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Untangling Perception of Fatigue and Fatigability: First Steps

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Abstract

Many terms have been used to distinguish fatigue caused by neuroinflammation and/or neurological damage from fatigue due to disability or side effects of medication (sometimes termed primary vs. secondary or central vs. peripheral fatigue). More recently a unified taxonomy has been proposed to distinguish between perception of fatigue and fatigability and for both physical and mental fatigue. The objective of this study was to estimate the extent to which perception of physical fatigue and perception of mental fatigue correlate with performance on tests that could serve as proxy measures for fatigability. The hypothesis was that perception of physical fatigue would correlate more highly with these proxy tests of physical fatigability than perception of mental fatigue. Data from 189 people with MS were available from a cross sectional study. A perception of physical fatigue latent variable was identified from 5 items that fit a unidimensional and hierarchical measurement model (Rasch model). A single indicator was found to best reflect perception of mental fatigue. Proxy measures for physical fatigability were the Six- Minute Walk Test (6MWT), the slope of the line linking time and oxygen consumption (VO_2 slope) and the stages achieved during the step-test of the Modified Canadian Aerobic Fitness Test (mCAFT). The correlations supported the original hypothesis. Physical fatigability correlated with perception of physical fatigue more than with perception of mental fatigue. The information can be used to untangle perception of fatigue and fatigability which will lead to better measurement of the fatigue construct, a prerequisite for developing effective interventions.

Keywords: Perception of fatigue; Fatigability; Physical capacity; Multiple Sclerosis; Six-Minute Walk Test; VO_2 peak

Abbreviations

CIS: Clinically Isolated Syndrome; CNS: Central Nervous System; EDSS: Expanded Disability Status Scale; FAMS: Functional Assessment of Multiple Sclerosis Quality of Life Instrument; FKS: Fatigue Index Kliniken Schmieder; MFIS: Modified Fatigue Impact Scale; FSS: Fatigue Severity Scale; mCAFT: Modified Canadian Aerobic Fitness Test; MFIS: Multidimensional Fatigue Inventory; MS: Multiple Sclerosis; 6MWT: Six-Minute Walk Test; PRO: Patient-reported outcome; QOL: Quality of life; VO_2 peak: Peak oxygen consumption; DMT: Disease Modifying Therapies

Introduction

Fatigue is the most common symptom of MS affecting virtually all [1]. Over 80% of people with MS report having fatigue [2] and 50% to 60% regard fatigue as the most distressing symptom affecting their quality of life (QOL) as it limits one's capacity to carry out physical and mental activities [3-5]. More than 80% of people with MS state that fatigue is the main problem preventing their ability to work [6,7]. This economic burden not only affects the individual, but also the health care system as outpatient visits and services are more frequent for MS patients with fatigue than for those without fatigue [8].

Though MS-related fatigue has distinct characteristics [9] (e.g., more severe, frequent, persistent and unpredictable), its cause is complex and remains unclear [10]. MS-related fatigue is linked to several factors including: dysregulation of the immune system [11,12], destruction, reorganization and compensation within the central nervous system (CNS) [13-16], and changes in the neuroendocrine [17] and neurotransmitter systems [18]. Secondary factors related to physical deconditioning [19,20], sleep problems [21,22], depression [23] and medication effects [24] also contribute to fatigue in people with MS.

Various definitions of fatigue appear in the literature. One of the most cited is from the Multiple Sclerosis Council for Clinical Practice Guidelines (MS Council), stating that fatigue is "a subjective lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual or desired activity" [25]. This definition highlights the individualized perception of fatigue and the fact that fatigue can impede not only physical function, but also mental function as expressed by inability to concentrate or think clearly.

Many terms have been also used to distinguish fatigue according to its pathogenesis. Primary fatigue refers to fatigue resulting from the disease process and secondary fatigue is due to disease-related manifestation or side effects of medication [5,20]. Due to the high degree of interdependence among MS symptoms affecting fatigue manifestation, it is difficult to differentiate primary fatigue from secondary fatigue.

Fatigue has also been classified as central or peripheral. Central

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fatigue is used to describe fatigue caused by reduced force generation triggered by events at or proximal to the anterior horn cells [26]. Peripheral fatigue, in contrast, is related to failure at or beyond the neuromuscular junction [26,27]. However, there is no consensus or strong evidence to anchor the use of these terms. For example, central fatigue was used to refer to multiple aspects of fatigue including the CNS cause of fatigue as manifested by performance changes, perceived changes in attention, and increased level of exhaustion [28].

