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The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue

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Abstract

Fatigue symptoms are reported by a majority of patients with multiple sclerosis (MS). Reliable assessment, however, is a demanding issue as the symptoms are experienced subjectively and as objective assessment strategies are missing. The objective of this study was to develop and validate a new tool, the Fatigue Scale for Motor and Cognitive Functions (FSMC), for the assessment of MS-related cognitive and motor fatigue. A total of 309 MS patients and 147 healthy controls were included into the validation study. The FSMC was tested against several external criteria (e.g. cognition, motivation, personality and other fatigue scales). The item-analysis and validation procedure showed that the FSMC is highly sensitive and specific in detecting fatigued MS patients, that both subscales significantly differentiated between patients and controls ($p < 0.01$), and that internal consistency (Cronbach's alpha $\alpha > 0.91$) as well as test–retest reliability ($r > 0.80$) were high. Cut-off values were determined to classify patients as mildly, moderately or severely fatigued. In conclusion, the FSMC is a new scale that has undergone validation based on a large sample of patients and that provides differential quantification and graduation of cognitive and motor fatigue.

Keywords

fatigue, fatigue assessment, fatigue scales, cognitive fatigue, motor fatigue, multiple sclerosis, patient reported outcome measure

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Introduction

Fatigue in the context of multiple sclerosis (MS) is a complex symptom with still obscure pathophysiology. According to several studies, 75–95% of all patients are affected[1,2] and 50–60% classify fatigue as one of the most serious symptoms interfering with the activities of daily living and thereby influencing quality of life.[3–5] In addition, fatigue is one of the main reasons for early retirement requests and inability to work,[6] pointing to the necessity of early and reliable evaluation. However, assessment of fatigue is difficult as it is experienced subjectively and as objective measurement tools are still missing. Patient reports support the assumption of fatigue not being unidimensional but being composed of different features,[2] some of which are cognitive and others more physical or motor-related. Although not being completely independent components, fatigue may occur with a physical or mental focus and as the knowledge about their relationship and the pathophysiological background is scarce, separate assessment of both components is advisable. Sometimes in conjunction with different assessment strategies, e.g. neurological interviews or fatigue diaries, questionnaires have become the gold standard in measuring fatigue. Although questionnaires offer the possibility to yield an essential database of processes that are not observable directly, their main disadvantage is the complete dependency on the subject's compliance, introspection, self-awareness, attention and willingness to overtly answer the questions. From a methodological point of view, items of a scale have to express clearly what a patient really experiences (= validity of a scale).

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Potential sources of conceptual heterogeneity among the existing MS-fatigue scales lie in the uncertainty among experts of which fatigue aspects a valid scale should include (e.g. motor performance, muscle strength, etc.). Thus, while there is a huge heterogeneity in the structure of the scales, some of them focus on the multidimensional facets of fatigue while others follow a domain-specific approach. Only a few scales have undergone validation, and even in those that have, the documented validation procedures did not fulfil accepted methodological criteria[7] in terms of appropriate sample size, inclusion of external criteria etc.[8,9] In addition to these inadequacies in the validation process, other obstacles appear already at the level of item generation. Only a few instruments are composed of items that have been determined by item analyses, which makes reliable assessment questionable. Finally, concerning the operationalization, in most scales the items are not suited to patients with lower education levels and/or those with additional cognitive impairments (i.e. length and complexity of sentences).

Given this background there is a need for an instrument to diagnose and quantify the core symptoms of fatigue reliably. The present study aimed at developing a new questionnaire that focuses on the two main reported domains of fatigue (i.e. cognitive and motor), that is easy to administer in clinical routine and allows for graduation of the symptoms by cut-off values.

Subjects and methods

Participants

A total of 354 MS patients and 151 control subjects entered the study. Only patients with clinically and laboratory definite MS according to McDonald's criteria and without relapse during the last 3 months were included. Immunomodulatory and symptomatic treatment should have been stable for 3 months and only participants without any history of any other (non-MS-related) neurological and/or psychiatric disorder were considered for participation. Out of the 354 patient data sets collected, 10.7% were excluded from further analyses because participants did not match the inclusions criteria, and 2.0% were rejected due to missing values exceeding 5% of the individual data set. Remaining isolated missing values under 5% were replaced by the expectation maximization algorithm (SPSS Missing Values Analysis 7.5, 1997 SPSS Inc.). This procedure was compared with the list-wise deletion alternative and revealed only minor differences in means and standard deviations. In the control group, 2.0% did not reach the inclusion criteria and 0.7% missing values were replaced by the above-mentioned algorithm.

