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# Relationship between poor decision-making process and fatigue perception in Parkinson's disease patients

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ABSTRACT

*Background:* Fatigue is a common non-motor symptom in Parkinson's disease patients. The reasons for its perception are not completely understood. One suggested possibility might be that perceived fatigue is related with abnormal interpretation of somatic symptoms. It has been described that somatic markers misinterpretation leads to poor decision-making. We hypothesized that fatigued Parkinson's disease patients would show poorer performance than non-fatigued in a decision-making task.
*Methods:* To test our hypothesis, 89 Parkinson's disease patients were assessed for the presence of fatigue using the Parkinson Fatigue Scale. All patients were also administered scales evaluating psychopathology and neuropsychological tests, including the Iowa Gambling Task.
*Results:* 33 (37.1%) patients fulfilled the established criteria for fatigue. In the univariate analysis, fatigued patients showed higher levels of anxiety (state: $p = 0.001$, trait: $p < 0.001$), impulsivity ($p = 0.051$), and depression ($p < 0.001$) than non-fatigued patients. No statistically significant differences in other neuropsychological test results (Stroop, Trail Making Test, Tower of London) were found between fatigued and non-fatigued patients except for the Iowa Gambling Task, in which fatigued patients showed poorer performance ($p = 0.001$) after controlling for confounding factors.
*Conclusions:* These results suggest that fatigued Parkinson's disease patients may present abnormal decision-making process, which may reflect abnormal processing of somatic markers when faced with an activity that requires effort.



## 1. Introduction

Fatigue is a wide-ranging symptom that is common in a variety of neurological, immunological, and psychiatric disorders, although its causal mechanisms are not well understood [1,2]. It is one of the most common and disabling non-motor symptoms occurring in Parkinson's disease (PD) patients, reported in up to two-thirds of this population [3]. However, the study of fatigue is a challenge because of its subjectivity, the lack of a universally accepted definition, and the need to differentiate between fatigability (objective changes in motor tasks performance) and the perception of fatigue (subjective sensations of fatigue) [4,5]. In this article, we use the term *fatigue* to refer to subjective sensations. Fatigue is defined as a difficulty to initiate and sustain physical and mental activities that require self-motivation in the absence of any clinically detectable motor weakness or dementia [2]. It is different from muscle weakness or apathy, and it is not merely a consequence of normal aging. Its evolution is not transient, and cannot be explained by prevailing circumstances [6]. As was described by Chaudhuri and Behan, to understand fatigue, we might regard voluntary effort as a variable affected by many control systems that regulate work output. These control systems can be divided into internal and external inputs. Internal inputs are related to motivational and emotional responses and are influenced by somatic changes and feedback from the motor, sensory, and cognitive systems. Thus, pathological fatigue is best understood as an enhanced perception of normal fatigue that can appear either as a consequence of dissociation between the internal and external input or from abnormal processing of some of their components [2]. According to this hypothetical model, when there is an abnormal processing of emotion-based somatic signals, fatigue may be generated as a result of abnormal internal inputs processing.

Effort activities have also been described as a decision-making process in which physical costs necessary to reach the objective are evaluated [7]. Some experiments have emphasized the relevance of dopamine, particularly in the ventral striatum, medial frontal cortex and dorsal anterior cingulate cortex, in mediating effort-related behavior [8]. Little is known of how such decisions are made by humans and their influence in pathological fatigue perception. According to

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Damasio's *somatic marker* hypothesis, emotion-based somatic signals arising from the body when a person evaluates the result of a decision are integrated in higher brain regions to regulate future decision-making processes [9,10]. Hence, according to this theory, abnormal processing of somatic markers could lead to incorrect decision-making. This process can be assessed with the Iowa Gambling Task. Although fatigue perception has been conceptualized as an abnormal decision-making process and incorrect interpretation of somatic symptoms has been considered a mechanism related with enhanced fatigue perception, the relationship between somatic markers processing and fatigue perception has not been analyzed in PD [2,7].

Individuals with PD display impairments in various cognitive tasks that primarily depend on the frontal lobes, and a growing number of studies have suggested that decision-making impairments are frequent in PD [11]. They may appear as a consequence of disruption of the reciprocal loop between the striatum and structures in the orbitofrontal cortex (OFC) following dopamine depletion [12]. There are no studies analyzing the relationship between decision-making impairment and fatigue perception in PD. However, in other disorders, such as multiple sclerosis or brain injury, fatigue perception has been related with abnormal reward processing [13,14].

As was mentioned above, according to the Chaudhuri hypothesis, numerous variables regulate work output. Changes in one of the elements of the complex chain of events that controls voluntary effort could affect the level of perceived exertion. Therefore, abnormal processing of the somatic inputs, as one of the key elements of the chain, could affect the normal integration of the different inputs implicated in effort perception and generate an increased sense of fatigue. Based on this empirical background, we hypothesized that PD patients with fatigue would have more difficulty than non-fatigued patients in decision-making processes. To test this hypothesis, the aim of the present study was to evaluate the relationship between decision-making processing and fatigue presence in PD patients. Other types of neuropsychological dysfunctions and the presence of certain psychopathological symptoms were also assessed to control their influence on the decision-making results.

