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# An objective measure combining physical and cognitive fatigability: Correlation with subjective fatigue in Parkinson's disease

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ABSTRACT

*Background:* Objective measures of physical and cognitive fatigability do not correlate with subjective Parkinson's disease (PD)-related fatigue. The relationship of subjective PD-related fatigue to tasks combining cognitive and motor effort has never been explored.
*Methods:* Forty-four right-handed, non-demented PD patients, 22 with (PD-F) and 22 without (PD-NF) fatigue, were tested using a sensor-engineered glove on their more affected hand. Patients performed sequential opposition finger movements following a metronome at 2 Hz for 5 min (cued task), and for another minute following a 2-min rest. The same task was repeated without sustained auditory cueing. Movement time (inter-tapping interval, ITI) and rate, touch duration, percentage of correct sequences and clinical measures (motor and fatigue severity, depression, sleep impairment and apathy) were analysed.
*Results:* In the cued task, motor performance worsened over time (significantly increased ITI and decreased movement rate on the third to fifth minute) in PD-F patients only. In the uncued task, motor performance deteriorated similarly in the two groups. PD-F and PD-NF patients differed in ITI and movement rate deterioration over time only in the cued task, independently from motor severity, depression and sleep impairment. The severity of subjective fatigue complaints significantly correlated with motor performance deterioration in the cued task.
*Conclusions:* PD-related fatigue is associated with performance on an externally cued, attention-controlled motor task, but not with an uncued version of the same task. The finding supports a link between PD-related fatigue and attention-demanding motor tasks, proposing a model of inducible fatigue applicable to future clinical and neuroimaging research.



## 1. Introduction

Parkinson's disease (PD)-related fatigue refers to self-reported, almost daily, significantly diminished energy levels or increased perceptions of effort that are disproportionate to attempted activities or general activity level [1]. It is an early manifestation diminishing quality of life, reported by approximately half of patients with PD [2]. Fatigue in PD is generally assessed by scales focusing on subjective complaints, rating their severity and/or screening for the presence of the fatigue 'trait' in individual patients [3]. Objective measures focused on performance fatigability, through either force generation protocols ('physical' fatigability) [4,5] or cognitive tasks predominantly engaging attention networks ('cognitive' fatigability) [6]. 'Physical' and 'cognitive' fatigability were always assessed independently, and neither correlated with subjective fatigue measures [4–6]. PD-related fatigue, however, reflects a complex construct. An interesting conceptualization of fatigue merges physical and cognitive elements, suggesting that it

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could represent failure to initiate and/or sustain attention-demanding physical activities requiring self-motivation [7].

Our group proposed a protocol to measure this particular type of activity, based on sequential finger opposition movements paced to a 2 Hz metronome signal and repeated continuously for 5 min [8]. This motor task requires high attentional demand related to both spatial (i.e., performing sequences in the correct finger order) and temporal (i.e., maintaining the correct frequency) aspects. When administered to healthy individuals, subjective fatigue was consistently reported at the end of performance [8]. After the 5-min period, participants were still able to complete the task but with lower temporal and spatial accuracy, recovering to baseline levels after a 1-min rest. Functional imaging studies showed a similarity between the neural correlates of this task in healthy subjects [9] and those of PD-related fatigue defined through subjective measures [10], i.e. changes in activity within motor and limbic loops of the cortico-basal ganglia network.

In this study we administered the same attention-demanding finger sequential task to PD patients with or without fatigue, screened through a validated, recommended and disease-specific subjective fatigue scale (the Parkinson Fatigue Scale). We hypothesized that i) the presence of subjective fatigue and its severity would be associated with task performance, and that ii) this effect would be independent of the main motor and non-motor domains potentially associated with PD-related subjective fatigue (motor severity, sleep disruption, depression) [11,12].

## 2. Methods

Participants gave their written informed consent prior to study inclusion. The experimental protocol was approved by the ethics committees of the University of Genoa and of the Research Ethics Committee London Centre, and was carried out in agreement with the Declaration of Helsinki.