Without a clear terminology, the measurement and treatment of fatigue remains limited [20]. To overcome these challenges, a unified taxonomy has recently been proposed by Kluger and colleagues to distinguish perception of fatigue from fatigability, and for both physical and mental fatigue [28].

Perception of fatigue is defined as "a subjective sensation of weariness, increasing sense of effort, mismatch between effort expanded and actual performance, or exhaustion" [28]. On the other hand, fatigability is defined as "the magnitude or rate of change in a performance criterion relative to a reference value or a given time of task performance or measure of mechanical output" [28]. Furthermore, perception of fatigue and fatigability can be both further classified to capture mental or physical dimensions.

The measurement of perception of fatigue can only be achieved through patient-reported outcomes (PROs). The most commonly used unidimensional scale of fatigue is the Fatigue Severity Scale (FSS) [29], and the most commonly used multidimensional scales are the Modified Fatigue Impact Scale (MFIS) [30] and the Multidimensional Fatigue Inventory (MFI) [31], although the latter measure was validated on patients with chronic fatigue and not on MS specifically [32]. Fatigue PRO measures vary widely in the way they ascertain perception of fatigue. Some scales capture the frequency, duration, severity, impact, or cause of fatigue, while others measure a mixture of these [33]. The heterogeneity of fatigue poses measurement challenges.

The measurement of fatigability requires testing performance on physical or mental tasks. Within the physical domain, fatigability can be measured through the decline in peak force, power, speed, or accuracy of performance of tasks. For example, electrical stimulations of the quadriceps, adductor pollicis and dorsal interosseous muscles has been applied to induce physiological fatigue and fatigability is measured through the decline in maximal force capacity, rate and speed in people with MS [34-37]. Decline in walking speed or grip strength have also been used as indicators of fatigability [38,39]. Similarly, cognitive fatigability is quantified through decline in processing speed, reaction time or accuracy over time after completing demanding cognitive tasks [40-43]. For example, Moyano and colleagues measured cognitive fatigability in people with MS by computing omissions and mistakes during flexibility and divided attention capacity testing [44].

With existing PROs, it is often difficult to distinguish between physical and mental fatigue and correlations with performance tests are disappointingly weak. Krupp and Elkins reported a decline in the cognitive performance on measures of verbal memory and conceptual planning in people with MS compared to a control group following effortful cognitive tasks. These changes in cognitive performance in the MS group did not correlate with changes in their self-reported level of fatigue [45]. On the same note, a recent study found that the decline of processing speed and working memory of people with MS did not correlate with their self-reported fatigue [40]. Similar findings were reported by studies on the effectiveness of medication in reducing fatigue in MS. In one trial, 3,4 diaminopyridine was found to be effective in reducing performance fatigability as measured by electrophysiological test, however, it failed to produce differences on the perception of fatigue as measured by the FSS [46]. Even scores obtained using the physical domain of the MFIS, one of the most commonly used MS-fatigue scales, failed to correlate with physical capacity as measured through the Six-Minute Walk Test (6MWT) [30]. This discrepancy between fatigability and perception of fatigue (either physical or mental) has been reported by many other studies [47-52]. In fact, studies have called for more clinical research to tackle the association between fatigability and perception of fatigue [20,28].

Objective

The global aim of this study is to contribute evidence towards the relationship between perception of fatigue as measured by PROs, and indicators of fatigability. The specific objective of this study is to estimate the extent to which perception of physical fatigue and perception of mental fatigue correlate with performance on tests that could serve as proxy measures for fatigability. The hypothesis is that perception of physical fatigue will correlate more highly with these proxy tests of physical fatigability than perception of mental fatigue.

Method

Study design and subjects

This is a secondary analysis of data arising from a cross-sectional study originally focused on gender differences in the life impact of (the new) MS [53,54]. The details of that study have been reported previously [53,55,56]. Briefly, participants were people with MS diagnosed after 1994 who were registered on clinic databases maintained by the three largest MS clinics in Montreal. A random sample was drawn from each center. Patients were excluded if they had a health condition diagnosed prior to MS that continued to exert an effect on function, if they had a relapse in the preceding month, if they were less than 18 years of age or if they had severe cognitive impairment. Data from 189 people were available (140 women and 49 men; mean age of 43 years). The sample was chosen to be generalizable to people being diagnosed and treated today.