Table 1. Demographic characteristics of the study cohort

Demographics	MS patients	Controls
N	309	147
Mean age	43.4 (SD = 9.9)	41.7 (SD = 12.9)
Sex		
Female	206	92
Male	103	55
Smoking		
No	62.1%	72.1%
Moderate	25.2%	22.4%
Strong	12.6%	5.4%
Handedness		
Right	86.4%	82.3%
Left	4.5%	11.6%
Both	9.1%	6.1%
Education		
Low	4.5%	2.0%
Medium	57.9%	54.4%
High	37.6%	43.6%

Note: *N*, number of subjects; SD, standard deviation.

Finally, a total of 309 MS patients with a mean age of 43.4 years (standard deviation (SD) = 9.95) and mean Expanded Disability Status Scale (EDSS) score of 3.4 (SD = 1.63) were considered for further statistical analyses. Two hundred and six subjects were female and 103 were male. One hundred and ninety nine had relapsing–remitting MS, 79 secondary progressive MS and 31 primary progressive MS. Furthermore, 147 healthy control subjects, 92 female and 55 male, with a mean age of 41.7 years without any history of psychiatric or neurological disorders participated in the study. By means of various demographic variables such as age, sex, education, handedness, smoking behaviour and profession, we tried to ensure collection of a representative healthy control sample (see Table 1).

All participants gave their informed written consent. None of the subjects refused participation due to length of testing. The study was approved by the local ethics committee of the University of Basel, Switzerland.

Item generation

In a first step, the most commonly used fatigue questionnaires (Fatigue Severity Scale (FSS),[8] Fatigue Assessment Instrument (FAI),[9] Fatigue Impact Scale (FIS),[4] Modified Fatigue Impact Scale (MFIS) from the MS Council,[2] (Fatigue Rating Scale (FRS),[10] and the Physical and Cognitive Fatigue scale[11]) were analysed on an item-to-item basis by sorting the individual items primarily according to the two-dimensional concept of motor and cognitive fatigue. Additional relevant

criteria in the item-selection process were that frequency and duration of individual symptoms should be reflected in the phrasing of the items and that fatigue as a state (actual preponderant symptoms) or trait (symptoms persisting over time) should be contained. After rephrasing and modifying those questions according to these criteria, additional items were created based on an expert-concerned-layperson interview approach with 10 neurologists, 10 physiotherapists and 10 MS patients as a pool-selection group. This step in the development process was aimed at providing a holistic view of the different fatigue aspects to further improve content validity.[7]

Semantic item analysis

For better practicability we chose to restrict the number of items to 10 per subscale. In a final step, 20 items (10 for cognitive and 10 for physical fatigue) that were consistently confirmed by the pool-selection group entered a stepwise semantic item analysis. First, 82 healthy controls were asked either in a directive way to rate the items on a dichotomous scale as measuring either cognitive or motor fatigue or in a so-called 'open-choice' manner to indicate by themselves what might be the focus of the individual item. Based on a qualitative analysis, items were either eliminated if they could not be clearly allocated by at least 75% of the raters to 'motor' or 'cognitive' aspects of fatigue or, if ambiguous, rephrased again. In a second step, the new item pool consisting of 20 items was further evaluated by 27 healthy controls and 45 MS patients in the same directive way as described above. The final evaluation resulted in a pool of 20 items that best distinguished and denominated the cognitive and motor aspects of fatigue. In addition, we tried to cover the four major components of fatigue as proposed by DeLuca[12] and Wessley et al.[13] by phrasing items that comprise behavioural/quantitative aspects of fatigue (e.g. items 3 and 8), the feeling state of the patient (all items), mechanisms inducing fatigue (items 5 and 11) and situative/contextual aspects (e.g. items 1, 8, 10 and 19). Thus, the final scale is composed of 20 items, whereby 10 items focus on cognitive and 10 items on motor fatigue. For each item the response pattern was fractionated on the basis of a five-point Likert scale (from 'absolutely agree' to 'absolutely disagree'). The instruction section asks the patient to assess fatigue symptoms *in general* instead of referring to a fixed time frame. This allows the *trait nature* of fatigue to be covered which should be independent of a given time frame that due to various confounding factors may not be representative. For the evaluation of specific treatment effects in a restricted time frame a B-version with a randomized order of the same items is available upon request from the corresponding author.

