EDITORIAL

The gap between academic advances and therapy development in motor neuron disease

AQ2 *Peter Bede*[a,b,c] *and Pierre-Francois Pradat*[c,d]

Despite the universal recognition of the fundamental clinical, genetic and pathological heterogeneity AQ5 of ALS, the expectation that the same drug may be effective across the entire spectrum of the disease has peculiarly persisted. In the era of precision medicine, the therapeutic imperative is to offer the appropriate drug to the correct patient at the optimal time. Academic studies in ALS have been hugely successful at characterizing specific cohorts with distinctive clinical, radiological and pathological features [1] and describing presymptomatic, peridiagnostic and late-stage disease burden patterns [2–4]. Cluster analyses of patients have consistently revealed distinct sub-populations based on a variety of biomarker metrics [5–7]. Yes, despite compelling evidence for biological heterogeneity, divergent pathomechanisms, and differing progression rates, the very same drug is uniformly prescribed for all patients with ALS in the clinical setting. Clinical trial designs in ALS also remain notoriously conservative focusing overwhelmingly on survival, respiratory function and the motor aspects of the disease, despite a plethora of academic studies highlighting comorbid frontotemporal [8–11], cerebellar [12], subcortical [13,14] and extrapyramidal dysfunction [15,16].

The timing of the therapeutic interventions is inherently defined by the speed of diagnosis, which in turn depends on local referral pathways and access to neuromuscular or motor neuron disease specialists. The considerable symptom-onset to diagnosis interval in ALS means that, by the time, patients are formally diagnosed in a tertiary referral centre, they are likely to have considerable disability and harbour a significant disease burden. Diagnostic delay not only limits the therapeutic benefit of established pharmacological interventions, but also impacts negatively on pharmacological trial participation. The phrase ''time is brain'' is used by stroke physicians to highlight the absolute urgency of intervening in neurovascular syndromes, but the very same message also applies to neurodegenerative processes. Misdiagnoses, misinterpretation of clinical signs, potentially unnecessary interventions are not uncommon during the diagnostic journey of ALS patients [17,18], delaying the confirmation of the diagnosis and enrolment in pharmaceutical trials.

Recent presymptomatic studies have confirmed considerable changes in specific genotypes [19–21], but these observations may be relatively unique the specific genetic variants evaluated and not readily representative of the presymptomatic phase of 'sporadic' cases, that is, patients not harbouring common, ALS-associated mutations such as *C9orf72*, *FUS*, *SOD1*, and so forth. These, seemingly 'sporadic' cases, represent the majority of patients attending our clinics. So, while the academic insights generated by recent presymptomatic studies confirm accruing disease burden long before symptom manifestation, the specific anatomical patterns described by these studies are likely to be genotype-specific. Notwithstanding these observations, emerging presymptomatic studies unequivocally highlight the urgency of intervening early and potentially extending the therapeutic window to the prodromal phase of the disease in selected patients. Two disease phases are increasingly distinguished in ALS [22] prior to meeting diagnostic criteria: the 'premanifest phase' referring to an interval spanning from the earliest biomarker evidence of the condition to symptom onset and the 'prodromal phase' when patients already have disease-associated symptoms but do not meet formal diagnostic criteria yet.

A number of scholarly concepts have been repeatedly proposed in ALS such as 'cognitive reserve' [23,24], 'motor reserve' [25], 'developmental factors' [20,26], 'abnormal energy metabolism'

[a]Computational Neuroimaging Group, School of Medicine, Trinity College, [b]Department of Neurology, St James's Hospital, Dublin, Ireland, [c]Department of Neurology, Pitié-Salpêtriére University Hospital and [d]Laboratoire d'Imagerie Biomédicale, Sorbonne University, CNRS, AQ3 INSERM, Paris, France

Correspondence to Peter Bede, Computational Neuroimaging Group, Biomedical Sciences Institute, Trinity College Dublin, Pearse Street, Dublin 2, Ireland. Tel: +353 1 410 3000; e-mail: bedep@tcd.ie AQ4

Curr Opin Neurol 2023, 36:000–000

DOI:10.1097/WCO.0000000000001179

[27], 'stage-wise propagation' [28], 'compensatory mechanisms' [3], 'sexual dimorphism' [29,30], 'prion-like propagation' [31], 'connectome-based propagation' [2], 'what wires together-dies together' [32], the 'D50 progression model' [33,34], and so forth, all riveting academic notions with compelling biological bases, which are yet to be developed into actionable clinical strategies. The translation of abstract academic concepts into viable strategies, such as early therapeutic intervention, cognitive rehabilitation, metabolic therapies, propagation prevention, and so forth seems a pressing priority.

