RESEARCH ARTICLE

Validity and reliability of the German multidimensional fatigue inventory in spinal muscular atrophy

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Abstract

Objective: Fatigue is a common and burdensome symptom of spinal muscular atrophy. Given its complex interactions, different dimensions of fatigue need to be investigated. The Multidimensional Fatigue Inventory is a widely used instrument that captures five distinct dimensions. The aim of this study was to investigate the validity and reliability of the German Multidimensional Fatigue Inventory in spinal muscular atrophy and to evaluate the presence of clinically relevant fatigue. **Methods**: One hundred and forty adult spinal muscular atrophy patients completed the Multidimensional Fatigue Inventory in a nationwide, multicenter, cross-sectional study. Structural validity was explored using principal component analysis. Cronbach's α was calculated to evaluate internal consistency. Convergent validity was assessed by correlation with a Visual Analog Scale for fatigue and the EuroQol-Five Dimension-Five Level Scale as a measure of quality of life. **Results**: The original five-component model of the questionnaire constituted an acceptable fit. Internal consistency and convergent validity of *general*, *physical*, *mental fatigue*, and *reduced activity* were good. We observed a floor effect for *mental fatigue*. While *physical fatigue* exceeded the cutoff for clinically relevant fatigue, all dimensions but *reduced motivation* correlated negatively with quality of life. Age, depression, and ≥4 copies of the *survival motor neuron 2* gene were associated with higher *general/physical fatigue*; unemployed participants reported higher scores for *reduced activity/motivation*. **Interpretation**: The Multidimensional Fatigue Inventory is a valid and reliable instrument to assess different dimensions of fatigue in spinal muscular atrophy. Fatigue is a relevant problem in spinal muscular atrophy and its assessment should be incorporated into standard care.

Introduction

Fatigue is a common symptom in spinal muscular atrophy (SMA) patients and is associated with reduced quality of life.[1–3] There is no single definition of the term fatigue, but it is mostly described as a sensation of tiredness, lack of energy, and feeling of constant exhaustion, also referred to as perceived fatigue. The underlying mechanisms are not fully understood and appear to be complex, involving psychological and somatic factors.[4,5] To evaluate treatment effectiveness and patient satisfaction, patient-reported outcome measures (PRO), such as fatigue, have recently moved into focus.[6,7] They capture the patient's subjective well-being, which may differ from clinical parameters, but is no less important. PROs are often elusive and challenging to quantify. This is reflected in the abundance of self-report questionnaires to assess fatigue. Instruments that are currently applied exhibit different properties and advantages and measure different aspects of fatigue (e.g., severity, phenomenology, or impact).[8,9] Among these, only the Fatigue Severity Scale (FSS) and the Visual Analog Scale (VAS) have been validated in SMA to some extent, to the best of our knowledge.[10] As both measures are unidimensional, there is a need for a validated instrument that captures different dimensions of fatigue in SMA.

A widely used instrument to assess the multidimensional aspects of fatigue in patients with neuromuscular diseases is the Multidimensional Fatigue Inventory (MFI).[11,12] Recently, we have shown increased *physical* and *general fatigue* as well as *reduced activity* in a small cohort of SMA patients applying the MFI.[3] However, the psychometric properties of the MFI have not been investigated in patients with SMA so far. Therefore, the aim of the present study was to investigate structural validity, internal reliability, and convergent validity as well as floor and ceiling effects of the MFI in adults with SMA and to collect preliminary data on the factors associated with fatigue in a larger cohort.

Methods

Study design, participants, and data acquisition

Seven German university hospitals participated in this nationwide, multicenter, cross-sectional study. Between February and August 2020, 140 SMA patients aged 18 years and above were recruited. The inclusion criteria comprised the diagnosis of SMA and sufficient German language skills to answer the questionnaires. The diagnosis was genetically confirmed for 137 participants (5q-associated), whereas three participants had not been genetically tested. All but three participants with 5q-SMA were receiving or had received intrathecal nusinersen treatments in the past. Sociodemographic and disease characteristics were obtained from medical records and completed during the assessment (Table 1). Fatigue and motor function were measured during routine visits to the sites. The Hammersmith Functional Motor Scale Expanded (HFMSE) (0–66 points, higher scores indicate better motor function) and the Revised Upper Limb Module (RULM) (0–37 points, higher scores indicate better motor function), two disease-specific scales that measure gross motor function and upper extremity function, respectively,[13,14] and the six-minute walk test (6WMT), which has been validated in ambulatory SMA patients,[15] were performed. Additionally, self-report questionnaires, such as the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) (0–48 points, higher scores indicate better function) and Spinal Muscular Atrophy Functional Rating Scale (SMAFRS) (0–50 points, higher scores indicate better function), which are frequently used in SMA,[16,17] were completed by the patients.

Study approval was obtained within the German Motor Neuron Disease Network (MND-NET) consortium from the local ethics boards of each site.[18] All participants gave written informed consent prior to their study participation.

