

might benefit from early initiation of therapy to prevent or delay progression to multiple sclerosis. Data from this study could also provide clues as to the causes and development of multiple sclerosis, because the interactions between genetic and environmental factors were analysed in children during the period of first exposure to environmental factors.

A major limitation inherent to this type of study is the likelihood of outcome misclassification because of insufficient follow-up. Because conversion to multiple sclerosis is dependent on time, the group with monophasic demyelination might include some children who would develop multiple sclerosis given extended follow-up. However, in Banwell and colleagues' study, the probability of misclassification was reduced by the fact that conversion to multiple sclerosis is most likely to happen within the first year after the acute demyelinating event.⁹

The Article by Banwell and colleagues⁴ will set a precedent for future prospective studies, in both paediatric and adult populations, through its integration of genetic, environmental, clinical, and radiological data, and its production of a refined assessment of the risk of multiple sclerosis at the time of a first event that is suggestive of CNS demyelination. As more knowledge is gained about the genetic and environmental factors that

determine the risk of multiple sclerosis, predictive models will be able to incorporate new predictors and analyse, in a multivariable manner, their individual or synergistic contributions to outcomes.

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I declare that I have no conflicts of interest.

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Towards a neuroimaging biomarker for amyotrophic lateral sclerosis

To be fully prepared for the emergence of neuroprotective drugs in amyotrophic lateral sclerosis (ALS), there is a clear need for the development of robust biomarkers for disease activity and for diagnosis and prognosis of this disorder.¹ Guidelines about the use of neuroimaging in the management of ALS have recognised the substantial contribution of MRI to the exclusion of mimic (largely spinal) disorders.² The increased sensitivity of MRI sequences to the inherent cerebral motor and extra-motor pathology now makes this technique a clear leader in the search for biomarkers. The Alzheimer's Disease Neuroimaging Initiative recognised the power of data sharing, and a similar multicentre collaborative approach might generate the large sample sizes that are needed to

fully explore the feasibility of MRI as a future outcome measure in therapeutic trials of ALS.

With the aim of establishing consensus about the various applications of MRI to the study of ALS, and to explore the possibility of multicentre collaboration, the first Neuroimaging Symposium in ALS (NISALS) was held at St Edmund Hall, Oxford University, UK, on Nov 3–5, 2010. It focused on four MRI techniques and recognised the need to balance a multiparametric approach (increasing the potential biomarker yield), with simplicity, reproducibility, and tolerability.

Voxel-based morphometry refers to the automated analysis of volumetric changes in grey or white matter in high-resolution three-dimensional T1-weighted MRI scans of the brain. This technique is the main MRI

Panel 1: Consensus guidelines on MRI protocol for studies of amyotrophic lateral sclerosis***Voxel-based morphometry***Essential*

- T1 (MP-RAGE or equivalent high-resolution three-dimensional pulse sequence)
- Isotropic voxels (maximum 1 mm³)

Desirable

- High GM–WM contrast

Diffusion tensor imaging*Essential*

- Minimum 12 gradient directions
- Isotropic voxels (maximum 2.5 mm slice thickness)
- T2, FLAIR (to consider other WM pathology such as cerebrovascular disease)
- Minimum b value 800 s/mm²

Desirable

- Axial acquisition (to maximise brainstem coverage)
- More than one cycle to allow averages to be calculated
- Cervical cord and brain
- Consideration of parallel imaging
- B0 field map

Functional MRI*Essential*

- Resting-state sequence (in addition to any task-based measure)

- EPI, isotropic voxels (maximum 3 mm slice thickness)
- Consistent, either eyes open–fixed target, or eyes closed–not asleep for resting-state acquisition

Desirable

- Axial acquisition (to maximise brainstem coverage)
- Pulse-waveform and respiratory-waveform monitoring to allow physiological noise correction
- Task-based protocol for both motor and cognitive functions
- B0 field map

Spectroscopy*Essential*

- Standardised methodology
- NAA-based measures within PMC

Desirable

- Myo-inositol, glutamate, and GABA measurements

*For all imaging methods, a minimum scanner field strength of 1.5T is essential, and 3.0T plus a multiple-channel head coil (12-channel to 32-channel) is desirable. MP-RAGE=magnetisation-prepared rapid gradient echo. GM=grey matter. WM=white matter. FLAIR=fluid-attenuated inversion recovery. EPI=echo planar imaging. NAA=N-acetyl aspartate. PMC=primary motor cortex.

measure of disease progression in both Alzheimer's disease and Huntington's disease. In ALS, voxel-based morphometry has been consistently sensitive (at a group level) to extra-motor, largely frontotemporal cerebral changes,¹ indicating the clinicopathological overlap of ALS with some types of frontotemporal dementia. However, the inconsistent findings of motor cortical atrophy and a paucity of large longitudinal MRI studies make the sensitivity of voxel-based morphometry to disease progression in ALS much more uncertain.

Diffusion tensor imaging—an MRI application that is sensitive to the direction of water movement—is used to detect pathology within neuronal white matter tracts. In ALS, this technique seems to accurately show the pathology that was historically noted in post-mortem histological studies.³ The most consistent results in ALS have come from studies using a diffusion tensor measure known as fractional anisotropy. This measure is a surrogate marker for disruption of the normal architecture of white matter tracts, in which water movement becomes less confined and unidirectional

(and the fractional anisotropy value is reduced). Fractional anisotropy is sensitive to involvement of both the cerebral and cervical corticospinal tracts, and of the extra-motor pathology.¹ However, overlapping changes are noted in other motor neuron disorders, such as hereditary spastic paraparesis. The true potential of diffusion tensor imaging as a diagnostic biomarker, or for monitoring disease progression, needs further longitudinal studies.

