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ARTICLE

Fatigue in Parkinson's disease: Brazilian validation of the modified fatigue impact scale

Fadiga na doença de Parkinson: validação brasileira da escala modificada de impacto da fadiga

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ABSTRACT

Background: The instruments that measure the impact of fatigue on physical, cognitive and psychosocial aspects has yet to be validated in Brazilian population with Parkinson's disease (PD). The aim of this study was to cross-culturally adapt and assess the psychometric properties of the Brazilian version of the Modified Fatigue Impact Scale (MFIS-PD/BR). **Methods:** Ninety PD individuals were recruited. The adaptation of the MFIS-PD was performed by translation and back translation methodology. Psychometric analysis was applied in order to perform the administration of the socio-clinical questionnaire, Mini-Mental State Examination (MMSE), Unified Parkinson's Disease Rating Scale (UPDRS Part I-IV), Hoehn-Yahr disability scale (HY), hospital anxiety and depression scale (HADS), Geriatric Depression Scale (GDS), fatigue severity scale (FSS), Parkinson Fatigue Scale (PFS-16), and MFIS-PD/BR with retest of the MFIS-PD/BR after 7 days. **Results:** The adaptation phase kept the same items of original MFIS-PD. The Cronbach's alpha for the MFIS-PD/BR was 0.878 when all responses items were scored. The test-retest intraclass correlation coefficients was above 0.80 ($p<0.01$) for the MFIS-PD/BR score, which was moderately correlated with the HADS, GDS, MDS-UPDRS score total and non-motor experiences of daily living, FSS and PFS-16. It was revealed the MFIS-PD/BR>29 points as cut-off point to indicate fatigued subjects with accuracy of 0.835 ($p<0.001$). **Conclusions:** The MFIS-PD/BR is valid and reproducible to use in assessing the fatigue symptom in Brazilian PD subjects.

Keywords: Parkinson Disease; Fatigue; Validation Studies; Psychometrics.

RESUMO

Introdução: Os instrumentos que mensuram o impacto da fadiga nos aspectos físicos, cognitivos e psicossociais ainda não foram validados na população brasileira com doença de Parkinson (DP). O objetivo deste estudo foi adaptar culturalmente e avaliar as propriedades psicométricas da versão brasileira da escala modificada de impacto da fadiga (MFIS-PD/BR). **Métodos:** Setenta indivíduos com DP foram recrutados. A adaptação do MFIS-PD foi realizada pela metodologia de tradução e retrotradução. Na análise psicométrica foi realizada a administração de questionário socioclínico, Miniexame do estado mental (*Mini-Mental State Examination* — MMSE), Escala Unificada de Avaliação da DP (*Unified Parkinson's Disease Rating Scale* — UPDRS Parte I-IV), escala de incapacidade Hoehn-Yahr (HY), escala hospitalar de ansiedade e depressão (*Hospital Anxiety and Depression Scale* — HADS), escala de depressão geriátrica (*Geriatric Depression Scale* — GDS), escala de gravidade da fadiga (*Fatigue Severity Scale* — FSS), escala de fadiga de Parkinson (*Parkinson Fatigue Scale* — PFS-16) e a MFIS-PD/BR com reteste após 7 dias. **Resultados:** A fase de adaptação manteve os mesmos itens do MFIS-PD original. O coeficiente alfa de Cronbach para o MFIS-PD/BR foi de 0,878 quando todos os itens das respostas foram pontuados. Os coeficientes de correlação intraclasse teste-reteste foram superiores a 0,80 ($p<0,01$) para o escore MFIS-PD/BR, que foi moderadamente correlacionado com o escore HADS, GDS, MDS-UPDRS, total e aspectos não-motores da vida diária, FSS e PFS-16. Foi revelado o ponto de corte do MFIS-PD/BR>29 pontos para indicar indivíduos fatigados com acurácia de 0,835 ($p<0,001$). **Conclusões:** O MFIS-PD/BR é válido e reprodutível para a avaliação do sintoma de fadiga em indivíduos brasileiros com DP.

Palavras-chave: Doença de Parkinson; Fadiga; Estudos de Validação; Psicometria.

INTRODUCTION

Fatigue is one of the most common and bothersome non-motor symptoms in Parkinson's disease (PD)[1,2,3] with prevalence estimates ranging from 15 to 78%[4,5]. It may manifest even during premotor stages of the disease and negatively impacts patients' quality of life[6].

Measuring fatigue is a difficult task. There is no universally accepted definition[1,7]. Common definitions include a sense of exhaustion or a subjective lack of physical and/or

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mental energy perceived by the individual, which interferes with usual or desired activity[4,8]. It is a complex and highly subjective symptom with many uncertainties regarding its pathophysiology. It is generally accepted that fatigue is multidimensional and may be comprised of distinct constructs including physical and cognitive aspects[4].

Specific diagnostic criteria for defining PD-related fatigue have been recently proposed to facilitate fatigue-related patient disability claims and medication coverage, and guide participant selection for clinical trials[2]. This variability of prevalence estimates is mostly due to the different instruments used to measure it[4]. For this reason, the assessment of fatigue severity in clinical and research contexts should be performed by standardized tools. The most prevalent method of assessing fatigue is by self-report rating instruments[9].

