Is Parkinson's disease an unique clinical entity? Rigid or tremor dominant PD: Two faces of the same coin

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ABSTRACT

Parkinson's disease is one of the most described neurodegenerative pathologies; though it is one of the most complex pathologies, is not fully understood, correctly identified, with its different types of presentation, its clinical course and the neural networks involved.

We report on a series consisting of 432 de novo PD diagnosed patients, and 457 control cases. We identify a possible independent relationship between two clinical PD presentation, akinetic-rigid and tremor-dominant, and cognitive and behavioral changes. A 24-months follow-up allows to identify new information still not fully explored.

1. Introduction

Parkinson's disease (PD) is a very heterogeneous neurodegenerative disorder. Probably, the principal basis of its ambiguous clinical presentation relies on the different and widespread dopaminergic neural networks impairment. Initially, all the symptoms have been referred to the brisk dysregulation of the striatonigral dopaminergic via, but more recently huger importance is given to the mesolimbic, the tuberoinfundibular and the mesocortical networks [1,2]. Previous work indicate different clinical subtypes of PD, with different courses and even prognosis, Unfortunately, the real neural mechanisms underlying these patterns, the clinical definition and the types of therapy are not recognized and many efforts have been undertaken to correctly approach these entities, both in a clinical context [3–6], and in a complex neuroimaging set [7–11]. One of the most well-conducted studies [12] argued that the akinetic rigid patients had an altered neural activity in the mesolimbic cortex and the tremor type in the cerebellar-thalamic projections.

Thus, there is a general clinical consensus on dividing empirically into two different motor subtypes of PD, although there is no consensus for the clinical distinctions. A well-designed, precursor study [13] have identified four patterns of clinical presentation in de novo PD patients: the benign form, also called pure motor, which shows a reduced bradykinesia, the mixed motor-non motor form, characterized by lower bradykinesia, axial alterations, behavior disturbances and a slow progression rate, the non-motor dominant type, with the lowest motor and the highest non-motor burden, and the motor dominant, with a faster progression disease [13]. We have previously reported different cognitive and behavioral profile in two groups of patients divided into two subgroups, as tremor dominant or akinetic-rigid type PD, with a follow up of 36 months [6]. This present study aims to implement the neuropsychological profile of the previous work, applying it in a *de novo* diagnosed group of PD patients, dividing them in two clinical patterns of presentation: akinetic-rigid and tremor type, employing a rigid score of UPDRS III and following them for 24 months.

2. Study design

Five hundred sixty-seven patients have been enrolled from January 15th, 2010, to January 15th, 2015. All the patients were visited and suspected of suffering from PD disease. They fulfilled the criteria of idiopathic PD [14,15]. Four hundred thirty-two patients of them underwent neuroimaging (CT head, 168 patients, 35.9% or MRI images, 299 patients, 64%), in order to exclude other degenerative disorders or significant small vessel disease, normal pressure hydrocephalus or brain tumors. All the patients

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underwent a DAT-SPECT [16]. Patients with previous psychiatric illness or central nervous system disorders and alcoholism were excluded. Additional exclusion criteria included the absence of a reliable caregiver and the neurological evidence of aphasic syndromes, which might have presented an obstacle to any understanding and compliance with the study.

Four hundred thirty-two patients have been enclosed and could be thoroughly studied. Patients were divided into two groups, one affected by predominant akinetic –rigid type of presentation, the other by the tremor-type presentation, in accordance to what we have previously described [6], where we have considered patients with declared PD patients, in off-state after an appropriate washout, and according to the classification by Abdo et al. [17] and by Rajput [18]. A "Tremor score" was derived as the mean of the sub-scores of items 20 and 21 (rest and action tremor) of UPDRS III [19]. A "Bradykinesia score" was defined as the mean of the sub-scores of items 23 to 26 (finger tap, handgrip, pronosupination, leg tap) of UPDRS III. The mean value of items 27 to 31 provided the "axial score."

