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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 it is likely to be underlined 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 gender 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: 1) the intensity at which sensation changed from unpainful to faintly painfull and 2) the intensity at which painful sensation was intolerable.

Results

No differences were found between the three groups for tactile and pain thresholds assessed in both hands and feet. Pain tolerance was significantly increased in all body district only in functional dystonia. Patients with continuous functional dystonia had higher pain tolerance compared to subjects with paroxysmal functional dystonia and idiopathic cervical dystonia. Spearman Rank Correlation did not demonstrate any 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 component of pain, as revealed by normal pain thresholds and increased pain tolerance. An abnormal connectivity between the motor and the limbic system might account for abnormal pain processing in functional dystonia.

INTRODUCTION

Functional neurological disorders (FND) have been recently better defined at pathophysiological level and distinguished from symptoms that are intentionally produced, such as malingering and factitious disorder[1]. FND 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, while the medial pathway projects to medial thalamic nuclei and limbic structures, such as 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 the sensory thresholds. In particular, the pain threshold (P-Th) evaluates the sensory-discriminative component of pain, whereas the 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 CD)[6] and it was recently demonstrated in functional dystonia (F-Dys), by testing of tactile temporal discrimination thresholds[7]. Yet, experimental data on pain perception are missing in both F-Dys and idiopathic cervical dystonia, which is often associated to pain. Only one study employing laser evoked potentials has revealed that the function of nociceptive pathways in cervical dystonia is comparable to healthy subjects[8].

Based on the evidence that in F-Dys there is an 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 an abnormal temporal processing of somatosensory stimuli[10] and a distorsion of cortical maps in the somatosensory cortex[11], which might determine an alteration of the sensory-discriminatory component of pain. Given these premises, in the present study we aimed to assess the sensory-discriminative and cognitive-emotional components of pain in idiopathic cervical dystonia and F-Dys, testing pain thresholds and pain tolerance in affected and unaffected body segments.

METHODS

We enrolled 10 patients with idiopathic cervical dystonia (CD), 12 patients with clinically definite F-Dys[12] and 16 healthy controls (HC) (13 females, 3 males; mean age = 34.6±10.8 years).

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

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 segments were recorded, including those without dystonia. Depression and anxiety were evaluated in patients and controls with 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 injection.

Tactile and pain thresholds were determined by the method of limits, according to a previous published protocol[5, 17]. The stimulus consisted of a square wave electrical pulse of 0.2 ms delivered by a current stimulator (Digitimer D360, Digitimer Ltd, UK) through AgCl surface skin ring electrodes. The anode was located 1.5 cm distally from the cathode. Hands and feet were tested separately in a random order across patients. Electrical stimuli of increasing intensity were delivered to the little finger and big toe of both sides. In brief, the lowest intensity of stimulus (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 intensity of electrical stimulus was increased by 0.5 mA steps until the subject reported a change in sensation from unpainful to ‘‘faintly painful’’ (pain threshold, P-Th). The patient was asked to point out his 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 (pain tolerance, P-Tol). If the subject did not report an intolerable pain sensation with 99 mA at 0.2 ms of stimulus duration, we increased the stimulus duration to 0.5 ms and 1 sec (3 subjects with F-Dys described in the results).

In order to avoid the pain-modulating effects of BoNT injections, the experiments were performed with a distance after the last botulinum treatment of at least 3 months.

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

STATISTICAL ANALYSIS

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

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

Differences in T-Th, P-Th and P-Tol among the 3 groups of subjects were explored by repeated measures analysis of variance (R-ANOVA) with “*group*” as between subjects factor (3 levels: HC, F-Dys and CD) and “*side*” (two levels: right, left) as within-subjects factor. The second aim of our study was to understand if 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 run a separate R-ANOVA with “*group*” as between subjects factor (three levels: continuous F-Dys, paroxysmal F-Dys, CD) and “side” (two levels: right, left) as 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 to age, age at onset, disease duration, BFM scale, pain scores of TWSTRS (severity, duration, disability due to pain), HAM-D and HAM-A.

Significance level was set at $p \leq 0.05$. Unless otherwise stated, data are given as mean ± standard deviation (SD).

RESULTS

Distribution of gender was comparable among the 3 groups (G-squared p-value = 0.6). Kruskall-Wallis analysis did not disclose any difference in age (*p*=0.08), although patients with CD were older compared to HC (*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 out of 12 patients with F-Dys have been chronically treated with BoNT, performed at least 3 months before the experiment. Supplementary table online shows details on each patient's oral medications.

Tables 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 two patients who also presented writer's cramp.