Measurement and procedure

Perception of fatigue: Fatigue was measured in this study using multi-item indexes: the RAND-36 [57,58], MFIS [30], MFI [31] and the Functional Assessment of Multiple Sclerosis Quality of Life Instrument (FAMS) [59] supplemented with 6 items from the FSS. Rasch analysis was applied to this pool of items to create a calibrated item bank supporting a fatigue measure (MS Gender). The wording of some items clearly targeted physical fatigue, while others mental or more general fatigue. To identify items that reflected physical and mental fatigue, a consensus exercise was carried out among fourteen clinical rehabilitation researchers to select items related to these two constructs. Items that were endorsed by ten raters as tapping these separate constructs were then cross-walked to the MFI [31]. The MFI was ideal for this purpose as its 20 items relating to five domains

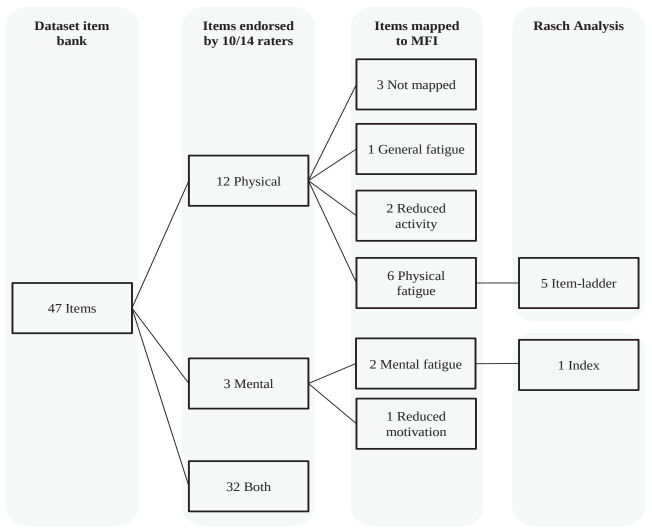

Figure 1: Process of Item Selection.

(general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue) has been validated on a very large sample (n=783) of people with fatigue symptom and healthy controls [32].

As the sum of ordinal rating scales does not create a legitimate total score [60,61], Rasch analysis was used to test the fit of items that mapped to the physical fatigue domain of the MFI to the Rasch measurement model. The items that fit, generated an MS-specific unidimensional, linear physical fatigue measure (Figure 1). Only two items mapped to the mental fatigue domain of the MFI and an ordinal index was created to tap perception of mental fatigue.

Fatigability: The participants were also tested on a number of performance measures of physical capacity that could be considered as proxy measures of fatigability as they required sustained physical performance, namely functional walking capacity and exercise capacity tests.

Functional Walking Capacity was measured using the Six-Minute Walk test (6MWT) [62]. In this standardized test participants were instructed to walk as far as possible in 6-minute time frame at their own pace in an enclosed 10 to 15 meter corridor. The total distance ambulated was measured and recorded. The 6MWT was reported to have high reliability and moderate validity [63].

Exercise capacity was measured using incremental graded cycle ergometer test which determines VO_2 peak (L/min) [64]. The test starts at a minimal workload of 10W followed by a gradual increase of 10W per minute. Participants were instructed to keep a constant peddling of 60rpm and the test was terminated once the participant was unable to maintain a peddling frequency of at least 45rmp. We took advantage of the fact that oxygen consumption is measured every 20 seconds creating a rich source of data to explain variation in peak VO_2. For this, we used the slope of the line linking time and oxygen consumption. The slope has been suggested as an indicator of the economy of performance [65]. For example, consider two people arriving at the same VO_2 peak; the one with the steeper slope has less economical performance suggesting more rapid fatigability [65].

An alternate method of measuring exercise capacity was also used, the Modified Canadian Aerobic Fitness Test (mCAFT), which can provide a more sensitive and ecologically meaningful proxy measure of physical fatigability. In this standardized test, subjects step on and off a double 20.3-cm wooden-step in series in time to a musical rhythm that becomes progressively more challenging every 3 minutes [66-69]. The starting stage is determined by the subject's age and gender and the final stage is determined once the subject achieved 85% of her/his age-predicted maximal heart rate [70]. Fatigability was inferred through the number of stages achieved: that is subtracting the initial stage from the final stage. The reliability and validity of the mCAFT in predicting exercise capacity has been shown to be high [66,71].

