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Motor control in complex regional pain syndrome: A kinematic analysis

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ABSTRACT

This study evaluated movement velocity, frequency, and amplitude, as well as the number of arrests in three different subject groups, by kinematic analysis of repetitive movements during a finger tapping (FT) task. The most affected hands of 80 patients with complex regional pain syndrome (CRPS) were compared with the most affected hands of 60 patients with Parkinson disease (PD) as well as the nondominant hands of 75 healthy control (HC) subjects. Fifteen seconds of FT with thumb and index finger were recorded by a 60-Hz camera, which allowed the whole movement cycle to be evaluated and the above mentioned movement parameters to be calculated. We found that CRPS patients were slower and tapped with more arrests than the two other groups. Moreover, in comparison with the hands of the HC subjects, the unaffected hands of the CRPS patients were also impaired in these domains. Impairment was not related to pain. Dystonic CRPS patients performed less well than CRPS patients without dystonia. In conclusion, this study shows that voluntary motor control in CRPS patients is impaired at both the affected as well as the unaffected side, pointing at involvement of central motor processing circuits.

1. Introduction

Complex regional pain syndrome (CRPS) may affect motor function, which cannot be attributed to the autonomic or trophic manifestations that occur in this condition [48–50]. In daily practice, CRPS patients often report difficulty with voluntary motor control, such as initiating movements [42]. Similar motor impairment has also been reported in other painful limb conditions and has been ascribed to alterations in central sensorimotor processing [11]. In CRPS, prominent structural and functional changes of the sensory [15,20,35,36] and motor cortex [24,26] have been found, the extent of which was shown to be related to the level of pain and motor impairment, respectively. It is unknown, however, how the initial noxious peripheral input in CRPS may lead to these changes.

Impaired motor control is generally characterized by the level of difficulty with movement initiation or by hesitations in ongoing movements, both of which can be seen as a form of akinesia; by slowness of movement performance, or bradykinesia; and by reduction of the movement amplitude, hypokinesia [29]. These abnormal motor features, which are well-known features of Parkinson's disease (PD), have occasionally been reported in CRPS [4,12,24,42,47], but have never been evaluated by objective kinematic analysis.

Analyzing the characteristics of voluntary motor control in CRPS may contribute to our understanding of how noxious input can affect central motor processing [28]. In this study, we therefore evaluated the different movement characteristics of the affected and unaffected hands of CRPS patients, and compared the findings with those from healthy subjects and PD patients. Additionally, we evaluated whether these movement parameters are related to pain and dystonia in CRPS.

2. Methods

2.1. Participants

Movement characteristics were evaluated in 80 CRPS type I patients (Table 1) who were recruited from 1 Department of Neurology (Leiden University Medical Center; $n = 50$) and 3 Departments of Anaesthesiology (Leiden University Medical Center: $n = 13$, VU

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University Medical Center: $n = 9$, Erasmus Medical University Center: $n = 8$). All patients fulfilled the International Association for the Study of Pain criteria for CRPS [30].

We also examined a convenience sample of 60 PD patients (Table 1) who were recruited from the Department of Neurology of the Leiden University Medical Center and who fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD [16]. Additionally, 75 healthy control (HC) subjects with normal function of both hands were evaluated. These control subjects were volunteers from the hospital staff or were partners, friends, or relatives of CRPS or PD patients.

Overall, patients were excluded if they had conditions other than PD or CRPS that could limit the function of their hands or if the maximum distance between thumb and index finger was $\leqslant$3 cm. CRPS patients with mild dystonia were included.

2.2. Data collection and measurement instruments

Demographic data and information on hand dominance were obtained from all participants. CRPS and PD patients rated the pain severity of their affected arm (or, if both arms were affected, of the most affected one) on a 0 to 10 numerical rating scale; CRPS patients additionally completed the McGill Pain Questionnaire to obtain more detailed information on pain experience. Furthermore, information on the presence of dystonia in the upper extremities of each CRPS patient was recorded by an independent clinician. In PD patients, motor impairments of the upper extremities were evaluated with the Short Parkinson Evaluation Scale/Scales for Outcomes in Parkinson's Disease scale [27], the motor section of which evaluates 10 items (among which are tremor, rigidity, rapid alternating movements) with a maximum score of 42. PD patients' disease severity was evaluated with the Hoehn and Yahr scale [18].

We used data from the nondominant hand of control subjects, because in general it is more difficult to perform rapid accurate movements with the nondominant hand, and these data may thus be considered to reflect the lower end of the spectrum of normal motor behavior. From PD patients, data from the most affected side were used, based on the highest Short Parkinson Evaluation Scale/Scales for Outcomes in Parkinson's Disease scores of the arms. From CRPS patients, depending on the comparison of interest, data from the affected or unaffected side were used. From the 21 CRPS patients with both arms affected, data from the most (or, if equal, earliest) affected hand were used. Because CRPS patients with 2 affected arms could not be included in analyses in which a comparison with the unaffected side was made, 59 patients remained for these research questions.

Table 1
Demographic and clinical information.

	HC	PD	CRPS	*P*
N	75	60	80	
Men (%)	34 (45)	39 (65)	9 (11)	<.001
Mean age, *y* (SD)	47.5 (14.6)	61.7 (10.4)	42.8 (11.6)	<.001
Mean disease duration, *y* (SD)	NA	8.1 (6.0)	5.7 (6.0)	.018
Hand dominance				
Right, N (%)	67 (89)	50 (83)	74 (93)	
Left, N (%)	7 (9)	4 (7)	5 (6)	
Ambidextrous, N (%)	1 (1)	6 (10)	1 (1)	
NRS pain, mean (SD)[a]	NA	0.9 (2.3)	6.4 (2.0)	<.001
CRPS				
Arms affected by CRPS				
Right, N (%)			33 (41)	
Left, N (%)			26 (33)	
Both, N (%)			21 (26)	
Observed dystonia most affected hand, N (%)[b]			29 (38)	
Pain rating index of McGill pain questionnaire, mean (SD)			28.2 (11.6)	
PD				
Hoehn and Yahr, N (%)[c]				
1		1 (1.6)		
2		35 (57.4)		
3		18 (30.0)		
4		3 (4.9)		
5		1 (1.6)		

CRPS = complex regional pain syndrome; HC = healthy control subjects; NRS = numerical rating scale; NA = not applicable; PD = Parkinson disease; PQ = pain questionnaire.
[a] Obtained from 47 CRPS patients, 59 PD patients.
[b] Obtained from 77 patients.
[c] Obtained from 58 patients.

