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The Parkinson disease pain classification system: results from an international mechanism-based classification approach

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Abstract

Pain is a common nonmotor symptom in patients with Parkinson disease (PD) but the correct diagnosis of the respective cause remains difficult because suitable tools are lacking, so far. We developed a framework to differentiate PD- from non-PD-related pain and classify PD-related pain into 3 groups based on validated mechanistic pain descriptors (nociceptive, neuropathic, or nociplastic), which encompass all the previously described PD pain types. Severity of PD-related pain syndromes was scored by ratings of intensity, frequency, and interference with daily living activities. The PD-Pain Classification System (PD-PCS) was compared with classic pain measures (ie, brief pain inventory and McGill pain questionnaire [MPQ], PDQ-8 quality of life score, MDS-UPDRS scores, and nonmotor symptoms). 159 nondemented PD patients (disease duration 10.2 ± 7.6 years) and 37 healthy controls were recruited in 4 centers. PD-related pain was present in 122 patients (77%), with 24 (15%) suffering one or more syndromes at the same time. PD-related nociceptive, neuropathic, or nociplastic pain was diagnosed in 87 (55%), 25 (16%), or 35 (22%), respectively. Pain unrelated to PD was present in 35 (22%) patients. Overall, PD-PCS severity score significantly correlated with pain's Brief Pain Inventory and MPQ ratings, presence of dyskinesia and motor fluctuations, PDQ-8 scores, depression, and anxiety measures. Moderate intrarater and interrater reliability was observed. The PD-PCS is a valid and reliable tool for differentiating PD-related pain from PD-unrelated pain. It detects and scores mechanistic pain subtypes in a pragmatic and treatment-oriented approach, unifying previous classifications of PD-pain.

Keywords: Pain, Parkinson disease, Questionnaire, Classification, Nociceptive, Neuropathic, Nociplastic

1. Introduction

Chronic pain (CP) (ie, pain lasting more than 3 months) affects 18% to 30% of the general population.[15,28] In Parkinson disease (PD), chronic pain is present in 20% of patients at the time of the diagnosis associated with the early motor stage and affects up to 80% during the course of the disease.[4,16,45] In addition, a Park Pain type has recently been described as one important nonmotor subtype.[40]

Pain in PD has been previously divided as (1) de novo pain temporally related to disease onset, the symptoms of the disease, or its treatment (PD-directly related pain), (2) previous chronic pain aggravated by the disease or its treatment (PD-indirectly related pain), or (3) pain that is neither caused nor aggravated by the disease (PD-unrelated pain).[35] A myriad of different pain syndromes has been described in PD, and several classification systems have

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been proposed.[10] These various pain types propositions were seldom validated[20,38] or formally tested,[41] which increases the difficulty in diagnosing and treating pain in PD patients. We aimed at incorporating these previous approaches to define PD-related pains and to distinguish them from PD-unrelated pains. According to previous classifications, pain is considered as PD-related when one of the following conditions applies: when occurring along with the first motor symptoms, when occurring/aggravated during the OFF stage, when occurring simultaneously with choreatic dyskinesia, or when improved by dopaminergic treatment.[9,20,38]

In one given disease entity, pain can be caused by different mechanisms, so that pain diagnosis and treatment is not etiology-driven, but, instead, mechanism-based.[2] In general, there are 3 main pain mechanisms of CP that account for most types of pain: nociceptive, neuropathic, and nociplastic pain.[21,30] In nociceptive pain, nociceptors are activated by mechanical, thermal, or mechanical stimuli related to actual or potential lesion to nonneural tissues. It includes most of the musculoskeletal (MSK) pain syndromes, such as osteoarthritis, and other inflammatory conditions where tissue lesion or inflammation predominates. Neuropathic pain is associated to a lesion or disease of the peripheral or central somatosensory system, with specific characteristics (tingling, burning, or electric-shock-like sensations) and location (neurologically plausible).[48] Nociplastic pain syndromes comprise instances where the nociceptive system is overactive without any evidence of somatosensory system lesion or peripheral activation of nociceptors due to actual or potential tissue damage.[27,30] Central sensitization (ie, increased responsiveness of a sensory neuron to normal or subthreshold inputs), which is not specific to a single pain type, plays the key role for the sensory gain of the somatosensory system in nociplastic pain. As depicted above, the proposition of Wasner and Deuschl for PD-related pains was followed for this validation and nociplastic pain as a third mechanistic descriptor was added,[51] as previously suggested by Marques et al., 2019.[30]

We have developed a new, mechanism-based classification to differentiate PD-related pain from PD-unrelated pain, with a further characterization of PD-related pain into 3 subgroups, to allow pathophysiology-based treatment to be performed.[13,35]

2. Methods

2.1. Design

This was an international, cross-sectional, multicenter study with a retest validation step.

2.2. Patients and consent

Consecutive inpatients and outpatients with or without pain and with the clinical diagnosis of PD according to the criteria of the United Kingdom PD Society Brain Bank were recruited[23] at the Department of Neurology of the Center for Neurorehabilitation in Valens, the Parkinson Center at the Center for Neurological Rehabilitation Zihlschlacht, the Department of Neurology of Kantonsspital St. Gallen in Switzerland, and the Hospital das Clínicas of the University of Sao Paulo in Brazil. Age-matched healthy individuals were also included to detect whether the PD-PCS can differentiate PD patients from controls by the pain level. Informed consent was obtained from all subjects before participation in the study. The study protocol was approved by the local institutional review boards in Switzerland (BASEC: 00502) and Brazil (0105/10).

