The contribution of disease severity, depression and negative affectivity to fatigue in multiple sclerosis: A comparison with ulcerative colitis

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Abstract

Background: Fatigue is one of the most common and troubling symptoms of multiple sclerosis (MS) and more severe and disabling than fatigue in other somatic populations. Although fatigue seems MS specific, its pathogenesis is still poorly understood. Objective: To study the disease specificity of fatigue in MS by comparing its level, its physical and psychological correlates to those of patients with ulcerative colitis (UC), a peripheral chronic auto-immune disease. We focused on the relative contribution of disease severity, depression and negative affectivity to fatigue in both patient samples. Methods: A total of 88 MS and 76 UC patients were included in this cross-sectional study. Fatigue, depression and negative affectivity were assessed respectively with the physical and mental fatigue subscales of the Multidimensional Fatigue Inventory, the depression subscale of the Hospital Anxiety and Depression Scale, and the neuroticism subscale of the Dutch NEO Five-Factor Inventory. The Expanded Disability Status Scale and the Colitis Activity Index were used to measure disease severity in MS and UC patients respectively. Results: While levels of both physical and mental fatigue were significantly higher in MS patients than in UC patients, there were no group differences in the contribution of disease severity, depression and negative affectivity to both physical and mental fatigue. Conclusion: Although levels of fatigue are higher for MS patients when compared with UC patients, the correlates of fatigue do not indicate MS specificity. As such our results support a transdiagnostic approach to fatigue in MS.

Keywords: Depression; Disease severity; Fatigue; Multiple sclerosis; Negative affectivity; Ulcerative colitis

Introduction

Fatigue is one of the most common and disabling symptoms of multiple sclerosis (MS), but its etiology is still poorly understood [1,2]. Up to 92% of the patients with MS complain of fatigue and over two-thirds of patients characterize it as the most troubling symptom [3]. Fatigue in MS is more severe and disabling compared to fatigue in healthy controls and several other somatic populations [4–9]. Usually, fatigue in MS presents as a chronic symptom, but it may also precede or accompany exacerbations [10–12]. Fatigue is frequently the presenting symptom at the time of diagnosis [5], and it is even reported as the only symptom of an acute relapse [13]. These findings suggest that fatigue is intrinsic to MS, but even though there is increasing evidence...
for the role of disease-related pathophysiological mechanisms to MS-related fatigue, these mechanisms can only explain a small part of the variance [1,2].

Since fatigue in MS is defined as a subjective experience [14], psychological variables are expected also to contribute to MS-related fatigue. Moreover, fatigue in a chronic illness often co-occurs with negative affect [15]. Compared to other chronic illnesses, depression is more common in MS and therefore, MS patients are especially at risk for fatigue [16–18]. There is also evidence that negative affectivity, also called neuroticism or emotional instability, plays an important role in the experience of chronic symptoms, including fatigue [19].

A few studies [4,7,20,21] have examined the impact of negative affectivity on fatigue in MS, and in only two of these cross-sectional studies significant associations between negative affectivity and fatigue have been found [4,20]. However, these significant results have to be interpreted with caution, because it is likely that depression has significantly influenced the outcome of personality assessments and in particular the level of negative affectivity [22]. To overcome this methodological problem, both Penner et al. [7] and Van der Werf et al. [21] controlled for depression and as a result, the relationship between negative affectivity and fatigue disappeared, which suggests that the effect of negative affectivity on fatigue is mediated by depression.

Given the possibility of both disease specific and non-specific explanations, the focus of the present study was on the disease specificity of fatigue in MS. Because fatigue is a common symptom in chronic diseases, that may be caused by many nonspecific factors [15], fatigue in MS patients should be compared to that in other chronic, and preferably nonneurological autoimmune diseases. For that reason, and in contrast to the study of Penner et al. [7], we did not include healthy participants, but patients with ulcerative colitis (UC). UC is an inflammatory bowel disease that like MS is chronic and intermittent, and starts between the ages of 20 and 40 [23]. Both MS and UC are characterized by a lifetime risk of relapses and are disabling diseases having a compromising effect on physical, mental and social wellbeing [24,25].

To study disease specificity of fatigue in MS, we first compared the levels of fatigue in both patient groups. Next, we explored the relative contribution of disease severity, depression and negative affectivity to fatigue in MS patients compared to UC patients. Besides overall relevance in both samples, we expected that both disease severity and depression contribute more to fatigue in MS patients than in UC patients, whereas we expected negative affectivity to contribute less to fatigue in MS patients than in UC patients.

