

SUPPLEMENTARY DATA

Cross-sectional and longitudinal assessment of the upper cervical spinal cord in motor neuron disease

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Supplementary Figures

Figure S1: CSA at baseline stratified for availability of follow-up data for ALS C9- patients.

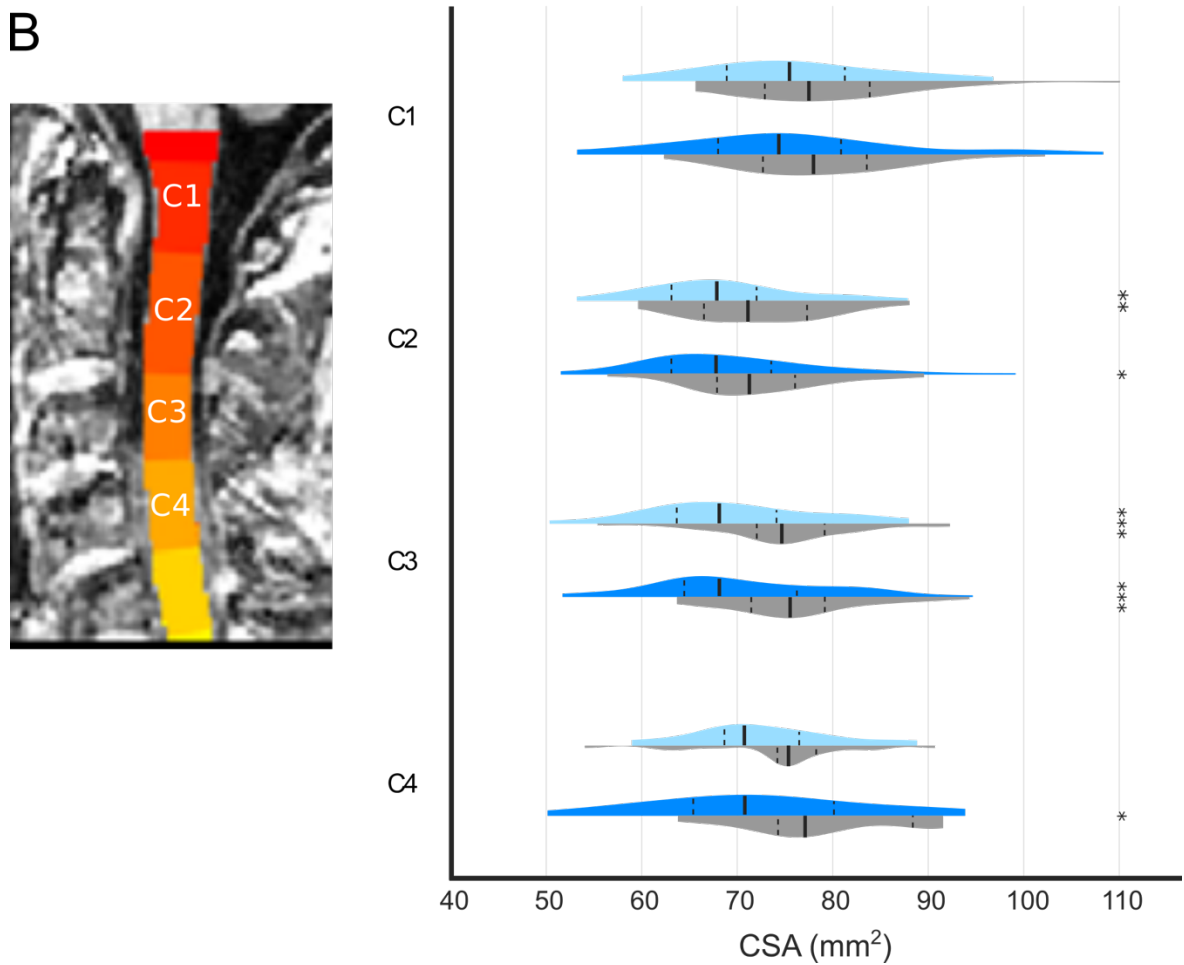
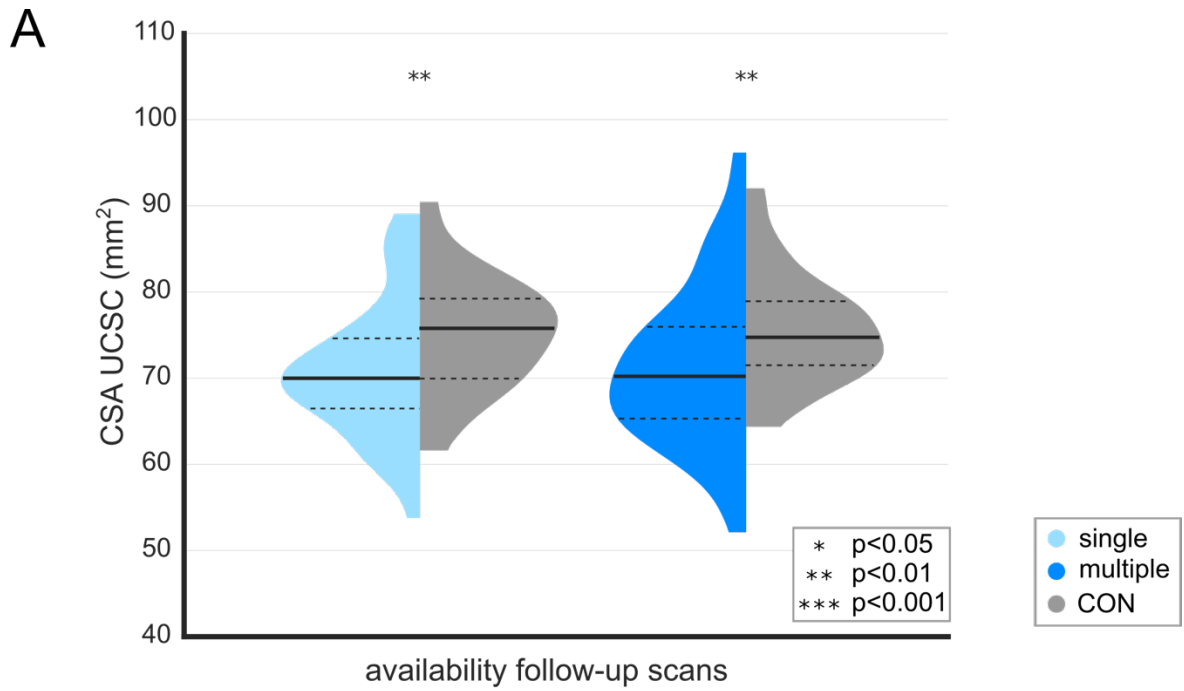
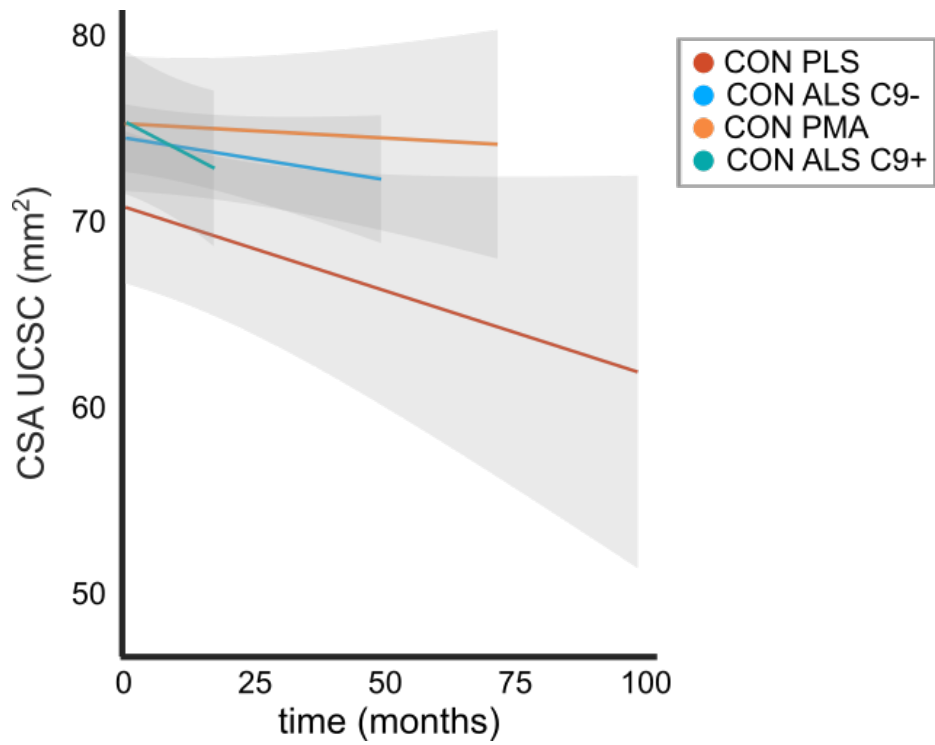


