**Fatigue in hypokinetic, hyperkinetic, and functional movement disorders**

Ilaria Antonella Di Vico, MD a\*#, Giovanni Cirillo, MD, PhD a,b,c\*, Alessandro Tessitore, MD, PhD c, Mattia Siciliano, PhD c,d, Massimo Venturelli, PhD a, [Cristian Falup-Pecurariu](https://pubmed.ncbi.nlm.nih.gov/?term=Falup-Pecurariu+C&cauthor_id=32296383), MD e, Gioacchino Tedeschi, MD c, Francesca Morgante, MD, PhD f, Michele Tinazzi, MD, PhD a#

a Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy;

b Division of Human Anatomy - Neuronal Networks Morphology Lab, University of Campania “Luigi Vanvitelli”, Naples, Italy;

c I Division of Neurology and Neurophysiopathology, Department of Medical and Surgical Sciences, University of Campania “Luigi Vanvitelli”, Naples, Italy;

d Department of Psychology, University of Campania "Luigi Vanvitelli", Caserta, Italy;

e Department of Neurology, Faculty of Medicine, Transilvania University, Brasov, Romania.

f Institute of Molecular and Clinical Sciences, St George's University of London, London, UK and Department of Clinical and Experimental Medicine, University of Messina, Italy.

\* *co-first authorship*

***# Co-corresponding authors:***

***Prof. Michele Tinazzi***

Neurology Unit, Movement Disorders Division,

Department of Neurosciences, Biomedicine and Movement Sciences,

University of Verona, Verona, Italy.

Tel: +39 0458122601

e-mail: michele.tinazzi@univr.it

***Dr. Ilaria A. Di Vico***

Neurology Unit, Movement Disorders Division,

Department of Neurosciences, Biomedicine and Movement Sciences,

University of Verona, Verona, Italy.

e-mail: ilariaantonella.divico@studenti.univr.it

**Declaration of interest**: All authors declare no potential competing financial and personal interests.

**Fundings**: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Abstract**

The emerging science of fatigue has soundly endorsed the need for its unified definition, shared terminology and increased recognition in neurological illnesses. Nevertheless, the real impact of fatigue remains under-recognized. Fatigue describes a sense of tiredness, lack of energy or need for increased effort often perceived as overwhelming, pervasive, and disabling. It is a common feature of chronic medical conditions and neurological diseases, including Parkinson’s disease (PD) and other hypokinetic, hyperkinetic, and functional movement disorders (FMD). While there is solid evidence for the burden of fatigue in PD, knowledge of fatigue in other movement disorders (MDS) is still limited. Lack of consensus definition, rigorous measures and the high prevalence of potential confounders such as apathy, depression and sleepiness are the main obstacles in studying fatigue in MDS. This review of the prevalence, impact, and clinical correlates of fatigue in common MDS summarizes current hypotheses for the pathophysiological mechanisms underlying fatigue and gives a brief overview of treatment options. Fatigue is a prevalent, disabling, primary non-motor symptom (NMS) in MDS, including atypical and secondary parkinsonisms, dystonia, essential tremor (ET) and a hallmark feature of FMD. We report the hypothesis that fatigue is a perceptual disorder of the sensorimotor system. Given therelevance of this burdensome symptom, fatigue deserves greater clinical and research attention to better understand its manifestation and pathophysiology and to improve diagnosis and treatment.

**Key words:**

Fatigue; Parkinson’s disease; Parkinsonisms; Dystonia; Essential Tremor; Functional Movement Disorders.

# 1. INTRODUCTION

Fatigue describes an overwhelming sense of tiredness, lack of energy or need for increased effort. It is pervasive, disproportionate to the performed activity, not relieved by rest or sleep and often interferes with mental and/or physical tasks [1,2]. It affects approximately 2-11% of the general population [3] and many patients with chronic medical conditions or neurological disorders. Fatigue is a frequent complaint in patients with hypokinetic disorders such as Parkinson’s disease (PD). Present in about half of PD patients [4], it is one of the most troublesome and disabling non-motor symptom (NMS), reduces quality of life (QoL), and limits physical and mental performance. In other movements disorders (MDS), however, including atypical parkinsonian syndromes, essential tremor (ET), dystonia, and functional movement disorders (FMD), fatigue might be an underestimated issue. Given the lack of existing evidence, we could not cover chorea and tics or other rarer MDS. Owing to its clinical presentation, multifactorial mechanisms and several potential confounders (i.e. concomitant depression, pain, apathy, multiple medications or comorbid illnesses), fatigue in PD and other MDS remains elusive, thus limiting treatment options.

This review gives an up-to-date overview of the epidemiology, pathophysiological mechanisms, current treatment and future perspective of fatigue in hypokinetic, hyperkinetic, and functional movements disorders. The potential unifying features of fatigue in MDS are discussed, emphasizing its importance in clinical practice and research. Literature search has been performed until June 2020. When possible, we referred to the most updated works. Better recognition of fatigue in MDS could help to elucidate its neural underpinnings and to develop tailored treatment strategies.

# 2. DEFINITION AND MEASURES

Currently, there is no consensus definition of fatigue in PD or other MDS and diagnostic criteria for PD-related fatigue remain a proposal [2]. However, a shared terminology would be central to achieving consistency and scientific progress [2,3,5]. Common definitionsare given in **Box 1**. Essential for a correct taxonomy of fatigue is to distinguish between fatigue and related constructs. *Fatigue* is a purely perceptive status, with a subjective and extremely individual nature, whereas *performance fatigability* refers to a decrease in muscle ability to exert force during exercise or work; as such, it is objective and physiologically measurable. Fatigue is a primary, independent symptom, established in the absence of causative factors of secondary fatigue (i.e., medications, chronic pain, physical deconditioning, anemia and so forth) or other NMS (e.g., depression, apathy or sleep disorders) that variably influence its occurrence [3]. Fatigue encompasses mental and/or physical domains, which do not necessarily correlate in severity [6,7]. *Mental fatigue* can arise from prolonged hypovigilance, sustained hypervigilance, unremitting intellectual activity, persistent emotional tension or it may occur with little or no mental exertion, whereas *physical fatigue* involves disproportionate physical exhaustion despite the incentive to perform a task. Furthermore, fatigue has also been classified as *peripheral* (correlated with a dysfunction originating at or distal to a neuromuscular junction) or *central* (arising from reduced muscle voluntary activation).However, the latter categorization can be confusing and should be used with caution or discarded because it makes inappropriate use of terms to describe performance fatigability and perception of fatigue interchangeably [3]. Efforts in improving consistency of fatigue designation, using a standardized definition is a priority in both clinical and research settings.

The subjective nature of fatigue eludes rigorous objective measures; reliable biomarkers absent, the only available tools are either questionnaires or self-reports. First-level screening for fatigue in PD can be done using the MDS-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [8] or the Non-Motor Symptom Assessment Scale (NMSS) during a holistic motor and non-motor assessment [9]. Fatigue in PD should be further evaluated with validated scales [10]. The Fatigue Severity Scale (FSS) [11] is a unidimensional scale recommended for both screening and grading severity in PD [12], also widely employed in multiple sclerosis (MS) trials [13], whereas the Parkinson Fatigue Scale (PFS) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale [9] are recommended for screening but only suggested for rating severity. Among multidimensional scales, the Multidimensional Fatigue Inventory (MFI) is the only that distinguishes five subdomains of fatigue (*reduced activity, reduced motivation, general, mental, and physical fatigue*); it is recommended for rating severity scale [9]. FSS and MFI were also validated in dystonia population, demonstrating satisfactory psychometric properties [34].

Importantly, no scale has proven superior to another. Accordingly, in the absence of a single specific clinical scale for fatigue in MDS, it is recommended selecting relevant fatigue measures coherent with the primary objective of the study and the use of multiple fatigue measures [1]. Moreover, none of these scales provide a clearly distinct measure of fatigue, irrespective of concurrent depression, anxiety, or apathy, whose high burden in MDS imposes a careful assessment with specific tools. Hence, it is crucial to address potential confounding symptoms through rigorous selection criteria or through a validated assessment of their severity (i.e. measures for depression, apathy, anxiety and sleep disturbances).