Methods

Patient samples

Eighty-eight MS patients and 76 UC patients were included in this cross-sectional study, which was conducted in the period from July 2004 to December 2006. The MS patients were recruited from the Department of Neurology of the Maastricht University Medical Centre (MUMC, Maastricht, The Netherlands), which performs both a local and regional function. Consecutively referred patients who presented at the outpatient clinic, aged 18–60 years, and diagnosed with clinically definite MS [26], were asked to participate in the study. The response rate was very high (>90%). The UC patients were selected with the help of the Inflammatory Bowel Disease (IBD) South Limburg database of the Department of Gastroenterology at the MUMC. UC patients who had been diagnosed using the Lennard-Jones criteria [27] were selected from the IBD database and matched with the MS patients on the basis of sex and age.

In order to study fatigue in patients in whom the disease was not active, we excluded patients who had had an exacerbation within the past 4 weeks. In the case of MS patients an exacerbation was defined as a sudden onset or increase within 24 h of a symptom that resolves fully or partially over the course of weeks and for which a neurologist was consulted. An exacerbation of UC was defined as a score of 10 or more on the Colitis Activity Index (CAI) [28] (see measurements). MS patients with a Kurtzke Expanded Disability Status Scale (EDSS) score >8 [29] were also excluded, because patients in this range of scores generally have impaired function of the upper limbs, which may interfere with psychological testing. Other exclusion criteria were: use of corticosteroids, somatic comorbidity, dementia or severe cognitive dysfunction and visual, verbal and/or motoric limitations that interfere with psychological testing.

Measurements

We used a multidimensional assessment approach, based on the physical and mental fatigue subscales of the Multidimensional Fatigue Inventory (MFI) [30]. Both of these subscales consist of four items with a 5-point response format with scores ranging from 4 to 20. The statements refer to aspects of fatigue during the past few days. Higher scores indicate more physical or mental fatigue. The MFI is generally used in the case of patients with chronic (neurological) diseases [4,31,32], and the Dutch language version has shown good reliability and validity [30]. In this study Cronbach’s alphas of both subscales were respectively .80 and .89 for the MS sample and .90 and .89 for the UC sample.

The EDSS [29], assessed by the patient’s own neurologist (R.H.), who is an experienced MS neurologist familiar with EDSS recording, provided data on disease severity in MS patients. The EDSS is divided into 8 functioning systems (pyramidal, cerebellar, brainstem, mental, bowel and bladder, visual-optic, sensory and others). Impairment in each system is graded separately by means of neurological examination. EDSS-scores range from 0 to 10, with 0 being normal neurological examination and 10 being death due to MS. The CAI was used to measure disease severity in the case of UC patients [28]. For practical reasons, one item
of the CAI (abdominal tenderness assessed by a clinician) was not included. We did use the other seven items of the CAI, including the number of daily liquid stools, presence of nocturnal diarrhea, occurrence of fecal incontinence, severity of abdominal pain, percentage of bowel movements with visible blood in the stool, perceived general well-being and the use of antidiarrheal medication. The total score of this version of the CAI ranges from 0 to 18. Both the EDSS and CAI are widely used as an outcome measure for monitoring the disease course. Higher scores on both measures indicate a higher level of disease severity.

The depression subscale of the Hospital Anxiety and Depression Scale (HADS) [33] was used to assess depressive complaints. This instrument has been especially designed to screen physically ill patients for the assessment of anxiety and depression; it does not include somatic symptoms. By making use of this instrument, we could ensure that fatigue and depression were measured as separate entities. The subscale depression consists of seven items (scores ranging from 0–21). Higher scores indicate more complaints of depression. Reliability and validity are adequate for the Dutch population [34]. In this study Cronbach’s alphas were, respectively, .85 for the MS sample and .82 for the UC sample.

Negative affectivity was assessed with the neuroticism subscale of the Dutch NEO Five-Factor Inventory, which is a reliable and valid personality questionnaire [35]. This subscale consists of 12 statements, rated on a five-point scale and resulting in total dimension scores ranging from 12 to 70. Higher scores indicate higher levels of neuroticism. Internal consistency of the neuroticism subscale in this study was high with Cronbach’s alphas of .86 in the MS sample and .88 in the UC sample.