The International Movement Disorders Society (IMDS) task force on fatigue-rating scales reviewed all nine fatigue-specific rating instruments that had been used in previous PD studies[7]. Only three scales, the Fatigue Severity Scale (FSS)[10], Parkinson Fatigue Scale (PFS-16)[11], and Multidimensional Fatigue Inventory (MFI)[12] were "recommended" for rating fatigue severity in PD. FSS and PFS-16 are one-dimensional instruments expressing a limited assessment of fatigue. MFI is a multidimensional instrument, however with focus on cancer-related fatigue aspects due to be developed originally for these patients. IMDS acknowledged that their recommendations were limited by the lack of published studies on certain scales[7], suggesting that research on alternative measures of fatigue in PD may be warranted. Schiehser et al.[9] subsequently provided validation of the Modified Fatigue Impact Scale (MFIS) for PD population, a scale which was not included in the IMDS manuscript[7,10].

MFIS[9] is a 21-item self-report measure of fatigue derived from the 40-item Fatigue Impact Scale (FIS)[13]. Originally, it was developed to assess fatigue in people with multiple sclerosis in clinical practice and researches[14]. In contrast to FSS, PFS-16, and MFI, MFIS is a multidimensional measure that assesses the impact of fatigue on physical, cognitive, and psychosocial functions. In addition, MFIS contains six additional items on each of the cognitive and physical subscales compared to MFI, suggesting the possibility of a stronger and more thorough assessment of these factors.

In Brazil, FSS[15] and PFS-16[16] have been widely used, despite the failings of their design and psychometric properties in Brazilian cross-cultural adaptation studies. These Brazilian versions did not fulfill the criteria for adequate sample size and design. Moreover, the psychometric properties of the Brazilian FSS adaptation were not assessed. This study was designed considering the quality of existing instruments, the lack of Brazilian PD-specific instrument for assessing fatigue with reported methodological and psychometric properties of design and administration that can satisfy the current standards for outcome measurements. The aim of the present study was to cross-culturally adapt and assess the psychometric properties of a Brazilian version of MFIS-PD.

METHODS

Design, location and setting

An observational cross-sectional study following the criteria proposed by Beaton et al.[17].

Participants were recruited from the physical therapy outpatient clinic at the Universidade Estadual de Londrina (State University of Londrina) in association with the Agape Social Care Center in Londrina, PR, Brazil. The study was approved by the Ethics Committee of the Universidade Estadual de Londrina, University Hospital (Opinion report No. 2.481.213). All participants voluntarily agreed to participate in the study and provided informed consent.

Participants

The study comprised a convenience sample including 90 individuals diagnosed with idiopathic PD by a board-certified neurologist specializing in movement disorders. The sample size was estimated in accordance with the criteria recommended for adaptation (20 subjects) and for validation study design (70 subjects)[17].

To be included in the study, participants must meet the following criteria: aged 50 years or older; diagnosis of idiopathic PD using the UK Brain Bank criteria[18]; Brazilian nationality; rated stage I-IV on Hoehn and Yahr disability scale (HY)[19]; regular use of antiparkinsonian medication; able to walk independently without gait aids; score ≥24 on the Mini-Mental Status Examination (MMSE)[20].

Individuals presenting other types of Parkinsonism or other associated neurological diseases, vestibular, cardiovascular, musculoskeletal, cognitive or comprehension disorders, visual or auditory impairment that could affect motor performance, or under treatment other than drug therapy or had surgery for PD such as deep brain stimulation were excluded. Individuals who missed the second interview or whose medication changed over the course of the study were considered losses.

Instrument

Modified Fatigue Impact Scale

MFIS measures the impact of fatigue on functioning by having participants rate 21 items on a scale from 0 (never) to 4 (almost always). Scores range from 0 to 84, with higher scores indicating greater impact of fatigue. The items can be aggregated into a total score (21 items) as well as three subscales: physical (9 items), cognitive (10 items), and psychosocial (2 items)[9].

Procedures

Patients were assessed using a socio-clinical questionnaire, MMSE[20], Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS, Part I-IV)[21], HY[19] by same examiner. Thus, they were included either in phase 1 or phase 2 of the study, according to the sequence of recruitment. All assessments were performed in the subjects at the same time of the day in the "on" phase of antiparkinsonian medication (approximately 1 hour after medication intake).

Phase 1: Cross-cultural adaptation of Modified Fatigue Impact Scale-Parkinson's Disease

MFIS was culturally adapted from English to Brazilian Portuguese language in accordance with the guidelines proposed by Beaton et al.[17]. The translations were performed by two native Portuguese translators independently. The translations were synthesized into a single Portuguese version by the translators and a third person (a healthcare professional). Subsequently, this Portuguese version was back-translated into English independently by two American translators. The backward translations were synthesized by the translators and compared with the MFIS[9]. The forward and backward translations were submitted to a bilingual expert committee (biostatistician, linguist, neurologists, psychologist, and physiotherapist) to analyze the equivalences. Subsequently, a trained interviewer administered the Brazilian version of MFIS (MFIS-PD/BR) to 20 PD subjects, in order to verify their comprehension of the instrument. At the end of this process, the MFIS-PD/BR was ready for psychometric testing [Additional file 1].

