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MRI as a frontrunner in the search for amyotrophic lateral sclerosis biomarkers?

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The opening sentence of many papers concerning amyotrophic lateral sclerosis (ALS) will inform the reader that it is a progressive, rapidly fatal neurodegenerative disorder characteristically involving loss of both lower motor neurons (LMNs) of the brainstem and spinal cord anterior horns, and upper motor neurons (UMNs) of the corticospinal tract (CST). Whilst true in essence, this does not encapsulate the clinico-pathological complexity of ALS, which, coupled with the insidious onset, significantly contributes to the consistent average diagnostic delay of nearly 1 year from symptom onset. Nor does it recognize the longer 'tail' of the survival curve beyond the median of 2–3 years from symptom onset, which frequently extends for 5–10 years across all clinically recognized phenotypes [1]. Both of these facets of ALS are compounded by the lack of diagnostic and prognostic biomarkers, although candidates are now emerging from a variety of sources [2]. A lack of markers sensitive to disease activity means that clinical trials rely on survival as a primary outcome measure, with a protracted time period and high financial cost as a result. The experience in multiple sclerosis highlights the need for robust biomarkers that will allow informed decisions about risk versus benefit for future therapeutic agents, in an environment where, ultimately, there may be multiple disease-modifying drugs.

Many would argue the *sine qua non* of ALS is LMN degeneration, and electromyography has a clear role in the detection of occult denervation in apparently unaffected muscles. In the purest use of the diagnostic term, ALS only refers to approximately 85% of cases within the wider umbrella term motor neuron disease, in which there is clear clinical or pathological evidence of both UMN and LMN involvement. A much smaller group of patients (~12%) may clinically have LMN-only involvement (termed progressive muscular atrophy), although pathological study reveals that occult CST involvement is still common in such cases. Rarer still is the UMN-only form of motor neuron disease (termed primary lateral sclerosis), which accounts for less than 3% of cases and is characterized by a consistently slow disease course over 10–20 years. Involvement of the wider cerebral cortex in ALS was recognized over 100 years ago, and the last two decades have galvanized the concept of a pathological continuum between ALS and some types of frontotemporal

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dementia, which share the same molecular signature, namely cytoplasmic inclusions of ubiquitinated TDP-43 [3].

Electromyography is not able to probe the UMN or extra-motor compartments of ALS pathology and, although transcranial magnetic stimulation has demonstrated significant utility in assessing the integrity of the CST, it is a highly operator-dependent technique, lacking widespread availability.

Neuroimaging has played a key role in the evolution of a modern, broader ‘cerebrally inclusive’ model of ALS pathogenesis over the last 30 years. Initial studies of cerebral blood flow using SPECT and PET were limited by spatial resolution, concern over repeated radiation exposure and lack of availability of centers with sufficient expertise. The successful clinical application of MRI arose from the quantum leap in computer processing power, permitting the rapid reconstruction of 3D images of high spatial resolution in an entirely noninvasively manner.

To date, MRI has made its greatest contribution to the diagnostic pathway in ALS through the exclusion of spinal ‘mimic’ pathology [4]. Within the brain, the initial excitement regarding the observation of CST hyperintensity (over 20 years ago) on standard T₂-weighted sequences in cases of ALS [5] gave way to the realization that this radiological sign is neither sensitive nor specific. The development of new acquisition protocols now permits the study of the brain, both structurally and functionally, with the hope of discovering sensitive and specific biomarkers for ALS [6]. At present, the techniques with the most promise are diffusion tensor imaging (DTI), voxel-based morphometry and resting-state functional MRI.

Diffusion tensor imaging can be used to perform neuropathology studies *in vivo* by exploiting the ability of MRI to provide information regarding the directionality of water. This is expected to be tightly confined and thus highly directional (anisotropic) within intact neuronal tracts and more freely diffusible (isotropic) in damaged tracts. In this way, DTI can provide information on the organization and integrity of cerebral white matter tracts, which have been long known to be consistently involved in ALS [7]. The fractional anisotropy is a quantifiable DTI measure and consistently reduced within the CST and corpus callosum of heterogeneous ALS patients [8], as well as in tracts projecting to frontotemporal areas, such as the uncinate fasciculus [9]. Fractional anisotropy has demonstrated prognostic value [10] and longitudinal studies suggest it also has monitoring potential [11].

