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Instrumented assessment of lower and upper motor neuron signs in amyotrophic lateral sclerosis using robotic manipulation: an explorative study

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is a lethal progressive neurodegenerative disease characterized by upper motor neuron (UMN) and lower motor neuron (LMN) involvement. Their varying degree of involvement results in a clinical heterogenous picture, making clinical assessments of UMN signs in patients with ALS often challenging. We therefore explored whether instrumented assessment using robotic manipulation could potentially be a valuable tool to study signs of UMN involvement.

Methods We examined the dynamics of the wrist joint of 15 patients with ALS and 15 healthy controls using a Wristalyzer single-axis robotic manipulator and electromyography (EMG) recordings in the flexor and extensor muscles in the forearm. Multi-sinusoidal torque perturbations were applied, during which participants were asked to either relax, comply or resist. A neuromuscular model was used to study muscle viscoelasticity, e.g. stiffness (k) and viscosity (b), and reflexive properties, such as velocity, position and force feedback gains (kv, kp and kf, respectively) that dominated the responses. We further obtained clinical signs of LMN (muscle strength) and UMN (e.g. reflexes, spasticity) dysfunction, and evaluated their relation with the estimated neuromuscular model parameters.

Results Only force feedback gains (kf) were elevated in patients ($p=0.033$) compared to controls. Higher kf, as well as the resulting reflexive torque (Tref), were both associated with more severe UMN dysfunction in the examined arm ($p=0.040$ and $p<0.001$). Patients with UMN symptoms in the examined arm had increased kf and Tref compared to controls (both $p=0.037$). Neither of these measures was related to muscle strength, but muscle stiffness (k) was lower in weaker patients ($p=0.012$). All these findings were obtained from the relaxed test. No differences were observed during the instructions comply and resist.

Conclusions This findings are proof-of-concept that instrumented assessment using robotic manipulation is a feasible technique in ALS, which may provide quantitative, operator-independent measures relating to UMN

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symptoms. Elevated force feedback gains, driving larger reflexive muscle torques, appear to be particularly indicative of clinically established levels of UMN dysfunction in the examined arm.

Keywords Amyotrophic lateral sclerosis, Upper motor symptoms, Biomarkers, Robotic manipulation, EMG

Background

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that is characterized by progressive degeneration of upper motor neurons (UMN) and lower motor neurons (LMN) [1]. Neurophysiological techniques can provide reliable evidence of subtle or subclinical LMN involvement to aid in diagnosis [2, 3]. Currently, imaging and neurophysiological techniques that could help assess UMN dysfunction, such as transcranial magnetic stimulation, are delivering promising results [4]. Still, contrasting results and substantial technical and methodological challenges persist [5–7], warranting the further exploration of alternative, potentially complementary techniques.

Instrumented assessment of limb motor function using small robotic manipulators has been implemented to study classic UMN signs, such as spasticity, in patients with UMN lesions or disorders including stroke, cerebral palsy and Parkinson's disease [8–17]. Analogous to clinical assessment, these techniques rely on the application of programmed external perturbations to a limb, after which the limb's response is quantified in terms of forces or torques, joint rotations or deviations and muscle activity using EMG. Neuromuscular models can, subsequently, be used to study the complex interaction between muscle viscoelastic properties, resulting from contraction, and reflexive properties, such as the afferent feedback from muscle spindles [12–14, 18–20]. These reflexive properties are modulated, at least in part, by the central nervous system [21] and may therefore be valuable measures to study and detect signs of UMN loss, such as increased tendon reflexes and spasticity [22]. The UMN syndrome in ALS is more complex, however, as loss of all classes of motor neurons in the anterior horn of the spinal cord can progressively disrupt the expression of symptoms emanating from UMN loss [23]. As such, it remains to be established whether estimates of reflexive properties are an informative measure to study UMN symptoms in ALS.

The goal of this study was, therefore, to explore instrumented assessment of ALS patients using robotic manipulation of the wrist. Our aims were: (1) to obtain and compare the reflexive and viscoelastic properties of patients to healthy controls and; (2) to explore if these neuromuscular properties can serve as measures to quantify signs of UMN loss. Here, we hypothesize that reflexive properties obtained from the wrist will be elevated in patients with UMN signs in the examined arm compared to those without. As muscle viscoelasticity is modulated by contraction, we, additionally, expect that patients with lower strength also exhibit reduced muscle viscoelasticity during all tests.

Methods

Study design

We performed a cross-sectional cohort study in a convenience sample of 15 consecutive patients with ALS at our outpatient clinic in the University Medical Center Utrecht between 2021 and 2022. To ensure that patients could perform the tasks with low physical burden, we excluded patients with severe weakness in the wrist joint, e.g. extensor or flexor carpi radialis (ECR, FCR) muscle strength ≤ 2 on the MRC scale [24]. Other reasons for exclusion were: presence of active psychiatric diseases,, frontotemporal dementia, concomitant neuropathy, brain injuries, epilepsy or other cerebral diseases, and any condition that may cause discomfort during motion of the wrist, that could influence the study results. Reference neuromuscular properties were derived from 15 gender-matched controls without neurological disorders. All patients and controls gave informed consent. The study was performed in accordance with the Declaration of Helsinki and was approved by the medical ethics committee of the University Medical Center Utrecht.

