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Research Report

Reduced sensory attenuation as a marker of pathological fatigue: Evidence from Parkinson's disease

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ABSTRACT

Fatigue is a prevalent and disabling nonmotor symptom in Parkinson's disease (PD), yet its underlying mechanisms remain poorly understood. A recent theoretical model proposes that fatigue may arise from impaired sensory attenuation, the normal reduction in perception of self-generated compared with externally generated stimuli. To test this hypothesis, we assessed sensory attenuation in 20 PD patients with fatigue ($PD_{Fatigue}$), 22 without fatigue ($PD_{NoFatigue}$), and 20 healthy controls (HC) using a force-matching task. Participants reproduced target forces on their left index finger under two conditions: by pressing directly on their own finger (direct condition) or using an external device (indirect condition). HC and $PD_{No\ fatigue}$ patients significantly overestimated the required force in the direct compared to the indirect condition, consistent with a normal sensory attenuation. In contrast, $PD_{Fatigue}$ patients showed no significant difference between conditions, indicating a selective impairment of sensory attenuation. Within the $PD_{Fatigue}$ group, reduced sensory attenuation was strongly associated with greater subjective fatigue and perceived effort, but not with motor symptom severity, disease duration, or other non-motor symptoms commonly co-occurring with fatigue. These findings provide empirical evidence that impaired sensory attenuation may be a fundamental mechanism underlying pathological fatigue in PD. Importantly, this impairment appears unique and specific to fatigue, as it does not correlate with other clinical features of PD or with other nonmotor symptoms. The selective link between sensory attenuation and fatigue offers a promising avenue for the development of targeted interventions and underscores the potential of sensory attenuation as a biomarker of pathological fatigue.

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1. Introduction

Fatigue is a pervasive and distressing symptom in Parkinson's disease, characterized by a subjective sense of exhaustion and sustained increase in perceived effort that is disproportionate to actual motor demands (Di Vico et al., 2021; Kluger et al., 2013; Siciliano et al., 2022).

Fatigue affects approximately 50% of patients with Parkinson's disease and is consistently rated among the most disabling nonmotor symptoms, often outweighing motor impairment in terms of subjective impact (Siciliano et al., 2018). It has been consistently identified as a major determinant of reduced quality of life in PD, limiting daily functioning and social engagement. It has also been associated with worse physical outcomes, such as reduced exercise capacity, higher risk of falls, and increased hospitalization (Barone et al., 2009; Elbers et al., 2014). It may appear even before motor onset and tends to persist or worsen over time (Siciliano et al., 2018).

The absence of targeted treatments reflects more than therapeutic inertia. It stems from a fundamental gap in our mechanistic understanding. Despite its clinical relevance, fatigue remains an "orphan" symptom, conceptually elusive and neglected in routine care. Unraveling its neurobiological substrates is therefore not only urgent but also the necessary step toward transforming an overlooked complaint into a measurable and treatable domain. Fatigue does not correlate consistently with motor severity, dopaminergic denervation, or treatment response, suggesting that distinct, non-dopaminergic mechanisms may be at play (Di Vico et al., 2025).

Neuroimaging and neurophysiological studies have begun to shed light on the mechanisms underlying fatigue. In particular, Siciliano and colleagues demonstrated that Parkinson's disease patients with fatigue show disrupted functional connectivity between motor and associative regions, including the supplementary motor area (SMA), a key hub involved in initiating and sustaining voluntary actions (Siciliano et al., 2020). Reduced SMA activation has been associated with a diminished sense of agency (i.e., the feeling of controlling one's own actions) and altered internal monitoring of movement, both of which may contribute to the subjective experience of effort (Haggard, 2005; Kuppuswamy, 2022; Zénon et al., 2015). These findings support the notion that fatigue reflects a dysfunction in higher-order motor control and internal action monitoring, rather than peripheral motor failure. A growing body of evidence further implicates altered glutamatergic and noradrenergic transmission, pointing toward a broader disruption of networks involved in motivation, effort estimation, and sensorimotor integration (Di Vico et al., 2025).

Importantly, fatigue is not unique to Parkinson's disease but represents a pervasive and disabling symptom across several neurological and systemic conditions, including multiple sclerosis, chronic fatigue syndrome, and stroke (Chaudhuri and Behan, 2004; Kluger et al., 2013). Understanding the mechanisms of fatigue in Parkinson's disease is therefore crucial not only for better characterizing this non-motor symptom, but also for providing a valuable framework for future comparisons across disorders.

In this context, a promising conceptual framework for understanding fatigue is the sensory attenuation model, which situates fatigue within the broader domain of predictive coding and internal models of motor control (Kuppuswamy, 2017). Rooted in the active inference framework (Friston et al., 2011), this model posits that fatigue may result from impaired attenuation of self-generated sensory input, a fundamental mechanism by which the brain filters expected consequences of voluntary action (Blakemore et al., 2000; Frith et al., 2000; Giannini et al., 2025). When this attenuation is disrupted, internally generated effort may be perceived as unexpectedly intense, leading to the subjective experience of fatigue (Kuppuswamy, 2017, 2022).

Building on this model, the current study investigated whether sensory attenuation contributes to pathological fatigue in Parkinson's disease. While abnormal sensory attenuation has been previously documented in Parkinson's disease patients (Macerollo et al., 2016), its role in the occurrence of pathological fatigue has not been explored. Indeed, direct evidence linking sensory attenuation and fatigue in Parkinson's disease is lacking (Kuppuswamy, 2022). This leaves open the question of whether abnormal sensory attenuation plays a role in pathological fatigue. To address this critical gap, we investigated sensory attenuation in patients with and without fatigue, alongside healthy controls.

Sensory attenuation is typically assessed using the force-matching task (FMT), in which participants are asked to reproduce a target force applied to their finger either by pressing on it directly (direct condition) or by using an external device (indirect condition). Healthy individuals consistently overestimate the target force when directly pressing on their own finger compared to when using an external device, due to the attenuation of the sensory consequences of the self-generated movement (McNaughton et al., 2023; Shergill et al., 2003). Conversely, in the indirect condition, healthy participants are more precise (McNaughton et al., 2023). Here, an external device mediates the force output, mimicking a less predictable, external sensory input and thereby preventing sensory attenuation. The condition is therefore commonly used as a control for both sensory sensitivity and any task-related bias (Wolpe et al., 2018). The FMT is now recognized as a well-established and reliable experimental paradigm and has been successfully used to investigate sensory attenuation across several disorders, including schizophrenia (Shergill et al., 2005), functional movement disorders (Pareés et al., 2014), and Parkinson's disease (Wolpe et al., 2016).

