

## Research article

# Serotonergic central tone in Parkinson's disease with fatigue: Evidence from the loudness dependence of auditory evoked potentials (LDAEP)

Caterina Pauletti<sup>a,\*</sup>, Daniela Mannarelli<sup>a</sup>, Nicoletta Locuratolo<sup>a</sup>, Andrea Maffucci<sup>a</sup>, Antonio Currà<sup>b</sup>, Lucio Marinelli<sup>c,d</sup>, Francesco Fattapposta<sup>a</sup>

<sup>a</sup> Department of Human Neurosciences, Sapienza University of Rome, Viale dell'Università 30, 00185 Rome, Italy

<sup>b</sup> Department of Medical-Surgical Sciences and Biotechnologies, A. Fiorini Hospital, Terracina, LT, Sapienza University of Rome, Polo Pontino, Latina, Italy

<sup>c</sup> Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, Italy

<sup>d</sup> Division of Clinical Neurophysiology, Department of Neuroscience, IRCCS Ospedale Policlinico San Martino, Genova, Italy

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## ABSTRACT

Central fatigue in Parkinson's disease (PD) is a common and disabling symptom that further worsens the patients' quality of life. A deficit in the serotonergic system may be implicated in the occurrence of fatigue in patients with PD as well as in those with other chronic conditions characterized by fatigue. The loudness dependence of auditory evoked potentials (LDAEP) is a neurophysiological tool that has proved to be effective in measuring the serotonergic central function in vivo. The aim of the present study was to assess central serotonergic activity in PD patients and to explore its possible association with the presence of fatigue. LDAEP was recorded in 38 PD patients (26 without fatigue – PDnF and 12 with fatigue – PDF) and 34 healthy controls. A significant difference between parkinsonian patients and controls emerged, with patients displaying stronger LDAEP values (which reflect a lower serotonergic central tone) than controls. By contrast, no differences in LDAEP emerged between PDF and PDnF. Our electrophysiological data confirmed the presence of a deficit in serotonergic central transmission in PD. An association between this deficit and fatigue was not demonstrated. It is likely that an altered dopamine/serotonin balance, rather than a serotonin deficit alone, is involved in the genesis of central fatigue. This complex and multifaceted symptom is related above all to a dysfunction in the striato-thalamo-cortical loop that connects the neostriatum to the frontal lobe and is strongly affected by motivation.

## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is typically characterized clinically by bradikinesia/akinesia, rigidity, tremor and postural instability. It is widely recognized that a plethora of motor and non-motor symptoms accompany and even precede this classic motor triad. These symptoms include central fatigue, which is a failure to initiate and maintain attentional and physical tasks that require self-motivation [1]. Central fatigue has been reported as a frequent and disabling symptom that affects up to 58% of PD patients [2] and further worsens the patients' quality of life [3].

It has been suggested that central fatigue, which includes mental and physical aspects, may be due to a dysfunction in the striato-thalamo-cortical loop connecting the neostriatum to the frontal lobe (prefrontal, cingulate, orbitofrontal cortices) [4]. Fatigue occurs in normal

physiological conditions whenever the cost of an action outweighs the expected benefit yielded by performance and is affected to a large extent by motivation. It has been hypothesised that deficits in stimulus evaluation and reward-related decision-making processes, which are related to the functional integrity of the mesolimbic system, eventually lead to central fatigue in PD [4,5]. These deficits may be mediated by a structural loss of dopaminergic cells, by a functional neurotransmitter imbalance resulting from reduced serotonin content at the basal ganglia level or other, as yet unclear, mechanisms. Pavese et al. recently reported that SERT levels in the basal ganglia and associated limbic circuits were reduced in PD patients with fatigue though not in those without fatigue, thereby indicating that fatigue in PD is associated with relative serotonergic denervation in these loci [6].

A neurophysiological tool that has proved to be effective in measuring serotonergic central function in vivo is the loudness

\* Corresponding author.

E-mail addresses: [caterina.pauletti@uniroma1.it](mailto:caterina.pauletti@uniroma1.it) (C. Pauletti), [andrea.maffucci@uniroma1.it](mailto:andrea.maffucci@uniroma1.it) (A. Maffucci).

