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Fatigue and processing speed are related in multiple sclerosis

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Background: Fatigue is common in multiple sclerosis (MS) and could be related to impaired processing speed caused by MS specific brain alterations. The objective of this study was to examine the relationship between processing speed and fatigue in patients with relapsing remitting MS.
Methods: Patients with EDSS score ≤3.5 were grouped as fatigued [Fatigue Severity Scale (FSS) score ≥5.0] or non-fatigued (FSS score ≤4.0). Patients with FSS scores ≥5 were categorized as primary or secondary fatigued according to various indices. A cognitive test battery obtained from Wechsler's Adult Intelligence Scale-III/ Wechsler's Memory Scale-III was applied.
Results: Processing speed (Digit Symbol Coding) was lower amongst all MS patients being 9.4(2.9) in primary fatigued, 8.3(2.8) in secondary fatigued and 10.3(2.7) in non-fatigued versus 12.3(3.0) in healthy controls. In the combined group of primary and secondary fatigued MS patients, processing speed was slower than that in non-fatigued MS patients and inversely related to fatigue ($r = -0.35$; $P < 0.05$). No such relationship could be established in non-fatigued MS patients or in healthy controls.
Conclusion: The degree of fatigue in MS is related to processing speed impairment and longitudinal studies should clarify their mutual dependency.

Introduction

Fatigue in multiple sclerosis (MS) is a lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual and desired activities [1]. Multiple aetiologies of MS-fatigue have been linked in a model encompassing both biological and psychological aspects. This model suggests that the inflammation and demyelination associated with the MS disease process trigger MS-fatigue, but that cognitive-behavioural variables, such as anxiety, depressed mood, reduced activity and deconditioning, can exaggerate fatigue [2].

Cognitive impairment occurs in 40–70% of patients with MS. Processing speed and working memory are essential features of the cognitive profile [3], but also e.g. free recall from long-term memory and abstract reasoning are frequently compromised [4].

Cognitive fatigability is a decline in performance during a neuropsychological testing session. A few study groups have actually demonstrated test performance fatigability amongst patients with MS, with [5] or without [6] a relationship to subjective fatigue.

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We hypothesized that MS patients with primary fatigue have impaired processing speed at baseline (cognitive fatigue) and increased test-performance fatigability (cognitive fatigability) whereas patients with secondary fatigue or without fatigue are less impaired.

Methods

Subjects

During the period May 2006–October 2007, patients who attended the MS-outpatient-clinic at Aarhus University Hospital or at the Hospital of Viborg County were recruited. Inclusion criteria were relapsing-remitting multiple sclerosis (MS), age of 18–55 years and an Expanded Disability Status Scale score (EDSS score) ≤3.5 [7]. Right handedness and normal function of the right arm were required. Exclusion criteria were clinical impression of dementia, concomitant major medical illness, clinical attack within 4 weeks, change of medical treatment within 3 weeks and living more than 65 km from the study site. Due to subsequent motor testing and MRI, pregnancy and contra-indications to MRI were also exclusion criteria.

Patients were stratified into two groups depending on the presence or absence of fatigue. Fatigue was quantified with the MS-specific questionnaire, the Fatigue

Severity Scale (FSS) [8]. Patients with a FSS mean score ≥5.0 were categorized as fatigued (F) and patients with a FSS mean score ≤4.0 as non-fatigued (NF) [9]. Patients with a FSS mean score between 4 and 5 were excluded. Subsequently, fatigue was categorized as primary fatigue (PF) or secondary fatigue (SF). Fatigued patients without fatigue-related symptoms or events were defined as primary fatigued. Fatigued patients who fulfilled any of the following items were categorized as secondary fatigued: *poor sleep* (Pittsburgh Sleep Quality Index > 5) [10], *poor well-being* (WHO-5 Well-being Index score ≤9) [11], *depression* (Major Depression Inventory score ≥26)[12], *pain* [two positive scores out of three; intensity (VAS score ≥3), frequency (at least once a week) and at least moderate pain according to The North American Research Committee on Multiple Sclerosis (NARCOM's) pain questionnaire] [13], *infection* (symptomatic infection within last 3 weeks, urinary tract infection upon examination (leucocytes $\geq 10^5$ or nitrite) and elevated C-reactive protein), *spasticity* (modified Ashworth scale score ≥3) [14] and tiredness due to pharmaceutical side-effects.