Whilst visible cerebral atrophy is not a common feature of ALS (including the motor strip surprisingly), the development of sophisticated analysis software, capable of detecting more subtle ‘volumetric’ changes in the gray and white matter brain regions (termed voxel-based morphometry), has revealed consistent extramotor changes in ALS patients [12]. It is not yet clear how these evolve over time and in relation to the variable clinical phenotype, but their combination with DTI changes may, in due course, allow the development of a ‘signature’ of changes specific and sensitive to the ALS brain [8].

Blood-oxygen-level-dependent functional MRI allows the noninvasive assessment of regional cerebral activity. Task-based studies confirmed earlier PET findings that the ‘boundaries’ of neuronal activity in the ALS brain in response to voluntary movement appear to be stretched [13]. Although this might, in theory, reflect compensatory mechanisms in response to neuronal death, a loss of wider motor network integration might be caused by another mechanism. It is now possible to study the brain as a series of interconnected networks by recording blood-oxygen-level-dependent changes during the resting state (resting-state functional MRI) and, indeed, early study supports the view of reduced network integrity in ALS [14]. The combination of this technique with DTI has

great potential to probe structural and functional connectivity simultaneously, with the tantalizing recent finding that the spread of pathology may be a function of this connectivity [15], offering both a biomarker and a novel therapeutic target. Studies of presymptomatic carriers of genes associated with ALS may reveal that this is among the earliest of pathological changes.

Magnetic resonance spectroscopy, although not a frontrunner in ALS MRI, has high sensitivity for nonspecific markers of neuronal loss, typically expressed as the ratio of *N*-acetylaspartate to creatine/choline. Magnetic resonance spectroscopy studies currently lack both standardization and the level of operator-independent analysis enjoyed by other techniques. Higher field strengths (e.g., 7 Tesla) offer the hope of quantification of metabolites, such as glutamate and GABA, which may have more specific relevance to excitotoxic themes in ALS pathogenesis [16].

The Alzheimer's Disease Neuroimaging Initiative (ADNI) [17] has highlighted the power of multicenter collaborative studies, and the early success in combining MRI and cerebrospinal fluid biomarkers represents a new era in the diagnostic and therapeutic assessment methodology of this disorder [18]. With this model in mind, Oxford University (UK) hosted international scientists at the first Neuroimaging Symposium in ALS (NISALS; November 2010), which led to the development of consensus guidelines on image acquisition and analysis [SUBMITTED FOR PUBLICATION], with the aim of retrospective data sharing to further explore the feasibility of MRI as a surrogate marker in future therapeutic trials for ALS.

With MRI looking so promising in ALS, what then are the major obstacles ahead? Most of the current data are based on cross-sectional studies. Longitudinal experiments in ALS are challenging as patients rapidly acquire physical disability, particularly bulbar and diaphragmatic weakness that often preclude lying flat in the scanner. However, such studies are essential if the full potential of MRI as a source of biomarkers is to be explored. MRI is also expensive compared with the standard questionnaire or physical examination-based disability outcome measures used in current therapeutic trials. However, a MRI-based biomarker might ultimately be extractable from sequences obtained during routine neurological investigation.

Significant technical hurdles must be overcome if MRI is to be translated into clinical use in ALS. Image acquisition characteristics vary between scanners and 'drift' over time on any given equipment. Standardization of acquisition is one positive step forward from the recent consensus meeting, but major challenges lie ahead in terms of standardizing image post-processing if multicenter data sharing is to be meaningful. Furthermore, current MRI findings in ALS are based on group comparisons, and large databases of healthy control images may be required to realize the goal of single-subject analysis.

At present, MRI cannot probe the LMN component of ALS. However, the cervical spinal cord has shown promise in relation to disability in ALS [19], and rapidly improving resolution might eventually permit detection of changes with the anterior horns, providing a simultaneous assessment of LMN involvement in relation to UMN loss.