The values of S-Th, P-Th and P-Tol in HC, CD, F-Dys recorded from the right and left hand and foot are displayed 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 the hands ($F_{2,35}$=3.766, *p*=0.033) and the feet ($F_{2,35}$=3.986, *p*= 0.028). No effect of the factor "*side"* (hands: $F_{2,35}$=0.68, *p*= 0.41; feet: $F_{2,35}$=0.16, *p*= 0.70) nor an interaction *"side*group"* (hand: $F_{2,35}$=1.27, *p*= 0.29; feet: $F_{2,35}$=0.02, *p*= 0.99) was found. Post-hoc analysis by unpaired t-test revealed a higher P-Tol in F-Dys compared to HC and CD, in the upper and lower limbs; no differences of P-Tol were found between CD and HC.

Figure 1 shows the individual values for P-Th and P-Tol in the 3 groups of subjects. For P-Tol, we had to increase the stimulus duration in 3 subjects with F-Dys who reported an unbearable stimulation at 0.5 ms (2 subjects for the right hand, right foot, left foot; 1 subject for the left hand) and 1 second (1 subject for all body districts.). As it was not possible to account for stimulus duration in the analysis only 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 if 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 (paroxysmal F-Dys) functional symptoms. There was no main effect of 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" or an interaction "*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 (Figure 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) (Figure 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, pain scores of the TWSTRS, BFM, HDRS, HARS (Table 3). Only HDRS was correlated to pain severity score of the TWSTRS in F-Dys.

DISCUSSION

Painful sensory modalities have been poorly examined in idiopathic cervical dystonia and functional dystonia, two conditions characterized by pain, likely to be underlined by a different mechanism. Tactile and pain thresholds were comparable between F-Dys, CD and HC, 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, as paroxysmal F-Dys and idiopathic cervical dystonia had comparable pain tolerance.

Pain is a frequent feature associated to cervical dystonia, occurring in up to 88.9% of patients naïve to BoNT and being correlated with severity of dystonic symptoms[3]. Whether pain in cervical dystonia is related to chronic muscular contraction or is generated by an alteration of transmission and processing of nociceptive stimuli has been matter of debate for a long time[8, 18-20]. Several sensory modalities have been explored in idiopathic isolated dystonia and one of the most frequently reported alteration is the prolonged temporal tactile discrimination threshold, which is a common feature to different types of dystonia, regardless the affected body segment [21, 22]. Pain is a sensory modality, which is 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 on pain-pressure thresholds were conducted in CD with opposite results. An earlier study found reduced pain-pressure thresholds in 9 patients with CD (6 of them 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 N2/P2 at laser evoked potential is comparable between CD and healthy subjects, regardless of stimulating a painful or painless area in dystonia[8].

The abnormality of pain tolerance only in patients with persistent dystonic functional 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, via 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, reporting 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 functional dystonia was included. Nevertheless, both these 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) the higher frequency of alexithymia, which refers to the inability to identify one's own emotions at a cognitive level[29]; 2) the lower interoceptive awareness, which is predictive of their tendency to focus on the external features of their body[30]. A similar reduced interoceptive sensitivity was also found in somatoform patients who disclosed increased pressure-pain tolerance[27].

A hypothesis to explain our findings in F-Dys is that the 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 has 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]. Noteworthy, deep brain stimulation or lesioning of the anterior cingulate cortex are able to decrease the affective response to noxious stimuli and are employed to treat major depression or intractable pain[34]. This hypothesis needs confirmation by further studies emplying functional neuroimaging with pain stimuli tasks as well ass assessment of emotional processing and alexithymia.

When interpreting our results, we should also consider recent theories on FND[35] postulating that two important mechanisms for generating these abnormal movements are self-focus attention and 'brain-expectations'. In fact, strong "top down" influences, such "prior beliefs" would tend to modify any "bottom up" sensory information. Moreover, excessive attention towards the body[36] might underlie the decrease in externally directed attention. These could influence the 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 have determined a reorganization of sensory areas, as it 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 to severity of depressive symptoms[5] and a similar association was found in patients with major depressive disorder[17]. 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]. Accordingly, we screened our sample for depression and anxiety and we could not find any correlation with pain tolerance, which also had an inverse pattern in F-Dys compared to subjects with major depression. Yet, we need to recognize that we did not employ 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 represents an important limitation, given the inter-subject 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 HC, the role of age on pain tolerance should be specifically addressed in future studies, as it 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 investigating pain processing in functional dystonia. Chronic treatment with botulinum toxin and oral medication might also have interfered with pain thresholds testing, although they were equally distributed between patients' groups.

