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ORIGINAL RESEARCH

Extra-motor cerebral changes and manifestations in primary lateral sclerosis

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Abstract

Primary lateral sclerosis (PLS) is classically considered a 'pure' upper motor neuron disorder. Motor cortex atrophy and pyramidal tract degeneration are thought to be pathognomonic of PLS, but extra-motor cerebral changes are poorly characterized. In a prospective neuroimaging study, forty PLS patients were systematically evaluated with a standardised imaging, genetic and clinical protocol. Patients were screened for ALS and HSP associated mutations, as well as *C9orf72* hexanucleotide repeats. Clinical assessment included composite reflex scores, spasticity scales, functional rating scales, and screening for cognitive and behavioural deficits. The neuroimaging protocol evaluated cortical atrophy patterns, subcortical grey matter changes and white matter alterations in whole-brain and region-of-interest analyses. PLS patients tested negative for known ALS- and HSP-associated mutations and *C9orf72* repeat expansions. Voxel-wise analyses revealed anterior cingulate, dorsolateral prefrontal, insular, opercular, orbitofrontal and bilateral mesial temporal grey matter changes and white matter alterations in the fornix, brainstem, temporal lobes, and cerebellum. Significant thalamus, caudate, hippocampus, putamen and accumbens nucleus volume reductions were also identified. Extra-motor clinical manifestations were dominated by verbal fluency deficits, language deficits, apathy and pseudobulbar affect. Our clinical and radiological evaluation confirms considerable extra-motor changes in a population-based cohort of PLS patients. Our data suggest that PLS should no longer be considered a neurodegenerative disorder selectively affecting the pyramidal system. PLS is associated with widespread extra-motor changes and manifestations which should be carefully considered in the multidisciplinary management of this low-incidence condition.

Keywords Primary lateral sclerosis · Cognition · Neuroimaging · Motor neuron disease · Frontotemporal degeneration

Glossary

ALS amyotrophic lateral sclerosis.
ALSFRS-r revised amyotrophic lateral sclerosis functional rating scale.
ANCOVA analysis of covariance.
ASS-m modified Ashworth spasticity scale score.
C9orf72 chromosome 9 open reading frame 72.
CNS-LS Center for neurological study-lability scale.
DTI Diffusion Tensor Imaging.
ECAS Edinburgh cognitive and behavioral screen.
ELQ emotional lability questionnaire.
EMM estimated marginal mean.
ELQ Emotional Lability Questionnaire.
FLAIR Fluid-attenuated inversion recovery.
FOV field of view.
FrSBe frontal systems behaviour scale.

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FWE familywise error.
GM grey matter.
HADS hospital anxiety and depression scale.
HC healthy control.
HSP hereditary spastic paraplegia.
IR-SPGR inversion recovery prepared spoiled gradient recalled echo.
IR-TSE inversion recovery turbo spin echo sequence.
LMN lower motor neuron.
Lt Left.
MND Motor neuron disease.
MNI152 Montreal Neurological Institute 152 standard space.
MRC Medical Research Council Scale for Muscle Strength.
PBA Pseudobulbar affect.
PCC Pathological crying and laughing.
PLS primary lateral sclerosis.
PUMNS Penn Upper Motor Neuron Score.
ROI region of interest.
Rt Right.
SD standard deviation.
SE-EPI spin-echo echo planar imaging.
SENSE Sensitivity Encoding.
SPIR spectral presaturation with inversion recovery.
T1W T1-weighted imaging.
TE Echo time.
TFCE threshold-free cluster enhancement.
TI Inversion time.
TIV total intracranial volume.
TR repetition time.
UMN Upper motor neuron.

