The Assessment of Motor Fatigability in Persons With Multiple Sclerosis: A Systematic Review

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Abstract

Background. Persons with multiple sclerosis (PwMS) are often characterized by increased motor fatigability, which is a performance change on an objectively measured criterion after any type of voluntary muscle contractions. This review summarizes the existing literature to determine which protocols and outcome measures are best to detect or study motor fatigability and the underlying mechanisms in MS. *Methods*. Two electronic databases, PubMed and Web of Science, were searched for relevant articles published until August 2016 with a combination of *multiple sclerosis*, *fatigability*, *muscle fatigue*, and *motor fatigue*. *Results*. A total of 48 articles were retained for data extraction. A variety of fatigability protocols were reported; protocols showed differences in type (isometric vs concentric), duration (15 to 180 s), and number of contractions (fixed or until exhaustion). Also, 12 articles reported motor fatigability during functional movements, predominantly assessed by changes in walking speed; 11 studies evaluated the mechanisms underlying motor fatigability, using additional electrical nerve or transcranial magnetic stimulation. Three articles reported psychometrics of the outcomes. *Conclusions*. The disparity of protocols and outcome measures to study different aspects of motor fatigability in PwMS impedes direct comparison between data. Most protocols use maximal single-joint isometric contractions, with the advantage of high standardization. Because there is no head-to-head comparison of the different protocols and only limited information on psychometric properties of outcomes, there is currently no gold standard to assess motor fatigability. The disability level, disease phenotype, and studied limb may influence the assessment of motor fatigability in PwMS.

Keywords

muscle fatigue, fatigability, motor fatigue, multiple sclerosis

Introduction

Multiple sclerosis (MS) is a progressive, chronic disease of the central nervous system, with symptoms such as weakness and fatigue.[1] Fatigue is often defined as a "subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities."[2] Fatigue is thus a subjective symptom that interferes with task performance in daily life. Kluger et al[3] proposed a unified taxonomy, where the symptom of fatigue is affected by perceptions of fatigue and performance fatigability. Performance fatigability can be studied within different domains. When studying the motor domain, the following definition of motor fatigability (adapted from Kluger et al[3]) can be used: "Motor fatigability is the magnitude or rate of change of motor performance on an objectively measured reference criterion after any type of voluntary activity or exercise" (p. 411). Several reviews on the assessment and treatment of fatigue in persons with MS (PwMS) or other neurological diseases exist.[4-6] In contrast, no overview has been reported of protocols and outcomes that can identify pathological motor fatigability in PwMS. Motor fatigability is, however, important to consider in PwMS because it affects the ability to perform sustained activities of daily living.[7] Furthermore, it will have an impact on the exercise capacity of PwMS, limiting the possibility to exercise regularly. The assessment of muscle weakness is routinely performed, but muscle weakness and

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motor fatigability are different concepts.[8] PwMS might not show muscle weakness on a single assessment of muscle strength, but they might show increased motor fatigability with a fast decline in muscle strength during longer or repeated test protocols.

Importantly, self-reported measures for fatigue do not provide a valid indicator of motor fatigability after physical activities or vice versa[9] because the 2 concepts are most often unrelated.[10,11] Consequently, it is important to quantify (pathological) motor fatigability applying objective, valid, reliable, and responsive outcomes.[10] To unravel the relation between motor fatigability and activities of daily living, it is, furthermore, important to include outcome measures on both the body function level and the activity level of the International Classification of Functioning, Disability and Health (ICF), when assessing fatigability.[12] It is not known if PwMS show motor fatigability after repeated and sustained muscle contractions of isolated joints, reflecting the "ICF body function level," as well as after functional activities such as walking, reflecting the "ICF activity level." From studies in healthy persons, it is known that motor fatigability is task specific and that protocol specifications affect the findings and the underlying mechanisms of motor fatigability.[13] In healthy individuals, different protocols are applied to assess different aspects of motor fatigability, where submaximal protocols most likely challenge the central nervous system and high-intensity exercises the peripheral neuromuscular system.[14,15] It is, however, not known if PwMS express pathological motor fatigability during all tasks or whether the results of different protocols can be compared.

Therefore, the aim of this systematic review was (1) to provide an extensive overview of the applied motor fatigability assessment protocols and outcome measures within the ICF framework to detect the most optimal assessment to quantify motor fatigability in PwMS and (2) to summarize the available information on psychometric properties for the located protocols, including the discriminant ability and the effect of exercise interventions.

Methods

Data Sources and Study Selection

To review the literature, the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were adopted.[16] The current review was registered on PROSPERO (CRD42016032320). Two databases (PubMed and Web of Science [WOS]) were searched using a combination of MeSH terms/keywords: multiple sclerosis AND (muscle fatigue OR fatigability OR motor fatigue). Literature searching started in September 2015, ended in November 2015, and was updated on August 23, 2016.

Studies were selected when they were written in English, published within the past 20 years, had undergone peer review, and enrolled ≥10 PwMS. Furthermore, studies had to generate/assess an objective parameter quantifying motor fatigability based on voluntary contractions. Interventional studies were only included when the intervention consisted of physical exercises. Descriptive, exploratory, or experimental full-length studies were included; conference papers, meeting reports, letters, and reviews were excluded.

All results were screened based on title and abstract by 2 independent reviewers (DS and CL). The entire text was read when the abstract did not provide sufficient information. In cases of disagreement between the 2 reviewers or if it was unclear whether a study should be included, a third reviewer (IL) was consulted. The reference lists of included articles were checked for further relevant articles.

Quality Assessment

The methodological quality was determined by the Downs and Black checklist.[17] Questions 6, 8, 14, 15, 19, 23, 24, and 26 were removed from the original scale when assessing observational studies because these questions were not applicable. A maximal score of 18 could, therefore, be assigned to observational studies as compared with 26 for randomized controlled trials. The score was converted to a percentage score for each study, with a score >65% indicating sufficient methodological quality.[18] Because the main goal of the review was to evaluate details of fatigability protocols, no studies were excluded based on the quality assessment.

Data Extraction

The following data were extracted from the selected articles: (1) study aim, ICF assessment level; (2) sample characteristics; (3) fatigability protocol specifications and outcome parameters; (4) information on psychometrics of outcomes; and (5) the main findings on motor fatigability in studies comparing healthy controls (HCs) with PwMS. Articles reporting protocols of a single muscle group or a single limb, during nonfunctional activities, were classified at the ICF body function level (category b 730-muscle power functions and b740-muscle endurance functions). Articles examining motor fatigability during functional activities were classified at the ICF activity level (d450-469-walking and moving). Details of the intervention and the effects on motor fatigability were documented from interventional studies.

Results

As presented in detail in Figure 1, 48 articles were included from the initial 494 hits (353 from WOS and 141 from

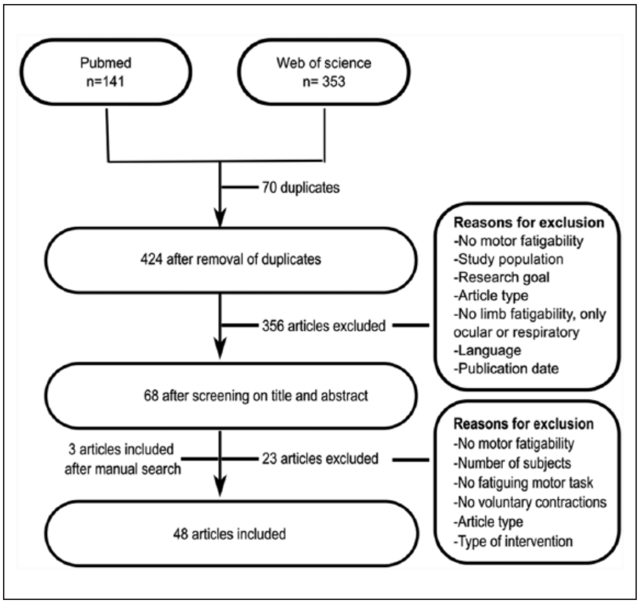

Figure 1. Schematic representation of the literature search.

PubMed). The data for quality assessment of the included studies are shown in Supplementary Tables 1 and 2. The results of the quality assessment for observational studies show that the scores range from 35% to 82% and for the interventional studies between 41% and 74%. The main problems of the observational studies were the lack of reporting of the following: the difference between asked and recruited participants (Q11 and Q12), the recruitment period (Q22), possible confounders (Q25), and the power of the study (Q27). For the interventional studies, all studies scored 0 on the representation of the study population (Q12), blinding of participants and assessors (Q14-15), and concealment of allocation (Q24). Furthermore, the reporting was also limited on the confounders (Q25), losses to follow-up (Q26), and the power of the study (Q27).

