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Loss of the ipsilateral silent period in amyotrophic lateral sclerosis is associated with reduced white matter integrity in the motor section of the corpus callosum

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ABSTRACT

Objective: Interhemispheric neurons in the motor section of the corpus callosum have an inhibitory effect on neurons of the contralateral motor cortex. Three quarters of patients with amyotrophic laterals sclerosis (ALS) show impaired transcallosal inhibition. We aimed to investigate whether structural changes co-occur with this functional impairment and to explore its phenotypic correlates.
Methods: The demographic, clinical, and neuropsychological data of 127 ALS patients were analysed. Transcallosal inhibition was assessed with an ipsilateral silent period (iSP) protocol using transcranial magnetic stimulation. Patients were categorised based on an iSP response or its loss, and the groups were characterised by demographic, clinical, and neuropsychological variables. Diffusion-weighted images from a subset of 63 patients were analysed using tractography, and white matter (WM) structural integrity metrics were compared across groups.
Results: 54 % of patients displayed iSP loss. The average free-water-corrected fractional anisotropy values within the callosal tract between the primary motor cortices were lower for patients with iSP loss compared to patients with an iSP response. There were no group differences based on other diffusivity metrics. The groups did not differ regarding any of the demographic, clinical, or neuropsychological variables.
Interpretation: We found reduced WM integrity in the motor section of the corpus callosum that differentiated ALS patients with iSP loss from patients with an iSP response, but with a small effect size. Nevertheless, the underlying pathological substrate and potential genetic drivers for these structural and functional changes in a subset of ALS patients remain to be satisfactorily investigated.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterised by combined dysfunction of upper and lower motor neurons. ALS has increasingly been recognised as a multisystem disorder with widespread neuropathological changes. The corpus callosum (CC) facilitates communication between the cerebral hemispheres and plays an important role in the coordination of voluntary movement. Patients with a disruption of transcallosal inhibitory signalling display involuntary movements that mirror contralateral voluntary movements, called mirror movements [1,2]. Both neuropathological and diffusion-weighted imaging studies have consistently shown structural changes to CC in ALS [3–6]. The integrity of callosal motor fibres can functionally be assessed by transcallosal inhibition, which is measured by transcranial magnetic stimulation (TMS). Deficits in transcallosal inhibition are common in ALS patients and have been suggested to have a high clinical value as an early diagnostic marker [2,7–11]. In cases with a low diagnostic certainty based on a clinical examination, assessing transcallosal inhibition may offer valuable information [2,9,10].

One measure of transcallosal inhibition is the ipsilateral silent period

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(iSP), which can be measured with a short single-pulse TMS protocol and has been found delayed or absent in 68–81 % of ALS patients, indicative of a reduced functional integrity of transcallosal inhibitory neurons in the motor section of the CC [7,9]. ALS patients with a loss of the iSP show more mirror movements compared with ALS patients with a preserved iSP response and healthy controls [11]. Furthermore, reduction in transcranial inhibition is correlated with a faster rate of disease progression [12]. However, no associations have been found between reduced transcranial inhibition and age [11,12], disease duration [11,12], sex [12], ratings on the revised ALS Functional Rating Scale (ALSFRS-R) [9,12], site of onset [9], or muscle strength in ALS patients [11]. It was our intent to extend these previous findings by utilising a large and representative sample that would enable a well-powered investigation of associations. The aim of this study was to correlate transcallosal inhibition with non-motor functioning in our ALS cohort. We opted to focus on non-motor functioning in the form of cognition and behaviour as cognitive and behavioural changes in ALS patients have been established as prominent non-motor symptoms [13] and have been associated with wide-spread structural changes [14–16]. No study seems to have investigated whether cognitive and behavioural changes are more likely to co-occur with impaired transcallosal inhibition. Furthermore, no previous studies have identified associations of structural integrity changes in white matter (WM) with this functional impairment [7,9].

To address this knowledge gap, we studied a large sample of ALS patients (i) to assess the structural correlates of pathological transcallosal inhibition in the callosal tract between motor cortices, and (ii) to compare the demographic, clinical, and neuropsychological profiles of ALS patients with intact and deficient transcallosal inhibition as assessed by an iSP protocol.