More than two decades after its first application to ALS, MRI is now well positioned to eventually deliver much needed biomarkers.

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Biography

Martin R Turner

Bibliography

1. Kiernan MC, Vucic S, Cheah B, et al. Amyotrophic lateral sclerosis. *Lancet*. 2010 (In Press). [PubMed: 21296405]
2. Turner MR, Kiernan MC, Leigh PN, Talbot K. Biomarkers in amyotrophic lateral sclerosis. *Lancet Neurol*. 2009; 8(1):94–109. [PubMed: 19081518]
3. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*. 2006; 314(5796):130–133. [PubMed: 17023659]
4. Filippi M, Agosta F, Abrahams S, et al. EFNS guidelines on the use of neuroimaging in the management of motor neuron diseases. *Eur. J. Neurol*. 2010; 17(4):526–e20. [PubMed: 20136647]
5. Goodin DS, Rowley HA, Olney RK. Magnetic resonance imaging in amyotrophic lateral sclerosis. *Ann. Neurol*. 1988; 23(4):418–420. [PubMed: 3382182]
6. Turner MR, Modo M. Advances in the application of MRI to amyotrophic lateral sclerosis. *Expert Opin. Med. Diagn*. 2010; 4(6):483–496. [PubMed: 21516259]
7. Smith MC. Nerve fibre degeneration in the brain in amyotrophic lateral sclerosis. *J. Neurol. Neurosurg. Psychiatry*. 1960; 23:269–282. [PubMed: 21610893]
8. 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):1645–1652. [PubMed: 21041787]
9. Sato K, Aoki S, Iwata NK, et al. Diffusion tensor tract-specific analysis of the uncinate fasciculus in patients with amyotrophic lateral sclerosis. *Neuroradiology*. 2010; 52(8):729–733. [PubMed: 20174788]
10. Agosta F, Pagani E, Petrolini M, et al. MRI predictors of long-term evolution in amyotrophic lateral sclerosis. *Eur. J. Neurosci*. 2010; 32(9):1490–1496. [PubMed: 21044177]
11. Sage CA, Peeters RR, Gorner A, Robberecht W, Sunaert S. Quantitative diffusion tensor imaging in amyotrophic lateral sclerosis. *Neuroimage*. 2007; 34(2):486–499. [PubMed: 17097892]
12. Chang JL, Lomen-Hoerth C, Murphy J, et al. A voxel-based morphometry study of patterns of brain atrophy in ALS and ALS/FTLD. *Neurology*. 2005; 65(1):75–80. [PubMed: 16009889]
13. Lule D, Ludolph AC, Kassubek J. MRI-based functional neuroimaging in ALS: an update. *Amyotroph. Lateral Scler*. 2009; 10(5–6):258–268. [PubMed: 19922112]
14. Mohammadi B, Kollewe K, Samii A, Krampfl K, Dengler R, Munte TF. Changes of resting state brain networks in amyotrophic lateral sclerosis. *Exp. Neurol*. 2009; 217(1):147–153. [PubMed: 19416664]
15. Verstraete E, van den Heuvel MP, Veldink JH, et al. Motor network degeneration in amyotrophic lateral sclerosis: a structural and functional connectivity study. *PLoS One*. 2010; 5(10):e13664. [PubMed: 21060689]
16. Rothstein JD. Current hypotheses for the underlying biology of amyotrophic lateral sclerosis. *Ann. Neurol*. 2009; 65(Suppl. 1):S3–S9. [PubMed: 19191304]
17. Mueller SG, Weiner MW, Thal LJ, et al. The Alzheimer's Disease Neuroimaging Initiative. *Neuroimaging Clin. N. Am*. 2005; 15(4):869–877. xi–xii. [PubMed: 16443497]

18. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol.* 2010; 9(11):1118–1127. [PubMed: 20934914]
19. Valsasina P, Agosta F, Benedetti B, et al. Diffusion anisotropy of the cervical cord is strictly associated with disability in amyotrophic lateral sclerosis. *J. Neurol. Neurosurg. Psychiatry.* 2007; 78(5):480–484. [PubMed: 17030586]