Study Objectives and Patient Characteristics

Study objectives were heterogeneous (Supplementary Table 3). In 23 articles, the objective was to assess motor fatigability in PwMS, whereas 11 articles aimed to detect underlying mechanisms. Also, 8 articles aimed to study the correlation between self-reported fatigue and motor fatigability, whereas 7 reported the influence of motor fatigability on other outcomes such as dual tasking, balance, motor cortex excitability, and brain activation patterns; 5 articles reported the effect of an intervention on motor fatigability; and 3 reported on the reliability of the applied outcomes for fatigability.

Most articles (n = 36) investigated the ICF body function level. Two articles reported both at ICF body function level and ICF activity level. Of the protocols at body function level, 20 examined the upper, 16 the lower, and 2 articles both upper and lower limbs. Motor fatigability protocols were reported by 12 articles at the ICF activity level. One of these combined outcomes at body function level with an exercise on activity level.

Table 1 summarizes sample characteristics. The sample size ranged from 10 to 208; 13 articles included all types of MS, 11 articles only included relapsing-remitting MS (RRMS), and 3 articles only secondary progressive MS. Three articles by the same author reported on PwMS with clinically isolated syndrome.[19-21] The average Expanded Disability Status Scale (EDSS) score ranged from 1.3 to 6. The studies that reported on self-reported subjective fatigue enrolled both fatigued and nonfatigued PwMS.

Fatigability Protocols

A schematic overview of type of protocols and frequency of application in clinical research in MS is provided in Figure 2. Table 2 documents the protocols' specifications.

Protocols Assessing Motor Fatigability at the ICF Body Function Level. In 30/38 protocols, isometric protocols were used (ICF category b7300-7301, 7400-7401). In all, 10 studies examined the lower limb and 18 the upper limb; 2 studies assessed both the upper and lower limbs. Most studies applied maximal voluntary contractions (MVCs) to assess motor fatigability. One study reported both maximal and submaximal protocols.[22] Generally, the duration of an MVC was predetermined (15 s,[23] 30 s,[8,11,19-21,24-26] 45 s,[27,28] 60 s,[29] 120 s,[30-36] 180 s[37-39]). In 1 study, the end point was not clearly defined ("until strength declined").[40] For protocols applying intermittent MVCs, the number of contractions ranged from 8 repetitions of 4 s[23] to 11 or 15 repetitive contractions without a specified duration,[24,40] the number of contractions that can be performed in 30 s,[8] 18 repetitions of 5 s,[41] and up to 2 minutes at 2 Hz (240 repetitions).[42]

Six articles reported submaximal isometric tasks of 10% to 50% of the MVC. One study evaluated a 60-s sustained contraction at 25%, 50%, 75%, and 100% MVC,[29] whereas 1 study applied 50% MVC until failure.[43] The 3 other protocols used repetitive contractions until inability to produce target force (eg, 30 s vs 30 s rest, or blocks of 44 s with 5 s rest)[35,44,45] or with a specified duration (6 minutes of exercises).[22]

Eight articles reported nonisometric protocols (ICF categories b7401 or 7402). Two studies required as many contractions as possible in a certain time frame.[46,47] Three other studies used an isokinetic protocol in the lower limbs, with 20 or 30 repetitions at 180°/s[48,49] or 50 repetitions at 60°/s.[50] One study reported squeezing a rubber ball maximally 10 times.[51] Motor fatigability during multijoint movements of the lower limb was assessed with leg presses until exhaustion.[52,53]

Table 1. Participant Characteristics of the PwMS in the Included Studies.

Article	Characteristics of the PwMS						Controls, n
	n	Subgroups	EDSS Scores	MS Type	Age	Perceived Fatigue	
Andreasen et al,[23] 2009	60	Primary fatigued (PF; n = 19) Secondary fatigued (SF; n = 20) Nonfatigued (NF; n = 21)	PF: 3 (1.0-3.5) SF: 2.5 (2.0-3.5) NF: 2.0 (1.5-3.5)	RR	PF: 43 (27-53) SF: 39 (24-52) NF: 39 (23-53)	PF FSS: 6.3 (5.0-7.0) SF FSS: 6.2 (5.0-7.0) NF FSS: 3.1 (1.0-4.0)	/
Broekmans et al,[48] 2010	25	Control group (C; n = 14) Experimental (E; n = 11)	4.3 ± 0.2	RR/SP/PP	47.9 ± 1.9	NR	/
Burschka et al,[56] 2012	37	Mild MS (n = 19) Moderate MS (n = 18)	Mild: 2 (0-3.5) Moderate: 4 (4-5)	RR/SP/CIS	39.7 ± 12.8	NR	25
de Souza-Teixeira et al,[52] 2009	13	/	NR	NR	43 ± 8	NR	/
Djaldetti et al,[11] 1996	30	With pyramidal lesions (n = 20) No pyramidal lesions (n = 10)	3.3 ± 2.5	RR/PP	37.4 ± 10.3	FSS: 4.9 (1.5-5.8)	13
Dodd et al,[53] 2011	71	Experimental (n = 36) Control (n = 35)	NR	RR	E: 47.7 ± 10.8 C: 50.4 ± 9.6	MFIS >38 41/71	/
Engelhard et al,[57] 2016	89	/	2,5 (0-6.5)	NR	46 (19-61)	MFIS: 29 (0-69)	29
Fay et al,[62] 2004	14	/	NR	NR	48.4 ± 6.3	NR	14
Greim et al,[51] 2007	79	/	2.51 ± 1.89	RR	35.2 ± 12.6	NR	51
Hameau et al,[50] 2016	30	Mild MS (n = 15) Moderate MS (n = 15)	Mild: 3.5 (2.5; 3.5) Moderate: 5 (4; 5.5)	RR/SP/PP	Mild: 46.9 ± 11 Moderate: 49.2 ± 9	Mild MFIS: 44 (17;53) Moderate MFIS: 58 (41;66)	/
Ickmans et al,[41] 2014	19	/	1.64 ± 1.02	NR	39.74 ± 10.74	CIS: 36.11 ± 11.36	32
Iriarte et al,[40] 1998	50	/	2.2 ± 1.9	NR	32.4 ± 9.8	FSS: 3.44 ± 1.45 FDS: 6.17 ± 3.31	50
Jonkers et al,[63] 2004	10	/	7.5 (6.5-7.5)	NR	54.5 (33-77)	NR	/
Kalron et al,[19] 2011	52	/	1.7 ± 1.3	CIS	35.2 ± 7.2	NR	28
Kalron et al,[20] 2012	52	Monosymptomatic (n = 35) Polysymptomatic (n = 17)	Mono: 1.3 ± 0.2 Poly: 2.6 ± 0.1	CIS	Mono: 3.1, SE 1.6 Poly: 39.4, SE 1.9	NR	28
Kalron et al,[21] 2013	52	1: Relapse within 1 year (n = 49) 2: No relapse (n = 25)	1: Mean 2.0 SE (0.2) 2: Mean 1.4 SE (0.2)	CIS	1: Mean 34.0, SE (2.0) 2: Mean 35.6, SE (1.5)	NR	/
Korkmaz et al,[64] 2011	33	Experimental (n = 16) Control (n = 17)	E: 4.84 ± 1.21 C: 3.94 ± 2.27	NR	E: 41.81 ± 8.43 C: 36.24 ± 10.08	NR	/
Lambert et al,[49] 2001	15	/	3.5 ± 0.3	NR	38.8 ± 10.0	NR	15
Latash et al,[29] 1996	11	/	3.7 ± 1.1	NR	41.3 ± 8.1	NR	11
Leone et al,[55] 2016	208	Subgroups for EDSS score	4.2 ± 3.6	RR/SP/PP	47.9 ± 10.7	MFIS: 40 ± 20	/
Liepert et al,[43] 2005	16	Fatigued (n = 8) Nonfatigued (n = 8)	MS-F: 3.1 ± 0.93 MS-NF: 2.9 ± 0.9	RR	MS-F: 42.5 ± 5 MS-NF: 40.3 ± 4.5	MS-F FSS: 5.3 ± 0.4 MS-NF FSS: 1.1 ± 0.2	6
McLoughlin et al,[54] 2014	34	/	3.5 (3-6)	NR	49.1 ± 10.4	NR	10
Perretti et al,[45] 2004	41	Fatigued (n = 32) Nonfatigued (n = 9)	Total: 3.2 ± 0.5 MS-F: 3.4 ± 1.0 MS-NF: 2.3 ± 0.5	RR	Total: 35.7 ± 10.1 MS-F: 37.7 ± 10 MS-NF: 28.7 ± 7.1	Total FSS: 43.1 ± 15.8 MS-F FSS: 51.6 ± 8.5 MS-NF FSS: 25.1 ± 11.8	13
Petajan and White,[37] 2000	32	Weak (n = 16) Normal strength (n = 16)	NR	NR	MS-W: 42.9 ± 9.9 MS-NW: 44.0 ± 10.3	NR	10
Phan-Ba et al,[58] 2012	81	EDSS 0-2 (n = 30) EDSS 2.5-3.5 (n = 21) EDSS 4.0-6.0 (n = 30)	Total group: 3.5 (0-6)	CIS/RR/SP/PP	40.16 ± 11.35	NR	30