The content validity was assessed by the expert committee, by verifying the conceptual, cultural, idiomatic, and semantic equivalences between MFIS-PD/BR and MFIS[9]. The group of 20 patients enrolled into cross-cultural adaptation only answered whether understood the items. This is only a small part of content validity that also includes face validity and extends to the degree to which the content of a questionnaire is adequate to be measured[17,22].

Phase 2: Assessment of psychometric properties

In this phase, 70 PD subjects were assessed. Testing-retesting was applied by examiners A and B, which administered MFIS-PD/BR separately with a one-hour interval; seven days later, examiner A performed the retest. Additionally, subjects also answered the Geriatric Depression Scale (GDS)[23], Hospital Anxiety and Depression Scale (HADS)[24], FSS[15], and PFS-16[16] to examiner B in a separate room. The time taken was recorded by a digital chronometer.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS®, Release 20.0) and MedCalc® (Release 19.1.3). The normality of data distribution was checked by means of the Shapiro-Wilk test. Based on the Instrument Review Criteria[25], the psychometric properties of the MFIS-PD/BR were analyzed. To consider data quality and acceptability satisfactory, missing data should comprise <5% of the data set[26]. The time taken to apply the MFIS-PD/BR and the score distributions of floor and ceiling effects were also taken into consideration in assessing the acceptability. A floor or ceiling effect was present if more than 15% of patients achieved the lowest or highest score in a questionnaire[27].

Cronbach's alpha was used to examine the internal consistency of items. It was analyzed by the measure of the average correlations among all items. Cronbach's alpha, item-total, and mean inter-item correlations were computed to ascertain internal consistency of MFIS for each scoring method. The rules of thumb provided by George and Mallery[28] were used to evaluate acceptability of Cronbach's alpha: alpha > 0.90 — excellent; > 0.80 — good; > 0.70 — acceptable; > 0.60 — questionable; < 0.50 — unacceptable.

Reliability was examined by the reproducibility and measurement error. Reproducibility was tested by means of testing-retesting using the intraclass correlation coefficient (ICC) and the Bland-Altman method with mean differences. ICC was calculated in two-way random effects model for agreement with optimal values were taken ICC≥0.70. Measurement error was assessed by calculating the standard error of the measurement (SEM). SEM agreement was derived from the error variance in the ICC formula[27].

The construct validity was tested through correlations between the MFIS-PD/BR and subscale scores of other instruments considering convergent validity and divergent validity. To evaluate convergent validity, the MFIS-PD/BR total score was compared to the FSS and PFS-16. To evaluate divergent validity, the MFIS-PD/BR total score was compared to several measures of disease related symptoms and disability (MDS-UPDRS, HY), psychological functioning (HADS, GDS) and cognitive performance (MMSE). Correlations were estimated using Pearson's (*rs*) or Spearman's correlation coefficients (*rho*). Coefficient values of 0.25 to 0.49 were deemed low correlations, values of 0.50 to 0.75 were moderate and values >0.75 were deemed high correlations[29].

A receiver operating characteristic (ROC) curve was drawn to provide a sensitivity, specificity ratio and accuracy of MFIS-PD/BR. For the clinical diagnosis of fatigue, it was considered the PFS-16≥3.3 points as cut-off point to indicate on diagnostic criteria for fatigue related PD[2].

The total amount of dopaminergic medication was expressed as the levodopa equivalent daily dosage (LEDD), determined by previously reported methods[6].

RESULTS

Ninety PD individuals were enrolled in the study (Table 1). The median disease duration is more than 50 months.

The MDS-UPDRS mean score indicated a moderate to severe impairment. More than 45% of sample showed clinically relevant fatigue (Table 2). The translation and back-translation versions were similar to the MFIS-PD original[9]. Use of the word 'fatigue' was avoided due to semantic ambiguity. Full equivalences of the MFIS-PD/BR were achieved. In pretesting, no subject demonstrated any problem in understanding the MFIS-PD/BR confirming the content and face validity. The MFIS-PD/BR kept the same number and allocation of items, domains, format and response patterns as original version[9]. It was completed in a median time of 2 minutes and 17 seconds (3.1–4.1). There were no missing data, ceiling (4.78% — first interview, 4.17% — retest), and nor floor effects (3.86% — first interview, 3.74% — retest).

The presence of clinical significant fatigue associated with increased scores in HADS total, HADS anxiety and HADS depression and GDS. Individuals with major disability (HY) and impairment (MDS-UPDRS total, part I, II and IV) scored higher in PFS-16. Medications (levodopa, dopaminergic drugs or antidepressants) did not associate with fatigue (Table 2).

