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Research Article

Intercultural Translation and Application of the German Version of King's Parkinson's Disease Pain Questionnaire in Fluctuating Parkinson's Disease

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Background. Pain is common in Parkinson's disease (PD) and impairs quality of life. The King's PD pain questionnaire (KPPQ) is a standardized, reliable, and valid self-administered questionnaire for screening of pain in PD. We developed a linguistically validated German version of the KPPQ and applied it to a cohort with fluctuating PD. *Methods*. The interculturally adapted German translation was performed according to internationally accepted procedures in coordination with the authors of the original publication but without further psychometric validation. After final approval by all translators and original authors, the German version was then tested for feasibility and comprehension in 30 PD patients. After final adaption, the German KPPQ together with the German quantitative KPPS were applied to an independent cohort of fluctuating PD patients within the VALIDATE-PD study. *Results*. The use of the German version of the KPPQ in clinical practice or in the VALIDATE-PD study revealed no significant problems of understanding. Sufficient datasets were available from 47 patients with motor fluctuations (24 (51%) males, 23 (49%) females; median (interquartile range (IQR)) age: 65 (58-73) years; median (IQR) Hoehn and Yahr stage: 2.5 [2-3]). Total pain was reported by 43 (92%) of participants with a median number of 4 (IQR: 2-5) pain subtypes. We did not observe any associations of total pain frequency, neither with gender nor with other demographic or clinical parameters. *Conclusions*. The German version of the KPPQ is recommended as a questionnaire for assessing the frequency of pain and its subtypes in PD in clinical studies and/or routine care.

1. Introduction

Pain is a common nonmotor symptom in Parkinson's disease (PD), which has received more and more attention during recent years, but is still insufficiently understood and frequently treated in an undifferentiated manner [1–4]. In PD, various types of pain may be present, such as dystonic, musculoskeletal, central, and radicular pain, which can accumulate in a single patient, further complicating the management of this nonmotor symptom [2–5]. Moreover, the underlying pathophysiological mechanisms are complex and include neuropathic, nociceptive, and nociplastic pain [2–4, 6]. However, detecting the presence of pain in its multiple modalities is necessary for adequate personalized management of PD. The absence of validated instruments for pain in PD either prevented the use of scales in clinical practice to characterize pain more accurately or led to the use of instruments that had not been validated. Consequently, the quantitative rater-/physician-based King's PD Pain Scale (KPPS) has been developed at King's College London [7], which has been validated and is already available in several languages including German [8–11]. In order to provide a patient-completed, easy-to-use, and time-efficient patient-based pain assessment tool for PD, the King's Parkinson's Disease Pain Questionnaire (KPPQ) was designed in correspondence to the rater-based KPPS [12]. The KPPQ assesses the frequencies of 14 items covering all major pain subtypes relevant in PD with a dichotomous outcome measure ("yes/no" responses by the patient). Previous psychometric validation studies showed that the KPPQ is a useful, reliable, and valid screening instrument for pain in PD [9, 12, 13]. Indeed, the diagnostic parameters of the KPPQ were very satisfactory as a whole with a global accuracy of 78% to 98% when compared to KPPS data [12]. We, here, report on the interculturally translated German version of the KPPQ and its application to a cohort with fluctuating PD as a subpopulation of PD patients for whom rather limited data on pain exists [14].

2. Participants and Methods

2.1. Study Protocol Approval and Patient Consents. We report, here, data on pain from the German cohort of the prospective, observational VALIDATE-PD study, which was conducted at two hospital centers in Germany (University Medicine Rostock and Movement Disorder Clinic Beelitz-Heilstätten) [15]. The study was approved by institutional review boards of both participating centers (ethic committee registry numbers A 2017-0115 for Rostock and AS 84 (bB)/2018 for Beelitz-Heilstätten). All participants provided written informed consent prior to study participation.

2.2. Intercultural Translation of the KPPQ into German Language. The King's PD pain questionnaire (KPPQ) [12] has been interculturally adapted according to internationally recognized and accepted procedures without further psychometric validation [16, 17]. This was done by ML, WJ, AS, and PO with the consent of and help from the authors of the original English language version (PO, AR, KRC, and PMM). Initially, the original was translated independently by two bilingual neuroscientists with a clinical focus on movement disorders (ML, WJ). Both versions were then compared, and a consensus version accepted by both translators was agreed upon. The translators tried to stay as close as possible to the original text so that a back-translation resulted in a version as similar as possible to the original.