Analysis

Rasch analysis was used to test the fit of the selected items to the Rasch model. Rasch analysis is an iterative process which tests ordering of response options, item fit, unidimensionality, and global fit [72]. Any item that did not fit the Rasch model statistically and theoretically was removed from the item pool and the steps repeated until all items fit and formed a measure [73,74]. All Rasch analyses were performed using the Rasch Unidimensional Measurement Model (RUMM2030) software [75].

Descriptive analyses were used to characterize patients and verify distribution of variables. Data were expressed as means ± standard deviation (SD) or as frequencies (percentages). For estimating the correlation between the perception of physical fatigue, perception of mental fatigue and fatigability (6MWT, VO_2 peak and step-test stage), pearson, polyserial and polychoric correlations were used. Pearson correlation was used to estimate the association between two continuous variables. Polyserial correlation was used when one of the variables was categorical with more than two classes, and polychoric correlation was used when both variables were categorical. The correlation estimates were considered significant if the 95% Confidence interval (CI) excluded the zero. Statistical analyses were performed using the Statistical Analysis Systems (SAS version 9.3).

Results

The database contained 47 items ascertaining perception of fatigue. As presented in Figure 1, twelve of those items were endorsed by 10 out of the 14 raters to cover physical fatigue, 3 items for the mental fatigue and 32 items reflected both physical and mental fatigue. During the next stage, 6 of the 12 items were mapped to physical fatigue domain of the MFI, two items to reduced activities, one item to general fatigue and 3 items did not map to any domain. As for the mental items, two items were mapped to the mental fatigue domain of the MFI and one item to reduced motivation domain.

After the application of Rasch analysis on the six potential physical fatigue items, one item "Physically, I feel only able to do a little" was deleted as it did not fit the Rasch Model (X^2 was 184.7). The 5 remaining items met the criteria for good fit with a non-significant Chi square probability value with Bonferroni correction (X^2 = 12.5, *p-Value* = 0.252) with appropriate local independency, unidimentionality, lack of DIF and good reliability (Person Separation Index of 0.828). As Rasch analysis converts ordinal responses to linear through a logit transformation, the score scale ranges from 0

Table 1: Items Measuring Perception of Physical Fatigue and Mental Fatigue.

Perception of Physical Fatigue	Perception of Mental Fatigue Index
None of the time Some of the time All of the time	<30 minutes at a time 30 to 90 minutes >90 minutes
1. I took longer to do things	How long can you sustain a mental activity before you have to rest?
2. I had to pace myself during the day	
3. I feel that I am in excellent condition	
4. I feel active	
5. I feel that physically I can take a lot	

Table 2: Demographic and clinical characteristics of sample (n = 189).

Variable [Norm]	Mean ± SD or N (%)
Age (year)	43.0 ± 10.2
Women/men	140/49 (74/26)
Definite MS/CIS	170/15 (92/8)
Year since diagnosis	6.2 ± 3.6
EDSS, median (IQR)	2.0 (1.0–3.5)
On DMT/not on DMT/no information	112/21/56 (59/11/30)
RAND-36 (Vitality 0-100)[66]*	49.5 ± 20.4

CIS: Clinically Isolated Syndrome; EDSS: Expanded Disability Status Scale; IQR: Interquartile Range; DMT: Disease Modifying Therapies; RAND-36: The Medical Health Outcomes Study.
*RAND-36 Vitality: higher value is more vitality, lower fatigue; norm for age 35-44 [76].

to 100 with higher scores representing more fatigue. These five items capturing perception of physical fatigue are presented in Table 1.

As presented in Figure 1, out of the two items on mental fatigue, one item was found to best reflect perception of mental fatigue and was transformed into a single mental fatigue index. The distribution of this index was not normally distributed; therefore, data were categorized into three classes as presented in Table 1. The other item "Did you have difficulties thinking clearly or forgetting things" was not included as it captures cognition rather than fatigue.

Table 2 presents information on the sample. The mean age was 43 years (SD: 10.2), there were three times more women as men, and about 60% of the participants were on Disease Modifying Therapies (DMTs). Time since diagnosis reflects the selection criterion of diagnosis after 1994. Also presented is the value on a generic measure of fatigue from the RAND-36 which was 49.5 (SD: 20.4) along with normative data for the age group 35-44 years [76].

