RESEARCH ARTICLE

Pain Processing in Functional and Idiopathic Dystonia: An Exploratory Study

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ABSTRACT: Background: Pain is often experienced by patients with functional dystonia and idiopathic cervical dystonia and is likely to be determined by different neural mechanisms.
Objective: In this exploratory study, we tested the sensory-discriminative and cognitive-emotional component of pain in patients with functional and idiopathic dystonia.
Methods: Ten patients with idiopathic cervical dystonia, 12 patients with functional dystonia, and 16 age- and sex-matched healthy controls underwent psychophysical testing of tactile and pain thresholds and pain tolerance. We delivered electrical pulses of increasing intensity to the index finger of each hand and the halluces of each foot. Pain threshold and pain tolerance were respectively defined as the (1) intensity at which sensation changed from unpainful to faintly painful and (2) intensity at which painful sensation was intolerable.
Results: No differences were found between the three groups for tactile and pain thresholds assessed in hands and feet. Pain tolerance was significantly increased in all body regions only in functional dystonia. Patients with continuous functional dystonia had higher pain tolerance compared to subjects with paroxysmal functional dystonia and idiopathic cervical dystonia. There was no correlation between pain tolerance and pain scores, depression, anxiety, disease duration, and motor disability in both groups.
Conclusions: Patients with functional dystonia have a dissociation between the sensory-discriminative and cognitive-emotional components of pain, as revealed by normal pain thresholds and increased pain tolerance. Abnormal connectivity between the motor and limbic systems might account for abnormal pain processing in functional dystonia.

Key Words: functional movement disorders; psychogenic dystonia; cervical dystonia; pain; emotions

Functional neurological disorders (FNDs) have recently been better defined at the pathophysiological level and distinguished from symptoms that are intentionally produced, such as malingering and factitious disorder.[1] FNDs are a source of major neurological disability, especially when they produce a motor disturbance, such as in functional dystonia (F-Dys). Patients affected by F-Dys often experience pain which is sometimes disproportionate to motor symptoms, and it frequently occurs in body segments not affected by involuntary movements.[2] Subjects with idiopathic cervical dystonia also experience painful sensations, especially in affected body parts.[3]

The large brain network accessed during nociceptive processing is now commonly referred to as the "pain matrix," and it includes lateral (sensory-discriminatory) and medial (affective-cognitive) neuroanatomical components.[4] The lateral pathway projects to lateral thalamus and then to primary and secondary somatosensory areas, whereas the medial pathway projects to medial thalamic nuclei and limbic structures, such as

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the anterior cingulate cortex and the insular cortex. Sensory-discriminative and cognitive-affective aspects of pain may be selectively assessed by simple and reliable psycophysical parameters, such as sensory thresholds. In particular, the pain threshold (P-th) evaluates the sensory-discriminative component of pain, whereas pain tolerance (P-tol) refers to the psychological perception of pain, a complex balance between cognitive and affective functions.[5] The contribution of the somatosensory system is well known in idiopathic dystonia, including cervical dystonia (CD),[6] and it was recently demonstrated in F-Dys by testing of tactile temporal discrimination thresholds.[7] Yet, there are no experimental data on pain perception in either F-Dys or idiopathic CD, which is often associated to pain. Only one study utilizing laser-evoked potentials has revealed that the function of nociceptive pathways in CD is comparable to healthy subjects.[8]

Based on the evidence that in F-Dys there is abnormal connectivity between motor and limbic areas,[9] we hypothesized an alteration of the cognitive-emotional component of pain in F-Dys. On the other hand, patients with idiopathic dystonia have abnormal temporal processing of somatosensory stimuli[10] and a distorsion of cortical maps in the somatosensory cortex,[11] which might produce an alteration of the sensory-discriminatory component of pain. Given these premises, we aimed to assess the sensory-discriminative and cognitive-emotional components of pain in idiopathic CD and F-Dys, testing pain thresholds and pain tolerance in affected and unaffected body segments.

Patients and Methods

We enrolled 10 patients with idiopathic CD, 12 patients with clinically definite F-Dys,[12] and 16 healthy controls (HCs; 13 women, 3 men; mean age: 34.6 ± 10.8 years).

