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# Abnormal sensory thresholds of dystonic patients are not affected by deep brain stimulation

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## Abstract

**Background:** Unlike motor symptoms, the effects of deep brain stimulation (DBS) on non-motor symptoms associated with dystonia remain unknown.

**Methods:** The objective of this study was to assess the effects of DBS on evoked experimental pain and cutaneous sensory thresholds in a crossover, double-blind on/off study and compare these results with those of healthy volunteers (HV).

**Results:** Sixteen patients with idiopathic dystonia (39.9 ± 13 years old, $n = 14$ generalized) with DBS of the globus pallidus internus underwent a battery of quantitative sensory testing and assessment using a pain top-down modulation system (conditioned pain modulation, CPM). Results for the more and less dystonic body regions were compared in on and off stimulation. The patients' results were compared to age- and sex-matched HV. Descending pain modulation CPM responses in dystonic patients (on-DBS, 11.8 ± 40.7; off-DBS, 1.8 ± 22.1) was abnormally low (defective) compared to HV (−15.6 ± 23.5, respectively $p = .006$ and $p = .042$). Cold pain threshold and cold hyperalgesia were 54.8% and 95.7% higher in dystonic patients compared to HV. On-DBS CPM correlated with higher Burke-Fahn-Marsden disability score ($r = 0.598$; $p = .014$). While sensory and pain thresholds were not affected by DBS on/off condition, pain modulation was abnormal in dystonic patients and tended to be aggravated by DBS.

**Conclusion:** The analgesic effects after DBS do not seem to depend on short-duration changes in cutaneous sensory thresholds in dystonic patients and may be related to changes in the central processing of nociceptive inputs.

## Significance

The sensory and pain thresholds were not affected by deep brain stimulation (DBS) on/off condition, but pain modulation was abnormal in dystonic patients. The analgesic effects seen after DBS do not seem to depend on short-duration changes

**Abbreviations:** BFM, Burke-Fahn-Marsden; BPI, brief pain inventory; CDT, cold detection threshold; CPM, conditioned pain modulation; CPT, cold pain threshold; C-TS, conditioned test stimulus; DBS, deep brain stimulation; DN4, Douleur neuropathique-4; FAB, frontal assessment battery; GPi, globus pallidus internus; HADS, Hospital Anxiety and Depression scale; HPT, heat pain threshold; HV, healthy volunteers; McGill, short-form McGill pain questionnaire; MDT, mechanical detection threshold; MH, mechanical hyperalgesia; MPT, mechanical pain threshold; NMS, non-motor symptoms; NPSI, Neuropathic Pain Symptom Inventory; PD, Parkinson's disease; QoL, quality of life; QST, quantitative sensory testing; SF-12, SF-12 quality of life questionnaire; SuC, pain rating to suprathreshold cold stimulation; SuH, pain rating to suprathreshold heat stimulation; TS, test stimulus; U-TS, unconditioned test stimulus; VAS, visual analogue scale; VDT, vibration detection threshold; WDT, warm detection threshold.

  

in sensory thresholds. They may be related to changes in the central processing of nociceptive inputs. This was the first effort to dissect the analgesic effects of DBS in dystonia.

## 1 | INTRODUCTION

Dystonia is a frequent movement disorder and impacts the patients' quality of life (QoL; (Stamelou et al., 2012). Part of the functional impairment found in dystonia is related to non-motor symptoms (NMS) (Ashkan et al., 2017; Kuyper et al., 2011; Page et al., 2007). Chronic pain is one of the most disabling and frequent complaints in dystonia (Kuyper et al., 2011; Stamelou et al., 2012). Dystonic patients suffer from altered somatosensory integration and plasticity (Hallett, 2011; Paracka et al., 2017). It is believed that sensory abnormality and pain in dystonia are part of a more widespread (GABA-A/dopamine) loss of inhibition and increase in brain plasticity (Stamelou et al., 2012).

Deep brain stimulation (DBS) targeting the globus pallidus internus (GPi) is the first-line treatment for refractory dystonia (Kupsch et al., 2006; Vidailhet et al., 2005), improving motor symptoms by 43%–65% (Cury et al., 2018) together with pain improvement. It has been suggested that pain amelioration is a considerable driver of postoperative improvements in QoL in dystonic patients (Eggink et al., 2018; Kupsch et al., 2006; Vidailhet et al., 2005). Pain relief after DBS treatment is not thought to be simply due to the alleviation of motor symptoms (Eggink et al., 2018) and could be due to increases in nociceptive thresholds, such as described in Parkinson's disease (PD), or instead, by boosting top-down pain modulatory/inhibitory systems (Cury et al., 2016). DBS is also thought to modify cortical plasticity, an effect that may relate to dystonia overall improvement (Ashkan et al., 2017). The better known modulatory descending pathways involve the midbrain periaqueductal grey matter, the rostral ventromedial medulla, as well as the spinal cord. These systems may be assessed by the conditioned pain modulation (CPM; Ren & Dubner, 2009). However, no study has assessed the mechanisms behind DBS effects on pain and sensory thresholds, nor evaluated pain modulatory systems in dystonia.

We report the first effort to dissect the potential analgesic effects of DBS in dystonia by measuring sensory and pain thresholds by quantitative sensory testing (QST), as well as pain descending modulatory responses by dynamic QST—a CPM paradigm, in a double-blind, crossover, on/off stimulation study with paired comparison with healthy volunteers (HV).

