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Relationship Between Perceived Fatigue and Performance Fatigability in People with Multiple Sclerosis: A Systematic Review and Meta-Analysis

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Abstract

Objective—Perceived fatigue (i.e., subjective perception of reduced capacity) is one of the most common and disabling symptoms for people with multiple sclerosis (MS). Perceived fatigue may also be related to performance fatigability (i.e., decline in physical performance over time), although study findings have been inconsistent.

Objective—To locate all studies reporting the relationship between perceived fatigue and fatigability in people with MS, determine the population correlation, and examine moderating variables of the correlation size.

Methods—In accordance with PRISMA guidelines, systematic searches were completed in Medline, PsychInfo, Google Scholar, and the Cochrane Library for peer-reviewed articles published between March 1983 and August 2016. Included articles measured perceived fatigue and performance fatigability in people with MS and provided a correlation between measures. Moderator variables expected to influence the relationship were also coded. Searches located 19 studies of 848 people with MS and a random-effects model was used to pool correlations.

Results—The mean correlation between fatigue and fatigability was positive, “medium” in magnitude, and statistically significant, $r = 0.31$ (95% CI = 0.21, 0.42), $p < .001$. Despite moderate between-study heterogeneity ($I^2 = 46\%$) no statistically significant moderators were found, perhaps due to the small number of studies per moderator category.

Conclusion—There is a significant relationship between perceived fatigue and fatigability in MS, such that people reporting elevated fatigue also are highly fatigable. The size of the relationship is not large enough to suggest fatigue and fatigability are the same construct, and both should continue to be assessed independently.

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Conflict of Interest

The authors declare no conflicts of interest.

Keywords

contraction; energy; exercise; perception; symptom; tired

Introduction

Fatigue is a frequent and debilitating symptom among people with multiple sclerosis (MS). Around 80% of people with MS report experiencing fatigue, making it the most common symptom (1–4), and nearly half report that fatigue is their most disabling symptom (5). Despite the high prevalence and consequences of fatigue in MS, the term fatigue is used inconsistently (6) and over 250 different instruments had been used to measure fatigue (7). Researchers have called for a need to better understand MS fatigue in narrative reviews (5, 8–11), but proposed measurement models have not been empirically tested.

Fatigue that is described by people with MS to clinicians may have both a mood and motor component (12), or operationalized as perceived fatigue and performance fatigability (8, 13). Perceived fatigue has been defined as a person's self-reported "subjective sensations" (8) of reduced capacity, and is measured using questionnaires (5, 13), such as the Fatigue Severity Scale (14) and Fatigue Impact Scale (15) or Modified Fatigue Impact Scale (16). People with MS may be asked to rate their quantity of physical and/or mental fatigue, or the impact that fatigue has on daily function (13). In contrast, fatigability is the decline in an objective measure of physical performance (requiring large muscle groups) over a discrete period of time, and is measured using a variety of physical tasks (6). Examples include a sustained muscle contraction during which the decline in force is quantified, or a timed walking test in which change in velocity is measured over time (8, 13). Although cognitive fatigue is also of concern in MS (9, 17), the focus here is on perceived fatigue and physical performance fatigability.

What remains unclear is whether perceived fatigue and fatigability are linked in MS. A 2013 review by Kluger and colleagues proposed a fatigue taxonomy, whereby perceived fatigue and performance fatigability are influenced by global fatigue, and that "perceptions of fatigue and performance fatigability have the potential to influence each other" (8). This relationship has frequently been tested in the literature and some studies have reported a significant correlation (12, 18–20), while others have not (21–24). However, studies have used a variety of perceived fatigue and performance fatigability measures, sometimes with small numbers of participants. Such issues may be mitigated with a meta-analysis, which may offer better evidence for or against this taxonomy proposed by Kluger and colleagues. Finding a strong relationship between perceived fatigue and fatigability could simplify MS fatigue measurement, potentially allowing researchers to use objective performance fatigability measures to estimate overall fatigue. In addition, a strong relationship would suggest that treating either perceived fatigue or performance fatigability could confer carry-over effects. On the other hand, a null or small relationship between perceived fatigue and fatigability further illustrates that a distinction between these constructs in research and clinical practice is necessary for scientific advancement and precise treatment.

The purpose of this systematic review and meta-analysis is to determine the association between perceived fatigue and fatigability in people with MS. A secondary purpose is to determine if study or participant features moderate the size of the relationship between fatigue and fatigability in the literature.

Methods

The present systematic review and meta-analysis was performed based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (25).

