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ORIGINAL COMMUNICATION

Dynamics of saccade parameters in multiple sclerosis patients with fatigue

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Abstract Fatigue is one of the most frequent and disabling symptoms in multiple sclerosis (MS). Its pathophysiology remains poorly understood and objective measures to quantify fatigue are unavailable to date. To investigate whether analysis of ocular motor movements can provide diagnostic information in MS patients with fatigue, 37 MS patients (21 female, age 44 ± 9 years) and 20 age- and gender-matched healthy controls were prospectively recruited. Fatigue was assessed with the fatigue severity scale (FSS). Twenty-five MS patients were fatigued (defined as FSS ≥4) and 12 MS patients were not. Subjects performed a saccadic fatigue task that required execution of uniform saccades over a period of 10 min. Saccadic amplitude, latency and peak velocities during the task were analysed and selected parameters were tested in a receiver operating characteristic (ROC) analysis. Fatigued patients showed a significantly larger decrease of saccadic peak velocity and amplitude when compared to patients without fatigue and healthy controls. Furthermore, fatigued patients showed significantly longer latencies compared to non-fatigued patients and healthy controls. Peak velocity change over time and latencies correlated with FSS scores. The best parameter to discriminate between fatigued and non-fatigued patients was peak velocity change over time (ROC; area under the curve = 0.857). Assessment of peak velocity, amplitude and latency in a saccade fatigue task is a promising approach for quantifying fatigue in MS patients.

Keywords Multiple sclerosis · Fatigue · Neuro-ophthalmology · Assessment of cognitive disorders · Diagnostic test assessment

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Introduction

Fatigue is one of the most common clinical symptoms of multiple sclerosis (MS) reported by more than 90 % of patients with substantial negative impact on quality of life and on employment status [1–7]. Up to two-thirds of patients consider fatigue to be their most disabling symptom [8]. It is characterized by an overwhelming sense of tiredness, lack of energy or feeling of exhaustion [9]. Fatigue overlaps with depression and cognitive dysfunction [10, 11] but may occur independently. Despite its enormous socioeconomic relevance and the burden for the individual patient, the pathomechanisms involved in fatigue are poorly understood and quantification of this subjective symptom is difficult. Thus, estimation of symptom severity relies on patients' complaints and self-assessed questionnaires [8, 10, 12–15]. Recently, quantification of horizontal saccades in MS patients exhibiting clinical signs of internuclear ophthalmoparesis (INO) was investigated as a model for studying fatigue [16]. In a fatigue test where participants were asked to execute horizontal saccades over a period of 10 min, deterioration of INO was observed in some patients and improvement was seen in others. However, patients were not tested for fatigue, so a possible association between subjective fatigue displayed on self-rated questionnaires and eye movement parameters was not investigated. The goal of our study was to investigate whether performance of MS patients without INO differs from healthy controls in a saccadic fatigue task, and whether fatigue scores affect saccade parameters.

Methods

Study participants

Thirty-seven MS patients fulfilling the 2005 panel criteria [17] were prospectively recruited from the outpatient clinic of the Clinical and Experimental Multiple Sclerosis Research Center at the Charité-University Medicine Berlin (Table 1). All patients met the following criteria: aged between 18 and 60 years; expanded disability status scale (EDSS) between 0 and 6.0 [18]; stable immunomodulatory therapy for ≥3 months; no acute relapse; and no systemic steroid treatment within 30 days prior to enrolment. All patients underwent a complete neurological examination by a board certified neurologist and were evaluated with the multiple sclerosis functional composite (MSFC) [19]. Patients with ocular motor deficits (e.g., saccadic dysmetria, nystagmus, and clinically apparent INO, such as slowing of the adducting eye or dissociated nystagmus) were not included. Fatigue was assessed by the fatigue severity scale (FSS) [8]. In accordance with previous reports [8, 12, 20], patients with scores ≥4 were classified as fatigued. Depression was measured by the 21-item version of the revised Beck depression inventory (BDI-IA) [21]. Healthy control individuals without neurological or psychiatric diseases were recruited via advertisement in the Charité intranet. Subjects with CNS-effective pharmacotherapy that might potentially influence performance on the saccadic fatigue task (e.g., benzodiazepines, tricyclic antidepressants, anticonvulsants, etc.) were not included. The study was approved by the ethics committee of the Charité-University Medicine Berlin and conducted in accordance with the Declaration of Helsinki. All patients and controls gave written informed consent.

