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RELATIONSHIP BETWEEN APATHY AND COGNITIVE FUNCTIONS IN PARKINSON'S DISEASE

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Abstract

Although apathy and cognitive impairment are among the frequently reported neuropsychiatric symptoms of Parkinson's disease (PD), the relationship between apathy and cognitive functions in Parkinson's disease has not been adequately explained. In this study, we aimed to reveal the relationship between apathy and cognitive impairment by evaluating the cognitive functions of PD patients with and without apathy, using neuropsychometric tests. The inclusion criteria for this study was diagnosis of PD according to the criteria of "United Kingdom Parkinson's Disease Society Brain Bank". Patients were distributed into groups based on their AES scores (cut-off point=38) and NPI Apathy subscores, together with the clinical evaluation. PD patients with apathy (n=32) were assigned to the a+PD group, and PD patients without apathy (n=45) to the a-PD group; age, education level, HYS and CDR stages were matched. The cognitive functions of the patients in both groups were evaluated using the following tests; personal and current information subtest of the WMS, orientation subtest of WMS, verbal fluency tests, abstraction skills tests, Stroop Test Çapa Version, Clock Drawing Test, visual memory subtest of WMS, logical memory subtest of WMS, Öktem-VMPT, BNT, BFRT, Yesavage GDS, NPI and MMSE were used. For the evaluation of the motor and non-motor clinical symptoms; the UPDRS, HYE, UM-PDHQ, and RBDSQ were used. Independent Sample t-test was carried out to compare the normally distributed variables between the PD groups with and without apathy, and for the non-normal distributed variables Mann-Whitney U test was utilized for comparison. Results of the statistical analysis showed, in PD patients with apathy; depression scores are increased; orientation and abstract thinking skills are impaired; and attention span, verbal fluency, performance in visual and logical memory tests, and cognitive flexibility are decreased. Overall, these findings suggest that clinical and cognitive features of PD patients with apathy differ from PD patients without apathy; and multifaceted decline is observed in neuropsychometric profile of parkinsonian apathy.

Keywords: *Apathy, cognitive functions, neuropsychological assessment, Parkinson's disease.*

1. Introduction

Parkinson's disease (PD) manifests a heterogeneous profile of clinical syndromes with motor and non-motor symptoms (Greenland et al., 2019). Non-motor symptoms may precede the diagnosis of PD, and the underlying pathophysiology has not yet been clearly elucidated (Schrag et al., 2015). Apathy is one of the frequently reported non-motor symptoms in PD and is defined as a decrease in emotional, behavioral, and cognitive components of goal-directed behavior, based on a lack of motivation, loss of interest, emotional bluntness, and lack of energy (Levy & Dubois, 2006; Marin et al., 1997; Marin et al., 1991).

Parkinsonian apathy is believed to involve several different pathophysiological mechanisms, depending on the stage of the disease and comorbid neuropsychiatric conditions (Santangelo et al., 2013). There are studies showing that frontal-subcortical system dysfunction, specifically damage to the prefrontal cortex-basal ganglia circuit leading to apathy. (Santangelo et al., 2018; Chase, 2011; Levy & Dubois 2006). The apathy symptom in Parkinson's disease is thought to be stemming from lesions in the ventral striatum and dopamine deficiency in the frontostriatal circuitry (Baggio et al., 2015; Levy & Dubois, 2006).

Neuropsychology studies show that executive dysfunction is the most consistent neuropsychological sign of apathy (Santangelo et al., 2018; Dirnberger & Jahanshahi, 2013; Brown & Pluck, 2000). Impairments in executive functions cause difficulties in directing attention to novel stimuli, problems in planning, and difficulties in manipulating internal and external stimuli (Lewy & Dubois, 2006). These impairments can lead to decreased cognitive interests and auto-activation deficits.

One of the reasons why the pathophysiological mechanism underlying the development of apathy in Parkinson's disease remains unclear is that it is difficult to evaluate apathy in Parkinson's patients due to motor symptoms such as the masked face, dystonia, and bradykinesia. Therefore, it is thought that applying apathy assessment scales to both the patient and their caregivers may provide more reliable results (Kirsch-Darrow et al., 2006). Another reason is that the clinical manifestations of apathy are multidimensional. In a study conducted by Pagonabarraga et al. (2015), apathy is classified into 3 sub-groups as emotional/affective apathy, cognitive apathy, and auto-activation apathy, after considering both the clinical manifestations of apathy and the findings of functional neuroimaging studies. Defining the subtypes of apathy and using specific neuropsychiatric assessment tools for each of these subtypes can help resolve different aspects of apathy at an individual patient-level (Leentjens et al., 2008; Schrag et al., 2007).

In this study, the neuropsychological assessment was performed in PD patients with and without apathy in order to determine the neuropsychological correlates of apathy in Parkinson's disease and thus contribute to clarifying the pathophysiological mechanism of apathy.

2. Methods

2.1. Participants

77 participants who were diagnosed with PD according to the United Kingdom Parkinson's Disease Society Brain Bank criteria were included in the study. Participants with suspected Parkinson-plus syndromes and a medical history of alcohol/substance abuse, stroke, head trauma, intoxication, and epileptic seizures were excluded from the study.