Data Searches

Google Scholar was used to conduct a search for articles published between March 1983 [release of the Poser criteria (26)] and August 2016. A Google Scholar “Advanced Search” was completed using all of the words “fatigue”, the exact phrase “multiple sclerosis”, and at least one of the following: “contraction”, “fatigability”, “force,” “exercise, or “motor fatigue”. In the Google Scholar search, all terms were separated by commas and entered with quotation marks around them. Similar searches were completed in Medline, PsychInfo, and the Cochrane Library (Supplements 1–3). The references of articles meeting the inclusion criteria were screened manually for other relevant literature (other sources). Searches and text reviews were completed by the first and second author, and were assisted by a systematic review/clinical librarian. The following criteria were required for inclusion: (i) the article reported data from an original study, rather than a review article; (ii) the study included people diagnosed with MS; (iii) perceived fatigue was measured; (iv) a measure of fatigability was included; and (v) data were sufficient for meta-analysis and presented in a peer-reviewed article written in English. Measures of perceived fatigue included visual analog scales (VAS) or questionnaires with evidence for reliability and validity that asked the participant to quantify their subjective intensity, or experience, of fatigue (6, 27). Measures of fatigability were defined as physical tasks in which a participant’s change in physical performance over time was recorded (6, 8). If there was debate whether a study had used a task meeting our *a priori* definition of fatigability, it was discussed with a multiple sclerosis fatigability researcher otherwise not involved in the systematic review. The study selection process is shown in a flow diagram (Figure 1).

Study Characteristics

The systematic review process resulted in 15 studies that met the inclusion criteria and were subsequently included in the meta-analysis. An additional 13 studies were located where authors indicated they measured perceived fatigue and fatigability but did not provide the correlation (but the study otherwise met the inclusion criteria). In these cases, the corresponding author of each paper was contacted via email with a request for the correlation or sufficient data to calculate it, and four authors (31%) responded. As a result, 19 studies were included in the meta-analysis, which provided data from a total of 848 persons with MS (median = 32). Descriptive study characteristics are presented in Table 1.

Moderator Selection and Coding

Prior to data extraction from studies, variables were chosen that could theoretically moderate the size of the correlation between perceived fatigue and fatigability. Selected moderators were related to participants (age, EDSS, MS type, sex) and studies themselves (fatigability measure, perceived fatigue measure, publication year).

Participant Features

Fatigue in MS has previously been linked to age, disability, MS type, and sex (28, 29), with some suggestion that disability is a driving factor (30). For this reason, data were extracted from articles to consider disability, measured using the extended disability status scale (EDSS)(31), and MS type as moderators (age and sex could not be included due to insufficient reporting in the articles). Mean EDSS was either extracted directly or estimated using established formulae (32) if only the median EDSS was provided. One study did not report EDSS (19). MS type was categorically coded as either relapsing-remitting only, relapsing-remitting and progressive (both primary and secondary), or not reported. One study included only secondary-progressive MS (33), and therefore was not coded for MS type since it was the only study in this category.

Study Features

There is no current “gold standard” measure of fatigue in MS, and some perceived measures correlate poorly with each other (34). The Fatigue Severity Scale (FSS)(14) and Modified Fatigue Impact Scale (MFIS)(16) were most often used, and sometimes both within the same study (19, 35), to measure perceived fatigue. Since these correlations were nested within the same studies, a sensitivity analysis (i.e., two independent meta-analyses) was conducted to determine if the correlations derived using the FSS and MFIS systematically differed prior to further analysis. Findings of the sensitivity analysis are reported in the *results* section.

The causes of fatigability also appear to be complex (6, 8, 36) and measurement of such in MS research has been varied. For example, tasks have included force changes of single finger contractions (19), repeated quadriceps contractions (24) and the 6-minute walk (37). Fatigability tasks were coded for moderation analyses in two ways to reflect this variability. First, tasks were coded as either a walking or machine contraction task (i.e., contraction type). Second, tasks were coded as either predominately upper- or lower-body (i.e., muscle group) since research has indicated that people with MS have similar upper-body strength to healthy control participants (38). Finally, publication year was considered as a moderator because changes in diagnostic criteria and tools over time may influence the heterogeneity of participants in study samples.

Statistical Analysis

Because the correlation coefficient is already standardized and unitless, it can be used as an effect size (i.e., r) in raw form (39). Thus, the first and second author independently derived 51 effects from the 15 studies obtained via systematic review by locating r directly in text or tables. To test the reliability of the effect size extractions, a two-way (effects $\times$ raters) intraclass correlation for absolute agreement was conducted. The result indicated perfect

agreement between authors, $ICC(2, 51) = 1.0$. Prior to further analysis, effects (if necessary) were reversed so that all positive value effects would indicate a positive relationship between perceived fatigue and fatigability.

