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Fatigue in Multiple Sclerosis is related to relapses, autonomic dysfunctions and introversion: A quasi-experimental study

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ABSTRACT

Background: Fatigue in Multiple Sclerosis (MS) might be partially due to inflammatory processes. If so, relapses should increase the fatigue level.
Methods: Two groups of MS patients participated in this study. One suffered from a relapse and was treated by Methylprednisolone. The other group experienced a deterioration of their neurological condition but no relapse and received neurological rehabilitation. We assessed fatigue before admission, at admission and after discharge (t1, t2, t3). Furthermore, autonomic dysfunctions, depressive mood, apathy and extraversion were assessed at admission. Changes in fatigue were analysed with ANCOVAs and fatigue levels were analysed with regression analyses using clinical data and scores for depressive mood, apathy, extraversion and autonomic dysfunctions.
Results: Only patients suffering from a relapse showed a significant increment in fatigue from t1 to t2. Regression analyses revealed that autonomic dysfunctions and introversion best explained the fatigue level.
Conclusions: This study shows that a relapse is accompanied by an increase in MS-related fatigue. Moreover, autonomic dysfunctions and introversion, more than depression and apathy, play a major role in the explanation of MS-related fatigue. This finding represents additional evidence for the relationship between inflammation, vagal afferent signaling, autonomic dysfunctions, introversion and the feeling of MS-related fatigue.

1. Introduction

Fatigue is one of the most frequently reported and consequential symptoms of Multiple Sclerosis (MS) (Krupp et al., 2010). Currently, there is no consensus concerning a definition of fatigue and there is no generally accepted objective measure for it. Recent reviews on fatigue define it as a feeling of tiredness, lack of energy, and/or loss of motivation (Sander et al., 2017b; Kluger et al., 2013). Recently, Hanken, Eling and Hildebrandt (Hanken et al., 2014) developed a model for explaining the emergence of subjective cognitive fatigue in MS. According to this model, a major mechanism for the development of fatigue is a binding of pro-inflammatory cytokines to vagal nerve endings signaling to the brain the existence of an inflammatory state. The peripheral activation of the vagal nerve is transferred to the dorsal nucleus and the solitary tract of the brain stem. Targeting also the locus coeruleus, the information is feed-forwarded to the hypothalamus triggering a process which is called sickness behavior with the feeling of fatigue as a central component. Recent studies have shown that the feeling of fatigue is correlated with neural activity in interoceptive brain areas (Harrison et al., 2009). Because the vagus nerve is a central component of this neuroinflammatory reflex it can be postulated that fatigue may be associated with other disorders related to its functioning. This assumption was recently supported by studies showing a correlation between MS-related cognitive fatigue and particular autonomic dysfunctions such as orthostatic intolerance, pupillomotor and bladder dysfunctions (Cortez et al., 2015; Sander et al., 2017a; Flachenecker et al., 2001). In another study, we could show a correlation between MS-related fatigue and heart rate variability, arguing for a relationship between afferent vagal signaling and the feeling of fatigue in MS (Sander et al., 2019).

A direct implication of our model is that the level of fatigue is a direct consequence of the degree of inflammatory processes. Therefore, events that increase inflammation, such as the occurrence of a relapse, should increase the fatigue level (Hautecoeur et al., 1997; Xu et al.,

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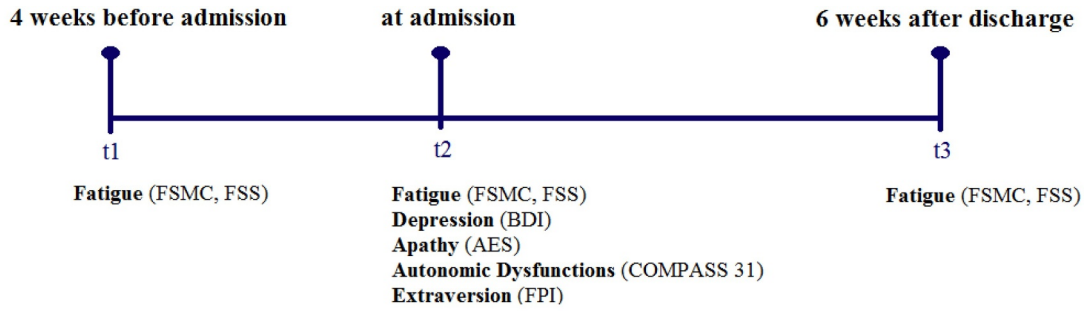


