

## Emergence of an imaging biomarker for amyotrophic lateral sclerosis – Is the endpoint near?

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A diagnostic and treatment biomarker for amyotrophic lateral sclerosis (ALS) remains a holy grail (REF Turner). From a neuroimaging perspective, diffusion tensor imaging (DTI) has been increasingly utilised to identify brain-related upper motor neuron changes in amyotrophic lateral sclerosis (ALS). In particular, the corticospinal tract, anterior corpus callosum and hippocampal fractional anisotropy (FA) white matter changes have been closely linked with ALS pathology (REF Kiernan) and associated with the underlying neuropathological spread of TDP-43 (REF Kassubek). Thus, DTI emerges as an ideal neuroimaging biomarker endpoint for disease modifying trials in ALS. However, most advanced trials are run on a multi-centre basis and currently it is not clear how DTI signatures across centres in ALS hold-up, in particular with varying imaging sequences and scanner variabilities.

The study by Müller and colleagues (REF) in the current issue of JNNP addresses this point directly, by conducting a multi-centre DTI study to investigate the potential factors influencing FA comparisons across sites and suggest a novel analysis protocol to reduce FA variability across centres. Müller and colleagues compiled DTI scans from 8 international sites with varying DTI protocols (eg. field strength (B0), echo time (TE), number of gradient directions, voxel size) encompassing a total of 253 ALS patients and 189 controls. . In addition, centre-specific factors such as actual scanner variability, scanning time, noise levels and participants age were identified that could affect the variability of the DTI scans.

Müller and colleagues developed a two-stage procedure to regress most of the centre-specific effects out from the results. In a first step, age, voxel size, echo time, number of gradients and field strength were regressed out of the FA maps of the controls and corrected FA maps for all controls were derived. FA maps of controls were then contrasted between centres and only FA maps of centres with less than 10,000 significant voxels between their controls were merged. In addition, residual centre-specific effects (eg. scan time, noise etc) were defined for controls. Secondly, 3-D linear corrections matrices were calculated and applied to the data sets of each site. The two-step procedure was initially performed for the controls scans only, followed by the ALS patients. The centre-corrected FA maps of each group (controls vs. ALS) were then contrasted via whole-brain-based spatial statistics (WBSS).

The results from this important series of analyses have established that the confounding factors (age, voxel size, echo time, gradient strength and field strength) exert a significant impact on the FA maps in controls and ALS patients. Regressing those factors out of the analysis reveals a more symmetric pattern between hemispheres for white matter changes. More importantly, the results show the classic white matter signature of ALS, with reduced FA in the corticospinal, corpus callosum, corticostriatal and hippocampal white matter tracts, aligning with pathological staging scheme for TDP-43 spread in ALS (REF Brettschneider; Tan)

The study by Müller and colleagues represents a critically important step in the development of DTI-derived biomarkers for ALS across multiple sites. Their findings clearly show that applying a two-step correction procedure to regress and account for centre-specific variability, it is possible to increase the sensitivity and specificity of the FA findings. More importantly, the FA results align with the neuropathological staging of TDP-43, relating the DTI changes with underlying pathological changes. Clearly, imaging across multiple sites is very challenging as the inherent variability across centres can significantly affect the signal-to-noise ratio of any imaging signature, which compromises their utility as endpoint measure for multi-site intervention studies. Various proposals have been designed to

overcome these multi-site imaging variability, ranging from shared protocols to 'travelling heads' (ie. one control which is scanned on all sites and all scanners are calibrated according to the controls' scan). The new approach by Müller and colleagues represents a move from dealing with such issues at data acquisition to the analysis stage. The promising findings suggest that it is possible to pool scans across sites, even if there exist significant differences across protocols, to facilitate multi-site collaboration. Such progress will not only impact on imaging collaborations across sites but also moves forward the tangible possibility that DTI may yet become a reliable trial endpoint measure in future disease modifying treatment trials in ALS.

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