The diagnosis of idiopathic dystonia was based on the International Parkinson and Movement Disorder Society recommendations[13] and the diagnosis of F-Dys on Gupta-Lang criteria.[12] Exclusion criteria were presence of clinically relevant cognitive impairment (Mini-Mental Status Examination score <24), diabetes mellitus, tendon areflexia, and polyneuropathy by nerve conduction studies. Severity of dystonia was evaluated with the Burke-Fahn-Marsden (BFM) scale[14] in all patients with F-Dys and CD. We also used the Psychogenic Movement Disorders Rating Scale (PMDRS) [15] in F-dys. In each patient, we retrieved demographic and clinical features (age at onset, disease duration, and affected body regions).

Pain was assessed using the pain score of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).[16] The TWSTRS includes pain scores for severity (0-10), duration (0-5), and pain-related disability (0-5). Moreover, all the different painful body regions were recorded, including those without dystonia. Depression and anxiety were evaluated in patients and controls with the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). In all patients treated with botulinum toxin (BoNT), the experiment was carried out at least 3 months after the last injection.

Tactile and pain thresholds were determined by the method of limits according to a previously published protocol.[5,17] The stimulus consisted of a square wave electrical pulse of 0.2 ms delivered by a constant current stimulator (Digitimer D360; Digitimer Ltd, Welwyn Garden City, UK) through AgCl surface skin ring electrodes. The anode was located 1.5 cm distal to the cathode. Hands and feet were tested separately in random order. Electrical stimuli of increasing intensity were delivered to the fifth finger and first toe bilaterally. In brief, the lowest stimulus intensity (0.5 mA) was increased by 0.5-mA steps until the subject perceived the electrical stimulus (tactile threshold; T-Th). When the subject perceived the electrical stimulus, we delivered decreasing stimuli with minimum difference in intensity (0.1 mA) until the correct T-Th was determined. We considered as exact T-Th the value to which the subject gave the same affirmative answer after four consecutive stimuli at the same intensity. Then, the stimulus intensity was increased by 0.5-mA steps until the subject reported a change in sensation from nonpainful to "faintly painful" (P-th). The subject was asked to point out the pain intensity on a Visual Analogue Scale (VAS) line ranging from 0 to 10. Finally, the intensity of electrical stimulus was increased by 1-mA steps until the subject reported an "intolerable" painful sensation (P-Tol). If the subject did not report an intolerable pain sensation with 99 mA at 0.2-ms stimulus duration, we increased the stimulus duration to 0.5 ms and 1 second (3 subjects with F-Dys described in the Results).

In order to avoid the pain-modulating effects of BoNT injections, the experiments were performed at an interval of $\geq$3 months after the last botulinum treatment.

The study was approved by the ethics committee of the University of Verona and conformed to the Declaration of Helsinki. All patients gave written informed consent before participation.

Statistical Analysis

Normal distribution of data was checked using the Kolmogorov-Smirnov test. In case of deviation from normality, nonparametric tests were used.

The Kruskal-Wallis test was used to compare HCs, F-Dys, and CD for age and education level. Disease duration in F-Dys and CD was compared using the Mann-Whitney U test.

TABLE 1. Clinical features of patients affected by functional and idiopathic cervical dystonia

