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Fatigue-Related Changes of Daily Function: Most Promising Measures for the Digital Age

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Abstract
Background: Fatigue is a prominent symptom in many diseases and is strongly associated with impaired daily function. The measurement of daily function is currently almost always done with questionnaires, which are subjective and imprecise. With the recent advances of digital wearable technologies, novel approaches to evaluate daily function quantitatively and objectively in real-life conditions are increasingly possible. This also creates new possibilities to measure fatigue-related changes of daily function using such technologies. ***Summary:*** This review examines which digitally assessable parameters in immune-mediated inflammatory and neurodegenerative diseases may have the greatest potential to reflect fatigue-related changes of daily function. ***Key Messages:*** Results of a standardized analysis of the literature reporting about perception-, capacity-, and performance-evaluating assessment tools indicate that changes of the following parameters: physical activity, independence of daily living, social participation, working life, mental status, cognitive and aerobic capacity, and supervised and unsupervised mobility performance have the highest potential to reflect fatigue-related changes of daily function. These parameters thus hold the greatest potential for quantitatively measuring fatigue in representative diseases in real-life conditions, e.g., with digital wearable technologies. Furthermore, to the best of our knowledge, this is a new approach to analysing evidence for the design of performance-based digital assessment protocols in human research, which may stimulate further systematic research in this area.

Introduction

Fatigue may be best described as "a multidimensional phenomenon in which the physiological, cognitive, motivational, and emotional state of the body is affected, resulting in impairment of an individual's ability to function in their normal capacity" [1]. For many diseases, fatigue is consistently ranked as one of the most debilitating symptoms with substantial impact on the health-related quality of life (HrQoL) [2–11] and one of the main causes for loss of employment [8, 12–17]. In 2006, the annual indirect costs (foregone productivity) of fatigue in the USA were estimated at over USD 100 billion [18]. In neurodegenerative and immune-mediated inflammatory diseases (IMIDs), fatigue is particularly common [19–21]. For example, about 50% of all people with Parkinson's disease (PD) [9, 10], more than 80% of those with Huntington's disease [22], 40–80% of those with active inflammatory bowel disease (IBD) [23], 75% of those with rheumatoid arthritis (RA) [24], 50–80% of those with systemic lupus erythematosus (SLE) [25, 26], and 67–88% of those with primary Sjogren's syndrome (PSS) [27, 28] report fatigue.

The strong influence fatigue has on HrQoL incorporating physical, mental, and social aspects [29] is most probably explained by its interaction with daily function. Daily function was recently defined as "*the performance of physical, behavioural, and cognitive activities and their individualized interaction with the environment*" [30]. Within the framework of the World Health Organization (WHO) International Classification of Function, Disability and Health (ICF model) [31], daily function has previously been associated with daily activities and social participation (shown in Fig. 1) [30].

Research and medical management in recent decades have focused on measurement of the body functions and structure domain (underlying pathogenesis), paying relatively little attention to disease-caused impairments of daily activities and social participation (often those which are most relevant from patients' perspective [29]). This has led many stakeholders involved in patient care and treatment development, including the European Medicines Agency (EMA) [32] and Food and Drug Administration (FDA) [33, 34], to call for the inclusion of objective measures of daily function in the assessment of therapeutic efficacy.

Daily function and its changes can be measured using perception, capacity, and performance measures (shown in Fig. 2) [30]. Perception measures assess how people perceive their symptoms, function, or disability. Most often, patient-reported outcomes (PROs) (typically standardized questionnaires) are used for this type of assessment. Capacity measures usually assess the ability of a person to complete a specific task with their best effort at the time of assessment. It is normally carried out in an instructed, supervised, and observed manner, mostly in professional environments. For example, the "five times sit-to-stand" test evaluates how fast a person can stand up from a chair [35]. Performance measures assess people's usual function. They can be collected, e.g.,