Table 3 presents the values on the measures of fatigue perception and on the indicators of fatigability along with the number of people assessed on each test, as this differed. The mean perception of physical fatigue was 43 (SD: 24.2). For perception of mental fatigue, the percentages of participants who were able to sustain mental activity for different time periods are given, ranging from 18.3% for less than 30 minutes to 44.6% for more than 90 minutes. The distance walked in 6 minutes (6MWT) averaged 454.7m (SD: 171.3), representing 80% of age- and sex-predicted distances [64]. The estimated oxygen peak uptake was 1.9L/min representing 23% of their age- and sex-predicted values [64]. The estimated VO_2 slope was 0.03L/min. The step-test stages that were achieved by participants ranged from 0 to 4. Percentage of participants who reached 0, 1, 2, 3, and 4 stages were 21.7%, 39.1%, 27.5%, 9.4% and 2.2% respectively.

Results of the correlation estimates between variables are presented in Table 4. In this table, correlation estimate, the 95% CI and the number of observation used are presented across the different variables. The direction of the scale explains a negative or a positive correlation between variables. For the perception of physical fatigue and the slope of VO_2, the higher the score the worst is the outcome. On the contrary, the higher scores reflect better outcomes for the perception of mental fatigue, 6MWT and step-test stage variables. The correlation between the perception of physical fatigue and the perception of mental fatigue was -0.44 (95% CI -0.55 to -0.31). A significant correlation was found between the perception of physical fatigue and 6MWT (-0.51, 95% CI -0.39 to -0.61), which was higher than the correlation between the perception of mental fatigue and the 6MWT (0.26, 95% CI 0.11 to 0.39). As for the VO_2 slope, its correlation with the perception of physical fatigue was 0.35 (95% CI 0.09 to 0.55), however it did not have a significant correlation with the perception of mental fatigue (-0.08, 95% CI -0.35 to 0.21). Similarly, the step-test stage had a significant correlation with the perception of physical fatigue (-0.22, 95% CI -0.37 to -0.05), and it did not have a significant correlation with the perception of mental fatigue (0.05, 95% CI -0.12 to 0.22).

Discussion

Five items were found to best reflect the construct of perception of physical fatigue, while one indicator was found to best reflect perception of mental fatigue. The results of this study supported our hypotheses. Although the correlations between proxy measures of physical fatigability and perception of physical fatigue were not strong (ranged -0.51 – 0.35; see Table 4), they were higher than such correlations with perceptional of mental fatigue (ranged -0.08 – 0.26; see Table 4).

Table 3: Values on Measures of Physical and Mental Fatigue and Indicators of Fatigability.

Variable	N of people assessed	Mean ± SD or N (%)
Physical fatigue* (0-100)	185	43±24.2
Mental fatigue (time to sustain mental activity)	175	
< 30 minutes		32 (18.3)
30 to 90 minutes		65 (37.1)
>90 minutes		78 (44.6)
6MWT (meters)	186	454.7±171.3
VO_2 Peak (L/min)	58	1.9±0.6
Slope of VO_2	58	0.03±0.01
Step-test stages achieved	138	
0		30 (21.7)
1		54 (39.1)
2		38 (27.5)
3		13 (9.4)
4		3 (2.2)

N: Number; 6MWT: Six-Minute Walk Test; VO_2 Peak: Peak oxygen consumption.
*Physical fatigue: higher is more fatigue.

Table 4: Correlation Matrix (95% CI), [N], *p-value.*

	Physical fatigue perception*	Mental fatigue perception†	6MWT†	VO_2 slope*	Step-test stage†
Physical fatigue perception*		-0.44 (-0.55 to -0.31) [171] *<.0001*	-0.51 (-0.39 to -0.61) [186] *<.0001*	0.35 (0.09 to 0.55) [57] *0.0072*	-0.22 (-0.37 to -0.05) [136] *0.0092*
Mental fatigue perception†			0.26 (0.11 to 0.39) [172] *0.0008*	-0.08 (-0.35 to 0.21) [49] *0.2817*	0.05 (-0.12 to 0.22) [126] *0.1074*
6MWT†				-0.30 (-0.51 to -0.04) [58] *0.1293*	0.31 (0.15 to 0.45) [137] *<.0001*
VO_2 slope*					-0.30 (-0.52 to -0.04) [56] *0.0638*
Step-test stage†					

CI: Confidence Interval; N: Number; 6MWT: Six-Minute Walk Test; VO_2 peak: Peak oxygen consumption.
*Higher score is worse.
†Higher score is better.