Eye movement recording and analysis

Eye movements were recorded by using infrared oculography (JAZZ-novo, Ober Consulting, Poznan, Poland). The JAZZ-novo system is a portable and light-weight, head-mounted system that records the average position of both eyes. Data were sampled at a frequency of 1,000 Hz. Subjects sat 50 cm away from a 22″ CRT-monitor with a 110-Hz-refresh rate. Stimuli were white dots (luminance, 12 Cd/m^2) seen against a homogenous, black background (luminance, 1 Cd/m^2). Experiments were run in an otherwise darkened room. Subjects performed an ocular motor "fatigue task" [16] that required stereotyped execution of horizontal 20°-saccades over a period of 10 min. Saccades were made in response to a circular visual stimulus (0.5°), alternating at 1.0 Hz between positions 10° to the left and 10° to the right of the midline.

Saccades were analysed offline, using Jazz Manager-Software (Ober Consulting, Poznan, Poland). Saccade latency was defined as the time from stimulus jump to corresponding saccade onset (as defined by a velocity criterion; threshold of 35°/s). As the stimuli appeared in a regular and temporally predictive manner, saccades were increasingly generated in anticipation of target onset. As those predictive saccades were executed before target appearance, their latencies were negative. [22]. Only saccades targeting a circular area around target location (radius, 4°; corresponding amplitude range for valid saccades, 16–24°) were included in the analysis of saccade amplitude, peak velocity and latency (exclusion rates, MS fatigue 16.7 %, MS non-fatigue 15.2 %, healthy controls 12.7 %). Mean values of these measures were calculated for saccades performed in six consecutive bins of 100 s. To evaluate the temporal dynamics of saccade parameters, differences in mean values between task bins were calculated.

Statistical analysis

Group differences in gender were analysed by using Pearson's Chi-square test. All other cohort statistics were

Table 1 Demographic and clinical characteristics

	MS non-fatigue (12)	MS fatigue (25)	Healthy controls (20)
Gender (%)			
Male	5 (41.7)	11 (44)	8 (40)
Female	7 (58.3)	14 (56)	12 (60)
Age			
Mean ± SEM (range)	45 ± 2 (31–57)	43 ± 2 (26–58)	41 ± 2 (25–57)
Visus			
Mean ± SEM (range)	1.03 ± 0.11 (0.36–1.6)	1.0 ± 0.06 (0.32–1.6)	0.92 ± 0.07 (0.45–1.6)
FSS			
Mean ± SEM (range)	2.58 ± 0.2 (1.11–3.89)	5.53 ± 0.1 (4.11–7)	1.69 ± 0.11 (1–2.44)
BDI			
Mean ± SEM (range)	7 ± 1 (1–15)	10 ± 1 (1–25)	2 ± 1 (0–9)
Time since diagnosis (months)			
Mean ± SEM (range)	86 ± 13 (33–160)	113 ± 17 (6–345)	
EDSS			
Median (range)	2.0 (0–6)	2.9 (0–6)	
MSFC			
Mean ± SEM (range)	0.06 ± 0.2 (−1.48–0.93)	−0.03 ± 0.14 (−1.6–1.1)	

FSS fatigue severity scale, *BDI* Beck depression inventory, *EDSS* expanded disability status scale, *MSFC* multiple sclerosis functional composite, *SEM* standard error of the mean

calculated using Mann–Whitney *U* tests. Baseline and overall group differences in the fatigue task were analysed using non-parametric Kruskal–Wallis tests. Time-dependent group differences in the fatigue task were analysed using Brunner's non-parametric analysis for longitudinal data [23]. Results from the Brunner analysis are given as group differences and group × time interaction effects from the ANOVA type model for small sample sizes. The correlation between FSS scores and results of the fatigue task were analysed using Spearman's Rho analyses. Finally, selected parameters from the fatigue task were tested for their discriminatory power between patients with low and high FSS scores using ROC analyses. Brunner analysis was performed with R Project 2.14.1 64-bit [24] using the macro F1_LD_F1.r. All other statistical analyses were performed with IBM SPSS Statistics 20 (IBM, Armonk, NY, USA). Throughout all figures, means and standard errors of the mean (SEM) were used. A p value <0.05 indicated statistical significance. All tests should be understood as constituting exploratory data analysis, in such a way that no previous power calculation or adjustments for multiple testing were made.