(continued)

Table 1. (continued)

Article	Characteristics of the PwMS						Controls, n
	n	Subgroups	EDSS Scores	MS Type	Age	Perceived Fatigue	
Romani et al,[27] 2004	60	Fatigued (n = 40) Nonfatigued (n = 20)	MS-F: 3.3 ± 2.5 MS-NF: 3.1 ± 2.3	RR	MS-F: 38.3 ± 8.1 MS-NF: NR	MS-F FIS: 75.4 ± 22.7 MS-NF FIS: 25.8 ± 13.4	/
Scheidegger et al,[42] 2012	23	/	3.15 ± 1.56	NR	39.7 ± 11.4	FSS: 37.2 ± 14.6	13
Schwid et al,[8] 1999	20	/	5.5 ± 1.3	NR	47.9 ± 7.4	NA	20
Sehle et al,[59] 2011	14	/	3.6 ± 1.33	NR	42 ± 7.6	FSMC: 64.3 ± 19.3	/
Sehle et al,[60] 2014	40	Fatigued (n = 29) Nonfatigued (n = 11)	Total 3.4 ± 1.3 MS-F: 3.8 ± 1.2 MS-NF: 2.4 ± 1.1	RR/PP/SP	Total: 45.9 ± 7.0 MS-F: 45.3 ± 7.0 MS-NF: 46.6 ± 7.6	MS-F FSMC motor: 38.6 ± 8.1 MS-NF FSMC motor: 27.4 ± 10.0	20
Sehle et al,[61] 2014	40	Fatigued (n = 29) Nonfatigued (n = 11)	Total: 3.4 ± 1.3 MS-F: 3.8 ± 1.2 MS-NF: 2.4 ± 1.1	RR/PP/SP	Total: 45.9 ± 7.0 MS-F: 45.3 ± 7.0 MS-NF: 46.6 ± 7.6	MS-F FSMC motor: 38.6 ± 8.1 MS-NF FSMC motor: 27.4 ± 10.0	20
Severijns et al,[24] 2015	30	EDSS <6 (n = 17) EDSS ≥6 (n = 13)	Total group: 4.0 (1.5-8.5)	RR/PP/SP	Total: 52 ± 12 EDSS <6: 49 ± 10 EDSS ≥6: 56 ± 12	MFIS: 35.6 ± 21.0	16
Severijns et al,[47] 2015	16	Weak (n = 8) Normal strength (n = 8)	6 (2-8)	RR/PP/SP	55 ± 8	MFIS: 42.3 ± 17.8	16
Severijns et al,[22] 2016	19	/	5 (1.5-7.5)	RR/PP/SP	56 ± 12	MFIS: 42.6 ± 16.6	19
Sheean et al,[28] 1997	21	/	5.4 ± 1.9	NR	39.8 (26-55)	NR	19
Skurvydas et al,[30] 2011	18	Men (n = 9) Women (n = 9)	Men: 3.4 ± 1.5 Women: 3.5 ± 1.6	SP	Men: 45.1 ± 4.1 Women: 41.1 ± 6.1	FSS Men: 5.6 ± 1.6 FSS Women: 5.5 ± 1.6	19
Steens et al,[31,32] 2012	20	/	2.5 (0-5)	RR	21-58	NR	20
Streckis et al,[33] 2014	18	Men (n = 9) Women (n = 9)	Men: 3.4 ± 1.5 Women: 3.5 ± 1.6	SP	Men: 45.1 ± 4.1 Women: 41.1 ± 6.1	Men FSS: 5.6 ± 1.6 Women FSS: 5.5 ± 1.6	/
Surakka et al,[25] 2004	28	/	2.1 ± 1	RR/SP	44 ± 7	FSS: 4.8 ± 1.4	/
Surakka et al,[26] 2004	95	Exercisers men (ME) Exercisers women (WE) Controls men (CM) Control women (CW)	WE: 2.0 ± 0.8 ME: 2.9 ± 1.2 CW: 2.5 ± 1.0 CM: 3.1 ± 1.2	RR/PP/SP	WE: 43 ± 6 ME: 45 ± 6 CW: 44 ± 7 CM: 44 ± 7	WE: FSS4.6 ± 1.6 ME: FSS4.6 ± 1.6 CW: FSS 4.7 ± 1.2 CM: FSS4.5 ± 1.1	/
Thickbroom et al,[44] 2006	23	/	2.2 ± 0.8	NR	41 ± 10	MFIS: 35 ± 17	15
Thickbroom et al,[46] 2008	10	/	2.05 ± 1.1	NR	41.3 ± 11.18	NR	13
White et al,[38] 2009	10	/	2.9 ± 1.9	NR	40.9 ± 11.3	NR	13
White et al,[39] 2013	11	/	1.9 (1.0-3.0)	RR	38.9 ± 6.9	FIS: 61 ± 39.1	11
Wolkorte et al,[35] 2015	19	/	1.2 ± 0.3	RR	39 (21-57)	FSS: 3.9 (1.6-6.2) MFIS: 27.3 (1-56)	19
Wolkorte et al,[34] 2015	86	/	NR	RR	41 (21-65)	FSS: 4.6 (1.3-7.0) MFIS: 38.3 (0-84)	/
Wolkorte et al,[36] 2016	25	/	5 (2.0-7.0)	SP	53 (41-65)	FSS: 5.1 (1.8-6.6) MFIS physical: 21.7 (9-32)	25

Abbreviations: CIS, checklist of individual strength; EDSS, Expanded Disability Status Scale; FDS, fatigue descriptive scale; FSS, Fatigue Severity Scale; FSMC, Fatigue Scale for Motor and Cognitive Functioning; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; MS-F, PwMS with subjective fatigue; MS-NF, PwMS without subjective fatigue; NR, not reported; PP, primary progressive MS; PwMS, persons with multiple sclerosis; RR, relapsing-remitting type of MS; SE, standard error; SP, secondary progressive MS; x, use of electrostimulation; /, data not available.