## 2. Methods

This is a cross-sectional, observational study in which 89 consecutive, medicated PD patients [mean age 62.30 (±9.32) years; 65.20% men] were recruited from a Movement Disorders outpatient clinic in a tertiary hospital. Disease severity was evaluated by the Unified Parkinson Disease Rating Scale (UPDRS) and Hoehn–Yahr staging [15,16]. We also recorded the clinical phenotype (akinetic-rigid, tremor, or mixed) and the presence of motor complications. All patients were referred for evaluation by a psychiatrist who was blinded to the clinical data. The psychiatric study was performed within one month after the neurological evaluation and included clinical and neuropsychological assessment. It was divided in two sessions, each lasting 1 h. All neuropsychological measures were assessed during the morning. The tests were performed in a natural manner, and for that reason, all patients were taking their usual treatment and were allowed to take psychostimulants, such as caffeine. The IGT was always applied at the end of the second evaluation. All patients experiencing motor fluctuations were evaluated during the on period.

The inclusion criteria were age older than 18 years, a complete clinical assessment, stable dose of antiparkinsonian and antidepressant medication during the past three months and informed consent to participate. Patients with severe unstable psychiatric disorders (psychotic episode, manic episode, major depressive episode or anorexia nervosa), those with a Mini Mental State Examination score lower than 26, and those with diseases other than PD related with fatigue were excluded.

### 2.1. Patient assessment

#### 2.1.1. Fatigue assessment

The Parkinson Fatigue Scale (PFS) was used to screen for fatigue [17]. It was specifically designed to measure fatigue in PD patients, taking into account possible overlapping with other symptoms of PD. For this reason it excludes emotional and cognitive features. It is a 16-item self-report instrument. The final score is based on the mean response across all the items and ranges from 1.0 to 5.0. Higher scores suggest greater perceived fatigue. Additionally, this instrument enables classification of patients as fatigued and non-fatigued. An alternative scoring method was also evaluated for this purpose, in order to have the highest sensitivity and good specificity [17]. To this end, we re-coded each item using a binary scoring method, in which the response "agree" and "strongly agree" were scored as *1*, and all other responses were scored as *0*. The final score was calculated by adding up the items. A cut-off score of ≥8 was used to indicate the presence of fatigue. The instrument was found to have good internal consistency, with a Cronbach's alpha coefficient of 0.95 in our sample.

#### 2.1.2. Neuropsychiatric assessment

The Spanish versions of the Hamilton Depression Scale (HAM-D) and the State-Trait Anxiety Inventory (STAI) were used to assess the severity of depressive and anxiety symptoms [18,19]. In addition, the Lille Apathy Rating Scale (LARS) was used to rate apathy, and the Barratt Impulsivity Scale (BISS-11) was completed to evaluate the impulsivity at the time of the assessment [20,21].

The Mini-Mental State Examination (MMSE) was used to evaluate global cognitive status [22].

#### 2.1.3. Neuropsychological measures

The Trail Making Test (TMT) was applied, using the Reitan administration format [23]. The TMT is a two-part pencil and paper test that requires individuals to connect a series of consecutively numbered circles in order (TMT-A) or to alternately connect consecutively numbered circles and lettered circles (TMT-B). TMT-A measures motor speed and visual scanning, whereas TMT-B additionally assesses cognitive flexibility, alternating attention, and the ability to inhibit a dominant but incorrect response. Scoring is based on the number of seconds required to complete parts A and B of the test. The higher the score, the poorer is the performance [24]. Calculation of the difference between the time scores of TMT-B and TMT-A is suggested for interpretation of executive deficits and to eliminate the influence of visual and motor abilities on performance [24].

The Stroop Color-Word Test was applied using the classical version based on card presentation. It consisted in two initial non-executive tasks in which the participant had to read aloud words representing the names of basic colors (STROOP-1) or name the color of different symbols printed in blue, red, and green (STROOP-2). The second block consisted in two Stroop interference conditions. In the first, the participant had to name the color of the ink in which the words blue, red, or green were printed, with the ink being different from the color indicated by the word (STROOP-3). In the second, the participant had to alternate this task with reading a word printed inside a rectangle (STROOP-4). For each condition, the number of correct responses given in 45 s was recorded [24]. The number of errors committed in the STROOP-3 and STROOP-4 were also recorded as a measure of cognitive flexibility and the capacity for response inhibition.

The Tower of London (ToL) was applied to assess deficits of visuospatial and planning ability. We used its classical version [25]. We calculated the number of correctly solved trials (the number of problems solved in minimum number of moves), the preplanning time (seconds between the presentation of each problem and the first touch of a ball) and the movement execution time (seconds between the first touch of a ball and the final solution of the problem).