Abbreviations: FSMC: Fatigue Scale for Motor and Cognition; FSS: Fatigue Severity Scale; BDI: Beck's Depression Inventory; AES: Apathy Evaluation Scale; COMPASS 31 = Composite Autonomic Symptom Scale 31; FPI: Freiburger Persönlichkeitsinventar.

Fig. 1. Study design.
Abbreviations: FSMC: Fatigue Scale for Motor and Cognition; FSS: Fatigue Severity Scale; BDI: Beck's Depression Inventory; AES: Apathy Evaluation Scale; COMPASS 31 = Composite Autonomic Symptom Scale 31; FPI: Freiburger Persönlichkeitsinventar. .

2013; Navikas and Review, 1996). Cross-sectional retrospective studies have shown that fatigue may precede the diagnosis of MS for several years (Berger et al., 2013; Disanto et al., 2018). But, unfortunately, hardly any studies investigated changes in fatigue severity and degree of inflammatory processes before, during and after a relapse and most of these studies did not use a longitudinal design with an appropriate comparison group (Flachenecker and Meissner, 2008; Sabanagic-Hajric et al., 2015).

The main aim of this study was to test our hypothesis that a relapse leads to an increase in fatigue. Hence, we investigated two groups of MS patients and collected data on fatigue changes over time. The first group was admitted to a hospital because of an acute relapse and the second was admitted to a rehabilitation center without suffering from a relapse: both groups became admitted to a health center (a psychosocial experience both groups have in common) but only one group suffered from an acute exacerbation of their autoimmune disease. According to our hypothesis, only the relapse group should show an increase in fatigue from before admission to the time at admission.

Another aim of this study was to shed light on possible neurophysiological underpinnings of fatigue in MS.

As summarized above, several pharmacological treatment strategies of fatigue in MS are strongly based on commonly held assumptions about the relation between neurotransmitter systems and depression and apathy (Miller and Soundy, 2017; Yang et al., 2017; Pardini et al., 2013; Loy et al., 2018). We therefore assessed depressive mood reflecting serotonergic dysfunction, apathy reflecting dopaminergic dysfunction, extraversion reflecting noradrenergic dysfunction and autonomic dysfunctions representing vagal disturbances and looked for potential predictors for MS-related fatigue.

2. Material and methods

2.1. Patients

One hundred thirty-six patients suffering from MS according to the McDonald criteria participated (Polman et al., 2011). 43 patients received treatment for MS relapses at the Department of Neurology of the Klinikum-Bremen-Ost, Bremen, Germany (relapse group) and 93 patients have been inpatients of the Rehabilitation Center Wilhelmshaven, Wilhelmshaven, Germany (rehabilitation group). Regarding the relapse group, only patients suffering from a relapse severe enough for being admitted to a hospital and receiving treatment with high doses of Methylprednisolone for five days were included in the study. Concerning the rehabilitation group, patients with an MS relapse or using corticosteroids during the last four weeks before admission were excluded. Patients received rehabilitation to reduce physical disability and to increase social integration. In the context of the rehabilitation program patients received extensive therapy including a mixture of physiotherapy, ergotherapy and speech therapy (individual and group therapy). Each patient received 4 to 5 therapy sessions per day depending on individual needs. Individuals under legal care and/or with a diagnosis of an additional neurodegenerative disease were excluded from the study. The study was approved by the ethical board of the Medical Society in Bremen and written informed consent was obtained from participants.

