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ORIGINAL REPORT

RELATIONSHIP BETWEEN FATIGUE AFTER ACQUIRED BRAIN INJURY AND DEPRESSION, INJURY LOCALIZATION AND AETIOLOGY: AN EXPLORATIVE STUDY IN A REHABILITATION SETTING

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Objective: **Fatigue after acquired brain injury may be related to the subcortico-frontal attention network. Depression is also strongly related to fatigue. This study investigates whether injury localization, diagnosis and depression are related to self-rated mental fatigue in patients with an acquired brain injury.**
Design: **Retrospective cross-sectional cohort study.**
Subjects: **Sixty-one patients diagnosed with stroke, subarachnoidal haemorrhage, traumatic brain injury, or brain tumour were included in the study.**
Methods: **Patients who underwent a multidisciplinary team assessment during September 2011 to June 2012, and who were assessed with the Mental Fatigue Scale, were included in the study.**
Results: **A significantly higher number of patients with posterior and non-specific lesions experienced fatigue compared with those with subcortical/frontal injuries. Fewer stroke patients experienced fatigue compared with the other patient groups. However, after logistic regression, only depression remained as an explanatory variable for self-rated fatigue. Nevertheless, although all patients with depression were fatigued, not all fatigued patients were depressed.**
Conclusion: **Although depression explains a high degree of fatigue after an acquired brain injury, mental fatigue after brain injury should be viewed as a condition partly separate from depression. Future extensive comparative studies are required, preferably including neuropsychological measures.**

Key words: fatigue; brain injury; stroke; traumatic brain injury; depression.

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LAY ABSTRACT

Fatigue is a common complaint following brain injury. This study investigated the impact of injury localization, diagnosis and depression on subjective fatigue experience in a group of patients in a rehabilitation unit. Patients with posterior and non-specific lesions were more fatigued than those with subcortical and frontal injuries. Stroke patients were less likely to experience fatigue than patients with other diagnoses. However, the differences in fatigue between injury localization and diagnostic groups were overshadowed by the strong relationship between depression and fatigue.

Mental fatigue is a common complaint after acquired brain injury (1, 2) and a major reason for reduced work capacity and leisure activity (1, 3–5).

However, fatigue is not a specific complaint and, in many cases, there are multifactorial causes for the symptom (6).

There is no clear correlation between self-rated fatigue after brain injury and time since injury (7–10), level of education, or sex (7, 10–12). Whether age is a contributing factor to fatigue is not conclusive. Some studies indicate that higher age leads to increased risk of fatigue after stroke (11), whereas Snaphaan et al. (13) found an increased risk of fatigue in younger patients with stroke.

On a functional level, reduced attention and processing speed have been associated with fatigue (14). Anatomically, disturbance of the non-motor function of the basal ganglia (15) and the fronto-subcortical attention-related network (16), including the thalamus and middle frontal gyrus (17), have been proposed to be crucial to the experience of mental fatigue. Thus, it is likely that patients with injuries in the frontal-subcortical network are more vulnerable to fatigue than those with other injury locations. Other cortical areas also appear to be relevant to fatigue related to brain injury, and Kohl et al. (18) have pointed out that superior parietal dysfunction should be included in a model of fatigue related to brain injury.

Nevertheless, the results of previous studies on the relationship between brain damage location and fatigue are not consistent; concerning stroke, no association has been found in some studies (11), while other studies have shown increased incidence of fatigue in subcortical damage (19–21). As for traumatic brain injury (TBI) and mild TBI, an association has been shown between impaired connectivity in frontal structures and self-rated fatigue (17, 18). In addition to primary brain injury related causes of fatigue, depression often co-occurs with fatigue after stroke, TBI and brain tumour (3, 11, 22–24). Depression and mental fatigue are subjective experiences, usually measured with different types of self-assessment scales, and the

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fact that the symptoms of the 2 states overlap makes it difficult to differentiate between them (25). High fatigue scores have also been found to coincide with high rates of depression (3, 24, 26). However, several studies have shown that fatigue after stroke, as well as after TBI, may occur independently of depression (3, 7, 8, 23, 24).

