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The association between perceived fatigue and actual level of physical activity in multiple sclerosis

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Abstract

Background: Both fatigue and reduced physical activity are important consequences of Multiple Sclerosis (MS). However, their mutual association is poorly understood.

Objectives: The objective of the study was to determine the relation between perceived fatigue and home-based recording of motor activity in patients with MS.

Methods: Found associations were checked for confounding by age, Expanded Disability Status Scales (EDSS), disease duration, sub-type of MS, anxiety, and depression. Forty-three ambulatory patients with MS were recruited. Ambulatory physical activity was recorded for 24 hours. Fatigue was assessed with the Fatigue Severity Scale (FSS), the Modified Fatigue Impact Scale (MFIS) and the Checklist Individual Strength (CIS20R). Linear regression was applied after which potential confounding factors were introduced in a multivariate regression model.

Results: No significant associations between physical activity and fatigue scores were found, except for the MFIS sub-scale 'physical activity' ($\beta_{physical\_activity}$ (β_{pa})=-0.044; SE=0.020). The association between physical activity and the FSS score was distorted by age, MS-type, anxiety and depression and the association between physical activity and the MFIS score by age and depression. The inverse association between MFIS sub-scale 'physical activity' and physical activity was significantly strengthened by adjusting for age (β_{pa}=-0.052; SE=0.019), sub type of MS (β_{pa}=-0.048; SE=0.020), anxiety (β_{pa}=-0.070; SE=0.023) and depression (β_{pa}=-0.083; SE=0.023).

Conclusion: In MS, there is no or at best a weak association between severity of perceived fatigue and physical activity. Depending on the fatigue questionnaire used, patient characteristics such as age, type of MS, depression and anxiety are factors that may affect this relationship.

Introduction

Fatigue is one of the most common symptoms in patients with multiple sclerosis (MS) and is reported by more than 53%[1] of all MS patients. Up to 40%[2] of patients with MS report fatigue as the most disabling problem, severely affecting daily activities and reducing quality of life. The exact aetiology of fatigue in MS is unknown, but it is well accepted that it is subjective and multidimensional in nature.[3-5] Both peripheral and central mechanisms[6,7] have been postulated to underlie fatigue, but so far these cannot satisfactorily explain fatigue in MS.[7,8]

Accumulating evidence indicates that patients with MS are less physically active than non-diseased people, but have quite a similar activity level as compared to patients with, for example, chronic fatigue syndrome, chronic obstructive pulmonary disease or cerebral palsy.[9] The observed reduction in the daily activities is often attributed to underlying impairments such as fatigue, muscle weakness, spasticity and ataxia.[7,10,11] However, the relation between fatigue and physical activity is unclear and complex, in which both factors seem to mutually influence each other. An impaired balance between, on the one hand, the capacity to produce effort (action) and, on the other hand, the tolerance to cope with increased effort (perception) is believed to worsen over the course of the disease, acknowledging that increased physical activity may enhance feelings of fatigue, whereas increased feelings of fatigue may also limit physical activity.[12] As a consequence, it has been hypothesized that being less active may lead to a vicious circle in which impaired fitness in turn may result in increased feelings of fatigue.[13] With that, increasing physical capacity has been seen as a cornerstone in the management of fatigue in patients with MS.[7] In addition, several studies in patients with MS also found significant associations of fatigue with variables such as age,[1] physical disability,[1,14,15] disease sub-type,[1] anxiety,[16] depression,[14,15] and health-related quality of life.[14] Motl and colleagues[10] found a small but significant association between fatigue and depression with self-reported physical inactivity (r=0.42) even when corrected for disease severity (Expanded Disability Status Scale [EDSS] score) or MS-disease course.

