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Validation of the fatigue scale for motor and cognitive functions in a danish multiple sclerosis cohort

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ABSTRACT

Background: Our objective was to validate the Danish translation of the Fatigue Scale for Motor and Cognitive Functions (FSMC) in multiple sclerosis (MS) patients.

Materials and methods: A Danish MS cohort (n = 84) was matched and compared to the original German validation cohort (n = 309) and a healthy control cohort (n = 147). The Modified Fatigue Impact Scale (MFIS) was used as reference scale and Becks Depression Inventory-Fast Screen (BDI-FS) and Expanded Disability Status Scale (EDSS) for confounding factors. We assessed internal consistencies; convergent, divergent, and predictive validity; partial correlations correcting for depression; significant differences between the mean scores of the cohorts; and sensitivity and specificity with receiver operating characteristic (ROC) curves.

Results: Excellent internal consistencies for the total scale and subscales were found (α = 0.91–0.95). Strong positive correlations between the two fatigue scales implied high convergent validity (total scores: r = 0.851, $p < 0.01$). The two cohorts corresponded well when divided into subgroups (EDSS score; age; gender). Correcting for depression did not result in any significant adjustments of the correlations. The area under the curve (AUC) for the ROC curves represented excellent accuracy (Danish MS cohort, AUC = 0.9190; German MS cohort, AUC = 0.9034).

Conclusion: The Danish translation of the FSMC has a high convergent validity with another measure of fatigue as well as excellent internal consistency and accuracy. It is found to be an applicable and recommendable measure of fatigue in Danish MS patients.

1. Introduction

Multiple sclerosis (MS) is a disease characterised by numerous neurological deficits including sensory and motor problems. Fatigue is the most commonly reported subjective symptom (65–95%), and often found to be the most debilitating (40%) (Bakshi, 2003; Minden et al., 2006). Together with depression, fatigue have a higher negative impact on quality of life (QoL) than physical complaints like spasticity and weakness (Amato et al., 2001). Fatigue in MS patients differs from normal tiredness experienced by healthy individuals. It is more severe, disabling, and more likely to interfere with them meeting their responsibilities (Krupp et al., 1988). Not only is the symptom itself a great burden to the patients, but the treatment of fatigue also presents a challenge. A major challenge in dealing with fatigue is that the aetiology and pathophysiology behind the symptom remains unclear (Rottoli et al., 2016) and there is no common unified definition among researchers and clinicians. A recently published study tried to limit this problem of inconsistency, by proposing the following definition for fatigue: "*The decrease in physical and/or mental performance that results from changes in central, psychological, and/or peripheral factors*" (Rudroff et al., 2016).

Monitoring fatigue as a symptom in clinical practice is based on the patient's own perception, and is most frequently done through self-report questionnaires. Due to both cultural and linguistic differences among countries, it is important to both translate and validate questionnaires in the native language of a patient population. Even though a number of different fatigue scales has been presented, most are only validated in English. In this study we wanted to validate a frequently

Abbreviations: FSMC, The fatigue scale for motor and cognitive functions;; MFIS, The modified fatigue impact scale; BDI-FS, Becks depression inventory-fast screen; EDSS, Expanded disability status scale

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used fatigue scale among MS patients in Denmark, namely the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009), and compare with the already well-established Modified Fatigue Impact Scale (MFIS) (1998). Both scales provide the possibility to subdivide the symptoms into the two entities of motor and cognitive fatigue.

2. Material & methods

2.1. Ethics

All procedures were performed according to the Declaration of Helsinki and with permission from the Regional Committees on Health Research Ethics for Southern Denmark (Reference number: S-20140034). The study was also approved by Danish Data Protection Agency (Reference number: 14/8330).

2.2. Participants

The study populations consisted of a Danish MS cohort (n = 84), a German MS cohort (n = 309), and a German healthy controls cohort (n = 147).

The Danish patient group was recruited, after written and oral informed consent, from the MS clinic at Odense University Hospital in 2014.

Inclusion criteria were: i) Clinically definite MS diagnosed by a specialist in Neurology according to the revised 2010 McDonald criteria (Polman et al., 2011), ii) age > 18 years, and iii) Danish as native language.

Exclusion criteria were: i) Other neurological diseases, ii) history of developmental disorders or other learning disability, iii) previous or present psychiatric diagnosis that is unlikely to be part of the patients' MS, iv) alcohol or drug abuse, and v) corticosteroids treatment within the last 4 weeks before evaluation. Information on age, gender, and Expanded Disability Status Scale (EDSS) (Kurtzke, 2015) score were also gathered.

All Danish study subjects completed the FSMC, the MFIS, and the Becks Depression Inventory-Fast Screen (BDI-FS) during a visit to the MS clinic.