2.3. Inclusion and exclusion criteria

Adult PD patients with or without pain that could stay in the ON-state during clinical assessments were included. Participants were screened for potential dementia using the Mini Mental Status Examination (MMSE, exclusion criterion, cutoff < 25). Patients with Deep Brain Stimulation (DBS) and LCIG pump therapy were also excluded.

2.4. Development of the scale

The Parkinson Disease Pain Classification System (PD-PCS) is a rater-based scale (**Fig. 1**, and Suppl. 1, available at http://links.lww.com/PAIN/B271 The generation of the sequence of steps and items was based on formal meeting with pain specialists (doctors, nurses, physiotherapists, and psychologists), as well as movement disorder experts. Its main aim was to: i. ascertain that pain is related to PD (irrespective of being directly- or indirectly-related) rather than unrelated to PD, ii. classify the existing pain into one of the 3 mechanistic descriptors of CP (ie, nociceptive, neuropathic, and nociplastic). A "severity" score was based on the intensity of pain (on a scale from 0 to 10), multiplied by its frequency and the impact in daily living (each using a 3-point Likert score) so that scores can range from 0 to 90 for each pain type.

Within each mechanistic pain descriptor (nociceptive, neuropathic, and nociplastic), classic pain-related situations in PD were included, based on classic case descriptions of pain in PD as well as previous tentative proposals to classify PD-related pain.[9,20,21,38,51] The *Douleur Neuropathique-4* questionnaire (DN-4) was used to classify pain as neuropathic.[5] We also took into account insights from recent studies suggesting that some particular types of musculoskeletal pain syndromes such as myofascial pain do occur in PD in a prevalent proportion of patients, being particularly responsive to DBS treatment.[12,13] The scoring system and a detailed discussion on its structure are included (Suppl. 1 and 2, available at http://links.lww.com/PAIN/B271 and http://links.lww.com/PAIN/B202). The final three-item-based model has been subject to previous peer review publications[30] and has benefited from presentations in workshops and inputs received at both international movement disorders and pain meetings.[13,21,35] Here, only pain related to PD was analyzed because we assumed that pain unrelated to PD corresponds to pain seen in the general population and because the PD-PCS aimed at assessing PD-related pains.

2.5. Patient assessment

Parkinson disease patients were clinically examined and underwent the UPDRS-III protocol by neurologists specialized in movement disorders. Raters assessed patient's pain with the classification tool in a standardized way (Suppl. 1, available at http://links.lww.com/PAIN/B271). The PD-PCS was assessed separately for each pain type associated with PD, and the main pain type mentioned in each group (nociceptive, neuropathic, and nociplastic) was documented and analyzed.

At baseline, general information concerning PD history was gathered. Medication intake was recorded (levodopa equivalents were calculated according to Tomlinson et al.[47]). Then, patients completed the following questionnaires and tests: PD-PCS, Brief Pain Inventory (BPI),[39] clock-drawing test,[37] QoL in PD questionnaire (PDQ-8),[31] hospital anxiety and depression scale (HADS),[26] McGill pain questionnaire short-form 1 (MPQ),[32] and the Wearing-off questionnaire-9 (WOQ-9).[43] Finally, the Movement Disorders Society revision of the unified Parkinson disease rating scale parts III and IV (MDS-UPDRS-III and -IV) were evaluated.[25]