Introduction

Primary lateral sclerosis (PLS) is a low-incidence motor neuron disease characterized by slowly progressive upper motor neuron (UMN) dysfunction (Statland et al. 2015). As clinical signs are dominated by striking upper motor neuron signs, and PLS has a much lower incidence than ALS, there is a prevailing notion that primarily lateral sclerosis solely affects the pyramidal system. The term 'PLS-plus' has been sporadically used to describe cases with extra-motor features (Gordon et al. 2006), but unlike in ALS (Burke, Elamin, et al. 2016; Elamin et al. 2013), no systematic studies have been performed to specifically characterize extra-motor disease burden in PLS. While extra-motor manifestations have been described in small case series, the prevalence and severity of these features are not well established. Despite the scarcity of neuropathological studies in PLS, extra-motor pathology has been intermittently described (Gazulla et al. 2019; Kobayashi et al., 2010). Sporadic reports of cognitive and behavioral impairment (Caselli et al. 1995; G. M. Grace et al. 2011; Le Forestier et al. 2001; Piquard et al. 2006) have been recently confirmed by larger case series (Agarwal et al. 2018; de Vries et al. 2019; de Vries et al. 2017). Motor cortex, corticospinal tract and corpus callosum degeneration have been consistently identified by computational imaging studies (Butman and Floeter 2007; Claassen et al. 2010; Finegan et al. 2019a; Muller et al. 2018; Pringle et al. 1992; van der Graaff et al. 2010), but reports of extra-motor involvement are surprisingly inconsistent (Chipika et al. 2020a). Perfusion abnormalities (Murphy et al. 2008), functional connectivity changes (Agosta et al. 2014) and diffusivity alterations (Canu et al. 2013) have been noted in PLS patients with cognitive impairment, but the majority of these studies suffer from sample size limitations. Brainstem (Bede et al. 2019), cerebellar (Finegan et al. 2019a; Tu et al. 2019), thalamic (Chipika et al. 2020b), and basal ganglia (Finegan et al. 2019b) degeneration have also been noted, but seldom linked to clinical manifestations (Floeter et al. 2014). The implications of cognitive and behavioral impairment are well established in other motor neuron diseases and associated with increased caregiver burden, limited compliance with assistive devices, increased fall risk, faster functional decline, shorter survival and a decreased likelihood of participation in clinical trials (Burke et al. 2017; Burke, Pinto-Grau, et al. 2016; Elamin et al. 2015; Elamin et al. 2011; Olney et al. 2005). As survival is much longer in PLS than in ALS (Finegan et al. 2019c), possible extra-motor manifestations are likely to have an enduring impact on multidisciplinary care, rehabilitation efforts, engagement with occupational and physiotherapy, ambulation safety and care preferences. The objective of this study is therefore the systematic evaluation of extra-motor disease burden in PLS using comprehensive cortical, subcortical and white matter analyses in a relatively large cohort of clinically and genetically well-characterized PLS patients. Based on the available literature, our hypothesis is that the multifaceted radiological analysis of quantitative imaging data reveals extra-motor changes in PLS.

Methods

Participants

Forty PLS patients were recruited from a population-based register, diagnosed based on the new consensus diagnostic criteria (Turner et al. 2020). MRI data from one hundred age-matched healthy controls were used for the interpretation of PLS imaging data. Healthy controls were unrelated to the participating PLS patients and had no established neurological or psychiatric diagnoses. The study was approved by the Ethics Committee of Beaumont Hospital, Dublin, Ireland and all participants provided informed consent prior to inclusion.

Clinical evaluation

Age, gender, education and handedness were recorded for each participant. Clinical data were collected at the time of MR imaging and included the total ALSFRS-r (Cedarbaum et al. 1999), ALSFRS sub-scores, symptom duration, Penn Upper Motor Neuron Score (PUMNS), modified Ashworth spasticity scale scores (Bohannon and Smith 1987), Edinburgh Cognitive and Behavioural ALS Screen (ECAS)(Abrahams et al. 2014), the Hospital Anxiety and Depression Scale (HADS) (Zigmond et al. 1983), the Frontal Systems Behavior Scale (J. Grace et al. 2002), the Emotional Lability Questionnaire (ELQ) and the Center for Neurological Study- Lability Scale (CNS-LS) (Moore et al. 1997; Newsom-Davis et al. 1999). The revised ALS functional rating scale (ALSFRS-r) provides a composite score of motor disability in four core domains; bulbar region, upper-limb/fine motor, lower-limb/gross motor and respiratory function (Cedarbaum et al. 1999). The Penn Upper Motor Neuron Score (PUMNS) appraises pathologically increased reflexes in the bulbar region and limbs (Bohannon and Smith 1987; Quinn et al. 2020). The Edinburgh Cognitive and Behavioural Screen (ECAS) evaluates cognitive performance across language, verbal fluency, executive, memory and visuospatial domains (Abrahams et al. 2014). It has been extensively validated in the Irish population and normative data are available (Pinto-Grau et al. 2017). The Frontal Systems Behavior Scale (FrSBe) questionnaire was completed by both 30 participating PLS patients and their caregivers. The FrSBe consists of 46 items across three subscales; apathy, disinhibition and executive dysfunction (Carvalho et al. 2013). Both 'before' and 'after' scores are awarded to identify disease-related behavioral change. Patients and family members were instructed to complete the questionnaire separately without conferring. Raw scores were converted to T-scores according to the published age, gender and education specific cut-offs. A T-score ≥ 65 on total score is indicative of behavioral impairment.

Magnetic resonance imaging

A 3D Inversion Recovery prepared Spoiled Gradient Recalled echo (IR-SPGR) pulse sequence was utilised to acquire T1-weighted images on a 3 Tesla Philips Achieva system with an 8-channel receive-only head coil. The following parameters were used for the IR-SPGR pulse sequence; TR/TE = 8.5/3.9 ms, TI =1060 ms, field-of-view (FOV): 256 × 256 × 160 mm, spatial resolution: 1 mm3, flip angle = 8°, SENSE factor = 1.5, acquisition time: 7 min 30 s. A spin-echo echo planar imaging (SE-EPI) sequence was used to acquire 32-direction DTI images; FOV = 245 × 245 × 150 mm, spatial resolution = 2.5 mm3, 60 slices were acquired with no interslice gap, TR/TE = 7639 / 59 ms, SENSE factor = 2.5, b-values = 0, 1100 s/mm^2. FLAIR images were also acquired for each participant to assess for vascular white matter lesion load and images were individually reviewed. FLAIR images were acquired in axial orientation using an Inversion Recovery Turbo Spin Echo (IR-TSE) sequence: FOV = 230 × 183 × 150 mm, spatial resolution = 0.65 × 0.87 × 4 mm, 30 slices with 1 mm gap, TR/TE = 11,000 / 125 ms, TI = 2800 ms, 120° refocusing pulse, with flow compensation and motion smoothing and a saturation slab covering the neck region. Imaging data were first explored in standard 'whole-brain' voxelwise analyses. Subsequently, region-of-interest (ROI) analyses were undertaken to assess a range of imaging metrics in clinically relevant anatomical regions.