The Cronbach's alpha for the MFIS-PD/BR was 0.878 when all responses items were scored. All item-total correlations were acceptable (Table 3). The mean inter-item correlation was 6.604 (Table 3). Good reliability was demonstrated. There was high agreement and small mean intra and interobserver differences (Table 4).

Table 1. Demographic and clinical characteristics for sample.

Variable	Adaptation sample (n=20)	Validation sample (n=70)
Demographics		
Age, years	63.80±6.47	68.40±10.21
Education, years	8 (4.25–11)	8 (4–12.75)
Sex (male: female)	13: 7	45: 25
Clinical features		
Disease duration, months	51 (31–92.75)	56.50 (27.25–96.25)
MMSE	27.50 (25.25–28.75)	26 (25–28)
HADS anxiety	5.85±2.99	6.76±3.77
HADS depression	6.30±3.18	6.73±3.16
HADS total score	12.15±5.20	13.50±5.83
GDS total score	3.5 (2–6.75)	4 (2–7)
HY, stage	2 (2–2.5)	2 (2–2.5)
HY, stage: 1/1.5/2/2.5/3/4/5 (n)	0/3/7/6/4/0/0	5/6/32/12/15/0/0
MDS-UPDRS – part I score	16.25±11.24	13.95±9.11
MDS-UPDRS – part II score	16.35±8.29	15.31±7.73
MDS-UPDRS – part III score	33.10±10.46	36.85±14.57
MDS-UPDRS – part IV score	5.20±5.47	4.75±5.03
MDS-UPDRS total score	70.90±27.90	70.87±28.56
LEDD (mg/ day)	519 (312.50–850)	500 (300–856.25)
Fatigue measures		
FSS total score	4.26±1.39	3.70±1.39
PFS-16 total score	3.20±0.83	3.03±0.80
MFIS-PD total score	31.05±19.91	30.25±17.81

n: number of individuals; MMSE: Mini-Mental State Examination; HADS: hospital anxiety depression scale; GDS: Geriatric Depression Scale; HY: modified Hoehn & Yahr stage; MDS-UPDRS: Movement Disorder Society - Unified Parkinson's Disease Rating Scale; LEDD: Levodopa Equivalent Daily Dosage; FSS: Fatigue Severity scale; PFS-16: Parkinson Fatigue Scale; MFIS-PD: Modified Fatigue Impact Scale.

Table 2. Comparison of Parkinson's disease fatigued and non-fatigued individuals.

Variable	Fatigued (n=32)	Non-fatigued (n=38)	p-value
Demographics			
Age, years	68.20±9.53	68.52±10.72	0.90
Education, years	9 (4–14.5)	8 (4–11)	0.52
Sex (male: female)	21 (65.6%): 11 (34.3%)	24 (63.1%): 14 (36.8%)	0.68
Clinical features			
Disease duration, months	63 (48 - 89.75)	51 (17.75–111)	0.21
MMSE	26 (23.25-27.75)	26.50 (25–28.75)	0.24
HADS anxiety	8.20±3.30	5.90±3.80	0.01
HADS depression	8.62± 2.84	5.60 ±2.81	0.00
HADS total score	16.83±4.77	11.50±5.53	0.00
GDS total score	5.5 (3.25–9)	3.5 (2–6)	0.01
HY, stage	2.37±0.64	2.03±0.52	0.02
MDS-UPDRS – part I score	20.75± 8.69	9.87±6.63	0.00
MDS-UPDRS - part II score	18.87±8.14	13.17±6.71	0.00
MDS-UPDRS – part III score	39.37±15.53	35.35±13.95	0.28
MDS-UPDRS – part IV score	6.91±5.80	3.45±4.05	0.00
MDS-UPDRS total score	85.91±29.68	61.85±23.98	0.00
LEDD (mg/ day)	500 (300–737.50)	487.50 (300–893.75)	0.81
Fatigue measures			
FSS total score	4.75±1.17	3.06±1.10	0.00
PFS-16 total score	3.84±0.45	2.55±0.52	0.00
MFIS-PD total score	42.87±17.55	22.67±13.19	0.00

n: number of individuals; MMSE: Mini-Mental State Examination; HADS: Hospital Anxiety Depression Scale; GDS: Geriatric Depression Scale; HY: Hoenh & Yahr, stage; MDS-UPDRS: Movement Disorder Society - Unified Parkinson's Disease Rating Scale; LEDD: Levodopa Equivalent Daily Dosage; FSS: Fatigue Severity Scale; PFS-16: Parkinson Fatigue Scale; MFIS-PD: Modified Fatigue Impact Scale.

*Presence of fatigue was identified by means of the PFS-16 cut-off point ≥3.3 points.

The MFIS-PD/BR correlated moderately with the instruments (total score) used to assess anxiety and depression (HADS, GDS), impairment (UPDRS score total and non-motor experiences of daily living) and fatigue (FSS, PFS-16) (Table 5). Anxiety, disability (HY), impairment (motor experiences of daily living, motor examination and motor complications) showed a low positive correlation with MFIS-PD/BR, whereas cognitive performance showed a low negative correlation with MFIS-PD/BR. In other words, higher anxiety, disability, lower cognitive performance, more severe or advanced disease were all associated with more fatigue. Analysis on ROC curve revealed the MFIS-PD/BR > 29 points as cut-off point to indicate fatigued subjects (Figure 1).