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dependence of auditory evoked potentials (LDAEP) [7,8]. Serotonergic tone is known to modulate sensory processing at the level of the primary auditory cortex, which is well represented by the N1/P2 complex of the auditory evoked potentials. The intensity of the auditory stimulus used to evoke the auditory potential normally influences the amplitude of the N1/P2 complex: louder tones evoke greater amplitudes of N1/P2, a phenomenon defined as loudness dependence of auditory evoked potentials [7].

Many preclinical and clinical studies have demonstrated an inverse relationship between LDAEP and serotonergic function: a strong LDAEP reflects low serotonergic activity whereas a weak LDAEP reflects high serotonergic activity [7,9]. This index has been used in a number of studies on neurological illnesses in which the serotonergic system is widely recognized to be involved, such as depression, migraine and obsessive compulsive disorder [10–11].

Data on the pathophysiology of central fatigue in PD are still controversial. The aim of the present study was to explore serotonergic central function in vivo and its possible role in the pathophysiology of central fatigue in PD. We hypothesized that if an alteration in serotonergic tone does contribute to the presence of fatigue in PD, then patients with fatigue would display stronger LDAEP values (which reflect a lower serotonergic tone) than patients without fatigue.

## 2. Subjects and methods

### 2.1. Subjects

Thirty-eight outpatients, with a confirmed diagnosis of idiopathic PD according to the UK Brain Bank diagnostic criteria [12], were recruited for the study. Exclusion criteria were: presence of dementia (age- and education-adjusted Mini-Mental State Examination score  $< 23.8$ , which is the cut-off for dementia according to Italian normative data) [13], depression (Beck Depression Inventory score  $> 9$ ) [14], or other neurological comorbidity (such as migraine, drug abuse, brainstem lesions), intake of SSRI,  $\beta$ -blockers, antiepileptic drugs or triptans, as these conditions are known to affect LDAEP. Thirty-four healthy age-matched volunteers, with unremarkable personal and family histories for psychiatric and neurological disorders, were consecutively recruited from non-consanguineous relatives of the outpatients as the control group.

All the patients were examined by at least two independent experienced neurologists. The severity of PD was assessed by means of the Hoehn and Yahr staging scale and motor disability was rated by means of the Unified Parkinson's Disease Rating Scale-subset III (UPDRS III), with both being assessed during the on phase. Moreover, the PD patients' quality of life was assessed by means of the 39-item Parkinson's Disease Questionnaire (PDQ-39) [15].

Fatigue was measured by means of the Fatigue Severity Scale (FSS), which is a patient-rated brief and easy unidimensional 9-item fatigue rating scale and the most frequently used fatigue-specific scale in chronic diseases [16]. Owing to its excellent psychometric properties and its validation in PD, it fulfils the criteria required for a recommended fatigue scale to assess the presence and the severity of this symptom in PD populations [17]. According to previous studies, an average score  $> 4$  was used to distinguish patients with fatigue from those without fatigue [2,16].

All the participants were right-handed and gave their written informed consent to the study. The study was approved by the local ethics committee.

### 2.2. Procedure

EEG recordings were performed in a quiet and electrically shielded room with the subject sitting in a comfortable armchair. EEG investigators, both during EEG recording and LDAEP analysis, were unaware of the patient group (with/without fatigue). Patients underwent EEG recording during the on phase. The active electrodes were placed in

F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 sites, according to the International 10–20 System. Two reference electrodes on the mastoids and the ground electrode were placed on the forehead. The vertical electrooculogram was recorded from above and below the left eye; a horizontal EOG was also performed from electrodes placed at the two external canthi. Electrode impedances did not exceed 3 K Ohm. A 0.01–30 Hz bandpass was used to filter EEG signals and EOG online. A Mizar Sirius EEG-EP multifunctional system was used for the stimulation and acquisition.

Auditory potentials were evoked by four runs of 250 stimuli each with a randomized inter-stimulus interval ranging from 500 to 900 ms. Tones of 1000 Hz and 50 ms duration (rise-fall times: 10 ms) were delivered binaurally through earphones at four different intensities (60, 70, 80 and 90 dB HL) in a pseudo-randomized order. Sounds were presented and controlled by a PC running system. Subjects were asked to fix a target in front of them in order to limit ocular artefacts; they were not informed about the sequence of different tones and were instructed to ignore them.