Healthy controls (HC) were recruited through the local newspaper, and the same general inclusion and exclusion criteria were applied. The study was conducted in accordance with Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and registered at ClinicalTrials.gov (NCT00342381). The regional scientific ethical committee and the Danish Data Protection Agency approved the protocol.

Study design

The day of examinations started with a case story review followed by EDSS scoring and neuropsychological examination. At the end of the day, patients were introduced to the questionnaires concerning secondary fatigue, answered at home and returned by mail within 2 weeks.

The EDSS was assessed in accordance with the Neurostatus (L. Kappos, version 03/2002). Experiences of fatigue during motor activity as well as complaints about fatigue limiting daily activities add to the pyramidal and the mental system scores of the EDSS. To enable studies of the relationship between fatigue (FSS) and disease severity, fatigue was excluded from the EDSS (corrEDSS). In the group of all fatigued MS patients, corrEDSS and EDSS were strongly related ($r = 0.88$; $P < 0.001$).

Neuropsychological measures

A test battery was constructed with tests from the Wechsler Adult Intelligence Scale (WAIS-III) and the Wechsler Memory Scale (WMS-III), representing four basic constructs: Procession Speed, Auditory Memory, Perceptual Organization and Verbal Comprehension [15].

The order of tests was: (i) Digit Symbol-Coding I (DSC I), (ii) Logical Memory I (LM I), (iii) Digit Symbol Copy (Copy), (iv) Matrix Reasoning (MR), (v) Vocabulary (V), (vi) Logical Memory II (LM II) and (vii) Digit Symbol Coding II (DSC II). DSC I and DSC II were identical. All examinations were conducted by the same physician trained by an experienced neuropsychologist. Administration and scoring was conducted under standardized conditions and in accordance with the WAIS-III and WMS-III manual. With the exception of Digit Symbol Copy, all WAIS-III/WMS-III data are scaled scores, raw scores being corrected for age [16]. Education was registered with 16 years as a maximum.

Digit symbol coding

Evidence suggests that speed of processing is the primary information processing deficit in MS [17]. Processing speed was examined with the Digit Symbol Coding as the first and the last neuropsychological test of the battery. The DSC-I score represents baseline cognitive fatigue whereas cognitive fatigability brought on during the neuropsychological test procedure was defined as [Digit Symbol Coding II scaled score] minus [Digit Symbol Coding I scaled score] (DSC II−I). Also, a more conservative parameter of processing speed was estimated: *Relative DSC* determined as Digit Symbol Coding I divided by the average of Matrix Reasoning and Vocabulary. A low Digit Symbol Coding I score compared to Matrix Reasoning and Vocabulary was interpreted as a MS-related reduction in processing speed. Digit Symbol Coding is composed of a series of numbers, each of which is paired with its own corresponding hieroglyphic-like symbol. Using a key, the examinee writes the symbol corresponding to its number.

Digit symbol copy

The Digit Symbol Copy (Copy) requires the examinee to copy symbols used in Digit Symbol Coding. The task is a measure of perceptual and grapho-motor speed and may affect the DSC scores. Raw scores were transformed to the corresponding cumulative percentage adjusted for age.

Logical memory I and II

Logical Memory I consists of two short stories which are orally presented. The examinee is instantly asked to retell the stories from memory. Approximately 30 min later the examinee is asked to retell both stories without being refreshed.

Matrix reasoning

Matrix Reasoning is a series of incomplete gridded patterns that the examinee completes from five possible choices. It is part of the perceptual organization index.

Vocabulary

Vocabulary consists of orally presented words that the examinee orally defines. It is the least sensitive factor because it represents tap crystallized intelligence considered to be relatively invulnerable to brain disease. This subtest reflects the pre-morbid verbal IQ score.

