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# Parkinson's Disease-related Pains are Not Equal: Clinical, Somatosensory and Cortical Excitability Findings in Individuals With Nociceptive Pain

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**Abstract:** **Chronic pain is a frequent and burdensome nonmotor symptom of Parkinson's disease (PD). PD-related chronic pain can be classified as nociceptive, neuropathic, or nociplastic, the former being the most frequent subtype. However, differences in neurophysiologic profiles between these pain subtypes, and their potential prognostic and therapeutic implications have not been explored yet. This is a cross-sectional study on patients with PD (PwP)-related chronic pain (ie, started with or was aggravated by PD). Subjects were assessed for clinical and pain characteristics through questionnaires and underwent quantitative sensory tests and motor corticospinal excitability (CE) evaluations. Data were then compared between individuals with nociceptive and non-nociceptive (ie, neuropathic or nociplastic) pains. Thirty-five patients were included (51.4% male, 55.7 ± 11.0 years old), 20 of which had nociceptive pain. Patients with nociceptive PD-related pain had lower warm detection threshold (WDT, 33.34 ± 1.39 vs 34.34 ± 1.72, *P* = .019) and mechanical detection threshold (MDT, 2.55 ± 1.54 vs 3.86 ± .97, *P* = .007) compared to those with non-nociceptive pains. They also presented a higher proportion of low rest motor threshold values than the non-nociceptive pain ones (64.7% vs 26.6%, *P* = .048). In non-nociceptive pain patients, there was a negative correlation between WDT and non-motor symptoms scores (r = –.612, *P* = .045) and a positive correlation between MDT and average pain intensity (r = .629, *P* = .038), along with neuropathic pain symptom scores (r = .604, *P* = .049). It is possible to conclude that PD-related chronic pain subtypes have distinctive somatosensory and CE profiles. These preliminary data may help better frame previous contradictory findings in PwP and may have implications for future trial designs aiming at developing individually-tailored therapies.**

***Perspective:*** ***This work showed that PwP-related nociceptive chronic pain may have distinctive somatosensory and CE profiles than those with non-nociceptive pain subtypes. These data may help shed light on previous contradictory findings in PwP and guide future trials aiming at developing individually-tailored management strategies.***

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**Key Words:** *Chronic pain, Parkinson's disease, pain measurement, pain threshold, cortical excitability*

Parkinson's disease (PD) is classically defined by motor signs.[1] However, since the seminal descriptions of the disease, non-motor symptoms (NMS) have also been acknowledged to play an important role in the disease.[2] NMS include chronic pain, olfactory disturbances, sleep abnormalities, mood and cognition complaints, constipation, and urinary incontinence, among others.[3–5] NMS may or may not be related to dopaminergic deficit. Some may respond to dopamine replacement therapy or deep brain stimulation, while others may not improve with motor symptom-targeted therapies, thus requiring specific treatments for their control.[6–8]

Within the last 20 years, a larger focus has been put into the characterization of NMS, such as chronic pain. Pain may predate the beginning of PD motor symptoms in up to 20% of patients and may affect as much as 80% during disease evolution.[9–11] Some NMS may cause similar losses in quality of life (QoL) to motor symptoms of PD.[12–14] It has been shown, for example, that despite deep brain stimulation being indicated based on the presence of refractory motor symptoms control, NMS such as pain also improves after surgery, and this correlates with better postoperative QoL. In fact, pain reduction has been found to be the main driver of QoL scores increase after surgery, to a higher degree than motor improvement itself.[8] Importantly, motor treatment strategies such as levodopa, apomorphine, or deep brain stimulation may improve pain in some patients and may transiently and partially improve somatosensory abnormalities, such as decreases in pain thresholds in patients with PD (PwP).[6,15,16] Additionally, other peptides and neurotransmitters systems have been reported to be altered in PwP, such as decreased noradrenaline in the locus coeruleus, reduced serotonin in the raphe nuclei, and increased glutamate in the subthalamic-pallidal and cortico-striatal projections. These abnormalities have been linked with gain in nociceptive processing in experimental studies.[17–21]

Despite the recent efforts in research and identification of PD-related pain, there is still a marked paucity of data regarding therapeutic interventions for their control, which is reflected in current evidence-based guidelines.[3] This is partly due to the fact that pain in PD is not a monotonic and homogeneous symptom. It has long been proposed to classify pain in PD according to motor status of patients, considering putative pain subtypes[22] or dimensions.[5] It was also suggested that pain in PD could be categorized according to the International Association for the Study of Pain mechanistic descriptors,[23,24] which was recently investigated by a validation study.[25] This research showed that PD-related chronic pain (ie, pain aggravated by or starting with PD[26,27]) could be classified as nociceptive, neuropathic, and/or nociplastic. Using this approach, it was observed that nociceptive pain is the most common PD-related pain subtype, present in about half of the patients. Nociceptive pain is generally more localized than its neuropathic and nociceptive counterparts, more frequently present in the trunk region, and is associated with levodopa-induced dyskinesia. Notably, it has been suggested that this type of pain would be more frequently responsive to dopamine replacement therapy.[6,25]

A mechanistic classification of PD-related pain may hold the key to a more personalized and assertive treatment of PwP. However, it remains undetermined whether each of its mechanistic classifications is associated with discrete somatosensory or cortical excitability profiles. Such associations could point to potential psychophysical or neurophysiological markers for different PD-related pain subtypes and could also lead to more specific ways of classifying patients for prognostic and therapeutic purposes. Here we compared clinical, quantitative sensory testing, and motor corticospinal excitability (CE) measurements of PwP-related nociceptive pain (ie, the most common pain mechanism in PD) to those with non-nociceptive pain (ie, neuropathic and nociplastic).