In conclusion, we reported a dissociation between the discriminative and affective dimension of pain in patients with persisten F-Dys, documented by a marked increase in pain tolerance in all body parts. Our data shed a light on the dissociation between pain perception and its emotional processing in patients with functional dystonia, which 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].

LEGEND TO FIGURES

Figure 1. Individual values for pain threshold and pain tolerance in functional dystonia (F-Dys) compared to idiopathic cervical dystonia (CD) and healthy controls (HC). CD = cervical dystonia; F-Dys= functional dystonia; HC = healthy controls; PT = pain threshold; P-Tol = Pain tolerance. Dotted and dashed lines respectively refer to the mean and standard deviation across the 3 groups.

Figure 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 cervical dystonia (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.

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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 it is likely to be underlined 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 gender 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: 1) the intensity at which sensation changed from unpainful to faintly painfull and 2) the intensity at which painful sensation was intolerable.

Results

No differences were found between the three groups for tactile and pain thresholds assessed in both hands and feet. Pain tolerance was significantly increased in all body district only in functional dystonia. Patients with continuous functional dystonia had higher pain tolerance compared to subjects with paroxysmal functional dystonia and idiopathic cervical dystonia. Spearman Rank Correlation did not demonstrate any 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 component of pain, as revealed by normal pain thresholds and increased pain tolerance. An abnormal connectivity between the motor and the limbic system might account for abnormal pain processing in functional dystonia.

INTRODUCTION

Functional neurological disorders (FND) have been recently better defined at pathophysiological level and distinguished from symptoms that are intentionally produced, such as malingering and factitious disorder[1]. FND 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, while the medial pathway projects to medial thalamic nuclei and limbic structures, such as 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 the sensory thresholds. In particular, the pain threshold (P-Th) evaluates the sensory-discriminative component of pain, whereas the 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 CD)[6] and it was recently demonstrated in functional dystonia (F-Dys), by testing of tactile temporal discrimination thresholds[7]. Yet, experimental data on pain perception are missing in both F-Dys and idiopathic cervical dystonia, which is often associated to pain. Only one study employing laser evoked potentials has revealed that the function of nociceptive pathways in cervical dystonia is comparable to healthy subjects[8].

Based on the evidence that in F-Dys there is an 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 an abnormal temporal processing of somatosensory stimuli[10] and a distorsion of cortical maps in the somatosensory cortex[11], which might determine an alteration of the sensory-discriminatory component of pain. Given these premises, in the present study we aimed to assess the sensory-discriminative and cognitive-emotional components of pain in idiopathic cervical dystonia and F-Dys, testing pain thresholds and pain tolerance in affected and unaffected body segments.

METHODS

We enrolled 10 patients with idiopathic cervical dystonia (CD), 12 patients with clinically definite F-Dys[12] and 16 healthy controls (HC) (13 females, 3 males; mean age = 34.6±10.8 years).

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

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 segments were recorded, including those without dystonia. Depression and anxiety were evaluated in patients and controls with 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 injection.

Tactile and pain thresholds were determined by the method of limits, according to a previous published protocol[5, 17]. The stimulus consisted of a square wave electrical pulse of 0.2 ms delivered by a current stimulator (Digitimer D360, Digitimer Ltd, UK) through AgCl surface skin ring electrodes. The anode was located 1.5 cm distally from the cathode. Hands and feet were tested separately in a random order across patients. Electrical stimuli of increasing intensity were delivered to the little finger and big toe of both sides. In brief, the lowest intensity of stimulus (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 intensity of electrical stimulus was increased by 0.5 mA steps until the subject reported a change in sensation from unpainful to ‘‘faintly painful’’ (pain threshold, P-Th). The patient was asked to point out his 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 (pain tolerance, P-Tol). If the subject did not report an intolerable pain sensation with 99 mA at 0.2 ms of stimulus duration, we increased the stimulus duration to 0.5 ms and 1 sec (3 subjects with F-Dys described in the results).

In order to avoid the pain-modulating effects of BoNT injections, the experiments were performed with a distance after the last botulinum treatment of at least 3 months.

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

STATISTICAL ANALYSIS

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

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

Differences in T-Th, P-Th and P-Tol among the 3 groups of subjects were explored by repeated measures analysis of variance (R-ANOVA) with “*group*” as between subjects factor (3 levels: HC, F-Dys and CD) and “*side*” (two levels: right, left) as within-subjects factor. The second aim of our study was to understand if 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 run a separate R-ANOVA with “*group*” as between subjects factor (three levels: continuous F-Dys, paroxysmal F-Dys, CD) and “side” (two levels: right, left) as 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 to age, age at onset, disease duration, BFM scale, pain scores of TWSTRS (severity, duration, disability due to pain), HAM-D and HAM-A.

