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Brazilian version of the Multidimensional Fatigue Inventory for Parkinson's disease

Versão brasileira do Inventário Multidimensional de Fadiga na doença de Parkinson

Josiane Lopes [a], Hayslenne Andressa Gonçalves de Oliveira Araújo [b], Suhaila Mahmoud Smaili [a] *

[a] Universidade Estadual do Centro-Oeste (UNICENTRO), Guarapuava, PR, Brazil
[b] Universidade Estadual de Londrina (UEL), Londrina, PR, Brazil

Introduction: The multidimensional fatigue inventory (MFI) has not been applied in Brazilian Parkinson`s disease (PD) population due to the lack of validation. **Objective:** The aim of this study was to cross-culturally adapt, to validate, and investigate the psychometric properties of Brazilian version of the MFI in PD. **Method:** Idiopathic PD individuals (N = 90) were recruited. The MFI was translated into Brazilian Portuguese using established forward-backward translation procedures, and the psychometric properties were evaluated. All individuals were assessed by socio-clinical questionnaire, Mini-Mental State Examination (MMSE), Unified Parkinson's Disease Rating Scale (MDS-UPDRS Part I-IV), Hoehn-Yahr disability scale (HY), hospital anxiety and depression scale (HADS), fatigue severity scale (FSS), Parkinson Fatigue Scale (PFS-16) and MFI-PD/ BR with retest of the MFI-PD/BR after seven days. **Results:** The adaptation phase kept the same items of original MFI-PD. No data missing, floor nor ceiling effects were found. The overall Cronbach's alpha coefficient for the 20 items was 0.81, ranging from 0.73 to 0.81 for each of the five subscales. Bland and Altman analysis showed no systematic differences between assessments. The intraclass correlation coefficient test-retest was higher or equal 0.70 ($p < 0.01$) for the MFI-PD/BR score, which was moderately correlated with the

*JL: PhD, e-mail: jolopes@unicentro.br
HAGOA: Doctoral student, e-mail: h.andressa.goa@hotmail.com
SMS: PhD, e-mail: suhailaneuro@gmail.com

HADS, MDS-UPDRS score (motor examination, motor and non-motor experiences of daily living and motor complications), FSS and PFS-16. It was revealed the MFI-PD/ BR > 55 points as cut-off point to indicate fatigued subjects with accuracy of 0.84 ($p < 0.001$). **Conclusion:** The MFI-PD/BR can be considered a valid and reproducible instrument for assessing PD-related fatigue.

Keywords: Parkinson Disease. Fatigue. Psychometrics.

Resumo

Introdução: *O inventário multidimensional da fadiga (MFI) não tem sido administrado em indivíduos brasileiros com doença de Parkinson (DP) devido à falta de validação.* ***Objetivo:*** *Adaptar transculturalmente, validar e investigar as propriedades psicométricas da versão brasileira do MFI na DP.* ***Método:*** *Foram recrutados indivíduos com DP (N=90). O MFI foi traduzido para o português falado no Brasil usando procedimentos de tradução e retrotradução e as propriedades psicométricas foram avaliadas. Todos os indivíduos foram avaliados por meio de um questionário sócio-clínico, mini-exame do estado mental (MEEM), escala modificada de avaliação na DP (MDS-UPDRS Parte I-IV), escala de incapacidade de Hoehn-Yahr (HY), escala de ansiedade e depressão (HADS), escala de gravidade de fadiga (FSS), escala de fadiga da DP (PFS-16) e MFI-DP/ BR com reteste do MFI-PD/BR em sete dias.* ***Resultados:*** *A adaptação manteve os mesmos itens do instrumento original do MFI-PD. Nenhum dado perdido, efeito chão ou teto foram encontrados. O coeficiente alpha de Cronbach de todos os 20 itens foram 0.81, variando entre 0.73 a 0.81 entre as cinco subescalas. A análise de Bland-Altman não demonstrou nenhuma diferença sistemática entre as avaliações. O coeficiente de correlação intraclasse teste-reteste foi maior ou igual a 0.70 ($p < 0.01$) para os escores do MFI-DP/BR com correlações moderadas com HADS, MDS-UPDRS escore (exame físico, experiências motoras e não motoras de atividades de vida diária e complicações motoras), FSS e PFS-16. Foi revelado MFI-DP/ BR > 55 pontos como ponto de corte para indicar indivíduos com fadiga com acurácia de 0.84 ($p < 0.001$).* ***Conclusão:*** *O MFI-DP/BR pode ser considerado um instrumento válido e reprodutível para avaliar fadiga na DP.*