## Methods

The study was performed at the University of São Paulo from November 2018 to January 2020 and was approved by the Institutions' Ethics Review Board (approval no. 1.016.522). All patients provided written informed consent before inclusion in the study. This study's sample was composed of subjects enrolled in the clinical trial registered as NCT03504748 at clinicaltrials.gov. Data from baseline assessments before trial initiation were collected and analyzed for the present study.

### *Patients*

Patients attending the movement disorder clinic with idiopathic PD and pain related to PD were consecutively assessed for eligibility. Idiopathic PD was diagnosed according to the Movement Disorders Society Clinical Diagnostic Criteria.[28] Inclusion criteria were: 1) ≥18 years old; 2) clinically established PD; and 3) PD-related chronic pain (ie, present most of the days for more than 3 months) of any mechanism (nociceptive, neuropathic, or nociplastic[25]). In particular, only PwP-related pains were included. Those with previously existing pains that were not chronic or were not aggravated by PD or which were neither influenced by hypo- or hyperkinetic states nor by dopamine replacement therapy state were not included.[15,24–26,29] Exclusion criteria were: undetermined diagnosis of idiopathic PD; inability to answer questions because of difficulty with verbal and written communication; the presence of significant

functional impairment secondary to cognitive decline or known major psychiatric illness; Mattis Dementia Rating Scale < 130;[30] active drug or alcohol abuse; the presence of risk factor for peripheral neuropathy (eg, diabetes mellitus or vitamin deficiency); the presence of previous chronic pain before (> 5 years) the diagnosis of PD, and which was not influenced by the emergence of PD symptoms; previous major stroke; thyroid abnormalities; or vitamin B12 deficiency (assessed routinely during outpatient care).

## Study Design

This was a cross-sectional observational exploratory study that examined pain phenotype, associated factors (QoL, PD motor, and NMS), somatosensory profile through quantitative sensory testing (QST), and motor CE in PwP-related nociceptive pain, compared to those with non-nociceptive (nociplastic and/or neuropathic) PD-related pain. Our hypothesis was that the most common pain mechanism in PD (nociceptive) would have different clinical, somatosensory, and cortico-neurophysiology profiles compared to non-nociceptive pain mechanisms.

Structured interviews, QoL and pain-specific questionnaires, and a standardized physical examination were performed during a routine medical visit to our outpatient clinic. Patients were invited for a second visit (< 15 days after the first) to undergo QST and CE measurements. These measurements were performed by a researcher who was blinded to the participants' history, pain subtype, and non-motor status.

## Clinical Assessments

Data about socio-demographic status, medical co-morbidities, analgesic, and psychotropic medication use were obtained through a structured interview. The duration of PD and the daily levodopa-equivalent dose were also recorded.[31] Hospital Anxiety and Depression Scale (HADS),[32,33] Non-Motor Symptoms Scale (NMSS),[34] and 8-item Parkinson Disease Questionnaire (PDQ-8)[35,36] were completed by subjects. Sequentially, patients were examined during their best "on" state and had their motor status classified according to part 3 of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS-III).[37] Cognitive status was assessed with the mini-mental state examination (MMSE).[38,39]

## Pain Assessment Scales

The following instruments were used for the characterization of PD-related chronic pain:

1. Parkinson Disease Pain Classification System (PD-PCS)[25]: This questionnaire allows for the classification of PD-related chronic pain as nociceptive, neuropathic, or nociplastic. Additionally, it produces a score based on pain intensity, frequency, and burden on daily living ranging from 0 (minimal) to 90 (maximum). In particular, nociplastic pain was defined in subjects with no clear nociceptive generators of pain and no possible neuropathic pain, as previously validated.[25,40]
2. Short-form of the McGill Pain Questionnaire[41,42]: It examines pain descriptors divided into 3 dimensions: sensory, affective, and evaluative. The total and dimension-specific scores (ranging from 0 to 15) are obtained by counting the words chosen by the subject.
3. Brief Pain Inventory (BPI)[43]: Measures current, least, average, and worst pain intensity in the last 24 hours with a 0 (none) to 10 (worst possible) numeric rating scale. It also measures pain interference on general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life. The total interference score ranges from 0 to 70, where higher scores mean higher interference.
4. Douleur Neuropathique 4 Questionnaire (DN-4)[44,45]: A screening test for neuropathic pain composed of 10 items. It ranges from 0 to 10 and is considered positive when ≥4.
5. Neuropathic Pain Symptom Inventory (NPSI)[46,47]: A qualitative and quantitative inventory that allows for discrimination and quantification of 5 distinct dimensions of neuropathic pain, that is, burning (superficial) spontaneous pain, pressing (deep) spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia. Its total score ranges from 0 to 100, with higher scores indicating more intense symptoms.

