Journal of Neurology (2024) 271:431–445
https://doi.org/10.1007/s00415-023-11994-7

ORIGINAL COMMUNICATION

Language deficits in primary lateral sclerosis: cortical atrophy, white matter degeneration and functional disconnection between cerebral regions

Ee Ling Tan[1] · Marlene Tahedl[1] · Jasmin Lope[1] · Jennifer C. Hengeveld[2] · Mark A. Doherty[2] · Russell L. McLaughlin[2] · Orla Hardiman[1] · Kai Ming Chang[1] · Eoin Finegan[1] · Peter Bede[1,3]

Received: 8 August 2023 / Revised: 6 September 2023 / Accepted: 8 September 2023 / Published online: 27 September 2023

Abstract

Background Primary lateral sclerosis (PLS) is traditionally regarded as a pure upper motor neuron disorder, but recent cases series have highlighted cognitive deficits in executive and language domains.

Methods A single-centre, prospective neuroimaging study was conducted with comprehensive clinical and genetic profiling. The structural and functional integrity of language-associated brain regions and networks were systematically evaluated in 40 patients with PLS in comparison to 111 healthy controls. The structural integrity of the arcuate fascicle, frontal aslant tract, inferior occipito-frontal fascicle, inferior longitudinal fascicle, superior longitudinal fascicle and uncinate fascicle was evaluated. Functional connectivity between the supplementary motor region and the inferior frontal gyrus and connectivity between Wernicke's and Broca's areas was also assessed.

Results Cortical thickness reductions were observed in both Wernicke's and Broca's areas. Fractional anisotropy reduction was noted in the aslant tract and increased radical diffusivity (RD) identified in the aslant tract, arcuate fascicle and superior longitudinal fascicle in the left hemisphere. Functional connectivity was reduced along the aslant track, i.e. between the supplementary motor region and the inferior frontal gyrus, but unaffected between Wernicke's and Broca's areas. Cortical thickness alterations, structural and functional connectivity changes were also noted in the right hemisphere.

Conclusions Disease-burden in PLS is not confined to motor regions, but there is also a marked involvement of language-associated tracts, networks and cortical regions. Given the considerably longer survival in PLS compared to ALS, the impact of language impairment on the management of PLS needs to be carefully considered.

Keywords Primary lateral sclerosis · Language · Frontotemporal dementia · MRI · Neuropsychology

Abbreviations

AF	Arcuate fascicle
ALS	Amyotrophic lateral sclerosis
ALSFRS	Amyotrophic lateral sclerosis functional rating scale
ASO	Antisense oligonucleotide
BOLD	Blood-oxygen-level-dependent (BOLD) signal
CIFTI	CIFTI "grayordinate" file format
CT	Cortical thickness
CSD	Constrained spherical deconvolution
DWI	Diffusion-weighted imaging
ECAS	Edinburgh Cognitive and Behavioural ALS Screen
ELQ	Emotional Lability Questionnaire
EPI	Echo-planar imaging
FA	Fractional anisotropy
FC	Functional connectivity
fMRI	Functional MRI
fODF	Fibre orientation distribution function
FOV	Field of view

Ee Ling Tan and Marlene Tahedl Contributed equally as joint first authors.

✉ Peter Bede
bedep@tcd.ie

[1] Room 5.43, Computational Neuroimaging Group (CNG), School of Medicine, Trinity College Dublin, Pearse Street, Dublin 2, Ireland

[2] Smurfit Institute of Genetics, Trinity College Dublin, Dublin, Ireland

[3] Department of Neurology, St James's Hospital, Dublin, Ireland

FSL	FMRIB´s Software Library
FTD	Frontotemporal dementia
GM	Grey matter
HADS	Hospital Anxiety and Depression Scale
HC	Healthy controls
IFO	Inferior occipito-frontal fascicle
ILF	Inferior longitudinal fascicle
IR-SPGR	Inversion recovery prepared spoiled gradient recalled echo
IQR	Interquartile range
LH	Left hemisphere
LMN	Lower motor neuron
ML	Machine learning
MND	Motor neuron disease
MNI152	Montreal Neurological Institute 152 standard space
NIV	Non-invasive ventilation
PEG	Percutaneous endoscopic gastrostomy
PLS	Primary lateral sclerosis
PT	Physiotherapy
RD	Radial diffusivity
RH	Right hemisphere
RIG	Radiologically inserted gastrostomy
ROI	Region of interest
rs-fMRI	Resting-state functional MRI
SC	Structural connectivity
SD	Standard deviation
SE-EPI	Spin-echo echo-planar imaging
SLF	Superior longitudinal fascicle
T	Tesla
T1w	T1-weighted imaging
TE	Echo time
TI	Inversion time
TR	Repetition time
UF	Uncinate fascicle
UMN	Upper motor neuron
VR	Voxel resolution
WM	White matter

Introduction

While frontotemporal dysfunction is a well-recognised clinical facet of ALS [1–4], cognitive manifestations of PLS are less well characterised. PLS is traditionally conceptualised as a "pure" upper motor neuron disorder, a view increasingly challenged by case series describing cognitive deficits [5, 6]. Larger PLS studies have recently highlighted that comorbid cognitive and behavioural manifestations are not uncommon [5–7], and more recently, a number of imaging studies have captured extensive frontotemporal, cerebellar and subcortical grey matter (GM) involvement [8, 9]. The most commonly described neuropsychological alterations in PLS include executive dysfunction, apathy, language deficits and deficits in social cognition [5–7], albeit specific domains are seldom evaluated in detail in dedicated prospective studies.

In light of the relative paucity of post-mortem studies [10], most of which focus on spinal and motor cortex involvement, computational neuroimaging is the most commonly utilised tool to characterise patterns of neurodegeneration in PLS [11]. Early PLS studies have primarily centred on the evaluation of corpus callosum, corticospinal tract and primary motor cortex pathology [12–14] and later studies have increasingly characterised intra- and inter-hemispheric disconnection [15–18]. Pre- and supplementary motor cortex involvement and brainstem alterations [17, 19] have been gradually characterised, and the most recent studies have revealed selective thalamic and amygdalar involvement as well [20–22]. Thalamic nuclei relay a number of corticocortical and corticobasal networks [23] mediating specific cognitive processes. The preferential degeneration of thalamic and amygdalar nuclei are likely contributors to the widespread neurocognitive changes observed clinically. While the hallmark clinical manifestations of PLS are progressive spasticity and pseudobulbar affect, recent studies also confirmed considerable cerebellar degeneration in PLS [8]. Albeit the physiological role of the cerebellum is typically merely associated with coordination and balance, its physiological role in mediating cognitive, emotional and behavioural processes and vulnerability in MNDs is increasingly recognised [8, 24]. Pseudobulbar affect is one of the commonest non-motor manifestation of PLS which is traditionally linked to cortico-medullary disconnection, but cerebellar and serotonergic factors are also thought to contribute [14, 25–28].

In ALS, genotype-associated cognitive and behavioural profiles are well recognised especially in association with *C9orf72* [29–32]. The high incidence and distinctive subtypes of cognitive phenotypes in ALS led to the development of classification schemes [33]. Disease-specific screening instruments [34–36] have been developed and validated to screen for neuropsychological (NP) deficits in the most commonly affected domains in ALS to trigger comprehensive NP assessments if required. More importantly, the survival and management implications of comorbid dementia have been extensively studied in ALS, but not in PLS. In ALS, there is a high incidence of comorbid cognitive and behavioural deficits [6, 37] and apathy [36] which are known to impact on adherence to medications, engagement with supportive interventions (PT/NIV/PEG), fall prevention strategies, participation in clinical trials and survival [38, 39]. Despite the compelling practical relevance of comorbid neuropsychological deficits, patients with PLS are not routinely screened for cognitive deficits and the radiological substrate of cognitive change in PLS remains poorly characterised. Our objective therefore is the systematic evaluation of the

integrity of language-associated cortical regions, relevant white matter (WM) tracts and the connectivity of relevant circuits. Accordingly, a prospective multimodal neuroimaging study has been carried out with 3D T1-weighted (T1w), diffusivity and functional MRI data and detailed clinical and genetic profiling.

Methods

Ethics approval

In accordance with the Ethics Approval of this research project by Beaumont Hospital, Dublin, all participants gave informed consent.

Participants

A total of 151 participants, 40 patients with PLS and 111 healthy controls (HC), were enrolled in this study. The demographic and clinical profiles of the two cohorts are summarised in Table 1**.** Age, sex, approximate date of symptom onset, symptom onset to scan interval, handedness, education, smoking history, BMI and site of disease onset were systematically recorded on the day of the scan, and the following instruments were also administered to all patients with PLS: (1) the ALS functional rating scale (ALSFRS-r), the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) [35], the Frontal Systems Behavior Scale (FrSBe), the Hospital Anxiety and Depression Scale (HADS) and the Emotional Lability Questionnaire (ELQ) [40] were uniformly administered. Healthy controls were unrelated to patients with PLS and had no family history of neurological disease. All subjects with PLS had "definite" PLS according to the new diagnostic criteria [41]. Participants with comorbid neuroinflammatory, neurovascular or psychiatric conditions and subjects who could not tolerate MRI scanning due to claustrophobia were excluded. Subjects with incidental radiological findings, such as hydrocephalus, meningiomas and previous strokes, were also excluded.

