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Faculté des sciences
médicales et paramédicales
Aix-Marseille Université

**Association entre taux de neurofilaments (NF-L) et modèles de
neurodégénérescence du cortex précentral dans la sclérose latérale
amyotrophique**

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Présentée et publiquement soutenue devant

**LA FACULTÉ DES SCIENCES MEDICALES ET PARAMEDICALES
DE MARSEILLE**

Le 28 Septembre 2022

Par Monsieur Antoine MOUTIEZ

Né le 21 avril 1994 à Villeneuve-D'ascq (59)

Pour obtenir le grade de Docteur en Médecine

D.E.S. de RADIOLOGIE ET IMAGERIE MEDICALE

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BRUDER Nicolas	GARCIA Stéphane	MILH Mathieu
BRUE Thierry	GARIBOLDI Vlad	MILLION Matthieu
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ELDIN Carole	MOTTOLA GHIGO Giovanna	
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LE CORROLLER Thomas (PU-PH)
PIRRO Nicolas (PU-PH)

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LAGIER Aude (MCU-PH) *disponibilité*

THOLLON Lionel (MCF) (60ème section)

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LABIT/BOUVIER Corinne (MCU-PH)
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MAUES DE PAULA André (MCU-PH)
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FRAISSE-MANGIALOMINI Jeanne (PRCE)

**BIOLOGIE ET MEDECINE DU DEVELOPPEMENT
ET DE LA REPRODUCTION ; GYNECOLOGIE MEDICALE 5405**

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ANTHROPOLOGIE 20

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DEGIOANNI/SALLE Anna (MCF)
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NICOLAS DE LAMBALLERIE Xavier (PU-PH)
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GOURIET Frédérique (MCU-PH)
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MARLINGE Marion (MCU-PH)
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 DUFOUR Jean-Charles (MCU-PH)
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 JOUVE Jean-Luc (PU-PH)
 LAUNAY Franck (PU-PH)
 MERROT Thierry (PU-PH)
 PESENTI Sébastien (PU-PH)
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DARIEL Anne (MCU-PH)

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4601

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RESSEGUIER Noémie (MCU-PH)

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OLIVE Daniel (PU-PH)
VIVIER Eric (PU-PH)

FERON François (PR) (69ème section)

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CHRETIEN Anne-Sophie (MCU PH)
DEGEORGES/VITTE Joëlle (MCU-PH)
DESPLAT/JEGO Sophie (MCU-PH)
JARROT Pierre-André (MCU PH)
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LAGIER Jean-Christophe (PU-PH)
MILLION Matthieu (PU-PH)
PAROLA Philippe (PU-PH)
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ELDIN Carole (MCU-PH)

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CASANOVA Ludovic (MCF Méd. Gén. Temps plein)

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FIERLING Thomas (MCF associé Méd. Gén. À mi-temps)

FORTE Jenny (MCF associé Méd. Gén. À mi-temps)

JANCZEWSKI Aurélie (MCF associé Méd. Gén. À mi-temps)

NUSSLI Nicolas (MCF associé Méd. Gén. À mi-temps)

ROUSSEAU-DURAND Raphaëlle

(MCF associé Méd. Gén. À mi-temps)

THERY Didier (MCF associé Méd. Gén. À mi-temps)

(nomination au 1/10/2019)

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RACCAH Denis (PU-PH)

VALERO René (PU-PH)

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CHABANNON Christian (PR) (66ème section)

SOBOL Hagay (PR) (65ème section)

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DENIS Danièle (PU-PH)

OTO-RHINO-LARYNGOLOGIE 5501

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FAKHRY Nicolas (PU-PH)

GIOVANNI Antoine (PU-PH)

LAVIEILLE Jean-Pierre (PU-PH)

MICHEL Justin (PU-PH)

NICOLLAS Richard (PU-PH)

TRIGLIA Jean-Michel (PU-PH) Surnombre

RADULESCO Thomas (MCU-PH)

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DUSSOL Bertrand (PU-PH)

JOURDE CHICHE Noémie (PU PH)

MOAL Valérie (PU-PH)

ROBERT Thomas (MCU-PH)

NEUROCHIRURGIE 4902

DUFOUR Henry (PU-PH)

FUENTES Stéphane (PU-PH)

REGIS Jean (PU-PH)

ROCHE Pierre-Hugues (PU-PH)

SCAVARDA Didier (PU-PH)

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FELICIAN Olivier (PU-PH)

PELLETIER Jean (PU-PH)

SUISSA Laurent (PU-PH)

MAAROUF Adil (MCU-PH)

PEDOPSYCHIATRIE; ADDICTOLOGIE 4904

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POINSO François (PU-PH)

GUIVARCH Jokthan (MCU-PH)

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MICALLEF/ROLL Joëlle (PU-PH)

SIMON Nicolas (PU-PH)

BOULAMERY Audrey (MCU-PH)

RANQUE Stéphane (PU-PH)

LE COZ Pierre (PR) (17ème section)

CASSAGNE Carole (MCU-PH)

MATHIEU Marion (MAST)

L'OLLIVIER Coralie (MCU-PH)

TOGA Isabelle (MCU-PH)

PHYSIOLOGIE 4402

PEDIATRIE 5401

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BARLOGIS Vincent (PU-PH)

BREGEON Fabienne (PU-PH)

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GABORIT Bénédicte (PU-PH)

DUBUS Jean-Christophe (PU-PH)

MEYER/DUTOUR Anne (PU-PH)

FABRE Alexandre (PU-PH)

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GIRAUD/CHABROL Brigitte (PU-PH)

BOUSSUGES Alain (PR associé à temps plein)

MICHEL Gérard (PU-PH)

BONINI Francesca (MCU-PH)

MILH Mathieu (PU-PH)

BOULLU/CIOCCA Sandrine (MCU-PH)

OVAERT-REGGIO Caroline (PU-PH)

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Title: Neurofilament light-chain levels interact with neurodegenerative patterns and motor neuron dysfunction in amyotrophic lateral sclerosis

Manuscript Type: Original Research Article

Abbreviations: Amyotrophic Lateral Sclerosis (ALS), neurofilament light-chains (NfL), cerebrospinal fluid (CSF), corticospinal tract (CST), revised ALS Functional Rating Scale (ALSFRS-R), transcranial magnetic stimulation (TMS), electromyography (EMG), compound muscle action potential (CMAP), motor evoked potential (MEP)

Key Results

We showed limb-specific thinning corresponding to the motor homunculus within the precentral cortex in amyotrophic lateral sclerosis (ALS) patients. Further, cerebrospinal fluid neurofilament light chain (NfL) levels negatively correlated with premotor cortical thickness, suggesting its key role in NfL accumulation in ALS. Finally, we found an interaction between serum NfL levels, cortical thinning, and disability according to motor evoked potential ratios, underlying the need for multimodal longitudinal assessments in advancing the understanding of prognostic value and pathophysiological mechanisms behind ALS neurodegeneration.