IBM SPSS version 24 was used with macros (40) to calculate the mean effect (r) and the 95% confidence interval (CI) with a random effects model (39). All correlations were transformed using Fisher's Z transform prior to analysis and then back-transformed for interpretation (39, 41). The magnitude (i.e., small = .10, medium = .25, large = .40) of r was interpreted based on convention (42). Positive effect sizes here indicate a positive relationship between perceived fatigue and fatigability, while negative effect sizes indicate a negative (i.e., inverse) relationship. Heterogeneity was tested using I^2 (43), and publication bias was examined using a funnel plot and Egger's test (44). N_+ was also calculated to determine the number of additional correlation coefficients equal to zero that would be necessary to nullify the overall relationship quantified here (45). The moderator analysis was conducted using macros (40) in SPSS to test if study or participant features influenced the size of the effect.

Results

Sensitivity Analysis

The mean effect for studies using the FSS ($k = 10$) was $r = 0.27$ (95% CI = 0.13, 0.41) and MFIS ($k = 8$) was $r = 0.19$ (95% CI = -0.11, 0.48). Although other perceived fatigue measures were sometimes used (e.g., Fatigue Impact Scale, Multidimensional Fatigue Inventory, VAS) none were used more than twice across the 19 studies, which precluded any preliminary sensitivity analysis. Although some studies (23, 46, 47) also included measures of acute perceived fatigue, these values were dropped due to the low number of effects ($k = 3$). Because the sensitivity analysis found that the mean effect did not differ depending on the perceived fatigue measure, effects were averaged together when multiple perceived fatigue measures were used within the same study. If subscale (e.g., MFIS-physical) means were reported in addition to an overall measure (e.g., MFIS-total) mean, the subscale correlation was not included in the average calculation. In other situations where multiple effects could be derived from the same study, effects were averaged to yield a single correlation for each study.

Primary Results

Nearly ninety-five percent (18/19) of the included studies reported a positive relationship between perceived fatigue and fatigability. Each effect size and the corresponding 95% CI is shown in a forest plot (Figure 2). The mean effect size was $r = 0.31$ (95% CI = 0.21, 0.42), $p < .001$. There was moderate heterogeneity between studies, $I^2 = 46\%$. A funnel plot (Figure 3) of the effects was asymmetrical. Visual inspection suggests that effects with smaller standard errors were more likely to be large and positive than negative, which may suggest publication bias. Egger's test for bias was also statistically significant, $F(1, 18) = 5.29$, $p = .034$. The number of additional correlations that would be necessary to nullify the result (N_+) was 323.

Moderator Analysis

The participants ranged in age from 12 to 65 years, and had an average EDSS of 3.6. Additional results from the moderator analysis are provided in Table 2. Participant EDSS did not moderate the association ($B = -.029$, $SE = .045$, $z = -.635$, $p = 0.524$) nor did MS type ($Q_B(2,16) = 1.261$, $p = .532$). The fatigability task features also did not moderate the association, as the contraction type ($Q_B(1,17) = 2.551$, $p = .110$) and muscle group ($Q_B(1,17) = 0.266$, $p = .871$) were not statistically significant. Finally, publication year did not significantly moderate the association ($B = .009$, $SE = .008$, $z = 1.144$, $p = 0.252$).

Discussion

Among people with MS, perceived fatigue and fatigability are significantly correlated and the size of the relationship is considered “medium” with a correlation of 0.31. Although narrative reviews had previously suggested that perceived fatigue and fatigability are linked in MS (5, 8), the results of experimental studies were mixed (12, 23). While the findings here clarify the existence of a relationship, the size of the correlation (and corresponding 95% CI) also suggests that measures of perceived fatigue and fatigability are not measuring the same underlying construct. A correlation of $> .60$ has classically been suggested as adequately large to argue for concurrent validity between two measures of the same construct (48). Investigators and clinicians should therefore include measures of both perceived fatigue and fatigability in their work and tentatively presume that each has a differing underlying mechanism.

Although there were small differences in the correlations between different levels of moderator variables (see Table 2), no moderator variable was statistically significant. This was unexpected given the moderate heterogeneity between studies, as evidenced by the I^2 value. However, the 95% CI around point estimates were wide, and the power of I^2 may be limited with a low number of studies, low average sample size, and low between-study variance (49). MS itself is also heterogeneous (50), and this may have contributed to sampling variability beyond what is normally expected in meta-analysis. Co-morbidities such as depression (9, 51), cognitive impairment (17, 52), and sleep disorders (53) may have influenced the relationship as well, but were not consistently reported in sufficient detail to be considered as effect moderators. Two included studies (12, 19) did find that accounting for depression strengthened the relationship between perceived fatigue and fatigability, suggesting depression should be considered as a covariate in future research. Additional studies need to be conducted to more accurately determine sources of heterogeneity between studies.