This preliminary version of the German translation was then clinically applied by AS and WJ to 30 patients with established PD diagnoses (refer to Table 1 for demographic and clinical characteristics including cognitive status). As described in the operating instructions of the questionnaire, the patients received the questionnaire from a doctor or nurse who asked additional questions as needed to help patients answer the questions. Feedback from patients was obtained by unstructured interviews discussing all questions of the KPPQ individually. Issues raised by the participants were taken into account into the first German version. Thereafter, this version was independently retranslated into the original English language by two bilingual neuroscientists (AS, PO) with special expertise in the field of movement disorders, and a consensus version was formed. This English version was then compared with the original version by all translators (PO, AS, ML, and WJ). Due to a few linguistic discrepancies between the original and the back-translated English version, the German version was slightly modified to suffice the consensus of all authors. In the final German consensus version of the KPPQ, synonyms were used instead of some of the German terms used in the first version. This version of the retranslation was then submitted to three lead authors of the original publication (AR, KRC, and PMM), who agreed to this version. Thus, a total of 4 authors of the original paper (AR, KRC, PO, and PMM) were involved in the validation.

2.3. Participants. The final German version of the KPPQ (Supplementary Figure S1) was used according to the operating instructions of the questionnaire to assess pain in a cohort of fluctuating PD patients from the VALIDATE-PD study (German cohort) [15]. Participants were screened between October 2017 and July 2019 according to the following criteria: Participants were eligible for the study if they were over 30 years old, had been diagnosed with PD according to the United Kingdom PD Society Brain Bank criteria, suffered from documented motor fluctuations as observed by the treating physician and/or documented on part 4 of the Movement Disorder Society-revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and were able to provide written informed consent. Motor complications included end-of-dose akinesia (wearing Off), On-Off phenomenon, delayed/no On response, Off period dystonia, peak-dose dyskinesia, and biphasic dyskinesia. Exclusion criteria comprised the existence of clinical signs for secondary or atypical parkinsonian syndromes, inability to complete questionnaires and/or patient diaries, lack of cooperation during the study procedures, presence of dementia (defined as scores on the Montreal Cognitive Assessment (MoCA) <21) [18] and/or relevant psychotic symptoms, ongoing treatment with advanced/invasive therapies (deep brain

Table 1: Demographic and clinical characteristics of study cohorts.

	Initial cohort for KPPQ translation process ($n = 30$)	Application cohort ($n = 47$)
Male/female, *n* (%)	20 (66%)/10 (33%)	24 (51%)/23 (49%)
Age, *median (IQR) in years*	76 (69-79)	65 (58-73)
Disease duration, *median (IQR) in years*	8 (4-10)	10 (8-15)
Symptom duration, *median (IQR) in years*	—	12 (9-17)
Duration of fluctuations, *median (IQR) in months*	—	61 (34-106)
Type of motor complication, *n (%)*		
End-of-dose akinesia	—	44 (94%)
On-Off phenomenon	—	31 (66%)
Delayed/no On response	—	36 (77%)
Off period dystonia	—	26 (55%)
Peak-dose dyskinesia	—	36 (77%)
Biphasic dyskinesia	—	9 (19%)
Medication		
Total LED (mg per day)[$], *median (IQR)*	—	1,325 (1,025-1,667)
Clinical scales		
MDS-UPDRS total score On state, *Median (IQR)*	—	64 (52-83)
Part I	—	13 (7-16)
Part II	—	16 (10-20)
Part III	—	28 (20-40)
Part IV	—	9 (7-11)
Hoehn & Yahr stage, *median (IQR)*	2.5 (2-3)	2.5 (2-3)
Cognitive status[#]		
Normal (MoCA score of ≥26)	14 (47%)	33 (70%)
Mild cognitive impairment (MCI; MoCA score of ≥21 and <26)	10 (33%)	14 (30%)
Dementia (MoCA score of <21)	6 (20%)	0 (0%)

Values are provided as number (percentage), or median (interquartile range (IQR)). MDS-UPDRS: Movement Disorder Society-revised version of the Unified Parkinson's Disease Rating Scale. [$]Levodopa equivalent doses (LED) were calculated according to Jost et al. [19]. [#]Cognitive status was screened using the Montreal Cognitive Assessment (MoCA) using the cut-off values reported by Dalrymple-Alford et al. in 2010 [18]: normal cognition, score of ≥26; mild cognitive impairment (MCI), score of ≥21 and <26; dementia, score of <21.

stimulation, subcutaneous apomorphine, and levodopa-carbidopa intestinal gel), and the presence of miscellaneous diseases impairing the patient's ability for consenting, participation, and judgment.