The Mental Fatigue Scale (MFS) (27) is a commonly used instrument for assessing mental fatigue in the field of rehabilitation medicine in Sweden, while the Hospital Anxiety and Depression Scale (HADS) (28), which is part of the Swedish National Quality Register of Rehabilitation, is frequently used in screening for depression.

In clinical practice, it is of value to know whether fatigue is related to the primary brain injury or to secondary factors, such as depression, as this may affect the choice of treatment.

The aim of this study was to investigate whether fatigue, measured with the MFS, was associated with brain injury localization, diagnosis, or depression in a clinical group of patients with acquired brain injury.

METHODS

Participants

The Outpatient Brain Injury Rehabilitation Unit at the Department of Rehabilitation Medicine Stockholm at Danderyd University Hospital receives patients between the ages of 18 and 65 years with moderate to severe acquired brain injury for assessment and treatment. All patients diagnosed with stroke, subarachnoidal haemorrhage, traumatic brain injury, and brain tumour, who underwent multidisciplinary team assessment at the Huddinge Unit during September 2011 to June 2012, and were assessed with the MFS, were included in the study. A total of 61 patients (27 women and 34 men) between 19 and 65 years of age (mean age 48 years; standard deviation 13 years) met the criterion and were included. Demographic data are shown in Table I.

The exclusion criterion was missing MFS data. A total of 22 patients were excluded for this reason. The reasons why MFS data were missing were: lack of knowledge of Swedish or aphasia ($n=5$), no neuropsychological investigation was accomplished during the assessment period ($n=5$), the paper form had disappeared ($n=5$), malingering, according to results of a malingering test ($n=1$) and unclear reason ($n=6$). There was no significant difference with regards to age, sex, and level of education between included and excluded patients.

Table I. Clinical and demographic data of the included population ($n=61$)

	n (%)	Median (range)
Men/women	34 (56)	27 (44)
Age, years		48 (19–65)
Education		
Elementary school	11 (18)	
Vocational high school	18 (30)	
Secondary education	9 (15)	
University/college	23 (38)	
Diagnosis		
Stroke	33 (54)	
TBI	17 (28)	
Other (tumour*, SAH)	11 (19)	
Lateralization		
Unclear	5 (8)	
Left	28 (46)	
Right	18 (30)	
Bilateral	10 (16)	
Latency, months		5 (2–62)
GOSE, median		5 (4–7)
GOSE=4	3 (5)	
GOSE=5	33 (54)	
GOSE=6	23 (38)	
GOSE=7	2 (3)	
MFS		13.5 (2–31)
HADS-D		5 (0–15)

*Among the tumours there were 3 meningioma and 1 pineal tumour grade 2, all treated with surgery only.
GOSE: Glasgow Outcome Scale Extended, MFS: Mental Fatigue Scale, HADS-D: Hospital Anxiety and Depression Scale, Depression Scale.

Measures

Mental Fatigue Scale (MFS). Mental fatigue was assessed with MFS, a multidimensional scale designed to capture mental fatigue in different patient groups with central nervous system (CNS) disease or injury, including stroke (4), TBI and brain tumour (27). The scale consists of 15 activity-based questions, including affective, cognitive and sensory symptoms, sleep, and variation throughout the day. Question number 15, on 24-h variations, is analysed separately and not included in the sum scores. The questions are rated on a 7-point scale based on intensity, frequency, and duration, where higher scores reflect more severe symptoms. Each item is rated between 0 and 3, with the option of rating between 2 scale steps; 0 corresponds to normal function; 1 indicates a problem; 2 pronounced symptoms; and 3 maximum symptom levels. The scale measures fatigue between 0 and 42, with a clinical cut-off score at 10.5 (29). The questions have been shown to have high internal consistency (Cronbach's alpha 0.94), and all items have been shown to correlate significantly with each other (27). The MFS has mainly been used to study mental fatigue in groups with TBI and stroke (4, 14).