Cohort characterization

Scores from ALS functional rating scale (ALSFRS-R) were used to characterize the patients' disease progression. The fine motor function (FMF) subdomain score of the ALSFRS-R was used to characterize disease progression in the cervical region. Neurological examinations were performed by an experienced physician. Presence of UMN symptoms in the cervical region, either on the left or right side, was determined according to the El-Escorial Criteria for ALS [25]. In the robotically manipulated arm, presence of UMN symptoms was defined by at least three elevated reflexes, or one pathologically elevated reflex of the triceps, biceps or brachioradial tendons, or the presence of clonus. Lastly, we determined a summed UMN score for the examined arm in a similar manner to the Penn UMN score [26], as follows: reflexes of the biceps, triceps or brachioradial tendon were scored as 0 (normal), 1 (elevated) or 2 (pathologically elevated); evocable Hoffman's sign, the presence of clonus anywhere in the limb and the presence of hypertonia in the limb were each scored as 1; otherwise a score of 0 was given. Hence, the UMN score ranged between 0 and 9. Muscle strength of the FCR and ECR was graded using the MRC scale

to document signs of LMN loss, with clinical weakness defined by MRC score lower than 5. Absolute strength of these muscles was determined during the study procedures, described below.

Study procedures

Recording setup and data acquisition

Participants were seated in a chair with their elbows slightly flexed and their feet supported, approximately 1 m from a screen. Instrumented assessment of the patients' wrists was performed using the Wristalyzer single-axis wrist manipulator (MOOG FCS, Nieuw Vennep, The Netherlands) [27] (Fig. 1A). This manipulator was programmed to provide a multi-sinusoidal torque perturbation signal [28, 29] (supplementary material). This type of signal consists of summation of multiple sinusoidal signals with pre-specified frequencies and random phases to elicit reflexive behavior. Wrist angles and torques in response to the perturbations were recorded directly by the Wristalyzer (Fig. 1B-D). Here, wrist angles were defined by the angular deviation from a neutral position, with flexion corresponding to positive angles and extension to negative angles. Activation of the ECR and FCR muscles was recorded using bipolar surface electrodes (Red Dot, 3 M Health Care, Germany) and the resulting EMG data was bandpass filtered (20–450 Hz, third-order Butterworth) and rectified. Maximum voluntary contraction tests were performed in flexion and

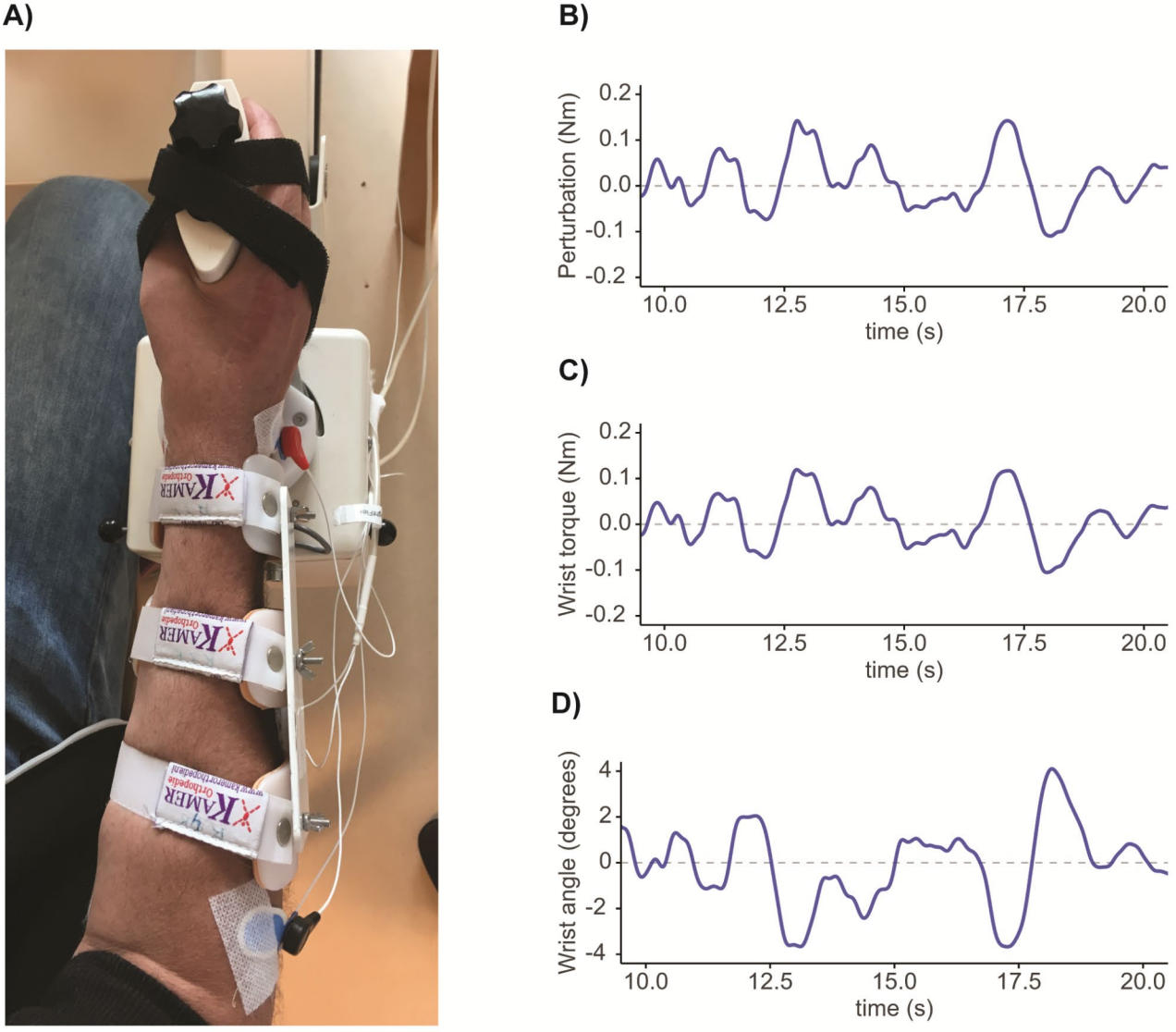

Fig. 1 Measurement setup and the mechanical responses to a torque perturbation. Plots depict: (**A**) setup of the wrist in the handle of the Wristalyzer; (**B**) the torque perturbation introduced by the Wristalyzer; (**C**) response torque produced by the participant's wrist and; (**D**) the introduced wrist angle. For legibility in this figure, signals are depicted as partial recording between 10–20 s seconds and Butterworth low-pass filtered at 3 Hz

extension (3x per direction), from which two EMG-to-torque ratios were determined [28]. Finally, muscle activation torque was calculated by summing the ECR and FCR signals scaled by their respective EMG-to-torque ratios.