Genetics

Participating patients with PLS underwent whole exome sequencing, as described previously [6]. Thirty-three ALS-associated genetic variants based on the ALS online

Table 1 The demographic and clinical profile of the study population

	PLS patients	HC	*t* test [W]$^{++}$/Chi-square [C2]$^{+++}$
Total number of subjects (missing data sets for CT/DWI^{+}/rs-fMRI)	40 (0/0/11)	111 (0/2/0)	n.a
Age [y, mean ± SD]	61.95 ± 10.21	59.36 ± 10.66	W: $t(71.20) = 1.36$, $p = 0.18$
Sex, F/M	15/25	57/56	C2: $X^2(1, N = 141) = 1.50$, $p = 0.22$
Handedness, R/L	36/4	106/7	C2: $X^2(1, N = 141) = 0.20$, $p = 0.66$
Years of education [y, mean ± SD]	12.38 ± 3.32	14.68 ± 3.52	W: $t(72.29) = -3.72$, $p < 0.001$*
Symptom duration [y, mean ± SD]	9.2 ± 5.7		
ELQ score—mean SD	12.34 ± 14.91		
ALSFRS-r—mean ± SD	33.88 ± 5.05		
ECAS total abnormal scores *n* (%)	9 (22.5%)		
ALS specific	9 (22.5%)		
ALS non-specific	6 (15%)		
Language	11 (27.5%)		
Verbal fluency	9 (22.5%)		
HADS mean (SD) total	8.1 (5.6)		
HADS mean (SD) anxiety	5.0 (4.1)		
HADS mean (SD) depression	3.2 (2.4)		
ELQ laughing	5.6 (7.4) abnormal: 31%		
ELQ crying	4.0 (6.2) abnormal: 25%		

ALSFRS amyotrophic lateral sclerosis functional rating scale, *CT* cortical thickness, *DWI* diffusion-weighted imaging, *ECAS* Edinburgh Cognitive and Behavioural ALS Screen, *ELQ* Emotional Lability Questionnaire, *F* female, *HADS* Hospital Anxiety and Depression Scale, *HC* healthy controls, *L* left-handed, *M* male, *PLS* primary lateral sclerosis, *R* right-handed, *rs-fMRI* resting-state functional magnetic resonance imaging, *SD* standard deviation, *y* years

$^{++}$Welch two-sample *t* tests were performed to test differences of age and years of education between all PLS vs. HC,

$^{+++}$Chi-square tests were performed to test differences of sex and handedness frequencies between all PLS vs. HC

*Significant at an alpha level of $p \leq 0.05$

database [42] and 70 hereditary spastic paraplegia (HSP)-associated genetic variants [43] were considered. Patients were also screened for hexanucleotide repeat expansion (HRE) in *C9orf72* using repeat-primed polymerase chain reaction (PCR) as previously described [44].

Neuroimaging

A 3 Tesla Philips Achieva platform was used for MR data acquisition. FLAIR images were acquired to identify incidental neurovascular or neuroinflammatory changes. FLAIR images were acquired axially with an Inversion Recovery Turbo Spin Echo (IR-TSE) sequence: TR/TE = 11,000/125 ms, TI = 2800 ms, FOV = 230 × 183 × 150 mm and spatial resolution = 0.65 × 0.87 × 4 mm. Three input raw-MR data sets were interrogated quantitatively in this study: 3D structural T1-weighted (T1w) images, diffusion-weighted images (DWI) and resting-state functional MRI (rs-fMRI). A 3D Inversion Recovery prepared Spoiled Gradient Recalled echo (IR-SPGR) sequence was used to acquire T1-weighted data with a field of view (FOV) of 256 × 256 × 160 mm, 160 sagittal slices with no interslice gap, flip angle (FA) = 8°, voxel resolution (VR) = 1 mm isotropic, SENSE factor = 1.5, TR/TE = 8.5/3.9 ms and TI = 1060 ms. A spin-echo echo-planar imaging (SE-EPI) pulse sequence with a 32-direction Stejskal–Tanner diffusion encoding scheme was used to acquire DWI data with a FOV = 245 × 245 × 150 mm, 60 axial slices with no interslice gaps, FA = 90°, VR = 2.5 mm isotropic, SENSE factor = 2.5, TR/TE = 7639/59 ms, dynamic stabilisation and spectral presaturation with inversion recovery (SPIR) fat suppression. An echo-planar imaging (EPI) sequence was implemented to evaluate fluctuations of the blood-oxygen-level-dependent (BOLD) signal at rest with eyes closed: a total of 220 volumes were acquired with a FOV = 233 × 233 × 120 mm, 30 axial slices with no interslice gap, FA = 90°, VR = 2.875 × 2.875 × 4 mm isotropic, SENSE factor = 2.5 and TR/TE = 2000/35 ms.

Cortical thickness estimation of Broca's and Wernicke's areas

3D T1w structural data were used for cortical thickness (CT) estimations in Broca's and Wernicke's areas. FreeSurfer's [45] "recon_all" pipeline was utilised for pre-processing including bias corrections, brain extraction, normalisation and generation of 2D cortical surface representations [46, 47]. Resulting surface data were subsequently converted into "CIFTI" file format with the help of Ciftify [48] which relies on Workbench [49] tools. Data were also input into the standard "fsl_anat" pipeline of FMRIB´s Software Library (FSL) [50] which encompasses bias correction, brain extraction and non-linear registration to the MNI152 2mm standard space. Resulting transformation matrices were subsequently used for image co-registration of DWI and functional data. A region-of-interest (ROI) label for "Broca's area" was generated by merging the "pars opercularis" and "pars triangularis" labels of the Desikan–Killiany (DK) atlas [51]. Wernicke's area was approximated based on the "banks of the superior temporal sulcus" of the DK atlas—incorporating parts of the superior temporal gyrus and posterior middle temporal gyrus [52]. While language functions are physiologically lateralised to the left hemisphere in right-handed people and in the majority of left-handed people [53, 54], metrics were also retrieved from the right hemisphere for further analyses.

Tractography of language-associated white matter tracts

Raw diffusion-weighted (DWI) data were used to generate tract-wise diffusivity values as a proxy of structural connectivity (SC). Pre-processing took place in MRtrix3 [55], including noise [56] and Gibb's Ringing artifacts removal [57], as well as motion, eddy current [58] and bias field corrections [59]. The integrity of the six most relevant language fibre tracts was appraised in each hemisphere: the arcuate fascicle (AF), inferior occipito-frontal fascicle (IFO), inferior longitudinal fascicle (ILF), superior longitudinal fascicle (SLF), uncinate fascicle (UF) [60, 61] as well as the frontal aslant tract (FAT) connecting the supplementary motor region/lateral superior frontal gyrus with the inferior frontal gyrus [62] (Fig. 1). Intraoperative brain stimulation and previous tractography studies have consistently highlighted the role of FAT in a variety of speech processes and language functions including speech initiation, sentence generation, verbal fluency, lexical decisions, orofacial movement coordination and speech inhibition [62] The TractSeg pipeline [63] was implemented to dissect AF, IFO, ILF, SLF and UF which relies on a neural network approach for the accurate segmentation of individual DWI data sets. TractSeg outputs three separate fibre bundles for SLF (SLF I, SLF II and SLF III) which were merged into a single SLF map. To estimate fibre orientation distribution (fODF) in each voxel and peaks of the spherical harmonic function, the constrained spherical deconvolution (CSD) approach of MRtrix3 [55] was used. The main advantage of CSD stems from its accuracy in crossing fibres regions [64–66]. Output fODFs were normalised [67] and spherical harmonic peaks retrieved to be fed into TractSeg. For frontal aslant tract segmentation, the relevant labels of the Glasser atlas [68] were utilised as end-ROIs [62]. The labels and DW images were aligned to the high-resolution T1w data and tractograms calculated between each pair of ROIs using a probabilistic algorithm to generate 5000 streamlines per tract, using the analogue options and parameters for estimating fODF and tractography as for TractSeg. The 12 tractograms were subsequently

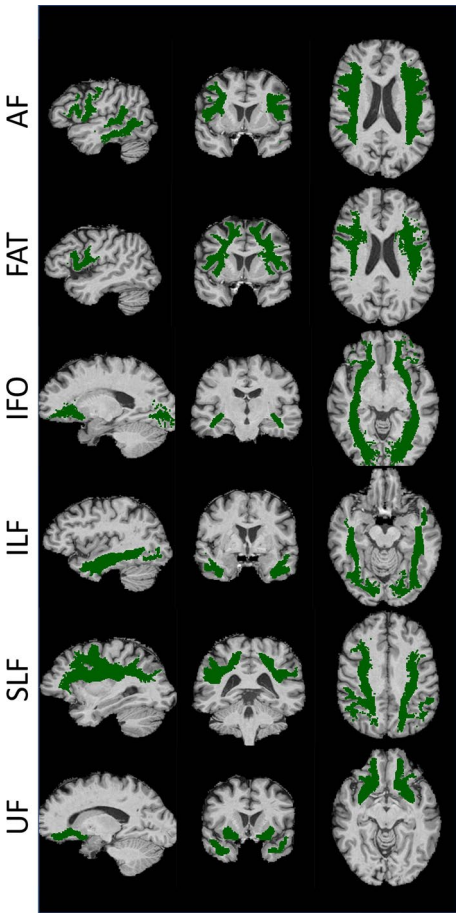

Fig. 1 Tractography of six language-associated tracts: arcuate fascicle (AF), frontal aslant tract (FAT), inferior occipito-frontal fascicle (IFO), inferior longitudinal fascicle (ILF), superior longitudinal fascicle (SLF) and uncinate fascicle (UF)

mapped onto track-weighted images implementing the track density imaging (TDI) method [69], where each streamline contributes a value of unity to the final track-weighted output map. These maps were binarised using a threshold of at minimum two streamlines per voxel. With the resulting binarised maps, the mean radial diffusivity (RD) and fractional anisotropy (FA) of each tract were estimated.

Functional connectivity between Broca's and Wernicke's areas and along the frontal aslant tract

Functional connectivity (FC) was estimated between Broca's and Wernicke's areas as well as between the supplementary motor region/lateral superior frontal gyrus and the inferior frontal gyrus. Rs-fMRI data were pre-processed using FSL's FEAT pipeline which includes brain extraction, intensity normalisation and slice time correction. Head-motion artifacts were corrected using FSL's ICA-based Automatic Removal Of Motion Artifacts (ICA- AROMA) [70]. Confounding effects of WM and cerebrospinal fluid (CSF) were regressed out. The resulting pre-processed functional images were transformed into MNI152 2mm standard space for subsequent group comparisons: First, linear co-registration of the native high-resolution data was performed using 6 degrees of freedom (DOFs), followed by non-linearly warping into standard space using 12 DOFs. FC was calculated in Matlab R2021b (The Mathworks, Natick, USA), using the CoSMoMVPA [71] and FieldTrip [72] toolboxes and defined as Fisher z-transformed Pearson's correlation between the time courses of the ROIs.