2.4. Clinical Assessments. Clinical assessments comprised registration of demographic and clinical characteristics including PD medication (levodopa equivalent dose was calculated according to Jost et al. [19]); cognitive screening with the MoCA [18]; clinical evaluation using the MDS-UPDRS [20, 21], PDQ-39 [22], and Beck's Depression Inventory version 2 (BDI-2) [23]; and assessment of pain using the German versions of the KPPQ and the King's PD Pain Scale (KPPS) [7, 8]. Clinical assessments including the KPPQ application were performed by experienced raters not involved in the translation process of the KPPQ (AB, ML, FG, and GE).

2.5. Statistical Analysis. Statistical analysis was performed using IBM SPSS Statistics software version 27 (IBM Corporation, New York, USA). Values are provided as *n* (%), mean ± standard deviation (SD), or median (interquartile range (IQR)), as appropriate. Group comparisons were performed using χ^2 test, Fisher's exact test, or Mann–Whitney *U*-test as appropriate without correction of α inflation. Since the KPPQ is a patient questionnaire with a dichotomous outcome measure ("yes/no" responses), percentage agreement rates and Cohen's κ statistics were used to assess inter-method agreement between KPPQ and KPPS pain frequency data (KPPS frequency score of 0 (no symptom) vs. ≥1 (symptom present)). As introduced by Martinez-Martin et al. [12], for the comparison of the KPPQ with the quantitative rater-based KPPS and other scales, the KPPQ total score was calculated by summing up the number of "yes" responses and KPPQ items were grouped into domains according to the KPPS [7, 8]. Correlations were then estimated using the Spearman rank correlation test, and a correlation coefficient of $|\rho| < 0.3$ was considered weak, $|\rho| = 0.3 - 0.59$ a moderate, and $|\rho| \geq 0.6$ a strong correlation. Pairwise exclusion was used for missing values. To estimate the screening potential of the German KPPQ, we calculated the diagnostic parameter sensitivity, specificity, accuracy, and balanced accuracy (average between

sensitivity and specificity) [24] of the KPPQ against the corresponding components of the KPPS. As most of the data was not normally distributed, we chose nonparametric tests for statistical comparisons. *P* values of <0.05 (two-tailed) were considered to be statistically significant.

3. Results

3.1. German Version of the KPPQ. In German-speaking countries, we prefer the term idiopathic Parkinson's syndrome rather than the abbreviation "PD" (or "PK" in the German language) for Parkinson's disease. Therefore, we have agreed on the name King's Pain Questionnaire for Parkinson's disease (in the German language: King's Schmerz-Fragebogen für Morbus Parkinson) in line with the previously translated KPPS [8]. The authors are aware that in the German-speaking countries, King's as the abbreviation of King's College London is not generally known, but this is part of the name of the original scale referring to its creators and their main affiliation. All other terms have been translated very closely and faithfully to the original; only the last question "Shooting pain/pins and needles down the limbs" was translated at the suggestion of a participant into "Einschießender/kribbelnder Schmerz entlang der Gliedmaßen," respectively "Shooting/tingling pain along the limbs," since this is a common term in German.

Neither the use of the first preliminary German version of the questionnaire in clinical practice with 30 patients (WJ, AS), nor the use of the final one with 47 patients of the VALIDATE-PD cohort revealed systematic problems of understanding. In the initial cohort of 30 participants, 21 (70%) of participants did not report any problems or comments, 5 (17%) participants submitted comments, and only 4 (13%) participants with PD-MCI experienced minor problems. Supervising neurologists reported no problems with the application of the questionnaire in 28 (94%) of participants; in one case, the term "off-Phasen (motor Off state)" and, in one case, the term "innere Organe (internal organs)" are needed to be explained. All relevant comments were included in the final version of the questionnaire. The final version of the interculturally adapted and linguistically validated questionnaire in the German language is shown in Supplementary Figure S1.

3.2. Participants. Sufficient datasets were available from 47 patients (refer to Table 1 for demographic and clinical characteristics). All patients displayed at least two types of motor complications, and the median number of motor complications was 5 (IQR: 2-7). Table 1 summarizes the various types of motor complications. All patients were treated with levodopa, 87% were in combination with COMT inhibitors, 70% were on MAO-B inhibitors (51% on safinamide), and 62% were on dopamine agonists. The median (IQR) total equivalent daily levodopa dose was 1,325 (1,025-1,667) mg. Of note, 14 (30%) of patients had joint or spinal osteoarticular degeneration.

