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Central fatigue and attentional processing in Parkinson's disease: An event-related potentials study

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HIGHLIGHTS

- P3a latency is longer and P3a amplitude lower specifically in Parkinson's disease (PD) patients with fatigue.
- Novelty processing, a basic part of adaptive decision-making behavior, is altered in PD with fatigue.
- Central fatigue in PD is related to the cognitive domain.

ABSTRACT

Objective: To verify whether central fatigue in patients with Parkinson's disease (PD) is associated with the presence of a more severe selective cognitive impairment.
Methods: Twenty-four PD patients without fatigue-PDnF, 11 with fatigue-PDF and 32 healthy volunteers underwent a P300 novelty task that elicits both the P3a and the P3b components.
Results: P3b latency was significantly longer in both PDF and PDnF than in controls. P3b amplitudes were comparable between groups. P3a latency and P3a amplitude were respectively significantly longer and lower in PDF than in either PDnF or controls.
Conclusion: The ability to discriminate the significant target stimulus, which requires the integrity of the dorsal attentional network and top-down control mechanisms, is compromised in parkinsonian patients irrespective of the presence of fatigue. PDF exhibited a difficulty in attentional orienting to salient novel stimuli, a bottom-up attentional control mechanism that is related to the functioning of the ventral attention network.
Significance: Fatigue seems to be specifically related to an impairment in the processing of novel stimuli, which is an essential part of adaptive decision-making behavior.

1. Introduction

The classical motor "triad" used to define the clinical picture of Parkinson's disease (PD) has been enriched by a wide range of motor and non-motor symptoms that appear to be more difficult to manage and to markedly worsen the quality of life of parkinsonian patients. These additional symptoms include fatigue, which has been reported to affect more than 50% of the parkinsonian population and constitutes a highly disabling disorder that develops early (Friedman et al., 2007).

Many researchers agree that fatigue in PD prevalently consists of central fatigue, which is a failure to initiate and maintain attentional and physical tasks that require self-motivation in the absence of, or not related to, cognitive and motor dysfunction (Chaudhuri and Behan, 2000).

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Although recent studies have improved our understanding of fatigue, data on the pathophysiological mechanisms underlying this symptom are not yet univocal.

It has been suggested that the disruption of the central networks related to volitional effort, such as the basal ganglia, and their connections via the thalamus to the frontal lobe (prefrontal, orbitofrontal, cingulate cortices), may play a role in central fatigue, as demonstrated by lesional studies, clinical studies and functional imaging studies in many chronic diseases in which this symptom plays a dominant role, such as chronic fatigue syndrome and multiple sclerosis, as well as in PD (Chaudhuri and Behan, 2004; Engström et al., 2013; Miller et al., 2014). Moreover, there is growing evidence that central fatigue may be associated with cognitive deficits in PD (Friedman et al., 2007). Indeed, fatigue, especially when moderate to severe, has been shown to be associated with cognitive impairment (Goldman et al., 2014). Fatigue in PD, in particular, appears to be related to attentional-executive deficits (Kluger et al., 2017; Pauletti et al., 2017) and decreased cerebral blood flow in the frontal lobe (Abe et al., 2000). Taken together, these observations also point to a possible role in the pathophysiology of central fatigue in PD of an altered striato-thalamo-prefrontal loop, which is known to be compromised by the pathological process of this disease.

An easy and reliable way to study selective attentional functions is by means of Event Related Potentials (ERPs). ERP components, which are recorded and analyzed on the EEG trace while a task is performed, provide a direct and continuous measure of the neurotransmission-mediated neural activity engaged during the task (Luck, 2014). They reflect neural processes that are completely task-dependent and can be quantified even in the absence of any overt response. In this perspective, they represent a reliable means of gaining information on attentional processing of stimuli, especially in movement disorders, in which the efficiency of cognitive processing may be confounded by the patients' motor impairments.

The P300 component of ERPs is elicited by stimuli that present a change in one of the core characteristics in a series of identical stimuli. To elicit a P3a component (which is more frontally expressed), the change must be unpredictable and rare; if it is also task-relevant, a P3b, which is more parietally expressed, appears in the ongoing EEG activity. The P3a therefore reflects attentional processes related to the attentional orientation to the novelty, engaging activity of the ventral attentional network, the attentional network, which includes the temporo-parietal junction (TPJ), the ventral frontal cortex, the anterior insula and the anterior cingulate cortex (ACC) (Coull, 1998; Petersen and Posner, 2012; Corbetta and Shulman, 2002). The P3b component instead reflects the activity of the dorsal attentional network, which includes the frontal eye fields (FEF), the inferior frontal junction and the superior parietal lobule (SPL), which exerts a central role on attentional control associated with the detection of targets and implements the mechanism that orients attention to the external environment by sending top-down biasing signals to a subset of sensory input (Corbetta and Shulman, 2002; Kim, 2014).

Several studies have demonstrated selective attentional deficits in PD using P3 components in both the auditory (Stanzione et al., 1991; Solís-Vivanco et al., 2015) and visual domains (Antal et al., 2000): the prolongation of P3b latency has been shown to be sensitive to the presence of dementia in PD (Seer et al., 2016); despite being less unequivocal, P3b amplitude findings point to a PD-related limitation of attentional processing resources that results in the P3b amplitude being selectively reduced in more highly demanding attentional tasks alone (Münte et al., 2015). The P3a, which is elicited both by the three-stimulus oddball task and by the distraction paradigm, has also been extensively studied in PD: although findings are somewhat contrasting, P3a amplitude attenuation has been interpreted as the electrophysiological correlate of PD-related behavioral deficits in adjusting rapidly and efficiently to novel environmental demands.