Assessment instruments

Measures of fatigue

Smets et al. initially developed and tested the MFI in Dutch patients with cancer and chronic fatigue syndrome.[19] The English version was translated into German,[20] and reference values for the German population were established in 2003.[21] It is a self-report instrument that measures how a patient felt "lately" on a 5-point Likert scale. The 20 items are categorized into five dimensions with four items each: *general fatigue*, *physical fatigue*, *mental fatigue*, *reduced motivation*, and *reduced activity*. Generally, it is recommended to calculate a sum score for each dimension, which ranges between 4 and 20 with higher scores indicating increased fatigue. The participants were asked to fill in the MFI during their first visit to the respective site within the recruitment period, and a short introductory instruction was given with the questionnaire.

Further, the participants were asked to rate their current fatigue on a Visual Analog Scale (VAS). The VAS consisted of a 100-mm-long horizontal line with the left end indicating "no exhaustion" and the right end indicating "extreme exhaustion." On the *X*-axis, the numbers

Table 1. Participant characteristics.

Participant characteristic	*N* (Percentage referring to the whole sample)	Mean (SD)	Median (Range)
Sex, female (*N*-valid = 140)	61 (43.6%)		
Age (years) (*N*-valid = 140)		36.3 (11.8)	34 (18–72)
Education ≥ 12 years (*N*-valid = 124)	96 (68.6%)		
Work situation, employed (*N*-valid = 134)	98 (70.0%)		
Relationship status, single (*N*-valid = 129)	75 (53.6%)		
Depression diagnosis (*N*-valid = 138)	14 (10.0%)		
SMA type (*N*-valid = 140)			
I	8 (5.7%)		
II	50 (35.7%)		
III	78 (55.7%)		
IV	4 (2.9%)		
SMN2 copy number (*N*-valid = 115)			
2	8 (5.7%)		
3	58 (41.4%)		
4	43 (30.7%)		
5	2 (1.4%)		
6	4 (2.9%)		
Use of wheelchair (*N*-valid = 140)	109 (77.9%)		
Scoliosis (*N*-valid = 139)	88 (62.9%)		
Use of NIV (*N*-valid = 140)	35 (25.0%)		
Use of PEG (*N*-valid = 140)	7 (5.0%)		
RULM (points, max. 37) (*N*-valid = 120)		20.9 (13.3)	20 (0–37)
HFMSE (points, max. 66) (*N*-valid = 120)		21.5 (23.4)	8.5 (0–66)
6MWT (meters) (*N*-valid = 38)		429 (188.4)	457.5 (18–785)
ALSFRS-R (points, max. 48) (*N*-valid = 128)		31.9 (10.4)	31 (1–48)
SMAFRS (points, max. 50) (*N*-valid = 57)		23.2 (19.2)	20 (0–49)
MFI (min. 4, max. 20) (*N*-valid = 140)			
General fatigue		9.5 (3.3)	9 (4–19)
Physical fatigue		11.0 (3.7)	11 (4–20)
Mental fatigue		7.4 (3.0)	7 (4–17)
Reduced activity		9.6 (3.3)	9 (4–18)
Reduced motivation		7.6 (2.7)	7 (4–16)
VAS fatigue (min. 0, max. 10) (*N*-valid = 138)		3.9 (2.4)	3.5 (0–10)

Depicted are the characteristics of the 140 participating adult SMA patients. Use of a wheelchair was defined as current use without a required minimum of hours/day. 6MWT, six-minute walk test; ALSFRS-R, amyotrophic lateral sclerosis functional rating scale-revised; HFMSE, hammersmith functional motor scale expanded; max., maximum; MFI, multidimensional fatigue inventory; min., minimum; *N*, number; NIV, noninvasive ventilation; *N*-valid, number of valid data for this variable; PEG, percutaneous endoscopic gastrostomy; RULM, revised upper limb module; SD, standard deviation; SMA, spinal muscular atrophy; SMAFRS, spinal muscular atrophy functional rating scale; SMN2, survival of motor neuron gene 2; VAS, visual analog scale.

"0" to "10" were written in the ascending order at a distance of 10 mm. The distance from "0" to the participants' marks was measured and rounded to one decimal place.

Measures of health-related quality of life (HRQoL)

The German version of the EuroQol-Five Dimension-Five Level Scale (EQ-5D-5L) was used to measure HRQoL. It is a standardized and well-validated self-report questionnaire, which captures the participant's health state "today." It comprises a vertical VAS as well as one question for each of the five dimensions as follows: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression.[22,23] The dimensions are scaled in five levels of perceived problems ranging from Level 1 "no problems" to Level 5 "unable/extreme problems." Together the stated levels for the five dimensions result in a distinct health state, which can be converted into an index value using the value set derived from a German reference sample.[24]

Statistics

Statistical analysis was performed using IBM Statistical Software Package of Social Science (SPSS; Chicago, IL,

USA, version 26). A two-tailed $p < .05$ was considered statistically significant for all analyses.