Palavras-chave: *Doença de Parkinson. Fadiga. Psicometria.*

Introduction

Fatigue is a problem for up to 75% of Parkinson`s disease (PD) patients [1, 2], and over half consider fatigue to be one of their 3 most disabling symptoms [3]. It may manifest even present during premotor stages of PD [4], and while most studies have found no significant association between fatigue and PD motor severity [5], other studies have reported significant correlations between increasing fatigue and increasing disease severity [1, 3, 6]. Fatigue negatively impacts on activities of daily living and quality of life in PD [4, 6] and is commonly associated with other non-motor symptoms such as sleepiness, anxiety, and depression [3].

The assessment of PD fatigue is not a easy task. It is a complex and highly subjective symptom with many uncertainties regarding its pathophysiology. One of the challenges is the lack of a widely accepted definition [7] and with that, differentiating its many dimensions such as motor, mental and social [3, 8, 9]. Fatigue usually refers to the difficulty initiating or sustaining voluntary activities [10]. Its multidimensionality is believed to result from a complex interplay between the underlying disease process, peripheral control systems, central control systems and environmental factors [3]. This complexity may be reflected in the large number of instruments that are currently available to measure fatigue in patients with PD [11].

Perceptions of fatigue are typically measured using self-reported scales of fatigue severity or impact [12, 13]. 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 [13]. Only three scales, the Fatigue Severity Scale (FSS) [14], Parkinson Fatigue Scale (PFS-16) [15], and Multidimensional Fatigue Inventory (MFI) [9] were recommended for rating fatigue severity in PD.

MFI is a commonly used instrument to assess the multidimensional aspects of fatigue in PD patients [9]. It is a self-report questionnaire that assesses general fatigue, physical fatigue, reduced activity, mental fatigue and reduced motivation. IMDS suggested the MFI as a screening instrument for fatigue and recommended the MFI for the assessment of fatigue severity in patients with PD [12]. In Brazil, FSS [16] and PFS-16 [17] have been widely used to assess PD fatigue. MFI provides a potential guide for PD fatigue assessment that can be used in research and clinical practice. Thus, this instrument is the possibility to complement the assessment of this symptom in other dimensions that are not assessment. However, it has limited Brazilian applicability due to the lack of a validated version.

Considering psychometric properties of design and administration that can satisfy the current standards for outcome measurements. From the possibility of applicability of MFI in Brazilian PD individuals, the aim of the present study was to cross-culturally adapt and investigate the psychometric properties of Brazilian version of the MFI in PD.

Method

Population and design

An observational cross-sectional study following the criteria proposed by Beaton et al. (2000) [18] was carried out. Participants were recruited from the physical therapy outpatient clinic at the State University of Londrina. The study was approved by the Ethics Committee of the State University of Londrina, University Hospital (Opinion report No. 2.481.213). All participants voluntarily gave written informed consent.

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) [18].

Subjects

Individuals were recruited according to the following criteria: aged 50 years or older; diagnosis of idiopathic PD using the UK Brain Bank criteria (Hughes et al., 1993) [19]; Brazilian nationality; Hoehn and Yahr disability scale (HY) stage I – IV [20]; stable use of antiparkinsonian medication; able to walk independently without gait aids; score ≥ 24 on the Mini-Mental Status Examination (MMSE) [21].

Individuals were excluded if they: a) 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; b) under treatment other than drug therapy or had surgery for PD such as deep brain stimulation; or c) had participated in a physiotherapy program two months before starting the trial. Individuals who missed the second interview or whose medication changed over the course of the study were considered losses.

Instrument

The Multidimensional Fatigue Inventory (MFI) was originally developed and validated in the Dutch language in patients with cancer and patients with chronic fatigue syndrome [9] and was translated and validated in English in patients with cancer [22]. The MFI is a self-report questionnaire that assesses the impact of fatigue and comprises five dimensions: general fatigue (GF), physical fatigue (PF), reduced activity (RA), mental fatigue (MF) and reduced motivation (RM). Each subscale contains four items, with two items formulated in a positive and two formulated in a negative direction. The addressed recall period is 'lately'. All items are scored on a five-point Likert scale ranging from 1 (yes, that is true) to 5 (no, that is not true). The negative formulated items must be recoded before adding up scores. The obtainable score within each subscale ranges from 4 (absence of fatigue) to 20 (maximum fatigue) [23].