Summary Statement

Our results promote the combination of MRI data with non-invasive clinical, electrophysiological and neurofilament light-chain serum assays for advancing the understanding of pathophysiological mechanisms driving amyotrophic lateral sclerosis neurodegeneration.

Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by rapid degeneration of upper and lower motor neurons leading to cortical atrophy in the brain, primarily in precentral areas. Recently, neurofilament light-chains (NfL) have been shown to be a robust diagnostic and prognostic biomarker with high specificity to ALS. The association between NfL, neuroradiological ratings of brain MRIs and cortical neurodegeneration, however, are not well understood. The goal of the study was to investigate the role of NfL serum and cerebrospinal fluid (CSF) measures as putative mediators between neuroradiological ratings, neurodegeneration in precentral areas and clinical disability measures in ALS. We included 31 patients diagnosed with ALS who had either a 3T (n = 20) or 7T (n = 11) MRI and serum (n = 25) or CSF (n = 16) NfL measurements. A blinded assessment of MRI anomalies was performed by trained neuroradiologists, and the associations and interactions between cortical thickness, NfL levels and clinical and electrophysiological scores were analyzed. We found higher serum NfL levels in ALS patients classed as having FLAIR hypersignal anomalies in the corticospinal tract (CST) ($p = 0.034$) and more global atrophy ($p\text{-value} = 0.012$). Quantitative analyses also showed significant associations between cortical thickness and bulbar and arm impairment which followed cortical distributions based on the motor homunculus. Finally, a significant interaction was observed between cortical thickness, serum NfL and motor evoked potential ratios for the upper right arm ($\text{FDR } p < 0.05$). Qualitative MRI anomalies seem to indicate higher NfL levels and might thus have a yet underestimated prognostic value. Further, serum NfL seems to be an important mediator between clinical symptoms and objective neuronal loss as determined by cortical thickness.

Key Words

Motor neuron disease, neurofilament light chains, neurodegeneration, MRI, electrophysiology

Introduction

Amyotrophic lateral sclerosis (ALS) is a lethal neurodegenerative disease involving upper and lower motor neurons. Clinical manifestations predominate initially in either limb (~65%), bulbar (~30%) or respiratory (~5%) territories (1). Atypical modes of presentation are not rare however, while evolution is heterogeneous, with disease occurring anywhere from a few months up to a decade (1,2). Brain MRI is an established tool used to map and quantify regional neuronal pathology and can be useful in the diagnosis of neurodegenerative diseases. ALS shows alterations primarily in motor cortex and tracts as well as in extra-motor areas including frontal and temporal lobes (3). In particular, cortical atrophy - a hallmark of neuronal death and represented by cortical thickness loss - tends to follow neuropathology patterns such as the distribution of the TDP-43 protein (4). From a clinical perspective, FLAIR signal anomalies of the corticospinal tract (CST) and atrophy in the central region have been evidenced as neuroradiological findings (5,6). However, MRI is not yet established as diagnostic or prognostic tool in ALS (7).

The association between heterogeneous phenotypes in ALS and brain pathology as detected by MRI hence remains moderate and suggests the presence of yet unknown or not completely understood pathophysiological mechanisms mediating this relationship. While progress is being made with more advanced mapping of clinical symptoms according to revised ALS Functional Rating Scale (ALSFRS-R) sub-scores (8,9), more precise, targeted mapping of correlations biomarkers is so far missing. Recent advances have demonstrated that the accumulation of neurofilament light chains (NfL) in the serum and cerebrospinal fluid (CSF), an indicator of axonal damage and neural death (10), is increased by more than nine-fold in ALS compared to controls (11). NfL seem a highly sensitive, robust biomarker for the diagnosis and prognosis of ALS (12,13) with relatively good specificity compared to

neuroinflammatory (14) and other neurodegenerative diseases (15). Thus, NfL seems a good candidate for being an informative mediator between definite neuronal loss in the cortex, neuroradiological rating and loss of function in ALS. Further, the potential of electrophysiological biomarkers such as transcranial magnetic stimulation (TMS) to depict upper motor neuron dysfunction has been well evidenced (16,17).

The goal of the study was to investigate the link between qualitative neuroradiological assessments or quantitative neurodegeneration in the precentral cortex, and either serum and CSF NfL levels on the one hand, or clinical and electrophysiological outcome measures on the other in a population of ALS patients.

Methods

Participants

We included retrospective data from 31 ALS patients prospectively recruited between 2013 and 2020. Inclusion criteria were patients who fulfilled the revised El Escorial diagnostic criteria (18). Exclusion criteria were comorbid neurological conditions or coexisting frontotemporal dementia.

Patients underwent clinical and electrophysiological examination, 3T or 7T MRI, and NfL assessments. 37 healthy controls with an equivalent 3T or 7T MRI served as a control group. The study had ethical approval and participants signed an informed consent before participating in the study.

Neurofilament Protocol

Serum and CSF NfL levels (pg/ml) were measured with the R-PLEX Human Neurofilament L Antibody Set from MesoScale Discovery (MSD) (F217X, MSD, USA) according to the manufacturer's instructions.

Clinical Examination

Patients' revised El Escorial diagnostic criteria (18) were: definite ALS (n=6), probable ALS (n=15), probable laboratory-supported ALS (n=2) and possible ALS (n=8). Clinical disability was quantified using ALSFRS-R and ALSFRS-R sub-scores (bulbar: items 1-3; arm: items 4-6; leg: items 7-9; respiratory: items 10-12). Disease duration since symptom onset, date of diagnosis, onset site and forced vital capacity were measured for all patients.

Electrophysiology Protocol

Transcranial magnetic stimulation (TMS) was performed using a Magstim 200 stimulator (Magstim) with a circular coil (9-cm diameter). The electromyography (EMG) machine Nicolet® Viking® EDX (Natus Medical Incorporated) was used to record surface EMG signals with bandpass filter 3–10,000 Hz, and perform electrical stimulation. Motor evoked potentials (MEPs) were recorded on both sides for upper limbs (abductor digiti minimi muscles) and lower limbs (tibialis anterior muscles). MEP ratios were calculated by dividing the MEP amplitude elicited by TMS by the amplitude of the same muscles' compound muscle action potential (CMAP) evoked by supramaximal electrical stimulation of the corresponding peripheral nerve (ulnar or fibular). TMS was not performed if CMAP amplitude was < 1mV.