## Quantitative Sensory Testing

Patients underwent a QST battery intended to assess large (A-ß) and small (A-δ, C) sensory fibers, including experimental pain (EP) measurements using mechanical and thermal suprathreshold stimuli. The QST assessments were conducted during the subjects' best "on" state. Tests were performed on both body thenar eminences. Mechanical detection thresholds (MDTs) and mechanical pain thresholds (MPT) were measured using von Frey monofilaments ranging from .008 to 300 g (NC 17775; Bioseb, France).[48,49] MPT was defined as the lowest pressure that was considered painful by the patient in 50% of 6 trials in ascending and descending orders.[49] Thermal thresholds were measured using a VSA-3000/TSA-2001 device (Medoc, Ramat Yishai, Israel). For the identification of the warm detection threshold (WDT) and cold detection threshold (CDT), the forced choice method was used to avoid bias due to increased motor reaction time related to bradykinesia and rigidity.[7,50] First, the temperature was increased or decreased at a rate of 1 °C/s from 32 °C to 35 °C (WDT) or 29 °C (CDT). After each trial, patients had 5 seconds to answer whether or not they perceived the stimulus. "Yes" answers led the software to lower the temperature difference to

1 °C and then to .3 °C subsequently, whereas "no" answers led to increases in temperature differences. The final threshold was calculated after 3 consecutive "yes" responses.[49] "Dumb" stimulations where no real thermal stimuli were delivered were inserted into the routine trials to investigate response bias. Heat and cold pain thresholds (HPT, CPT) were assessed using the method of limits (thermal ramps of 1 °C/s starting from skin temperature, ie, around 32 °C, measured with a contactless thermometer[49]). Interstimulus intervals were 6 to 8 seconds for detection thresholds, 15 to 20 seconds for HPT, and 20 to 30 seconds for CPT. All thermal thresholds were expressed as absolute temperature values. Suprathreshold heat stimulations (SuH) were also performed, with temperature increasing at a linear rate of 2 °C/s from 32 °C and kept constant for 2 seconds at 2 different target temperatures (46 and 48 °C, in random order, provided HPT was < 46 °C).[51] EP intensity was scored on a visual analog scale (VAS, 0–100 mm) and averaged. Suprathreshold cold stimulation (SuC) was performed by decreasing the temperature from 32 °C to 10 °C and 5 °C (provided CPT was < 5 °C).[51] The 2 SuH (for 46 and 48 °C) and SuC (for 10 and 5 °C) VAS scores were respectively averaged to obtain a single value for SuH and SuC.[51] Temperatures did not exceed 50 °C for heat or 0 °C for cold stimuli to avoid thermal lesions. Group comparisons were performed comparing patients with nociceptive and non-nociceptive pains.

## Motor CE

CE measurements were obtained during the patients' best "on" state. Magnetic stimulation was applied with the PROX100 Mag (Magventure Tonika Elektronic, Farum, Denmark) using a coil (MC-125, Magventure Tonika Elektronic, Farum, Denmark) oriented at a tangent to the scalp and covering the region corresponding to the hand M1 representation (first dorsal interossei muscle).[52–56] Motor CE consisted of determining rest motor threshold (RMT) based on the % of maximal stimulator output (MSO), motor evoked potentials (MEPs) at 120% and 140% above the MSO, short interval intracortical inhibition (SICI), and intracortical facilitation (ICF) in each hemisphere. MEP-derived parameters were recorded with an electromyography amplifier module (Magventure Tonika Elektronic, Denmark) and surface electrodes (Biom Alpine, Skovlunde, Denmark). The RMT was defined as the lowest pulse intensity eliciting a MEP of at least 50 μV in 50% of 20 trials.[54] Intracortical modulation was investigated according to a paired pulses protocol. Paired pulses were delivered, with the intensity of the conditioning stimulus set at 80% of the RMT and the intensity of the test stimulus at 120% of the RMT. Interstimulus intervals of 2 and 4 ms were used to investigate SICI and of 10 and 15 ms to investigate ICF. For each paired pulse, the results of 8 trials were averaged, and the changes in conditioned MEP amplitude were expressed as a percentage of the unconditioned MEP amplitude. The mean percentage inhibition and facilitation were respectively averaged and used for analyses.

## Data Analysis Strategy

PD-related pain was divided into 2 groups: nociceptive and non-nociceptive (ie, neuropathic and/or nociplastic). Pain characteristics, NMSS and motor symptoms scale, and QoL scores were compared between these groups. Differences between groups in raw CE and QST results were also examined. QST and CE data were further compared for left-right differences and according to the most and least-affected motor side. In case results were similar ($P > .2$), they were pooled for further analyses. Additionally, QST results were classified as low, normal, or high, according to normative data from sex and age-matched healthy volunteers assessed at our laboratories under the same methodology and reported elsewhere.[57] CE parameters were similarly classified, considering normative data available at https://tinyurl.com/cortical-excitability.[49] This allowed for calculating the proportion of patients with altered results in each pain group. Continuous data were expressed as mean, standard deviation, minimal and maximal values; and categorical variables as absolute frequency and percentages. For between-group comparisons, the chi-square test was applied for categorical variables and the Mann-Whitney test for continuous ones. Spearman coefficients were used to assess the correlation between the variables. Statistical significance was set at $P < .05$, and Bonferroni correction for multiple comparisons was used when adequate. Correlation analyses between relevant CE and QST results were made with clinical data. All statistical calculations were performed using the software Statistical Package for the Social Sciences version 20.0.0 (SPSS Inc, Chicago, IL). As this is, to the best of our knowledge, the first study to explore the differences between different pain mechanisms in PD, a convenience sample was used consisting of patients prospectively referred for our Institution's movements disorders clinic. It was expected that nociceptive pain would account for at least 55% of patients, thus allowing for comparisons between nociceptive and non-nociceptive PD-related pains. Based on previous studies assessing QST and CE changes in subtypes of asymmetric pain syndromes within the same diagnostic entity, a minimum sample size of 32 was deemed necessary, with the inclusion of 3 more patients (10%) to account for potential data loss or inclusion failure/dropouts between the first and second visit.[51,58–61]