In this study, MFS was analysed as both a dichotomous (> 10) and a continuous variable.

The scale is similar to the Comprehensive Psychopathological Rating Scale (CPRS) (30), an instrument designed to evaluate change in psychiatric disorders over time of treatment. Four items, "concentration difficulties", "lack of initiative", "irritability", and "decreased sleep" overlap and are identical in both scales (29). Analysis of the internal structure of the scales revealed 5 components with an eigenvalue > 1, where items from MFS mainly loaded on the same component, including overlapping items "lack of initiative" and "concentration difficulties". Other overlapping items, i.e. "irritability" and "decreased sleep" loaded on other components, as well as the item "increased sleep" (29).

Based on this analysis, and with the purpose of obtaining a fatigue measure without psychopathological confounders, a separate "core fatigue" measure, where the items "irritability", "increased sleep", and "decreased sleep" were excluded from the sum of scores, was applied in this study.

Hospital Anxiety and Depression Scale (HADS). Symptoms of depression were assessed with the HADS (28). HADS is a self-assessment form that includes 14 items divided into 2 subcategories; 1 for anxiety and 1 for depression. Each item is rated on a 4-point Likert scale (0–3). Both subscales range from 0 to 21, where scores between 8 and 10 indicate the possible presence of anxiety or depression, while a score over 10 more clearly indicates the occurrence of such conditions. In this study, HADS depression (HADS-D) was analysed both as a dichotomous and a continuous variable. Scores above 7 are considered clinically relevant (31) and was chosen as a cut-off for depression in the calculations.

Glasgow Outcome Scale Extended (GOSE). The extended version of Glasgow Outcome Scale (GOS) (32), GOSE (33), is a scale designed to assess the outcome after brain injury. The classification is based on a structured interview and the scale has 8 steps; 1 corresponds to "dead" and 8 to "good recovery". The measure includes physical, as well as cognitive and emotional, aspects. GOSE was used to classify the severity of brain injury.

Procedure

In accordance with normal procedure, psychologists or physicians administered MFS, HADS, and GOSE during a 2-week team assessment period.

Based on magnetic resonance tomography (MRT) or computed tomography (CT) findings by independent neuroradiologists, participants were classified into 1 of 3 injury location categories. Group 1 included those with injuries in frontal, subcortical, and brain stem structures, with or without posterior involvement; Group 2 included those with solely posterior injuries; and Group 3 included those with non-specific/unclear injuries.

Statistics/data analysis

Non-parametric statistics were used: χ^2, Fisher's exact test, Kruskal–Wallis test, Spearman's rank correlation and logistic regression (forward stepwise). Significance levels of 0.05 (2-tailed) were accepted. As the study is explorative, no Bonferroni corrections were made. To evaluate the generalizability of the results a *post hoc* power analysis was carried out. With a power of 80% and a significance level of $p=0.05$, a total of 87 participants would have been required to obtain satisfying power in the sub-group analysis of injury localization and fatigue. As to sub-group analyses of diagnosis and fatigue, a total of 57 participants was satisfactory. The statistical package IBM SPSS, version 23, was used.

Ethics

The study is a register study approved by the ethics review board of Stockholm, Sweden, (reg. no. 2016/408-32). The study was performed according to the principles of the Declaration of Helsinki 1978.

RESULTS

Study population

A majority of the patients included in the study had moderate to severe brain injuries. Clinical data is presented in Table I.