As described elsewhere [6], we enriched the data with the MDS-UPDRS [20] sub-scores: 2.9 (Turning in bed; 0–4); 2.10 (Tremor; 0–4); 3.3 (Rigidity of neck and four extremities; 0–4); 3.4 (Finger taps; 0–4); 3.5 (Hand movements; 0–4); 3.6 (Leg agility; 0–4); 3.13 (postural tremor of hands; 0–4); 3.14 (Kinetic tremor of hands; 0–4); 3.15 (Rest tremor amplitude; 0–4); 3.16 (Constancy of rest tremor; 0–4).

We defined as Akinetic-rigid prevalent type the patient who obtained an average summary score of 2.9, 3.3, 3.4, 3.5, 3.6 was more than 14, and at the same time his average summary scores in 2.10, 3.13, 3.14, 3.15, 3.16 was less than 10; on the contrary, we defined as Tremor prevalent type if the average summary score of 2.9, 3.3, 3.4, 3.5, 3.6 was at average less than 10, and at the same time their average scores in 2.10, 3.13, 3.14, 3.15, 3.16 was more than 14 [6].

The progression rate was calculated as UPDRS III/disease duration.

We have recruited 457 controls, not affected by PD; among them, 125 suffered from cervicogenic headache, 275 from migraine and 57 suffered from chronic low back pain.

The present study was conducted following the Declaration of Helsinki, and under the Ethics Guidelines (Point 4 of the CEUR Declaration) of the Committee of the University-Hospital of Trieste, and written informed consent was obtained from all the participants.

3. Outcome measures

Complete neurological and neuropsychological examinations have been performed for each patient at the recruitment time, and then, every six months for 24 months.

Akinetic-rigid and tremor-dominant profiles have been evaluated by UPDRS and MDS-UPDRS [19,20].

The main outcomes of the study were:

1. Global performance, which was assessed using the Montreal Cognitive Assessment (MoCA; score 0–30; 30 = normal) [21].
2. Frontal Assessment Battery (FAB; score: 0–18; 18 = normal) [22,23].
3. Beck's Depression Inventory (version for Italian population) (score: 0–39; total score 10–19 indicated mild depression; total score 20–29 indicated moderate depression; >30 indicated severe depression) [24,25].
4. Hamilton Anxiety Rating Scale (HAM-A) (score: 0–56; a total score comprised 0–17, estimated mild anxiety; 18–24: mild to moderate anxiety; 25–30 severe anxiety) [26].
5. Apathy Evaluation Score (AES-C) (clinical examination; score: 18–72; higher scores reflect increasing apathy) [27].
6. Stroop Test (reading, color naming, and interference mistakes) [28,29].
7. Language and executive functions evaluated by Semantic Word fluency and phonemic fluency test; on semantic fluency tasks participants were asked to name as many animals, fruits and vegetables as possible in three minutes time; On phonemic tasks, subjects were asked to produce as many words as possible that began with T, P and S. Responses were recorded on audiotape and repeated words were not counted [30].

The equivalent daily dose of levodopa was calculated according to the international standard converting measure (30) as follows: dose of levodopa plus dose of dopamine agonists multiplied by equivalents (=1 × levodopa dose + 0.75 × controlled release dose + 0.33 × entacapone + 20 × ropinirole dose + 100 × pramipe xole + 10 × selegiline + 1 × amantadine) [31].

Visits were scheduled every six months. The complete pattern of cognitive and behavioral tests was performed at the beginning and every six months, after 24 months of follow-up.

3.1. Statistical analysis

Statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS, version 19.8). The difference in baseline characteristics between the two PD groups considered and controls patients were assessed by ANOVA test, for categorical variables; in case the ANOVA results were found significant, the multiple comparison analysis was also done by the Tukey test, to examine those groups, which were significantly different for each other. These tests were repeated at 24-months evaluation.

A Wilcoxon signed-rank was applied for the differences at baseline in UPDRS I-IV, in the separate UPDRS III subscores, in the MDS-UPDRS selected criteria and for the neuropsychological variables. The same was repeated at 24 months.

The linear regression method was applied to analyze the independent association of the disease status (Akinetic rigid or tremor dominant); all the variables predetermined as possible confounders (age, education, gender) and those showing significant univariate association with disease status ($p < 0.05$) were entered in the regression models. All the assumptions of these models were verified, and all the tests were two-tailed (when relevant). A post-hoc multiple comparison Benjamini-Hochberg correction was performed, determining an alfa = 0.00178. This was done for each status at baseline and 24-months.