# Results

## General Clinical Characteristics

Thirty-eight patients were screened for enrollment, and 35 were included (Fig 1). Subjects were 55.7 ± 11.0 years

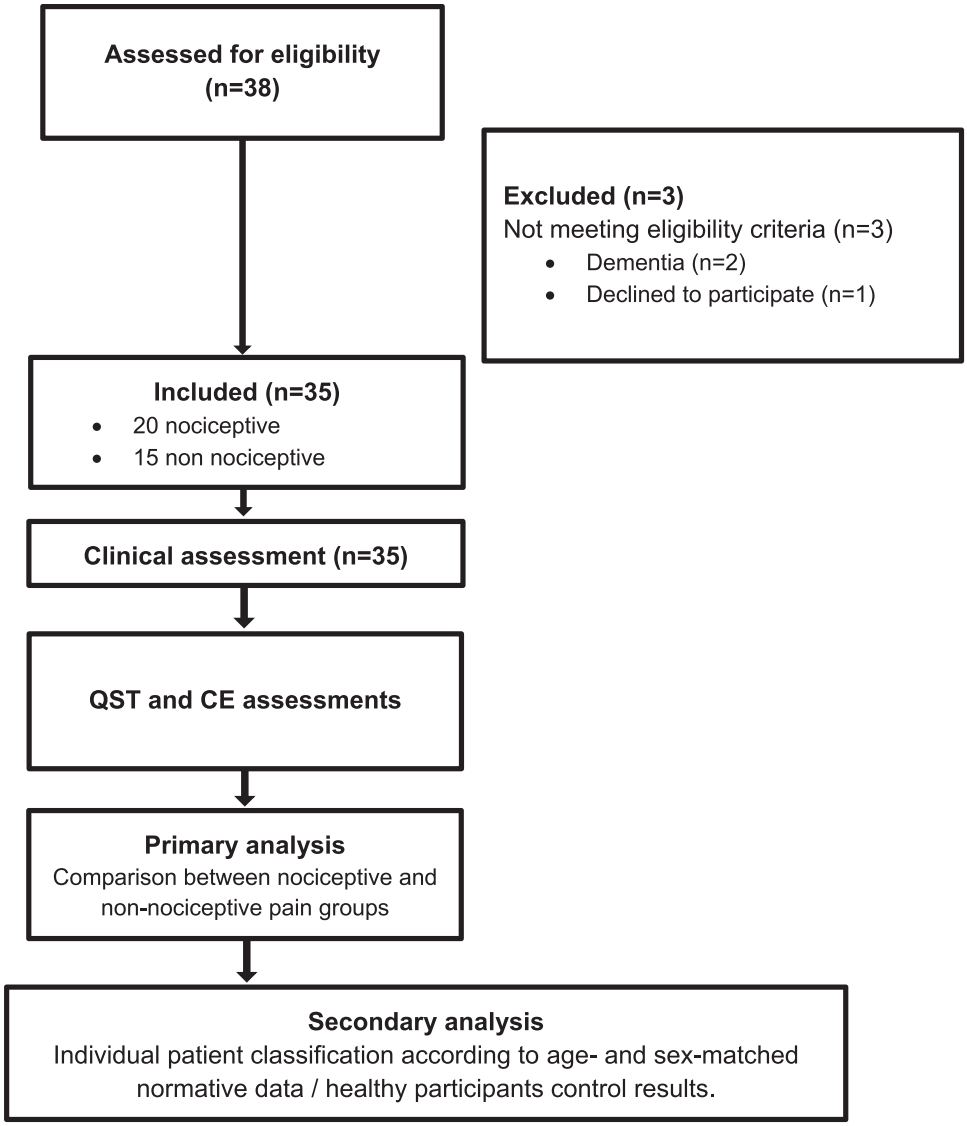


**Figure 1.** STROBE flowchart showing the patient selection for this study. STROBE, Strengthening the reporting of OBservational studies in Epidemiology.

old, and around half (51.4%) were male. The mean PD duration was 8.9 ± 7.0 years, and the most symptomatic motor side was the right hemibody (45.7%). The mean UPDRS-III score was 39.8 ± 16.3, and the daily levodopa-equivalent dose was 890.2 ± 689.8 mg. The mean score for PDQ-8 was 42.9 ± 21.3, for NMSS was 129.4 ± 60.4, and for MMSE was 26.8 ± 2.2. Individuals with PD-related nociceptive pain had higher UPDRS-III scores than those with non-nociceptive pain ($P$ = .022, Table 1).