Figure S2: Sagittal view of three brain MRI's as example for image quality necessary for upper cervical spinal cord examination.



Figure S3: Longitudinal change in CSA for each control group, as reported in the main text.



Supplementary Tables

Table S1: Demographic and clinical characteristics of ALS C9- patients at baseline stratified for availability of follow-up data.

	Single scan	Multiple scans
n	44	64
Gender (%)		
Male	27 (61.4)	32 (50.0)
Female	17 (38.6)	32 (50.0)
Age at 1st MRI (median, range)	68.7 (51.0 – 78.5)	62.4 (30.6 – 80.6)
Site of onset (%)		
Bulbar	14 (31.8)	16 (25.0)
Spinal	30 (68.2)	48 (75.0)
Disease duration^a (median, range)	12.5 (2.9 – 58.1)	14.4 (3.9 – 174.4)
Type (%)		
Sporadic	44 (100)	64 (100)
Familial	0 (0.0)	0 (0.0)
ALSFRS-R score (median, range)	38 (23 – 46)	41 (26 – 47)

^a Disease duration was measured from disease onset until date of the first MRI in months.

Table S2: Mean age and gender for the patient groups and their matched controls.

	n	Age at 1st MRI	Gender	
		Mean (range)	Male (%)	Female (%)
ALS C9-	108	63.1 (30.6-80.6)	59 (54.6)	49 (45.4)
CON ALS C9-	108	63.8 (30.9-79.4)	59 (54.6)	49 (45.4)
ALS C9+	26	57.7 (40.6-67.0)	17 (65.4)	9 (34.6)
CON ALS C9+	26	57.8 (38.7-67.1)	17 (65.4)	9 (34.6)
PLS	28	61.7 (36.1-78.3)	17 (60.7)	11 (39.3)
CON PLS	28	62.0 (39.9-78.3)	17 (60.7)	11 (39.3)
PMA	56	63.4 (22.6-80.1)	46 (82.1)	10 (17.9)
CON PMA	56	63.6 (30.9-78.4)	46 (82.1)	10 (17.9)

Table S3. Distribution of scan visits.

	ALS C9-	ALS C9+	PLS	PMA	CON
Baseline scan	108	26	28	56	114
Scan 2	58	17	17	40	54
Scan 3	33	6	15	25	-
Scan 4	23	5	10	18	-
Scan 5	13	4	10	17	-

Table S4: Demographics and clinical characteristics of study participants classified according to cervical spinal cord segment measured.

