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Data Article

Progressive brainstem pathology in motor neuron diseases: Imaging data from amyotrophic lateral sclerosis and primary lateral sclerosis



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ABSTRACT

A standardised, single-centre, longitudinal imaging protocol was used to evaluate longitudinal brainstem alterations in 100 patients with amyotrophic lateral sclerosis (ALS) with reference to 33 patients with primary lateral sclerosis (PLS), 30 patients with frontotemporal dementia (FTD) and 100 healthy controls. "Brainstem pathology in amyotrophic lateral sclerosis and primary lateral sclerosis: A longitudinal neuroimaging study" [1] ALS patients were scanned twice; 4 months apart. T1-weighted imaging data were acquired on a 3 T Philips Achieva MRI system, using a 3D Inversion Recovery prepared Spoiled Gradient Recalled echo (IR-SPGR) sequence. Raw MRI data underwent meticulous quality control before pre-processing. A Bayesian segmentation algorithm was utilised to parcellate the brainstem into the medulla oblongata, pons and mesencephalon before estimating the volume of each segment. Vertex-based shape analyses were carried out to characterise anatomical patterns of atrophy. Brainstem volume loss in ALS was dominated by medulla oblongata atrophy, but significant pontine pathology was also detected. Brainstem volume

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reductions were more significant in PLS than in ALS after correcting for demographic variables and total intracranial volume. Shape analyses revealed bilateral ‘flattening’ of the medullary pyramids in ALS compared to healthy controls. Our data demonstrate that computational neuroimaging readily detects brainstem pathology in vivo in both amyotrophic lateral sclerosis and primary lateral sclerosis.

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Specifications Table

Subject	Neuroscience (Neurology)
Specific subject area	Neurology
Type of data	Raw volumetric data, Box plots, Radar graph, 3D anatomical figures
How data were acquired	Imaging data were acquired on a Philips Achieva 3T MRI scanner (Philips Medical Systems, Best, The Netherlands) with an 8-channel head coil.
Data format	Raw volumetric brainstem characteristics; medulla oblongata, pons and mesencephalon volume profiles
Parameters for data collection	3D–T1-weighted sequence: spatial resolution: $1 \times 1 \times 1$ mm, Field of view: $256 \times 256 \times 160$ mm, TR/TE = 8.5/3.9 ms, TI = 1060 ms, flip angle = 8°, SENSE factor = 1.5.
Description of data collection	The protocol, consent forms, recruitment procedures, and data management were approved by the institutional ethics committee. All participants provided informed consent prior to inclusion.
Data source location	Participating ALS patients were diagnosed according to the El Escorial research criteria, PLS patients were diagnosed according to the Gordon criteria, FTD patients were diagnosed according to the Rascovsky criteria. MRI data were acquired on a 3 T Philips Achieva system with uniform pulse sequence settings and anonymised. Institution: Computational neuroimaging group, Trinity Biomedical Sciences Institute, Trinity College Dublin City/Town/Region: Dublin Country: Ireland
Data accessibility	Raw brainstem volumes and segmental volumetric profiles have been uploaded to ‘Mendeley Data’ https://doi.org/10.17632/4t8c4bmw5p.3
Related research article	Authors: Peter Bede, Rangariroyashe H. Chipika, Eoin Finegan, Stacey Li Hi Shing, Mark A. Doherty, Jennifer C. Hengeveld, Alice Vajda, Siobhan Hutchinson, Colette Donaghy, Russell L. McLaughlin, Orla Hardiman Title: Brainstem pathology in amyotrophic lateral sclerosis and primary lateral sclerosis: a longitudinal neuroimaging study Journal: Neuroimage Clinical https://doi.org/10.1016/j.nicl.2019.102054

Value of the Data

- Volumetric brainstem data in ALS and PLS reveal medulla oblongata and pons atrophy compared to healthy and disease controls
- The dataset provides evidence of phenotype-specific brainstem profiles in motor neuron diseases and is consistent with post mortem studies, pathological TDP-43 staging systems, and the clinical profile of the phenotypes.
- The presented data demonstrate that ALS-specific imaging signatures can be captured in the brainstem based on T1-weighted datasets alone.
- This dataset may be useful for biomarker development for pharmaceutical trials in motor neuron diseases.