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

Patients included had segmental/generalized dystonia of inherited/idiopathic (Albanese et al., 2013) aetiology who underwent GPi-DBS. Patients' evaluation and data collection were done in the Functional Neurosurgical Outpatient Clinic. This study began in November 2017, and patients were evaluated until April 2018. Exclusion criteria were patients younger than 18 years old, those having received botulinum toxin injections over at least the preceding 3 months, who did not consent to participate, or those who could not have their DBS turned off. Patients with continuous pain medication were also excluded. The study size was established by calculating the standard deviation of the warm detection threshold (WDT) from Paracka et al. (2017), using an error margin of 1.8% for comparing data in a confidence interval of 95%.

### 2.2 | Study design

Patients assessed under their usual treatment underwent a neurological examination and completed pain, mood, cognitive and QoL questionnaires. Afterwards, a double-blind, randomized controlled investigation (Figure 1a) was performed to assess the effects of DBS on sensory and pain thresholds using QST and pain descending modulation by CPM. Another switched the DBS between on/off (namely on-DBS or off-DBS, respectively), using www.randomizer.org. After a 30-min wash-out, QST and CPM were performed again. Thus, patients were always evaluated with the same QST/CPM battery in the off and on-DBS conditions. QST parameters and CPM effect in dystonic patients were also compared to reference values obtained from age- and sex-matched HV from our laboratory's normative database (Aparecida da Silva et al., 2018).

### 2.3 | Patients' clinical and functional status assessments

Patients were assessed by the motor and disability parts of the Burke-Fahn-Marsden (BFM) scale, with higher scores indicating worse dystonia and worse disability (Burke

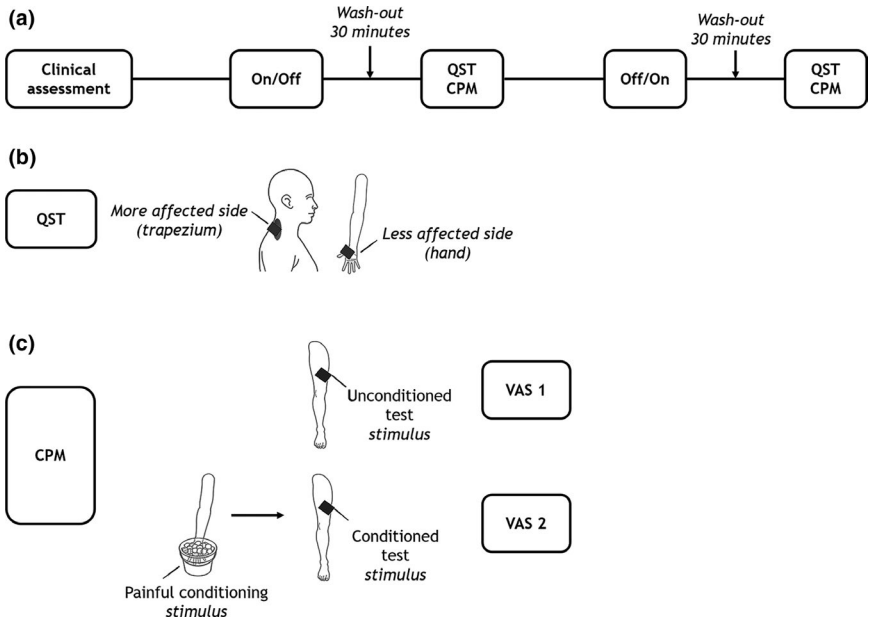


**FIGURE 1** Cross-sectional and double-blind randomized evaluation using QST and CPM. (a) Patients underwent a clinical assessment (cross-sectional study) using the following validated tools and questionnaires: Burke-Fahn-Marsden scale, Neuropathic Pain Symptom Inventory, Douleur Neuropathique-4, Brief Pain Inventory, short-form McGill Pain Questionnaire, Frontal Assessment Battery, the Hospital Anxiety and Depression Scale and SF-12 Quality of Life Questionnaire. Afterward, a double-blind, randomized controlled study was performed to assess the effects of deep brain stimulation on sensory and pain thresholds using QST and CPM. An unblinded researcher maintained or changed the DBS status (on-DBS or off-DBS respectively), as previously randomized. After a 30-min wash-out, QST and CPM were performed. (b) The QST battery was applied in the thenar eminence of the asymptomatic ([no dystonia]/less symptomatic [less dystonic]) limb (hand) and in the most affected (most dystonic) trapezium. (c) The CPM battery was done with a thermal test stimulus applied to the left anterior thigh. The unconditioned test stimulus was the pain intensity measured by the Visual Analogue Scale (VAS, 0–100 mm) to a stimulus set at 5°C above the heat pain threshold (HPT) applied for 5 s (VAS 1). The conditioned test stimulus was the pain intensity (VAS 2) to the same stimulus described above while the patients submerged their right hand in a 4°C water bath with ice blocks and cold water (painful conditioning stimulus). CPM effect is calculated as follows: [VAS 2] − [VAS 1], as the expected response in HVs is VAS 1 > VAS 2, it is usually a negative number. CPM, conditioned pain modulation; DBS, deep brain stimulation; QST, quantitative sensory test

et al., 1985). Previous disease and medication histories were obtained. Clinical and neurologic examinations were performed. Chronic pain was assessed in all patients. Oral medication was not changed during the evaluation. The hospital anxiety and depression scale (HADS) (Botega et al., 1995; Zigmond & Snaith, 1983), SF-12 QoL questionnaire (SF-12) (Camelier, 2004) and the frontal assessment battery (FAB) were used to determine mood, QoL and cognitive variables (Dubois et al., 2000).