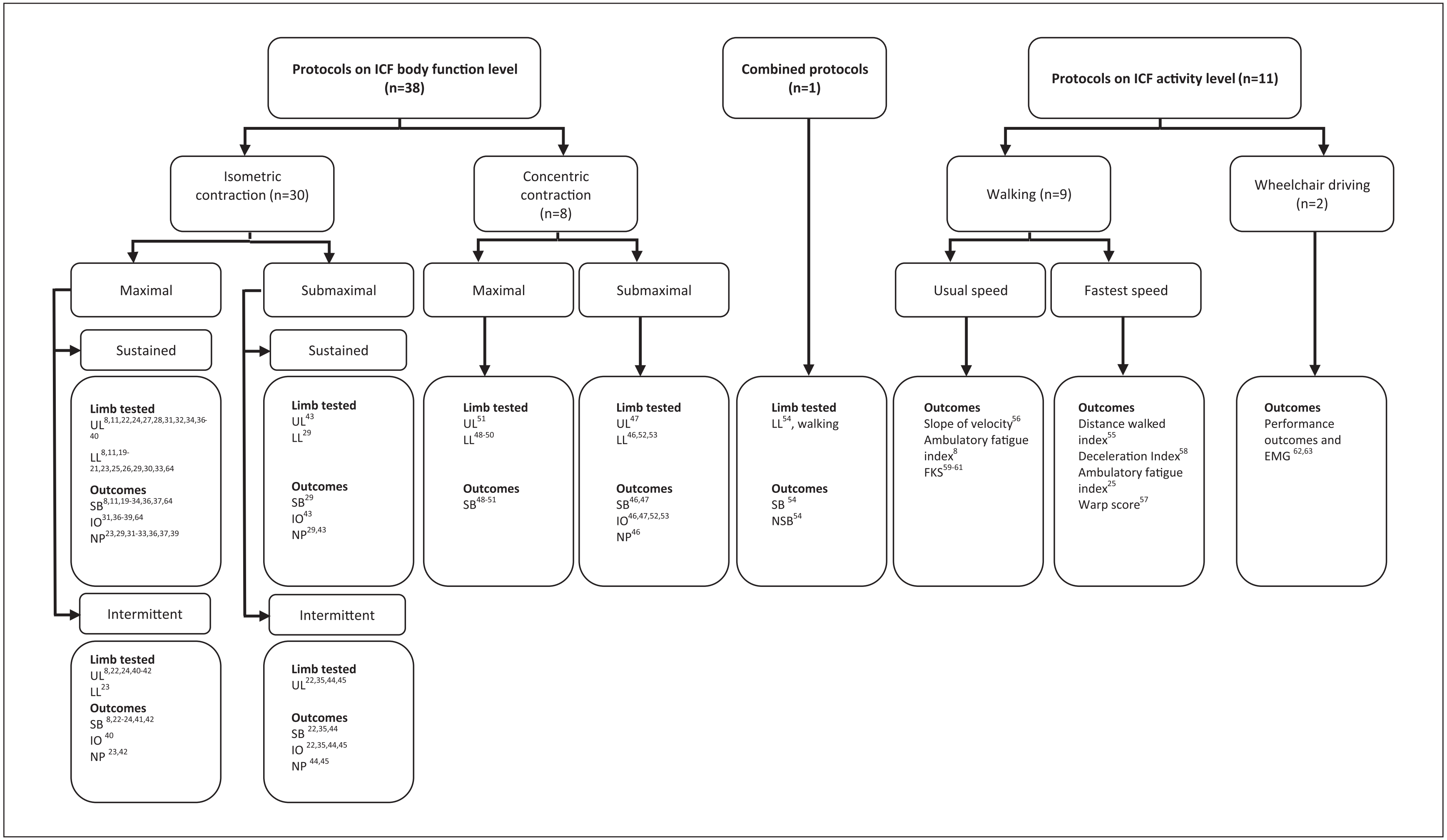

Figure 2. A schematic overview of the type of experimental protocols used to assess motor fatigability in multiple sclerosis.
Abbreviations: EMG, electromyography; FKS, Fatigue index Kliniken Schmieder; ICF, International Classification of Functioning, Disability and Health; IO, indirect outcomes for motor fatigability; LL, lower limb; NP, neurophysiological outcomes; SB, strength-based outcomes; UL, upper limb.

Table 2. Specifications of the Protocols and Outcome Measures for Motor Fatigability.

Article	Protocol Specifications						Description of the Motor Outcome Assessments	HC-MS	Main Findings for the Difference Between PwMS and HCs
	Activity	Intensity	Duration	ES	TMS	Measurement System			
Andreasen et al,[23] 2009	Isometric quadriceps contraction	100% MVC	8 Repetitions of 4 s /2 s rest; 15 s	x	/	Biodex System 3 Pro (Biodex Medical Systems, NY, USA)	Decline in strength, peripheral activation, and central activation after 4 and 8 contractions, and after 15 s MVC	NA	/
Broekmans et al,[48] 2010	Isokinetic knee extension	100% MVC	20 Repetitions at 180°/s	/	/	Biodex System 3 Pro (Biodex Medical Systems, NY, USA)	Average work of the last 6 s versus the first 6 s	NA	/
Burschka et al,[56] 2012	Walking	Usual speed	6 Minutes or 12 minutes	/	/	Hallway of 20 m, stopwatch	Slope of the minute-by-minute velocity profile during walking, modeled as a linear or quadratic trend	3/4	The linear slope of decline in walking speed was lower in severe PwMS for both the 6MWT and 12MWT and the quadratic trend only after 6MWT. For mild MS, the quadratic trend was different after 6MWT and the linear trend after 12MWT
de Souza-Teixeira et al,[52] 2009	Leg extensions	40% MVC	Until exhaustion	/	/	Load cell (ERGO, Globus, Codogne, Italy)	The maximal number of repetitions	NA	/
Djaldetti et al,[11] 1996	Isometric contraction of m. biceps and m. iliopsoas	100% MVC	30 s	/	/	Isometric stain gauge, attached to a mechanical system	Fatigue index as the ratio between the observed area under the curve and the hypothetical area under the curve. General fatigue index is the average of the 2 muscles, 2 limbs, over 2 examinations	1/1	The general fatigue index in PwMS was 11% higher than in HCs
Dodd et al,[53] 2011	Leg press and reversed leg press	50% MVC	Until exhaustion	/	/	NR	The maximal number of repetitions	NA	/
Engelhard et al,[57] 2016	Walking	As fast as possible	6 minutes	/	/	Actigraph GT3X	Warp score, which measures the stretch needed to align gait cycles within 1 minute, and distance score, which measures the similarity of gait cycles in 1 minute	NR	/
Fay et al,[62] 2004	Manual wheelchair driving	Speed of 1 m/s	5 minutes	/	/	Instrumented rear wheel, SMARTwheel	Velocity, propulsion frequency, push angle, phase duration, propulsion patterns, push rim force, work, work loss	4/8	Velocity, push angle, and work and work loss after 5 minutes of wheelchair driving changed more in PwMS than in HCs
Greim et al,[51] 2007	Hand grip	100% MVC	10 Repetitions	/	/	Rubber ball	Decline in maximal strength	1/1	Fist tightening strength declined 8% more in PwMS after 10 trials
Hameau et al,[50] 2016	Isokinetic knee extension	100% MVC	50 Repetitions of 60°/s	/	/	ConTrex-MJ dynamometer (ConTrex AG, Switzerland)	Slope as the rate of decline in normalized peak torque represented by the slope of the linear regression	NA	/
Ickmans et al,[41] 2014	Isometric hand grip contraction	100% MVC	18 Repetitions of 5 s/5 s rest	/	/	Hydraulic hand dynamometer (JAMAR, Masan, Japan)	Maximal hand grip strength	0/1	There were no significant differences between HCs and PwMS in strength decline after 18 repetitions
Iriarte and de Castro,[40] 1998	Isometric and isotonic hand grip contraction	100% MVC	11 Repetitions; sustained contraction	/	/	A standard manual dynamometer	Line of fatigability by dividing the values of the sum of the first 2 trials by the sum of the last 2 trials. Length of time for a maximal contraction until a decrease in strength is seen	2/2	Fatigability slope was 0.2 units higher in PwMS, and time to fatigue was on average 4 s longer in HCs
Jonkers et al,[63] 2004	Joystick wheelchair driving	7 Functional tasks	Functional tasks: time necessary	/	/	Eight-channel bipolar EMG (MP3000P8, Mega electronics, Finland)	EMG median frequency and maximal rectified EMG over 0.5 s during the reference steering tasks of 3 minutes	NA	/
Kalron et al,[19] 2011	Isometric knee/ankle extension/flexion	100% MVC	30 s	/	/	Isokinetic dynamometer (Cybex 6000, Ronkonkoma, NY, USA)	Fatigue index as the ratio between the observed area under the curve and the hypothetical area under the curve, when the maximal value is determined within the first 5 s of the trial	8/8	All the fatigue indices were significantly different between HCs and PwMS, with an average difference of 8%
Kalron et al,[20] 2012	Isometric knee/ankle extension/ flexion	100% MVC	30 s	/	/	Isokinetic dynamometer (Cybex 6000, Ronkonkoma, NY)	Fatigue index as the ratio between the observed area under the curve and the hypothetical area under the curve, when the maximal value is determined within the first 5 s of the trial	8/8	All the fatigue indices were higher in polysymptomatic PwMS than HCs in both legs (on average 11%-15%), except for the right ankle dorsiflexion. For monosymptomatic PwMS, left knee extension and dorsiflexion were not different, but on average, FI were 7% to 4% higher

(continued)

Table 2. (continued)

