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Parkinson's Disease-related Fatigue: A Case Definition and Recommendations for Clinical Research

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Abstract

Fatigue is one of the most common and disabling symptoms in Parkinson's disease (PD). Since fatigue was first described as a common feature of PD 20 years ago, little progress has been made in understanding its causes or treatment. Importantly, PD patients attending the 2013 World Parkinson Congress voted fatigue as the leading symptom in need of further research. In response, the Parkinson Disease Foundation and ProjectSpark assembled an international team of experts to create recommendations for clinical research to advance this field. The working group identified several areas where shared standards would improve research quality and foster progress including terminology, diagnostic criteria, and measurement. Terminology needs to (1) clearly distinguish fatigue from related phenomena (e.g. sleepiness, apathy, depression); (2) differentiate subjective fatigue complaints from objective performance fatigability; and (3) specify domains affected by fatigue and causal factors. We propose diagnostic criteria for PD-related fatigue to guide participant selection for clinical trials and add rigor to mechanistic studies. Recommendations are made for measurement of subjective fatigue complaints, performance fatigability, and neurophysiologic changes. We also suggest areas where future research is needed to address methodological issues and validate or optimize current practices. Many limitations in current PD-related fatigue research may be addressed by improving methodological standards, many of which

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are already being successfully applied in clinical fatigue research in other medical conditions (e.g. cancer, multiple sclerosis).

Keywords

Parkinson's disease; fatigue; case definition; clinical research

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting about 1% of the population over the age of 50.¹ Traditionally, research focus has been on the motor aspects of the disease, such as tremor, rigidity and akinesia. During the last 2 decades, however, attention has shifted to the many non-motor symptoms common in PD, including fatigue. Several studies have shown that fatigue is a major problem for approximately half of PD patients. It tends to develop early, including in the pre-motor period, and is reported by one-third of patients as the single most disabling symptom.^{2, 3} Fatigue is a leading cause of disability claims related to PD and, even in retired individuals, limits the ability to maintain hobbies and participate in social activities.⁴

Despite the enormous impact of fatigue in PD, its pathophysiology remains unknown. Studies generally do not find significant associations between disease duration, stage or motor symptoms and fatigue suggesting the involvement of nonmotor networks.² Fatigue is often associated with depression,² but these symptoms frequently occur independently and fatigue may persist following successful treatment of depression.⁵ Fatigue in PD is also inconsistently associated with sleep disorders and is dissociable from daytime somnolence.⁶⁻⁸ Proposed physiologic mechanisms include increased circulating pro-inflammatory cytokines, dysfunction in nigrostriatal and extrastriatal dopaminergic pathways, involvement of non-dopaminergic (particularly serotonergic) pathways, executive/prefrontal pathology and involvement of the autonomic nerve system.⁹⁻¹³ While intriguing, studies to date are generally limited by small sample sizes, failure to control for potential confounding factors and explain only a small portion of the variance in fatigue. Treatment options for fatigue in PD are similarly limited. There are very few published reports on the treatment of fatigue in PD and a recent systematic review concluded that insufficient evidence exists to support the management of fatigue in PD with any pharmacologic or nonpharmacologic treatments.¹⁴

Thus, there is a clear need for further basic and clinical research on PD-related fatigue. Importantly, PD patients attending the 2013 World Parkinson Congress voted fatigue as the leading symptom in need of further research. In response, the Parkinson Disease Foundation and ProjectSpark assembled an international team of experts to create recommendations for clinical research to forward this field. The working group identified several high-priority areas where shared standards would improve research quality and foster progress including terminology, case definition, and measurement. The goal of this paper is to make recommendations regarding terminology, measurement and a working case definition of PD-related fatigue based on discussions from this working group.

Working Group Strategy

Prior to meeting, the working group identified topics critical to advancing clinical research in PD-related fatigue. At the working group meeting summaries of the available literature from PD-related fatigue were presented and gaps identified. The group also reviewed research from other medical conditions where methodology or findings may be more advanced including cancer-related fatigue, multiple sclerosis and chronic fatigue syndrome. In the absence of evidence, we relied on expert opinion based on the clinical and research experiences of the group and specifically highlight these areas as in need of additional research.