Ninety-nine patients responded to the follow-up (77% of the relapse group and 71% of the neurological rehabilitation group). 74% of these patients suffered from a relapsing-remitting, 26% from a secondary progressive disease course.

2.2. Study design

MS patients were interviewed at admission at the respective health center. First, information about their current level of fatigue, depression and apathy was collected (t2). Also, information about autonomic symptoms and extraverted behavior was assessed. Second, patients were asked about their past level of fatigue of four weeks ago (t1). Six weeks after discharge, patients were phoned to collect information about their current level of fatigue (t3; see Fig. 1).

2.3. Assessment

The clinical status of the patients was assessed with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983).

To assess fatigue, we used the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009). The FSMC is a self-report questionnaire composed of 20 items, evaluating motor and cognitive fatigue. It has a 5-point scale for each item (from "I completely agree" to "I completely disagree"). The maximum total score is 100, the maximum total scores for respectively cognitive and motor fatigue are 50. Total scores beyond 62 indicate severe fatigue, scores beyond 33 or 31 indicate severe cognitive or motor fatigue, respectively.

We also used the Fatigue Severity Scale (FSS) (Krupp et al., 1989) consisting of nine items with higher scores representing stronger fatigue. It has a 7-point scale for each item (from "I completely agree" to "I completely disagree"). The maximum average score is 7, a score beyond 5 is usually regarded as indicating severe fatigue. The FSS does not distinguish between different aspects of fatigue, and it is somewhat biased towards assessing motor fatigue (Sander et al., 2017b).

To assess the severity of autonomic symptoms we used the Composite Autonomic Symptom Scale 31 (COMPASS 31), consisting of 31 questions, (Sletten et al., 2012) covering six domains including

orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor activity.

Depressive symptoms were assessed using the Beck Depression Inventory Scale (BDI) (Hautzinger et al., 1995). We used the items A-O, the psychological items, to calculate the score for mood impairment, whereas the P-U items represent the somatic score.

The Apathy Evaluation Scale (AES) has been validated in several neurological diseases including a recent evaluation in MS patients and it can reliably discriminate apathetic from non-apathetic individuals (Raimo et al., 2014). We used the self-report version which has 18 items. A higher score represents a higher level of apathy.

Extraversion was assessed with a 14 items scale of the "Freiburger Persönlichkeitsinventar", a personality questionnaire, which was constructed based on a firm theoretical background. It is used frequently in German language countries (Fahrenberg et al., 2010). Individuals with high scale scores describe themselves as social contact seeking and impulsive, whereas individuals with low scores tend to avoid social contacts, appear as calm and serious, controlled and introvert.

2.4. Statistical evaluation

To analyze the relation between fatigue and relapses repeated measures analyses of covariance (ANCOVAs) were performed on the fatigue scores, with GROUP (relapse group versus rehabilitation group) as between-subject factor and Time (t1, t2, t3) as within subject factor (Greenhouse-Geisser correction was used for calculating the significance level).

Hierarchical regression analyses were used to analyze predicted fatigue status on the basis of autonomic dysfunction and psychological questionnaires. In a first step, the variables Age, Gender, Education, Disease duration, Expanded Disability Status Scale (EDSS) and Group (relapse group versus rehabilitation group) were included into the regression analysis as covariates. We then added the total score of the COMPASS 31 and the scores of the other questionnaires using forward regression analyses to see which of them would improve the explained variance. For the BDI, we used the sum score of the psychological items for the regression analysis. The dependent variable was the fatigue level (FSMC score, FSS score) at the three time points. Correcting for multiple testing, the significance level was set to $0.05/6 < 0.009$.

We finally performed a principal component analysis (with varimax rotation) to analyze which particular questionnaires load on the same factor as the fatigue scores.

3. Results

Table 1 provides information about the two groups. The two groups differed significantly only on Age and Disease duration. Therefore, Age and Disease duration were included as covariates in the ANCOVA.