Experimental protocol

First, we assessed participants' wrist strength by performing maximum voluntary contraction tests in both flexion and extension (6s duration, 3x per direction). Wrist strength was characterized by the maximal flexion and extension torques and the sum of these two measures. Then, we performed a protocol consisting of one passive test and various active tests, presented by Mugge et al. [20]. This protocol was selected to explore multiple modalities of motor control behaviour. The instructions for the tests were as follows:

(1) minimize muscle activity to ensure passive behavior (relaxed test);

(2–3) maintain a bias force of 5% and 10% of MVC by complying with the perturbations (compliance test) and;

(4) maintain a fixed posture by resisting the perturbations (resistance test).

These tests were explained in depth and practiced in order to familiarize participants with the sensations introduced by the perturbation. Hereafter, each test was recorded 3 times for averaging purposes (3×4 test, 12 total recordings). To assure approximate linear behavior, the amplitude of the perturbation signal was modulated such that the resulting wrist angles were small (SD ~ 1°). Performance during the active tasks was quantified by the standard deviation of wrist torque during compliance tests and wrist angles during the resistance tasks. Visual feedback was supplied on screen to minimize drift from target force for the compliance tests or position for the resistance tests.

Estimation of reflexive and muscle viscoelastic properties

Model and parameter description

We used the extensive neuromuscular model incorporated in NMCLab to quantify the contributions of various physiological structures to the overall joint dynamics [18]. The model scheme and equations are provided in the supplementary material. This model determines muscle torque as a result of changes in muscle length using a viscoelastic element with stiffness (k) and viscosity (b), and a reflexive pathway. This latter pathway consists of a muscle spindle represented by a velocity and position feedback gain (kv, kp) and a Golgi tendon organ represent by a force feedback gain (kf). Muscle viscoelastic and reflexive properties were estimated for each test (4×5 parameters). Neural delays of the proprioceptive feedback (τ_{MS} – muscle spindle, τ_{GTO} – Golgi tendon organ), wrist inertia (I) and muscle activation dynamics (fa, β) were considered test independent (see supplementary data). Finally, the combined reflexive response after a deviation was obtained by incorporating muscle activation dynamics. The root-mean-square of the reflexive torque (Tref) was obtained from simulation as an additional simple endpoint to evaluate the effect of combined changes in reflexive properties.

Parameter estimation procedure and validation

Parameter estimates were obtained by fitting the model onto the wrist dynamics, which were obtained using a closed-loop frequency domain identification procedure [19]. We characterized participants' wrist dynamics by two frequency response functions for each task. First, the joint admittance described the relation between wrist torque and rotations. The joint admittance is best interpreted as the level of compliance to disturbances. A joint with low admittance will be stiff (e.g. resistance test), whereas a joint with high admittance will be compliant (e.g. relaxed or compliance test). Second, we determined the reflexive impedance, which describes the relation between wrist angles and muscle activation torque. We then fitted the neuromuscular model onto the obtained wrist dynamics by minimizing the following criterion function:

$$\begin{aligned} E = & \sum_i \sum_f {\gamma_{T\theta}}^2 \left| \log(\widehat{H}_{T\theta}) - \log(H_{T\theta}) \right| \\ & + q {\gamma_{\theta A}}^2 \left| \log(\widehat{H}_{\theta A}) - \log(H_{\theta A}) \right| \end{aligned} \quad (3)$$

Here, $H_{T\theta}(f)$, $\hat{H}_{T\theta}(f)$, $H_{\theta A}(f)$, and $\hat{H}_{\theta A}(f)$ denote the modeled and measured joint admittance and reflexive impedance of each test (i) at frequency (f), respectively. The criterion was weighted by the coherences ${\gamma_{T\theta}}^2(f)$ and ${\gamma_{\theta A}}^2(f)$, to reduce reliance on frequencies with noisy or non-linear estimates. The reflexive impedance error was weighted by q to yield approximately 25% of the total error. We assessed the goodness-of-fit of the optimized models for each test using the variance accounted for (VAF), which is reduced by either noise or unmodeled behavior.

Statistical analysis

Participant characteristics were compared using t-tests for normal distributed data or Mann-Whitney U tests for non-normal distributed data. Categorical data were compared with Fisher's exact test. Differences between the neuromuscular parameters and Tref of patients and controls were evaluated per performed test using t-tests. The relation between patients' clinical characteristics and the neuromuscular parameters and Tref was examined using linear regression models for continuous variables; Mann-Whitney U tests were used for non-continuous variables with Holm's correction to address multiple comparisons.

Data are presented as median [IQR], unless otherwise stated. *P*-values < 0.05 were considered significant.

All signal processing and modeling analyses were performed using MATLAB (The MathWorks Inc. (2022), Natick, Massachusetts); all statistical analyses were performed using R (R core team (2020), R foundation for statistical computing, Vienna, Austria).

Results

Individual patient characteristics are provided in Table 1. Briefly, patients were older than controls (mean (sd) = 64 (6) versus 52 (13) years, $p = 0.005$) with a disease duration since symptom onset of 35 [19–48] months. ALSFRS-R scores were 41 [39-42] and clinical signs of weakness in either flexor or extensor direction were present in 6/15 patients. Despite the occasional presence of asymmetric clinical signs of weakness in either flexion or extension direction, no significant difference was observed in the ratio of maximum flexion and extension torques between patients and controls ($p = 0.17$). Of the 15 included patients, signs of UMN dysfunction in the cervical region according to the El-Escorial Criteria were present in 12 patients; 6 of these 12 exhibited signs of UMN dysfunction in the robotically manipulated arm. The remaining 3 patients had no signs of UMN dysfunction in the cervical region. Of note, 13/15 patients received riluzole (50 mg, 2dd), a glutamate inhibitor, as part of their regular medication for ALS.

