


# Correlation of force control with regional spinal DTI in patients with cervical spondylosis without signs of spinal cord injury on conventional MRI

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## Abstract

**Objectives** The aim of this study was to investigate spinal cord structure in patients with cervical spondylosis where conventional MRI fails to reveal spinal cord damage.

**Methods** We performed a cross-sectional study of patients with cervical spondylosis without conventional MRI findings of spinal cord damage and healthy controls. Subjects were studied using spinal diffusion tensor imaging (DTI), precision grip and foot force-tracking tasks, and a clinical examination including assessment of neurological signs. A regional analysis of lateral and medial spinal white matter across multiple cervical levels (C1–C5) was performed.

**Results** DTI revealed reduced fractional anisotropy (FA) and increased radial diffusivity (RD) in the lateral spinal cord at the level of greatest compression (lowest Pavlov ratio) in

patients ( $p < 0.05$ ). Patients with spondylosis had greater error and longer release duration in both grip and foot force-tracking. Similar spinal cord deficits were present in patients without neurological signs. Increased error in grip and foot tracking (low accuracy) correlated with increased RD in the lateral spinal cord at the level of greatest compression ( $p \leq 0.01$ ).

**Conclusions** Spinal DTI can detect subtle spinal cord damage of functional relevance in cervical spondylosis, even in patients without signs on conventional T2-imaging and without neurological signs.

## Key Points

- DTI reveals spinal cord changes in cervical spondylosis with few symptoms
- DTI changes were present despite normal spinal cord on conventional MRI
- DTI parameters correlated with force control accuracy in hand and foot
- Spinal DTI is a promising technique for patients with cervical spondylosis

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**Keywords** Spinal cord · Cervical spondylosis · Force control · Diffusion tensor imaging · Pavlov ratio

## Abbreviations and acronyms

AD	Axial diffusivity
ADC	Apparent diffusion coefficient
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
N	Newton
RD	Radial diffusivity
ROI	Region of interest
SD	Standard deviation

## Introduction

In cervical spondylotic myelopathy the spinal cord is damaged by chronic compression and altered vascular supply resulting in associated neurological symptoms and functional deficits in gait, manual dexterity and sphincter control [1, 2]. Early diagnosis and follow-up remain clinically challenging because of the poor sensitivity of neurological signs [3, 4]. Clinical signs are insufficient to confirm compression-induced spinal cord damage and MRI is routinely performed. However, clinical symptoms in cervical spondylosis are not systematically associated with spinal anatomical MRI signs [5, 6]. Diffusion tensor imaging (DTI) is a promising imaging method for quantifying spinal cord structure and some recent studies suggest that DTI could provide useful biomarkers in various spinal pathologies [7–9]. In cervical spondylosis with neurological symptoms, spinal DTI is more sensitive than conventional imaging [6, 10–13] and spinal cord damage detected with DTI can relate to severity of symptoms [14–16]. However, studies relating DTI parameters to quantitative measures of sensorimotor function in cervical spondylosis are lacking, in particular in patients with mild disability where clinical signs have poor sensitivity [4]. Studies in patients without signs of damage on conventional MRI at any cervical level are also lacking. Thus, this study investigated the structure–function relationship in cervical spondylosis patients without conventional MRI evidence of spinal cord damage, i.e. increased signal intensity on T2-weighted imaging of spinal cord. A visuomotor task was used to quantify voluntary force modulation in grip and foot force-tracking. We hypothesized that DTI would detect spinal damage in cervical spondylosis patients without signs on conventional T2-weighted imaging. We also predicted that the degree of structural (DTI assessed) spinal cord damage would correlate with reduced force control in both grip and foot tracking.

## Materials and methods

### Subjects

Sixteen patients (11 women, 5 men) with clinical symptoms of cervical spondylosis (neck pain with/without neurological symptoms, and absence of comorbid disorders) without MRI evidence of spinal cord damage on T2-weighted imaging were recruited from a rehabilitation and spinal disease clinic (Service de Médecine Physique et de Réadaptation, Hôpital Cochin, Paris). Twenty age-matched healthy volunteers (12 women, 8 men) without history of arthritis, neck pain or any radiating symptoms served as control group. Patients with spondylosis and controls had a mean±SD age of 53±9 and 53±6 years, respectively ( $p=0.88$ ). The patients' clinical status data are detailed in Table 1. The study received

institutional review board approval and all subjects provided informed consent.

### Clinical measures

All subjects were questioned regarding traumatic history, pain characteristics and sphincter control. They underwent a standardized clinical cervical spine exam including cervical spine mobility (flexion, extension, side bending and rotation), palpation of trigger points and Spurling's manoeuvre. Pain intensity was rated on a visual analogue scale. Neurological assessment included muscle strength, surface and deep sensitivity, tendon reflexes, pyramidal reflexes, proprioception and gait patterns. We used the functional independence measure (FIM) and the European myelopathy score (EMS) to evaluate disability [17]. Three trials of maximal voluntary grip force were performed using the JAMAR<sup>®</sup> hand dynamometer and the maximum retained. A clinical measure of manual dexterity was obtained using the Moberg pick-up test (Table 1) [18]. Patients without neurological symptoms were classified as subclinical patients.