Statistical modelling

RStudio (R version 4.2.2) was used for statistical inferences. Differences in means of age and education between patients (aggregating across subgroups) and HC were examined using Welch two-sample *t* tests. Sex and handedness rations were compared using Chi-square testing. To test differences in neuroimaging metrics between patients and HC, a one-way analysis of variance (ANOVA) omnibus test was implemented, correcting for the confounding effects of age, sex, handedness and years of education. To account for multiple comparisons, for CT and FC, we considered *p* values below $0.05/2 = 0.025$ as significant (correcting for two ROIs); for WM tractography, we considered *p* values below $0.05/6 = 0.008$ as significant, correcting for the number of tracts evaluated (6).

Data availability

Statistical outputs and additional data processing details can be requested from the corresponding author. Individual patient clinical and neuroimaging data cannot be made available due to institutional regulations and departmental policies.

Results

Subjects

In total, data from 40 PLS patients and 111 HC were evaluated. While complete structural, diffusivity and fMRI data were available from the majority of subjects, 11 patients with PLS had no rs-fMRI data and 2 healthy controls out of the 111 healthy subjects had no diffusion-weighted data available (Table 1). Welch two-sample t-testing indicated adequate matching for age [$t(71.20) = 1.36$, $p = 0.18$]; however, PLS patients had significantly fewer years of education [$t(72.29) = -3.72$, $p < 0.001$]. As indicated above, education was included as a covariate in our statistical models.

Chi-square testing revealed no significant differences in sex distributions [$X^2(1, N=141)=1.50$, $p=0.22$] and distributions of handedness [$X^2(1, N=141)=0.20$, $p=0.66$] between the study groups. Patients with PLS tested negative for GGGGCC hexanucleotide expansions in *C9orf72* and the panel of HSP and ALS-associated genetic variants.

Cortical thickness

To assess cortical thickness differences of language-associated regions between PLS and HC, we used analysis of variance (ANOVA), corrected for age, sex, handedness and years of education. CT differences were evaluated in two regions of interest (ROIs), Broca's and Wernicke's areas. To correct for multiple comparisons with regard to the two ROIs, we adjusted the alpha level $p<0.05/2=0.025$. Results are illustrated in Fig. 2, and the details of the statistical comparisons are presented in Table 2. Significantly reduced cortical thickness was detected in Broca's area in patients with PLS compared to controls [$F(1, 147)=49.11$, $p<0.001$]. The thickness of the right-hemispheric equivalent of Broca's area was also significantly lower in PLS [$F(1, 147)=53.46$, $p<0.001$]. Wernicke's area also exhibited significantly lower CT in PLS compared to controls [$F(1, 147)=36.13$, $p<0.001$], as well as in its right-hemispheric equivalent [$F(1, 147)=3.80$, $p<0.001$]. These findings suggest that both Broca's and Wernicke's areas are affected in PLS, which is, however, not specific to the left hemisphere since similar atrophy was also detected in the equivalent brain regions in the right hemisphere.

White matter microstructure alterations

To evaluate differences in white matter (WM) integrity in language-associated tracts between PLS and HC, we used ANOVA, correcting for age, sex, handedness and years of education. We contrasted differences in radial diffusivity (RD) and fractional anisotropy (FA) in 6 language-associated tracts on each hemisphere: (1) arcuate fascicle (AF), (2) frontal aslant tract (FAT), (3) inferior occipito-frontal fascicle (IFO), (4) inferior longitudinal fascicle (ILF), (5) superior longitudinal fascicle (SLF) and (6) uncinate fascicle (UF). To correct for multiple comparisons investigating these six tracts, we adjusted the alpha level $p<0.05/6=0.008$. We illustrate the results of these comparisons in Fig. 3 and provide statistical details in Table 2. In the left hemisphere, significantly lower FA [$F(1, 143)=14.06$, $p<0.001$] and higher RD [$F(1, 143)=28.90$, $p<0.001$] was identified in the aslant tract in patients with PLS. Additionally higher RD was detected in the AF [$F(1, 147)=19.85$, $p<0.001$], and the SLF [$F(1, 147)=19.10$, $p<0.001$]. In the right hemisphere, reduced FA was identified in the frontal aslant tract [$F(1, 143)=16.20$, $p<0.001$] and SLF [$F(1, 147)=10.23$, $p=0.002$] in patients with PLS compared to controls. Additionally, higher RD was detected in all investigated tracts with the exception of the SLF [$F(1, 147)=2.58$, $p=0.11$]. These findings indicate that language-associated tracts, the frontal aslant tract in particular, are affected in PLS in both hemispheres, and RD is more sensitive than FA in detecting white matter integrity alterations.

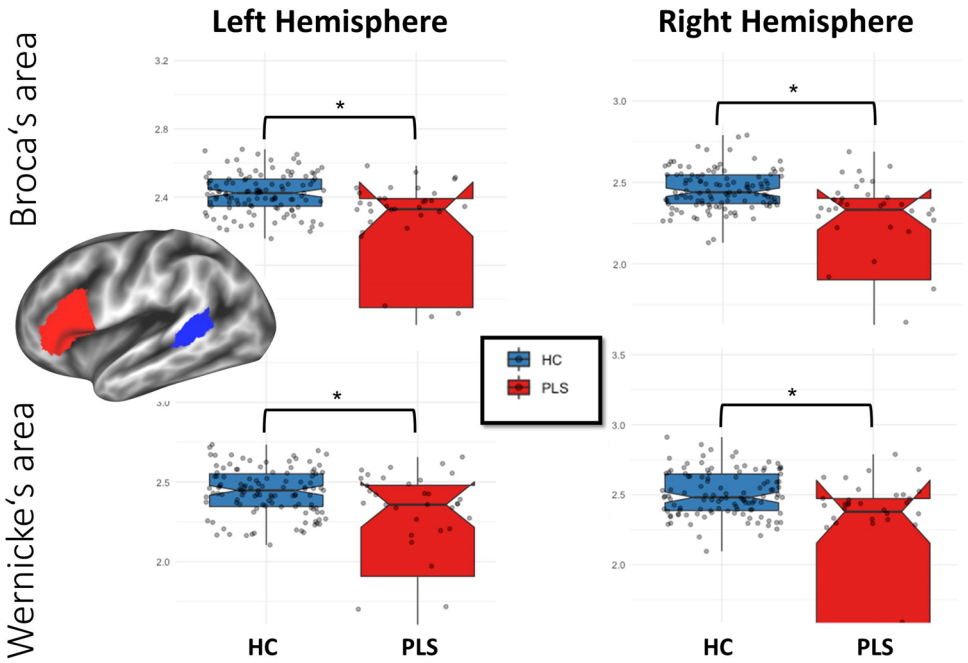

Fig. 2 Cortical thickness differences between patients with PLS (PLS) and healthy controls (HC). *Statistically significant group differences

Table 2 Statistical details of radiological comparisons

Neuroimaging metric	General linear model, testing main effect "neuroimaging metric"					
	Left hemisphere			Right hemisphere		
	Sum square	*F* value	*p* value	Sum square	*F* value	*p* value
Cortical thickness						
Broca's area	2.066	49.11	**< 0.001***	2.66	53.46	**< 0.001***
Wernicke's area	2.644	36.13	**< 0.001***	3.80	43.41	**< 0.001***
Fractional anisotropy						
Arcuate fascicle	1.48e−3	4.89	0.03	4.90e−4	0.85	0.36
Aslant tract	1.68e−2	14.06	**< 0.001***	1.47e−2	16.20	**< 0.001***
Inferior occipito-frontal fascicle	9.00e−5	0.13	0.72	1.80e−4	0.34	0.56
Inferior longitudinal fascicle	1.00e−5	0.01	0.92	4.40e−4	0.47	0.49
Superior longitudinal fascicle	1.87e−3	4.31	0.04	6.78e−3	10.23	**0.002***
Uncinate fascicle	1.50e−4	0.17	0.68	2.50e−4	0.46	0.50
Radial diffusivity						
Arcuate fascicle	1.40e−8	19.85	**< 0.001***	6.92e-9	8.87	**0.003***
Aslant tract	1.39e-7	28.90	**< 0.001***	1.44e-7	33.57	**< 0.001***
Inferior occipito-frontal fascicle	1.08e-8	6.87	0.01	2.71e-8	19.84	**< 0.001***
Inferior longitudinal fascicle	4.51e-9	5.20	0.024	1.59e−8	12.03	**< 0.001***
Superior longitudinal fascicle	2.03e−8	19.11	**< 0.001***	4.87e−9	2.58	0.11
Uncinate fascicle	5.84e−9	4.83	0.023	1.19e−8	11.88	**< 0.001***
Functional connectivity						
Broca's–Wernicke's areas	0.003	0.07	0.79	0.07	1.72	0.19
Aslant tract: source-to-target	0.33	8.27	**0.005***	0.306	6.22	**0.014***

Radiological differences between individuals with PLS patients and healthy controls

*Bold font indicate significant *p* values at the corrected alpha levels (for CT and FC: $p < 0.05/2 = 0.025$, correcting for two ROIs for WM analyses: $p < 0.05/6 = 0.008$, correcting for six tracts)

ANOVA analysis of variance, *CT* cortical thickness, *FC* functional connectivity, *PLS* primary lateral sclerosis, *ROI* region of interest, *WM* white matter

