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ORIGINAL COMMUNICATION

Clinical and demographic correlates of apathy in Parkinson's disease

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Abstract

Objective To better understand the demographic, neuropsychiatric, cognitive, and motor predictors of apathy in Parkinson's disease (PD).

Method 112 participants (M_{age} = 68.53 years; $M_{disease\ duration}$ = 6.17 years) were administered the Apathy Scale (AS), Beck Depression Inventory-II (BDI-II), Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Trail Making Test (TMT), Wechsler Adult Intelligence Scale-IV Matrix Reasoning subtest, letter (F-A-S) and category (Animals) fluency, and Hopkins Verbal Learning Test-Revised. Psychosis was assessed. A stepwise logistic regression analysis was performed to investigate the ability of demographic factors and clinical assessments to predict nonapathetic (AS ≤ 13) versus apathetic (AS > 13) group membership.

Results The regression analysis yielded a robust model in which older age, less education, elevated BDI-II, current psychosis, higher MDS-UPDRS Part III (motor score), and slower TMT-B performance predicted membership in the apathetic group, with a correct classification rate of 77.5% (Nagelkerke $R^2 = 0.48$, $p < .001$). Depression ($OR = 9.20$, $p < .001$) and education ($OR = 0.66$, $p = 0.002$) contributed significantly to the overall model. A linear regression with AS score as the outcome variable was similar, but TMT-B additionally contributed significantly ($p = 0.02$) to the overall model, $F(6, 86) = 12.02$, $p < .001$, adjusted $R^2 = 0.42$.

Conclusions Of the factors examined, depression, education, and executive functioning were the strongest correlates of apathy in PD. These results support the idea that common underlying frontosubcortical disruptions in this population contribute to apathy, depression, and executive dysfunction.

Keywords Parkinson's disease · Apathy · Depression · Cognition · Executive function

Introduction

Apathy, an internal lack of motivation, can manifest as a standalone syndrome or symptom of depression [1]. It is a complex multifactorial construct influenced by both neurobiological and psychosocial underpinnings [2]. It is a common neuropsychiatric feature of Parkinson's disease (PD), with reported prevalence rates as high as 70% [3, 4]. Apathy in individuals with PD is related to disease severity, has been implicated in a number of adverse disease outcomes (e.g., disability), and can have a significant negative impact on both patient and caregiver quality of life [4–6].

The pathophysiological mechanisms of apathy in PD are multifactorial and incompletely understood [7]. Its high frequency in this population suggests that it may be related to frontosubcortical dysfunction as part of the overarching disease process [8, 9]. It has been postulated that apathy is related to insufficient dopamine transmission in the mesocorticolimbic pathway, which disrupts reward circuitry (i.e., the orbital prefrontal cortex—ventral striatum circuit) [4, 10]. Dysfunction of cholinergic, serotonergic, and noradrenergic pathways have also been implicated in apathy [1, 11].

Prior studies have sought to identify the clinical and demographic correlates of apathy in PD [1, 4, 12]. Older age, lower education, and possibly male sex have each been associated with apathy in this population [13–15]. While some have found a positive association between PD motor symptoms and apathy [14–18], others have failed to do so [19–21]. Perhaps the most consistent findings are those demonstrating a significant relationship between apathy,

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depression, and executive functioning [9, 12]. A recent meta-analysis indicated that apathy increased risk of comorbid depression by 2.3 times [12]. Still, apathy can occur without depression [15, 22] and it is generally understood that apathy and depression are overlapping yet distinct constructs [7].

While a growing body of literature has examined demographic, neuropsychiatric, and motor correlates of apathy in PD [8, 14, 15, 17, 19–21], few investigations have done so in well-defined cohorts without dementia [23]. Moreover, only some have utilized more robust regression modeling, as opposed to means comparisons or correlational analyses [14, 15, 17–21]. One study that did utilize regression analysis found that cognitive measures of initiation, sex, and age were retained in a stepwise linear model [21]. However, the authors did not incorporate several important variables, including disease duration, pharmacological treatment, psychosis, or measures of cognition in domains other than executive functioning. To our knowledge, only Skorvanek and colleagues [18] have comprehensively examined the relative influence of demographic, psychiatric, motor, and cognitive variables on apathy in the same PD sample. These authors found depression and levodopa equivalent dose (LED) to be the most robust risk factors of apathy [18]. Given the prevalence of apathy and its adverse impact on outcomes in this population, a better understanding of its demographic and clinical correlates is warranted. The present study sought to more comprehensively define and understand the *relative* influence of the demographic, psychiatric (including mood and psychosis), motor, and cognitive predictors of apathy in individuals with PD without dementia.