Results

Out of 37 total patients, 25 were fatigued and 12 were not, as defined by FSS score. Healthy controls, MS patients with fatigue and MS patients without fatigue did not differ with respect to gender, age and visual acuity (all $p > 0.22$; Table 1). Furthermore, fatigued and non-fatigued patients did not differ in EDSS ($p = 0.09$), MSFC ($p = 0.73$), PASAT ($p = 0.47$), BDI ($p = 0.19$) and time since diagnosis ($p = 0.53$) (Table 1).

Differences in saccade latency, amplitude and peak velocity

Figure 1 shows representative saccades made at the beginning and the end of the fatigue task for a healthy control and a fatigued MS patient. In overall mean performance, fatigued patients showed a larger latency compared to non-fatigued patients and healthy controls (Kruskal–Wallis test, $p = 0.004$), whereas amplitude ($p = 0.89$) and peak velocity ($p = 0.46$) did not differ between groups (Table 2). Brunner analysis confirmed the overall difference in latency ($p = 0.004$) across all time bins. While healthy controls and non-fatigued patients did not differ in the generation of predictive saccades with increasingly negative latencies, fatigued MS patients showed markedly longer latencies during the entire task. Furthermore, fatigue patients showed a more pronounced decrease of saccadic peak velocity ($p = 0.002$) and amplitude ($p = 0.042$) when compared to patients without fatigue and healthy controls over time (Fig. 2; Table 2).

Correlation of latency, amplitude and peak velocity with FSS in MS patients

Inspection of the data shows a similar decrease of saccade peak velocity between bin 1 and 2 in all groups. We therefore calculated the correlation of FSS scores with