Significance level was set at $p \leq 0.05$. Unless otherwise stated, data are given as mean ± standard deviation (SD).

RESULTS

Distribution of gender was comparable among the 3 groups (G-squared p-value = 0.6). Kruskall-Wallis analysis did not disclose any difference in age (*p*=0.08), although patients with CD were older compared to HC (*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 out of 12 patients with F-Dys have been chronically treated with BoNT, performed at least 3 months before the experiment. Supplementary table online shows details on each patient's oral medications.

Tables 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 two patients who also presented writer's cramp.

The values of S-Th, P-Th and P-Tol in HC, CD, F-Dys recorded from the right and left hand and foot are displayed 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 the hands ($F_{2,35}$=3.766, *p*=0.033) and the feet ($F_{2,35}$=3.986, *p*= 0.028). No effect of the factor "*side"* (hands: $F_{2,35}$=0.68, *p*= 0.41; feet: $F_{2,35}$=0.16, *p*= 0.70) nor an interaction *"side*group"* (hand: $F_{2,35}$=1.27, *p*= 0.29; feet: $F_{2,35}$=0.02, *p*= 0.99) was found. Post-hoc analysis by unpaired t-test revealed a higher P-Tol in F-Dys compared to HC and CD, in the upper and lower limbs; no differences of P-Tol were found between CD and HC.

Figure 1 shows the individual values for P-Th and P-Tol in the 3 groups of subjects. For P-Tol, we had to increase the stimulus duration in 3 subjects with F-Dys who reported an unbearable stimulation at 0.5 ms (2 subjects for the right hand, right foot, left foot; 1 subject for the left hand) and 1 second (1 subject for all body districts.). As it was not possible to account for stimulus duration in the analysis only 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 if 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 (paroxysmal F-Dys) functional symptoms. There was no main effect of 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" or an interaction "*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 (Figure 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) (Figure 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, pain scores of the TWSTRS, BFM, HDRS, HARS (Table 3). Only HDRS was correlated to pain severity score of the TWSTRS in F-Dys.

DISCUSSION

Painful sensory modalities have been poorly examined in idiopathic cervical dystonia and functional dystonia, two conditions characterized by pain, likely to be underlined by a different mechanism. Tactile and pain thresholds were comparable between F-Dys, CD and HC, 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, as paroxysmal F-Dys and idiopathic cervical dystonia had comparable pain tolerance.

Pain is a frequent feature associated to cervical dystonia, occurring in up to 88.9% of patients naïve to BoNT and being correlated with severity of dystonic symptoms[3]. Whether pain in cervical dystonia is related to chronic muscular contraction or is generated by an alteration of transmission and processing of nociceptive stimuli has been matter of debate for a long time[8, 18-20]. Several sensory modalities have been explored in idiopathic isolated dystonia and one of the most frequently reported alteration is the prolonged temporal tactile discrimination threshold, which is a common feature to different types of dystonia, regardless the affected body segment [21, 22]. Pain is a sensory modality, which is 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 on pain-pressure thresholds were conducted in CD with opposite results. An earlier study found reduced pain-pressure thresholds in 9 patients with CD (6 of them 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 N2/P2 at laser evoked potential is comparable between CD and healthy subjects, regardless of stimulating a painful or painless area in dystonia[8].

The abnormality of pain tolerance only in patients with persistent dystonic functional 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, via 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, reporting 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 functional dystonia was included. Nevertheless, both these 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) the higher frequency of alexithymia, which refers to the inability to identify one's own emotions at a cognitive level[29]; 2) the lower interoceptive awareness, which is predictive of their tendency to focus on the external features of their body[30]. A similar reduced interoceptive sensitivity was also found in somatoform patients who disclosed increased pressure-pain tolerance[27].

A hypothesis to explain our findings in F-Dys is that the 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 has 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]. Noteworthy, deep brain stimulation or lesioning of the anterior cingulate cortex are able to decrease the affective response to noxious stimuli and are employed to treat major depression or intractable pain[34]. This hypothesis needs confirmation by further studies emplying functional neuroimaging with pain stimuli tasks as well ass assessment of emotional processing and alexithymia.

When interpreting our results, we should also consider recent theories on FND[35] postulating that two important mechanisms for generating these abnormal movements are self-focus attention and 'brain-expectations'. In fact, strong "top down" influences, such "prior beliefs" would tend to modify any "bottom up" sensory information. Moreover, excessive attention towards the body[36] might underlie the decrease in externally directed attention. These could influence the 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 have determined a reorganization of sensory areas, as it 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 to severity of depressive symptoms[5] and a similar association was found in patients with major depressive disorder[17]. 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]. Accordingly, we screened our sample for depression and anxiety and we could not find any correlation with pain tolerance, which also had an inverse pattern in F-Dys compared to subjects with major depression. Yet, we need to recognize that we did not employ 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 represents an important limitation, given the inter-subject 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 HC, the role of age on pain tolerance should be specifically addressed in future studies, as it 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 investigating pain processing in functional dystonia. Chronic treatment with botulinum toxin and oral medication might also have interfered with pain thresholds testing, although they were equally distributed between patients' groups.