Procedures

The subjects were assessed using a socio-clinical questionnaire, MMSE [21], Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS, Part I - IV) [24], HY [19] by same examiner. Following this, 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 the MFI-PD

The MFI was culturally adapted from English to Brazilian Portuguese language in accordance with the guidelines proposed by Beaton et al. [18]. 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). After, this Portuguese version was back-translated into English independently by two American native translators. The backward translations were synthesized by the translators and compared with the MFI [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 the MFI (MFI-PD/ BR) to 20 PD subjects to verify their comprehension of the instrument. At the end of this process, the MFI-PD/BR was ready for psychometric testing and keep the same items and structure as proposed in study performed by Baptista et al. [25].

The content validity was assessed by the expert committee, by verifying the conceptual, cultural, idiomatic and semantic equivalences between the MFI-PD/BR and MFI [9]. It was checked in this PD group if they understood all items of the instrument. 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 [18, 26].

Phase 2: Assessment of psychometric properties

Seventy PD subjects were assessed. Testing-retesting was applied by two examiners, physiotherapists (A and B) administered the MFI-PD/BR separately with a one-hour interval and then, seven days later, examiner A performed the retest. Additionally, subjects also answered the Hospital Anxiety and Depression Scale (HADS) [27], FSS [16] and PFS-16 [17] to examiner B in a separate room. The time taken was recorded by a digital chronometer.

Statistical analyses

Data were analyzed with the Statistical Package for the Social Sciences (SPSS®, Release 20.0), and MedCalc® (Release 19.1.3). A two-tailed significance level of 0.05 was used for all tests. The normality of data distribution was checked by means of the Shapiro-Wilk test. Data quality and acceptability satisfactory were considered if missing data comprise < 5 % of the data set [28]. The time taken to apply the MFI-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 [29].

The reliability was examined by the internal consistency, reproducibility, and measurement error. Cronbach's alpha was used to examine the internal consistency of items. The reproducibility was tested by means of testing-retesting using the intraclass correlation coefficient (ICC) and the Bland-Altman method with mean differences. The 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 [29].

The construct validity was tested through correlations between the MFI-PD/ BR and subscale scores of other instruments considering convergent validity and divergent validity. To evaluate convergent validity, the MFI-PD/ BR total score was compared to the FSS and PFS-16. To evaluate divergent validity, the MFI-PD/ BR total score was compared to several measures of disease related symptoms and disability (MDS-UPDRS, HY), psychological functioning (HADS) 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 [30].

A receiver operating characteristic (ROC) curve was drawn to provide a sensitivity, specificity ratio and accuracy of MFI-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 [6].

The total amount of dopaminergic medication was expressed as the levodopa equivalent daily dosage (LEDD), determined by previously reported methods [4].

Results

Ninety PD individuals were enrolled in the study. The baseline characteristics of the adaptation and validation sample are described in 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 who participated of validation phase showed clinically relevant fatigue (Table 2). The translation and back-translation versions were similar to the MFI-PD original [23]. All equivalences of the MFI-PD/BR were achieved. In pretesting, there was no problem in understanding the MFI-PD/BR confirming the content and face validity. The instrument kept the same number and allocation of items, domains, format and response patterns as original version [9, 23]. It was completed in a median time of 5 minutes and 47 seconds (4.1 – 6.8). No missing data, ceiling (2.78% – first interview, 3.17% – retest), and nor floor effects (2.86% – first interview, 3.94% – retest) were found for the MFI-total and subscales.

The presence of clinical significant fatigue associated with increased scores in HADS total and in its subscales: anxiety and depression. Individuals with major disability (HY) and impairment (MDS-UPDRS total, part I, II and IV) scored higher in PFS-16. There was no association between the fatigue and medication usage for DP (levodopa, dopaminergic drugs or antidepressants) (Table 2).

The Cronbach`s alpha for the MFI-PD/ BR was 0.81 when all responses items were scored. All item-total correlations were acceptable (Table 3). The mean inter-item correlation was 0.70 (Table 3). Good reliability was demonstrated. No systematic differences were found between the observers administration and interviews. There was high agreement and small mean intra and interobserver differences (Table 4).

The MFI-PD/BR correlated moderately with HADS (total score) and its subscale depression, impairment (UPDRS score total and non-motor experiences of daily living) and fatigue (FSS, PFS-16) (Table 5). Disability (HY), impairment (motor experiences of daily living, motor examination and motor complications) showed a low positive correlation with MFI-PD/BR. In other words, higher depression, disability, and advanced stages of PD, more fatigue is perceived by subject. Analysis on ROC curve revealed the MFI-PD/ BR > 55 points as cut-off point to indicate fatigued subjects with value of accuracy of 0.84 [0.72; 0.91](p < 0.001), sensitivity=100% and 1-Specificity=60%.