The structural validity of the MFI was investigated by means of principal component analysis (PCA) to measure the degree to which the subscales of the MFI reflect different dimensions of fatigue. A participant to item ratio of 5:1[25] was used to calculate the minimum sample size and led to the desired number of at least 100 participants. The suitability of the data for PCA was determined using the Kaiser–Meyer–Olkin measure (≥0.6) and Bartlett's test. As a first step, the number of components to be extracted was set to five to assess the suitability of the original five-component model. The obtained components were rotated oblique using the direct oblimin procedure (with Kaiser normalization) as the components were expected to correlate. The criterion for component loading was set at ≥0.4[26] with the term "loading" describing the relative contribution of an item to a component. To name the extracted components, the theme of the item with the highest loading in the pattern matrix was adapted for each component. An alternative four-component model was investigated (defined number of four extracted components) in the same manner.

Reliability in terms of internal consistency was assessed by calculating the Cronbach's α coefficient for each subscale. It was considered good if >0.7.[27] Further, interitem correlations and corrected item–total correlations were calculated and considered acceptable if ranging between 0.3 and 0.7.[28] Convergent validity was tested by examining Spearman rank correlations of the MFI subscales with the VAS fatigue and the scores on the generic HRQoL measure EQ-5D-5L. Floor and ceiling effects were assumed if more than 15% of the study participants opted for the highest or lowest possible score in a MFI subscale.[29]

To study the association of sociodemographic and disease characteristics with the MFI dimensions, data distribution was evaluated visually on normal probability plots and by Shapiro–Wilk tests. To control for confounding, the data were checked for outliers and cluster formation and, if necessary, the analyses were adapted accordingly. As not all data were normally distributed, Mann–Whitney *U* and Kruskal–Wallis tests for independent samples were calculated to determine the differences in metric variables between two multiple groups, respectively. In case of a significant result in the Kruskal–Wallis test, pairwise comparisons with Bonferroni correction were performed and corrected significances were reported. Correlations were studied by means of Spearman rank correlation.

This report was structured following the reporting guidelines to strengthen the reporting of observational studies in epidemiology (STROBE).[30]

Results

Sample characteristics

Table 1 summarizes the participant characteristics. In total, 163 patients were confirmed eligible and approached. Of these, 23 patients did not respond or refused to participate in the study. Reasons for nonparticipation were not specified. Finally, 140 patients were enrolled in Essen ($N = 35$), Hanover ($N = 30$), Dresden ($N = 20$), Munich ($N = 16$), Ulm ($N = 16$), Berlin ($N = 16$), and Rostock ($N = 7$) and analyzed. The sample consisted mainly of SMA type II and type III patients ($N = 50$, $N = 78$, respectively). The median age was 34 years (range: 18–72 years), 43.6% of the participants were female, 77.9% of the participants were using a wheelchair, and 25.0% needed noninvasive ventilation.

None of the participants had more than 5% missing data (two or more missing item answers). Six participants had one missing item on the MFI. Omitted items included item 1 ($N = 1$), item 2 ($N = 1$), item 5 ($N = 2$), item 12 ($N = 1$), and item 13 ($N = 1$). In the case of a missing item, the value was replaced with the mean of the respondent's completed answers within the same dimension.

The highest scores were reported for *physical fatigue* with a median score of 11, followed by *reduced activity* and *general fatigue* (both median = 9). *Reduced motivation* and *mental fatigue* (both median = 7) presented with lower scores (Table 1). No statistically significant differences in fatigue scores were found between the participating sites for *general fatigue, mental fatigue, reduced activity*, and *reduced motivation*. Regarding *physical fatigue*, participants enrolled at the Hannover site presented with higher scores (median = 13) compared with participants enrolled at the Ulm (median = 9, $p = 0.047$, t test statistic = −3.1) and Berlin sites (median = 9, $p = 0.031$, $t = -3.2$). The Ulm and Rostock participants were mainly composed of type III and type IV SMA patients (Ulm: 92.9%; Rostock: 92.9%), whereas Berlin and Munich enrolled mostly type II (and type I) SMA patients (Berlin: 56.3%, Munich: 68.8%). The Ulm participants had higher RULM scores compared with Munich and Essen ($p = 0.006$, $t = -3.6$; $p = 0.021$, $t = -3.3$, respectively), higher HFMSE scores compared with Munich and Essen ($p < 0.001$, $t = -4.5$; $p = 0.001$, $t = -4.0$, respectively), and higher ALSFRS-R scores compared with Munich, Berlin, and Essen ($p = 0.001$, $t = -4.0$; $p = 0.045$, $t = -3.1$; $p = 0.016$, $t = -3.4$, respectively). There were no significant differences between the centers regarding education, work situation, relationship status, or prevalence of depression in the enrolled patients.