1. Data

Despite pathognomonic bulbar involvement in motor neuron diseases [2–4], the majority of imaging studies in ALS and PLS focus on cortical and spinal cord signatures [5–9]. In this dataset we present the volumetric brainstem profile of 100 patients with amyotrophic lateral sclerosis (ALS), 33 patients with primary lateral sclerosis (PLS), 30 patients with frontotemporal dementia (FTD), and 100 age-matched healthy controls (HC) [1] (Table 1). Relevant demographic (age, gender, education and handedness) and clinical (ALSFRS-r) characteristics [10,11] are presented in the companion article [1]. Raw volumetric data for each brainstem segment are available online at Mendeley Data; <https://doi.org/10.17632/4t8c4bmw5p.3> Longitudinal brainstem changes in ALS [12] are presented in boxplots (Fig. 1). Reference volumetric data are shown for PLS patients [13], disease controls [14,15] and healthy controls [16] to aid the interpretation of ALS-associated brainstem changes. Based on estimated marginal means corrected for age, gender, total intracranial volumes and education, the comparative profile of the study groups are further illustrated in radar plots with reference to healthy controls (Fig. 2). Focal atrophy patterns are presented as three-dimensional vertex projections (Fig. 3).

Table 1

Data categories and measures.

Data categories	Specific measures
Segmental brainstem volumes	Medulla oblongata volume (mm ³) Pons volume (mm ³) Mesencephalon volume (mm ³)
Vertex contrast between ALS patients and healthy controls	Vertex locations of individual participants are projected on the surface of an average brainstem template as scalar values. Permutation based non-parametric statistics were used for group comparisons including age, gender and education. Resulting statistical maps are displayed on 3D mesh templates to showcase focal shape deformations.

ALS = amyotrophic lateral sclerosis; ALSFRS-R = amyotrophic lateral sclerosis functional rating scale-revised; PLS = Primary lateral sclerosis.

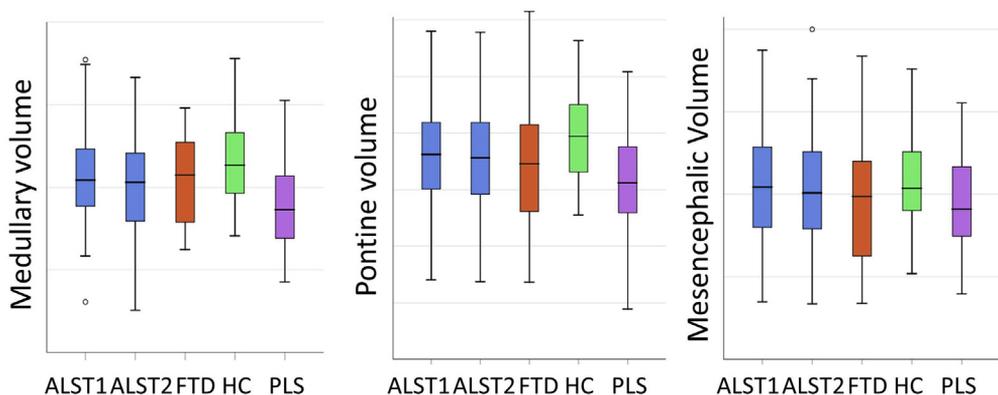


Fig. 1. The comparative volumetric brainstem profile of patients with amyotrophic lateral sclerosis at time-point 1 (ALST1), patients with amyotrophic lateral sclerosis at time-point 2 (ALST2), frontotemporal dementia (FTD), healthy controls (HC) and patients with primary lateral sclerosis (PLS).

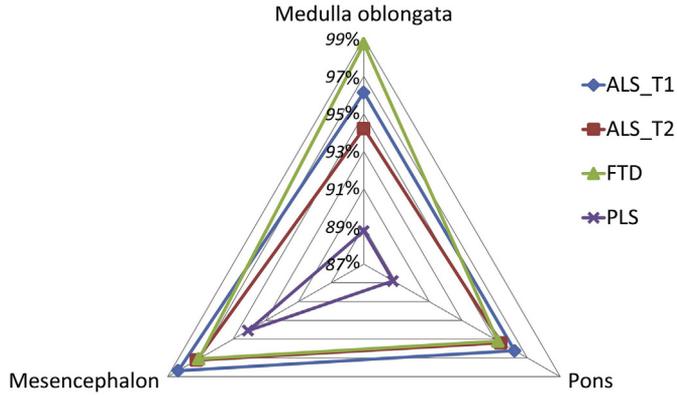


Fig. 2. The segmental brainstem profile of ALS, PLS and FTD with reference to healthy controls. 100% represents the estimated marginal mean of healthy controls for each structure. Estimated marginal means of volumes were calculated with the following values Age = 59.59, Gender = 1.43, Education = 13.63, TIV = 1435355.28.