The results are presented as mean changes from baseline with standard deviations, and P-values where appropriate.

4. Results

As reported in Tables 1 and 2, at baseline patients have been divided into two groups according to the UPDRS III sub-items and to MDS-UPDRS, virgin from therapy. Baseline UPDRS was different in the two groups concerning UPDRS I ($p < 0.05$) and UPDRS III ($p < 0.01$) (Table 1). Two hundred thirteen patients were

Table 1
Global UPDRS at baseline (mean and SD).

UPDRS	Group A (Akinetic-Rigid)	Group B (Tremor)	Between groups-p
UPDRS I (0–16)	7.2 (2.1)	4.1 (1.1)	P < 0.05
UPDRS II (0–52)	14.1 (3.5)	8.9 (4.1)	P = 0.067
UPDRS III (0–56)	17.9 (2.3)	8.5 (3.2)	P < 0.01
UPDRS IV (0–23)	1.7 (0.2)	1.1 (0.1)	P = 0.76

included in the akinetic-rigid profile (with this called Group A) and 219 in the tremor-profile (with this called Group B). 457, not PD patients have been defined as group C (Tables 2 and 3). Patients at baseline evaluation had never assumed any PD therapy. The demographic values, i.e., age, gender, and educational levels were not significantly associated with the two disease states (Table 4). One-way analysis of variance (ANOVA) method was applied to explore the statistical difference among mean value in the two groups of PD and control (Table 5). Group A and B (akinetic-rigid and tremor dominant PD variants) did worse in the FAB test ($p < 0.01$), were more depressed, according to the Beck test ($p < 0.01$), more anxious (HAM-A, $p < 0.01$) and more apathetic (AES-C, $p < 0.01$). They made more interference mistakes in the Stroop test ($p < 0.01$) and produced fewer words, both in the phonological fluency and in the semantic tests ($p < 0.01$). We have examined the six neuropsychological variables, FAB, Beck's, HAM-A, AES-C, Stroop interference mistakes, and phonological and semantic fluency: we found them significantly different in the two groups, which suggested that at least one average out of the two was statistically different from the other. The Multiple-comparison Tukey test was done to explore such variables (Table 6). In multivariate analysis, akinetic-rigid profile was independently associated with FAB scores ($p < 0.05$), Beck's scores ($p < 0.01$), HAM-A ($p < 0.05$), AES-C ($p < 0.01$), interference mistakes of Stroop test ($p < 0.01$) and phonological and semantic production ($p < 0.01$) (Table 7), after corrections for multiple comparison. In multivariate analysis, the tremor-dominant profile was independently associated with FAB scores ($p < 0.05$), HAM-A ($p < 0.05$), AES-C ($p < 0.01$), and phonological and semantic production ($p < 0.01$) (Table 8), after corrections for multiple comparisons.

Table 2
UDRS III at baseline: subscores.

UPDRS III	Group A	Group B	Between-groups test
Tremor scores (0–8) (items 20–21)	2.1 (1.1)	5.1 (1.1)	P < 0.01
Bradykinesia scores (0–16) (items 23–26)	10.6 (1.2)	2.1 (1.2)	P < 0.01
Axial scores (0–20) (items 27–31)	5.2 (1.3)	1.3 (0.2)	P < 0.01

Table 3
MDS-UPDRS Criteria employed to divide the two groups (see text).