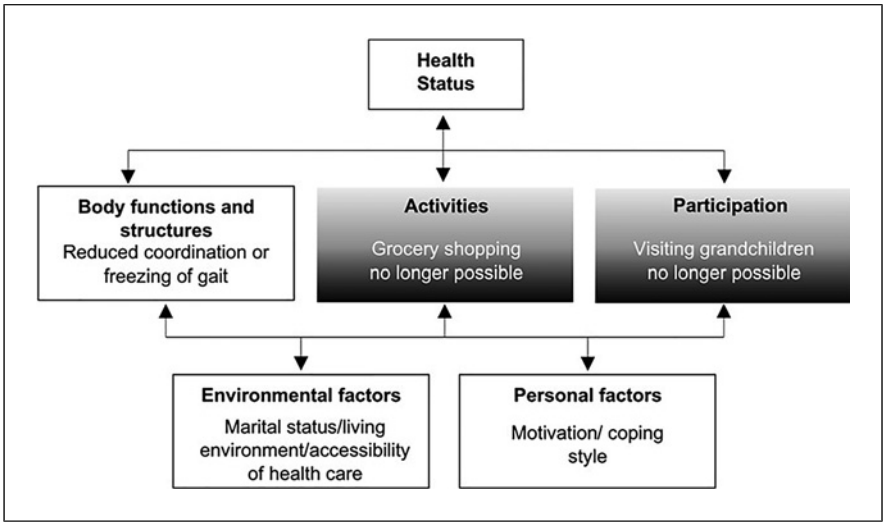

Fig. 1. World Health Organization International Classification of Function, Disability and Health (ICF) with the 5 domains (in bold) and limitations caused by fatigue as an example (normal text) of how a specifically reduced health status can affect the different domains. Daily function is mainly represented by the activities of daily living (ADL) and the participation in societal role domains. The different degrees of grey symbolize that the two domains can be assessed with different assessment types (see also Fig. 2). Adapted from https://neurogeriatrics-kiel.com/about-us.

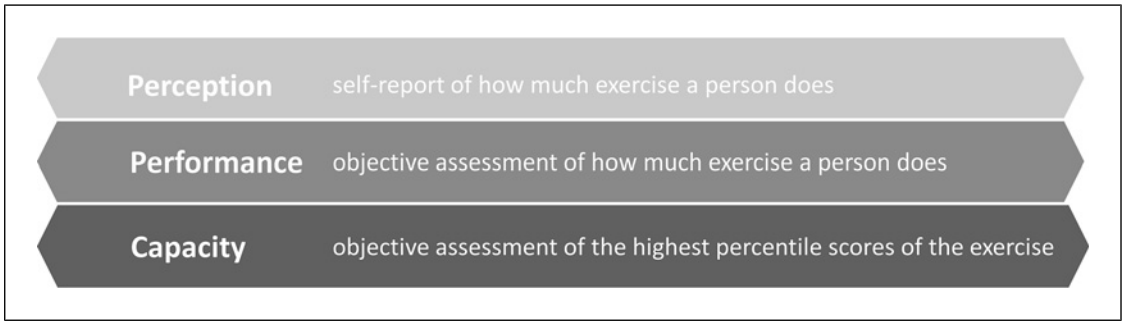

Fig. 2. Types of assessment for daily function (in bold), with an example for a specific aspect of daily function (physical activity, normal text). Adapted from https://neurogeriatrics-kiel.com/about-us.

using digital devices in the usual environment, without instructing users to perform specific tasks. While perception and capacity measures are commonly used in diagnostics and treatment efficacy evaluation, performance measures are not yet part of assessment batteries on a regular basis in clinical trials and in standard medical care. However, performance measures most probably have the highest potential among the three assessment strategies to provide the most relevant, objective, and accurate information about daily function. In addition, digital technologies that track daily function parameters (e.g., smartphones, smartwatches) are developing rapidly and are used by a large part of the population. Therefore, they already have a high level of acceptance among potential study participants and patients, especially if the factors of low effort of use, low disruption to the users' daily life, and good support from the study team are taken into account [36]. Consequently, the identification of daily-function-associated (surrogate) parameters of fatigue that can potentially be evaluated with digital tools in the usual environment of patients [37] could inform future research in this area.