2. Methods

2.1. Participants

In this single centre retrospective study, we analysed data from 127 patients who were recruited between 01/2011 and 10/2023 by the department of neurology of the Rostock University Medical Centre and completed a transcranial magnetic stimulation (TMS) assessment. Patients were classified according to the modified El Escorial criteria for ALS [17] ($n = 127$). A subsample of 9 cases additionally met the Rascovsky criteria for frontotemporal dementia [18]. All patients received a clinical and neurological examination and were characterised on the ALSFRS-R [19]. Exclusion criteria included a history of brain injury, epilepsy, or psychiatric illness.

2.2. Neuropsychological assessment

The neuropsychological assessment included the German versions of the Montreal cognitive assessment (MoCA) [20], the Edinburgh cognitive and behavioural ALS screen (ECAS) [21,22], and the Frontal System Behaviour Scale (FrSBe) [23]. Cognitive and behavioural impairments were classified according to the revised Strong criteria. Cognitive deficits were assessed with ECAS based on norms from a Swiss and German sample [22]. A behavioural classification was based either on the age- and education-normed informant version of FrSBe [23], or on clinical observation by an experienced neuropsychologist, or both.

2.3. TMS acquisition

Motor evoked potentials (MEP) were recorded from the abductor pollicis brevis (APB) or the first dorsal interosseous (FDI) muscle of each hand with a circular coil (outside diameter 9 cm) connected to a Magstim 200 stimulator (Magstim Co., UK) in a Micromed EP system (Micromed, Germany). Voluntary electromyography activity was recorded with silver/silver chloride surface electrodes in a belly-tendon montage and monitored by audiovisual feedback. The point of optimal excitability was determined.

ISP was recorded with a 7 cm diameter figure-of-eight coil by stimulating at 1.5 times the resting motor threshold while patients maintained a maximum tonic activation of the ipsilateral muscle and relaxed the contralateral muscle. 10 trials per hemisphere were recorded and the latency was averaged after offline rectification.

Peripheral motor latency was measured using foraminal electromagnetic stimulation with a round coil centered over the C7/C8 cervical spine and the central motor conduction time (CMCT) was calculated by subtracting the shortest recorded peripheral nerve component from the shortest total corticomotor latency. CMCT was considered abnormal if longer than 9 ms [24,25].

2.4. MRI acquisition and preprocessing

MRI datasets were available for 63 ALS patients, none of whom had a concurrent dementia diagnosis. Diffusion-weighted imaging data were acquired on two scanners at the Rostock University Medical Centre (Rostock, Germany): a 3 Tesla Siemens Skyra Fit scanner (2018–2022) or a Siemens Vida scanner (2022−2023). The MRI diffusion sequence was applied with the following parameters: repetition time = 12,100 ms, echo time = 88 ms, field of view = 240 mm, isotropic resolution = 2 mm, b-values = 700 and 1000 s/mm^2, diffusion directions per b-value = 30, b0 images = 10, slices = 72, phase encoding AP. The data were processed in FSL (www.fmrib.ox.ac.uk/fsl, version 6.0.3). Pre-processing included brain-tissue extraction [26] and correction for eddy currents and motion [27].

T_1-weighted MR images were acquired with a magnetization prepared rapid gradient echo sequence with the following parameters: 192 sagittal slices, field of view = 256 × 256 mm^2, image matrix = 256 × 256, isotropic voxel size = 1 mm^3, echo time = 4.37 msec, repetition time = 2500 msec, flip angle = 7°. The data were segmented with cat12 [28] in SPM12.

2.5. Estimation of diffusivity metrics

A bi-tensor model was fitted to the eddy-corrected diffusion data using the Diffusion Imaging in Python algorithm [29], which allowed the estimation of free water fraction (FWf), free water-corrected fractional anisotropy (fwFA), free water-corrected mean diffusivity (fwMD), free water-corrected axial diffusivity (fwAD), and free water-corrected radial diffusivity (fwRD). For comparison purposes, a one-compartment tensor model was fitted to estimate the equivalent non-free-water-corrected maps using FSL's dtifit [30] (FA, MD, AD, RD). The analyses with non-corrected data are included in the supplementary material.