3.3. Pain Characteristics in Fluctuating Patients as Assessed by KPPQ. When various subtypes of pain in fluctuating PD were assessed using the KPPQ, pain was reported by 43 (92%) of participants with a median number of 4 (IQR: 2-5) pain subtypes (Table 1; please note that the ordering of the questions of the KPPQ follows the ordering of the KPPS for easy comparison of the two scales). Most frequent pain subtypes were "1. Pain around joints" (62% of all participants), "5. Off period dystonia in a specific region" and "8. Pain while turning in bed" (both 57%), "6. Generalized Off period pain" (43%), and "7. PLM or RLS-associated pain" (36%). Although the KPPQ does not contain domains and total pain frequency, we calculated domain/total frequency scores for the comparison with the KPPS (similar to Martinez-Martin et al. [12]). On the domain level, the most frequent pain domain was "D3. Fluctuation-related pain" (68% of all participants) followed by "D1. Musculoskeletal pain" (62%) and "D4. Nocturnal pain" (52%; Table 2).

We did not observe differences in total pain frequency in KPPQ assessment between female and male participants (100% in females vs. 83% in males; $P = 0.109$, Fisher's exact test), but significant higher frequencies in females for the pain subtype domains "D3. Fluctuation-related pain" (83% in females vs. 54% in males; $P = 0.037$) and "D4. Nocturnal pain" (78% in females vs. 50% in males; $P = 0.044$, both χ^2 test).

We then compared the pain frequencies as reported by the original approach of the self-administered KPPQ ("yes/no" responses) with those assessed by the treating neurologist/physician using dichotomized frequency data of the KPPS (score of 0 vs. ≥1; Table 2). On the item level, we detected high agreement rates of the two scales regarding pain subtype frequencies between 59% and 98% with corresponding Cohen's κ values ranging between -0.035 and 0.789. On the domain level, we found consistent agreement rate rates between 62% and 87% (Cohen's κ values: 0.034-0.515). The total scores showed an agreement rate of pain frequency of 85% (Cohen's κ value: 0.141).

The KPPQ total score (sum of all "yes" responses) showed moderate correlations with the KPPS total score, the MDS-UPDRS pain item, and the PDQ-39 sum score as well as with the subscores "Bodily discomfort," "Mobility," "Activities of daily living," "Emotional well-being," and "Social Support" (Table 3). No associations were found with the presence/absence of joint or spinal osteoarticular degeneration. We did not detect any further associations between KPPQ total score and age, disease duration, duration of fluctuations, or disease severity (MDS-UPDRS part III motor score or total score) in our cohort (Table 3).

The results of the KPPQ screening parameters were satisfactory, with accuracy values ranging from 60% to 98% and balanced accuracy values from 53% to 97% (see Supplementary Table S1 for all details).

3.4. Pain Characteristics in Fluctuating Patients as Assessed by KPPS. In addition, we explored how the KPPS performed in relation to distribution of scores by gender and quality of life. The KPPS does not only assess pain frequency, but also pain severity leading to compound frequency × severity scores for each pain subtype, domain, and total score. Using these compound scores, we

Table 2: Pain characteristics reported on the KPPQ and KPPS in participants with fluctuating Parkinson's disease ($n = 47$).