# 3. HYPOKINETIC MOVEMENT DISORDERS

## 3.1 Parkinson’s disease (PD)

Fatigue affects up to half of PD patients [4] and is the single most disabling symptom in one third [15]. Fatigue in PD has been consistently reported as one of the strongest predictors of QoL, also in early stages of the disease [11,15,16]. Fatigue influences multiple areas of daily living (e.g., emotional well-being, mobility, social functioning) and can increase the risk of institutionalization [16]. Fatigue in PD has been correlated with lower functional capacity for exercise, physical conditioning and more sedentary behaviour [17].

There is no clear association between PD-related fatigue and disease severity and progression or dopaminergic therapy. It can occur early in the course of PD or also sometimes in premotor stages [18], does not correlate with motor symptom severity [4], and is only weakly associated with drug-related effects [19]. Nonetheless, there is a close, somewhat inextricable relationship with other NMS such as apathy, anxiety, and disorders of the sleep-weak cycle [20]. From a behavioral perspective, fatigue and apathy share a reduction in self-initiated voluntary actions and deficits in motivational systems. Nevertheless, while motivational dysfunctions related to the activational system may play a greater role in fatigue, directional system deficits may predominate in apathy [21]. Indeed, apathetic patients are not normally interested in performing actions while in fatigue; despite wanting to act, they feel unable. Interestingly, despite this complex interplay with other NMS, many studies have demonstrated how fatigue in PD can occur in isolation with unique qualitative characteristics. Opposite to the prevailing clinical view, depression has recently been reported to have no signiﬁcant effect on fatigue prevalence [4]. This lack of correlation underscores the need to frame fatigue as an independent NMS of PD.

Specific impairment in the processing of novel stimuli in ventral attention network functioning has been demonstrated in PD patients with fatigue [22], thus suggesting a role for impaired cognition in fatigue, although no measures of global cognition significantly correlated with fatigue [4]. A recent study has also demonstrated that subjective memory decline (defined as memory complaints despite normal objective cognitive performance) and fatigue are associated in PD [23]. Autonomic nervous system dysfunction exacerbates the perception of fatigue [24]. A positive correlation has been reported between fatigue and orthostatic hypotension, and the scores for the two autonomic symptom questionnaires, the Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms (SCOPA-AUT) and the modified version of the Mayo Clinic Composite Autonomic Symptom Score (COMPASS) scale, in particular orthostatic intolerance [25,26]. Cardiac sympathetic denervation (demonstrated with 123I-meta-iodobenzylguanidine (123I-mIBG) scintigraphy) has been linked to fatigue [27–29], as has impairment of the parasympathetic cardiovascular axis, although the deep breathing test scores partially overlapped between the fatigued and the non-fatigued PD patients [28].

## 3.2 Other parkinsonian syndromes

In the seven studies that explored fatigue in atypical and secondary parkinsonisms [30–36] (Table 1), fatigue resulted a predominant non-motor feature of parkinsonian syndromes, present in up to 80% of patients with multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and vascular parkinsonism (VP), in 70% with dementia with Lewy bodies (DLB) and in almost 55% with corticobasal degeneration (CBD) [31]. Evaluation with the NMSS showed that sleep/fatigue disturbances were among the most commonly affected domains; the prevalence of fatigue (sub-item) was 61.0% in patients with MSA [36] and 68% or 65.8 % in those with PSP [30,33]. The clinical sub-type did not influence fatigue occurrence, and similar rates of prevalence and severity were found in the MSA-P (MSA with predominately parkinsonism), MSA-C (MSA with predominately cerebellar ataxia) [36], PSP-Richardson syndrome (PSP-RS), and PSP-parkinsonism (PSP-P) group [30]. Fatigue and sleep disturbances were correlated with poor QoL in the MSA-P and the MSA-C group [32,36] but not in the PSP group [32].

Correlation studies have showed that sleep/fatigue disorders are linked to mood/cognition and urinary dysfunction in MSA-P patients and with mood/cognition and cardiovascular disturbances in MSA-C patients [32]. In patients with PSP, sleep/fatigue was not modulated by age, age at onset, and disease duration. Conversely, fatigue resulted positively correlated with cognitive impairment, PSP-history, disease severity, and severity of bulbar symptoms but not with of parkinsonian symptom severity, as assessed by the UPDRS part III [30,32,37].

# 4. HYPERKINETIC MOVEMENT DISORDERS

## 4.1 Dystonia

To date, six studies (Table 2) have addressed fatigue in idiopathic dystonia affecting different body parts (generalized, segmental cervical, cranial, and other focal dystonia) [38], cervical dystonia (CD)[39–41], myoclonus dystonia (MD) due to epsilon sarcoglycan (SCGE) mutation [42], dopa-responsive dystonia (DRD) associated to ﻿GTP-cyclohydrolase 1 (GCH-1) mutation [43]. A Standardized tools for fatigue assessment was used in four out of the six studies [38,41–43] and a comprehensive ad hoc NMS questionnaire (﻿Dystonia Non-Motor Symptoms Questionnaire - DNMSQuest) in the other two [39,40]. Severe-to-moderate fatigue was reported in 46% of patients with dystonia and was perceived as one of the three most disabling symptoms in 37% [38]. Fatigue was rated as one of the five most burdensome symptoms and the second most disturbing one after tremor [40]. Fatigue was more prevalent in patients with generalized dystonia, CD, and focal dystonia (not cranial) than in those with segmental and cranial dystonia; between 50% and 70% of patients with CD reported fatigue significantly more often than the controls [38,39,41]. Reduced activity, mental fatigue, and reduced motivation were the domains most severely affected in over 50% of patients, while generalized fatigue was present in 42% and physical fatigue in 36%.

Fatigue has also been noted in other dystonia groups: 58% of those with DRD [43] and 42% of those with MD [42], although marginally under the cut-off for clinically significant fatigue [42]. Fatigue is a leading cause of diminished QoL in patients with dystonia, in which it affects the physical and mental components of QoL, irrespective of the co-occurrence of depression, pain, and sleep disturbances [38,40–43].

Analysis of clinical correlates has showed a strong correlation between fatigue in all its dimensions and neuropsychiatric comorbidities. While controlling for depression and anxiety, FSS scores remained significant, indicating the independent nature of fatigue in dystonia. Moreover, fatigue was positively correlated with bodily pain and tiredness, and negatively with sleep problems [38]. A weak association was found between fatigue and scores for jerks-tremor in patients with CD [41]. In patients with DRD, age at onset of dystonia and severity of motor symptoms (parkinsonian or dystonic) were associated with fatigue, which was more severe in younger and symptomatic patients than in older or asymptomatic patients [43].

4.2 Essential tremor (ET)

Three studies have investigated fatigue in ET [44–46] (Table 2). Fatigue has been described in 30% to 52.5% of patients with ET [44,45]. Almost 100% of ET patients reported disturbances in the domain sleep/fatigue on the NMSS [46]. Fatigue was far more prevalent and severe in patients with ET (prevalence 8-25%) than in the healthy controls [44,45]. Despite the higher rates and scores for fatigue in ET, no significant differences with healthy controls were found after subjects with moderate or severe depression were excluded [46], suggesting that fatigue in ET may be largely modulated by depression. Fatigue was correlated with depression [44,45] and other NMS like sleep quality, pain, and anxiety [44], whereas it was not signiﬁcantly correlated with age at onset, duration of tremor, and tremor severity. Fatigue was also positively correlated with the sleep/fatigue of the NMSS, age and age at disease onset. In general, the prevalence of non-motor abnormalities did not differ for gender, family history of tremor, use of medications, marital status, employment status or comorbidities [44]. Sleep/fatigue disturbances were shown to be predictors of poor emotional well-being [46], and fatigue had negative effects on physical and mental health and QoL.

# 5. FUNCTIONAL MOVEMENT DISORDERS (FMD)

Fatigue is one of the most common self-reported symptoms in patients with FMD. Accurate data on its prevalence are lacking, and only one study has directly compared fatigue in FMD in a historical cohort of 217 controls with neuromuscular disorders (NMD) [47]. The prevalence of fatigue, assessed via the Checklist Individual Strength was higher in FMD than in NMD patients (78% and 53%, respectively); the more severely affected subdomains were motivation, concentration, and physical activity. Another study showed that FMD patients were also more severely fatigued than age- and sex-matched healthy controls [48]. Other studies have reported high rates of fatigue among FMD patients, although measures of fatigue were not reported (Table 3). In a feasibility study on rehabilitation, after patients with prominent fatigue were excluded, half (N=30) still rated fatigue as severe to extreme, 45% (N=27) slight to moderate, and absent in only 5% (N=3). In another study that excluded patients with prominent fatigue, the reported prevalence of fatigue was 59.6% in a cohort of 47 patients [49]. Severe fatigue is known to impede good outcome of intense rehabilitation in such patients; when dominant, it was an exclusion criterion in intervention trials [49,50]. Moreover, some patients in the intervention group reported exacerbation of chronic fatigue related to treatment intensity, which resolved spontaneously within days.