Terminology

Although fatigue is often viewed as a “non-specific symptom” we believe that a more scientifically productive viewpoint is to treat fatigue as a complex construct requiring precision in terms of phenomenology and terminology. The lead author and his colleagues previously published recommendations for a unifying taxonomy for clinical research in fatigue in neurological populations which was designed specifically with PD-related fatigue in mind.¹⁵ The goal of this taxonomy is to facilitate scientific progress by providing shared terminology and accurate descriptions of phenomenology. The key aspects of this taxonomy are: 1) Distinguishing fatigue from related constructs (e.g. sleepiness); 2) Recognizing that subjective fatigue complaints and objective fatigability of performance are dissociable phenomena; 3) Utilizing strict criteria to define clinical significance; 4) Specifying what performance domains are affected by fatigue (e.g. motor, cognitive); and 5) Identifying causal factors by function and neuroanatomic location. We will briefly review these points as they relate to clinical research in PD-related fatigue.

One of the challenges of studying fatigue in PD is the high prevalence of potentially confounding symptoms including daytime somnolence, apathy, and depression. While these symptoms are frequently comorbid with fatigue they are distinct phenomena and are dissociable. On a phenomenological level, fatigue is described by PD patients as a lack of energy or a need for increased effort needed to attempt daily activities that is distinct from sleepiness (they do not feel a need to take a nap), lack of motivation (they want to do activities but do not have energy) and depression (they report fatigue may lead to frustration but that their mood is not driving fatigue). Epidemiologic studies support this distinction in that many PD patients with fatigue do not have depression, apathy or daytime sleepiness and regression models suggest that patients with comorbid symptoms (e.g. depression and fatigue) may differ from patients with isolated fatigue.^{2, 16} As these symptoms likely have different biological underpinnings and different responses to treatment it is critical that clinical studies deal with potential confounds through participant selection criteria (e.g. exclusion of patients meeting DSM criteria for active major depression or proposed criteria for apathy¹⁷) and/or collecting data on confounding symptom severity to allow for more complex modeling (e.g. using validated depression¹⁸, sleep quality,¹⁹ or sleepiness²⁰ scales as covariate in regression models).

Fatigue and fatigability are normal physiologic reactions to prolonged or intense activity. In healthy individuals fatigue is predictable, transient, responds to rest and does not interfere with daily activities. Fatigue may be clinically significant if it is chronic, unpredictable, poorly responsive to rest, out of proportion to activities performed, present at rest or interfering with daily activity. Currently there is no consensus for how to define clinically significant fatigue in PD. The majority of studies that make this distinction do so by choosing a cut-point on a fatigue scale. Below we propose diagnostic criteria inspired by DSM-style criteria currently in use for defining cancer-related fatigue and chronic fatigue syndrome.^{21, 22} A related issue is the potential for fatigue in PD to be secondary to other causes (e.g. low testosterone, anemia, comorbid medical illness, medications) as opposed to PD pathology. Clinical researchers may address this issue through selection criteria (e.g. exclusion of patients with heart failure), screening for common causes of fatigue (e.g. hypothyroidism, anemia) and a careful history to determine if fatigue onset was associated with any specific medical or non-medical events (e.g. starting a beta-blocker medication). Of note, while sleepiness is associated with the use of dopamine agonists, there is no evidence that dopaminergic medications increase fatigue. In fact, there is preliminary data to suggest that PD medications and deep brain stimulation may actually improve fatigue in some patients.²³⁻²⁵

A fundamental distinction in this taxonomy is between perceptions of fatigue, often described as an increased sense of effort or decreased energy; and performance fatigability, an objective decrement in performance induced by continued activity. These symptoms are clearly dissociable in PD. Although PD patients demonstrate more rapid fatigability on both motor and cognitive tasks, this fatigability does not correlate with subjective fatigue complaints.²⁶⁻²⁸ Other studies have notably shown an increased sense of effort for PD patients performing motor tasks compared with healthy controls even when performance is similar, suggesting that fatigue complaints may be driven more by altered perception than performance limitations.²⁹ Further work associating objective measures with subjective complaints is needed to better understand the phenomenology of PD-related fatigue.