In conclusion, we reported a dissociation between the discriminative and affective dimension of pain in patients with persisten F-Dys, documented by a marked increase in pain tolerance in all body parts. Our data shed a light on the dissociation between pain perception and its emotional processing in patients with functional dystonia, which 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].

LEGEND TO FIGURES

Figure 1. Individual values for pain threshold and pain tolerance in functional dystonia (F-Dys) compared to idiopathic cervical dystonia (CD) and healthy controls (HC). CD = cervical dystonia; F-Dys= functional dystonia; HC = healthy controls; PT = pain threshold; P-Tol = Pain tolerance. Dotted and dashed lines respectively refer to the mean and standard deviation across the 3 groups.

Figure 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 cervical dystonia (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.

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DOCUMENTATION OF AUTHOR ROLES

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
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FM: 1A, 1B, 2A, 2B, 2C, 3B

AM: 1B, 1C, 2B, 3A, 3B

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LR: 2B, 2C, 3B

CA, CT: 1C, 3B

PG: 2C, 3B

MT: 1A, 3B

FULL FINANCIAL DISCLOSURE FOR THE PREVIOUS 12 MONTHS

FM

Stock ownership in medically related fields	none
Intellectual property rights	none
Consultancies	Medtronic and Chiesi
Expert testimony	none
Advisory boards	none
Employment	none
Partnerships	none
Contracts	none
Honoraria	UCB Pharma, Medtronic, Lundbeck, Chiesi, Abbvie, Allergan, Merz
Royalties	FM receives royalties from Springer for her book "Disorders of movement"
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Other	none