Fatigue significantly affected self-rated health, and fatigue severity affected QoL after adjusting for the overlap with depressive symptoms [47]. Correlation studies in FMD linked depression and anxiety to all fatigue subdomains; motor severity was correlated with fatigue severity and physical activity but not with concentration and motivation.

#  6. PATHOPHYSIOLOGY OF FATIGUE: WHAT HAVE WE LEARNT FROM PARKINSON’S DISEASE?

Since the majority of mechanistic studies has been carried out in patients with PD, one of the fundamental question to answer is whether these results might serve as a model to understand the pathophysiology of fatigue in other MDS. To the best of our knowledge, three main pathophysiological mechanisms have been implicated in the genesis of fatigue in PD: (***i***) cortical-subcortical circuitry abnormalities; (***ii***) neurotransmitter imbalance; and (***iii***) neuroinflammatory mechanisms.

Corticothalamic–basal ganglia network dysfunction is well-recognized in the pathophysiology of many MDS, and basal ganglia-frontal loop impairment has been largely implicated in PD-related fatigue [51]. Imaging studies involving fatigued PD patients have demonstrated reduced perfusion in the frontal lobe and altered connectivity of the supplementary motor area (SMA) [52,53]. Based on these findings, cortical mechanisms of fatigue seem to be related more to impaired motor planning and movement preparation rather than to motor execution. In line with this hypothesis, abnormally greater corticomotor neuronal excitability was reported during and after a fatiguing exercise in PD patients compared to healthy controls [54], suggesting abnormal basal ganglia output to the cortex [55]. Changes of brain connectivity may be a strategy to overcome basal ganglia dysfunction. Advanced magnetic resonance imaging (MRI) studies using voxel-based morphometry have shown increased connectivity in the prefrontal and posterior cingulate cortices within the default mode network in the absence of structural gray or white matter differences in fatigued PD patients [52]. However, it is unclear whether this is a cognitive compensatory mechanism of motor hypoconnectivity or a maladaptive phenomenon [52].

Consistent with the negligible association between motor severity and disease duration [4] and the poor response of fatigue to dopaminergic treatment [56], dopaminergic degeneration in the nigrostriatal circuit has been linked with fatigue only in patients with early PD [19,57,58], while a role for extrastriatal dopaminergic dysfunction in the insular cortex has been proposed [58]. In contrast, several studies have suggested that serotonergic dysfunction can lead to the development of fatigue, depression, and anxiety [7], implicating a shared neurobiological mechanism. Serotonergic denervation in the basal ganglia and associated limbic circuits (ventral striatum, thalamus, amygdala, cingulate cortex) was reported in fatigued PD patients [58], and fatigue severity was negatively and significantly correlated with serotonin (5-HT) levels in the cerebral spinal ﬂuid [25]. Notably, serotonergic dysfunction has also been reported in non-PD fatigued patients [59].

Systemic inflammation is a commonly overlooked denominator for fatigue in multiple diseases, including neurological (e.g., MS, PD, amyotrophic lateral sclerosis) and non-neurological disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus). Studies to date have produced conflicting results and no biomarkers have been found. Elevated peripheral cytokines, including tumor necrosis factor alpha and interleukin-6, have been shown in PD patients [60]. Neuroinflammation has been implicated in fatigue per se, and increased levels of proinflammatory mediators have been found to correlate with more severe NMS in PD [61,62].

# In light of these findings, fatigue seems to be more a disorder of movement preparation rather than of movement execution. Its neural signature could be a perturbation in neurotransmitter balance at the fronto-basal ganglia loop that leads to impairment of the integration of sensory, motor, and affective inputs and results in disruption of the perceptual aspects of movement such as motivation to act or perceived effort [58]. Altered perception of effort is embedded in fatigue definition [3] and refers to the higher prediction of sensory consequences of movement compared to the actual sensory input derived from muscle contraction, with impairment of sensory attenuation. Aberrant sensory attenuation of self-generated movements has been identified as the primary cause of abnormal fatigue and as a disease-independent mediator of fatigue [21]. Importantly, aberrant sensory attenuation is an established correlate of disorders of agency that imply a lack (external attribution) of perceived effort [63], placing fatigue within the spectrum of agency-related disorders. This hypothesis aligns nicely with recognition of the high levels of fatigue in disorders like FMD, in which the neural underpinning is a disrupted sense of agency among other causes. Further studies are needed to clarify this hypothesis, identifying reliable biomarkers of fatigue and whether they are disease-specific or common across multiple conditions.

# 7. IS TREATMENT POSSIBLE?

Lack of uniformity in the clinical assessment, unclear pathogenic mechanisms, and paucity of compelling evidence have meant scarce recommendations for the treatment of fatigue. To date, few studies exclusively in PD patients, have included fatigue as a primary outcome measure or selected patients according to fatigue severity as measured with fatigue-specific tools. Moreover, fatigue scores barely reaching the cut-off for clinically relevant fatigue may have contributed to the lack of effect for most interventions [56]. As a result, findings are sparse and sometimes conflicting.

Experimental research has identified a potential role in fatigue treatment for drugs modulating dopaminergic neurotransmission, although no compelling evidence exists so far. Dopaminergic therapy ameliorated motor performance fatigability in patients with PD [54] and slowed progression of fatigue in early PD compared to placebo but without a dose-response effect [19]. In the large ADAGIO study cohort, rasagiline 1 or 2 mg showed a small, albeit statistically significant, effect on fatigue compared to placebo in recently diagnosed drug-naïve PD patients [64].

Low rates of fatigue were reported in a large Japanese study that involved patients with mild to moderate PD treated with pramipexole [65] and patients treated with transdermal rotigotine patch; however, fatigue has been reported among the possible side effects of pramipexole therapy [66–68].

The clinical efficacy of psychostimulants (caffeine, methylphenidate) in PD-related fatigue is controversial and concerns about long-term use of pharmacological psychostimulants have been raised (drug dependency, psychotic symptoms, behavioral sensitization) [69]. A randomized controlled trial (RCT) on methylphenidate in a small group of PD patients reported lower fatigue scores following a 6-week treatment period [70]. However, no statistically significant differences were found between methylphenidate and placebo on the FSS and the MFI total score, thus a pharmacological benefit is uncertain [56].

Despite successful clinical application of modafinil for the treatment of daytime sleepiness in PD patients [71], evidence to support its use to treat PD-related fatigue is insufficient [69].

Doxepin, a tricyclic antidepressant, was found to considerably reduce fatigue (and insomnia) in PD patients at a daily dosage of 10 mg [72]; however , because the small sample size (N=12) limits the quality of evidence in this study these findings need to be confirmed in studies with a larger sample.

Amantadine, a weak N-methyl-d-aspartate receptor antagonist with antiviral effects, is commonly employed in the treatment of fatigue in multiple sclerosis [5]. It has been only marginally assessed in PD-related fatigue. In the EASED study, administration of Amantadine Extended Release, a long-acting, extended-release capsule formulation of amantadine taken once daily at bedtime, was not found to have a significant effect on fatigue [73].

Common sense and clinical practice might suggest a potential role for physical exercise in treating fatigue, but RCTs and interventional studies have produced conflicting results and no design for an ideal exercise prescription program has been forthcoming. The efficacy of aerobic exercise in PD-related fatigue was demonstrated in a pilot RCT that tested a protocol of home-based treadmill training (20–40 min, four times a week for 6 weeks) [74]. Moreover, high-intensity exercise prescription [75] and aerobic walking, fitness, and motor function [76] effectively reduced fatigue severity in PD patients. However, these results were not supported by the Park-in-Shape study, which found no beneficial effect after 6 months (30–45 min, three times per week) of high-intensity aerobic exercise [77]. A possible explanation for these disappointing results is the ceiling effect of relatively good baseline FSS scores. Poor efficacy of a 12-week, mixed exercise program (aerobic, strength, ﬂexibility) in reducing fatigue in PD patients was also reported in a single-blinded study compared to usual care [78]. Importantly, however, since lack of mobility and a sedentary lifestyle have been linked to fatigue [78] and could potentially perpetuate fatigue symptoms, assessing the effects of physical exercise in the management of fatigue is warranted.

