

# The tough body at the epicentre of amyotrophic lateral sclerosis

The corpus callosum is a signpost to the interhemispheric highways underpinning the widespread cerebral pathology that typifies the syndrome of ALS

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The brain has become axiomatic to understanding pathogenesis in amyotrophic lateral sclerosis (ALS), not least given the clinical, molecular and genetic overlap with frontotemporal dementia.<sup>1</sup> ALS, although defined in part by its lower motor neuron degeneration, now appears misfiled alongside the neuromuscular disorders. The corpus callosum (CC, latin translation: tough body) is a pervasive cerebral integrator, and a consistent part of the *in vivo* cerebral white matter MRI signature of ALS,<sup>2</sup> noted in *post mortem* studies many decades prior to diffusion tensor imaging (DTI).<sup>3,4</sup> The JNNP paper by Zhang *et al*<sup>5</sup> uses advanced MRI analysis to explore symmetrical interhemispheric functional connectivity in ALS in relation to the regional anatomy of the CC.

Loss of interhemispheric connectivity in ALS was initially demonstrated in patients using transcranial magnetic stimulation.<sup>6</sup> The identification of regionally coherent MRI blood oxygenation level-dependent signals in a task-free state (resting-state functional MRI) has been a major driver in understanding brain function as a series of network-based processes. This technique first identified interhemispheric impairment between bilateral subregions of the primary motor cortex in ALS.<sup>7</sup> MR tractography can be used to parcellate the CC and create a cross-sectional 'key' to all structurally connected regions of the brain.<sup>8</sup> Zhang *et al* combined aspects of both approaches, creating a novel voxel mirrored homotopic map to study the symmetrical functional connectivity of regions in relation to the position of their interhemispheric fibres within five regions along the midline sagittal plane of the CC. The central motor cortical interhemispheric fibres were the most

consistently involved in combined functional and structural analyses, the latter in keeping with a previous study that focused on this CC regionality,<sup>9</sup> and the area where the inflammatory infiltrates appear concentrated.<sup>10</sup>

Subcortical structures, including the putamen, also showed reduced symmetrical functional connectivity and between the superior temporal gyri, the latter aligning with the recognition of consistent verbal fluency impairments in ALS. Cognition was not explored in this study (those with significant cognitive impairment were excluded), though more anterior regions of the CC have been previously linked to measures of frontal lobe dysfunction in ALS.<sup>11</sup> Nonetheless, symmetrical functional connectivity changes were noted by Zhang *et al* in multiple bihemispheric regions connected through anterior and posterior parts of the CC, as one would predict with the concept of ALS as a widespread cerebral network disorder, despite its motor-predominant phenotype.

The authors point out that the brain is not symmetrical, which may distort phenotype correlations in relation to voxel mirrored homotopic connectivity. The onset of symptoms in ALS is typically focal and strikingly asymmetric for most of the two-thirds of patients where it begins in a limb. Limb dominance influences laterality of first weakness in upper limb-onset ALS,<sup>12</sup> and there is a higher probability of contralateral versus ipsilateral sequential limb involvement.<sup>13,14</sup> The DTI white matter signature is consistently symmetrical however.<sup>15</sup> This may reflect group-level analysis in what is a clinically heterogeneous syndrome. Furthermore, there is an average diagnostic delay of ~1 year in ALS, so that bihemispheric pathology (if not symptoms as well) may be established by the time individuals reach the MRI scanner. With evolving ideas about trans-synaptic transmission of pathology in ALS, a natural question is whether the CC facilitates interhemispheric spread. A potentially disease-modifying effect of callosotomy in

the presymptomatic period is then a compelling concept, and potentially testable in appropriate non-human models.

In the context of assessing the effects of other therapeutic interventions, the CC, uniquely spanning the breadth of ALS cerebral pathology, warrants further assessment as both a phenotype stratifying and potentially pharmacodynamic biomarker.

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