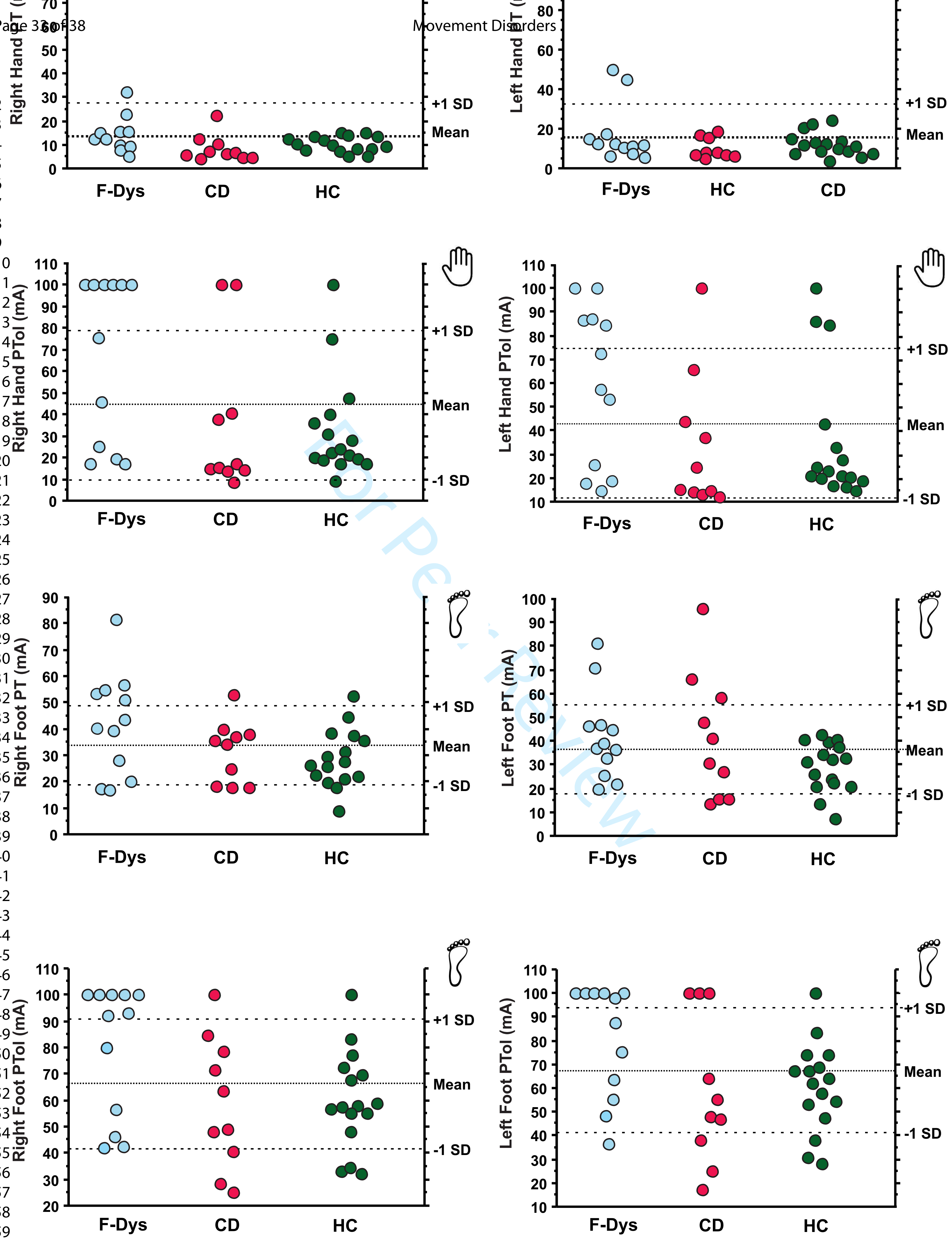
LR

Stock ownership in medically related fields	none
Intellectual property rights	none
Consultancies	none
Expert testimony	none
Advisory boards	none
Employment	none
Partnerships	none
Contracts	none
Honoraria	Chiesi
Royalties	none
Grants:	none
Other	none

AM, EA, CA, CT, PG, MT

Stock ownership in medically related fields	none
Intellectual property rights	none
Consultancies	none
Expert testimony	none
Advisory boards	none
Employment	none
Partnerships	none
Contracts	none
Honoraria	none

Royalties	none
Grants:	none
Other	none


Right Hand PT
Left Hand PT
F-Dys
CD
HC
+1 SD
Mean
-1 SD
Right Hand PTol (mA)
Left Hand PTol (mA)
Right Foot PT (mA)
Left Foot PT (mA)
Right Foot PTol (mA)
Left Foot PTol (mA)