Table 2. Summary of cognition- and motor-related item contents

Item key cognitive subscale	Item key motor subscale
Concentration	Skilfulness
Decision making/executive functions	Stamina/resting periods
Learning	Stress and physical power
Occupational demands	Social environment
Stress and concentration	Muscles/strength
Heat and thinking	Physical stamina
Thinking/motivation/drive	Drive/motivation
Verbal fluency	Speed reduction
Attention/stamina	Reactivity
Memory	Heat and physical energy

The item key for both subscales is shown in Table 2. The scale itself is presented in the Appendix (available online as supplementary file).

Validity

To assess convergent and discriminant validity, the FSMC was tested against several external criteria estimated to be of relevance for motor and/or cognitive fatigue:

(a) To assess convergent validity, different fatigue ratings often used in clinical routine and/or clinical trials were included:
- Rating for fatigue by neurologists according to the global clinical impression and documented via standardized, quantified neurological examination (Neurostatus; see http://www.neurostatus.net).
- Two commonly used fatigue scales: FSS,[8] an instrument focussing primarily on motor fatigue and the MFIS[2] which assesses motor, cognitive and psychosocial components of fatigue.

(b) To specify discriminant validity, depression as a factor often discussed to be substantially related to fatigue was included via:
- rating for depression by neurologists according to the global clinical impression;
- Beck Depression Inventory (BDI);[14]

(c) To test for convergent and discriminant validity, the relation between cognitive/motor fatigue and cognitive performance/motor function was assessed via the following:
- Neuropsychological testing: Brief Repeatable Battery of Neuropsychological Tests (BRB-N),[15] Faces Symbol Test (FST),[16] Multiple Sclerosis Neuropsychological Questionnaire (MSNQ-patient and informant report).[17] For the MSNQ-informant report, proxies consisted of spouses, significant

others or close relatives. All patients had a person who belonged to one of the three categories.
- Testing of upper and lower extremity function: 9HPT and 25-foot-walk of the Multiple Sclerosis Functional Composite (MSFC).[18]

For each participant the whole assessment procedure lasted 2 hours.

All data were analysed using standard statistical software (SPSS, version 11.0.4). Owing to the large sample size examination of the distributions was performed via inspection of box-plots for all analysed data instead of application of the Kolmogorov–Smirnoff test. From this inspection no obvious signs of deviation from a normal distribution were detected. Thus, parametric tests were used for further data analyses.

Results

Reliability

Cronbach's alpha as a measure for internal consistency was computed for both subscales and the total scale. In the patient group, $\alpha = 0.93$ for the cognitive subscale, $\alpha = 0.91$ for the motor subscale and $\alpha = 0.95$ for the entire scale. In the control group, $\alpha = 0.87$ for the cognitive subscale, $\alpha = 0.83$ for the motor subscale and $\alpha = 0.91$ for the total scale.

To analyse test–retest reliability, 294 patients out of the whole sample completed the FSMC again after an interval of 4 weeks. Bivariate correlations between the first and second measurement revealed the following significant correlation coefficients: 0.85 for the cognitive FSMC subscale, 0.86 for the motoric FSMC subscale and 0.87 for FSMC total scale.

Validity

Bonferroni-corrected *t*-tests ($p = 0.0025$) for independent samples revealed significant differences between MS-patients and healthy controls for each item of the two subscales ($p < 0.0001$; $1.01 < d < 2.13$).