All recordings were averaged off-line. ERP averages were computed separately for each stimulus intensity level. The analysis epoch was 600 ms with a 100 ms pre-stimulus baseline. A first automatic procedure was used to reject trials containing drift deflection of more than  $\pm 100$  mV in any channel including EOG. A further offline analysis was performed to exclude ocular artefacts (eye movements/blinks) according to a standard algorithm [18] implemented in our analyzer software (ERPLAB Toolbox; available at <http://erpinfo.org/erplab>). Trials containing artefacts were eliminated by computing the cross covariance between the single-trial EOG waveform and a 200 ms step function and rejecting trials in which the maximum covariance exceeded a  $\pm 15$  mV threshold. The mean number of sweeps was  $212.1 \pm 13.3$  for each intensity stimulus.

To calculate the LDAEP, the N1 (between 50 and 150 ms post-stimulus) and P2 (between 120 and 200 ms post-stimulus) components were identified for each stimulus intensity at the Cz site. The N1 and P2 amplitudes were measured. The N1/P2 ASF slope was calculated as the linear amplitude/stimulus intensity function slope for block averages ( $\mu\text{V}/\text{dB}$ ).

## 3. Statistical analyses

Data are expressed as means ( $\pm$ standard deviation) for continuous variables and as proportions for categorical variables. The Shapiro-Wilk test was used to assess the normal distribution of the data.

The demographic and psychological characteristics of the three groups (parkinsonians with fatigue: FSS  $\geq 4$  (PDF), parkinsonians without fatigue: FSS  $< 4$  (PDnF) and healthy controls (HC)) were compared using univariate ANOVA. Differences in the clinical characteristics between the two PD groups (PDF and PDnF) were tested by means of the U Mann-Whitney test for continuous variables and chi-squared Fisher exact test for categorical data.

To verify whether serotonergic central tone, as indexed by LDAEP, was altered in PD, LDAEP values in the parkinsonian population were first compared with those in controls by means of Student's *t*-test. Once the PD population was split into two groups according to the presence of fatigue, univariate ANOVA was used to test the differences between the three groups (PDF, PDnF, HC) in LDAEP values. A Bonferroni correction was then applied.

Spearman's rank correlation coefficient was performed to detect any correlations between the clinical variables and LDAEP.

A  $p < 0.05$  was considered statistically significant. The analyses were performed using the SPSS statistical package (Version 25.0).

## 4. Results

All the subjects completed the task. On the basis of the FSS cut-off, 12 (31.6%) of the 38 patients experienced fatigue (PDF), while the remaining 26 (68.4%) did not (PDnF). No difference emerged in clinical

impairment measures (age at onset, disease duration, UPDRS III and HY scores) between PD groups, with the exception of levodopa equivalent daily dosage (LEDD): LEDD was significantly higher in PDF than in PDnF ( $p = 0.005$ ). The demographic and clinical characteristics of all the subjects who took part are shown in Tables 1 and 2.

#### 4.1. LDAEP

Grand Average of ERP responses to tones of varying intensity for the three groups (PDF, PDnF and controls), are displayed in Fig. 1A.

A significant difference between parkinsonian patients and controls emerged ( $p = 0.002$ ; PD:  $0.96 \pm 0.7$ ; controls:  $0.47 \pm 0.45$ ) (Fig. 1B).

When the PD population was split into two groups according to the presence of fatigue, ANOVA revealed a significant main “group” effect ( $F_{2,69} = 5.14$ ;  $p = 0.08$ ;  $\eta = 0.13$ ; PDF:  $0.99 \pm 0.83$ ; PDnF:  $0.94 \pm 0.70$ ). After Bonferroni’s correction, no significant difference emerged between the two groups of patients whereas both groups were significantly different from controls (PDF vs PDnF:  $p = 1.0$ ; controls vs PDnF:  $p = 0.019$ ; controls vs PDF:  $p = 0.050$ ) (Fig. 1C and Fig. 2).

#### 4.2. Correlations

No significant correlations were detected between the LDAEP values and clinical characteristics in the PD population, with the exception of the LEDD ( $r = 0.33$ ;  $p = 0.04$ ).

Fatigue significantly correlated directly with UPDRS III ( $r = 0.31$ ;  $p = 0.05$ ), LEDD ( $r = 0.52$ ;  $p = 0.001$ ) and quality of life (PDQ39) ( $r = 0.44$ ;  $p = 0.006$ ).

### 5. Discussion

The aim of the present study was to assess central serotonergic activity in PD patients and to explore its possible association with the presence of fatigue.

First of all, our results confirmed the presence of a deficit in serotonergic central tone in PD patients. PD patients, regardless of the presence of fatigue, displayed stronger LDAEP values, which are indicative of a lower serotonergic activity level.