MRI Protocol

The 3T protocol included a three-dimensional Magnetization-Prepared Rapid Gradient Echo T1-weighted (MPRAGE; TR/TE/IT = 2300/2.98/900 ms; 160 sagittal slices, 1 mm³ isotropic) and FLAIR (TR/TE/IT = 5000/395/1800 ms; 160 sagittal slices, 1 mm³ isotropic), and was acquired using a 32-channel (32Rx/1Tx) head coil (Siemens). The 7T MRI protocol included a 3D Magnetization Prepared 2 Rapid Acquisition Gradient Echoes T1-weighted (MP2RAGE; TR/TE/TI1/TI2 = 5000/3/900/2750 ms, 256 sagittal slices, 0.6 mm³ isotropic), FLAIR (TR/TE/IT = 8500/466/2400 ms; 192 sagittal slices, 0.8 mm³ isotropic) and a sagittal 2D magnetization-prepared turbo-FLASH (fast low-angle shot) B1+ mapping (19) (TR/TE = 2000/14 ms, 14 axial sections, slice thickness 5 mm, in plan resolution of 3.9 × 3.9 mm²) and was acquired using a 32-channel (32Rx/1Tx) head coil (Nova).

Image Processing

7T MP2RAGE images were denoised (20). T1w images were skull-stripped using HD-BET (21). FreeSurfer was used to manually correct brain masks and estimate wholebrain cortical thickness. Individual data were smoothed with a FWHM of 10mm and registered to the fs-average brain (<https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all>).

Blinded neuroradiological rating

A blinded assessment of patient and control MRIs was performed by two trained radiologists (AM and BT). Atrophy for whole brain (global), precentral, frontal, parietal, and temporal lobes was reported as “No”, “Mild”, or “Marked” for each hemisphere. The occipital lobe was used as a reference given relative lack of atrophy in this area in ALS. Atrophy of the precentral gyrus was reported only when very marked given it being the primary atrophic zone in ALS. CST atrophy was determined based on the peduncles and pons. Atrophy to both was rated as “Yes”, only one as “Undetermined” and neither as “No”. FLAIR CST anomalies were reported using a window of 0/210 at 3T and 50/400 at 7T. MRIs with significant movement were rated as “Artefacts” and removed from subsequent analyses. Following initial rating, the radiologists reviewed the corresponding images and provided a consensus rating when discordance occurred. This rating was used for investigating statistical associations. Participants were also grouped into those with no anomalies or at least one anomaly across all ratings.

Statistics

Demographic and clinical data were analyzed using R (Version 1.2.5033). Differences between control and patient characteristics were determined using two-sample t-tests.

Associations were examined with Pearson's correlations. An increase or decrease in mean values over ordered groups (e.g., no vs. mild vs. marked atrophy) was analysed with the Jonckheere-Terpstra tests. Any missing values marked as NA were omitted from analyses in pair-wise fashion.

Spatial patterns of cortical thickness between patients and controls were analysed using FreeSurfer's surface based GLM analyses (mri_glmfit and mri_glmfit-sim). Between patient analyses were restricted to the precentral area from the Desikan-Killiany Atlas (? .aparc.annot: precentral) (22). Association between patients' cortical thickness and ALSFRS-R sub-scores, MEP ratios, and serum or CSF NfL levels were also examined using GLMs. All models were adjusted for age, sex and scanner (3T or 7T) and allowed random intercepts. An unadjusted p-value below < 0.05 was used to explore the results. FDR cluster correction was run with a p-value < 0.05 using 1000 permutations.

Results

Demographic and clinical data

Data from 31 ALS patients and 37 healthy controls were analyzed. Patients' data included a 3T (n = 20) or 7T (n = 11) MRI, NfL serum (n = 25) or CSF (n = 16) samples, clinical examinations (n=31) and electrophysiological assessments (n = 29). Controls' data included a 3T (n = 26) or 7T (n = 15) MRI. As hypothesized, we observed decreased cortical thickness in patients compared to controls (**Supplementary Figure 1**).

Patients' demographic and clinical details can be found in **Table 1**. The control group had a mean age of 50 (\pm 11) years; with median and range 51 [27-66] years, and sex ratio 1:1 male to female. Two-sample t-tests comparing age and sex between controls and patients showed no difference for sex ($p = 0.237$), but a difference for age (p -value = 0.039). Log NfL values were used for analyses due to the non-normal distribution of raw serum NfL levels according to Shapiro-Wilkes ($W = 0.3$, $p < 0.001$). Pearson's correlation showed a positive correlation between serum and CSF NfL levels ($r = 0.64$, $p = 0.010$).

Neuroradiological rating

Raw results from radiologists' blinded ratings of T1w or FLAIR MRIs can be seen in **Supplementary Table 1**. Concordance between the raters was 92.4% for control hemispheres, and 83.7% for patient hemispheres (p -value < 0.001). Concordance across patients and controls for each image-area can be seen in **Supplementary Table 2**. Raw values following the radiologists' consensus can be found in **Supplementary Table 3**. Global Atrophy was rated "No" in 64 control and 42 patient hemispheres, "Mild" in 6 control and 5 patient hemispheres and "Marked" in 0 control and 5 patient hemispheres. FLAIR anomalies were rated as "Yes" in 0 control and 7 patient hemispheres and "No" in 52 control

and 43 patient hemispheres. At least one anomaly was found in 1 control and 16 patients. Subsequent analyses exploring the link between serum NfL and consensus ratings found higher serum NfL levels in patients with FLAIR hypersignal ($p = 0.045$) and an association with global atrophy (p -value = 0.014, alternative hypothesis: increasing serum NfL levels with increasing anomalies) (**Figure 1**). Nonetheless, anomalies were rare and serum NfL values did not differ between patients with no or at least one anomaly ($p = 0.39$).

Mapping disability scores with cortical atrophy

To determine whether patterns of cortical atrophy were associated with limb-specific clinical symptoms or electrophysiology results in expected precentral areas, associations were performed between ALSFRS-R sub-scores and MEP ratios. **Figure 2** shows the association between ALSFRS-R scores and cortical thickness. For ALSFRS-R bulbar scores, one cluster in the right (G_precentral: Size = 2723mm², MNI (x) = 44.2, MNI (y) = -9.2, MIN (z) = 45.6, p value = 0.002) and left (G_precentral: Size = 1422mm², MNI (x) = -45.2, MNI (y) = -10.0, MIN (z) = 50.5, p value = 0.002) hemisphere survived cluster-wise correction.

ALSFRS-R arm scores survived cluster-wise correction in the right hemisphere (G_precentral: Size = 1076mm², MNI (x) = 59.9, MNI (y) = 4.9, MIN (z) = 19.3, p value = 0.02). Results from MEP ratios (**Figure 3**) showed a similar distribution, with decreased cortical thickness in upper leg-regions of the precentral cortex being associated with decreased leg MEP ratios.