## 2.4 | Outcome measures

### 2.4.1 | Pain assessment scales

Below are the questionnaires used for pain assessment (Cury et al., 2016; Lopes et al., 2018). These scales and questionnaires were applied only once, with patients under their usual treatment, thus, before the QST/CPM on/off study:

(i) The Short-form McGill pain questionnaire (McGill) in which pain descriptors are categorized into three dimensions of pain: sensory, affective and evaluative. There is an item for pain intensity by the visual analogue scale (VAS, 0–100 mm, where 0 means no pain and 100 stands for maximal pain imaginable) (Ferreira et al., 2013);
(ii) The Brief Pain Inventory (BPI) short-form gives two main scores: pain severity score and pain interference score in daily activities (Ferreira et al., 2011);
(iii) The Douleur Neuropathique-4 (DN4) assesses a possible neuropathic component of the pain. Scores of ≥4 are considered positive (Santos et al., 2010);
(iv) Neuropathic Pain Symptom Inventory evaluates different clusters of descriptors and varies from 0–10 (de Andrade et al., 2011).

### 2.4.2 | Psychophysics assessment

*Quantitative sensory testing*

The tests performed were already extensively used (Cury et al., 2016; Kaziyama et al., 2020; Lopes et al., 2018). Briefly, stimuli were applied on the thenar eminence of the asymptomatic

limb (i.e. not dystonic or less dystonic) and the skin over the most dystonic trapezium (Figure 1b). Mechanical detection thresholds (MDT) and mechanical pain thresholds (MPT) were measured using von Frey monofilaments (NC 17775; Bioseb). The vibration detection threshold (VDT) was measured using a graduated tuning fork (Rydel-Seiffer tuning fork; Martin; Martina et al., 1998). Thermal thresholds were assessed using a TSA-2001 device (Medoc) with a 20 × 35 mm thermode. For thermal detection thresholds (WDT; cold detection threshold, CDT), the forced-choice method (Cury et al., 2016; Lopes et al., 2018) was, again, used to avoid bias due to lower motor reaction time (Cury et al., 2016). Heat and cold pain thresholds (HPT, CPT) were established through a method of limits (1°C/s from 32°C; Coghill & Yarnitsky, 2015). Experimental pain was studied by suprathreshold heat (SuH) and cold (SuC) stimulations (Cury et al., 2016; Lopes et al., 2018). Stimulations above (46°C and 48°C) and below (5°C and 10°C) heat and cold pain thresholds, respectively, were delivered for 2s and VAS scores were recorded.

*CPM*

Dynamic QST, CPM (Figure 1c), was explored with a painful thermal test stimulus (set at 5°C above HPT for 5 s) applied to the left anterior thigh. This was performed both before (unconditioned test stimulus) and after (conditioned test stimulus) the delivery of a painful conditioning stimulus at the contralateral upper limb—immersion in 4°C water until pain reached a VAS of at least 60/100 mm (i.e. cold pressor test); (Aparecida da Silva et al., 2018; Lopes et al., 2018). CPM is based on the modulatory effect that a painful conditioning stimulus (i.e. the upper limb immersion in cold water) has on a painful test stimulus applied in a different body segment (i.e. heterotopic); (Yarnitsky et al., 2015). Thus, it is calculated as the change in pain intensity, measured by VAS, by the subtraction of the conditioned test stimulus and the unconditioned test stimulus. Therefore, normal individuals have negative CPM values, as a normal response is to have a lower pain intensity after the painful conditioning stimulus is delivered.

## 2.5 | Statistical analysis

Data were expressed as mean ± *SD* (min–max). Non-normal data for independent variables were evaluated using the Mann–Whitney test, and dependent variables with the Wilcoxon non-parametric test. No correction for family wise errors was performed for this exploratory study (Bender & Lange, 2001), except when main results from multiple tests had to be combined for one final conclusion and decision. Correlation analyses were performed by Spearman's correlation. The following comparisons were made: (i) Over the less affected body region (hand)—off versus on-DBS for each QST parameter; (ii) Over the more affected body region (trapezium)—off versus on-DBS for each QST parameter; (iii) In the off-DBS condition—hand versus trapezium for each QST parameter; (iv) In the on-DBS condition—hand versus trapezium for each QST parameter; (v) CPM effect (off versus on-DBS condition); (vi) The on- and off-DBS QST (hand only) and CPM effect were compared to HV's. A subanalysis was performed comparing the QoL, BFM, FAB and HADS scales between patients with and without chronic pain using the Mann–Whitney test for independent samples. QST/CPM analyses were correlated with BFM, pain intensity (BPI), HADS and SF-12 scores. All statistical calculations were performed using the Statistical Package for the Social Sciences software (SPSS, version 20.0.0; SPSS Inc.), and statistical significance was set at $p < .05$).