To achieve a higher accuracy of registration within the analyses, an unbiased group template was estimated from the FA images of all patients using Advanced Normalization Tools' (ANTs) buildtemplate function [31]. The transformations from this step were applied to warp the diffusivity maps into group template space for voxel-level SPM analyses.

2.6. Regions of interest

Six region of interest (ROI) masks were used to guide the probabilistic tractography. Both the right and the left precentral gyrus upper limb area from the Brainnetome Atlas [32] were used as seed and target regions. To constrain the tractography to the motor section of the CC, the equivalent CC mask from the Brainnetome Atlas [32] was included as the waypoint, and the masks of external capsule, internal capsule, and superior longitudinal fasciculus from the Johns Hopkins University (JHU) WM atlas [33] were used as exclusion masks. All masks were in the JHU WM atlas standard space.

All ROIs were transformed into each individual's T_2 space by

applying two transformations in one step. The group template was registered to the mean FA image from the JHU WM atlas. The inverse transformation of this step and the inverse transformation from the group template creation step were applied to warp the ROIs into each patient's T_2 space. All transformations were estimated with ANTs' non-linear SyN registration algorithm [34].

2.7. Tractography

The diffusion parameters were calculated with FSL's BedpostX using the eddy-corrected DWI data and a standard ball-and-sticks model with three fibres modelled per voxel [35,36]. FSL's ProbtrackX was used for probabilistic tracking by generating 5000 random samples from the seed ROI [35,36]. Two tractograms were calculated for every patient, starting on the right and left side. The equivalent ROI in the opposite hemisphere was used as the target. Per patient, the two tractograms were combined and transformed into the group template space to estimate a group tract.

The group tract was created by incorporating all voxels that were included in at least 90 % of the individual patient tracts based on visual inspection (Fig. 1). Subsequently, the group tract was transformed back into each patient's T_2 space, and average diffusivity metrics were extracted from voxels belonging to the tract for each participant.

To control for unspecific individual differences in diffusivity metrics, a control mask was created for each patient by subtracting the group tract from the patient's whole-brain WM segment (from running cat12 on T_1-weighted images). Per diffusivity metric, the mean value of the voxels belonging to the control mask was entered as a covariate in statistical analyses.

2.8. Statistical analysis

The statistical analyses were completed in Jeffreys's Amazing Statistics Program (https://jasp-stats.org) and R (https://www.r-project.org/). We selected Bayes factor (BF) hypothesis testing. The calculation of BF enables a quantification of evidence, which may either support or oppose an effect of interest. The data can either support the presence of an effect ($BF_{10} \geq 3$), the absence of an effect ($BF_{10} < 0.33$), or offer inconclusive evidence (BF_{10} between 0.3 and 3). After determining the presence or absence of an effect, the posterior distribution of the plausible standardised parameter values for the estimated effect can be examined. The mean of this posterior distribution gives a point estimate for the parameter value and a credible interval summarises the probability distribution for the plausible parameter values for this effect of interest. The width of the credible interval implies the level of reliability of the estimation, and the inclusion of 0 in the credible interval indicates the plausibility of lack of effect.

The whole sample was categorised based on whether they showed iSP response or its loss. The equivalence of the iSP response vs iSP loss groups was compared on numerous demographic, clinical, and neuropsychological variables. The equivalence of groups on categorical variables was compared utilising Bayesian chi-squared tests (independent multinomial sampling plan), and on standardised continuous variables using Bayesian *t*-tests. For each demographic, clinical, and neuropsychological variable, the presence of an effect was evaluated by inspecting the BF_{10}, after which the mean and the 95 % credible interval of the posterior distribution for this estimated effect was determined.