Validity of reflexive and muscle viscoelastic estimates

The dynamics of participants' wrists were estimated from the recordings using two frequency response functions: joint admittance and reflexive impedance. Median coherence of the joint admittance was > 0.95, indicating high linearity and low noise. Coherences of the reflexive impedance were lower, with the lowest coherence observed during the relaxed test (median = 0.63). Model fits, as indicated by Variance Accounted For (VAF) of the simulated wrist torque, were higher for relaxed and resistance tests (95% [89-96%] and 98% [97-98%]) than for the compliance tests (69% [59-83%], at 5% bias; and 65% [57-70%], at 10% bias). VAFs of the simulated wrist angles were generally lower than those of the wrist torque, with the best VAFs again observed during the relaxed and resistance tests (91% [73-96%] and 67% [51-72%]). VAFs of the wrist angles were very low during the compliance tests (32% [6-52%] at 5% bias and 21% [11-36%] at 10% bias), which could be expected as this task can be effectively performed in various positions. Overall, no differences were found between the VAFs obtained from controls or patients in any of the tests. Figure 2 depicts representative model fits (e.g. median VAF) during the relaxed and resistance tests.

Differences between estimated neuromuscular parameters of patients and controls

Parameters with no dependence on the performed test, such as wrist inertia or the muscle activation dynamics, did not differ between patients and controls. A summary

Table 1 Clinical characteristics of the individual participating patients

	Age / Sex	Disease duration (months)	Symptom onset	ALSFRS-*R*/ FMF	UMN signs cervical region/ examined arm	UMN score	Tone	Strength flexion/ extension (Nm)	MRC flexion/ extension
1	59 / F	18.8	Bulbar	30/8	Yes/Yes	5	Normal	9.4/2.0	5/4
2	63 / M	19.5	Spinal	42/11	No/No	0	Normal	14.1/3.6	5/5
3	63 / M	35.4	Spinal	41/8	Yes/No	3	Normal	14.2/2.7	4/4
4	55 / M	44.0	Spinal	45/10	Yes/No	0	Normal	13.3/3.4	5/5
5	65 / F	71.7	Spinal	42/11	Yes/No	2	Hypotone	6.1/2.0	4/5
6	76 / M	39.2	Spinal	42/10	Yes/Yes	4	Normal	15.5/4.3	5/5
7	64 / M	47.6	Spinal	38/9	Yes/Yes	9	Hypertone	14.5/4.1	5/4
8	64 / F	31.1	Bulbar	39/12	Yes/Yes	4	Normal	8.8/2.1	5/4
9	66 / F	98.1	Respiratory	26/7	Yes/No	4	Normal	9.1/3.0	5/5
10	55/ M	48.7	Spinal	42/11	Yes/No	0	Normal	14.6/3.6	5/4
11	67 / F	19.1	Spinal	39/9	Yes/Yes	5	Normal	8.1/2.7	5/5
12	59 / F	13.1	Spinal	38/10	Yes/Yes	7	Normal	9.4/2.9	5/5
13	64 / M	15.1	Spinal	43/11	No/No	0	Normal	16.3/2.8	5/5
14	66 / F	79.1	Spinal	41/10	No/No	3	Normal	9.9/2.3	5/5
15	71 / M	10.2	Bulbar	43/12	Yes/No	3	Normal	16.1/4.4	5/5

Disease duration = duration from symptom onset until participation in months; ALSFRS-R = ALS function rating scale score (ranging from 0–48); FMF = fine motor function score, a subdomain of the ALSFRS-R; UMN signs in the cervical region according to the El-Escorial criteria; classification of UMN signs in the examined arm and the UMN score are provided in the methods; Strength = maximum voluntary contraction torque; MRC = medical research council score

