

Supplementary material

Table A1. Summary of MRI system, acquisition parameters and vertebral coverage across participating sites.

Site	MRI scanner	Contrast, Orientation	Vertebral coverage (median, range)	TR (ms)	TE (ms)	FOV(mm ²)	Number of slices, slice thickness (mm)
Aix-Marseille University, Hôpital La Timone, Marseille, France (n = 15)	3T	T ₂ *w, Axial	C1-C7	849	23	179x179	40, 3.00
		T ₂ w, Sagittal	C1-C7	3000	68	261x261	15, 2.50
Brigham and Women's Hospital, Boston, USA (n = 80)	3T	T ₂ w, Axial	C1-C7	5070	101	179x179	47, 3.00
Karolinska University Hospital, Stockholm, Sweden (n = 51)	Siemens Trio 3T	T ₂ *w, Axial	C1-C7	561	17	179x179	30, 4.40
Massachusetts General Hospital, Boston, USA (n = 18)	7T	T ₂ *w, Axial	C1-C7	500	7.8	219x210	36, 3.00
National Institutes of Health Clinical Center, Maryland, USA (n = 29)	Siemens Skyra 3T	T ₂ *w, Axial	C1-C7	560	17	260x195	28, 5.00
		T ₂ w, Sagittal	C1-C7	6000	27	384x384	30, 1.00
New York University Langone Medical Center, New York, USA (n = 151)	Siemens 3T	T ₂ w, Axial	C1-C7	4000	107	200x156	60, 4.86
		T ₂ w, Sagittal	C1-C7	3000	103	180x135	32, 3.90

French Observatory of Multiple Sclerosis, France (n = 32)	3T	T ₂ *w, Axial	C1-C3	992	29	198x179	16, 4.55
		T ₂ w, Sagittal	C1-C7	4720	74	338x338	12, 4.80
San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy (n = 115)	Philips 3T Achieva	T ₂ *w, Axial	C1-C7	47	6.5	150x150	40, 2.50
		T ₂ w, Sagittal	C1-C7	2933	70	250x250	14, 2.50
University Hospital of Montpellier, France (n = 15)	Siemens Skyra 3T	T ₂ *w, Axial	C1-C7	849	23	179x179	40, 3.30
		T ₂ w, Sagittal	C1-C7	3000	68	261x261	15, 2.75
University Hospital of Rennes, Rennes, France (n = 51)	Siemens Verio 3T	T ₂ *w, Axial	C1-C7	849	23	179x179	40, 3.30
		T ₂ w, Sagittal	C1-C7	3000	68	261x261	15, 2.75
University College London, London, UK (n = 39)	3T	T ₂ *w, Axial	C1-C3	23	5	240x240	10, 5.00
		T ₂ w, Sagittal	C1-C7	4000	80	256x256	12, 3.00
Zuckerberg San Francisco General Hospital, San Francisco, USA (n = 25)	3T	T ₂ *w, Axial	C1-C7	3516	72	179x179	36, 3.30
Vanderbilt University Medical Center, Nashville, USA (n = 23)	Philips Achieva 3T	T ₂ *w, Axial	C2-C5	753	7	162x162	14, 5.00
		T ₂ w, Sagittal	C1-C7	2500	100	251x251	18, 2.00

Table A2. Lesion frequency for different populations, defined by patient phenotype.

	Phenotype				Total cohort
	CIS	RRMS	SPMS	PPMS	n=642
	n=31	n=416	n=84	n=73	
C1-C3	1.37 (1.35, 1.4)	2.74 (2.71, 2.77)	3.02 (2.98, 3.05)	3.49 (3.46, 3.53)	2.75 (2.73, 2.78)
C4-C7	1.23 (1.21, 1.25)	1.93 (1.91, 1.94)	1.96 (1.95, 1.98)	1.91 (1.89, 1.93)	1.89 (1.88, 1.91)
DC	1.41 (1.38, 1.44)	2.48 (2.45, 2.51)	2.48 (2.45, 2.52)	2.60 (2.56, 2.65)	2.42 (2.39, 2.46)
LF	1.06 (1.04, 1.08)	1.53 (1.52, 1.55)	1.73 (1.71, 1.75)	1.91 (1.88, 1.93)	1.57 (1.55, 1.59)
VF	0.15 (0.15, 0.16)	0.40 (0.39, 0.41)	0.37 (0.37, 0.38)	0.33 (0.32, 0.34)	0.37 (0.36, 0.38)

Lesion frequency (%) averaged value (confidence interval at 95%) in multiple regions of interest of the cervical spinal cord, for different populations. For a given population (i.e. each column), values in violet indicate higher median values comparing (i) C1-C3 vs. C4-C7, (ii) DC vs. LF vs. VF. No statistical tests were performed for lesion frequency between regions of interests. Abbreviations: MS, multiple sclerosis; CIS, clinically isolated syndrome; RRMS, relapsing-remitting MS; PPMS, primary progressive MS; SPMS, secondary progressive MS; DC, dorsal columns; LF, lateral funiculi; VF, ventral funiculi. Phenotype was not available for all subjects.