Voxel-wise t-tests of the group tract's diffusivity metrics were carried out between patients with iSP loss versus iSP response in SPM12 in Matlab (https://www.fil.ion.ucl.ac.uk/spm/). To control for unspecific individual differences in WM integrity, the parameter value in whole-brain WM excluding the group tract was included as a covariate. Further covariates included age and sex. The WM diffusivity metrics within the group tract were also compared in volume of interest (VOI) analyses between the groups using Bayesian univariate analysis of covariance (ANCOVA), while controlling for age, sex, and the whole-brain diffusivity metric from the respective control mask. For each diffusivity metric, the BF_{10} for group effect was calculated as well as the mean and the 95 % credible interval of the posterior distribution for the estimated effect.

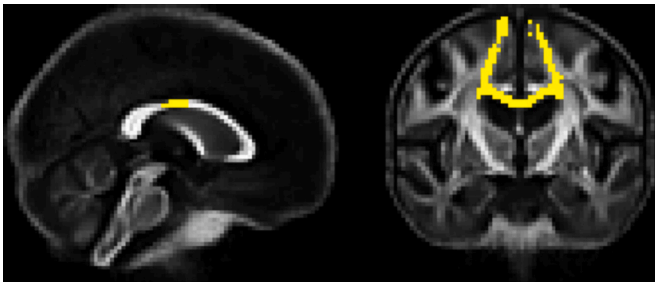

Fig. 1. Group tract between the primary motor cortices projected onto the group template.

3. Results

54 % of the patients had iSP loss. The iSP response was measured in the APB muscle in 59 patients (46 %) and in the FDI muscle in 68 patients (54 %). The proportion of patients with iSP loss was 64 % when assessing the APB muscle compared to 46 % when assessing the FDI muscle. For patients with an iSP response, the average latency was 43.276 (± 6.517) when measuring from the left hand and 43.954 (± 4.812) when measuring from the right hand. A small proportion of patients showed a loss of iSP on one side and an iSP response on the other side (3 with iSP loss only on the right side, 3 on the left). In seven patients, measurement was only possible on one side due to advanced lower motor neuron damage. CMCT was abnormally slow in 17 % of patients on the left side and in 19 % of patients on the right side.

The demographic and clinical characterisation of the sample can be found below (Table 1). There was moderate evidence that age, sex, phenotypic composition, years of education, and the distribution of Strong classification did not differ between the groups. There was strong evidence that the CMCT on the left side was higher in the iSP loss group than in the iSP response group. Additionally, there was strong evidence that the genetic composition did not differ between the groups ($BF_{10} = 0.040$). In terms of cognitive and behavioural metrics, there was anecdotal to moderate evidence that MoCA score, ECAS total and subscores, FrSBe total and subscores did not differ between the groups (all BF_{10} between 1.8 and 0.2, data shown in supplementary table S1). Despite the sample size of 127 patients, our findings were inconclusive with respect to both the existence (H_A) or absence (H_0) of group differences between patients with iSP loss and patients with an iSP response on the remaining variables (BF_{10} between 0.3 and 3).

The free-water-corrected data offered strong support that ALS patients with iSP loss had lower fwFA values within the WM tract connecting primary motor cortices ($BF_{10} = 53.741$). The sequential analysis of the level of support (BF_{10} value) for the alternative hypothesis of a group difference with an increasing number of cases is plotted in Fig. 2B. The posterior distribution for the effect of a group was centred at 0.28 (95 % credible interval of 0.11–0.45), indicating a small effect (Fig. 2C). There was no strong evidence for the presence or absence of group differences based on other free-water-corrected diffusivity metrics (Table 2). The equivalent analyses with non-free-water-corrected data can be found in the supplementary material (Table S2). The sequential analysis plot and posterior distribution for fwMD can be found in Fig. 2. Voxel-based analyses of the diffusivity metrics in the group tract did not result in any clusters of group differences at the significance threshold of $p < 0.001$. The figure with non-corrected data is included in the supplementary material (Fig. S1).

Table 1
The demographic and clinical characterisation of the sample.