# 3 | RESULTS

## 3.1 | Sample description

Sixteen patients, 39.9 ± 13.8 (18.0–61.0) years, were included ($n = 14$ generalized, $n = 2$ segmental; four women). A family history of dystonia was present in 25.0% of the patients, and 43.8% had consanguinity. Seven patients, all with generalized dystonia, underwent genetic analyses: DYT1, $n = 2$; DYT6, $n = 3$; and DYT16, $n = 2$. Age at dystonia onset was 17.8 ± 14.9 (4.0–54.0).

Patients were evaluated 3.7 ± 3.8 (0.3–12.3) years after DBS surgery. They had a total BFM motor score of 48.0 ± 21.1 (20.0–78.0) and a disability score of 10.0 ± 5.0 (2.0–19.0; Table S1). We compared the right and left arm component subscores of the BFM scale for generalized dystonia patients and did not find any significant statistical difference (Figure S1). Nine patients (56.3%) reported current chronic pain. Only one reported the presence of chronic pain before dystonia. The BPI pain severity index was 3.3 ± 1.9 (0.0–6.2), and pain interference in daily activities was 2.4 ± 2.7 (0.0–8.7; Table S2). Two patients had a positive DN4 (both with a score of 4). Four patients (25.0%) had anxiety scores higher than 8.0, and none had major depression (score > 9.0) on the HADS. SF-12's bodily pain ($p = .023$) and mental health ($p = .042$) subscores were significantly worse in patients with chronic pain compared with pain-free dystonic patients (Table S1). Also, patients with chronic pain had worse total ($p = .005$), depression ($p = .008$) and anxiety ($p = .023$) scores in the HADS (Table S1).

## 3.2 | Sensory and modulatory pain assessment

Quantitative sensory testing results in the off-DBS condition were not significantly different from the on-DBS in comparisons within the same body part (hand or trapezium, Table 1).

**TABLE 1** Quantitative sensory test (QST) values on the more (trapezium) and less (hand) affected body region and in the on- and off-DBS conditions. The table shows the results of the following comparisons: (i) off versus on-DBS for QST parameters in the hand (p-hand); (ii) off versus on-DBS for QST parameters in the trapezium (p-trapezium); (iii) analysis of hand versus trapezium for QST parameters in the off-DBS condition (p-off); and (iv) analysis of hand versus trapezium for QST parameters in the on-DBS condition (p-on). Results are presented as mean ± *SD* (min–max). Significance set at $*p < 0.05$; $**p < 0.01$

| | Off-DBS | | On-DBS | | Off versus on-DBS | | Hand versus Trapezium | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | **Hand** | **Trapezium** | **Hand** | **Trapezium** | **p-hand** | **p-trapezium** | **p-off** | **p-on** |
| CDT (°C) | 30.7 ± 1.2 (27.9–31.8) | 30.0 ± 1.8 (26.4–31.9) | 30.7 ± 0.8 (29.1–31.9) | 30.1 ± 1.6 (28.7–31.9) | 0.975 | 0.900 | 0.083 | 0.061 |
| WDT (°C) | 33.5 ± 1.5 (32.3–37.4) | 34.3 ± 1.8 (32.2–37.4) | 33.3 ± 0.8 (32.4–35.3) | 34.3 ± 1.6 (32.1–37.6) | 0.682 | 0.979 | 0.155 | 0.007** |
| HPT (°C) | 45.9 ± 2.7 (41.5–50.0) | 45.0 ± 3.1 (39.0–49.3) | 46.0 ± 2.5 (42.4–49.8) | 45.6 ± 3.5 (37.7–49.4) | 1.000 | 0.453 | 0.326 | 0.717 |
| CPT (°C) | 16.1 ± 7.7 (0.8–29.6) | 13.5 ± 9.6 (0.0–26.1) | 16.6 ± 6.2 (5.3–24.5) | 15.1 ± 9.4 (0.0–28.2) | 0.959 | 0.140 | 0.233 | 0.587 |
| SuH (VAS) | 39.8 ± 28.6 (2.5–90.5) | 36.5 ± 28.3 (1.5–90.5) | 39.5 ± 28.7 (4.0–87.5) | 48.3 ± 32.1 (2.0–93.5) | 0.518 | 0.191 | 0.313 | 0.155 |
| SuC (VAS) | 43.6 ± 30.1 (2.5–87.5) | 35.5 ± 31.4 (0.0–100.0) | 53.6 ± 32.8 (3.0–99.0) | 42.2 ± 33.1 (0.0–100.0) | 0.083 | 0.233 | 0.011* | 0.021* |
| MDT ($g/mm^2$) | 1.8 ± 0.2 (1.7–2.3) | 2.0 ± 0.5 (1.7–3.3) | 1.8 ± 0.4 (1.7–3.3) | 1.9 ± 0.7 (1.7–4.5) | 0.655 | 0.783 | 0.059 | 0.180 |
| MPT ($g/mm^2$) | 104.0 ± 42.5 (25.0–137.3) | 98.9 ± 48.4 (6.8–137.3) | 114.0 ± 36.4 (39.1–137.3) | 117.0 ± 38.5 (31.6–137.3) | 0.043 | 0.108 | 0.715 | 0.833 |
| MH (VAS) | 5.8 ± 8.5 (0.0–22.0) | 6.7 ± 12.9 (0.0–51.0) | 7.9 ± 12.6 (0.0–45.0) | 5.2 ± 12.0 (0.0–46.0) | 0.262 | 0.248 | 0.859 | 0.089 |
| Mechanical dynamic allodynia (0–100) | 0.0 ± 0.0 (0.0–0.0) | 0.0 ± 0.0 (0.0–0.0) | 0.0 ± 0.0 (0.0–0.0) | 0.0 ± 0.0 (0.0–0.0) | 1.000 | 1.000 | 1.000 | 1.000 |
| VDT (μm) | 7.6 ± 0.6 (6.0–8.0) | 6.6 ± 1.0 (5.0–8.0) | 7.7 ± 0.7 (6.0–8.0) | 6.4 ± 1.2 (3.0–8.0) | 0.589 | 0.589 | 0.020* | 0.002** |