In conclusion, high-quality evidence studies are needed to assess the treatment of fatigue in PD and other MDS.

# 8. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Fatigue is a prevalent and disabling NMS in MDS. It is a component of the clinical spectrum of neurodegenerative and secondary parkinsonisms (VP), dystonia (genetic, acquired, focal or generalized), ET (even if it seems to be strictly related to mood disorder) and FMD. Lack of consensus definition, rigorous measures and the high prevalence of potentially confounders challenge fatigue research and clinical recognition in MDS. According to the current evidence, we hypothesize that fatigue might be a perceptual disorder of the sensorimotor system. Therefore, since no specific treatment options are currently recommended, our future activity aims to identify new specific fatigue-related markers using advanced imaging techniques or neurophysiological paradigms. Bursting clinical and experimental research, we believe that comprehension of fatigue phenomenology and pathophysiology will improve the diagnosis and pave the way for new targeted therapeutic options.

**Figure**



**Box 1**

1. **Fatigue**: subjective overwhelming sense of tiredness, lack of energy or need for increased effort.
* **Mental Fatigue** cognitivefatigue that limits initiating and/or endurance in mental activities
* **Physical Fatigue** physical sense of tiredness that limits initiating and/or endurance of physical tasks
* **Primary Fatigue:** isolated fatigue not related to secondary causative factors
* **Secondary Fatigue:** fatigue caused by medical conditions or other non-motor symptoms
1. **Performance fatigability**: objective decline in performance physiologically measurable during motor or cognitive tasks
* **Mental Performance fatigability**: cognitivefatigability during mental activities
* **Physical Performance fatigability**: fatigability during physical tasks
* **Central Performance fatigability**: fatigability induced by central mechanisms (from brain to spinal cord)
* **Peripheral** **Performance fatigability**: fatigability induced by mechanisms above the neuromuscular junction

**Table 1**. Frequency and severity of fatigue in hypokinetic parkinsonian syndromes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Subjects/****Patients** | **Age****(Mean ± SD)** | **Disease Duration** **(Mean ± SD)** | **Measures of Fatigue** | **Fatigue Frequency and/or Severity in:** |
| **PSP** | **MSA** | **CBD** | **VP** | **DLB** | **PD** | **HC** |
| Colosimo et al., 2010 | N=1302 * *N=30 PSP*
* *N=34 MSA*
* *N=11 CBD*
* *N=83 VP*
* *N=14 DLB*
* *N=1130 PD*
 | PSP 63.5±8.7MSA 63.5±8.7CBD 70.1±10.2VP 74.2±7.1DLB 63.5±8.7PD 67.3±9.4 | PSP 3.5±3.1MSA 3.5±1.8 CBD 2.5±1.1 VP 4.4±3.4DLB 4.2±3.1PD 6.6±5.1 | One-item question:“Fatigue limiting the patient’s day activities” | FrequencyN=24, 80.0% | FrequencyN=28, 82.4% | FrequencyN=10, 54.6% | FrequencyN=65, 79.3% | FrequencyN=6, 71.4% | FrequencyN=669, 59.4% | / |
| Radicati et al., 2017 | N=50 PSP N=100 PD  | PSP 69.82±9.04PD 69.19±8.27 | PSP 3.80±2.06PD 3.83±2.25 | NMSSSleep/fatigue(domain) | Frequency92%Severity27.50 | / | / | / | / | Frequency89%Severity16.25 | / |
| NMSS Fatigue(sub-item) | Frequency68% | Frequency67% |
| Ou et al., 2016 | N=27 PSP N=27 PD N=27 HC | PSP 65.1±8.4PD 65.3±8.4HC 65.6±8.4 | PSP 3.6±2.1PD 3.6±1.9/ | NMSSSleep/fatigue (domain) | Frequency100%Severity12.4±9.5 | / | / | / | / | Frequency88.9%Severity11.1±9.5 | Frequency59.3%Severity3.0±4.5 |
| Chaithra et al., 2020 | N=76 * *N=53 PSP-RS*
* *N=16 PSP-P*
* *N=7 other PSP*
 | 62.04± 7.10 | 2.68±2.10 | NMSSSleep/fatigue(domain) | Frequency82.90%Severity7.84±6.44 (PSP)Frequency86.79%Severity8.23±6.54 (PSP-RS)Frequency87.50%Severity8.19±5.82(PSP-P) | / | / | / | / | / | / |
| NMSS Fatigue (sub-item) | Frequency65.80%Severity3.71±3.78(PSP)Frequency69.81%Severity4.28±3.91(PSP-RS)Frequency68.75%Severity3.25±3.39 (PSP-P) |
| Wang et al., 2019 | N= 55 MSA * *N=18 RBD +*
* *N=37 RBD -*
 | 62.80±10.55  |  | FSS |  | Severity21.15 (11-28)(MSA)Severity21.28(10-31.25)(MSA RBD+)Severity21.08 (12-27.05)MSA RBD-) | / | / | / | / | / |
| Zhang et al., 2016 | N= 172 MSA * *N=76 MSA-P*
* *N=96 MSA-C*
 | 60.03±7.03 | 2.72±1.60 | NMSSSleep/fatigue (domain)  |  | FrequencyN=150, 87.2%Severity9.91±7.95 (MSA)FrequencyN=68, 89.5% Severity11.22±8.67 (MSA-P)FrequencyN= 82, 85.4%Severity8.87±7.21 (MSA-C) | / | / | / | / | / |
| NMSS Fatigue (sub-item) | FrequencyN=105,61.0% Severity3.09±3.39(MSA)FrequencyN=47,61.8% Severity3.58±3.65(MSA-P)FrequencyN=58,60.4%Severity2.71 ± 3.14(MSA-C) |

**Table legend***:* ***PSP***, progressive supranuclear palsy; ***PSP-RS****,* PSP-Richardson syndrome; ***PSP-P***, PSP-parkinsonism; ***MSA***, multiple system atrophy; ***MSA-P***, MSA-parkinsonian subtype; ***MSA-C***, MSA cerebellar subtype; ***RBD***, rapid eye movement behaviour disorders; ***CBD****,* corticobasal degeneration; ***VP****,* vascular parkinsonism; ***DLB****,* dementia with Lewy bodies; ***PD****,* Parkinson’s disease;***HC****,* healthy controls; ***NMSS***, Non-Motor Symptom Scale; ***FSS***, Fatigue Severity Scale.

**Table 2**. Frequency and severity of fatigue in hyperkinetic MDS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Subjects/****Patients** | **Age****(Mean ± SD)** | **Disease Duration****(Mean ± SD) or****Median (range)** | **Measures of****Fatigue** | **Fatigue Frequency and/or Severity in:** |
| **GD** | **CD** | **SD** | **CrD** | **Other FD** | **DRD** | **M-D** | **ET** | **HC** |
| Wagle Shukla et al., 2016 | N= 91* 9: GD;
* 18: SD,
* 64: FD
 | 60 ± 17 | 7.5 ±8 | FSS | Frequency56%Severity3.9±1.8 | Frequency50%Severity4.1±1.9 | Frequency39%Severity3.5±2.1 | Frequency38%Severity3.7±1.7 | Frequency67%Severity3.6±1.4 | / | / | / | / |
| MFI | Severity |
| GF 12.6±2.5PF 13.4±3.2MF 12.2±1.4RA 12.8±1.9RM 12.9±1.8 | GF 12.2±2.8PF 11.5±2.1MF 12.5±2.1RA 12.8±1.5RM 12.9±2.0 | GF 11.1±2.9PF 11.7±2.2MF 7.2±5.3RA 12.7±1.7RM 13.5±2.3 | GF 11.8±3.5PF 11.8±2.8MF 12.8±2.4RA 12.7±1.3RM 12.1±1.5 | GF 12±4.0PF 11±3.5MF 11.3±3.2RA 12±1.0RM 13.3±2.5 |
| Smit et al., 2017a | N= 40 CD | 54.1 | 13.1 ± 11.2 | NMS questionnaire | / | Frequency76.3% | / | / | / | / | / | / | / |
| Smit et al., 2017b | N= 44 CDN= 43 HC | CD 54±10.6HC 54±11.3 | 13.3 ± 11.2/ | FSS | / | Severity4.4±1.7 | / | / | / | / | / | / | Severity2.7±1.4 |
| Kingelhoefer et al., 2014 | N= 102 CD | 59.19±1.21 | 10.99±7.10 | NMS questionnaire | / | Frequency51.0 % | / | / | / | / | / | / | / |
| Timmers et al., 2017 | N= 22 DRDN= 21 HC | DRD 45.2HC 46.2 | 27.4 (20.8)/ | FSS | / | / | / | / | / | Frequency36%Severity35.0±16.2 | / | / | FrequencyN=5, 24%Severity27±14.0 |
| Timmers et al., 2019 | N= 41 M-DN= 51 CDN= 19 DRDN= 53 HC | M-D 48.7±15.7CD 54.2±10.6DRD 51.1±15.6HC 53.4±12.9 | M-D 45 (7–73)CD 10 (1–52)DRD 40 (18–71)/ | FSS | / | Frequency73%Severity39.6±15.7 | / | / | / | Frequency58%Severity36.9±18.1 | Frequency42%Severity35.0±15.7 | / | Frequency15%Severity24.0±12.4 |
| Chandran et al., 2012 | N=50 ETN=50 HC | ET 40.7± 16.2HC 42.3±15.3 | 8.4±10.0/ | PFS | / | / | / | / | / | / | / | Frequency30% Severity5.8±0.8 | Frequency8%Severity2.5±0.4 |
| Sengul et al., 2014 | N=45 ETN=35 HC | ET 24.55±7.16HC 24.80±5.43 | 4.36±3.94/ | FSS | / | / | / | / | / | / | / | Frequency52.5%Severity39.05±16.94  | Frequency25.0%Severity27.34±13.21 |
| Shalash et al., 2019 | N=40 ETN=30 HC | ET 45.20±18.10HC 43.43±17.27 | 10.40±7.86/ | NMSS(Sleep/fatigue domain) | / | / | / | / | / | / | / | Frequency100%Severity10.53 ± 6.07 | Frequency80%Severity4.10 ± 3.52 |