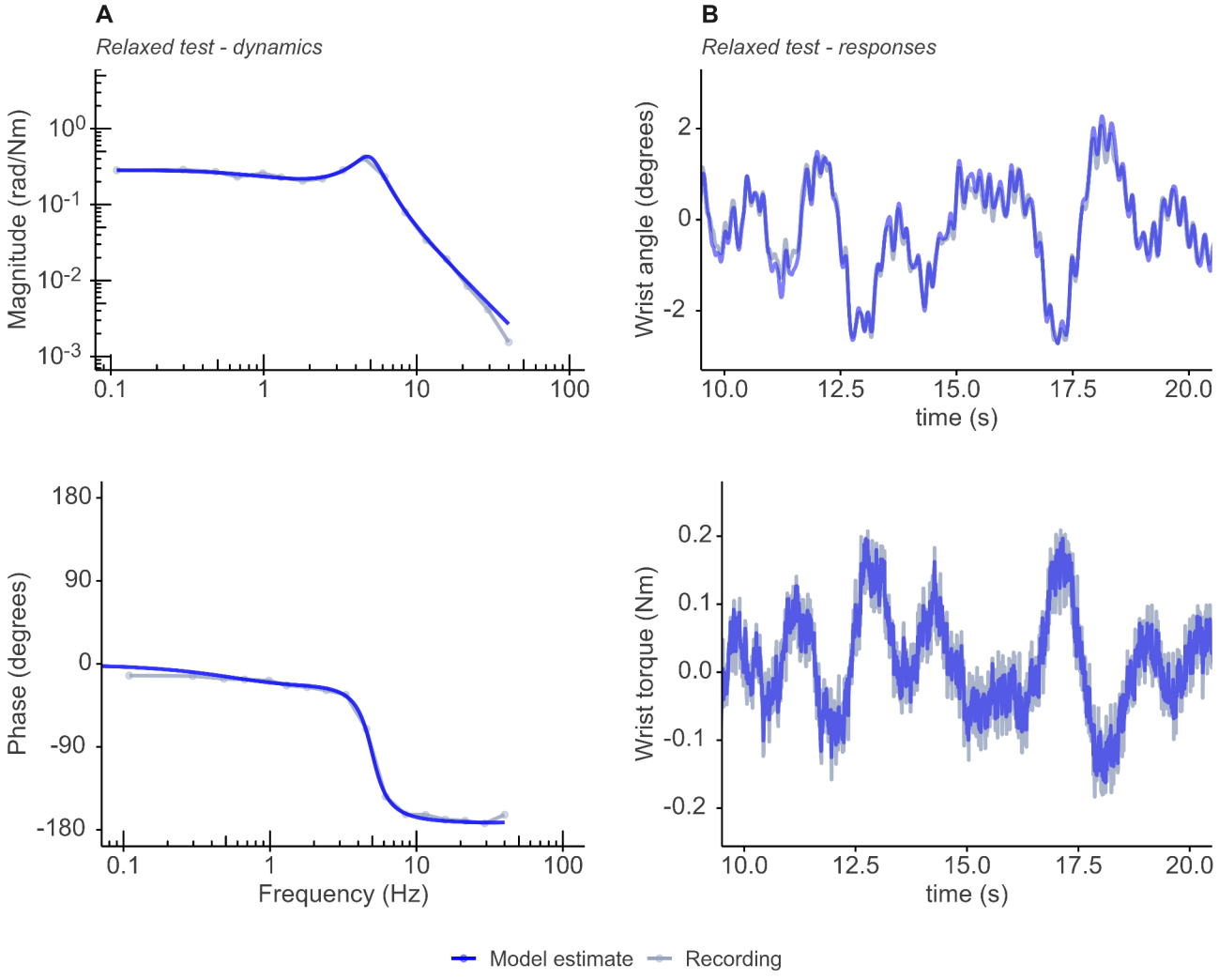

Fig. 2 Representative model fit on the corresponding joint admittance and the resulting model simulation. Plots depict: (**A**) frequency response function (magnitude at the top, phase at the bottom) of joint admittance from the relaxed test and the simulated joint admittance from the neuromuscular model of an ALS patient; (**B**) the corresponding recorded wrist angle and wrist torque, as well as the simulations obtained from the model to the deviations above, displayed from 10–20 s

of the estimated neuromuscular properties is provided in Table 2.

During the relaxed test, we found no overall difference in the muscle viscoelasticity between patients and controls, indicated by muscle stiffness (k: patients=3.95 [1.84–4.67] Nm/rad; controls=4.59 [3.49–5.71] Nm/rad, p=0.12) and viscosity (b: patients=0.07 [0.05–0.09] Nms/rad; controls=0.09 [0.08–0.10] Nms/rad, p=0.10). During the resistance test, similarly, no noteworthy overall group differences were observed in muscle stiffness (k: patients=8.21 [6.41–8.99] Nm/rad; controls=9.38 [6.84, 11.25] Nm/rad, p=0.14) or viscosity (b: patients=0.14 [0.11–0.18] Nms/rad; controls=0.17 [0.14–0.24] Nms/rad, p=0.11). Of the reflexive properties, only the force feedback gain during the relaxed test was significantly elevated in patients (kf: patients=0.59 [0.21–0.79]; controls=0.03 [-0.08-0.45], p=0.033). In line with this observation, higher reflexive torques Tref were observed in patients (Tref: patients=0.042 [0.029–0.052] Nm; controls=0.015 [0.008–0.028] Nm, p=0.021). No further group differences were observed.

Association between clinical measures, muscle viscoelastic and reflexive properties

We identified a significant relation between kp and age in patients and controls during the relaxed test (p=0.031), for which we accounted by adding age as covariate in the subsequent analyses of this neuromuscular property. Other estimated neuromuscular properties were not related to age in patients and controls. In relaxed tests, a difference in muscle stiffness was observed between male and female controls (k: male=5.13 [4.59–7.26]; female=3.19 [2.62–4.01], p=0.012) and patients (k: male=4.49 [3.70–5.53]; female=1.50 [1.19–3.46],

Table 2 Reflexive and intrinsic properties of the study cohort during all tasks

Characteristic	ALS, $N=15$	Controls, $N=15$
Relaxed test		
b (Nms/rad)	0.07 [0.05–0.09]†	0.09 [0.08–0.10]
k (Nm/rad)	3.95 [1.84–4.67]	4.59 [3.49–5.71]
kv (Nms/rad)	0.10 [-0.04-0.16]	0.03 [0.00-0.13]
kp (Nm/rad)	-0.29 [-0.81-0.14]	-0.39 [-0.98- -0.07]
kf (-)	0.59 [0.21–0.79]*	0.03 [-0.08-0.45]
Compliance test (5% bias)		
b (Nms/rad)	0.10 [0.06–0.13]	0.11 [0.07–0.15]
k (Nm/rad)	4.76 [4.17–9.28]	6.37 [4.53–8.51]
kv (Nms/rad)	0.21 [0.15–0.56]	0.27 [0.12–0.63]
kp (Nm/rad)	-3.14 [-4.88-5.68]	1.72 [-2.01-6.11]
kf (-)	-0.33 [-0.45- -0.17]	-0.34 [-0.65- -0.05]
Compliance test (10% bias)		
b (Nms/rad)	0.12 [0.08–0.14]	0.12 [0.10–0.15]
k (Nm/rad)	5.91 [4.97–7.65]	7.85 [6.25–10.29]
kv (Nms/rad)	0.69 [0.34–0.92]	0.42 [0.29–0.70]
kp (Nm/rad)	-4.28 [-6.20-2.64]	2.36 [-5.16-6.57]
kf (-)	-0.49 [-0.67- -0.31]	-0.50 [-0.77- -0.28]
Resistance test		
b (Nms/rad)	0.14 [0.11–0.18]	0.17 [0.14–0.24]
k (Nm/rad)	8.21 [6.41–8.99]	9.38 [6.84–11.25]
kv (Nms/rad)	0.61 [0.33–0.86]	0.55 [0.42–1.09]
kp (Nm/rad)	-1.63 [-5.05-0.19]	-1.86 [-2.49-1.85]
kf (-)	-1.00 [-1.07- -0.77]	-0.76 [-1.15- -0.53]
Test-independent		
I ($x10^{-3}$ kgm^2)	4.7 [4.3–5.7]	4.6 [4.3–5.1]
τ_{GTO} (ms)	25 [22–34]	24 [21 32]
τ_{MS} (ms)	25 [23–28]	25 [21–29]
f_a (Hz)	4.97 [3.53–5.66]	5.35 [3.32–6.64]
β (-)	4.01 [2.95–4.45]	3.08 [2.80–4.31]