Grey matter analyses

Voxel-based morphometry was carried out in FMRIB's FSL environment (Douaud et al. 2007; Good et al. 2001) using standard pre-processing steps; skull-removal, motion-corrections and tissue-type segmentation. Grey-matter partial volume data were aligned to the MNI152 standard space, a study-specific GM template was created to which the grey matter images from each subject were co-registered. To evaluate cortical grey matter changes in PLS compared to healthy controls, permutation based non-parametric inference was utilized using the threshold-free cluster enhancement (TFCE) method. The design matrix included study group membership and the following demeaned covariates; age, gender, years of education and total intracranial volumes.

White matter analyses

Pre-processing of raw diffusion data included eddy current corrections and skull removal (Schuster, Elamin, et al. 2016). Subsequently, a tensor model was fitted to the diffusion data to create maps of fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD). The tract-based statistics (TBSS) pipeline of the FSL image analysis suite was utilized for non-linear registration and skeletonization of diffusion images (Smith et al. 2006). FA, AD, MD and RD images were merged into a 4D file and a mean FA mask was created. Permutation-based non-parametric statistics was used to characterize the voxelwise diffusivity profile of PLS patients in contrast to healthy controls. Covariates included age, gender and years of education.

Subcortical great matter segmentation

The subcortical segmentation and registration tool FIRST of the FMRIB's Software Library was utilized to segment subcortical grey matter structures (Patenaude et al. 2011). Volumes of subcortical grey matter structures were estimated as described previously (Bede, Finegan, et al. 2018; Bede, Omer, et al. 2018). Total intracranial volume was included

as an additional covariate for the comparisons of subcortical grey matter volumes.

Region of interest analyses

The standard pipelines of the FreeSurfer image analysis suite (B. Fischl 2012) was used for cortical thickness measurements including the removal of non-brain tissue, segmentation of the subcortical white matter and deep grey matter structures, intensity normalization, tessellation of the grey matter-white matter boundary, and automated topology correction (Fischl and Dale 2000). The labels of the Desikan-Killiany atlas were utilized to retrieve average cortical thickness values (Schuster, Hardiman, et al. 2016). White matter integrity metrics were retrieved from skeletonized FA, AD, MD and RD maps using atlas-defined labels for the corpus callosum, corticospinal tracts, frontal lobe, cerebellum, forceps major, occipital lobe, parietal lobe, thalamus, temporal lobe and forceps minor (Schuster, Elamin, et al. 2016; Wakana et al. 2007). Values for bilateral structures were averaged.

Genetic testing

Twenty-eight of the 40 PLS patients underwent whole genome sequencing and were screened for ALS and HSP-associated mutations. Thirty-three PLS were screened for *C9orf72* GGGGCC repeat expansions using repeat-primed polymerase chain reaction.

Statistical analyses

Demographic variables for PLS and healthy control groups were compared with independent samples t-tests for continuous variables and Chi-square and Fisher's exact test for categorical variables. All assumptions were verified. Statistical analysis of clinical data was performed using IBM SPSS Statistics Version 26. Voxel-wise imaging data were analyzed using non-parametric permutation-based statistics with FMRIB's Randomise. Region-of-interest imaging statics were performed on raw data retrieved from individual scans. Regional cortical thickness, subcortical grey matter volumes and white matter metrics were interpreted using IBM SPSS v. 26. Assumptions of normality were examined using the Kolmogorov-Smirnov test. Skewness and kurtosis were assessed separately for each study group. Since all variables followed a normal distribution, parametric statistics were applied. Group differences in imaging metrics retrieved from ROIs were examined using multivariate analysis of covariance (MANCOVA) with age, gender and education as covariates.

Results

Clinical characteristics

The demographic of all participants and the clinical characteristics PLS patients are presented in Table 1. Thirty-nine of the 40 patients reported symptom onset in the lower limbs. Pathologically increased reflexes were identified in all body regions, but UMN burden was particularly high in the lower limbs with a mean UMN score of 9.8 (max = 14). Spasticity was also higher in the lower limbs than upper limbs with a mean ASS-m of 3.3 and 2.6 respectively. Pseudobulbar affect was identified in 17 patients (42%) based on established thresholds for CNS-LS and ELQ. Nine patients (22.5%) showed evidence of cognitive impairment based on the total ECAS score. Language (28%) and verbal fluency (22.5%) deficits were most common, followed by memory impairment (12.5%). Abnormal performance in executive (7.5%) and visuospatial domains (2.5%) were uncommon based on our screening assessment with ECAS. Self and family-reported behavioral change was evident in one third of patients. Self-reported and caregiver-reported behavioral changes were remarkably concordant across all subscales. Apathy was the most commonly identified behavioral change.