The aim of the present study was to verify the hypothesis according to which central fatigue in PD patients is associated with the presence of a more severe selective cognitive impairment. This impairment is presumed to be related to the activation of brain areas that represent the cortical target of the striato-thalamo-prefrontal loop, which has been considered to play a role in the pathophysiology of central fatigue. We hypothesized that if fatigue is associated with a deficit related to the striato-thalamo-prefrontal loop, P300 parameters would be compromised to a greater extent in patients with fatigue than in those without.

2. Methods

2.1. Design

We used a cross-sectional design to compare a group of PD patients with and without fatigue with an age-matched control group.

2.2. Subjects

Patients with a confirmed diagnosis of idiopathic PD according to the UK Brain Bank diagnostic criteria (Gibb and Lees, 1988), were consecutively recruited from the outpatient clinic of the Department of Human Neuroscience, Sapienza University of Rome. Exclusion criteria were: (1) 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; Measso et al., 1993); (2) comorbid psychiatric diagnoses; (3) use of psychoactive medication, drugs or excessive use of alcohol. Thirty-six outpatients (28 males, 8 females) were enrolled for the study. Thirty-two healthy age-matched volunteers (20 males, 12 females), with unremarkable personal and family histories for psychiatric and neurological disorders, were consecutively recruited from among non-consanguineous relatives of the outpatients as the control group.

All the patients were examined by two independent experienced neurologists during the "on" phase. The severity of PD was assessed by means of the Hoehn and Yahr staging scale while motor disability was rated by means of the Unified Parkinson's Disease Rating Scale-subset III (UPDRS III). The main clinical characteristics of the PD population are shown in Tables 1 and 2. Fatigue was measured by means of the Fatigue Severity Scale (FSS) (Krupp et al., 1989). When the seven-grade Likert scale is used, a cut-off of 4 indicates the presence of fatigue, with higher scores indicating a higher severity of fatigue.

Moreover, the PD patients' quality of life was assessed by means of the 39-item Parkinson's Disease Questionnaire (PDQ-39) (Peto and Jenkinson, 1995) and their quality of sleep by means of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989).

The experimental procedure was approved by the institutional review board of Sapienza University of Rome, and conducted in accordance with the Declaration of Helsinki. All the participants were right-handed and gave their written informed consent to the study.

2.3. Procedure

Each subject underwent an ERP evaluation consisting of an auditory P300 Novelty Task.

Table 1
Demographic variables and clinical characteristics of PD patients and controls.

	PDF (n = 11)	PDnF (n = 24)	Controls (n = 32)	*p*	*p*		
					PDF vs PDnF	PDF vs HC	PDnF vs HC
M/F	9/2	18/6	20/12	-	1.0*	.29*	.39*
Age (yrs)	68.3 ± 9.8 (73)	65.2 ± 6.8 (66.5)	62.8 ± 9.3 (64)	.14	–	–	–
Education (yrs)	10.2 ± 4.0 (13)	14 ± 4.2 (13)	13 ± 3.8 (13)	.08	–	–	–
MMSE	28.7 ± 1.4 (29.3)	28.5 ± 2.0 (30)	28.7 ± 1.7 (30)	.87	–	–	–
STAI Y-1	38.7 ± 5.2 (40.0)	34.8 ± 8.6 (32.5)	33.0 ± 4.6 (33)	**.03**	**.008**	**.004**	.79
STAI Y-2	46.3 ± 7.4 (47)	34.7 ± 6.5 (33.5)	34.2 ± 5.8 (33)	**<0.001**	**<0.001**	**<0.001**	.86
BDI	12.0 ± 3.2 (11)	6.3 ± 5.0 (5.5)	5.3 ± 2.8 (6)	**<0.001**	**.01**	**<0.001**	.76

Data are expressed as mean ± standard deviation (median).
Significant values ($p < 0.05$) are highlighted in bold.
Kruskal-Wallis test.
MMSE: mini mental state examination; STAI: state trait anxiety inventory; BDI: Beck depression scale.
* Fisher exact test for categorical data.

Table 2
Clinical characteristics of PD population.

	PDF (n = 11)	PDnF (n = 24)	U	*p*
Age at onset	62.7 ± 10.7 (64)	62.2 ± 7.8 (64)	109	.53
Disease duration yrs	5.6 ± 4.5 (4)	3.8 ± 2.8 (3)	88	.16
HY (%)				1.0*
1	8 (72.7%)	17 (70.8%)		
2	3 (27.3%)	7 (29.2%)		
UPDRS III	15.2 ± 4.2 (13)	15.0 ± 5.8 (13)	113.5	.64
Onset side R (%)	5 (45.5%)	14 (58.3%)		.71*
Predominant motor symptom n (%)				.86*
Tremor	6 (54.5%)	15 (62.5%)		
Rigidity	4 (36.4%)	7 (29.2%)		
Mixed	1 (9.1%)	2 (8.3%)		
LEDD (mg/die)	500.0 ± 195.3 (465)	349.8 ± 212.4 (300)	76	.07
Levodopa usage nr (%)	8 (72.7%)	11 (45.8%)		.17*
Dopamine agonist usage nr (%)	7 (63.6%)	19 (79.2%)		.42*
MAOBI usage (nr)	3 (27.3%)	11 (45.8%)		.46*
FFS	5.5 ± 1.2 (5.8)	2.4 ± 0.8 (2.5)	0	**<0.001**
PSQI	9.0 ± 5.2 (9)	5.6 ± 3.3 (5)	68.5	.07
PDQ39	29.5 ± 8.7 (31)	16.6 ± 11.6 (13)	35.5	**.001**

Data are expressed as mean ± standard deviation (median).
Significant values ($p < 0.05$) are highlighted in bold.
Mann-Whitney *U* test.
HY: Hohen-Yahr stage; UPDRS III: Unified Parkinson's disease rating scale part III; LEDD: Levodopa equivalent daily dose; FFS: Fatigue severity scale; PSQI: Pittsburgh sleep quality index; PDQ-39: Parkinson's Disease Questionnaire. MAOBI, Monoamine oxidase-B inhibitor.
* Fisher exact test.