Abbreviations: CDT, cold detection threshold; CPT, cold pain threshold; DBS, deep brain stimulation; HPT, heat pain threshold; MDT, mechanical detection threshold; MH, mechanical hyperalgesia; MPT, mechanical pain threshold; SuC, pain rating to suprathreshold cold stimulation; SuH, pain rating to suprathreshold heat stimulation; VAS, visual analogue scale 0–100 mm; VDT, vibration detection threshold; WDT, warm detection threshold.

When comparing changes between the more (trapezium) and less (hand) affected body regions in the off-DBS condition, we found that the pain rating to experimental pain cold stimulus was significantly higher on the hand (43.6 ± 30.1 vs. 35.5 ± 31.4; $p$ =.011), and similar findings were obtained in the on-DBS status in the hand (SuC: 53.6 ± 32.8) compared to the trapezium (42.2 ± 33.1; $p$ =.021). Similarly, the VDT was significantly lower on the trapezium compared to the hand in the off-DBS status (7.5 ± 0.6 vs. 6.6 ± 1.0, $p$ =.020; respectively), as well as in the on-DBS conditions: 7.7 ± 0.7 vs. 6.4 ± 1.2, $p$ =.002 for the hand and trapezium, respectively. In the on-DBS, WDT was significantly lower on the hand (33.2 ± 0.8) compared to the trapezium (34.3 ± 1.6; $p$ =.007; respectively).

Concerning the less affected body region (hand), both the MDT and MPT were higher in dystonic patients compared to HV, regardless of the DBS conditions (Table 2). CPT and experimental pain cold stimulus (SuC) were significantly higher (i.e. cold allodynia and cold hyperalgesia) in dystonic patients when in the on-DBS condition. CPT was 54.8% higher, while SuC was 95.7% higher when compared to HV.

The patient's CPM values in the off-DBS state were not significantly different from the on-DBS (Table 3). Still, both on- and off-DBS values were significantly higher (i.e. less effective CPM) when compared to reference data from HV (Table 3). We found a correlation between higher on-DBS CPM and higher BFM disability score ($r$ = .598, $p$ =.014), and with higher off-DBS CPM and lower SF-12 vitality score ($r$ = −.655, $p$ =.008). Other pre-planned correlation analyses were not significant.

## 4 | DISCUSSION

Abnormal afferent sensory processing has long been acknowledged in dystonia (Sanger et al., 2001). We found that chronic pain is still a common complaint in dystonic patients, even under DBS. Patients with pain had more severe mood symptoms and worst QoL. Dystonic patients presented cold allodynia and cold hyperalgesia, as well as a significant *A-β*/*A-δ*-dependent deficits related to mechanical detection and pain thresholds, respectively, which occurred even in the body area less affected by dystonia. Since cold allodynia and cold hyperalgesia may also depend on central alterations in sensory processing, these data suggest that dystonic patients have both peripheral and central sensory abnormalities occurring even in the least affected body regions.

We also found that the more affected dystonic body region (i.e. the skin over the trapezium) presented more altered sensory thresholds results (i.e. higher WDT, cold hyperalgesia) when compared to the less affected hand. Although this may be, in part, due to the difference between glabrous and

**TABLE 2** Comparison between patients and healthy volunteers concerning hand QST parameters. The table shows the results of the following comparisons: (i) HV versus patients off-DBS for QST parameters in the hand (p HV vs. off); (ii) HV versus patients on-DBS for QST parameters in the hand (p HV vs. on). Results are presented as mean ± *SD* (min–max). Significance set at *$p < 0.05$; **$p < 0.01$

