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# TRACKING LONGITUDINAL EVOLUTION OF AMYOTROPHIC LATERAL SCLEROSIS USING DIFFUSION TENSOR MRI

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## INTRODUCTION

- ✓ Identifying predictors of progression and survival in amyotrophic lateral sclerosis (ALS) is important for both every-day clinical management and design of treatment trials.
- ✓ The high sensitivity of magnetic resonance imaging (MRI) to the brain motor and extramotor ALS pathology makes this technique pivotal in the search for such biomarkers. Particularly, diffusion tensor (DT) MRI has revealed damage to white matter tracts, which faithfully matches post-mortem neuropathological studies in ALS [1,2].
- ✓ To date, most of the MRI data in ALS are based on cross-sectional studies of small samples of patients.

## OBJECTIVE

**To explore longitudinal clinical, cognitive, and structural brain changes in patients with ALS.**

## MATERIALS AND METHODS

**Table 1.** Demographic features of patients and healthy controls.

| | ALS | HC | p |
|---|---|---|---|
| **Number** | 33 | 40 | - |
| **Gender, males (%)** | 23 (70%) | 21 (53%) | 0.16 |
| **Age at MRI (years)** | 60.2 ± 9.9 | 61.8 ± 8.5 | 0.93 |
| **Age at onset (years)** | 58.0 ± 14.2 | - | - |
| **Disease duration (months)** | 18.1 ± 13.0 | - | - |

Values denote means ± standard deviations or frequencies (%). Abbreviations: ALS= amyotrophic lateral sclerosis; HC= healthy controls.

Thirty-three ALS patients and 40 healthy controls were enrolled. Patients were followed prospectively with clinical and MRI scans every 3 months, and underwent neuropsychological evaluations every 6 months, for a maximum follow up of 1 year.

**Clinical and cognitive assessments**. Clinical evaluation included the ALSFRS-r, Medical Research Council (MRC) and ALS severity scale to assess motor disability. The degree of upper motor neuron (UMN) involvement was graded using the UMN score. Cognitive assessment was performed using the MMSE, verbal fluency tests, and the Test of Attentional Performance.

**MRI analysis.** All subjects underwent DT MRI on a 3 T scanner (Philips Medical Systems, Intera).

**Statistical analysis.** Longitudinal linear models were used to assess clinical and cognitive variable changes over time. Tract based spatial statistics (TBSS) analyses were applied to investigate progressive white matter (WM) damage.

## RESULTS

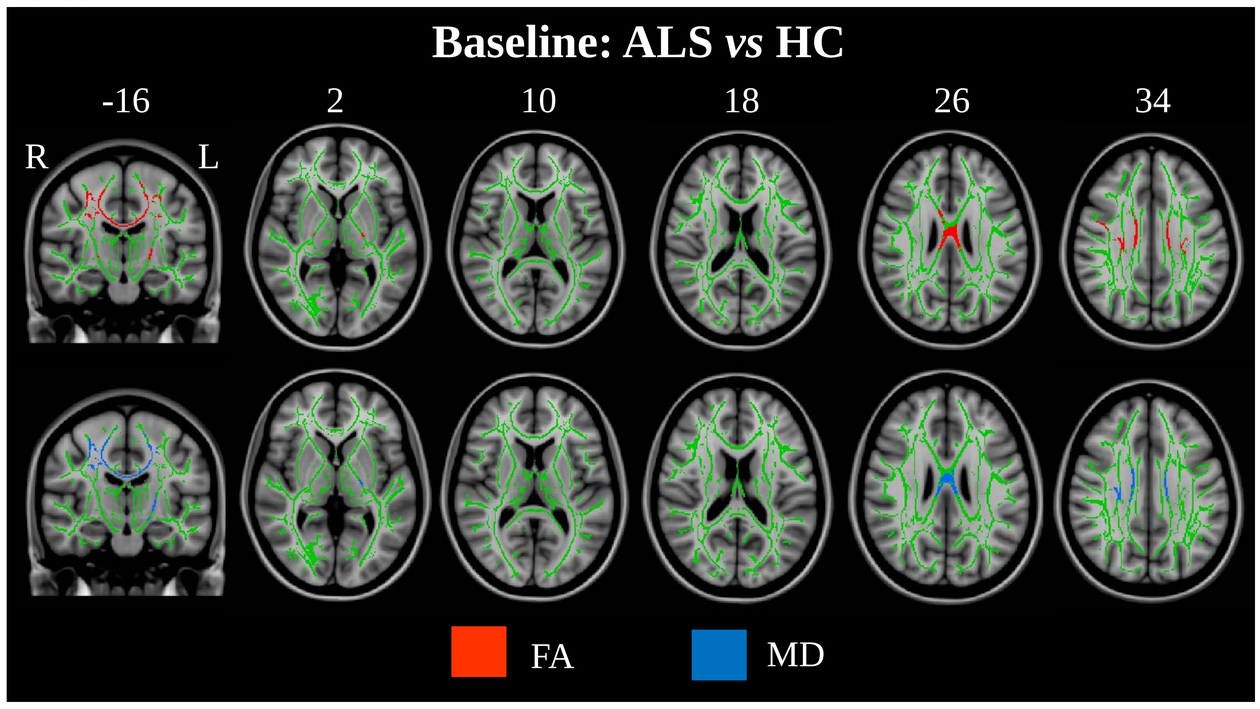
**Table 2.** Baseline clinical and cognitive features of ALS patients and mean rate of decline over follow-up.