2.3. Evaluation of movement characteristics

Movement characteristics were assessed by means of a finger tapping (FT) task in which participants were instructed and encouraged to oppose the thumb and index finger as fast as possible and with the widest possible amplitude. All participants were able to watch their active hand. The movements were recorded with a digital color video camera that had a sampling rate of 60 Hz (Basler A601fc, Basler, AG, Ahrensburg, Germany). The camera was mounted on a stand above the area where the task was performed and was connected to a computer equipped with video tracking software (EthoVision Color-Pro 3.0, Noldus Information Technology, Wageningen, The Netherlands) (Fig. 1). For each hand, 15 s of data were recorded. The software was calibrated to convert the pixels to distance in the approximated plane of the finger movement. A small strip of 1-cm-wide adhesive green tape was attached around the tip of the thumb; blue tape was used for the tip of the index finger. The video tracking software program calculated the *X*, *Y* coordinates of the centers of the colored tape at both fingertips and the distance between them as a function of time. From the distance between the fingertips, the following parameters were calculated to characterize bradykinesia, hypokinesia, and akinesia using custom-made scripts in Matlab 7.5 (The MathWorks Inc., Natick, MA).

2.3.1. Bradykinesia

→ Mean velocity (*velocity*; cm/s), which is the total path length divided by the total time (15 s).
→ *E*/*F ratio*, defined as the mean positive velocity, i.e., the mean velocity over the time segments with a positive velocity, divided by the mean negative velocity, reflecting the extension and flexion phase of the FT movement, respectively.

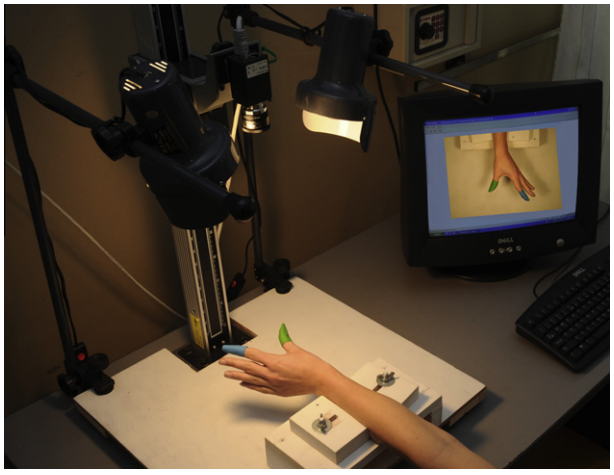

Fig. 1. The experimental setup.

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→ Median frequency (*frequency*; Hz), which is derived from the power spectral density of the distance signal [44]. By definition, the signal power above and below the median frequency is equal.
→ Change in frequency over time (*Δfreq*; Hz/s); the time–frequency characteristics of the signal are calculated using the wavelet transform [45]. At each time instant, the median frequency is calculated and the change in median frequency with time is obtained with linear regression between 1 and 14 s.

2.3.2. Hypokinesia

→ Mean maximum amplitude (*amplitude*; cm); the average distance between thumb and index finger when the velocity crosses zero and the fingers are open, calculated between 1 and 14 s.
→ Change in amplitude over time (*Δampl*; cm/s); the change in distance between the fingers as a function of time, obtained by linear regression between 1 and 14 s.

2.3.3. Akinesia/irregularity

→ Surplus in the number of times when the velocity changes sign (*surplusnull*; in counts [N]); there should be 2 moments where the velocity is null and changes sign per movement cycle: when thumb and index finger touch and at the moment the widest amplitude is reached. Based on the median frequency, the number of velocity sign changes is calculated; a surplus in this number reflects holds or reversals in movement direction, thus indicating hesitations as a measure of akinesia.
→ The variability in amplitude, *CVampl* (CV = coefficient of variation); the standard deviation of the *amplitude* (i.e., the SD of the distances between thumb and index finger when the velocity crosses zero and the fingers are open), normalized with the mean maximum amplitude, giving *CVampl*.

If the number of missing samples per series was ⩾10% (i.e., if digit identification failure occurred in ⩾90 of the 900 frames), the parameters were considered to be estimated inaccurately and data from that hand of the participant were removed from the analysis. The study was approved by the medical ethics committees of the involved hospitals, and all participants gave their written consent.

2.4. Statistical analysis

Sociodemographic and clinical variables were compared between groups as appropriate. For the comparison of the FT parameters between groups, a one-way analysis of covariance was used, with the separate parameters as dependent variables, group as factor (based on subject group, i.e., comparison of HC, PD, and CRPS, and comparison of CRPS patients with and without dystonia), and age and gender as covariates, because these factors are known to influence FT rate [3]. The Least Significant Difference method was used for post hoc analysis to compare between groups. Differences between the two hands of CRPS patients were assessed with the paired samples *t* test. None of the parameters of interest were normally distributed, as was revealed by inspection of the normality curves and the Kolmogorov–Smirnov test. Nevertheless, parametric testing by 1/-way analysis of covariance and *t* test was considered appropriate because it is shown to be reasonably robust to type I errors in case of large and approximately equal sample sizes, 2-sided testing, and acceptable homogeneity of variance ratios for all parameters checked, all of which applied to our study [6,40]. The significance threshold was set at 0.05. All analyses were performed with PASW Statistics 17.0 (SPSS Inc., Chicago, IL).