We hypothesized that fatigue in Parkinson's disease would be associated with impaired sensory attenuation, as demonstrated by a reduced overestimation of target forces in the direct condition in fatigued patients but not in healthy control or non-fatigued patients. Demonstrating a specific link between sensory attenuation and fatigue could help clarify the mechanisms underlying pathological fatigue in Parkinson's disease and inform the development of more targeted therapeutic approaches.

2. Materials and methods

2.1. *Participants*

Given the absence of prior studies exploring the interplay between sensory attenuation and fatigue in Parkinson's disease, the sample size was computed on a priori standard values by using G-Power 3 (Faul et al., 2007). We chose an anticipated effect size f of .25, which is suitable for within-between designs and is considered medium, according to the convention established by Cohen for estimating effect size in the absence of previous data (Cohen, 1988). The α error probability was set at .05 and power ($1-\beta$) at .90, yielding a required sample size of 54 participants. To ensure a balanced design across groups and to meet the target sample size established by the a priori power analysis, we set a minimum recruitment goal of 20 participants per group.

Forty-two patients with a diagnosis of idiopathic Parkinson's disease and 20 healthy controls (HC) participated in the study. Patients were enrolled at the Neurology Unit, Movement Disorders Division, University of Verona, Italy. Recruitment took place during routine neurological assessments conducted by the neurologist (I.DV.), who evaluated patient eligibility based on the study's inclusion and exclusion criteria as part of the standard clinical evaluation. Demographic and clinical information, including disease duration and Levodopa Equivalent Daily Dose (LEDD), was collected during these visits. To be eligible, patients had to present no upper-limb tremor that could interfere with the experimental task and a Hoehn & Yahr (H&Y) score <2.5, indicating early-stage disease with predominantly unilateral motor symptoms (Goetz et al., 2004). Exclusion criteria included a Montreal Cognitive Assessment (MoCA; Conti et al., 2015) score <21, reflecting cognitive impairment, and any history of severe psychiatric disorders. Patients meeting these criteria were then invited to participate in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the committee for approval of research on humans (Comitato di Approvazione della Ricerca sulla Persona-CARP). Written informed consent was obtained from all participants prior to their inclusion in the study.

2.2. *Clinical assessment*

Pathological fatigue was determined on the day of testing using the Fatigue Severity Scale (FSS), a 9-item self-report questionnaire widely applied in clinical settings to evaluate persistent fatigue over the past two weeks (Krupp et al., 1989; Siciliano et al., 2019). The FSS stands as the only recommended scale for the screening and grading of fatigue severity in Parkinson's Disease and other neurological disorders (Di Vico et al., 2025; Friedman et al., 2007; Herlofson & Larsen, 2002; Krupp et al., 1989). The established clinical cut-off of FSS ≥36 is widely used to identify pathological fatigue and is supported by consistent empirical evidence (Friedman et al., 2010; Herlofson & Larsen, 2002; Krupp et al., 1989). Using this validated criterion, we classified patients as experiencing clinically significant fatigue ($\text{PD}_{\text{Fatigue}}$) or not ($\text{PD}_{\text{No Fatigue}}$) and verified that no healthy participants exceeded the threshold indicative of pathological fatigue (Herlofson & Larsen, 2002; Krupp et al., 1989). This dichotomous classification allowed us to directly address our main research question: whether sensory attenuation differs specifically in individuals with clinically significant fatigue. To further characterize fatigue in our sample, we used other scales in addition to the FSS. The Parkinson's Disease Fatigue Scale (PFS) assessed the severity of fatigue and its impact on daily activities and social interactions (Brown et al., 2005; Siciliano et al., 2019). Additionally, the Multidimensional Fatigue Inventory (MFI) provided a broader evaluation of fatigue across five dimensions: global fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity (Smets et al., 1995). As no formally validated Italian version of this scale is currently available, we used an Italian translation that has previously been employed in studies involving clinical populations (e.g., Sandri et al., 2025; Trojsi et al., 2023).

Moreover, to account for potential confounding factors often co-occurring with fatigue (Nassif & Pereira, 2018; Siciliano et al., 2022), we administered scales for other non-motor symptoms. In particular, sleep disturbances were evaluated with the Parkinson's Disease Sleep Scale (PDSS-2), with a threshold of ≥18 indicating poor sleep quality (Arnaldi et al., 2016; Chaudhuri et al., 2002; Trenkwalder et al., 2011); excessive daytime sleepiness was assessed via the Epworth Sleepiness Scale (ESS), where a cut-off score of ≥10 defined excessive daytime somnolence (Johns, 1991; Vignatelli et al., 2003); depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS) using a cut-off score ≥11 to indicate clinically relevant symptoms in either domain (Costantini et al., 1999; Zigmond & Snaith, 1983). Finally, apathy was measured with the Apathy Evaluation Scale-Self report version (AES-S), with a score ≥40 indicative of clinically significant apathy (Marin et al., 1991; Santangelo et al., 2014). Severity of motor symptoms was assessed by means of the Unified Parkinson's Disease Rating Scale–Part III (UPDRS–III) (Antonini et al., 2013; Goetz et al., 2008).

2.3. *Procedure*

Sensory attenuation was assessed in a single session using the FMT (McNaughton et al., 2023; Palmer et al., 2016; Pareés et al., 2014; Shergill et al., 2003, 2005; Wolpe et al., 2018). After completing the FMT, we proceeded with the clinical assessment. The FMT and the clinical assessment were conducted with patients in their “off” medication state, meaning they abstained from dopamine therapy for at least 12 h prior to the experimental session.

The FMT was implemented using a custom-built apparatus developed by our research group. The device consisted of a stepper motor controlled via a program coded in MATLAB 2014. A small platform was mounted on the motor shaft so that, when the motor was activated, the platform moved downward, activating a mechanical lever. Participants placed their left hand palm-up with the index finger securely taped to a support positioned beneath the lever. A force sensor embedded in the lever recorded both the target and matched forces during the stimulation and matching phases. During the stimulation phase, a target force was applied to the participants' left index finger for a fixed duration of 3 sec. Immediately afterward, participants matched the target force under two conditions (Fig. 1A). In the direct condition, they directly applied the force over their left index finger with their right index finger (Fig. 1B). In the indirect condition, participants pressed a touch-sensitive button that activated the motor, causing the lever to progressively advance toward the finger to apply force, with no detectable delay. When participants released the button, the