One factor that may have possibly influenced the size of the estimated correlation is the apparent conflation of fatigability in some perceived fatigue measures used in MS research. In their key review, Kluger and colleagues note that, “perceptions of fatigue and fatigability are not only distinct but also potentially independent” (8). But, the FSS and MFIS (accounting for 84%, or 16/19 of the perceived fatigue measures used in the included studies) both have items that appear to query fatigability. The FSS includes items such as “exercise brings on my fatigue”, “fatigue interferes with my physical functioning”, and “my fatigue prevents sustained physical functioning”. The MFIS asks if “because of my fatigue”

participants “have trouble maintaining physical effort for long periods”, “muscles feel much weaker than they should” and if participants are “less able to complete tasks that require physical effort”. On the other hand, including questions that target physical fatigue has strengthened the content validity evidence for these measures (54). While asking about the consequences or impact of fatigue may have influenced the reported correlation, this is uncertain given that so few studies included other fatigue measures.

Only three studies (23, 46, 47) measured perceived fatigue “right now”, and this low number prevented timing of fatigue assessment from being considered as a moderator. Perceived fatigue may be variable both within (55) and between (56) days in people with MS. Of the most common measures from studies included in this meta-analysis, the MFIS asks “how much of a problem fatigue has caused them during the past month, including the day of testing” (15). The FSS is not anchored by a time period and instead asks for “agreement” with items regarding fatigue (14), although it is sometimes “based on the previous week” (57). Circadian variation in physical performance (58) may influence the fatigability tasks. The correlations obtained in the included studies were likely influenced by including “chronic” perceived fatigue measures and fatigability measures based on “right now” performance. Future studies will likely obtain a more precise estimate of the relationship between perceived fatigue and fatigability by using “right now” perceived fatigue measures, such as VAS used in some studies (23, 46).

Several limitations should be considered when interpreting results of this systematic review and meta-analysis. There was some indication of publication bias based on funnel plot inspection and Egger’s test. This could have occurred if authors did not publish or report small, statistically non-significant, or negative relationships between perceived fatigue and fatigability. The systematic review located 13 studies that had collected data to compute a correlation but did not report it, and only four authors responded to requests for data. Therefore, the true relationship between perceived fatigue and fatigability could be smaller than that reported here, although future studies will need to confirm this possibility.

The analysis was unable to identify significant effect moderators despite heterogeneity that existed between studies. It is possible this occurred because the hypothesized mechanisms of both perceived fatigue and fatigability are uncertain, although numerous suggestions have been presented (9, 11, 12, 30). Knowledge of a mechanism could drive study design and result in less between-study heterogeneity, although such varied decisions cannot necessarily be captured by a moderator analysis. For example, one study reported only obtaining a statistically significant relationship after controlling for maximum force (12), although not all studies accounted for maximum force. Although the purpose of the systematic review and meta-analysis was not to explore perceived fatigue and fatigability mechanisms, a better understanding of this area could lead to improved future study design and analysis. It has also been suggested that fatigability may drive perceived fatigue in some people with MS but not others (59), potentially further adding heterogeneity that cannot be explained by a moderator analysis. In sum, studies used many different fatigability tasks (see table 1) that may have varied on multiple parameters. Coming to agreement on one or several fatigability tasks, in a process similar to that of the Multiple Sclerosis Outcome Assessments Consortium (60) for example, could reduce variability in future research.

An important caveat is that these findings apply only to people with MS, but the framework of this systematic review and meta-analysis could benefit the study of other diseases. For example, exploratory factor analysis of symptom questionnaires related to post-exertional malaise (PEM) in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) found that PEM is linked to both generalized fatigue and muscle-specific fatigue (61). Although not measured objectively, muscle-specific fatigue may be related to fatigability and could be studied as such in people with ME/CFS to learn more about PEM.

