV**
- **SIENAX 2.0** for quantification of normalized WM, GM and total brain volumes

Statistical analysis

- Deformation of **template and atlas of SC WM** regions on the T_2-weighted image



Statistical analysis:

- Group comparisons
- Associations of MRI variables with EDSS explored by age-, sex- and phenotype-adjusted linear models
- Multivariable linear models with step-wise variable selection to identify independent predictors of EDSS

Results

	HC (n=32)	MS (n=111)	MS vs HC p value	RRMS (n=57)	PMS (n=54)	PMS vs RRMS p value
Men/Women	15/17	47/64	0.65○	24/33	23/31	0.90○
Mean age (SD) [years]	40.1 (14.4)	45.3 (10.6)	0.13+	40.5 (9.6)	50.3 (9.2)	<0.001+
Median disease duration (IQR) [years]	-	14 (4-22)	-	8 (2-16)	19 (11-24)	<0.001*
Median EDSS score (IQR)	-	4.0 (1.5-6.0)	-	1.5 (1.0-2.5)	6.0 (5.0-6.5)	<0.001*

Results

RRMS *vs* HC

- SC lesions (HC had no SC lesions)
- Lower WM and global SC cross-sectional areas
- Similar global and regional fractional anisotropy (FA)
- Higher brain T_2-LV
- Lower NBV and WMV

PMS *vs* RRMS

- Lower GM and global SC cross-sectional areas
- Higher global and regional SC nT_2-LV
- Lower global and regional FA
- Higher brain T_2-LV
- Lower NBV, WMV and GMV

Univariate associations

		RRMS patients Beta (p value)	PMS patients Beta (p value)
Brain [mL]	T_2-LV	**0.382 (<0.001)**	**0.152 (<0.01)**
	GMV	**-0.315 (0.001)**	**-0.216 (<0.01)**
	WMV	**-0.191 (0.02)**	-0.051 (0.46)
	NBV	**-0.298 (<0.001)**	**-0.191 (0.02)**
SC cross-sectional areas [mm^2]	GM	-0.111 (0.32)	**-0.219 (0.02)**
	WM	-0.056 (0.46)	-0.091 (0.23)
	Global	-0.147 (0.12)	-0.050 (0.45)
SC nT_2-LV	GM	**0.195 (0.02)**	0.052 (0.47)
	WM	**0.190 (0.01)**	0.030 (0.71)
	Dorsal columns	0.056 (0.48)	-0.082 (0.28)
	Lateral funiculi	**0.260 (<0.001)**	0.046 (0.55)
	Global	**0.196 (0.01)**	-0.023 (0.78)
SC FA	GM	**-0.216 (<0.01)**	**-0.172 (0.01)**
	WM	**-0.352 (<0.001)**	**-0.152 (0.02)**
	Dorsal columns	**-0.225 (0.02)**	**-0.134 (0.05)**
	Lateral funiculi	**-0.394 (<0.001)**	**-0.167 (<0.01)**
	Global	**-0.362 (<0.001)**	**-0.158 (<0.01)**
	Lesions	-0.153 (0.13)	-0.113 (0.07)

Univariate associations

		RRMS patients Beta (p value)	PMS patients Beta (p value)	Heterogeneity among phenotypes p value	MS Patients phenotype-adjusted Beta (p value)
Brain [mL]	T_2-LV	0.382 (<0.001)	0.152 (<0.01)	**0.04**	**0.207 (<0.001)**
	GMV	-0.315 (0.001)	-0.216 (<0.01)	0.40	**-0.254 (<0.001)**
	WMV	-0.191 (0.02)	-0.051 (0.46)	0.19	**-0.110 (0.04)**
	NBV	-0.298 (<0.001)	-0.191 (0.02)	0.35	**-0.241 (<0.001)**
SC cross-sectional areas [mm^2]	GM	-0.111 (0.32)	-0.219 (0.02)	0.45	**-0.177 (0.01)**
	WM	-0.056 (0.46)	-0.091 (0.23)	0.75	-0.074 (0.17)
	Global	-0.147 (0.12)	-0.050 (0.45)	0.40	-0.083 (0.12)
SC nT_2-LV	GM	0.195 (0.02)	0.052 (0.47)	0.20	**0.111 (0.04)**
	WM	0.190 (0.01)	0.030 (0.71)	**0.04**	0.094 (0.09)
	Dorsal columns	0.056 (0.48)	-0.082 (0.28)	0.21	-0.015 (0.78)
	Lateral funiculi	0.260 (<0.001)	0.046 (0.55)	**0.04**	**0.166 (<0.01)**
	Global	0.196 (0.01)	-0.023 (0.78)	**0.04**	**0.099 (0.08)**
SC FA	GM	-0.216 (<0.01)	-0.172 (0.01)	0.66	**-0.191 (<0.001)**
	WM	-0.352 (<0.001)	-0.152 (0.02)	0.07	**-0.217 (<0.001)**
	Dorsal columns	-0.225 (0.02)	-0.134 (0.05)	0.43	**-0.164 (<0.01)**
	Lateral funiculi	-0.394 (<0.001)	-0.167 (<0.01)	**0.03**	**-0.246 (<0.001)**
	Global	-0.362 (<0.001)	-0.158 (<0.01)	**0.05**	**-0.225 (<0.001)**
	Lesions	-0.153 (0.13)	-0.113 (0.07)	0.74	**-0.125 (0.02)**

Multivariate analysis

Independent predictors of EDSS in RRMS patients (R^2=0.53):

- SC lateral funiculi nT_2-LV (B=0.56; p<0.001)
- NBV (B=-0.41; p<0.01)

Independent predictors of EDSS in PMS patients (R^2=0.49):

- SC lesion-free dorsal column FA (B=-0.52; p<0.01)
- SC GM atrophy (B=-0.36; p=0.03)

Best predictors of phenotype with logistic multiple regression analysis (AUC=0.97):

- SC GM atrophy (OR=0.23; p=0.001)
- SC global nT_2-LV (OR=2.35; p=0.05)

Conclusions

- **Cervical SC** suffers from **macroscopic and microscopic damage in MS**, more severe in PMS compared to RRMS

- **Cervical SC involvement** in MS is **highly correlated with disability**

- Different MRI measures contribute to explain **disability in RRMS and PMS**:
  - **SC lateral-funiculi T_2-LV** and **brain atrophy** in **RRMS**
  - **SC dorsal-column FA** and **GM atrophy** in **PMS**

- Cervical SC MRI involvement is an **accurate predictor of MS phenotype**: **cross-sectional GM atrophy** and **T_2-LV** are the main predictors