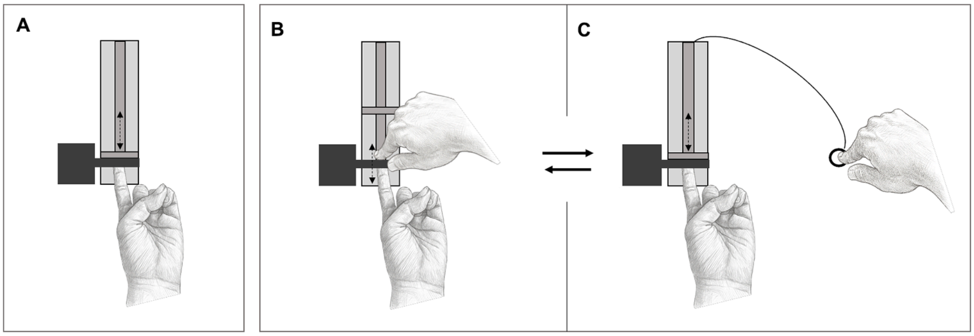

Fig. 1 – Experimental set-up. In each trial, participants underwent a stimulation phase in which they received a target force on the left index finger through a lever moved by a motor (A). Immediately following, they were asked to match this force under two different conditions. In the direct condition (B), they used their right index finger to directly press on their own left index finger. In the indirect condition (C), they matched the target force by operating the motor with a touch-sensitive button.

lever immediately stopped moving (Fig. 1C). The matching phase lasted up to 6 sec. If no change in the applied force was detected for 500 msec, the system automatically advanced to the next trial. The matched force was defined as the mean force recorded during the final 500 msec of the reproduction phase, when the response was considered stable (McNaughton et al., 2023). This allowed for the minimization of possible confounding effects arising from altered force production in PD, such as increased force irregularities or prolonged time to peak (Stelmach et al., 1989). Three different target forces, increasing by 1 N (1N, 2N, 3N), were randomly delivered in both conditions. We used multiple target forces primarily to reduce the risk of habituation across trials, while also enabling the exploration of potential force-dependent differences in sensory attenuation, consistent with previous findings (Palmer et al., 2016). Each condition comprised three blocks of 12 trials (36 trials in total), with four repetitions for each target force. Participants were given a 1-min rest between blocks and a 5-min break between the two conditions. Force data was acquired at 1000 Hz using an FSR 402 force sensing resistor (single-part repeatability of ±2%) integrated into a bridge resistor circuit. The analog signal was digitized via a 16-bit data acquisition system (NI USB-6210, National Instruments). Across a maximum force range of 10 N, this setup provided a theoretical resolution of .00015 N (.0015%). For post-processing, the raw data was first passed through a 50 Hz notch filter to eliminate power-line interference, and subsequently smoothed using a second-order, zero-phase maximally flat low-pass Butterworth filter with a 10 Hz cutoff frequency.

To eliminate potential auditory cues from the motor, participants wore noise-canceling headphones throughout the task. The headphones were also used to deliver three auditory signals marking the key phases of each trial: the onset of the stimulation phase (“stimulation”), and the beginning (“go”) and end (“stop”) of the matching phase. Throughout each trial, participants were instructed to maintain gaze on a central fixation point displayed on a computer screen. Following a 12-trial familiarization phase, participants completed the direct and indirect conditions in a counterbalanced order.

The primary outcome measure was the sensory attenuation index (SA index), calculated for each trial and target force as the ratio between the force reproduced by the participant (F_{matched}) and the target force (F_{target}):

$$\text{SA index} = \frac{F_{\mathrm{matched}}}{F_{\mathrm{target}}}$$

This measure was averaged across trials, after removing outliers (i.e., trials in which the ratio exceeded ±2 SD from the mean ratio computed across the 12 trials for each target) to give the mean attenuation for each target force in each condition (Pareés et al., 2014). On this measure, a score of 1 suggests accurate estimation of the target force, while a score higher than 1 indicates overestimation and a score lower than 1 indicates underestimation. Typically, the SA index is higher in the direct condition than in the indirect, indicating greater overestimation when directly pressing on the finger compared to operating an external device, which suggests proper sensory attenuation. Conversely, a lack of significant difference between the two conditions would suggest impaired sensory attenuation. To thoroughly explore this disparity between conditions across groups, we calculated the delta SA as follows:

$$\text{Delta SA} = \text{SA index}_{\mathrm{direct}} - \text{SA index}_{\mathrm{indirect}}$$

where SA $\text{index}_{\mathrm{direct}}$ and SA $\text{index}_{\mathrm{indirect}}$ are the average of SA indices across target forces, in the direct and indirect conditions, respectively. The delta SA quantifies the difference in force estimation between conditions, with lower scores reflecting a poorer ability to distinguish self-from externally applied forces.

Following the direct and indirect conditions, we used ten-cm-long Visual Analog Scales (VAS) to capture subjective experiences during the experiment. We measured state fatigue (from 0 = “not at all” to 10 = “maximal fatigue”) and physical effort experienced in performing the task (from 0 = “no effort” to 10 = “maximal effort”). This allowed us to explore the interplay between sensory attenuation and perceived fatigue and effort, a key component of the sensory attenuation model of fatigue. Additionally, we measured perceived accuracy (0 = "poor" to 10 = "very good") and the feeling of control over the task (0 = "not at all" to 10 = "total control"). These measures were included to investigate the relationship between sensory attenuation and the subjective experience of control, supported by findings that impaired sensory attenuation is linked to a diminished sense of control over actions (Blakemore et al., 2002).

2.4. *Data analysis*

Statistical analyses were performed using IBM SPSS Statistics 25. Age and gender distribution were analyzed by means of a *t*-test and a chi-squared test, respectively. Clinical variables were analyzed by means of the Kruskal–Wallis test and the Mann–Whitney *U* test.

To explore whether sensory attenuation differed between groups and across conditions, SA indices were analyzed by means of 3 × 2 × 3 rmANOVA with Group ($\mathrm{PD}_{\mathrm{Fatigue}}$, $\mathrm{PD}_{\mathrm{No\ Fatigue}}$, HC) as between subject factor, and Condition (direct, indirect) and Target Force (1N, 2N, 3N) as within-subject factors. Assumptions of normality, homogeneity of variances, and sphericity were systematically checked. With the exception of minor deviations, these assumptions were adequately met, and repeated-measures ANOVA is well established to be robust to such moderate violations, particularly with balanced group sizes (Blanca et al., 2017, 2018; Rasch & Guiard, 2004; Rogan & Keselman, 1977; Schmider et al., 2010). Greenhouse–Geisser corrections were applied when necessary (Blanca et al., 2023; Greenhouse & Geisser, 1959). All main effects and interactions remained statistically significant after correction, confirming the robustness of the findings. To ensure that minor assumption violations did not bias the results, we conducted non-parametric robustness checks. These analyses yielded a comparable pattern of significant and non-significant effects, further supporting the stability of the findings. Full assumption checks and supporting analyses are reported in the Supplementary materials. Post-hoc comparisons of estimated marginal means were conducted using Wald *z*-tests with Bonferroni correction for multiple comparisons. Additionally, a one-way ANOVA was performed with Group ($\mathrm{PD}_{\mathrm{Fatigue}}$, $\mathrm{PD}_{\mathrm{No\ Fatigue}}$, HC) as the between-subject factor to explore whether the delta SA differed across groups. Homogeneity of variances was confirmed (Levene's test, $p > .05$). Welch's ANOVA, which does not assume equal variances, was also computed and yielded a consistent group effect ($p = .029$), confirming the robustness of the results. When a significant main effect was found, Bonferroni-corrected pairwise *t*-tests were used for post-hoc comparisons. Non-significant results were further examined using Bayesian paired and independent-samples *t*-tests.