Pt	Sex	Age (y)	Disease Duration (y)	Affected Body District	BFM- Mov	BFM- Dis	Pain Score[a]	Pain Duration (y)[a]	Pain Disability[a]	HARS	HDRS
F-Dys											
1	M	42	4	Generalized - Px	0	0	5.25	2	2	25	19
2	W	51	37	Generalized - CT	0	0	1.75	2	4	7	21
3	W	38	28	Generalized - CT	0	0	7.25	5	3	18	13
4	M	43	22	Generalized - CT	0	0	2.75	2	2	18	12
5	W	58	15	Neck + UL + trunk - Px	12	11	8.5	3	2	45	23
6	W	25	6	Neck + UL - CT	5	1	3.25	5	2	6	11
7	M	50	2	Neck + trunk - CT	18	4	2.5	2	2	5	9
8	M	35	3	Neck - CT	7	4	4	2	1	11	15
9	W	37	1	Face - Px	0	4	5.25	2	2	8	13
10	W	23	0.6	Face - Px	1	8	5	4	4	22	21
11	W	36	9	Face + UL-Tr - Px	16	4	5	2	2	3	5
12	W	16	0.3	Face + UL-Tr - Px	8	4	6.75	5	2	18	19
Mean ± SD	4 M/8 W	37.8 ± 12.2	10.66 ± 12.2	—	5.6 ± 6.7	3.3 ± 3.5	4.8 ± 2.0	3.0 ± 1.3	2.3 ± 0.9	15.5 ± 11.8	15.1 ± 5.5
Idiopathic CD											
1	W	37	3	Neck - UL[b]	6	4	4	10	5	4	8
2	M	22	1	Neck	5	1	4	4	3	3	4
3	W	63	14	Neck	7	0	12	3.5	2	2	11
4	W	57	4	Neck - UL[b]	4	0	11	3.25	2	2	7
5	W	72	9	Neck	9	1	12	6	5	3	13
6	W	39	15	Neck	4	0	7	4.5	2	2	7
7	W	66	16	Neck	1.5	0	7	5	1	2	16
8	M	51	26	Neck	5	2	4	2.5	1	1	17
9	W	54	16	Neck	0.5	0	6	3.5	5	2	7
10	M	27	10	Neck	4	0	5	4	3	0	14
Mean ± SD	3 M/7 W	48.8 ± 16.9	11.4 ± 7.6	—	4.6 ± 2.5	0.8 ± 1.3	7.2 ± 3.3	3.9 ± 2.9	2.6 ± 1.6	2.0 ± 1.2	10.4 ± 4.4
P value		0.06	0.4	—	0.7	0.06	0.6	0.8	0.7	[a]**0.0001**	0.06

Comparisons by Mann-Whitney U test.
[a]Pain subscores from the Toronto Western Spasmodic Torticollis Rating Scale (version 1).
[b]Writer's cramp
BFM-Mov, Burke-Fahr-Marsden Movement scale; BFM-Dis, Burke-Fahr-Marsden Disability scale; CT, continuous; M, man; y, years; Pt, patient; Px, paroxysmal; UL, upper limb; UL-Tr, upper limb tremor; W, woman.

TABLE 2. Tactile and pain thresholds in functional and cervical idiopathic dystonia and HCs

	Body Site	F-Dys	Idiopathic Dystonia	HCs	Main Effects, *F* value, *P* value
Tactile threshold (mA)	RH	2.03 ± 0.58	1.573 ± 0.45	1.67 ± 0.41	Group: $F_{2,35} = 2.012$; $P = 0.1494$
	LH	1.93 ± 0.41	1.816 ± 0.37	1.78 ± 0.33	Side: $F_{2,35} = 1.614$; $P = 0.2125$
					Group*side: $F_{2,35} = 1.953$; $P = 0.1574$
	RF	7.15 ± 4.2	5.862 ± 1.35	5.01 ± 1.05	Group: $F_{2,35} = 2.741$; $P = 0.0807$
	LF	6.19 ± 1.50	5.397 ± 1.38	4.98 ± 1.49	Side: $F_{2,35} = 1.638$; $P = 0.2105$
					Group*side: $F_{2,35} = 0.524$; $P = 0.5977$
Pain threshold (mA)	RH	20.96 ± 23.64	8.55 ± 5.56	10.53 ± 3.39	Group: $F_{2,35} = 1.171$; $P = 0.3219$
	LH	17.12 ± 14.63	19.38 ± 8.74	12.31 ± 5.86	Side: $F_{2,35} = 1.126$; $P = 0.2959$
					Group*side: $F_{2,35} = 2.125$; $P = 0.1346$
	RF	41.97 ± 21.27	31.73 ± 1.60	28.78 ± 11.42	Group: $F_{2,35} = 2.084$; $P = 0.1416$
	LF	41.88 ± 20.31	41.12 ± 6.46	29.12 ± 10.69	Side: $F_{2,35} = 1.552$; $P = 0.2222$
					Group*side: $F_{2,35} = 1.361$; $P = 0.2712$
Pain tolerance (mA)	RH	66.8 ± 38.09	36.26 ± 35.22	32.97 ± 23.79	Group: $F_{2,35} = 3.766$; **$P = 0.033$***
	LH	59.88 ± 33.27	34.10 ± 29.04	35.60 ± 28.06	Side: $F_{2,35} = 0.68$, $P = 0.41$
					Group*side: $F_{2,35} = 1.27$, $P = 0.29$
	RF	79.05 ± 25.25	58.97 ± 24.82	60.12 ± 18.53	Group: $F_{2,35} = 3.986$, **$P = 0.028$***
	LF	80.41 ± 23.74	59.50 ± 31.03	60.70 ± 18.84	Side: $F_{2,35} = 0.16$, $P = 0.70$
					Group*side: $F_{2,35} = 0.02$, $P = 0.99$

LF, left foot; LH, left hand; RF, right foot; RH, right hand.
*Bolded values are statistically significant.