2.3.1. Control measures

Before the ERP session, depression and anxiety, which are considered as potential attentional biases, were assessed by means of validated self-administered questionnaires (Beck Depression Inventory, BDI (Beck et al., 1961), and state-trait anxiety inventory, STAI Y-1, STAI Y-2 (Spielberger, 1983).

2.3.2. ERP evaluation

2.3.2.1. P300 – Novelty task. A series of auditory stimuli were administered. Stimuli were represented by frequent standard stimuli consisting of a 500 Hz tone (probability of occurrence: 0.8) and infrequent target stimuli consisting of a 1000 Hz tone (probability of occurrence: 0.1). The duration of both types of stimuli was 200 ms, the rise-fall time 10 ms, and the intensity 80 dB SPL. Novel stimuli, consisting of unique, non-repeating sound effects ("novels") either generated in the lab using a microphone, such as recordings of typical environmental sounds (e.g. a key in a lock, a glass on a table), or sampled from a sound effects compact disc (Kimble et al., 2000), were also administered (probability of occurrence: 0.1) These novel sounds were clipped to a length of 200 ms and were unidentifiable and ambiguous, with a frequency ranging from 500 to 1000 Hz. The intensity of all the stimuli, including the novel sounds, was checked using a calibrated sound-level meter (Radio Shack 33-2055) and adjusted so that the intensity perceived by the subject was 80 dB. The intensity and frequency range of all the stimuli (standard, target and novel) fell within the range of pure tone average normality for all the subjects. No target trial was followed by novel trials or vice versa in order to reduce the added effect of stimuli probability.

The subjects were told that they would hear a series of stimuli in which target tones were randomly interspersed. They were asked to ignore all other sounds and silently count the target tones, stating how many they had counted at the end of task. The interstimulus interval varied randomly between 2 and 3 s. The task lasted approximately 15 min.

2.3.2.2. EEG recording. The subjects were seated in a comfortable chair in a faradized and light-attenuated room. Electrical brain activities were recorded by means of Ag/AgCl electrodes placed at the F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 sites, according to the International 10-20 System. The EEG signals were referred to linked mastoids and grounded at Fpz. The vertical electro-oculogram (VEOG) was recorded from above and below the left eye; a horizontal EOG (HEOG) 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 online

EEG signals and EOG. An analog/digital converter at a sampling rate of 1024 Hz was used in order to digitize data, which were stored on a hard disk. We used a Mizar Sirius EEG-EP multifunctional system.

2.3.2.3. ERP analysis. EEG data were clipped offline into epochs of 800 ms with a baseline correction of 100 ms before each stimulus. A first automatic procedure was used to reject trials containing drift deflection exceeding ±100 μV in any channel including EOG, according to clinical guidelines (Duncan et al., 2009). A further offline analysis was performed to exclude ocular artifacts (eye movements/blinks), according to a standard algorithm (Woodman and Luck, 2003) implemented in our analyzer software (ERPLAB Toolbok). Trials containing artifacts were eliminated by computing the cross covariance between the single-trial EOG waveform and a 200-ms step function and rejecting trials on which the maximum covariance exceeded a ±15 μV threshold. Lastly, the detection of artifacts was verified by visual inspection. Artifact rejection accounted for 27.4 ± 10.9/400 (6.9%) of the trials in the patient group and 23.2 ± 5.7/400 (5.8%) in the control group.

Moreover, frequent trials following a novel or target trials were eliminated from further analyses.

For each subject, all the artifact-free trials were averaged per stimulus (Standard, Target, Novel) and filtered using a low-pass digital filter of 20 Hz.

The mean number of trials included was comparable between groups (PDF: 294.4 ± 10.8/400 (73.6%), PDnF: 296.9 ± 10.9/400 (74%), controls: 295.5 ± 6.9/400 (73.8%); $F_{2-64} = 0.36$, $p = 0.70$).

Similarly, the mean number of trials was comparable between groups also for each condition (standard stimuli: PDF: 229.9 ± 3.5; PDnF: 229.9 ± 3.9; controls: 227.7 ± 2.3; $F_{(2,64)} = 2.8$, $p = 0.07$; target stimuli: PDF: 32.3 ± 4.3; PDnF: 33.7 ± 4.1; controls: 34.1 ± 2.6; $F_{(2,64)} = 1.1$, $p = 0.34$; novel stimuli: PDF: 32.2 ± 4.3; PDnF: 33.3 ± 3.8; controls: 33.8 ± 3.3; $F_{(2,64)} = 0.78$, $p = 0.46$).

Electrical activity was measured at all the electrode sites and Fz, Cz and Pz were chosen for the analysis because ERP responses were largest in the midline locations. The P3b amplitude was defined as the mean voltage between 250 and 500 ms in the target responses; similarly, the P3a amplitude was defined as the mean voltage between 250 and 500 ms in the novel responses (Luck, 2014). The P3 latencies, defined as the midpoint latency of the same temporal window (between 250 and 500 ms), were calculated for the P3b on the target responses and for the P3a on the novel responses. The difference waves (DW) were also estimated by subtracting the grand average of the standard tones from the grand average of the novel tones and from the grand average of the target tones in each participant. The P3d amplitude were defined as the mean voltage between 250 and 500 ms on the two DWs. The P3d latencies, defined as the midpoint latency of the same temporal window (between 250 and 500 ms), were also on the two DWs.

The accuracy of the target counting, measured as the difference between the number of targets reported by participants and the real number of targets present along the task (errors) was also calculated as a performance measurement.