Principal component analysis: To confirm the conceptualization of the FSMC into the dimensions 'motor fatigue' and 'cognitive fatigue', a principal component analysis with Varimax rotation and Kaiser normalization was computed. For the patient cohort, two main factors could be extracted with the first factor explaining 35.7% of variance and a second factor explaining 25.7% of variance. Out of the 20 items, the 10 cognitive items uniquely loaded on the first factor, seven motor items loaded on the second factor and three motor items loaded on both factors.

Convergent and discriminant construct validity: Bivariate correlations to test for convergent validity showed high correlations between the FSMC and the two existing fatigue scales FSS and MFIS, and a lower correlation to the fatigue scoring by treating neurologists (see Table 3 for details).

To determine discriminant validity, correlations were computed between FSMC and (a) depression measured either by BDI or rated by neurologists, (b) disease severity measured by EDSS, (c) physical functionality as measured by the Nine Hole Peg (9-HP) test and the 25-foot-walk test (Table 4) and (d) cognitive performance (Table 5). Depression correlated with both subscales of the FSMC. These correlations were slightly weaker than those obtained between depression and fatigue measured by MFIS and FSS. While EDSS only correlated substantially with the physical aspects of fatigue, cognitive test performance was weakly to moderately correlated to motor as well as to cognitive fatigue (Table 4). Table 5 reports correlation coefficients where the relation between fatigue and at least one of the cognitive measures was more than 0.16.

Since depression was strongly related to both cognitive and motor fatigue, partial correlations controlling for depression were computed to clarify the adjusted relation between fatigue, the above-mentioned other disease variables and cognition. Details are given in Tables 3–5.

As the MSFC is a clinically important outcome measure for MS trials we additionally computed *z*-transformed MSFC values from the PASAT (Paced auditory serial addition test), 9-HP test and the 25-foot-walk test. The total *z*-score was then correlated with the different fatigue measures. It turned out that the MSFC correlated highest with the FSMC motor scale ($r = -0.342$**) and the MFIS motor scale ($r = -0.258$**), followed by the FSMC cognitive scale ($r = -0.206$**), the FSS ($r = -0.142$*) and the MFIS cognitive scale ($r = -0.130$*). More specifically, highest correlations were found between PASAT and FSMC sum score ($r = -0.25$**), FSMC motor score ($r = -0.20$**) and FSMC cognitive score ($r = -0.27$**).

Sensitivity and specificity: As for MS-fatigue objective criteria to verify the presence of fatigue are missing, the different fatigue scales with their subscales were chosen as predictor variables for the group variable (MS/controls) in a logistic regression. Based on the resulting classification table, the percentage of patients correctly diagnosed as MS patients ('sensitivity') and the percentage of controls correctly classified as not being MS patients ('specificity') could be identified. As fatigue is a well-established symptom in MS that, by definition, is not present in healthy subjects, the mentioned 'sensitivity' and 'specificity' values indicate the ability of the scales in relating fatigue to the underlying diagnosis of MS.

Table 3. Correlations between different fatigue assessments in the patient cohort

	FSMC_M	MFIS_C	MFIS_M	MFIS_S	FSS_S	FbN
FSMC_C	0.710**	0.832**	0.560**	0.771**	0.684**	0.444**
FSMC_M		0.555**	0.804**	0.763**	0.794**	0.497**
FSMC_S		0.756**	0.732**	0.829**	0.797**	0.508**

Note: Pearson correlation, 2-tailed, **p < .01; FbN, fatigue rated by neurologists; FSMC, Fatigue Scale for Motor and Cognitive Functions; MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; _C, cognitive subscale; _M, motor subscale; _S, sum score of scale.