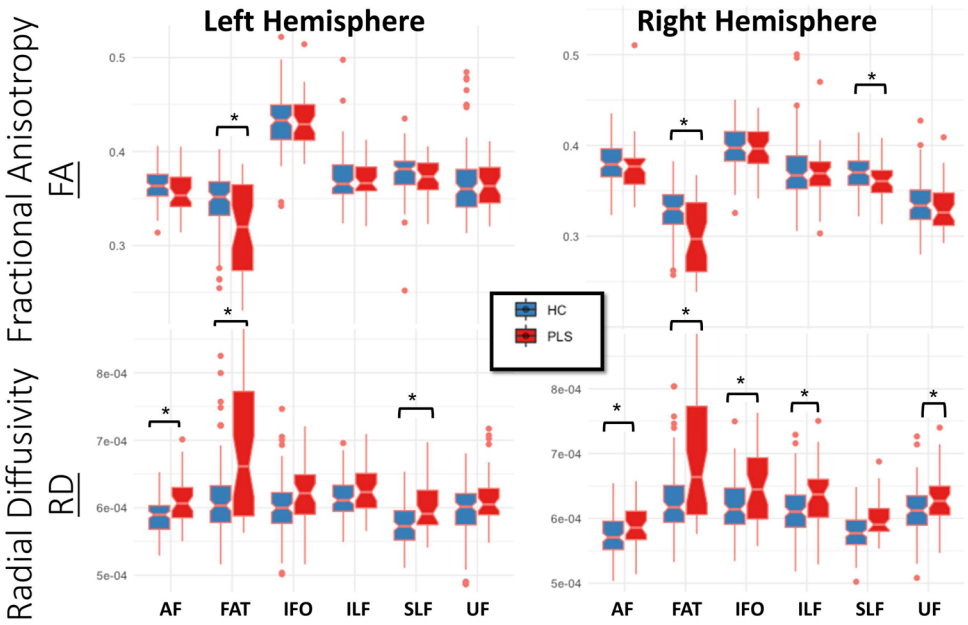

Fig. 3 Fractional anisotropy (FA) and radial diffusivity (RD) differences between patients with PLS (PLS) and healthy controls (HC) in the arcuate fascicle (AF), frontal aslant tract (FAT), inferior occipito-frontal fascicle (IFO), inferior longitudinal fascicle (ILF), superior longitudinal fascicle (SLF) and uncinate fascicle (UF) *Statistically significant group differences

Functional connectivity

Functional connectivity (FC) differences in language-associated circuits between PLS and HC were explored using ANOVA, correcting for age, sex, handedness and years of education. Differences in partial correlations of BOLD time courses were evaluated between two ROI pairs in each hemisphere: (1) between Broca's and Wernicke's areas and their equivalents in the right hemisphere, and (2) between supplementary motor area/lateral superior frontal gyrus and the inferior frontal gyrus, i.e. along the frontal aslant tract. Please note that the confounding effects of WM and CSF time courses were regressed out. To correct for multiple comparisons investigating the two circuits, the alpha level was adjusted to $p < 0.05/2 = 0.025$. The outcomes of the comparisons are illustrated in Fig. 4, and statistical details are provided in Table 2. Reduced functional connectivity was detected along the frontal aslant tract in patients with PLS both in the left [$F(1, 134) = 8.27$, $p = 0.005$] and right [$F(1, 134) = 6.22$, $p = 0.014$] hemispheres. Functional connectivity between Broca's and Wernicke's areas was not reduced in the left [$F(1, 134) = 0.07$, $p = 0.789$] or right hemispheres [$F(1, 134) = 1.72$, $p = 0.192$]. These findings demonstrate functional disconnection between the supplementary motor region and the inferior frontal gyrus along the aslant tract in both hemispheres.

Discussion

Our data indicate that brain regions mediating a variety of language functions under physiological circumstances are heavily affected in PLS. We detected not only cortical thickness reductions in both Wernicke's and Broca's areas but also structural connectivity changes in the frontal aslant tract, arcuate and superior longitudinal fascicles of the left hemisphere. Furthermore, decreased functional connectivity was identified between the supplementary motor region and the inferior frontal gyrus.

Our study benefits from a multimodal, structural, functional approach and our findings based on raw DWI and rs-fMRI data are consistent. For example, we detect FA reductions and increased RD in the frontal aslant tract (Fig. 3) suggestive of impaired structural connectivity and we also detect decreased functional connectivity between the supplementary motor region and the inferior frontal gyrus (Fig. 4) suggestive of impaired functional integrity along the aslant tract. The appraisal of multiple diffusivity metrics, instead of just assessing FA, is also beneficial, as radial diffusivity alterations capture the involvement of more tracts than by assessing FA alone (Fig. 3). The impact of sexual dimorphism and education on brain morphology is well recognised both in healthy individuals and ALS [73, 74]; therefore, sex and education have been incorporated in all of our statistical models. Interestingly, the majority of imaging changes are relatively symmetric and cortical thickness alterations, and structural and functional connectivity changes were also

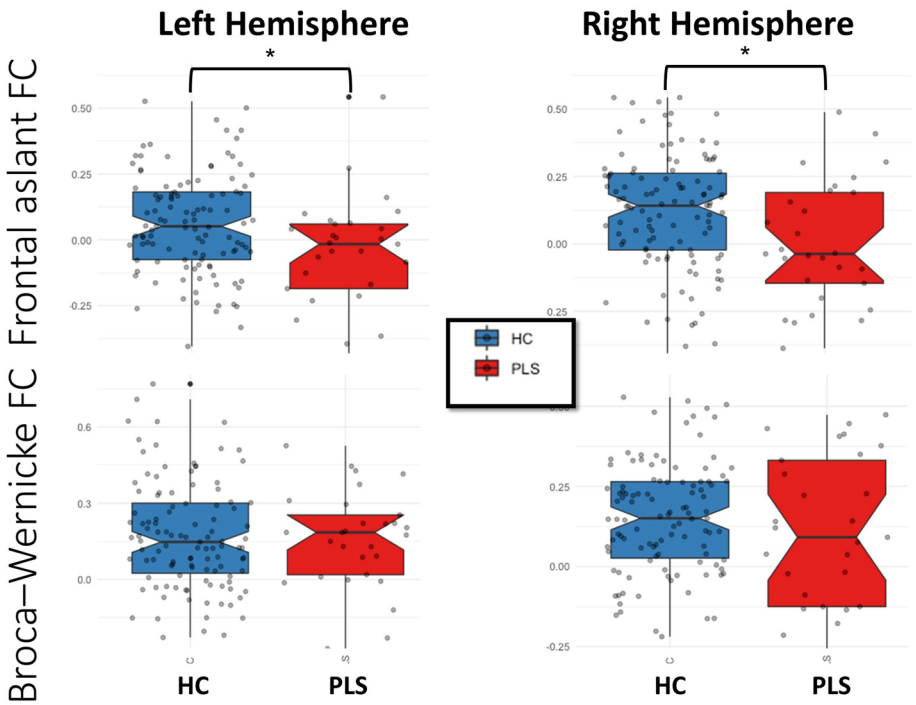

Fig. 4 Functional connectivity differences between patients with PLS and healthy controls (HC) *Statistically significant group differences

noted in the right hemisphere. Broca's area atrophy in MNDs have previously been associated with hexanucleotide expansions in *C9orf72* [75], and also noted in PLS [6]. In this study we demonstrate Broca's area atrophy in PLS patients who tested negative for *C9orf72* HREs and also identify Wernicke's area cortical thickness reductions. While PLS is not associated with frank semantic deficits clinically, the radiological changes underline the rationale for thorough neuropsychological testing beyond cursory screening for cognitive deficits. In view of that caveats of pursuing direct clinico-radiological correlations [76], we have intentionally only performed descriptive radiological analyses. Neuropsychological deficits in MNDs should not be linked to a single grey or white matter metric as these typically stem from the dysfunction of multi-synaptic networks [23] including cortical, subcortical and white matter components [77, 78].

While our data demonstrate widespread frontotemporal change and the involvement of long association fibres, the exact chronology of motor and extra-motor involvement is not entirely clear. The majority of participants have a relatively long symptom duration; therefore, it remains to be established if frontotemporal change in PLS is a late-stage secondary phenomenon or if it preceded motor cortex involvement. The post-mortem literature of PLS with regard to extra-motor involvement is relatively scarce. The few longitudinal imaging studies in PLS also primarily focus on motor connectome degeneration [17, 19, 79], but there is imaging evidence of relatively early and progressive frontotemporal involvement in PLS [11–13]. Interestingly, studies of "probable" PLS, i.e. cohorts with a symptom duration less than 4 years, do not typically capture frontotemporal change, but identify primary motor cortex changes, suggesting that motor cortex and corticospinal tract degeneration likely precedes frontotemporal disease burden expansion [80, 81].

There are a number of misconceptions around PLS, one of which is that it is a relatively benign clinical entity, which is only true in comparison to ALS [82]. While PLS carries a better prognosis than ALS [83, 84], it does exhibit a relentlessly progressive clinical and radiological progression. Another misconception around PLS is that it is a clinically homogeneous condition with stereotyped clinical symptoms and clinical trajectory. The findings of this study highlight that despite unifying clinical symptomatology (spasticity, gait impairment, pseudobulbar affect), patients with PLS may exhibit varying degree of cognitive or behavioural change and that PLS may be more heterogeneous clinically than previously thought. Disease heterogeneity in universally recognised in ALS and the prognostic and survival implications of cognitive change in ALS have been extensively studied [39]. In general, prognostic indicators and predictive markers have been extensively studied in ALS and much less so in PLS [85–88]. The recognition of clinical heterogeneity in ALS inspired cluster analyses of large data sets [89–91] to identify unique phenotypes with distinctive radiological, clinical and genetic profiles. Furthermore, given the relatively high incidence of cognitive change in ALS, sub-phenotypes have been defined based on the impairment in specific domains [33]. In PLS, terminology such as "PLS-plus" or "PLS-FTD" has been previously coined, but no uniformly utilised or defined based on psychometric measures. The appraisal of extra-motor involvement and detection of cognitive change is not merely an academic pursuit. The practical implications of cognitive change have been widely studied in ALS, and there is ample evidence that frontotemporal dysfunction impacts on compliance with assistive devices [92], adherences to therapies, may impact on caregiver burden and influence end-of-life decisions. It is also conceivable that marked frontotemporal change has ramifications for clinical trial participation. Clinical experience suggests that logopenic and agrammatic speech may be mistaken for apathy or depression and pseudobulbar affect mistaken for disinhibition [25]. Accordingly, raising awareness of language deficits may be useful for early screening for these manifestations, triggering expert assessments and interventions by speech pathologists or speech and language therapists.