**Table legend***:* ***GD***, generalized dystonia; ***CD****,* Cervicaldystonia*;* ***SD***, segmental dystonia; ***CrD****,* cranial dystonia;***FD***, focal dystonia; ***DRD****,* Dopa-responsive dystonia*;* ***M-D****,* Myoclonus-dystonia*;* ***ET***, Essential Tremor; ***HC****,* healthy controls; ***FSS****,* Fatigue Severity Scale; ***MFI****,* Multidimensional Fatigue Inventory; ***NMS****,* Non-motor symptom; ***PFS***, *Parkinson’s disease fatigue scale*; ***NMSS***, *Non-Motor Symptoms Scale****; GF****,* General Fatigue; ***PF****,* Physical Fatigue; ***MF****,* Mental Fatigue; ***RA****,* Reduced Activity; ***RM****,* Reduced Motivation.

**Table 3**. Frequency and severity of fatigue in functional movement disorders (FMDs)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study**  | **Subjects/patients**  | **Age****(Mean ± SD)**  | **Disease Duration (Mean ± SD)** | **Measures of Fatigue**  | **Fatigue frequency and/or severity in:** |
| **FMDs** | **NMDs** | **HC** |
| Věchetová et al., 2018 | N=61 FMDN=61 HC | FMD 45.1±13HC 43.5±12 | 5.7±5 | FSS | Severity5.4±1 | / | Severity3.2±1 |
| Gelauff et al., 2020 | N=181 FMDN=217 NMD | FMD 48 ± 15NMD 42 ± 10 | *n. r.**n. r.* | Fatigue (CIS) | Severity scores ≥ 3578%Motivation15±10Concentration21±15Physical activity14±9 | Severity scores ≥ 3553%Motivation11±8Concentration12±13Physical activity9±8 | / |
| Nielsen et al., 2015 | N=47 FMD | 44.2±14.1 | 5.5±6.7 | Self-rating fatigue  | FrequencyN=28, 59,6% | / | / |
| Nielsen et al., 2017 | N=60 FMD | 44.2±14.1 | 5.8±7.3 | Self-rating fatigue | FrequencyNoneN=3, 5%Slight to moderateN=27, 45%Severe to extremeN=30, 50% | / | / |

**Table legend**: ***FMDs***, Functional Movement Disorders; ***NMDs***, neuromuscular disorders; ***HC***, healthy controls; ***FSS***, fatigue severity scale; ***CIS*** checklist individual strength; ***n.r.***, not reported.

# References

[1] B.M. Kluger, K. Herlofson, K.L. Chou, J.S. Lou, C.G. Goetz, A.E. Lang, D. Weintraub, J. Friedman, Parkinson’s disease-related fatigue: A case definition and recommendations for clinical research, Mov. Disord. 31 (2016) 625–631. https://doi.org/10.1002/mds.26511.

[2] B.M. Kluger, Fatigue in Parkinson’s Disease, in: Int. Rev. Neurobiol., 2017: pp. 743–768. https://doi.org/10.1016/bs.irn.2017.05.007.

[3] B.M. Kluger, L.B. Krupp, R.M. Enoka, Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy, Neurology. 80 (2013) 409–416. https://doi.org/10.1212/WNL.0b013e31827f07be.

[4] M. Siciliano, L. Trojano, G. Santangelo, R. De Micco, G. Tedeschi, A. Tessitore, Fatigue in Parkinson’s disease: A systematic review and meta-analysis, Mov. Disord. 33 (2018) 1712–1723. https://doi.org/10.1002/mds.27461.

[5] I.K. Penner, F. Paul, Fatigue as a symptom or comorbidity of neurological diseases, Nat. Rev. Neurol. 13 (2017) 662–675. https://doi.org/10.1038/nrneurol.2017.117.

[6] J.-S. Lou, Physical and Mental Fatigue in Parkinsonʼs Disease, Drugs Aging. 26 (2009) 195–208. https://doi.org/10.2165/00002512-200926030-00002.

[7] A. Chaudhuri, P.O. Behan, Fatigue and basal ganglia, J. Neurol. Sci. 179 (2000) 34–42. https://doi.org/10.1016/S0022-510X(00)00411-1.

[8] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M.B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A.E. Lang, A. Lees, S. Leurgans, P.A. LeWitt, D. Nyenhuis, C.W. Olanow, O. Rascol, A. Schrag, J.A. Teresi, J.J. van Hilten, N. LaPelle, P. Agarwal, S. Athar, Y. Bordelan, H.M. Bronte-Stewart, R. Camicioli, K. Chou, W. Cole, A. Dalvi, H. Delgado, A. Diamond, J.P. Dick, J. Duda, R.J. Elble, C. Evans, V.G. Evidente, H.H. Fernandez, S. Fox, J.H. Friedman, R.D. Fross, D. Gallagher, C.G. Goetz, D. Hall, N. Hermanowicz, V. Hinson, S. Horn, H. Hurtig, U.J. Kang, G. Kleiner-Fisman, O. Klepitskaya, K. Kompoliti, E.C. Lai, M.L. Leehey, I. Leroi, K.E. Lyons, T. McClain, S.W. Metzer, J. Miyasaki, J.C. Morgan, M. Nance, J. Nemeth, R. Pahwa, S.A. Parashos, J.S.J.S. Schneider, A. Schrag, K. Sethi, L.M. Shulman, A. Siderowf, M. Silverdale, T. Simuni, M. Stacy, M.B. Stern, R.M. Stewart, K. Sullivan, D.M. Swope, P.M. Wadia, R.W. Walker, R. Walker, W.J. Weiner, J. Wiener, J. Wilkinson, J.M. Wojcieszek, S. Wolfrath, F. Wooten, A. Wu, T.A. Zesiewicz, R.M. Zweig, Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results, Mov. Disord. 23 (2008) 2129–2170. https://doi.org/10.1002/mds.22340.

[9] K.R. Chaudhuri, P. Martinez-Martin, A.H.V. Schapira, F. Stocchi, K. Sethi, P. Odin, R.G. Brown, W. Koller, P. Barone, G. MacPhee, L. Kelly, M. Rabey, D. MacMahon, S. Thomas, W. Ondo, D. Rye, A. Forbes, S. Tluk, V. Dhawan, A. Bowron, A.J. Williams, C.W. Olanow, International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson’s disease: The NMSQuest study, Mov. Disord. 21 (2006) 916–923. https://doi.org/10.1002/mds.20844.