Association between NFL levels, electrophysiology and cortical thickness

The spatial origin of NFL associated with cortical neurodegeneration is shown in **Figure 4**. Results showed negative correlation between NFL levels in either CSF or serum with cortical

thickness i.e., reduced cortical thickness with increasing NfL. Further, we explored the interaction between serum NfL levels and MEP ratios for each limb compared to cortical thickness in the contralateral hemisphere. Results can be seen in **Figure 5**. Overall, we found positive interactions, indicating that the inverse effect of serum NfL values on cortical thickness is stronger (i.e., the slope of the linear model is steeper) in patients with lower MEP values (higher disability). These interactions were found across upper limb and bulbar premotor and motor areas. The interaction between right upper limb MEP ratio, NfL and cortical thickness survived cluster correction in the left hemisphere (G_precentral: Size = 633mm², MNI (x) = -58.7, MNI (y) = 0.8, MIN (z) = 20.1, p value = 0.04).

Discussion

Our study investigated clinical and research grade MRI outcomes as bridging techniques between disability and neuronal loss in a group of ALS patients. Serum NfL levels, currently the most promising blood biomarker in neurodegenerative diseases, served as a marker of ongoing neuronal loss and were associated with precentral area cortical thickness. Moreover, we found a significant interaction between NfL and cortical thickness with electrophysiological outcomes - an objective measure of upper motor neuron dysfunction. Despite low observations of anomalies during neuroradiological rating, our results suggest that visibility of FLAIR anomalies increases with higher serum NfL levels - which are linked to poorer prognosis.

Radiological ratings linked to serum biomarker in ALS

To date, qualitative MRI ratings have usually been found to be neither sensitive nor specific for diagnosing ALS, resulting in a tendency towards using clinical and electrophysiological scores (6). Here, while detection of anomalies was rare, perhaps due to MRIs being performed at the beginning of patients' disease courses, we found a meaningful association between serum NfL levels and FLAIR CST signal anomalies and global atrophy. These results are in line with a previous study suggesting that CST hyperintensities on FLAIR images represent a marker of axonal degeneration (5), the same pathophysiological process as NfL (10). These results may support the prognostic value of qualitative MRI assessments in ALS. Further studies with longitudinal data and increased sample size might be necessary to clearly define the link between atrophy and NfL. Additionally, our study focused on precentral areas, yet changes in subcortical and extra-motor structures, the most frequent longitudinal changes in ALS (23), or spinal cord atrophy, were not explored.

Spatial distribution of ALS symptoms

We demonstrated that the association between precentral cortical thinning and limb ALSFRS-R sub-scores and MEP ratios followed a distribution generally respecting the motor homunculus. As with previous results, the spatial distribution was observed bilaterally (3,5), and associations were prominent bulbar scores (8,9). We also observed overlap of sub-scores into other motor homunculus regions. One explanation could be the non-specific nature of ALSFRS-R sub-scores (24,25), yet we also observed overlap for MEP ratios. Alternatively, studies have suggested apparent spreading of symptoms to adjacent motor regions (5,8). This may be in line with recent challenges to the somewhat misinterpreted strict segmentation of the homunculus across sensorimotor areas (26), with increasing suggestions of a more distributed, overlapping profile particularly between body regions with higher physical proximity (27,28).

Interaction between motor dysfunction and NfL

Finally, we demonstrated an interaction with a negative association between cortical thickness and serum NfL levels, that was stronger in patients with decreased right arm MEP ratios. Serum NfL may thus be a useful marker of ongoing neurodegeneration, which is associated with cortical atrophy and electrophysiological measures of motor neuron function. A longitudinal study in ALS patients showed serum NfL levels indicated CST degeneration (29). Further, NfL increase pre-symptom before remaining elevated and stable throughout the disease course (30). Here we extend arguments for multimodal assessments in ALS (25) by presenting the opportunities of combining non-invasive markers of neurodegeneration and muscle function. Further studies investigating longitudinal evolutions of these markers

alongside CST degradation or quantitative DTI would be essential in fully detailing the link between NFL, symptoms and neurodegeneration in order to create standardized maps of cortical degradation in disease states (31,32).

Limitations

Our main limitation was reduced power due to a small data set. Further, our cohort was mainly spinal onset patients (bulbar onset: $n = 6$) with higher disability in the lower limbs according to both ALSFRS-R and MEP. Ultimately, this could have impacted on the current results. We also used 3T and 7T MRI data which have differing sensitivities to anomalies and cortical thickness. The use of identical, standardized surface-based post-processing and inclusion of MRI scanner as a covariate in statistical analyses aimed to reduce the potential bias associated. Further, due to the low levels of bulbar onset patients ($n=6$), our cohort was largely spinal onset patients with higher disability in the lower limbs according to both ALSFRS-R sub-scores and MEP ratios. Ultimately, this could have impacted on the current results. Further, NfL may also be linked to neurodegeneration within the spinal cord which we did not explore. Finally, while age was incorporated into statistical analyses, FLAIR anomalies and global atrophy become more apparent with age, even in healthy controls. The blinded rating assessments may thus have been influenced by this.

Conclusion

Our study evidenced the benefit of using radiological qualitative measurements alongside quantitative MRI assessment of cortical thickness in ALS. Further, we demonstrated the usefulness of combining non-invasive markers such as serum NfL and clinical and limb-specific symptom evaluations with MRI for a detailed mapping of ongoing neurodegeneration. This step towards improved understanding of ALS pathophysiology extends arguments promoting multimodal standardized approaches (25) in advancing diagnostic and prognostic capabilities of these methods.

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Group	Patients
	n = 31 (/31)
Age (years)	56 (\pm 12); 57 [26-77]
Sex ratio (M/F)	35%
Disease Duration (months)	23 (\pm 23); 13 [5-100]
Age Diagnosed (years)	54 (\pm 12); 56 [25-75]
Onset site	Bulbar, n=7; upper limb, n=7, lower limb, n=17
Vital capacity (%)	95 (\pm 20); 97 [59-130]
	n = 25 (/31)
Serum NfL (pg/ml)	1121 (\pm 2774); 402 [65-14273]
	n = 16 (/31)
CSF NfL (pg/ml)	34802 (\pm 20734); 31121 [5101-74038]
	n = 29 (/31)
MEP ratio Left Arm (%)	35 (\pm 25); 43 [0-76]
MEP ratio Right Arm (%)	34 (\pm 25); 36 [0-72]
MEP ratio Left Leg (%)	15 (\pm 22); 0 [0-63]
MEP ratio Right Leg (%)	15 (\pm 21); 0 [0-69]
	n = 31 (/31)
ALSFRS-R (/48)	38 (\pm 5); 39 [23-47]
ALSFRS-R Arm (/12)	9 (\pm 3); 9 [3-12]
ALSFRS-R Bulbar (/12)	11 (\pm 2); 12 [4-12]
ALSFRS-R Leg (/12)	7 (\pm 3); 6 [2-12]

Table 1. Demographic and clinical details of amyotrophic lateral sclerosis (ALS) patients. Data are shown as mean (\pm standard deviation); median [range]. serum NfL = serum neurofilament light chain, CSF NfL = corticospinal fluid neurofilament light chain, MEP = motor evoked potentials, ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Recovery Scale Revised.

