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Modulation of alertness by sustained cognitive demand in MS as surrogate measure of fatigue and fatigability

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ABSTRACT

Objective: This study used reaction time (RT) as an objective marker of cognitive fatigue and fatigability in patients with multiple sclerosis (MS).
Method: RT was measured in fifteen healthy controls and in thirty MS patients with cognitive fatigue identified with the Fatigue Scale for Motor and Cognitive Function (FSMC). Secondary fatigue was excluded through the Epworth Sleepiness Scale and the Beck Depression Inventory. RT was measured at rest (t1), following a 2.5 hour test session inducing high cognitive load (t2), and a one hour recovery period (t3).
Results: At rest mean RT was longer in patients than in controls (391 ms vs 205 ms). After exerting cognitive load (t2), RT in patients increased dramatically but remained unchanged in controls. After the recovery period (t3), RT returned to baseline levels in most patients. Patients further showed a significant correlation between RT and FMSC scores at t1, t2 and t3.
Conclusion: RT performance is a suitable surrogate marker for assessing fatigue. RT is sensitive to cognitive load and the recovery from cognitive demand. It hence represents an objective index for fatigability which can inform the management and treatment of MS.

1. Introduction

Fatigue is a very common symptom in multiple sclerosis (MS) that is experienced by up to 90% of patients [1,2]. It is often the most disabling symptom with regard to quality of life, social participation, and the ability to work [3]. In many cases the impact of fatigue in the work environment is so severe that patients have to take early retirement [4]. Fatigue causes therefore not only distress for the affected individual but also represents a substantive economic burden. It is a long lasting discussion whether or not fatigue is more prevalent and more sustained in MS or whether fatigue constitutes a relatively generic symptom of brain disease or brain damage. Supporting the latter argument recent studies have identified fatigue as a major problem in stroke, traumatic brain injury and Parkinson disease [5]. A better understanding of fatigue and its impact on functional ability and wellbeing is therefore paramount. However, in contrast to its clinical importance, fatigue is a poorly defined construct and hence difficult to measure. This is because various clinical characteristics of the condition act as potential confounds, such as cognitive deficits, depression, physical deconditioning or spasticity [6]. In addition, secondary causes such as sleep disturbances or side effects of medication may aggravate the level of fatigue experienced by the patient. This is a complicated matter, since depression, sleep disturbance, cognitive deficit and fatigue might interact and augment each other. Driven in part by the poor definition and challenges involved in measuring fatigue, effective treatment and management of this symptom is limited [7].

Kluger et al. recently proposed a new taxonomy and a novel assessment for fatigue [8]. Specifically, he suggested distinguishing between *fatigue*, defined as the subjective perception, and *fatigability*, defined as objectively measurable changes in performance. In addition, Genova et al. distinguished between a state component and a trait component of fatigue [9]. ""*State*" fatigue refers to a transient condition, which can change with time, and can fluctuate based on both internal and external factors. …."*Trait*" fatigue refers to a more stable state in an individual, and is not likely to change significantly over time [9]." In the present study we combined fatigue self-rating tools with reaction times as a psychophysical measure of alertness to determine an objective measure of fatigue, and to investigate how fatigue is modulated by sustained cognitive demand. Assuming that fatigue is indexed by slower reaction times, we hypothesized that increased RT following cognitive load

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Table 1
Clinical data.

	Patients with fatigue		Patients without fatigue		Healthy controls	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
N	30		5		15	
Females	22 (73%)		2 (40)		11 (73%)	
Age	44.7 ± 7.1	31–55	45.3 ± 6.1	42–53	43.6 ± 11.0	28–59
EDSS	3.8 ± 1.2	2–6	3.7 ± 0.6	3–4.5		
Years since onset	12.1 ± 8.3	1–31	15 ± 5.2	8–21		
Years since diagnosis	9.9 ± 6.7	1–23	13.6 ± 6.8	4–21		
BDI-II	10.3 ± 6.1	1–22	6.6 ± 5.5	2–16		
Epworth Sleepiness Scale	8.2 ± 2.1	3–10	5.4 ± 3.0	1–9		
FSMC motor	39 ± 6.6	20–50	30.4 ± 7.0	21–40		
FSMC cognitive	36.5 ± 8.2	22–50	18.2 ± 6.3	9–25		
FSMC total	75.6 ± 13.5	43–100	49.4 ± 10.6	36–61		

would provide an objective measure of fatigability. The cognitive load intervention comprised a 2.5 h standardized sequence of cognitive tests which is performed as a routine procedure in the clinic to assess cognitive strengths and deficits [10]. This test battery allowed us to capture the impact of cognitive load on fatigability [8]. In addition, we studied fatigue recovery by retesting participants 1 h after completing the cognitive test battery. Through this paradigm we were able to determine the immediate and sustained impact of cognitive demanding situations on fatigue.