Fatigue throughout the group

Forty-four patients (67%) met the fatigue criterion (MFS> 10.5), while 20 patients did not. As to sex, educational level, GOSE score, lateralization and latency, no differences were found between the patients who met the criterion of mental fatigue and those who did not. However, the fatigued patients were younger ($p=0.049$) and rated significantly more symptoms of depression ($p=0.000$, HADS-D) compared with non-fatigued patients. There was also a negative correlation between age and fatigue when measured as a continuous variable ($r=-291$, $p=0.023$).

Relationship between fatigue and injury location

There was a significant difference in fatigue due to injury location ($p=0.035$) when the fatigue measure was used as a continuous variable. Patients with posterior and non-specific injuries rated higher levels of fatigue than those with subcortical/frontal lesions (Fig. 1). However, when the measure was dichotomized, there was no difference between the groups ($p=0.167$). The different injury location groups did not differ with respect to the other variables: age, sex, latency, educational level, GOSE and HADS-D.

Relationship between fatigue and diagnosis

There was a significant difference in fatigue depending on the cause of injury, independently of whether the fatigue measure (MFS) was used as a continuous or as a categorical variable (Table II). Stroke patients were less fatigued than patients with TBI or other diagnosis (Table II and Fig. 2). There was no significant difference in GOSE, latency, and age between the diagnostic groups, but there was a tendency that patients with TBI were younger and more depressed (Table II).

Relationship between fatigue and depression

Eighteen patients (29.5%) met the criterion of depression (1 case of missing data). There was a significant positive correlation between depression and self-rated

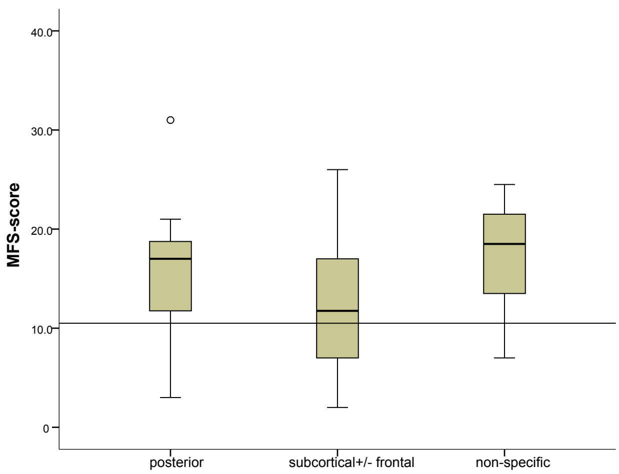

Fig. 1. Comparison of rated scores in Mental Fatigue Scale (MFS) based on injury location ($n=61$).

Table II. Demographic and clinical data related to diagnosis

	Stroke $n=33$	TBI $n=17$	Other $n=11$	*p*-value
Sex (men/women), *n* (%)	22 (67)/11 (33)	9 (53)/8 (47)	3 (27)/8 (73)	0.068
Age, years, median (range)	53 (21–65)	40 (19–65)	52 (36–65)	0.073
Education				0.580
Localization, *n* (%)				0.294
Cortical+/– subcortical	23 (70)	10 (59)	5 (46)	
Posterior	7 (21)	2 (12)	3 (27)	
Diffuse	3 (9)	5 (29)	3 (27)	
Lateralization, *n* (%)				0.000
Unclear	0	4 (24)	1 (9)	
Left	22 (67)	4 (24)	2 (18)	
Right	10 (30)	2 (12)	6 (55)	
Bilateral	1 (3)	7 (41)	2 (18)	
Latency, months, median (range)	4 (2–30)	6.0 (3–62)	5 (3–15)	0.316
GOSE, median (range)	5 (4–7)	5 (4–7)	5 (5–6)	0.857
MFS continuous, median (range)	10.5 (2–25)	17 (3.5–24.5)	18.5 (7–31)	0.004
MFS categorical (fatigue/non-fatigued), *n*	17/16	14/3	10/1	0.016
Core fatigue, median	8.5	14.5	15.5	0.007
HADS-D continuous, median (range)	4 (0–15)	7.0 (0–11)	6 (2–13)	0.077

χ^2 test/Fischer's exact test and Kruskal–Wallis test for independent groups were used for group comparison.
GOSE: Glasgow Outcome Scale Extended, MFS: Mental Fatigue Scale, HADS-D: Hospital Anxiety and Depression Scale, Depression scale.

mental fatigue ($r=0.715$, $p=0.000$). The correlation remained when only the core fatigue items of MFS were used ($r=0.654$, $p=0.000$).

