Title: Towards a neuroimaging biomarker in amyotrophic lateral sclerosis

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Towards a neuroimaging biomarker in amyotrophic lateral sclerosis

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To be fully prepared for the emergence of candidate neuroprotective drugs in Amyotrophic Lateral Sclerosis (ALS), the development of robust biomarkers of disease activity, as well as those for diagnosis and prognosis in a notoriously heterogeneous disorder, is axiomatic [1]. Guidelines on the use of neuroimaging in the management of ALS recognised the enormous contribution of magnetic resonance imaging (MRI) in the exclusion of ‘mimic’ (largely spinal) disorders [2], but the expanding repertoire of MR sequences with sensitivity to the inherent cerebral motor and extra-motor pathology, now makes it a frontrunner in the search for biomarkers. The Alzheimer Disease Neuroimaging Initiative (ADNI) recognised the power of data-sharing, and a similar multi-centre collaborative approach might generate the large sample sizes needed to fully explore the feasibility of MRI as a future outcome measure in ALS therapeutic trials.

The 1st Neuroimaging Symposium in ALS (NISALS) was held at St. Edmund Hall, Oxford University, UK on 3rd-5th November 2010. The initial focus was on four MRI techniques, recognising the need to balance a multi-parametric approach (increasing the potential biomarker yield), with simplicity, reproducibility and tolerability.

1. **Voxel-based morphometry** (VBM) refers to the automated analysis of volumetric grey or white matter changes in high resolution 3D T1-weighted images of the brain, and is currently the primary MRI measure of disease progression in both Alzheimer’s and Huntington’s diseases. In ALS, VBM has been consistently sensitive (at a group level) to extra-motor, largely fronto-temporal cerebral changes (reviewed in [1]), reflecting the clinicopathological overlap of ALS with some types of frontotemporal dementia. However, the surprising lack of consistent motor cortical atrophy, and a paucity of large longitudinal MRI studies, makes the sensitivity of VBM to disease progression in ALS much more uncertain.

2. **Diffusion tensor imaging** (DTI) is an established tool for the detection of pathology within white matter neuronal tracts, and in ALS appears to accurately reflect the pathology observed historically in post-mortem histological studies
The most consistent results in ALS have come from studies using a DTI measure of white matter integrity known as fractional anisotropy (FA), which is sensitive to involvement of both the cerebral and cervical corticospinal tract, as well as extra-motor regions (reviewed in [1]). However, overlapping changes are observed in other motor neuron disorders such as hereditary spastic paraparesis, and results from longitudinal studies of FA change in ALS are conflicting at present, so that the true potential of DTI as a diagnostic biomarker or in monitoring disease progression requires further study.

3. **Functional MRI** using blood oxygenation level-dependent (BOLD) contrast has, like PET studies a decade prior, provided evidence for widespread alterations in cortical activity as a consistent feature of ALS pathology. More recently however, the exploration of the task-free resting state image of discrete cortical networks (resting state functional MRI, rs-fMRI) heralds a new era exploring ALS as a ‘system’ failure of interconnected networks. Application of rs-fMRI to ALS patients suggests that reduced inter-hemispheric functional connectivity between motor cortices is a feature of early clinical disease [4], a finding consistent with the structural callosal involvement seen using DTI [3].

4. **Magnetic resonance spectroscopy** (MRS) has proved sensitive to cerebral pathology in ALS using common proton-based cerebral metabolites, mainly N-acetylaspartate, commonly expressed as a ratio with creatine or choline (reviewed in [1]). Higher field strengths (3T and above) permit greater separation of metabolite peaks, with the potential to study those with more specific relevance to ALS pathogenesis, for example glutamate and GABA, as well as myo-inositol. A lack of acquisition standardisation, including single versus multi-voxel sampling, and the technical expertise needed to perform high quality MRS are currently barriers to multi-centre collaboration.

The combination of different MRI techniques may improve sensitivity and specificity for ALS, demonstrated in a study of heterogeneous patients where combining grey matter VBM and DTI improved both indices to 90% [3]. MRI also permits the linking of
structure with function in ALS, through the combination of rs-fMRI with DTI and VBM [5]. The study of pre-symptomatic individuals carrying mutations in genes linked to the ~5% of familial ALS cases is regarded as a priority, as it is the only way to study key events around the ‘clinical horizon’ at present, which may be where the optimal therapeutic window lies.

Consensus was reached on ‘essential’ and ‘desirable’ MRI protocols (Table 1) and clinical information (Table 2) for future ALS studies, with an aim for multi-centre 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 VBM, DTI and rs-fMRI to disease progression in ALS, with a view to a prospective multi-centre study comparing modalities.