	N	iSP response	iSP loss	BF_{10}	Mean (95 % CI)
Group size: count (%)	127	58 (45.7 %)	69 (54.3 %)		
Muscle: APB/FDI	127	21/37	38/31	2.036	0.182 (0.017, 0.349)
Age: mean (SD)	127	64.0 (11.7)	64.0 (11.1)	0.190	0.002 (−0.172, 0.170)
Sex: male/female	127	38/20	46/23	0.232	−0.014 (−0.200, 0.163)
Education years: mean (SD)	125	13.1 (2.8)	12.8 (2.5)	0.225	−0.049 (−0.221, 0.122)
Months since onset: median (IQR)	118	15.0 (7.3–25.0)	13.0 (7.8–28.0)	0.385	0.102 (−0.078, 0.284)
Delta FS: median (IQR)	113	0.7 (0.4–1.2)	0.7 (0.3–1.4)	0.417	0.109 (−0.075, 0.292)
Site of onset: bulbar/spinal	119	19/32	17/51	0.673	−0.136 (−0.326, 0.050)
Phenotype: count (%)				0.155	
Classical ALS		40 (69 %)	49 (71 %)		
UMND		9 (16 %)	9 (13 %)		
LMND		5 (8 %)	7 (10 %)		
Not classifiable	119	4 (7 %)	4 (6 %)		
CMCT: median (IQR)					
left	107	7.3 (6.6–7.9)	7.7 (6.5–9.2)	5.987	0.238 (0.051, 0.422)
right	108	7.2 (6.3–8.3)	7.6 (6.9–9.1)	1.588	0.185 (0.002, 0.371)
Strong criteria: count (%)	105			0.128	
ALSni		19 (40 %)	24 (41 %)		
ALSci		16 (34 %)	18 (31 %)		
ALSbi		6 (13 %)	3 (5 %)		
ALScbi		6 (13 %)	13 (22 %)		

APB, abductor pollicis brevis muscle; BF_{10}, Bayes factor for the presence of group difference; CI, credible interval; CMCT, Central motor conduction time; Delta FS, the progression rate in ALS Functional Rating Scale-Revised (ALSFRS-R); FDI, first dorsal interosseous muscle; IQR, inter-quartile range; iSP, ipsilateral silent period; LMND, lower motor neuron dominant variants (including progressive muscle atrophy, flail arm, flail leg); N, sample size; SD, standard deviation; UMND, upper motor neuron dominant variants (including primary lateral sclerosis).

4. Discussion

We assessed transcallosal inhibition with the iSP protocol in a relatively large sample of ALS patients. In accordance with previous publications, we observed iSP loss in 54 % of the patients in our sample [7,9]. Furthermore, we were also able to demonstrate a structural neuroimaging correlate of this functional impairment, owing to a different methodological approach than in previous studies. The average fwFA values within the callosal tract between the primary motor cortices were lower for patients with iSP loss compared to patients with an iSP response. This group difference had a small effect size, and its detection seemed to require a larger sample size than was available in previous studies [7,9], as suggested by the sequential analysis. Therefore, the small effect size demonstrated by our hypothesis-directed analyses is not in opposition to the negative findings of previous studies.

Even though fwFA is minimally affected in the motor section of the corpus callosum in patients with iSP loss, other WM integrity metrics did not differ between patients with intact iSP and iSP loss, and a voxel-level group comparison within this callosal tract between the primary motor cortices did not identify any clusters. Regardless of this, a large proportion of ALS patients shows a marked disruption of the transcallosal inhibitory reaction. High rates of both increased latency of the iSP response and its complete loss have been described in ALS samples compared to control participants [7–9,11]. Thus, it would seem that even slight structural changes, which may not always be successfully identifiable with standard imaging analyses, may suffice to disrupt the normal transcallosal inhibition response. As also demonstrated by the previous studies, the functional TMS measurement is clearly a more sensitive index of transcallosal inhibition changes than structural metrics.