Item/domain	KPPQ[§]	KPPS		KPPQ vs. KPPS frequency		
	Frequency[#], *n* (%)	Frequency[#], *n* (%)	Frequency × severity score, median[$]	Frequency × severity score, IQR[$]	Agreement rate (%)	Cohen's κ[¶]	*P* value*
1. Pain around joints	29 (62%)	29 (62%)	2 (17%)	0 (0%)-6 (50%)	77%	0.52	1.000
Domain 1. Musculoskeletal pain	29 (62%)	29 (62%)	2 (17%)	0 (0%)-6 (50%)	77%	0.52	1.000
2. Pain deep within the body	7 (15%)	3 (6%)	0 (0%)	0 (0%)-0 (0%)	91%	0.13	0.289
3. Pain related to internal organ	7 (15%)	5 (11%)	0 (0%)	0 (0%)-0 (0%)	91%	0.25	0.727
Domain 2. Chronic pain	11 (23%)	6 (13%)	0 (0%)	0 (0%)-0 (0%)	74%	0.19	0.388
4. Dyskinetic pain	10 (21%)	15 (32%)	0 (0%)	0 (0%)-3 (25%)	81%	0.52	0.180
5. Off period dystonia in a specific region	27 (57%)	25 (53%)	1 (8%)	0 (0%)-6 (50%)	83%	0.23	0.815
6. Generalized Off period pain	20 (43%)	8 (17%)	0 (0%)	0 (0%)-0 (0%)	62%	0.15	0.008
Domain 3. Fluctuation-related pain	32 (68%)	32 (68%)	6 (17%)	0 (0%)-9 (25%)	70%	0.32	1.000
7. PLM or RLS-associated pain	17 (36%)	7 (15%)	0 (0%)	0 (0%)-0 (0%)	66%	0.02	0.155
8. Pain while turning in bed	27 (57%)	22 (47%)	0 (0%)	0 (0%)-8 (67%)	59%	0.20	0.359
Domain 4. Nocturnal pain	30 (64)	24 (52%)	1 (4%)	0 (0%)-7 (29%)	62%	0.32	0.210
9. Pain when chewing	5 (11%)	2 (4%)	0 (0%)	0 (0%)-0 (0%)	94%	0.54	0.250
10. Pain due to grinding teeth	4 (9%)	1 (2%)	0 (0%)	0 (0%)-0 (0%)	89%	-0.04	0.375
11. Burning sensation in the mouth	2 (4%)	3 (6%)	0 (0%)	0 (0%)-0 (0%)	98%	0.79	1.000
Domain 5. Orofacial pain	8 (17%)	6 (13%)	0 (0%)	0 (0%)-0 (0%)	87%	0.50	0.687
12. Burning pain in the limbs	6 (13%)	4 (9%)	0 (0%)	0 (0%)-0 (0%)	83%	0.11	0.727
13. Generalized lower abdominal pain	11 (23%)	1 (2%)	0 (0%)	0 (0%)-0 (0%)	79%	0.13	0.002
Domain 6. Discoloration, oedema/swelling	16 (34%)	4 (9%)	0 (0%)	0 (0%)-0 (0%)	64%	0.03	0.013
14. Shooting pain/pins & needles	10 (21%)	14 (30%)	0 (0%)	0 (0%)-2 (17%)	70%	0.22	0.424
Domain 7. Shooting pain/pins & needles	10 (21%)	14 (30%)	0 (0%)	0 (0%)-2 (17%)	70%	0.22	0.424
Total score	43 (92%)	42 (90%)	12 (7%)	7 (4%)-24 (14%)	85%	0.14	1.000

KPPQ: King's Parkinson's Disease Pain Questionnaire; KPPS: King's Parkinson's Disease Pain Scale; PLM: periodic limb movements; RLS: restless leg syndrome. [§]We included domains into the KPPQ and ordered the questions of the KPPQ according to the ordering of the KPPS for easy comparison of the two scales. [#]Number and proportion of participants with a positive response (score ≥ 1). [$]Numbers in parentheses are percentages of respective maximum item/domain/total score. [¶]Cohen's κ statistics were used to assess intermethod agreement between dichotomous KPPQ and KPPS pain frequency data. *P values from the McNemar test.

Table 3: Correlations of the KPPQ total score and the KPPS total score ($n = 47$).

	KPPQ total score, ρ	KPPS total score, ρ
With other pain measures		
KPPQ total score	—	0.50***
KPPS total score	0.50***	—
MDS-UPDRS, part I, item 9 (pain)	0.32*	0.40**
PDQ-39 subscore 8 "Bodily discomfort"	0.35*	0.52***
With PD-related measures		
Symptom duration, *years*	0.17	0.21
Disease duration, years	-0.02	-0.03
Duration of fluctuations, *months*	-0.06	-0.08
MDS-UPDRS total score On state	0.11	0.14
Part I	0.17	0.20
Part II	0.09	0.00
Part III	-0.05	0.02
Part IV	0.11	0.20
Hoehn & Yahr staging	0.16	0.13
PDQ-39 sum score	0.42**	0.24*
PDQ-39 subscore 1 "Mobility"	0.43**	0.33*
PDQ-39 subscore 2 "Activities of daily living"	0.32*	0.02
PDQ-39 subscore 3 "Emotional well-being"	0.38**	0.28
PDQ-39 subscore 4 "Stigma"	0.21	-0.06
PDQ-39 subscore 5 "Social support"	0.35**	-0.07
PDQ-39 subscore 6 "Cognition"	0.07	0.17
PDQ-39 subscore 7 "Communication"	-0.12	0.00
Levodopa equivalent dose (LED)	-0.17	-0.20
With other measures		
Beck's Depression Inventory version 2 (BDI-2)	0.20	0.11
MoCA	0.22	0.02

Values are correlation coefficients ρ from Spearman's rank correlation tests. KPPQ: King's Parkinson's Disease Pain Questionnaire; KPPS: King's Parkinson's Disease Pain Scale; MDS-UPDRS: Movement Disorder Society-revised version of the Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; PDQ-39: 39-item Parkinson's disease questionnaire. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ as provided by Spearman's rank correlation analyses.