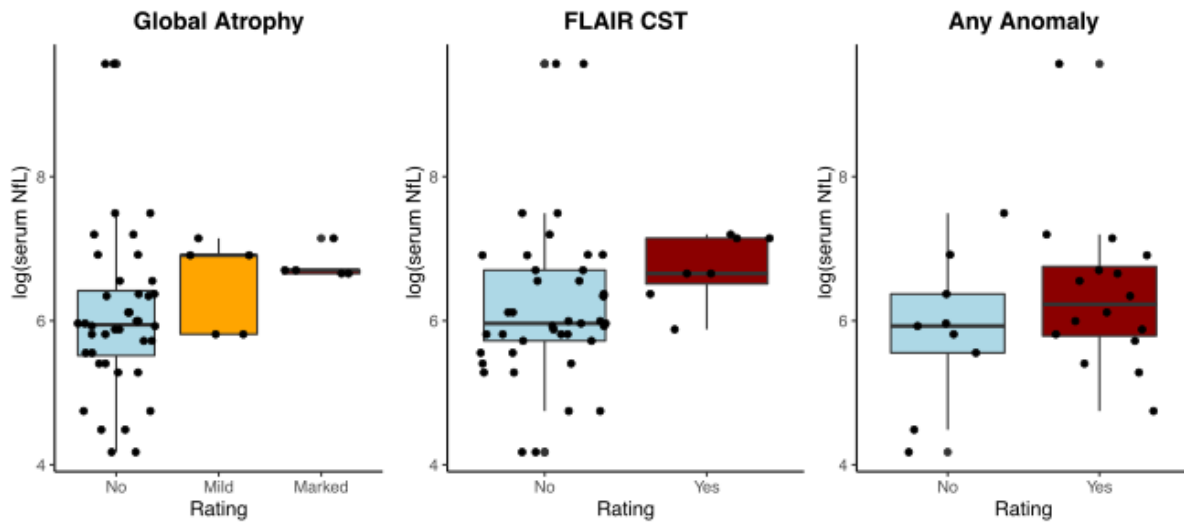


Figure 1. Association between serum neurofilament light chain (NfL) levels and anomalies based on neuroradiological ratings for each hemisphere in ALS patients. Graphs show consensus ratings compared to log serum NfL values for **A.** Global Atrophy, **B.** FLAIR in corticospinal tract (CST), and **C.** instances of at least on anomaly found on any image.

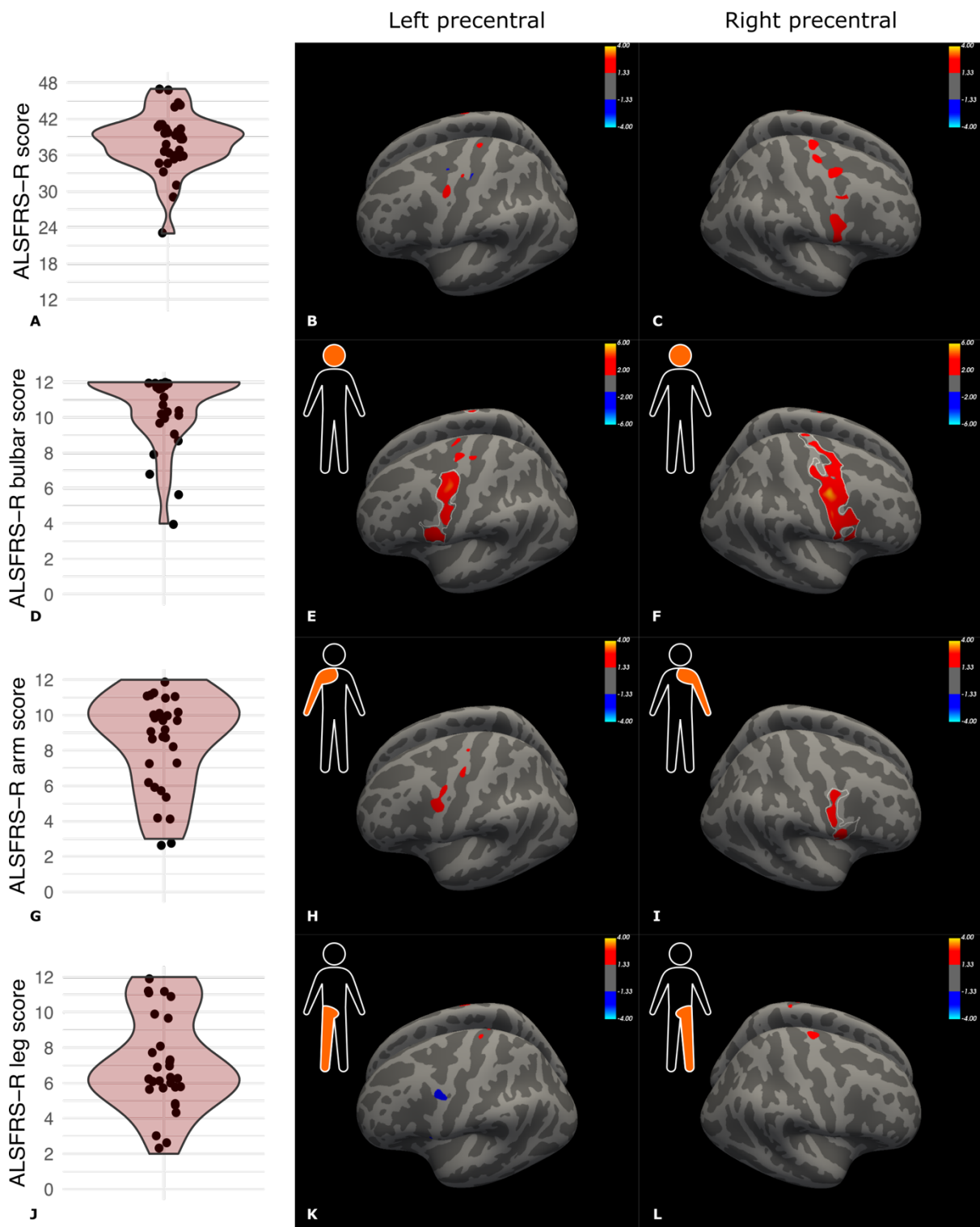


Figure 2. Amyotrophic Lateral Sclerosis Functional Recovery Scale Revised (ALSFRS-R) score and sub-score distributions (violin graphs) and corresponding general linear model (GLM) comparison for patients' precentral cortical thickness and ALSFRS-R scores for **A. - C.** global score and **D. - F.** bulbar, **G. - I.** arm and **J. - L.** leg region sub-scores. Note that while ALSFRS-R sub-scores are not lateralized, GLM correlations for the left precentral cortex were presumed to be