Structural validity

The PCA results are presented in Tables 2 and 3. Kaiser–Meyer–Olkin measure (KMO = 0.85) and Bartlett's test (Chi-square = 1114.22, df = 190, $p < .001$) indicated adequate suitability of the data for PCA. Regarding the original five-component model, all five components had an eigenvalue above 1.0, and together they explained 62.2% of the variance. In the pattern matrix, all four items intended for *physical fatigue* (items 2, 8, 14, and 20) loaded exclusively on component 1. For *mental fatigue*, *general fatigue*, and *reduced activity*, three of the four items loaded properly on the component, whereas only two of the items intended for *reduced motivation* (items 4 and 15) loaded on the corresponding component. Four items loaded on different components compared with the original MFI dimensions: items 1 and 3 loaded on *physical fatigue* instead of *general fatigue* and *reduced activity*, respectively, item 19 loaded on *general fatigue* instead of *mental fatigue*, and item 18 loaded on the *reduced activity* instead of *reduced motivation*. Three items loaded >0.4 across two different components (items 12, 13, and 18). Item 9 did not load >0.4 on any component. The highest loadings were congruent between pattern and structure matrix, though there was more cross-loading, and item 9 loaded on *physical fatigue* in the structure matrix. Communalities were good, only item 9 had a value <0.4. The component correlation matrix showed a moderate correlation between components 1 and 4 ($r = 0.35$).

We recalculated the PCA omitting item 9, as it did not load on any component in the pattern matrix. KMO measure and Bartlett's test still indicated adequate suitability of the data, and the five extracted factors now explained 64.0% of the total variance. Item loadings in the pattern and structure matrix only marginally changed without shift of the highest loadings or new cross-loadings (data not shown).

As we were not able to fully replicate the original five-component model in our sample, we next extracted four components (Table 3). The components were identified as follows: *physical and general fatigue* (component 1) with three items originally intended for each *physical* and *general fatigue* loading on it, *mental fatigue* (component 2) with all four items loading on it, *reduced activity* (component 4) with three items (6, 10, and 17) loading as intended, and *reduced motivation* (component 3) with only one item (15) loading properly on the component. Items 3 and 4 loaded on *physical fatigue* instead of *reduced activity* and *reduced motivation*, respectively, whereas Items 5 and 18 loaded on *reduced activity* instead

Table 2. Principal component analysis: original five-component model, pattern, and structure matrices.

	Pattern matrix—components						Structure matrix—components				
Item	1 *Physical fatigue*	2 *Mental fatigue*	3 *General fatigue*	4 *Reduced activity*	5 *Reduced motivation*	Item	1 *Physical fatigue*	2 *Mental fatigue*	3 *General fatigue*	4 *Reduced activity*	5 *Reduced motivation*
01	0.772					**20**	**0.804**				
03	0.758					**01**	0.789				
20	**0.753**					**03**	0.778				
02	**0.751**					**14**	**0.725**		0.413		
14	**0.669**					**02**	**0.721**				
08	**0.403**					**08**	**0.505**				
09						**09**	0.486				
07		**0.872**				**07**		**0.872**			
11		**0.832**				**11**		**0.841**			
13		**0.606**	0.408			**13**		**0.719**	0.571		
19			0.689			**19**		0.492	0.727		
05			**0.585**			**16**	0.513		**0.695**		
16			**0.575**			**05**	0.415		**0.660**	0.427	
12	0.452		**0.481**			**12**	0.590		**0.627**		
06				**0.774**		**06**				**0.795**	
10				**0.680**		**10**			0.416	**0.748**	
17				**0.565**		**17**		0.413		**0.653**	
18			0.411	0.536		**18**			0.530	0.633	
15					**0.827**	**15**					**0.819**
04					**0.676**	**04**					**0.724**

Depicted are absolute loadings > 0.4. Items in bold type load highest on the component they were intended for in the original version of the MFI by Smets et al.

Table 3. Principal component analysis: four-component model, structure, and pattern matrices.

	Pattern matrix—components					Structure matrix—components			
Item	1 *Physical and general fatigue*	2 *Mental fatigue*	3 *Reduced motivation*	4 *Reduced activity*	Item	1 *Physical and general fatigue*	2 *Mental fatigue*	3 *Reduced motivation*	4 *Reduced activity*
20	**0.815**				**20**	**0.824**			
01	**0.806**				**01**	**0.793**			
03	0.764				**03**	0.762			
14	**0.714**				**14**	**0.738**			
02	**0.649**				**12**	**0.647**	0.542		
12	**0.546**				**02**	**0.653**			
04	0.447				**16**	**0.594**	0.481		0.502
16	**0.413**				**08**	**0.500**			
08					**09**	0.486			0.447
09					**04**	0.456			
07		**0.796**			**13**	0.404	**0.806**		0.415
11		**0.758**			**07**		**0.797**		
13		**0.733**			**11**		**0.753**	0.405	
19		**0.679**			**19**		**0.701**		
15			**0.588**		**15**			**0.590**	
10				**0.760**	**10**				**0.785**
06			0.474	**0.720**	**18**				0.719
18				0.655	**06**			0.442	**0.691**
17				**0.610**	**17**				**0.665**
05				0.421	**05**	0.490			0.580

Depicted are absolute loadings >0.4. Items in bold type load highest on the component they were intended for in the original version of the MFI by Smets et al.

of *general fatigue* and *reduced motivation*, respectively. Item 6, though loading highest on component 4, also loaded on *reduced motivation*. Items 8 and 9 did not load >0.4 on any component. In the structure matrix, seven items loaded across different components, but the maximum loading was consistent between pattern and structure matrix for all items. All communalities besides those for Items 8 and 9 were >0.4. The component correlation matrix showed that component 1 was moderately correlated with components 2 and 4 ($r = 0.32$, $r = 0.42$, respectively). Together, the four components explained 56.7% of the total variance.