Method

Participants

This study used baseline data from 112 participants collected as part of a larger prospective longitudinal investigation of neuropsychiatric symptoms in PD at an academic medical center. The cohort is comprised of a well-defined convenience sample of individuals with PD followed in our neurology clinics. Inclusion criteria were: (1) meets UK Brain Bank Criteria for diagnosis of PD with the exception that subjects were not excluded if they had more than one relative with PD [24], (2) disease onset between the ages of 30 and 85 years of age, and (3) participant was able and willing to provide informed consent. Exclusion criteria were: (1) a clinical diagnosis of dementia [25], and (2) advanced PD or comorbid disease that would interfere with the study.

Measures

Demographic information, including age, education, sex, ethnicity, and disease duration was obtained. Use of acetylcholinesterase inhibitors, antidepressants, antipsychotics, and/or dopaminergic medications was also collected. Hoehn and Yahr scale stage [26] was assigned and LED [27] was calculated for each participant.

Apathy was assessed using the Apathy Scale (AS) [28]. The AS is a validated 14-item measure adapted from Marin's Apathy Evaluation Scale [29] and designed specifically to assess apathy in PD. It is considered acceptable for use with both cognitively normal and cognitively impaired individuals [30]. The AS contains questions about daily life over the past four weeks related to various manifestations of apathy. For each question, the participant responds with "not at all" (0 points), "slightly" (1 point), "some" (2 points), or "a lot" (3 points). The total score ranges from 0 to 42, with a cutoff of ≥ 14 indicating a higher likelihood of clinically significant apathy in PD [28].

Depression was assessed using the Beck Depression Inventory-II (BDI-II). The BDI-II is a 21-item measure with possible scores ranging from 0 to 63 [31]. A cutoff of ≥ 14 is typically used to indicate a higher likelihood of clinically significant depression. The Frontal Systems Behavior Scale (FrSBe) was used to assess behavioral symptoms. It is a 46-item questionnaire that yields demographically-corrected T scores for Apathy, Disinhibition, and Executive Dysfunction subscales as well as a total score [32]. T scores of 65 or greater are considered clinically elevated [32]. The presence or absence of current psychosis was determined using NINDS-NIMH diagnostic criteria [33]. Motor symptomatology was assessed using Part III of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [34].

Cognition was assessed using the Montreal Cognitive Assessment (MoCA), Trail Making Test Parts A (TMT-A) and B (TMT-B), Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) Matrix Reasoning (MR) subtest, letter (F-A-S) and category (Animals) fluency, and Hopkins Verbal Learning Test-Revised (HVLT-R). The MoCA is a brief global cognitive screening measure sensitive to mild cognitive impairment and well-validated for use in PD [35, 36]. Items are categorized into eight domains (visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation) and the total score can range from 0 to 30. The TMT-A is a measure of psychomotor processing speed involving visual scanning and sequencing. The TMT-B is a measure of mental flexibility similar to TMT-A, but with the added complexity of mental set shifting [37]. The WAIS-IV MR subtest is

a pattern completion measure of abstract visual reasoning [38]. Letter and category fluency are both measures of verbal fluency [39, 40]. The HVLT-R is a measure of verbal list learning and memory [41]. Demographically-corrected T scores for the TMT-A, TMT-B, letter fluency, and category fluency were derived from Heaton and colleagues [42], while normative data for the WAIS-IV MR and HVLT-R were derived from the respective test manuals.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics, version 24 (SPSS, IBM Corporation, Armonk, NY). Means, medians, standard deviations, ranges, 95% confidence intervals, and histograms were generated for all continuous variables, and frequencies and percentages were generated for all categorical variables. Statistical assumptions for all analyses were tested to ensure accurate interpretation of the results. The level of statistical significance was set at $\alpha = 0.05$. A one-way multivariate analysis of variance (MANOVA) for continuous variables, and Chi-square tests for categorical variables were conducted to assess for significant differences between nonapathetic (AS total score ≤ 13) and apathetic (AS total score > 13) groups for all demographic and clinical factors of interest. Demographic variables included age (years), education (years), disease duration (years), and sex (male versus female). Psychiatric variables included mood (BDI-II), behavioral regulation (FrSBe self-reported current Apathy, Disinhibition and Executive Dysfunction subscale and total T scores), and psychosis (presence or absence of current psychosis). Cognitive variables included MoCA education-corrected total score, and T scores for TMT-A, TMT-B, WAIS-IV MR, letter and category fluency, and HVLT-R total learning and delayed recall. Motor symptoms (MDS-UPDRS Part III score), current dopamine agonist and antidepressant use, and LED were also included.