Functional MRI with blood oxygenation level-dependent (BOLD) contrast has, like PET studies a decade before, provided evidence for widespread alterations in cortical activity as a consistent feature of ALS pathology. Task-free resting-state imaging of discrete cortical networks (resting-state functional MRI [rs-fMRI]) provides a new technique to explore ALS as a system failure of interconnected networks. Application of rs-fMRI to patients with ALS suggests that reduced interhemispheric functional connectivity between motor cortices is a feature of early clinical disease,⁴ a finding that is consistent with structural callosal involvement, which is seen with diffusion tensor imaging.³

Panel 2: Consensus guidelines for the clinical dataset for MRI studies in amyotrophic lateral sclerosis

Demographics

Essential

- Date of birth
- Sex

Desirable

- Handedness
- Date of death (retrospectively)

Diagnostic aspects

Essential

- Diagnosis (ALS, other motor neuron disease, control)
- Date of symptom onset (first weakness, month, and year)
- Date of diagnosis by neurologist (ALS tertiary centre)
- Family history

Desirable

- Revised El Escorial EMG staging
- Genotype for familial cases
- Comorbidities

Clinical features

Essential

- Site of first weakness (bulbar, upper limb R/L, lower limb R/L, respiratory, trunk)

- ALSFRS-R score (with subscores)
- A simple cognitive battery, including verbal (letter) fluency, to classify patients as: ALS-CU, ALS-CI, or ALS-FTD (Strong/Neary criteria)

Desirable

- Pattern and timing of regional spread of symptoms
- Distribution of clinical UMN (and LMN) findings within territories, considering:
 - (1) A pathological reflex sum score;³
 - (2) Tapping speed (finger and foot bilaterally);
 - (3) Spasticity measure (eg, Ashworth score)
- Forced vital capacity (% predicted)
- Detailed neuropsychological profile and behavioural assessment (eg, FrSBE)
- Any atypical findings (eg, sphincter or sensory symptoms)
- Concomitant medications (riluzole at any time)

ALS=amyotrophic lateral sclerosis. EMG=electromyography. R/L=right/left. ALSFRS-R=revised amyotrophic lateral sclerosis functional rating scale. ALS-CU=ALS cognitively unimpaired. ALS-CI=ALS cognitively impaired. ALS-FTD=ALS with frontotemporal dementia. LMN=lower motor neuron. UMN=upper motor neuron. FrSBE=frontal system behaviour scale.

Magnetic resonance spectroscopy is sensitive to cerebral pathology in ALS and uses common proton-based cerebral metabolites, mainly N-acetyl aspartate, generally expressed as a ratio with creatine or choline.¹ High field strengths (3T and greater) allow increased separation of metabolite peaks, with the potential to study metabolites with specific relevance to the pathogenesis of ALS—eg, glutamate, GABA, and myo-inositol. The absence of acquisition standardisation, including single-voxel versus multivoxel sampling, and the technical expertise needed to do high-quality magnetic resonance spectroscopy, are present barriers to multicentre collaboration.

The combination of different MRI techniques might improve sensitivity and specificity for ALS, as shown in a study of heterogeneous patients in which the combination of grey-matter voxel-based morphometry and diffusion tensor imaging resulted in 90% for both indices.³ MRI also allows structure and function in ALS to be associated via the combination of rs-fMRI with diffusion tensor imaging and voxel-based morphometry.⁵ A study of presymptomatic individuals carrying mutations in genes linked to familial ALS, which accounts for about 5% of all cases, is regarded as a priority because this is the only way at present to study

key events that occur around clinical onset, which might be where the optimum therapeutic window lies.

Consensus was reached about essential and desirable protocols for MRI (panel 1) and clinical information (panel 2) for future studies of ALS, with aims for multicentre and, crucially, longitudinal studies. The first stage for MRI-based collaboration will involve exploration of the feasibility of pooling longitudinal data to establish an estimate of the sensitivity of voxel-based morphometry, diffusion tensor imaging, and rs-fMRI to disease progression in ALS, with a view to a prospective multicentre study comparing imaging techniques.

A biomarker-focused approach is now a priority in ALS research, preceding the emergence of various disease-modifying drugs, the discovery of which might facilitate more efficient therapeutic trials. The first NISALS has catalysed a growing international spirit of collaboration with the hope of translation into a better future for patients.

Martin R Turner, Julian Grosskreutz, Jan Kassubek, Sharon Abrahams, Federica Agosta, Michael Benatar, Massimo Filippi, Laura H Goldstein, Martijn van den Heuvel, Sanjay Kalra, Dorothée Lulé, Bahram Mohammadi, for the first Neuroimaging Symposium in ALS (NISALS)

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We thank Kevin Talbot and Nick Fox for their active support of the first NISALS and for their comments on the first version of this manuscript. We declare that we have no conflicts of interest. MRT is supported by the Medical Research Council/Motor Neuron Disease Association (MRC/MNDA) Lady Edith Wolfson Clinician Scientist Fellowship. The Motor Neuron Disease Association (UK) and Oxford Radcliffe Hospitals National Health Service Trust Charitable Funds provided funding for the Oxford NISALS meeting. Costs for venue hire were met by the MRC/MNDA Lady Edith Wolfson Clinician Scientist Fellowship (MRT). Travel and accommodation costs were borne by individual delegates.

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