Subjective measures were analyzed by means of non-parametric test. More precisely, Kruskal–Wallis test was applied to compare perceived fatigue, effort, performance, and control across groups separately for each condition. The Wilcoxon signed-rank test was used to assess differences between direct and indirect conditions in each group.

The Spearman coefficient correlations were used to explore 1) the relation between the amount of SA in each condition (SA $\mathrm{index}_{\mathrm{direct}}$, SA $\mathrm{index}_{\mathrm{indirect}}$) and subjective measures; 2) the potential association between delta SA, disease severity, disease stage, LEDD, and other nonmotor symptoms. These analyses were performed separately for each group.

Effect sizes were estimated using eta squared (η^2) and partial eta squared (ηp^2) for main effects and interactions, Cohen's *d* for parametric paired and independent-samples tests, and Pearson's *r* for non-parametric pairwise comparisons (Cohen, 1988; Keppel, 1991; Lakens, 2013). Statistical significance was set at $p < .05$, with Bonferroni-corrected *p*-values reported where applicable.

3. Results

3.1. *Demographic and clinical data*

With the FSS score, we identified 20 patients with pathological fatigue who formed the $\mathrm{PD}_{\mathrm{Fatigue}}$ group. The remaining 22 patients formed the $\mathrm{PD}_{\mathrm{No\ Fatigue}}$ group. All groups ($\mathrm{PD}_{\mathrm{Fatigue}}$, $\mathrm{PD}_{\mathrm{No\ fatigue}}$, and HC) were comparable for age, gender distribution, and cognitive level (all, $p > .810$). Disease duration, disease stage, severity of motor symptoms, and LEDD were similar between $\mathrm{PD}_{\mathrm{Fatigue}}$ and $\mathrm{PD}_{\mathrm{No\ fatigue}}$ groups (all, $p > .278$) (Table 1).

The FSS score was significantly different across the groups ($H_{(2)} = 40.073$, $p < .001$, $\eta^2 = .646$), with a higher score in $\mathrm{PD}_{\mathrm{Fatigue}}$ compared to both $\mathrm{PD}_{\mathrm{No\ fatigue}}$ ($Z = -5.545$, Bonferroni-corrected $p < .001$, $r = -.854$) and HC ($Z = -5.412$, Bonferroni-corrected $p < .001$, $r = -.856$). These results confirmed that patients of the $\mathrm{PD}_{\mathrm{Fatigue}}$ group were experiencing a significantly higher level of fatigue compared to the other groups, as measured with the FSS. Further evidence supporting these findings came from additional measures of fatigue. The Kruskal–Wallis test yielded statistical significance for the PFS ($H_{(2)} = 34.867$, $p < .001$, $r = .745$) and the MFI's global ($H_{(2)} = 24.989$, $p < .001$, $r = .650$), physical ($H_{(2)} = 28.232$, $p < .001$, $r = .675$), mental fatigue ($H_{(2)} = 7.337$, $p = .026$, $r = .344$) due to higher scores in the $\mathrm{PD}_{\mathrm{Fatigue}}$ group compared to both the $\mathrm{PD}_{\mathrm{No\ Fatigue}}$ (PFS: $Z = -4.599$, Bonferroni-corrected $p < .001$, $r = .709$; MFI Global fatigue, $Z = -4.135$, Bonferroni-corrected $p < .001$, $r = -.636$; MFI Physical fatigue: $Z = -4.047$, Bonferroni-corrected $p < .001$, $r = -.622$; MFI mental fatigue: $Z = -2.395$, Bonferroni-corrected $p = .034$, $r = -.370$) and HC (PFS: $Z = -5{,}412$, Bonferroni-corrected $p < .001$, $r = -.856$; MFI Global fatigue: $Z = -4.535$, Bonferroni-corrected $p < .001$, $r = -.717$; MFI Physical fatigue: $Z = -4.976$, Bonferroni-corrected $p < .001$, $r = -.787$; MFI mental fatigue: $Z = -2.284$, Bonferroni-corrected $p = .046$, $r = -.359$). The three groups did not differ in terms of anxiety ($H_{(2)} = 4.900$, $p = .086$, $\eta^2 = .049$), depression ($H_{(2)} = 4.953$, $p = .084$, $\eta^2 = .050$), apathy ($H_{(2)} = 1.542$, $p = .463$, $\eta^2 = .025$), or daytime somnolence ($H_{(2)} = .803$, $p = .669$, $\eta^2 = .013$). We found no significant difference in overall sleep quality (PDSS-2 total score) between $\mathrm{PD}_{\mathrm{Fatigue}}$ and $\mathrm{PD}_{\mathrm{No\ Fatigue}}$ groups ($Z = -1.866$, $p = .062$, $r = -.288$). A significant difference was observed only on the PDSS-2 subscale for nocturnal Parkinson's disease motor symptoms (e.g., muscle cramps in arms and legs), with the $\mathrm{PD}_{\mathrm{Fatigue}}$ group reporting a greater score ($Z = -2.186$, $p = .029$, $r = -.337$) (Table 2).

Table 1 – Demographical and clinical characteristics.

	HC ($n = 20$)	PD$_{\text{No Fatigue}}$ ($n = 22$)	PD$_{\text{Fatigue}}$ ($n = 20$)	*p*-value
Age (years)				
Mean (SD)	64.80 (10.43)	61.65 (9.32)	64.10 (8.37)	.586
Sex				
Female, *n* (%)	9 (30)	8 (36)	9 (45)	.615
Male, *n* (%)	14 (70)	14 (64)	11 (55)	
MoCA	27.10 (1.89)	26.77 (2.05)	26.90 (2.38)	.810
Disease duration (months)				
Mean (SD)	NA	4.23 (2.84)	4.37 (3.13)	.909
Most affected side				
Right, *n* (%)	NA	12 (54)	6 (30)	
Left, *n* (%)	NA	10 (45)	14 (70)	
PD subtype				
Akinetic-rigid, *n* (%)	NA	0 (0)	1 (5)	
Tremor- dominant, *n* (%)	NA	13 (59)	11 (55)	
Bradykinetic-rigid, *n* (%)	NA	9 (41)	8 (40)	
UPDRS-III				
Mean (SD)	NA	18.50 (6.67)	19.65 (10.42)	.980
H&Y				
Mean (SD)	NA	1.89 (.51)	1.90 (.38)	.864
LEDD				
Mean (SD)	NA	407.45 (214.16)	473.55 (255.56)	.364

MoCA: Montreal Cognitive Assessment; UPDRS-III: Unified Parkinson's Disease Rating Scale–Motor subscale; H&Y: Hoen and Year; LEDD: Levodopa Equivalent Daily Dose; NA: Not Available.