It is well established that the pathology of PD extends beyond the neuronal loss of the dopaminergic neurons of the *substantia nigra*. In particular, neuronal loss and Lewy bodies in the raphe nuclei, which provide serotonin innervation to the entire brain, including the core structures of the cortico-basal ganglia-thalamo-cortical loop, are believed to be present in the early phases of the disease, i.e. in Braak stage 2, even before the involvement of the *substantia nigra pars compacta* [19,20]. These data are further supported by in vivo neuroimaging

**Table 2**

Clinical characteristics of PD population.

	PDF (n = 12)	PDnF (n = 26)	U	p
Age at onset	62.8 ± 7.9 (65; 50–74)	59.8 ± 7.9 (60; 42–71)	125	
Disease duration (yrs)	5.8 ± 5.5 (4; 1–20)	3.4 ± 3.2 (2; 1–15)	116	0.200
UPDRS III	20.3 ± 11.2 (17; 11–47)	14.8 ± 5.8 (14; 5–26)	111	0.156
HY (%)				0.539*
1	5 (41.7%)	12 (46.2%)		
2	7 (58.3%)	14 (53.8%)		
Predominant motor symptom (%)				0.438**
Tremor	3 (25%)	11 (42.3%)		
Rigidity	4 (33.3%)	9 (34.6%)		
Mixed	5 (41.7%)	6 (23.1%)		
LEDD (mg/die)	612.8 ± 312.1 (475; 240–1235)	340.2 ± 201.0 (300; 100–775)		<b>0.005</b>
FSS	5.2 ± 1.2 (4.9; 4.2–8.0)	2.5 ± 0.8 (2.6; 1.1–3.9)	0	<b>&lt;0.001</b>
PSQI	8.3 ± 4.5 (8; 3–16)	5.0 ± 3.3 (3.5; 2–14)	52	<b>0.031</b>
PDQ39	33.8 ± 21.2 (29; 13–96)	17.0 ± 13.6 (12.5; 1–54)	61	<b>0.003</b>

Data are expressed as mean ± standard deviation (median; range).

Mann-Whitney U test Kruskal-Wallis test; \*chi-squared test; \*\*Fisher exact test. Significant values ( $p < 0.05$ ) are highlighted in bold.

UPDRS III: Unified Parkinson’s disease rating scale part III; HY: Hohen-Yahr stage; LEDD: Levodopa equivalent daily dose; FFS: Fatigue severity scale; PSQI: Pittsburgh sleep quality index; PDQ-39: Parkinson’s Disease Questionnaire.

studies that have revealed reduced serotonin transporter binding in PD patients compared with healthy controls [21].

Moreover, several studies have demonstrated that degeneration of the serotonergic system in PD is implicated in the development of tremor and levodopa induced dyskinesias, as well as in non-motor symptoms, such as depression, psychosis and sleep disorders, thereby indicating that this neurotransmitter plays an important role in the pathology and clinical manifestation of PD [22].

Interestingly, our electrophysiological data are in line with these observations, even in patients who are in the early disease stages (as revealed by the 1–2 HY stages in our population) and do not suffer from depression, which indicates that serotonergic dysfunction is present even when the clinical picture of PD is mild.

Nonetheless, our study appears to have failed to demonstrate an association between a deficit in serotonergic activity and the presence of fatigue. Indeed, LDAEP values in PD patients with fatigue were

**Table 1**

Demographic variables and clinical characteristics of PD patients and controls.