The ANCOVA for the total score of the FSMC revealed no main effects but there was a significant interaction between GROUP and TIME [F (df 1.925): 3.493, $p = 0.034$] (see Fig. 2). Using the FSS scores as dependent variable, the ANCOVA showed a main effect for GROUP [F(1,91): 13.532, $p < 0.001$] with the rehabilitation group presenting higher fatigue scores. Additionally, we found a significant interaction effect between GROUP and TIME [F(df 1.242): 4.146, $p = 0.036$].

Following our quasi-experimental design, we focused on the difference in fatigue severity accompanying an acute relapse. Post hoc dependent *t*-tests revealed that patient groups differed in their fatigue level at t1 (FSS $p < 0.001$; FSMC $p = 0.002$) and partially at t2 (FSS $p = 0.04$), but not at t3. The relapse group showed a significant increase of fatigue from t1 to t2 (change on FSS: $p = 0.037$; change on FSMC $p = 0.012$), whereas patients of the rehabilitation group did not show any significant change in fatigue. The change in fatigue from t2 to t3 was not significant for both groups (see Table 2).

To exclude a potential effect of steroids on fatigue severity in the relapse group, we divided this group into subgroups corresponding to the number of days they received steroid treatment (0 days, 1 day, 2 days, 3 days, 4 days and longer). Comparing these groups taken together with the non-relapse group using a univariate analysis of variance at t2 showed no differences for the FSMC ($p = 0.474$) but groups differed on the FSS ($p = 0.046$). This finding corresponds to the results of the ANCOVA reported above. On the other hand, the same analysis showed significant differences at t1 (as expected by the ANCOVA) but not at t3 (as expected). We repeated this analysis for the four other questionnaires, which had been assessed only at t2. There were no significant effects for the number of days being treated with steroids on the COMPASS 31, the FPI and the AES (each $p > 0.29$). The groups did show a difference on the psychological items of the BDI ($p = 0.024$) but post-hoc *t*-test did not show an effect for the number of days of steroid treatment.

These post-hoc analyses indicate that the number of days treated with steroids did not influence the findings of the ANCOVA reported above.

To make sure that our results are not influenced by the difference in age and disease course we also tried to match both groups by excluding older patients with a secondary chronic disease course from the non-relapse group (blind for their fatigue scores). Excluding 12 patients from this group, the difference in age between the groups was not significant anymore (*t*-test: $p = 0.11$) and the groups were similar with respect to their disease course (Chi Square test: $p = 0.48$). The ANOVA for repeated measurement still showed the significant interaction between GROUP and TIME for the FSMC ($p = 0.03$) and the FSS ($p = 0.021$). It should also be mentioned that after the exclusion of older and secondary chronic patients, the t1 score dropped slightly (FSMC: 69, FSS: 4.9). The somewhat lower scores on t1 had no impact on the results arguing against a ceiling effect.