In a recent qualitative study, Kayes et al. reported that fatigue is seen by MS patients as a barrier to taking part in physical activity[17] related to the previously mentioned vicious cycle. On the other hand, Vercoulen et al.[18] found no significant correlation for patients with MS between physical activity (assessed with an actometer), and perceived fatigue assessed with the Checklist Individual Strength subscale 'Subjective Fatigue'. Therefore, a potential found relationship of physical activity with fatigue might be specific to the type of fatigue questionnaire used, as questionnaires typically evaluate different underlying constructs of fatigue.[19,20] In addition, the method used to monitor physical activity by using self-report scales[21] or activity monitoring[21-23] may affect found relationships between physical activity and fatigue. Therefore, the first objective of the present study was to explore the relationship between the actual amount of physical activity performed over a 24-hour period in MS patients' own community setting, and, self-reported perceived fatigue as assessed by three commonly applied self-report questionnaires (i.e. Fatigue Severity Scale [FSS], Modified Fatigue Impact Scale [MFIS] and Checklist Individual Strength [CIS20R]) including their sub-scales.

We hypothesized that the strength of associations may depend on the questionnaire used, but that overall higher fatigue scores would be significantly inversely associated with physical activity assessed with 24 hours activity monitoring (24h-AM). Additionally, we correct for possible confounders, such as age, disability status, disease duration, disease sub-type, depression and anxiety. Our second objective was to investigate whether the associations between physical activity and fatigue were confounded by factors such as age, disability status, disease duration, disease sub-type, depression and anxiety, as previous studies have not addressed this. We hypothesized that the association between actual levels of physical activity and perceived fatigue was significantly distorted by these variables.

Methods

Subject selection

Patients with MS were recruited from the MS center of the VU University Medical Center (VUmc), the Netherlands from a local outpatient database and by referrals from the neurology department. Patients met the following inclusion criteria: (1) older than 18 years; (2) a definite diagnosis of MS;[24] (3) an EDSS score below 6.5,[25] indicating that patients were ambulatory; (4) no co-morbidity that could influence fatigue and/or mobility; and (5) written informed consent.

Activity monitoring

The assessment of daily physical activities was done by means of a portable activity monitor (AM, Vitaport3). In a previous study, we showed that 24-h AM is a reliable method to measure physical activity in ambulatory patients with MS.[26] The applied methodology was published previously.[26] The obtained signals from the AM were analysed and classified into postures and motions according to the method of Bussmann and colleagues.[27] Subsequently, motions were grouped into a single category defined as 'dynamic activity' (expressed in hours), which contained sit to stand and stand to sit transitions, walking, stair walking and cycling. The variable dynamic activity was used in the present study as a direct correlate of physical activity in the home and community setting.

Questionnaires

Three Dutch versions of self-report questionnaires, the FSS, the MFIS, and the CIS20R, were used to assess fatigue. The FSS[19,28] is a nine-item self-report questionnaire to assess the severity of fatigue and its impact on an individual's daily functioning.

The MFIS is a shortened Dutch version of the 40-item Fatigue Impact Scale[5] and assesses the perceived impact of fatigue on the sub-scales physical, cognitive and psychosocial functioning during the past 4 weeks.

The CIS20R3,[29] assesses fatigue during the past 2 weeks and consists of four sub-scales: subjective experience of fatigue; reduction in motivation; reduction in activity and reduction in concentration.

The Hospital Anxiety and Depression Scale (HADS)[30] is a self-report rating scale of 14 items. It is designed to measure anxiety and depression (seven items for each subscale).

Assessments

Six research assistants were trained to apply the AM. Assessments were done on all days of the week. The AM was applied and removed in the participants' own home. Twenty-four-hour monitoring was executed twice. Research assistants visited the participants on day 1 (application AM) and day 2 (pick up AM) and a week later on day 8 (application AM) and day 9 (pick up AM).

All participants were instructed to continue their usual daily activities performed in their own environment (i.e. home and community) and use their walking devices or orthoses as they would normally do, but to refrain from showering and swimming. Participants were told that the system measures body movement, but no elaborate explanation of the purpose of the study and the function of the AM was given until the end of the final measurement session.

At the assessment days 1 and 8, the participants also filled in three fatigue questionnaires and the HADS. To prevent carry-over effects, the three fatigue questionnaires were offered in a random sequence (i.e. MFIS/FSS/CIS20R, CIS20R/MFIS/FSS, and FSS/CIS20R/MFIS). In random order, half of the participants completed the questionnaires in the morning, the other half of the participants in the afternoon to control for influences of diurnal fluctuations in perception of fatigue.