## PD-related Pain Features

PD-related pain mean duration was 8.1 ± 8.2 years. Pain preceded the PD diagnosis in 8 (22.8%), appeared after the PD diagnosis in 14 (40.0%), and began simultaneously with motor PD symptoms in 13 (37.2%) cases. Twenty patients had nociceptive and 15 non-nociceptive pain (neuropathic n = 7; nociplastic n = 8). In patients with nociceptive pain, the most common pain locations were the cervical region (75%), followed by shoulders (65%) and arms (55%). In patients with predominant neuropathic pain, it was predominant in the cervical region (85.7%), followed by the legs (71.4%), and then the hands (57.1%). Conversely, among those with a predominant nociplastic type, the most common site was the right arm and the right leg (75% each) (Fig 2). The qualitative assessment showed that the more prevalent pain areas were on the shoulder girdle/neck in nociceptive PD-related pain, while the limbs were more frequently affected in non-nociceptive pain patients.

## QST Results

QST measurements were not different between right and left hemibodies ($P$ > .20). Additionally, there was no association between any QST variable

**Table 1. General Demographic Characteristics of Parkinson's Disease-related Chronic Pain Patients**

| | NOCICEPTIVE (N = 20) | NON-NOCICEPTIVE (N = 15) | P |
|---|---|---|---|
| Age (years) | 57.70 (11.04) 36–80 | 53.00 (10.70) 32–68 | .254 |
| Female | 10 (50) | 7 (46.7) | .845 |
| Pain side | | | |
| Right | 9 (45) | 7 (46.7) | .922 |
| Left | 11 (55) | 8 (53.3) | |
| Time since PD diagnosis (years)† | 8.3 ± 4.9 (1.5–17) | 9.8 ± 9.3 (.5–31) | .934 |
| Duration of pain (years)† | 9.1 ± 8.6 (.25–30) | 6.8 ± 7.6 (.5–26) | .382 |
| Time relationship between chronic pain and PD symptoms | | | |
| Chronic pain first | 6 (30) | 2 (13.3) | .431 |
| PD symptoms first | 8 (40) | 6 (40.0) | |
| Chronic pain and PD symptoms began simultaneously | 6 (30) | 7 (46.7) | |
| Daily levodopa-equivalent dose (mg)† | 806.1 ± 847.2 (0–2,558) | 986.3 ± 463.3 (300–1,860) | .313 |
| UPDRS-III score† | 47.4 ± 10.3 (29–64) | 33.3 ± 17.9 (12–74) | .022* |
| MMSE score† | 27.1 ± 2.02 (21–30) | 26.4 ± 2.5 (22–30) | .458 |

NOTE. Data presented as n (%), unless otherwise specified. PD, Parkinson's Disease
*$P < .05$.
†Data presented as mean ± standard deviation (minimum–maximum).

and the side most affected by PD motor symptoms. Therefore, results from both hemibodies were merged for subsequent analyses.

When compared with healthy individuals, matched by age and sex, the CDT (30.15 ± 1.70 vs 29.35 ± 1.91, $P = .019$), CPT (11.83 ± 6.54 vs 8.98 ± 6.10, $P = .044$), and MDT (3.07 ± 1.50 vs 1.93 ± 0.77, $P = .001$) were higher in PD patients, while WDT (33.14 ± 1.59 vs 34.33 ± 1.30, $P = .010$) and HPT (44.60 ± 3.15 vs 45.83 ± 2.46, $P = .001$) were lower in these patients (Table 2). When considering the subtype of PD-related pain, patients with the nociceptive pain subtype had lower WDT (33.34 ± 1.39 vs 34.34 ± 1.72, $P = .019$) and MDT (2.55 ± 1.54 vs 3.86 ± .97, $P = .007$) than the non-nociceptive one (Table 3). However, the frequency of abnormal QST parameters was similar between these groups.