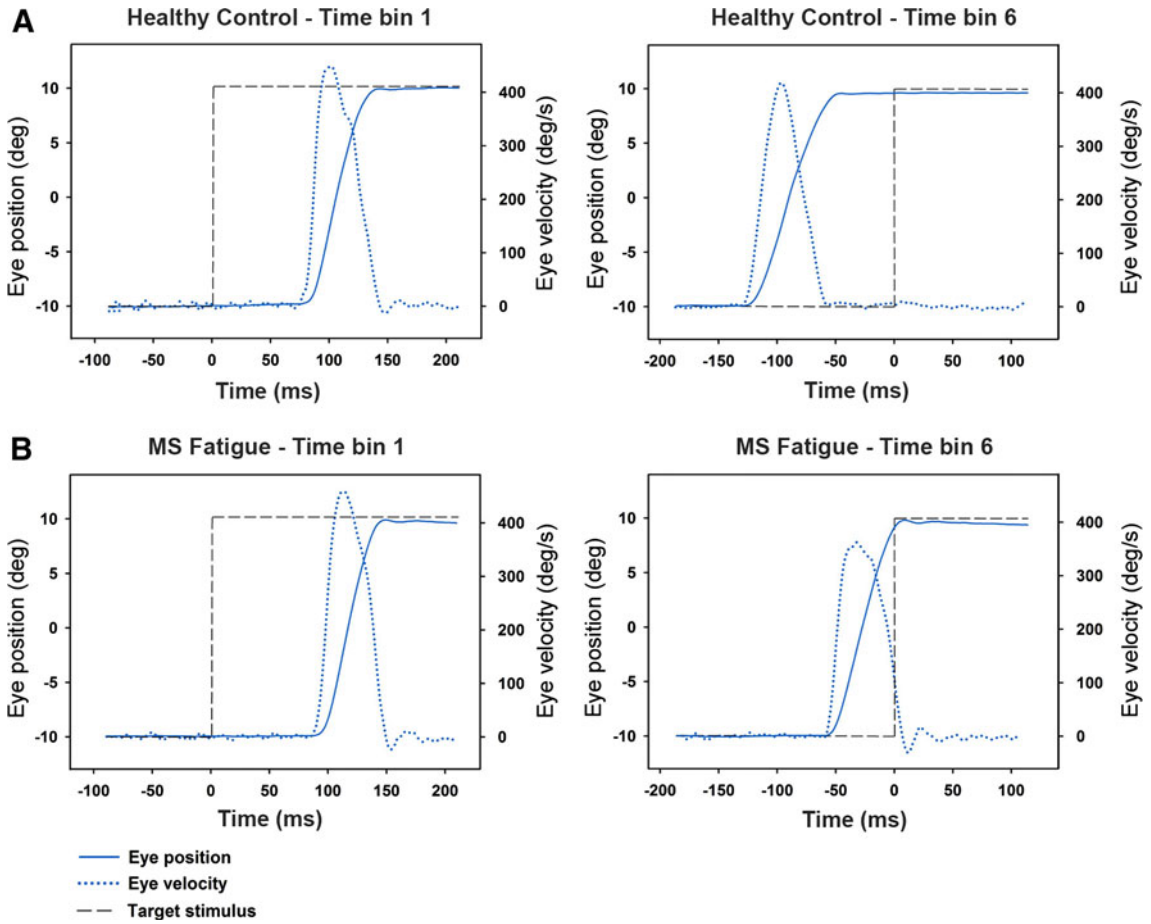

Fig. 1 Representative recordings of horizontal saccades. Data of a healthy control (**a**) and an MS patient with fatigue (**b**) are shown for saccades made at the beginning (time bin 1, *left*) and the end (time bin 6, *right*) of the saccade fatigue task. The control subject **(a)** shows no relevant change of saccade amplitude or peak velocity between time bin 1 and time bin 6. For saccade latencies, a marked reduction is observed with negative latencies at time bin 6 (predictive saccades). The fatigued MS patient also shows little difference in saccade amplitude between time bins 1 and 6, while peak velocity is substantially reduced. Saccade latencies are reduced to a much lesser extent in comparison to the healthy control subject

change in peak velocity between bin 6 and 2. Change in peak velocity correlated with FSS scores in MS patients (Spearman's Rho analysis, Rho $= -0.468$, $p = 0.004$). Correlation of saccade latency with FSS scores was strongest in bin 4 (Spearman's Rho $= 0.385$, $p = 0.019$). A correlation between change in amplitude and FSS failed to reach significance (bin 6 minus bin 2, Rho $= -0.300$, $p = 0.071$). Importantly, MSFC did not show a significant correlation with any of the observed parameters (latency, bin 4, Rho $= 0.131$, $p = 0.438$; change in peak velocity, bin 6 minus bin 2, Rho $= 0.177$, $p = 0.294$; change in amplitude, bin 6 minus bin 2, Rho $= -0.17$, $p = 0.314$). For a summary of correlation analyses see Table 3.

ROC analysis in MS patients

Parameters that showed the highest group differences in the previous analyses were selected for further ROC curve analysis, i.e., amplitude change between time bin 6 and 2, peak velocity change between time bin 6 and 2, and latency at bin 4. From these parameters, peak velocity change discriminated best between MS patients with and without fatigue (AUC $= 0.857$, SE $= 0.062$, $p = 0.001$), followed by latency (AUC $= 0.785$, SE $= 0.075$, $p = 0.006$) and amplitude change (AUC $= 0.727$, SE $= 0.097$, $p = 0.027$). This means, in our cohort, MS patients would be classified as fatigued or non-fatigued at a peak velocity change cutoff of -37.3°/sec with a sensitivity of 60 % at a specificity of 92 % (supplementary Fig. 1).

Discussion

Our study is the first to correlate ocular motor fatigue with subjective fatigue in MS patients and healthy controls. The most relevant findings are a significantly larger decrease of

Table 2 Saccade parameters (mean ± SEM)

