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STRUCTURAL ORGANIZATION OF THE BRAIN CONNECTOME IN PATIENTS WITH PRIMARY LATERAL SCLEROSIS

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INTRODUCTION AND OBJECTIVE

✓ Primary lateral sclerosis (PLS) has a slower rate of progression and a more benign prognosis than the more common form of motor neuron disease (MND), amyotrophic lateral sclerosis (ALS). Graph theory provides a powerful framework to describe the topological organization of the brain. Network research might contribute to the understanding of the pathophysiology of MND and reveal connectivity profiles associated with different clinical outcomes. This study aimed at investigating structural neural pathways organization in patients with PLS relative to ALS using an advanced network-based approach.

METHODS

✓ This study included 29 patients with PLS, 29 patients with ALS and 29 age- and sex- matched healthy controls. PLS and ALS patients were well matched for disease severity based on ALS functional rating scale-revised. Using a 3.0 T scanner, brain MRI scans were obtained from all subjects.

Table 1. Demographic and clinical findings in healthy controls and in patients with ALS and PLS.

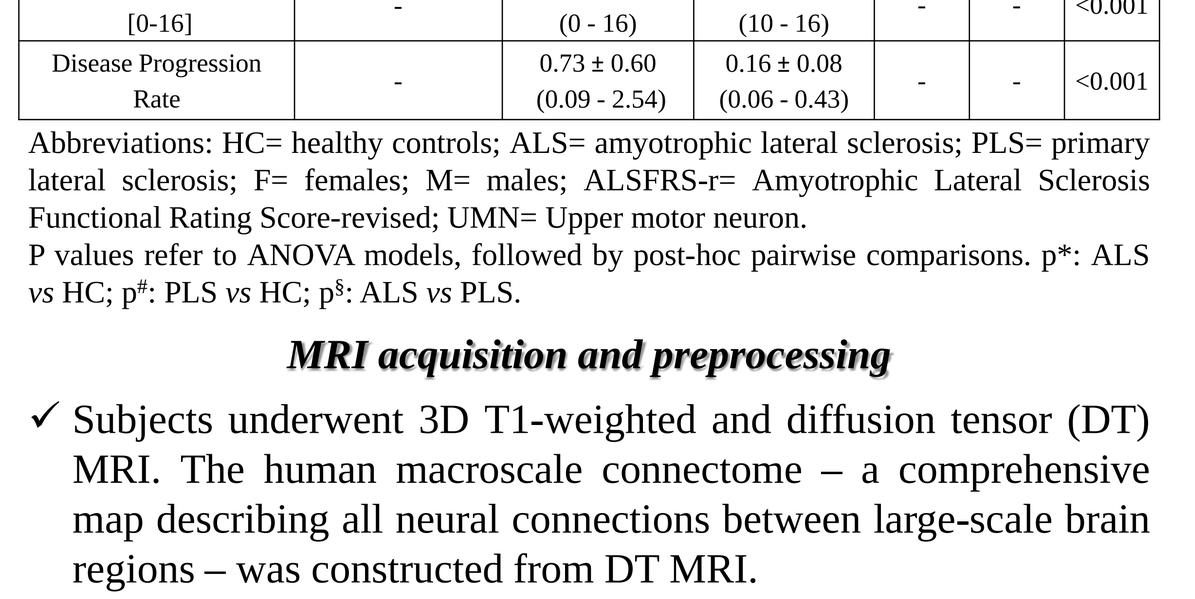
	HC	ALS	PLS	p*	p#	p§
N	29	29	29			
Age [years]	63.60 ± 7.61 (44.70 - 78.76)	63.90 ± 8.51 (45.27 - 77.49)	63.44 ± 6.89 (46.62 - 73.03)	1.00	1.00	1.00
Gender [F/M]	14/15	16/13	15/14	1.00	0.793	1.00
Clinical variables						
Disease duration [months]	-	21.76 ± 18.18 (2 - 66)	82.31 ± 62.09 (8 - 247)	-	-	<0.001
ALSFRS-r [0-48]	-	36.72 ± 7.82 (16 - 46)	37.97 ± 5.10 (22 - 44)	-	-	0.48
UMN Score [0-16]	-	10.24 ± 4.54 (0 - 16)	13.94 ± 2.11 (10 - 16)	-	-	<0.001
Disease Progression Rate	-	0.73 ± 0.60 (0.09 - 2.54)	0.16 ± 0.08 (0.06 - 0.43)	-	-	<0.001

Abbreviations: HC= healthy controls; ALS= amyotrophic lateral sclerosis; PLS= primary lateral sclerosis; F= females; M= males; ALSFRS-r= Amyotrophic Lateral Sclerosis Functional Rating Score-revised; UMN= Upper motor neuron.
P values refer to ANOVA models, followed by post-hoc pairwise comparisons. p*: ALS *vs* HC; p#: PLS *vs* HC; p§: ALS *vs* PLS.