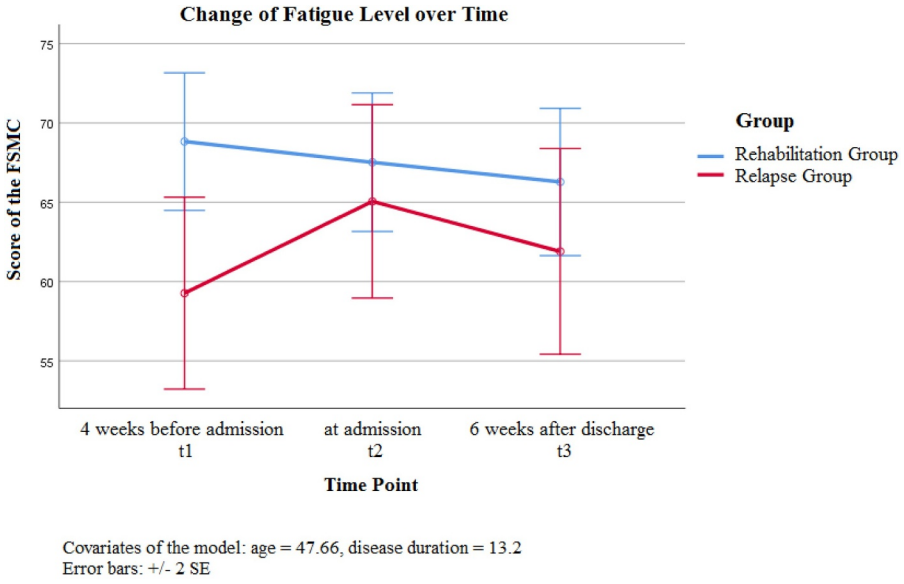
Table 2 presents the results of the regression analyses. The variable Group only played a significant role as a predictor for fatigue at t1. At admission (t2), the variable Group did not enter the regression analyses. The regression analyses revealed that only two variables explained fatigue level at the three time points: the score of the COMPASS 31 and the extraversion score of the FPI. A high level of autonomic dysfunctions and a low score on extraversion were associated with high fatigue scores (see Fig. 3 for the relation between fatigue at t2 and autonomic dysfunctions and Fig. 4 for the relation between fatigue at t2 and

Table 1
Data of patient groups.

	Relapse group	Rehabilitation group
n	34	65
Gender (male/female)	12/22	17/48
Disease course (rr/sc)	29/5	44/21
Age in years (SD)*	43 (14)	50 (8)
Years of education (SD)	11 (2)	11 (1)
EDSS (SD)	4.6 (2.1)	4.0 (2.2)
Disease duration in years (SD)*	10.1 (9.6)	14.7 (9.4)
FSMC score at t1 (SD)*	58 (20)	70 (15)
FSS score at t1 (SD)*	3.6 (1.6)	5.7 (3.2)
FSMC score at t2 (SD)	63.3 (18.9)	67.6 (16.6)
FSS score at t2 (SD)*	4.0 (1.6)	4.7 (1.5)
AES score at t2 (SD)	16 (8)	16 (8)
BDI psy score t2 (SD)	7.4 (5.7)	6.6 (4.4)
COMPASS 31 score at t2 (SD)	19.6 (12)	21.5 (11.5)
Extraversion score FPI at t2 (SD)	6.0 (3.2)	5.1 (3.0)
FSMC score at t3 (SD)	60.5 (18)	66.5 (18)
FSS score at t3 (SD)	4.1 (1.6)	4.7 (1.5)

Abbreviations: *n* = Number; rr = Relapsing remitting; sc = Secondary chronic; SD = Standard deviation; EDSS = Expanded disability symptom scale; FSMC = Fatigue Scale for Motor and Cognitive Functions; FSS = Fatigue Severity Scale; AES = Apathy Evaluation Scale; BDI Beck's Depression Inventory, psy = psychological; COMPASS 31 = Composite Autonomic Symptom Scale 31; FPI = Freiburger Persönlichkeitsinventar.

* significant difference ($p < 0.05$).



Abbreviations: FSMC: Fatigue Scale for Motor and Cognition.

Fig. 2. Change of the Fatigue Scale for Motor and Cognitive Functions over time for Multiple Sclerosis patients suffering from a relapse leading to hospitalization (relapse group) and for Multiple Sclerosis Patients without a relapse that have been admitted to a rehabilitation center (rehabilitation group).
Abbreviations: FSMC: Fatigue Scale for Motor and Cognition.

extraversion for the entire patient group).

Because the scores of the COMPASS 31 and the FPI played a significant role in explaining fatigue, we performed a median split for these variables and repeated the ANCOVAs to analyze their possible interaction with fatigue changes from t1 to t2. We did not find a significant main effect for the FPI score or the COMPASS 31 score, nor did we find a significant interaction effect between these variables and changes in fatigue. Nevertheless, the addition of these variables did not change the main results of the ANCOVAs.

