Journal of Psychosomatic Research 100 (2017) 1–7

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Review article

Relationship between perceived fatigue and performance fatigability in people with multiple sclerosis: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Contraction
Energy
Exercise
Perception
Symptom
Tired

ABSTRACT

Background: 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), $p < 0.001$. 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.

1. 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

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http://dx.doi.org/10.1016/j.jpsychores.2017.06.017
Received 18 February 2017; Received in revised form 23 June 2017; Accepted 23 June 2017

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.

2. 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].

2.1. 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 (Fig. 1).

2.2. 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.

2.3. 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).

2.3.1. 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.

2.3.2. 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.

2.4. 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 × raters) intraclass correlation for absolute agreement was conducted. The result indicated perfect agreement between authors,