2.3. Scales

All scales are self-evaluation questionnaires constructed as Likert scales, with 1–5 points per item for the FSMC, 0–4 points per item for the MFIS, and 0–3 points per item for the BDI-FS.

The FSMC consists of 20 items, with a subdivision of 10 motor and 10 cognition focused items. Cut-off values for grading of fatigue were based on the original validation data (Penner et al., 2009). A score of ≥ 43 equals mild, ≥ 53 equals moderate, and ≥ 63 equals severe fatigue. The total possible score ranges from 20 to 100 points. Cut-off values for the cognitive subscale were ≥ 22 for mild, ≥ 28 for moderate, and ≥ 34 for severe cognitive fatigue. For the motor subscale: ≥ 22 for mild, ≥ 27 for moderate, and ≥ 32 for severe motor fatigue (Penner et al., 2009).

The MFIS consists of 21 items, where 9 are related to motor, 10 to cognition, and 2 to psychosocial aspects of fatigue. The cut-off value defining fatigue related to MS is 38 points (Flachenecker et al., 2002), and the total possible score is between 0 and 84 points.

For assessment of depression we used BDI-FS. The scale consists of 7 items and cut-off values for interpretation are provided, where 0–4 points equals minimal depression, 4–8 equals mild, 9–12 equals moderate, and 10–21 equals severe (Smarr and Keefer, 2011).

2.4. Statistical analysis

Statistical validation was based on the recommendations of Bland and Altman (Bland and Altman, 2002).

Descriptive statistics were calculated for mean age, gender distribution, and mean EDSS score. The distribution of fatigue severity was calculated for each of the cohorts.

Due to the large sample size, manual inspection of box plots was performed to evaluate Gaussian distribution. Based on this, the data did not deviate from a normal distribution, and parametric tests were applied.

Cronbach's alpha was used for calculating internal consistency. Good consistency was defined as $\alpha \geq 0.8$.

Validity of the content was based on calculations on convergent and divergent validity. For convergent validity, we performed bivariate correlation analyses between the FSMC and the MFIS, both total and subscales. Divergent validity was assessed through correlations between fatigue scales and i) BDI-FS and ii) EDSS scores. Pearson correlation coefficient was used to calculate the correlations between the FSMC and MFIS. The correlations between the fatigue scales and the BDI-FS and EDSS score was calculated by the same method, as well as partial correlations correcting for the possible confounding effect of depression.

Predictive validity was calculated by comparing the cohorts through unpaired *t*-tests. First, we divided the patients into subgroups based on i) EDSS score (≤ 3 points for mild disability; 3.5–6 points for moderate disability; ≥ 6.5 points for severe disability), ii) age (10 year-intervals), and iii) gender. Next, we compared matched subgroups from the two MS cohorts and calculated the statistical significance.

The statistical significance of mean scores of individual items and of the total sums in both scales were estimated using two-sampled *t*-tests with unequal variances and post-hoc Bonferroni correction (for FSMC: $p < 0.0025$; for FSMC total and subscales: $p < 0.0167$; for MFIS: $p < 0.0024$; for MFIS total and subscales: $p < 0.0125$).

Moreover, we calculated the sensitivity and specificity for different cut-off values of the FSMC using MFIS as reference variable. Receiver operating characteristic (ROC) curves were plotted for these numbers.

The statistical analysis was done using STATA 14.0 and GraphPad PRISM 7. All p-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics

The study cohorts were well-matched in age, gender distribution, and mean EDSS score (Table 1). Even though the Danish cohort (n = 84) was smaller than the German (n = 309), they had a similar distribution when subdividing into the different fatigue severities according to the cut-off values (Table 1).

3.2. Reliability of the FSMC

Internal consistency of the whole questionnaire was calculated and compared to the original validation paper (Penner et al., 2009). In the Danish patient group; $\alpha = 0.95$ for the total scale, $\alpha = 0.93$ for the cognitive subscale, and $\alpha = 0.91$ for the motor subscale. None of the Cronbach's alpha values with missing item showed a higher value, indicating that removing any of the questions, would not increase the internal consistency of the questionnaire.

3.3. Validity of the FSMC

The two fatigue scales and related subscales correlated well. The cognitive subscales ($r = 0.8521$, $p < 0.0001$) as well as the motor subscales ($r = 0.774$, $p < 0.0001$) had strong positive correlation coefficients, concluding with a high convergent validity (Table 2).

Except from the cognitive subscales, all scales including subscales showed slightly weak, but significant, correlations with depression through the BDI-FS score (Table 3). Disability measured by EDSS scores showed the same trend; however, with a somewhat stronger correlation