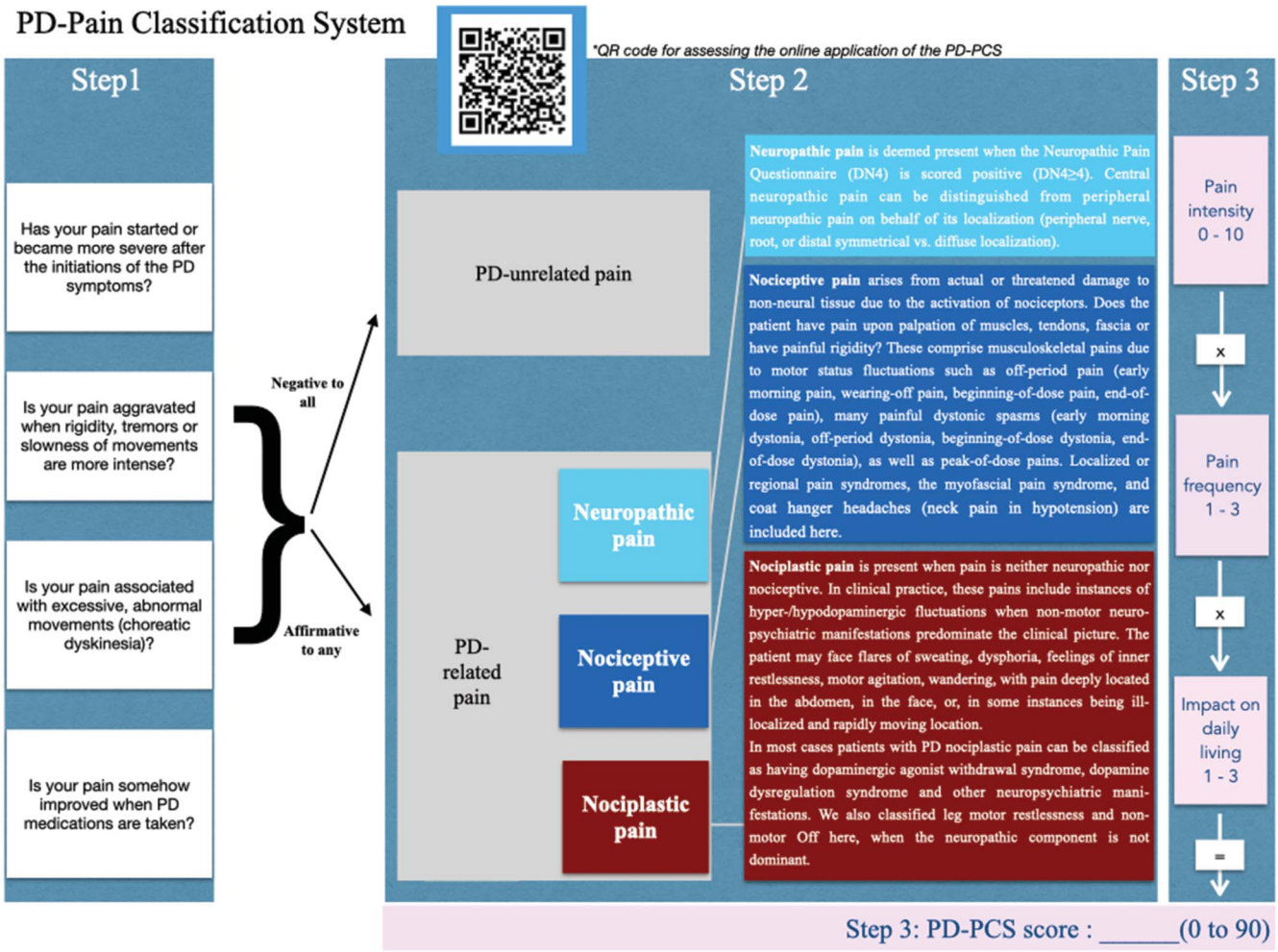

Figure 1. The PD-Pain Classification System (PD-PCS) with a complementary QR code for a web-based online version.

A part of the questionnaires was reassessed at a second visit after 7 days (5-10 days) by the same rater to determine intrarater reliability and simultaneously by a second rater blinded to the assessments of the first rater to determine interrater reliability. Patients were assessed by PD-PCS, BPI, and MPQ. In addition, the Clinical Global Impression of Change (CGIC) was assessed by the patient (Patient's Global Impression of Change [PGIC]) and by the physician (CGIC) to determine if patients were stable at the second visit for intrarater comparisons.[7]

2.6. Sample Size

By using the 10-times-item rule and counting 8 (PD-PCS) items, 80 PD patients with pain would be needed. An extra 20% of patients was recruited to account for lost data, thus sample size was adjusted to 100. Because about 60% of the patients were expected to suffer from pain, 150 patients were included to reach 100 patients with pain. A subsample of 40 patients with pain was considered enough for calculating reliability at a second visit. A sample of 40 non-PD healthy controls, so as to have one control for about 2 patients with pain, was included.

2.7. Data analyses

Data from the single centers was collected by the leading centers and transferred to the Biomedical Research Center (CAECIHS-UAI), National Research Council (CONICET), Buenos Aires, Argentina, for analyses. Comparisons between controls and patients of numerical or categorical variables were performed by Student *t*-test or chi-square test, or their nonparametric homologues when assumptions were not met.

2.8. Validation analysis

(1) Acceptability: proportion of missing data, score distribution, skewness, and floor and ceiling effects were evaluated. Floor and ceiling effects were calculated as the proportion of cases with PD-PCS scores below 5% or above 95% of total scores, respectively, in patients with pain as assessed by the BPI;
(2) Internal consistency was evaluated by intraclass correlation coefficient (ICC);
(3) Intrarater and interrater reliability was assessed by Kappa scores for dichotomous variables or ICC for continuous variables. For these analyzes, only patients identified as "stable" by the CGIC were included;
(4) Criterion validity was explored by correlating PD-PCS scores with BPI and MPQ scores using the Pearson correlation technique;
(5) Convergent construct validity was further assessed by correlating the presence and intensity of each type of pain as assessed by the PD-PCS with MDS-UPDRS part IV, PDQ-8, HADS, and WOQ-9;