There was no correlation between severity of depression (HADS-D as a continuous variable) and severity of brain injury or time since injury. However, there was a tendency for younger patients to rate higher degrees of depression ($r=–253$, $p=0.05$).

As several factors correlated with fatigue, a logistic regression with age, injury location, diagnosis, lateralization, and depression (continuous variable) in the model was accomplished, which was acceptable according to Nagelkerke R-square (0.545). After logistic regression, depression remained only as an explanatory variable for self-rated mental fatigue (Table III).

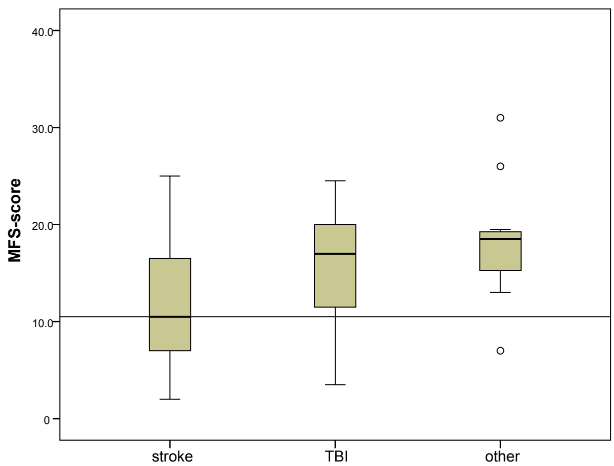

Fig. 2. Comparison of the Mental Fatigue Scale Scores (MFS) between different diagnostic groups ($n=61$).

Table III. Final results of logistic regression analysis (stepwise forward) of fatigue (Mental Fatigue Scale) with the variables age, injury location, diagnosis, lateralization, and depression (Hospital Anxiety and Depression Scale, Depression scale; HADS D continuous variable) included in the model

	OR	95% CI	Wald χ^2	df	*p*-value
HADS-D	1.898	1.351–2.666	13.667	1	0.000
Constant	0.171		7.464	1	0.006

CI: confidence interval; OR: odds ratio.

Post hoc *analysis of depression*

Out of clinical interest, the distribution of fatigue and depression was investigated. All patients who were depressed (HADS> 8) rated 10, 5 or higher in MFS, but more than half (56%, $n=23$) of the patients who met the criterion of mental fatigue were not depressed (Fig. 3).

There was no difference in age, sex, latency between injury and rehabilitation, injury location or diagnosis between those who were mentally fatigued, but not depressed ($n=23$), and those who were fatigued and depressed ($n=18$).

DISCUSSION

The aim of this study was to investigate whether injury location and diagnosis were crucial to the experience of mental fatigue. It was found that patients with solely posterior and non-specific lesions rated more mental fatigue than patients with frontal and subcortical lesions. Furthermore, stroke patients rated significantly less fatigue than those with TBI or other diagnosis. However, there was, in accordance with previous studies (3, 24), a clear connection between self-rated fatigue and symptoms of depression. When included in regression analysis, depression accounted