Table 3. Corrected item-total correlations and Cronbach's alpha (α) if item is deleted from the Modified Fatigue Impact scale (MFIS/PD-BR).

MFIS/PD-BR - Item	Mean (SD)	CITC	α
1. I have been clumsy and uncoordinated.	0.90 (0.95)	0.401	0.851
2. I have had to pace myself in my physical activities.	2.18 (1.61)	0.056	0.855
3. I have been less motivated to do anything that requires physical effort.	1.37 (1.32)	0.675	0.848
4. I have trouble maintaining physical effort for long periods.	1.45 (1.33)	0.683	0.848
5. My muscles have felt weak	1.93 (1.52)	0.544	0.849
6. I have been physically uncomfortable.	1.71 (1.37)	0.570	0.849
7. I have been less able to complete tasks that require physical effort.	1.71 (1.30)	0.693	0.848
8. I have limited my physical activities.	1.60 (1.51)	0.735	0.846
9. I have needed to rest more often or for longer periods.	1.71 (1.53)	0.622	0.848
10. I have been less alert	1.18 (1.18)	0.680	0.848
11. I have had difficulty paying attention for long periods of time.	1.25 (1.33)	0.700	0.848
12. I have been unable to think clearly.	1.15 (1.23)	0.622	0.849
13. I have been forgetful.	1.64 (1.37)	0.503	0.849
14. I have had difficulty making decisions	0.90 (1.19)	0.566	0.849
15. I have been less motivated to do anything that requires thinking	1.29 (1.32)	0.747	0.847
16. I have had trouble finishing tasks that require thinking.	1.14 (1.46)	0.738	0.847
17. I have had difficulty organizing my thoughts when doing things at home or at work.	1.09 (1.34)	0.805	0.847
18. My thinking has been slowed down.	1.65 (1.43)	0.675	0.847
19. I have had trouble concentrating.	0.98 (1.09)	0.668	0.849
20. I have been less motivated to participate in social activities.	1.59 (1.43)	0.647	0.848
21. I have been limited in my ability to do things away from home.	1.71 (1.65)	0.629	0.847

SD: standard deviation; CITC: Corrected item-total correlation; α: measure if item deleted.

DISCUSSION

This study presents the first attempt to provide the Brazilian validation of MFIS investigating its psychometric properties in individuals with idiopathic PD. The MFIS appears to be a promising measure for evaluating fatigue in PD[4].

Each society has its own beliefs and behavior and, in the cross-cultural adaptation process these particularities must be considered[30].The steps for the cross-cultural adaptation process proposed[17] were followed and all equivalences, content and face validity between the original MFIS[9] and MFIS-PD/BR were achieved. The cross-cultural adaptation of MFIS-PD/BR kept similar results of equivalences as the Brazilian version of MFIS adapted to multiple sclerosis patients performed by Pavan et al.[31].Through assuring these equivalences, it was expected to maintain the psychometric properties of the MFIS-PD/BR as properly documented in prior study[9].

For an instrument to be considered appropriate for clinical or research use, it is necessary to evaluate, at least, its acceptability, reliability, and validity[30,32]. MFIS-PD/BR showed a good level of acceptability and required few minutes to fill out. Acceptability is supported when the scores observed are also well distributed[25]. There is no information about the acceptability property in validation process of MFIS in PD in other idioms.

The reliability of the MFIS-PD/BR was good and showed small SEM on all domains. The SEM allows one to make statements about the precision of test scores of individual examinees. The lower the difference, the better is an instrument to obtain more realistic scores[27]. The Bland-Altman analysis demonstrated that there was low individual variability with satisfactory limits of agreement, such that the subjects answered the items similarly seven days later. These results suggest that the MFIS-PD/BR is a stable instrument with low systematic difference indicating good concordance between the first and the last interview and the two observers. The original MFIS[9] did not show the Bland-Altman analysis.

A valid instrument, it truly reflects the concept that it should measure[22]. Investigating the validity of PD fatigue instruments is a complex task due the unclear definition and multidimensional factors. There are three main different aspects of validity: content, criterion, and construct validity[33]. Content and face validity have already been commented when describing the stage of cross-cultural adaptation. Since no gold standard exists for fatigue instruments,

Table 4. Reproducibility of the MFIS-PD/BR.