Differences in T-Th, P-th, and P-Tol among the three groups were explored by repeated-measures analysis of variance (R-ANOVA) with "*group*" as a between-subjects factor (three levels: HC, F-Dys, and CD) and "*side*" (two levels: right, left) as a within-subjects factor. The second aim of our study was to understand whether pain thresholds were different in patients with F-Dys according to the temporal pattern of dystonic symptoms, namely patients with persistent versus paroxysmal symptoms. Accordingly, for each psychophysical variable (T-Th, P-th, and P-Tol), we ran a separate R-ANOVA with "*group*" as a between-subjects factor (three levels: continuous F-Dys, paroxysmal F-Dys, and CD) and "side" (two levels: right, left) as a within-subjects factor.

Conditional on a significant *F* value, post-hoc unpaired *t* tests were performed to demonstrate differences between groups in each body site. Correction for multiple comparisons was not conducted, given the exploratory nature of the study.

In F-Dys and CD, correlational analysis was performed by Spearman rank correlation using P-tol values averaged between the right and left hand or foot. We verified whether P-Tol values were correlated with age, age at onset, disease duration, BFM scale, pain scores of TWSTRS (severity, duration, and disability attributed to pain), HAM-D, or HAM-A. Significance level was set at $P \leq 0.05$. Unless otherwise stated, data are given as mean ± standard deviation (SD).

Results

The sex distribution was comparable among the three groups (G-squared *P* value = 0.6). Kruskall-Wallis analysis did not reveal any difference in age ($P = 0.08$), although patients with CD were older compared to HCs ($P = 0.01$). Age was comparable between HC and F-dys ($P = 0.5$) and tended to be higher in CD compared to F-Dys ($P = 0.06$). All patients with CD and 4 of 12 patients with F-Dys had been treated chronically with BoNT, but at least 3 months had elapsed before the study. The supplementary table (online) shows details of each patient's oral medications.

Table 1 reports the features of patients with F-Dys and CD. At the time of the assessment, the two groups were comparable for age of onset (F-Dys, 27.3 ± 12.1 years; CD, 37.5 ± 15.8; $P = 0.5$), disease duration ($P = 0.7$), level of anxiety ($P = 0.9$), and depression ($P = 0.8$). Among F-Dys, 4 patients had an exclusive involvement of facial muscles and the movement disorder was paroxysmal in 6 patients. The mean PMDRS score was 23.3 + 2.8. CD patients had isolated cervical dystonia, except for 2 patients who also presented writer's cramp.

The values of T-Th, P-th, and P-Tol in HCs, CD, and F-Dys recorded from the right and left hands and feet are shown in Table 2. For both S-Th and P-th, R-ANOVA did not show any effect of the factor "*group*." No effect of group was found for pain intensity at pain threshold level by VAS (hands, $F_{2,35} = 0.56$; $P = 0.57$; feet, $F_{2,35} = 1.31$; $P = 0.29$). An effect of the factor "*group*" was found for P-Tol in both hands and feet. No effect of the factor "*side*" nor an interaction of "*side*group*" was found. Post-hoc analysis by unpaired *t* test revealed a higher P-Tol in F-Dys compared to HCs and CD, in the upper and lower limbs; no differences in P-Tol were found between CD and HCs.