Internal consistency

The Cronbach's α coefficients of four of the five subscales were acceptable (*general fatigue*: 0.76, *mental fatigue*: 0.79, *physical fatigue*: 0.75, and *reduced activity*: 0.71), whereas *reduced motivation* showed an inadequate value of 0.45. If *general* and *physical fatigue* were combined into a single score, Cronbach's α for this new subscale increased to 0.84. Only the removal of item 8 would have slightly increased Cronbach's α of the respective subscale (*physical fatigue*) to 0.76.

Interitem correlations for all subscales but *reduced motivation* were acceptable and ranged between 0.2 and 0.7 (*general fatigue*: 0.30–0.62, *physical fatigue*: 0.29–0.66, *reduced activity*: 0.26–0.49, *mental fatigue*: 0.29–0.62, and *reduced motivation*: 0.04–0.31). The lowest correlations were found between item 15 and items 9 and 18 as well as item 4 and items 9 and 18, suggesting the presence of two distinct components within the *reduced motivation* subscale. The combined *general/physical fatigue* subscale showed interitem correlations ranging between 0.16 and 0.68. Item scale correlations were ≥ 0.4 for all subscales (including the combined *general/physical fatigue* subscale) with the exception of *reduced motivation* (range: 0.21–0.34).

All pairwise correlations between the MFI subscales were statistically significant and ranged from 0.37 to 0.62 (Table 4).

Convergent validity

The initial five-component model of the MFI had good convergent validity with the VAS scale. Spearman rank correlation coefficients ranged between 0.40 (*mental fatigue*) and 0.70 (*general fatigue*) (Table 5). The relationship between MFI and HRQoL (EQ-5D-5L) yielded a significant negative correlation with the EQ-5D-5L VAS ("health state today") for all dimensions but *reduced motivation*. While the dimensions *general fatigue, physical*

Table 4. Pairwise correlations between MFI dimensions.

N = 140	*General fatigue*	*Physical fatigue*	*Mental fatigue*	*Reduced activity*	*Reduced motivation*
General fatigue	1.000	**0.618****	**0.512****	**0.561****	**0.483****
Physical fatigue		1.000	**0.367****	**0.571****	**0.475****
Mental fatigue			1.000	**0.394****	**0.423****
Reduced activity				1.000	**0.551****
Reduced motivation					1.000

Depicted are r_S (Spearman rho) values for bivariate correlations. Significant correlations are printed in bold type. MFI, multidimensional fatigue inventory; *N,* number; $^{**}p < 0.01$ (two-tailed).

Table 5. Correlation of the MFI dimensions with VAS fatigue and HRQoL.

	VAS fatigue	VAS HRQoL (numeric)	EQ-5D-5L Mobility	EQ-5D-5L Self-Care	EQ-5D-5L Usual Activities	EQ-5D-5L Pain/ Discomfort	EQ-5D-5L Anxiety/ Depression
General fatigue	**0.704****	**−0.401****	−0.165	−0.131	**0.274****	**0.355****	**0.465****
N	138	120	139	139	139	137	139
Physical fatigue	**0.571****	**−0.444****	−0.130	−0.080	**0.402****	**0.360****	**0.316****
N	138	120	139	139	139	137	139
Mental fatigue	**0.396****	**−0.178***	−0.077	−0.017	0.161	**0.195***	**0.395****
N	138	120	139	139	139	137	139
Reduced activity	**0.525****	**−0.269****	−0.005	0.019	**0.253****	**0.252****	**0.323****
N	138	120	139	139	139	137	139
Reduced motivation	**0.460****	−0.134	−0.147	**−0.181***	0.151	0.136	**0.256****
N	138	120	139	139	139	137	139

Depicted are r_S (Spearman rho) values for bivariate correlations. Significant correlations are printed in bold type. EQ-5D-5L, EuroQol-5 Dimensions-5 Level Scale; HRQoL, health-related quality of life; MFI, multidimensional fatigue inventory; *N,* number; VAS, visual analog scale; $^{*}p < 0.05$ (two-tailed); $^{**}p < 0.01$ (two-tailed).

fatigue, and *reduced activity* correlated with the indicated levels of problems regarding Usual Activities, Pain/Discomfort, and Anxiety/Depression, *mental fatigue* correlated with the latter two. *Reduced motivation* only correlated positively with Anxiety/Depression and even negatively with Self-Care. Correlations with the EQ-5D-5L index values were not calculated, as the index values showed a cluster formation in the described cohort.