Procedure

All the participants were evaluated at the Department of Psychology of the MUMC, where they completed the questionnaires. General information necessary for the description and comparison of the two patient groups was collected. This included sex and age, as well as the level of premorbid intelligence, which was measured with the Dutch version of the National Adult Reading Test [36]. Medical histories of the MS and UC patients (disease course, disease duration) were collected from the hospital database. Disease duration was defined as the interval between the day of the (clinically definite) diagnosis and evaluation. The UC patients completed the CAI at inclusion. For the MS patients, EDSS scores were collected from the hospital database. If there was no recent (>3 months before inclusion) EDSS score available, the treating neurologist was consulted for reassessment. The medical ethics committee of the MUMC approved the project and each participant gave informed consent.

Data analyses

Based on the significant results obtained from a sample of 80 MS patients in a comparable study [20], we assumed that the number of patients included in the present study was sufficient. Data were checked for missing values, normality, outliers, and extremes. Square root transformation was used for abnormally distributed variables before parametric testing. Differences in characteristics between the MS and UC group and self-report measures were analyzed by means of independent sample Student t tests and chi-square analyses. Because of the different ranges of both of the disease severity measures (0–10 versus 0–18), the scores of the MS disease severity measure (EDSS) were linearly transformed to the range of the CAI (EDSS score/10×18) in order to be able to directly compare the mean of disease severity in both patient samples.

Furthermore, Pearson correlation coefficients were calculated for both groups in order to examine interrelationships between independent variables (age, sex, disease duration, disease severity, depression, negative affectivity) and dependent variables (physical and mental fatigue). Fatigue levels in both patient groups were compared with the help of multiple regression analyses that were conducted in the total sample using a forced entry method with physical and mental fatigue as outcome measures and age, sex, disease duration, disease severity, depression, negative affectivity, and disease as independent variables. In order to assess the contribution of disease severity, depression and negative affectivity to fatigue in both patient groups, we conducted multiple regression analyses in the MS and UC sample separately.

Next, we tested the impact of disease as a moderator between respectively disease severity, depression and negative affectivity on the one hand and physical and mental fatigue on the other. In line with the procedure specified by Baron and Kenny [37], interaction terms were calculated (disease severity×disease, depression×disease, and negative affectivity×disease) and entered in a second step. Before computing the interaction terms, all independent variables were centered (dichotomic variables) or transformed into standardized values (continuous variables) to avoid artificially induced multicollinearity. Because of the disease specific measurement of disease severity, we calculated standardized scores for both patient groups separately. The assumptions of regression analysis (absence of multicollinearity, homoscedasticity, normal distribution of the residuals and absence of “influential cases”) were checked for all models. \( P<.05 \) was considered significant. Analyses were carried out using SPSS version 12.0.1 for Windows (SPSS, Chicago, IL).

Results

Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of both patient groups. Most of the MS patients (66%) had a relapsing remitting disease course, 18% had secondary progressive MS and 16% primary progressive
Table 1
Demographic and clinical characteristics (mean, (S.D.)) of both patient groups

<table>
<thead>
<tr>
<th></th>
<th>Multiple sclerosis (n=88)</th>
<th>Ulcerative colitis (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%female/%male)</td>
<td>30/70</td>
<td>32/68</td>
</tr>
<tr>
<td>Age in years</td>
<td>43.6 (9.0)</td>
<td>45.3 (8.8)</td>
</tr>
<tr>
<td>Premorbid intelligence</td>
<td>102.0 (9.4)</td>
<td>103.1 (9.8)</td>
</tr>
<tr>
<td>Disease severity</td>
<td>6.4 (3.5)</td>
<td>3.5 (2.1)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>5.7 (6.2)</td>
<td>10.1 (7.0)</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>14.4 (3.7)</td>
<td>11.1 (4.8)</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>12.3 (4.6)</td>
<td>9.7 (4.6)</td>
</tr>
<tr>
<td>Depression</td>
<td>5.6 (4.0)</td>
<td>4.0 (3.6)</td>
</tr>
<tr>
<td>Negative affectivity</td>
<td>32.0 (8.6)</td>
<td>31.0 (9.0)</td>
</tr>
</tbody>
</table>

⁎⁎ Because of the different range of both disease severity measures, the scores of the MS disease severity measure (EDSS) were linearly transformed into the range of the CAI (0–18) for reasons of comparison.