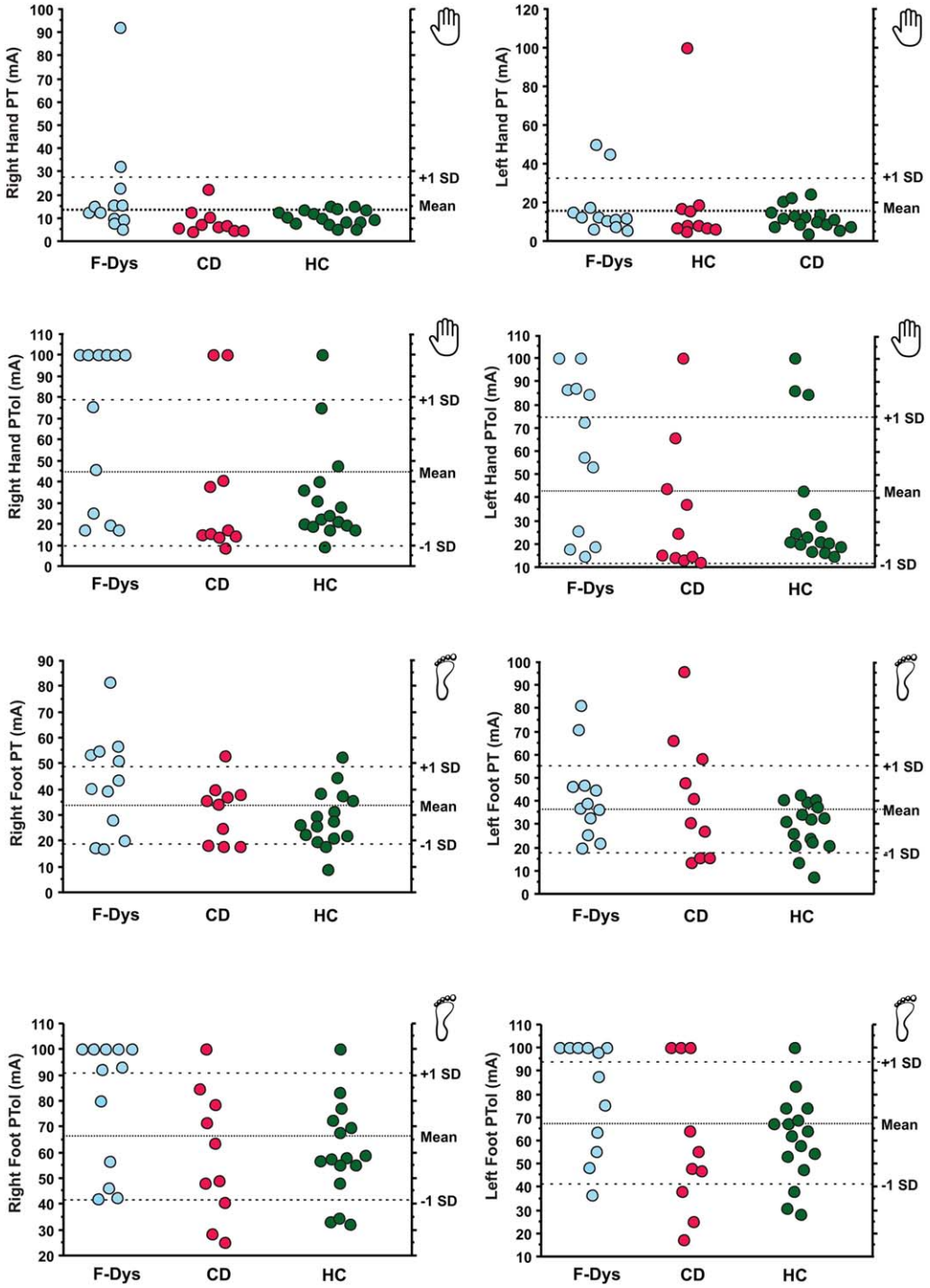

FIG. 1. Individual values for pain threshold and pain tolerance in F-Dys compared to idiopathic CD and HCs. Dotted and dashed lines, respectively, refer to the mean and standard deviation across the three groups. PT, pain threshold. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 1 shows the individual values for P-th and P-Tol in the three groups of subjects. For P-Tol, we had to increase the stimulus duration in 3 subjects with F-Dys who reported unbearable stimulation at 0.5 ms (2 subjects for the right hand, right foot, and left foot; 1 subject for the left hand) and 1 second (1 subject for all body areas). Because it was not possible to account for stimulus duration in the analysis for 3 subjects, a value of 100 mA (corresponding to the maximal allowed stimulation with 0.2-ms pulse width) was set as P-Tol in these subjects.