observed significantly higher frequency × severity total KPPS scores in females as compared to male participants (median (IQR) score of 16 [11–33] in females versus 10 [4–21] in males; $P = 0.013$, Mann–Whitney U test), as well as higher frequency × severity scores in females in the pain subtype domains "D3. Fluctuation-related pain" ($P = 0.048$) and "D4. Nocturnal pain" ($P = 0.039$, both Mann–Whitney U test). Spearman correlation analyses revealed a weak correlation of the total KPPS score with the PDQ-39 sum score, but moderate correlations with the PDQ-39 subscores "Bodily discomfort" and "Mobility" as well as the MDS-UPDRS pain item (Table 3). No associations were detected with the presence/absence of joint or spinal osteoarticular degeneration. Spearman rank correlation analyses revealed no further significant associations between total pain and pain subtype frequency × severity scores and age, disease duration, duration of fluctuations, or disease severity (MDS-UPDRS part III motor score or total score) in our cohort (Table 3).

4. Discussion

The King's Parkinson's disease Pain Questionnaire (KPPQ) is the first specific self-administered pain questionnaire for PD. It is a reliable and valid scale for the assessment of pain in PD patients particularly for use in clinical routine. We, here, report the German version of the KPPQ and its application in a cohort of fluctuating PD patients. Of note, we used accepted standard procedures for intercultural translation and adaptation of patient-administered questionnaires [16, 17] and did not perform a comprehensive psychometric validation of the German version. However, the correlations of the KPPQ results with those of other PD-specific pain assessments as well as the diagnostic parameters of the KPPQ were very similar as compared to the results reported by the previous larger KPPQ validation studies [9, 12, 13].

Pain is a subjective, physiological, and psychological experience, which is further influenced by sociocultural factors [25]. In PD, pain is an important and frequently

reported nonmotor symptom in all disease stages, which has been reported to impair health-related quality of life. Pain has recently received some attention as an early symptom but, foremost, is a major problem in middle and advanced stages of PD. The current prevalence is 40-85% with chronic pain being present in about two-thirds of patients [1]. The wide range of pain prevalence in PD might be related to methodological differences in assessing pain (e.g., different pain assessment tools) and cohort compositions, lack of distinction of pain related and unrelated to PD, and—particularly—differences in the definition of (chronic) pain. In general, chronic pain is currently defined as pain that persists or recurs for longer than three months [26]. In PD, studies applying clear pain classifications distinguishing chronic from intermittent (nonchronic) pain are largely lacking. The herein applied KPPS uses the term "Chronic pain" for its subtype domain 2, although this scale assesses pain only for the last month [7]. Thus, repeated applications of the KPPS or the KPPQ are needed to capture chronic pain in PD according to the current definitions.

Although the data on pain predictors in PD are heterogeneous, major predictors seem to include female gender, longer disease duration, younger age at disease onset, and higher levodopa equivalent daily dose [10, 27, 28]. Nonetheless, it has been challenging to assess pain in PD so far. Previous pain scales have neither been validated for PD nor do they take into account the specific characteristics of this disease. Therefore, the introduction of the KPPS as a quantitative measure of pain for clinical studies and treatment monitoring as well as the KPPQ as a self-administered questionnaire mainly for clinical routine closed a gap and quickly developed into an internationally established test. After first presenting the KPPS in the German language [8], we now translated the PD-specific self-administered questionnaire for pain—the KPPQ—in order to provide an easy and fast instrument to assess the frequency of pain and its subtypes in PD for German patients.

Even though the application of the German version of the KPPQ in our VALIDATE-PD cohort had the main goal to test the usability/practicability of the questionnaire, the results on pain frequencies with a focus on fluctuating PD patients are of special interest. Indeed, 90-92% of patients in our cohort of fluctuating PD reported one or more types of pain. Recently published cross-sectional studies also using the KPPQ or KPPS in patients with PD found that 45-85% of participants experience pain [9, 10, 27, 29–32]. Since general demographic and clinical characteristics of the cohorts in these studies are similar to our cohort, the high prevalence of pain in our cohort might be related to the fact that we only included fluctuating PD patients with a rather long disease duration and did not exclude patients with other types of pain as in most previous studies. However, the fact that the prevalence of "1. Pain around joints" in the present study (62% of patients in both pain assessments) was the same range as that reported in previous studies (53-84% of patients), which excluded patients with conditions potentially associated with PD-unrelated pain such as osteoarthritis [9, 10, 27, 29–32], does not support the notion that our pain data are relevantly confounded by PD-unrelated pain. Since our study as well as most of the previous investigations has only applied the pain assessment tools once to the participants, there are limited data available on the duration and chronicity of PD pain and its subtype. Notable, the term "Chronic pain" herein thus refers only to the pain subtype domain 2 of the KPPS.