Table A3. Lesion frequency for different populations, defined by patient EDSS and disease duration.

	Mild EDSS			Moderate EDSS			Severe EDSS			Total Cohort (n=642)
	Short DD (n=132)	Moderate DD (n=62)	Long DD (n=25)	Short DD (n=64)	Moderate DD (n=84)	Long DD (n=70)	Short DD (n=5)	Moderate DD (n=30)	Long DD (n=77)	
C1-C3	2.43 (2.40, 2.46)	1.54 (1.52, 1.55)	2.44 (2.40, 2.48)	3.28 (3.24, 3.32)	3.29 (3.26 - 3.33)	2.57 (2.54, 2.60)	4.5 (4.42, 4.59)	4.41 (4.36, 4.46)	3.40 (3.36, 3.43)	2.75 (2.73, 2.78)
C4-C7	2.18 (2.16, 2.20)	1.53 (1.51, 1.54)	1.26 (1.24, 1.28)	1.85 (1.83, 1.87)	2.42 (2.39, 2.44)	1.40 (1.38, 1.41)	1.89 (1.85, 1.94)	1.80 (1.77, 1.82)	1.97 (1.95, 1.99)	1.89 (1.88, 1.91)
DC	2.33 (2.29 , 2.36)	1.40 (1.38, 1.43)	2.11 (2.07, 2.16)	3.06 (3.01, 3.11)	2.99 (2.95, 3.03)	2.06 (2.02, 2.09)	1.27 (1.22, 1.31)	3.19 (3.13, 3.25)	2.83 (2.79, 2.87)	2.42 (2.39, 2.46)
LF	1.60 (1.58, 1.62)	1.31 (1.30, 1.33)	1.05 (1.03, 1.08)	1.52 (1.50, 1.54)	1.87 (1.85, 1.89)	1.33 (1.31, 1.34)	2.43 (2.37, 2.48)	2.02 (1.99, 2.04)	1.80 (1.78, 1.83)	1.57 (1.55, 1.59)
VF	0.46 (0.45, 0.47)	0.19 (0.18, 0.20)	0.27 (0.26, 0.29)	0.44 (0.43, 0.45)	0.44 (0.43, 0.45)	0.24 (0.23, 0.25)	1.05 (0.99, 1.10)	0.44 (0.42, 0.45)	0.34 (0.33, 0.35)	0.37 (0.36, 0.38)

Lesion frequency (%) averaged value (confidence interval at 95%) in multiple regions of interest of the cervical spinal cord, for different populations. EDSS and disease duration (DD) were only available for 549 individuals. For a given population (i.e. each column), values in violet indicate higher median values comparing (i) C1-C3 vs. C4-C7, (ii) DC vs. LF vs. VF. EDSS scores categories: mild (0-2.5), moderate (3-5.5) and severe (≥ 6), and DD categories: short (0-5 years) moderate (5-15 years), long (≥ 15 years). No statistical tests were performed for lesion frequency between regions of interests. Abbreviations: DC, dorsal columns; LF, lateral funiculi; VF, ventral funiculi.

Table A4. Significant phenotypic differences in cervical cord lesion distributions, and significant correlation between lesion distribution and an increase of EDSS.

Analysis	Vertebral level	Region of interest	t-value at local maxima	P-value, FWE corrected
Differences between RRMS versus SPMS patients				
	C3	LF	4.5	0.031
Differences between RRMS versus PPMS patients				
	C3	LF	5.0	0.011
	C3	Central cord area	4.3	0.020
Differences between SPMS versus PPMS patients				
	None	None	None	Not significant
Correlation with an increase of EDSS				
	C1	LF	5.2	< 0.001
	C1	Central cord area	5.2	< 0.001
	C2	LF	5.4	< 0.001
	C2	Central cord area	5.2	< 0.001
	C3	LF	5.0	< 0.001
	C3	Central cord area	5.5	< 0.001
	C4	LF	4.3	< 0.001
	C5	LF	3.7	0.003
<p>The peak t-value of each significant voxels cluster ($p < 0.05$, FWE corrected) is indicated as well as its location in terms of vertebral level and cross-sectional region of interest. Group comparisons analysed cord locations where the lesion frequencies were lower in one group versus another: RRMS versus SPMS, RRMS versus PPMS, and SPMS versus PPMS. Group comparisons were adjusted for age, while correlation with EDSS was corrected for age and disease duration. Abbreviations: EDSS, Expanded Disability Status Scale; FWE, family-wise error; MS, multiple sclerosis; RRMS, relapsing-remitting MS; PPMS, primary progressive MS; SPMS, secondary progressive MS; LF, lateral funiculi.</p>				

Table A5. Lesion volumes in grey and white matter for different phenotype populations.