To understand whether the increased P-Tol was influenced by the temporal course of functional dystonic manifestation (persistent or paroxysmal), we conducted a further analysis comparing CD patients to F-Dys with persistent (continuous F-Dys) and paroxysmal

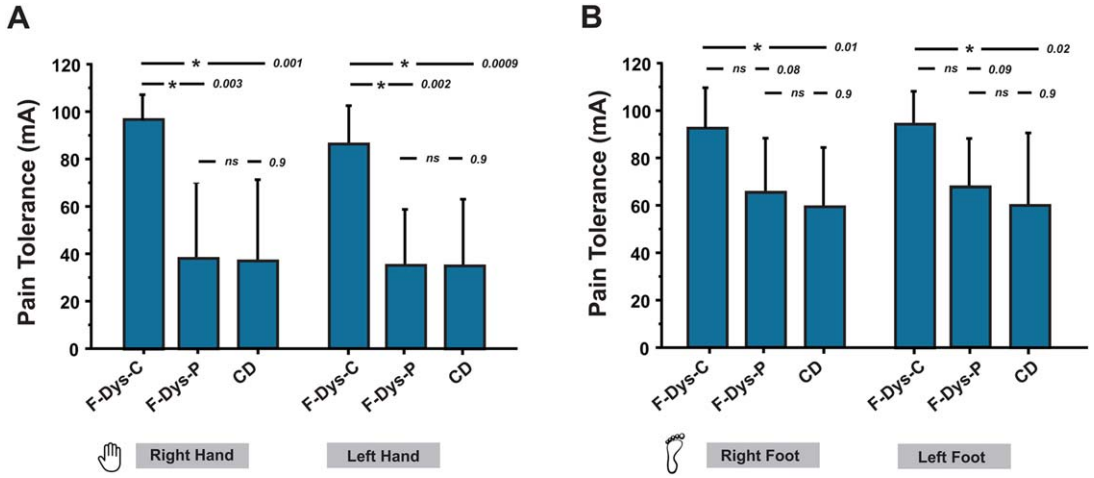

FIG. 2. Pain tolerance was significantly increased in the both hands of subjects with persistent functional dystonia (F-Dys-C) compared to paroxysmal functional dystonia (F-Dys-P) and CD. Pain tolerance was increased in both feet of F-Dys-C compared to CD; the difference between F-Dys-C and F-Dys-P did not reach statistical significance when considering P-Tol in both feet. *ns*, not significant. [Color figure can be viewed at wileyonlinelibrary.com]

(paroxysmal F-Dys) functional symptoms. There was no main effect for the factor "*group*" both for S-Th in hands ($F_{2,19} = 1.41$; $P = 0.27$) and feet ($F_{2,19} = 2.11$; $P = 0.16$) and P-th in hands ($F_{2,19} = 0.82$; $P = 0.45$) and feet ($F_{2,19} = 0.99$; $P = 0.39$). Neither a significant effect of "side" nor an interaction of "*side*group*" were found for S-Th and P-th in the hands and feet.

For P-Tol, we found a "*group*" effect ($F_{2,19} = 9.89$; $P = 0.001$), but neither an effect of "side" ($F_{2,19} = 1.63$; $P = 0.21$) nor an interaction "*side*group*" ($F_{2,19} = 0.4$; $P = 0.67$). This effect was determined by a higher P-Tol in both hands and feet of F-Dys with continuous F-Dys compared to paroxysmal F-Dys and CD (Fig. 2). Similar results for P-Tol were disclosed also in the lower limbs, as revealed by a main effect of "*group*" ($F_{2,19} = 4.15$; $P = 0.03$), but neither an effect of "side" ($F_{2,19} = 0.06$; $P = 0.81$) nor an interaction "*side*group*" ($F_{2,19} = 0.01$; $P = 0.98$; Fig. 2).

In CD and F-Dys, Spearman rank correlation did not show any correlation between P-tol in hands and feet with age, disease duration, and pain scores of the TWSTRS, BFM, Hamilton Depression Rating Scale (HDRS), or Hamilton Anxiety Rating Scale (HARS;

TABLE 3. Correlations between pain tolerance and demographic and clinical data in functional and cervical idiopathic dystonia