We finally analysed the shared variation of the questionnaires by a principle component analysis. The principle component analysis showed that the fatigue scores shared common variance with the score of the COMPASS 31 and the extraversion score of the FPI, whereas the psychological item score of the BDI and the apathy score loaded together on a separate factor (see Table 3).

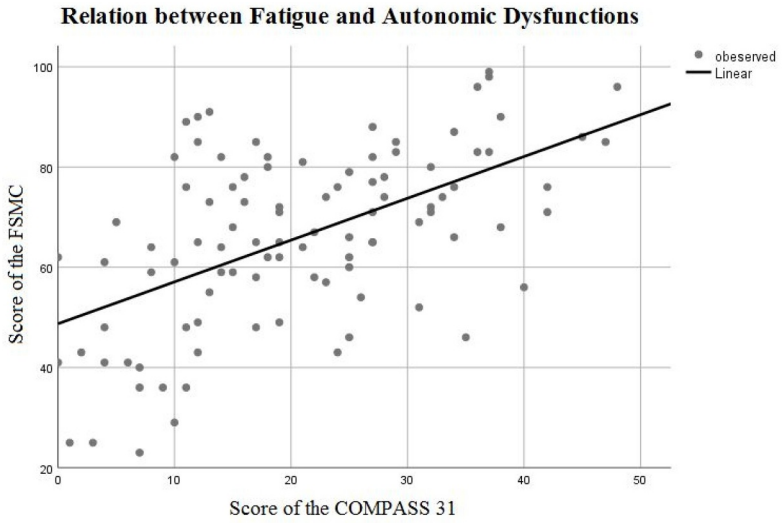
4. Discussion

The present study investigated fatigue changes in MS patients over time, showing that relapses leading to hospitalization are associated with an increase in subjective fatigue. Independent of the fatigue score used, MS-related fatigue increased from t1 to t2 in the relapse group but not in the rehabilitation group. Previous studies have also shown that during a relapse fatigue increases (Sabanagic-Hajric et al., 2015; Nickerson et al., 2015; Maurer et al., 2016) and that fatigue may even be the only clinical symptom of a relapse (Flachenecker and Meissner, 2008). But none of these studies assessed pre-relapse fatigue and had a follow-up, which would enable to detect changes in fatigue accompanying the occurrence of relapses. Furthermore, previous studies did not include comparable control groups. We compared the development of fatigue in the relapse group with that in the rehabilitation group, both consisting of MS patients that are admitted to a health

Table 2
Results of the regression analyses.

Fatigue Scale	F score	Corrected *R*-square	Single significant variables
FSMC t1			
Model 1	F(4.169): $p = 0.001$	0.170	EDSS, GROUP
Model 2	F(8.661): $p < 0.001$	0.366	GROUP, COMPASS 31
Model 3	*F(11.260): $p < 0.001$*	*0.469*	*GROUP, COMPASS31, FPI*
FSMC t2			
Model 1	F(2.114): $p = 0.060$	0.067	None
Model 2	F(5.711): $p < 0.001$	0.262	COMPASS 31
Model 3	*F(7.243): $p < 0.001$*	*0.349*	*COMPASS 31, FPI*
FSMC t3			
Model 1	F(2.664): $p = 0.020$	0.097	EDSS
Model 2	F(7.349): $p < 0.001$	0.323	COMPASS 31
Model 3	*F(8.820): $p < 0.001$*	*0.402*	*COMPASS 31, FPI*
FSS t1			
Model 1	F(3.287): $p = 0.006$	0.129	none
FSS t2			
Model 1	F(1.257): $p = 0.285$	0.016	none
Model 2	F(4.178): $p = 0.001$	0.193	FPI
Model 3	*F(11.260): $p < 0.001$*	*0.257*	*FPI, COMPASS 31*
FSS t3			
Model 1	F(1.110): $p = 0.001$	0.007	none
Model 2	F(3.450): $p = 0.003$	0.156	FPI
Model 3	*F(3.925): $p = 0.001$*	*0.201*	*FPI, COMPASS 31*

Abbreviations: FSMC = Fatigue Scale for Motor and Cognitive Functions; FSS = Fatigue Severity Scale; EDSS = expanded disability symptom scale; COMPASS 31 = Composite Autonomic Symptom Scale 31; FPI = Freiburger Persönlichkeitsinventar.