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)
Sex, n (%)	5.85 ± 2.99	6.76 ± 3.77
HADS anxiety	6.30 ± 3.18	6.73 ± 3.16
HADS depression	12.15 ± 5.20	13.50 ± 5.83
HADS total score	2 (2 – 2.5)	2 (2 – 2.5)
HY, stage	0/ 3/ 7/ 6/ 4/ 0/ 0	5/ 6/ 32/ 12/ 15/ 0/ 0
HY, stage: 1/1.5/2/2.5/ 3/4/5 (n)	16.25 ± 11.24	13.95 ± 9.11
MDS-UPDRS – part I score	16.35 ± 8.29	15.31 ± 7.73
MDS-UPDRS - part II score	33.10 ± 10.46	36.85 ± 14.57
MDS-UPDRS – part III score	5.20 ± 5.47	4.75 ± 5.03
MDS-UPDRS – part IV 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
MFI-PD total score	60.94 ± 12.80	58.05 ± 12.34
MFI general fatigue	12.71 ± 3.86	12.50 ± 3.70
MFI physical fatigue	14.59 ± 3.85	13.09 ± 3.43
MFI reduced activity	13.88 ± 3.03	13.23 ± 2.79
MFI mental fatigue	10.88 ± 3.23	10.95 ± 3.33
MFI reduced motivation	8.88 ± 2.57	9.37 ± 2.47

Note: SD = n, number of individuals; MMSE, mini-mental state examination; HADS, hospital anxiety 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; MFI-PD, multidimensional fatigue inventory.

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

Variables (n=319)	Fatigued (n = 32)	Nonfatigued (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
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
MFI-PD total score	66.67 ± 7.71	52.88 ± 11.73	0.00
MFI general fatigue	14.17 ± 3.08	10.43 ± 3.23	0.00
MFI physical fatigue	15.33 ± 2,25	11,93 ± 3.54	0.00
MFI reduced activity	14.17 ± 2.53	12.40 ± 3.06	0.02
MFI mental fatigue	12.33 ± 2.83	9.93 ± 3.28	0.00
MFI reduced motivation	10.66 ± 2.88	8.20 ± 2.37	0.00

Note: 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; MFI-PD, multidimensional fatigue inventory. *Presence of fatigue was identified by means of the PFS-16 cut-off point ≥ 3.3 points.

Table 3 - Corrected item-total correlations and Cronbach's alpha (α) if item or subscale are deleted from the Multidimensional Fatigue Inventory (MFI/PD-BR)

MFI/PD-BR – Item and subscale	Mean (SD)	CITC	α
1. I feel fit.	2.95 (1.25)	0.61	0.84
2. Physically I feel only able to do a little.	3.50 (1.06)	0.48	0.84
3. I feel very active.	2.92 (1.11)	0.45	0.84
4. I feel like doing all sorts of nice things.	1.83 (1.01)	0.17	0.85
5. I feel tired.	3.25 (1.23)	0.44	0.84
6. I think I do a lot in a day.	3.03 (1.22)	0.42	0.84

(to be continued)

(conclusion)

7. When I am doing something, I can keep my thoughts on it.	2.44 (1.19)	0.34	0.85
8. Physically I can take on a lot.	3.34 (1.21)	0.63	0.84
10. I think I do very little in a day.	3.34 (1.27)	0.43	0.84
11. I can concentrate well.	2.52 (1.19)	0.58	0.84
12. I feel rested.	2.31 (1.22)	0.51	0.84
13.I takes a lot of effort to concentrate on things.	2.88 (1.16)	0.41	0.84
14. Physically I feel I am in a bad condition.	3.06 (1.24)	0.64	0.84
15. I have a lot of plans.	2.64 (1.21)	0.19	0.85
16. I tired easily.	3.33 (1.33)	0.63	0.84
17. Physically I feel only able to do a little.	3.77 (1.06)	0.29	0.85
18. I don`t feel like doing anything	2.30 (1.25)	0.39	0.85
19. My thoughts easily wander.	3.00 (1.20)	0.26	0.85
20.Physically I feel I am in a excellent condition	3.30 (1.19)	0.64	0.84
MFI-PD total score	58.04 (12.33)	1.00	0.81
MFI general fatigue	11.82 (3.64)	0.80	0.73
MFI physical fatigue	13.20 (3.52)	0.85	0.73
MFI reduced activity	13.06 (2.98)	0.69	0.76
MFI mental fatigue	10.82 (3.31)	0.61	0.76
MFI reduced motivation	9.12 (2.82)	0.45	0.79