[10] J.H. Friedman, G. Alves, P. Hagell, J. Marinus, L. Marsh, P. Martinez-Martin, C.G. Goetz, W. Poewe, O. Rascol, C. Sampaio, G. Stebbins, A. Schrag, Fatigue rating scales critique and recommendations by the Movement Disorders Society Task Force on rating scales for Parkinson’s disease, Mov. Disord. 25 (2010) 805–822. https://doi.org/10.1002/mds.22989.

[11] D.A. Gallagher, A.J. Lees, A. Schrag, What are the most important nonmotor symptoms in patients with Parkinson’s disease and are we missing them?, Mov. Disord. 25 (2010) 2493–2500. https://doi.org/10.1002/mds.23394.

[12] R.G. Brown, A. Dittner, L. Findley, S.C. Wessely, The Parkinson fatigue scale, Park. Relat. Disord. 11 (2005) 49–55. https://doi.org/10.1016/j.parkreldis.2004.07.007.

[13] H. Beckerman, I.C. Eijssen, J. van Meeteren, M.C. Verhulsdonck, V. de Groot, Fatigue Profiles in Patients with Multiple Sclerosis are Based on Severity of Fatigue and not on Dimensions of Fatigue, Sci. Rep. 10 (2020) 4167. https://doi.org/10.1038/s41598-020-61076-1.

[14] S.B. Yellen, D.F. Cella, K. Webster, C. Blendowski, E. Kaplan, Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system, J. Pain Symptom Manage. 13 (1997) 63–74. https://doi.org/10.1016/S0885-3924(96)00274-6.

[15] P. Barone, A. Antonini, C. Colosimo, R. Marconi, L. Morgante, T.P. Avarello, E. Bottacchi, A. Cannas, G. Ceravolo, R. Ceravolo, G. Cicarelli, R.M. Gaglio, R.M. Giglia, F. Iemolo, M. Manfredi, G. Meco, A. Nicoletti, M. Pederzoli, A. Petrone, A. Pisani, F.E. Pontieri, R. Quatrale, S. Ramat, R. Scala, G. Volpe, S. Zappulla, A.R. Bentivoglio, F. Stocchi, G. Trianni, P. Del Dotto, The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson’s disease, Mov. Disord. 24 (2009) 1641–1649. https://doi.org/10.1002/mds.22643.

[16] K. Herlofson, J.P. Larsen, The influence of fatigue on health-related quality of life in patients with Parkinson’s disease, Acta Neurol. Scand. 107 (2003) 1–6. https://doi.org/10.1034/j.1600-0404.2003.02033.x.

[17] C.E. Garber, J.H. Friedman, Effects of fatigue on physical activity and function in patients with Parkinson’s disease, Neurology. (2003). https://doi.org/10.1212/01.WNL.0000055868.06222.AB.

[18] C. Pont-Sunyer, A. Hotter, C. Gaig, K. Seppi, Y. Compta, R. Katzenschlager, N. Mas, D. Hofeneder, T. Brücke, A. Bayés, K. Wenzel, J. Infante, H. Zach, W. Pirker, I.J. Posada, R. Álvarez, L. Ispierto, O. De Fàbregues, A. Callén, A. Palasí, M. Aguilar, M.J. Martí, F. Valldeoriola, M. Salamero, W. Poewe, E. Tolosa, The onset of nonmotor symptoms in parkinson’s disease (the onset pd study), Mov. Disord. 30 (2015) 229–237. https://doi.org/10.1002/mds.26077.

[19] G. Schifitto, J.H. Friedman, D. Oakes, L. Shulman, C.L. Comella, K. Marek, S. Fahn, Fatigue in levodopa-naïve subjects with Parkinson disease, Neurology. 71 (2008) 481–485. https://doi.org/10.1212/01.wnl.0000324862.29733.69.

[20] A.D. Krystal, Psychiatric Disorders and Sleep, Neurol. Clin. (2012). https://doi.org/10.1016/j.ncl.2012.08.018.

[21] A. Kuppuswamy, The fatigue conundrum, Brain. 140 (2017) 2240–2245. https://doi.org/10.1093/brain/awx153.

[22] C. Pauletti, D. Mannarelli, N. Locuratolo, A. Currà, L. Marinelli, F. Fattapposta, Central fatigue and attentional processing in Parkinson’s disease: An event-related potentials study, Clin. Neurophysiol. 130 (2019) 692–700. https://doi.org/10.1016/j.clinph.2019.01.017.

[23] M. Siciliano, L. Trojano, R. De Micco, A. Russo, G. Tedeschi, A. Tessitore, Subjective memory decline in Parkinson’s disease patients with and without fatigue, Parkinsonism Relat. Disord. 70 (2020) 15–19. https://doi.org/10.1016/j.parkreldis.2019.11.017.

[24] J.H. Friedman, R.G. Brown, C. Comella, C.E. Garber, L.B. Krupp, J.S. Lou, L. Marsh, L. Nail, L. Shulman, C.B. Taylor, Fatigue in Parkinson’s disease: A review, Mov. Disord. 22 (2007) 297–308. https://doi.org/10.1002/mds.21240.

[25] L.J. Zuo, S.Y. Yu, F. Wang, Y. Hu, Y.S. Piao, Y. Du, T.H. Lian, R.D. Wang, Q.J. Yu, Y.J. Wang, X.M. Wang, P. Chan, S. Di Chen, Y. Wang, W. Zhang, Parkinson’s disease with fatigue: Clinical characteristics and potential mechanisms relevant to α-synuclein oligomer, J. Clin. Neurol. 12 (2016) 172–180. https://doi.org/10.3988/jcn.2016.12.2.172.

[26] J.H. Ahn, M. Kim, J.K. Mun, Y. Cho, J.S. Kim, J. Youn, J.S. Kim, J.W. Cho, The Dysfunctional Autonomic Function and “Dysfunctional” Fatigue in Drug Naïve Parkinson’s Disease, J. Parkinsons. Dis. (2020). https://doi.org/10.3233/JPD-201919.

[27] T. Nakamura, M. Hirayama, T. Hara, T. Hama, H. Watanabe, G. Sobue, Does cardiovascular autonomic dysfunction contribute to fatigue in Parkinson’s disease?, Mov. Disord. 26 (2011) 1869–1874. https://doi.org/10.1002/mds.23744.

[28] E. Olivola, L. Brusa, C. Rocchi, O. Schillaci, C. Liguori, R. Cerroni, M. Pierantozzi, A. Chiaravalloti, A. Stefani, F. Stocchi, Does fatigue in Parkinson’s disease correlate with autonomic nervous system dysfunction?, Neurol. Sci. 39 (2018) 2169–2174. https://doi.org/10.1007/s10072-018-3569-x.

[29] K.L. Chou, S. Gilman, N.I. Bohnen, Association between autonomic dysfunction and fatigue in Parkinson disease, J. Neurol. Sci. 377 (2017) 190–192. https://doi.org/10.1016/j.jns.2017.04.023.

[30] S.P. Chaithra, S. Prasad, V.V. Holla, A. Stezin, N. Kamble, R. Yadav, P.K. Pal, The Non-Motor Symptom Profile of Progressive Supranuclear Palsy, J. Mov. Disord. 13 (2020) 118–126. https://doi.org/10.14802/jmd.19066.

[31] C. Colosimo, L. Morgante, A. Antonini, P. Barone, T.P. Avarello, E. Bottacchi, A. Cannas, M.G. Ceravolo, R. Ceravolo, G. Cicarelli, R.M. Gaglio, L. Giglia, F. Iemolo, M. Manfredi, G. Meco, A. Nicoletti, M. Pederzoli, A. Petrone, A. Pisani, F.E. Pontieri, R. Quatrale, S. Ramat, R. Scala, G. Volpe, S. Zappulla, A.R. Bentivoglio, F. Stocchi, G. Trianni, P. Del Dotto, L. Simoni, R. Marconi, Non-motor symptoms in atypical and secondary parkinsonism: The PRIAMO study, J. Neurol. 257 (2010) 5–14. https://doi.org/10.1007/s00415-009-5255-7.

[32] C.N. Lee, M. Kim, H.M. Lee, J.W. Jang, S.M. Lee, D.Y. Kwon, K.W. Park, S.B. Koh, The interrelationship between non-motor symptoms in Atypical Parkinsonism, J. Neurol. Sci. 327 (2013) 15–21. https://doi.org/10.1016/j.jns.2013.01.034.

[33] F.G. Radicati, P. Martinez Martin, C. Fossati, K.R. Chaudhuri, M. Torti, C. Rodriguez Blazquez, L. Vacca, F. Stocchi, Non motor symptoms in progressive supranuclear palsy: prevalence and severity, Npj Park. Dis. 3 (2017). https://doi.org/10.1038/s41531-017-0037-x.