Table 2 – Mean and standard deviation (SD) of clinical scales assessing fatigue, sleep, and mood.

	HC^{a} ($n = 20$)	PD$_{\text{No Fatigue}}$^{b} ($n = 22$)	PD$_{\text{Fatigue}}$^{c} ($n = 20$)	*p*-value
Fatigue				
FSS	21.05 (7.34)^{c}	20.64 (8.48)^{c}	46.80 (6.44)^{a,b}	<.001
PFS	1.57 (.57)^{c}	1.96 (.82)^{c}	3.54 (.68)^{a,b}	<.001
MFI				
Global fatigue	8.55 (3.52)^{c}	8.96 (3.99)^{c}	14.70 (2.45)^{a,b}	<.001
Physical fatigue	7.70 (2.89)^{c}	9.09 (3.58)^{c}	14.15 (2.70)^{a,b}	<.001
Mental fatigue	8.95 (2.61)^{c}	8.73 (3.01)^{c}	11.30 (3.37)^{b,c}	.026
Reduced motivation	8.20 (3.44)	7.41 (3.26)	9.30 (3.66)	.239
Reduced activity	8.85 (4.53)	8.59 (3.53)	11.10 (3.54)	.051
Sleep problems				
PDSS-2				
PDSS-2 total score	NA	11.77 (6.98)	16.80 (8.39)	.062
Motor symptoms at night	NA	2.27 (2.96)	4.20 (3.59)	.053
PD symptoms at night	NA	1.50 (1.87)^{c}	3.55 (3.05)^{b}	.029
Disturbed sleep	NA	8.00 (3.82)	9.05 (3.80)	.447
ESS	5.60 (4.16)	6.05 (3.15)	6.65 (4.28)	.669
Mood				
HADS				
Anxiety	6.30 (4.14)	4.27 (3.13)	6.70 (4.19)	.086
Depression	4.15 (3.25)	4.00 (2.96)	6.05 (2.86)	.084
AES	29.25 (6.80)	28.41 (6.49)	31.10 (6.56)	.463

FSS: Fatigue severity scale; PFS: Parkinson's disease Fatigue Scale; Multidimensional Fatigue Inventory; PDSS-2: Parkinson's Disease Sleep Scale-2; ESS: Epworth Sleepiness Scale; HADS: Hospital Anxiety and Depression Scale; AES: Apathy Evaluation Scale. Superscripted letters ($^{a,\ b,\ c}$) denote significant post-hoc comparisons between groups, where a = healthy controls (HC), b = Parkinson's disease patients without fatigue (PD$_{\text{No Fatigue}}$), c = Parkinson's disease patients with fatigue (PD$_{\text{Fatigue}}$).

3.2. *Sensory attenuation*

The rmANOVA revealed a significant main effect of Condition ($F_{(1,\ 59)} = 19.474$, $p < .001$, $\eta p^2 = .248$), and of Target force ($F_{(1,\ 118)} = 29.313$, $p < .001$, $\eta p^2 = .332$). Also, the Condition × Target force interaction yielded statistical significance ($F_{(2,\ 118)} = 40.124$, $p < .001$, $\eta p^2 = .405$), due to a higher overestimation of the target force in the direct compared to the indirect condition at all force levels (all Bonferroni-corrected $p < .003$) except 3N (Bonferroni-corrected $p = .069$), and to a progressive decrease of SA index across force levels in the direct condition (SA index, 1N > 2N > 3N; all Bonferroni-corrected $p < .001$). Additional details are provided in Supplementary Fig. 1 and Supplementary Tables 1 and 2

Even more interestingly, we found a significant Group × Condition interaction ($F_{(2,\ 59)} = 3.658$, $p = .032$, $\eta p^2 = .110$). Post-hoc comparisons revealed that the HC and the $PD_{No\ fatigue}$ exhibited a significant difference between conditions with a higher overestimation in the direct compared to the indirect condition (HC: direct, 1.429 ± .576; indirect, 1.004 ± .123; Wald $Z_{(59)} = 4.427$, Bonferroni-corrected $p < .001$, Cohen's $d = 1.176$. $PD_{No\ Fatigue}$: direct, 1.271 ± .374; indirect, 1.029 ± .128; Wald $Z_{(59)} = 2.752$, Bonferroni-corrected $p = .011$, Cohen's $d = .669$), irrespective of the target force. Crucially, the $PD_{Fatigue}$ group showed no significant difference between direct (1.140 ± .257) and indirect conditions (1.083 ± .218, Wald $Z_{(59)} = .594$, Bonferroni-corrected $p = .555$, Cohen's $d = .158$; Fig. 2). The lack of difference between conditions in this group suggests a reduced ability to differentiate between self-generated and externally applied forces, indicating impairment of sensory attenuation mechanisms (Pareés et al., 2014). These results were further corroborated by a Bayesian paired-samples t-test indicating weak evidence in favor of the null hypothesis ($BF_{10} = .343$), suggesting that the data do not provide substantial support for a difference between conditions. Further details on post-hoc analyses are available in Supplementary Table 3.

To further explore this relevant finding, we analyzed the delta SA (representing the magnitude of the difference between conditions) across groups. These analyses revealed that delta SA was significantly different across groups ($F_{(2,59)} = 3.658$, $p = .032$, $\eta p^2 = .111$) due to a lower delta SA in the $PD_{Fatigue}$ group (.057 ± .272) compared to the HC group (.4250 ± .599, $t_{(38)} = 2.53$, Bonferroni-corrected $p = .016$, Cohen's $d = .802$), highlighting an impairment of sensory attenuation in patients with fatigue (Fig. 3).