Mechanistic studies must be careful in attributing a causal relationship between physiologic markers and fatigue. Even in studies monitoring performance fatigability over time physiologic changes may reflect: 1) Functional deterioration of systems associated with performance³⁰; 2) Engagement of systems associated with perceptions or monitoring of effort and fatigue^{31, 32}; 3) Learning or other time-dependent processes not associated with fatigue³³; or 4) Engagement of compensatory processes to maintain performance.³⁴⁻³⁹ Terminology should thus clearly identify the neuroanatomic location and function of physiological factors as well as the domains of function affected. While the term “central fatigue” has been used to indicate central nervous system causes of fatigue it may also be used to refer to subjective fatigue and cognitive fatigability and should thus be used with caution.¹⁵

Proposed Diagnostic Criteria

There may be advantages to addressing PD-related fatigue as a distinct syndrome including: 1) Reducing participant heterogeneity in clinical and mechanistic studies; and 2) Providing a

diagnostic category to facilitate fatigue-related patient disability claims and medication coverage.⁴⁰ Potential downsides would include making the diagnosis of fatigue in PD more complex and limiting enrollment in clinical trials. As a motivating example, depression can also be viewed as either a symptom or syndrome but the majority of scientific advances in neurobiology, genetics and treatment have resulted from studies of syndromes such as major depressive disorder.⁴¹ In the field of clinical fatigue research, chronic fatigue syndrome (CFS) and cancer-related fatigue have moved towards syndromic diagnostic criteria with noted benefits regarding quality of clinical research and patient advocacy.^{21, 22}

In advocating for diagnostic criteria to define PD-related fatigue we propose that there are distinctive neurobiological features which drive fatigue in this population and may be utilized in the development of biomarkers and therapeutic targets. This assumption is supported by the observation that PD patients characterize their fatigue associated with PD as qualitatively different than normal physiological fatigue.⁴² Table 1 outlines our proposed working case definition of PD-related fatigue. This definition was based on published studies of fatigue in PD, our collective clinical experience, and review of the case definitions for cancer-related fatigue and CFS.^{21, 22, 43} Our major goals in creating this definition were to: 1) Differentiate persons with clinically significant fatigue from those experiencing normal physiological fatigue; and 2) To exclude patients with fatigue from causes other than PD. As this case definition is based on indirect evidence and expert opinion, further studies will be needed to directly validate these criteria including qualitative, psychometric and neurobiological studies. The utility of this case definition should also be evaluated through clinical trials applying these criteria for trial inclusion.

Measurement

In line with the fatigue taxonomy described above, we cannot recommend a single global fatigue measure. Rather, there is a need to choose relevant fatigue measures based on what aspects of fatigue are being studied which in turn depend on the research questions of a particular study. Fatigue measures may be categorized into three general domains: 1) Measures of perceptions of fatigue and subjective fatigue complaints; 2) Measures of performance fatigability; and 3) Physiologic factors associated with fatigue or fatigability.

Measures of Perceptions of Fatigue

In 2010 a Movement Disorders Society (MDS) Task Force published a review of subjective fatigue rating scales as well as recommendations for use.⁴⁴ Here we will briefly summarize the most commonly used and highly recommended fatigue rating scales in PD. Some authors have suggested that measures of overall activity should be considered in interpreting fatigue complaints due to the possibility that some persons may avoid/restrict activities to minimize fatigue complaints.⁴⁵ In addition to the measures of subjective fatigue complaints (trait), physiological studies may also consider single item visual analogue scales to measure momentary (state) perceptions of fatigue.⁴⁶