The primary analysis was a stepwise Wald logistic regression, performed to investigate the ability of the demographic, neuropsychiatric, and motor variables to predict nonapathetic versus apathetic group membership. Variables for which there was a significant difference between groups from the aforementioned means comparisons were included as predictors with three exceptions. First, age was automatically retained as a covariate in the final model because of prior evidence indicating its strong association with apathy [4, 23]. Second, the FrSBe variables were not included because this data was only available for 76 (68%) participants. Third, MoCA score was not included, given that scores from a more comprehensive battery of cognitive tests were used. Predictors were entered by block in the following order: age, remaining demographics, mood, psychosis, motor symptoms, and cognition. The classification rate cut value was set at 0.33 because it is the ratio of participants with apathy to total sample. A follow-up exploratory stepwise forward linear regression analysis was then performed to investigate the ability of demographic, neuropsychiatric, and motor variables to predict AS score. The same predictors were entered by block as described above with AS score as the outcome variable. Entry and exit criteria were set at $p < .15$ and $p > .16$, respectively, for both regression analyses.

Results

Descriptive information is presented in Table 1, along with the results of the mean comparison analyses. Participants had a mean age of 68.53 (8.13) years, 95% CI [67.01, 70.06], and were generally college-educated ($Mdn = 16$ years, interquartile range = 14–18) with a median disease duration of 5.51 years (interquartile range = 3.47–8.02). The majority was male (60.7%), and self-identified as White and Non-Hispanic (99.1%). Hoehn and Yahr stages were relatively early overall, ranging from 1.0 to 3.0. The majority was in Stage 2, $n = 72$ (64.9%). Forty participants (36.0%) were on an antidepressant, three (2.7%) were taking an antipsychotic medication, and 33 (29.5%) were on dopamine agonist therapy.

The mean MoCA score was 24.20 (2.88) overall, which is above published cutoffs for detecting dementia in PD [43, 44]. Mean T-scores for TMT-A, TMT-B, WAIS-IV MR, and letter and category fluency were all in the average range, while HVLT-R total learning and delayed recall were in the low average range overall.

The mean AS score was 10.26 (6.36), range = 0–27, and 32 (28.6%) participants had significantly elevated AS scores, $M = 18.59$ (3.65), range = 14–27. The mean BDI-II score was within the normal range overall, $M = 10.01$ (7.39), range = 0–41. Of the 32 participants in the apathetic group, 17 had BDI-II scores above the cutoff of > 13 suggestive of clinical depression, $M = 22.53$ (7.87), range = 14–41. Mean FrSBe scores were all within normal limits in the nonapathetic group. In the apathetic group, the Executive Dysfunction subscale was borderline elevated, $M = 64.50$ (16.74), and the Apathy subscale was significantly elevated, $M = 70.08$ (15.67).

Pearson r correlations were moderate between the AS and the FrSBe Apathy subscale ($r = 0.59$), and moderate, but weaker, between the AS and MDS-UPDRS apathy question (item 1.5; $r = 0.43$). Pearson r correlations were also moderate between the AS and other measures of mood and frontally-mediated behavior. The BDI-II yielded the highest correlation ($r = 0.58$), followed by the FrSBe Executive Dysfunction subscale ($r = 0.46$), and FrSBe Disinhibition subscale ($r = 0.33$).