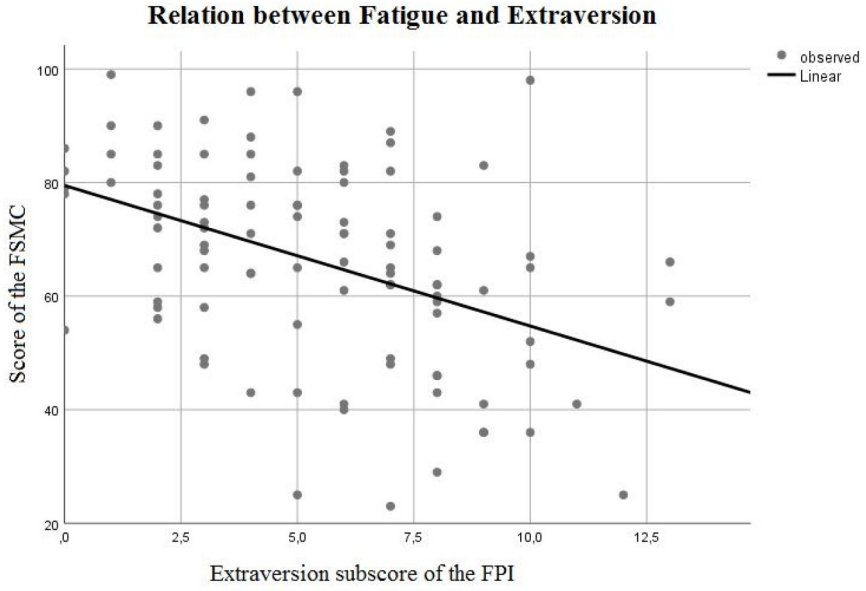


Abbreviations: FSMC: Fatigue Scale for Motor and Cognition; COMPASS 31 = Composite Autonomic Symptom Scale 31.

Fig. 3. Relation between the Fatigue Scale of Motor and Cognitive Functions and the Composite Autonomic Symptom Scale 31 in the whole group of Multiple Sclerosis patients.
Abbreviations: FSMC: Fatigue Scale for Motor and Cognition; COMPASS 31 = Composite Autonomic Symptom Scale 31.

center because of a worsening of neurological symptoms. The inclusion of a control group and a follow-up measurement in our study enabled us to demonstrate that fatigue increases with the occurrence of a relapse, indicating the influence of relapse-associated inflammation in the generation of the feeling of fatigue in MS patients.

Trying to explain the fatigue scores before admission, at admission and after discharge from the respective health center with regression analyses, we found that experiencing autonomic dysfunctions plays an important role for the fatigue level. This finding is an extension of our earlier studies and those of others (Cortez et al., 2015; Sander et al., 2017a; Flachenecker and Meissner, 2008). According to our model, vagal afferents play a major role in the generation of MS-related fatigue. Autonomic dysfunctions are associated with vagal dysfunctions and these dysfunctions are related to the involvement of the vagal nerve in the neuro-immunological reflex (Pavlov and Tracey, 2012). The results of the present study further evidence a relationship between inflammation, autonomic dysfunctions and fatigue. The association between autonomic failure and fatigue was found irrespective of the



Abbreviations: FSMC: Fatigue Scale for Motor and Cognition; FPI = Freiburger Persönlichkeitsinventar.

Fig. 4. Relation between the Fatigue Scale of Motor and Cognitive Functions and the extraversion subscore of the Freiburger Persönlichkeitsinventar in the whole group of Multiple Sclerosis Patients.
Abbreviations: FSMC: Fatigue Scale for Motor and Cognition; FPI = Freiburger Persönlichkeitsinventar.