MDS-UPDRS	Group A	Group B	Between-groups test
2.9 (Turning in bed; 0–4)	**2.7 (1.1)**	1.6(1.2)	P < 0.01
2.10 (Tremor; 0–4)	1.1 (0.1)	*2.8 (0.2)*	P < 0.01
3.3 (Rigidity of neck and four extremities; 0–4)	**2.3 (0.4)**	0.9 (0.1)	P < 0.01
3.4 (Finger taps; 0–4)	**2.3 (1.1)**	1.4 (1.1)	P < 0.01
3.5 (Hand movements; 0–4)	**2.5 (0.7)**	0.8 (0.1)	P < 0.01
3.6 (Leg agility; 0–4)	**2.3 (0.1)**	0.9 (0.2)	P < 0.01
3.13 (postural tremor of hands; 0–4)	0.1 (0.2)	*2.5 (1.1)*	P < 0.01
3.14 (Kinetic tremor of hands; 0–4)	0.3 (0.1)	*2.3 (1.1)*	P < 0.01
3.15 (Rest tremor amplitude; 0–4)	0.4 (0,1)	*2.6 (1.2)*	P < 0.01
3.16 (Constancy of rest tremor; 0–4)	0.3 (0.1)	*2.6 (0.2)*	P < 0.01

Table 6
Multiple comparison analysis (Tukey test) of various neuropsychological parameters in the three groups.

Variables	Mean Differences	SE of mean differences	p-value
FAB			
A vs C	−4.5	−0.11	0.01
B vsC	−3.5	−0.76	0.01
BECKS			
A vs C	+15.6	0.23	0.01
B vs C	+4.0	0.64	0.05
HAM-A			
A vs C	+6.2	0.71	0.05
B vs C	+20.3	2.73	0.01
AES-C			
A vs C	+15.6	2.35	0.01
B vs C	+9.4	1.98	0.01
Stroop Interf. Mistakes			
A vs C	+18.6	0.83	0.01
B vs C	+9.4	0.74	0.05
Phonol. fluency			
A vs C	−30.6	−0.56	0.01
B vs C	−20.2	−0.78	0.01
Semantic Fluency			
A vs C	−24.2	−3.41	0.01
B vs C	−13.2	−0.71	0.01

Table 4
Comparison of mean values of epidemiological variable in the two PD groups and control (Means and SD).

Variables	Group A	Group B	Group C	F chi2 Value	DF	p-value
Age (years)	59.1 (2.7)	61.2 (2.1)	60.7 (1.3)	2.66	2.24	0.63
Educ. Lev (years)	8.4 (1.3)	8.7 (1.1)	8.9 (1.7)	0.56	3.11	0.45
Gender M/F	116/97	121/98	221/236	0.79	2.31	0.79

Table 5
Comparison of mean values of age, educational level, and neuropsychological tests in the two PD groups and controls (Means and SD).

Characteristics	Group A	Group B	Controls	F chi2 value	DF	p-value
MOCA	28.3 (1.7)	27.9 (1.9)	28.1 (1.3)	0.98	2.31	0.36
FAB test	12.3 (2.5)	12.9 (1.7)	16.6 (1.2)	0.87	2.43	0.01
Beck's Test	28.3 (1.3)	17.8 (1.7)	12.7 (1.9)	0.74	2.9	0.01
HAM-A Test	22.3 (2.7)	36.3 (1.3)	16.1 (2.1)	0.08	2.02	0.01
AES-C	27.3 (1.7)	21.1 (2.1)	11.7 (2.1)	0.37	2.42	0.01
Stroop test						
reading (correct)	86.5 (2.7)	89.1 (2.1)	92.3 (7.7)	0.75	2.41	0.36
color naming (correct)	71.7 (3.1)	73.1 (2.1)	83.8 (2.3)	0.77	2.34	0.54
interference mistakes (wrong)	31.9 (2.1)	22.7 (3.1)	13.3 (1.7)	0.89	2.48	0.01
Phonol. Fluency (sum 3 min)	20.7 (2.9)	31.1 (2.9)	51.3 (3.5)	0.82	2.71	0.01
Sem. Fluency (sum 3 min)	32.5 (2.1)	43.5 (3.5)	56.7 (4.5)	0.84	2.77	0.01

Table 7
Linear regression results considering independent associations with MDS-UPDRS Akinetic-Rigid profile (2.9, 3.3, 3.4, 3.5, 3.6 >10 and 2.10, 3.13, 3.14, 3.15, 3.16 <10).