Statistical analysis

For all analyses, the mean scores over the two consecutive assessments were determined for physical activity, FSS, MFIS, and CIS20R scores, as no significant differences were found between the two assessments (t-test, p-values >0.05). Frequency distributions of physical activity, FSS, MFIS, and CIS20R scores were checked for normality by visual inspection of histograms.

Standard linear regression analyses were used to assess the bivariate associations between, on the one hand, physical activity as the dependent variable in the model and, on the other hand FSS, MFIS or CIS20R, including their sub-scales as the independent variable. Subsequently, we adjusted each derived association model for age, EDSS, disease duration, disease sub-type, HADS depression, and HADS anxiety, separately. If the unstandardized regression coefficient of physical activity with perceived fatigue measured by the different fatigue questionnaires changed by more than 15% after the variable was added to the model, the variable was considered to be a covariate that confounded the relationship between physical activity and perceived fatigue. Finally, all variables that distorted this relationship significantly were added to a last association model in order to determine the significant adjusted association between the independent variable, physical activity and the dependent variables (i.e. measures of fatigue). Statistical significance was taken two-sided at the 0.05 level with respect to the linear correlations' deviation from a zero slope. All data were analysed with SPSS statistical package (version 16.0).

Results

Patient characteristics

Forty-five patients with MS were included in the study of which 43 (mean age 48.7 years, median EDSS score 3.5) were used for analyses. Table 6.1 shows characteristics of the MS patients.

Table 6.1 Participants characteristics (N=43)

	Mean (SD)	Min–Max (range)
Age (years)	48.7 (7.0)	38–64 (26)
Disease duration (years)	14.3 (9.2)	2–51 (49)
Physical activity (minutes)	126 (48)	41–233 (192)
	Number	Percentage
Gender, male/female	13/30	30/70
MS type, RR/SP/PP	26/10/7	61/23/16
	Median scores (IQR)	Min–Max (range) scores
EDSS	3.5 (2.5)	1–6 (5)
HADS depression*	4.5 (6.25)	0–17 (17)
HADS anxiety*	4 (4.62)	0–16.5 (16.5)
FSS	52 (6)	15–63 (48)
MFIS	41 (17.5)	1–74.5 (73.5)
MFIS physical	21.5 (5.5)	1–32 (31)
MFIS cognitive	17 (8.5)	0–35.5 (35.5)
MFIS psychosocial	4 (2.5)	0–8 (8)
CIS20R	78.5 (19)	31.5–121.5 (90)
CIS20R subjective feeling	32.5 (12.5)	9.5–56 (46.5)
CIS20R concentration	20.5 (6.5)	5–31.5 (26.5)
CIS20R motivation	13.5 (6)	4–25 (21)
CIS20R activity	12 (6)	3–20.5 (17.5)

* N=30.
SD, standard deviation; M, male; F, female; MS, multiple sclerosis; EDSS, Expanded Disability Status Scale; RR, relapse remitting; SP, secondary progressive; PP, primary progressive, IQR; inter quartile range; HADS, Hospital Anxiety and Depression Scale; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; CIS20R, Checklist Individual Strength.

All participants were able to walk at least 100 metres without resting with or without intermittent or constant unilateral assistance. None of the participants used a wheelchair. All participants gave informed consent, in accordance with the ethical standards of the Declaration of Helsinki. The medical ethics committee of the VUmc approved the study. All data were normally distributed upon visual inspection. Table 6.1 shows that, on average over the two 24h-AM assessments, patients exhibited 126 minutes of dynamic physical activity.

The AM data of two MS patients (4.4% of total assessments) could not be used for analysis because of a malfunctioning sensor. All but two participants had a measurement interval of seven days according to the measurement protocol. System failure and assessor illness resulted in a 6- and 14-day interval in these instances. In general, the 24h-AM was well tolerated by the subjects, without adverse events, and no practical problems were reported by participants.

Linear regression analyses

No significant bivariate standardized (β_s) and unstandardized (β_{pa}) regression coefficients were found between physical activity and FSS, MFIS and CIS20R scores, including the sub-scales, with exception of the MFIS sub-scale 'physical activity' (β_s=-0.325, β_{pa}=-0.044; SE=0.020).