| | Baseline mean ± SD | Mean % change baseline-month 12 |
|---|---|---|
| **ALSFRS-R score** | 40.1 ± 1.4 | -32.0 |
| **Total MRC score** | 105.4 ± 2.9 | -18.2 |
| **ALS Severity Scale – bulbar speech** | 8.7 ± 0.4 | -27.2 |
| **ALS Severity Scale – swallow score** | 9.0 ± 0.4 | -7.7 |
| **ALS Severity Scale – lower extremity** | 7.4 ± 0.4 | -39.6 |
| **ALS Severity Scale – upper extremity** | 7.4 ± 0.4 | -37.9 |
| **UMN score** | 9.4 ± 1.0 | 25.3 |
| **MMSE** | 28.3 ± 0.5 | -5.9 |
| **Phonemic fluency** | 29.9 ± 9.9 | -4.5 |
| **Semantic fluency** | 39.4 ± 11.2 | -2.6 |
| **Sustained attention (total omissions)** | 19.7 ± 1.9 | 75.5 |
| **Behavioral control (median RT)** | 624.3 ± 104.2 | 17.8 |
| **Interference tendency (median RT)** | 595.1 ± 40.9 | 14.9 |

**Abbreviations.** ALSFRS-R: ALS Functional Rating Scale-Revised; MMSE: Mini Mental State Examination; MRC: Medical Research Council; RT: reaction times; UMN: Upper Motor Neuron.

## RESULTS

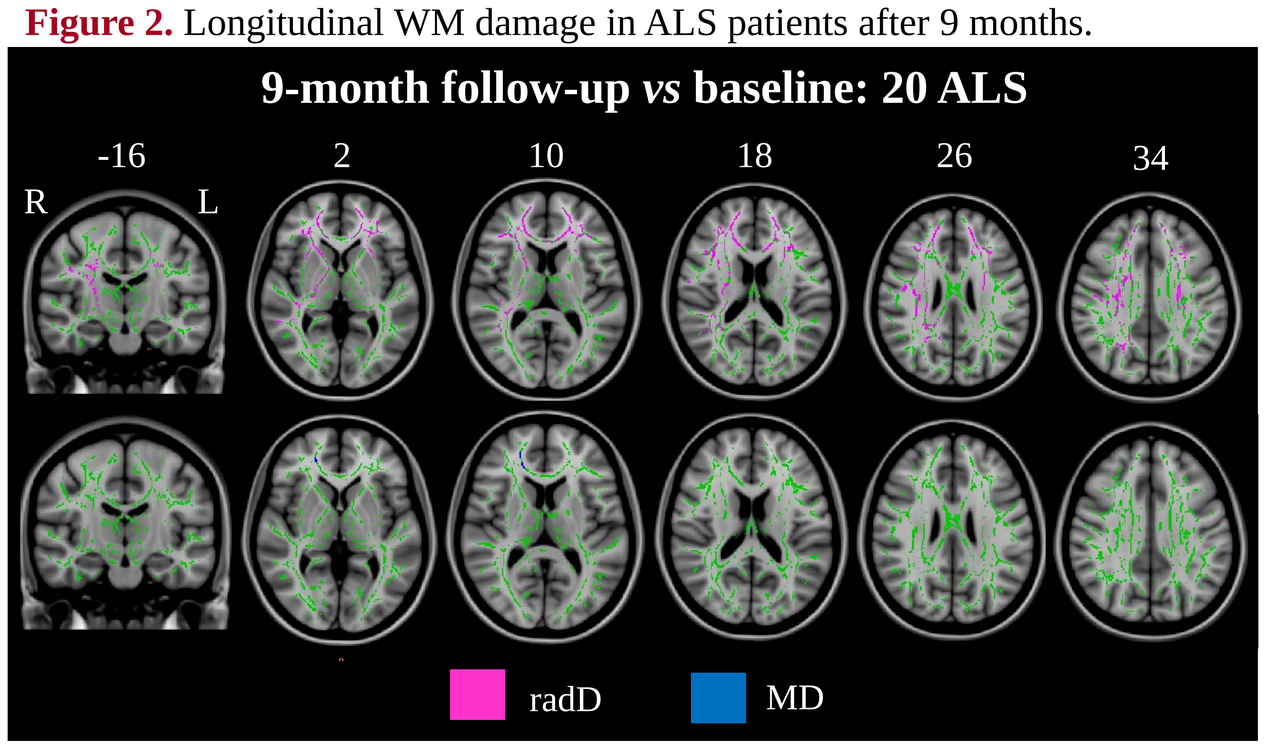
**Figure 1.** WM damage in ALS patients compared with healthy controls at baseline.