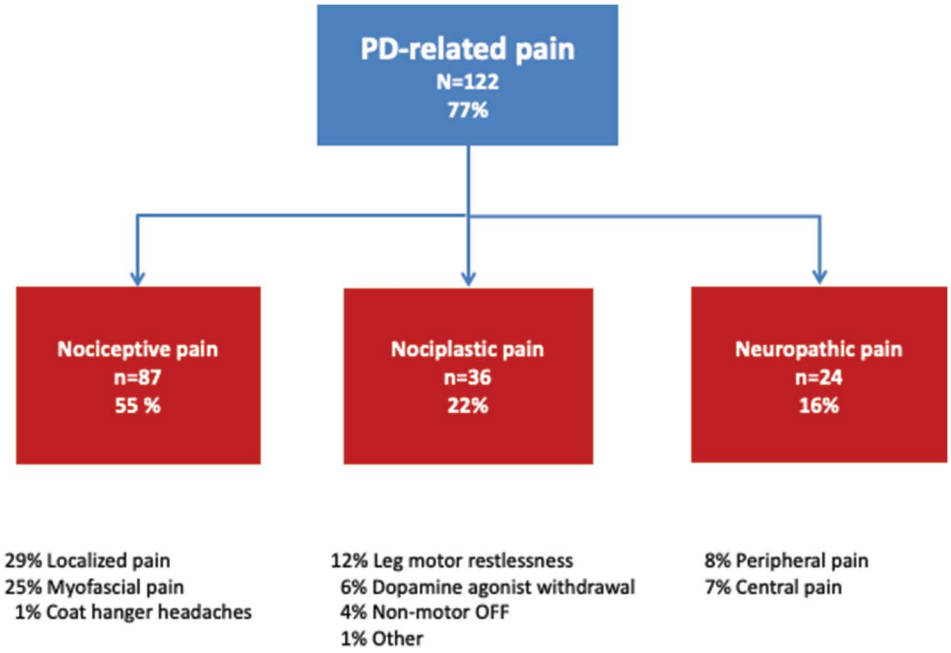

Figure 2. Prevalence of nociceptive, neuropathic and nociplastic pains with respect to the defined pain syndrome at the first visit (in % of the total sample, n=159). PD, Parkinson disease.

(6) Known-group validity was assessed by comparing the scores from the 3 pain types (subgroups of the PD-PCS) according to QoL and disease characteristics;
(7) Internal validity was assessed by a principal component analysis with nonorthogonal rotation of pain syndromes intensity scores, as calculated by the PD-PCS.

3. Results

3.1. Clinical features and acceptability

One hundred fifty-nine PD patients and 37 healthy controls were recruited in 4 clinical centers: in Sao Paulo, Brazil (Hospital das Clínicas, Universidade de São Paulo), and in the Eastern part of Switzerland (Center for Neurorehabilitation in Valens, Center for Neurological Rehabilitation Zihlschlacht, and Department of Neurology of Kantonsspital St. Gallen). Main characteristics of patients and control are shown in **Table 1**.

There was no difference in age between groups, but PD patients were more frequently males, less frequently active workers, had higher HADS anxiety and depression scores, and higher clock scores. Classification of PD-pain was possible for all patients. Assessment with full scale (step 1, step 2 with pain type determination and pain location with the manikin, and step 3 score calculation for the determined mechanistic pain descriptor) took less than 7 minutes in 85% of cases and less than 10 minutes in the remaining ones. As shown in **Table 1**, 93% of PD patients were affected by pain as assessed by the BPI vs 6% of controls ($P < 0.01$). Regarding the PD-PCS, PD-related pain was present in 122 patients (77%), with 24 (15%) suffering from more than one syndrome at the same time. PD-related pain with nociceptive, neuropathic, or nociplastic components was diagnosed in 87 (55%), 25 (16%), or 35 (22%), respectively (the respective pain syndromes are given in **Figure 2**. Most frequent mixed pain syndromes concerned nociceptive pain combined with nociplastic (n = 12.7%) or neuropathic pain (n = 9.6%). The pain characteristics according to the DN4 are given for each pain mechanism in Suppl. Table 1 (available at http://links.lww.com/PAIN/B202).

Pain unrelated to PD (ie, neither caused or aggravated by PD) was present in 35 (22%) patients vs 2 (5%) controls ($P < 0.01$).

The number of affected body regions by nociceptive, neuropathic, or nociplastic pain was 4.8 ± 5.2, 8.5 ± 5.8, and 10.1 ± 8.9, respectively ($P < 0.01$). Affected body regions are shown in Suppl. Table 2 (available at http://links.lww.com/PAIN/B202). In patients with pain according to the BPI, floor effects for nociceptive, neuropathic, nociplastic, and total scores were present in 4%, 4%, 20%, and 32% of cases, respectively. Ceiling effects for these scores in patients with pain were observed in 6%, 0%, 0%, and 0% of cases, respectively. Skewness was 0.98, 2.53, 2.90, and 0.79 for PD-PCS nociceptive, neuropathic, nociplastic, and total scores, respectively. Samples from Brazil and Swiss were similar, apart for the following results: compared to the Swiss, Brazilians were younger (60 ± 12 vs 71 ± 8 $P < 0.05$), had higher UPDRS III (41.2 ± 14.9 vs 28.9 ± 12.6 $P < 0.05$), and suffered more frequently from LIDs (56% vs 24%, $P < 0.01$). Regarding PD-PCS, Swiss patients suffered more frequently from nociplastic pain (33% vs 13% $P < 0.01$), and had higher PD-PCS total scores (41.2 ± 14.9 vs 28.9 ± 12.6 $P < 0.05$). All other characteristics and results were not different between the samples.

3.2. Internal consistency

Consistency of nociceptive, neuropathic, nociplastic severity scores, as assessed by ICC, was 0.08 ($P = 0.90$). This confirms that the scale is not unidimensional because it assessed the presence of different kinds of pain.