2.4. Statistical analyses

Data are expressed as means (±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: FFS ≥ 4 (PDF), parkinsonians without fatigue: FFS < 4 (PDnF) and healthy controls (HC)) were compared using the Kruskal-Wallis test. 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 Fisher exact test for categorical data.

As regards the P3 amplitudes and latencies, the responses to the target and the novel stimuli were analyzed separately by means of a mixed model ANOVA for repeated measures, the "electrode" (Fz, Cz, Pz) being the within-subject factor and the "group" (PDF, PDnF and controls) the between-subject factor. Similarly, P3d amplitudes and latencies on the two DWs (target-standard, novel-standard) were analyzed separately by means of a mixed model ANOVA for repeated measures, the "electrode" (Fz, Cz, Pz) being the within-subject factor and the "group" (PDF, PDnF and controls) the between-subject factor. If required, a post-hoc Bonferroni's correction was subsequently applied.

Degrees of freedom were adjusted, when necessary, using the Greenhouse-Geisser epsilon coefficient for possible violations of the sphericity assumption; corrected p values are reported. Effects sizes were measured by calculating the partial eta squared (η_p^2).

Differences in accuracy, expressed as the as the difference between the number of targets reported by participants and the real number of targets present along the task, were tested by means of a Kruskal-Wallis test.

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

Moreover, whenever a significant group difference emerged in the psychological or clinical characteristics, that particular factor was incorporated as a covariate into a post-hoc ANCOVA to directly check for any significant contribution made by the factor to the group difference observed in the ERPs parameters.

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

3. Results

One patient displayed high scores in depression (BDI = 43) and anxiety (STAI Y-2 = 75) scales and was therefore excluded from further analyses. On the basis of the FFS cut-off for the presence of fatigue, 11 (31.4%) of the 35 patients experienced fatigue (PDF) while 24 (68.6%) did not (PDnF) (a clear bimodality in the distribution of scores was not present). The demographic and clinical characteristics of both the patients and controls as well as the control measures results are shown in Tables 1 and 2. None of the patients was taking amantadine, COMT inhibitors, anticholinergic agents, and safinamide.

3.1. ERPs

All the patients and controls completed the task, with P3 waves being elicited in 100% of the subjects, as demonstrated by t-tests against a voltage value of 0 (P3a $t_{(66)} = 17.8$, Cohen's $d = 2.17$, $p < 0.0001$; P3b $t_{(66)} = 18.6$, Cohen's $d = 2.27$, $p < 0.0001$). Fig. 1 shows the Grand Average of the P300 components obtained for patients and controls. Table 3 shows P300 mean amplitude and latency values for each group.

3.1.1. Response to target stimuli (naming P3b)

As regards P3b latency, ANOVA revealed a main effect of the "group" factor ($F_{(2,64)} = 4.8$, $p = 0.01$, $\eta_p^2 = 0.13$). After Bonferroni's correction, a significant difference was detected between PDF and controls ($p = 0.02$), with PDF displaying longer latencies than controls. A difference bordering on significance was detected between PDnF and controls ($p = 0.08$), with PDnF also displaying longer latencies than controls. No differences emerged between PDF and PDnF ($p = 1.0$) (Fig. 2B). ANOVA did not reveal any effect of the "electrode" factor ($F_{(2,128)} = 0.4$, $p = 0.68$, $\varepsilon = 0.9$, $\eta_p^2 = 0.006$). A significant effect of the "electrode"x"group" interaction emerged ($F_{(4,128)} = 4.7$,

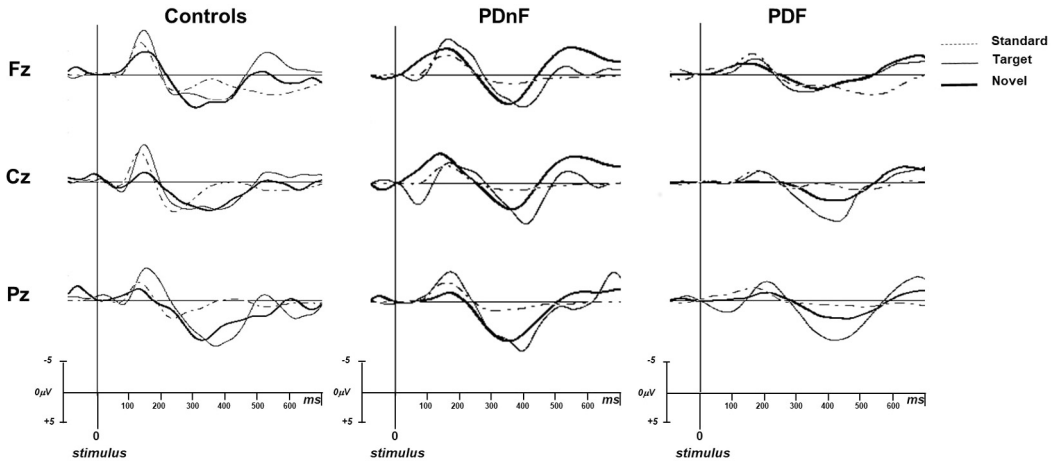

Fig. 1. ERPs traces in mid-line scalp locations for the standard (dashed line), target (thin line) and novel stimulus (thick line) for PDF, PDnF and controls.

Table 3
Mean P3 amplitudes and latencies (for target and novel stimuli) of PD patients and controls.