In conclusion, this meta-analysis of 19 studies found a statistically significant and “medium” relationship between perceived fatigue and fatigability in people with MS. While others have suggested that perceived fatigue and fatigability may not be closely related (62), this meta-analysis strengthens an inconsistent body of literature and provides directions for future research. The findings also add empirical support for the fatigue and fatigability model proposed by Kluger and colleagues, at least in the case of MS. In practice, clinicians should measure both perceived fatigue and fatigability, and cannot safely assume that performance on physical tasks is reflective of perceived fatigue. The presenting symptom may also influence treatment choice as (for example) modafinil is used for perceived fatigue (63), and preliminary reports suggest dalfampridine may improve fatigability (64). Independent measurement and treatment of perceived fatigue and fatigability would then be expected to improve understanding of the relationship between the constructs and their mechanisms, further improving treatment options for people with MS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil.* 1984; 65(3):135–8. [PubMed: 6703889]
2. Wood B, van der Mei IA, Ponsonby AL, Pittas F, Quinn S, Dwyer T, et al. Prevalence and concurrence of anxiety, depression and fatigue over time in multiple sclerosis. *Multiple sclerosis.* 2013; 19(2):217–24. DOI: 10.1177/1352458512450351 [PubMed: 22729988]
3. Vercoulen JHMM, Hommes OR, Swanink CMA, Jongen PJH, Fennis JFM, Galama JMD, et al. The measurement of fatigue in patients with multiple sclerosis: a multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. *Archives of Neurology.* 1996; 53:642–9. [PubMed: 8929171]
4. Branas P, Jordan R, Fry-Smith A, Burls A, Hyde C. Treatments for fatigue in multiple sclerosis: a rapid and systematic review. *Health Technology Assessment.* 2000; 4(27)
5. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Multiple sclerosis.* 2003; 9:219–27. [PubMed: 12814166]
6. Enoka RM, Duchateau J. Translating Fatigue to Human Performance. *Med Sci Sports Exerc.* 2016; doi: 10.1249/MSS.0000000000000929

7. Hjollund NH, Andersen JH, Bech P. Assessment of fatigue in chronic disease: a bibliographic study of fatigue measurement scales. *Health and quality of life outcomes*. 2007; 5:12.doi: 10.1186/1477-7525-5-12 [PubMed: 17326844]
8. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy. *Neurology*. 2013; 80:409–16. [PubMed: 23339207]
9. Kos D, Kerckhofs E, Nagels G, D'Hooghe MB, Ilsbrouckx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabilitation and neural repair*. 2008; 22(1):91–100. DOI: 10.1177/1545968306298934 [PubMed: 17409388]
10. Bol Y, Duits AA, Hupperts RM, Vlaeyen JW, Verhey FR. The psychology of fatigue in patients with multiple sclerosis: a review. *Journal of psychosomatic research*. 2009; 66(1):3–11. DOI: 10.1016/j.jpsychores.2008.05.003 [PubMed: 19073287]
11. Vucic S, Burke D, Kiernan MC. Fatigue in multiple sclerosis: mechanisms and management. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2010; 121(6):809–17. DOI: 10.1016/j.clinph.2009.12.013 [PubMed: 20100665]
12. Steens A, de Vries A, Hemmen J, Heersema T, Heerings M, Maurits N, et al. Fatigue perceived by multiple sclerosis patients is associated with muscle fatigue. *Neurorehabilitation and neural repair*. 2012; 26(1):48–57. DOI: 10.1177/1545968311416991 [PubMed: 21856990]
13. Krupp LB. Fatigue in multiple sclerosis: definition, pathophysiology and treatment. *CNS Drugs*. 2003; 17(4):225–34. [PubMed: 12665396]
14. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*. 1989; 46:1121–3. [PubMed: 2803071]
15. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: Initial validation of the fatigue impact scale. *Clinical Infectious Diseases*. 1994; 18(Supplement 1):S79–S83. [PubMed: 8148458]
16. Guidelines MSCfCP. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. 1998
17. DeLuca J, Genova HM, Hillary FG, Wylie G. Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI. *Journal of the neurological sciences*. 2008; 270(1-2):28–39. DOI: 10.1016/j.jns.2008.01.018 [PubMed: 18336838]
18. Greim B, Benecke R, Zetl UK. Qualitative and quantitative assessment of fatigue in multiple sclerosis (MS). *J Neurol*. 2007; 254(Suppl 2):II58–64. DOI: 10.1007/s00415-007-2014-5 [PubMed: 17503131]
19. Wolkorte R, Heersema DJ, Zijdewind I. Muscle Fatigability During a Sustained Index Finger Abduction and Depression Scores Are Associated With Perceived Fatigue in Patients With Relapsing-Remitting Multiple Sclerosis. *Neurorehabilitation and neural repair*. 2015; 29(8):796–802. DOI: 10.1177/1545968314567151 [PubMed: 25605633]
20. Iriarte J, de Castro P. Correlation between symptom fatigue and muscular fatigue in multiple sclerosis. *European Journal of Neurology*. 1998; 5:579–85. [PubMed: 10210893]
21. Sharma KR, Kent-Braun JA, Mynhier MA, Weiner MW, Miller RG. Evidence of an abnormal intramuscular component of fatigue in multiple sclerosis. *Muscle & Nerve*. 1995; 18:1403–11. [PubMed: 7477063]
22. Surakka J, Romberg A, Ruutiainen J, Virtanen A, Aunola S, Maentaka K. Assessment of muscle strength and motor fatigue with a knee dynamometer in subjects with multiple sclerosis: a new fatigue index. *Clinical rehabilitation*. 2004; 18:652–9. [PubMed: 15473117]
23. McLoughlin JV, Barr CJ, Crotty M, Sturnieks DL, Lord SR. Six minutes of walking leads to reduced lower limb strength and increased postural sway in people with Multiple Sclerosis. *NeuroRehabilitation*. 2014; 35(3):503–8. DOI: 10.3233/NRE-141143 [PubMed: 25248444]
24. Andreasen AK, Jakobsen J, Petersen T, Andersen H. Fatigued patients with multiple sclerosis have impaired central muscle activation. *Multiple sclerosis*. 2009; 15(7):818–27. DOI: 10.1177/1352458509105383 [PubMed: 19465444]
25. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care