	ALS C9-	ALS C9+	PLS	PMA	CON
C1 (n (%))	108 (100)	26 (100)	28 (100)	56 (100)	114 (100)
Age at first MRI	64.6 (30.6-80.6)	59.7 (40.6 – 67.0)	60.2 (36.1 – 78.3)	63.1 (22.6 – 80.1)	65.0 (30.8-79.4)
Sex (male/female)	59 / 49	17 / 9	17 / 11	46 / 10	63 / 51
Site of onset (bulbar/spinal)	30 / 78	5 / 21	3 / 25	0 / 56	-
Disease duration^a (median, range)	14.4 (2.9-174.4)	11.5 (3.3-68.3)	90.6 (23.5-224.9)	20.3 (4.6-467.4)	-
C2 (n (%))	108 (100)	26 (100)	28 (100)	58 (100)	114 (100)
Age at first MRI	64.6 (30.6-80.6)	59.7 (40.6 – 67.0)	60.2 (36.1 – 78.3)	63.1 (22.6 – 80.1)	65.0 (30.8-79.4)
Sex (male/female)	59 / 49	17 / 9	17 / 11	46 / 10	63 / 51
Site of onset (bulbar/spinal)	30 / 78	5 / 21	3 / 25	0 / 56	-
Disease duration^a (median, range)	14.4 (2.9-174.4)	11.5 (3.3-68.3)	90.6 (23.5-224.9)	20.3 (4.6-467.4)	-
C3 (n (%))	108 (100)	21 (80.8)	21 (75.0)	48 (85.7)	114 (100)
Age at first MRI	64.6 (30.6-80.6)	62.2 (40.6 – 67.0)	60.2 (36.1 – 75.0)	63.8 (46.4 – 80.1)	65.0 (30.8-79.4)
Sex (male/female)	59 / 49	12 / 9	10 / 11	38 / 10	63 / 51
Site of onset (bulbar/spinal)	30 / 78	5 / 16	2 / 19	0 / 48	-
Disease duration^a (median, range)	14.4 (2.9-174.4)	11.5 (3.3-68.3)	78.8 (23.5-224.9)	21.7 (4.6-467.4)	-
C4 (n (%))	49 (43.4)	7 (26.9)	8 (28.6)	18 (32.1)	49 (43.0)
Age at first MRI	67.3 (46.4-80.6)	63.1 (48.0 – 66.6)	67.8 (36.1 – 75.0)	70.2 (49.4 – 80.1)	67.0 (45.0-79.4)
Sex (male/female)	19 / 30	2 / 5	3 / 5	11 / 7	20 / 29
Site of onset (bulbar/spinal)	15 / 34	2 / 5	0 / 8	0 / 18	-
Disease duration^a (median, range)	14.1 (4.6-174.4)	14.2 (6.0-21.2)	82.2 (37.1-214.2)	26.5 (9.4-467.4)	-

^a Disease duration was measured from disease onset until date of the first MRI in months.

Table S5 Baseline CSA of the average over segments C2 and C3.

	CSA	CSA	Δ CSA	p-value	FDR-corrected
	PAT	CON			p-value
ALS C9-	69.12 \pm 7.35	74.14 \pm 7.35	5.02	<0.001	<0.001
ALS C9+	71.58 \pm 6.79	76.40 \pm 7.12	4.76	0.019	0.028
PLS	65.81 \pm 6.76	72.45 \pm 6.85	6.64	0.002	0.006
PMA	70.29 \pm 8.50	74.88 \pm 8.86	4.60	0.002	0.008

Table S6 Longitudinal CSA of the average over segments C2 and C3.

	Δ CSA	p-value	FDR-corrected
			p-value
ALS C9-	0.005	0.004	0.044
ALS C9+	0.002	0.703	0.999
PLS	<0.001	0.998	0.999
PMA	0.002	0.217	0.434

Table S7 Baseline correlations between CSA and ALSFRS-R scores.