Participants were assigned to a+PD group (n=32) and the a-PD (n=45) group as a result of clinical evaluation, scores from the AES (cut-off point=38), and the NPI apathy subscale. Groups were matched by age, education level, HYE, and CDR stages. The Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn Yahr Parkinson's Rating Scale (HYS), University of Miami Parkinson's Disease Hallucination Scale (UM-PDHQ), and REM Sleep Behavior Disorder Screening Questionnaire (RBSQ) were used to evaluate clinical symptoms. All participants were right-handed.

2.2. Data collection

Data were collected by demographic information form and neuropsychometric inventory. The neuropsychometric inventory includes personal and current information subtest of the Wechsler Memory Scale (WMS), orientation subtest of WMS, verbal fluency tests, abstraction skills tests, Stroop Test Çapa Version, Clock Drawing Test (CDT), visual memory subtest of WMS, logical memory subtest of WMS, Öktem Verbal Memory Processes Test (VMPT), Boston Naming Test (BNT), Benton Face Recognition Test (BFRT), Yesavage Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI) and Mini-Mental State Examination (MMSE). Neuropsychological assessment was completed in approximately 2 hours.

2.3. Statistical analysis

SPSS (statistical package for social science) 25.0 for Windows was used for statistical analysis. For the variables that met the normality criteria, parametric tests were applied, and for the variables that did not meet the criteria non-parametric tests were applied. In cases where the variables were normally distributed, the Independent samples t-test was used, and in cases where the variables were not normally distributed, the Mann-Whitney U test was used. The significance value was accepted as $p < .05$.

3. Results

Statistical analysis results showed that UPDRS total scores ($t(75) = -2.110$, $p < .05$), GDS scores ($t(75) = -3.209$, $p < .01$), AES scores ($t(75) = -15.234.110$, $p < .001$), NPI total scores ($U = 484$, $p < .05$), and NPI caregiver distress scores ($U = 520$, $p < .05$) of the a+PD group were significantly higher than the a-PD group. The demographic and clinical characteristics of the participants are shown in Table 1.

Table 1. Demographic and clinical characteristics of sample.

	a+PD n = 32	a-PD n = 45		
	Mean (SD)	Mean (SD)	*t*	*p*-value
Age (years)	72.22 (6.65)	68.67 (9.57)	-1.810	.074
Gender (female/male)[a]	14/18	17/28		.598
Education (years)	5.66 (4.67)	7.37 (4.14)	1.694	.094
Duration of disease (months)[b]	87.19 (54.05)	89.55 (58.30)		.882
UPDRS total score	50.41 (17.05)	41.51 (19.02)	-2.110	.038*
Hoehn and Yahr Stages[a,c]	Stage 2	Stage 2		.908
GDS	13.16 (7.93)	8.09 (5.93)	-3.209	.002**
AES	45.31 (8.18)	22.33 (2.88)	-15.234	<.001***
CDR[a,c]	1.0	1.0		.130
NPI total score (frequency × severity)[b]	19.81 (14.78)	12.98 (12.81)		.015*
NPI caregiver distress score[b]	11.06 (8.32)	7.69 (7.13)		.038*
UM-PDHQ	2.41 (4.03)	3.02 (3.86)	.677	.500
RBDSQ	4.06 (2.29)	4.04 (2.31)	-0.034	.973

Note. *p < .05; **p < .01; ***p < 0.001; AES = Apathy Evaluation Scale, CDR = Clinical Demantia Rating, GDS = Yesavage Geriatric Depression Scale, NPI = Neuropsychiatric Inventory, RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire, SD = Standard Deviation, UM-PDHQ = University of Miami Parkinson's Disease Hallucination Scale, UPDRS = Unified Parkinson Disease Rating Scale.

[a] Chi-square test was used.

[b] Mann-Whitney U test was used.

[c] Median values are shown.

WMS personal and current information scores ($t(75)$ = 2.875, p < .01), WMS personal and current information scores ($t(75)$ = 2.774, p < .0), forward digit span ($t(75)$ = 2.554, p < .05), reverse digit span ($t(75)$ = 3.664, p < .001), visual memory immediate scores ($t(74)$ = 2.381, p < .05), logical memory immediate scores ($t(74)$ = 2.977, p < .01), logical memory delayed ($t(74)$ = 4.682, p < .001), phonetic fluency scores (U = 412, p < .05), semantic fluency scores ($t(75)$ = 3.579, p < .01), alternating word fluency scores ($t(75)$ = 5.239, p < .001), Stroop interference scores (U = 383, p < .05) binary similarities test scores ($t(75)$ = 3.307, p < .001), CDT scores ($t(75)$ = 2.510, p < .05), and BNT scores ($t(75)$ = 3.756, p < .001) of the a+PD group were significantly lower than the a-PD group. The neuropsychometric findings of the groups are shown in Table 2.