Variables	Beta	95%CI	p
Age	0.38	0.7–1.1	0.38
Educ. Lev.	0.64	0.2–1.3	0.076
Gender M/F	0.78	0.3–1.2	0.61
MOCA	0.74	1.1–2.7	0.76
FAB	0.64	2.1–3.4	0.05
BECKS	0.12	0.02–0.45	0.01
HAM-A	0.23	0.07–1.16	0.05
AES-C	0.13	0.05–0.23	0.01
Stroop Interf. Mistakes	0.17	0.03–0.73	0.01
Phonol. Fluency	0.32	0.03–0.89	0.01
Semantic Fluency	0.23	0.04–1.1	0.01

Table 8
Linear regression results considering independent associations with MDS-UPDRS Tremor-dominant profile (2.9, 3.3, 3.4, 3.5, 3.6 <10, average scores in 2.10, 3.13, 3.14, 3.15, 3.16 >14).

Variables	Beta	95%CI	p
Age	0.43	0.8–1.2	0.42
Educ. Lev.	0.74	0.3–1.3	0.066
Gender M/F	0.75	0.5–1.2	0.65
MOCA	0.73	1.4–2.5	0.56
FAB	0.53	2.4–3.2	0.05
BECKS	0.43	0.2–0.41	0.56
HAM-A	0.12	0.07–2.1	0.01
AES-C	0.14	0.02–0.15	0.01
Stroop Interf. Mistakes	0.17	0.33–1.73	0.34
Phonol. Fluency	0.34	0.01–0.67	0.01
Semantic Fluency	0.21	0.02–1.13	0.01

The Wilcoxon signed-rank test between groups (Table 9) put in evidence that in Group A there was a higher level of depression, apathy, a significant number of interference mistakes and a lower production in the phonological and semantic fluency (all $p < 0.01$) when compared to Group B, who had a higher level of anxiety ($p < 0.01$).

During the follow-up, the PD patients of both groups received appropriate therapy. The mean L-dopa equivalent dosage (LEDD) was higher, at the end of the follow-up in Group A (LEDD of Group A: 987. 3 (200.5) mg/daily; Group B received 650.4 (125, 4) mg/daily. Group A showed a more severe disease. In Group A patients received at the end of the follow-up, 84 patients received dopamine-agonists, 56 Levo-Dopa, 73 Entacapone, even combined. Group B patients received the following drugs: 98 patients received dopamine-agonists, 98 Levo-Dopa, and 23 Entacapone, even combined.

After the 24-months follow-up, UPDRS was different in the two groups, now tested in ON and OFF condition, with a between-group comparison in both condition; in ON, Group A did worse only in UPDRS III (Table 10); in off, Group A did worse than B in UPDRS I ($p < 0.05$) and UPDRS III ($p < 0.01$) (Table 10).

One-way analysis of variance (ANOVA) method was applied to explore the statistical difference among mean value in the two groups of PD and control (Table 11). Group A and B did worse in the FAB test ($p < 0.01$), were more depressed, according to the Beck test ($p < 0.01$), more anxious (HAM-A, $p < 0.01$) and more apathetic (AES-C, $p < 0.01$). They made more interference mistakes in the Stroop test ($p < 0.01$) and produced fewer words, both in the phonological fluency and in the semantic tests ($p < 0.01$). The results are similar to those obtained at baseline. We have examined the six neuropsychological variables, FAB, Beck's, HAM-A, AES-C, Stroop interference mistakes, and phonological and semantic fluency: we found them significantly different in the two groups, which suggested that at least one average out of the two was statistically different from the other. The Multiple-comparison Tukey test was done to explore such variables (Table 12).

In multivariate analysis, akinetic-rigid profile was independently associated with FAB scores ($p < 0.01$), Beck's scores ($p < 0.01$), AES-C ($p < 0.01$), Interference mistakes of Stroop test ($p < 0.01$) and phonological and semantic production ($p < 0.01$) (Table 13), after corrections for multiple comparison. In multivariate analysis, the tremor-dominant profile was independently associated with HAM-A ($p < 0.01$), AES-C ($p < 0.01$), and phonological and semantic production ($p < 0.01$) (Table 14), after corrections for multiple comparisons. The Wilcoxon signed-rank test between groups (Table 15) put in evidence that in Group A there was a higher level of depression, apathy, a significant number of interfer-

Table 9
Wilcoxon signed rank test, between groups at baseline (Means and SD).