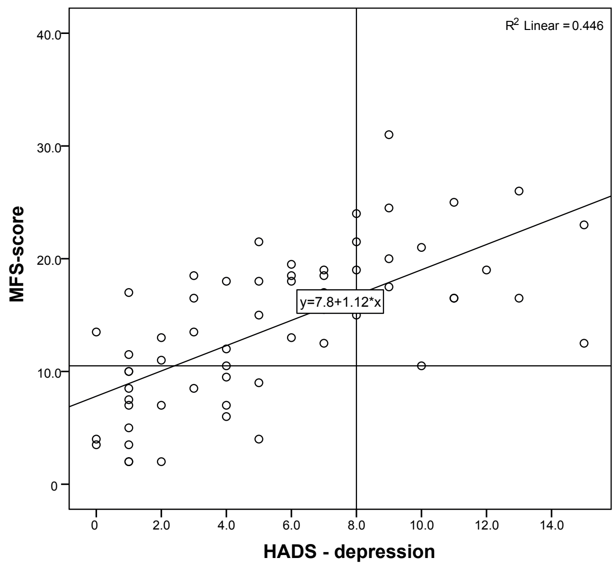

Fig. 3. Scatter plot: rated points in Mental Fatigue Scale (MFS) and rated points in Hospital Anxiety and Depression Scale (HADS) Depression Scale ($n = 61$).

for the greater part of the variance of self-rated mental fatigue and was the only remaining explanation for self-rated fatigue.

Thus, the theory of the importance of disturbance within a more or less defined subcortical/frontal network as a determinant of fatigue experience was not supported in the study, but coincides partly with the findings of Kohl et al. (18), indicating that the parietal lobe may also be relevant for fatigue.

Although the parietal lobe is part of the attention-related network (34), which theoretically can be linked to fatigue, it is difficult from a neuroanatomical perspective to explain why patients with posterior and non-specific lesions reported more fatigue than those with frontal and subcortical injuries. As for the non-specific injuries, a possible interpretation is that those tend to be widespread, disturbing attention-related networks. A lower degree of reported fatigue in frontally injured patients, on the other hand, might be due to injury-related lack of insight with understatement of fatigue.

It was found that stroke patients rated lower levels of mental fatigue than other diagnostic groups, including TBI, a finding that lacks support in the literature. Johansson et al. (27) found no significant difference in the MFS total score between stroke and TBI patients. However, differences in fatigue levels between different diagnosis groups are not well studied. In contrast to the participants in Johansson's study our participants were unselected rehabilitation patients. A possible explanation for the difference seen in our study could be that stroke patients, regardless of sequelae, are perhaps referred to rehabilitation more automatically and at an earlier stage than patients with TBI or other diagnoses, who might not be referred unless they have pronounced symptoms, such as fatigue or depression. The results showed no significant differences regarding latency from injury to rehabilitation, between the groups. Nevertheless, in numerical terms, the median for the latency between injury and assessment was 4 months for stroke patients and 6 months for patients with TBI. Another hypothesis may be that stroke causes focal damage to the brain, while TBI and the other groups (SAH and tumour) usually cause more widespread injuries, and in the case of TBI, diffuse axonal injuries, that may interfere with fatigue-related networks. In the whole group, there was a significant negative relationship between age and fatigue. In previous studies, including one with MFS as fatigue measure (29), age has most often not been shown to be related to fatigue, either in stroke, TBI or SAH. In cases where an association has been seen, it has gone in the opposite direction, with higher age increasing the incidence of fatigue. Snaphaan et al. (13), on the other hand, found an increased risk of fatigue in younger stroke patients, which might mirror high demands on functioning and activity in younger people, making them more vulnerable to fatigue.

However, the differences in fatigue levels between localization and between diagnosis groups were overshadowed by the strong relationship between depression and fatigue; an association that is convincingly supported in the literature (11, 22, 24).

The strong relationship between fatigue and depression seen in this study could be explained by the fact that MFS is theoretically based on a psychiatric model (35), and does not primarily emanate from an anatomical or functional perspective. The strong correlation also remained when the core fatigue measure was used, i.e. when the items shown to relate to anxiety/depression in Johansson & Rönnbäck's (29) component analysis of MFS and CPRS were excluded. This indicates that the relationship does not depend on single confounding variables; in this case, psychiatric items in the fatigue form.