In this study, we did not correlate perception of physical and mental fatigue with mental fatigability as the dataset did not include a proxy of such a performance measure. Neumann and colleagues used the same taxonomy that was proposed by Kluger and colleagues to develop a better understanding of mental fatigue and fatigability in MS [42]. In their study, the perception of mental fatigue, as measured through the cognitive subscale of the Fatigue Scale for Motor and Cognitive Function (FMSC), was correlated with mental fatigability as measured through the reaction time. Even though their study concluded that perception of mental fatigue (i.e., cognitive subscale of the FMSC) had a significant correlation with mental fatigability (i.e., reaction time) at r=0.54 and a p-value=0.002, their CI ranged from 0.03 to 0.82 [42]. Therefore, their lower limit of the CI indicates a very weak association which could reflect that items in the cognitive subscale of the FMSC might not adequately reflect the perception of mental fatigue constructs or that the association is, in fact, weak.

Another study found that perception of mental fatigue was a "function of time", rather than a function of load (the complexity of the task) or domain (the type of the task, e.g., processing speed vs. working memory). In other words, the longer the task, the more self-reported mental fatigue [40].

The association between what the patients are reporting in terms of their perception of fatigue and their performance on physical and cognitive activities was found to be non-uniform. One hypothesis is that the *effort* in producing a task, which is reflected in the perception of fatigue, might not be reflected in the performance. That is, there is a complex feedback loop between effort and perception of fatigue, which is not captured by performance-based measures. Task effort results in increasing the perception of fatigue which in turn feeds back and makes additional increase in the task effort until the task is terminated [40]. In our study, this effort may be best reflected by the slope of VO_2.

The effect of time and effort on fatigue is best reflected from a patient's point of view. The spoon theory, was generated by a person with Systemic Lupus Erythematosus (SLE), though is applicable to any chronic condition [77]. This theory illustrates how individuals with chronic conditions need to plan their activities and daily tasks based on the number of "spoons", i.e., the energy reserve they have [77]. Spoons exemplify a unit of measurement reflecting how much energy an individual has to spend on tasks throughout a given day. Each task or activity costs a certain number of spoons, that when run out, cannot be replaced until the next day. This theory emphasizes the importance of monitoring and balancing daily tasks in concordance to the available number of spoons and highlights the need for adopting different strategies for an efficient spending of these spoons [77]. As was illustrated in the slope of VO_2, some patients spent all of their "spoons" in a short period of time and reached their peak oxygen consumption quickly (i.e., steeper slope), while other patients were more efficient and spent their energy over a longer period of time before reaching their VO_2 peak (i.e., lower/gradual slope).

New approaches are under development for quantifying fatigability and better linking it to perception of fatigue. For example, Sehle and colleagues developed the Fatigue Index Kliniken Schmieder (FKS) that measures physical fatigability through the monitoring of gait changes (acceleration patterns and variability) during a walking test [78]. Eye movements are also indicated as a proxy measure for fatigability, in particular, increased eye movement disconjugacy after repetitive horizontal saccades was found to be a "promising" approach for measuring fatigue in people with MS [79,80].

There are a number of limitations in this study. Data were based on a cross-sectional study, thus participants were assessed at one point in time, and the data may not necessarily reflect all time points. The sample size was different for the different outcome measures owing to missing data and the fact that not all participants were able to perform the exercise capacity tests. Moreover, this study only addressed association between two measurement approaches (PRO and performance indicators) and did not address explanation of either phenomenon. Further work is warranted in the area as many factors may be involved in the relationship including mood, disability status, and sleep disorders.

Conclusion

Overall, linking perception of fatigue to fatigability has been shown to be a challenging process as many studies have failed to show such a relationship. This current study aimed at providing the initial steps to untangle the association between perception of fatigue and fatigability by selecting items and performance measures that further distinguish and differentiate mental and physical components. The use of a strong theoretical framework in defining perception of physical or mental fatigue along with Rasch analysis were helpful in identifying items that best link perception of physical fatigue to physical fatigability. Our next steps are to build on those items to strengthen the measurement of the constructs.

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