		PDF (n = 11)	PDnF (n = 24)	Controls (n = 32)
Target (P3b)				
Lat (ms)	Fz	378.5 ± 26.4	372.8 ± 26.7	353.8 ± 15.0
	Cz	382.7 ± 34.9	368.4 ± 27.4	357.6 ± 14.0
	Pz	371.1 ± 24.9	370.1 ± 23.2	362.4 ± 16.6
Amp (μV)	Fz	4.6 ± 2.3	7.7 ± 3.0	7.6 ± 3.8
	Cz	6.3 ± 3.4	9.2 ± 3.7	7.8 ± 3.2
	Pz	8.1 ± 5.1	10.0 ± 4.1	9.0 ± 3.6
Novel				
Lat (ms)	Fz	353.7 ± 27.0	338.6 ± 25.2	327.6 ± 18.5
	Cz	357.1 ± 27.3	337.1 ± 23.3	328.3 ± 20.4
	Pz	348.4 ± 26.3	340.6 ± 26.8	334.9 ± 20.3
Amp (μV)	Fz	3.0 ± 1.2	6.1 ± 3.0	6.2 ± 2.0
	Cz	5.3 ± 2.8	7.8 ± 3.7	7.1 ± 2.1
	Pz	6.6 ± 3.5	8.0 ± 3.3	7.2 ± 2.6

Data are expressed as mean ± standard deviation.

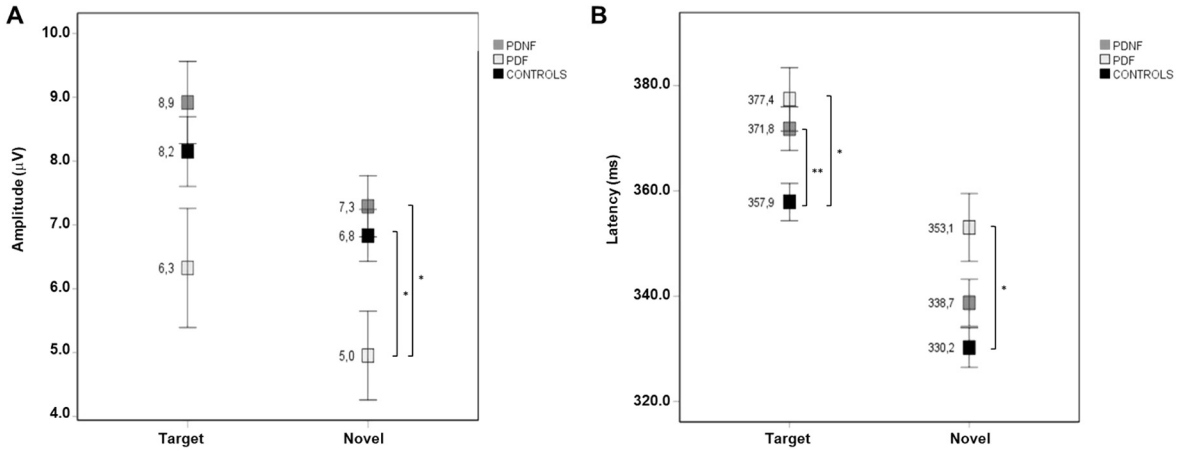

Fig. 2. Amplitudes (part A) and latencies (part B) of P3 components presented separately for novel (p3a) and target (p3b) stimuli. Error bars indicate ± 1SE. $^{*}p < 0.05$ and $^{**}p < 0.1$, both after Bonferroni correction.

$p = 0.01$; $\eta_p^2 = 0.13$); after Bonferroni's correction, a significant difference was detected between controls and both PDF and PDnF on Fz and Cz.

As regards the P3b amplitude, ANOVA did not reveal a main effect of the "group" factor ($F_{(2,64)} = 2.8$, $p = 0.07$, $\eta_p^2 = 0.08$) (Fig. 2A), but did reveal a main effect of the "electrode" factor ($F_{(2,128)} = 14.6$, $p < 0.001$, $\eta_p^2 = 0.18$), with higher amplitudes emerging for parietal sites than for frontal sites (Fig. 3B). The "electrode" × "group" interaction was not significant ($F_{(4,128)} = 1.2$, $p = 0.31$, $\eta_p^2 = 0.03$).

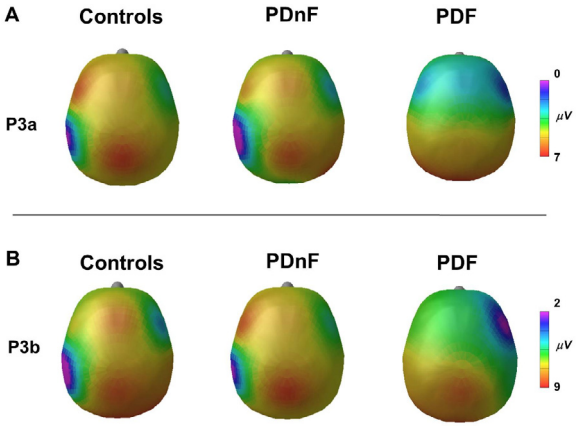

Fig. 3. Topographic maps in terms of amplitude of P3a (A) and P3b (B) in controls, Parkinson's disease patients without fatigue (PDnF) and Parkinson's disease patients with fatigue (PDF).

3.1.2. Response to novel stimuli (naming P3a)

As regards the P3a latency, ANOVA revealed a main effect of the "group" factor ($F_{(2,63)} = 4.8$, $p = 0.012$, $\eta_p^2 = 0.13$). After Bonferroni's correction, a significant difference was detected between PDF and controls ($p = 0.01$), with PDF displaying longer latencies than controls. No differences emerged between PDnF and PDF ($p = 0.2$) or controls ($p = 0.48$) (Fig. 2B). ANOVA did not reveal any effect of the "electrode" factor ($F_{(2,126)} = 0.2$, $p = 0.79$, $\varepsilon = 0.76$, $\eta_p^2 = 0.004$). A significant effect of the "electrode" × "group" interaction emerged ($F_{(4,126)} = 2.8$, $p = 0.03$; $\eta_p^2 = 0.08$); after Bonferroni's correction, a significant difference was detected between controls and PDF on both Fz and Cz.