### Visuomotor precision grip and toe force-tracking

Accurate control of precision grip force is necessary for dexterous manipulation. Control of toe force is important for balance and gait. Precision grip and toe control was measured using a force-tracking task [19, 20]. Subjects performed a visuomotor ramp-hold-and-release task (Fig. 1, example traces at 3 N). The task comprised six blocks each consisting of four ramp-hold-and-release target force trajectories from 0 N to 3, 6 or 9 N. Before each ramp, the target remained for 3 s at 0 N. The target force then ramped up linearly for 2 s to reach the steady-state force level, which lasted 4 s, after which the target force dropped instantaneously to 0 N (release). Between blocks, there was a 5-s pause with a black screen. Each subject performed a pseudo-randomized order of two blocks at each force level (i.e. eight trials per force level). Subjects were instructed to minimize the distance (error) between the applied (cursor) and the target force. All subjects were familiarized with the task before testing. Collection of all 24 trials took 12 min. The following force control measures were extracted for each trial, according to previous definitions:

(i) Relative error (Ns): the total error (the absolute sum of positive error above and negative error below target) between the applied force and the target force trajectory, normalized to the target force level. (ii) Release duration (ms): the time taken to abruptly reduce the grip force (from 75 % to 25 % of the target force) at the end of the hold period. (iii) Timing of force onsets (beginning of ramp) and offsets (end of hold) [21].

**Table 1** Clinical tests in healthy controls and in cervical spondylosis patients

	Pain			Neck ext. (cm)	Neurological signs					EMS	Dext right/ left (s)	MaxF right/ left (kg)
	Cerv. (mm)	Rad. (mm)	NP (mm)		Mot def	Abn Ref	Sens def	Sphincter	Gait			
Pat1	0	35	40	15	Y	N	Y	Y	Y	2	16/17	35/34
Pat2	10	0	35	18	Y	N	Y	Y	Y	1	18/14	24/24
Pat3	88	40	54	17	N	Y	N	Y	N	1	14/20	48/46
Pat4	50	40	60	19	N	N	N	N	N	0	13/12	20/24
Pat5	70	60	50	16	N	N	N	N	Y	0	16/16	36/34
Pat6	0	0	80	21	Y	N	Y	N	N	0	14/17	76/62
Pat7	80	70	40	17	Y	N	N	N	Y	1	23/16	30/44
Pat8	50	0	50	17	Y	Y	N	N	Y	0	11/14	28/30
Pat9	70	50	0	20	N	N	N	N	Y	1	23/30	38/37
Pat10	0	50	20	15	Y	N	Y	N	Y	1	18/14	24/24
Pat11	0	40	60	19	N	Y	Y	N	N	0	14/19	32/28
Pat12	30	0	0	17	N	N	N	N	N	0	15/15	24/26
Pat13	35	25	0	18	N	N	N	N	Y	0	15/12	28/32
Pat14	60	60	45	18	N	N	N	N	N	0	15/14	38/32
Pat15	30	30	0	18	N	N	N	N	N	0	12/13	34/37
Pat16	35	45	0	17	N	N	N	N	N	0	15/20	32/32
Pats mean±SD/freq	38±30	34±23	33±27	18±2	Y=6 N=10	Y=3 N=13	Y=5 N=11	Y=3 N=13	Y=8 N=8	0=10 1=5 2=1	16±3/16±5	34±14/34±10
Control mean±SD/freq	3±12	0±0	1±4	20±1	Y=1 N=19	Y=1 N=19	Y=0 N=20	Y=0 N=20	Y=2 N=18	'0'=20	15±3/15±3	38±10/36±9
<i>P</i> value	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.14	0.19	<b>0.007</b>	<b>0.04</b>	<b>0.008</b>	<b>0.003</b>	0.45/0.27	0.41/0.68

Presence of sphincter and gait trouble is described under neurological signs. Group differences marked in bold