From a radiological perspective, extra-motor disease burden in ALS is very well characterised [93–100], including presymptomatic extra-motor changes [1, 31, 101], and the identified anatomical patterns are often linked to the distribution of pathological TDP-43 [102, 103]. Radiological descriptions in ALS complement the wealth of neuropsychology studies, which typically detect executive dysfunction, language deficits, memory impairment, disinhibition, apathy and deficits in social cognition [34, 36, 39, 100, 104, 105]. Study designs in ALS are likely transferable to future PLS studies and there are obvious methodological lessons from existing ALS papers, such as the nuanced characterisation of cognitive change, assessment of longitudinal profiles and the study of the practical implications of frontotemporal dysfunction with regard to survival, decision making and adherence to MDT interventions.

ALS and PLS share a number of core clinical and radiological features, including corticospinal tract involvement, corpus callosum degeneration, brainstem and cerebellar atrophy [8, 106]. The reliable distinction of early-stage upper motor neuron predominant ALS from PLS on clinical grounds can be challenging, hence the minimum symptom duration criterion of subsequent diagnostic criteria for PLS. Given their overlapping radiological signatures [83], machine learning frameworks had difficulty reliably distinguishing ALS from PLS based on cerebral MRI data alone [107]. While individual subject classification into diagnostic, phenotypic or prognostic categories is a relatively new field of MND research, a multitude of statistical approaches have been successfully trialled to date [78, 108, 109]. From a

methodological perspective, imaging studies in PLS primarily rely on structural and diffusivity data [11, 18], sometimes rs-fMRI is incorporated [15, 16] in the protocols, but unlike in ALS, paradigm-based or motor imagery fMRI is seldom utilised [110, 111]. MR spectroscopy is also underutilised in PLS, despite its potential to reveal early metabolic changes, possibly preceding structural degeneration [112].

This study is not without limitations. Only cross-sectional analyses have been conducted; therefore, the longitudinal evolution of pathological change in language-associated areas cannot be inferred from these data; the chronology of motor and language involvement also remains to be established. Another shortcoming of this study is that no *post-mortem* data are available for the anatomical alignment of histopathology and imaging data which would be an important cross-validation step. Notwithstanding these limitations, our clinical and imaging data demonstrate that pathology in PLS is not confined to motor regions and that multiple language-associated brain regions are significantly affected. Unlike in ALS, where the impact of cognitive deficits has been widely studied, the practical ramifications of neuropsychological deficits in PLS remain to be evaluated, so that multidisciplinary care can be tailored to individual patient profiles. The traditional view of PLS as a relatively "benign", clinically homogeneous, "motor-system only" disease needs to be urgently challenged and frontotemporal disease-burden needs to be comprehensively characterised both in vivo and post-mortem.

Conclusions

PLS should no longer be regarded as pure UMN disorder with the exclusive involvement of the primary motor cortex and the descending corticospinal tracts. Our data add to the accruing clinical and neuroimaging evidence that PLS is a multi-system disorder with considerable frontotemporal, subcortical and cerebellar involvement.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-023-11994-7.

Acknowledgements The authors are most grateful for the participation of each patient and healthy control. We also thank all patients who expressed interest in this research study but were unable to participate due to medical or logistical reasons. We also express our gratitude to the caregivers and families of each patient for facilitating attendance at our neuroimaging centre. Without their generosity this study would have not been possible.

Author contributions The manuscript was drafted by ELT, MT, JL, KMC and PB. ELT, MT, KMC, EF and PB were involved in study conceptualisation. EF, OH and PB performed clinical assessments. ELT, MT, JL, KMC and PB contributed to MR data processing and analyses. RLMcL, MAD and JCH performed genetic analyses.

Funding This study was supported by the Spastic Paraplegia Foundation, Inc. (SPF). Professor Bede is also sponsored 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, The Hayes Family Charitable Fund and the Iris O'Brien Foundation. RLMcL, MAD and JCH are supported by the MND Association (898-792) and Science Foundation Ireland (17/CDA/4737).

Declarations

Conflicts of interest The authors have no financial or non-financial interests to disclose.

Ethics approval This study was approved by the Ethics (Medical Research) Committee—Beaumont Hospital, Dublin, Ireland (IRB).

References

1. Lulé DE, Müller HP, Finsel J, Weydt P, Knehr A, Winroth I, Andersen P, Weishaupt J, Uttner I, Kassubek J, Ludolph AC (2020) Deficits in verbal fluency in presymptomatic C9orf72 mutation gene carriers—a developmental disorder. J Neurol Neurosurg Psychiatry 91(11):1195–1200. https://doi.org/10.1136/jnnp-2020-323671
2. Trojsi F, Di Nardo F, Siciliano M, Caiazzo G, Femiano C, Passaniti C, Ricciardi D, Russo A, Bisecco A, Esposito S, Monsurrò MR, Cirillo M, Santangelo G, Esposito F, Tedeschi G (2020) Frontotemporal degeneration in amyotrophic lateral sclerosis (ALS): a longitudinal MRI one-year study. CNS Spectr. https://doi.org/10.1017/s109285292000005x
3. Trojsi F, Corbo D, Caiazzo G, Piccirillo G, Monsurro MR, Cirillo S, Esposito F, Tedeschi G (2013) Motor and extramotor neurodegeneration in amyotrophic lateral sclerosis: a 3T high angular resolution diffusion imaging (HARDI) study. Amyotroph Lateral Scler Frontotempor Degener 14(7–8):553–561. https://doi.org/10.3109/21678421.2013.785569
4. Christidi F, Karavasilis E, Rentzos M, Velonakis G, Zouvelou V, Xirou S, Argyropoulos G, Papatriantafyllou I, Pantolewn V, Ferentinos P, Kelekis N, Seimenis I, Evdokimidis I, Bede P (2020) Neuroimaging data indicate divergent mesial temporal lobe profiles in amyotrophic lateral sclerosis, Alzheimer's disease and healthy aging. Data Brief 28:104991. https://doi.org/10.1016/j.dib.2019.104991
5. de Vries BS, Rustemeijer LMM, van der Kooi AJ, Raaphorst J, Schröder CD, Nijboer TCW, Hendrikse J, Veldink JH, van den Berg LH, van Es MA (2017) A case series of PLS patients with frontotemporal dementia and overview of the literature. Amyotroph Lateral Scler Frontotempor Degener 18(7–8):534–548. https://doi.org/10.1080/21678421.2017.1354996
6. Finegan E, Shing SLH, Chipika RH, Chang KM, McKenna MC, Doherty MA, Hengeveld JC, Vajda A, Pender N, Donaghy C, Hutchinson S, McLaughlin RL, Hardiman O, Bede P (2021) Extra-motor cerebral changes and manifestations in primary lateral sclerosis. Brain Imaging Behav 15(5):2283–2296. https://doi.org/10.1007/s11682-020-00421-4
7. de Vries BS, Spreij LA, Rustemeijer LMM, Bakker LA, Veldink JH, van den Berg LH, Nijboer TCW, van Es MA (2019) A neuropsychological and behavioral study of PLS. Amyotroph Lateral Scler Frontotempor Degener 20(5–6):376–384. https://doi.org/10.1080/21678421.2019.1620284