Cortical Grey matter profiles

Voxel-wise analyses revealed widespread multifocal extramotor atrophy including the bilateral anterior cingulate, dorsolateral prefrontal cortex, insula, operculum, orbitofrontal and anterior mesial temporal regions. (Fig. 1). Region-of-interest cortical thickness analyses also demonstrated cortical thinning in multiple frontotemporal regions. (Table 2a). Significant atrophy was identified in multiple frontal lobe regions including orbitofrontal, caudal middle frontal, cingulate and insular areas. Considerable fusiform gyrus, temporal pole, transverse temporal, and superior temporal changes were also identified. Within the parietal lobe, precuneus and supramarginal cortical thinning was observed.

Subcortical grey matter profiles

The volumetric comparisons of subcortical grey regions are shown in Table 2b. The thalamus was the most significantly affected subcortical grey matter structure, followed by the caudate and hippocampus. The putamen and accumbens were also affected, but no significant globus pallidus or amygdala atrophy was observed.

White matter profiles

Significant, symmetrical white matter alterations were identified in PLS group, primarily involving the corticospinal tracts

Table 1 The demographic and clinical profile of study participants

	PLS *n* = 40	HC *n* = 100	*p* value
Age- years (SD)	61.7 (9.7)	57.6 (11.9)	.06
Sex- Male n (%)	25 (63%)	52 (52%)	.174
Education-yrs.	12.3 (3.3)	14.3 (3.3)	.001
Duration-years (SD) [Range]	9.2 (5.7) [4–25.7]		
Region of Onset	Lower Limbs: 39 (98%)		
	Bulbar: 1 (2%)		
ALSFRS-R mean (SD)	35.4 (5.4)		
Bulbar	9.4 (2.1)		
Upper Limbs	9.1 (1.9)		
Lower Limbs	5.7 (1.6)		
Respiratory	11.2 (1.3)		
UMN Score Total mean (SD)	19.9(6.3)		
Bulbar Sub-score (max = 4)	1.7(1.4)		
Upper Limbs Sub-score (max = 14)	8.3(3.4)		
Lower Limbs Sub-score (max = 14)	9.8(2.5)		
Spasticity ASS-m mean (SD) max = 5			
Upper Limbs	2.6(0.7)		
Lower Limbs	3.3(1.6)		
MRC Upper limb max = 80	79.4 (1.9)		
Lower limb max = 60	59.6 (2.6)		
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%)		
Executive	3 (7.5%)		
Memory	5 (12.5)		
Visuospatial	1 (2.5%)		
FrSBe	**% Abnormal before/after**		
Total- self	10% / 37%		
Apathy-self	7% / 47%		
Disinhibition- self	7% / 20%		
Executive – self	10% / 27%		
Total- Family	10% / 33%		
Apathy- Family	7% / 43%		
Disinhibition- Family	13% / 28%		
Executive - Family	7% / 27%		
HADS Mean (SD)			
Total	8.1 (5.6)		
Anxiety	5.0 (4.1)		
Depression	3.2 (2.4)		
Pathological crying and laughing (PBA)			
CNS-LS	13.0 (7.2) abnormal: 39%		
ELQ-Laughing	5.6 (7.4) abnormal: 31%		
ELQ-Crying	4.0 (6.2) abnormal: 25%		

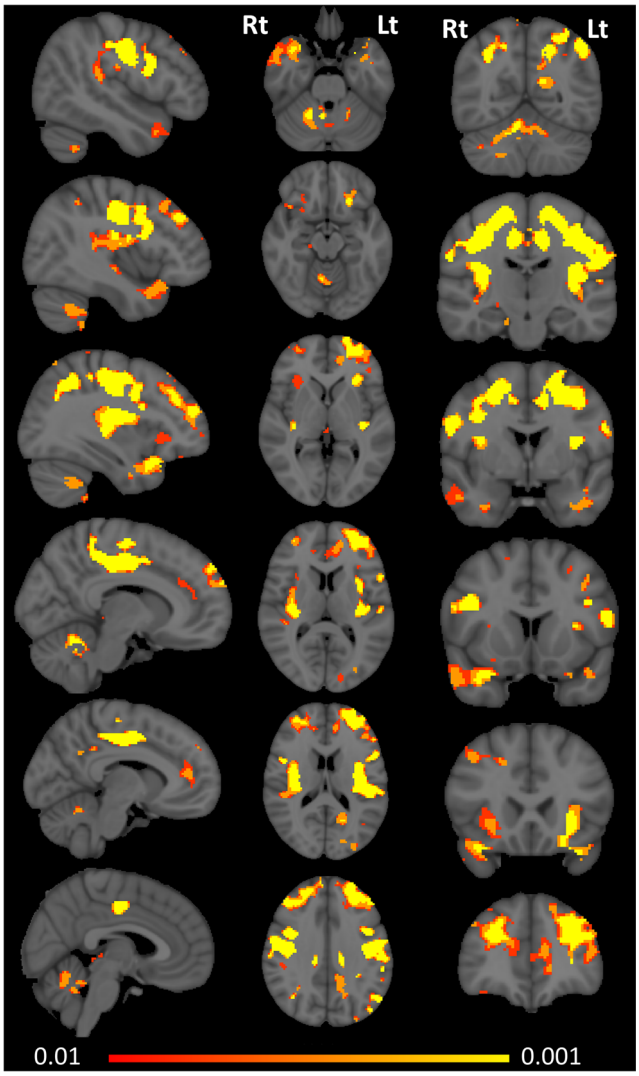

Fig. 1. Motor and extra-motor grey matter pathology in PLS at $p < 0.01$ FWE TFCE.