3. Results

Age was not evenly distributed between the groups, with PD patients being significantly older than HC subjects and CRPS patients ($P < .001$) (Table 1). Gender was also unevenly distributed between diagnostic categories, with women being overrepresented in the CRPS group ($P < .001$).

3.1. Comparison between the most affected side of patients with CRPS and PD and the nondominant hand of HC subjects

Data from 69 HC subjects, 55 PD patients, and 73 CRPS patients remained for analysis, because the color tracking software could not track the fingertips in ⩾10% of the frames in 6 HC subjects, 5 PD patients, and 7 CRPS patients (Table 2, Fig. 2). In 1 CRPS patient, the E/F ratio markedly exceeded all other E/F ratios, but because it involved an unlikely but not necessarily impossible value, we decided to adjust this value to the highest observed score, rather than to exclude it (the E/F ratio of 1.95 was adjusted to 1.31, 1/100th higher than 1.30, the second highest value).

Overall, there was a significant effect of group on all parameters measured, except for *E/F ratio* and *amplitude*.

3.1.1. Bradykinesia

CRPS patients performed the FT task more slowly ($P < .001$) and at a lower rate ($P < .001$) than PD patients and HC subjects, whereas PD patients were in turn slower than HC subjects ($P < .001$). In all groups, the velocity in the flexion phase exceeded the velocity in the extension phase, resulting in an *E/F ratio* < 1. Post hoc analysis showed that change in frequency over time only differed between the HC and the PD group ($P = .006$), the latter

Table 2
Comparison between nondominant hand of HC subjects and (most) affected hand of PD and CRPS patients.

	HC ($n = 69$)	PD ($n = 55$)	CPRS ($n = 73$)	F (2,192)	P	Post hoc
Bradykinesia						
Velocity (cm/s)	50.5 (12.0)	31.8 (14.8)	22.3 (14.4)	65.0	<.001	All
E/F ratio[a]	0.88 (0.11)	0.86 (0.15)	0.84 (0.19)	2.4	.097	
Frequency (Hz)	4.17 (0.65)	3.09 (1.03)	1.99 (1.19)	73.3	<.001	All
Δfreq (Hz/s)	0.013 (0.068)	−0.011 (0.080)	−0.004 (0.049)	4.9	.008	PD > HC
Hypokinesia						
Amplitude (cm)	8.19 (1.55)	7.15 (2.51)	7.31 (2.72)	2.9	.060	
Δampl (cm/s)	−0.005 (0.043)	−0.049 (0.080)	−0.006 (0.079)	4.7	.010	PD > HC/ CRPS
Akinesia/irregularity						
Surplus null (n)	12.9 (13.5)	33.5 (25.3)	57.2 (49.1)	25.4	<.001	All
CVampl	0.119 (0.038)	0.171 (0.073)	0.119 (0.061)	14.2	<.001	PD > HC/ CRPS

Parameters are expressed as mean (±SD). *P* values are uncorrected for multiple testing (between analyses).
Δ = change over time (changes in frequency or amplitude per second); CRPS = complex regional pain syndrome; CVampl = coefficient of variation of amplitude (calculated as SD divided by mean); E/F ratio = extension/flexion velocity ratio; HC = healthy control subjects; PD = Parkinson's disease.
[a] Adjusted value in 1 case.

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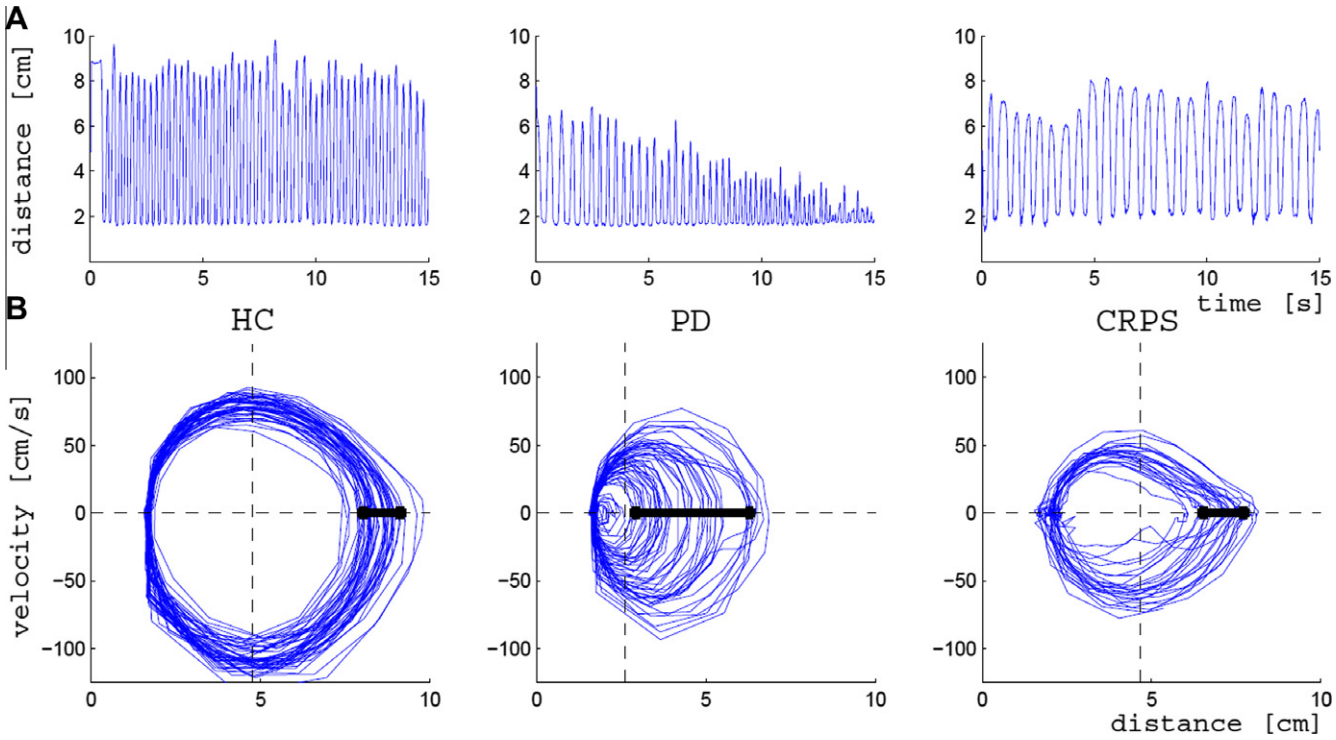