- interventions: Explanation and elaboration. *Annals of Internal Medicine*. 2009; 151(4):W-65–W-94. [PubMed: 19622512]
26. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology*. 1983; 13(3): 227–31. [PubMed: 6847134]
 27. O'Connor PJ. Evaluation of four highly cited energy and fatigue mood measures. *Journal of psychosomatic research*. 2004; 57(5):435–41. DOI: 10.1016/j.jpsychores.2003.12.006 [PubMed: 15581646]
 28. Colosimo C, Millefiorini E, Grasso MG, Vinci F, Fiorelli M, Koudriavtseva T, et al. Fatigue in MS is associated with specific clinical features. *Acta Neurol Scand*. 1995; 92(5):353–5. [PubMed: 8610485]
 29. Ghajarzadeh M, Jalilian R, Eskandari G, Sahraian MA, Azimi A, Mohammadifar M. Fatigue in multiple sclerosis: relationship with disease duration, physical disability, disease pattern, age and sex. *Acta neurologica Belgica*. 2013; 113(4):411–4. DOI: 10.1007/s13760-013-0198-2 [PubMed: 23616230]
 30. Kroencke DC, Lynch SG, Denney DR. Fatigue in multiple sclerosis: relationship to depression, disability, and disease pattern. *Multiple sclerosis*. 2000; 6:131–6. [PubMed: 10773860]
 31. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*. 1983; 33(11):1444–52. [PubMed: 6685237]
 32. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005; 5:13.doi: 10.1186/1471-2288-5-13 [PubMed: 15840177]
 33. Skurvydas A, Brazaitis M, Andrejeva J, Mickeviciene D, Streckis V. The effect of multiple sclerosis and gender on central and peripheral fatigue during 2-min MVC. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2011; 122(4):767–76. DOI: 10.1016/j.clinph.2010.10.005 [PubMed: 21036661]
 34. Flachenecker P, Kumpfel T, Kallmann B, Gottschalk M, Grauer O, Rieckmann P, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Multiple sclerosis*. 2002; 8:523–6. [PubMed: 12474995]
 35. Motta C, Palermo E, Studer V, Germanotta M, Germani G, Centonze D, et al. Disability and Fatigue Can Be Objectively Measured in Multiple Sclerosis. *PLoS One*. 2016; 11(2):e0148997.doi: 10.1371/journal.pone.0148997 [PubMed: 26863109]
 36. Gandeiva SC. Spinal and supraspinal factors in human muscle fatigue. *Physiological Reviews*. 2001; 81(4):1725–89. [PubMed: 11581501]
 37. Engelhard MM, Dandu SR, Patek SD, Lach JC, Goldman MD. Quantifying six-minute walk induced gait deterioration with inertial sensors in multiple sclerosis subjects. *Gait & posture*. 2016; 49:340–5. DOI: 10.1016/j.gaitpost.2016.07.184 [PubMed: 27479220]
 38. Schwid SR, Thornton CA, Pandya S, Manzur KL, Sanjak M, Petrie MD, et al. Quantitative assessment of motor fatigue and strength in MS. *Neurology*. 1999; 53:743–50. [PubMed: 10489035]
 39. Lipsey, MW., Wilson, DB. *Practical meta-analysis*. Thousand Oaks, CA: SAGE Publications; 2001.
 40. Wilson, DB. *Meta-analysis macros for SAS, SPSS, and Stata*. <http://mason.gmu.edu/~dwilsonb/ma.html>2006
 41. Hedges, LV., Olkin, I. *Statistical methods for meta-analysis*. New York: Academic Press; 1985.
 42. Cohen J. A power primer. *Psychological bulletin*. 1992; 112(1):155–9. [PubMed: 19565683]
 43. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *British Medical Journal*. 2003; 327(6):557–60. [PubMed: 12958120]
 44. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal*. 1997; 315:629–34. [PubMed: 9310563]
 45. Rosenberg MS. The file-drawer problem revisited: A general weighted method for calculating fail-safe numbers in meta-analysis. *Evolution*. 2005; 59(2):464–8. [PubMed: 15807430]
 46. Karpatkin H, Cohen ET, Rzetelny A, Parrott JS, Breismeister B, Hartman R, et al. Effects of Intermittent Versus Continuous Walking on Distance Walked and Fatigue in Persons With Multiple

