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MOTOR NEURON DISEASE

Improved imaging biomarkers in amyotrophic lateral sclerosis

The neuropathology associated with amyotrophic lateral sclerosis (ALS) is well-characterized in motor neurons, spinal cord and motor cortex, but less is known about how this disease affects the brain over time. Now, a study published in *Brain* elucidates the longitudinal course of structural brain changes associated with ALS, revealing potential imaging markers.

"The majority of studies of brain atrophy in ALS over the last decade have been small and, typically, cross-sectional," says Martin Turner, who led the study. Although previous experiments have revealed how the disease affects groups of patients, cross-sectional data alone has little diagnostic or prognostic value in individual patients. With this limitation in mind, Turner and colleagues used voxel-based morphometry and diffusion tensor imaging to measure both grey and white matter changes cross-sectionally and longitudinally.

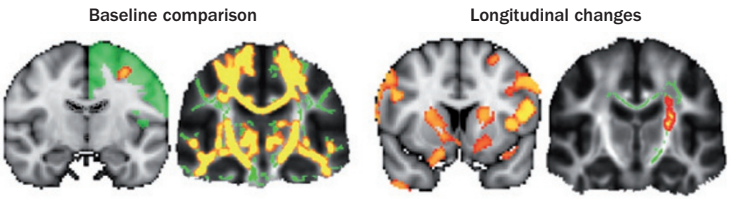
The authors recruited 60 patients with sporadic ALS and compared their brain scans with those from 36 healthy controls. Patients with ALS showed decreased fractional anisotropy and increased mean diffusivity in the rostral corticospinal tracts and in the motor fibres of the corpus callosum. These measurements of lost white matter integrity correlated with clinical ratings of upper motor neuron dysfunction. Voxel-based morphometry revealed disease-related reductions in grey matter volume in the frontal and primary motor regions of the left hemisphere.

The participants with ALS were offered follow-up MRI every 6 months, and the authors assessed longitudinal brain changes in 27 patients by comparing the baseline scan with a final scan up to 2 years later. Few changes were observed in white matter pathology between baseline and follow-up, and the clinical severity of upper motor neuron dysfunction also remained mostly stable. By contrast, extensive changes were seen in grey matter, with atrophy progressing not only in the frontotemporal and motor regions affected at baseline, but in the thalamus and caudate nucleus as well.

The results suggest that the early stages of ALS are dominated by white matter loss, which is followed by widespread degeneration of grey matter loci. The authors hope that establishing this temporal pattern of white and grey matter pathology might reduce diagnostic delay in ALS. "Overall, this study suggests that the major value of measuring white matter integrity is as a diagnostic biomarker, whereas grey matter change is a marker of progression," concludes Turner.

The authors are currently trying to increase diagnostic accuracy and improve patient stratification in ALS by combining their imaging protocol with analyses of blood and cerebrospinal fluid. Improving the detection and monitoring of ALS could be useful in future clinical trials.

Alex Chase



At baseline, patients with ALS mainly show white matter pathology. Longitudinally, ALS progression is dominated by grey matter atrophy. Within each pair of brain images, significant reductions in grey matter volume (left) and white matter integrity (right) are shown in yellow, orange and red, with predefined regions of interest shown in green. Image courtesy of M. Turner.

Original article Menke, R. A. *et al*. Widespread grey matter pathology dominates the longitudinal cerebral MRI and clinical landscape of amytrophic lateral sclerosis. *Brain* doi:10.1093/brain/awu162