and the corpus callosum. Cerebellar, fornix, brainstem and temporal lobe alterations were also captured. Fig. 2. ROI analyses also demonstrated widespread diffusion abnormalities in the PLS group (Table 3). Across all diffusion metrics, the most significant changes were observed in the corticospinal tracts and in the body of the corpus callosum. Thalamic white matter involvement was also detected across all diffusivity measures. While no white matter region-of-interest was entirely preserved, parietal and occipital lobe involvement was relatively spared.

Discussion

The study confirms widespread extra-motor pathology in PLS which is consistent with the growing literature of cognitive and behavioral changes in this condition. Our imaging analyses provide evidence of widespread frontotemporal cortical changes, subcortical grey matter degeneration and extra-motor white matter pathology.

Our imaging data confirm the motor cortex (Butman and Floeter 2007; Finegan 2019a; Schuster et al. 2013), corpus callosum (Muller et al. 2012; van der Graaff et al. 2011) and corticospinal tract (Salameh et al. 2013; Suh et al. 2006; Tzarouchi et al. 2011) findings of previous imaging papers in PLS (Clark et al. 2018; Müller et al. 2018; Turner et al. 2007). However, the novelty of our study is the description of widespread, multifocal and symmetric frontotemporal degeneration is a cohort of established PLS patients. PLS is not classically regarded as part of the ALS-FTD spectrum, yet, our cohort of *C9orf72* negative PLS patients exhibit patterns of grey matter atrophy reminiscent of FTD (Bede, Omer, et al. 2018; Omer et al. 2017) involving insular, orbitofrontal, superior temporal regions as well as primary language regions; the pars opercularis and pars triangularis of the inferior frontal lobe. Considerable anterior and posterior cingulate pathology is also evident on both whole-brain morphometry and region-of-interest cortical thickness analyses. Despite the anatomical concordance of morphometric and ROI approaches, one of the benefits of the standard VBM method is its ability to highlight the strikingly symmetric patterns of grey matter degeneration at a given statistical threshold. (Fig. 1.) ALS studies often identify some degree of frontotemporal pathology (Christidi et al., 2019; Christidi et al. 2017; Omer et al. 2017), but they are remarkably inconsistent with regard to extra-motor pathology depending on the phenotypes and genotypes included (Bede, Querin et al. 2018; Christidi, Karavasilis, Rentzos, et al. 2018; Nasseroleslami et al. 2019). ALS is a relatively heterogeneous condition, especially with regard to frontotemporal pathology (Burke, Pinto-Grau, et al. 2016; Elamin et al. 2017). Our radiological and clinical findings suggest that heterogeneity in PLS may be much less prominent than previously suggested and patients exhibit relatively uniform frontotemporal changes (Zhai et al. 2003). The relative homogeneity of PLS patients is also evidenced by their invariably long survival, symmetric lower limb onset, limited respiratory involvement and fairly stereotypical disability profiles.

Our voxelwise and ROI white matter analyses not only confirm the pathognomonic degeneration of the pyramidal tracts, but capture extra-motor white matter changes across multiple diffusivity metrics. Tract-based spatial statistics readily capture the degeneration of the body of the corpus callosum, but the ROI analyses also demonstrate the forceps minor (anterior forceps) and forceps major (posterior forceps) are also significantly affected. The tract-based analysis of AD, MD and RD captured considerable fornix pathology which has not been previously reported in PLS. The fornix is a key output tract of the hippocampus and its degeneration has been linked to memory deficits in ALS (Christidi et al. 2019). The observation that both the hippocampus and its output bundle

Table 2 **(a)**: The cortical thickness profile (mm) of PLS patients and healthy controls (HC) **(b)** Subcortical grey matter volumes of PLS and HC groups(mm^3). Regions are ranked in order of statistical significance from the most affected region to the least affect region. Estimated marginal means (EMM) and standard error(SE) are adjusted for age (58.7), gender (1.45) and education. Subcortical grey matter volumes are additionally adjusted for total intracranial volume. Significant between group differences are presented in bold