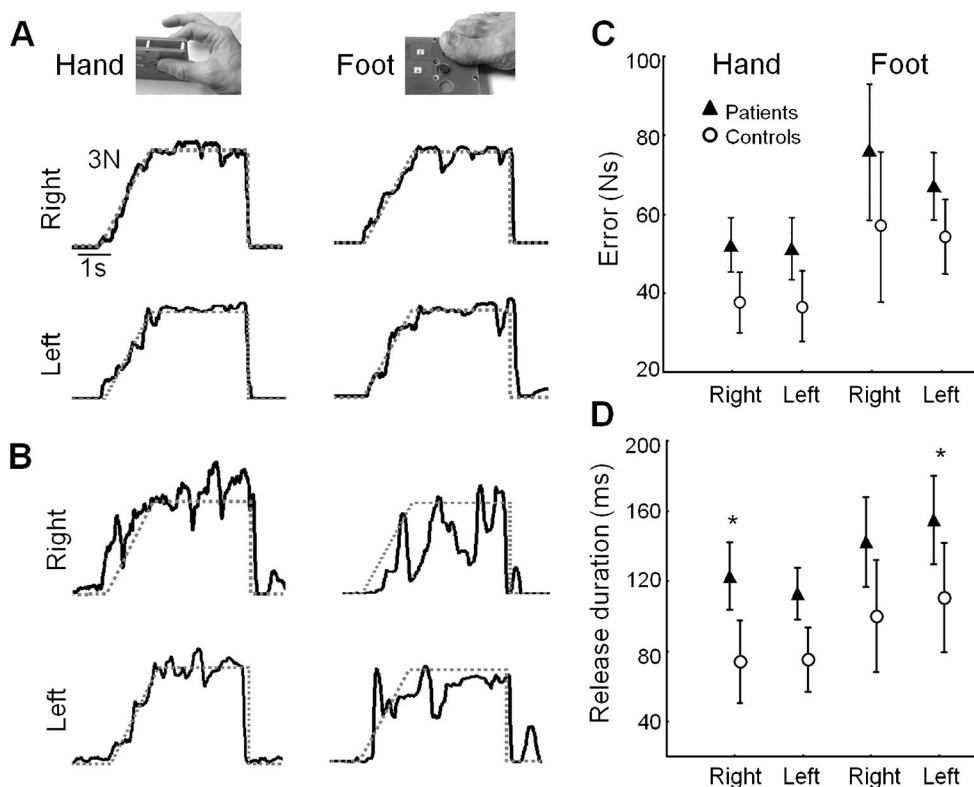
*Pat* patient, *Cerv* cervical, *Rad* radicular, *NP* neuropathic, *ext* extension, *Mot def* motor deficit, *Abn ref* abnormal reflexes, *Sens def* sensory deficit, *EMS* European myelopathy score (0 = normal functioning; 1 = grade 1, 2 = grade 2), *Dext* pick-up test in s, *MaxF* maximal power grip force

**DTI**

Participants underwent a single imaging session in a 1.5-T Siemens Avanto scanner (Siemens, Erlangen, Germany) with collection of DTI-weighted images of the cervical spinal cord (C1–C5). The sensitivity encoding (SENSE) single-shot echo-planar imaging (EPI) sequence with SENSE factor 2 was used to reduce distortions. In the sagittal diffusion-weighted sequence 25 non-collinear gradient directions were applied with two *b* values (*b*=0 and 900 s/mm<sup>2</sup>; TR/TE 2000/95 ms; field of view 18 cm, image matrix 128×128; 12 slices with slice thickness of 3 mm; slice gap=0; voxel size 1.4×1.4×3 mm). Spatial presaturation bands were applied anterior and posterior to the vertebral column to reduce ghosting from fat outside the spinal column. The sequence was repeated four times, lasting 4 min 26 s in total. Diffusion tensor images were averaged across the four acquisitions before analysis to increase signal-to-noise ratio. Imaging parameters were similar to those used in previous spinal DTI studies [19, 22]. Sagittal

and axial fast spin echo T2-weighted images were also obtained from C1 to C5 and used to evaluate T2 signal integrity and degree of spinal stenosis (by an experienced radiologist, AF).

All diffusion images were examined for movement, distortion or eddy current artefacts before analysis. Visible artefacts were present in one patient and one control, subsequently excluded from DTI analysis. Fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD) and radial diffusivity (RD) values were calculated voxel-by-voxel using MedINRIA (1.9.0) software (<http://www-sop.inria.fr/asclepios/software/MedINRIA>). AD describes the principal eigenvector (λ1) and RD the mean of the remaining two eigenvectors perpendicular to λ1 (λ2+λ3/2) [23]. Regions of interest (ROIs) covering the entire spinal white and grey matter were drawn on *b*0 images (axial views). ROIs included (1) the lateral part and (2) the medial part of the spinal cord on both sides (Fig. 2c). The lateral ROI was defined so as to include the lateral corticospinal tract (CST) and the medial ROI was defined as the remaining part of the spinal cord (e.g. Fig. 2c–e) [19].