8. Finegan E, Siah WF, Li Hi Shing S, Chipika RH, Hardiman O, Bede P (2022) Cerebellar degeneration in primary lateral sclerosis: an under-recognized facet of PLS. Amyotroph Lateral Scler Frontotempor Degener. https://doi.org/10.1080/21678421.2021.2023188
9. Finegan E, Li Hi Shing S, Chipika RH, Doherty MA, Hengeveld JC, Vajda A, Donaghy C, Pender N, McLaughlin RL, Hardiman O, Bede P (2019) Widespread subcortical grey matter degeneration in primary lateral sclerosis: a multimodal imaging study with genetic profiling. NeuroImage Clin 24:102089. https://doi.org/10.1016/j.nicl.2019.102089
10. Mackenzie IRA, Briemberg H (2020) TDP-43 pathology in primary lateral sclerosis. Amyotroph Lateral Scler Frontotempor Degener. https://doi.org/10.1080/21678421.2020.1790607
11. Pioro EP, Turner MR, Bede P (2020) Neuroimaging in primary lateral sclerosis. Amyotroph Lateral Scler Frontotempor Degener 21(sup1):18–27. https://doi.org/10.1080/21678421.2020.1837176
12. Tahedl M, Li Hi Shing S, Finegan E, Chipika RH, Lope J, Hardiman O, Bede P (2021) Propagation patterns in motor neuron diseases: Individual and phenotype-associated disease-burden trajectories across the UMN-LMN spectrum of MNDs. Neurobiol Aging 109:78–87. https://doi.org/10.1016/j.neurobiolaging.2021.04.031
13. Tahedl M, Li Hi Shing S, Finegan E, Chipika RH, Lope J, Murad A, Hardiman O, Bede P (2021) Imaging data reveal divergent longitudinal trajectories in PLS, ALS and poliomyelitis survivors: group-level and single-subject traits. Data Brief 39:107484. https://doi.org/10.1016/j.dib.2021.107484
14. Tahedl M, Tan EL, Siah WF, Hengeveld JC, Doherty MA, McLaughlin RL, Hardiman O, Finegan E, Bede P (2023) Radiological correlates of pseudobulbar affect: corticobulbar and cerebellar components in primary lateral sclerosis. J Neurol Sci 451:120726. https://doi.org/10.1016/j.jns.2023.120726
15. Agosta F, Canu E, Inuggi A, Chio A, Riva N, Silani V, Calvo A, Messina S, Falini A, Comi G, Filippi M (2014) Resting state functional connectivity alterations in primary lateral sclerosis. Neurobiol Aging 35(4):916–925
16. Agosta F, Canu E, Riva N, Galantucci S, Chiò A, Silani V, Iannaccone S, Calvo A, Comola M, Falini A, Comi G, Filippi M (2012) Sensorimotor functional connectivity alterations and their relationship with microstructural white matter integrity in primary lateral sclerosis. Dement Geriatr Cogn Disord 34:159
17. Tahedl M, Tan EL, Shing SLH, Chipika RH, Siah WF, Hengeveld JC, Doherty MA, McLaughlin RL, Hardiman O, Finegan E, Bede P (2023) Not a benign motor neuron disease: longitudinal imaging captures relentless motor connectome disintegration in primary lateral sclerosis. Eur J Neurol 30(5):1232–1245. https://doi.org/10.1111/ene.15725
18. Agosta F, Galantucci S, Riva N, Chio A, Messina S, Iannaccone S, Calvo A, Silani V, Copetti M, Falini A, Comi G, Filippi M (2014) Intrahemispheric and interhemispheric structural network abnormalities in PLS and ALS. Hum Brain Mapp 35(4):1710–1722. https://doi.org/10.1002/hbm.22286
19. Bede P, Chipika RH, Finegan E, Li Hi Shing S, Doherty MA, Hengeveld JC, Vajda A, Hutchinson S, Donaghy C, McLaughlin RL, Hardiman O (2019) Brainstem pathology in amyotrophic lateral sclerosis and primary lateral sclerosis: a longitudinal neuroimaging study. NeuroImage Clin 24:102054. https://doi.org/10.1016/j.nicl.2019.102054
20. Chipika RH, Christidi F, Finegan E, Li Hi Shing S, McKenna MC, Chang KM, Karavasilis E, Doherty MA, Hengeveld JC, Vajda A, Pender N, Hutchinson S, Donaghy C, McLaughlin RL, Hardiman O, Bede P (2020) Amygdala pathology in amyotrophic lateral sclerosis and primary lateral sclerosis. J Neurol Sci 417:117039. https://doi.org/10.1016/j.jns.2020.117039
21. Chipika RH, Finegan E, Li Hi Shing S, McKenna MC, Christidi F, Chang KM, Doherty MA, Hengeveld JC, Vajda A, Pender N, Hutchinson S, Donaghy C, McLaughlin RL, Hardiman O, Bede P (2020) "Switchboard" malfunction in motor neuron diseases: Selective pathology of thalamic nuclei in amyotrophic lateral sclerosis and primary lateral sclerosis. NeuroImage Clin 27:102300. https://doi.org/10.1016/j.nicl.2020.102300
22. Chipika RH, Siah WF, Shing SLH, Finegan E, McKenna MC, Christidi F, Chang KM, Karavasilis E, Vajda A, Hengeveld JC, Doherty MA, Donaghy C, Hutchinson S, McLaughlin RL, Hardiman O, Bede P (2020) MRI data confirm the selective involvement of thalamic and amygdalar nuclei in amyotrophic lateral sclerosis and primary lateral sclerosis. Data Brief. https://doi.org/10.1016/j.dib.2020.106246
23. Bonelli RM, Cummings JL (2007) Frontal-subcortical circuitry and behavior. Dialogues Clin Neurosci 9(2):141–151
24. Chipika RH, Mulkerrin G, Pradat PF, Murad A, Ango F, Raoul C, Bede P (2022) Cerebellar pathology in motor neuron disease: neuroplasticity and neurodegeneration. Neural Regen Res 17(11):2335–2341. https://doi.org/10.4103/1673-5374.336139
25. Finegan E, Chipika RH, Li Hi Shing S, Hardiman O, Bede P (2019) Pathological crying and laughing in motor neuron disease: pathobiology, screening, intervention. Front Neurol 10:260. https://doi.org/10.3389/fneur.2019.00260
26. Bede P, Finegan E (2018) Revisiting the pathoanatomy of pseudobulbar affect: mechanisms beyond corticobulbar dysfunction. Amyotroph Lateral Scler Frontotempor Degener 19(1–2):4–6. https://doi.org/10.1080/21678421.2017.1392578
27. Trojsi F, Di Nardo F, D'Alvano G, Caiazzo G, Passaniti C, Mangione A, Sharbafshaaer M, Russo A, Silvestro M, Siciliano M, Cirillo M, Tedeschi G, Esposito F (2023) Resting state fMRI analysis of pseudobulbar affect in amyotrophic lateral sclerosis (ALS): motor dysfunction of emotional expression. Brain Imaging Behav 17(1):77–89. https://doi.org/10.1007/s11682-022-00744-4
28. Christidi F, Karavasilis E, Ferentinos P, Xirou S, Velonakis G, Rentzos M, Zouvelou V, Zalonis I, Efstathopoulos E, Kelekis N, Evdokimidis I (2018) Investigating the neuroanatomical substrate of pathological laughing and crying in amyotrophic lateral sclerosis with multimodal neuroimaging techniques. Amyotroph Lateral Scler Frontotempor Degener 19(1–2):12–20. https://doi.org/10.1080/21678421.2017.1386689
29. Li Hi Shing S, McKenna MC, Siah WF, Chipika RH, Hardiman O, Bede P (2021) The imaging signature of C9orf72 hexanucleotide repeat expansions: implications for clinical trials and therapy development. Brain Imaging Behav. https://doi.org/10.1007/s11682-020-00429-w
30. McKenna MC, Lope J, Tan EL, Bede P (2022) Pre-symptomatic radiological changes in frontotemporal dementia: propagation characteristics, predictive value and implications for clinical trials. Brain Imaging Behav. https://doi.org/10.1007/s11682-022-00711-z
31. Bede P, Lulé D, Müller HP, Tan EL, Dorst J, Ludolph AC, Kassubek J (2023) Presymptomatic grey matter alterations in ALS kindreds: a computational neuroimaging study of asymptomatic C9orf72 and SOD1 mutation carriers. J Neurol. https://doi.org/10.1007/s00415-023-11764-5
32. Trojsi F, Siciliano M, Femiano C, Santangelo G, Lunetta C, Calvo A, Moglia C, Marinou K, Ticozzi N, Ferro C, Scialò C, Sorarù G, Conte A, Falzone YM, Tortelli R, Russo M, Sansone VA, Chiò A, Mora G, Silani V, Volanti P, Caponnetto C, Querin G, Sabatelli M, Riva N, Logroscino G, Messina S, Fasano A, Monsurrò MR, Tedeschi G, Mandrioli J (2019) Comparative analysis of C9orf72 and sporadic disease in a large multicenter ALS population: the effect of male sex on survival of C9orf72

positive patients. Front Neurosci 13:485. https://doi.org/10.3389/fnins.2019.00485
33. Strong MJ, Abrahams S, Goldstein LH, Woolley S, McLaughlin P, Snowden J, Mioshi E, Roberts-South A, Benatar M, HortobaGyi T, Rosenfeld J, Silani V, Ince PG, Turner MR (2017) Amyotrophic lateral sclerosis—frontotemporal spectrum disorder (ALS-FTSD): revised diagnostic criteria. Amyotroph Lateral Scler Frontotempor Degener 18(3–4):153–174. https://doi.org/10.1080/21678421.2016.1267768
34. Elamin M, Pinto-Grau M, Burke T, Bede P, Rooney J, O'Sullivan M, Lonergan K, Kirby E, Quinlan E, Breen N, Vajda A, Heverin M, Pender N, Hardiman O (2017) Identifying behavioural changes in ALS: validation of the Beaumont Behavioural Inventory (BBI). Amyotroph Lateral Scler Frontotempor Degener 18(1–2):68–73. https://doi.org/10.1080/21678421.2016.1248976
35. Abrahams S, Newton J, Niven E, Foley J, Bak TH (2014) Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotempor Degener 15(1–2):9–14. https://doi.org/10.3109/21678421.2013.805784
36. Radakovic R, Stephenson L, Colville S, Swingler R, Chandran S, Abrahams S (2016) Multidimensional apathy in ALS: validation of the Dimensional Apathy Scale. J Neurol Neurosurg Psychiatry 87(6):663–669. https://doi.org/10.1136/jnnp-2015-310772
37. Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S, Lynch C, Pender N, Hardiman O (2012) The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry 83(1):102–108
38. Elamin M, Bede P, Byrne S, Jordan N, Gallagher L, Wynne B, O'Brien C, Phukan J, Lynch C, Pender N, Hardiman O (2013) Cognitive changes predict functional decline in ALS: a population-based longitudinal study. Neurology 80(17):1590–1597. https://doi.org/10.1212/WNL.0b013e31828f18ac
39. Elamin M, Phukan J, Bede P, Jordan N, Byrne S, Pender N, Hardiman O (2011) Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. Neurology 76(14):1263–1269
40. Newsom-Davis IC, Abrahams S, Goldstein LH, Leigh PN (1999) The emotional lability questionnaire: a new measure of emotional lability in amyotrophic lateral sclerosis. J Neurol Sci 169(1–2):22–25
41. Turner MR, Barohn RJ, Corcia P, Fink JK, Harms MB, Kiernan MC, Ravits J, Silani V, Simmons Z, Statland J, van den Berg LH, Mitsumoto H (2020) Primary lateral sclerosis: consensus diagnostic criteria. J Neurol Neurosurg Psychiatry 91(4):373–377. https://doi.org/10.1136/jnnp-2019-322541
42. Abel O, Shatunov A, Jones AR, Andersen PM, Powell JF, Al-Chalabi A (2013) Development of a smartphone app for a genetics website: the Amyotrophic Lateral Sclerosis Online Genetics Database (ALSoD). JMIR Mhealth Uhealth 1(2):e18–e18. https://doi.org/10.2196/mhealth.2706
43. Klebe S, Stevanin G, Depienne C (2015) Clinical and genetic heterogeneity in hereditary spastic paraplegias: from SPG1 to SPG72 and still counting. Revue Neurol 171(6–7):505–530. https://doi.org/10.1016/j.neurol.2015.02.017
44. Byrne S, Elamin M, Bede P, Shatunov A, Walsh C, Corr B, Heverin M, Jordan N, Kenna K, Lynch C, McLaughlin RL, Iyer PM, O'Brien C, Phukan J, Wynne B, Bokde AL, Bradley DG, Pender N, Al-Chalabi A, Hardiman O (2012) Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a C9orf72 repeat expansion: a population-based cohort study. Lancet Neurol 11(3):232–240. https://doi.org/10.1016/S1474-4422(12)70014-5
45. Fischl B (2012) FreeSurfer. Neuroimage 62(2):774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021
46. Fischl B, Sereno MI, Dale AM (1999) Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 9(2):195–207. https://doi.org/10.1006/nimg.1998.0396
47. Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9(2):179–194. https://doi.org/10.1006/nimg.1998.0395
48. Dickie EW, Anticevic A, Smith DE, Coalson TS, Manogaran M, Calarco N, Viviano JD, Glasser MF, Van Essen DC, Voineskos AN (2019) Ciftify: a framework for surface-based analysis of legacy MR acquisitions. Neuroimage 197:818–826. https://doi.org/10.1016/j.neuroimage.2019.04.078
49. Marcus DS, Harms MP, Snyder AZ, Jenkinson M, Wilson JA, Glasser MF, Barch DM, Archie KA, Burgess GC, Ramaratnam M, Hodge M, Horton W, Herrick R, Olsen T, McKay M, House M, Hileman M, Reid E, Harwell J, Coalson T, Schindler J, Elam JS, Curtiss SW, Van Essen DC (2013) Human Connectome Project informatics: quality control, database services, and data visualization. Neuroimage 80:202–219. https://doi.org/10.1016/j.neuroimage.2013.05.077
50. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM (2012) FSL. Neuroimage 62(2):782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015
51. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31(3):968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021
52. Binder JR (2015) The Wernicke area: modern evidence and a reinterpretation. Neurology 85(24):2170–2175. https://doi.org/10.1212/wnl.0000000000002219
53. Szaflarski JP, Binder JR, Possing ET, McKiernan KA, Ward BD, Hammeke TA (2002) Language lateralization in left-handed and ambidextrous people: fMRI data. Neurology 59(2):238–244. https://doi.org/10.1212/wnl.59.2.238
54. Buchsbaum BR, Baldo J, Okada K, Berman KF, Dronkers N, D'Esposito M, Hickok G (2011) Conduction aphasia, sensory-motor integration, and phonological short-term memory - an aggregate analysis of lesion and fMRI data. Brain Lang 119(3):119–128. https://doi.org/10.1016/j.bandl.2010.12.001
55. Tournier JD, Smith R, Raffelt D, Tabbara R, Dhollander T, Pietsch M, Christiaens D, Jeurissen B, Yeh C-H, Connelly A (2019) MRtrix3: a fast, flexible and open software framework for medical image processing and visualisation. Neuroimage 202:116137. https://doi.org/10.1016/j.neuroimage.2019.116137
56. Veraart J, Fieremans E, Novikov DS (2016) Diffusion MRI noise mapping using random matrix theory. Magn Reson Med 76(5):1582–1593. https://doi.org/10.1002/mrm.26059
57. Kellner E, Dhital B, Kiselev VG, Reisert M (2016) Gibbs-ringing artifact removal based on local subvoxel-shifts. Magn Reason Med 76(5):1574–1581. https://doi.org/10.1002/mrm.26054
58. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23(Suppl 1):S208-219. https://doi.org/10.1016/j.neuroimage.2004.07.051
59. Tustison NJ, Avants BB, Cook PA, Zheng Y, Egan A, Yushkevich PA, Gee JC (2010) N4ITK: improved N3 bias correction. IEEE Trans Med Imaging 29(6):1310–1320. https://doi.org/10.1109/tmi.2010.2046908
60. Friederici AD (2015) White-matter pathways for speech and language processing. Handb Clin Neurol 129:177–186. https://doi.org/10.1016/b978-0-444-62630-1.00010-x
61. Middlebrooks EH, Yagmurlu K, Szaflarski JP, Rahman M, Bozkurt B (2017) A contemporary framework of language