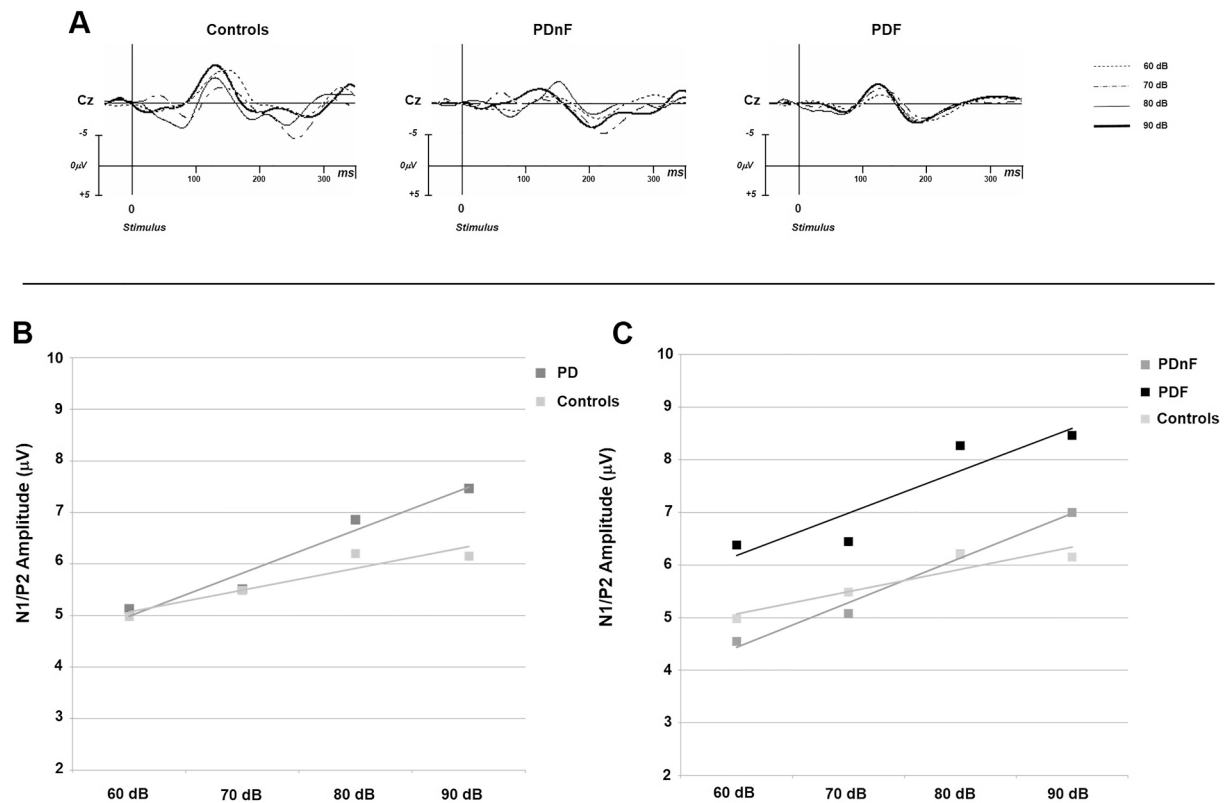
	PDF (n = 12)	PDnF (n = 26)	Controls (n = 34)	p	p°		
					PDF vs PDnF	PDF vs HC	PDnF vs HC
Age (yrs)	68.4 ± 6.4 (69.5)	63.0 ± 7.2 (62)	64.2 ± 7.2 (64)	0.097	–	–	–
Sex (M/F)	7/5	18/8	17/17	0.32*			
Education (yrs)	11 ± 5 (13)	12.7 ± 3.5 (13)	14.7 ± 4.5 (18)	<b>0.026</b>	0.805	<b>0.039</b>	0.201
MMSE	28.3 ± 1.6 (27.7)	28.8 ± 2.1 (30)	27.9 ± 2.0 (28.5)	0.544	–	–	–
STAI Y-1	36.5 ± 5.0 (34)	33.2 ± 7.0 (33)	33.5 ± 6.8 (32.5)	0.460	–	–	–
STAI Y-2	40.9 ± 7.6 (39.5)	33.1 ± 5.8 (31.5)	34.6 ± 6.1 (33.5)	<b>0.010</b>	<b>0.008</b>	<b>0.036</b>	1.000

Data are expressed as mean ± standard deviation (median).

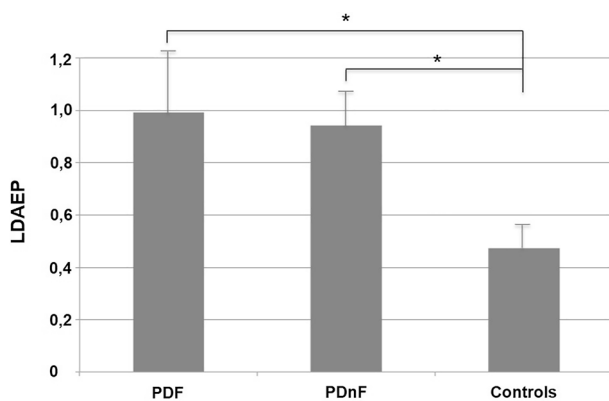
°ANOVA, after Bonferroni correction; \*chi-squared test.