As regards the P3a amplitude, ANOVA revealed a main effect of the "group" factor ($F_{(2,63)} = 4.0$, $p = 0.02$, $\eta_p^2 = 0.13$). After Bonferroni's correction, a significant difference emerged between PDF and both controls ($p = 0.02$) and PDnF ($p = 0.06$), with PDF displaying lower amplitudes. No difference emerged between PDnF and controls (Fig. 2A). ANOVA also revealed a main effect of the "electrode" factor ($F_{(2,126)} = 21.6$, $p < 0.001$, $\varepsilon = 0.82$, $\eta_p^2 = 0.26$), with higher amplitudes emerging for parietal sites than for frontal sites. The "electrode" × "group" interaction was bordering on significance ($F_{(4,126)} = 2.2$, $p = 0.07$; $\eta_p^2 = 0.07$). After Bonferroni's correction, a significant difference was detected between PDF and both PDnF and controls on Fz (PDF vs PDnF: $p = 0.002$; PDF vs controls: $p = 0.001$). No significant differences were detected at Cz and Pz (Fig. 3A).

3.1.3. Additional ERP results

The Grand Average of the DWs is depicted in Supplementary Fig. 1.

As regards P3d latency on the target-standard DW, ANOVA revealed a main effect of the "group" factor ($F_{(2,64)} = 4.8$, $p = 0.01$, $\eta_p^2 = 0.13$). After Bonferroni's correction, a significant difference was detected between PDF and controls ($p = 0.016$), with PDF displaying longer latencies than controls. No differences emerged between PDnF and PDF ($p = 0.6$) or controls ($p = 0.1$) (Supplementary Fig. 2). ANOVA revealed a significant effect of the "electrode" factor ($F_{(2,128)} = 3.8$, $p = 0.04$, $\varepsilon = 0.7$, $\eta_p^2 = 0.05$), with longer latencies at Pz. The "electrode" × "group" interaction was not significant ($F_{(4,128)} = 0.2$, $p = 0.9$; $\eta_p^2 = 0.007$).

As regards the P3d amplitude on the target-standard DW, ANOVA did not reveal a main effect of the "group" factor ($F_{(2,64)} = 0.8$, $p = 0.5$, $\eta_p^2 = 0.02$) (Supplementary Fig. 2), but did reveal a main effect of the "electrode" factor ($F_{(2,128)} = 15.1$, $p < 0.001$, $\eta_p^2 = 0.19$), with higher amplitudes emerging for parietal sites than for frontal sites. The "electrode" × "group" interaction was not significant ($F_{(4,128)} = 0.5$, $p = 0.7$, $\eta_p^2 = 0.01$).

As regards the P3d latency on the novel-standard DW, ANOVA revealed a main effect of the "group" factor ($F_{(2,64)} = 4.23$, $p = 0.019$, $\eta_p^2 = 0.12$). After Bonferroni's correction, a significant difference was detected between PDF and controls ($p = 0.015$), with PDF displaying longer latencies than controls. No differences emerged between PDnF and PDF ($p = 0.2$) or controls ($p = 0.8$) (Supplementary Fig. 2). ANOVA did not reveal any effect of the "electrode" factor ($F_{(2,128)} = 0.9$, $p = 0.4$, $\varepsilon = 0.72$, $\eta_p^2 = 0.014$). The "electrode" × "group" interaction was not significant ($F_{(4,128)} = 0.6$, $p = 0.65$; $\eta_p^2 = 0.02$).

As regards the P3d amplitude on the novel-standard DW, ANOVA revealed a main effect of the "group" factor ($F_{(2,64)} = 3.8$, $p = 0.03$, $\eta_p^2 = 0.11$). After Bonferroni's correction, a significant difference emerged between PDF and both controls ($p = 0.03$) and PDnF ($p = 0.05$), with PDF displaying lower amplitudes. No difference emerged between PDnF and controls (Supplementary Fig. 2). ANOVA also revealed a main effect of the "electrode" factor ($F_{(2,128)} = 7.9$, $p = 0.001$, $\eta_p^2 = 0.11$), with higher amplitudes emerging for parietal sites than for frontal sites. The "electrode" × "group" interaction was not significant ($F_{(4,128)} = 0.8$, $p = 0.5$; $\eta_p^2 = 0.25$).

3.2. Performance measure

Non-significant differences emerged between groups in accuracy (PDF: 0.9 ± 1.5; PDnF: 0.79 ± 1.1; controls: 0.56 ± 0.9; $F_{(2,64)} = 0.52$, $p = 0.59$).

3.3. Correlations

The severity of fatigue significantly inversely correlated with the P3 amplitude in frontal sites, both for the target stimulus ($r = -0.36$, $p = 0.03$) and for the novel stimulus ($r = -0.39$, $p = 0.01$).

Fatigue also significantly directly correlated with quality of life (PDQ39) ($r = 0.74$, $p < 0.001$) but did not correlate with any other clinical characteristics.

Psychophysiological parameters (P3 amplitudes and latencies) did not significantly correlate with any clinical characteristics in the sample of parkinsonian patients (disease duration or severity, age at onset, LEDD) (correlations between P3a amplitude and disease duration are displayed in Supplementary Table 2). The accuracy significantly correlated with the UPDRS III ($r = 0.41$, $p = 0.014$).

As regards control measures: the severity of fatigue significantly correlated with depression scores ($r = 0.57$, $p < 0.01$) and trait anxiety score ($r = 0.7$, $p < 0.01$), but did not correlate with state anxiety score ($r = 0.26$, $p = 0.13$). Anxiety and depression scores did not correlate with P3 parameters either in the control group or in the PD patients group.