processing in the human brain in the context of preoperative and intraoperative language mapping. Neuroradiology 59(1):69–87. https://doi.org/10.1007/s00234-016-1772-0
62. La Corte E, Eldahaby D, Greco E, Aquino D, Bertolini G, Levi V, Ottenhausen M, Demichelis G, Romito LM, Acerbi F, Broggi M, Schiariti MP, Ferroli P, Bruzzone MG, Serrao G (2021) The frontal aslant tract: a systematic review for neurosurgical applications. Front Neurol 12:641586. https://doi.org/10.3389/fneur.2021.641586
63. Wasserthal J, Neher P, Maier-Hein KH (2018) TractSeg—fast and accurate white matter tract segmentation. Neuroimage 183(June):239–253. https://doi.org/10.1016/j.neuroimage.2018.07.070
64. Tournier JD, Calamante F, Connelly A (2007) Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. Neuroimage 35(4):1459–1472. https://doi.org/10.1016/j.neuroimage.2007.02.016
65. Tournier JD, Yeh CH, Calamante F, Cho KH, Connelly A, Lin CP (2008) Resolving crossing fibres using constrained spherical deconvolution: validation using diffusion-weighted imaging phantom data. Neuroimage 42(2):617–625. https://doi.org/10.1016/j.neuroimage.2008.05.002
66. Farquharson S, Tournier JD, Calamante F, Fabinyi G, Schneider-Kolsky M, Jackson GD, Connelly A (2013) White matter fiber tractography: why we need to move beyond DTI. J Neurosurg 118(June):1367–1377
67. Raffelt D, Dhollander T, Tournier JD, Tabbara R, Smith R, Pierre E, Connelly A (2017) Bias field correction and intensity normalisation for quantitative analysis of apparent fibre density. Proc ISMRM 26:3541
68. Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, Ugurbil K, Andersson J, Beckmann CF, Jenkinson M, Smith SM, Van Essen DC (2016) A multi-modal parcellation of human cerebral cortex. Nature 536(7615):171–178. https://doi.org/10.1038/nature18933
69. Calamante F, Tournier JD, Jackson GD, Connelly A (2010) Track-density imaging (TDI): super-resolution white matter imaging using whole-brain track-density mapping. Neuroimage 53(4):1233–1243. https://doi.org/10.1016/j.neuroimage.2010.07.024
70. Pruim RHR, Mennes M, van Rooij D, Llera A, Buitelaar JK, Beckmann CF (2015) ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 112:267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064
71. Oosterhof NN, Connolly AC, Haxby JV (2016) CoSMoMVPA: multi-modal multivariate pattern analysis of neuroimaging data in Matlab/GNU Octave. Front Neuroinform 10:27. https://doi.org/10.3389/fninf.2016.00027
72. Oostenveld R, Fries P, Maris E, Schoffelen JM (2011) FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011:156869. https://doi.org/10.1155/2011/156869
73. Trojsi F, Di Nardo F, Caiazzo G, Siciliano M, D'Alvano G, Passaniti C, Russo A, Bonavita S, Cirillo M, Esposito F, Tedeschi G (2021) Between-sex variability of resting state functional brain networks in amyotrophic lateral sclerosis (ALS). J Neural Transm (Vienna) 128(12):1881–1897. https://doi.org/10.1007/s00702-021-02413-0
74. Bede P, Elamin M, Byrne S, Hardiman O (2014) Sexual dimorphism in ALS: exploring gender-specific neuroimaging signatures. Amyotroph Lateral Scler Frontotempor Degener 15(3–4):235–243. https://doi.org/10.3109/21678421.2013.865749
75. Bede P, Bokde AL, Byrne S, Elamin M, McLaughlin RL, Kenna K, Fagan AJ, Pender N, Bradley DG, Hardiman O (2013) Multiparametric MRI study of ALS stratified for the C9orf72 genotype. Neurology 81(4):361–369. https://doi.org/10.1212/WNL.0b013e31829c5eee
76. Verstraete E, Turner MR, Grosskreutz J, Filippi M, Benatar M (2015) Mind the gap: the mismatch between clinical and imaging metrics in ALS. Amyotroph Lateral Scler Frontotempor Degener 16(7–8):524–529. https://doi.org/10.3109/21678421.2015.1051989
77. McKenna MC, Corcia P, Couratier P, Siah WF, Pradat PF, Bede P (2021) Frontotemporal pathology in motor neuron disease phenotypes: insights from neuroimaging. Front Neurol 12:723450. https://doi.org/10.3389/fneur.2021.723450
78. McKenna MC, Murad A, Huynh W, Lope J, Bede P (2022) The changing landscape of neuroimaging in frontotemporal lobar degeneration: from group-level observations to single-subject data interpretation. Expert Rev Neurother 22(3):179–207. https://doi.org/10.1080/14737175.2022.2048648
79. Bede P, Pradat PF, Lope J, Vourc'h P, Blasco H, Corcia P (2022) Primary lateral sclerosis: clinical, radiological and molecular features. Revue Neurol 178(3):196–205. https://doi.org/10.1016/j.neurol.2021.04.008
80. Finegan E, Li Hi Shing S, Siah WF, Chipika RH, Chang KM, McKenna MC, Doherty MA, Hengeveld JC, Vajda A, Donaghy C, Hutchinson S, McLaughlin RL, Hardiman O, Bede P (2020) Evolving diagnostic criteria in primary lateral sclerosis: the clinical and radiological basis of "probable PLS." J Neurol Sci 417:117052. https://doi.org/10.1016/j.jns.2020.117052
81. Finegan E, Siah WF, Shing SLH, Chipika RH, Chang KM, McKenna MC, Doherty MA, Hengeveld JC, Vajda A, Donaghy C, Hutchinson S, McLaughlin RL, Hardiman O, Bede P (2020) Imaging and clinical data indicate considerable disease burden in 'probable' PLS: patients with UMN symptoms for 2–4 years. Data Brief. https://doi.org/10.1016/j.dib.2020.106247
82. Bede P, Siah WF (2021) The diagnostic challenge of primary lateral sclerosis: the integration of clinical, genetic and radiological cues. Eur J Neurol. https://doi.org/10.1111/ene.15049
83. Finegan E, Chipika RH, Shing SLH, Hardiman O, Bede P (2019) Primary lateral sclerosis: a distinct entity or part of the ALS spectrum? Amyotroph Lateral Scler Frontotempor Degener 20(3–4):133–145. https://doi.org/10.1080/21678421.2018.1550518
84. Finegan E, Chipika RH, Li Hi Shing S, Doherty MA, Hengeveld JC, Vajda A, Donaghy C, McLaughlin RL, Pender N, Hardiman O, Bede P (2019) The clinical and radiological profile of primary lateral sclerosis: a population-based study. J Neurol 266(11):2718–2733. https://doi.org/10.1007/s00415-019-09473-z
85. Elamin M, Bede P, Montuschi A, Pender N, Chio A, Hardiman O (2015) Predicting prognosis in amyotrophic lateral sclerosis: a simple algorithm. J Neurol 262(6):1447–1454. https://doi.org/10.1007/s00415-015-7731-6
86. Schuster C, Hardiman O, Bede P (2017) Survival prediction in amyotrophic lateral sclerosis based on MRI measures and clinical characteristics. BMC Neurol 17(1):73. https://doi.org/10.1186/s12883-017-0854-x
87. Grollemund V, Chat GL, Secchi-Buhour MS, Delbot F, Pradat-Peyre JF, Bede P, Pradat PF (2020) Development and validation of a 1-year survival prognosis estimation model for amyotrophic lateral sclerosis using manifold learning algorithm UMAP. Sci Rep 10(1):13378. https://doi.org/10.1038/s41598-020-70125-8
88. Westeneng HJ, Debray TPA, Visser AE, van Eijk RPA, Rooney JPK, Calvo A, Martin S, McDermott CJ, Thompson AG, Pinto S, Kobeleva X, Rosenbohm A, Stubendorff B, Sommer H, Middelkoop BM, Dekker AM, van Vugt J, van Rheenen W, Vajda A, Heverin M, Kazoka M, Hollinger H, Gromicho M, Körner S, Ringer TM, Rödiger A, Gunkel A, Shaw CE, Bredenoord AL, van Es MA, Corcia P, Couratier P, Weber M, Grosskreutz