Article	Protocol Specifications						Description of the Motor Outcome Assessments	HC-MS	Main Findings for the Difference Between PwMS and HCs
	Activity	Intensity	Duration	ES	TMS	Measurement System			
Kalron et al,[21] 2013	Isometric knee/ankle extension/ flexion	100% MVC	30 s	/	/	Isokinetic dynamometer (Cybex 6000, Ronkonkoma, NY, USA)	Fatigue index as the ratio between the observed area under the curve and the hypothetical area under the curve when the maximal value is determined within the first 5 s of the trial	NA	/
Korkmaz et al,[64] 2011	Isometric knee extension and ankle dorsiflexion	100% MVC	NR	/	/	NR	Strength decline. Amplitude, RMS, MNF, and MDF of the EMG signal of m. quadriceps femoris and m. tibialis anterior	NA	/
Lambert et al,[49] 2001	Isokinetic knee extension and flexion	100% MVC	3 Sets of 30 contractions at 180°/s	/	/	Cybex Norm dynamometer	Fatigue index was calculated as the work performed during the last 15 contractions divided by the work done in the first 15 repetitions	1/2	Fatigue index was significantly higher in PwMS for knee flexion (10%) but not for knee extension
Latash et al,[29] 1996	Isometric knee extension	25%-50%-75%-100% MVC	60 s	x	/	Kin-Com 500H (Chattex Corp, Chattanooga)	Drop of torque more than 60 s. Central fatigue: changes in torque after electrical stimulation	2/2	The drop of torque and the changes in central fatigue were significantly higher in PwMS after 75% and 100% contractions, not after 25% and 50% contractions
Leone et al,[55] 2016	Walking	Fastest speed	6 minutes	/	/	A 30-m hallway, stopwatch	Distance walked index as a ratio between the walked index at minute 6 versus minute 1	NA	/
Liepert et al,[43] 2005	Isometric hand grip	50% MVC	Until failure	x	P-P	Bistim device (Magstim, Dyfed, UK)	Exercise duration; M-wave amplitude for flexor digitorum superficialis; MEP amplitude, intracortical inhibition, and facilitation	1/5	The exercise duration was 7 s shorter in PwMS with fatigue than in HC. There were no significant differences in the other parameters
McLoughlin et al,[54] 2014	Walking	Fastest speed	6 minutes	/	/	Isometric strain gauge, 10-m hallway	Strength before and after 6 minutes walking. Balance before and after 6 minutes walking	NR	There was a decline in knee extension strength and ankle dorsiflexion strength in PwMS only, but a direct statistical comparison was not performed
Perretti et al,[45] 2004	Isometric pinch grip	50% MVC	30 s/30 s rest, until strength <50% MVC	/	P-P	Pinch gauge (B and L Engineering, California, USA)	Number of repetitions until the participant was unable to maintain 50% MVC, MEP amplitude	1/2	The number of repetitions was equal in both groups. MEP amplitude decreased in HC to 64% and in PwMS to 86% of the initial value
Petajan and White,[37] 2000	Isometric hand grip	100% MVC	3 minutes	/	P-P	Custom-built hydraulic force transducer	Strength decline; time at which force declined to 50%; changes in central motor conduction time and MEP amplitude	2/4	Time to 50% decline in force was significantly longer in HCs, with a difference of 13 s on average. The central motor conduction time increased in PwMS after exercise, not in controls
Phan-Ba et al,[58] 2012	Walking	Fastest speed	timed 500 MW	/	/	3-m Broad corridor	Deceleration index: ratio between the walking speed of the timed 25-foot walk and the speed during the last 100 m of the 500-m walk	0/1	The deceleration index is not significantly lower in PwMS
Romani et al,[27] 2004	Isometric thumb adduction	100% MVC	45 seconds	x	Pre	Custom-made sling attached to force transducer	DF%: percentage decrement of force. DCA%: percentage decrement in central activation.	NA	/
Scheidegger et al,[42] 2012	Isometric abduction of the little finger	100% MVC	2-Minute repetitions at 2 Hz	x	IB	Viking select EMG force transducer (Sensotec, USA), Magstim 200 stimulator	Percentage decline in maximal strength. Central conduction index: calculated as the ratio between the first curve of the triple stimulation versus the second curve	2/2	The strength declined more in PwMS than in HCs (difference of 8% on average). The central conduction index was 40% higher in PwMS than in HCs
Schwid et al,[8] 1999	Isometric hand grip, elbow extension, knee extension, ankle dorsiflexion, walking	100% MVC; usual speed	30 s; 30 Contractions; 500 MW	/	/	Rigid frame attached to force transducer; digital grip dynamometer (Sammons preston, IL)	4 Different static fatigue indices. Dynamic fatigue index: ratio between the maximal strength in the first versus the last contractions Ambulatory fatigue index: the ratio between the velocity in the last versus the first 50-m lap on a 500-m walk	16/18	All fatigue indices showed more fatigability of PwMS compared with HCs. For the static fatigue indices, the average difference for the elbow extensors was 7%, for the hand grip 19%, for the knee extensors 19%, and for the dorsiflexors 22%. The dynamic fatigue index differed with 8% and the ambulatory index with 15%

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Table 2. (continued)

Article	Protocol Specifications						Description of the Motor Outcome Assessments	HC-MS	Main Findings for the Difference Between PwMS and HCs
	Activity	Intensity	Duration	ES	TMS	Measurement System			
Sehle et al,[59] 2011	Walking on treadmill	Usual speed	Until 1 minute after asking to stop	/	/	Wireless AS200 system (Lutz Mechtronic Technology, Austria)	Based on the number of gait parameters that showed a significant change in mean or SD, a fatigue index was calculated	NA	/
Sehle et al,[60] 2014	Walking on treadmill	Usual speed	One minute after reaching a Borg score of 17, maximal 60 minutes	/	/	Wireless AS200 system (Lutz Mechtronic Technology, Austria)	Fatigue Index Kliniken Schmieder is an index of change based on the difference between 2 attractors and the deviations away from the attractors of the 3-dimensional accelerations of the foot	1/1	The fatigue index Kliniken Smieder ranged from 0.5 to 125 in the PwMS and from 0.3 to 3.9 in HCs
Sehle et al,[61] 2014	Walking on treadmill	Usual speed	One minute after reaching a Borg score of 17, maximal 60 minutes	/	/	Wireless AS200 system (Lutz Mechtronic Technology, Austria)	Fatigue Index Kliniken Schmieder is an index of change based on the difference between 2 attractors and the deviations away from the attractors of the 3-dimensional accelerations of the foot	NR	/
Severijns et al,[24] 2015	Isometric hand grip	100% MVC	30 s and 15 repetitive contractions	/	/	Digital JAMAR hand grip module (E-link, Biometrics Ltd, UK)	Static fatigue index: ratio based on the area of strength decline over 30 s to the hypothetical area when no strength loss is seen Dynamic fatigue index: the ratio between the maximal strength in the first 3 versus the last 3 contractions	1/2	The static fatigue index was 42% for PwMS and 29% in HCs. The dynamic fatigue index was 21% in PwMS and 18% in HCs
Severijns et al,[47] 2015	Isotonic shoulder anteflexion	Weight of 2.5 N	15 minutes	/	/	Haptic Master. Trigno Wireless EMG (Delsys)	Pre-post comparison of maximal shoulder anteflexion strength, number of movements in 3 minutes, path of movement and EMG RMS and MDF of the anterior deltoid	0/5	None of the parameters showed a significant Group × Time interaction effect; thus the change was identical for PwMS and HCs
Severijns et al,[22] 2016	Isometric hand grip exercises	25% MVC 100% MVC	3 × 6 minutes 30 s or 30 repetitions	/	/	Digital JAMAR (E-link, Biometrics Ltd, UK). Trigno Wireless EMG (Delsys)	Decline in maximal hand grip strength; median frequency and root mean square of the EMG of wrist flexors and extensors; static and dynamic fatigue index	3/7	Strength declined more in HCs for the dominant hand (4% difference), but not for the nondominant hand. EMG outcomes were not different between groups. The static fatigue index was 10% increased in PwMS and the dynamic fatigue index only for the nondominant hand
Sheean et al,[28] 1997	Isometric thumb adduction	100% MVC	45 s	x	P-P	EMG disk electrodes Magnetic stimulation: custom build	Rate of decline in strength; changes in central activation; stimulated twitch force pre-post. MEP amplitude and central motor conduction time	2/5	Decline in strength in PwMS was higher (45%) than in HCs (18%). The decline in central activation was 48% in PwMS and 9% in HCs. The change in stimulated twitch force, MEP amplitude, and conduction time was not different between groups
Skurvydas et al,[30] 2011	Isometric knee extension	100% MVC	2 minutes	x	/	Isokinetic dynamometer (System 3, Biodex medical system, NY)	Fatigue index for maximal strength, voluntary activation and twitch force, based on the differences from pre to post	2/3	No difference in muscle fatigability, based on muscle torque. Different underlying mechanism, shown by the 46%-52% higher fatigue index for voluntary activation and the 20%-40% lower fatigue index for peripheral fatigue in PwMS.
Steens et al,[31] 2012	Isometric index finger abduction	100% MVC	2 minutes	x	/	Digitimer DS7, Welwyn Garden City, UK	Muscle fatigue index (strength), peripheral fatigue (resting twitch), central fatigue (superimposed twitch), residual EMG (EMG amplitude)	1/4	The decline in central activation was 12% higher in PwMS. Other indices did not show significant differences
Steens et al,[32] 2012	Isometric index finger abduction	100% MVC	2 minutes	x	Pre	Digitimer DS7, Welwyn Garden City, UK	Muscle fatigue index (strength), peripheral fatigue (resting twitch), central fatigue (superimposed twitch), residual EMG (EMG amplitude)	1/4	The peripheral fatigue was 18% higher in male HCs compared with male PwMS. Other parameters were not significantly different
Streckis et al,[33] 2014	Isometric knee extension	100% MVC	2 minutes	x	/	Isokinetic dynamometer (System 3, Biodex medical system, NY)	Fatigue index for maximal strength, voluntary activation and twitch force, based on the differences from pre to post	NA	/

