

**Structural and functional connectome alterations across King's stages in amyotrophic lateral sclerosis**

Edoardo Gioele Spinelli, Alma Ghirelli, Silvia Basaia, Camilla Cividini, Nilo Riva, Tommaso Russo, Elisa Canu, Veronica Castelnovo, Massimo Filippi, Federica Agosta

**State of the art.** The absence of objective and reproducible markers of disease progression in amyotrophic lateral sclerosis (ALS) is a major limitation in study enrolment and design. This study explored structural and functional connectivity rearrangements within and among brain networks underlying the clinical spreading of ALS to propose objective measures mirroring disease progression.

**Methodology.** 104 ALS patients and 61 healthy controls underwent brain MRI on a 3T scanner. Patients were stratified in four groups, according to the King's staging system. No patient had comorbid frontotemporal dementia. Structural and functional connectivity values within and between different anatomical brain regions were obtained using diffusion tensor and resting-state functional MRI data, respectively. Comparisons between groups were performed using age- and sex-adjusted ANOVA models, Bonferroni-corrected for multiple comparisons.

**Results.** Compared with controls, a progressive reduction of structural connectivity within nodes of the sensorimotor network was observed in ALS patients across King's stages 2, 3 and 4 ( $p < 0.006$ ). Patients in stages 3 and 4 also showed loss of structural connectivity between frontal and sensorimotor regions ( $p = 0.001$ ), whereas patients in milder stages were comparable with controls. A disruption of functional connectivity between frontal and temporal regions was found only in stage 4 ( $p = 0.025$ ).

**Conclusion.** Brain MRI can quantify increasing disruption of structural connectivity in sensorimotor and frontal networks in ALS, mirroring disease spreading described by the King's staging. Frontotemporal functional disconnection only characterizes advanced disease stages.

**Funding:** Italian Ministry of Health (GR-2011-02351217; GR-2013-02357415; RF-2011-02351193), AriSLA (ConnectALS), European Research Council (StG-2016\_714388\_NeuroTRACK), Foundation Research on Alzheimer Disease.

**Conflicts of interest**

No conflicts of interest.