Data presented as median [IQR]. b=muscle viscosity; k=muscle stiffness; kv=velocity feedback gain; kp=position feedback gain; kf=force feedback gain; I=inertia; τ_{GTO} =neural delay of golgi tendon organ feedback; τ_{MS}=neural delay of muscle spindle feedback; f_a = eigen-frequency activation dynamics; β=relative damping activation dynamics; $^{\dagger}p<0.10$, $^{*}p<0.05$ between controls and ALS patients

$p=0.021$). This gender-effect likely resulted from strength differences, as muscle stiffness was higher in stronger patients (coefficient (SE): 0.32 (0.13), $p=0.026$, Fig. 3A). A similar relation between strength, gender and muscle viscosity was observed in patients (Fig. 3B). During the resistance tests, we found a relation between muscle stiffness and muscle strength in controls that was not observed in patients (coefficient (SE): controls=0.46 (0.19), $p=0.032$; patients=0.14 (0.16), $p=0.427$). We observed no differences between any of the neuromuscular properties of patients with MRC≤4 or MRC=5 in either flexion or extension.

When comparing patients based on UMN symptoms, we only observed differences in neuromuscular properties from the relaxed test (Fig. 4). Force feedback gains in patients with UMN symptoms in the examined arm were elevated compared to controls (kf: patients=0.78 [0.52–1.70]; controls=0.03 [-0.08-0.45], $p=0.037$). This reflexive property was also associated with the UMN score of the examined limb (coefficient (SE)=0.14 (0.07), $p=0.040$). Importantly, we found no association between patients' muscle strength and kf (coefficient (SE)=0 (0.05), $p=0.951$) or clinical signs of weakness and kf ($p=0.689$). The summary measure of the reflexive muscle torque Tref was associated with the UMN score (coefficient (SE) x 10^{-3} = 9.48 (1.81), $p<0.001$). Additionally, Tref was larger in patients with UMN symptoms in the examined arm compared to controls (Tref: patients=0.057 [0.045–0.079] Nm; controls=0.015 [0.008–0.028] Nm, $p=0.037$). Multivariable analysis showed that kp and kf, but not kv, were strong determinants of Tref (coefficient (SE): kp = -0.033 (0.01); kf=0.044 (0.01), both $p<0.001$).

Discussion

In this study, we explored instrumented assessment of the wrists of patients with ALS using robotic manipulation. We show that the presence and severity of UMN signs in the examined arm was related to the force feedback gain, as well as the reflexive contribution to the wrist response. Importantly, estimates of muscle viscoelastic properties were on muscle strength, but the force feedback gain was not. These combined findings may serve as proof-of-concept that clinical signs of UMN and LMN loss can be separately captured using instrumented assessment.

Patients were all able to comply with the tests performed during the assessment protocol without requiring extra rest. The protocol was generally perceived as engaging, with the game-like nature of the active tests being especially compelling to the participants. Relaxed and resistance tests felt the most natural to participants, generally only requiring one training run. Excellent VAFs were obtained for these two tests, that were in line with a previous study using a similar protocol in healthy subjects [20]. Although that same study also produced lower VAFs during the compliance tests, those produced in our study were substantially lower. As postulated by the authors, compliance tests may elicit non-linear responses that are not captured by the implemented linear neuromuscular model. This assumption of linearity is an important limitation, addressed later in this section. Potentially, our incorporation of bias torques to maintain while complying with the perturbations may have further lowered the reliability of the parameter estimates during this task. Upon further inspection of the compliance tests, we found that participants tended to drift away from the neutral position during training. This process likely inflated the standard deviation of the handle position, causing the researchers to reduce the power of the perturbation signal. In some instances, mainly at 5% bias, these perturbations were not sufficient to elicit