	Age	Disease Duration	P-Tol Hand	P-Tol Foot	Pain Severity	Pain Duration	Pain Disability	BFM	HDRS
F-Dys									
Disease duration	0.52								
P-Tol hand	0.39	0.48							
P-Tol foot	0.18	0.23	**0.78****						
Pain severity[a]	−0.15	−0.23	−0.44	−0.38					
Pain duration[a]	−0.47	−0.21	−0.1	−0.05	0.48				
Pain disability[a]	0.11	0.09	−0.02	0.01	−0.05	0.30			
BFM	−0.11	−0.28	0.07	0.14	0.01	0.06	−0.40		
HDRS	−0.08	−0.19	−0.52	−0.10	**0.63***	0.30	−0.18	−0.20	
HARS	0.18	0.02	−0.40	−0.28	0.58	0.25	−0.30	−0.38	**0.89****
CD									
Disease duration	0.35								
P-Tol hand	−0.25	−0.09							
P-Tol foot	−0.22	−0.22	0.19						
Pain severity[a]	0.28	−0.16	−0.15	−0.07					
Pain duration[a]			−67	0.54	0.62				
Pain disability[a]			−0.04	0.57	**0.73***	−0.53			
BFM	0.15	−0.44	−0.33	0.61	0.34	0.56	0.47		
HDRS	0.38	−0.03	−0.45	−0.16	0.51	0.24	−0.26	0.27	
HARS	0.36	0.55	0.06	−0.32	0.36	−0.38	−0.46	0.12	0.51

[a]Pain subscores from the Toronto Western Spasmodic Torticollis Rating Scale (version 1).
Values are Spearman rho: *$P < 0.05$; **$P < 0.01$.
BFM-Mov, Burke-Fahr-Marsden Movement scale.

Table 3). Only HDRS was correlated with pain severity score of the TWSTRS in F-Dys.

Discussion

Painful sensory modalities have been poorly examined in idiopathic CD and F-Dys, two conditions characterized by pain, but likely to be caused by a different mechanism. Tactile and pain thresholds were comparable between F-Dys, CD, and HCs, whereas pain tolerance was higher in F-Dys. This increase occured in both the upper and lower limbs only in subjects with persistent F-Dys, because paroxysmal F-Dys and idiopathic CD had comparable pain tolerance.

Pain is a frequent feature associated with CD; it occurs in up to 88.9% of patients naïve to BoNT and is correlated with severity of dystonic symptoms.[3] Whether pain in CD is related to chronic muscle contraction or is generated by an alteration of transmission and processing of nociceptive stimuli has been a matter of debate for a long time.[8,18-20] Several sensory modalities have been explored in idiopathic isolated dystonia. One of the most frequently reported alterations is prolonged temporal tactile discrimination threshold, which is a feature common to different types of dystonia, regardless of the affected body segment.[21,22] Pain is a sensory modality transmitted by A-δ and C fibers and can be explored using a variety of stimuli, including pain thresholds evoked by thermal sensation and mechanical pressure. Electrical stimulation at high intensity as per pain threshold testing can stimulate small diameter, high-threshold cutaneous afferents (A-delta), and even C-fibers.[23] When considering perception of mechanical painful stimuli, two studies of pain-pressure thresholds were conducted in CD with opposite results. An earlier study found reduced pain-pressure thresholds in 9 patients with CD (6 were never treated with BoNT) compared to 5 healthy subjects.[19] However, when assessing a larger sample of 39 patients with CD, Kutvonen and coworkers found normal pain-pressure thresholds.[20] The normality of pain thresholds and tolerance in our CD sample parallels these early findings, obtained with pressure painful stimuli, and supports the view that at least cutaneous nociceptive pathways are normal in patients with idiopathic CD chronically treated with BoNT. Overall, they are in keeping with the evidence that the amplitude of the N2/P2 peak of laser-evoked potentials is comparable between CD and healthy subjects, regardless of stimulating a painful or painless area.[8]

The abnormality of pain tolerance only in patients with persistent functional dystonic symptoms supports the recent view that there are distinct phenotypes among F-Dys.[24] However, data on pathophysiological differences among F-Dys phenotypes are not available. The increase of pain tolerance, together with the normality of pain threshold, suggests a dissociation between the sensory-discriminative and cognitive-affective components of pain in persistent F-Dys. These two dimensions of pain are regulated by separate, but parallel, neural systems, respectively the lateral pain system (sensory-discriminative dimension of pain) and the medial pain system (cognitive-affective dimension of pain).[25] The lateral system projects to the primary somatosensory cortex through the lateral thalamic nuclei, whereas the medial system projects to several brain regions, including the cingulate cortex and limbic system through the medial medial thalamic nuclei. The two systems are functionally segregated and can be separately assessed by applying nociceptive stimuli of different intensities.[26] The dissociation of the two systems in F-dys is in keeping with two previous studies that reported increased pain tolerance and normal sensory-discriminative thresholds in patients with multisomatoform disorders.[27,28] The category "somatoform" refers to DSM-IV TR, which included in this entity somatization and conversion disorder, pain, hypochondria, and body dysmorphic disorder. Clinical features of subjects in these previous reports were not specified; therefore, it is not possible to ascertain whether any functional movement disorder and, more specifically, F-Dys was included. Nevertheless, both studies reported averaged values from the right and the left hand and did not assess lower limbs.