Although it is clear from the literature that pain is associated with longer disease duration and is fluctuating with motor fluctuations [1, 5, 10, 27, 28, 33, 34], it still remains enigmatic whether pain is more frequent in fluctuating PD patients. In a previous small study comparing motor nonfluctuators with motor fluctuators, we did not detect any differences in pain frequency using the Non-Motor Symptoms Scale and Questionnaire [35]. A German study using a self-developed PD pain questionnaire displayed also a high frequency of pain with 95% of patients reporting any type of pain [36]. The reason for the high prevalence is not fully clear, because the demographic data of this study is comparable to the other pain studies, and no information on motor fluctuations was reported [36]. Together, we found a high prevalence of pain in fluctuating PD, but there are no conclusive data available on the comparison of nonfluctuating and fluctuating PD with respect to pain frequency and severity.

In our study, the most common type of pain was "D3. Fluctuation-related pain" (68% in both pain instruments), which is in contrast to most previous studies showing "1. Pain around joints" as the most frequent pain subtype (40–84%) [9, 10, 27, 29–32]. This difference most likely reflects the cohort composition in our study, which exclusively selected fluctuating PD patients.

Available data on the influence of gender on pain frequency and severity are inconclusive [7, 9, 10, 27–32], which might not only be related to differences in study designs and sample sizes, but also in the sociocultural background of the various study cohorts [25]. In our KPPQ assessment, we found no association of the total pain frequency and gender, but higher frequency in females of "D3. Fluctuation-related pain" and "D4. Nocturnal pain." Consistent with previous data [12, 27], we detected a moderate association of KPPQ and KPPS sum scores with PDQ-39 as a measure of health-related quality of life. Further predictors of pain in PD might include longer disease duration, younger age at disease onset, higher levodopa equivalent daily doses, and deep brain stimulation, but the data are somewhat contradictory [7, 9, 10, 27, 28, 31, 32, 37, 38]. We did however not find further associations of pain measures and demographic and clinical data in our cohort. This could be related to the rather selected and small-sized patient cohort.

Importantly, both pain assessments have been validated exclusively for pain directly related to PD, and in the initial validation studies as well as in most subsequent reports, only PD patients with no other aetiology for pain, particularly osteoarthritis, were included [7, 10, 12, 27, 29]. This is an important aspect, since up to 30% of the general population experience pain, and excluding all other aetiologies of pain would exclude at least a third of PD patients with pain that could potentially be aggravated in PD. As already discussed, the present study did not explicitly exclude other pain

aetiologies and 30% of participants had joint or spinal osteoarticular degeneration as a major cause of pain. However, we did not observe associations of pain frequency and/or severity with the concomitant diagnosis of osteoarthritis.

This study has several limitations. Firstly, we used accepted standard procedures for intercultural translation and adaptation of patient-administered questionnaires [16, 17] but did not perform a comprehensive psychometric validation of the German version of the KPPQ. We compared the KPPQ results with data of the rater-based KPPS as a gold standard for PD pain assessment and other PD-related measures but did not determine reliability measures such as test-retest or intraclass correlation coefficient (ICC) estimation. Secondly, we applied the German KPPQ to a rather small cohort of highly selected late-stage PD patients suffering from motor complications. This small sample size is due to the difficult recruitment of late-stage PD patients. Together, these special characteristics of our selected cohort limit the results of our study including the validation data to fluctuating PD patients. However, the application of standard procedures for intercultural translation of patient-administered questionnaires in conjunction with the fact that our results are similar to previous results of larger validation studies of the KPPQ in other languages [9, 12, 13] leads us to the assumption that the presented German version of the KPPQ is an intercultural comparable and valid tool to assess pain in PD.

5. Conclusion

We developed a linguistically validated German version of the King's PD pain questionnaire (KPPQ) English original, which has been applied to a cohort of fluctuating PD patients. Although the KPPQ may not take into account the entire complexity of pain in PD and, in many areas, still follow the traditional terminology used in pain therapy but not a mechanism-based classification approach [6], it offers an intercultural comparable, valid, simple, and convenient way of assessing the occurrence of the most commonly observed pain syndromes in PD.

Data Availability

The main data supporting our results in this study are almost all available in the manuscript and Supplementary Information. We are sorry that the raw data from the hospitals cannot be made publicly available because of hospital regulation restrictions and privacy concerns to protect our patients. Anonymized data might be accessible for research purposes from the corresponding author upon reasonable request.