Significant values ( $p < 0.05$ ) are highlighted in bold.

MMSE: Mini Mental State Examination; STAI: state trait anxiety inventory.



**Fig. 1.** Grand average of N1 and P2 auditory evoked potentials in response to tones of varying intensity at Cz, for controls, PDnF and PDF (A). LDAEP as the slope of linear regression of the N1/P2 peak-to-peak amplitude by increasing sound intensity (dB) in PD patients and controls (B) and in PDF, PDnF and controls (C).



**Fig. 2.** The N1/P2 loudness dependence of auditory evoked potentials of PDF, PDnF and controls. The data are presented as mean  $\pm$  ES. \* Statistically significant difference at  $p < 0.05$ .

comparable to those in PD patients without fatigue, indicating that the serotonergic central tone is similar in the two parkinsonian populations.

This observation is not in line with previous report by Pavese et al. [6] that demonstrated an association between fatigue in PD and reduced serotonergic function. It should however be borne in mind that LDAEP is a functional measure of central serotonergic transmission in cortical areas, and does not necessarily represent the number of serotonin transporters and receptors but is instead an electrophysiological response to variations in the intensity of acoustic stimuli, which is mediated above all by serotonin.

Moreover, our PD patients were all on medication and the fact that the two groups were taking significantly different amounts of levodopa replacement therapy (LEDD dosages being taken by PDF were nearly twice as high as those being taken by PDnF) despite the clinical

impairment being similar in both groups, further highlights the complexity of central fatigue.

Indeed, numerous interactions are known to exist between dopaminergic and serotonergic neurons, particularly under pharmacological stimulation. Striatal 5HT receptors and SERT may modulate the levodopa metabolism in dopamine in serotonergic neurons, and serotonin may depress dopamine activity and release within the basal ganglia [23,24]. On the other hand, an increased dopamine level, which induces oxidative stress, or chronic levodopa intake may damage serotonergic neurons, thereby causing deficits in the serotonergic system [25,26].

Within this context, the serotonergic tone that we measured by means of LDAEP may be the result of a serotonin/dopamine imbalance rather than a measure of serotonergic denervation per se.

In fact, even though the variation of LDAEP in response to changes in serotonin neurotransmission has been explored in pharmacological, brain imaging, and genetic studies, and it is likely to reflect a long-term serotonergic activity rather than acute changes in monoamine activity, recent studies showed that also dopamine levels could modulate LDAEP in healthy and pathological populations [27,28].

Moreover, the hypothesis that a neurotransmitter imbalance rather than an isolated neurotransmitter deficit underlies central fatigue is supported by the observation that dopaminergic or serotonergic drugs are not sufficient to treat fatigue fully, even though the data available on the efficacy of treatments for fatigue are still inconsistent [29].

This study has some limitations. First, our PDF sample was relatively small, which means caution must be taken in generalizing these results to all PD subjects with fatigue.

Second, fatigue was measured by means of a self-administered, subjective scale, i.e. the FSS. Although this scale is “recommended” both for screening purposes and to rate severity, the MDS task force on rating scales for PD [17] has stated that the correct assessment of fatigue, which is a difficult symptom to define let alone to measure, remains challenging.

## 6. Conclusions

To conclude, central fatigue is a multifaceted symptom that is strongly affected by motivation but whose pathophysiology is still poorly understood. Deficits in the attention and affective sets linked to motor preparation and execution, which are crucially dependent on the integrity of dorsal and ventral striato-pallidal-thalamo-cortical circuits are thought to play a major role in its development.

The genesis of central fatigue is more likely to be due to an altered dopamine/serotonin balance than to a serotonin deficit, with dopamine and serotonin probably acting in a synergic manner and playing complementary roles in the reinforcement and control processes that sustain decision making behaviors.

Further studies are needed to shed more light on the pathophysiology and possible therapeutic options in patients with this symptom.

## CRedit authorship contribution statement

**Caterina Pauletti:** Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Visualization. **Daniela Mannarelli:** Methodology, Investigation, Writing - original draft, Visualization. **Nicoletta Locuratolo:** Investigation, Writing - review & editing. **Andrea Maffucci:** Investigation, Data curation. **Antonio Currà:** Writing - review & editing. **Lucio Marinelli:** Writing - review & editing. **Franco Fattapposta:** Conceptualization, Supervision, Writing - review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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