(continued)

Table 2. (continued)

Article	Protocol Specifications						Description of the Motor Outcome Assessments	HC-MS	Main Findings for the Difference Between PwMS and HCs
	Activity	Intensity	Duration	ES	TMS	Measurement System			
Surakka et al,[25] 2004	Isometric knee extension/ flexion	100% MVC	30 s	/	/	Knee muscle dynamometer (Ab HUR, Finland)	Comparison of 3 different fatigue indices based on the area under the curve	NA	/
Surakka et al,[26] 2004	Isometric knee extension/ flexion walking	100% MVC fastest speed	30 s; 500 MW	/	/	Knee muscle dynamometer (Ab HUR, Finland)	Fatigue index, based on the area under the curve; ambulatory fatigue index	NA	/
Thickbroom et al,[44] 2006	Isometric index finger abduction	40% MVC	7 s/3 s rest for 120 repetitions/until exhaustion	/	P-P	Strain gauge (Grass instruments, Model FT03) Magstim 200 stimulator	Degree of force loss after exercise Changes in MEP threshold, latency, and amplitude and in silent period duration. EMG RMS	2/6	MEP amplitude increased more in PwMS than in HCs (33% difference), and the silent period duration was 30 ms longer in PwMS after exercise
Thickbroom et al,[46] 2008	Ankle dorsiflexion	Fastest speed	5 Bouts of 15 s	/	IB	Dynamometer attached to foot support, Magstim 200	Percentage reduction in force. Tap rate changes. MEP amplitude changes	2/3	The strength declined more in PwMS than in HCs (15% difference), and the MEP amplitude increased more in PwMS (45% on average)
White et al,[38] 2009	Isometric hand grip	100% MVC	3 minutes	/	/	NR	Time to attain 50% of the peak force	1/1	Time to 50% decline in force was significantly longer in HCs, with an average difference of 38 s
White et al,[39] 2013	Isometric thumb abduction	100% MVC	3 minutes	/	P-P	EMG: Synergy (Viasys) Magstim 200² (Wales, UK), Force transducer	Time to 50% of the peak force.MEP amplitude and latency, central motor conduction time, motor threshold, silent period with TMS	NR	/
Wolkorte et al,[34] 2015	Isometric index finger abduction	10% MVC 30% MVC	12 Blocks; blocks of 44 s until failure	/	/	Custom-built force transducer, sintered Ag/ AgCl electrodes	The decline in intermittent maximal strength The number of blocks until fatigue (30% MVC task) EMG RMS. force variability	1/4	The number of blocks at 30% MVC was not significantly lower in PwMS compared with HCs. The force variability increased more in PwMS
Wolkorte et al,[35] 2015	Isometric index finger abduction	100% MVC	2 minutes	/	/	Custom-built force transducer	Muscle fatigability as the ratio between the average strength in the first versus the last 6 s	NA	/
Wolkorte et al,[36] 2016	Isometric index finger abduction	100% MVC	2 minutes	x	/	Custom-built force transducer, sintered Ag/ AgCl electrodes	Muscle fatigue (index based on strength) Peripheral fatigue (index based on rest twitch) Central fatigue (index based on superimposed twitch) Residual EMG (index based on EMG amplitude)	4/4	Significant differences for muscle fatigue (10% difference), peripheral fatigue (30% difference), decline in EMG and increase in central fatigue (25% difference)

Abbreviations: EMG, electromyography; ES, additional use of electrical stimulation; HCs, healthy controls; HC-MS, number of significantly different outcomes; IB, TMS during the exercise; m, metres; MDF, median frequency; MEP, motor evoked potential; MNF, mean frequency; MS, multiple sclerosis; MVC, maximal voluntary contraction; MWT, minutes walking test; NR, not reported; NA, not applied; NS, not significant; P-P, pre-exercise and postexercise; PwMS, persons with multiple sclerosis; RMS, Root mean square; TMS, additional use of transcranial magnetic stimulation.

A total of 10 studies applied additional electrical stimulation of the nerve innervating the target muscle to determine underlying mechanisms.[23,27-33,36,42] Two studies interspersed the voluntary exercises with transcranial magnetic stimulation (TMS) to gain further insight into corticospinal excitability,[42,46] and 6 studies used TMS before and after a fatigability protocol.[28,37,39,43-45]

Protocols Assessing ICF Activity Level. In 10 studies, walking for a fixed time (6 or 12 minutes),[54-57] a fixed distance (500 m),[8,25,58] or until voluntary exhaustion[59-61] at either comfortable or fastest walking speed was applied. Three walking studies used a treadmill[59-61]; 7 studies tested free overground walking.[8,25,54-58] One study examined motor fatigability during 5 minutes wheelchair driving at a speed of 1 m/s in a manual wheelchair,[62] whereas another used a functional steering task with a joystick-driven wheelchair, mimicking daily life activities.[63]

Outcome Measures: The Quantification of Motor Fatigability and Underlying Mechanisms

Table 2 summarizes the identified outcomes to document motor fatigability. Overall, the outcomes could be categorized as (1) strength-based outcomes, (2) indirect outcomes, and (3) neurophysiological outcomes.

Strength-Based Outcomes. The majority of the isometric protocols (29/48) used strength-based outcomes to assess motor fatigability. Despite the different names (eg, "percent decrement of force," "static fatigue index," "rate of decline in strength"), most outcomes directly measure the strength decline. Indices of motor fatigability are mostly based on the ratio between the initial and the final strength during sustained (23/48) or repetitive contractions (8/48). For the sustained contractions, an index was also based on the area under the curve or the slope of the strength decline.[8,11,19-21,24-26] Some articles only reported a statistical comparison of the maximal strength, assessed before and after a specific task, rather than an index.[22,29,47,64] This approach was also used in one study after walking.[54] During isokinetic protocols, the ratio between the work done during the first contractions versus the last contractions[48,49] or the slope of torque decline[50] was used.

Indirect Outcomes. Four articles reported indirect outcomes based on endurance time. For example, 3 studies reported the time until MVC declined to 50% of the initial MVC.[37-39] Five studies evaluated the "number of repetitions": for example, the number of contractions until the participant was unable to maintain 50% MVC,[45] the number of repetitions performed in a fixed amount of time,[47] or until inability to maintain a target force[35,52,53] were reported. The performance such as the change in tapping speed[46] and the trajectory of movements[47] during single-joint movements was described as an indirect measure of motor fatigability.

After walking, indices were based on walking velocity or distance, such as the deceleration index,[58] distance walked index,[55] and ambulatory fatigue index.[8] Four studies calculated an index based on gait kinematics.[57,59-61] The performance outcomes after manual wheelchair driving were velocity and propulsion frequency.[62] Electromyography (EMG) was used in 9 studies.[22,31,32,35,36,44,47,63,64] Four studies reported the median or mean frequency of the EMG signal,[22,47,63,64] whereas the remaining 6 studies reported a measure of the EMG amplitude (eg, root mean square).

Neurophysiological Outcomes. Besides the assessment of motor fatigability as such, neurophysiological outcomes were reported in 17 studies to explore underlying mechanisms of motor fatigability (Table 2). The twitch interpolation technique[65] was frequently applied to determine the changes in central and peripheral activation of the muscles under investigation[23,27-33,36,42,43] and used as an indication of a loss of central drive (central fatigue) or peripheral muscle fatigue.[66]

Psychometric Properties

The only information on psychometrics in PwMS that was detected with the current literature search was related to reliability of the outcome measures. No information was detected on the validity and responsiveness of motor fatigability measures. The discriminant ability, however, might partially represent construct validity.