| Variable | HV | Dystonic Off | Dystonic On | p HV versus off | p HV versus on |
|---|---|---|---|---|---|
| CDT (°C) | 30.6 ± 0.9 (27.7–31.4) | 30.7 ± 1.2 (27.9–31.8) | 30.7 ± 0.8 (29.1–31.9) | 0.171 | 0.897 |
| WDT (°C) | 33.5 ± 0.7 (32.4–35.1) | 33.5 ± 1.5 (32.3–37.4) | 33.3 ± 0.8 (32.4–35.3) | 0.128 | 0.254 |
| HPT (°C) | 44.6 ± 3.4 (37.7–49.6) | 45.9 ± 2.7 (41.5–50.0) | 46.0 ± 2.5 (42.4–49.8) | 0.402 | 0.491 |
| CPT (°C) | 10.7 ± 6.4 (0.5–22.3) | 16.1 ± 7.7 (0.8–29.6) | 16.6 ± 6.2 (5.3–24.5) | 0.056 | 0.023* |
| SuH (VAS) | 24.4 ± 23.3 (0.0–65.0) | 39.8 ± 28.6 (2.5–90.5) | 39.5 ± 28.7 (4.0–87.5) | 0.073 | 0.080 |
| SuC (VAS) | 27.4 ± 27.8 (0.0–82.5) | 43.6 ± 30.1 (2.5–87.5) | 53.6 ± 32.8 (3.0–99.0) | 0.086 | 0.019* |
| MDT (g/mm$^2$) | 0.0 ± 0.1 (0.0–0.4) | 1.8 ± 0.2 (1.7–2.3) | 1.8 ± 0.4 (1.7–3.3) | 0.0001** | 0.0001** |
| MPT (g/mm$^2$) | 81.0 ± 117.2 (1.4–300.0) | 104.0 ± 42.5 (25.0–137.3) | 114.0 ± 36.4 (39.1–137.3) | 0.032* | 0.023* |
| MH(VAS) | 3.1 ± 8.7 (0.0–30.0) | 5.8 ± 8.5 (0.0–22.0) | 7.9 ± 12.6 (0.0–45.0) | 0.196 | 0.184 |
| Mechanical dynamic allodynia (0–100) | 0.0 ± 0.0 (0.0–0.0) | 0.0 ± 0.0 (0.0–0.0) | 0.0 ± 0.0 (0.0–0.0) | 1.000 | 1.000 |

Abbreviations: CDT, cold detection threshold; CPT, cold pain threshold; DBS, deep brain stimulation; HPT, heat pain threshold; MDT, mechanical detection threshold; MH, mechanical hyperalgesia; MPT, mechanical pain threshold; SuC, pain rating to suprathreshold cold stimulation; SuH, pain rating to suprathreshold heat stimulation; VAS, visual analogue scale 0–100 mm; WDT, warm detection threshold.

**TABLE 3** Conditioned pain modulation (CPM) parameters. The table shows the results of the following comparisons: (i) off versus on-DBS for CPM variables (p-on vs. off), (ii) CPM of HV versus patients in the off-DBS condition (p HV vs. off), and (iii) in the on-DBS condition (p HV vs. on). Results are presented as mean ± *SD* (min–max). Significance set at $*p < 0.05$; $**p < 0.01$

| | Off-DBS | On-DBS | HV | p on versus off | p HV versus off | p HV versus on |
|---|---|---|---|---|---|---|
| HPT (°C) | 47.1 ± 2.4 (43.6–49.9) | 47.0 ± 2.1 (42.7–49.6) | — | 0.469 | — | — |
| U-TS (VAS) | 59.8 ± 35.6 (10.0–100.0) | 57.5 ± 33.0 (9.0–100.0) | — | 0.727 | — | — |
| C-TS (VAS) | 58.9 ± 35.2 (7.0–100.0) | 45.8 ± 37.0 (0.0–100.0) | — | 0.382 | — | — |
| C-TS total duration | 40.9 ± 12.0 (29.5–66.6) | 42.1 ± 21.9 (26.0–115.0) | — | 0.460 | — | — |
| C-TS unpleasantness (VAS)[a] | 70.7 ± 31.0 (13.0–100.0) | 59.3 ± 38.3 (10.0–100.0) | — | 0.182 | — | — |
| CPM effect[b] | 1.8 ± 22.1 (−34.0–50.0) | 11.8 ± 40.7 (−86.0–97.0) | −15.6 ± 23.5 (−62.0–28.0) | 0.683 | 0.042* | 0.006** |
| CPM[c] | 20.3 ± 81.1% (−63.0%–230.0%) | 66.8 ± 199.8% (−90.0%–720.0%) | −43.1 ± 29.7% (−96.0%–35.0%) | 0.826 | 0.001** | 0.0001** |

Abbreviations: CPM, conditioned pain modulation; C-TS, conditioned test stimulus; HV, healthy volunteers; TS, test stimulus; U-TS, unconditioned test stimulus.

[a]Conditioned-TS unpleasantness is the pain's VAS of the hand after water bath with ice blocks was finished;

[b]''Raw'' CPM effects were calculated as (C-TS) − (U-TS);

[c]CPM was calculated as a ratio: {[(C-TS) − (U-TS)]/[U-TS]} × 100.

non-glabrous skin or due to intrinsic discriminatory threshold differences between the hand and the shoulder, these results were relatively consistent. They did not occur for other sensory thresholds, suggesting an actual abnormality related to the dystonic state. Turning on or off the DBS had no significant effect on painful or non-painful sensory thresholds, on evoked pain ratings, or conditioned top-down modulation of pain.

In our sample, 56.3% of patients had chronic pain even after DBS treatment. Pain is a frequent complaint and impacts a patient's QoL (Page et al., 2007; Stamelou et al., 2012). Nevertheless, most studies on dystonia and pain have focused on cervical dystonia and other focal dystonias, with a high prevalence of pain (67%–75%); (Kuyper et al., 2011; Stamelou et al., 2012). In patients with inherited/idiopathic generalized dystonia, a randomized clinical trial with 40 patients showed a reduction in pain (VAS) in on-DBS patients versus no change in sham-stimulation (63% vs. 0%) at 3 months, which was maintained at 6 months and 5 years (Eggink et al., 2018; Kupsch et al., 2006; Volkmann et al., 2012).