MRI acquisition and preprocessing

✓ Subjects underwent 3D T1-weighted and diffusion tensor (DT) MRI. The human macroscale connectome – a comprehensive map describing all neural connections between large-scale brain regions – was constructed from DT MRI.

✓ Tissue segmentation was performed on T1 images using Freesurfer (v. 5.3).



A) Parcellation of the segmented gray matter mask into 83 distinct brain regions based on Desikan atlas adding basal ganglia. DT MRI was performed to reconstruct the white matter tracts forming the structural brain network. **B)** Parcellated gray matter was co-registred to subject DT MRI. **C)** From the total collection of reconstructed streamlines those that touched both regions *i* and *j* were selected. Then, from the selected fiber streamlines, the average fractional anisotropy (FA) and mean diffusivity (MD) values were computed as the average over all points. These values were incorporated into cells c(*i*,*j*) in the matrix.

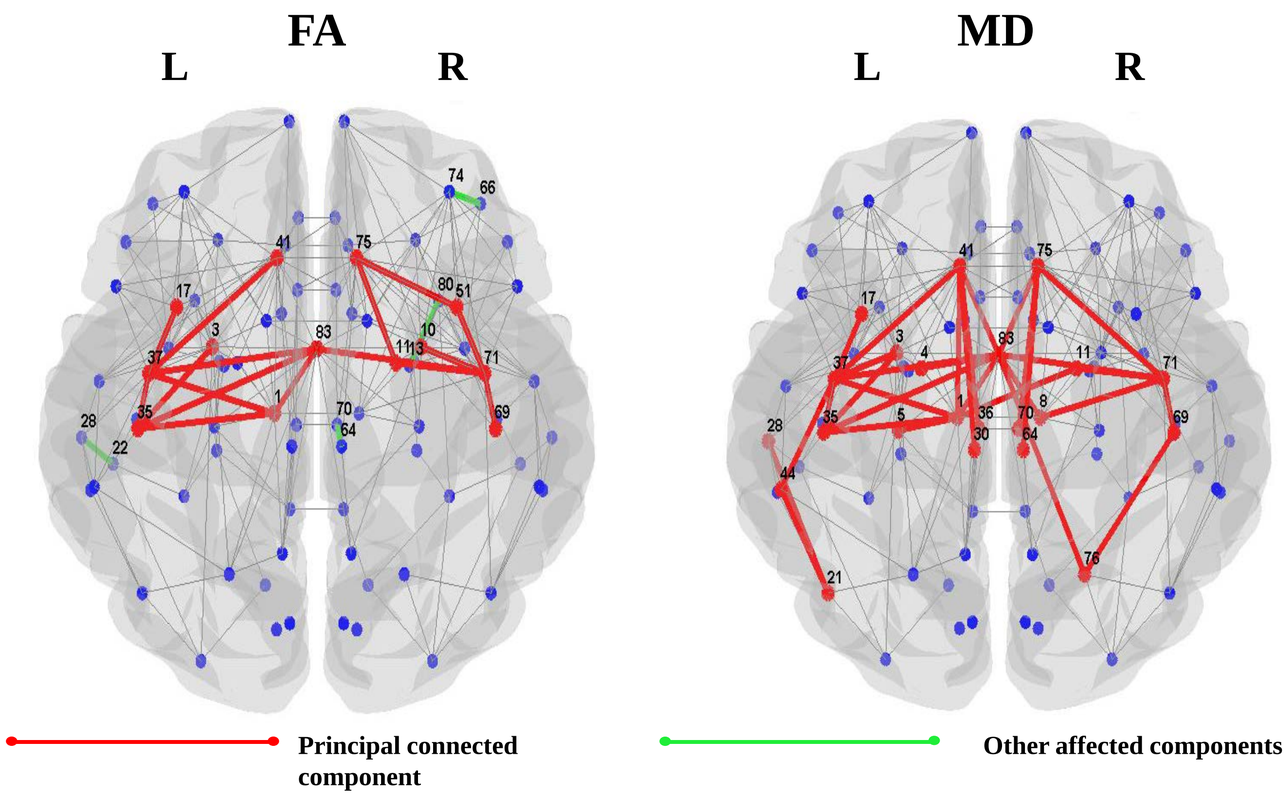
METHODS

✓ The affected structural connections in patients with ALS and PLS relative to healthy controls and each other were investigated using Network-Based Statistic ($p<0.01$, 10.000 permutations).