3.3. Assessment of reliability

Interrater reliability and intrarater reliability were assessed in patients who came to the second visit and were not considered to exhibit relevant clinical changes in pain as assessed by CGIC. Patients were assessed by the same researcher (n = 17, intrarater assessment) and

Table 1

Pain in healthy controls and in Parkinson disease patients.

	Healthy controls (n = 37)	PD (n = 159)	*P*
Males	16 (43%)	99 (62%)	0.04
Age (yr)	65.0 ± 11.5	65.1 ± 11.6	0.96
Right handedness	35 (95%)	156 (98%)	0.22
Married	24 (65%)	112 (70%)	0.51
Active	13 (35%)	13 (8%)	<0.01
PD duration (yr)	—	10.2 ± 7.6	—
MDS-UPDRS III score	—	35.5 ± 15.2	—
MDS-UPDRS IV score	—	6.1 ± 4.6	—
LIDs	—	66 (42%)	—
Daily % score	—	0.6 ± 0.9	—
Off-time	—	113 (72%)	—
Daily % score	—	1.1 ± 1.0	—
WOQ-9 score	—	4.8 ± 2.6	—
Clock score	1.0 ± 0.1	2.8 ± 1.5	<0.01
PDQ-8 score	—	28.2 ± 23.5	—
HADS-A score	2.7 ± 2.9	7.5 ± 4.1	<0.01
HADS-D score	1.4 ± 2.2	7.4 ± 4.5	<0.01
Antiparkinsonian drugs			
Levodopa	—	146 (92%)	
Agonists	—	75 (47%)	
Other	—	86 (54%)	
Levodopa equivalent dose	—	1050 ± 635	
Pain			
Pain reported at BPI	2 (6%)	148 (93%)	<0.01
Maximum pain score	—	7.2 ± 2.6	—
Minimum pain score	—	1.7 ± 2.2	—
Average pain score	—	5.1 ± 2.3	—
Ongoing pain score	—	2.9 ± 2.9	—
MPQ sensory	—	13.3 ± 7.8	—
MPQ affective	—	5.1 ± 4.4	—
MPQ total	—	18.5 ± 11.4	—
PD-PCS			
No pain		37 (23%)	
PD-unrelated pain	2 (5%)	35 (22%)	<0.01
PD-related pain		122 (77%)	
PD-related pain component:			
Nociceptive	0	87 (55%)	<0.01
Score	0	22.6 ± 29.1	<0.01
Neuropathic	0	25 (16%)	<0.01
Score	0	7.3 ± 19.1	<0.01
Nociplastic	0	35 (22%)	<0.01
Score	0	6.0 ± 16.4	<0.01
One component	—	98 (62%)	—
Two components	—	22 (14%)	—
Three components	—	2 (1%)	—
PD-PCS total score	0	36.0 ± 35.1	<0.01

Mean ± SDs are shown. Comparisons were performed by means of χ^2 or *t*-tests.

BPI, brief pain inventory; HADS-A and HADS-D, Hospital Anxiety and Depression scale—Anxiety and depression scores; LIDs, levodopa-induced dyskinesia; MDS-UPDRS III-IV, Movement Disorders Society Revision of the Unified Parkinson's Disease Rating Scale parts III and IV; MPQ, McGill Pain Questionnaire; PD, Parkinson disease PD-PCS, Parkinson's Disease—Pain Classification System; PDQ-8, Quality of life in Parkinson's Disease questionnaire; WOQ-9, Wearing-off questionnaire-9.

by a different one (n = 24, interrater assessment). Overall, PD-PCS severity score showed statistically significant intrarater (ICC= 0.62) and interrater reliability (ICC = 0.59). Data on reliability of subscores are given in **Table 2 and 3**.

3.4. Criterion validity

The PD-PCS total score showed significant association with BPI and MPQ scores (**Table 4**).

Table 2

PD-PCS scores and other pain measures in PD patients assessed on 2 occasions 7 d apart (n = 48).

	Visit 1	Visit 2	Δ V2 − V1	P
PD-PCS				
PD-unrelated	8 (17%)	5 (11%)	—	0.45
Nociceptive pain	27 (56%)	34 (71%)	—	0.09
Score	26.5 ± 30.0	30.2 ± 28.3	4.2 ± 26.1	0.30
Neuropathic pain	11 (23%)	5 (10%)	—	0.07
Score	9.5 ± 20.2	4.6 ± 14.2	−5.1 ± 20.7	0.09
Nociplastic pain	9 (19%)	13 (27%)	—	0.22
Score	3.8 ± 12.7	7.1 ± 21.7	3.3 ± 22.1	0.14
PD-PCS total score	40.6 ± 34.3	43.9 ± 32.2	3.3 ± 30.2	0.39
Brief pain inventory				
Maximum pain	7.9 ± 2.0	7.5 ± 2.2	−0.4 ± 2.5	0.35
Minimum pain	1.4 ± 1.6	1.8 ± 2.0	0.4 ± 2.1	0.18
Average pain	5.5 ± 2.0	5.7 ± 2.4	0.2 ± 2.3	0.65
Ongoing pain	2.7 ± 2.8	3.0 ± 2.9	0.2 ± 3.3	0.68
McGill pain questionnaire				
Sensory	14.6 ± 7.6	14.6 ± 8.2	−0.1 ± 6.5	0.91
Affective	6.1 ± 4.4	6.6 ± 4.7	0.6 ± 3.1	0.21
Total score	20.7 ± 11.0	21.1 ± 12.1	0.4 ± 8.1	0.72
Change scores				
PGIC	—	3.3 ± 1.4	—	—
Improvement	—	26 (54%)	—	—
No change	—	17 (35%)	—	—
Worsening	—	5 (10%)	—	—
CGIC	—	3.4 ± 1.1	—	—
Improvement	—	23 (48%)	—	—
No change	—	20 (42%)	—	—
Worsening	—	5 (10%)	—	—

Mean ± SDs are shown. Numerical variables were compared by paired *t* test and the categorical ones by McNemar test.