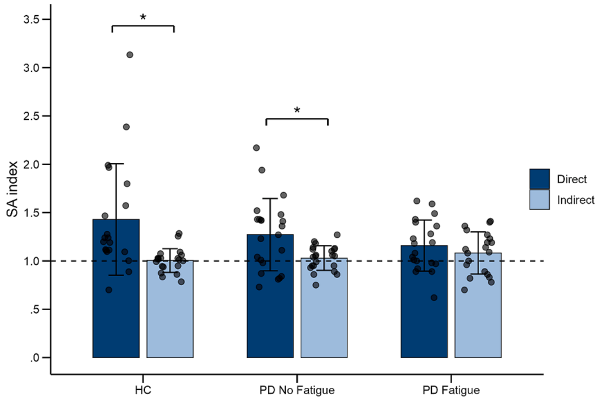

Fig. 2 – Mean sensory attenuation index in direct and indirect conditions across all groups. Healthy controls (HC) and Parkinson's disease patients without fatigue ($PD_{No\ Fatigue}$) showed significantly higher overestimation of the target force in the direct (dark blue) compared to the indirect (light blue) conditions. In contrast, patients with fatigue ($PD_{Fatigue}$) showed similar sensory attenuation index in both conditions. Asterisks indicate statistically significant differences ($p < .05$). The dashed line denotes optimal performance, corresponding to accurate reproduction of the target force. Dots represent individual data. Error bars indicate standard deviations.

3.3. *Subjective ratings*

Subjective measures of state fatigue, effort, accuracy, and control were comparable across all groups and conditions, with no significant differences observed either between conditions within each group (all, $p > .064$) or across groups (all, $p > .055$). Complete results of the Kruskal–Wallis and Wilcoxon-signed rank tests are reported in Supplementary Table 6.

3.4. *Correlations between SA and subjective ratings*

In the $PD_{Fatigue}$ group, the SA $index_{direct}$ was negatively correlated with the subjective ratings of fatigue ($\rho = -.681$, $p = .001$; Bonferroni-corrected significant threshold, $p = .012$), suggesting that the higher the perceived state fatigue, the lower the amount of sensory attenuation in the direct condition (Fig. 4A and B). The correlation between SA $index_{direct}$ and effort was of moderate strength ($\rho = -.512$, $p = .021$), suggesting a trend toward an association between higher perceived effort reduced sensory attenuation. Furthermore, we observed a statistically significant positive correlation between the SA $index_{direct}$ and subjective ratings of control experienced during the direct condition ($\rho = .655$, $p = .002$), suggesting that a higher SA index is associated with a greater feeling of control.

No significant correlation between the amount of SA and subjective ratings has been found in the HC group (all $p > .093$) or in the $PD_{No\ Fatigue}$ group (all $p > .147$; further details are available in Supplementary Tables 6 and 7).

3.5. *Correlations between delta SA and clinical variables*

In the $PD_{Fatigue}$ group, we found a significant positive correlation between delta SA and LEDD ($\rho = .554$, $p = .011$). This

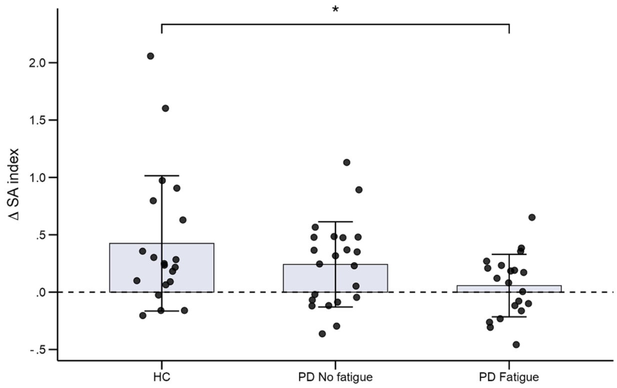

Fig. 3 – Mean delta sensory attenuation across the three groups. Parkinson's disease patients with fatigue ($PD_{Fatigue}$) showed a significantly lower delta SA (Δ SA index) compared to healthy controls (HC). Asterisks indicate statistically significant differences ($p < .05$). The dashed line denotes optimal performance, corresponding to accurate reproduction of the target force. Dots represent individual data. Error bars indicate standard deviations.

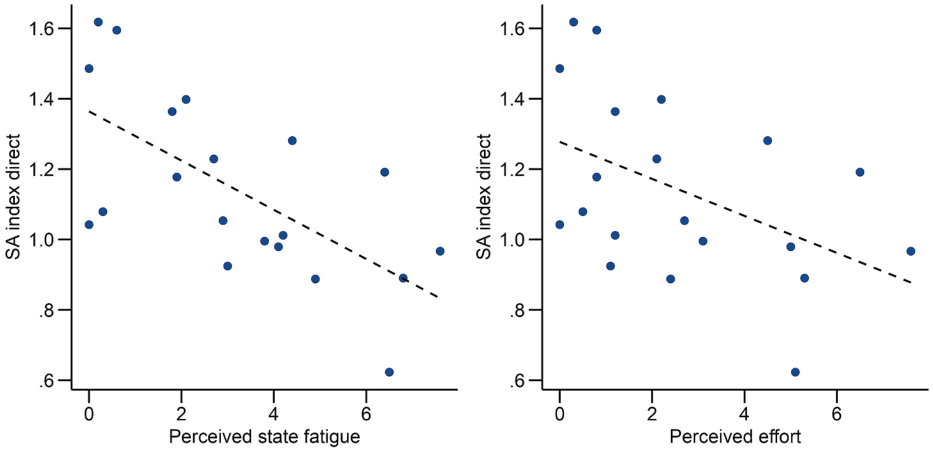

Fig. 4 – Correlations between sensory attenuation and perceived state fatigue and effort in the direct condition in the $PD_{Fatigue}$ group. Spearman's correlations revealed that as the sensory attenuation index in the direct condition (SA $index_{direct}$) decreased, there was an increase in the perceived levels of state fatigue (A) and effort (B) in the $PD_{Fatigue}$ group.

indicates that higher levodopa equivalent daily doses were associated with greater SA in the direct condition compared to the indirect condition within this group (Fig. 5).

This correlation was exclusive to $PD_{Fatigue}$ group, as it was not significant in the $PD_{No\ Fatigue}$ group ($p = .783$). Furthermore, we found no significant correlations between delta SA and other clinical factors typically associated with fatigue, including mood disorders and sleep disturbances, across any of the groups studied, with the exception of a modest association with nocturnal Parkinson's disease motor symptoms in the $PD_{Fatigue}$ group ($\rho = .480$, $p = .032$) (See Supplementary Table 8 for further details). This lack of correlation rules out a potential confounding interaction between delta SA and conditions like depression, anxiety, apathy, or sleep problems, irrespective of whether pathological fatigue was present ($PD_{Fatigue}$) or not ($PD_{No\ Fatigue}$ and HC).