⁎ P<.01 (two tailed).

Table 2
Pearson correlations of all measures with fatigue in both patient groups

<table>
<thead>
<tr>
<th></th>
<th>Multiple sclerosis (n=88)</th>
<th>Ulcerative colitis (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Physical fatigue</td>
<td>Mental fatigue</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.024</td>
<td>0.138</td>
</tr>
<tr>
<td>Age</td>
<td>0.193</td>
<td>−0.019</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.267⁎</td>
<td>0.078</td>
</tr>
<tr>
<td>Disease severity</td>
<td>0.387⁎</td>
<td>−0.039</td>
</tr>
<tr>
<td>Depression</td>
<td>0.507⁎</td>
<td>0.366⁎</td>
</tr>
<tr>
<td>Negative affectivity</td>
<td>0.350⁎</td>
<td>0.422⁎</td>
</tr>
</tbody>
</table>

⁎⁎ Expanded Disability Status Scale in MS and Colitis Activity Index in UC.

⁎ P<.05.

⁎⁎ P<.01 (2-tailed).

MS. The average EDSS score was 3.5 (S.D.=1.9, range 0–7.5). In the UC sample, the mean CAI was 3.5 (S.D.=2.1, range 0–9). Compared to the UC group, the MS had higher ratings on disease severity, but shorter disease duration. On average, the MS patients had higher scores on physical fatigue, mental fatigue and depression than the UC patients. Levels of negative affectivity were equal in both patient groups.

Zero-order relationships between all measures and fatigue in both patient groups

The correlations between all independent variables and physical and mental fatigue in both patient groups are presented in Table 2. In both groups, disease severity was significantly related to physical fatigue (MS: r=0.387; P<.01, UC: r=0.641; P<.01). Furthermore, in the case of both MS and UC patients, negative affectivity was significantly related to both physical (MS: r=0.350; P<.01, UC: r=0.522; P<.01) and mental fatigue (MS: r=0.422; P<.01, UC: r=0.569; P<.01). Also, depression was significantly related to both physical (MS: r= 0.507; P<.01, UC: r= 0.521; P<.01) and mental fatigue (MS: r=0.521; P<.01, UC: r=0.554; P<.01) in both patient groups.

Multiple regression analyses predicting physical and mental fatigue

As shown in Table 3, disease independently contributed to both physical fatigue (β=−0.326; P<.01) and mental fatigue (β=−0.196; P<.01). This supported our first hypothesis that MS patients report significantly higher levels of both physical and mental fatigue compared to UC patients, also after controlling for negative affectivity, depression, disease severity, disease duration, sex, and age. The contribution of disease severity, depression and negative affectivity to fatigue in both samples is shown in Table 4. In both the MS and UC sample, disease severity was contributing to physical fatigue, but not to mental fatigue, explaining respectively about 6% and 26% of the variance. Depression was the largest independent contributor to physical fatigue in the MS group, accounting for about 14% of the variance, whereas depression accounted for about 9% of the variance of mental fatigue. In the UC sample,
depression explained about 7% and 10% of the variance of respectively physical and mental fatigue. In both MS and UC patient groups, negative affectivity only contributed to mental fatigue and not to physical fatigue, explaining respectively about 7% and 12% of the variance.

To test whether the factor disease would have a moderating effect on the relationships between disease severity, depression and negative affectivity on the one hand, and fatigue on the other hand, interaction terms were calculated and added to the second step (data not shown). The addition of these three interaction effects did not result in a significant increment of $R^2$ above that associated with the main effect model for both physical and mental fatigue ($F$-change=2.319, $P=.078$; $F$-change=0.337, $P=.799$). These results mean that the contribution of disease severity, depression and negative affectivity to fatigue does not significantly differ between the patient groups.

**Discussion**

The aim of the present study was to improve the understanding of fatigue and its disease specificity in MS by comparing its level and correlates to those of UC patients, a comparable but peripheral autoimmune disease. The correlates referred to the relative contribution of disease severity, depression and negative affectivity to both physical and mental fatigue. The levels of both physical and mental fatigue were significantly higher in MS than in UC, suggesting MS specificity. The correlates, however, did not differ between both samples, suggesting a lack of MS specificity.