CGIC, clinical global impression of change; PD, Parkinson disease; PD-PCS, Parkinson's Disease—Pain Classification System; PGIC, Patient's Global Impression of Change.

3.5. Convergent construct validity

Correlations between PD-PCS scores and other variables are shown in **Table 4**. Nociceptive, neuropathic, nociplastic, and total PD-PCS scores correlated with the presence of levodopa-related motor complications, PDQ-8, and HADS anxiety scores. Nociceptive, neuropathic, and total PD-PCS scores also correlated with HADS depression scores. Nociceptive, neuropathic, and total scores also correlated with BPI and MPQ scores (**Table 5**).

3.6. Known-group and internal validity

A multinomial logistic regression analysis was used to assess factors associated with pain mechanism (Suppl. Table 3, available at http://links.lww.com/PAIN/B202). Results showed that nociceptive pain was related to WOQ-9 score (OR, 95% CI= 1.43, 1.15-1.76) and BPI pain score now (1.27, 1.04-1.55), neuropathic pain to WOQ-9 score (1.83, 1.27-2.65), HADS-A score (1.29, 1.01-1.64), BPI pain score now (1.51, 1.13-2.04), and MPQ sensory score (1.19, 1.01-1.40), and nociplastic pain score to WOQ-9 score (1.47, 1.12-1.92). When QoL, through PDQ-8, was stratified according to low (<8), intermediate (9-16), high (17-42), or very high (>42) scores, pain unrelated to PD had a somewhat similar distribution across all strata, whereas PD-related pain patients were concentrated in the more affected strata. The PD-PCS showed that these differences were even more significantly clear for the nociceptive and neuropathic mechanistic pain descriptors (Suppl. Table 4, available at http://links.lww.com/PAIN/B202). Correlations between nociceptive, neuropathic, or nociplastic scores with the total PD-PCS scores were all significant (Pearson's $r = 0.74$, 0.46, or 0.29, respectively). A principal component analysis revealed 2 factors accounting for 73% of variance. Nociceptive and neuropathic pain loaded positively each one in a different factor, whereas nociplastic pain loaded negatively on both factors.

Table 3

Intrarater and interrater reliability.

	Intrarater (n = 17)	Interrater (n = 24)
Nociceptive pain[a]	0.60*	0.40*
Nociceptive score[b]	0.37*	0.65*
Neuropathic pain[a]	0.43*	0.33
Neuropathic score[b]	0.34*	0.69*
Nociplastic pain[a]	0.43*	0.23
Nociplastic score[b]	0.50*	0.04
PD-PCS total score[b]	0.62*	0.59*

Kappa scores (a) or intraclass correlation coefficients (b) are shown (*$P < 0.05$). Only patients with no change on Clinical Global Impression of Change (CGIC) and Patient's Global Impression of Change (PGIC) were selected for these analyses.

PD-PCS, Parkinson's Disease—Pain Classification System.

4. Discussion

We here present an international validation study of a unifying classification system for pain in PD. This system was able to differentiate PD-related pain from PD-unrelated pain, providing a mechanistic and treatment-oriented classification of PD-related pain based on pain pathophysiology. This categorization system showed moderate intrarater and interrater reliability, which probably reflects the difficulties of assessing pain in PD. Moderate correlations with commonly used pain questionnaires and other scales confirmed criterion and convergent construct validity. On average, patients presented with moderate pain intensity. One fourth of them had chronic pain that was not directly related to PD, which is in line with the prevalence of pain in the general population.[15] Pain related to PD was present in 77% of the sample and comprised a single type of pain in 62%, 2 types in 14%, and 3 in 1% of the patients. Interestingly, mixed pain (overlap of neuropathic and nociceptive pain) is relatively common in the general population,[21] but has never been formally described in PD. The result that 15% of patients with pain directly related to PD have more than one pain type is clinically relevant and may impact not only on treatment approaches, but also the design of future trials.[21]

The PD-PCS score was significantly correlated with those from commonly used questionnaires such as the BPI and the MPQ. It also showed correlations with QoL and mood scores. Interestingly, the total score of the PD-PCS correlated with the MDS-UPDRS-IV score, but not with the motor score. This finding may be related to the fact that all patients were assessed in the "ON" state. Alternatively, the dissociation between motor and pain state has been described in several instances[11,12,14] and argue against a unique musculogenic origin of pain in PD. Our present data suggest that the 3 pain types identified by the PD-PCS are actually different pain syndromes, sharing different characteristics and probably reflecting different mechanistic backgrounds and possibly different responses to treatment. For instance, we found that higher nociceptive pain scores were found in patients with worse QoL, whereas this was not true for nociplastic pain. Also, as expected, patients with nociceptive pain had more localized pain (ie, shoulder)

Table 4

Correlations between PD-PCS scores and other variables at Visit 1 in Parkinson disease patients (n = 159).