MFIS/PD-BR (subscale)	ICC	[95% CI]	SEM	Bland-Altman			
				d	95%CI of d	SD of d	95%LC
MFIS (Physical)							
Intra-observer	0.88	0.81 - 0.93	2.84	-0.18	-1.39 -1.01	0.75	-11.69 – 11.32
Interobserver	0.86	0.77 - 0.91	5.52	-1.31	-2.66 - 0.03	0.05	-14.22 – 11.59
MFIS (Cognitive)							
Intra-observer	0.96	0.93 - 0.97	1.96	-0.57	-1.51 - 0.35	0.22	-9.50 – 8.34
Interobserver	0.92	0.87 - 0.95	5.60	-1.32	-2.68 - 0.03	0.05	-14.32 – 11.66
MFIS (Psychosocial)							
Intra-observer	0.89	0.84 - 0.93	1.12	0.15	-0.50 - 0.81	0.63	-6.14 – 6.45
Interobserver	0.84	0.75 - 0.90	2.06	-0.15	-0.65 - 0.34	0.53	-4.95 – 4.64
MFIS (Total)							
Intra-observer	0.93	0.88 - 0.95	8.84	-0.60	-2.80 -1.58	0.58	-21.56 – 20.34
Interobserver	0.92	0.88 - 0.95	9.93	-2.79	-5.15 - (-0.44)	0.02	-25.31 – 19.72

MFIS-PD: Modified Fatigue Impact Scale; ICC: Intraclass correlation coefficient; CI: confidence interval; SEM: standard error of measurement *d*: mean difference; SD: standard deviation; LC: limits of agreement.

Table 5. Correlation between MFIS-PD/BR and other variables.

Variable	MFIS-PD/BR Correlation	p-value
Demographics		
Age, years	0.10⁺	0.43
Education, years	-0.03⁺⁺	0.78
Sex (male; female)	-0.14⁺	0.24
Clinical features		
Disease duration, months	0.06⁺⁺	0.60
MMSE	-0.33⁺⁺	0.00
HADS anxiety	0.26⁺	0.03
HADS depression	0.64	0.00
HADS total score	0.52	0.00
GDS total score	0.56⁺	0.00
HY, stage	0.32⁺	0.01
MDS-UPDRS – part I score	0.64⁺	0.00
MDS-UPDRS – part II score	0.33⁺	0.00
MDS-UPDRS – part III score	0.29⁺	0.01
MDS-UPDRS – part IV score	0.36⁺	0.00
MDS-UPDRS total score	0.51⁺	0.00
LEDD (mg/ day)	0.00⁺⁺	0.99
Fatigue measures		
FSS total score	0.56⁺	0.00
PFS-16 total score	0.71⁺	0.00

⁺Pearson correlation; ⁺⁺Spearman correlation.
MFIS-PD: Modified Fatigue Impact Scale; MMSE: Mini-Mental State Examination; HADS: Hospital Anxiety Depression Scale; GDS: Geriatric Depression Scale; HY: Hoenh & Yahr, stage; MDS- UPDRS: Movement Disorder Society - Unified Parkinson's Disease Rating Scale; LEDD: Levodopa Equivalent Daily Dosage; FSS: Fatigue Severity Scale; PFS: Parkinson Fatigue Scale.

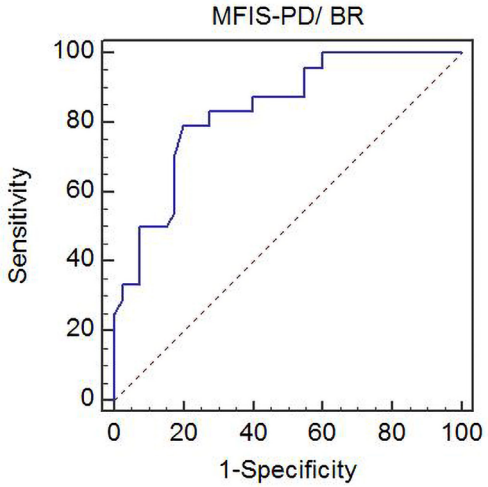

Figure 1. Receiver operating characteristic (ROC) curve and the cut-off point for MFIS-PD/BR to detect fatigue in PD subjects (n=70). Sensitivity=79.2%; 1-Specificity=80%; Standard error=0.05; Accuracy=0.83 [0.72–0.91] (p<0.001).

criterion validity was not evaluated. Construct validity was defined as the degree to which scores of a questionnaire are consistent with other instruments which measures the similar (convergent validity) or associated (divergent validity) constructs[22]. Convergent validity of MFIS-PD/BR was established with the FSS and PFS-16, suggesting a moderate level of association. In contrast, Schiehser et al.[9] evidenced the strong level of association of MFIS with the fatigue subscale of the Positive and Negative Affect Schedule (PANAS-X)[34]. There is no Brazilian validated PANAS-X limiting its administration on this current study.

The adequate divergent validity was established between MFIS-PD/BR and motor and non-motor symptoms, cognitive performance, disease severity, anxiety, and depression. MFIS did not correlate with sex, age, education, disease duration, and antiparkinsonian medicine. These results are in line with data showed by the study that validated the MFIS for PD[9], except the weak association between levodopa levels and fatigue. In the present study, the individuals reported the dose of levodopa levels and many of them use other antiparkinsonian medicine associated. Other studies also confirmed the association of the presence or severity of fatigue (HY) and LEDD[35,36,37].