Fig. 2. The 15-s finger tapping cycle of 1 exemplary subject from each group. (A) The amplitude, i.e., distance between the thumb and index finger, as a function of time. Note the decrement in amplitude over time in the PD patient and the decreased frequency in the CRPS patient. (B) The velocity, i.e., the first derivative of distance, against amplitude. Each line represents 1 FT cycle. A subject starts with open fingers, i.e., high amplitude and no velocity. During the closing of the fingers, the amplitude decreases and consequently the velocity is negative, until the fingers are closed and velocity is zero. With opening of the fingers, the (positive) velocity increases and decreases until the fingers are open maximally and velocity is zero again.

showing a decrease over time, whereas HC subjects showed an increase over time.

3.1.2. Hypokinesia

The mean maximum amplitude was lower in PD and CRPS patients than in HC subjects, but the difference only just failed to reach significance ($P = .06$). PD patients showed a larger decrease in amplitude over time than both the HC and the CRPS groups ($P = .01$).

3.1.3. Akinesia/irregularity

CRPS patients showed more arrests during the FT task than HC subjects and PD patients ($P < .001$), whereas PD patients performed worse than HC subjects ($P = .029$). Amplitude for the PD patients was more irregular than in both the HC and the CRPS groups ($P < .001$).

3.2. Comparison between the affected and the unaffected sides of patients with CRPS

Of 59 CRPS patients with one unaffected hand, data from 11 patients could not be used because at least at one side the fingers could not be tracked in ⩾10% of the frames, leaving 48 patients for analysis (Table 3).

3.2.1. Bradykinesia

The FT task with the affected hand was performed more slowly ($P < .001$) and at a lower rate ($P < .001$) than with the unaffected hand. *E/F ratio* and *Δfreq* did not differ between the 2 sides.

3.2.2. Hypokinesia

Amplitude was smaller at the affected side ($P = .035$), whereas the change in amplitude over time did not differ between the two sides.

Table 3
Comparison between CRPS patients' affected and unaffected hands.

	Affected ($n = 48$)	Unaffected ($n = 48$)	P
Bradykinesia			
Velocity (cm/s)	24.2 (15.3)	35.2 (18.9)	<.001
E/F ratio	0.82 (0.19)	0.81 (0.15)	.582
Frequency (Hz)	2.16 (1.24)	2.98 (1.21)	<.001
Δfreq (Hz/s)	−0.004 (0.058)	0.010 (0.051)	.166
Hypokinesia			
Amplitude (cm)	7.46 (2.90)	8.11 (3.36)	.035
Δampl (cm/s)	−0.002 (0.088)	−0.020 (0.077)	.253
Akinesia/irregularity			
Surplus null (n)	43.6 (33.1)	32.4 (31.9)	.066
CVampl	0.116 (0.065)	0.116 (0.056)	.997

Parameters are expressed as mean (±SD). *P* values are uncorrected for multiple testing (between analyses).
E/F ratio = extension/flexion velocity ratio; Δ = change over time (changes in frequency or amplitude per second); CRPS = complex regional pain syndrome; CVampl = coefficient of variation of amplitude (calculated as SD divided by mean).

3.2.3. Akinesia/irregularity

With their affected hand, CRPS patients tapped with more arrests, but this difference only just failed to reach significance ($P = .066$). The variability in amplitude was equal at both sides.

3.3. Comparison between the unaffected side in patients with CRPS and the nondominant hand of HC subjects

Due to finger tracking failures in ⩾10% of the frames, 5 of a total of 59 CRPS patients with one unaffected side and 6 of 75 HC subjects were excluded (Table 4).

3.3.1. Bradykinesia

The unaffected CRPS patients' hands performed the task more bradykinetically than the nondominant hands of HC subjects,

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Table 4
Comparison between nondominant hand of HC subjects and unaffected hand of CRPS patients.

	HC (n = 69)	CRPS (n = 54)	F (1,119)	P
Bradykinesia				
Velocity (cm/s)	50.5 (12.0)	35.8 (18.2)	18.2	<.001
E/F ratio	0.88 (0.11)	0.81 (0.14)	10.8	<.001
Frequency (Hz)	4.17 (0.65)	3.03 (1.22)	33.3	<.001
Δfreq (Hz/s)	0.013 (0.068)	0.009 (0.053)	0.4	.551
Hypokinesia				
Amplitude (cm)	8.19 (1.55)	8.15 (3.32)	0.4	.548
Δampl (cm/s)	−0.005 (0.043)	−0.016 (0.076)	0.3	.561
Akinesia/irregularity				
Surplus null (n)	12.9 (13.5)	31.1 (30.8)	13.5	<.001
CVampl	0.119 (0.038)	0.118 (0.056)	0.1	.708

Parameters are expressed as mean (±SD). P values are uncorrected for multiple testing (between analyses).
CRPS = complex regional pain syndrome; E/F ratio = extension/flexion velocity ratio; Δ = change over time (changes in frequency or amplitude per second); CVampl = coefficient of variation of amplitude (calculated as SD divided by mean); HC = healthy control subjects.

illustrated by a lower velocity (P < .001) and frequency (P < .001). The E/F ratio was smaller in the CRPS group (P < .001).