A key contrast of academic studies and clinical care lies their focus on an entire patient population versus an individual patient. Academic studies are inherently cohort studies and rely on group-level observations, characterising phenotype-associated or genotype-associated traits. Clinical care on the other hand centres on the diagnosis and support of specific individuals and relies heavily on the accurate interpretation of single-subject data. Where academic studies describe 'typical' disease burden patterns and 'representative' longitudinal trajectories inferred from hundreds of patients, the quest of a clinician is accurately classifying a single patient into relevant diagnostic, phenotypic and prognostic categories. Accordingly, numerous machine-learning initiatives have been published recently using a variety of models to categorize patients into clinically relevant subgroups [35–39]. Although these have shown promise to discriminate patients from controls, the distinction of patients from 'disease controls' proved more challenging [40], and the search for reliable prognostic indicators also continues [41–43].

Although the majority of MND studies focus on ALS, other motor neuron diseases such as SBMA [44,45], adult spinal muscular atrophy [46,47], HSP [48,49], primary lateral sclerosis [50,51] and low-incidence entities such as postpolio syndrome [52,53] are increasingly evaluated in large prospective multimodal studies. Non-ALS motor neuron diseases have received relatively limited research attention in the past, despite their notable quality-of-life ramifications. The new consensus diagnostic criteria in PLS [54] has given impetus to PLS research [55–57], where extramotor changes [58,59] and frontotemporal dysfunction is increasingly recognized [60]. Ultimately, the study of non-ALS motor neuron diseases or 'restricted phenotypes' offers important methodological and conceptual lessons and may also serve as 'disease control' groups for ALS studies. Similarly, there are ample methodological learning opportunities from other neurodegenerative conditions, especially FTLD; concepts, study-frameworks, multisite designs, data repositories, and so forth, which could be readily adopted in ALS/MND [61,62].

Despite the contrast between academic achievements and the limited therapeutic options in motor neuron disease at present, it is likely that recent scholarly advances will filter down to practical clinical applications. Instead of small research groups working in isolation, large international consortia increasingly spearhead research efforts thanks to effective protocol harmonization and data-sharing arrangements. There are increasing funding opportunities for low-incidence conditions, and patient advocacy groups and charities not only support research but also help to identify the most pressing research priorities. The sheer number of recent publications in the field, the high academic standard of studies and the engrossing array of innovative approaches indicate an unrelenting research momentum, a likely harbinger of therapeutic breakthrough.

Acknowledgements

None. AQ6

Financial support and sponsorship

This study was sponsored by the Spastic Paraplegia Foundation (SPF). P.B. is also supported by the Health Research Board (HRB EIA-2017-019 and JPND-Cofund-2-2019-1), the Irish Institute of Clinical Neuroscience (IICN), the EU Joint Programme – Neurodegenerative Disease Research (JPND), the Andrew Lydon scholarship, and the Iris O'Brien Foundation. Professor P.-F.P. is supported by the EU Joint Programme – Neurodegenerative Disease Research (JPND), l'Association pour la Recherche sur la SLA (ARSLA) and l'Agence Nationale pour la Recherche (ANR).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Iyer PM, Mohr K, Broderick M, *et al.* Mismatch negativity as an indicator of cognitive sub-domain dysfunction in amyotrophic lateral sclerosis. Front Neurol 2017; 8:395. AQ7
2. Meier JM, van der Burgh HK, Nitert AD, *et al.* Connectome-based propagation model in amyotrophic lateral sclerosis. Ann Neurol 2020; 87:725–738.
3. Abidi M, de Marco G, Couillandre A, *et al.* Adaptive functional reorganization in amyotrophic lateral sclerosis: coexisting degenerative and compensatory changes. Eur J Neurol 2020; 27:121–128.
4. Tahedl M, Tan EL, Chipika RH, *et al.* Brainstem-cortex disconnection in amyotrophic lateral sclerosis: bulbar impairment, genotype associations, asymptomatic changes and biomarker opportunities. J Neurol 2023. AQ8
5. Tan HHG, Westeneng HJ, Nitert AD, *et al.* MRI clustering reveals three ALS subtypes with unique neurodegeneration patterns. Ann Neurol 2022; 92:1030–1045.
6. Dukic S, McMackin R, Costello E, *et al.* Resting-state EEG reveals four subphenotypes of amyotrophic lateral sclerosis. Brain 2022; 145:621–631.
7. Bede P, Murad A, Lope J, *et al.* Clusters of anatomical disease-burden patterns in ALS: a data-driven approach confirms radiological subtypes. J Neurol 2022; 269:4404–4413.