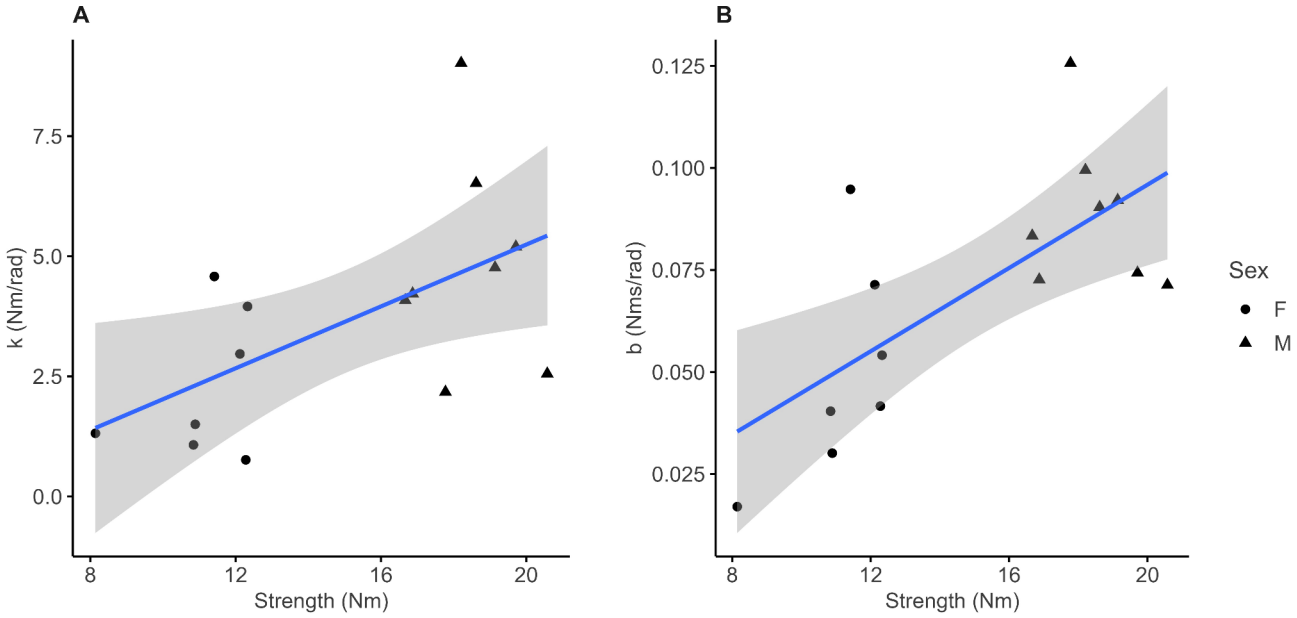

Fig. 3 The relation between absolute muscle strength measures, gender and the estimated viscoelastic properties in patients. Plots depict: (**A**) muscle stiffness (k) and; (**B**) muscle viscosity (b). Both measures are plotted against the underlying muscle strength defined as the summed maximum flexor and extensor torques. Male patients (triangles were all stronger than female patients (circles)

the sought after compliant behaviour as observed from the joint admittance, which rather resembled the joint admittances from the relaxed or resistance tests. Based on these analyses of validity, only parameter estimates obtained during the relaxed and resistance test are considered in this discussion.

Our study shows that the presence of clinical signs of UMN loss in the examined arm corresponded to changes in the reflexive properties of the wrist. Force feedback gain kf was elevated in patients with signs of UMN loss in the examined arm compared to controls. As a result, the reflexive torque in response to the applied perturbation was also elevated. It is important to consider whether changes in kf may have been caused by LMN loss. In ALS specifically, the loss of all classes of motor neurons in the spinal cord over which UMN symptoms are typically expressed, poses a challenge for detecting subtle changes in function [23]. We found no relation between kf and either absolute muscle strength or clinical signs of weakness. Rather, patients with lower maximum torque production had lower muscle viscoelasticity, although this was primarily driven by gender differences. This finding indicates that the major effect of LMN loss, e.g. weakness and atrophy, could potentially be separated from the effects of UMN loss with this instrumented approach. However, assessment of patients with more severe clinical weakness than those in this study is necessary.

One study showed that γ-motor neurons, which regulate muscle spindle tension, also degenerate in patients with ALS alongside α-motor neurons [30]. This finding could not be confirmed in a morphometric study of ALS [31], however, and subsequent mouse model studies found that γ-motor neurons are relative spared [32, 33]. Additionally, a histological study in patients found that the primary innervation of type Ia/II afferents to the muscle spindles was intact [34], whereas in $SOD1^{G93A}$ and $TDP43^{A315T}$ mouse models the opposite was observed [33]. The latter study also suggested that Ib-afferents to the golgi tendon organs were relatively spared [33]. Based on these studies, reflexive properties related to muscle spindle function may also be susceptible to the loss of LMN, thereby potentially explaining why no altered position or velocity feedback gains were identified in ALS patients. Future work should include disease controls with exclusive UMN loss, such as patients with primary lateral sclerosis (PLS), to provide further insights into the effect of degeneration of LMN networks on the established reflexive properties. Interestingly, if LMN loss indeed impairs the integration of Ia/II afferent feedback in small instrumented tasks, but not the integration of Ib afferent feedback, quantification of these reflex properties may help better discriminate patients with ALS or PLS, which remains a diagnostic challenge [35].

Our study had several limitations. Due to the exploratory nature of this study, the sample size was relatively small and the groups of patients with or without UMN symptoms in the arm or cervical region were biased towards those with symptoms. Assessment in larger patient groups with various degrees of LMN and UMN loss, as well as disease controls with isolated UMN loss, should be addressed in future work. Older adults (>65 years) generally have lower muscle viscoelasticity than