Table 2. Neuropsychological characteristics of a+PD and a-PD groups.

		a+PD n=32	a-PD n=45		
		Mean (SD)	Mean (SD)	*t*	*p*-value
General Cognitive Function	MMSE	20.00 (3.91)	21.29 (5.12)	1.248	.216
Personal and Spatial Orientation	WMS personal and current information	3.78 (1.58)	4.71 (1.25)	2.875	.005**
	WMS orientation	2.88 (1.79)	3.91 (1.33)	2.774	.008**
Digit Span	Forward digit span	4.22 (0.94)	4.80 (1.01)	2.554	.013*
	Reverse digit span	1.97 (1.18)	2.89 (1.03)	3.644	<.001***
Verbal Memory	VMPT learning	49.03 (20.47)	59.00 (22.76)	1.974	.052
	VMPT delayed recall	3.78 (2.95)	4.67 (3.30)	1.211	.221
	VMPT recognition	4.88 (3.00)	6.24 (3.21)	1.896	.062
Visual Memory	Visual memory immediate	3.81 (2.22)	5.48 (3.84)	2.381	.020*
	Visual memory delayed	2.50 (2.0)	3.77 (3.57)	4.840	.052
Logical Memory	Logical memory immediate	8.88 (3.28)	11.68 (4.93)	2.977	.007**
	Logical memory delayed	6.19 (4.03)	11.41 (5.29)	4.682	<.001***
Executive Functions	Phonetic fluency[a]	13.59 (8.15)	20.66 (11.81)		.011*
	Semantic fluency	10.56 (4.18)	14.78 (5.65)	3.579	.001**
	Alternating word fluency	2.34 (1.89)	5.07 (2.67)	5.239	<.001***
	Stroop interference score[a]	110.23 (56.25)	85.33 (38.66)		.029*
	Proverb interpretation task	1.97 (1.38)	2.33 (0.93)	1.300	.199.
	Binary similarities test	6.09 (2.25)	7.69 (1.96)	3.307	.001**
	CDT	1.88 (1.33)	2.67 (1.33)	2.510	.014*
Language	BNT	19.19 (5.85)	23.77 (4.78)	3.756	.001**
Visuospatial function	BFRT	37.78 (5.72)2	38.77 (5.58)	0.749	.456

Note. $*p < .05$; $**p < .01$; $***p < 0.001$; BFRT = Benton Face Recognition Test, BNT = Boston Naming Test, CDT = Clock Drawing Test, MMSE = Mini Mental State Examination, VMPT = Öktem Verbal Memory Process Test
[a] Mann-Whitney U test was used.

4. Discussion

Previous studies showed that apathy in PD is associated with depression (Oguru et al., 2010, Starkstein et al., 2009; Kirsch-Darrow et al., 2006), executive dysfunction (Lee, 2020; Sinha et al., 2013), anxiety (Santangelo et al., 2013; Gallagher & Schrag, 2012) and personality traits (Pluck & Brown, 2002). Our findings showed that the depression scores of the a+PD group were higher than the a-PD group. This finding was expected given the overlapping symptomatology of apathy and depression. However, there is no consensus on the relationship between depression and apathy in the literature. While some researchers argue that apathy emerges as a sign of depression (Starkstein et al., 2009; Pluck & Brown, 2002), others argue that apathy should be considered a separate syndrome independent of depression (Kirsch-Darrow et al., 2006).

In our study, it was found that the verbal fluency scores of the a+PD groups were lower compared to the a-PD group. In previous studies, verbal fluency tests are shown to be tasks that are sensitive to frontal and language functions, and reflect the impairment in verbal fluency, executive dysfunction, and loss of language functions (Whiteside et al., 2016; Herrera et al., 2012). It was also reported that verbal fluency was lower in patients with PD (Henry et al., 2004). This finding was interpreted as a marker of progressive impairment of executive functions in PD patients without dementia (Azuma et al., 2003). Consistent with previous findings, Santangelo et al. (2007) claimed that decreased phonological fluency may predict the development of dementia in PD patients. In addition, the a+PD group had a higher Stroop interference score compared to the a-PD group. This finding can be explained in relation to the deterioration in inhibition and cognitive flexibility skills (Santangelo et al., 2018).

Impairment in memory and learning processes observed in PD patients was interpreted as secondary type memory deficit attributed to frontal dysfunction (Ivory et al., 1999). Similarly, in our study, visual memory and logical memory functions of a+PD were observed to be impaired compared to the a-PD group. This finding may indicate loss of memory functions and impairment in attention functions. Our results show that the proverb interpretation task and binary similarities test scores of the a+PD group were lower than the a-PD group. These findings can be explained by the abstraction skills of PD patients with apathy being impaired. In addition, it was observed that the personal and current information and orientations of the a+PD group were lower than the a-PD group. Finally, the higher NPI scores of the a+PD group compared to the a-PD group indicate that parkinsonian apathy creates extra distress for caregivers.

Considering that neuropsychometric assessment is a performance-based measurement and can be affected by motivation level, parkinsonian apathy is associated with multi-domain cognitive impairment in which executive dysfunction is prominent.

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