		Phenotype					Total cohort n=231
			CIS n=21	RR n=154	SP n=29	PP n=23	
Absolute Lesion Volume, mm³	GM	<i>Mean</i>	8.41	38.36	37.20	41.19	35.49
		<i>SD</i>	13.78	70.90	41.75	57.88	63.43
		<i>Median</i>	2.15	9.83	18.28	19.38	11.09
		<i>IQR</i>	10.54	44.35	40.34	38.98	41.10
	WM	<i>Mean</i>	50.30	110.19	135.40	143.02	110.52
		<i>SD</i>	53.87	148.67	127.78	133.41	139.48
		<i>Median</i>	42.38	54.37	85.52	89.61	62.01
		<i>IQR</i>	65.57	118.34	94.84	117.49	116.89
Normalised Lesion Volume	GM	<i>Mean</i>	0.006	0.026	0.025	0.028	0.024
		<i>SD</i>	0.009	0.048	0.028	0.039	0.043
		<i>Median</i>	0.001	0.007	0.012	0.013	0.008
		<i>IQR</i>	0.007	0.030	0.027	0.026	0.028
	WM	<i>Mean</i>	0.009	0.019	0.023	0.025	0.019
		<i>SD</i>	0.009	0.026	0.022	0.023	0.024
		<i>Median</i>	0.007	0.009	0.015	0.015	0.011
		<i>IQR</i>	0.011	0.020	0.016	0.020	0.020
<p>Absolute and normalised lesion volume mean, SD, median, and IQR values in the grey and white matter of the cervical spinal cord, for different phenotype populations. Normalised lesion volumes represent the proportion of a region affected by lesions. For a given population (i.e. each column), coloured values indicate higher mean (violet) and median (red) values comparing GM vs. WM. Abbreviations: MS, multiple sclerosis; CIS, clinically isolated syndrome; RRMS, relapsing-remitting MS; PPMS, primary progressive MS; SPMS, secondary progressive MS; GM, grey matter; WM, white matter; SD, standard deviation; IQR, interquartile range. Phenotype was not available for all subjects.</p>							

Table A6. Lesion volumes in white matter regions for different phenotype populations.

			Phenotype				Total cohort n=642
			CIS n=31	RRMS n=416	SPMS n=84	PPMS n=73	
Absolute Lesion Volume, mm³	DC	<i>Mean</i>	36.42	65.28	65.46	68.30	63.83
		<i>SD</i>	60.	97.52	85.62	102.63	94.51
		<i>Median</i>	11.44	24.33	33.22	28.84	26.48
		<i>IQR</i>	42.6	82.80	76.19	74.96	78.99
	LF	<i>Mean</i>	42.33	61.63	69.68	76.28	63.05
		<i>SD</i>	61.57	85.81	79.20	95.66	85.36
		<i>Median</i>	18.10	27.85	46.72	45.26	32.79
		<i>IQR</i>	51.85	74.18	67.95	68.67	75.29
	VF	<i>Mean</i>	3.07	8.13	7.61	6.62	7.57
		<i>SD</i>	7.61	17.53	19.67	11.31	16.96
		<i>Median</i>	0.	0.70	0.79	1.94	0.56
		<i>IQR</i>	0.56	7.42	6.76	7.79	6.70
Normalised Lesion Volume	DC	<i>Mean</i>	0.019	0.034	0.034	0.036	0.034
		<i>SD</i>	0.032	0.051	0.045	0.054	0.050
		<i>Median</i>	0.006	0.013	0.018	0.015	0.014
		<i>IQR</i>	0.022	0.044	0.040	0.040	0.042
	LF	<i>Mean</i>	0.016	0.023	0.026	0.029	0.024
		<i>SD</i>	0.023	0.032	0.030	0.036	0.032
		<i>Median</i>	0.007	0.010	0.018	0.017	0.012
		<i>IQR</i>	0.019	0.028	0.026	0.026	0.028
	VF	<i>Mean</i>	0.003	0.007	0.006	0.005	0.006
		<i>SD</i>	0.006	0.014	0.016	0.009	0.014
		<i>Median</i>	0.	0.001	0.001	0.002	0.
		<i>IQR</i>	0.	0.006	0.006	0.006	0.005

Absolute and normalised lesion volume mean, SD, median, and IQR values in multiple regions of interest of the cervical spinal cord (DC, LF, VF), for different phenotype populations. Normalised lesion volumes represent the proportion of a region affected by lesions. For a given population (i.e. each column), coloured values indicate higher mean (violet) and median (red) values comparing DC vs. LF vs. VF. Abbreviations: MS, multiple sclerosis; CIS, clinically isolated syndrome; RRMS, relapsing-remitting MS; PPMS, primary progressive MS; SPMS, secondary progressive MS; DC, dorsal columns; LF, lateral funiculi; VF, ventral funiculi; SD, standard deviation; IQR, interquartile range. Phenotype was not available for all subjects.