Methods

As part of the review of the question posed above, the authors conducted systematic literature searches for several diseases. Note that these were not performed uniformly across all diseases due to the varying amounts of existing literature (see also limitations). The following search terms were entered into PubMed (and for IBD also into Embase, Medline, Cochrane, Web of Science, PsycINFO, and Google Scholar): Fatigue AND "Parkinson's Disease/Huntington's Disease/Inflammatory Bowel Disease/Crohn's Disease/Ulcerative Colitis/Rheumatoid Arthritis/Systemic Lupus Erythematosus/Primary Sjogren's Syndrome" AND "daily function/ADL/activities of daily living/participation." The abstracts of all hits were rated according to their potential to report about fatigue-related changes of daily function (the concept of interest), using a self-developed scale with a score from 0 to 5 (online suppl. Table 1; for all online

suppl. material, see https://doi.org/10.1159/000536568). All abstracts that obtained a rating of ≥1 were included in the full-text search. Reference lists of these full-text papers were also screened for potentially interesting papers. From full papers with ≥4 points ("core papers"), the following parameters were extracted: number of participants, gender ratio, mean age, mean disease duration, main outcomes from disease-specific scores, fatigue measure used in the study, daily function measure used in the study, and measures that show a significant association between fatigue and daily function concepts of interest. Approval by the local Ethics Committee was waived because no original data were collected in this study.

Results

The literature search revealed 5,150 hits. After screening the abstracts, 950 full-text articles were selected and evaluated. Out of the 100 studies that met the criteria of a core paper, 93 investigated fatigue-related changes of daily function by using perception ($N = 77$) and capacity measures ($N = 16$), and only a minority of the studies used performance measures ($N = 7$). Online supplementary Table 2 gives an overview of the search results.

Perception studies primarily indicate that worsening in physical activity, independence of daily living, social participation, and mental status are associated with fatigue. Fatigue-related changes of physical activity were reported for people with PD [38], IBD [39], RA [40], SLE [41, 42], and PSS [43–45]. Fatigue-related changes in leisure activities were reported for PD [38], IBD [39], RA [40], and SLE [42]. In SLE, sedentary lifestyle was also associated with fatigue [41]. Two studies in PSS revealed fatigue-related changes in strenuous and moderate physical activities [43, 45]. Fatigue-related changes in independence of daily living, which was mainly investigated as part of PROs assessing activities of daily living, were observed in PD [46–48], IBD [21, 49, 50], RA [51, 52], SLE [42, 53–55], and PSS [44]. Fatigue-related changes in social participation were observed for social interaction [21, 40, 42, 44, 52, 56–60], communicational aspects [48, 51, 55, 60], and working life [16, 22, 40, 54, 61–65]. More specifically, fatigue was linked to changes in speech production in PD [48], changes in the ability to follow a conversation in IBD and RA [51, 60], and changes in the ability to use the phone or smartphone in SLE [55]. Regarding working life, fatigue-related changes of work efficiency (reduced labour productivity, partly due to working while sick [presenteeism]) were reported for IBD, RA, and SLE [16, 40, 54, 63–65]. Increased absence from the workplace due to fatigue-related changes (absenteeism) was reported for IBD [65] and RA [16]. Unemployment was associated with fatigue in patients with Huntington's disease [22]. Results for IBD and PSS were less clear [17, 61, 62, 66]. Fatigue-related changes of emotional well-being were reported for PD [47, 48, 67], IBD [59, 68], RA [51], and SLE [42]. An overview of the core studies using perception measures for fatigue-related changes of daily function is provided in Table 1 and online supplementary Table 3.