- Sclerosis: A Randomized Crossover Trial. *Journal of neurologic physical therapy : JNPT*. 2015; 39(3):172–8. DOI: 10.1097/NPT.0000000000000091 [PubMed: 26050076]
47. Severijns D, Lemmens M, Thoelen R, Feys P. Motor fatigability after low-intensity hand grip exercises in persons with multiple sclerosis. *Multiple Sclerosis and Related Disorders*. 2016; 10:7–13. DOI: 10.1016/j.msard.2016.08.007 [PubMed: 27919502]
 48. Cronbach LJ, Meehl PE. Construct validity in psychological tests. *Psychological bulletin*. 1955; 52(4):281–302. [PubMed: 13245896]
 49. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta analysis: Q statistic or I2 index? *Psychol Methods*. 2006; 11(2):193–206. [PubMed: 16784338]
 50. Lucchinetti CF, Bruck W, Rodriguez M, Lassmann H. Distinct patterns of multiple sclerosis pathology indicates heterogeneity of pathogenesis. *Brain Pathology*. 1996; 6:259–74. [PubMed: 8864283]
 51. Flensner G, Ek AC, Landtblom AM, Soderhamn O. Fatigue in relation to perceived health: people with multiple sclerosis compared with people in the general population. *Scand J Caring Sci*. 2008; 22(3):391–400. DOI: 10.1111/j.1471-6712.2007.00542.x [PubMed: 18840223]
 52. Flensner G, Ek A-C, Söderhamn O. Lived experience of MS-related fatigue—a phenomenological interview study. *International Journal of Nursing Studies*. 2003; 40(7):707–17. DOI: 10.1016/s0020-7489(03)00010-5 [PubMed: 12965162]
 53. Veauthier C, Paul F. Sleep disorders in multiple sclerosis and their relationship to fatigue. *Sleep medicine*. 2014; 15(1):5–14. DOI: 10.1016/j.sleep.2013.08.791 [PubMed: 24360534]
 54. Amtmann D, Bamer AM, Noonan V, Lang N, Kim J, Cook KF. Comparison of the psychometric properties of two fatigue scales in multiple sclerosis. *Rehabilitation psychology*. 2012; 57(2):159–66. DOI: 10.1037/a0027890 [PubMed: 22686554]
 55. Morris ME, Cantwell C, Vowels L, Dodd K. Changes in gait and fatigue from morning to afternoon in people with multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry*. 2002; 72:361–5.
 56. Stringer EA, Baker KS, Carroll IR, Montoya JG, Chu L, Maecker HT, et al. Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: evidence of inflammatory pathology. *Journal of Translational Medicine*. 2013; 11(93):1–11. [PubMed: 23281771]
 57. Learmonth YC, Dlugonski D, Pilutti LA, Sandroff BM, Klaren R, Motl RW. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. *Journal of the neurological sciences*. 2013; 331(1-2):102–7. DOI: 10.1016/j.jns.2013.05.023 [PubMed: 23791482]
 58. Carrier J, Monk TH. Circadian Rhythms of Performance: New Trends. *Chronobiology International*. 2009; 17(6):719–32. DOI: 10.1081/cbi-100102108
 59. Iriarte J, Subira ML, de Castro P. Modalities of fatigue in multiple sclerosis: Correlation with clinical and biological factors. *Multiple sclerosis*. 2000; 6:124–30. [PubMed: 10773859]
 60. Rudick RA, Larocca N, Hudson LD, Msoac. Multiple Sclerosis Outcome Assessments Consortium: Genesis and initial project plan. *Multiple sclerosis*. 2014; 20(1):12–7. DOI: 10.1177/1352458513503392 [PubMed: 24057430]
 61. McManimen SL, Sunnquist ML, Jason LA. Deconstructing post-exertional malaise: An exploratory factor analysis. *Journal of health psychology*. 2016; doi: 10.1177/1359105316664139
 62. Dobkin BH. Fatigue versus activity-dependent fatigability in patients with central or peripheral motor impairments. *Neurorehabilitation and neural repair*. 2008; 22(2):105–10. DOI: 10.1177/1545968308315046 [PubMed: 18285599]
 63. Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2002; 72:179–83.
 64. Espejo C, Montalban X. Dalfampridine in multiple sclerosis: from symptomatic treatment to immunomodulation. *Clinical immunology*. 2012; 142(1):84–92. DOI: 10.1016/j.clim.2011.06.004 [PubMed: 21742559]

Figure 1.
Study selection flow diagram.