Ethical Approval

The study was approved by the institutional review boards of all participating centers (ethic committee registry numbers A 2017-0115 for Rostock and AS 84 (bB)/2018 for Beelitz-Heilstätten.

Consent

All participants gave written informed consent to participate in the study and were advised both orally and in writing of the nature of the study.

Conflicts of Interest

M. Löhle has received honoraria for presentations from Novartis Pharma. W.H. Jost has received honoraria from AbbVie, BIAL, Merz, STADA/Britannia, and Zambon outside the submitted work. A. Bremer has nothing to disclose. F. Gandor has received honoraria from AbbVie, BIAL, Merz, and STADA outside the submitted work. A. Rizos has received salary support from the National Institute of Health Research (NIHR) Clinical Research Network (CRN) South London and the International Parkinson and Movement Disorder Society (MDS) and honorarium from Britannia Pharmaceuticals Ltd. P. Martinez-Martin has received honoraria from Bial, for participation in a course, and from the International Parkinson and Movement Disorder Society for activities during the International Congress 2022 and for directing the Clinical Outcome Assessment Program. K.R. Chaudhuri has received funding from Bial and Scion, Britannia Pharmaceuticals, AbbVie, UCB, GKC Britannia Pharmaceuticals, AbbVie, UCB, GKC as well as EU Horizon program, Parkinson's UK, NIHR, Parkinson's Foundation, Wellcome Trust, Kirby Laing Foundation, and MRC. He has received honoraria for lectures, expert advice or expert testimony from AbbVie, Britannia Pharmaceuticals, UCB, Zambon, Novartis, Boehringer Ingelheim, Bial, Kyowa Kirin, SK Pharma, GKC, GMC, Cynapsus, Lobsor, Stada, Zambon, Profile Pharma, Synovion, Roche, Theravance Biopharma, Scion, Acadia, 4D Pharma, and Medtronic. He has received royalties from Oxford University Press, Cambridge Publishers, and MAPI Institute. P. Odin has received funding from AbbVie, Lund University Medical Faculty, Multipark, the Swedish Parkinson Foundation, Health Care Region Skåne, and Åhlens Foundation. He has received honoraria for lectures and expert advice from AbbVie, Bial, Britannia, Ever Pharma, Global Kinetics, Lobsor, Nordic Infucare, Stada, and Zambon. He has received royalties from UNIMED Verlag. G. Ebersbach has received honoraria for advisory boards, consultancy, and presentations from AbbVie Pharma, BIAL, Biogen GmbH, Desitin Pharma, STADA Pharma, Neuroderm Inc., Licher GmbH, UCB Pharma, and Zambon Pharma. He has received royalties from Kohlhammer Verlag and Thieme Verlag. A. Storch has received funding from the Deutsche Forschungsgemeinschaft (German Research Association) and the Helmholtz-Association outside the present study. He has received honoraria for presentations/advisory boards/consultations from Global Kinetics Corporation (manufacturer of the PKG®), Desitin, Lobsor Pharmaceuticals, STADA, Bial, RG Gesellschaft, Zambon, Novo Nordisk, and AbbVie outside the present study. He has received royalties from Kohlhammer Verlag and Elsevier Press. He serves as an editorial board member of Stem Cells International.

Authors' Contributions

Conceptualization was conducted by M.L., W.H.J., A.B., A.R., P.M.-M., K.R.C., P.O., G.E., and A.S. Funding acquisition was conducted by P.O. and A.S. Organization of research was conducted by M.L., A.B., P.O., and A.S. Execution of research/clinical assessments was conducted by M.L., W.H.J., A.B., F.G., G.E., and A.S. Data curation was conducted by M.L., W.H.J., and A.S. Translation of questionnaire was conducted by M.L., W.H.J., A.R., P.M.-M., K.R.C., P.O., and A.S. Statistical methodology was conducted by M.L. and A.S. Execution of statistical analyses was conducted by M.L. and A.S. Writing of the original draft was conducted by A.S. Manuscript review and editing were conducted by M.L., W.H.J., A.B., F.G., A.R., P.M.-M., K.R.C., P.O., and G.E. All authors have read and agreed to the published version of the manuscript. The corresponding author had the final responsibility for the decision to submit for publication.

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Supplementary Materials

Supplementary Table S1: estimation of the screening potential of pain items and domains of the KPPQ when using the KPPS as the gold standard external criterion. Supplementary Figure S1: German version of the King's Parkinson's disease Pain Questionnaire (KPPQ). *(Supplementary Materials)*

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