Although several previous studies did not find any association between disease severity, as measured with the EDSS, and fatigue [38–41], our study revealed that disease severity was an independent contributor to physical fatigue only, which is in line with other findings [7]. Contrary to our expectations, the groups did not differ when it came to the contribution of disease severity to fatigue. Hence, both MS and UC patients experienced more fatigue with increasing disease severity. In line with related studies in MS, which also used the so-called exclusive approach of measuring depression [41,42], depression explained a moderate amount of the variance of both physical and mental fatigue in both patient samples. Given the problem that fatigue is a symptom of depression, we used the HADS, which excludes somatic items to ensure that fatigue and depression were measured as separate entities. This is often not the case in related studies [7,43–45].

Whereas it became clear that depression was contributing to both physical and mental fatigue, in both patient samples negative affectivity contributed to mental fatigue only. Although we did find significant correlations between negative affectivity and both physical and mental fatigue, the associations with physical fatigue disappeared after controlling for sex, age, disease duration, disease severity and depression. Our findings are in contrast with the results of Penner et al. [7], who did not find a relationship between negative affectivity and either physical or mental fatigue after controlling for disease severity as measured with the EDSS and depression. Several factors can explain these contradictory results, including the use of different instruments to assess fatigue and depression. Penner et al. [7] revealed that MS patients had elevated levels of negative affectivity compared to the healthy controls, and assumed that the increase of negative affectivity is related to the MS disease itself. In our study, levels of negative affectivity were equal in both patient groups. This is in accordance with other results [4] that suggest that elevated levels of negative affectivity are a feature of chronic illness and therefore are not specific for MS. Our results support the need for a multidimensional operationalization of fatigue, at least in a physical and mental dimension, as well as the importance of controlling for depression as a confounder.

Comparison of the independent contributors of physical and mental fatigue in both MS and UC patients revealed that there were no significant differences between these two patient groups. Given the fact that both MS and UC are autoimmune diseases, these findings could lead to a new hypothesis that immune system dysregulation is related to fatigue. However, attempts to correlate MS-related fatigue with immune system activation, assessed by circulating levels of cytokines, have so far led to inconsistent results [46,47]. To examine the hypothesis that MS-related fatigue is caused by ongoing inflammation, future studies should focus on fatigue during exacerbations instead of chronic fatigue.

Several methodological limitations to this study need to be mentioned. Firstly, the representativeness and comparability of both patient samples can be a point of discussion. The recruitment procedure of both patient samples was different, which might cause a selection bias interfering with the present results. Secondly, the cross-sectional design of our study makes it impossible to infer causality from the associations found and therefore, we cannot definitely answer the question whether depression and negative affectivity are risk factors for fatigue in MS or visa versa. To the best of our knowledge, no longitudinal studies that focus on the relationship between negative affectivity and fatigue have been conducted in MS patients. However, there is major evidence that negative affectivity predicts several physical conditions, as has been shown in a large longitudinal cohort twin study [19]. With regard to depression, our findings are in line with two available intervention studies that suggest that fatigue is caused by depression [48,49]. Also, recent longitudinal findings ($n=2768$) support this relationship between fatigue and depression in MS [50]. Thirdly, it is possible that strong associations between self-reported variables, such as depression, negative affectivity and fatigue are the result of similar methods of measurement. Fourthly, the measurement of disease severity in both patient groups merits
further consideration. Although both the EDSS and the CAI are widely used as outcome scales for monitoring the disease course of respectively MS and UC patients, both of these scales are partly subjective. An overall biomarker of disease activity may enhance comparability across groups, but as yet no such valid and reliable biomarker is available.

Our study is unique in comparing MS patients with UC patients, a control group of chronic patients with an autoimmune disease without obvious central nervous system involvement. Although the ideal control group is always a point of discussion, UC patients are especially appropriate as controls because UC is also a chronic, intermittent, and disabling disease, that most often starts between the ages of 20 and 40 [23]. Furthermore, fatigue and depression are common symptoms in both MS and UC [32,51,52], and UC is not characterized by chronic pain such as rheumatoid arthritis.

To disentangle the complex etiology of MS-related fatigue, future research may focus on comparison with other clinical samples which have fatigue as a symptom. If there is additional evidence for nonspecificity of fatigue in MS, we should use a transdiagnostic approach to fatigue. Such an approach may help to develop specific interventions and to improve the overall management of fatigue in MS patients.

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