Capacity studies suggest that mobility capacity, aerobic capacity, supervised mobility performance, and cognitive capacity are the daily function concepts of interest most closely associated with fatigue. More specifically, fatigue-related changes of mobility capacity were shown for IBD [69], RA [70, 71], and SLE [72]. In IBD and PSS, negative associations between fatigue and maximal isokinetic [69] and isometric muscle strength [72] were shown. The results for RA were less clear [70, 71, 73]. Fatigue-related changes of aerobic capacity were found in PSS [74] and SLE [75], but not in PD [38] and RA [76]. Changes in supervised mobility performance related to fatigue were detected in IBD [77], PD [38], and SLE [72]. In PD, e.g., fatigue was associated with a longer time to perform the TUG [38], but not with the SPPB total score [78] and the 6MWT distance [79]. The 6MWT, however, correlated with fatigue in IBD [77]. For SLE [72], but not for RA [73], an association between repeated sit-to-stand movements and fatigue was shown. Fatigue-related changes in cognitive capacity, more specifically verbal episodic memory (recognition discriminability), were shown in PD [80]. No fatigue-related changes in cognitive capacity were found for PSS [81]. It is important to note that the fatigue scale used in the latter study does not contain any item assessing mental fatigue. Table 1 and online supplementary Table 4 give an overview of the core studies using capacity measures for fatigue-related changes of daily function.

Performance studies suggest that unsupervised daily mobility performance, as measured using digital wearable technologies, is associated with fatigue. For example, in PD, a mean step count of <4,200/day was associated with fatigue [82]. In IBD, fatigue was related to a reduction of daily mean motility (intensity of daily physical activity) [77]. Studies with RA patients showed an association of fatigue with decreased daily activity as measured with the number of accelerations measured during repeated 5-min periods [83] as well as the stand-to-sit ratio [84]. In SLE, fatigue was shown to be related to the ratio of moderate to vigorous physical activity, as measured using vector magnitude per minute [85]. An overview of the studies using performance measures for fatigue-related changes of daily function is provided in Table 1 and online supplementary Table 5.

Table 1. Most promising parameters to measure fatigue-related changes of daily function

Daily function concept of interest	Sub-category	Association with fatigue	No association with fatigue
Assessed with perception measures			
Physical activity	Leisure activity	PD [38] IBD [39] RA [40, 42]	IBD [89]
	Strenuous physical activity	PD [38] PSS [43–45]	
	Moderate physical activity	PSS [43, 45]	
	Sedentary lifestyle	SLE [41]	
Independence of daily living	ADL	PD [46–48] IBD [21, 49, 50] RA [51, 52] SLE [42, 53–55] PSS [44]	
Participation	Social interaction	PD [90] IBD [21, 57–60] RA [40, 52] SLE [42] PSS [44]	
	Communication		
	Speech production	PD [48]	
	Follow conversations	IBD [60] RA [51]	
	Use telephone	SLE [55]	
	Working life		
	Work efficiency loss	IBD [63, 65] RA [16, 40] SLE [54, 64]	
	Absenteeism	IBD [65] RA [16]	
	Unemployment	HD [22] IBD [61] PSS [62]	IBD [66] PSS [17]
Mental status	Emotional well-being	PD [47, 48, 67] IBD [59, 68] RA [51] SLE [42]	
Assessed with capacity measures			
Cognitive capacity		PD [80]	PSS [81]
Aerobic capacity		SLE [75] PSS [74]	PD [38] RA [76]
Mobility capacity		IBD [69] RA [70, 71] SLE [72]	RA [71, 73]
Supervised mobility performance		PD [38, 91] IBD [77] SLE [72]	PD [78, 79] RA [73]
Assessed with performance measures			
Unsupervised mobility performance		PD [82] IBD [77] RA [83, 84] SLE [85]	

Concepts of interest and their sub-categories of fatigue-related changes in daily function that are potentially interesting for the development of digital performance parameters, divided into perception, capacity, and performance measures. ADL, activities of daily living; HD, Huntington's disease; IBD, inflammatory bowel disease; PD, Parkinson's disease; PSS, primary Sjogren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Discussion