**Fig. 1** Visuomotor force-tracking in a healthy control subject (**a**) and a patient with cervical spondylosis (**b**; same subjects as in Fig. 2). Precision grip (*left*) and toe (*right*) force-tracking examples with force recording (*black line*) and target force trajectory (*dotted grey line*). Note less accuracy relative to the target force in the patient in both grip and foot force-tracking tasks. **c** Mean error for the patients and controls (Newton seconds, N s; mean±95 % confidence intervals) in grip and foot force-

tracking tasks separately for the right and left sides. **d** Mean release duration for the patients and controls (ms; mean±95 % confidence intervals) in grip and foot force-tracking tasks. Note the greater error (force modulation) and the longer release duration in the patient group. *Open circles* controls, *filled triangles* patients. \* $p<0.05$  group difference on each side in post hoc comparison

To limit the partial volume effect (i.e. inclusion of voxels containing cerebrospinal fluid, CSF) we verified that ROI placement on the  $b_0$  image did not contain voxels extending into CSF (voxels covering both were removed). Only voxels with diffusion predominantly in the craniocaudal direction on FA colour maps were included. Two raters (PL and FO) separately performed ROI measurements, and reliability of DTI parameters within these ROIs were evaluated using intraclass correlation coefficients (ICC). ICC>0.7 was considered to reflect good reliability. Deterministic tractography using DTItrack (MedINRIA software, with FA>0.2) with seed regions covering whole spinal cord at C2 and C5 levels was used to ensure anatomical correspondence between tracked fibres and T2-weighted images.

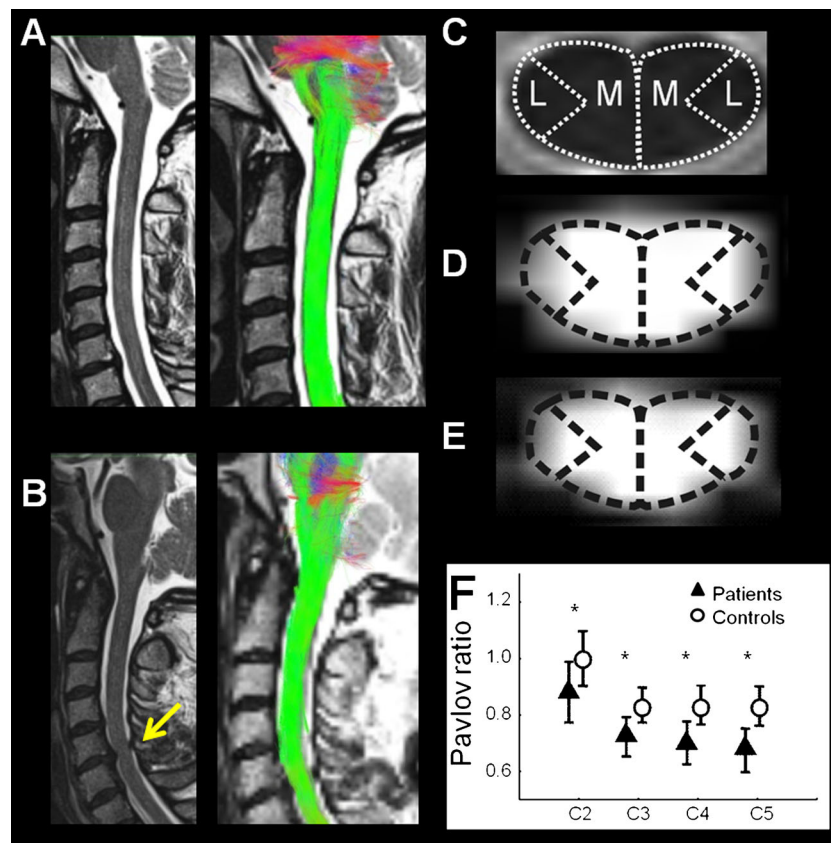
### Pavlov's ratio

The degree of spinal stenosis was measured on sagittal T2-weighted images according to Pavlov's ratio, i.e. the ratio of the diameter of the spinal canal to the diameter of the vertebral body [24]. The lowest Pavlov ratio for each subject was used

to define the cervical level with greatest spinal compression (greatest stenosis).

### Statistics

Group differences in clinical variables were evaluated using the Chi-square and Mann–Whitney  $U$  tests. Group differences in DTI parameters (FA, ADC, AD and RD) were evaluated using general linear model ANOVAs with two within-group factors: LEVEL (C1–C5) and ROI (medial/lateral), and one between-group factor GROUP. DTI parameters across sides (left/right) correlated ( $r>0.79$ ) and values were pooled for ANOVA. A second separate ANOVA of DTI parameters was confined to the level of greatest stenosis (according to Pavlov's ratio) and performed with one within-group (ROI) and one between-group (GROUP) factor. Group differences in Pavlov's ratio were also analysed using ANOVA (with factors LEVEL and GROUP). Force data were analysed using Matlab v7 (The MathWorks, Inc., Natick, MA, USA). Differences in force-tracking parameters (error, release duration, onsets and offsets) were analysed separately using ANOVA with two within-subject factors (HAND/FOOT, and SIDE: right, left)