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

Table 4 - Reproducibility of the MFI-PD/BR

				Bland-Altman			
MFI/PD-BR (subscale)	**ICC**	**[95% CI]**	**SEM**	**d**	**95%CI of d**	**SD of d**	**95%LC**
MFI (General Fatigue)							
Intra-observer	0.82	0.72 - 0.88	2.97	-0.67	-1.21 – (-0.12)	0.01	-5.90 – 4.55
Interobserver	0.70	0.56 - 0.81	3.83	0.09	-0.62 - 0.81	0.79	-6.81 – 7.00
MFI (Physical fatigue)							
Intra-observer	0.79	0.68 - 0.87	3.02	0.10	-0.44 - 0.66	0.69	-5.15 – 5.37
Interobserver	0.76	0.63 - 0.84	3.29	1.01	0.40 - 1.62	0.00	-4.85 – 6.89
MFI (Reduced Activity)							
Intra-observer	0.79	0.65 - 0.87	2.40	-0.17	-0.77 - 0.42	0.56	-5.92 – 5.57
Interobserver	0.78	0.63 - 0.86	2.70	0.25	-0.42 - 0.92	0.46	-6.20 – 6.70
MFI (Mental fatigue)							
Intra-observer	0.74	0.60 – 0.83	3.16	-0.12	-0.72 – 0.47	0.67	-5.82 – 5.57
Interobserver	0.72	0.67 - 0.88	3.03	0.32	-0.30 – 0.96	0.30	-5.73 – 6.39
MFI (Reduced Motivation)							
Intra-observer	0.77	0.53 – 0.87	2.17	-0.25	-0.93 – 0.43	0.47	-6.84 - 6.34
Interobserver	0.75	0.59 – 0.85	2.58	-0.04	-0.68 - 0.59	0.88	-6.17 - 6.08
MFI (Total)							
Interobserver	0.89	0.82 - 0.93	7.53	-1.10	-2.47 - 0.25	0.10	-14.16 – 11.94
Intra-observer	0.85	0.76 - 0.90	9.51	1.64	-0.09 - 3.38	0.06	-14.99 – 18.27

Note: MFI-PD, multidimensional fatigue inventory; 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 MFI-PD/BR and other variables

Variable	MFI-PD/BR	
	Correlation	p-value
Demographics		
Age, years	0.087+	0.496
Education, years	0.143++	0.260
Sex (male: female)	-0.112+	0.378
Clinical features		
Disease duration, months	0.079++	0.534
MMSE	-0.242++	0.054
HADS anxiety	0.244+	0.052
HADS depression	0.644+	0.000
HADS total score	0.507+	0.000
HY, stage	0.365+	0.003
MDS-UPDRS – part I score	0.592+	0.000
MDS-UPDRS - part II score	0.406+	0.001
MDS-UPDRS – part III score	0.431+	0.000
MDS-UPDRS – part IV score	0.284+	0.023
MDS-UPDRS total score	0.569+	0.000
LEDD (mg/day)	0.072++	0.570
Fatigue measures		
FSS total score	0.662+	0.000
PFS-16 total score	0.728+	0.000

Note: + Pearson correlation; ++ Spearman correlation. MFI-PD, multidimensional fatigue inventory; MMSE, mini-mental state examination; HADS, hospital anxiety 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.

Discussion

The MFI has already been validated in Brazil for Hodgkin's Lymphoma Survivors [25], however, the current study presents the first attempt to validate the instrument in idiopathic PD subjects. Considering the high prevalence of fatigue in PD, many instruments were developed and submit to psychometric studies but the available existing instruments only provided a limited understanding of the level of fatigue. There is a continuous necessity to have other instruments to complement all aspects of fatigue. The MFI appears to be a promising measure for evaluating fatigue in PD [1].

The frequency of fatigue in this study confirmed the high prevalence demonstrated in various studies, with worldwide rates of up to 75% [1, 2], and Brazilian rates of around 41.3 to 67.4% [16, 17]. This is a subjective finding with great perception sense involved and a considerable variability in the description of fatigue. Common definitions include a sense of exhaustion or a subjective lack of physical and/ or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activity [31]. However, these terms may be differently interpreted depending on subject's cultural background [32].

