Spinal cord MRI predictive of disease progression and subtypes in Motor Neurone Disease

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Introduction:

Motor Neurone Disease (MND) is a debilitating and progressive disorder that affects motor neurons (MNs) in the brain and/or spinal cord. Clinical presentation of MND varies, with different subtypes of MND having distinct clinical features and prognoses. MND subtypes include upper/lower (U/L) dominant and mixed disease phenotypes including Primary Lateral Sclerosis (PLS), Progressive Bulbar Palsy (PBP), and Flail Limb

Phenotype (FLP). Each disease subtype has clinical features that define disease progression, spread, and prognoses[1,2].

Uncovering the relationship between neuronal degeneration patterns and MND subtype classification is important for more accurate diagnoses and improved patient care/planning for patient progression[3]. However, this has not been well explored in the spinal cord (SC).

To better understand MND disease heterogeneity, we investigated relationships between newly standardised SC MRI metrics (using the Spinal Cord Toolbox [SCT] [4]), clinical scores, and the different forms of the disease over time. We aim to explore these relationships to better predict disease prognosis and classify diagnostic features.

Methods:

We used a 3T human MRI scanner (PrismaFit, Siemens Healthineers) to scan 22 patients twice over six months with the default SCT imaging and post-processing protocols, which includes diffusion and anatomical MRI scan protocols[5] (Fig. 1).

We collected clinical data including the PLS Functional Rating Scale (PLSFRS)[6] and other neuropsychological/clinical metrics from patients diagnosed with different subtypes of MND of N=(UMN dominant:3, LMN dominant:6, mixed L/UMN:7, PBP:3, PLS:3), as clinically assessed at the Royal Brisbane and Women's Hospital, Australia.

To investigate whether clinical scores and/or diagnosis are related and predictive of the change in different MRI metrics (which are a corollary of neuronal degeneration and faster decline) in patients over time, we conducted Bayesian linear mixed effects (LME) analyses using Stan[7] implemented in R[8], entering formal diagnosis and clinical scores (PLSFRS) as fixed effects, and time as a random effect. MRI spinal cord metrics (Fractional Anisotropy [FA], Magnetisation Transfer Ratio [MTR], spinal cord volume and surface area) were our parameters of interest.

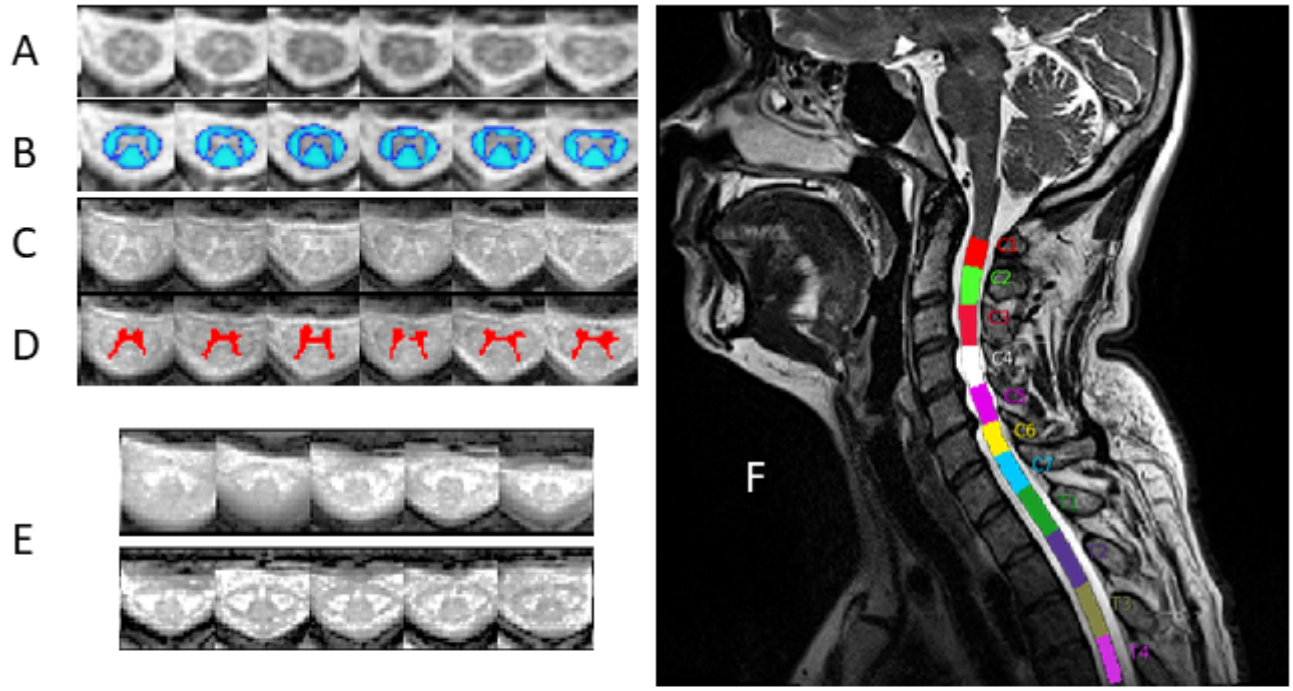

Fig. 1: Using SCT, we extracted Fractional Anisotropy (FA) and Magnetisation Transfer Ratio [A] along the white matter tracts (B) of the SC (vertebrae 2-5 [F]), and grey matter (C and D) and white matter segmentations of the SC along vertebrae 2-5, and cord surface area from C1-C7 (F). E shows marked GM degeneration in one MND patient.