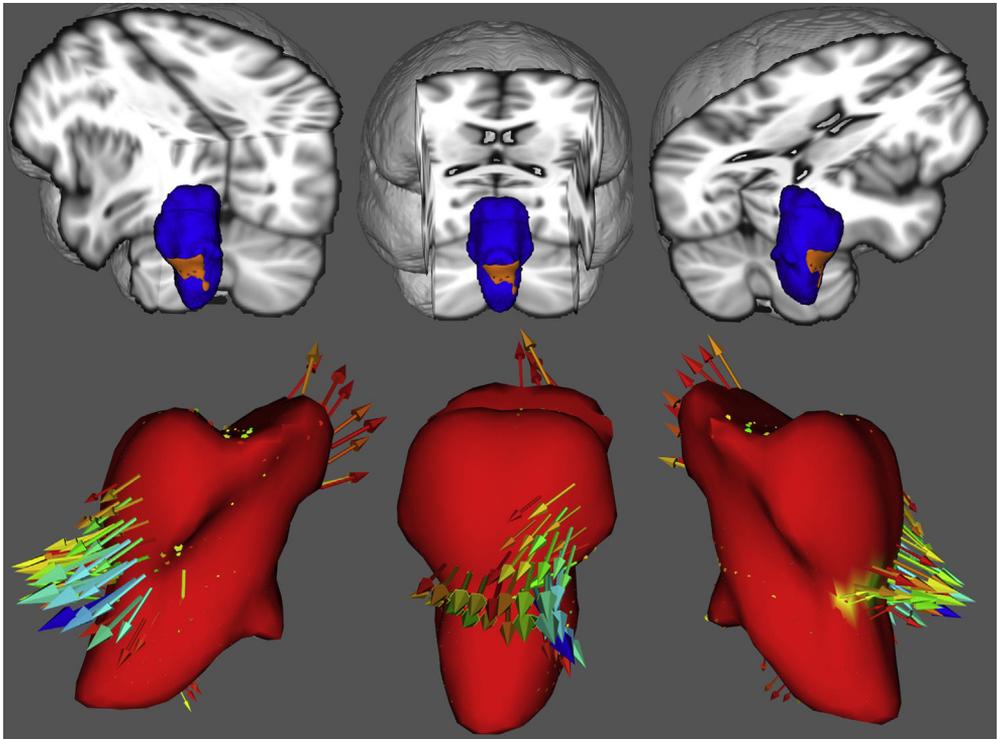


Fig. 3. Anatomical patterns of atrophy in ALS compared to healthy controls based on vertex-analyses after corrections for demographic variables. **Top:** Vertex analyses; brainstem mesh is shown in blue and shape deformations are highlighted in orange at $p < 0.05$ FWE **Bottom:** Surface-based vertex analyses; the brainstem mesh template is shown in red.

2. Experimental design, materials, and methods

This protocol was approved by the institutional ethics committee and each participant provided informed consent. Recruitment, anonymisation and data management procedures followed

institutional and EU data handling guidelines (GDPR). Patients were recruited from a national motor neuron disease clinic to participate in a standardised imaging protocol [8]. Participating ALS patients were diagnosed according to the El Escorial research criteria, PLS patients were diagnosed according to the Gordon criteria and FTD patients according to the Rascovsky criteria [17]. The study was designed to characterise brainstem degeneration in ALS and PLS with a view to identify distinguishing imaging characteristics for diagnostic classification applications [18,19]. T1-weighted images were acquired with a spatial resolution of $1 \times 1 \times 1$ mm and field of view of $256 \times 256 \times 160$ mm using a 3D Inversion Recovery prepared Spoiled Gradient Recalled echo (IR-SPGR) sequence; repetition time (TR) = 8.5 ms, echo time (TE) = 3.9 ms, Inversion time (TI) = 1060 ms, flip angle = 8° , SENSE factor = 1.5. Whole brainstem volumes and total intracranial volumes (TIV) were estimated using FSL-FIRST [20] of the FMRIB's Software Library (FSL) [7,14].

The brainstem of each participant was further segmented into the medulla oblongata, pons, and mesencephalon using a Bayesian parcellation algorithm implemented in version 6.0 of the FreeSurfer image analysis suite. Analyses of covariance (ANCOVA) were used to explore intergroup volumetric differences using age, education, gender and TIV as covariates [11]. To illustrate disease-specific volumetric traits in ALS and PLS, the estimated marginal mean of each segment was plotted on a radar chart with reference to healthy controls.

As volumetric profiling only detects global volume reductions, additional vertex analyses were performed to characterise focal shape deformations in ALS compared to healthy controls. FMRIB's subcortical segmentation and registration tool FIRST was used for shape analyses to map surface-projected atrophy patterns in the brainstem. ALS patients at their second time point exhibited considerable bilateral flattening of the medullary pyramids above the pyramidal decussation (Fig. 3).

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Conflict of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter Bede is the associate editor of Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, member of the UK Motor Neuron Disease Association (MND) Research Advisory Panel, the steering committee of the Neuroimaging Society in ALS (NiSALS) and the patron of the Irish Motor Neuron Disease Association (IMNDA).

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