We found that among patients with pain, two fulfilled the DN4 screening test for neuropathic pain. The current diagnostic criteria for neuropathic pain imply that pain is located in an area of sensory deficits caused by a disease or lesion to the somatosensory system. While we have found that there are somatosensory abnormalities in dystonic areas (i.e. higher WDT), the task to ascertain that dystonic patients have actual lesion of disease directly causing these abnormalities remains to be determined. We also found a higher MDT (*A-β* fibre-dependent) and MPT in both DBS conditions, as well as higher CPT and SuC (*A-δ* fibre-dependent) in the on-DBS state compared to HV. Few studies have explored small-fibre sensory changes in dystonia. The sample sizes were usually small, and QST measurements were commonly based on reaction-time-dependent measurements, which may bias sensory assessment in motor disorders (Lopes et al., 2018). One study found increased WDT, CDT and MPT in the affected side of focal hand dystonia patients (Suttrup et al., 2011). Another study reported reduced CDT and WDT and enhanced dynamic mechanical allodynia in distant body parts (i.e. hands) and increased CPT and allodynia in the shoulder in patients with cervical dystonia (Paracka et al., 2017). In cervical dystonia, pain-pressure thresholds were twice as high as in HV (Lobbezoo et al., 1996). In general, higher thermal detection thresholds have also been reported (Paracka et al., 2017), as well as abnormal *A-δ*-dependent heat evoked responses in dystonic patients when compared to HV (Suttrup et al., 2011). These conflicting results might be related to the fact that, in some of these studies, the body area chosen to perform QST was the same where dystonia was located (Suttrup et al., 2011), while in others, the region less affected by the disease was studied (Paracka et al., 2017). In some instances, one cannot ascertain the dystonic status of the region included in the QST study (Paracka et al., 2017). Table 4 shows the comparisons between these studies and the present one. Here, we chose to study the less and more dystonic body regions to disentangle these variables. Also, to date, no study applied reaction-time-independent QST methods to

**TABLE 4** QST studies in dystonia. This table shows the previous QST studies in dystonia and their comparison to this one

| Study | Sample size and characteristics | DBS | Areas tested | Use of reaction-time independent methods for thermal detection threshold determination | Main QST findings | Main CPM findings |
|---|---|---|---|---|---|---|
| Paracka et al. (2017) | 20 patients with inherited or idiopathic dystonia (8 with generalized dystonia; 5 with segmental dystonia with upper limb involvement and 7 with cervical dystonia, CD) | No | Back of the hand in all patients and at the shoulder in patients with CD | No | Decreased CDT, and allodynia on both hands (worse in the limb with dystonia); CD: reduced CDT, WDT, increased allodynia (hand) and increased CPT and allodynia (shoulder) | Not evaluated |
| Suttrup et al. (2011) | 10 patients with idiopathic hand dystonia | No | Dorsum of the hand bilaterally in patients and the right side in HV | No | Increased WDTs, CDTs, and MPT (patients vs. HV); Increased WDTs and CDTs in the intraindividual (patients) comparison | Not evaluated |
| Lobbezoo et al. (1996) | 9 patients with CD | No | The sternocleidomastoid and upper trapezius muscles | No | Pain-pressure thresholds two times lower than in HV | Not evaluated |
| Present study | 16 patients with inherited or idiopathic dystonia (14 with generalized dystonia and 2 with segmental dystonia) | Yes | Thenar eminence of the asymptomatic limb (i.e., not dystonic or less dystonic) and the skin over the most dystonic trapezium. Thenar eminence in HV | Yes | Increased MDT and MPT were higher in the patients, regardless of the DBS conditions; Increased CPT and SuC in patients in the on-DBS condition | On- and off-DBS CPM effects were abnormally high (defective) when compared to HV |

Abbreviations: CD, cervical dystonia; CDT, cold detection threshold; CPM, conditioned pain modulation; CPT, cold pain threshold; DBS, deep brain stimulation; HV, healthy volunteers; MDT, mechanical detection threshold; MPT, mechanical pain threshold; QST, quantitative sensory testing; SuC, pain rating to experimental pain cold stimulus; WDT, warm detection threshold.

determine sensory detection thresholds in dystonia. This is an important methodological issue when studying diseases that cause motor impairment that can bias the reaction time due to the motor deficits intrinsically associated with the studied pathology. Also, to the best of our knowledge, no previous attempt has been made to evaluate DBS's effect on sensory and pain thresholds, and we found no effect between the on- and off-DBS status.

The pathophysiology of dystonia involves not only basal ganglia's dysfunction but also an abnormal function of structures like the cerebellum and other areas (Lozeron et al., 2016). It is indeed considered a network disorder (Lehericy et al., 2013). Transcranial Magnetic Stimulation (TMS) has been used to evaluate abnormal excitability in dystonia. Paired pulse TMS has been explored in dystonia, and task-specific focal hand dystonia has received the most attention due to the assessment of the M1 hand representation. It had been found that dystonic patients have defective intracortical inhibition, as assessed by GABA-A-dependent short-interval intracortical inhibition (Espay et al., 2006; Ridding et al., 1995).