Since most scales and questionnaires have been developed in English-speaking countries, a validation process is required before these instruments can be used in other countries. Therefore, for these instruments to be considered appropriate for clinical or research use, it is necessary to evaluate all psychometric properties [16, 33]. Different societies have its own beliefs and behavior and, in the cross-cultural adaptation process these particularities must be considered [32]. According to the cross-cultural adaptation process proposed [18] all equivalences, content and face validity between the original MFI and MFI-PD/BR were achieved assuming the maintenance of the psychometric properties of the MFI-PD/BR as properly documented in prior study [23].

The MFI-PD/BR showed a good level of acceptability and required few minutes to fill out. For an instrument to be considered appropriate to investigate a sign/ symptom of a patient, it is necessary to evaluate, at least, its acceptability, reliability, and validity [32, 33]. Acceptability refers to the distribution of score as a symmetric way [34]. The acceptability of MFI-PD/BR is in accordance with the original MFI [23] only in GF and RM subscales that was not observed floor nor ceiling effects, too. Elbers et al. [23] mentioned that the found floor effect for the MF subscale and the ceiling effects for the PF and RA subscales should be considered when evaluating one of these aspects of fatigue. Furthermore, these results suggest that mental fatigue and physical fatigue are two different aspects of fatigue and further confirm previous findings that mental fatigue and physical fatigue are different symptoms in PD [7, 35].

In agreement of study that validated MFI for PD [23], the current study evidenced the reliability of MFI-PD/

BR as good and showed small SEM on all subscales. The SEM allows one to make statements about the precision of test scores of individual examinees. The lower difference, the better is an instrument to obtain more realistic scores [29]. 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 MFI-PD/BR is a stable instrument with low systematic difference indicating good concordance between the first and the last interview and the two observers. Elbers et al. [23] also evidenced the same Bland-Altman analysis confirming the stability of MFI to assess fatigue in PD.

When an instrument is valid, it truly reflects the concept that it should measure [26]. Investigating the validity of PD fatigue instruments is a complex task due the unclear definition and multidimensional factors. On this current study three aspects of validity was analyzed: content, criterion, and construct validity [11]. Content validity has already been commented on, in describing the stage of cross-cultural adaptation. Since no gold standard exists for fatigue instruments, criterion validity was not evaluated. The degree to which scores of a questionnaire are consistent with other instruments which measures the similar (convergent validity) or associated (divergent validity) constructs was defined as construct validity [26]. Convergent validity of the MFI-PD/BR was established with the FSS and PFS-16, suggesting a moderate level of association. The adequate divergent validity was established between MFI-PD/BR and severity of PD, motor aspects (experiences of daily living, examination, and complications) and depression feeling.

In the study of validation of MFI for PD subjects [23] was investigate only the structural validity where assume that MFI is validate for PD, however is not possible to establish any association with this current study. The results of the current study is in line with other studies that investigate the construct validity of the MFI in patients with cancer [36, 37]. It was not investigate the structural validity of MFI because it is not necessary to test again for the same disease if it is confirmed in the study of validation of MFI for PD subjects [23].

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 [17, 38, 39]. Similar to the current study, low-to-high correlations were found between the fatigue (PFS-16) and depression measures [40, 41].

This is the first study to calculate the cut-off point for the MFI-PD. 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 [23]. 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 [38] as the similar subscales of MFI-PD.

There are some limitations of this study need to be pointed out. It was accomplished a monocentric study with a convenience sample. A validation study requires many possibilities of changes to generalize the finds to the other parts of country whose speaks the idiom. It is important to observe that the sample of the present study was fairly early in disease course, which indicates a limitation to generalize the results to more advanced PD subjects. 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 were no other Brazilian specific instruments for assessing PD fatigue. With regard to use of the HADS instruments, it is important to consider that they are generic measurements, and may fail to address important areas of impact that are disease-specific.

Further research is necessary in order to be able to administer the MFI-PD/BR. Future studies could correlate it with imaging examinations, investigate samples composed by patients in hospital or more advanced stages of PD, analyze outcomes such as sleep and quality of life. A longitudinal study with a greater length of follow-up among those expected to change could determine the responsiveness of the MFI-PD/BR during the treatment protocol with the purpose to reduce fatigue.

Conslusion

MFI-PD/BR is a reliable and valid instrument to assess the multidimensional aspects of fatigue in Brazilian patients with PD. It holds the relevant psychometric

properties and satisfies the modern standards for outcome measurements relating to the symptom of fatigue in PD. 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.

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