Results are overlaid on the Montreal Neurological Institute standard brain and displayed at p<0.05 Family Wise Error-corrected. FA= fractional anisotropy; MD= mean diffusivity; R=right; L=left.

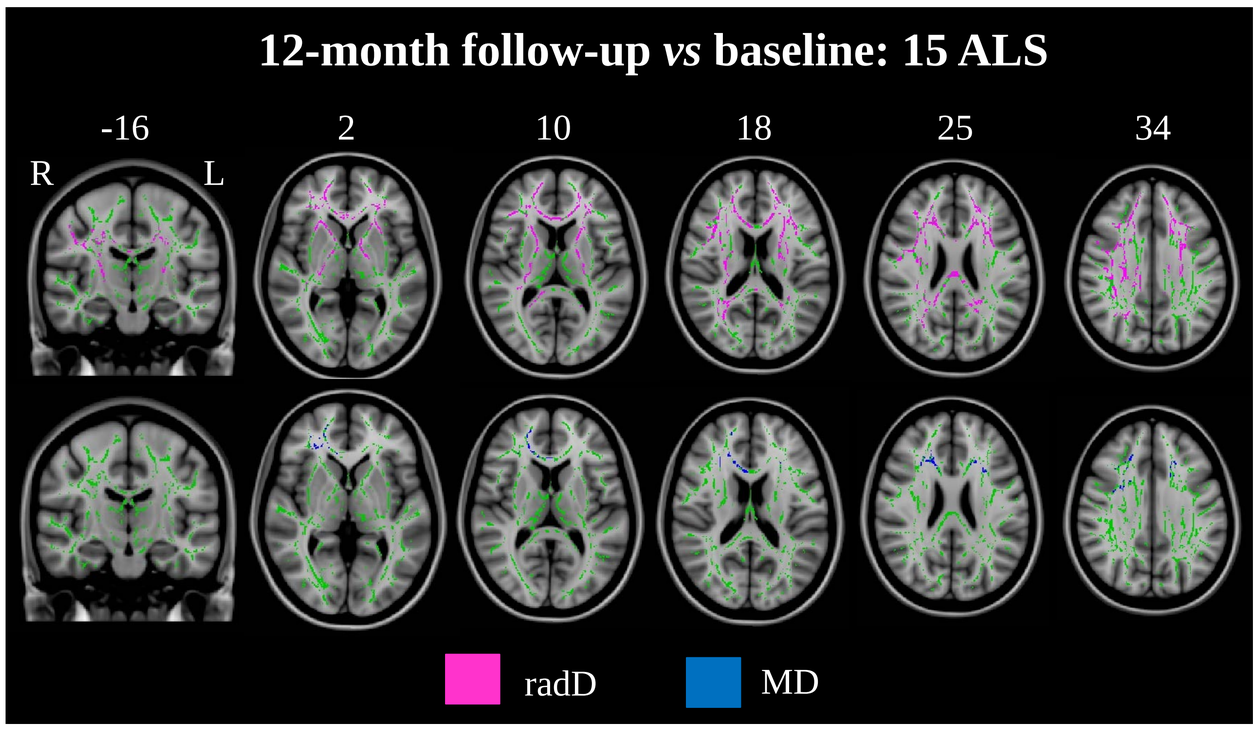
**Longitudinal TBSS analysis.** No significant longitudinal WM alterations were found in ALS patients at 3- and 6-month follow-ups relative to baseline.

**Figure 2.** Longitudinal WM damage in ALS patients after 9 months.




Results are overlaid on the Montreal Neurological Institute standard brain and displayed at p<0.05 Family Wise Error-corrected. MD= mean diffusivity; radD= radial diffusivity; R=right; L=left.

**Figure 3.** Longitudinal WM damage in ALS patients after 12 months.




Results are overlaid on the Montreal Neurological Institute standard brain and displayed at p<0.05 Family Wise Error-corrected. MD= mean diffusivity; radD= radial diffusivity; R=right; L=left.

## CONCLUSIONS

- ✓ We found a significant progression of WM damage in ALS patients, evolving as a widespread structural network degeneration.
- ✓ Our results suggest that MRI provides a powerful tool to track in vivo the disease spreading evolution related to pathological propagation patterns in ALS.
- ✓ WM metrics may offer useful markers to monitor disease progression and test the efficacy of new experimental treatments as they become available.

## REFERENCES

1. Agosta et al., Hum Brain Mapp 2007. 2. Filippini et al., Neurology 2010.

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