	Bin 1	Bin 2	Bin 3	Bin 4	Bin 5	Bin 6	All bins
Latency (ms)							
MS fatigue	17.01 ± 16.91	−7.50 ± 18.88	−8.71 ± 21.86	−25.06 ± 28.99	−29.92 ± 32.49	−54.52 ± 34.48	−18.12 ± 22.58
MS non-fatigue	−42.31 ± 20.77	−88.13 ± 33.5	−105.31 ± 36.09	−157.24 ± 30.94	−158.65 ± 38.79	−160.31 ± 40.46	−118.66 ± 29.91
Healthy controls	−48.93 ± 22.15	−78.48 ± 24.1	−120.48 ± 20.02	−136.09 ± 23.22	−163.67 ± 24.44	−161.68 ± 25.63	−118.22 ± 20.22
Peak velocity (deg/s)							
MS fatigue	427.58 ± 15.21	407.45 ± 15.5	394.44 ± 15.13	382.02 ± 16.13	372.06 ± 17.13	360.58 ± 18.48	390.69 ± 15.87
MS non-fatigue	411.36 ± 19.58	387.59 ± 19.74	388.13 ± 21.51	380.34 ± 20.37	381.39 ± 20.41	377.38 ± 21.91	387.7 ± 20.15
Healthy controls	443.09 ± 12.48	418.54 ± 13.64	408.79 ± 13.95	412.99 ± 13.74	408.35 ± 13.34	404.79 ± 14.47	416.09 ± 13.37
Amplitude (deg)							
MS fatigue	20.31 ± 0.31	20.17 ± 0.18	19.95 ± 0.2	19.77 ± 0.2	19.57 ± 0.22	19.22 ± 0.3	19.83 ± 0.19
MS non-fatigue	19.9 ± 0.3	19.72 ± 0.29	19.64 ± 0.32	19.53 ± 0.26	19.55 ± 0.34	19.56 ± 0.34	19.65 ± 0.29
Healthy controls	20.28 ± 0.17	19.92 ± 0.31	19.94 ± 0.31	19.92 ± 0.31	19.85 ± 0.31	19.79 ± 0.3	19.96 ± 0.3

saccade peak velocity and amplitude in MS patients with fatigue compared to non-fatigued MS patients and healthy controls over the course of a 10-min saccade fatigue task. Moreover, throughout the task, saccade latencies were longer in MS patients with fatigue than in non-fatigued patients and healthy controls. Latency and peak velocity changes over time correlated with FSS scores, with peak velocity changes over time discriminating best between fatigued and non-fatigued patients. These differences between MS patients with and without fatigue cannot be explained by a higher degree of neurological disability, cognitive impairment or depression in the fatigued group since EDSS, MSFC (taken as a whole, and PASAT in particular) and BDI did not differ between groups.

The study of saccades has a long tradition in MS research (e.g., [25, 26]). Recently, Matta et al. [16] applied a saccade fatigue test to investigate ocular disconjugacy in MS patients with INO. The authors found a change in conjugacy between minute 1 and minute 10 of the saccade test in the majority of patients. Interestingly, conjugacy increased (i.e., INO worsened) in patients with mild INO while it decreased in patients with more severe INO. The authors concluded that these seemingly paradoxical results may be explained by adaptive mechanisms of vergence in patients with more severe INO. While Matta et al. [16] focused on patients with INO and did not assess fatigue in their cohort, we investigated whether saccade parameters are differentially affected in MS patients with and without fatigue. We therefore prospectively recruited MS patients without apparent ocular motor dysfunction and analysed saccade parameters depending on the presence of fatigue. While we found significant differences between fatigued MS patients and control groups for all three saccade parameters, their dynamics were different. Although we observed a similar decrease of saccade latency over time in all three groups, latency was significantly longer in fatigued MS patients during the first 100 s and remained significantly longer throughout the subsequent time bins. A different pattern emerged for saccade amplitude and peak velocity. Both parameters did not differ at the beginning of the task, but decreased more rapidly in fatigued MS patients over the course of the task. Hence, amplitude and peak velocity are parameters that appear to reflect a susceptibility to exertion, i.e., a response to the fatiguing nature of the tasks. Given that peak velocity is a function of amplitude, a decrease in peak velocity during the fatigue task might be due to progressive reduction of amplitude. However, inspection of the data (Table 2; Fig. 2) suggests that peak velocity did drop more than would be expected by the reduction of saccade amplitude. Moreover, ROC analysis identified change in peak velocity during the fatigue task as the saccade parameter that discriminated best between fatigued and non-fatigued patients. Regarding