Reliability. Three studies investigated the reliability of motor fatigability outcomes. Schwid et al[8] and Surakka et al[26] reported on the reliability of static fatigue indices, based on a 30-s sustained isometric contraction. The static fatigue index with the best reliability in PwMS (intraclass correlation coefficients [ICCs] range = 0.71-0.96) that best discriminated between HCs and PwMS was calculated by dividing the total area under the strength curve by the hypothetical area under the curve, when no strength decline would occur (ie, the multiplication of maximal strength times contraction duration from 5 s after the start of the contraction). Other fatigue indices showed lower ICCs.[8] A fatigue index based on a ratio between the initial strength and the final strength had ICCs of 0.46 to 0.77. A fatigue index, based on the area under the first 5 s versus the last 5 s had ICCs of 0.5 to 0.73. A fatigue index, based on the area under the curve of the entire contraction period, showed ICCs of 0.64 to 0.93. A slightly modified static fatigue index also showed good reliability (ICC of 0.68-0.86).[26] Lambert et al[49] reported poor to moderate reliability of an index based on the work performed during the first 15 versus the last 15 contractions of an isokinetic protocol consisting of 30 maximal contractions at 180°/s (ICCs from 0.36 to 0.51). In accordance, poor reliability of a dynamic fatigue index was reported, with ICCs from 0.20 to 0.44.[8] One report showed poor reliability of an ambulatory fatigue index determined during a 500-m walk (ICC = 0.21-0.36).[8]

Discriminant Ability Between (Subgroups of) PwMS and HCs. Table 2 shows that 34/48 articles enrolled PwMS and HCs. Not all studies compared groups statistically; 24 articles reported a statistically significant difference between HCs and PwMS, and 17 of these used isometric (repetitive or sustained) MVCs. Of these 17, strength-based outcomes showed a group difference for motor fatigability in the upper limb,[22,24,28,36,40,42,51] the lower limb,[19,20,29] and in both the upper and lower limbs.[8,11] The number of times that an outcome showed a difference between PwMS and HCs is shown in Table 3. Three protocols with sustained MVCs investigated the difference between subgroups of PwMS and found that motor fatigability was related to disability level (EDSS score),[24] the presence of pyramidal signs,[11] and the involvement of more than 1 functional system.[20] Wolkorte et al[36] further found that secondary progressive PwMS show more motor fatigability compared with RRMS. Seven articles reported nonsignificantly different strength-based outcomes, and 6 of these studied the upper limb (hand grip or intrinsic hand muscles), with a sustained contraction of 2 minutes[31,32] or 3 minutes[37,38] or with intermittent isometric hand grip contractions.[24,41] One article studied knee extension with a sustained contraction of 2 minutes.[30] Out of 6 studies with nonsignificant results, 4 included PwMS with RRMS or mild MS (average EDSS < 3.5). Of the latter studies, 5 using a sustained MVC did, however, report significantly different neurophysiological outcomes. Intermittent concentric maximal contractions elicited a greater decline in strength in the upper limb compared with HCs.[51] One study, using maximal concentric knee contractions, showed only a difference in total work, not for the work index.[49] One study reported different motor fatigability between mild and moderate MS, assessed with the decline in peak torque after 50 isokinetic knee extensions.[50]

For the submaximal protocols contractions, only 1 strength outcome (force variability) differentiated HCs from PwMS for the upper limb,[35] whereas no difference in decline in strength, the number of contractions, or exercise duration was observed. One submaximal foot tapping protocol did detect a difference in strength decline between PwMS and HCs.[46] Significant differences were reported for motor fatigability during walking[8,54,56,61] and after 5 minutes of wheelchair driving.[62] Three walking studies showed that PwMS with higher EDSS levels experienced more motor fatigability.[55,56,58]

The Effect of Exercise Interventions on Motor Fatigability. Although there is no study investigating responsiveness of outcomes for motor fatigability, a limited number of exercise intervention studies revealed that motor fatigability can be improved. Five studies evaluated the effects of different exercise interventions on motor fatigability (Supplementary Table 4). Studies aimed to improve motor fatigability of the lower limb.[25,48,52,53,64] Interventions included progressive resistance training,[52,53] inpatient rehabilitation followed by home exercises,[25] electrical stimulation,[64] and whole body vibration.[48] Three intervention studies showed improvements of motor fatigability based on the number of repetitions,[52] the knee flexion fatigue index,[25] and the quadriceps peak torque after a 30-s sustained contraction.[64]

Discussion

The main findings of this systematic review are that (1) most assessments of motor fatigability at the ICF body function level are based on isometric maximal contractions; (2) the assessments of motor fatigability at the ICF activity level are predominantly based on changes in performance during a functional activity; (3) the majority of the studies at both the body function level and activity level were able to discriminate between PwMS and HCs; and (4) information on the psychometrics of the applied fatigability protocols is limited.

Selecting the Right Protocol and Outcomes When Assessing Motor Fatigability

The included study protocols differed substantially on protocol components, such as the type, intensity, and duration of the fatiguing task; type of movement; and the assessed limb or body part. Because motor fatigability is task specific,[67] these components will influence the assessment of motor fatigability.

Body Function Level. Most protocols assessed isometric MVCs, which is probably explained by the physiological definition of fatigability that most of the studies adopted.[14,68] Furthermore, isometric contractions have the advantage that they can be highly standardized. In addition, participants quickly fatigue when they perform MVCs, making strength deficits easier to detect.[69] The duration of most protocols is generally fixed, which is preferable, because protocols performed until volitional exhaustion show poor reliability.[70] The maximal contraction duration was 3 minutes,[37-39] but most applied 30 s. Most studies assessed motor fatigability with strength-based measures. These are easy to interpret, but results of different contraction times are difficult to compare because other mechanisms are likely responsible for the quick decline in strength within 30 s compared with over a longer period.[34,71] Nonetheless, the reliability of fatigue indices does not seem to depend on protocol length in HCs.[72] Numerous calculation methods exist for fatigability indices.

Table 3. Summary of the Number of Studies With a Statistical Comparison Between HCs and PwMS in Which Outcomes Indicated an Increased Motor Fatigability in PwMS.

Protocols at ICF body function level		Isometric								Concentric			
		Maximal				Submaximal							
		Sustained		Intermittent		Sustained		Intermittent		Maximal		Submaximal	
Outcomes		UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL
Strength-based outcomes	Static fatigue index	4/4	4/4										
	Ratio of initial vs final strength	2/4	1/2	4/6			0/1	0/3		1/1		0/1	1/1
	Force variability							1/1					
	Fatigue index, based on work loss										0/1		
Indirect outcomes	Time to 50% MVC	2/2											
	Endurance time	1/1				1/1							
	Number of repetitions							0/2					
	Performance changes											0/1	0/1
	EMG RMS index	1/2						0/3					
Neurophysiological outcomes	Central activation change	3/4	2/2				0/1						
	Twitch force change	2/4	1/1										
	MEP amplitude	0/1						2/2					1/1
	Central conduction index	1/2		1/1									

Protocols at ICF activity level	Walking		
Outcomes	Usual Speed	Fastest Speed	Wheelchair Driving
Slope of decline velocity	1/1		
Fatigue index for walking speed	1/1	0/1	
Biomechanical variables	1/1		1/1

Abbreviations: EMG, electromyography; ICF, International Classification of Functioning, Disability and Health; LL, lower limb; MVC, maximal voluntary contraction; PwMS, persons with multiple sclerosis; UL, upper limb.

Using a ratio of the initial versus the final force level might cause problems because the force variability increases during the final stage of a sustained contraction.[73] This problem may, however, be overcome by looking at the total area under the curve after sustained contractions.[26] Studies evaluating the underlying mechanisms of motor fatigability require standardized (high-intensity) isometric contractions, often supplemented by TMS[39,42-46] or peripheral nerve stimulation[23,27,28,30-33,36,42] before and after the fatiguing task. An in-depth discussion on the underlying mechanisms of motor fatigability is provided in a recently published review.[74] Motor fatigability is most often assessed during sustained contractions; however, intermittent contractions seem more relevant for daily life. Although isokinetic protocols are sparsely used,[48-50] these might be interesting because they are even more energetically demanding.[14] One should take into account that also here, results on motor fatigability of sustained contractions cannot be interchanged with intermittent contractions because the physiological reaction in the muscle tissue is different[14] and possibly, also, the brain activation patterns.[75] Some results might indicate that intermittent contractions are less suitable to determine pathological motor fatigability because these do not differentiate PwMS from HCs.[24]

The majority of the protocols used maximal muscle contractions. Only 6 studies applied a submaximal isometric protocol.[22,29,35,43-45] One could argue that intermittent submaximal contractions more closely simulate real-world situations.[76,77] Submaximal protocols might be difficult to standardize because these might be influenced more by problems with selective motor control requiring more concentration. To evaluate changes in muscle output caused by submaximal exercises, a submaximal fatiguing exercise interrupted with brief maximal contractions might be applied[78] as has been done in a few studies.[35,46,47] Furthermore, PwMS with muscle weakness may already perform near their maximal strength during activities of daily living (ADL); thus, when asking a submaximal percentage of their strength, this might be underestimating the problem of fatigability in daily life. A further challenge to this approach relates to the higher absolute strength usually exerted by HCs. This causes reduced blood perfusion in HCs and, thus, increases the peripheral fatigue, although the proportional strength is identical, which contributes to sex-related differences in fatigability.[79] Indirect outcomes such as performance measures[47] have the advantage that they are directly related to the task. However, the interpretation is more difficult because they cannot be attributed to 1 muscle group.