**Fig. 2** Diffusion tensor imaging and spinal stenosis in cervical spondylosis patients without conventional MRI findings of spinal cord damage. **a, b** *Left*: Sagittal T2-weighted images showing cervical spinal cord anatomy and fibre tracking in a control subject (*top*) and a cervical spondylosis myelopathy (CSM) patient (*bottom*; patient 7 in Table 1). Note the presence of spondylosis stenosis at C4–C5 and C5–C6 (*arrow*) levels in the patient. *Right*: fibre tracking shows ascending and descending spinal cord fibres (*green* craniocaudal FA direction) in both

subjects. **c** Axial  $b_0$  image illustrating positioning of medial (*M*) and lateral (*L*) ROIs. **d, e** Axial view at C5 level of FA map with lateral and medial spinal cord ROIs in a healthy control (*top*) and a patient (*bottom*; same subjects as in **a, b**). **f** Pavlov's ratio (mean ± 95 % confidence intervals) was lower in patients than controls at all levels (C2–C5) indicating reduced spinal canal space in CSM patients. \*Significant post hoc comparisons. *Open circles* controls, *black triangles* cervical spondylosis patients

and a between-subject factor (GROUP). Post hoc tests were performed using Fisher LSD test. The level of significance was set to  $p \leq 0.05$  for ANOVAs and post hoc tests. Relations between force-tracking and DTI parameters were investigated using Pearson's correlation tests. Force-tracking performance was similar on both sides in controls and patients and data were pooled across hands for correlation analyses. Correlation tests were limited to variables showing significant group differences and corrected for multiple comparisons (Bonferroni,  $p < 0.0125$ ). Statistical analysis was performed using Statistica 10 (StatSoft, Inc., Tulsa, OK, USA).

## Results

### Clinical characteristics and anatomical MRI

All 16 patients reported cervical neck pain and most had a combination of radicular and neuropathic pain (Table 1). Seven patients (44 %) complained of night awakening secondary

to pain and 11 patients (69 %) reported previous cervical trauma. Patients had significantly reduced neck extension by about 2 cm. In terms of neurological signs, sensory deficits, sphincter and gait trouble were significantly more frequent in the patient group (Table 1). This was not the case for motor deficits and reflexes. However, five (31 %) patients had no neurological signs (subclinical patients) and three (19 %) patients had only one sign. Eight patients (50 %) had small reduction in independence according to FIM (patients:  $124 \pm 4$ , controls:  $126 \pm 0$ ;  $P = 0.01$ ) and ten patients (63 %) were classified as 'normal functioning' according to EMS, confirming mild disability. Patients did not differ in age, gender, functional dexterity (pick-up task) or maximal grip force (Table 1).

Anatomical MRI showed signs of cervical spinal canal stenosis in 13 (81 %) patients and in four (20 %) controls. None of the patients had signs of spinal cord compression. Patients also showed more signs of herniated discs than age-matched controls (Table 2). In patients, stenosis was most frequent at C5–C6 (81 %) followed by C4–C5 (44 %, example Fig. 2b).

**Table 2** Cervical spine findings on T1 and T2-weighted imaging

	Spinal canal stenosis	Osteoarthritis signs	Herniated disc	Levels affected
Pat1	Y	Y	Y	C2–C6
Pat2	Y	Y	Y	C5–C6
Pat3	Y	Y	N	C2–C7
Pat4	N	N	N	
Pat5	Y	N	Y	C5–C6
Pat6	N	N	Y	C5–C6
Pat7	N	N	N	
Pat8	Y	Y	N	C5–C7
Pat9	Y	N	Y	C3–C7
Pat10	Y	Y	Y	C4–C6
Pat11	Y	Y	Y	C5–C6
Pat12	Y	N	Y	C4–C6
Pat13	Y	Y	Y	C5–C7
Pat14	Y	Y	N	C3–C6
Pat15	Y	N	Y	C5–C6
Pat16	Y	N	Y	C3–C7
Pats freq	Y=13	Y=8	Y=11	
	N=3	N=8	N=5	
Control freq	Y=5	Y=4	Y=3	
	N=15	N=16	N=17	
Fisher's exact <i>P</i>	<b>0.002</b>	0.08	<b>0.002</b>	

Images from each patient and healthy subject were assessed by an experienced radiologist (AF). Spinal canal stenosis was considered present when sagittal T2-weighted images showed locally absent CSF and axial images showed flattening of spinal cord. Calcification of posterior ligament and osteophytes were noted as arthritic signs. Herniated discs were noted when visible on both sagittal and axial T2-weighted images. Group differences marked in bold

Pat patient

Quantification of stenosis according to Pavlov's ratio showed the same pattern with the majority of patients showing lowest ratios (least canal space) at C5 (69 %). Three patients (19 %) had lowest ratio at C4 and two patients (12 %) at C3. ANOVA comparison of groups showed lower Pavlov ratios in patients than controls (GROUP:  $F=13.4$ ,  $p<0.001$ ; Fig. 2f). Post hoc tests showed diminished spinal canal space at all cervical levels in patients ( $p<0.05$ ).