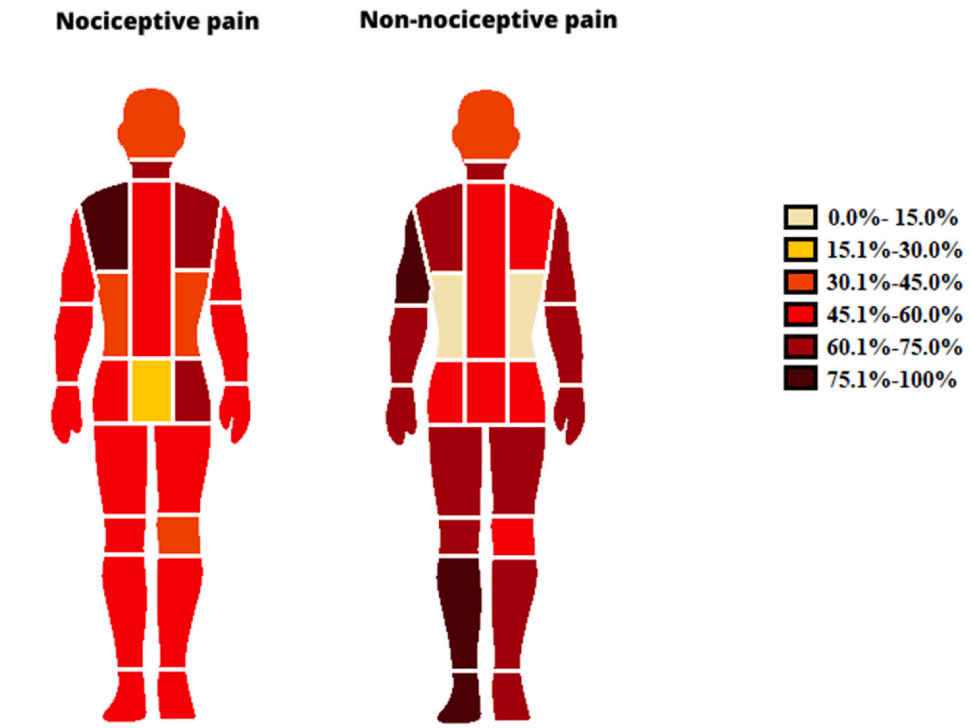


**Figure 2.** Spatial distribution of pain in PD patients, according to its type (nociceptive vs non-nociceptive pain). Lighter colors indicate the less affected body regions and dark colors are the most affected ones. Pain sites from the back and front parts of the body were averaged.

**Table 2. Quantitative Sensory Test Measures in Patients With Parkinson's Disease-related Chronic Pain and Age and Sex-Matched Healthy Volunteers**

| QUANTITATIVE SENSORY TEST MEASURES | PATIENTS WITH PARKINSON DISEASE-RELATED CHRONIC PAIN | HEALTHY VOLUNTEERS | P |
|---|---|---|---|
| Cold detection threshold (°C) | 30.15 ± 1.70 (24.85–31.90) | 29.35 ± 1.91 (21.20–31.20) | .019* |
| Warm detection threshold (°C) | 33.14 ± 1.59 (31.65–39.0) | 34.33 ± 1.30 (32.70–38.50) | .010* |
| Cold pain threshold (°C) | 11.83 ± 6.54 (0–24.95) | 8.98 ± 6.10 (0–28) | .044* |
| Heat pain threshold (°C) | 44.60 ± 3.15 (38.85–49.9) | 45.83 ± 2.46 (40.45–49.55) | .001** |
| Mechanical detection threshold (g/mm$^2$) | 3.07 ± 1.50 (.04–6.0) | 1.93 ± .77 (1.5–5.0) | .001** |
| Mechanical pain threshold (g/mm$^2$) | 17.44 ± 9.41 (3.09–59.0) | 31.75 ± 44.22 (4.0–159.5) | .662 |

NOTE. Data presented as mean ± standard deviation (minimum–maximum).
*$P < .05$.
**$P < .0083$ according to Bonferroni correction for multiple pairwise comparisons.
Healthy volunteers (n = 40) from our laboratory reference data.

**Table 3. Quantitative Sensory Test Measures Between Patients With Nociceptive and Non-nociceptive Parkinson's Disease-related Chronic Pain**

| QUANTITATIVE SENSORY TEST | NOCICEPTIVE PAIN | NON-NOCICEPTIVE PAIN | P |
|---|---|---|---|
| Cold detection threshold (°C) | 30.25 ± 1.54 (26.60–31.50) | 29.77 ± 2.02 (24.85–31.90) | .572 |
| Warm detection threshold (°C) | 33.34 ± 1.39 (31.65–37.90) | 34.34 ± 1.72 (32.40–39.00) | .019* |
| Cold pain threshold (°C) | 11.66 ± 6.40 (0–24.95) | 12.57 ± 6.90 (2.53–22.85) | .742 |
| Heat pain threshold (°C) | 44.18 ± 3.05 (38.85–49.40) | 45.27 ± 3.19 (30.15–49.65) | .347 |
| Mechanical detection threshold (g/mm$^2$) | 2.55 ± 1.54 (.04–5.00) | 3.86 ± .97 (3.00–6.00) | .007** |
| Mechanical pain threshold (g/mm$^2$) | 18.41 ± 11.64 (3.09–59.00) | 16.09 ± 3.22 (7.50–19.00) | .220 |

NOTE. Data presented as mean ± standard deviation (minimum–maximum).
*$P < .05$.
**$P < .0083$, according to Bonferroni correction for multiple pairwise comparisons.

**Table 4. Cortical Excitability Values Between Patients With Parkinson's Disease-related Chronic Pain and Healthy Volunteers**

| | PATIENTS WITH PARKINSON DISEASE-RELATED CHRONIC PAIN | HEALTHY INDIVIDUALS | P |
|---|---|---|---|
| RMT (%) | 47.56 ± 8.35 (31.5–63.5) | 48.31 ± 9.18 (30–78) | .846 |
| MEP at 120% (μV) | 1,137.7 ± 1,606.2 (61–6,375) | 418.22 ± 439.38 (29–2,700) | .001* |
| MEP at 140% (μV) | 1780.70 ± 2,117.78 (57.1–8,450) | 1,058.86 ± 974.09 (79–5,200) | .027** |
| MEP140/MEP120 | 2.46 ± 1.66 (.72–9.55) | 3.98 ± 5.01 (.30–42.27) | .081 |
| SICI | 1.17 ± .68 (.20–2.54) | .85 ± .71 (.03–5.14) | .004* |
| ICF | 2.12 ± 1.88 (.40–8.77) | 1.92 ± 1.68 (.01–9.87) | .777 |

NOTE. Data presented as mean ± standard deviation (minimum–maximum). RMT is reported as maximal stimulator output 0–100%.
*$P < .0083$.
**$P < .05$, according to Bonferroni correction for multiple pairwise comparisons.
Healthy volunteer data based on 100 sex and age range matched form our laboratory.