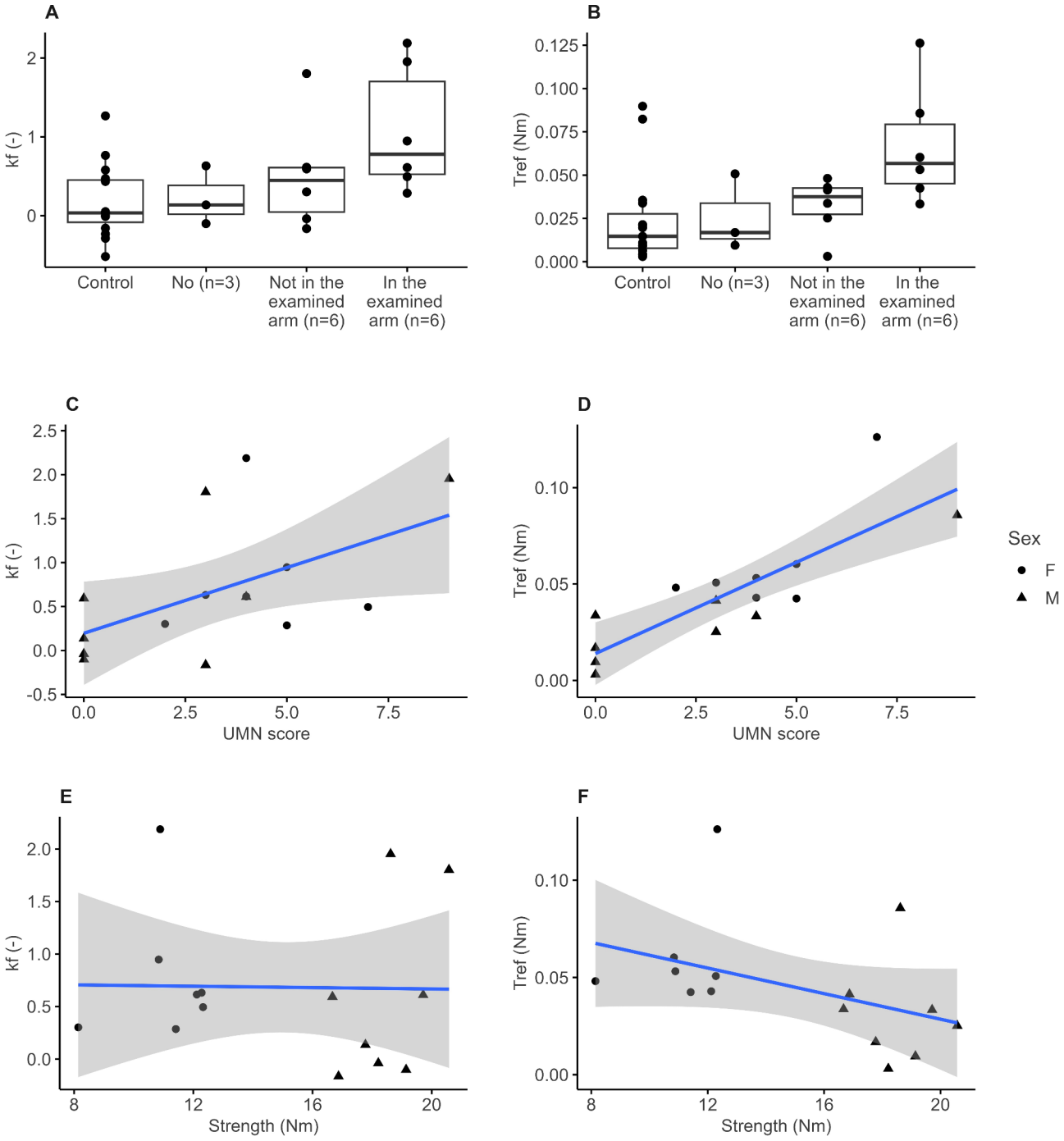

Fig. 4 The relation between UMN symptoms, muscle strength and the estimated reflexive properties of patients. Plots depict: **A-B**) force feedback gain (kf) and reflexive torque (Tref), respectively, stratified by the presence of upper motor neuron (UMN) symptoms in the cervical region; **C-D**) kf and Tref compared to the UMN score, grading severity in the examined arm, and; **E-F**) kf and Tref compared to wrist strength, defined by the summed maximum flexor and extensor torque

younger adults [36]. Yet, we found no age-effects on muscle-viscoelastic properties in either patients or controls and, consequently, the age differences in our cohort are unlikely to have influenced our findings. For future studies, however, it is advisable to age-gender match the patients and controls, especially if age ranges are large. Additionally, we performed relatively simple motor tests that might not capture the full spectrum of motor planning dysfunction that was found in another exploratory study of robotic testing in ALS patients [37]. To explore multiple facets of motor control, we utilized an established linear neuromuscular model that approximated

the wrist as a rotation actuator and, therefore, assumed that the flexor and extensor have comparable neuromuscular properties. While flexor muscles tend to be preferentially affected in ALS [38], maximum flexor- to extensor torque ratios were comparable between patients and controls in our study. We recommend that future studies evaluate nonlinear, antagonistic muscle models to separately evaluate the characteristics of these two muscles over larger ranges of motion, which is inherently nonlinear [39–41].

Conclusions

Developing effective biomarkers of UMN dysfunction remains a key challenge in ALS research, particularly for improving diagnosis and tracking disease progression during trials [42]. However, promising imaging and neurophysiological techniques, such as electroencephalography, do not yet provide individualized data that can be used as measure of UMN dysfunction [43]. This study provides proof-of-concept results that a short instrumented assessment protocol can yield quantitative, operator-independent, non-invasive measures that correspond to clinical signs of UMN and LMN loss.

Abbreviations

ALS	Amyotrophic lateral sclerosis
ALSFRS	Amyotrophic lateral sclerosis functional rating scale (revised)
ECR	Extensor carpi radialis
EMG	Electromyography
FCR	Flexor carpi radialis
FMF	Fine motor function score
LMN	Lower motor neuron
MRC	Medical research council score
PLS	Primary lateral sclerosis
SE	Standard Error
UMN	Upper motor neuron
VAF	Variance accounted for

Supplementary Information

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Supplementary Material 1

Author contributions

DJLSG: conceptualization of study design, acquisition and analysis of data, drafting and revision of manuscript. JJP: acquisition and analysis of data. BTHMS, WM and ACS: conceptualization of study design, analysis of data, drafting and revision of manuscript. HSG, FCTvdH and LHvdBerg: conceptualization of study design, drafting and revision of manuscript. All authors read and approved the manuscript.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and was approved by the medical ethics committee of the University Medical Center Utrecht.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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