Table A7. Lesion volumes in motor and sensory tracts for different populations, defined by patient EDSS.

		Mild EDSS	Moderate EDSS	Severe EDSS	Total cohort		
		n=230	n=226	n=126	n=642		
Absolute Lesion Volume, mm³	Motor tracts	<i>Mean</i>	42.99	47.58	55.60	47.34	
		<i>SD</i>	62.05	67.46	56.87	63.21	
		<i>Median</i>	19.73	24.31	39.36	25.70	
		<i>IQR</i>	54.87	49.78	63.12	54.24	
	Sensory tracts	<i>Mean</i>	75.31	93.74	98.75	86.10	
		<i>SD</i>	104.34	127.03	117.38	114.91	
		<i>Median</i>	35.44	47.67	55.86	43.33	
		<i>IQR</i>	85.61	110.55	97.61	95.49	
	Normalised Lesion Volume	Motor tracts	<i>Mean</i>	0.017	0.018	0.022	0.018
			<i>SD</i>	0.024	0.026	0.022	0.025
			<i>Median</i>	0.008	0.009	0.015	0.010
			<i>IQR</i>	0.021	0.019	0.024	0.021
Sensory tracts		<i>Mean</i>	0.024	0.030	0.031	0.027	
		<i>SD</i>	0.033	0.040	0.037	0.036	
		<i>Median</i>	0.011	0.015	0.018	0.014	
		<i>IQR</i>	0.027	0.035	0.031	0.030	

Absolute and normalised lesion volume mean, SD, median, and IQR values in motor and sensory tracts of the cervical spinal cord, for different populations defined by patient EDSS. Normalised lesion volumes represent the proportion of a region affected by lesions. For a given population (i.e. each column), coloured values indicate higher mean (violet) and median (red) values comparing motor vs. sensory tracts. EDSS score categories: mild (0-2.5), moderate (3-5.5) and severe (≥ 6). Abbreviations: EDSS, Expanded Disability Status Scale; IQR, interquartile range; SD, standard deviation. EDSS score was not available for all subjects.

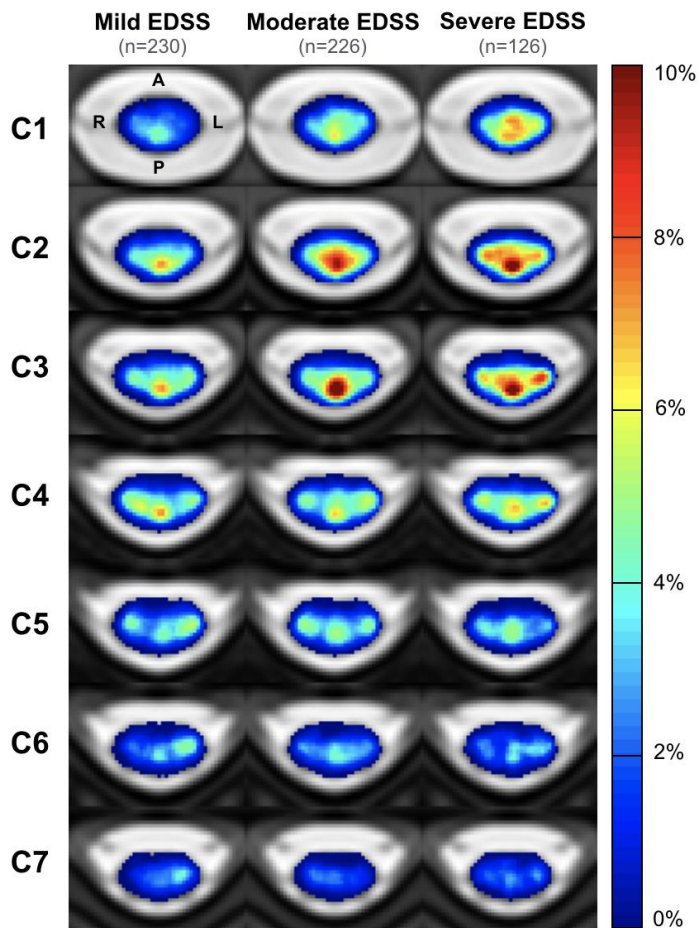


Figure A1. Frequency of MS lesions the cervical spinal cord for patients grouped by EDSS score categories. EDSS score categories: mild (0-2.5), moderate (3-5.5) and severe (≥ 6). EDSS, Expanded Disability Status Scale. A: anterior; P: posterior; L: left; R: right.