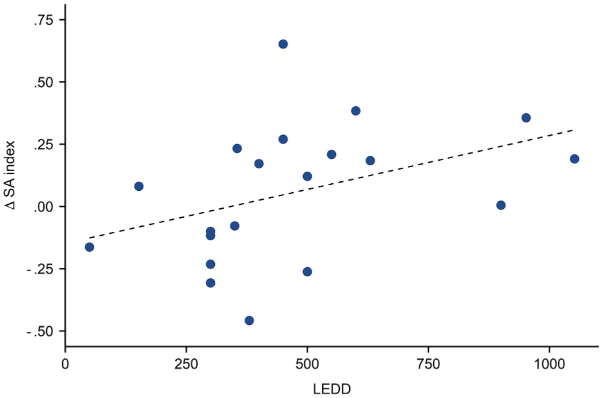

Fig. 5 – Correlation between delta sensory attenuation and levodopa dose in $PD_{Fatigue}$ group. A significant positive correlation between the delta sensory attenuation (Δ SA index) and levodopa equivalent daily dose (LEDD) was observed in the $PD_{Fatigue}$ group, suggesting that a greater delta between the direct and indirect conditions was associated with a higher LEDD.

4. Discussion

Our study demonstrates a selective impairment of sensory attenuation in Parkinson's disease patients with pathological fatigue. In the force-matching task, on average, only fatigued patients failed to overestimate the target force in the direct compared to the indirect condition. Conversely, this overestimation was present at the group level in both healthy controls and non-fatigued patients. A greater overestimation in the direct condition reflects intact sensory attenuation, whereby self-generated stimuli are perceived as less intense than externally generated ones (Palmer et al., 2016; Wolpe et al., 2018). The absence of this effect in fatigued patients suggests a disruption in sensory attenuation mechanisms and a diminished capacity to differentiate self-from externally generated forces (Pareés et al., 2014).

These findings offer preliminary behavioral evidence in support of the sensory attenuation model of fatigue. According to this model, a reduction in sensory attenuation may represent a plausible mechanism contributing to the subjective experience of pathological fatigue (Kuppuswamy, 2017, 2022). In this framework, impaired sensory attenuation could make motor acts feel unexpectedly intense or effortful, thereby contributing to subjective fatigue. Our results align with this hypothesis by showing reduced sensory attenuation in the fatigued group. Moreover, within this group, we observed a significant negative correlation between sensory attenuation and perceived fatigue in the direct condition, indicating that higher levels of state fatigue were associated with lower sensory attenuation. We also found a trend toward a negative correlation between sensory attenuation and perceived effort, suggesting a potential link between altered effort perception and impaired sensory attenuation. Together, these observations point to a possible mechanistic relationship between sensory attenuation and pathological fatigue, warranting further investigation.

Crucially, since, on average, impaired sensory attenuation was found only in the group of Parkinson's disease patients with fatigue but not in those without, we conclude that abnormal sensory attenuation may be a hallmark of pathological fatigue rather than a feature of Parkinson's disease itself. This conclusion is further corroborated by the absence of significant correlations between sensory attenuation and motor symptom severity in patients with fatigue. This finding suggests that the impaired sensory attenuation in these patients is not directly modulated by the severity of their motor symptoms, which stands in contrast to the observations of Wolpe and collaborators (Wolpe et al., 2018), who found a negative correlation between sensory attenuation and motor severity in Parkinson's disease. The discrepancy is likely due to methodological differences: Wolpe and collaborators tested patients in their “on” medication state, whereas our study tested them in their “off” state (Wolpe et al., 2018). This difference in dopaminergic state would critically influence experimental outcomes and highlights a crucial role for the dopaminergic system in modulating sensory attenuation in Parkinson's disease, a relationship that warrants further investigation. Another important observation suggesting that abnormal sensory attenuation is specifically linked to pathological fatigue rather than Parkinson's disease itself is the lack of significant correlation between disease duration and sensory attenuation in fatigued patients. This finding is a common observation in the literature exploring pathological fatigue, consistently showing that this nonmotor symptom is unrelated to disease duration or motor severity (Friedman et al., 2007; Havlikova et al., 2008). When considering our results alongside previous literature on fatigue, it becomes apparent that sensory attenuation and fatigue share commonalities, such as their consistent independence from Parkinson's disease severity.

Our data expand upon previous work showing reduced sensory attenuation in PD by uncovering a critical distinction: fatigue status matters. Earlier EEG studies reported globally diminished sensory attenuation in PD patients in the off-medication state (Macerollo et al., 2016; Pavese et al., 2010). However, by stratifying patients according to the presence or absence of fatigue, we demonstrate that this alteration is not uniform across PD but rather selectively characterizes those with fatigue. This distinction offers a novel interpretation of past findings and opens the door to targeted investigations in other neurological conditions where fatigue is prominent, such as multiple sclerosis or functional neurological disorders.

What are the neural underpinnings underlying the interplay between sensory attenuation and fatigue? The pathophysiology of fatigue relies on sensorimotor predictive processes, involving brain regions affected by Parkinson's disease, such as the basal ganglia and the prefrontal cortex (Pavese et al., 2019; Redinbaugh & Saalmann, 2024; Roelcke et al., 1997). These two interconnected brain regions are crucial for generating predictions about the sensory consequences of motor acts, a core component of sensory attenuation (Blakemore et al., 1998; Kuppuswamy, 2017, 2022; Redinbaugh & Saalmann, 2024). Therefore, the link between sensory attenuation and fatigue in Parkinson's disease could be explained by abnormal functioning of brain regions involved in predictive processes. Such impairments would compromise the ability to distinguish between internally and externally generated sensations (Harrison et al., 2021; McNaughton et al., 2023). Understanding the intricate interplay between sensory attenuation and fatigue would, however, necessitate a more comprehensive neurobiological perspective, considering both the involved neural circuits and their neurochemical modulation (Kuppuswamy et al., 2022). While specific brain regions like the basal ganglia and prefrontal cortex are part of the predictive processing circuitry, the dopaminergic system profoundly influences their function. Relevant to this, reduced dopamine input to cortical and subcortical brain structures, especially within the sensorimotor network, is a hallmark of Parkinson's disease (Sharman et al., 2013). Previous research suggests that dopamine administration can enhance sensory attenuation, with studies in Parkinson's disease demonstrating a positive correlation between dopamine levels and the magnitude of sensory attenuation (Macerollo et al., 2016; Wolpe et al., 2018). Consistent with these findings, we observed a significant correlation between the dopamine equivalent daily dose and the degree of sensory attenuation in the direct condition. Notably, this correlation was specific to patients with fatigue and was not present in those without. In line with this, using positron emission tomography, Pavese and collaborators found insular dopaminergic dysfunction in Parkinson's disease patients with fatigue but not in those without fatigue, indicating a possible involvement of this dysfunction in the pathophysiology of fatigue (Pavese et al., 2010). Integrating our behavioral findings with these studies, we can speculate that dopaminergic dysfunction may play a role in the interplay between fatigue and sensory attenuation. We must, however, interpret our results with caution, as patients were only assessed in their “off” state. Moreover, evidence regarding the benefits of levodopa for fatigue remains inconsistent (Nassif & Pereira, 2018). While some studies have reported that dopaminergic drugs may slow the progression of fatigue (Ongre et al., 2017), others have found dopamine to be ineffective in alleviating it (Elbers et al., 2015), and some have even suggested that fatigue could be an adverse effect of dopaminergic agonists (Pogarell et al., 2002). In addition, a recent meta-analysis found no evidence supporting a role for the dopaminergic system in modulating fatigue (Di Vico et al., 2025). These findings leave open the question of the precise contribution of dopamine depletion to pathological fatigue. Future studies assessing sensory attenuation in patients with fatigue in their “off” and “on” medication states, as well as in more advanced stages of the disease, when dopamine depletion is more pronounced, are needed to further clarify the role of dopamine in mediating the relationship between sensory attenuation and fatigue.