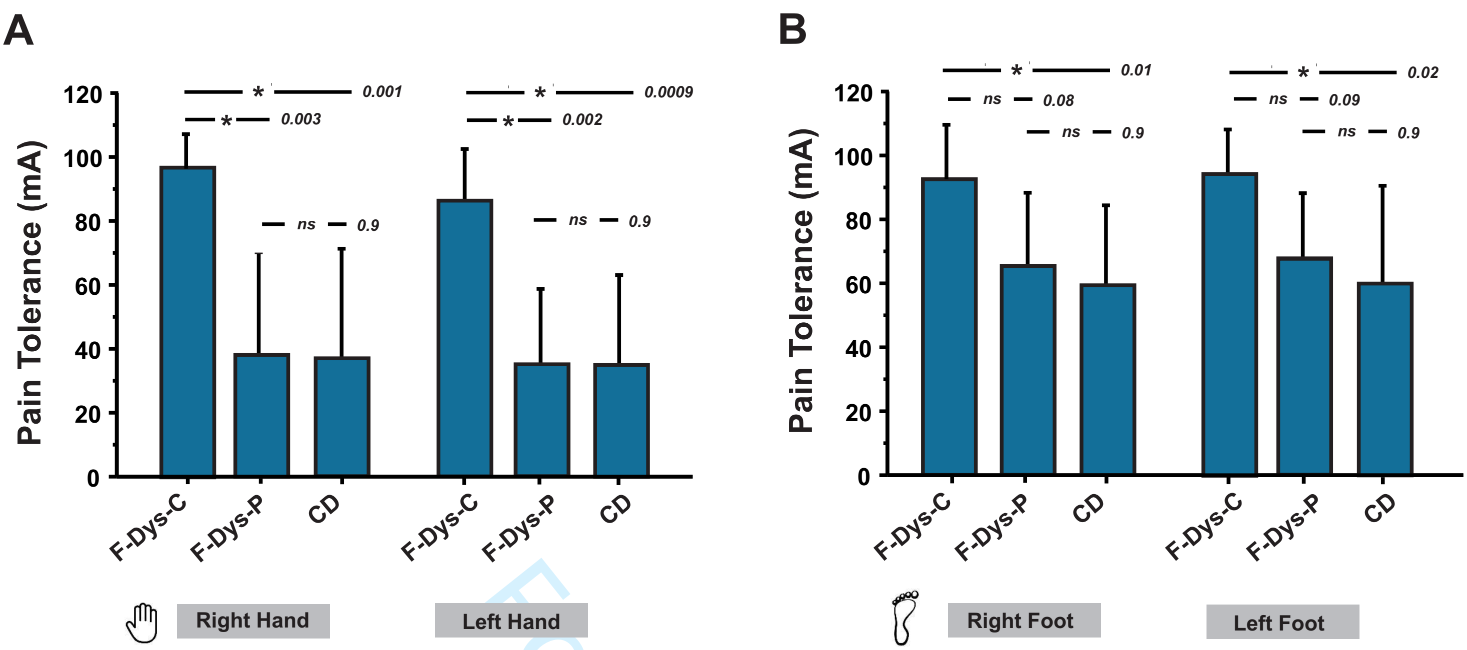

A
Pain Tolerance (mA)
120
100
80
60
40
20
0
* 0.001
* 0.003
ns 0.9
* 0.0009
* 0.002
ns 0.9
F-Dys-C
F-Dys-P
CD
F-Dys-C
F-Dys-P
CD
Right Hand
Left Hand
B
Pain Tolerance (mA)
* 0.01
ns 0.08
ns 0.9
* 0.02
ns 0.09
ns 0.9
F-Dys-C
F-Dys-P
CD
F-Dys-C
F-Dys-P
CD
Right Foot
Left Foot

Table 1: Clinical features of patients affected by Functional and Idiopathic Cervical Dystonia

Pt	Gender	Age (y)	Disease duration (y)	Affected Body District	BFM-Mov	BFM-Dis	Pain score¶	Pain Duration¶	Pain Disability¶	HARS	HDRS
				FUNCTIONAL DYSTONIA							
1	M	42	4	Generalized - Px	0	0	5.25	2	2	25	19
2	F	51	37	Generalized - CT	0	0	1.75	2	4	7	21
3	F	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	F	58	15	Neck+UL+trunk - Px	12	11	8.5	3	2	45	23
6	F	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	F	37	1	Face - Px	0	4	5.25	2	2	8	13
10	F	23	0.6	Face - Px	1	8	5	4	4	22	21
11	F	36	9	Face + UL-Tr - Px	16	4	5	2	2	3	5
12	F	16	0.3	Face + UL-Tr - Px	8	4	6.75	5	2	18	19
Mean ± SD	4 M/8 F	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 CERVICAL DYSTONIA							
1	F	37	3	Neck – UL*	6	4	4	10	5	4	8
2	M	22	1	Neck	5	1	4	4	3	3	4
3	F	63	14	Neck	7	0	12	3.5	2	2	11
4	F	57	4	Neck - UL*	4	0	11	3.25	2	2	7
5	F	72	9	Neck	9	1	12	6	5	3	13
6	F	39	15	Neck	4	0	7	4.5	2	2	7
7	F	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	F	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 F	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	***0.0001**	0.06

BFM-Mov= Burke Fahr Marsden Movement scale; BFM-Dis= Burke Fahr Marsden Disability scale; CT = Continuous; F=female; HARS= Hamilton Anxiety Rating Scale; HDRS=Hamilton Depression Rating Scale; M=male; y= years; pt= patient; Px = paroxysmal; SD= Standard Deviation; UL= upper limb; UL-Tr = upper limb tremor. * Writer's cramp. ¶ Pain sub-scores from the Toronto Western Spasmodic Torticollis Rating Scale (version 1). Comparisons by Mann-Whitney U test.

Table 2: Tactile and Pain Thresholds in Functional and Cervical Idiopathic Dystonia and Healthy Controls

	Body site	Functional Dystonia	Idiopathic Dystonia	Healthy controls	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 Side: $F_{2,35}$= 1.614; *p* = 0.2125 Group*side: $F_{2,35}$= 1.953; *p* = 0.1574
	LH	1.93 ± 0.41	1.816 ± 0.37	1.78 ± 0.33	
	RF	7.15 ± 4.2	5.862 ± 1.35	5.01 ± 1.05	Group: $F_{2,35}$ = 2.741; *p* = 0.0807 Side: $F_{2,35}$ = 1.638; *p* = 0.2105 Group*side: $F_{2,35}$= 0.524; *p* = 0.5977
	LF	6.19 ± 1.50	5.397 ± 1.38	4.98 ± 1.49	
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 Side: $F_{2,35}$ = 1.126; *p* = 0.2959 Group*side: $F_{2,35}$= 2.125; *p* = 0.1346
	LH	17.12 ± 14.63	19.38 ± 8.74	12.31 ± 5.86	
	RF	41.97 ± 21.27	31.73 ± 1.60	28.78 ± 11.42	Group: $F_{2,35}$= 2.084; *p* = 0.1416 Side: $F_{2,35}$ = 1.552; *p* = 0.2222 Group*side: $F_{2,35}$= 1.361; *p* = 0.2712
	LF	41.88 ± 20.31	41.12 ± 6.46	29.12 ± 10.69	
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 Side: $F_{2,35}$ = 0.68, *p* = 0.41 Group*side: $F_{2,35}$ =1.27, *p* = 0.29
	LH	59.88 ± 33.27	34.10 ± 29.04	35.60 ± 28.06	
	RF	79.05 ± 25.25	58.97 ± 24.82	60.12 ± 18.53	Group: $F_{2,35}$=3.986, *p* = 0.028 Side: $F_{2,35}$=0.16, *p*= 0.70 Group*side: $F_{2,35}$=0.02, *p*= 0.99
	LF	80.41 ± 23.74	59.50 ± 31.03	60.70 ± 18.84	

