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Short communication

Cognitive correlates of "pure apathy" in Parkinson's disease

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ABSTRACT

Introduction: Previous studies exploring the association between apathy and cognitive deficits in Parkinson's disease (PD) employed scales and questionnaires for apathy, which did not control for the possible confounding effect of motor symptoms. Here we investigated the cognitive correlates of "pure apathy" by the Dimensional Apathy Scale, which allows us to assess apathy minimizing the influence of motor symptoms.
Methods: Consecutive PD outpatients referred to our centre were screened. All participants underwent a neuropsychological battery to assess verbal memory, executive functions and visuospatial abilities, apathy and depressive symptoms.
Results: We enrolled 56 non-depressed and non-demented PD patients, of whom 28 were apathetic and 28 were not. The two groups did not differ on demographic and clinical aspects; apathetic PD patients performed worse than non-apathetic PD patients on the part A, B and B-A of Trail Making Test and the interference task of Stroop test. No significant differences were found on memory and perceptual visuospatial tasks.
Conclusions: Our results demonstrated that "pure apathy" is associated with more severe executive dysfunctions such as alteration of set-shifting and inhibitory control, which are mediated by prefrontal cortex and subcortical regions (i.e. basal ganglia). Our findings also supported the hypothesis that co-occurrence of apathy and executive deficits may be the epiphenomenon of damage in prefrontal-striatal cortical circuitries connecting dorsolateral prefrontal cortex, anterior cingulate cortex and basal ganglia.

1. Introduction

Apathy has been defined as a distinct psychiatric syndrome characterized by "simultaneous diminution in the cognitive and emotional concomitants of goal directed behaviour" and by a loss of motivation as the main symptom [1]. The prevalence of apathy in Parkinson's Disease (PD) ranges from 13.9% to 70% [2] and is associated with higher age, an increased risk of comorbid depression, more severe motor symptoms and disability [3]. Apathy has been related to three types of disruptive processing in PD (i.e. emotional, motor and cognitive) [4,5]. In particular, the emotional apathy refers to a decrease of goal-directed behaviors due to a difficulty in linking affective and emotional signals with ongoing and forthcoming behaviors. The Auto-activation dimension of apathy seems to be due to the dissociation between spontaneous and voluntary behavioral production induced by an external stimulation. "Cognitive inertia" refers to the reduction of goal-directed behaviors due to decrease of the cognitive functions needed to elaborate the plan of actions. In detail, apathy has been related to more severe cognitive decline assessed by Mini-Mental State Evaluation (MMSE) [3], and associated with impairment of some cognitive functions [2]. As for executive functions, apathetic patients performed worse than non-apathetic ones on specific frontal tests tapping spatial planning and cognitive flexibility [see review, 2]. In the domain of memory, some studies did not find significant differences between apathetic and non-apathetic PD patients on short-term and long-term memory tasks, whereas others found that apathetic patients performed worse on the long-term memory tasks [see review, 2]. Visuospatial functions and language abilities in PD patients with apathy were poorly explored with conflicting results [see review, 2]. The inconsistency in findings may be attributed to the methodological differences between studies. Indeed, some studies excluded PD patients with dementia and/or depression in comorbidity, while other studies included them. Moreover, in all previous studies exploring the association between apathy and cognitive deficits in PD, apathy was assessed through questionnaires and scales (i.e. Apathy Evaluation Scale, Lille Apathy Evaluation Rating Scale), which did not control for the possible confounding effect of severity of

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Table 1
Comparison between apathetic and non-apathetic PD patients on demographic, clinical, cognitive and behavioral variables.

	PD + A	PD-A			
	Mean ± SD	Mean ± SD	U	p	ES (r)
Age (ys)	68.3 ± 8.7	64.6 ± 7.6	297.500	0.121	−0.207
Education (ys)	9.0 ± 4.0	10.8 ± 4.0	289.000	0.082	−0.232
Disease Duration (ys)	7.7 ± 3.4	8.6 ± 4.0	266.000	0.847	−0.025
UPDRS-III	16.7 ± 7.8	14.8 ± 6.7	199.000	0.361	−0.122
Hoehn&Yahr	2.5 ± 0.6	2.2 ± 0.7	198.000	0.081	−0.233
Levodopa Equivalent Daily Dose	907.2 ± 447.2	798.3 ± 442.2	205.000	0.378	−0.117
Montreal Cognitive Assessment	20.2 ± 3.6	21.5 ± 3.2	278.500	0.137	−0.198
DAS total score	34.5 ± 3.7	20.2 ± 6.5	15.000	< **0.001**	−0.826
Beck Depression Inventory - II	9.5 ± 5.0	7.3 ± 4.3	294.000	0.107	−0.215

PD, Parkinson's Disease; PD + A, PD patients with apathy; PD-A, PD patients without apathy; ES, Effect size; ys, years; UPDRS, Unified Parkinson's Disease Rating Scale; DAS, Dimensional Apathy Scale.

motor symptoms. Therefore, taking into account the abovementioned limitations, we performed a study in non-demented and non-depressed PD patients to investigate the cognitive correlates of apathy evaluated by means of the Dimensional Apathy Scale (DAS), a specific questionnaire which allows to evaluate the presence of apathy minimizing the influence of PD motor symptoms [6], according to the criterion D of the diagnostic clinical criteria proposed for apathy (for the reference, see supplemental material 1).