8. Christidi F, Karavasilis E, Velonakis G, *et al.* The clinical and radiological spectrum of hippocampal pathology in amyotrophic lateral sclerosis. Front Neurol 2018; 9:523.
9. Chipika RH, Christidi F, Finegan E, *et al.* Amygdala pathology in amyotrophic lateral sclerosis and primary lateral sclerosis. J Neurol Sci 2020; 417:117039.
10. Burke T, Elamin M, Bede P, *et al.* Discordant performance on the 'Reading the Mind in the Eyes' Test, based on disease onset in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2016; 17:467–472.
11. Finegan E, Chipika RH, Li Hi Shing S, *et al.* Pathological crying and laughing in motor neuron disease: pathobiology, screening. Interv Front Neurol 2019; 10:260.
12. Bede P, Chipika RH, Christidi F, *et al.* Genotype-associated cerebellar profiles in ALS: focal cerebellar pathology and cerebro-cerebellar connectivity alterations. J Neurol Neurosurg Psychiatry 2021; 92:1197–1205.
13. Chipika RH, Finegan E, Li Hi Shing S, *et al.* Switchboard'' malfunction in motor neuron diseases: selective pathology of thalamic nuclei in amyotrophic lateral sclerosis and primary lateral sclerosis. NeuroImage Clinical 2020; 27:102300.
14. Proudfoot M, Bede P, Turner MR. Imaging cerebral activity in amyotrophic lateral sclerosis. Front Neurol 2018; 9:1148.
15. Abidi M, de Marco G, Grami F, *et al.* Neural correlates of motor imagery of gait in amyotrophic lateral sclerosis. J Magn Reson Imaging 2021; 53:223–233.
16. Feron M, Couillandre A, Mseddi E, *et al.* Extrapyramidal deficits in ALS: a combined biomechanical and neuroimaging study. J Neurol 2018; 265:2125–2136.
17. Cellura E, Spataro R, Taiello AC, La Bella V. Factors affecting the diagnostic delay in amyotrophic lateral sclerosis. Clin Neurol Neurosurg 2012; 114:550–554.
18. Zoccolella S, Beghi E, Palagano G, *et al.,* SLAP registry. Predictors of delay in the diagnosis and clinical trial entry of amyotrophic lateral sclerosis patients: a population-based study. J Neurol Sci 2006; 250:45–49.
19. Chipika RH, Siah WF, McKenna MC, *et al.* The presymptomatic phase of amyotrophic lateral sclerosis: are we merely scratching the surface? J Neurol 2021; 268:4607–4629.
20. Lulé DE, Müller HP, Finsel J, *et al.* Deficits in verbal fluency in presymptomatic C9orf72 mutation gene carriers-a developmental disorder. J Neurol Neurosurg Psychiatry 2020; 91:1195–1200.
21. Querin G, Bede P, El Mendili MM, *et al.,* Predict to Prevent Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis Study Group. Presymptomatic spinal cord pathology in c9orf72 mutation carriers: a longitudinal neuroimaging study. Ann Neurol 2019; 86:158–167.
22. Benatar M, Turner MR, Wuu J. Defining presymptomatic amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2019; 20:303–309.
23. Temp AGM, Prudlo J, Vielhaber S, *et al.* Cognitive reserve and regional brain volume in amyotrophic lateral sclerosis. Cortex 2021; 139:240–248.
24. Costello E, Rooney J, Pinto-Grau M, *et al.* Cognitive reserve in amyotrophic lateral sclerosis (ALS): a population-based longitudinal study. J Neurol Neurosurg Psychiatry 2021; 92:460–465.
25. Bede P, Bogdahn U, Lope J, *et al.* Degenerative and regenerative processes in amyotrophic lateral sclerosis: motor reserve, adaptation and putative compensatory changes. Neural Regen Res 2021; 16:1208–1209.
26. Bede P, Siah WF, McKenna MC, Li Hi Shing S. Consideration of C9orf72-associated ALS-FTD as a neurodevelopmental disorder: insights from neuroimaging. J Neurol Neurosurg Psychiatry 2020.
27. Vandoorne T, De Bock K, Van Den Bosch L. Energy metabolism in ALS: an underappreciated opportunity? Acta Neuropathol 2018; 135:489–509.
28. Kassubek J, Muller HP, Del Tredici K, *et al.* Diffusion tensor imaging analysis of sequential spreading of disease in amyotrophic lateral sclerosis confirms patterns of TDP-43 pathology. Brain 2014; 137(Pt 6):1733–1740.