Floor and ceiling effects

There was no floor/ceiling effect for the dimensions *general fatigue, physical fatigue, reduced activity*, or *reduced motivation*. Regarding *mental fatigue*, 19.3% of the participants ($N = 27$) had opted for the lowest possible score, suggesting a floor effect.

Association with sociodemographic and disease characteristics

There were no significant differences in the MFI subscales between female and male participants. Similarly, there were no significant differences after participant stratification according to wheelchair use, scoliosis, NIV, PEG, education (< 12 years vs. ≥ 12 years), or relationship status (single vs. in partnership). Further, the correlation analysis did not reveal an association of fatigue scores (*general, physical*, and *mental fatigue, reduced activity*, and *reduced motivation*) with any motor function or disability measure (RULM, HFMSE, 6MWT, ALSFRS-R, and SMAFRS).

In contrast, age correlated positively with *general* and *physical fatigue* ($N = 140$, $r_S = 0.198$, $p = 0.019$; N = 140, $r_S = 0.211$, $p = 0.012$). Participants with SMA types III and IV reported more *general fatigue* compared with types I and II (median = 10 vs. 8, $N = 140$, Mann–Whitney $U = 2855.5$, $p = 0.042$). Similarly, participants with five or six *SMN2* copies and thus a milder phenotype tended to report higher fatigue scores in all dimensions, though there were only six participants with five or six *SMN2* copies in the whole sample. If dichotomized in participants with < 4 and ≥ 4 *SMN2* copies, there were significant differences for *physical fatigue* (median = 10 vs. 12, $N = 114$, Mann–Whitney $U = 2001.5$, $p = 0.016$).

Further, employed participants (full-time, part-time, or freelance) reported less fatigue in the *reduced activity* dimension (median = 9 vs. 12, $N = 134$, Mann–Whitney $U = 1203.0$, $p = 0.005$) and the *reduced motivation* dimension (median = 7 vs. 8, $N = 134$, Mann–Whitney $U = 1347.0$, $p = 0.035$) compared with participants who did not work (including students and pensioners). Participants who had been diagnosed with depression or were taking antidepressants reported more *general fatigue* (median = 12 vs. 9, $N = 138$, Mann–Whitney $U = 1177.0$, $p = 0.029$) and *physical fatigue* (median = 13 vs. 10, $N = 138$, Mann–Whitney $U = 1151.5$, $p = 0.045$). For *mental fatigue*, significance was slightly missed (median = 9 vs. 7, $N = 138$, Mann–Whitney $U = 1142.0$, $p = 0.051$). However, only 14 participants had a diagnosis of depression.

Discussion

The primary objective of this study was to investigate the validity and reliability of the German version of the Multidimensional Fatigue Inventory in adult patients with SMA. As the main result, the original five-component model of the MFI was replicable in our large sample. In addition, Cronbach's α, interitem correlations, and Spearman rank correlations with VAS for fatigue and HRQoL suggested good internal consistency and convergent validity for *general fatigue*, *physical fatigue*, *reduced activity*, and *mental fatigue*.

Given the comparably low number of items per dimension in the original MFI (four items per dimension), the correct loading of three or four items per component can be considered satisfactory in PCA.[31] This applied to *physical, mental*, and *general fatigue* as well as *reduced activity* in the five-component model in our sample. Four items loaded on different components compared with the original MFI, whereas two items loaded > 0.4 across two different components. Keeping in mind the relatively high component correlations (namely between components 1 and 4) and the commonly reported difficulties in distinguishing between *physical* and *general fatigue*,[32,33] these items might not contribute to one component/dimension exclusively. For example, the wording of item 1 ("I feel fit," *general fatigue*) may be understood ambiguously and rated in relation to physical fitness rather than in general. Consequently, we decided not to consider these aberrant loadings as item misfits.

General fatigue, physical fatigue, mental fatigue, and *reduced activity* presented with good internal consistency. In contrast, *reduced motivation* exhibited low interitem and item scale correlations and an unacceptable Cronbach's α. This has previously been reported for *reduced motivation* in chronic diseases such as postpolio syndrome.[12,34] In fact, in our sample, the *reduced motivation* dimension was better suited for a two-component model. The theme of the positively phrased items (4: "I feel like doing all sorts of nice things"; 15: "I have a lot of plans") appears to differ especially from item 9 ("I dread having to do things"), which includes aspects of anxiety. Deleting item 9 led to a slightly improved fit of the five-component model. These findings are in line with psychometric studies of the MFI in Swedish populations, indicating a low correlation of item 9 (and 18) with *reduced motivation*, which points out the need for further investigation of this item.[32,35]

The combination of *general* and *physical fatigue* into one dimension has previously been postulated by Elbers et al., who validated the MFI in patients with Parkinson's disease.[33] Moreover, Hagelin et al. found a strong correlation between *general* and *physical fatigue* in cancer patients.[32] Importantly, the developers of the MFI also acknowledged this alternative four-component model as equally acceptable and suggested combining both dimensions if future research supported this.[36] Especially patients with severe motor impairments—such as in our study cohort—might find it hard to distinguish between general and physical aspects of fatigue, as they tend to rate their "fitness" primarily in terms of physical aspects. Statements such as "I feel fit" (item 1, originally included in the *general fatigue* dimension) and "Physically I feel I am in an excellent condition" (item 14, *physical fatigue*) may be rated similarly. Applied to our data, a four-component model did not improve structural validity. In fact, in the four-component model, fewer items loaded on the components as intended.