·Figure 1

Results:

Results revealed that clinical diagnosis is significantly related to change in MRI metrics, while PLSFRS scores were not. We found changes in SC metrics are related and predictive of disease diagnosis in LMN dominant, PLS, and mixed MN patients, but not for UMN dominant and PBP patients. We found that the relationship between MRI metrics and diagnosis was significant over time (posterior M = 6.78, 95% CI = 0.73,11.68, Fig. 2). Unique alterations in FA were significantly related to each diagnostic subgroup, independently.

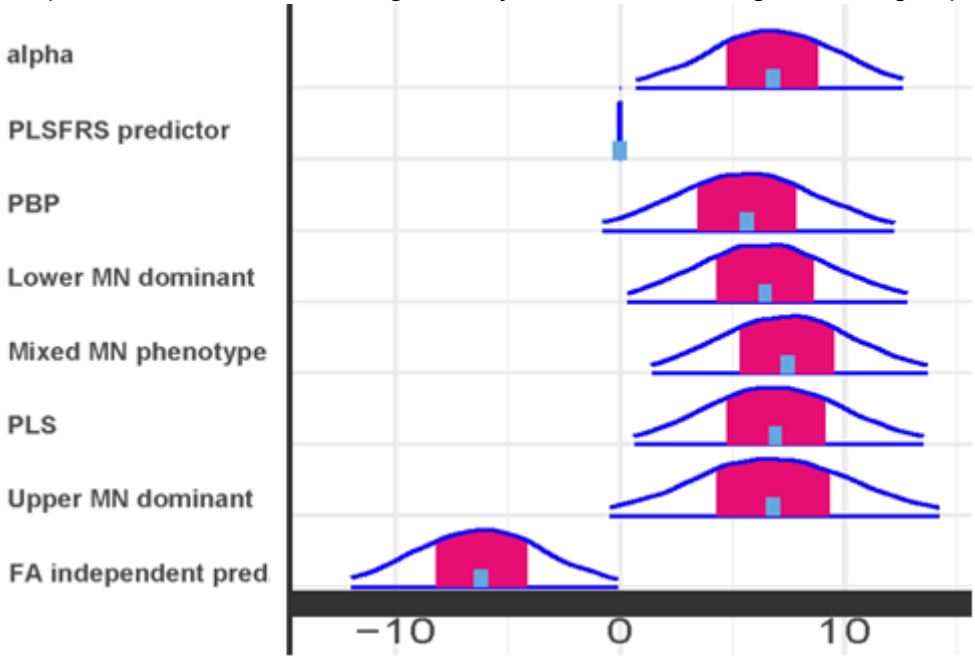

Fig. 2: Prior posterior densities (blue), 95% credible intervals (CIs; horizontal blue) and 50% posterior interval (pink) for variables in the LME model. Y axis shows names of predictors/variables entered into the model. The alpha distribution describes the overall relationship of the outcome variables (MR metrics) across levels of our predictor variables (clinical scores and diagnoses) and is significant, while PLSFRS as a predictor of MRI metrics is not. The following 5 rows represent each diagnosis and its relationship to the MRI metrics, wherein if the CIs pass 0, the relationship is significant. The sigma of FA, which describes the residual variance of FA after accounting for the fixed effects indicates the model is predicting a non-0 effect, or a relationship between the diagnosis and FA independently.

·Figure 2

Conclusions:

These are the first results of a larger study examining the subtypes of MND: "Biomarkers of Long surviving MND (BeLong)", which includes both brain and spinal cord MRI.
We found that a clinical diagnosis is related to changes in SC metrics, while decreases in clinical scores (PLSFRS) are not, which suggests the need for more robust clinical assessment tools[9].
Results indicate that disease subtypes in MND are related differentially to SC MRI metrics including FA, MTR, and SC volume. There was a statistically significant relationship between these metrics and LMN dominant forms of the disease, but not UMN dominant forms of the disease, save for PBP. However, PBP is related to lower MN degeneration in the brain stem (i.e., not the area of the SC assessed here).
Examining relationships between clinical features and SC metrics is crucial for studying both the disease heterogeneity of MND and how its spread is related to diagnosis. We found that SC metrics examined using MRI are strongly related to disease subtype classification, which indicates promise for incorporating these tools clinically.

Disorders of the Nervous System:

Neurodegenerative/ Late Life (eg. Parkinson's, Alzheimer's) [1]

Modeling and Analysis Methods:

Bayesian Modeling
Classification and Predictive Modeling

Neuroanatomy, Physiology, Metabolism and Neurotransmission:

Neuroanatomy Other [2]

Keywords:

DISORDERS
Modeling
Motor
Spinal Cord
Other - Amyotrophic Lateral Sclerosis

[1|2]Indicates the priority used for review

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Not applicable

Please indicate which methods were used in your research:

Neurophysiology
Structural MRI
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Behavior
Neuropsychological testing

For human MRI, what field strength scanner do you use?

3.0T

Which processing packages did you use for your study?

FSL
Free Surfer
Other, Please list - Spinal cord toolbox, ANTs

Provide references using author date format

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