Figure 2.

Forest plot of effect sizes. Negative values indicate an inverse relationship between perceived fatigue and fatigability, while positive values indicate a direct relationship. The author name on the left indicates the corresponding study with the corresponding correlation and 95% confidence interval across on the right. The dot pictorially represents the correlation, the size of the dot indicates weight, and the horizontal line shows the confidence interval. The dashed line indicates the mean correlation.

Figure 3. Funnel plot of effect sizes. Each correlation is on the x-axis and standard error is on the y-axis. In the absence of publication bias a funnel shape is created by the spread of effect sizes.

Table 1

Characteristics of Included Studies

Lead author (year)	n	MS Type	Mean EDSS	Perceived Fatigue Measure	Fatigability Measure
Allart (2015)	109	RR, SP, PP	5.75	FSS & VAS	2 min walk (calculated index)
Andreasen (2009)	55	RR	2.48	FSS & MFIS-20	Repeated MVCs using right quadriceps
Burschka (2012)	37	RR, SP	3.09	Wuerzbürger Fatigue Inventory	6 min walk, 12 min walk
Englehard (2016)	89	–	3.00	MFIS-total	6 min walk (warp)
Greim (2007)	79	RR	2.51	MFIS-total	Successive hand dynamometer MVCs
Iriarte (1998)	50	–	2.20	FSS & Fatigue Descriptive Scale	Successive hand dynamometer MVCs
Karparkin (2015)	27	RR, SP, PP	3.75	FSS	6 min walk
McLoughlin (2014)	34	–	4.01	MFIS-total	in knee extension & ankle dorsiflexion strength after 6 min walk
Motta (2016)	80	RR, SP	3.30	FSS & MFIS	Gait variability index
Severijns (2015)	32	RR, SP, PP	5.45	VAS	30s isometric shoulder contraction
Severijns (2015)	30	RR, SP, PP	4.51	MFIS	Successive hand dynamometer MVCs
Severijns (2016)	18	RR, SP, PP	4.74	MFIS-total	Intermittent hand dynamometer MVCs
Sharma (1995)	28	RR, progressive	5.10	FSS	Foot dorsiflexion MVCs
Skurvydas (2011)	18	SP	3.45	FSS	Knee extensor MVC (calculated index)
Steens (2012)	20	RR	2.50	FSS	Successive MVCs with first dorsal interosseus muscle
Surakka (2004)	28	RR, SP, PP	2.10	FSS	Isometric torque of knee flexors and extensors
White (2000)	6	–	3.10	Fatigue Impact Scale	Timed 25 ft walk before and after hot exercise
Wolkorte (2015)	83	RR	–	FSS & MFIS-physical	Index Finger abduction MVC
Wolkorte (2016)	25	RR, SP	3.93	MFIS-physical	Successive MVCs of right index finger (dorsal interosseus muscle)

Note. FSS = Fatigue Severity Scale, MFI = Multidimensional Fatigue Inventory, MFIS = Modified Fatigue Impact Scale, MVC = maximum voluntary contraction, n = study sample size, PP = primary progressive, RR = relapsing-remitting, SP = secondary progressive, VAS = visual analog scale.

Table 2

Results for Moderator Variables

Effect Moderator	Number of Effects	Effect Size <i>d</i> (95% CI)	<i>P</i> Value
Participant Characteristics			
MS Type			
RR only	4	.324 (.214 to .485)	.532
RR + progressive (PP, SP)	10	.349 (.214 to .485)	
Not reported	3	.203 (−.014 to .421)	
Study Characteristics			
Contraction Type			
Machine contraction	13	.254 (.135 to .373)	.110
Walking	5	.417 (.256 to .579)	
Muscle Group			
Upper-body task	8	.301 (.148 to .454)	.871
Lower-body task	10	.318 (.188 to .448)	

^{a, b} moderator levels with a different superscript differ significantly. The *p* value is for q-between. PP = primary progressive, RR = relapsing-remitting, SP = secondary progressive.