	Nociceptive score	Neuropathic score	Nociplastic score	PD-PCS total score
MDS-UPDRS-III score	0.08	0.13	−0.07	0.10
MDS-UPDRS-IV score	0.22**	0.04	0.15	0.28**
LIDs daily %	0.18**	0.07	−0.02	0.18**
Off-time daily %	0.12	0.07	0.10	0.19**
WOQ-9 score	0.06	0.18**	0.20**	0.27**
Clock score	0.03	0.02	0.00	0.04
PDQ-8 score	0.24**	0.18**	0.16**	0.39**
HADS-A	0.25**	0.19**	0.16**	0.40**
HADS-D	0.22**	0.18**	0.05	0.33**
BPI worst	0.33**	0.16**	0.03	0.40**
BPI weakest	0.25**	0.06	−0.04	0.22**
BPI average	0.31**	0.16**	0.16**	0.43**
BPI now	0.28**	0.18**	−0.01	0.32**
MPQ sensory	0.31**	0.35**	0.08	0.49**
MPQ affective	0.31**	0.22**	0.07	0.43**
MPQ total	0.33**	0.32**	0.08	0.50**

Pearson correlation coefficients are shown (*$P < 0.05$, **$P < 0.01$).

BPI, brief pain inventory; HADS-A and HADS-D, Hospital Anxiety and Depression scale—Anxiety and depression scores; LIDs, levodopa-induced dyskinesia; MDS-UPDRS III-IV, Movement Disorders Society Revision of the Unified Parkinson's Disease Rating Scale parts III and IV; MPQ, McGill Pain Questionnaire; PD-PCS, Parkinson's Disease—Pain Classification System; PDQ-8, Quality of life in Parkinson's Disease questionnaire; WOQ-9, Wearing-off questionnaire-9.

compared to those with nociplastic pain, who had widespread pain featuring on average twice the number of pain regions in the body than that reported by nociceptive pain patients. This finding is in line with the spatially widespread nature of the pain types (central, nonmotor off) classified under the nociplastic umbrella compared to regional MSK pain classified as nociceptive.[1,21] In general, nociceptive pain was more commonly located in the trunk and lower back, whereas neuropathic pain and nociplastic pain were rather found in the lower limbs and on both upper and lower limbs, respectively. Finally, visceral pain may also be considered a nociplastic rather than nociceptive pain, in line with a more accepted view in this regard.[3,49]

However, it is known that PD lowers pain thresholds, so that patients with more severe motor disease have, in general, more altered pain sensitivity.[34,36] Also, it has been repetitively shown that both dopamine replacement therapy,[6,22,29,42] and DBS[12,14] can partially reverse these changes. Pain in PD was originally related to increased muscle rigidity. Indeed, the musculoskeletal origin of pain in PD has been initially put forth, but later evidence challenged this hypothesis because many patients with severe rigidity do not have pain. Moreover, severity of motor symptoms does not differ between patients with or without pain[24] and pain begins before motor symptoms in a significant proportion of patients.[16,17] Finally, there is a lack of correlation between motor improvement and pain relief with DBS treatment.[12] These findings speak in favor of a specific role of dopamine as a modulator of sensory and pain processing involved in PD-related pain. However, whether dopamine-related mechanisms are more involved in nociceptive, neuropathic, or nociplastic mechanisms of PD-related pain remain to be determined. In this view, maybe nearly all PD-related pain syndromes may involve dopamine-based dysfunction in the central nervous system (CNS), but they cannot be considered to be what is usually called "central neuropathic pain." In fact, "central neuropathic pain" is defined by the finding of lesions in the CNS specifically affecting the somatosensory structures and leading to the occurrence of pain with "neuropathic" characteristics (tingling, burning, and electric shock-like sensations).[48] Dopamine-related mechanisms in PD-related pain probably go beyond this restrictive view of central neuropathic pain. Therefore, what is usually called "central PD pain"[41] needs to be urgently revised.[30] In fact, most patients suffering from "central PD pain"

Table 5

Correlation of changes in PD-PCS scores with other pain measures.

	Nociceptive score	Neuropathic score	Nociplastic score	Total
BPI worst	0.13	−0.06	0.14	0.26
BPI weakest	−0.01	0.10	−0.16	−0.05
BPI average	0.21	−0.09	−0.20	0.01
BPI now	0.37**	−0.22	−0.27	−0.01
MPQ sensory	0.24	0.10	0.03	0.30**
MPQ affective	0.17	−0.22	0.19	0.17
MPQ total	0.26	0.00	0.09	0.31**

Pearson correlation coefficients are shown. *$P < 0.05$, **$P < 0.01$.