Importantly, we did not find significant correlations between reduced sensory attenuation in Parkinson's disease patients with fatigue and other nonmotor symptoms such as depression, anxiety, and sleep disturbances, which often co-occur with and are thought to exacerbate the subjective experience of fatigue (Nassif & Pereira, 2018; Siciliano et al., 2022). These findings suggest that mood disorders and sleep problems may not be significant confounding factors for sensory attenuation in our group of patients experiencing fatigue. Furthermore, they lend additional indirect support to the hypothesis that fatigue may represent a primary symptom with a distinct underlying mechanism, likely involving sensory attenuation. This is in line with previous findings suggesting that, although mood disorders and sleep problems are associated with fatigue, they do not entirely overlap with it (Hagell & Brundin, 2009). In fact, fatigue often persists as an independent symptom in Parkinson's disease, presented even in non-depressed and well-rested patients (Friedman et al., 2007). Along this line, our findings consistently highlight a specific association between fatigue and sensory attenuation, which seems not to be influenced by other clinically relevant characteristics, like severity of disease, mood abnormalities, and sleep problems.

Finally, and interestingly, we found a significant correlation between sensory attenuation and perceived control in the direct condition, particularly in patients experiencing fatigue. This correlation indicates that, within this group, a diminished overestimation of the target force was associated with a lower perception of control over the task. This observation strongly suggests that sensory attenuation plays a crucial role in modulating the subjective experience of control over movements for those experiencing fatigue, with important implications for an individual's experience of self-agency (i.e., the feeling of being in control of one's own movement) (Shergill et al., 2005).

We acknowledge some limitations in our study. First, the study findings lead to a crucial question that our current experimental design cannot answer: Is the loss of sensory attenuation a “trait” present before the onset of fatigue in Parkinson's disease, or does it emerge as a consequence of fatigue? While the sensory attenuation model of fatigue posits sensory attenuation as a key mechanism underlying fatigue, direct evidence establishing the temporal relationship between the loss of sensory attenuation and pathological fatigue remains elusive and warrants longitudinal study. Second, although our findings provide significant evidence on the interplay between sensory attenuation and fatigue, the role of perceived effort is only marginally explored. A new experimental design, allowing for the direct assessment of sensory attenuation, pathological fatigue, and perceived effort across tasks demanding differential levels of exertion, is therefore needed. Adding perceived effort to the equation would indeed provide evidence supporting the mechanism linking sensory attenuation and fatigue. Third, we acknowledge the absence of an independent measure of perceptual sensitivity (e.g., passive force estimation or discrimination paradigms) as a limitation of the present study. However, several methodological safeguards, such as the use of an optimized 500 ms force window, the comparable motor performance across groups, and the requirement of fine motor control in both direct and indirect conditions, substantially reduce the likelihood that perceptual or motor factors confounded our results. Even so, incorporating dedicated perceptual control tasks in future work will help further substantiate this interpretation. Fourth, although the study was adequately powered to detect the primary Group × Condition effect, the sample size may have limited statistical power to detect small-to-moderate three-way interactions involving target force; therefore, null higher-order interactions involving target force should be interpreted with caution. Finally, neuroimaging and neurophysiological investigations are needed to explore the neural underpinnings of altered sensory attenuation in patients with Parkinson's disease experiencing fatigue, identifying the specific brain networks underlying the sensory attenuation model of fatigue.

These limitations notwithstanding, this research sheds new light on the pathophysiology of fatigue by providing preliminary evidence of the link between sensory attenuation and pathological fatigue in Parkinson's disease, thereby opening the way for further investigations. While validation studies employing larger samples and replication cohorts are needed to confirm and extend these findings, our results suggest that impaired sensory attenuation may represent a measurable candidate biomarker to aid in diagnosing, monitoring, and potentially predicting fatigue severity in individuals with Parkinson's disease. This possibility may also be relevant to other neurological conditions in which pathological fatigue stands as one of the most common nonmotor symptoms (i.e., multiple sclerosis, functional neurological disorders), although further evidence will be essential before drawing firm conclusions. Ultimately, a clearer understanding of the mechanisms contributing to fatigue could pave the way for more effective and targeted therapeutic strategies. Such approaches might aim to enhance sensory attenuation processes, thereby refining the perception of effort and diminishing the persistent feeling of fatigue. This, in turn, could lead to important improvements in the quality of life for individuals who suffer from pathological fatigue.

CRediT authorship contribution statement

Angela Marotta: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing-review and editing, Writing-original draft. **Emanuela Pizzolla:** Data curation, Formal analysis, Investigation, Writing-original draft. **Ilaria Di Vico:** Writing-review and editing, Resources. **Michele Tinazzi:** Writing-review and editing, Resources. **Mehran Emadi Andani:** Methodology, Resources, Software, Writing-review and editing. **Mirta Fiorio:** Supervision, Conceptualization, Methodology, Funding acquisition, Writing-review and editing.

Ethical considerations

All participants signed a written informed consent form before taking part in the study, following the Declaration of Helsinki.

Competing interests

All authors declare no financial or non-financial competing interests.

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Scientific transparency statement

DATA: All raw and processed data supporting this research are publicly available: https://osf.io/w93en/overview?view_only=26725eb9b4214213bdcb9c906dcfce61 Data contained in the manuscript or supplemental files.

CODE: All analysis code supporting this research is publicly available: https://osf.io/w93en/overview?view_only=26725eb9b4214213bdcb9c906dcfce61.

MATERIALS: No study materials supporting this research are publicly available.

The authors provided the following justification for restricting access to materials: *'The code associated to the device is under evaluation for patenting.'*

DESIGN: This article reports, for all studies, how the author(s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.

PRE-REGISTRATION: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

For full details, see the *Scientific Transparency Report* in the supplementary data to the online version of this article.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2026.04.001.

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