Convergent validity was assessed by Spearman rank correlation of the subscales with a VAS for fatigue. Though it would have been desirable to test convergent validity with other measures of fatigue, we decided to use the VAS as it has frequently been applied for this purpose.[19,37] The results were satisfactory and showed a positive correlation with all dimensions of the MFI. As anticipated, quality of life (also measured on a VAS) correlated strongest with *general* and *physical fatigue*. *Reduced motivation* did not correlate with the quality of life and higher fatigue in this dimension even was associated with fewer problems in the Self-Care dimension of the EQ-5D-5L. This emphasizes the need to exercise caution regarding the interpretation of *reduced motivation* as a fatigue dimension equal to, for example, *physical* or *mental fatigue*.

Regarding the presence of clinically relevant fatigue, only *physical fatigue* exceeded the cutoff defined by Singer et al. for patients aged < 60 years (≥ 11 points).[38] While the questions in the MFI covering *physical fatigue* and

reduced activity mostly aim at physical aspects and are presumably answered with regard to actual function by the patients, the questions covering *mental fatigue*, and *reduced motivation* are abstract and aim at cognitive processing. As SMA patients suffer from severe motoric symptoms but not from cognitive impairments,[38] they may report high *physical fatigue*, but cognitive constructs such as motivation or mental exhaustion may be less relevant. Regarding the association of the different fatigue dimensions with sociodemographic characteristics, age correlated positively with *general* and *physical fatigue*, which is in line with previous studies of fatigue in general.[21,39] Further, participants who had been diagnosed with depression reported higher scores in the dimensions *general* and *physical fatigue*. An association of depression, especially with *mental* and *general fatigue*, is well known for several neurological diseases.[40,41] Moreover, a higher number of *SMN2* copies was associated with higher *physical fatigue* scores. In a previous monocentric study, we found that SMA patients with ≥ 4 *SMN2* copies reported higher scores for *reduced activity* but not *physical fatigue*.[3] A possible explanation for this discrepancy may be that in the present study more participants with < 4 *SMN2* copies —and thus, a more severe phenotype— were included and median *physical fatigue* was lower. Component correlations between *physical fatigue* and *reduced activity* might also contribute to this finding, though further investigation is needed. Interestingly, we found no correlation of motor function scores with any fatigue dimension, most importantly not with *physical fatigue*. This lack of relation is well known,[5] but a conclusive explanation is missing. We hypothesize that first, the functional assessments are not sensitive enough to capture all impairments reported by SMA patients, as already shown for endurance or independence.[42] The lack of relation to functional assessments further indicates that *physical fatigue* may include physical aspects not covered by the functional assessments. Therefore, (physical) fatigue is a symptom distinct from the motor function which should be assessed in SMA routine care. Next, we found that employed participants reported less fatigue in the dimensions *reduced activity* and *reduced motivation*. While the association with *reduced motivation* should be interpreted with caution, it is not surprising that employment status and fatigue are associated in general. Higher fatigue scores were associated with unemployment after traumatic brain injury and in multiple sclerosis.[43,44] Further, *general fatigue, mental fatigue*, and *reduced motivation* have been shown to predict a return to work during breast cancer treatment.[45]

The strength of our study is the comparably large sample size, especially bearing in mind that SMA is an orphan disease and large sample sizes are usually only achieved through multicenter (as done here) or international cooperation. The overall low number of missing data and the large number of sociodemographic characteristics studied are further advantages.

However, some limitations should be acknowledged. First, we did not intend to conduct a full psychometric analysis of the MFI, so we did not assess parameters such as test–retest reliability, interrater reliability, and minimally clinically important difference. Second, we did not perform personal interviews and therefore cannot determine the face validity of the MFI. Though, the small number of missing items and the absence of a systematic pattern for these missing items allows the conclusion that the MFI was well accepted by SMA patients. Regarding bias and imprecision, we have to take the possibility of selection bias into account as patients without fatigue more likely may have refrained from participating in the study. This may have contributed to an overestimation of fatigue scores. Further, the sociodemographic data were mostly collected prior to enrollment in our study and not with the purpose to investigate fatigue possibly leading to imprecision.

Although our sample was representative of adult SMA patients receiving nusinersen in Germany in terms of sex, age, SMA type, and physical impairments,[46,47] it may differ from the entirety of SMA patients especially compared with the pre-nusinersen era. Also, there were differences between the recruiting sites. Participants enrolled at the Ulm site suffered from a milder phenotype and reported, along with participants from Berlin, lower *physical fatigue* scores than the participants enrolled at Hannover. We do not expect these differences to impact our findings regarding the psychometric properties of the MFI, but this should be kept in mind when comparing studies conducted in different centers.