Characteristics	Group A	Group B	Wilcoxon signed rank test A vs B between test	p-value
MOCA	28.3 (1.7)	27.9 (1.9)	+0.4	0.36
FAB test	12.3 (2.5)	12.9 (1.7)	−0.6	0.34
Beck's Test	28.3 (1.3)	17.8 (1.7)	+10.5	0.01
HAM-A Test	22.3 (2.7)	36.3 (1.3)	−14	0.01
AES-C	27.3 (1.7)	21.1 (2.1)	+6.2	0.01
Stroop test				
reading (correct)	86.5 (2.7)	89.1 (2.1)	−2.6	0.36
color naming (correct)	71.7 (3.1)	73.1 (2.1)	−1.4	0.54
interference mistakes (wrong)	31.9 (2.1)	22.7 (3.1)	+9.2	0.01
Phonol. Fluency (sum 3 min)	20.7 (2.9)	31.1 (2.9)	−10.4	0.01
Sem. Fluency (sum 3 min)	32.5 (2.1)	43.5 (3.5)	−11	0.01

Table 10
24-months results in UPDRS, in on and off. Values are mean (SD).

	Group A	Group B	Between groups p	Group A	Group B	Between groups p
UPDRS	In ON			In OFF		
UPDRS I (0–16)	10.7 (1.3)	7.2 (1.2)	0.56	12.3 (1.1)	9.2 (1.1)	<0.05
UPDRS II (0–52)	15.3 (2.5)	14.2 (1.6)	0.65	32.1 (1.9)	28.1 (1.4)	0.54
UPDRS III (0–56)	24.6 (2.3)	18.3 (2.3)	0.05	35.4 (4.3)	24.5 (2.3)	<0.01
UPDRS IV (0–23)	5.6 (2.2)	5.8 (1.1)	0.43	11.2 (2.5)	13.2 (2.8)	0.54

Table 11
Comparison of mean values of age, educational level, and neuropsychological tests in the two PD groups and controls (Means and SD).

Characteristics	Group A	Group B	Controls	F chi2 value	DF	p-value
MOCA	25.3 (1.7)	26.9 (1.9)	28.7 (1.1)	0.75	2.36	0.086
FAB test	9.3 (2.5)	10.9 (1.7)	16.8 (0.7)	0.87	2.43	0.01
Beck's Test	34.6 (2.6)	18.9 (12)	13.4 (0. 4)	0.45	2.9	0.01
HAM-A Test	18.4 (1.2)	43.1 (3.4)	18.3 (1.3)	0.09	2.3	0.01
AES-C	45.5 (4.2)	33.1 (4.7)	11.1 (1.9)	0.43	2.78	0.01
Stroop test						
reading (correct)	87.1 (2.4)	88.5 (6.3)	93.4 (2.4)	0.67	2.32	0.34
color naming (correct)	68.2 (1.5)	69.5 (3.2)	84.7 (4.1)	0.56	2.12	0.65
interference mistakes (wrong)	46.5 (7.5)	37.6 (3.6)	16.7 (5.1)	0.78	2.33	0.01
Phonol. Fluency (sum 3 min)	13.4 (2.9)	28.7 (1.4)	50.7 (4.2)	0.98	2.65	0.01
Sem. Fluency (sum 3 min)	23.4 (4.3)	37.6 (4.1)	53.4 (6.1)	0.44	2.32	0.01

Table 12
Multiple comparison analysis (Tukey test) of various neuropsychological parameters in the three groups.

Variables	Mean Differences	SE of mean differences	p-value
FAB			
A vs C	−7.5	−0.34	0.01
B vsC	−5.9	−0.89	0.01
BECKS			
A vs C	+21.2	0.45	0.01
B vs C	+5.5	0.87	0.05
HAM-A			
A vs C	+0.1	0.11	0.45
B vs C	+24.8	3.56	0.01
AES-C			
A vs C	+34.4	4.23	0.01
B vs C	+22	2.45	0.01
Stroop Interf. Mistakes			
A vs C	+29.8	1.45	0.01
B vs C	+20.9	2.11	0.01
Phonol. fluency			
A vs C	−37.3	−2.56	0.01
B vs C	−20.9	−0.78	0.01
Semantic Fluency			
A vs C	−30	−3.81	0.01
B vs C	−22	−1.34	0.01

Table 13
Linear regression results considering independent associations with MDS-UPDRS Akinetic-Rigid profile (2.9, 3.3, 3.4, 3.5, 3.6 >10 and 2.10, 3.13, 3.14, 3.15, 3.16 <10) AT 24 MONTHS.