Table 3
Results of the principal component analysis.

	Fatigue and ANS dysfunction	Depressive Mood and Apathy
FSMC (at admission)	,904	,269
FSS (at admission)	,876	-,094
COMPASS 31	,678	,256
FPI (extraversion)	-,543	-,526
BDI (psy score)	,057	,866
AES (total score)	,161	,790

Rotation-method: Varimax with Kaiser-normalization.
Abbreviations: ANS: Autonomic Nervous System; FSMC: Fatigue Scale for Motor and Cognition; FSS: Fatigue Severity Scale; COMPASS 31 = Composite Autonomic Symptom Scale 31; FPI: Freiburger Persönlichkeitsinventar; BDI: Beck's Depression Inventory; psy: psychological; AES: Apathy Evaluation Scale.

investigated group (relapse group, rehabilitation group) and therefore seems to be a major contributor to fatigue in MS.

Fatigue was, to some extent, also consistently explained by the level of extraversion. Patients with a high level of extraversion reported lower fatigue. A recent review on personality traits and MS-related fatigue showed that extraversion might be a moderating factor for experiencing fatigue (Schreiber et al., 2015). Ramirez-Maestre and Rosa Esteve (2013) argued for a similar role of extraversion for experiencing less pain in patients with chronic pain. According to our model, fatigue in MS represents the current inflammatory state of the organism, resembling symptoms of sickness behavior. Fatigue signals the organism to interrupt an ongoing interaction with the environment (to enhance the efficacy of the immune system) by distracting attention away from the environment to an internal state. Withdrawal from the environment is another main component of sickness behavior. In animals, artificially induced sickness behavior leads to a global reduction of activity in orexinergic neurons, of locomotion and exploration and a fragmentation of the sleep-wake cycle (Gaykema and Goehler, 2009; Gaykema and Goehler, 2011; Gaykema et al., 1998). The finding that introversion, but not extraversion was related to higher fatigue can have various reasons. Keeping it in line with our model, it might reflect a tendency that fatigued patients refrain from the environment focusing on internal signals. In this respect, less extraversion might not be a (personality) factor influencing the feeling of fatigue, but the feeling of fatigue might lead to an enduring tendency of attending to interoceptive signals (resulting in introversion). And this would argue for the development of orexinergic, histaminergic or maybe noradrenergic treatment strategies for MS-related fatigue.

A limitation of our study is the retrospective assessment of fatigue for t1, i.e. 4 weeks before admission to the respective health center. However, this procedure was used for both groups and therefore should not have influenced the intra-group development of fatigue. A second limitation of the investigation may be that we did not assess autonomic failure and extraversion for all three measurement points. This is impossible because questions of the Compass 31 assess autonomic dysfunctions during the last year. The concept of extraversion is defined as trait variable in the FPI and the questions for its assessment rely on undefined time spans. Therefore, we could not assess potential changes in autonomic dysfunctions and extraversion over time. Last, but not least, age and disease duration differed between the groups. The reasons for admission to a hospital and to a rehabilitation unit differ and there appears to be a tendency that older and secondary chronic patients are admitted to a rehabilitation unit more frequently. Consequently, it seems quite plausible that our two groups differed in age and disease course as a result of these policies in dealing with these conditions. Because we used age and disease course as control variables for our analyses and as we also made an additional attempt to match our two groups for age and disease course, we do not believe that this difference played a major role for our findings.

The strength of our investigation is the quasi-experimental design: we looked for a condition that would change fatigue according to our model and compared MS-relapse patients with MS patients also being admitted for neurological problems, but no relapse. Fatigue significantly increased in the relapse group and not in the other group. This provides credibility to the results and supports our model. However, the explained variance of the regression analyses was smaller than 50% pointing to a multidimensional background of the feeling of fatigue.

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Data statement

Original data is available on request.

Declaration of Competing Interest

The authors confirm that there are no conflicts of interest, no sponsoring and patent holdings related to this article.

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