Despite the strong correlation between fatigue and depression, *post-hoc* analysis showed that fatigue and depression are not necessarily concomitant; more than half of the mentally fatigued patients did not meet the depression criterion. This finding corresponds with the results of previous studies (8, 24, 27) and supports the notion that fatigue and depression should be considered as separate phenomena. This is clinically relevant, as the assumption that all fatigued brain injury patients are depressed may lead to incorrect treatment choices. However, all patients who were depressed were also fatigued; indicating that depression related to brain damage is a considerable risk factor for fatigue.

It is important to consider that in this study mental fatigue, as well as depression, was self-rated, and that scores above the cut-off limit on HADS-D do not necessarily equal clinical depression. Another possible explanation for the high degree of correlation of measures could be "response style", i.e. a general tendency to rate low or high in self-assessment forms.

The assumption of the importance of response style is supported by the fact that we did not find any natural cut-off limits for HADS-D and MFS in *post hoc* analyses. Hence, depression was used as a continuous variable in the regression analysis and one can question the relevance of using cut-off values.

MFS is designed to be a multidimensional instrument, as opposed to unidimensional scales, which are constructed to derive a single score. While unidimensional scales often are brief and easy to use, multidimensional scales could give more extensive information, in capturing different aspects of fatigue (36). Previous studies by Johansson et al. have shown that the variables in MFS have a strong internal correlation (27). This suggests that the instrument may not give a very multidimensional picture of fatigue, and one could question the large number of items. A less extensive questionnaire would require less effort to complete, probably without reducing the validity and informational value of the instrument.

A methodological weakness in this study concerns the division of patients into injury localization groups. In many cases, the injury was not limited to a single area (frontal, subcortical or posterior), but transcended the borders. Furthermore, the number of patients in whom the injury could not be clearly identified, was relatively large. Based on the theory of the importance of a subcortical frontal network for fatigue experience, all participants with verifiable injuries subcortically, frontally or in combination and with or without posterior involvement, were sorted into a single group. Consequently, this group became much larger than the group with purely posterior injuries.

The method of dividing the brain into separate anatomical substructures to capture a complex phenomenon, such as fatigue, is questionable, given the knowledge of the importance of the connectivity of the cortical network for brain function. A more appropriate method may be to study the connection between functional networks and fatigue using functional magnetic resonance imaging (fMRI) (16), although fMRI is not an option in most clinical practices. Most clinicians have to rely on MRI and the results of questionnaires.

The results of this study highlight the importance of interpreting the results of MFS with caution, since depression may be an important explanatory factor in cases of high scores. Nevertheless, all fatigue is not depression, and it is thus important to investigate both conditions in order to fully understand the patient's symptoms.

In the brain-injured population, there are also individuals who, due to impaired insight, have difficulty evaluating their fatigue. Unfortunately, this study did not include neuropsychological variables that could have contributed to further understanding.

The participants in this study were consecutive, in the sense that it was a register study on the patients subject to rehabilitation in the unit. However, there is a risk of selection bias, as the Department of Rehabilitation Medicine Stockholm is highly specialized and preferably offers rehabilitation to patients with severe and complex injuries; a group in which significant fatigue could be more likely. Therefore, the results of this study should be generalized only to patients with moderate to severe injuries.

The relatively small sample size is a limitation in the study, leading to small subgroups for injury location, which might negatively affect the generalizability of these results. While the *post hoc* power analysis showed satisfying power concerning diagnosis and fatigue; i.e. stroke patients being less fatigued than patients with other diagnoses, the power calculations indicated that the number of subjects was too small to draw any firm conclusions on the relationship between injury localization and fatigue. Therefore, more extensive and comparative studies are required, preferably including neuropsychological measures, which might help identify what distinguishes fatigued patients without depression from fatigued patients with depression, as this may be indicative of choice of treatment.

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