Table 1 Neuropsychiatric, Motor, and Demographic Differences Between Nonapathetic and Apathetic Groups

Domain	Variable	Nonapathetic		Apathetic		Overall		*p*	η^2
		n	*M* (SD)	*n*	*M* (SD)	*n*	*M* (SD)		
Apathy	Apathy scale	80	6.93 (3.50)	32	18.59 (3.65)	112	10.26 (6.36)	< 0.001	0.69
Cognition[a]	MoCA	79	24.71 (2.82)	32	22.94 (2.68)	111	24.20 (2.88)	0.003	0.08
	Trail making test part A	78	44.38 (11.63)	32	43.50 (9.02)	110	44.13 (10.90)	0.70	< 0.01
	Trail making test part B	75	48.69 (10.02)	30	43.70 (10.77)	105	47.27 (10.44)	0.03	0.05
	WAIS-IV matrix reasoning	78	54.49 (9.89)	31	49.78 (8.60)	109	53.15 (9.74)	0.02	0.05
	Letter fluency	79	48.52 (11.55)	31	43.52 (10.62)	110	47.11 (11.48)	0.04	0.04
	Category fluency	79	47.52 (12.09)	32	45.28 (11.90)	111	46.87 (12.02)	0.38	0.01
	HVLT-R total learning	79	43.76 (10.20)	32	38.66 (1.56)	111	42.29 (10.05)	0.01	0.05
	HVLT-R delayed recall	79	42.32 (13.55)	32	36.19 (11.65)	111	40.55 (13.27)	0.03	0.04
Behavioral regulation[a]	FrSBe Disinhibition	50	50.70 (11.63)	26	57.58 (19.94)	76	53.05 (15.22)	0.06	0.05
	FrSBe Apathy	50	57.60 (11.37)	26	70.08 (15.67)	76	61.87 (14.20)	< 0.001	0.18
	FrSBe dysexecutive	50	55.62 (13.21)	26	64.50 (16.74)	76	58.66 (15.01)	0.01	0.08
	FrSBe total	50	55.92 (12.78)	26	70.42 (17.72)	76	60.88 (16.11)	< 0.001	0.18
Motor symptoms	MDS-UPDRS Part III	80	26.24 (13.94)	32	32.19 (13.30)	112	27.94 (13.96)	0.04	0.04
Demographics	Age (years)	80	68.24 (8.36)	32	69.28 (7.61)	112	68.53 (8.13)	0.54	< 0.01
	Education (years)	80	16.63 (2.41)	32	14.91 (2.74)	112	16.13 (2.61)	0.001	0.09
	Disease duration (years)	80	6.41 (3.95)	32	5.56 (3.72)	112	6.17 (3.89)	0.30	0.01
	Levodopa equivalent dose	80	603.76 (376.60)	32	712.08 (311.62)	112	634.71 (361.22)	0.15	0.02
		n (%)		*n* (%)		*n* (%)		*p*	Cramer's V
	Sex (*n* male)	44 (55.0)		24 (75.0)		68 (60.7)		0.05	0.18
	Dopamine agonist (*n* yes)	26 (32.5)		7 (21.9)		33 (29.5)		0.27	0.11
	Antidepressant (*n* yes)	27 (34.2)		13 (40.6)		40 (36.0)		0.52	0.06
Mood	Depressed (*n* yes)	8 (10.1)		17 (53.1)		25 (22.5)		< 0.001	0.47
Psychosis	Current psychosis (*n* yes)	24 (30.0)		16 (50.0)		40 (35.7)		0.046	0.19

MoCA Montreal Cognitive Assessment, *WAIS-IV* Wechsler Adult Intelligence Scale-Fourth Edition, *HVLT-R* Hopkins Verbal Learning Test-Revised, *FrSBe* Frontal Systems Behavior Scale Self-Rating Form current symptoms, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale. Nonapathetic = Apathy Scale (AS) score ≤ 13, apathetic = AS score > 13; depressed = Beck Depression Inventory-II score > 13