The Fatigue Severity Scale (FSS)⁴⁷ is a unidimensional, 9-item fatigue inventory that asks patients to rate statements regarding the impact of fatigue on various domains of function on

a 7-point scale (strongly disagree to strongly agree). It is the most commonly used fatigue scale across all conditions and the only scale to receive “recommended” ratings from the MDS Task Force for both screening and severity ratings. The Multidimensional Fatigue Inventory (MFI)⁴⁸ is a 20-item scale that asks patients to rate statements regarding feelings of effort and capacity on a 7-point Likert scale (“Yes, that is true” to “No, that is not true”). An advantage of the MFI is that it provides validated subscores for five dimensions of fatigue (general, physical, mental, reduced activity and reduced motivation).⁴⁹ The MFI received a “suggested” rating for screening and “recommended” rating for severity. The Parkinson Fatigue Scale (PFS)⁴² is a 16-item scale that asks patients to rate statements regarding both the subjective experience and impact of fatigue on a 5-point scale (strongly disagree to strongly agree). The PFS originated from statements by PD patients who experienced fatigue and received a “recommended” rating for screening and “suggested” rating for severity. The Modified Fatigue Impact Scale (MFIS)⁵⁰ is a 21-item scale that rates the impact of fatigue on function using a 5-point scale (never to always) and provides a total score in addition to physical, cognitive and psychosocial subscores. While not included in the MDS Task Force paper it has been subsequently validated in PD and is recommended for use by the Multiple Sclerosis Council for Clinical Practice Guidelines.⁵¹ Based on performance in clinical trials, the MFIS may also be more responsive to change than some other available scales.⁵²

Measures of Performance Fatigability

Objective performance fatigability is typically measured by either a) assessing performance at baseline on a task and measuring change in one or more aspects of performance during continued performance of that task; or b) assessing performance on a probe task at rest and the reassessing performance on these probe tasks after completion of a distinct fatiguing task. In the motor domain, fatigability is commonly assessed using motor tasks such as finger tapping (looking at rate) or force generation.²⁷ Two force generation protocols are commonly used to assess physical fatigability: intermittent submaximal force exercise protocol and the continuous maximum force exercise protocol.⁵³ While PD patients demonstrate accelerated fatigability on both types of motor tasks and report increased effort, no correlations have been found between these measures of fatigability and subjective complaints.^{27, 29}

Fatigability may also be induced by cognitive tasks and assessed in the cognitive domain by examining changes in response time or accuracy. To date, a single study using a prolonged version of the Attention Network Task (ANT) found accelerated cognitive fatigue in PD patients versus controls but failed to find a correlation with subjective fatigue complaints.²⁶ Studies examining fatigability using different tasks or outcome measures may be worth pursuing as studies from other neurologic disorders suggest that not all cognitive domains are equally associated with fatigue.³² Studies in other populations also suggest that change in intraindividual variability of response times may be a more sensitive metric than mean response time or accuracy.^{31, 54}

Measuring Physiologic Factors

Studies of physiologic factors frequently examine subjective fatigue complaints but more detailed mechanistic studies also investigate physiologic changes associated with momentary perceptions of fatigue or the development of cognitive or motor fatigability.^{39, 46}

Physiological factors with potential associations with PD-related fatigue include changes in cortical excitability, reduced central motor drive, autonomic dysfunction, metabolic function, respiratory function and inflammation.^{9, 13, 27, 55-57}