Results of our literature review in IMID and ND suggest that fatigue and daily function are strongly and negatively correlated. Among the different aspects of interest within daily function, physical activity (e.g., to initiate leisure activity or maintain strenuous activities), independence of daily living (e.g., washing or dressing oneself), social participation (e.g., participation in social life, conversations, and working life impairments), and mental status were most consistently associated with fatigue-related changes of daily function across the diseases reviewed. There is also substantial evidence that fatigue-related changes in daily function impact physical ability (e.g., physical or cognitive capacity) and mobility performance, aspects of socialization (e.g., through impaired communication skills), and emotional well-being [48, 67]. The relationship between fatigue and daily function impairment is likely bidirectional, but this is beyond the scope of this paper to discuss such relationship in detail.

As expected, a substantial majority of studies investigating changes in fatigue-related daily function used perception-based assessment tools. The balance between core studies that have shown significant associations between measures of fatigue and daily functioning compared to studies that have not shown significant associations (see also Table 1) argues, at least indirectly, for the value of perception measures in this context. The disadvantages of this type of assessment remain the subjectivity of the assessment and the dependence on the memory and motivation of the study participant. A particular disadvantage for the question addressed here is that the currently available perception measures usually depict multidimensional constructs (e.g., HrQoL) and are accordingly based on a large number of questions, which are only partially relevant for the study of fatigue.

Few studies used capacity measures to investigate fatigue-related changes of daily function, and they give surprisingly inconsistent results (Table 1). This inconsistency may base on the fact that this type of assessment usually requires an artificial setup and often captures data over a very short period of time. A systematic review comparing mobility assessments made in unsupervised surroundings (comparable to the performance category presented here) with supervised setups (i.e., hospitals or research laboratories, which reflect typically measures of the capacity category) highlights large disparities, even when using the same measures, between results based on the two methods for mobility assessment in neurological diseases [86]. Some doubt thus arises as to whether capacity measures are actually suitable for adequately depicting fatigue-related changes of daily function across different conditions and diseases. This may be because capacity assessment often focuses on measuring the best effort an individual can achieve, and fatigue is a phenomenon characterized by not only its chronicity and severity, but also its variability and inability to sustain an effort. Therefore, a fatigued individual may be able to achieve a single best effort that is not significantly different from their best effort when not fatigued.

It is also noteworthy that different fatigue PROs are used in different studies. While in general there are good correlations between assessments using different fatigue PROs, the question items within individual fatigue PROs differ with some covering different aspects/dimensions of fatigue whereas some may focus on a particular dimension (e.g., mental or physical) of fatigue or its impact. The choice of the fatigue PROs used in the study can have key impact on the research findings. For example, the lack of association observed in one study [81] between cognitive symptoms and fatigue among PSS patients is likely due to their use of Fatigue Severity Scale and SF-36 vitality domain as measures of fatigue – as neither fatigue assessment tool evaluates mental fatigue. This is in contrast to the findings reported by Segal et al. [87] which showed that cognitive symptoms are associated with mental fatigue.

Interestingly, the few core papers in our literature evaluation that used performance measures reported comparable correlations across diseases (Table 1). Although these studies only covered a small part of daily function (here classified as "unsupervised mobility performance"), this observation argues strongly in favour of using continuous and objective digital parameters to assess daily function and to measure associations with symptoms such as fatigue on this important aspect of daily life. As a next step, it makes sense to define additional concepts of interest of daily function for the development of the most appropriate performance-based tools to evaluate the relationship between fatigue and daily function. Ideally, this can be achieved through passive data to minimize potential burden to collection, without directly "bothering" the study participant. In this way, data relevant to everyday life can be collected practically without a placebo effect and without important losses. Promising parameters that can be measured with established and validated digital tools are specific aspects of mobility (such as quantitative and qualitative parameters of walking, turning, and sit-to-stand and stand-to-sit performance); accelerometer- and gyroscope-containing sensors on the feet, the low back, and the wrist are particularly suitable for recording. Other promising digital parameters can be obtained by measuring the physiology of the human body. These include

(chest) electrocardiogram and (wrist) photo plethysmography. Building on the findings of this structured review, it is advisable to systematically examine fatigue-assessing patient-rated instruments, including questionnaires, scales, surveys, and diaries. The objective should be to identify items from these instruments that could potentially be objectively measured using digital technology.