Variables	Beta	95%CI	p
Age	0.45	0.6–1.3	0.56
Educ. Lev.	0.65	0.5–1.4	0.056
Gender M/F	0.78	0.3–1.2	0.61
MOCA	0.45	0.1–2.3	0.053
FAB	0.41	2.2–3.2	0.01
BECKS	0.10	0.01–0.67	0.01
HAM-A	0.26	0.09–1.34	0.54
AES-C	0.09	0.02–0.43	0.01
Stroop Interf. Mistakes	0.12	0.02–0.87	0.01
Phonol. Fluency	0.14	0.01–1.89	0.01
Semantic Fluency	0.32	0.01–1.9	0.01

ence mistakes and a lower production in the phonological and semantic fluency (all $p < 0.01$) when compared to Group B, who had a higher level of anxiety ($p < 0.01$). The results confirmed what we have found at baseline. In the present analysis, the classification accuracy rate of the logistic model was 58.9%, which was higher than the proportional by chance accuracy; the criteria for the classification accuracy were satisfied.

Table 14
Linear regression results considering independent associations with MDS-UPDRS Tremor-dominant profile (2.9, 3.3, 3.4, 3.5, 3.6 <10, average scores in 2.10, 3.13, 3.14, 3.15, 3.16 >14) AT 24 MONTHS.

Variables	Beta	95%CI	p
Age	0.42	0.7–1.2	0.56
Educ. Lev.	0.73	0.3–1.4	0.059
Gender M/F	0.75	0.5–1.2	0.65
MOCA	0.72	1.2–3.7	0.067
FAB	0.43	2.1–4.5	0.067
BECKS	0.32	0.2–0.56	0.67
HAM-A	0.09	0.05–2.6	0.01
AES-C	0.11	0.04–0.34	0.01
Stroop Interf. Mistakes	0.17	0.33–1.73	0.054
Phonol. Fluency	013	0.23–0.67	0.01
Semantic Fluency	0.14	0.32–1.13	0.01

Table 15
Wilcoxon Signed Rank Test between groups in the two PD groups (Means and SD).

Characteristics	Group A	Group B	Wilcoxon signed rank test (A vs B between groups)	p-value
MOCA	25.3 (1.7)	26.9 (1.9)	−1.6	0.28
FAB test	9.3 (2.5)	10.9 (1.7)	−1.6	0.23
Beck's Test	34.6 (2.6)	18.9 (12)	+15.7	0.01
HAM-A Test	18.4 (1.2)	43.1 (3.4)	−24.7	0.01
AES-C	45.5 (4.2)	33.1 (4.7)	+12.4	0.01
Stroop test				
reading (correct)	87.1 (2.4)	88.5 (6.3)	−1.4	0.45
color naming (correct)	68.2 (1.5)	69.5 (3.2)	−1.3	0.72
interference mistakes (wrong)	46.5 (7.5)	37.6 (3.6)	+8.9	0.01
Phonol. Fluency (sum 3 min)	13.4 (2.9)	28.7 (1.4)	− 15.3	0.01
Sem. Fluency (sum 3 min)	23.4 (4.3)	37.6 (4.1)	−14.2	0.01

5. Discussion

This cross-sectional study, covering 432 PD patients and 457 neurological control-patients confirms and expands previous studies [4,5,6,13].

Our objectives were:

1. Confirm previous hypotheses of cognitive and behavioral differences of two clinical motor variants of PD, without dementia
2. Identify a possible independent relationship between the two variants (akinetic-rigid and tremor-dominant) and cognitive and behavioral changes, such as frontal executive functions, divided attention, lexical strategies, depression and behavior in these two groups.