3.4. CoVariates

The control measures that resulted significantly different between groups, were used as covariates in a post-hoc ANCOVA. After controlling for BDI, STAI Y-1 and STAI Y-2, a significant group effect on P3a amplitude at frontal site ($F_{(2,61)} = 5.7$, $p = 0.005$, $\eta_p^2 = 0.16$) still remained. After Bonferroni correction, a significant difference emerged between PDF and both PDnF ($p = 0.008$) and controls ($p = 0.005$), with PDF displaying lower amplitudes (adjusted means controlled by psychological variables: PDF = 2.9; PDnF = 6.1; controls = 6.3).

Similarly, after controlling for BDI, STAI Y-1 and STAI Y-2, a significant group effect still remained also on P3d amplitude on the novel-standard DW, at frontal site ($F_{(2,61)} = 3.7$, $p = 0.003$, $\eta_p^2 = 0.11$). After Bonferroni correction, a significant difference emerged between PDF and both PDnF ($p = 0.07$) and controls ($p = 0.025$), with PDF displaying lower amplitudes (adjusted means

controlled by psychological variables: PDF = 1.8; PDnF = 5.9; controls = 6.6).

Moreover, given the fact that PDF group showed a tendency for higher LEDD and for longer disease duration compared with PDnF group, and considering the consistent association between p3a amplitude and disease duration in PD (Solís-Vivanco et al., 2015; Cavanagh et al., 2017), LEDD and disease duration were also used as covariates in a post-hoc ANCOVA: a significant "group" effect remained on P3a amplitude, ($F_{(1,30)} = 12.1$, $p = 0.02$, $\eta_p^2 = 0.29$; LEDD effect: $F_{(1,30)} = 4.9$, $p = 0.03$; disease duration effect: $F_{(1,30)} = 3.7$, $p = 0.07$; adjusted means PDF = 3.1; PDnF = 6.4), as well as on P3d amplitude on the novel-standard DW ($F_{(1,30)} = 11.9$, $p = 0.002$, $\eta_p^2 = 0.285$; LEDD effect: $F_{(1,30)} = 0.3$, $p = 0.62$; disease duration effect: $F_{(1,30)} = 1.9$, $p = 0.17$; adjusted means PDF = 2.1; PDnF = 6.3).

Finally, also PDQ-39 was included as covariate in a post-hoc ANCOVA: a significant "group" effect remained on P3a amplitude ($F_{(1,30)} = 6.9$, $p = 0.014$, $\eta_p^2 = 0.19$; PDQ-39 effect: $F_{(1,30)} = 0.018$, $p = 0.89$; adjusted means PDF = 3.0; PDnF = 6.1), as well as on P3d amplitude on the novel-standard DW ($F_{(1,30)} = 4.8$, $p = 0.04$, $\eta_p^2 = 0.14$; PDQ-39 effect: $F_{(1,30)} = 0.004$, $p = 0.95$; adjusted means PDF = 2.3; PDnF = 5.5).

4. Discussion

The aim of the present study was to explore the association between fatigue and information processing in patients with PD.

Parkinsonian patients, irrespective of the presence of fatigue, exhibited a delayed P3b latency, which indicates that they took longer to evaluate and detect the significant target stimulus. The fact that there was no difference in accuracy between groups indicates that the behavioral performance was not compromised even though they took longer to process the target stimulus processing. The amount of attention assigned to the task, as shown by the P3b amplitude, was comparable in the two groups.

The allocation of attention relies on multiple factors, such as the physical properties of stimuli, their context, their proximity to sensory templates actively stored in working memory as well as the voluntary regulation of attention to specific events, respectively bottom-up and top-down control factors (Corbetta and Shulman, 2002).

P3b mainly reflects brain activity related to attention and working memory that is engaged during the categorization of an event, i.e. the process that leads to change/update the internal representation of the environment designed to correctly decide whether an external stimulus matches the mental model of the stimulus and to make an appropriate response (context updating theory) (Polich, 2007). The representations involved in the selection of task-relevant stimuli and responses are controlled by top-down voluntary signals and are linked to the activity of the dorsal fronto-parietal network, which includes the FEF, SPL, right supramarginal gyri as well as regions anterior/superior to the intraparietal sulcus (Corbetta and Shulman, 2002; Huang et al., 2012; Rossi et al., 2014).

Parkinsonian patients are known to have an executive cognitive deficit (impairment in set-shifting, planning, inhibition and updating functions) caused by the disruption of the mesocortical dopaminergic system (Dubois and Pillon, 1997; Owen, 2004). In this perspective, our results are in line with the current literature. Indeed, both the PDF and PDnF groups presented similarly prolonged P3b latencies, which indicates that fatigue and top-down mechanisms of attentional discrimination of the stimulus are not correlated.

A better insight into the association between cognition and fatigue was gained as regards the psychophysiological response to the novel stimulus. The p3a component was prolonged and significantly lower in amplitude in PDF patients alone. The p3a component is the neural marker of the process of the orienting response to salient stimuli. Novel stimuli are in fact salient by definition and determine an involuntary switch in attention allocation, as occurs, for instance, when attention is suddenly captured by an unexpected event beyond the immediate perceptual field (Linden, 2005), which represents a bottom-up mechanism of redirecting attentional resources. It relies on the integrity of the ventral attention network, which acts as a circuit breaker for the dorsal network by involving the TPJ, and for auditory stimuli by involving ventral frontal areas, the inferior frontal gyri (anterior and left posterior), angular gyrus and posterior cingulate cortices (Rossi et al., 2014).

Our data point to a specific dysfunction in PDF patients that is linked to the ventral network and to the ability to redirect attention through bottom-up mechanisms.