Table 6.2 shows that adjustments for age, type MS, HADS depression and anxiety resulted in significant negative regression coefficients (β_{pa}) for FSS and MFIS, and for the MFIS sub-scale 'physical activity'.

Table 6.2 also illustrates the proportional change of the bivariate unstandardized regression coefficients for physical activity (β_{pa}), and FSS, MFIS and MFIS sub-scale 'physical activity' that showed a distortion beyond the 15% after adjusting for the significant candidate determinants. Initially, for the FSS, no significant bivariate association was found. However, adjustment for age, MS-type, anxiety (HADS-A) and depression (HADS-D) resulted in a significant (proportional) increment of the unstandardized regression coefficients between physical activity and FSS ranging from 17.4% up to 69.6%, respectively. Similarly, the association between physical activity and MFIS became significant after adjusting for age and depression (HADS-D), with a proportional change of 41.6% and 83.3%, respectively.

The inverse association of the MFIS sub-scale 'physical activity' was significantly strengthened by adjusting for age, sub type of MS, anxiety (HADS-A) and depression (HADS-D), resulting in an increment of the negative regression coefficient from -0.052 for age to -0.083 for depression.

Correcting the associations for significant covariates in one multivariate regression model resulted in a proportional increment of 80% in the relationship between physical activity and the MFIS sub-scale 'physical activity', an increment of 56% for physical activity and FSS, and 8.3.% for physical activity and MFIS. No significant bivariate associations were found for physical activity and CIS-20R or sub-scales, and all associations remained insignificant after controlling for the different covariates. In addition, disability status (EDSS) showed a small but significant association with MFIS (r=0.33, p=0.03), but not with the FSS (r=0.19, p=0.23) and the CIS20R (r=0.06, p=0.71).

Table 6.2 Proportional change in the significant unstandardized β coefficients of Dynamic activity adjusted for confounders (N=43)

	FSS		MFIS		MFIS physical	
Independent variable	β_{pa}	Proportional change (%) β_{pa}	β_{pa}	Proportional change (%) β_{pa}	β_{pa}	Proportional change (%) β_{pa}
Fatigue questionnaires	-0.023 (NS)	-	-0.012 (NS)	-	-0.044[a]	-
Adjusted covariates	-	-	-	-	-	-
Age	-0.027[a]	17.4	-0.017[a]	41.6	-0.052[a]	18.2
Disease duration	-	-	-	-	-0.044[a]	0
Type MS	-0.028[a]	21.7	-	-	-0.048[a]	9.1
Depression (HADS-D)*	-0.038[a]	65.2	-0.022[a]	83.3	0.083[b]	88.6
Anxiety (HADS-A)*	-0.039[a]	69.6	-	-	-0.070[b]	59.1
All significant covariates	-0.036[a]	56.6	-0.022[a]	83.3	-0.080[b]	81.8

[a] Correlation is significant at the 0.05 level (2-tailed).
[b] Correlation is significant at the 0.01 level (2-tailed).
* N=30.
β_{pa}, unstandardized regression coefficient for physical activity; MS, multiple sclerosis; HADS, Hospital Anxiety and Depression Scale; HADS-D, depression subscale of the Hospital Anxiety and Depression Scale; HADS-A, anxiety subscale of the Hospital Anxiety and Depression Scale; NS, not significant; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; CIS20R, Checklist Individual Strength.

Discussion

To the best of our knowledge, this is the first study that has explored the relation between multiple self-report fatigue measures and the actual performed physical activities in MS patients' own community environment monitored for 24 hours, taking possible confounders, such as age, disability status, disease duration, disease sub-type, depression and anxiety into consideration.

In contrast with our first hypothesis, we did not find a significant inverse association between physical activity and fatigue as assessed with the questionnaires. Only the MFIS sub-scale 'physical functioning' showed a small significant inverse relationship with the actual amount of physical activity. The significant regression coefficient β_{pa} of -0.044 suggests that a one-point increment on the MFIS sub domain physical activity score is associated with an average decline of 5.5 minutes in subjects' physical activity over 24 hours. Interestingly, Vercoulen et al.[18] also failed to show significant associations between the CIS20R sub-scale 'subjective fatigue' and physical activity. In accordance with our second hypothesis we found that, depending on the fatigue questionnaire used, the association became stronger after correcting for factors such as age, depression and anxiety. Although disability status (EDSS) showed a small but significant association with fatigue (MFIS), it did not significantly influence the association between physical activity and fatigue.