related to right limb symptoms, and vice-versa for the right precentral cortex, as depicted by the orange shading on the silhouette. The colour scale (signed \log_{10} p-values) indicates decreased cortical thickness with decreasing (less normal) ALSFRS-R scores in red (and vice versa negative associations in blue). Uncorrected threshold of 1.3 corresponding to a \log_{10} of $p = 0.05$. Significant clusters surviving cluster-wise p value (CWP) correction ($p < 0.05$) are outlined in white.

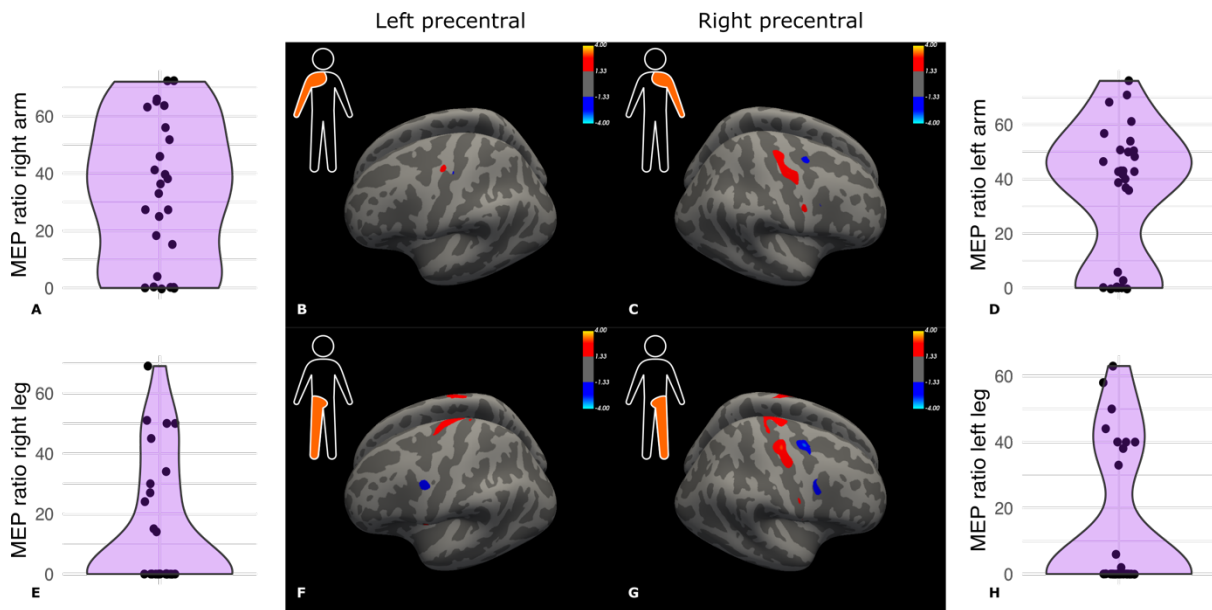


Figure 3. Motor evoked potential (MEP) ratio distributions (violin plots) across patients and corresponding general linear model (GLM) comparison for patients' precentral cortical thickness and electrophysiology MEP ratios for **A. - B.** upper right limb, **C. - D.** upper left limb, **E. - F.** lower right limb, **G. - H.** lower left limb. Correlations for the left precentral area were performed with right limb measures, and vice-versa for the right precentral area, following the orange shading on the silhouettes. The colour scale (signed log₁₀ p-values) indicates decreased cortical thickness with decreasing (less normal) MEP ratios in red (and vice versa negative associations in blue). Uncorrected threshold of 1.3 corresponding to a log₁₀ of $p = 0.05$. Significant clusters surviving cluster-wise p value (CWP) correction ($p < 0.05$) are outlined in white.

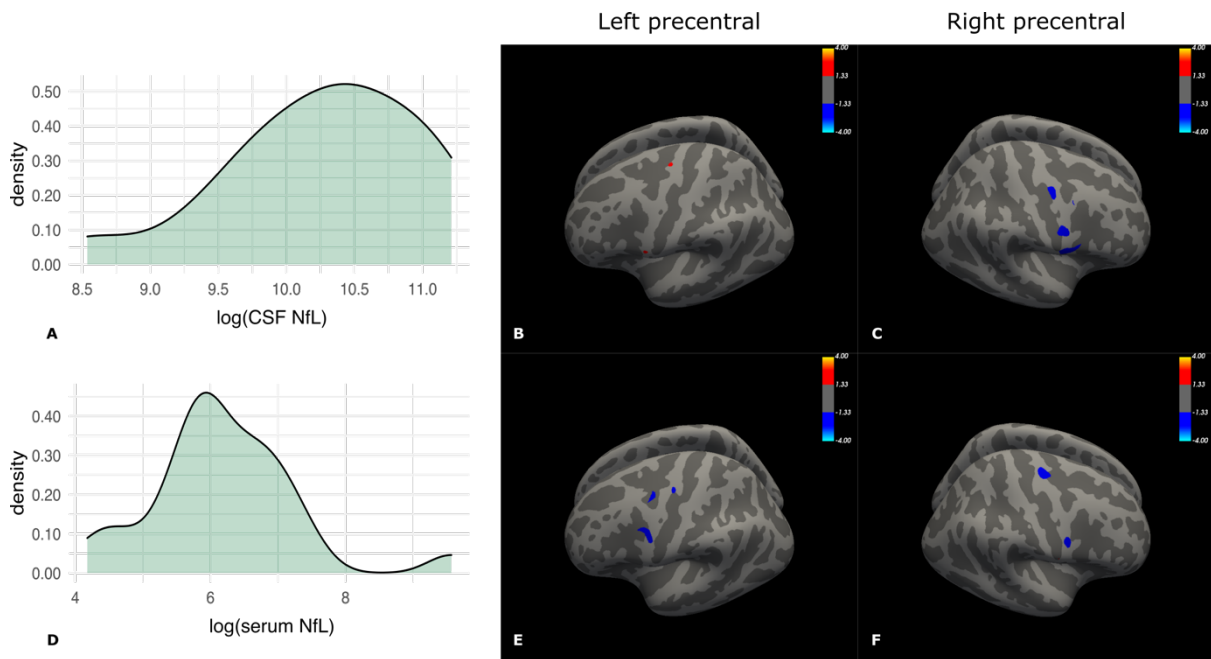


Figure 4. Distribution of log cerebrospinal fluid (CSF) and serum neurofilament light-chain (NfL) levels across patients with corresponding general linear model (GLM) comparison for patients' precentral cortical thickness and log NfL levels in **A. - C.** CSF and **D. - F.** serum. The colour scale (signed log₁₀ p-values) indicates decreasing cortical thickness with increasing NfL scores in blue (and vice versa positive associations in red). Uncorrected threshold of 1.3 corresponding to a log₁₀ of $p = 0.05$. Of note, negative correlation in the left precentral area situates around the premotor cortex. Significant clusters surviving cluster-wise p value (CWP) correction ($p < 0.05$) are outlined in white.