LF= Left Foot; LH= Left Hand; RF= Right Foot; RH= Right Hand

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
					Functional Dystonia				
Disease duration	.52								
P-Tol hand	.39	.48							
P-Tol foot	.18	.23	**.78****						
Pain severity [¶]	-.15	-.23	-.44	-.38					
Pain duration [¶]	-.47	-.21	-.1	-.05	.48				
Pain disability [¶]	.11	.09	-.02	.01	-.05	.30			
BFM	-.11	-.28	.07	.14	.01	.06	-.40		
HDRS	-.08	-.19	-.52	-.10	**.63***	.30	-.18	-.20	
HARS	.18	.02	-.40	-.28	.58	.25	-.30	-.38	**.89****
	Age	**Disease duration**	**P-Tol hand**	**P-Tol foot**	**Pain severity**	**Pain duration**	**Pain disability**	**BFM**	**HDRS**
					Cervical Dystonia				
Disease duration	.35								
P-Tol hand	-.25	-.09							
P-Tol foot	-.22	-.22	.19						
Pain severity [¶]	.28	-.16	-.15	-.07					
Pain duration [¶]			-67	.54	.62				
Pain disability [¶]			-.04	.57	**.73***	-.53			
BFM	.15	-.44	-.33	.61	.34	.56	.47		
HDRS	.38	-.03	-.45	-.16	.51	.24	-.26	.27	
HARS	.36	.55	.06	-.32	.36	-.38	-.46	.12	.51

BFM-Mov= Burke Fahr Marsden scale; HARS= Hamilton Anxiety Rating Scale; HDRS=Hamilton Depression Rating Scale; [¶]Pain sub-scores from the Toronto Western Spasmodic Torticollis Rating Scale (version 1). Values are Spearman's rho; *p<0.05, ** p<0.01

Supplementary Table. Concomitant medication in Functional and Idiopathic Cervical Dystonia

Pt	Gender	Age (y)	Affected Body District	Medication
Functional Dystonia				
1	M	42	Generalized - Px	Botulinum Toxin Duloxetine 30 mg/daily Clonazepam 2 mg/daily
2	F	51	Generalized - CT	Botulinum Toxin Escitalopram 10 mg/daily Clonazepam 2 mg/daily
3	F	38	Generalized – CT	-
4	M	43	Generalized – CT	-
5	F	58	Neck+UL+ trunk - Px	Botulinum Toxin Lorazepam 1 mg/daily
6	F	25	Neck + UL – CT	Botulinum Toxin Clonazepam 1 mg/daily
7	M	50	Neck + trunk - CT	-
8	M	35	Neck - CT	Paroxetine 10 mg/daily
9	F	37	Face - Px	-
10	F	23	Face - Px	-
11	F	36	Face + UL-Tr - Px	Clonazepam 2 mg/daily
12	F	16	Face + UL-Tr - Px	Clonazepam 1 mg/daily
Idiopathic Cervical Dystonia				
1	F	37	Neck – UL*	Botulinum toxin
2	M	22	Neck	Botulinum toxin Clonazepam 2 mg/daily
3	F	63	Neck	Botulinum toxin
4	F	57	Neck - UL*	Botulin toxin Clonazepam 3 mg/daily
5	F	72	Neck	Botulinum toxin
6	F	39	Neck	Botulinum toxin
7	F	66	Neck	Botulinum toxin Lorazepam 1 mg/daily
8	M	51	Neck	Botulinum toxin Escitalopram 10 mg/daily
9	F	54	Neck	Botulinum toxin Paroxetine 20 mg/daily
10	M	27	Neck	Botulinum toxin Clonazepam 2 mg/daily

CT = Continuous; Px = paroxysmal; UL= upper limb; UL-Tr = upper limb tremor. * Writer's cramp