The present findings are remarkable for a number of reasons. First, the absent relationship between, on the one hand, physical activity, and, on the other hand, severity of fatigue assessed with these commonly used scales further challenges the assumption that patients who are reporting more fatigue will automatically show less physical activity, i.e. a downward directed spiral between inactivity and fatigue. The weak associations between fatigue and physical activity we found are in line with the complex nature of individual decisions made by MS patients to engage in physical activity.[17] Our finding further suggests that central fatigue in MS is a perceptual problem in which patients will rather compensate or even overcompensate their daily tasks than yield to feelings of fatigue. Therefore, therapeutic approaches for the treatment of fatigue should probably be accompanied by cognitive behavioural therapy, in which patients learn to restructure their living habits, including sufficient intervals of resting.[31] In addition, the findings in the present study confirm that fatigue management in MS should comprise identification and treatment of other factors that are expected to contribute to fatigue, such as depression and anxiety. Second, observed differences found for the relations between the three fatigue measures and physical activity, ranging from weak but statistically significant on the MFIS sub-scale 'physical activity' to no significant associations at all for the CIS20R, emphasize that these measures have different properties reflecting different underlying constructs of fatigue and that fatigue is multidimensional.[19] This finding is further underpinned by the low correlation coefficients found for concurrent validity between these measurements.[19] Comprehensive fatigue assessment should therefore include a test battery of different questionnaires.[3] The findings further emphasize that there is an urgent need for consensus on a uniform definition of fatigue which is currently lacking[7] and with that, a golden standard to measure fatigue in MS. Third, the weak mutual relationship may have important consequences for future trials aimed at influencing fatigue by breaking through the proposed vicious circle between perception of fatigue and physical activity.[17] At minimum, the weak inverse relationship found in the present study suggests that a mean additional dose of 33 minutes spontaneous dynamic physical activities per day would be associated with a mean reduction of three points on the MFIS domain physical activity. However, studies that investigated longitudinal dose–response effects of physical training on fatigue are lacking in MS.

The present study has some limitations. First, only ambulatory MS patients were included (i.e. EDDS score below 6.5). Further studies with larger patient groups are needed to include non-ambulatory MS patients, using a more elaborate AM setup with accelerometers on the arms to measure wheelchair propulsion activity. Secondly, there may be other variables that distort the relationship between physical activity and fatigue that we have not assessed and therefore not included in our adjusted linear regression models, like, for example, pain, cognitive impairments and quality of life. Third, the present study is cross sectional, whereas it is conceivable that dynamic activity and fatigue outcomes are not stable but time-dependent and sensitive to daily, weekly or seasonal variations. Future studies should focus on elucidating the longitudinal construct validity of fatigue by assessing how changes in factors such as depression and anxiety are quasi-causally related with changes in perceived fatigue and actual levels of physical activity by applying an intensive repeated measurement design over a prolonged period of time. As a consequence, the daily within-subject variability of fatigue will be reduced. These models with repeated measurements in time may also help to unravel the longitudinal relationship of fatigue being an antecedent or consequence of physical activity by assessing physical activity and instantaneous fatigue simultaneously. This may be done by means of a Visual Analogue Scale (VAS), scoring current fatigue (e.g. hourly) in combination with continuous activity monitoring.

The latest technological developments applying using wireless sensor systems with higher sample frequencies and longer battery life facilitate longer and more detailed registration periods. Further research is needed to determine the optimal frequency and exact formulation of the VAS-fatigue question(s). Finally, the present study does not give an answer to which type of activities (e.g. cycling, walking, stair-walking, transfers) participants change due to fatigue.

Conclusion

The relationship between fatigue and physical activity is not a uniform, clear and straightforward association. Fatigue assessed with total scores of the FSS, MFIS, or CIS20R is not significantly related to physical activity, questioning the existence of a vicious circle of inactivity mediated only by fatigue. Dependent on the fatigue questionnaire used, patient characteristics such as age, type of MS, depression and anxiety are important confounders in the understanding of the relationship of physical activity and fatigue.

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