(a) Cortical Region	Group EMM (SE)		p value	Rank
	PLS	HC		
Precentral	2.308 (.024)	2.540 (.015)	**.0000000000004**	1
Superior Frontal	2.509 (.023)	2.654 (.014)	**.0000005**	2
Paracentral	2.246 (.026)	2.402 (.016)	**.000002**	3
Medial Orbitofrontal	2.296 (.020)	2.410 (.012)	**.000003**	4
Posterior Cingulate	2.390 (.021)	2.506 (.013)	**.00001**	5
Caudal Middle Frontal	2.369 (.023)	2.489 (.015)	**.00003**	6
Lateral Orbitofrontal	2.527 (.022)	2.640 (.014)	**.00004**	7
Fusiform	2.619 (.020)	2.716 (.012)	**.00005**	8
Frontal Pole	2.504 (.031)	2.653 (.019)	**.0001**	9
Superior Temporal	2.688 (.025)	2.806 (.015)	**.0001**	10
Isthmus Cingulate	2.312 (.027)	2.440 (.017)	**.0001**	11
Insula	2.850 (.028)	2.980 (.017)	**.0001**	12
Rostral Middle Frontal	2.239 (.019)	2.324 (.012)	**.0003**	13
Rostral Anterior Cingulate	2.707 (.025)	2.812 (.016)	**.0006**	14
Inferior Temporal	2.664 (.023)	2.762 (.015)	**.0006**	15
Pars Orbitalis	2.545 (.029)	2.663 (.018)	**.001**	16
Temporal Pole	3.646 (.039)	3.792 (.024)	**.002**	17
Transverse Temporal	2.277 (.033)	2.400 (.020)	**.002**	18
Precuneus	2.288 (.020)	2.363 (.013)	**.003**	19
Pars Triangularis	2.360 (.022)	2.439 (.014)	**.003**	20
Pars Opercularis	2.471 (.024)	2.554 (.015)	**.005**	21
Supramarginal	2.434 (.021)	2.502 (.013)	**.007**	22
Caudal Anterior Cingulate	2.516 (.032)	2.610 (.020)	**.014**	23
Middle Temporal	2.765 (.025)	2.835 (.015)	**.022**	24
Banks Superior Temporal Sulcus	2.492 (.026)	2.555 (.016)	**.047**	25
Parahippocampal	2.709 (.042)	2.799 (.026)	.078	26
Inferior parietal	2.360 (.020)	2.401 (.013)	.091	27
Lingual	1.944 (.019)	1.981 (.012)	.094	28
Entorhinal	3.387 (.048)	3.450 (.030)	.273	29
Superior Parietal	2.117 (.022)	2.137 (.013)	.440	30
Peri-calcarine	1.594 (.021)	1.578 (.013)	.506	31
Cuneus	1.834 (.021)	1.849 (.013)	.539	32
Post-central	2.030 (,018)	2.023 (.011)	.773	33
Lateral Occipital	2.139 (.019)	2.138 (.012)	.965	34
(b)Subcortical Grey Matter				
Thalamus	6881 (81)	7440 (50)	**.00000006**	1
Caudate	3257 (55)	3483 (34)	**.0008**	2
Hippocampus	3568 (65)	3802 (40)	**.003**	3
Putamen	4482 (65)	4669 (40)	**.018**	4
Accumbens	398 (15)	440 (9)	**.021**	5
Globus Pallidus	1697 (34)	1775 (21)	.058	6
Amygdala	1134 (33)	1192 (21)	.154	7

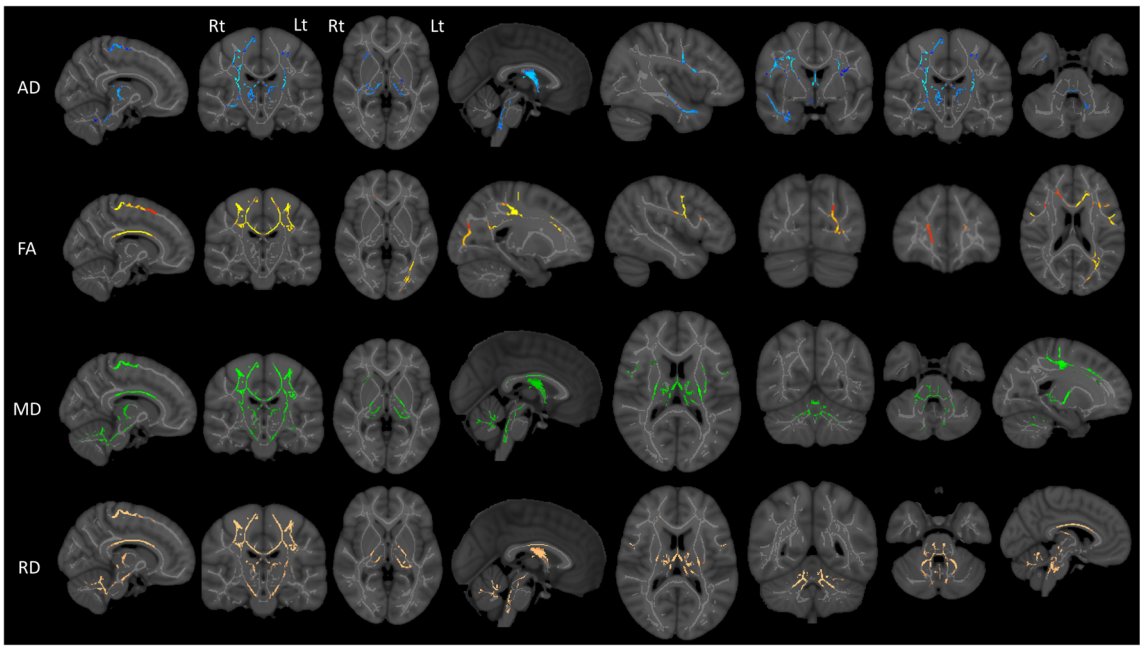

Fig. 2 Tract-based diffusivity alterations in PLS at $p < 0.0125$ FWE TFCE. Regions of reduced fractional anisotropy (FA), increased axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD) are presented