### Diffusion parameters

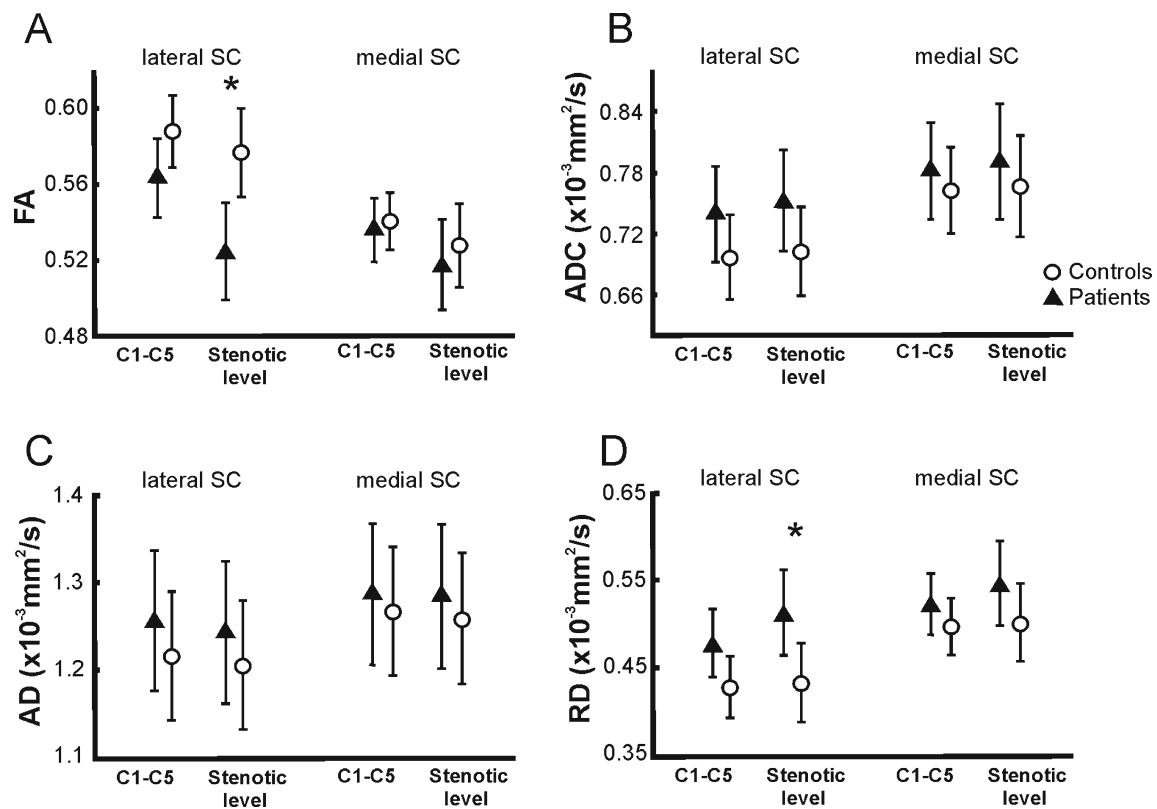
All subjects showed good quality FA, FAdir maps and fibre tracking from C1 to C5 (examples Fig. 2). Inter-rater reliability was good for FA, ADC, AD and RD (ICC 0.93, 0.94, 0.98 and 0.75, respectively), without systematic bias between raters (paired *t* test,  $p>0.1$ ). Whole spinal cord ROIs included a similar number of voxels in patients ( $40\pm 8$ ) and controls ( $41\pm 8$ ,  $P=0.64$ ), as did lateral spinal cord ROIs ( $8\pm 1$  voxels in patients and  $9\pm 2$  voxels in controls,  $P=0.84$ ).

ANOVA across all spinal levels (C1–C5) showed an effect of ROI and LEVEL on all parameters, consistent with previous studies [19, 25, 26]. FA was greater in the lateral than in the medial spinal cord (ROI:  $F=62.9$ ,  $p<0.001$ ) and higher at

C1–C3 compared to C4–C5 (LEVEL:  $F=13.4$ ,  $p<0.001$ ). ADC was reduced in the lateral ROI (ROI:  $F=68.9$ ,  $p<0.001$ ) and lower at higher cervical levels (LEVEL:  $F=9.3$ ,  $p<0.001$ ). Patients and controls both showed this pattern and groups were similar in all parameters when analysed across all spinal levels. However, when confining the ANOVA to the level of greatest stenosis significant group differences were found. FA was reduced in patients (GROUP:  $F=4.1$ ,  $p=0.05$ ) and differed between lateral and medial ROIs (GROUP\*ROI,  $F=9.9$ ,  $p=0.004$ ). Post hoc comparison showed a significant reduction of about 9 % in the lateral ROI only ( $p=0.003$ , Fig. 3a). RD showed an inverse pattern tending to be increased in patients and regionally different (GROUP:  $F=3.9$ ,  $p=0.06$ ; GROUP\*ROI:  $F=3.7$ ,  $p=0.06$ ). Post hoc tests showed a 16 % increase in RD confined again to the lateral ROI ( $p=0.02$ , Fig. 3d). ADC and AD showed no GROUP differences (Fig. 3b, c). The five subclinical patients showed the exact same group differences ( $p<0.05$ ).