3.3.2. Hypokinesia

No significant differences were found in *amplitude* or *Δampl* between the two groups.

3.3.3. Akinesia/irregularity

The unaffected side in CRPS patients showed more arrests than the nondominant hands of the HC group (P < .001), whereas the *CVampl* was similar in both groups.

3.4. Comparison between CRPS patients with and without observed dystonia

Twenty-nine of the 80 CRPS patients had dystonia in their most affected hand. Because of missing dystonia scores for three patients and finger tracking failure of ⩾10% in 2 nondystonic and 4 dystonic CRPS patients, data from 25 CRPS patients with observed dystonia and 46 CRPS patients without dystonia remained for analysis (Table 5).

Table 5
Comparison between CRPS patients with and without observed dystonia of their most affected hand.

	Dystonia (n = 25)	No dystonia (n = 46)	F (1, 67)	P
Bradykinesia				
Velocity (cm/s)	16.2 (11.7)	25.6 (14.7)	7.1	.010
E/F ratio[a]	0.88 (0.19)	0.82 (0.18)	1.1	.304
Frequency (Hz)	1.59 (0.80)	2.23 (1.31)	5.1	.027
Δfreq (Hz/s)	−0.007 (0.050)	−0.004 (0.057)	0.1	.782
Hypokinesia				
Amplitude (cm)	6.40 (2.44)	7.84 (2.78)	4.0	.051
Δampl (cm/s)	−0.011 (0.057)	−0.005 (0.090)	0.1	.782
Akinesia/irregularity				
Surplus null (n)	67.1 (47.4)	50.1 (47.9)	1.9	.176
CVampl	0.121 (0.064)	0.117 (0.061)	0.0	.905

Parameters are expressed as mean (±SD). P values are uncorrected for multiple testing (between analyses).
CRPS = complex regional pain syndrome; E/F ratio = extension/flexion velocity ratio; Δ = change over time (changes in frequency or amplitude per second); CVampl = coefficient of variation of amplitude (calculated as SD divided by mean).
[a] Adjusted value in 1 case.

3.4.1. Bradykinesia

Dystonic patients were slower (P < .001) and tapped at a lower rate (P < .001) than did CRPS patients without dystonia, whereas the *E/F ratio* did not differ.

3.4.2. Hypokinesia

There was a trend toward a smaller *amplitud*e in dystonic patients, but this difference did not reach statistical significance (P = .051). Change in amplitude over time did not differ significantly.

3.4.3. Akinesia/irregularity

There were no differences in the number of arrests and amplitude variability during FT between dystonic and nondystonic patients.

An overview of all FT parameter (sub) group means is represented in Fig. 3

3.5. Relationships between movement performance parameters and pain scores in CRPS

Exploring correlations between the various kinematic parameters and pain measured by the numerical rating scale and the pain rating index score derived from the McGill Pain Questionnaire showed only a significant correlation for pain rating index with *surplusnull* (r = .353, P = .003).

4. Discussion

This is the first study to describe various kinematic characteristics of FT movements in CRPS. A strong point of our kinematic evaluation method is the visualization and quantification of the full movement cycle during FT; most previous studies extracted data from the contact phase only. To verify the parameters acquired through this novel setup, an additional control group of PD patients was included because bradykinesia, hypokinesia, and akinesia have been extensively studied in these subjects. The most prominent kinematic findings in PD, namely slowness of movement with declining velocity and amplitude over time, as well as hesitations in ongoing movements, were all replicated quantitatively in our study, confirming the validity of this method in assessing FT movement characteristics.

We found a strikingly reduced velocity and frequency of FT movements performed with more arrests in CRPS patients compared with both control groups. A reduced FT frequency of the affected hand has also been described previously in a small group of CRPS patients by Maihöfner et al. [24]. Furthermore, our analysis showed that CRPS patients with dystonia are more bradykinetic and hypokinetic than those without dystonia, indicating a more severely impaired voluntary motor control in this subgroup of CRPS patients. Because it was recently shown that the duration of the extension phase exceeds the flexion phase during FT [1,7], we verified these findings in our study. All groups tapped with a lower velocity during the extension than during the flexion phase, although we found no differences in E/F ratios between groups.

Interestingly, our findings point at a significantly impaired motor performance of CRPS patients' unaffected hands when compared with the nondominant side of HC subjects. These findings corroborate those of another study that compared kinematic characteristics of writing in CRPS patients with HC subjects [37]. On the affected, nondominant upper extremity, patients showed movement disorders including akinesia, muscle spasms, and dystonia, whereas the dominant extremity was free of any symptoms and signs. However, when performing a drawing task with the unaffected dominant extremity, the CRPS patients were slower and showed greater variability of segment length and of movement time per segment than