Data concerning factors associated with fatigue in PD are still scarce and contradictory. In contrast of results of the present study, some studies have found association between fatigue and education level, time from diagnosis, female gender, advanced age, severity of PD, and advanced HY disease stages[16,37,38]. Similar to the current study, low-to-high correlations were found between the fatigue (PFS-16) and depression measures[16,39,40] and anxiety assessments[16,40].

Before the current study, no cut-off point for the MFIS-PD had been calculated. It was stated that it is impossible to calculate the sensitivity and specificity because of the absence of a gold standard instrument which measure fatigue symptom[9]. Therefore, it was used PFS-16 to screen who feels fatigue associated PD to drawn the ROC curve because PFS-16 captures the effects of fatigue considering the subjective experience of fatigue and the impact of this symptom on daily functioning, such as socialization and work[37] as the similar domain of MFIS-PD.

Some limitations of this study need to be pointed out. These include the monocentric design and the sample. It is important to observe that the sample of the present study was fairly early in disease course, suggesting that generalizability of these results to more advanced PD patients may be limited. Moreover, the lack of a control group of healthy participants did not allow the comparison of the fatigue severity between PD patients and the general population. Another limitation is that FSS and PFS-16 were used as comparator instruments despite their problems regarding reliability and validity. These were administered in the present study because there was no other Brazilian specific instrument for assessing PD fatigue. With regard to use of the HADS and GDS instruments, it is important to emphasize that they are generic measurements, and may fail to address important areas of impact that are disease-specific.

Nonetheless, the present study supported the reliability and validity of MFIS for PD individuals in Portuguese version spoken in Brazil that satisfies the modern standards for outcome measurements relating to the symptom of fatigue in PD. It contains the relevant psychometric properties to assess fatigue in PD, can be administered rapidly and is easily comprehended. It can be used in clinical settings as well as in any design of research study thus promoting their use in cross-sectional and longitudinal clinical studies and fostering cross-cultural studies for a deeper understanding of this distressing, common, and underestimated non-motor symptom.

References

1. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. Neurology. 2013 Jan;80(4):409-16. https://doi.org/10.1212/WNL.0b013e31827f07be
2. Kluger BM, Herlofson K, Chou KL, Lou JS, Goetz CG, Land AE, et al. Parkinson's disease-related fatigue: a case definition and recommendations for clinical research. Mov Disord. 2016 May;31(5):625-31. https://doi.org/10.1002/mds.26511
3. Herlofson K, Kluger BM. Fatigue in Parkinson's disease. J Neurol Sci. 2017 Mar;374:38-41. https://doi.org/10.1016/j.jns.2016.12.061
4. Siciliano M, Trojano K, Santangelo G, De Micco R, Tedeschi G, Tessitore A. Fatigue in Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2018 Nov;33(11):1712-23. https://doi.org/10.1002/mds.27461
5. Kluger BM, Garimella S, Garvan C. Minimal clinically important difference of the Modified Fatigue Impact Scale in Parkinson's disease. Parkinsonism Relat Disord. 2017 Oct;43:101-104. https://doi.org/10.1016/j.parkreldis.2017.07.016
6. Stocchi F, Abbruzzese G, Ceravolo R, Cortelli P, D'Amelio M, De Pandis MF, et al. Prevalence of fatigue in Parkinson disease and its clinical correlates. Neurology. 2014 Jul;83(3):215-20. https://doi.org/10.1212/WNL.0000000000000587
7. Friedman JH, Alves G, Hagell P, Marinus J, Marsh L, Martinez-Martin P, et al. Fatigue rating scales critique and recommendations by the Movement Disorders Society task force on rating scales for Parkinson's disease. Mov Disord. 2010 May;25(7):805-22. https://doi.org/10.1002/mds.22989
8. Spirgi S, Meyer A, Calabrese P, Gschwandtner U, Fuhr P. Effects of cognitive performance and affective status on fatigue in Parkinson's disease. Dement Geriatr Cogn Disord Extra. 2019;9(3):344-51. https://doi.org/10.1159/000498883
9. Schiehser DM, Ayers CR, Liu L, Lessig S, Song DS, Filoteo JV. Validation of the Modified Fatigue Impact Scale in Parkinson's disease. Parkinsonism Relat Disord. 2013 Mar;19(3):335-8. https://doi.org/10.1016/j.parkreldis.2012.11.013
10. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989 Oct;46(10):1121-3. https://doi.org/10.1001/archneur.1989.00520460115022
11. Brown RG, Dittner A, Findley L, Wessely SC. The Parkinson fatigue scale. Parkinsonism Relat Disord. 2005 Jan;11(1):49-55. https://doi.org/10.1016/j.parkreldis.2004.07.007
12. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995 Apr;39(3):315-25. https://doi.org/10.1016/0022-3999(94)00125-o
13. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994 Jan;18 Suppl 1:S79-83. https://doi.org/10.1093/clinids/18.supplement_1.s79

14. Multiple Sclerosis Council for Clinical Practice Guidelines. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. Washington, D.C.: Paralyzed Veterans of America, 1998.