### Force control

Visuomotor precision grip and toe force-tracking was more variable in patients (Fig. 1a, b). The ANOVA showed a



**Fig. 3** Regional spinal DTI parameters of lateral and medial spinal cord across C1–C5 levels and at the level of greatest stenosis. **a** FA (mean ± 95 % confidence intervals) was lower in patients in the lateral spinal cord, only at the level of greatest stenosis ( $p=0.003$ ). No significant difference in FA was found in the medial spinal cord. **b** Patients had similar spinal

ADC values as controls in both whole spinal cord and regionally at the level of greatest stenosis. **c** Axial diffusivity (AD) was also comparable across groups. **d** RD was higher in the lateral spinal cord in patients at the level of greatest stenosis only ( $p=0.02$ ). *Open circles* controls, *black triangles* cervical spondylosis patients, \*significant group differences

significant effect of GROUP ( $F=5.5$ ,  $P=0.03$ ) with patients producing 38 % more error in grip and 27 % more error in foot tracking (Fig. 1c). Post hoc tests showed significantly higher error in both grip and foot tracking in the patients (mean across right and left sides,  $p<0.05$ ). The average error was greater in foot compared to grip tracking (HAND/FOOT:  $F=44.8$ ,  $p<0.001$ ). In patients, error in grip tracking correlated with error in foot tracking ( $R=0.82$ ,  $p<0.001$ ).

Patients also took significantly longer to release force (57 % longer in grip and 42 % longer in foot tracking) compared to controls (GROUP:  $F=16.4$ ,  $p<0.001$ ; Fig. 1d). Post hoc tests showed longer release duration across both hands and feet in patients ( $p<0.05$ ). The effect of HAND/FOOT was not significant ( $F=0.21$ ,  $p=0.66$ ), although mean grip and foot release duration was 30 and 31 ms longer than in controls, respectively. In patients, grip release duration did not correlate with foot release duration ( $R=0.25$ ,  $p=0.35$ ). Timing of force onsets and offsets was similar in patients and controls ( $p>0.5$ ).

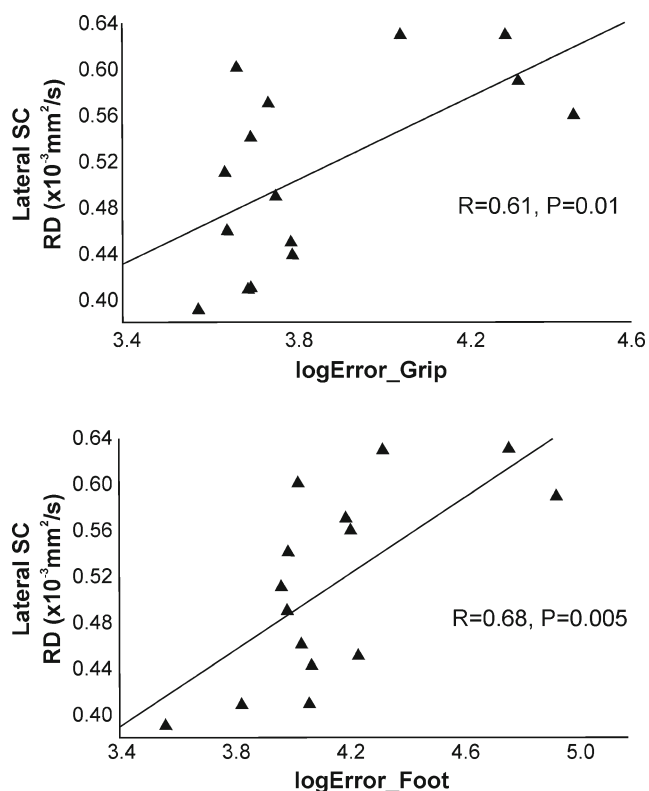
Subclinical patients also showed increased error ( $p=0.05$ ) and prolonged release duration ( $p<0.001$ ) compared to controls.

### Relation between force control and DTI parameters

In the patients, RD in the lateral spinal cord at the level of greatest stenosis correlated positively with grip and foot tracking error (Fig. 4). FA (in this ROI) showed a tendency for negative correlation ( $R=-0.49$ ,  $p=0.06$  and  $R=-0.56$ ,  $p=0.03$ , respectively). Thus, patients with more accurate foot tracking (less error) had higher FA and lower RD values than less accurate patients. No relations were found between release duration and diffusion parameters.

### Discussion

Our findings extend previous work on the sensitivity of spinal DTI by providing quantitative evidence of impaired spinal cord structure–function in cervical spondylosis patients without conventional MRI evidence of spinal cord damage with few or lacking neurological signs. The degree of (DTI-assessed) spinal damage correlated with the accuracy in voluntary grip and foot force control: patients with greatest cervical damage were least accurate.