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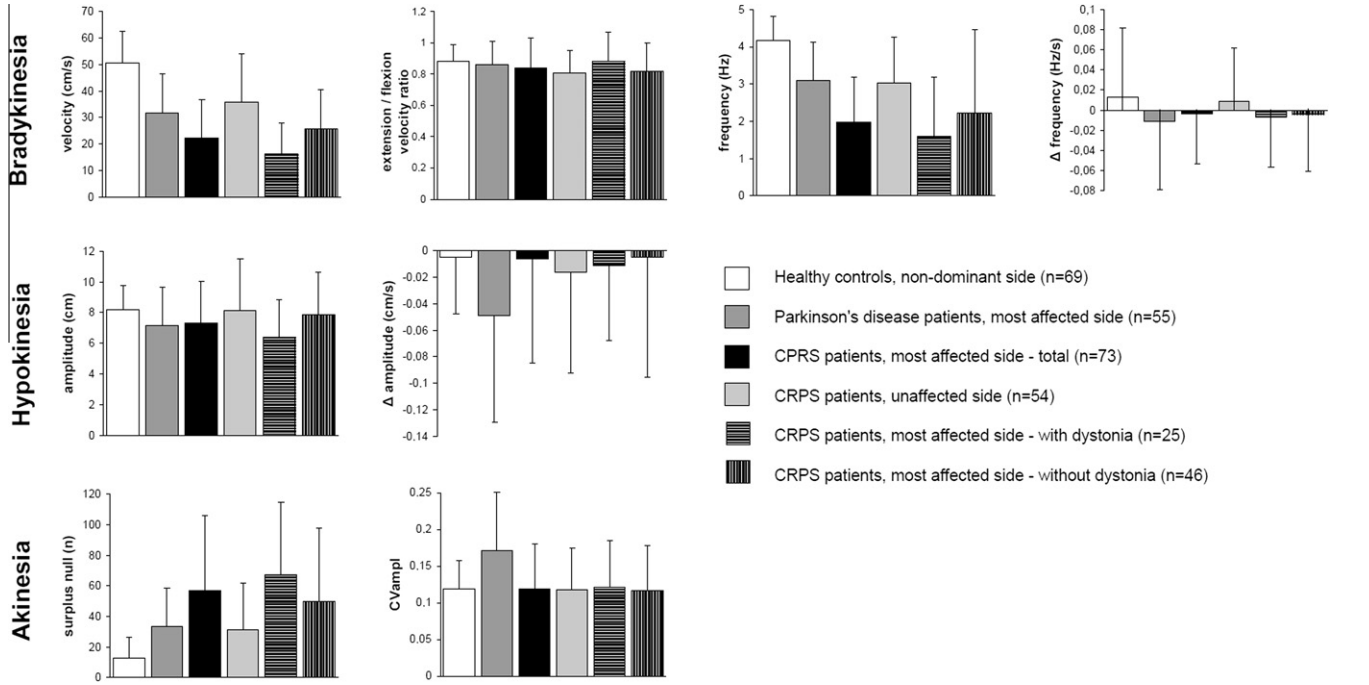

Fig. 3. Histograms showing the mean (±1 SD) of all parameters for the 3 subject groups, reflecting the data in Table 2 through Table 5. The last 2 bars in each plot represent the most affected side of 2 subgroups of the CRPS patients: with and without dystonia.

control subjects, whereas motor preprogramming was normal. Collectively, both studies show impaired motor processing not being limited to the affected side, an indication for underlying changes in the central nervous system in CRPS.

Based on findings from studies that mostly used experimentally induced pain paradigms, several theories have been proposed on the role of pain in motor processing ([2,19,23,31,38] see [17] for review). However, except for a significant but low correlation with the excess in number of arrests (*surplus null*), we found no relation between pain and the various kinematic parameters. Previous studies also failed to demonstrate a relation between pain and disturbances of movement in CRPS patients [4,24,42]. These findings may be explained in terms of long-term maladaptive changes of the central nervous system that may accompany pain ([31,46,51] see [17] for review). The question remains, however, at which level or levels of the central nervous system these maladaptive changes are mediated, because in CRPS central nervous system changes may involve both the spinal cord and cortical areas.

Central sensitization, an important mechanism underlying the chronification of pain in disorders such as CRPS, is associated with an increased excitability of spinal neurons [39,53]. The molecular and physiological changes that underpin central sensitization may occur within hours after peripheral inflammation or nerve injury on the ipsilateral side and within 24 h on the contralateral side of the spinal cord [39,53]. Because central sensitization has been shown to influence spinally mediated motor programs such as nociceptive withdrawal reflexes and simple motor learning tasks, it is conceivable that it also affects voluntary motor control [8,9,34,52].

Additionally, an increasing number of studies have found prominent supraspinal changes in CRPS. In motor cortical areas, a functional imaging study showed a reorganization of central motor circuits corresponding with the affected side in CRPS [24], whereas during FT with the affected arm, an increased activation at the ipsilateral side was found. This has been suggested to result from dysfunction of transcallosal connections between primary motor cortices of hemispheres [41] and may contribute to the motor disturbances in the contralateral unaffected upper extremity in CRPS patients, as found both in the study by Ribbers et al. [37] and in our study. Interestingly, in CRPS patients, FT is associated with an increased activation of parts of the frontal cortex (mainly brain areas 8, 9, 10, and 46) corresponding with the affected side [24]. These cortical regions are involved in the planning and execution of motor behavior, and their increased activation during FT may indicate a compensatory mechanism for the failing motor control and/or motor planning associated with CRPS.

Aside from changes in motor and premotor areas, myriad studies have shown prominent changes of sensory processing in the brain in CRPS. These changes predominantly involve disturbances in body-related cortical maps of the affected body part (see [33] for review). Objective studies using brain imaging and neurophysiological methods have shown a decreased hand representation at the primary somatosensory cortex [10,20,25,36], whereas other more subjective studies have shown attention deficits and body perception disturbances of the affected and, in a few cases, of the unaffected limb in those with CRPS [13,21,32]. Studies by Schwoebel et al. and Moseley et al. found increased response times for imagery movements in patients with chronic unilateral arm pain and CRPS, respectively, illustrating that the presence of pain is associated with alterations in the body schema [32,43]. This indicates that our findings are probably explained not only by changes in efferent motor control, but also by changes in sensory input, higher-order sensory processing, and sensorimotor integration. Interestingly, both studies reported improvement of response times with motor imagery-based interventions, such as mirror feedback and training of hand laterality recognition. It would therefore be interesting to evaluate whether these methods could also be used to achieve similar improvements in FT. Lewis et al. recently showed the importance of vision in updating the body schema, thereby improving position accuracy in CRPS affected extremities [22]. Interestingly, in agreement with our findings and supporting the notion of problems in central processing, the unaffected side of CRPS patients also showed impairments in limb position accuracy in comparison with healthy control subjects.