29. Trojsi F, Di Nardo F, Caiazzo G, *et al.* Between-sex variability of resting state functional brain networks in amyotrophic lateral sclerosis (ALS). J Neural Transm (Vienna) 2021; 128:1881–1897.
30. Bede P, Elamin M, Byrne S, Hardiman O. Sexual dimorphism in ALS: exploring gender-specific neuroimaging signatures. Amyotroph Lateral Scler Frontotemporal Degener 2014; 15:235–243.
31. Kanouchi T, Ohkubo T, Yokota T. Can regional spreading of amyotrophic lateral sclerosis motor symptoms be explained by prion-like propagation? J Neurol Neurosurg Psychiatry 2012; 83:739–745.
32. Bak TH, Chandran S. What wires together dies together: verbs, actions and neurodegeneration in motor neuron disease. Cortex 2012; 48:936–944.
33. Steinbach R, Batyrbekova M, Gaur N, *et al.* Applying the D50 disease progression model to gray and white matter pathology in amyotrophic lateral sclerosis. NeuroImage Clin 2020; 25:102094.
34. Dieckmann N, Roediger A, Prell T, *et al.* Cortical and subcortical grey matter atrophy in amyotrophic lateral sclerosis correlates with measures of disease accumulation independent of disease aggressiveness. NeuroImage Clin 2022; 36:103162.
35. Bede P, Murad A, Hardiman O. Pathological neural networks and artificial neural networks in ALS: diagnostic classification based on pathognomonic neuroimaging features. J Neurol 2021; 269:2440–2452.
36. Behler A, Müller HP, Ludolph AC, *et al.* A multivariate Bayesian classification algorithm for cerebral stage prediction by diffusion tensor imaging in amyotrophic lateral sclerosis. NeuroImage Clin 2022; 35:103094.
37. van der Burgh HK, Schmidt R, Westeneng HJ, *et al.* Deep learning predictions of survival based on MRI in amyotrophic lateral sclerosis. NeuroImage Clin 2017; 13:361–369.
38. Westeneng HJ, Debray TPA, Visser AE, *et al.* Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. Lancet Neurol 2018; 17:423–433.
39. Behler A, Müller HP, Del Tredici K, *et al.* Multimodal in vivo staging in amyotrophic lateral sclerosis using artificial intelligence. Ann Clin Translat Neurol 2022; 9:1069–1079.
40. Bede P, Murad A, Lope J, *et al.* Phenotypic categorisation of individual subjects with motor neuron disease based on radiological disease burden patterns: a machine-learning approach. J Neurol Sci 2021; 432:120079.
41. Grollemund V, Chat GL, Secchi-Buhour MS, *et al.* Development and validation of a 1-year survival prognosis estimation model for amyotrophic lateral sclerosis using manifold learning algorithm UMAP. Sci Rep 2020; 10:13378.
42. Grollemund V, Le Chat G, Secchi-Buhour MS, *et al.* Manifold learning for amyotrophic lateral sclerosis functional loss assessment: development and validation of a prognosis model. J Neurol 2021; 268:825–850.
43. Schuster C, Hardiman O, Bede P. Survival prediction in amyotrophic lateral sclerosis based on MRI measures and clinical characteristics. BMC Neurol 2017; 17:73.
44. Pradat PF, Bernard E, Corcia P, *et al.,* French Kennedy's Disease Writing Group. The French national protocol for Kennedy's disease (SBMA): consensus diagnostic and management recommendations. Orphanet J Rare Dis 2020; 15:90.
45. Querin G, Bede P, Marchand-Pauvert V, Pradat PF. Biomarkers of spinal and bulbar muscle atrophy (SBMA): a comprehensive review. Front Neurol 2018; 9:844.
46. Querin G, Lenglet T, Debs R, *et al.* The motor unit number index (MUNIX) profile of patients with adult spinal muscular atrophy. Clin Neurophysiol 2018; 129:2333–2340.
47. Querin G, El Mendili MM, Lenglet T, *et al.* The spinal and cerebral profile of adult spinal-muscular atrophy: a multimodal imaging study. NeuroImage Clin 2019; 21:101618.
48. Mulkerrin G, França MC Jr, Lope J, *et al.* Neuroimaging in hereditary spastic paraplegias: from qualitative cues to precision biomarkers. Expert Rev Mol Diagn 2022; 22:745–760.