A biomarker-focused era has arrived in ALS research, preceding the emergence of multiple disease-modifying drugs, the discovery of which may be facilitated through more efficient therapeutic trials. The 1st NISALS has catalysed a growing international spirit of collaboration with the hope of translation into a better future for patients.
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Competing interests
There are none.

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Table 1

Consensus guidelines on MRI protocol for ALS studies.

<table>
<thead>
<tr>
<th>MRI modality</th>
<th>Essential</th>
<th>Desirable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scanner field strength</strong></td>
<td>1.5T</td>
<td>3T</td>
</tr>
<tr>
<td><strong>Voxel-based morphometry</strong></td>
<td>T1 (MP-RAGE or equivalent high resolution 3D pulse sequence);</td>
<td>High GM–WM contrast</td>
</tr>
<tr>
<td></td>
<td>Isotropic voxels: max. 1mm³</td>
<td></td>
</tr>
<tr>
<td><strong>Diffusion tensor imaging</strong></td>
<td>Gradient directions: min. 12</td>
<td>Axial acquisition (to maximise brainstem coverage)</td>
</tr>
<tr>
<td></td>
<td>Isotropic voxels: max. 2.5mm³ slice thickness</td>
<td>More than one cycle to allow ‘averaging’</td>
</tr>
<tr>
<td></td>
<td>T2, FLAIR (to consider other WM pathology e.g. cerebrovascular disease)</td>
<td>Cervical cord as well as brain</td>
</tr>
<tr>
<td><strong>Functional MRI</strong></td>
<td>Resting state sequence (in addition to any task-based paradigm)</td>
<td>Axial acquisition (to maximise brainstem coverage)</td>
</tr>
<tr>
<td></td>
<td>EPI, isotropic voxels, max. 3mm slice thickness</td>
<td>Pulse and respiratory waveform monitoring to allow physiological noise correction</td>
</tr>
<tr>
<td></td>
<td>Consistent, either ‘eyes open-fixed target’ or ‘eyes closed-not asleep’ for resting state acquisition</td>
<td>Task-based protocol for both motor and cognitive functions</td>
</tr>
<tr>
<td><strong>Spectroscopy</strong></td>
<td>Standardised methodology</td>
<td>Myo-inositol, Glutamate and GABA measurements</td>
</tr>
<tr>
<td></td>
<td>NAA-based measures within PMC</td>
<td></td>
</tr>
</tbody>
</table>

EPI – echo planar imaging
FLAIR – fluid attenuation inversion recovery
GM – grey matter
MP-RAGE - magnetization prepared rapid gradient echo
PMC – primary motor cortex
WM – white matter
Table 2

Consensus guidelines on the clinical dataset for MRI studies in ALS.

<table>
<thead>
<tr>
<th>Category</th>
<th>Essential</th>
<th>Desirable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>Date of birth&lt;br&gt;Gender</td>
<td>Handedness&lt;br&gt;Date of death (retrospectively)</td>
</tr>
<tr>
<td><strong>Diagnostic aspects</strong></td>
<td>Diagnosis (ALS, other MND, control)&lt;br&gt;Date of symptom onset (first weakness, month and year)&lt;br&gt;Date of diagnosis by neurologist (ALS tertiary centre)&lt;br&gt;Family history</td>
<td>Revised El Escorial EMG staging&lt;br&gt;Genotype for familial cases&lt;br&gt;Co-morbidities</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Site of first weakness (bulbar, upper limb R/L, lower limb R/L, respiratory, trunk)&lt;br&gt;ALSFRS-R score (with sub-scores)&lt;br&gt;A simple cognitive battery, including verbal (letter) fluency, to classify patients as: ALS-cu, ALS-ci or ALS-FTD (Strong/Neary criteria)</td>
<td>Pattern and timing of regional spread of symptom&lt;br&gt;Distribution of clinical UMN (and LMN) findings within territories, considering:&lt;br&gt;a. A ‘pathological reflex’ sum score (e.g. [3])&lt;br&gt;b. Tapping speed (finger and foot bilaterally)&lt;br&gt;c. Spasticity measure (e.g. Ashworth score)&lt;br&gt;Forced vital capacity (% predicted)&lt;br&gt;Detailed neuropsychological profile and behavioural assessment (e.g. FrSBE)&lt;br&gt;Any atypical findings e.g. sphincter or sensory symptoms&lt;br&gt;Concomitant medications (riluzole at any time)</td>
</tr>
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</table>

ALS-cu – ALS cognitively unimpaired<br>ALS-ci – ALS cognitively impaired<br>ALS-FTD – ALS with frontotemporal dementia<br>FrSBE – Frontal System Behaviour Scale
References