[34] R. Ou, W. Song, Q. Wei, K. Chen, B. Cao, Y. Hou, B. Zhao, H. Shang, Non-motor symptoms in progressive supranuclear palsy, Mov. Disord. 31 (2016) S55. https://doi.org/http://dx.doi.org/10.1002/mds.26688.

[35] H. Wang, R. An, Y. Chen, X. Mu, B. Yang, Q. Zhao, H. Huang, P. Ning, Q. Shen, D. Xie, H. Lu, J. Zhou, Y. Xu, Clinical features of multiple system atrophy with or without rapid eye movement behavior disorder: a cross-sectional study in southwest China, Clin. Auton. Res. 30 (2020) 239–245. https://doi.org/10.1007/s10286-019-00651-7.

[36] L.Y. Zhang, B. Cao, R.W. Ou, Q.Q. Wei, B. Zhao, J. Yang, Y. Wu, H.F. Shang, Non-motor symptoms and the quality of life in multiple system atrophy with different subtypes, Park. Relat. Disord. 35 (2017) 63–68. https://doi.org/10.1016/j.parkreldis.2016.12.007.

[37] R. Ou, W. Song, Q. Wei, K. Chen, B. Cao, Y. Hou, B. Zhao, H. Shang, Characteristics of Nonmotor Symptoms in Progressive Supranuclear Palsy, Parkinsons. Dis. 2016 (2016). https://doi.org/10.1155/2016/9730319.

[38] A.W. Shukla, R. Brown, K. Heese, J. Jones, R.L. Rodriguez, I.M. Malaty, M.S. Okun, B.M. Kluger, High rates of fatigue and sleep disturbances in dystonia, Int. J. Neurosci. 126 (2016) 928–935. https://doi.org/10.3109/00207454.2015.1085035.

[39] L. Klingelhoefer, D. Martino, P. Martinez-Martin, A. Sauerbier, A. Rizos, W. Jost, T.T. Warner, K.R. Chaudhuri, Nonmotor symptoms and focal cervical dystonia: Observations from 102 patients, Basal Ganglia. 4 (2014) 117–120. https://doi.org/10.1016/j.baga.2014.10.002.

[40] M. Smit, A.L. Bartels, A. Kuiper, A.S.J. Kamphuis, V. Han, M.A.J. Tijssen, The Frequency and Self-perceived Impact on Daily Life of Motor and Non-motor Symptoms in Cervical Dystonia, Mov. Disord. Clin. Pract. 4 (2017) 750–754. https://doi.org/10.1002/mdc3.12510.

[41] M. Smit, A.S.J. Kamphuis, A.L. Bartels, V. Han, R.E. Stewart, I. Zijdewind, M.A. Tijssen, Fatigue, Sleep Disturbances, and Their Influence on Quality of Life in Cervical Dystonia Patients, Mov. Disord. Clin. Pract. 4 (2017) 517–523. https://doi.org/10.1002/mdc3.12459.

[42] E.R. Timmers, M. Smit, A. Kuiper, A.L. Bartels, S. van der Veen, A.M.M. van der Stouwe, P. Santens, B. Bergmans, M.A.J. Tijssen, Myoclonus-dystonia: Distinctive motor and non-motor phenotype from other dystonia syndromes, Park. Relat. Disord. 69 (2019) 85–90. https://doi.org/10.1016/j.parkreldis.2019.10.015.

[43] E.R. Timmers, A. Kuiper, M. Smit, A.L. Bartels, D.J. Kamphuis, N.I. Wolf, B.T. Poll-The, T. Wassenberg, E.A.J. Peeters, T.J. de Koning, M.A.J. Tijssen, Non-motor symptoms and quality of life in dopa-responsive dystonia patients, Park. Relat. Disord. 45 (2017) 57–62. https://doi.org/10.1016/j.parkreldis.2017.10.005.

[44] V. Chandran, P.K. Pal, J.Y.C. Reddy, K. Thennarasu, R. Yadav, N. Shivashankar, Non-motor features in essential tremor, Acta Neurol. Scand. 125 (2012) 332–337. https://doi.org/10.1111/j.1600-0404.2011.01573.x.

[45] Y. Sengul, H.S. Sengul, S.K. Yucekaya, S. Yucel, B. Bakim, N.K. Pazarcı, G. Özdemir, Cognitive functions, fatigue, depression, anxiety, and sleep disturbances: assessment of nonmotor features in young patients with essential tremor, Acta Neurol. Belg. 115 (2015) 281–287. https://doi.org/10.1007/s13760-014-0396-6.

[46] A.S. Shalash, H. Mohamed, A.H. Mansour, A. Elkady, H. Elrassas, E. Hamid, M.H. Elbalkimy, Clinical Profile of Non-Motor Symptoms in Patients with Essential Tremor: Impact on Quality of Life and Age-Related Differences, Tremor Other Hyperkinet. Mov. (N. Y). 9 (2019). https://doi.org/10.7916/tohm.v0.736.

[47] J.M. Gelauff, E.M. Kingma, J.S. Kalkman, R. Bezemer, B.G.M. van Engelen, J. Stone, M.A.J. Tijssen, J.G.M. Rosmalen, Fatigue, not self-rated motor symptom severity, affects quality of life in functional motor disorders, J. Neurol. (2018). https://doi.org/10.1007/s00415-018-8915-7.

[48] G. Věchetová, M. Slovák, D. Kemlink, Z. Hanzlíková, P. Dušek, T. Nikolai, E. Růžička, M.J. Edwards, T. Serranová, The impact of non-motor symptoms on the health-related quality of life in patients with functional movement disorders, J. Psychosom. Res. 115 (2018) 32–37. https://doi.org/10.1016/j.jpsychores.2018.10.001.

[49] G. Nielsen, L. Ricciardi, B. Demartini, R. Hunter, E. Joyce, M.J. Edwards, Outcomes of a 5-day physiotherapy programme for functional (psychogenic) motor disorders, J. Neurol. 262 (2015) 674–681. https://doi.org/10.1007/s00415-014-7631-1.

[50] G. Nielsen, M. Buszewicz, F. Stevenson, R. Hunter, K. Holt, M. Dudziec, L. Ricciardi, J. Marsden, E. Joyce, M. Edwards, Randomised feasibility study of physiotherapy for patients with functional motor symptoms, J. Neurol. Neurosurg. Psychiatry. 88 (2017) 484–490. https://doi.org/10.1136/jnnp-2016-314408.

[51] A. Chaudhuri, P.O. Behan, Fatigue in neurological disorders, Lancet. 363 (2004) 978–988. https://doi.org/10.1016/S0140-6736(04)15794-2.

[52] A. Tessitore, A. Giordano, R. De Micco, G. Caiazzo, A. Russo, M. Cirillo, F. Esposito, G. Tedeschi, Functional connectivity underpinnings of fatigue in “Drug-Naïve” patients with Parkinson’s disease, Mov. Disord. 31 (2016) 1497–1505. https://doi.org/10.1002/mds.26650.

[53] M. Siciliano, R. De Micco, A. Giordano, F. Di Nardo, A. Russo, G. Caiazzo, A. De Mase, M. Cirillo, G. Tedeschi, L. Trojano, A. Tessitore, Supplementary motor area functional connectivity in “drug-naïve” Parkinson’s disease patients with fatigue, J. Neural Transm. 127 (2020) 1133–1142. https://doi.org/10.1007/s00702-020-02219-6.

[54] J.S. Lou, G. Kearns, T. Benice, B. Oken, G. Sexton, J. Nutt, Levodopa improves physical fatigue in Parkinson’s disease: A double-blind, placebo controlled, crossover study, Mov. Disord. 18 (2003) 1108–1114. https://doi.org/10.1002/mds.10505.

[55] E.M. Khedr, O. Galal, A. Said, M. Abd-Elsameea, J.C. Rothwell, Lack of post-exercise depression of corticospinal excitability in patients with Parkinson’s disease, Eur. J. Neurol. 14 (2007) 793–796. https://doi.org/10.1111/j.1468-1331.2007.01858.x.

[56] R.G. Elbers, J. Verhoef, E.E.H. van Wegen, H.W. Berendse, G. Kwakkel, Interventions for fatigue in Parkinson’s disease, Cochrane Database Syst. Rev. 2015 (2015). https://doi.org/10.1002/14651858.CD010925.pub2.