### 2.1. Subjects

Patients with idiopathic PD were recruited from the National Parkinson's Disease Centre of Excellence, King's College Hospital, London, and the IRCCS, San Martino Hospital, University of Genoa, Italy. PD patients were screened according to selection criteria, and based on presence/absence of subjective fatigue, obtaining equally sized groups of patients with (PD-F) and without (PD-NF) subjective fatigue. Inclusion criteria were: a diagnosis of PD according to the UK Parkinson's Disease Society Brain Bank criteria; Hoehn & Yahr stages 1–3; stable dopaminergic medications for $\geq$1 month. Exclusion criteria were: co-existing neurological illnesses causing weakness, dyspraxia, or sensory impairment in the dominant hand; co-existing rheumatological or orthopaedic illnesses limiting range of motion of hand joints; Mini-Mental State Examination corrected score <27; hearing impairment hindering perception of the metronome tone.

Subjective fatigue complaints were screened using the Parkinson's Fatigue Scale 16-item scale (PFS-16) [13]; an average score $\geq$2.95 was used to discriminate patients experiencing subjective fatigue from those who did not. This threshold was found to distinguish these two groups of PD patients with a sensitivity of 81% and specificity of 85.7% [13]. All participants were taking L-dopa alone or in combination with a dopamine agonist, and were tested 60–90 min after their first administration of L-dopa and/or dopamine agonist in the morning. All participants were right-handed on the Edinburgh Handedness Inventory [14].

Experimental procedures were administered to each subject by the same research assistant. Disease severity was determined using the Unified Parkinson's Disease Rating Scale (UPDRS)-revised version, Motor score (part 3) [15]. Patients were also administered the Beck Depression Inventory-2 (BDI-2) [16], Parkinson's Disease Sleep Scale (PDSS) [17], and Apathy Scale [18].

### 2.2. Motor tasks

#### 2.2.1. Attention-demanding motor task following an acoustic cue (Cued task)

Participants sat comfortably in a quiet room, wearing a sensor-engineered glove (Glove Analyzer System, eTT s.r.l., Italy) on their more affected hand. They were instructed to execute the following motor sequence: opposition of thumb to index, medium, ring and little fingers (SEQ). The task was practiced at their own pace and the training ended generally within 2 min, when they were able to execute the task correctly. Participants were then asked to perform the task following an acoustic cue paced at 2 Hz (cued task) for 5 min (5-min TASK), to stay motionless for about 2 min, and perform an additional 1-min TASK section. An eyes-closed paradigm was chosen to avoid confounding due to integration of acoustic and visual information (Fig. 1).

#### 2.2.2. Control experiment (Uncued task)

A control experiment (uncued task) was performed by 17 PD-F and 20 PD-NF patients, in order to disentangle motor performance worsening induced by bradykinesia in the 5-min TASK from attentional control requested for the cued task. At least 7 days after the first experiment, subjects performed the uncued task, in which they listened to the acoustic cue paced at 2 Hz for 30 s and subsequently, when the tone stopped, tapped fingers in a sequential order, trying to maintain the same rhythm as accurately as possible for 5 min. Likewise, after a pause of about 2 min, they listened motionless to the acoustic cue for 30 s and, when the tone stopped, they tapped fingers in a sequential order, trying to maintain the same rhythm for 1 min. Like during the cued task, patients kept their eyes closed throughout the whole task (Fig. 1).

### 2.3. Data analysis

Data were processed using a customized software. Finger opposition movements were described by: (i) *inter-tapping interval* (ITI), i.e. the time elapsing from end of contact between the thumb and another finger to the beginning of the subsequent contact; (ii) *touch duration* (TD), i.e. the contact time between the thumb and another finger. From these parameters we calculated the *movement rate* as 1/(TD + ITI)*1000, i.e the number of contacts per second (Hz). The *percentage of correct sequences* (% CORR-SEQ) was also computed; incorrect sequences were not analysed for the other parameters. Each parameter was analysed in 1-min bins; for each minute, we calculated the average values of ITI, TD, rate and % CORR-SEQ.

### 2.4. Statistical analysis

#### 2.4.1. Demographic and clinical data

Gender differences between groups (PD-F, PD-NF) were assessed by chi-square test. Differences between groups for all other demographic and clinical characteristics were analysed by unpaired *t* or Mann-Whitney U tests, depending on data distribution (assessed by the Kolmogorov-Smirnov test).

#### 2.4.2. Motor tasks

Since data were normally distributed, parametric tests were applied. Each parameter (ITI, TD, movement rate, %CORR-SEQ) was entered in a two-way repeated measures analysis of variance (RM-ANOVA) with the factor GROUP (PD-F, PD-NF) as between-subjects

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