INVITED EDITORIAL

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# Open imaging protocols, amyotrophic lateral sclerosis and other neurodegenerative disorders

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## The pros and cons of using standardised protocols

The evaluation of imaging biomarker efficiency is a complicated task when it is based on real-world data derived from a single centre [1]. Over the last decade, there have been more than 125 registered trials investigating treatment effects and monitoring disease progression in amyotrophic lateral sclerosis [2]. Despite that, fixed protocols aimed at measuring imaging biomarkers' effect size, sensitivity, and specificity remain out of reach. The problem with imaging biomarker discovery and validation is the tremendous variability in the clinical course of this disease [3]. Since clinical course variability is primarily due to multiple mechanisms and progression-driving factors, it may be more productive to look at a syndrome affecting a pathway rather than a more specific gene-protein interaction [4]. The disease severity and duration variability mean that the imaging biomarkers might contribute to the diagnosis. However, image-derived measures alone will not be sufficient to detect the disease. Nonetheless, an abnormal finding in an imaging study is not necessarily associated with clinical progression, and might not be present in some patients at the beginning of the disease course. The main problems are the small sample size, the low power to detect the difference, and restricted funding for the reference dataset. The small sample size is a particular challenge because amyotrophic lateral sclerosis is rare. However, open reference datasets are available [5] and enable the comparison of clinical patient populations to extensive standardised, high-quality imaging data [6].

## Automatic *vs.* manual extraction of regions of interest (ROI)

Manual identification of critical landmarks is feasible in small clinical datasets, but is more difficult when encompassing extensive population studies. Research presented in this issue has manually extracted anatomical landmarks and average values [1]. Achieving reproducibility of these measurements using automatic registration-based methods would represent a significant advance [7]. Software solutions for extracting quantitative markers and landmarks of the motor system are progressing at pace. The clinical community needs to be aware of the methods, already widely available, for analysing large datasets of brain images for research purposes and the achievement of tangible improvements using high-performance computing platforms (HPC) and federated machine learning [8].

A recent achievement in brain tumour research highlights the potential. It is critical to use quantitative parameters that include cortical thickness, cortico-spinal tract coherence measures, and brain and lateral ventricle volumes obtained from reference populations of healthy controls matched for age and gender. Such measures enable clinicians to track the evolution of the brain injury in question well before the damage becomes apparent and irreversible [7, 9]. Efforts to harness the global community of researchers interested in neurodegenerative diseases to share protocols, image processing pipelines, and DNA-based biomarkers, are already underway in what is known as the 'United Consortium' [10]. Aggregating imaging resources from multiple sites using centralised high-performance computing (HPC) enables the

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discovery of new structural features and validation of existing structural biomarkers on large datasets [11]. A Canadian project has already started to combine and aggregate data from patients diagnosed with amyotrophic lateral sclerosis and other neurodegenerative diseases and controls. MRI datasets have been collected and analysed using a distributed database [12].

## Biological precision *vs.* technical feasibility

The source of the abnormal signal captured in the recent study by Maj et al. came from an altered white matter tract signal, and possibly myelination [1]. Identifying and measuring demyelination of the cortico-spinal pathway has been attempted using various magnetic resonance imaging methods. Currently, a precise imaging-histological correlation is hard to reach within a reasonable timeframe applicable to patient-focused clinical protocols. However, hope lies in synthetic MRI methods based on multi-dynamic multi-echo (MDME) sequences. It is important to determine how various pathologies will affect the measurements based on T2-relaxation before comprehensive clinical implementation begins [13]. Diffusion-weighted imaging remains the most commonly available sequence that measures radial diffusivity and apparent diffusion coefficient feasible on most modern clinical MRI scanners with an acceptable acquisition duration time.

In summary, it is essential to understand that the goal of standardising MRI data acquisition in this field should unite all neurologists and all clinicians. Ontario Neurodegenerative Disease Research Initiative (ONDRI), a Canadian research community, has identified all neurodegenerative diseases as a global challenge and is using all available technology to facilitate the search for a solution in the form of a unified platform for the acquisition and analysis of structural brain biomarkers [14].

MRI acquisitions using widely available standardised protocols will enable analysis using validated software processing pipelines [15, 16]. The results will allow the evaluation of single-subject results against a large and growing database of morphological biomarkers for tracking the course of the clinical disease. This will lead to a better prognosis and improve the detection of progression in every patient, leading to the faster discovery of therapeutic agents.