Table 4. Correlations and partial correlations controlling for depression shown in parentheses between fatigue and other disease variables

	BDI	DbN	EDSS	9HPmean	25FWmean
FSMC_C	0.47**	0.21**	0.13* (0.09)	0.03 (0.01)	0.04 (0.01)
FSMC_M	0.42**	0.23**	0.38** (0.38**)	0.22* (0.24**)	0.22** (0.22**)
FSMC_S	0.49**	0.24**	0.27** (0.25**)	0.15* (0.14*)	0.14* (0.12*)
MFIS_C	0.52**	0.29**	0.03 (−0.03)	0.01 (−0.03)	0.01 (−0.03)
MFIS_M	0.47**	0.27**	0.34** (0.33**)	0.22** (0.22**)	0.21** (0.20**)
MFIS_S	0.56**	0.31**	0.21** (0.19**)	0.13* (0.11*)	0.13* (0.12*)
FSS_S	0.45**	0.26**	0.26** (0.24**)	0.11 (0.09)	0.14* (0.12*)
FbN	0.30**	0.37**	0.18** (0.16**)	0.07 (0.05)	0.15** (0.15**)

Note: Pearson correlation, 2-tailed, **p < .01, *p < .05; _C, cognitive subscale; _M, motor subscale; _S, sum score of scale; FbN, fatigue rated by neurologists; DbN, depression rated by neurologists; FSMC, Fatigue Scale for Motor and Cognitive Functions; MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; BDI, Beck Depression Inventory; EDSS, Expanded Disability Status Scale; 9HPmean, mean value of nine hole peg test; 25FWmean, mean value of 25 footwalk test.

Table 5. Correlations and partial correlations controlling for depression shown in parentheses between fatigue and cognitive outcome measures

	MSNQ_P	MSNQ_I	FST_90s	SDMT	PASAT
FSMC_C	0.61** (0.52**)	0.38** (0.31**)	−0.16** (−0.17**)	−0.33** (−0.30**)	−0.27** (−0.26**)
FSMC_M	0.39** (0.26**)	0.26** (0.18**)	−0.26** (−0.28**)	−0.34** (−0.31**)	−0.20** (−0.18**)
FSMC_S	0.54** (0.44**)	0.35** (0.27**)	−0.23** (−0.25**)	−0.36** (−0.34**)	−0.25** (−0.24**)
MFIS_C	0.65** (0.57**)	0.38** (0.31**)	−0.10 (−0.10)	−0.27** (−0.24**)	−0.18** (−0.15**)
MFIS_M	0.32** (0.16**)	0.24**(0.15**)	−0.18** (−0.20**)	−0.29**(−0.25**)	−0.10 (−0.06)
MFIS_S	0.54** (0.41**)	0.34** (0.26**)	−0.16** (−0.17**)	−0.31** (−0.28**)	−0.15** (−0.12*)
FSS_S	0.39** (0.26**)	0.24** (0.15**)	−0.09 (−0.09)	−0.19** (−0.14*)	−0.04 (−0.00)
FbN	0.23** (0.13*)	0.13* (0.07)	−0.09 (−0.08)	−0.16** (−0.13*)	0.01 (−0.04)

Note: Pearson correlation, 2-tailed, **p < .01, *p < .05; _C, cognitive subscale; _M, motor subscale; _S, sum score of scale; FbN, Fatigue estimated by neurologists; MSNQ_P, Multiple Sclerosis Neuropsychological Questionnaire Patient Report; MSNQ_I, Multiple Sclerosis Neuropsychological Questionnaire Informant Report; FST_90s, Faces Symbol Test Performance after 90 seconds; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Test.

In this concern, the logistic regression revealed high 'sensitivity' and 'specificity' scores for both FSMC subscales. A comparison between the FSMC and the two other fatigue scales (FSS, MFIS) showed that the values for specificity, in particular, distinguished the new scale from the other fatigue instruments (Table 6).

To test for relevant differences in receiver operating characteristic (ROC) areas between the FSMC and the two other fatigue scales, 90% confidence intervals (CIs) were computed for the ROC areas of the individual tests to find out if the overlap between the FSMC and the two other scales was below 30% of the 90% CI width. According to Cumming and Finch[19], it has been assumed that for one-tailed hypotheses with $\alpha = 0.05$, an overlap below 30% can be regarded as reflecting a substantial difference between the

individual measures. As shown in Figure 1, there was either no overlap (exemplified for the cognitive subscales) or an overlap not exceeding the critical value of 30%.

In addition we plotted the ROC curves of the three different scales into one figure to allow a direct comparison of the area under the curve between the different instruments. As shown in Figure 2, the FSMC is not only superior with respect to the total scale but also with respect to the two different subscales.