## *Cortical Excitability*

CE measurements were also not different between hemibodies ($P > .20$, Supplementary Table 1). Additionally, the hemibodies more affected by PD motor symptoms presented with similar results to the ones less affected. PwP frequently had abnormal values for RMT (91.6%), MEP at 120% (68.8%), MEP at 140% (81.2%), SICI (84.4%), and ICF (62.5%) when compared to normative values from a healthy individuals' cohort, matched by age and sex. Furthermore, group-average values for MEP at 120%, MEP at 140%, and SICI were significantly higher among PD patients than healthy controls (Table 4). Subjects with nociceptive PD-related pain presented with a higher proportion of low RMT values than the non-nociceptive pain ones (64.7% vs 26.6%, $P = .048$). No difference was found between these groups regarding other CE parameters (Supplementary Table 2).

## Correlation Analyses

The CE and QST variables that were significantly different between nociceptive and non-nociceptive PD-related pain groups (ie, WDT, MDT, and RMT) were included in correlation analyses aimed at identifying associations with motor and non-motor findings (ie,

NMSS, PD-PCS, UPDRS-III, PDQ-8, NPSI, and HADS scores), according to the 2 pain subgroups. No significant correlations were found between the QST and CE measures and the questionnaires/scales scores for the nociceptive pain group. However, the non-nociceptive PD-related pain individuals showed a negative correlation between WDT and NMS score ($r = -.612$, $P = .045$). Also, in these patients, MDT positively correlated with BPI average pain intensity subscore ($r = .629$, $P = .038$) and total NPSI score ($r = .604$, $P = .049$). There was also a trend for the positive correlation between MDT and UPDRS-III score ($r = .626$, $P = .053$).

## Discussion

Here we report that patients with different types of PD-related pain mechanisms, based on clinical classification, also present different profiles of somatosensory and CE responses, which were additionally intercorrelated. PwP have been the object of CE studies for more than 3 decades, and the same is true for QST assessments.[62] Previous studies focused the clinical assessment on motor signs of the disease and not on the profile of the pain symptoms. It has been shown that PwP have higher MEPs than healthy controls,[63] along with decreased ICF and inhibition.[64] MEPs are related to the strength of motor corticospinal projections[65] and have been reported to be decreased in instances of cerebral stroke,[66] compressive myelopathy, or motor neuron disease,[52] and to be increased in PwP.[63] Intracortical inhibition is dependent on $GABA_A$ receptors[65,67] and has been found to be reduced in PD and to be normalized by dopamine intake[68–73] or Deep Brain Stimulation (DBS),[74] while ICF is dependent on glutamate N-methyl-D-aspartate receptors and has been reported to be either normal or decreased in PwP.[73,75–78] Regarding their somatosensory profile, PwP have lower thermal detection and pain thresholds, and these abnormalities are commonly reported to be modulated toward normality by levodopa intake or DBS.[7,79]

Here we report the first attempt to characterize CE and QST profiles of PwP presenting PD-related chronic pain. When analyzed together, irrespective of their pain subtype, previous psychophysics and motor CE findings in PwP with and without pain were confirmed in comparison to healthy individuals. Notably, thermal detection thresholds were lower (ie., hyperesthesia), as well as thermal pain thresholds (ie, thermal allodynia), while MDTs were increased. While somatosensory denervation has been reported in PD,[80–82] the functional significance of these findings argues for an allodynia and hyperesthesia state in PD patients. Furthermore, our CE assessments showed higher MEP amplitudes and defective intracortical inhibition at a group level. Interestingly, the findings that PwP with PD-related chronic pain have similar QST and CE changes compared to PwP in general is probably related to the fact that chronic pain affects up to 80% of PwP so that at the group level, it is possible that patients with chronic pain drive the changes in both groups to the same direction when data from healthy individuals are used as a control.

However, when comparing patients with nociceptive pain with those with non-nociceptive pain, original findings were revealed. Nociceptive pain patients showed lower WDT and MDT compared to patients with non-nociceptive pains. Additionally, nociceptive pain was associated with a higher proportion of patients with low RMT (64.7%) compared to non-nociceptive pain (22.6%). RMTs are dependent on neuronal membrane excitability, being increased by drugs that block voltage-gated sodium channels,[83,84] and are not affected by N-methyl-D-aspartate or Gamma-aminobutyric acid blockage.[78,84,85] RMTs are known to be decreased in instances of structural damage to the corticospinal tract (stroke, advanced motor neuron disease, or spinal cord injury) and increased in instances of hyperexcitability of corticospinal systems such as early stages of amyotrophic lateral sclerosis and untreated generalized epilepsy patients.[86,87] PD studies not reporting on the presence of chronic pain or the proportion of nociceptive pain patients among participants reported conflicting results, finding both increases and decreases in RMT in PwP.[62] Interestingly, in non-nociceptive pain patients, higher (close to healthy individuals) WDTs were strongly associated with lesser NMS and their abnormal MDTs (ie, higher sensory loss) correlated with higher scores in motor, pain, mood, and QoL scores. Additionally, in the non-nociceptive pain group, higher cortical RMTs correlated with higher motor scores of PD. WDTs are dependent on C-fiber conduction and integration, while MDTs are mainly mediated by large-myelinated A-beta fibers.