Most protocols on body function level assess the upper limbs, which contrasts the fact that, clinically, motor fatigability is mostly reported in the lower limbs—for example, during walking.

Clinically, it could be hypothesized that fatigability in the lower limbs influences activities of daily living more profoundly and, thus, is reported more frequently because fatigued legs require rest by sitting down or lying. This fatigue effect might only be reported in the upper limbs after very specific tasks, such as sewing, which require continuous activation. One could further argue that investigating motor fatigability in the upper limbs is less relevant because the upper limbs are normally less impaired by the disease process.[8] The reason that most of the research is performed on the upper limbs, is probably caused by the fact that many studies included neurophysiological investigations for the mechanisms of fatigability. These investigations are technically more straightforward to perform accurately in the upper limbs than in the lower limbs because relevant muscles can more easily be accessed and stimulated. Furthermore, when investigating the lower limbs, a more profound effect of deconditioning (besides the disease effect of MS) can be expected. Until now, only 1 study compared motor fatigability in the upper limb and the lower limb,[8] stating that these are related in PwMS. This information is contrasted by a study in HCs, stating that there is no relation between hand grip fatigability and fatigability of the knee extensors.[80] In short, the generalizability of motor fatigability across upper and lower limb muscles is unknown. More can probably be learned in future studies comparing upper- and lower-limb fatigability.

Activity Level. Fatigability determined on the body function level might be more precise and has several advantages, such as the ability to determine underlying mechanisms within the same tasks (strength decline combined with neurophysiological measurements). However, the investigation at the ICF activity level might be more relevant for daily life because these activities are most often closer linked to quality of life. Most studies attempting to evaluate motor fatigability at ICF activity level have applied walking paradigms.[8,25,56,58-61] These protocols seem relevant for clinical practice, but the interpretation is complicated because outcomes based on physical performance during functional activities, such as the deceleration in walking speed, give no information on underlying causes. Observing changes in gait dynamics seems an attractive approach and has been applied during walking on a treadmill at maximal speed.[60,61] However, it is not straightforward to interpret changes in kinematics as an increase in motor fatigability (decreased neural drive) versus an increased manifestation of underlying impairments of spasticity or ataxia. To overcome this, some studies use EMG parameters as an additional indirect measure of motor fatigability. During sustained submaximal static contractions, notable changes occur as the signal amplitude (RMS) increases and shifts in the EMG spectrum toward lower frequencies take place. Both parameters are used as markers of muscle fatigue. However, EMG variables could not discriminate HCs from PwMS in several studies.[31,47] Furthermore, it has been argued that amplitude characteristics are not reliable[14,81,82] and that the use of EMG outcomes during dynamic contractions is often difficult to interpret. McLoughlin et al[54] tried to integrate the ICF body function level and the ICF activity level by assessing strength and balance before and after a 6-minute walking paradigm and showed that PwMS showed greater loss of strength and balance after 6 minutes walking than HCs.

Is Motor Fatigability Increased in MS?

Overall, the literature shows that motor fatigability is increased in PwMS. As discussed above, the ability to detect differences between HCs and PwMS seems to be related to the type of tasks (sustained or intermittent), contraction intensity (maximal or submaximal), and the limbs examined (upper or lower limb). Furthermore, it is likely that not all PwMS show abnormal motor fatigability, as reported earlier.[24,55] Strength-based outcomes were not always sufficiently sensitive to detect differences in mildly impaired PwMS, despite different neurophysiological outcomes[32]; 7 studies found no significant difference between HCs and PwMS for strength-based parameters. Maximal protocols, which could not discriminate HCs and PwMS, used a low number of repetitive hand grip contractions[24,41] or a long isometric contraction for 2 or 3 minutes,[30,31] where individuals are in the plateau phase of strength decline. Further explanations for the lack of discrimination might be the small samples, MS phenotype,[36] or disability level of the participants.[24]

Of note, none of the submaximal protocols, assessing the upper limb with strength outcomes, discriminated HCs from PwMS, whereas 1 lower limb study did show a more profound force decline after a foot tapping exercise.[46] This may again suggest a different response between upper and lower limbs, caused by earlier and more substantial impairments in the lower limbs of PwMS.[8]

Limitations in the Current Literature Review

The aim of this review was to detect the best protocol to assess and study motor fatigability. Therefore, we narrowed the literature search to included studies that specifically mentioned motor fatigue, muscle fatigue, or fatigability. This was done to avoid nonrelevant articles but might have excluded studies where motor fatigability was a secondary outcome. The quality checklist of the included studies showed that a substantial part of the included research suffered from methodological issues. Previously, Meyer et al[18] used a cutoff score of 65% for inclusion. However, if we used this value as a cutoff, only 22 studies would have been retained, leading to exclusion of several relevant protocols and outcomes.

Clinical Assessment of Motor Fatigability

In 1977, it was already stated that it was necessary to investigate muscle endurance as an additional index of paresis.[83] Later, it was stated that some PwMS do not show strength deficits acutely but experience abnormal motor fatigability over time.[37] To be able to use a protocol in a clinical setting, the protocol should be feasible, quick, easy to interpret, and reliable. Based on the current review, no single protocol can be recommended for clinical use because of the lack of comparison of protocols head to head and the lack of knowledge on psychometrics. To detect the PwMS prone to a slight increase in motor fatigability, a strenuous approach is needed by determining the change in strength during sustained MVCs. Currently, the only outcome that has documented sufficient reliability in PwMS is a fatigue index based on the area under the curve of a sustained MVC of 30 s.[8] Previously, it was stated that documenting the difference in strength before and after an exercise protocol is clinically feasible.[68] This is a feasible approach for physical exercises or daily life activities. With this approach, one should take into account that submaximal exercises might not elicit increased motor fatigability when they are executed at the participant's own relative strength. Furthermore, PwMS are likely to use a higher percentage of their maximal strength in daily life compared with HCs.[84] Unfortunately, the current clinical tools to assess muscle strength do not include standard protocols and outcomes measures for motor fatigability. Furthermore, the lack of cutoff values for this kind of protocols hinders clinical interpretation.

Recommendations for Future Research

This literature review revealed a number of limitations that need to be kept in mind when interpreting the existing studies and designing future studies. To begin with, one should clearly define the concept that is assessed.[3,7] Second, the existing psychometrics information only included limited information on the reliability of a few protocols.[8,26] Related to this, no cutoff value exists to determine if motor fatigability is pathological. Future studies should identify norm values for motor fatigability obtained from a large, well-described population-based group of HCs. Third, before collecting norm data, a consensus has to be reached on the best protocol. This is not possible at the moment because of the almost complete lack of studies comparing different protocols head to head. Fourth, future intervention studies should evaluate patients with established motor fatigability at study entry, based on well-defined cutoff values, and perform comparisons of different interventions. Some research suggests that submaximal exercises are better to target the central nervous system.[85] Because pathological motor fatigability in PwMS seems more related to central mechanisms, submaximal exercises with a high number of repetitions or a long duration might attenuate motor fatigability. There is already (limited) information on the influence on white matter structure of, for example, task-specific training in PwMS.[86] However, for the improvement of strength, high-intensity exercises are advised. It was suggested that motor fatigability can be improved by increasing the muscle mass with strength training,[87,88] which might also increase neural drive in PwMS[89] and, thus, improve motor fatigability indirectly. Fifth, there is limited information on the relation between motor fatigability in different muscle groups[8] and on the relation between motor fatigability on the different levels of the ICF. Although there seems to be a relation between motor fatigability on body function level and gait parameters,[19] there are no reports explicitly examining the relation between motor fatigability on body function level and activity level. It might be expected that motor fatigability affects functional tasks when sustained or high-intensity muscle activity is required. The clinical meaning of protocols and outcomes for motor fatigability (ie, the relation to quality of life or the participation in society) was not studied so far. It is, however, important that the influence of motor fatigability on daily functioning is elucidated because daily life functioning has a large impact on the quality of life of the patient.[90] Finally, the difference between PwMS and HCs in underlying mechanisms of motor fatigability have predominantly been studied in the upper limbs, with only 2 reports evaluating the lower limbs.

Conclusion

A variety of protocols and outcome measures are applied to study different aspects of motor fatigability in PwMS, thus challenging comparability across studies. Most protocols use maximal single-joint isometric contractions, with the advantage of high standardization. Protocols determining motor fatigability during submaximal or functional activities might, however, be more relevant for PwMS. Because of the lack of head-to-head comparisons of the different protocols and a lack of information on psychometric properties, no gold standard is currently available to determine increased motor fatigability in PwMS.

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