Supplemental upper extremity motor testing

The 9 Hole Peg Test (9-HPT) was used as a quantitative test of upper extremity motor speed and coordination [18]. It was administered in accordance with MSFC Manual (Edition, January 2001). Data are the inverted average of the two right hand performances.

Depression and well-being

The Well-being Index (WHO-5) has been derived from a WHO project (WHO 1990) and was used as a screening tool with a score ≤9 as indicative of depression [11]. The MDI is used for diagnosis of depression which requires the presence of core symptoms. But as a rating tool a MDI-score of 20–24 indicates mild depression [12].

Sleep

Sleep efficiency was assessed with the PSQI. The questionnaire is composed of seven components including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication as well as daytime dysfunction during the last month rated as a global score ranging from 0–21 with a score >5 indicating poor sleep [10].

Statistics

ANOVA was used to compare demographic data, disease duration, time since last attack, the neuropsychological scaled-scores and 9-HPT. In case of significance, pairwise analyses were conducted (*t*-test). Kruskal–Wallis tests were applied for analysis of scores of EDSS, FSS, MDI, WHO-5 and PSQI. Spearman's rank correlation was used to establish relationships between disability scores, neuropsychological parameters and scores obtained with the various questionnaires.

Results

Recruitment

Medical records of 906 patients were screened. One hundred and ninety-five case reports fulfilled the inclusion criteria and patients were contacted by mail. One hundred and sixteen patients responded and 23 were excluded following interview (Fig. 1). To ensure a similar number of participants in the three study groups, responders with secondary fatigue were not included during the period 1 August–31 October 2007. A total of 78 subjects were enrolled including 60 patients with MS and 18 healthy, non-fatigued control subjects.

Fatigue

Amongst patients with MS 19 were primary fatigued, 20 secondary fatigued and 21 non-fatigued (see Appendix S1 for confirmation). There were no differences with respect to gender, age or years of education between the four groups (Table 1). Disease duration was similar between patient groups, but 'time since last attack' was shorter for secondary fatigued than non-fatigued patients.

The non-fatigued patients had a lower EDSS score than fatigued patients, but after correction for fatigue

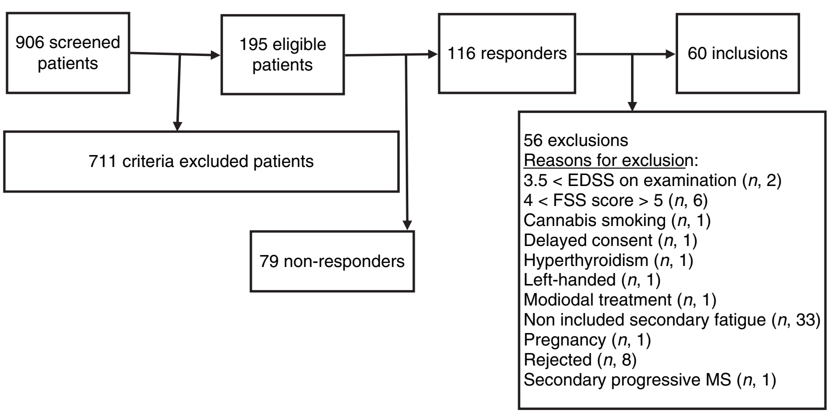

Figure 1 Recruitment of patients.

Table 1 Demographics, disability scores and treatment in patients with MS and healthy controls

	PF (*n*, 19)	SF (*n*, 20)	NF (*n*, 21)	HC (*n*, 18)
FSS score	6.3 (5.0–7.0)***	6.2 (5.0–7.0)***	3.1 (1.0–4.0)	2.8 (1.8–4.3)
Age (years)	43 (27–53)	39 (24–52)	39 (23–53)	40 (23–54)
Education (years)	13 (10–16)	13 (10–16)	15 (9–16)	15 (11–16)
Disease duration (years)	5.0 (1–14)	3.5 (0–16)	3.0 (0–9)	
Time since attack (years)	2 (0–7)	1 (0–6)*	3 (0–10)	
EDSS score	3.0 (1.0–3.5)**	2.5 (2.0–3.5)**	2.0 (1.5–3.5)	0 (0–2)
CorrEDSS score	2.5 (1.0–3.5)	2.0 (1.5–3.5)	2.0 (1.5–3.5)	
INFβ-1a/INFβ-1b/GA/NT	0.42/0.16/0.11/0.32	0.40/0.15/0.10/0.35	0.71/0.05/0.00/0.24	