Recently, the concept of body space matrix was forwarded and it was demonstrated that the positioning of an extremity in this matrix influences central body regulation processes as swelling,

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temperature, and pain level [14,33]. It is conceivable that this may influence motor control as well. In the context of the present study, it is therefore relevant to consider that the position of the hands under the camera led to the execution of the motor tasks near the midline, which may have affected the performance to some extent.

Our study had some potential limitations. First, although there is no uniform, generally accepted definition of akinesia, the most commonly used description comprises, aside from hesitations in ongoing movements, difficulty in initiating movements. Unfortunately, we were unable to measure this feature of voluntary motor control in a valid manner with this setup; it may, however, add valuable information and should therefore be included in future studies. Second, the performance of the FT task may be affected by the attention problems that have been described in CRPS, although we encouraged each subject to perform the FT task fully focused, with close attention of the researcher, and decided to limit the total time of the FT task to 15 s, thereby reducing potential problems with attention and fatigue as much as possible. However, we cannot completely rule out that differences in motor performance between groups could in part be explained by differences in attention, although we consider this unlikely, because it could, in our opinion, explain differences in frequency and velocity but not hesitations. Third, the duration of the FT task in our study may have been too short to measure decrement of the movement parameters [5]. Nevertheless, a significant decrement in amplitude and frequency was detected in PD patients within this period, showing that 15 s is long enough to capture changes over time in PD, although it cannot be ruled out that this may have been too short to detect decrements in the two other groups. Finally, because it was an explorative study, only the presence or absence of dystonia was recorded in our study and we were therefore unable to relate the severity of dystonia to the severity of impaired motor function, an issue that should be addressed in a future study.

In conclusion, our results show prominent bradykinesia and akinesia at both the affected and the unaffected side in CRPS patients, suggesting impaired central processing of fine movements. Motor impairment was unrelated to pain, which may reflect long-term maladaptive changes of the central nervous system that can accompany pain. CRPS patients with dystonia performed less well than those without dystonia, indicating a more pronounced central motor processing deficit in these patients.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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References

[1] Agostino R, Currà A, Giovannelli M, Modugno N, Manfredi M, Berardelli A. Impairment of individual finger movements in Parkinson's disease. Mov Disord 2003;18:560–5.

[2] Arendt-Nielsen L, Graven-Nielsen T, Svarrer H, Svensson P. The influence of low back pain on muscle activity and coordination during gait: a clinical and experimental study. Pain 1996;64:231–40.

[3] Arnold G, Boone KB, Lu P, Dean A, Wen J, Nitch S, McPherson S. Sensitivity and specificity of finger tapping test scores for the detection of suspect effort. Clin Neuropsychol 2005;19:105–20.

[4] Birklein F, Riedl B, Sieweke N, Weber M, Neundörfer B. Neurological findings in complex regional pain syndromes—analysis of 145 cases. Acta Neurol Scand 2000;101:262–9.

[5] Bronte-Stewart HM, Ding L, Alexander C, Zhou Y, Moore GP. Quantitative digitography (QDG): A sensitive measure of digital motor control in idiopathic Parkinson's disease. Mov Disord 2000;15:36–47.

[6] Cribbie RA, Keselman HJ. The effects of nonnormality on parametric, nonparametric, and model comparison approaches to pairwise comparisons. Educ Psychol Meas 2003;63:615–35.

[7] Currà A, Agostino R, Dinapoli L, Bagnato S, Manfredi M, Berardelli A. Impairment of individual finger movements in patients with hand dystonia. Mov Disord 2004;19:1351–7.

[8] Ferguson AR, Bolding KA, Huie JR, Hook MA, Santillano DR, Miranda RC, Grau JW. Group I metabotropic glutamate receptors control metaplasticity of spinal cord learning through a PKC-dependent mechanism. J Neurosci 2008;28:11939–49. <http://www.jneurosci.org/content/28/46/11939>.

[9] Ferguson AR, Crown ED, Grau JW. Nociceptive plasticity inhibits adaptive learning in the spinal cord. Neuroscience 2006;141:421–31.

[10] Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995;375:482–4.

[11] Frettlöh J, Hüppe M, Maier C. Severity and specificity of neglect-like symptoms in patients with complex regional pain syndrome (CRPS) compared to chronic limb pain of other origins. Pain 2006;124:184–9.

[12] Galer BS, Butler S, Jensen MP. Case reports and hypothesis: a neglect-like syndrome may be responsible for the motor disturbance in reflex sympathetic dystrophy (Complex Regional Pain Syndrome-1). J Pain Symptom Manage 1995;10:385–91.

[13] Galer BS, Jensen M. Neglect-like symptoms in complex regional pain syndrome: results of a self-administered survey. J Pain Symptom Manage 1999;18:213–7.

[14] Gallace A, Torta DM, Moseley GL, Iannetti GD. The analgesic effect of crossing the arms. Pain 2011;152:1418–23.

[15] Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. Neuron 2008;60:570–81. <http://www.sciencedirect.com/science/article/pii/S0896627308007484>.

[16] Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745–52. <http://jnnp.bmj.com/content/51/6/745.long>.

[17] Hodges PW, Tucker K. Moving differently in pain: a new theory to explain the adaptation to pain. Pain 2011;152:S90–8.

[18] Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17:427–42.

[19] Johansson H, Sojka P. Pathophysiological mechanisms involved in genesis and spread of muscular tension in occupational muscle pain and in chronic musculoskeletal pain syndromes: a hypothesis. Med Hypotheses 1991;35:196–203.

[20] Juottonen K, Gockel M, Silén T, Hurri H, Hari R, Forss N. Altered central sensorimotor processing in patients with complex regional pain syndrome. Pain 2002;98:315–23.