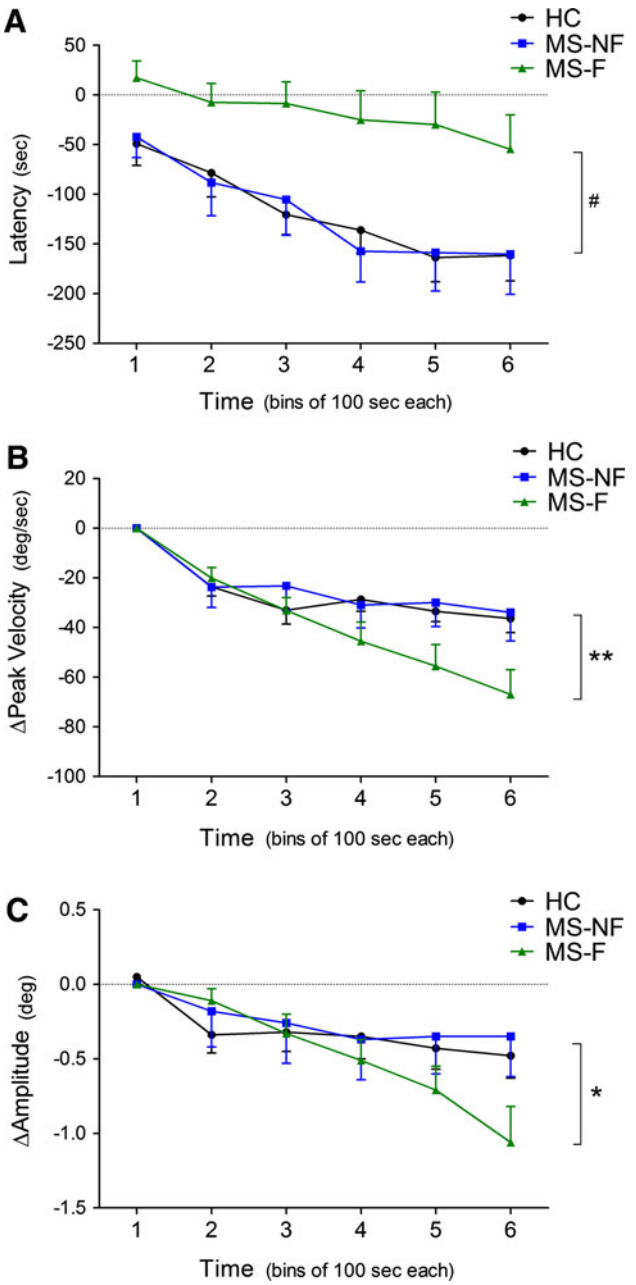

Fig. 2 Saccade parameters across the 10-min saccade fatigue task. Fatigued MS patients (MS-F) showed a longer saccade latency across all bins ($^{\#}$ $p = 0.004$, Kruskal–Wallis test, mean of all bins) and a larger decrease of amplitude (* $p = 0.042$, Brunner's non-parametric analysis for longitudinal data [23]) and saccade peak velocity (** $p = 0.002$, Brunner analysis) than non-fatigued MS patients (MS-NF) and healthy controls (HC)

the underlying pathophysiological mechanisms of these dynamic changes, neurophysiological evidence indicates that ocular motor fatigue is of premotor origin, rather than of muscular or brainstem origin [27, 28]. These premotor processes likely reflect altered cortical or cerebellar influences that might result in a decreasing ability to sustain attention [27]. This hypothesis is supported by recent studies that have found an association between fatigue and deficits of attention [12, 29]. On the contrary, baseline saccade latency seems to reflect an a priori difference between fatigued MS patients and controls, and suggests a failure in the predictive generation of saccades. Interestingly, failure in predictive motor timing has also been associated with cerebellar pathology [30, 31]. Thus, the results in the saccadic fatigue task appear to be specifically related to the symptom of fatigue. Additional (functional) MRI studies that were not part of our investigations may contribute to further clarification.