Quantification and graduation of fatigue: Cut-off values for the FSMC total score and the differential scores as expressed in the subscales were determined by SDs from the mean values of the healthy control group. As one SD corresponded to the optimal value received by ROC analyses for sensitivity and specificity, a further graduation of the fatigue symptoms was undertaken by two and three SDs. Thus, according to the cut-off values in Table 6, MS patients can be categorized as mildly, moderately and severely fatigued (Table 7).

Table 6. Comparison of ROC analysis results for the different fatigue scales

Scales	Sensitivity	Specificity	ROC-Area
FSMC_S	88.7	83.0	0.93
FSMC_C	86.4	66.7	0.88
FSMC_M	89.0	86.4	0.94
MFIS_S	87.1	71.4	0.89
MFIS_C	83.8	59.2	0.82
MFIS_M	88.0	77.6	0.91
FSS_S	86.7	69.4	0.89

Note: FSMC_S, sum score of FSMC; FSMC_C, cognitive score of FSMC; FSMC_M, physical score of FSMC; abbreviations for the other scales respectively.

Discussion

Since fatigue belongs to the core symptoms in MS, reliable assessment in clinical routine is required. However, fatigue symptoms may vary among patients in frequency and pattern and may also be influenced by some environmental and psychosocial conditions. Therefore, assessment of fatigue still remains a challenging endeavour. Numerous factors add to the complexity of this task. First, the illness has a variable course; second, there is no definite diagnostic laboratory test or biomarker; third, fatigue is common to many other illnesses. Moreover, and unlike many other MS-related symptoms, fatigue cannot necessarily be inferred by some clinical apparent markers (e.g. paresis). Most importantly, fatigue appears to have physical as well as mental components.

Taking into account these restrictions, one promising method to assess fatigue is given by self-report measures. Although fatigue questionnaires represent a gold-standard in clinical practice, some of the existing scales suffer from methodological limitations regarding validation procedures and scale conceptions. With the FSMC we aimed at better assessing the respective contribution and inter-correlation of physical and mental fatigue. This segregation of physical and mental fatigue might further help to better understand the influence of potential confounding variables and finally contribute

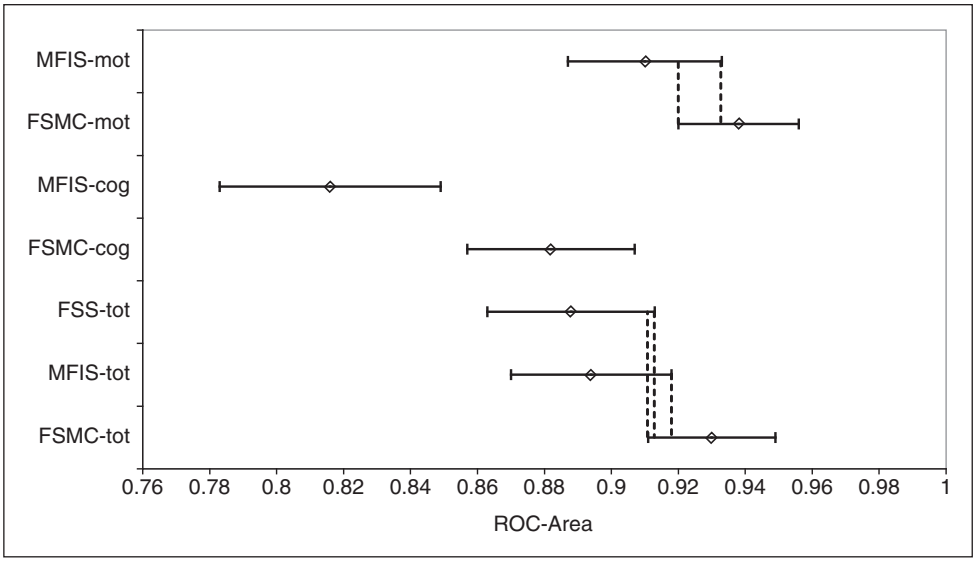

Figure 1. Overlap for the 90% confidence intervals of the receiver operating characteristic (ROC) areas between the Fatigue Scale for Motor and Cognitive Functions (FSMC) total scale and its subscales and the Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS), respectively.

to a better understanding of the mechanisms which underlie the different fatigue domains.