Values are median (range).
*$P < 0.05$ vs. NF; **$P < 0.01$ vs. NF; ***$P \le 0.001$ vs. NF and HC.
MS, multiple sclerosis; PF, primary fatigued; SF, secondary fatigued; NF, non-fatigued; HC, healthy control; FSS, Fatigue Severity Scale. EDSS, Expanded Disability Status Scale; CorrEDSS, corrected EDSS; INFβ-1a, inteferon β-1a; INFβ-1b, interferon β-1b; GA, glatiramer acetate; NT, no treatment.

(corrEDSS) scores were similar. In the group of all MS patients, FSS was related to EDSS ($r = 0.42$, $P < 0.001$) but not to corrEDSS ($r = 0.07$; $P = 0.6$).

Amongst patients with secondary fatigue four fulfilled three out of seven criteria, one fulfilled two criteria and 15 fulfilled one criterion, only. Twelve secondary fatigued patients had poor sleep, six complained of pain, four of poor well-being, three of medical induced fatigue, two had a high depression score and two were treated for urinary tract infection.

Depression, well-being and sleep

Table 2 shows the scores of well being (WHO-5), mental depression (MDI) and sleep quality (PSQI). Secondary fatigued patients had a lower WHO-5 score than primary fatigued patients, but without any relation to the FSS score. No participant fulfilled diagnostic criteria for depression including core symptoms. One primary fatigued patient had a MDI score of 20 and six secondary fatigued patients either had a MDI score ≥20 and/or a WHO-5 score ≤9. The correlation between FSS and MDI in the combined group of 39 primary and secondary fatigued patients was $r = 0.40$; $P = 0.01$. The PSQI score was higher amongst secondary fatigued patients as compared to primary fatigued patients. However, no correlation could be established between scores of sleep quality (PSQI) and subjective fatigue (FSS).

Processing speed and fatigue

Digit Symbol Coding I was significantly reduced in all MS groups, being 9.4 (2.4) [mean (SD)] in primary fatigue, 8.3 (2.8) in secondary fatigue and 10.3 (2.7) in non-fatigue versus 12.3 (3.0) in healthy controls (Table 3). However, there was no difference in processing speed between primary fatigued and secondary fatigued MS patients. In the combined group of primary and secondary fatigued MS patients processing speed was slower than in non-fatigued MS patients (8.8 (2.9) for fatigued 12.3 (3.0) for non-fatigued, $P < 0.05$). Also, the Digit Symbol Coding I score was inversely related to subjective fatigue (FSS) in the combined group of fatigued MS patients ($r = -0.35$; $P < 0.05$) (Fig. 2), whereas no such relationship could be established in non-fatigued MS patients nor in healthy controls.

Also, Relative Digit Symbol Coding was inversely related to subjective fatigue (FSS) in the combined group of fatigued MS patients ($r = -0.34$; $P < 0.05$).

EDSS and Digit Symbol Coding I were related amongst all patients ($r = -0.37$; $P < 0.01$), but there was no correlation between corrEDSS and Digit Symbol Coding I ($r = -0.21$; $P = 0.11$).

Table 2 Scores of sleep quality (PSQI), well being (WHO-5) and depression (MDI)

	PF	SF	NF	HC
PSQI	2 (1–5) SF***	6 (2–14) NF**; HC**	3 (1–9)	4 (1–8)
WHO-5	18 (10–24) SF*; NF*; HC**	14.5 (5–21) NF***; HC***	20 (12–25)	19 (14–24)
MDI	8 (0–20) NF**; HC**	11.5 (1–36) NF**; HC**	5 (0–12)	3 (1–17)

Values are median (range).
*$P < 0.05$ vs. SF and NF; **$P < 0.01$; ***$P \le 0.001$ vs. SF, NF and/or HC.
PF, primary fatigued; SF, secondary fatigued; NF, non-fatigued; HC, healthy control; PSQI, Pittsburgh Sleep Quality Index; WHO-5, WHO Well-being Index; MDI, Major Depression Inventory.