J, Ludolph AC, Petri S, de Carvalho M, Van Damme P, Talbot K, Turner MR, Shaw PJ, Al-Chalabi A, Chiò A, Hardiman O, Moons KGM, Veldink JH, van den Berg LH (2018) Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. Lancet Neurol 17(5):423–433. https://doi.org/10.1016/s1474-4422(18)30089-9

89. Bede P, Murad A, Lope J, Hardiman O, Chang KM (2022) Clusters of anatomical disease-burden patterns in ALS: a data-driven approach confirms radiological subtypes. J Neurol. https://doi.org/10.1007/s00415-022-11081-3
90. Dukic S, McMackin R, Costello E, Metzger M, Buxo T, Fasano A, Chipika R, Pinto-Grau M, Schuster C, Hammond M, Heverin M, Coffey A, Broderick M, Iyer PM, Mohr K, Gavin B, McLaughlin R, Pender N, Bede P, Muthuraman M, van den Berg LH, Hardiman O, Nasseroleslami B (2022) Resting-state EEG reveals four subphenotypes of amyotrophic lateral sclerosis. Brain J Neurol 145(2):621–631. https://doi.org/10.1093/brain/awab322
91. Tan HHG, Westeneng HJ, Nitert AD, van Veenhuijzen K, Meier JM, van der Burgh HK, van Zandvoort MJE, van Es MA, Veldink JH, van den Berg LH (2022) MRI clustering reveals three ALS subtypes with unique neurodegeneration patterns. Ann Neurol. https://doi.org/10.1002/ana.26488
92. Olney RK, Murphy J, Forshew D, Garwood E, Miller BL, Langmore S, Kohn MA, Lomen-Hoerth C (2005) The effects of executive and behavioral dysfunction on the course of ALS. Neurology 65(11):1774–1777. https://doi.org/10.1212/01.wnl.0000188759.87240.8b
93. Bede P, Chipika RH, Tan EL (2023) Imaging extra-motor dysfunction in motor neuron disease: achievements and controversies. Amyotroph Lateral Scler Frontotempor Degener. https://doi.org/10.1080/21678421.2023.2232406
94. Bede P, Iyer PM, Schuster C, Elamin M, McLaughlin RL, Kenna K, Hardiman O (2016) The selective anatomical vulnerability of ALS: 'disease-defining' and 'disease-defying' brain regions. Amyotroph Lateral Scler Frontotempor Degener 17(7–8):561–570. https://doi.org/10.3109/21678421.2016.1173702
95. Lule D, Diekmann V, Muller HP, Kassubek J, Ludolph AC, Birbaumer N (2010) Neuroimaging of multimodal sensory stimulation in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 81(8):899–906. https://doi.org/10.1136/jnnp.2009.192260
96. Trojsi F, Di Nardo F, Santangelo G, Siciliano M, Femiano C, Passaniti C, Caiazzo G, Fratello M, Cirillo M, Monsurrò MR, Esposito F, Tedeschi G (2017) Resting state fMRI correlates of theory of mind impairment in amyotrophic lateral sclerosis. Cortex 97:1–16. https://doi.org/10.1016/j.cortex.2017.09.016
97. Trojsi F, Di Nardo F, Caiazzo G, Siciliano M, D'Alvano G, Ferrantino T, Passaniti C, Ricciardi D, Esposito S, Lavorgna L, Russo A, Bonavita S, Cirillo M, Santangelo G, Esposito F, Tedeschi G (2020) Hippocampal connectivity in amyotrophic lateral sclerosis (ALS): more than Papez circuit impairment. Brain Imaging Behav. https://doi.org/10.1007/s11682-020-00408-1
98. Christidi F, Argyropoulos GD, Karavasilis E, Velonakis G, Zouvelou V, Kourtesis P, Pantoleon V, Tan EL, Daponte A, Aristeidou S, Xirou S, Ferentinos P, Evdokimidis I, Rentzos M, Seimenis I, Bede P (2023) Hippocampal metabolic alterations in amyotrophic lateral sclerosis: a magnetic resonance spectroscopy study. Life (Basel, Switzerland). https://doi.org/10.3390/life13020571
99. Christidi F, Karavasilis E, Rentzos M, Velonakis G, Zouvelou V, Xirou S, Argyropoulos G, Papatriantafyllou I, Pantolewn V, Ferentinos P, Kelekis N, Seimenis I, Evdokimidis I, Bede P (2019) Hippocampal pathology in amyotrophic lateral sclerosis: selective vulnerability of subfields and their associated projections. Neurobiol Aging 84:178–188. https://doi.org/10.1016/j.neurobiolaging.2019.07.019
100. Christidi F, Karavasilis E, Rentzos M, Kelekis N, Evdokimidis I, Bede P (2018) Clinical and radiological markers of extra-motor deficits in amyotrophic lateral sclerosis. Front Neurol 9:1005. https://doi.org/10.3389/fneur.2018.01005
101. Chipika RH, Siah WF, McKenna MC, Li Hi Shing S, Hardiman O, Bede P (2021) The presymptomatic phase of amyotrophic lateral sclerosis: are we merely scratching the surface? J Neurol 268(12):4607–4629. https://doi.org/10.1007/s00415-020-10289-5
102. Kassubek J, Muller HP, Del Tredici K, Brettschneider J, Pinkhardt EH, Lule D, Bohm S, Braak H, Ludolph AC (2014) Diffusion tensor imaging analysis of sequential spreading of disease in amyotrophic lateral sclerosis confirms patterns of TDP-43 pathology. Brain J Neurol 137(Pt 6):1733–1740. https://doi.org/10.1093/brain/awu090
103. Müller HP, Del Tredici K, Lulé D, Müller K, Weishaupt JH, Ludolph AC, Kassubek J (2020) In vivo histopathological staging in C9orf72-associated ALS: a tract of interest DTI study. NeuroImage Clin 27:102298. https://doi.org/10.1016/j.nicl.2020.102298
104. Burke T, Pinto-Grau M, Lonergan K, Elamin M, Bede P, Costello E, Hardiman O, Pender N (2016) Measurement of social cognition in amyotrophic lateral sclerosis: a population based study. PLoS ONE 11(8):e0160850. https://doi.org/10.1371/journal.pone.0160850
105. Burke T, Elamin M, Bede P, Pinto-Grau M, Lonergan K, Hardiman O, Pender N (2016) Discordant performance on the 'reading the mind in the eyes' test, based on disease onset in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotempor Degener 17(7–8):467–472. https://doi.org/10.1080/21678421.2016.1177088
106. Bede P, Chipika RH, Christidi F, Hengeveld JC, Karavasilis E, Argyropoulos GD, Lope J, Li Hi Shing S, Velonakis G, Dupuis L, Doherty MA, Vajda A, McLaughlin RL, Hardiman O (2021) Genotype-associated cerebellar profiles in ALS: focal cerebellar pathology and cerebro-cerebellar connectivity alterations. J Neurol Neurosurg Psychiatry 92(11):1197–1205. https://doi.org/10.1136/jnnp-2021-326854
107. Bede P, Murad A, Lope J, Li Hi Shing S, Finegan E, Chipika RH, Hardiman O, Chang KM (2021) Phenotypic categorisation of individual subjects with motor neuron disease based on radiological disease burden patterns: a machine-learning approach. J Neurol Sci 432:120079. https://doi.org/10.1016/j.jns.2021.120079
108. Tahedl M, Chipika RH, Lope J, Li Hi Shing S, Hardiman O, Bede P (2021) Cortical progression patterns in individual ALS patients across multiple timepoints: a mosaic-based approach for clinical use. J Neurol 268(5):1913–1926. https://doi.org/10.1007/s00415-020-10368-7
109. McKenna MC, Tahedl M, Lope J, Chipika RH, Li Hi Shing S, Doherty MA, Hengeveld JC, Vajda A, McLaughlin RL, Hardiman O, Hutchinson S, Bede P (2021) Mapping cortical disease-burden at individual-level in frontotemporal dementia: implications for clinical care and pharmacological trials. Brain Imaging Behav. https://doi.org/10.1007/s11682-021-00523-7
110. Abidi M, Pradat PF, Termoz N, Couillandre A, Bede P, de Marco G (2022) Motor imagery in amyotrophic lateral Sclerosis: An fMRI study of postural control. NeuroImage Clinical 35:103051. https://doi.org/10.1016/j.nicl.2022.103051
111. Abidi M, de Marco G, Grami F, Termoz N, Couillandre A, Querin G, Bede P, Pradat PF (2021) Neural correlates of motor imagery of gait in amyotrophic lateral sclerosis. J Magn Reson Imaging 53(1):223–233. https://doi.org/10.1002/jmri.27335

112. Christidi F, Karavasilis E, Argyropoulos GD, Velonakis G, Zouvelou V, Murad A, Evdokimidis I, Rentzos M, Seimenis I, Bede P (2022) Neurometabolic alterations in motor neuron disease: insights from magnetic resonance spectroscopy. J Integr Neurosci 21(3):87. https://doi.org/10.31083/j.jin2103087