are affected illustrates the concomitant degeneration of interconnected brain regions (Bak and Chandran 2012). Tract-based spatial statistics also identified diffusivity changes within the thalamus, which is typically by either evaluated by volumetric (Finegan et al. 2020c) or vertex-wise (Finegan et al. 2019d) approaches relying on T1-wieghted raw data. In this study we found both thalamic diffusivity alterations – reduced FA, increased AD, MD, RD - as well as volume reductions on structural analyses. Both imaging and post mortem studies suggest that thalamic changes are driven by the focal degeneration of specific nuclei as opposed to global atrophy (Chipika et al. 2020b; Chipika et al. 2020c). One the benefits of combining whole-brain and ROI analyses is the ability to rank the most affected and least affected brain regions. Similarly to ALS (Bede et al. 2016), PLS also exhibits a strikingly selective pattern of frontotemporal vulnerability with the relative sparing of postcentral and lateral occipital brain regions. Despite the considerable symptom duration profile of this cohort, parietal and occipital white matter involvement is limited in this patient group. The white matter changes identified in the brainstem (Fig. 2.) are not surprising in light of the UMN burden and pseudobulbar manifestations observed in the cohort and are consistent with dedicated brainstem studies (Bede et al. 2020; Bede et al. 2019). Cerebellar grey matter atrophy has been previously described (Finegan et al. 2019a) based on imaging data, but it is seldom assessed specifically clinically. The clinical relevance of cerebellar pathology may be underestimated in PLS where a significant proportion of patients use walking aids for safe ambulation and may be at a relatively high risk of falls. Cerebellar pathology was also detected on tract-based and ROI white matter analyses. While the clinical detection of subtle cerebellar signs may be confounded by prominent pyramidal signs the target evaluation of cerebellar function may be judicious. Cerebellar degeneration has also been implicated in the aetiology of pseudobulbar affect through impaired gate-control mechanisms (Bede and Finegan 2018; Christidi, Karavasilis, Ferentinos, et al. 2018; Finegan et al. 2019b; Floeter et al. 2014).

While direct correlations between imaging metrics and neuropsychological performance are often considered contentious (Verstraete et al. 2015), the clinical profile of the patients shows remarkable concordance with our imaging findings. The considerable paracentral gyrus cortical thinning is in line with the lower limb predominant motor disability of our cohort as the medial segment of the motor cortex provides the somatotopic representation of the lower limbs in the motor homunculus. The language deficits observed on our screening tests are also concordant with the degenerative changes of the pars opercularis and pars triangularis. The high prevalence of apathy observed in our cohort may be anatomically linked to the considerable volume reductions identified in the accumbens nucleus, which, under physiological conditions, mediates motivation and contributes to reward processing (Ikemoto et al. 1999; Machts et al. 2015). Linking impairments in specific cognitive domains to single cortical or subcortical regions however is simplistic, as the majority of cognitive functions are mediated by multi-synaptic corticobasal networks (Bonelli and Cummings 2007; O'Callaghan et al. 2013). A high prevalence of language and verbal fluency deficits was identified while memory and visuospatial deficits were relatively uncommon. The identified verbal fluency

Table 3 Regional white matter metrics are presented as estimated marginal means (standard error). Regions are listed in rank order of statistical significance. Estimated marginal means (EMM) and standard error (SE) are adjusted for age (58.7), gender (1.45) and education. Significant between group differences are presented in bold