Our results indicate that the MFI is a valid and reliable instrument to assess different dimensions of fatigue in adult SMA patients. The original five-component model showed an acceptable fit for the data and all dimensions but *reduced motivation* had good internal consistency and convergent validity. We recommend the use of the original version of the MFI, although we found evidence that the reduction of individual items may lead to slightly improved psychometric properties. Fatigue is a relevant problem in SMA and has a negative impact on quality of life. The assessment of fatigue should therefore be incorporated into the clinical standard of SMA care, the MFI being the tool of choice to assess its different dimensions. If current treatment options such as SMN repletion therapies are addressing the pathological mechanisms underlying fatigue remains to be determined in future studies involving a longitudinal controlled design.

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Ethics Approval

The study has been approved by the local ethics review boards in Hanover (no. 6269), Essen (18-8285-BO), Dresden (EK393122012), Munich (16/14), Berlin (EA1/219/15), Ulm (19/12), and Rostock (A 2014–0021) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for Publication

All study participants gave their written informed consent to the publication of anonymized cohort data.

Author Contributions

Conceptualization—SP, OSK; Methodology—CB, SP, OSK; Software—all (CB, AO, NHT, BS, MF, IC, RG [Ramona Griep], ZU, CDW, CK, HAS, GW, AH, PL, MD, ACL, TM, RG [René Günther], TH, SP, OSK); Validation—CB, AH, PL, MD, ACL, TM, RG (René Günther), TH, SP, OSK; Formal Analysis—CB, NHT, OSK; Investigation—all (CB, AO, NHT, BS, MF, IC, RG [Ramona Griep], ZU, CDW, CK, HAS, GW, AH, PL, MD, ACL, TM, RG [René Günther], TH, SP, OSK); Resources—all (CB, AO, NHT, BS, MF, IC, RG [Ramona Griep], ZU, CDW, CK, HAS, GW, AH, PL, MD, ACL, TM, RG [René Günther], TH, SP, OSK); Data curation – all (CB, AO, NHT, BS, MF, IC, RG (Ramona Griep), ZU, CDW, CK, HAS, GW, AH, PL, MD, ACL, TM, RG (René Günther), TH, SP, OSK); Writing—original draft preparation—CB, AO, SP, OSK; Writing—review and editing—all (CB, AO, NHT, BS, MF, IC, RG (Ramona Griep), ZU, CDW, CK, HAS, GW, AH, PL, MD, ACL, TM, RG (René Günther), TH, SP, OSK); Visualization—CB, NHT; Supervision—AH, PL, MD, ACL, TM, RG (René Günther), TH, SP, OSK; Project administration—AO, AH, PL, MD, ACL, TM, RG (René Günther), TH, SP, OSK; all authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Deidentified data will be shared on reasonable request with any qualified investigator.

Conflict of Interest

CB reports no disclosures. AO has received honoraria as a speaker/consultant from the German Neuromuscular Society "Deutsche Gesellschaft fuer Muskelkranke (DGM e.V.), Impulze GmbH, and Biogen GmbH. She is being supported by PRACTIS—Clinician Scientist Program of Hannover Medical School, funded by the German Research Foundation (DFG, ME 3696/3-1, 2020–2021). NHT reports no disclosures. BS reports personal fees from Biogen, outside the submitted work. MF reports nonfinancial support from Biogen, outside the submitted work. IC reports no disclosures. RG (Ramona Griep) reports no disclosures. ZU reports speaker honoraria and research support from Biogen outside the submitted work. CDW is being supported by the Clinician Scientist Program (CSP) of Ulm University, funded by the German Charcot Foundation. She has received honoraria from Biogen as an advisory board member and for lectures and as an advisory board member and consultant from Hoffmann-La Roche. She also received travel expenses from Biogen. CK has received honoraria as a speaker/consultant from Biogen, Roche, Ipsen, and Merz Pharma. HAS reports no disclosures. GW reports no disclosures. AH is supported by the Hermann und Lilly Schilling Stiftung für medizinische Forschung im Stifterverband. He has received personal fees and nonfinancial support from Biogen and Desitin during the conduct of the study; and grants from the Helmholtz Foundation, the Federal Ministry of Education and Research, Innovationsausschuss des G-BA, the German Neuromuscular Society, and the Schilling-Stiftung outside the submitted work. PL reports no disclosures. MD received personal fees from Biogen, Roche, Sanofi-Genzyme, and Alnylam. ACL reports no disclosures. TM reports personal fees from Mitsubishi Tanabe Pharma, Biogen, ITF Pharma, and study support from Cytokinetics, Apellis Pharmaceuticals, Orphazyme, and Orion Pharma. TM further is a founder of the digital management and research platform "APST" and holds shares in Ambulanzpartner Soziotechnologie APST GmbH. RG (René Günther) received research support from Biogen and consultant honoraria from Biogen and Roche. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. TH has received grants from the Federal Ministry of Education

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