This literature review also shows that digital technologies may be helpful in providing objective assessment of communicative and participatory function, although further research is needed before such technologies can be employed in routine clinical practice and in clinical trials. For example, parameters such as frequency or durations of usage of communication platforms and social apps on one's personal mobile phone can give indications of the levels of social activity of the user.

A particularly interesting aspect arising from the above discussion is the possibility of making direct comparisons between measures of perception, capacity, and performance of daily function, preferably on a similar concept of interest. This would help better understand how self-assessments by patients, clinical evaluations, and performance in daily life correlate or differ. Unfortunately, only a few studies found in the present literature review analysed associations across different daily function assessment approaches, and further research is needed to determine the extent to which these different assessment approaches are correlated [30].

To the best of our knowledge, this review provides a new approach to analysing evidence for the design of performance-based digital assessment protocols in human research, and we hope that it will stimulate further systematic research in this area. However, it has also its limitations. Firstly, it includes a literature search that was conducted mainly in the PubMed database, thus cannot claim to be comprehensive, and was not similar across all diseases. This method was chosen because we were primarily interested in the type of measures the studies used for the assessment of daily function and its relationship with fatigue. We consider this to be legitimate, as no quantitative claims were made between diseases and no statistical analyses were performed. Secondly, the primary objective of this work (daily function manifestations of fatigue) was not the primary objective of most studies found in our literature search. Therefore, we cannot ultimately exclude misinterpretations of extracted data. We have therefore kept the concepts of interest as general as possible. Thirdly, this review does not comment on what digital devices, algorithms, signal processing techniques, and analytical approaches, including artificial intelligence/machine learning, have been and should be used to detect and predict fatigue within the concept of interest (daily function). We believe this is work that should follow and take into account the results of this review. Finally, many factors may influence the interplay between fatigue and daily function, such as disease severity, comorbidities, mental health, emotional well-being, pain, and sleep [52, 73, 81, 88]. Future studies should thus take such potential confounders into consideration.

Conclusion

For a better understanding of daily function and how it changes with fatigue, we advocate a digital and performance-based assessment of concepts of interest within daily function to be applied in future studies and clinical trials. We provide evidence in IMID and ND that changes in physical activity, independence of daily living, social participation, working life, mental status, cognitive capacity, aerobic capacity, and supervised and unsupervised mobility performance have a high potential to reflect fatigue-related changes of daily function. Further research should look into how disease-specific and other factors may affect fatigue-related changes of daily function in diseases associated with fatigue.

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Statement of Ethics

No statement of ethics was required for this work.

Conflict of Interest Statement

Meenakshi Chatterjee received stock from employer from Johnson and Johnson and is a full-time employee and shareholder of Johnson and Johnson. Lori Ann Warring is a full-time employee of Johnson and Johnson. Geert van Gassen is a full-time employee of Takeda Belgium. Teemu Ahmaniemi is a full-time employee of VTT Technical Research Centre of Finland Ltd. Michael Chambers received contract funding for all activities related to IDEA-FAST, including contribution to this study/manuscript. Joaquim Ferreira received grants from Angelini, BIAL and AbbVie, and consulting fees or honoraria from Lundbeck, BIAL, Biogen, AbbVie ONO, SK Chemicals, and Zambon. Janneke van der Woude holds grants from AbbVie, Takeda, Pfizer, Galapagos, and

Celltrion, and received consulting fees or honoraria from ZonMw, Tramedico, Falk Benelux, and Pfizer. Wan-Fai Ng has provided consultation services for Novartis, GlaxoSmithKline, AbbVie, BMS, Sanofi, MedImmune, argenx, Janssen, Resolve Therapeutics, and UCB.

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Author Contributions

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Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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