One common approach when analyzing differences in QST parameters is to relate them to the potential lesions of specific components of the somatosensory system. In PwP, peripheral neuropathy and a decrease in the density of intraepidermal nerve fiber density have been classically reported,[80–82] and putatively linked to Lewy body deposition in peripheral nerves. In this line, non-nociceptive pain patients presented higher detection thresholds. Since this group included patients with possible neuropathic pain, and since in this group strong correlations were found between more altered QST results and more intense motor and neuropathic symptoms, and also worse QoL, one could argue for a continuum of disease burden according to the type of PD-related pain present. Nociceptive pain patients would have more discrete somatosensory changes and more frequently low RMT, while non-nociceptive patients would have more pronounced somatosensory alterations and higher RMTs, which globally correlated with more severe motor and NMS. In this view,

nociceptive pain would occur in patients with less affected somatosensory and clinical abnormalities, while non-nociceptive pains would be related to more pronounced nigrostriatal denervation and heavier disease burden, with more impactful motor, and NMS and higher RMT. On the other hand, these findings could also be interpreted within a dual-hit hypothesis of PD, which suggests that a neurotrophic agent could access the Central Nervous System via nasal-temporal routes and the gastroenteric-dorsal motor nucleus pathway. It is possible that people with longstanding active peripheral pain generators (eg, Musculoskeletal factors) would have nociceptive signals amplified by the gain in the somatosensory system triggered by the installation and development of PD caused by the spread of pathological findings through the Central Nervous System. It is supposed that projection pathways related to bottom-up integration and top-down modulation of nociceptive processing via noradrenaline, serotonin, and dopamine would play a major role in the disturbance of the somatosensory processing seen in PwP with chronic pain.[88–90] While tempting, this interpretation needs to be tempered, and one needs to recall that motor treatment strategies such as dopamine replacement therapy and DBS have significant impacts on clinical pain, somatosensory, and CE parameters in PD. It has been recently shown, for example, that levodopa supplementation would relieve a great part of Musculoskeletal/nociceptive pains in PwP, while neuropathic pain has been shown not to respond to DBS, which was also more efficacious for nociceptive pains in PD.[6,8] This means that the CE and somatosensory changes described here are not solely the result of PD interference upon cortical and sensory systems but may also be dependent on the effects of treatment. The present study was not designed to tease out these variables, but it highlights a very important point: clinically based classifications of mechanisms of PD-related pains identify groups of patients not only with different pain characteristics but also with distinct somatosensory and cortical neurophysiology profiles. This opens 2 important lines of consideration. One relates to the importance of reporting whether PD patients included in neurophysiology and psychophysics studies have PD-related chronic pain, and if they do, which type. Given the contradictory reports on RMT and ICF in PD, it may well be the case that the presence of pain and different proportions of distinct pain subtypes may have influenced previous studies and induced undesired bias in the assessments.[62] Another point relates to treatment trial design. Given the low number of positive studies offering possibilities to treat pain in PD, one could argue that part of this unsuccess is related to the fact that different pain types in PD have different pain mechanisms, which are unlikely to be tackled by one single therapeutic approach. This means that trialists should focus on specific pain types of PD when designing therapeutic or prevention studies. This strategy has already started to be employed and has shown positive practical implications.[91]

This exploratory cross-sectional study has a long list of limitations. The main ones are related to the sample size. This was a convenience sample of patients, prospectively addressed for a neuromodulation trial and assessed at the baseline before any intervention. Furthermore, compared to most PwP and previously published studies in this field, the average age in our sample was somewhat lower and with large variation (ie, 55.7 ± 11.0 years old), which may limit the generalizability of our findings. Bias related to expectation and presence of chronic pain more severe than that found in the average patients is not possible to exclude. Also, a longitudinal evaluation would have allowed for the characterization of how the present findings would behave over time. While pain classification in PwP was shown to be reliable in time,[19] CE and QST assessments have rarely been assessed in PD over different time points under controlled conditions. Additionally, the aim of the study was to characterize the main and most prevalent pain mechanism in PD, that is, nociceptive pain. It means that nociplastic and neuropathic pain patients were merged into the non-nociceptive pain group. Thus, the present study does not provide individual information about the specific characteristics of these 2 pain mechanisms in PD patients. Finally, dopa-sensitivity was not reassessed during data collection, and, therefore, the association between this phenomenon and QST and CE measurements was not examined.

## Conclusions

PwP have different chronic pain types, which are not only related to distinctive clinical characteristics but also to somatosensory and cortical neurophysiology differences. These differences may partially explain variability in previous reports on PD patient samples with unknown pain status and may have significant implications for trial designs aiming at developing personalized and more assertive pain management strategies.

## Disclosures

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## Appendix A. Supplementary Data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2023.07.005.

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