[57] K.L. Chou, V. Kotagal, N.I. Bohnen, Neuroimaging and clinical predictors of fatigue in Parkinson disease, Park. Relat. Disord. 23 (2016) 45–49. https://doi.org/10.1016/j.parkreldis.2015.11.029.

[58] N. Pavese, V. Metta, S.K. Bose, K.R. Chaudhuri, D.J. Brooks, Fatigue in Parkinson’s disease is linked to striatal and limbic serotonergic dysfunction, Brain. 133 (2010) 3434–3443. https://doi.org/10.1093/brain/awq268.

[59] A.J. Cleare, C. Messa, E.A. Rabiner, P.M. Grasby, Brain 5-HT 1A receptor binding in chronic fatigue syndrome measured using positron emission tomography and [11C] WAY-100635, Biol. Psychiatry. 57 (2005) 239–246. https://doi.org/10.1016/j.biopsych.2004.10.031.

[60] M.K. McCoy, T.N. Martinez, K.A. Ruhn, D.E. Szymkowski, C.G. Smith, B.R. Botterman, K.E. Tansey, M.G. Tansey, Blocking soluble tumor necrosis factor signaling with dominant-negative tumor necrosis factor inhibitor attenuates loss of dopaminergic neurons in models of Parkinson’s disease, J. Neurosci. 26 (2006) 9365–9375. https://doi.org/10.1523/JNEUROSCI.1504-06.2006.

[61] D. Lindqvist, S. Hall, Y. Surova, H.M. Nielsen, S. Janelidze, L. Brundin, O. Hansson, Cerebrospinal fluid inflammatory markers in Parkinson’s disease - Associations with depression, fatigue, and cognitive impairment, Brain. Behav. Immun. 33 (2013) 183–189. https://doi.org/10.1016/j.bbi.2013.07.007.

[62] J.R. Pereira, L.V. dos Santos, R.M.S. Santos, A.L.F. Campos, A.L. Pimenta, M.S. de Oliveira, G.G. Bacheti, N.P. Rocha, A.L. Teixeira, P.P. Christo, P.L. Scalzo, IL-6 serum levels are elevated in Parkinson’s disease patients with fatigue compared to patients without fatigue, J. Neurol. Sci. 370 (2016) 153–156. https://doi.org/10.1016/j.jns.2016.09.030.

[63] G. Lafargue, N. Franck, Effort awareness and sense of volition in schizophrenia, Conscious. Cogn. (2009). https://doi.org/10.1016/j.concog.2008.05.004.

[64] O. Rascol, C.J. Fitzer-Attas, R. Hauser, J. Jankovic, A. Lang, J.W. Langston, E. Melamed, W. Poewe, F. Stocchi, E. Tolosa, E. Eyal, Y.M. Weiss, C.W. Olanow, A double-blind, delayed-start trial of rasagiline in Parkinson’s disease (the ADAGIO study): Prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes, Lancet Neurol. 10 (2011) 415–423. https://doi.org/10.1016/S1474-4422(11)70073-4.

[65] A. Morita, Y. Okuma, S. Kamei, F. Yoshii, T. Yamamoto, S. Hashimoto, H. Utsumi, T. Hatano, N. Hattori, M. Matsumura, K. Takahashi, S. Nogawa, Y. Watanabe, T. Miyamoto, M. Miyamoto, K. Hirata, Pramipexole reduces the prevalence of fatigue in patients with Parkinson’s disease, Intern. Med. 50 (2011) 2163–2168. https://doi.org/10.2169/internalmedicine.50.5456.

[66] O. Pogarell, T. Gasser, J.J. Van Hilten, S. Spieker, S. Pollentier, D. Meier, W.H. Oertel, Pramipexole in patients with Parkinson’s disease and marked drug resistant tremor: A randomised, double blind, placebo controlled multicentre study, J. Neurol. Neurosurg. Psychiatry. 72 (2002) 713–720. https://doi.org/10.1136/jnnp.72.6.713.

[67] K.M. Shannon, J.P. Bennett, J.H. Friedman, Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson’s disease, Neurology. 49 (1997) 724–728. https://doi.org/10.1212/WNL.49.3.724.

[68] A. Antonini, L. Bauer, E. Dohin, W.H. Oertel, O. Rascol, H. Reichmann, M. Schmid, P. Singh, E. Tolosa, K.R. Chaudhuri, Effects of rotigotine transdermal patch in patients with Parkinson’s disease presenting with non-motor symptoms - results of a double-blind, randomized, placebo-controlled trial, Eur. J. Neurol. 22 (2015) 1400–1407. https://doi.org/10.1111/ene.12757.

[69] R.G. Elbers, H.W. Berendse, G. Kwakkel, Treatment of Fatigue in Parkinson Disease, JAMA. 315 (2016) 2340. https://doi.org/10.1001/jama.2016.5260.

[70] D.A. Mendonça, K. Menezes, M.S. Jog, Methylphenidate improves fatigue scores in Parkinson disease: A randomized controlled trial, Mov. Disord. 22 (2007) 2070–2076. https://doi.org/10.1002/mds.21656.

[71] T.M. Rodrigues, A.C. Caldas, J.J. Ferreira, Pharmacological interventions for daytime sleepiness and sleep disorders in Parkinson’s disease: Systematic review and meta-analysis, Park. Relat. Disord. 27 (2016) 25–34. https://doi.org/10.1016/j.parkreldis.2016.03.002.

[72] S. Rios Romenets, L. Creti, C. Fichten, S. Bailes, E. Libman, A. Pelletier, R.B. Postuma, Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson’s disease - A randomized study, Park. Relat. Disord. 19 (2013) 670–675. https://doi.org/10.1016/j.parkreldis.2013.03.003.

[73] R. Pahwa, C.M. Tanner, R.A. Hauser, K. Sethi, S. Isaacson, D. Truong, L. Struck, A.E. Ruby, N.L. Mcclure, G.T. Went, M.J. Stempien, Amantadine extended release for levodopa-induced dyskinesia in Parkinson’s disease (EASED Study), Mov. Disord. 30 (2015) 788–795. https://doi.org/10.1002/mds.26159.

[74] C.G. Canning, N.E. Allen, C.M. Dean, L. Goh, V.S.C. Fung, Home-based treadmill training for individuals with Parkinson’s disease: A randomized controlled pilot trial, Clin. Rehabil. 26 (2012) 817–826. https://doi.org/10.1177/0269215511432652.

[75] N.A. Kelly, M.P. Ford, D.G. Standaert, R.L. Watts, C.S. Bickel, D.R. Moellering, S.C. Tuggle, J.Y. Williams, L. Lieb, S.T. Windham, M.M. Bamman, Novel, high-intensity exercise prescription improves muscle mass, mitochondrial function, and physical capacity in individuals with Parkinson’s disease, J. Appl. Physiol. 116 (2014) 582–592. https://doi.org/10.1152/japplphysiol.01277.2013.

[76] E.Y. Uc, K.C. Doerschug, V. Magnotta, J.D. Dawson, T.R. Thomsen, J.N. Kline, M. Rizzo, S.R. Newman, S. Mehta, T.J. Grabowski, J. Bruss, D.R. Blanchette, S.W. Anderson, M.W. Voss, A.F. Kramer, W.G. Darling, Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting, Neurology. 83 (2014) 413–425. https://doi.org/10.1212/WNL.0000000000000644.

[77] N.M. van der Kolk, N.M. de Vries, R.P.C. Kessels, H. Joosten, A.H. Zwinderman, B. Post, B.R. Bloem, Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson’s disease: a double-blind, randomised controlled trial, Lancet Neurol. 18 (2019) 998–1008. https://doi.org/10.1016/S1474-4422(19)30285-6.

[78] C. Winward, C. Sackley, C. Meek, H. Izadi, K. Barker, D. Wade, H. Dawes, Weekly exercise does not improve fatigue levels in Parkinson’s disease, Mov. Disord. 27 (2012) 143–146. https://doi.org/10.1002/mds.23966.

**Figure legend**

**Figure 1.** Schematic representation of fatigue-related mechanisms.

Fatigue might be related to imbalance between sensory attenuation (reduced) and prediction of error (increased) in the pre-movement stage, that ultimately leads to an increased perception of effort due to higher error precision. This might be underpinned by three main mechanisms, including cortico-subcortical dysfunction, neuroinflammation and neurotransmitter imbalance, that are responsible for chronic perceived fatigue.