15. Valderramas S, Feres AC, Melo A. Reliability and validity study of a Brazilian-Portuguese version of the fatigue severity scale in Parkinson's disease patients. Arq Neuropsiquiatr. 2012 Jul;70(7):497-500. https://doi.org/10.1590/s0004-282x2012000700005

16. Kummer A, Scalzo P, Cardoso F, Teixeira AL. Evaluation of fatigue in Parkinson's disease using the Brazilian version of Parkinson's Fatigue Scale. Acta Neurol Scand. 2011 Feb;123(2):130-6. https://doi.org/10.1111/j.1600-0404.2010.01364.x

17. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000 Dec;25(24):3186-91. https://doi.org/10.1097/00007632-200012150-00014

18. Hughes AJ, Daniel SE, Blankson S, Lees AJ. A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol. 1993 Feb;50(2):140-8. https://doi.org/10.1001/archneur.1993.00540020018011

19. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967 May;17(5):427-42. https://doi.org/10.1212/wnl.17.5.427

20. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State" - A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98. https://doi.org/10.1016/0022-3956(75)90026-6

21. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008 Nov;23(15):2129-70. https://doi.org/10.1002/mds.22340

22. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol. 2010 Jul;63(7):737-45. https://doi.org/10.1016/j.jclinepi.2010.02.006

23. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982-1983;17(1):37-49. https://doi.org/10.1016/0022-3956(82)90033-4

24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

25. Scientific Advisory Committee of the Medical Outcomes Trust. Instrument review criteria. Washington, D.C.: Scientific Advisory Committee, 1995.

26. Smith SC, Lamping DL, Banarjee S, Harwood R, Foley B, Smith P, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. Health Technol Assess. 2005 Mar;9(10):1-93, iii-iv. https://doi.org/10.3310/hta9100

27. Terwee CB, Bot SD, De Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007 Jan;60(1):34-42. https://doi.org/10.1016/j.jclinepi.2006.03.012

28. George D, Mallery P. SPSS for Windows step by step: a simple guide and reference, 11.0 update. 4th ed. Boston: Allyn & Bacon, 2003.

29. Fisk JD, Brown MG, Sketris IS, Metz LM, Murray TJ, Stadnyk KJ. A comparison of health utility measures for the evaluation of multiple sclerosis treatments. J Neurol Neurosurg Psychiatry. 2005 Jan;76(1):58-63. https://doi.org/10.1136/jnnp.2003.017897

30. Weeks A, Swerissen H, Belfrage J. Issues, challenges, and solutions in translating study instruments. Eval Rev. 2007 Apr;31(2):153-65. https://doi.org/10.1177/0193841X06294184

31. Pavan K, Marangoni B, Mendes MF, Tilbery CP, Lianza S. Esclerose múltipla: adaptação transcultural e validação da escala modificada de impacto de fadiga. Arq Neuro-Psiquiatr. 2007;65(3a):669-73. https://doi.org/10.1590/S0004-282X2007000400024

32. Guillemim F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol. 1993 Dec;46(12):1417-32. https://doi.org/10.1016/0895-4356(93)90142-n

33. Elbers RY, Rietberg MB, van Wegen EE, Verhoef J, Kramer SF, Terwee CB et al. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. Qual Life Res. 2012 Aug;21(6):925-44. https://doi.org/10.1007/s11136-011-0009-2

34. Watson D, Clark LA. The PANAS-X: manual for the positive and negative affect schedule e expanded form. Iowa: University of Iowa, 1994.

35. Çilga G, Genç A, Çolakoğlu BD, Kahraman T. Turkish adaptation of Parkinson fatigue scale and investigating its psychometric properties. Int J Rehabil Res. 2019 Mar;42(1):20-5. https://doi.org/10.1097/MRR.0000000000000314

36. Sáez-Francàs N, Hernández-Vara J, Corominas Roso M, Alegre Martín J, Casas Brugué M. The association of apathy with central fatigue perception in patients with Parkinson's disease. Behav Neurosci. 2013 Apr;127(2):237-44. https://doi.org/10.1037/a0031531

37. Martinez-Martin P, Wetmore JB, Arbelo JM, Catalán MJ, Valldeoriola F, Rodriguez-Blazquez C. Validation study of the Parkinson's Fatigue Scale in advanced Parkinson's disease. Patient Relat Outcome Meas. 2019;10:141-52. https://doi.org/10.2147/PROM.S196042

38. Bensing JM, Hulsman RL, Schreurs KM. Gender differences in fatigue: biopsychosocial factors relating to fatigue in men and women. Med Care. 1999 Oct;37(10):1078-83. https://doi.org/10.1097/00005650-199910000-00011

39. Hagell P, Rosblom T, Pålhagen S. A Swedish version of the 16-item Parkinson Fatigue Scale (PFS-16). Acta Neurol Scand. 2012 Apr;125(4):288-92. https://doi.org/10.1111/j.1600-0404.2011.01560.x

40. Fu R, Cui SS, Du JJ, Huang P, He YC, Gao C, et al. Validation of the Parkinson Fatigue Scale in Chinese Parkinson's disease patients. Brain Behav. 2017 May;7(6):e00712. https://doi.org/10.1002/brb3.712