49. Rezende TJ, de Albuquerque M, Lamas GM, *et al.* Multimodal MRI-based study in patients with SPG4 mutations. PLoS One 2015; 10:e0117666.
50. Finegan E, Li Hi Shing S, Chipika RH, *et al.* Widespread subcortical grey matter degeneration in primary lateral sclerosis: a multimodal imaging study with genetic profiling. NeuroImage Clin 2019; 24:102089.
51. Bede P, Pradat PF, Lope J, *et al.* Primary lateral sclerosis: clinical, radiological and molecular features. Revue Neurol (Paris) 2021; 178:196–205.
52. Li Hi Shing S, Chipika RH, Finegan E, *et al.* Postpolio syndrome: more than just a lower motor neuron disease. Front Neurol 2019; 10:773.
53. Li Hi Shing S, Lope J, Chipika RH, *et al.* Extra-motor manifestations in postpolio syndrome (PPS): fatigue, cognitive symptoms and radiological features. Neurol Sci 2021; 42:4569–4581.
54. Turner MR, Barohn RJ, Corcia P, *et al.* Primary lateral sclerosis: consensus diagnostic criteria. J Neurol Neurosurg Psychiatry 2020; 91:373–377.
55. Finegan E, Li Hi Shing S, Siah WF, *et al.* Evolving diagnostic criteria in primary lateral sclerosis: the clinical and radiological basis of 'probable PLS'. J Neurol Sci 2020; 417:117052.
56. Pioro EP, Turner MR, Bede P. Neuroimaging in primary lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2020; 21:18–27.
57. Mitsumoto H, Turner MR, Ajroud-Driss S, *et al.* Preface: promoting research in PLS: current knowledge and future challenges. Amyotroph Lateral Scler Frontotemporal Degener 2020; 21:1–2.
58. Finegan E, Shing SLH, Chipika RH, *et al.* Extra-motor cerebral changes and manifestations in primary lateral sclerosis. Brain Imaging Behav 2021; 15: 2283–2296.
59. Bede P, Finegan E. Revisiting the pathoanatomy of pseudobulbar affect: mechanisms beyond corticobulbar dysfunction. Amyotroph Lateral Scler Frontotemporal Degener 2018; 19:4–6.
60. de Vries BS, Rustemeijer LMM, van der Kooi AJ, *et al.* A case series of PLS patients with frontotemporal dementia and overview of the literature. Amyotroph Lateral Scler Frontotemporal Degener 2017; 18:534–548.
61. McKenna MC, Lope J, Tan EL, Bede P. Presymptomatic radiological changes in frontotemporal dementia: propagation characteristics, predictive value and implications for clinical trials. Brain Imaging Behav 2022.
62. McKenna MC, Murad A, Huynh W, *et al.* The changing landscape of neuroimaging in frontotemporal lobar degeneration: from group-level observations to single-subject data interpretation. Expert Rev Neurother 2022; 22:179–207.

WCO

Manuscript No. WCO360418

Current Opinion in Neurology
Typeset by Thomson Digital
for Wolters Kluwer

Dear Author,

During the preparation of your manuscript for typesetting, some queries have arisen. These are listed below. Please check your typeset proof carefully and mark any corrections in the margin as neatly as possible or compile them as a separate list. This form should then be returned with your marked proof/list of corrections to the Production Editor.

QUERIES: to be answered by AUTHOR/EDITOR?

QUERY NO.	QUERY DETAILS	RESPONSE
<AQ1>	As per style, the short title/running head can have a maximum of 65 characters including spaces and author names, and abbreviations/acronyms only as exceptions. Please check the suggested short title for appropriateness.	
<AQ2>	Please confirm whether surnames/ family names (red) have been identified correctly in the author byline.	
<AQ3>	Affiliations have been set as per style. Please check for accuracy of information.	
<AQ4>	Please check and confirm the corresponding author's name and relevant details for appropriateness.	
<AQ5>	Please define ALS at the first instance of occurrence in the text.	
<AQ6>	Please check the Acknowledgements section for the accuracy of presentation of the content.	
<AQ7>	References have been updated using PubMed. Please check.	
<AQ8>	Please update [4,26].	