[21] Lewis JS, Kersten P, McCabe CS, McPherson KM, Blake DR. Body perception disturbance. a contribution to pain in complex regional pain syndrome (CRPS). Pain 2007;133:111–9.

[22] Lewis JS, Kersten P, McPherson KM, Taylor GJ, Harris N, McCabe CS, Blake DR. Wherever is my arm? Impaired upper limb position accuracy in complex regional pain syndrome. Pain 2010;149:463–9.

[23] Lund JP, Donga R, Widmer CG, Stohler CS. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. Can J Physiol Pharmacol 1991;69:683–94.

[24] Maihöfner C, Baron R, DeCol R, Binder A, Birklein F, Deuschl G, Handwerker HO, Schattschneider J. The motor system shows adaptive changes in complex regional pain syndrome. Brain 2007;130:2671–87. <http://brain.oxfordjournals.org/content/130/10/2671.long>.

[25] Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. Neurology 2003;61:1707–15.

[26] Maihöfner C, Seifert F, Markovic K. Complex regional pain syndromes: new pathophysiological concepts and therapies. Eur J Neurol 2010;17:649–60.

[27] Marinus J, Visser M, Stiggelbout AM, Rabey JM, Martínez-Martín P, Bonuccelli U, Kraus PH, van Hilten JJ. A short scale for the assessment of motor impairments and disabilities in Parkinson's disease: the SPES/SCOPA. J Neurol Neurosurg Psychiatry 2004;75:388–95. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1738938>.

[28] Marinus J, Moseley GL, Birklein F, Baron R, Maihöfner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol 2011;10:637–48.

[29] Marsden CD. Slowness of movement in Parkinson's disease. Mov Disord 1989;4:S26–37.

[30] Merskey H, Bogduk N. Complex regional pain syndrome, type 1. In: Merskey H, Bogduk N, editors. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press; 1994. p. 41–2.
[31] Moseley GL, Nicholas MK, Hodges PW. Does anticipation of back pain predispose to back trouble? Brain 2004;127:2339–47. <http://brain.oxfordjournals.org/content/127/10/2339.long>.
[32] Moseley GL. Distorted body image in complex regional pain syndrome. Neurology 2005;65:773.
[33] Moseley GL, Gallace A, Spence C. Bodily illusions in health and disease: physiological and clinical perspectives and the concept of a cortical 'body matrix'. Neurosci Biobehav Rev 2011. doi:10.1016/j.neubiorev.2011.03.013.
[34] Parsons AM, Honda CN, Jia Y, Budai D, Xu X-J, Wiesenfeld-Hallin Z, Seybold VS. Spinal NK1 receptors contribute to the increased excitability of the nociceptive flexor reflex during persistent peripheral inflammation. Brain Res 1996;739:263–75.
[35] Pleger B, Tegenthoff M, Ragert P, Förster A-F, Dinse HR, Schwenkreis P, Nicolas V, Maier C. Sensorimotor retuning [corrected] in complex regional pain syndrome parallels pain reduction. Ann Neurol 2005;57:425–9.
[36] Pleger B, Tegenthoff M, Schwenkreis P, Janssen F, Ragert P, Dinse HR, Völker B, Zenz M, Maier C. Mean sustained pain levels are linked to hemispherical side-to-side differences of primary somatosensory cortex in the complex regional pain syndrome I. Exp Brain Res 2004;155:115–9.
[37] Ribbers GM, Mulder T, Geurts AC, den Otter RA. Reflex sympathetic dystrophy of the left hand and motor impairments of the unaffected right hand: impaired central motor processing? Arch Phys Med Rehabil 2002;83:81–5.
[38] Roland M. A critical review of the evidence for a pain-spasm-pain cycle in spinal disorders. Clin Biomech 1986;1:102–9.
[39] Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Bonventre JV, Woolf CJ. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001;410:471–5.
[40] Sawilowsky SS, Blair RC. A more realistic look at the robustness and type II error properties of the t-test to departures from population normality. Psychol Bull 1992;111:352–60.
[41] Schnitzler A, Kessler KR, Benecke R. Transcallosally mediated inhibition of interneurons within human primary motor cortex. Exp Brain Res 1996;112:381–91.
[42] Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. Neurology 1990;40:57–61.
[43] Schwoebel J, Friedman R, Duda N, Coslett HB. Pain and the body schema: evidence for peripheral effects on mental representations of movement. Brain 2001;124:2098–104. <http://brain.oxfordjournals.org/content/124/10/2098.long>.
[44] Spyers-Ashby JM, Bain PG, Roberts SJ. A comparison of fast Fourier transform (FFT) and autoregressive (AR) spectral estimation techniques for the analysis of tremor data. J Neurosci Methods 1998;83:35–43.
[45] Torrence C, Compo GP. A Practical Guide to Wavelet Analysis. Bull Am Meteor Soc 1998;79:61–78. <http://www.esrl.noaa.gov/psd/people/gilbert.p.compo/Torrence_compo1998.pdf>.
[46] Tsoa H, Galea MP, Hodges PW. Reorganization of the motor cortex is associated with postural control deficits in recurrent low back pain. Brain 2008;131:2161–71. <http://brain.oxfordjournals.org/content/131/8/2161.long>.
[47] Van Hilten JJ, Blumberg H, Schwartzman RJ. Movement disorders and dystrophy—pathophysiology and measurement. In: Wilson P, Stanton-Hicks M, Harden N, editors. CRPS: current diagnosis and therapy. Seattle: IASP Press; 2005. p. 119–37.
[48] Van Hilten JJ. Movement disorders in complex regional pain syndrome. Pain Med 2010;11:1274–7.
[49] Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012–6.
[50] Verdugo RJ, Ochoa JL. Abnormal movements in complex regional pain syndrome: assessment of their nature. Muscle Nerve 2000;23:198–205.
[51] Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686–8.
[52] Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci Lett 1986;64:221–5.
[53] Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999;353:1959–64.

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