		ALS C9-	ALS C9+	PLS	PMA
Total ALSFRS-R	UCSC	r=0.098,	r=0.226,	r=0.557,	r=-0.168,
		p=0.315	p=0.324	p=0.009	p=0.258
	C1	r=0.040,	r=0.199,	r=0.547,	r=-0.193,
		p=0.686	p=0.329	p=0.003	p=0.157
	C2	r=0.112,	r=0.212,	r=0.541,	r=-0.211,
		p=0.252	p=0.298	p=0.003	p=0.122
	C3	r=0.114,	r=0.247,	r=0.463,	r=-0.081,
		p=0.243	p=0.279	p=0.034	p=0.589
C4	r=0.155,	r=-0.322,	r=0.349,	r=0.239,	
	p=0.286	p=0.482	p=0.396	p=0.356	
Spinal ALSFRS-R sub-score	UCSC	r=0.024,	r=0.249,	r=0.558,	r=-0.127,
		p=0.807	p=0.276	p=0.009	p=0.393
	C1	r=-0.002,	r=0.214,	r=0.525,	r=-0.196,
		p=0.981	p=0.294	p=0.004	p=0.151
	C2	r=0.026,	r=0.263,	r=0.491,	r=-0.184,
		p=0.791	p=0.193	p=0.008	p=0.179
	C3	r=0.031,	r=0.295,	r=0.466,	r=-0.032,
		p=0.755	p=0.194	p=0.033	p=0.832
C4	r=0.073,	r=-0.334,	r=0.471,	r=0.358,	
	p=0.618	p=0.465	p=0.238	p=0.158	

bold p-values denote significance.

Table S8 Longitudinal correlations between CSA of UCSC and ALSFRS-R scores.

	ALS C9-	ALS C9+	PLS	PMA
Total ALSFRS-R	r=0.318,	r=0.316,	r=0.677,	r=0.233,
	p<0.001	p=0.134	p<0.001	p=0.016
Spinal ALSFRS-R sub-score	r=0.375,	r=0.374,	r=0.784,	r=-0.254,
	p<0.001	p=0.097	p=0.002	p=0.016

bold p-values denote significance.

Table S9 Comparison of white matter tracts in terms of FA, RD and MD for the patient groups.

		ALS C9-	ALS C9+	PLS	PMA
fmajor	FA	0.920	0.562	0.849	0.451
	MD	0.371	0.442	0.450	0.752
	RD	0.672	0.397	0.686	0.533
fminor	FA	0.432	0.141	0.395	0.825
	MD	0.152	0.002	0.249	0.309
	RD	0.225	0.006	0.662	0.530
ATR	FA	0.709	0.699	0.384	0.595
	MD	0.307	0.004	0.864	0.727
	RD	0.532	0.024	0.623	0.799
CAB	FA	0.190	0.298	0.998	0.625
	MD	0.114	0.626	0.475	0.713
	RD	0.101	0.791	0.573	0.598
CCG	FA	0.476	0.234	0.106	0.596
	MD	0.136	0.030	0.324	0.799
	RD	0.195	0.046	0.081	0.566
CST	FA	<0.001	0.245	0.541	0.585
	MD	<0.001	0.046	0.003	0.892
	RD	<0.001	0.099	0.071	0.987
ILF	FA	0.438	0.540	0.473	0.641
	MD	0.646	0.410	0.127	0.995
	RD	0.781	0.340	0.524	0.917
SLFP	FA	0.313	0.738	0.333	0.839
	MD	0.176	0.019	0.429	0.927
	RD	0.211	0.093	0.426	0.877
SLFT	FA	0.809	0.481	0.133	0.560
	MD	0.262	0.100	0.973	0.994
	RD	0.447	0.487	0.440	0.867
UNC	FA	0.080	0.638	0.796	0.627
	MD	0.161	0.067	0.325	0.903
	RD	0.083	0.184	0.605	0.761

fmajor = forceps major; fminor = forceps minor; ATR = anterior thalamic radiation; CAB = cingulum-angular bundle; CCG = cingulum-cingulate gyrus bundle; CST = corticospinal tract; ILF = inferior longitudinal fasciculus; SLFP = superior longitudinal fasciculus-parietal terminations; SLFT = superior longitudinal fasciculus-temporal terminations; UNC = uncinata fasciculus

bold p-values denote significance after 10,000 permutations.