Our study has several limitations:

1. It is a single-center study
2. It has been designed as a cross-sectional study
3. The number of patients is small to interfere
4. It has no pathological or functional neuroimaging confirm

It has some strengths:

1. This is the first study which divided at the diagnosis the two clinical PD variants
2. All the patients can be thoroughly studied in a standardized way
3. All the patients attended the best-standardized procedure to implement the PD diagnosis
4. We can employ an accepted standardized procedure to distinguish the two PD variants
5. Our data were the first, which relate PD variants, before therapy to neuropsychological specific profiles.

Therefore, to the best of our knowledge, this is the first study which enrolled PD patients, virgin from therapies, differentiated them *ab initio* in two clinical variants, and found out a specific neuropsychological profile for each of the two variants.

Akinetic-rigid patients had severe axial and motor impairment, their clinical course is worse (considering their LEDD, i.e.), but they had more frontal executive alterations, they had more impairment in divided attention and control operative procedure and worse semantic and phonological production (even if not demented at the end of the study), they were more depressed, more apathetic. On the contrary, tremor-dominant patients did show some degree of depression, but more anxiety, and had lower production of verbal fluency, when compared to controls, even if much better than akinetic-rigid patients.

The differences between the two clinical phenotypes of presentation have been reported with many different explications: there are some works which stressed on the different dopaminergic defects and concomitant white matter disease which often is associated with white matter alterations [2,10,32,33]. In our works, the accurate selection of neuroimaging excluded all the suspected white matter alterations, which could somehow mislead, due to superimposing factors (white matter alterations and degenerative disorders).

Some other studies tended to focus on dopamine levels in *globus pallidus*; firstly they have been described in primates [34,35], but soon afterward, the theory has been somehow extended into human beings [36]. It can be argued that there is a loss of dopaminergic projections to the dorsal putamen in akinetic-rigid patients; on the contrary, there is a severe dopaminergic loss to the lateral putamen and the caudate nucleus in the dominant tremor profile.

More recent functional studies (i.e., [7–9,11,12]) try to define the functional impairment of the two distinct profile. One of the most well-conducted studies [12], employing resting-state fMRI and the regional homogeneity method has defined the neural activity in akinetic-rigid and tremor-dominant patients. Results are quite surprising: akinetic-rigid subjects seemed to have an increased regional homogeneity in the right amygdala, left putamen, bilateral angular gyrus, bilateral medial prefrontal cortex and a reduced one in left posterior cingulate gyrus and *precuneus* and bilateral thalamus. On the other hand, tremor dominant patients showed higher regional homogeneity in the bilateral angular gyrus, in the left posterior cingulate and *precuneus*, in the cerebellum, with a decrease in the right putamen and the primary sensory cortex, associated to a reduced the activity of the cerebellum vermis. Therefore, to summarize their impingent work, these authors argued that the Akinetic-rigid patients had an altered neural activity in the mesolimbic cortex and the tremors-type in the cerebellar-thalamic projections.

Of course, all these studies had been done to evaluate motor aspects of the PD variants. Anything has been done concerning the clinical and neuropsychological aspects of the two entities. Nevertheless, the differences which we observed are quite surprising and present throughout the entire follow-up. The suggested imbalance of the mesolimbic cortex, as proposed by Zhang et al. [12] in the akinetic-rigid patients can help to explain the findings we have found: apathy, deficit of divided attention, lack of verbal access and production rely on secure neural networks, which is supported by basal ganglia through their intimate projections to mesolimbic cortex [37–41].

The conclusions of our works seem somehow eradicated on a profound difference, starting from the very first part of the disease history of PD, between the two variants, without any other possibility, at the moment to be explained. These aspects should lead to a suggestion for neurologists and caregivers to better evaluate and identify neuropsychological differences, and follow-up them.

More studies will be needed to implement further knowledge.

Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CRediT authorship contribution statement

Rita Moretti: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Paola Caruso:** Investigation, Writing - review & editing. **Giovanni Monguzzi:** Methodology. **Alessia Sala:** Methodology, Investigation. **Matteo Dal Ben:** Writing - original draft. **Silvia Gazzin:** Conceptualization, Formal analysis, Investigation.

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