Two psychological features of patients with FND might explain the increased pain tolerance in F-Dys: (1) a higher frequency of alexithymia, which refers to the inability to identify one's own emotions at a cognitive level[29]; (2) lower interoceptive awareness, which is predictive of a tendency to focus on the external features of the body.[30] A similar reduced interoceptive sensitivity was also found in somatoform patients who were found to have increased pressure-pain tolerance.[27]

A hypothesis to explain our findings in F-Dys is that increased pain tolerance might be caused by abnormalities in limbic areas involved in emotion and pain processing (anterior cingulate cortex) and implicated in assigning emotional salience (amygdala, anterior insula, and posterior cingulate cortex). Indeed, abnormalities in areas involved in emotion recognition and processing have been shown in patients with FND.[31-33] Moreover, FND subjects have reduced activity and lower connectivity of the right temporoparietal junction (an area involved in generating an appropriate sensory prediction signal) with sensorimotor and limbic regions, such as the anterior cingulate cortex and right ventral striatum.[32] It is noteworthy that DBS or lesioning of the anterior cingulate cortex decreases the affective response to noxious stimuli and is used to treat major depression or intractable pain.[34] This hypothesis needs

confirmation by further studies using functional neuroimaging with pain stimuli tasks as well as assessment of emotional processing and alexithymia.

When interpreting our results, we should also consider recent theories on FND[35] that postulate two important mechanisms for generating these abnormal movements: self-focus attention and "brain-expectations." In fact, with strong "top-down" influences, such "prior beliefs" would tend to modify any "bottom-up" sensory information. Moreover, excessive attention toward the body[36] might underlie a decrease in externally directed attention. These could influence cognitive appraisal of pain tolerance. However, this mechanism would not entirely explain the dissociation between pain threshold and tolerance in F-Dys.

Finally, chronic functional dystonia might be related to a reorganization of sensory areas, as has been demonstrated in complex pain regional syndrome type I, a condition that should be included into the functional symptoms spectrum based on clinical and neurophysiological evidence.[37] When dealing with pain, it is also fundamental to discuss the role of emotions and mood on pain processing. Indeed, decreased pain thresholds and pain tolerances in Parkinson's disease were correlated with severity of depressive symptoms,[5] and a similar association was found in patients with major depressive disorder.[17] Accordingly, we screened our sample for depression and anxiety, and we could not find any correlation with pain tolerance. Moreover, pain tolerance had an inverse pattern in F-Dys compared to subjects with major depression. Regarding the relationship between anxiety and pain tolerance, the literature has been controversial on this topic, with reports of decreased pain tolerance in post-traumatic stress disorder[38] or lack of correlation between anxiety and pain tolerance in patients with juvenile fibromyalgia.[38] Yet, we need to recognize that we did not use measures of state anxiety and depression that have been found to modulate pain perception.

We recognize that the small sample size of this exploratory study is an important limitation, given the intersubject variability of psychophysical data, especially in the lower limbs. Even though we could not find any correlation between age and pain tolerance in F-Dys, CD, and HCs, the role of age on pain tolerance should be specifically addressed in future studies, as has been done for parameters of somatosensory processing, such as tactile temporal discrimination thresholds.[39,40] Moreover, objective measures such as pain-evoked potentials or galvanic skin response should be added to P-Tol assessment in future studies to investigate pain processing in F-Dys. Chronic treatment with BoNT and oral medication might also have interfered with pain threshold testing, although they were equally distributed between patient groups.

In conclusion, we report a dissociation between the discriminative and affective dimensions of pain in patients with persisten F-Dys, documented by a marked increase in pain tolerance in all body parts. Our data shed light on the dissociation between pain perception and its emotional processing in patients with F-Dys. This might be used to develop novel rehabilitation protocols, given the profound disability caused by pain and its negative impact on the selection for current physiotherapy protocols.[41]

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Supporting Data

Additional Supporting Information may be found in the online version of this article.