BPI, brief pain inventory; MPQ, McGill Pain Questionnaire; PD-PCS, Parkinson's Disease—Pain Classification System.

actually have a complex clinical presentation,[18,50] where pain occurs in diverse areas of the body, in a context of dysphoria, motor restlessness, akathisia, and cognitive acceleration, frequently in association with dopamine oscillation syndrome.[8,33] Because these patients lack clear lesion to the somatosensory system, they do not have a "neuropathic" pain syndrome *stricto sensu,* and more likely present nociplastic pain. Our data further support this view, as has been previously put forth by Marques et al., 2019.[30] Indeed, patients with nociplastic pain had more widespread pain areas and more intense pain burden, usually caused by dopamine agonist withdrawal syndrome, dopaminergic dysregulation syndrome,[33,50] nonmotor off periods, and visceral pain attacks.[44]

There have been several attempts to classify pain in PD. The first one was Quinn's pain classifications, which segregated PD-related from PD-unrelated pain, but had not been organized as a questionnaire.[38] This first classification proposed that PD-related pain was associated with fluctuations of the disease and/or dopaminergic treatment. It included pain preceding diagnosis of PD, off-period pain, painful dystonic spasms, and peak-of-dose pain. We used several of these characteristics in step 1 of the PD-PCS to classify pain as PD-related, and most instances of pain during motor off-periods were classified as nociceptive in the PD-PCS because in all instances, there are excessive painful contractions conveyed by muscle innervation.[19,46] The Non-Motor Symptoms Scale (NMS) proposed an association of pain with PD by an exclusion of further causes and when pain occurs in the off-stage and improves by dopaminergic treatment.[9] The most common pain classification by Ford summarized 5 different forms (musculoskeletal, dystonic, central, neuropathic, and akathisia[20]) when pain occurs in relation with the cardinal symptoms of PD as well as with akathisia and dystonia. He further suggested to consider the impact of dopaminergic medication without addressing if pain was PD-related or PD-unrelated. In one recent approach, pain was classified into neuropathic, nociceptive, and miscellaneous pains.[51] Here, we used the definition of PD-related pains based on the classification of Quinn, additionally including the effects of dopaminergic use in pain,[38] with a further classification of PD-related pains based on the classification of Wasner and Deuschl.[51] This allows the distinction between PD-related and PD-unrelated pain. To date, there is one PD pain scale, the King's Parkinson Disease Pain Scale.[10] It has been validated exclusively for PD-directly related pain, and proposes 7 pain domains (musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, orofacial pain, discoloration/oedema/swelling, and radicular pain). Importantly, in the King's scale, only patients with no other etiology for their pain were included. This is an important issue because up to 30% of the general population have chronic pain, and excluding all other etiologies of pain would exclude at least a third of PD patients with pain that could potentially be aggravated by PD (classified here as pain indirectly related to PD). Also, so far, it has not been shown whether the different King's Parkinson Disease Pain Scale domains constitute actual distinct pain mechanisms or simply subitems of larger pain groups. We propose that our approach is comparable to previous classifications and scales because it provides an umbrella mechanistic classification of pain in PD that can be further refined into different PD pain types as proposed by Marques 2019[30] and the King's approach.[10] With a validated classification system, the treatment of pain in PD could in future be based on the exact subtype of pain, which so far has not been possible because the existing classifications have either not been validated or are not mechanism-based.

5. Conclusions

In summary, we presented the validation of a hierarchical approach for the diagnostic classification of pain in PD in an attempt to unify previous efforts to classify PD-related pain. Based on 4 questions, the questionnaire establishes a relation of pain with PD before subdividing it into 3 pain types according to mechanistic descriptors (nociceptive, neuropathic, and nociplastic) and providing scores. The refinement of the characterization of pain in PD should help improve pain in PD patients in a more pragmatic and symptom-oriented manner.

Conflict of interest statement

V. Mylius received honoraria from LicherMT, Boston Scientific, and Abbvie. SPL received honoraria from IPMDS and consulted for Merz Pharmaceuticals. F. Brugger received research grants from Baasch-Medicus Foundation and Forschungskommission Kantonsspital St. Gallen, and a travel grant from Abbvie Switzerland. A. Rizos received salary support from the Institute for National Health Research (NIHR) Clinical Research Network (CRN) South London and honoraria from Britannia Pharmaceuticals Ltd. K.R. Chaudhuri received honoraria for advisory boards by AbbVie, UCB, Pfizer, Jazz Pharma, GKC, Bial, Cynapsus, Novartis, Lobsor, Stada, Medtronic, Zambon, Profile, Sunovion, Roche, Therevance, and Scion, honoraria for lectures by AbbVie, Britannia, UCB, Mundipharma, Zambon, Novartis, Boeringer Ingelheim, Neuroderm, and Sunovion, grants (investigator-initiated) by Britania Pharmaceuticals, AbbVie, UCB, GKC, and Bial, academic grants by EU (Horizon 2020), IMI, Parkinson UK, NIHR, PDNMG, Kirby Laing Foundation, NPF, and MRC. L. Timmermann received payments as a consultant for Boston Scientific, and honoraria as a speaker on symposia sponsored by UCB, Desitin, Boston Scientific, and Abbott. R. Gonzenbach received honoraria from Almirall, Bayer, Sandoz, Biogen, Roche, Novartis, and Sanofi. G. Kägi received honoraria from Bayer. D. Ciampi de Andrade consulted for Merk, Grunenthal, Cristalia, and Novartis, and investigator-initiated research grant from Grunenthal, Mundipharma, Pfizer, and Abbott. The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B202 and http://links.lww.com/PAIN/B271.

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