2. Methods

2.1. Participants

Consecutive PD outpatients referred to our centre were screened and included in the study if they met the following inclusion criteria: 1) a diagnosis of idiopathic PD according to clinical diagnostic criteria; 2) absence of dementia or cognitive global dysfunctioning defined according to an age- and education adjusted score on the Italian version of the Montreal Cognitive Assessment < 15.5 (MoCA [7]); 3) absence of major depression according to DSM-5 clinical criteria.

Demographic features, disease duration, Levodopa Equivalent Daily Dose (LEDD) and severity of motor symptoms assessed by both part III of Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr staging were recorded.

All participants gave their written informed consent to participate to the study, which was approved by the local ethics committee.

2.2. Neuropsychological and behavioural evaluation

PD patients underwent the Italian version of the Dimensional Apathy Scale (DAS), a self-rated questionnaire validated in PD [8], which assesses apathy in neurological diseases minimizing the effect of motor symptoms. The DAS consists of 24 items rated on a 4-point Likert scale (total score ranging 0–72) and of three subscales: (1) executive subscale assessing apathetic impairments associated with planning, attention or organisation; (2) emotional subscale assessing apathy associated with altered emotion integration; and (3) behavioural/cognitive initiation subscale assessing apathy associated with loss of self-generation of behaviours or cognition. The DAS allows to identify apathetic from non-apathetic PD patients. Therefore, a cut-off score equal or greater than 29 was used to identify PD cases with apathy.

All participants also underwent a neuropsychological battery to assess verbal memory (by immediate and delayed recall of the Rey Auditory Verbal Learning Test, RAVLT), executive functions (by the time scores of part A, B of the Trail Making Test (TMT) and the difference between Part A and B (TMT:B-A), the interference task of the Stroop Test) and visuospatial abilities (by the form H of the Benton Judgment of Line Orientation, BJLOT). Moreover, PD patients completed the Beck Depression Inventory-II (BDI-II), a questionnaire assessing depressive symptoms. The references of clinical criteria, clinical and neuropsychiatric scales, and cognitive tests are reported in Supplemental Material 1.

2.3. Statistical analysis

Demographic, clinical, neuropsychological (i.e. cognitive, apathy and depression scores) variables were compared between patients with apathy (PD + A) and patients without apathy (PD-A) with Mann-Whitney *U* Test and Quade's rank analysis of covariance (a nonparametric equivalent of analysis of covariance, ANCOVA), as appropriate. The critical alpha level for all analyses was set at 0.05 but was corrected according to Bonferroni procedure (0.05/7 = 0.007). Moreover, to control a possible confounding effect of the educational level, clinical variables, global cognitive status, we performed a linear regression analysis where educational level, UPDRS, H&Y, MoCA scores were entered as independent variables and the total DAS score as dependent variable. All analyses were performed with IBM SPSS-20.

3. Results

We screened 74 consecutive PD outpatients; out of these, 10 were excluded due to major depression, 6 due to dementia and 2 due to co-occurrence of depression and dementia. Therefore, we enrolled 56 non-depressed and non-demented PD patients. According to the cut-off score of DAS, we identified 28 apathetic and 28 non-apathetic PD patients; the occurrence of apathy was confirmed by an interview based on the clinical criteria for apathy (for the reference see Supplemental material 1). The two groups did not differ on demographic and clinical aspects, MoCA and BDI-II (Table 1). In order to control the effect of motor symptoms severity, educational level, and global cognitive status, a linear regression analysis (corrected R2 = 0.039, F(4, 37) = 1.412, p = 0.249) was performed showing that H&Y score (Beta = −0.005, t = −0.024, p = 0.981, 95% Confidence Intervals: −4.751 to −5.639), UPDRS score (Beta = 0.093, t = 0.548, p = 0.587, 95% Confidence Intervals: −0.296 to −0.515), educational level (Beta = −0.061, t = −0.346, p = 0.731, 95% Confidence Intervals: −0.827 to 0.586) and MoCA score (Beta = −0.303, t = −1.611, p = 0.116, 95% Confidence Intervals: −1.425 to 0.163) were not significantly related to DAS total score. These findings indicated that severity of motor symptoms, global cognitive dysfunction and educational level did not contribute to apathy.

As for cognitive tests, apathetic PD patients performed worse than non-apathetic PD patients on the part A, B and B-A of the TMT and the interference task of the Stroop test (Table 2). No statistically significant differences were found on the remaining cognitive tests.

To control the potential effect of depressive symptoms on the relationship between cognitive performance and apathy scores, we performed Quade's rank analysis of covariance. In this analysis, the group

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