Table 3 Neuropsychological scaled scores and motor functional test scores

	PF	SF	NF	HC
Vocabulary	10.2 (2.8)	10.4 (2.7)	10.6 (2.4)	10.8 (2.9)
Matrix Reasoning	12.5 (3.6)	13.2 (2.6)	13.1 (2.4)	13.6 (1.8)
Logical Memory I	12.2 (2.4)	11.4 (2.7)	11.9 (3.2)	12.5 (2.4)
Logical Memory II	12.1 (2.3)	10.9 (2.1)	12.4 (2.9)	12.6 (2.5)
Digit Symbol Coding I	9.4 (2.9) HC**	8.3 (2.8) HC***; NF*	10.3 (2.7) HC*	12.3 (3.0)
Digit Symbol Coding II-I	3.0 (1.9)	2.4 (1.0)	2.6 (1.1)	2.7 (1.2)
Digit Symbol Copy	33.6 (20.5)	28.4 (19.7)	31.4 (17.5)	43.1 (11.5)
Nine Hole Peg Test	0.054 (0.01)	0.054 (0.01)	0.055 (0.01)	0.059 (0.01)

Values are mean (SD).
$*P < 0.05$ vs. NF or HC; $**P < 0.01$ vs. HC; $***P < 0.001$ vs. HC.
PF, primary fatigued; SF, secondary fatigued; NF, non-fatigued; HC, healthy control.

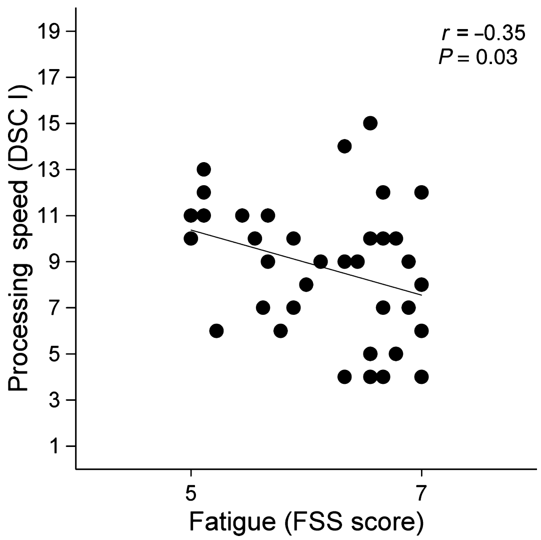

Figure 2 Relationship between processing speed (DSC I) and fatigue (FSS) in 39 fatigued patients with multiple sclerosis.

Motor performance as assessed by Digit Symbol Copy and 9-HPT was similar in all four groups of MS patients and healthy controls.

Fatigability of processing speed performance

Digit Symbol Coding scores improved with repetition. Mean Digit Symbol Coding II-I scores were 3.0 (1.9) in primary fatigue, 2.4 (1.0) in secondary fatigue, 2.6 (1.1) in non-fatigue and 2.7 (1.2) in healthy controls. There was no difference between primary and secondary fatigued MS patients nor between fatigued and non-fatigued MS patients.

Other neuropsychological performances

In Table 3 the scaled scores are given for Vocabulary, Matrix Reasoning and Logical Memory I and II. Vocabulary, Matrix Reasoning, Logical Memory I and Logical Memory II were similar in all groups. After correction for mutual dependency of the neuropsychological parameters during multiple linear regressions it was not possible to demonstrate any defect within these domains. Logical Memory II was related to FSS in the group of all study subjects ($r = -0.24$; $P < 0.05$), but this relationship did not apply to MS patients.