RESULTS

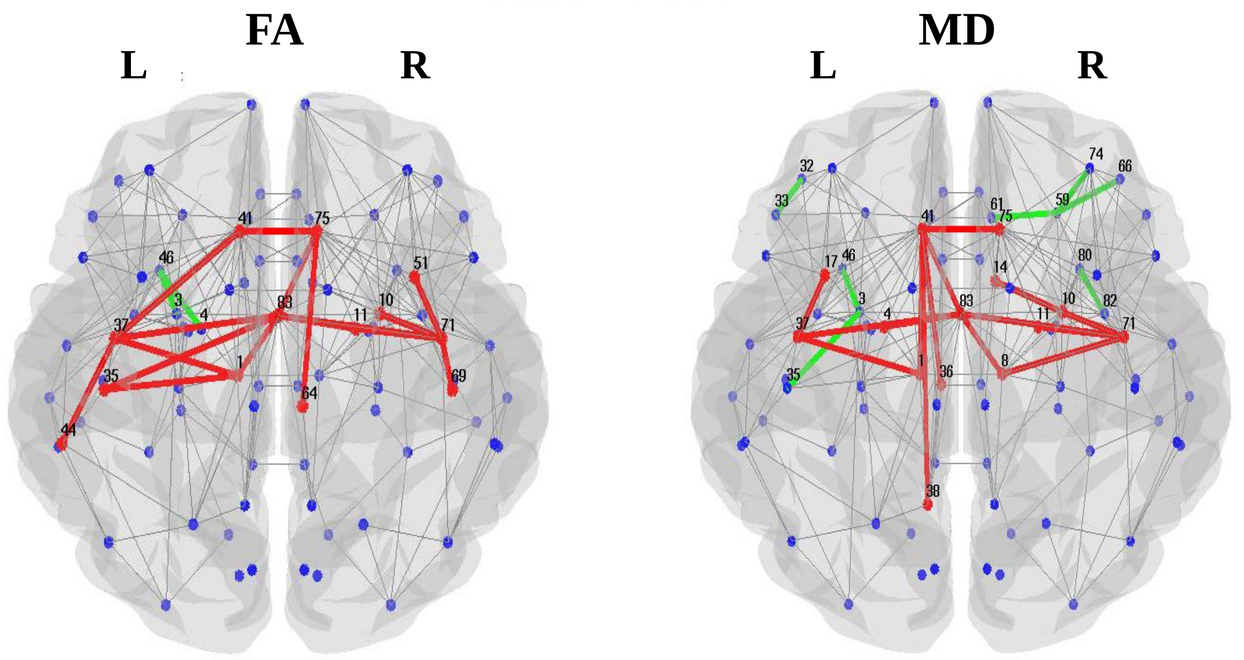
✓ Widespread structural connectivity changes were observed in PLS patients relative to controls. Decreased FA and increased MD were found within the sensorimotor/basal ganglia networks, including precentral and postcentral gyri, brainstem and the left thalamus, bilateral putamen and pallidum.

PLS *vs* HC



✓ Regional analysis showed that ALS patients manifested a decreased FA and an increased MD relative to controls in connections linking precentral and postcentral gyri, SMA, brainstem and superior frontal gyri bilaterally.

ALS *vs* HC



✓ No differences were found between PLS and ALS subjects.

DISCUSSION AND CONCLUSIONS

✓ This study showed motor and extra-motor structural network degeneration in PLS, suggesting that graph analysis might represent a powerful approach to detect both UMN degeneration and extra-motor brain changes associated with the disease.

✓ Results showed that the pattern of structural abnormalities was similar inALS and PLS patients. Therefore, the pattern of structural alterations is likely to reflect the UMN involvement across the MND spectrum.

✓ Network-based advanced MRI analyses hold the promise to provide an objective *in vivo* assessment of MND related pathological changes, delivering potential diagnostic and prognostic markers to be used in the clinical practice.

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