Region	PLS	HC	p value	Rank
Fractional Anisotropy				
Corpus Callosum (body)	.590 (.006)	.644 (.004)	**.0000000001**	1
Corticospinal Tract	.497 (.004)	.519 (.002)	**.000001**	2
Frontal Lobe	.375 (.003)	.393 (.002)	**.000008**	3
Cerebellum	.371 (.002)	.383 (.001)	**.00003**	4
Forceps Major	.712 (.004)	.729 (.003)	**.001**	5
Occipital Lobe	.358 (.003)	.371 (.002)	**.0009**	6
Parietal Lobe	.415 (.004)	.429 (.002)	**.001**	7
Thalamus	.322 (.002)	.331 (.002)	**.001**	8
Temporal Lobe	.357 (.003)	.366 (.002)	**.018**	9
Forceps Minor	.645 (.006)	.656 (.004)	.113	10
Axial Diffusivity				
Corticospinal Tract	.001156 (.000005)	.001123 (.000003)	**.0000002**	1
Thalamus	.001173 (.000015)	.001085 (.00001)	**.000005**	2
Cerebellum	.000961 (.000005)	.000941 (.000003)	**.001**	3
Occipital Lobe	.001021 (.000005)	.001034 (.000003)	**.025**	4
Forceps Minor	.001615 (.000014))	.001579 (.000009)	**.030**	5
Frontal Lobe	.001084 (.000006)	.00107 (.000003)	**.043**	6
Temporal Lobe	.001027 (.000005)	.001018 (.000003)	.093	7
Forceps Major	.001569 (.000011)	.001551 (.000007)	.177	8
Corpus Callosum (body)	.001568 (.0000103)	.0015629 (.000006)	.641	9
Parietal Lobe	.00112 (.000005)	.001119 (.000003)	1	10
Mean Diffusivity				
Corpus Callosum (body)	.000888 (.000009)	0.000834 (.000006)	**.00000000001**	1
Corticospinal Tract	.000719 (.000004)	.000684 (.000002)	**.000000002**	2
Cerebellum	.000673 (.000004)	.00065 (.000002)	**.000006**	3
Thalamus	.000885 (.000013)	.000807 (.000008)	**.000002**	4
Frontal Lobe	.000766 (.000006)	.000742 (.000003)	**.001**	5
Forceps Major	.000779 (.000007)	.000755 (.000004)	**.006**	6
Temporal Lobe	.000737 (.000004)	.000723 (.000003)	**.014**	7
Forceps Minor	.000861 (.000011)	.000833 (.000007)	**.027**	8
Parietal Lobe	.000754 (.000005)	.000744 (.000003)	.088	9
Occipital Lobe	.000729 (.000005)	.000728 (.000003)	.845	10
Radial Diffusivity				
Corticospinal Tract	.000501	.000465 (.000003)	**.0000000002**	1
Corpus Callosum (body)	.000548	.000469 (.000006)	**.000000002**	2
Cerebellum	.000529	.000505 (.000002)	**.0000001**	3
Thalamus	.000741	.000667 (.000008)	**.000002**	4
Frontal Lobe	.000607	.000578 (.000004)	**.00005**	5
Forceps Major	.000384	.000357 (.000004)	**.001**	6
Temporal Lobe	.000591	.000576 (.000003)	**.0079**	7
Parietal Lobe	.000572	.000556 (.000003)	**.021**	8
Forceps Minor	.000484	.00046 (.000006)	**.046**	9
Occipital Lobe	.000583	.000575 (.000003)	.174	10

deficits cannot be attributed to spastic dysarthria as the ECAS corrects for motor disability through the 'verbal fluency index'. Although the ECAS assessment can be undertaken in either spoken or written format, all patients in this cohort were able to complete it verbally. In our experience, anarthria is not a common clinical feature of PLS despite the presence of some degree of spastic dysarthria (Yunusova et al. 2019). Unlike in ALS, where executive dysfunction is the commonest cognitive

deficit (Christidi, Karavasilis, Rentzos, et al. 2018), impaired executive function was not readily identified on ECAS in our cohort of PLS patients. By contrast, patients and family consistently reported executive dysfunction on FrSBe.

While the neuropsychological profile of ALS has been extensively studied, disease-specific screening instruments have been developed, large longitudinal studies have been undertaken, cognitive profiles linked to specific genotypes and imaging changes, extra-motor changes in PLS remain woefully underrecognized and they are not routinely tested for. It is clear that the considerable apathy detected in a significant minority of our patients is likely to impact on the quality of life of the patients, their caregivers and affect the management of this cohort. The recognition of language deficits in PLS is also hugely relevant with regard to maintaining interpersonal communication and employment. We must acknowledge the limitations of the cognitive screening tests utilized in this cohort which does not substitute comprehensive neuropsychological testing. Furthermore, the prolonged mean symptom duration in this PLS group must be considered when interpreting the prevalence and pattern of extra-motor features in comparison with previous studies in ALS with much shorter symptom duration. We also concede that a multi-timepoint study design, enrolling from first presentation, would provide crucial longitudinal insights, in particular with respect to the chronology of motor and extra-motor involvement (Chipika et al. 2019). A recent natural history study of PLS revealed ceiling-effects; progressive UMN degeneration in the first 8 years followed by a plateau (Floeter and Wu 2020). A recent analysis of imaging data of patients with a symptom duration of less than 4 years suggests motor cortex pathology without detectable extra-motor atrophy (Finegan et al. 2020a; Finegan et al. 2020c), but large perspective studies are needed to verify if precentral gyrus changes truly precede extra-motor expansion. We also acknowledge that the comparison of a single patient group to healthy controls only permits the description of group-level changes as opposed to the precision categorization of individual MND patients (Bede et al. 2017; Grollemund et al. 2019; Querin et al. 2018; Verde et al. 2020). Despite these limitations, our data provide compelling evidence of considerable frontotemporal pathology in a population-based sample of *C9orf72* negative PLS patients.

Conclusions

Primary lateral sclerosis is associated with widespread frontotemporal and subcortical pathology and neuropsychological deficits. Accordingly, it should no longer be regarded as a pure upper motor neuron disorder. Patients should be meticulously screened for cognitive deficits and apathy, and the impact of these deficits on decision making and clinical management should be urgently studied in dedicated prospective research protocols.

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Drafting the paper: EF, PB.

Compliance with ethical standards

Conflict of interest none declared.

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