We further compared the patients with intact and deficient transcallosal inhibition regarding numerous demographic, clinical, and neuropsychological variables. We found an association with the CMCT, which was prolonged in ALS patients with iSP loss. Slowed corticospinal conduction has been commonly reported in ALS [37] and related to changes in WM metrics [38]. Besides this, we found anecdotal to strong evidence for the absence of a group effect for all other assessed variables, implying that the impairment of transcallosal inhibition is a specific characteristic in ALS patients that offers information distinct from demographic, clinical, and neuropsychological data. The motor section of the corpus callosum has been highlighted as one of the most markedly involved regions in ALS patients in diffusion imaging as well as post-mortem pathologic studies [5,39]. However, the reasons for the individual differences in the extent of WM structural changes in ALS patients and the impaired transcallosal inhibition that occurs in some of them need further investigation.

Some limitations of this study need to be considered. First, we chose to focus on the clear-cut dichotomous categorisation of transcallosal inhibition impairment to ensure an expectation of a high pathological load in the iSP loss group, which would be vital for discovering any possible co-occurrences with white matter structural changes. This choice of excluding the investigation of iSP latency values could have resulted in reduced sensitivity in identifying changes to the transcallosal inhibition. It should, however, also be noted, that the implications of increased iSP latency remain somewhat unclear. Second, whereas the iSP was measured from the FDI muscle at the start of data collection, the target was changed halfway through to the APB muscle, which has been shown to offer a more valid measurement [40]. Accordingly, a larger proportion of ALS patients in our sample showed a loss of iSP when measuring from the APB muscle (64 %) compared to the FDI muscle (46 %). Therefore, the overall prevalence of iSP loss may remain underestimated based on our data. Third, the presence of mirror movements as a clinical correlate of transcallosal inhibition impairment was not explored in our sample.

A valid measurement of iSP is only possible with sufficient innervation of the target muscle, which is a potential problem in ALS patients with advanced lower motor neuron degeneration. Indeed, in 6 % of our sample, measurement was only possible on one side due to the extent of lower motor neuron damage. Thus, future investigations should include compound muscle action potential amplitudes and muscle strength estimations to quantify the lower motor neuron degeneration and its influence on iSP measurement. Additionally, future studies could compare ALS to other neurodegenerative diseases in which patients display mirror movements and disrupted transcallosal inhibition such as asymmetric parkinsonian disorders as in early Parkinson's disease or corticobasal syndrome.

5. Conclusion

ALS patients with impaired transcallosal inhibition as assessed by the iSP showed reduced integrity of WM connections between the motor cortices. We identified no further phenotypical correlates of iSP loss, despite the relatively large sample size and the examination of numerous demographic, clinical, and neuropsychological parameters. Therefore, the reasons underlying these structural and functional changes in more

