Elsevier Editorial System(tm) for The Lancet Neurology
Manuscript Draft

Manuscript Number:

Title: Towards a neuroimaging biomarker in amyotrophic lateral sclerosis

Article Type: Commentary (Reflection & Reaction)

Corresponding Author: Dr Martin R Turner, PhD

Corresponding Author's Institution: University of Oxford

First Author: Martin R Turner, PhD

Order of Authors: Martin R Turner, PhD; 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; Other members of The 1st NISALS

Manuscript Region of Origin: UNITED KINGDOM

Towards a neuroimaging biomarker in amyotrophic lateral sclerosis

Martin R Turner[1]
Julian Grosskreutz[2]
Jan Kassubek[3]
Sharon Abrahams[4]
Federica Agosta[5]
Michael Benatar[6]
Massimo Filippi[5]
Laura H. Goldstein[7]
Martijn van den Heuvel[8]
Sanjay Kalra[9]
Dorothée Lulé[3]
Bahram Mohammadi[10]
& other members of 'The 1st NISALS'*

*Other contributors to The 1st Neuroimaging Symposium in ALS (NISALS): Nazem Atassi[11], Peter Bede[12], Habib Benali[13], Christian Enzinger[14], Christian Gaser[2], Laura Jelsone-Swain[15], Hans-Peter Müller[3], Richard W. Orrell[16], Pierre-François Pradat[17], Johannes Prudlo[18], Stefan Ropele[14], Rakesh Sharma[1], Vincenzo Silani[19], Andrew Simmons[7], Stephen Smith[1], Stefan Teipel[18], Ahmed Toosy[16], Stella Tsermentseli[7], Philip Van Damme[20], Esther Verstraete[8], Robert Welsh[15], Matthias Wittstock[17]

[1]Nuffield Department of Clinical Neurosciences, University of Oxford, UK
[2]Friedrich-Schiller-University of Jena, Germany
[3]Department of Neurology, University of Ulm, Germany
[4]Human Cognitive Neuroscience, Centre for Cognitive Aging and Cognitive Epidemiology, Euan MacDonald Centre, University of Edinburgh, UK
[5]Neuroimaging Research Unit, Department of Neuroscience, Scientific Institute and University San Raffaele, Milano, Italy
[6]Department of Neurology, Miller School of Medicine, University of Miami, USA
[7]King's College London, Institute of Psychiatry, UK

[8]Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, The Netherlands

[9]Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

[10]CNS-Lab, International Neuroscience Institute, Hannover & Department of Neurology, University of Lübeck, Germany

[11]Massachusetts General Hospital-Harvard Medical School, Boston, USA

[12]Trinity College Dublin, Ireland

[13]INSERM, Paris, France

[14]Department of Neurology, Medical University of Graz, Austria

[15]University of Michigan, USA

[16]UCL Institute of Neurology, University College London, UK

[17]Hôpital de la Pitié-Salpêtrière, Paris, France

[18]Department of Psychiatry, University of Rostock and DZNE, Germany

[19]Department of Neurology, Universita' degli Studi di Milano - IRCCS Istituto Auxologico Italiano, Milano, Italy

[20]University of Leuven, Belgium

Corresponding author: Dr Martin Turner
Nuffield Department of Clinical Neurosciences
West Wing Level 3, John Radcliffe Hospital
Oxford OX3 9DU
UK
Tel: +44 (0)1865 231893
Fax: +44 (0)1865 231885
martin.turner@clneuro.ox.ac.uk

Counts: Manuscript: 825
Refs: 5
Tables: 2

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

[3]. 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.

Acknowledgements

The authors are grateful to Professors Kevin Talbot and Nick Fox for their active support of the 1st NISALS, and their comments on the initial version of this manuscript. MRT is supported by the Medical Research Council/Motor Neuron Disease Association Lady Edith Wolfson Clinician Scientist Fellowship.

Competing interests

There are none.

Financial disclosures

The Motor Neuron Disease Association (UK) and Oxford Radcliffe Hospitals NHS Trust Charitable Funds provided funding for the Oxford NISALS meeting. Venue hire costs were met by the MRC/MNDA Lady Edith Wolfson Clinician Scientist Fellowship (MRT). Travel and accommodation costs were borne by individual delegates.

Table 1

Consensus guidelines on MRI protocol for ALS studies.

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

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.

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

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

References

[1] Turner MR, Kiernan MC, Leigh PN, Talbot K. Biomarkers in amyotrophic lateral sclerosis. Lancet Neurol. 2009 Jan;8(1):94-109.

[2] Filippi M, Agosta F, Abrahams S, Fazekas F, Grosskreutz J, Kalra S, et al. EFNS guidelines on the use of neuroimaging in the management of motor neuron diseases. Eur J Neurol. 2010 Apr;17(4):526-e20.

[3] Filippini N, Douaud G, Mackay CE, Knight S, Talbot K, Turner MR. Corpus callosum involvement is a consistent feature of amyotrophic lateral sclerosis. Neurology. 2010;75(18):1645-52.

[4] Jelsone-Swain LM, Fling BW, Seidler RD, Hovatter R, Gruis K, Welsh RC. Reduced interhemispheric functional connectivity in the motor cortex during rest in limb-onset Amyotrophic Lateral Sclerosis. Frontiers in Systems Neuroscience. 2010 epub 2010-December-31;1:12.

[5] Verstraete E, van den Heuvel MP, Veldink JH, Blanken N, Mandl RC, Hulshoff Pol HE, et al. Motor network degeneration in amyotrophic lateral sclerosis: a structural and functional connectivity study. PLoS One. 2010;5(10):e13664.