Interestingly, some reports on changes in cortical excitability due to peripheral neuropathic pain have also reported this same abnormality (Lefaucheur et al., 2006) that can be attenuated (or partially restored) after effective pain treatment. Whether both neuropathic pain and dystonia share a common mechanistic ground or simply have similar non-specific changes in intracortical measurements remains to be determined. Of note, these changes occur in both the affected and non-affected hemispheres in focal dystonia, while it is shown to be localized to the contralateral M1 in cases of neuropathic pain (Ridding et al., 1995). In dystonia, there is an increase in the activity of the indirect pathway and abnormal discharges of GPi neurons. Contrary to PD, the direct pathway in dystonia also seems to have increased activity. The traditional view of the basal ganglia circuitry did not include and direct connection between the cortex and the GPi. Nevertheless, a hyperdirect pathway, the cortico-pallidal, seems to play an important role, as already proven in many different studies (Cacciola et al., 2016, 2018). GPi-DBS improves motor symptoms in dystonia, not only due to reducing the abnormal plasticity but also DBS is likely to influence the hyperdirect cortico-pallidal (Cacciola et al., 2016; Ni et al., 2018) paths.

We also reported the original finding that dystonic patients have an abnormally low (i.e. defective) pain modulatory function, as assessed by CPM. Both on- and off-DBS values were significantly higher (i.e. less effective CPM) compared to reference data from HV. The experience of pain depends not only on the quality and intensity of the peripheral stimulus but also on the status of pain modulatory systems. CPM assesses one of the branches of the various top-down networks that modulate sensory and painful stimuli and is dependent on descending projections from the brain cortex and brainstem to the spinal cord, which is responsible for the creation of spatial contrast between two co-occurring nociceptive stimuli in two different body parts. Our CPM changes could be seen as the nociceptive equivalent of the spatial discrimination threshold that has been so extensively described in dystonia (Sanger et al., 2001). Such differences were less frequently explored in generalized dystonia, which was present in most of our patients. Our data are in accordance with the theory proposed by Hallett (2011), suggesting that both motor and NMS in dystonia are related to an inhibition loss, with increased plasticity (Hallett, 2011; Stamelou et al., 2012). This would explain defective QST parameters seen even on the less affected body region in dystonic patients compared to HV. Also, it would justify the deficits found when comparing the more and less affected body areas in patients. Furthermore, pain modulatory system was highly defective in dystonic patients, with worse loss of counter-irritation nociceptive modulation, where strong facilitation occurred instead of inhibition. Our findings, which show that altered CPM was strongly correlated with dystonic disability scores, further support this view.

The present study has limitations. This study has a sample of 16 patients, in which not all of them have generalized dystonia. The cross-sectional nature of pain and non-motor assessments precludes more profound interpretations on the correlations between pain, QoL and motor symptoms and might have failed to show potential changes seen after surgery. Also, sessions were performed after a relatively short period in the on- and off-DBS condition; therefore, despite the use of many thresholds, modulatory pain measurements, and assessments, most of the on/off comparisons were not significant. Indeed, Vidailhet and colleagues (2005) intended to evaluate patients after a 10 hr wash-out period in the off-DBS condition. However, after 3 hr in the off status, a patient had breathing difficulties, and another one had recurrent dystonic spasms after 7 hr (Vidailhet et al., 2005). In regard to this scenario, our Ethics Committee suggested only a 30-min wash-out phase. We also need to consider that DBS itself modulates brain networks and could modulate pain processing in dystonia. To circumvent this problem, we included the HV in our experimental design. Although our CPM methodology has been already applied previously and is in accordance with current recommendations (Aparecida da Silva et al., 2018; Lopes et al., 2018; Yarnitsky et al., 2015), we acknowledge that a control conditioning setup (e.g. with warm water) could be used during the unconditioned test stimulus should be further explored and could provide new insights into our results. Also, different from PD, in which a short period without DBS stimulation may be enough to reveal initial motor and non-motor phenomena, in some patients, dystonic motor symptoms may have very robust therapeutic inertia after DBS activation, so that some patients might experience weeks without changes of motor symptoms after the

therapy is discontinued (Kupsch et al., 2011). It is possible that NMS of dystonia may also take a long time to vanish once DBS is turned off, similar to what is known for motor symptoms, and this could explain in part the negative on/off-DBS comparisons.

We have shown that in a sample of patients with predominant generalized dystonia under DBS, a significant proportion of individuals still have pain. Alterations of CPM were correlated with QoL and motor symptoms. Some sensory changes were confirmed to occur differentially between the more and less affected dystonic limb and were worse in patients compared to HV, while no sensory parameters were modified by acute short-lasting DBS changes. These data support the integrative view, which proposes that motor and NMS of dystonia are part of a generalized lack of spatial discrimination in motor, sensory and cognitive/affective loops. It is our belief that future studies could aim to assess CPM and QST in a prospective fashion. Moreover, a thorough classificatory system for pain in dystonia could help evaluate treatment responses and assist clinical evaluation.

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Not applicable.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted from November 2017 to April 2018 and approved by Comitê de Ética para Análise de Projetos de Pesquisa do Hospital das Clínicas da Faculdade Medicina da Universidade de São Paulo (CAPPESq, #48607515.5.0000.0068). All patients gave written informed consent.

## AUTHORS' CONTRIBUTIONS

CL and VAS executed experiments, and CL drafted the manuscript. CL and EL organized and analysed data. CL, VAS, EL, SCBC, NL, RG, ERB, MJT and DCA reviewed and revised the manuscript. RGC, ERB, MJT and DCA conceptualized the project. All authors approved the final version of the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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