Although CNS factors are hypothesized to play a key role in PD-related fatigue, studies utilizing neuroimaging to understand PD-related fatigue are limited. The clinical relationship of dopaminergic loss to PD-related fatigue is unclear and most studies do not find a strong relationship between severity of motor symptoms and fatigue or dopaminergic therapies. However, in the ELLDOPA cohort of untreated early PD patients treatment with levodopa was associated with less progression of fatigue over 40 weeks and fatigue improvement was reported in one-third of de novo PD patients who subsequently started on dopamine replacement therapy in the Parkinson's Progression Markers Initiative (PPMI) cohort.^{2, 24, 58} Despite this, [¹²³I]-β-CIT imaging of striatal dopamine transporter uptake did not differ between high and low fatigue patients in the ELLDOPA cohort.⁵⁸ Another study also showed no difference in ¹⁸F-dopa uptake between 10 fatigued PD subjects and 10 non-fatigued PD subjects but revealed serotonin transporter binding in the caudate, putamen, ventral striatum and thalamus was decreased in fatigued compared to non-fatigued patients.¹¹ The role of other neurotransmitter systems (e.g. norepinephrine, acetylcholine GABA, glutamate), morphologic changes in grey and white matter, and regional brain activity and functional connectivity have yet to be explored in PD-related fatigue but are associated with fatigue in other neurologic disorders and should be pursued.^{39, 59-61}

Summary and Directions for Future Research

Table 2 provides a summary of recommendations relevant to the conduct and reporting of clinical research on PD-related fatigue. Future studies are needed to substantiate and optimize these recommendations, including: 1) Psychometric and qualitative studies for the proposed working case definition of PD-related fatigue; 2) Phenomenological and epidemiological studies to better understand the underlying construct of PD-related fatigue, including possible fatigue subtypes¹⁶; 3) Physiologic studies to elicit mechanisms, identify therapeutic targets and provide neurobiological validation of PD-related fatigue diagnosis; and 4) Clinical trials to validate the therapeutic utility and clinical meaningfulness of outcome measures and diagnostic classifications.

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Table 1
Proposed Criteria for diagnosis of Parkinson's Disease-related fatigue

Patients must report significantly diminished energy levels, or increased perceptions of effort which are disproportionate to attempted activities or general activity level. Symptoms must be present for most of the day, every day or nearly every day during the previous month. In addition, patients must have four or more of the symptoms from section A as well as meet criteria in sections B, C, and D.	
A. Symptoms	
1	Symptoms may be induced by routine activities of daily living.
2	Symptoms may occur with little or no exertion.
3	Symptoms limit the type, intensity or duration of activities performed by the patient.
4	Symptoms are not reliably relieved by rest or may require prolonged periods of rest.
5	Symptoms may be brought on by cognitive tasks or situations requiring sustained attention including social interactions.
6	Patients avoid rigorous activities due to fear of experiencing worsening of symptoms.
7	Mild to moderate exertion may induce a worsening of symptoms lasting hours to days.
8	Symptoms have a predictable diurnal pattern regardless of activities performed (e.g. worsening in the afternoon).
9	Symptoms are unpredictable and may have a sudden onset.
B. The patient experiences clinically significant distress or impairment in social, occupational or other important areas of function as a result of fatigue.	
C. There is evidence from the history and physical examination suggesting fatigue is a consequence of PD.	
D. The symptoms are not primarily a consequence of comorbid psychiatric disorders (e.g. depression), sleep disorders (e.g. obstructive sleep apnea) or medical conditions (e.g. anemia, congestive heart failure).	

Table 2
Summary of Recommendations for Terminology and Measurement for Clinical Research on PD-related Fatigue

1	Studies should define fatigue related terminology or refer to prior publications regarding taxonomy/definitions.
2	Fatigue should be distinguished from related symptoms (e.g. depression, sleepiness, apathy). Depending on the goals of the study this may be addressed through exclusion criteria or inclusion of measures of related symptoms for covariates in analyses.
3	Studies should address potential secondary causes of fatigue including other medical conditions (e.g. heart failure), psychiatric conditions (e.g. major depressive disorder), and medications (e.g. beta blockers) through subject selection criteria or covariates.
4	Studies should specify how clinically significant fatigue is defined using a case definition or a cut-point on a fatigue scale or other fatigue measure.
5	Studies should choose specific fatigue outcome measures based on their research question(s).
6	Studies of physiologic factors associated with fatigue should specify what aspects of fatigue they are associated with and how these factors may relate to fatigue (e.g. contributory, compensatory) if known.