# Whole-Brain HARDI investigation in Bulbar- and Spinal-onset Amyotrophic Lateral Sclerosis

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**Background and aims:** Amyotrophic Lateral Sclerosis (ALS) is regarded as a multisystem disorder from early stages; different disease onsets are related to different pathological hallmarks and different prognosis. Microstructural features underlying these differences, although widely investigated in vivo using advanced neuroimaging approaches, have not been still completely elucidated. In particular, the DTI model has been proven not specifically suitable for exploring WM regions with multiple fiber orientations, including corticospinal tracts (CSTs) and several associative fiber tracts, thus stimulating the adoption of higher order diffusion models in the context of high angular resolution diffusion imaging (HARDI) [1,2], that are more sensitive to intravoxel orientation heterogeneity. Using magnetic resonance (MR) HARDI, we aimed at revealing possible divergent microstructural patterns between ALS patients with limb (ALS-L) vs. bulbar (ALS-B) onsets at an early stage of the disease.

**Methods:** We studied 22 patients with ALS, 11 with ALS-B and 11 with ALS-L, in stages 1 or 2 according to the King's staging system [3], and 18 age and sex-matched healthy controls (HCs). Patients were clinically investigated and both patients and controls underwent a 60-min neuropsychological battery, aiming to asses a broad range of cognitive skills. Statistical mapping of HARDI-derived parameters and tractography measures were performed using the Q-ball imaging diffusion data model.

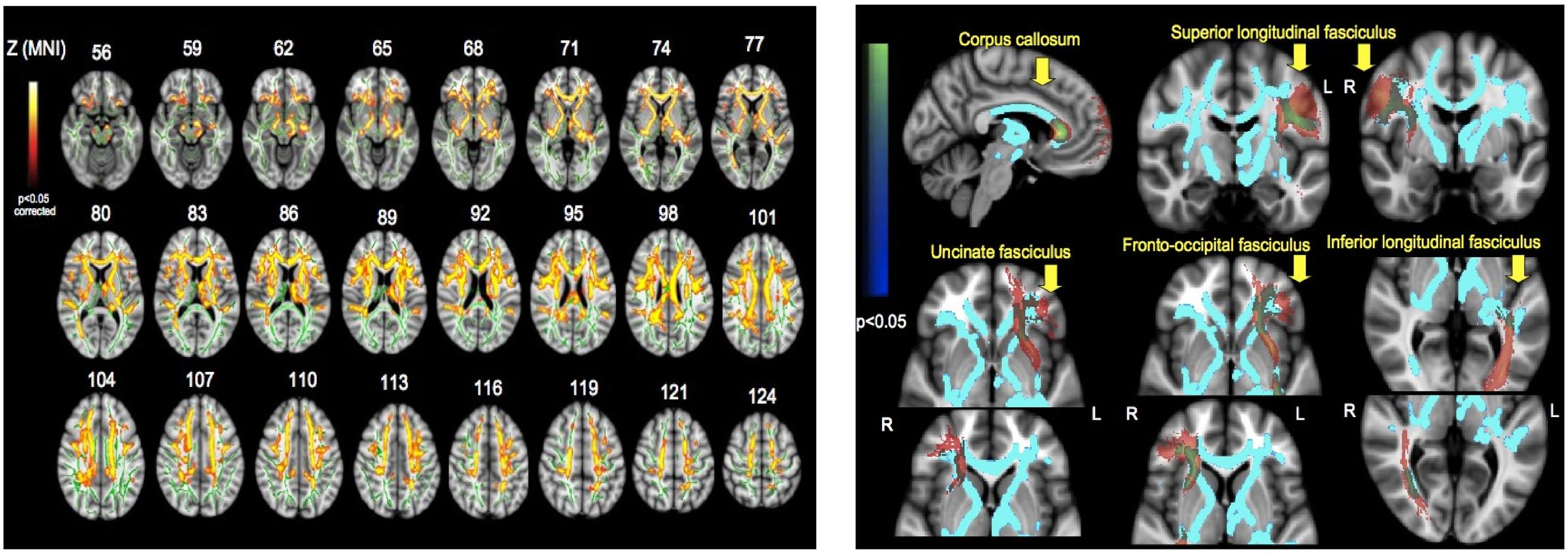


**Fig.1** Comparison between statistic parametric maps of ALS-B patients compared to ALS-L ones. GFA decrease (red-yellow and blue scales, $p<0.05$, corrected) is evident in both motor and extra-motor (i.e., cingulated gyri, and inferior fronto-occipital, superior and inferior longitudinal and uncinate fasciculi) areas.

**Results:** No significant differences were identified for any of the demographic (age and gender) and clinical, neuropsychological and behavioural variables between patients and HCs and between the two patient groups. When compared to HCs, the ALS group showed a highly significant decrease of generalized fractional anisotropy (GFA) and fiber length and density in the corticospinal tracts and in the corpus callosum ($p<0.05$, corrected for multiple comparisons). Comparing ALS-B and ALS-L patients, larger areas of decreased GFA were found in ALS-B patients in several bilateral associative fiber tracts in frontal, temporal and parietal lobes.

**Conclusions:** HARDI allowed detecting differentially altered whole-brain patterns of WM microstructure in ALS-L and ALS-B, revealing that, in early stages of disease, ALS-B may be associated with a more widespread WM degeneration than ALS-L, in line with the hypothesis that ALS-B represents a biologically more aggressive form of the disease. Moreover, the used approach underlined the preclinical existence of disease-related microstructural abnormalities, that may precede both cognitive and behavioural impairment in the two different disease phenotypes, and that would be more sensitively identified by an HARDI technique.

**References**

[1] Tuch DS, Reese TG, Wiegell MR, Wedeen VJ. Diffusion MRI of complex neural architecture. Neuron 2003;40:885-95.
[2] Rose S, Pannek K, Bell C, Baumann F, Hutchinson N, Coulthard A, McCombe P, Henderson R. Direct evidence of intra- and interhemispheric corticomotor network degeneration in amyotrophic lateral sclerosis: an automated MRI structural connectivity study. NeuroImage 2012;59:2661-9.
[3] Balendra R, Jones A, Jivraj N, Steen IN, Young CA, Shaw PJ, et al. Use of clinical staging in amyotrophic lateral sclerosis for phase 3 clinical trials. JNNP 2015;86:45-9.