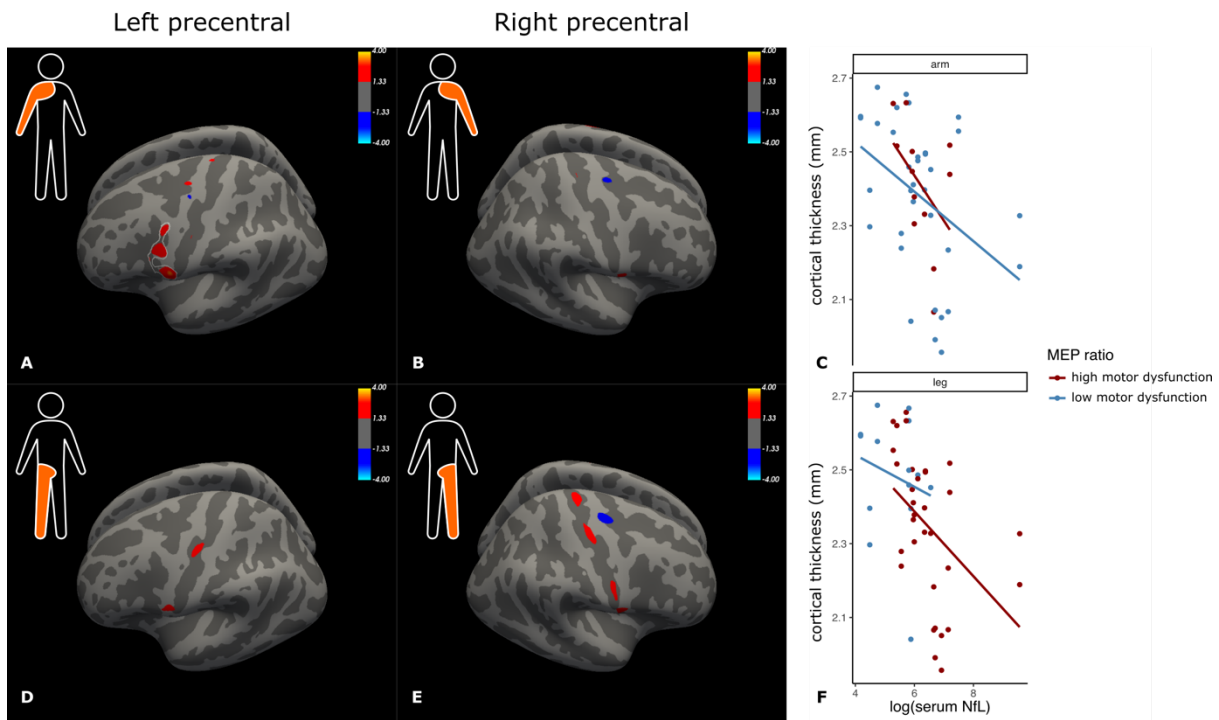
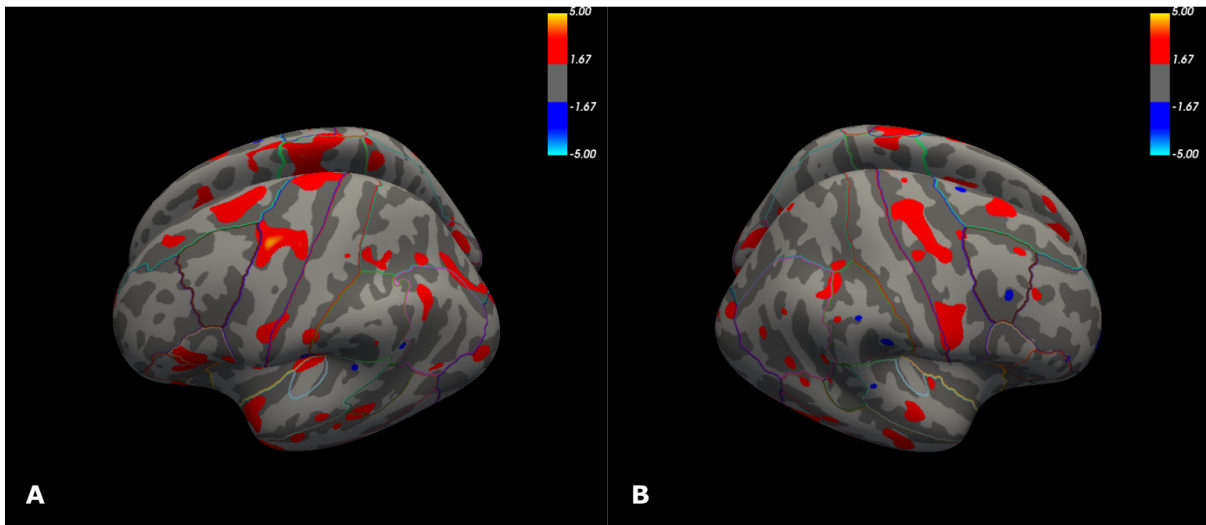


Figure 5. General linear model (GLM) demonstrating the interaction between patients' precentral cortical thickness, neurofilament light-chain (NfL) levels and motor evoked potential (MEP) ratios in **A.** upper right limb **B.** upper left limb and **C.** lower left limb **D.** lower right limb. Panels on the right depict scatter plots and linear model estimations for the interaction between serum NfL and cortical thickness according to MEP ratios for the upper limb (arm) and lower limb (leg) split into either high upper motor dysfunction (low MEP ratios) or low upper motor dysfunction (high MEP ratios). The colour scale (signed log₁₀ p-values) when red indicates that higher MEP values were associated with a lower effect of serum NfL on cortical thickness. Uncorrected threshold of 1.3 corresponding to a log₁₀ of $p = 0.05$. Significant clusters surviving cluster-wise p value (CWP) correction ($p < 0.05$) are outlined in white.