**Fig. 4** Relation between spinal cord structure and error during force-tracking in cervical spondylosis patients. RD in the lateral spinal cord at level of greatest stenosis correlated with error in precision grip (*top*) and foot tracking (*bottom*; error log transformed). Higher error was present in patients with higher RD values

Although the patient group showed more signs of spinal stenosis and cervical arthritis than the age-matched control group (Table 2), no signs of spinal cord damage were present on conventional T2-weighted imaging at any cervical level. Despite normal-appearing T2-weighted imaging, DTI showed reduced FA in the lateral spinal cord at the cervical level of greatest compression (stenosis) in the spondylosis patients. This was also the case in subclinical patients without neurological signs. Spinal damage confined to the area of greatest compression agrees with previous animal studies [27] and with recent DTI studies in cervical spondylotic myelopathy [6, 14, 15]. In this study, the reduced FA in the lateral spinal cord was primarily due to increased RD. RD reflects diffusion perpendicular to the axon and informs on myelin content, whereas AD, which was not affected, is more related to axonal changes [23]. The reduced RD suggests detectable changes in myelin content in the lateral spinal cord confined to the level of maximal stenosis.

The CST is the major descending tract in the lateral spinal cord and our findings suggest that damage was most pronounced in the lateral white matter [28]. We thus hypothesize that the lateral CST is affected in early cervical spondylotic myelopathy. This is coherent with human postmortem findings in showing white matter changes occurring mainly in the

lateral CST [29]. It is also consistent with abnormal motor, but normal sensory-evoked potentials in cervical spondylosis with neurological symptoms [30]. Similarly, a recent animal model of cervical myelopathy showed early occurring corticospinal degeneration and compromised spinal cord microvasculature [27]. This pattern of initial damage to CST axons may be due to an increased vulnerability of large myelinated fibres as suggested by animal and human studies [31, 32].

Accuracy in grip and foot force control correlated with degree of spinal cord damage, i.e. with RD in the lateral spinal cord as assessed by DTI (Fig. 4). This confirmed our hypothesis of a cervical spinal structure–function relationship in patients with cervical spondylosis. This hypothesis was grounded on the assumption that the CST is essential for adequate force control in both the upper and lower limbs. Functionally, the CST provides major excitatory input to hand and foot motoneuron pools and force control deficits in chronic spinal cord injury are likely due to impaired motor unit modulation (accuracy), including impaired ability to stop motor unit activity (release duration) [33, 34]. In this study, the patients were less accurate in force control (greater error) and showed prolonged release duration in both feet and hands. This extends previous findings showing that force control impairments may be present even in cervical spondylosis patients without neurological signs [35, 36]. Anatomically, the CST represents the predominant tract in the lateral spinal cord and we have previously shown a correlation between FA in the lateral cervical spinal cord and accuracy of force control in the precision grip in a larger sample of healthy subjects (same task as in this study) [19]. The present findings show the presence of such a spinal cord structure–function relationship in spondylosis patients. This is in line with recent findings showing a correlation of severity of clinical symptoms with reduced FA at the level of greatest spinal canal stenosis [15] and extends these findings by showing that the spinal DTI changes relate to specific deficits in force control, a key function of the corticospinal tract. In addition we show that this correlation is present in patients without conventional MRI signs of spinal cord damage, which has not been specifically tested before.

In a more general perspective, our findings add to growing evidence that spinal DTI can be used to probe the structural integrity of spinal white matter and that altered integrity (assessed by DTI parameters) may have functional consequences. For example, sensory function has been found to correlate with DTI integrity of posterior tracts, and fine finger movements with CST integrity [6, 37]. Furthermore, DTI measures also correlate with symptom severity and functional deficits in other disorders affecting the spinal cord such as amyotrophic lateral sclerosis [7], syringomyelia [38], multiple sclerosis [8] and spinal cord injury [25, 37, 39].

These results should be considered within the limitations of the current study. Limitations concern the sample size and DTI methods: although a relatively small sample of patients was



included (all, however, without signs of spinal cord damage on T2-weighted imaging), power was sufficient to detect group DTI and behavioural differences. Relatively poor spatial DTI resolution is not uncommon: we employed a previously used sequence [19, 22] with similar resolution to previous studies [40, 41]. Spinal imaging remains difficult because of the small size and physiological motion of the spinal cord and optimizing the imaging methods remains a major challenge [9, 16, 42]. ROIs were defined manually; nonetheless, results showed good reliability across two separate raters [19, 22]. Furthermore, our findings agree with previous studies in other pathologies showing a correlation between spinal CST integrity and motor function [7, 8, 37].

In conclusion, this study shows that DTI is sensitive for detection of spinal cord damage in cervical spondylosis without conventional MRI evidence of spinal cord damage. The correlation of quantitative force control measures with the regional changes in spinal DTI parameters suggests that these structural changes are functionally relevant and can impact sensorimotor control in both the hand and foot. Spinal DTI may be more sensitive for the detection of spinal damage than the use of neurological signs and could be used early in the course of cervical spondylosis to improve diagnosis and medical management.

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