The observation of differences in saccade parameters between fatigued and non-fatigued MS patients adds to previous attempts to develop objective measures of fatigue. A recent study showed that FSS scores are an independent predictor of the alertness subtest of the test for attentional performance (TAP) [12, 32]. Here, we extend these results by demonstrating that analysis of eye movements in a short fatigue test may serve as a quantitative tool to objectify self-reported fatigue. In fact, saccade measures correlated with FSS scores and discriminated well between fatigued and non-fatigued patients. The need for an objective measure of fatigue is already evident from its high prevalence in MS patients and the resulting negative impact on their quality of life, including a substantial socioeconomic burden. Moreover, scores from current fatigue questionnaires, i.e., the FSS and Modified Fatigue Impact Scale (MFIS), are only moderately correlated [7, 11]. This suggests that these measures may not fully capture the different dimensions of fatigue, may be based on different fatigue constructs or may be prone to bias of self-reporting [11]. New objective measures of fatigue are also needed as endpoints in clinical trials [11, 33]. This need is highlighted by the fact that clinical trials investigating the efficacy of treatment strategies in fatigue have yielded conflicting results (e.g., [34, 35]). Furthermore, the proposed ocular motor fatigue task might also be implemented to objectively assess fatigue in other diseases, e.g., chronic fatigue syndrome [36]. Advantages of the saccade fatigue task for use in clinical practice and studies are its brevity and simplicity with respect to task instructions, task setup, data acquisition and analysis. The use of a miniaturized, portable eye-movement recording device further allows for a rapid bedside performance of the task in clinical settings. However, the compact construction does not allow for a separate measurement of both eyes. Hence, although only patients without clinically apparent INO were enrolled, our system cannot detect developing INO during the fatigue task, and this might have contributed to the observed changes in saccade amplitude and peak velocity in MS patients with and without fatigue. Furthermore, mild ocular motor deficits might not have been detected in the neurological examination [37]. In future studies, application of

Table 3 Correlation analysis

	FSS score		MSFC	
	Rho	*p* value	Rho	*p* value
Peak velocity	*−0.468*	*0.004*	0.177	0.294
Amplitude	−0.3	0.071	−0.17	0.314
Latency	*0.385*	*0.019*	0.131	0.438

Correlation analysis (Spearman's Rho analysis) for saccade peak velocity (change between bin 6 and 2), saccade amplitude (change between bin 6 and 2), and saccade latency (bin 4) with FSS scores and MSFC

Saccade peak velocity and latency were significantly correlated with FSS scores in MS patients (values in italics)

Importantly, no significant correlation of the MSFC with any of the saccade parameters was observed

the saccade fatigue task should be extended to patients with ocular motor deficits to evaluate how these deficits influence performance in the task. Monocular eye movement recordings could be employed to further explore the pathophysiological mechanisms of ocular motor fatigue.

In summary, the proposed oculomotor fatigue task represents a first and promising step towards an objective testing of fatigue severity, both in clinical practice and clinical trials. In addition to assessing cognitive measures of fatigue with the TAP, the analysis of saccade parameters might serve to improve the clinical characterization of the multidimensional fatigue syndrome and help to disentangle fatigue from associated neuropsychological symptoms, e.g., cognitive impairment and depression.

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Conflicts of interest There is no conflict of interest from any author regarding this study.

Ethical standard This study has been approved by the appropriate ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

References

1. Minden S, Frankel D, Hadden L et al (2006) The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. Mult Scler 12(1):24–38
2. Lerdal A, Celius E, Moum T (2003) Fatigue and its association with sociodemographic variables among multiple sclerosis patients. Mult Scler 9(5):509–514
3. Bakshi R (2003) Fatigue associated with multiple sclerosis: diagnosis, impact and management. Mult Scler 9(3):219–227
4. Krupp L (2006) Editorial. Mult Scler 12(4):367–368
5. Patrick E, Christodoulou C, Krupp LB (2009) Longitudinal correlates of fatigue in multiple sclerosis. Mult Scler 15(2):258–261
6. Smith MM, Arnett Pa (2005) Factors related to employment status changes in individuals with multiple sclerosis. Mult Scler 11(5):602–609
7. Téllez N, Río J, Tintoré M et al (2005) Does the modified fatigue impact scale offer a more comprehensive assessment of fatigue in MS? Mult Scler 11(2):198–202
8. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46(10): 1121–1123
9. Comi G, Leocani L, Rossi P, Colombo B (2001) Physiopathology and treatment of fatigue in multiple sclerosis. J Neurol 248(3):174–179
10. Krupp LB, Elkins LE (2000) Fatigue and declines in cognitive functioning in multiple sclerosis. Neurology 55(7):934–939
11. Flachenecker P, Kümpfel T, Kallmann B et al (2002) Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Mult Scler 8(6):523–526
12. Weinges-Evers N, Brandt AU, Bock M et al (2010) Correlation of self-assessed fatigue and alertness in multiple sclerosis. Mult Scler 16(9):1134–1140
13. Morrow SA, Weinstock-Guttman B, Munschauer FE, Hojnacki D, Benedict RHB (2009) Subjective fatigue is not associated with cognitive impairment in multiple sclerosis: cross-sectional and longitudinal analysis. Mult Scler 15(8):998–1005
14. Bailey A, Channon S, Beaumont JG (2007) The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. Mult Scler 13(1):73–80
15. Schwid SR, Thornton CA, Pandya S et al (1999) Quantitative assessment of motor fatigue and strength in MS. Neurology 53(4):743–750
16. Matta M, Leigh RJ, Pugliatti M, Aiello I, Serra A (2009) Using fast eye movements to study fatigue in multiple sclerosis. Neurology 73(10):798–804
17. Polman CH, Reingold SC, Edan G et al (2005) Diagnostic criteria for multiple sclerosis : 2005 revisions to the "McDonald Criteria". Ann Neurol 11:840–846
18. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33(11):1444–1452
19. Cutter GR, Baier ML, Rudick RA et al (1999) Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 122(5):871–882
20. Kos D, Nagels G, D'Hooghe MB, Duportail M, Kerckhofs E (2006) A rapid screening tool for fatigue impact in multiple sclerosis. BMC Neurol 6:27
21. Beck AT, Steer RA (1984) Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol 40(6): 1365–1367
22. Leigh RJ, Zee DS (2006) The neurology of eye movements. Oxford University Press, Oxford