## References


1. Maj E, Jamroży M, Bielecki M, et al. Role of DTI-MRI parameters in diagnosis of ALS: useful biomarkers for daily practice? Tertiary centre experience and literature review. Neurol Neurochir Pol. 2022 [Epub ahead of print], doi: 10.5603/PJNNS.a2022.0070, indexed in Pubmed: 36426927.
2. Wong C, Stavrou M, Elliott E, et al. Clinical trials in amyotrophic lateral sclerosis: a systematic review and perspective. Brain Commun. 2021; 3(4): fcab242, doi: 10.1093/braincomms/fcab242, indexed in Pubmed: 34901853.
3. Shinotoh H, Armon C. Validation of MRI biomarker of white matter degeneration for ALS clinical trials: One small step. Neurology. 2020; 95(8): 327–328, doi: 10.1212/WNL.0000000000010252, indexed in Pubmed: 32646957.
4. Hewamadduma CA, Hoggard N, O'Malley R, et al. Novel genotype-phenotype and MRI correlations in a large cohort of patients with mutations. Neurol Genet. 2018; 4(6): e279, doi: 10.1212/NXG.0000000000000279, indexed in Pubmed: 30533525.
5. Nugent AC, Thomas AG, Mahoney M, et al. The NIMH intramural healthy volunteer dataset: A comprehensive MEG, MRI, and behavioral resource. Sci Data. 2022; 9(1): 518, doi: 10.1038/s41597-022-01623-9, indexed in Pubmed: 36008415.
6. Griffanti L, Gillis G, O'Donoghue MC, et al. Adapting UK Biobank imaging for use in a routine memory clinic setting: The Oxford Brain Health Clinic. Neuroimage Clin. 2022; 36: 103273, doi: 10.1016/j.nicl.2022.103273, indexed in Pubmed: 36451375.
7. Zhang H, Avants BB, Yushkevich PA, et al. High-dimensional spatial normalization of diffusion tensor images improves the detection of white matter differences: an example study using amyotrophic lateral sclerosis. IEEE Trans Med Imaging. 2007; 26(11): 1585–1597, doi: 10.1109/TMI.2007.906784, indexed in Pubmed: 18041273.
8. Pati S, Baid U, Edwards B, et al. Federated learning enables big data for rare cancer boundary detection. Nat Commun. 2022; 13(1): 7346, doi: 10.1038/s41467-022-33407-5, indexed in Pubmed: 36470898.
9. Keihaninejad S, Zhang H, Ryan NS, et al. An unbiased longitudinal analysis framework for tracking white matter changes using diffusion tensor imaging with application to Alzheimer's disease. Neuroimage. 2013; 72: 153–163, doi: 10.1016/j.neuroimage.2013.01.044, indexed in Pubmed: 23370057.
10. Adams HHH, Evans TE, Terzikhan N. The Uncovering Neurodegenerative Insights Through Ethnic Diversity consortium. Lancet Neurol. 2019; 18(10): 915, doi: 10.1016/S1474-4422(19)30324-2, indexed in Pubmed: 31526750.
11. Knol M, Poot R, Evans T, et al. Genetic variants for head size share genes and pathways with cancer. , doi: 10.1101/2020.07.15.191114.
12. Picher-Martel V, Magnussen C, Blais M, et al. CAPTURE ALS: the comprehensive analysis platform to understand, remedy and eliminate ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2022 [Epub ahead of print]: 1–7, doi: 10.1080/21678421.2022.2041668, indexed in Pubmed: 35195049.
13. Yoo RE, Choi SH, Youn SW, et al. Myelin Content in Mild Traumatic Brain Injury Patients with Post-Concussion Syndrome: Quantitative Assessment with a Multidynamic Multiecho Sequence. Korean J Radiol. 2022; 23(2): 226–236, doi: 10.3348/kjr.2021.0253, indexed in Pubmed: 35029073.
14. Ramirez J, Holmes MF, Scott CJM, et al. ONDRI Investigators. Ontario Neurodegenerative Disease Research Initiative (ONDRI): Structural MRI Methods and Outcome Measures. Front Neurol. 2020; 11: 847, doi: 10.3389/fneur.2020.00847, indexed in Pubmed: 32849254.
15. Laansma MA, Bright JK, Al-Bachari S, et al. ENIGMA-Parkinson's Study. International Multicenter Analysis of Brain Structure Across Clinical Stages of Parkinson's Disease. Mov Disord. 2021; 36(11): 2583–2594, doi: 10.1002/mds.28706, indexed in Pubmed: 34288137.
16. ENIGMA DTI protocols. https://enigma.ini.usc.edu/protocols/dti-protocols/ (20.12.2022).