The results of our validation study have shown that both subscales provide good reliability, sensitivity and specificity values. The concept of the scale with its two components has been verified by the factor analysis. In terms of convergent validity, high intercorrelations were found between the FSMC and the two other fatigue instruments FSS and MFIS.

Differentiating physical from cognitive aspects of fatigue in MS may also play an important role for treatment studies. A differentiation between individual fatigue profiles might help to elucidate differential treatment efficacy on specific dimensions (e.g. positive effects on physical fatigue components does not necessarily imply efficacy on mental fatigue symptoms and vice versa). The need for a proper distinction between mental and physical aspects was exemplified in a study by Ford and coworkers.[20] The authors could demonstrate that while depression was significantly correlated with mental fatigue there was no such relation to physical components. Our study results, however, clearly support the hypothesis that depression is related to both cognitive and motor fatigue. This was true for all three fatigue inventories applied (FSMC, FSS, MFIS) and points to a strong relationship between fatigue and depression.

Comparable to the fatigue rating (see Table 3), treating neurologists rated the degree of depression to be lower than indicated by the patients' self-reports assessed via BDI. This result clearly demonstrates the inconsistency between self- and external evaluation and might be of relevance in the treatment process on depression and fatigue in MS.

Since in our study fatigue and depression turned out to be strongly interlinked, we conducted a partial correlation analysis to control for depression and thus allowing a more detailed insight into the relation between fatigue, other disease variables and cognitive performance. When the influence of depression was controlled for, EDSS and physical functions only correlated with motor but not with cognitive fatigue. From these results it can be concluded that motor fatigue is closely related to physical function as indicated by high EDSS scores and decreased 9-HP test and 25-foot-walk performance.

When applying a comprehensive neuropsychological screening to assess the cognitive core functions mostly affected in MS we found cognitive test performance to be only slightly related to fatigue. The highest correlation coefficients were detected between the MSNQ self-reports and cognitive fatigue thus indicating that the subjective self-evaluation of the patients is consistent for fatigue and cognitive performance. However, among the different objective test measures only three tests, the FST_90s (Faces Symbol Test after 90 seconds), the SDMT (Symbol Digit Modalities Test) and the PASAT showed relevant correlations. From these

Table 7. Cut-off values for the FSMC

FSMC Sum Score	≥43	Mild fatigue
	≥53	Moderate fatigue
	≥63	Severe fatigue
FSMC Cognitive Score	≥22	Mild cognitive fatigue
	≥28	Moderate cognitive fatigue
	≥34	Severe cognitive fatigue
FSMC Physical Score	≥22	Mild motor fatigue
	≥27	Moderate motor fatigue
	≥32	Severe motor fatigue