Discussion

In this study, the relation between fatigue and cognition was examined in a group of mildly to moderately disabled patients with relapsing remitting MS. It was hypothesized that patients with primary fatigue have reduced processing speed compared to secondary fatigued and to non-fatigued patients with MS. The measure of processing speed was Wechsler's Digit Symbol Coding [4]. Primary, secondary and non-fatigued MS patients had mean performances that were 2–4 scaled scores lower than healthy controls, indicating that processing speed was impaired in MS in general. There was no difference in processing speed between primary and secondary fatigued patients. However, in the combined group of primary and secondary fatigued patients processing speed was slower than in non-fatigued MS patients. Furthermore, there was a significant inverse relationship between fatigue in MS and processing speed even after weighing the Digit Symbol Coding score to account for the influence of other cognitive parameters (Relative DSC I). Consequently, we conclude that fatigue is related to processing speed impairment in MS.

It has been suggested that the written Symbol Digit Modalities Test should be used with caution in MS because of its sensitivity to upper extremity weakness and in-coordination [18]. The performance at the 9-Hole Peg Test was similar amongst MS patients and healthy controls. Therefore, it is unlikely that the present findings of impaired Digit Symbol Coding are due to physical disabilities. With regard to information processing, processing speed is the primarily impaired neuropsychological function in MS [17]. With the present observation of preservation of Vocabulary, Matrix Reasoning and Logical Memory I and II in all groups of MS patients, the poor Digit Symbol Coding performance observed most likely reflects a disease related reduction of processing speed. Alternatively, a disease effect on memory function can influence the Digit Symbol Coding score [19].

Conventional magnetic resonance (MR) imaging studies suggest that fatigue is related to cerebral grey and white matter atrophy, MR spectroscopy suggests a relation to diffuse axonal dysfunction, and functional MR imaging suggests disruption of cortico-subcortical circuits as a neuropathological substrate of fatigue in MS [20].

Primary fatigued patients had higher well-being scores (WHO-5) than secondary fatigued patients without any relationship between well-being and fatigue (FSS). At the time of investigation 7 out of 39 (18%) fatigued patients had a substantial high depression score or a low well being score. However, none of the fatigued patients could be diagnosed as depressed (MDI), the depression score being similar in secondary fatigue and primary fatigue.

Few studies have been designed to distinguish between fatigue and non-fatigue in MS [21,22]. Furthermore, previous studies unable to establish a relationship between subjective fatigue and objective cognitive test fatigability examined the complaints of fatigue at the time of the neuropsychological examination, so-called 'state' fatigue, as opposed to 'trait' fatigue, refering to the overall experience of fatigue during daily life [22,23]. In a pilot study Schwid *et al.* compared cognitive performance at the start and end of a test requiring sustained attention [5]. They found that cognitive test fatigability was related to the FSS score, reflecting recent subjective fatigue without any relationship to fatigue rated every hour for 48 hours. In this study, tests were administered with a 'natural break' in-between. We speculate whether cognitive fatigability (DSC II-I) would have been manifest if a more demanding test battery had been applied. During a sustained neuropsychological task the compensatory neuronal capacity might be exceeded and, thereby, the cognitive fatigability will appear.

Marrie *et al.* [24] demonstrated a non-linear relationship between subjective and objective cognitive complaints in patients with MS. They suggested that patients with severe and/or long-standing cognitive impairment lack insight into their deficits. Furthermore it is difficult to distinguish between fatigue and severe physical impairments [25] leading us to recruit mildly to moderately disabled patients, only. A complete neuropsychological examination had enabled the construction of individual indices corrected for gender, ethnicity and age. We decided, however, to apply a short test battery that was extensive enough to reflect pre-morbid performance and the influence of MS on cognitive functioning [15]. Additional tests of interest could be information processing tasks that relies less on visual function e.g. verbal fluency and examination of visuospatial function [26]. Also, a stratification of educational level without the application of an upper limit as used in this study should be considered. Eventually, the high Digit Symbol Coding score amongst healthy controls could imply that the group is not fully representative for the healthy population.

Fatigue in MS may worsen due to variables such as physical disability, sleep quality and depression. However, this study supports the concept that fatigue in mildly to moderately disabled MS patients is associated with discrete cognitive impairment in domains sensitive to the pathology of MS [2]. Longitudinal studies are needed to clarify whether progression of processing speed impairment is related to worsening of fatigue in multiple sclerosis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Fatigue scores in MS patients and healthy controls.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

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