23. Brunner E, Domhof S, Langer F (2002) Nonparametric analysis of longitudinal data in factorial experiments. Wiley, New York
24. R Development Core Team RFFSC (2008) R: a language and environment for statistical computing. R foundation for statistical computing, Vienna. 1(10): ISBN 3-900051-07-0. Available at: http://www.r-project.org
25. Frohman EM, Frohman TC, Zee DS, McColl R, Galetta S (2005) The neuro-ophthalmology of multiple sclerosis. Lancet Neurol 4(2):111–121
26. Downey DL, Stahl JS, Bhidayasiri R et al (2002) Saccadic and vestibular abnormalities in multiple sclerosis: sensitive clinical signs of brainstem and cerebellar involvement. Ann NY Acad Sci 956(4):438–440
27. Straube A, Robinson FR, Fuchs AF (1997) Decrease in saccadic performance after many visually guided saccadic eye movements in monkeys. Investig Ophthalmol Vis Sci 38(13):2810–2816
28. Prsa M, Dicke PW, Thier P (2010) The absence of eye muscle fatigue indicates that the nervous system compensates for non-motor disturbances of oculomotor function. J Neurosci 30(47): 15834–15842
29. Flachenecker P, Meissner H (2008) Fatigue in multiple sclerosis presenting as acute relapse: subjective and objective assessment. Mult scler 14(2):274–277
30. Bo J, Block HJ, Clark JE, Bastian AJ (2008) A cerebellar deficit in sensorimotor prediction explains movement timing variability. J Neurophysiol 100(5):2825–2832
31. Bares M, Lungu O, Liu T et al (2007) Impaired predictive motor timing in patients with cerebellar disorders. Exp Brain Res 180(2):355–365
32. Zimmermann P, Fimm B (2002) A test battery for attentional performance. In: Leclercq M, Zimmermann P (eds) Applied neuropsychology of attention: theory, diagnosis and rehabilitation. Psychology Press, London, pp 110–151
33. Möller F, Poettgen J, Broemel F et al (2011) HAGIL (Hamburg Vigil Study): a randomized placebo-controlled double-blind study with modafinil for treatment of fatigue in patients with multiple sclerosis. Mult scler 17(8):1002–1009
34. Stankoff B, Waubant E, Confavreux C et al (2005) Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology 64(7):1139–1143
35. Rammohan KW, Rosenberg JH, Lynn DJ et al (2002) Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry 72(2):179–183
36. Prins JB, van der Meer JWM, Bleijenberg G (2006) Chronic fatigue syndrome. Lancet 367(9507):346–355
37. Frohman TC, Frohman EM, O'Suilleabhain P et al (2003) Accuracy of clinical detection of INO in MS: corroboration with quantitative infrared oculography. Neurology 61(6):848–850