2. Method

2.1. Participants

Patients were recruited from a neurological rehabilitation unit (Kliniken Schmieder -Clinic for Neurology and Neurological Rehabilitation, Konstanz, Germany). Inclusion criteria comprised diagnosis of MS according to McDonald's criteria [11] and cognitive fatigue defined as ≥22 on the cognitive domain of the Fatigue Scale for Motor and Cognitive Functions (FSMC, [12]). Exclusion criteria were other neurological or psychiatric diseases, a value of >10 on the Epworth Sleepiness Scale as well as a score of >20 in the Beck Depression Inventory II [13]. A total of 30 patients and 15 healthy controls participated in the study. All participants signed informed consent prior to the experiment. The protocol was approved by the local ethics committee of the University of Konstanz and adhered to the Declaration of Helsinki.

The patient group comprised 22 females (73.3%) and 8 males aged 44.7 ± 7.1 years (range 31–55). Twenty three patients (76%) had a relapsing remitting course of MS, one (3%) a primary progressive, and six (20%) a secondary progressive form. The average score on the Expanded Disability Status Scale (EDSS) was 3.8 ± 1.2 (range 2.0 to 6.0). The EDSS scale spans from 0 (no symptoms) to 10 (death through MS). Three on the EDSS indicates the border between light and moderate symptoms. Time interval since initial symptom onset was 12.1 ± 8.3 years (range 1–31), time since diagnosis 9.0 ± 6.7 years (range 1–23). The mean value on the Beck Depression Inventory (BDI II) was 10.3 ± 6.1 (range 1–20). Cut-off values of the BDI II, ranging from 0 to 63 are 9, 14, 20 and 29 for minimal, light, moderate and severe depression, respectively. The mean Epworth Sleepiness Scale (ESS) was 8.2 ± 2.1 and ranged from three to ten. Values >10 indicate pathological sleepiness.

Main demographic and clinical data as well as distribution of fatigue severity are compiled in Table 1. The control group consisted of 15 healthy age- and sex-matched volunteers aged 43.6 ± 11 years (range 28–59, eleven female). We did not manage to collect data from MS patients with a comparable EDSS without fatigue, since most patients with a demand for rehabilitation and an EDSS of about 3.8 have fatigue. The data including those five MS patients with no fatigue were included and are displayed in Table 2, but due to the low number no statistics were performed.

Table 2
Fatigue according to the FSMC.

	Frequency (n)	Frequency (%)
Mild cognitive fatigue mild	6	20
Moderate cognitive fatigue	3	10
Severely cognitive fatigue	21	70
No motor fatigue	1	3.3
Mild motor fatigue	0	0
Moderate motor fatigue	3	10
Severe motor fatigue	26	86.3
Mild total fatigue	2	6.7
Moderate total fatigue	5	16.7
Severe total fatigue	23	76.7

2.2. Subjective rating of fatigue and clinical ratings

The Fatigue Scale for Motor and Cognitive Functions (FSMC) was used to subjectively assess fatigue [12]. A score ≥22 on the motor subscale indicates mild motor fatigue, ≥27 moderate motor fatigue and ≥32 severe motor fatigue. The cut-off values for the cognitive subscale are as follows: a score ≥22 reflects mild cognitive fatigue, ≥28 moderate cognitive fatigue and ≥34 severe cognitive fatigue [14]. The composite FSMC score differentiates three levels, mild (score ≥ 43), moderate (score ≥ 53) and severe (score ≥ 63) fatigue. Depression was assessed through the German version of the Beck Depression Inventory II (BDI) [13]. Daytime sleepiness was measured by the German version Epworth Sleepiness Scale (ESS) [15].

2.3. Assessment of performance

The alertness subtest of the computerized test battery for attention performance (TAP-M/version mobility) was used to capture changes in cognitive performance [16]. The test comprised a simple reaction time task lasting approximately 3 min. Two blocks of 20 trials were presented. In each trial a white X appeared on the screen for a maximum duration of 2000 ms and participants were asked to execute a speeded response with their right index finger as soon as the letter X appeared. In one block of trials, an acoustic warning signal (a beep) was presented prior to the X. The interval between this warning signal and X varied randomly between 100 and 1000 ms from trial to trial. In the other block of trials, the warning was signal omitted. Performance was indexed by median reaction time (RT). Blocks with and without warning signal were ordered in an ABBA design. Because the RT results for trials with and without the warning signal were virtually identical, we collapsed the results across the two blocks in all analyses reported in this manuscript.[1]

[1] A three-way analysis of variance with the factors Group (patients vs. controls) × test time (t1, t2 vs. t3) × warning signal (with vs. without) on RT yielded no significant effect of factor warning signal or any significant interaction with this factor, all *Fs* < 1.55.