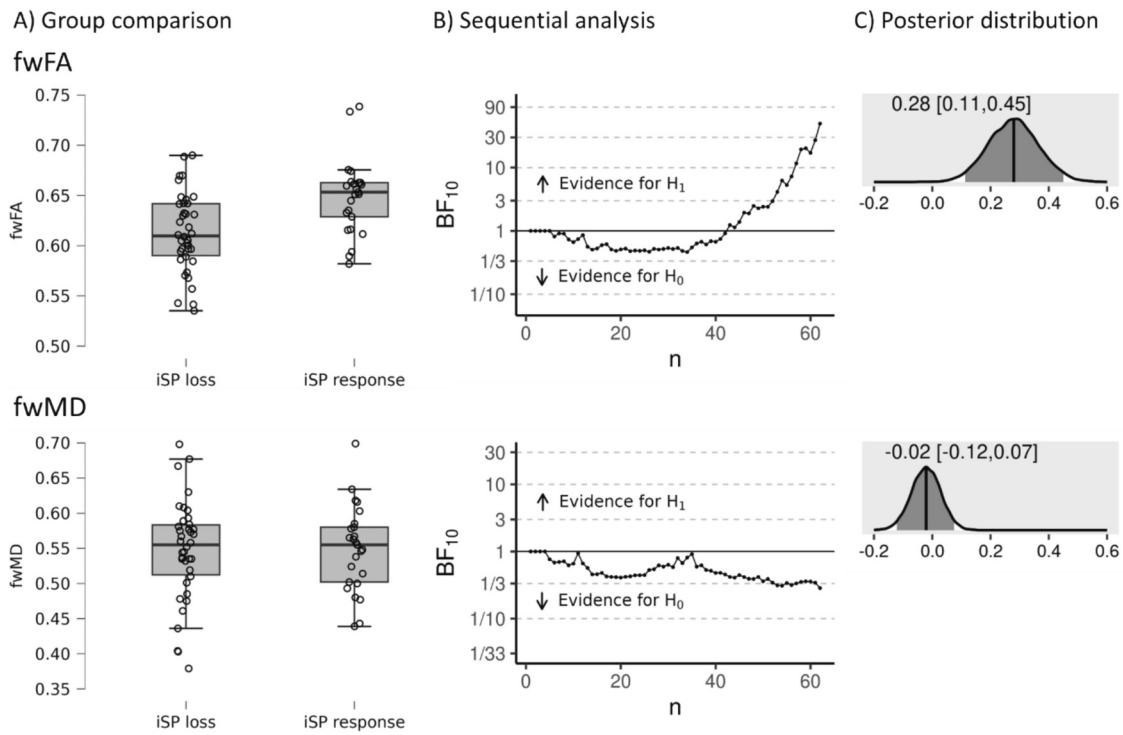

Fig. 2. Comparison of diffusivity metrics within the WM tract connecting primary motor cortices in patients with and without a loss of iSP. A) Box plots of fwFA values and fwMD values for the groups. In each box plot, the central line corresponds to the median, the upper and lower borders of the box to the 25th and 75th percentiles, respectively, and the length of the whiskers to 1.5 times the interquartile range. The fwMD values have been multiplied by 1000. B) Sequential analyses demonstrating the internal coherence of Bayesian ANCOVA for fwFA and fwMD data. The alternative hypothesis that the groups differ on the diffusivity metric reached a level of strong support ($BF_{10} > 10$) with the sequential inclusion of 58 cases for fwFA data. After the inclusion of all cases, there was very strong evidence for group differences on the fwFA metric and moderate evidence for a lack of group differences on fwMD metric. C) The posterior distributions of standardised parameter estimates for the effect of group for fwFA and fwMD data by Bayesian ANCOVAs. The median is marked with a solid line, the 95 % credible intervals are marked in grey, and the values are stated in each plot.

Table 2
The free-water-corrected diffusivity metrics and group differences.

Diffusivity metric	iSP response group mean (SD)	iSP loss group mean (SD)	BF_{10}
fwFA	0.649 (0.037)	0.613 (0.039)	53.741
fwMD	0.549 (0.061)	0.546 (0.072)	0.281
fwRD	0.329 (0.045)	0.346 (0.052)	1.107
fwAD	1.015 (0.112)	0.970 (0.129)	0.498
FWf	0.220 (0.043)	0.222 (0.043)	0.481

BF_{10}, Bayes factor for the effect of group in Bayesian ANCOVA including age, sex, and metric value in control mask as covariates; fwAD, free-water-corrected axial diffusivity; FWf, free-water fraction; fwFA, free-water-corrected fractional anisotropy; fwMD, free-water-corrected mean diffusivity; fwRD, free-water-corrected radial diffusivity; iSP, ipsilateral silent period; SD, standard deviation. The values for fwMD, fwRD and fwAD have been multiplied by 1000.

than half of all ALS patients remain to be satisfactorily investigated, and further research (genetic investigations, in particular) would be beneficial.

Ethical statements

The study was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients gave their written informed consent, and the study was approved by the local medical ethics committee.

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CRediT authorship contribution statement

Annaliis Lehto: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Julia Schumacher:** Writing – review & editing, Methodology. **Elisabeth Kasper:** Writing – review & editing, Conceptualization. **Stefan Teipel:** Writing – review & editing. **Andreas Hermann:** Writing – review & editing, Funding acquisition, Conceptualization. **Johannes Prudlo:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

S.T. served on advisory boards of Lilly, Eisai, and Biogen, and is member of the independent data safety and monitoring board of the ENVISION study (Biogen).

Data availability

The data analysed in the current study can be received from the corresponding author upon reasonable request from qualified investigators.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.123267.

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