Supplementary File

Left hemisphere

Right hemisphere



Supplementary Figure 1. General linear model (GLM) comparison between control and patient cortical thickness for the left and right hemisphere. The colour scale (signed \log_{10} p-values) indicates decreased cortical thickness in the patient group compared to the control group in red (positive associations are in blue). Uncorrected threshold of 1.3 corresponding to a \log_{10} of $p = 0.05$.

Group	Area	Rater	Abnormalities
P	Atrophy CST	A	No: 43; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 4; Undetermined: 5;
P	Atrophy CST	B	No: 52; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	FLAIR CST	A	No: 45; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 3; Undetermined: 2;
P	FLAIR CST	B	No: 47; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 5; Undetermined: 1;
P	Frontal	A	No: 44; Mild: 8; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Frontal	B	No: 52; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Global	A	No: 38; Mild: 10; Marked: 4; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Global	B	No: 41; Mild: 6; Marked: 4; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Parietal	A	No: 32; Mild: 18; Marked: 2; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Parietal	B	No: 50; Mild: 2; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Precentral	A	No: 42; Mild: 2; Marked: 8; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Precentral	B	No: 52; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Temporal	A	No: 52; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Temporal	B	No: 52; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
P	Precentral Signal	A	No: 48; Mild: 0; Marked: 0; Iso: 4; Hyper: 0; Yes: 0; Undetermined: 0;
P	Precentral	B	No: 50; Mild: 0; Marked: 0; Iso: 2; Hyper: 0; Yes: 0;

	Signal		Undetermined: 0;
C	Atrophy CST	A	No: 61; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 4; Undetermined: 3;
C	Atrophy CST	B	No: 67; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 1;
C	FLAIR CST	A	No: 47; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 5;
C	FLAIR CST	B	No: 60; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Frontal	A	No: 70; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Frontal	B	No: 70; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Global	A	No: 58; Mild: 4; Marked: 8; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Global	B	No: 66; Mild: 4; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Parietal	A	No: 64; Mild: 6; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Parietal	B	No: 68; Mild: 2; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Precentral	A	No: 66; Mild: 0; Marked: 4; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Precentral	B	No: 70; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Temporal	A	No: 68; Mild: 2; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Temporal	B	No: 70; Mild: 0; Marked: 0; Iso: 0; Hyper: 0; Yes: 0; Undetermined: 0;
C	Precentral Signal	A	No: 0; Mild: 2; Marked: 0; Iso: 1; Hyper: 67; Yes: 0; Undetermined: 0;
C	Precentral	B	No: 0; Mild: 0; Marked: 0; Iso: 0; Hyper: 68; Yes: 0;

	Signal		Undetermined: 0;
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Supplementary Table 1. Rating scores for each different area and image type examined between rater (A or B) for both patients (P) and controls (C). CST = corticospinal tract.

Hemisphere	Area	Group	Concordance
Left	Atrophy CST	C	94%
Left	Atrophy CST	P	88%
Left	FLAIR CST	C	88%
Left	FLAIR CST	P	84%
Left	Frontal	C	100%
Left	Frontal	P	85%
Left	Global	C	83%
Left	Global	P	77%
Left	Parietal	C	89%
Left	Parietal	P	65%
Left	Precentral	C	94%
Left	Precentral	P	81%
Left	Temporal	C	94%
Left	Temporal	P	100%
Left	Precentral Signal	C	100%
Left	Precentral Signal	P	96%
Right	Atrophy CST	C	86%
Right	Atrophy CST	P	77%
Right	FLAIR CST	C	92%
Right	FLAIR CST	P	84%
Right	Frontal	C	100%
Right	Frontal	P	85%
Right	Global	C	83%

Right	Global	P	73%
Right	Parietal	C	89%
Right	Parietal	P	65%
Right	Precentral	C	94%
Right	Precentral	P	81%
Right	Temporal	C	100%
Right	Temporal	P	100%
Right	Precentral Signal	C	97%
Right	Precentral Signal	P	96%

Supplementary Table 2. Concordance between raters for each different are and image type examined for both patients (P) and controls (C) according to hemisphere. CST = corticospinal tract.

Group	Area	Abnormalities
P	Atrophy CST	Artefact: 0; Iso: 0; Hyper: 0; Mild: 0; Marked: 0; No: 48; Yes: 4;
P	FLAIR CST	Artefact: 0; Iso: 0; Hyper: 0; Mild: 0; Marked: 0; No: 43; Yes: 7;
P	Frontal	Artefact: 0; Iso: 0; Hyper: 0; Mild: 5; Marked: 0; No: 47; Yes: 0;
P	Global	Artefact: 0; Iso: 0; Hyper: 0; Mild: 5; Marked: 5; No: 42; Yes: 0;
P	Parietal	Artefact: 0; Iso: 0; Hyper: 0; Mild: 12; Marked: 2; No: 38; Yes: 0;
P	Precentral	Artefact: 0; Iso: 0; Hyper: 0; Mild: 3; Marked: 0; No: 49; Yes: 0;
P	Temporal	Artefact: 0; Iso: 0; Hyper: 0; Mild: 0; Marked: 0; No: 52; Yes: 0;
P	Precentral Signal	Artefact: 0; Iso: 2; Hyper: 50; Mild: 0; Marked: 0; No: 0; Yes: 0;
C	Atrophy CST	Artefact: 2; Iso: 0; Hyper: 0; Mild: 0; Marked: 0; No: 64; Yes: 4;
C	FLAIR CST	Artefact: 0; Iso: 0; Hyper: 0; Mild: 0; Marked: 0; No: 52; Yes: 0;
C	Frontal	Artefact: 0; Iso: 0; Hyper: 0; Mild: 0; Marked: 0; No: 70; Yes: 0;
C	Global	Artefact: 0; Iso: 0; Hyper: 0; Mild: 6; Marked: 0; No: 64; Yes: 0;
C	Parietal	Artefact: 0; Iso: 0; Hyper: 0; Mild: 8; Marked: 0; No: 62; Yes: 0;
C	Precentral	Artefact: 0; Iso: 0; Hyper: 0; Mild: 0; Marked: 0; No: 70; Yes: 0;
C	Temporal	Artefact: 0; Iso: 0; Hyper: 0; Mild: 0; Marked: 0; No: 70; Yes: 0;
C	Precentral Signal	Artefact: 2; Iso: 0; Hyper: 68; Mild: 0; Marked: 0; No:

		0; Yes: 0;
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Supplementary Table 3. Rating scores following radiologists' joint consensus for each different areas and image type examined for both patients (P) and controls (C). CST = corticospinal tract.

SERMENT D'HIPPOCRATE

« Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque. »