PD patients, given the disrupted integration in the basal ganglia-cortical loops due to the pathophysiological process of the disease, typically have difficulty in initiating and performing an act (either purely motor or cognitive) because of an inability to internally generate the appropriate motor, sensory and motivational cues; they consequently rely to a large extent on external cues to overcome this shortcoming (Brown and Marsden, 1988). Our data suggest that fatigue is associated to the inability to process external stimuli correctly, given the alteration of the bottom-up stimulus-driven mechanisms reflected by prolonged P3a latency, in addition to the top-down, self-generated, internal mechanism alteration reflected by prolonged P3b latency.

In healthy subjects, the onset of fatigue is designed to lead to the abandonment of a behavior when the energetic costs continue to exceed the perceived rewards of task performance (Boksem and Tops, 2008). Fatigue relies on mechanisms of evaluation and comparison of the costs and benefits of a motor/mental activity by balancing its energetic cost with the subject's volitional and motivational drive (Tinaz et al., 2016).

Several critical areas are involved in the mechanism of reward-related and effort-based decision making, such as the ventral tegmental area, the striatum, the insula, the ACC, the orbitofrontal cortex, the amygdala and the accumbens, all of which are known to be affected to some extent by the progressive neurodegeneration in PD and constitute the mesolimbic dopaminergic pathway, which is also activated in novelty processing. The integration of novel stimuli is in fact an essential part of adaptive decision-making behavior, and novelty is a potent learning signal that represents an exploration "bonus" for rewards (Wittmann et al., 2008; Krebs et al., 2009; Koster et al., 2016).

Within this perspective, central fatigue in PD almost appears to be a cognitive symptom, or at least one that is associated with the attentional domain. This observation is in keeping with recent resting-state functional magnetic resonance imaging studies in which PD-related fatigue was found to be associated with altered neural activity within the areas involved in the attention and salience networks (Zhang et al., 2017), and in the default mode network (Tessitore et al., 2016).

Several neurotransmitters have been implicated in the pathogenesis of fatigue. As in other studies related to fatigue, only a mild relationship emerged from our data between this symptom and dopamine replacement therapy. PDF showed specifically an impairment in the novelty P3, that reflects the activity of the network for rapidly orienting to novel stimuli or events (Ranganath and Rainer, 2003). A main role of dopamine in novelty processing has been hypothesized: it has been suggested that sensory-driven dopaminergic responses provide reinforcement signals that are necessary to create neural sensitivity to novel stimuli, therefore playing a critical role novelty detection (Redgrave and Gurney, 2006). On the other hand the effect of dopamine manipulation on novelty-related components is weak and it seems to be receptor

dependent (Kenemans and Kähkönen, 2011) and data are still controversial. Moreover a study by Pavese et al. (2010) demonstrated that fatigue is associated with reduced serotonergic function in the basal ganglia and limbic structures and that insular dopaminergic dysfunction could also play a role in it.

Taken together this data indicate that fatigue is probably a complex phenomenon that could depend on more than one neurotransmitter, and provide explanation on why fatigue does not well respond to any specific drug so far. Unfortunately our data do not contribute to shed light on the biochemical aspects of fatigue, that is still a matter of debate.

This study has certain limitations. First, our PDF population significantly differed from PDnF and controls in depression values. Depressed individuals may display reduced brain responses to novel sounds (Bruder et al., 2009), and a link between neuropsychiatric symptoms and cognitive decline has been described in PD (Lee et al., 2012). It is worth bearing in mind that our PDF sample did not display a clinically relevant level of depression (BDI < 16), and that in our sample depression and anxiety scores did not seem to be responsible for the reduced attention ability found in PDF. Even though several studies have reported that fatigue in PD is often associated with other non-motor symptoms, including depression and anxiety, fatigue has been found to affect non-depressed, non-demented, and non-sleepy PD patients to the same extent as PD patients with these problems (Friedman et al., 2007). Our PDF population significantly differed from PDnF also in other clinical aspects (anxiety, LEDD, PDQ-39). Even if the group effect on attentional parameters was preserved after controlling the data for all these variables, we are not able to exclude that they, as well as other variables such as disease duration that are known to influence psychophysiological parameters (Solís-Vivanco et al., 2015), could have played a role in compromising the attentional orienting in these patients. However our results indicate fatigue as one of the clinical characteristics associated to an alteration of attentional orienting in PD.

Second, the cross-sectional design allowed us to detect an association between fatigue and cognitive functions without, however, exploring any cause-effect relationship. Third, although making a sharp distinction between top-down and bottom-up mechanisms is useful for outline purposes, it should be borne in mind that top-down control mechanisms are also engaged in the processing of novel stimuli and that the two attentional networks operate on a parallel and continual basis rather than on an alternative basis (Kim, 2014). Lastly, the study is based exclusively on psychophysiological measures of attention, with the exception of the MMSE, rather than on a wide spectrum of cognitive measures. However, ERPs do have the considerable advantage of being able to provide reliable information without being dependent on motor performance, a feature that is particularly relevant in movement disorders.

In conclusion, the present data provide evidence of a specific alteration in attentional processing of information in PDF that is related to novelty processing. Central fatigue is a multifaceted symptom, that includes wide affective, executive and behavioral areas beyond attention. Further studies are needed to confirm the hypothesis that central fatigue is related also to the cognitive area rather than exclusively to the motor area.

Declaration of interest

None of the authors have potential conflicts of interest to be disclosed.

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Authors' roles

CP: Conception, design and execution of the research project analysis and interpretation of data, writing the first draft.

DM: Organization and execution of the research project, analysis and interpretation of data, review of the manuscript.

NC: execution of the research project, review of the manuscript.

AC: interpretation of data, review of the manuscript.

LM: interpretation of data, review of the manuscript.

FF: Conception and organization of the research project, interpretation of data, review of the manuscript.

All authors have read and approved the final version of the manuscript.

Appendix A. Supplementary material

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