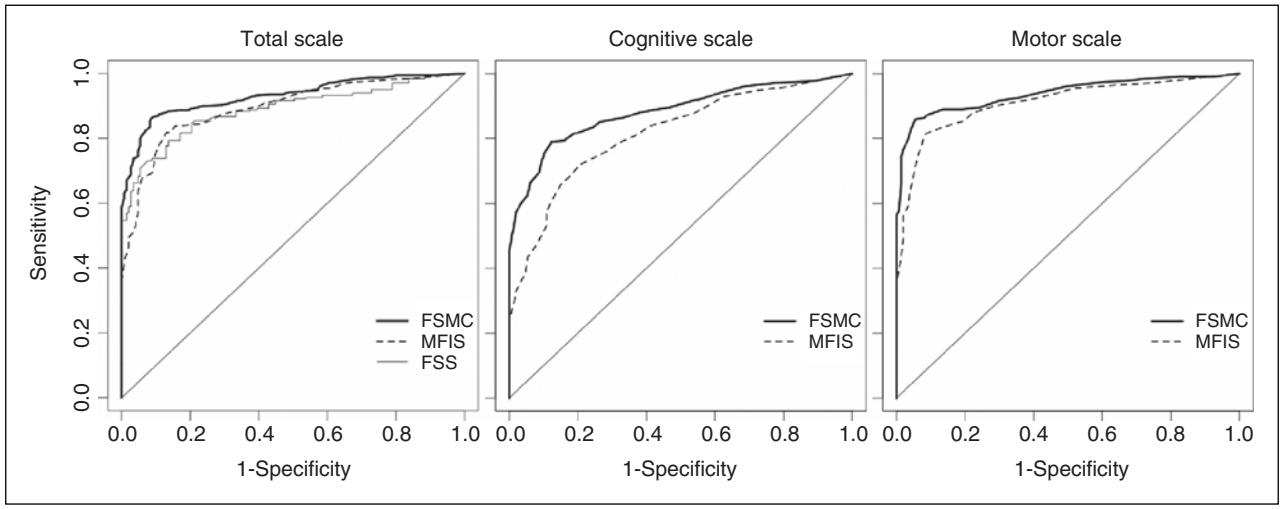

Figure 2. Receiver operating characteristic areas plotted into one figure for the three total scales and for the cognitive and motor scale of the Fatigue Scale for Motor and Cognitive Functions (FSMC) and Modified Fatigue Impact Scale (MFIS), respectively.

results it can be inferred that only tests sensitive for information processing speed and working memory may be related to fatigue while verbal and spatial short- and long-term memory as well as executive functions are not influenced. Interestingly, both cognitive and motor fatigue were found to be related to these tests underlining the interrelation between cognitive and motor fatigue even for cognitive processing. By controlling for depression, we were able to unmask the robust correlation between MSNQ patient and informant report and cognitive fatigue. Among the cognitive test variables, the SDMT turned out to correlate highest with cognitive and motor fatigue, followed by the PASAT and FST_90s. A qualitative comparison between the three fatigue scales showed that for the FSMC both subscales consistently correlated with all three cognitive outcome measures, while MFIS and FSS did not show a comparable consistency over all three cognitive outcome measures. These findings might be interpreted in favour of the sensitivity of the FSMC with respect to cognitive and motor aspects of neuropsychological tests. While the FST_90s is highly dependent on intact hand function, which is reflected by higher correlations with motor fatigue, the SDMT measures mainly information processing speed requiring a fast vocal output, thus showing a correlative relationship to both fatigue aspects. PASAT however is primarily a test for higher cognitive functioning that is reflected by a stronger relation to the cognitive fatigue component. Being aware of the only small to modest correlation coefficients overall one can note that the FSMC was at least able to distinguish *consistently* between motor and cognitive aspects of fatigue and which was slightly less influenced by depression.

By logistic regression we found higher levels of sensitivity and specificity for the FSMC when compared with MFIS and FSS. As the ROC area reflects the relation between sensitivity and specificity values, 90% CIs for the ROC areas were computed and the overlap between the scales was analysed. By applying this method it could be demonstrated that the ROC areas for the FSMC were the largest and that the overlap of the 90% CI between FSMC, MFIS and FSS was less than 30%. In addition we plotted the ROC curves into one figure to allow for direct comparison between the different areas under the curve. Although differences are small, the FSMC consistently showed the largest ROC area when compared with MFIS and FSS. Thus, it can be concluded that the FSMC's values for sensitivity and specificity were superior to the values obtained by the MFIS and FSS. To support reliable fatigue assessment, cut-off values for the FSMC total scale and both subscales were determined by SDs from the mean values of a healthy control population. By means of these cut-off values, we were able to establish a subdivision from mild, moderate to severe fatigue for both domains as well as for the composite fatigue score. This approach clearly distinguishes the new scale from other existing instruments and thus offers the possibility to grade fatigue symptoms as they may change over time.

In conclusion, the FSMC represents a new patient reported outcome measure for measuring mental and physical fatigue. Sensitivity and specificity scores allow reliable assessment and the statistically identified cut-off values provide detailed quantification of fatigue in clinical routine. As the FSMC additionally underwent a professional linguistic validation procedure for more than 20 languages including the steps (a) backward and forward translations, (b) clinician's review, (c) cognitive debriefing and (d) international harmonization, this instrument might offer new perspectives for international research programs on fatigue in MS.

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