[a]T scores were utilized for all cognitive and FrSBe variables except MoCA

Compared to participants in the nonapathetic group, those in the apathetic group were significantly less educated ($p = 0.001$), and more likely to present with psychosis ($p = 0.046$), significantly elevated depression (BDI-II > 13, $p < .001$) and greater motor symptomatology (MDS-UPDRS Part III, $p = 0.04$). They also had significantly higher FrSBe Apathy and Executive Dysfunction subscale scores ($p < .001$ and $p = 0.01$, respectively), as well as higher FrSBe total

scores ($p < .001$). Of the cognitive variables, apathetic participants had significantly lower MoCA ($p = 0.003$), TMT-B ($p = 0.03$), WAIS-R MR ($p = 0.02$), letter fluency ($p = 0.04$), and HVLT-R (p's = 0.01 and 0.03 for total learning and delayed recall, respectively) scores. Age, sex, disease duration, LED, current dopamine agonist therapy, current antidepressant use, the FrSBe Disinhibition subscale, TMT-A, and category fluency were not significantly different between groups (all p's > 0.05).

The logistic regression analysis yielded a robust final model (see Table 2). Older age, less education, elevated BDI-II score, the presence of current psychosis, higher MDS-UPDRS Part III score, and poorer TMT-B performance significantly predicted membership in the apathetic group, with a correct classification rate of 77.5% (Nagelkerke $R^2 = 0.48$, $p < .001$, Hosmer–Lemeshow $p = 0.56$). However, only elevated depression ($OR = 9.20$, $p < .001$) and education ($OR = 0.66$, $p = 0.002$) contributed significantly to the overall model. As a means of corroborating these findings, a similar analysis was performed in which the FrSBe Apathy subscale T score (using a cutoff of ≥ 65) replaced the AS as the determinant of group membership. This produced a very similar final model in which older age, less education, elevated BDI-II score, the presence of current psychosis and poorer TMT-B performance significantly predicted membership in the apathetic group, with a correct classification rate of 86.6% (Nagelkerke $R^2 = 0.41$, $p < .001$, Hosmer–Lemeshow $p = 0.96$). Elevated BDI-II score ($p = 0.03$), education ($p = 0.02$), and TMT-B ($p = 0.01$) contributed significantly to the overall model.

Results of the follow-up exploratory linear regression analysis yielded a final model in which older age, less education, elevated BDI-II score, the presence of current psychosis, higher MDS-UPDRS Part III score, and poorer TMT-B performance were significantly associated with higher AS scores, $F(6, 86) = 12.02$, $p < .001$, adjusted $R^2 = 0.42$. See Table 3. In this parametric iteration, education ($B = -0.69$, $p = 0.001$), depression ($B = 6.45$, $p < .001$), and TMT-B ($B = -0.14$, $p = 0.02$) contributed significantly to the overall model.

Table 2 Stepwise Wald Logistic Regression Model Predicting Apathetic versus Nonapathetic Group Membership

Final Predictors	Statistics						Final Overall Model			
	B	*SE*	Wald	*p*	*OR*	95% CI	Nagelkerke R^2	*p*	Hosmer–lemeshow	Classification rate[a]
Age (years)	0.06	0.04	2.52	0.11	1.06	[0.99, 1.14]	0.48	< 0.001	0.56	77.5%
Education (years)	− 0.42	0.13	9.69	0.002	0.66	[0.50, 0.86]				
Depression	2.22	0.67	10.97	< 0.001	9.20	[2.47, 34.22]				
Current psychosis	0.81	0.60	1.81	0.18	2.24	[0.69, 7.22]				
MDS-UPDRS III	0.01	0.03	0.21	0.65	1.01	[0.96, 1.06]				
Trails B	− 0.07	0.04	3.69	0.05	0.93	[0.87, 1.00]				

SE = standard error; *OR* = odds ratio; CI = confidence interval; Trails B = Trail Making Test Part B; MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III; depression = depressed versus not depressed using Beck Depression Inventory-II cutoff of > 13; current psychosis = psychosis verses no psychosis

[a]Cut value = 0.33

Table 3 Stepwise Forward Linear Regression Model of Neuropsychiatric, Motor, and Demographic Predictors of Apathy

Final Predictors	Statistics							Final overall model			
	B	*SE*	*t*	*p*	95% CI for *B*	Tolerance	VIF	Adjusted R^2	*F*	*df*	*p*
Age (years)	0.12	0.07	1.86	0.07	[− 0.01, 0.25]	0.90	1.11	0.42	12.02	6, 86	< 0.001
Education (years)	− 0.69	0.21	− 3.32	0.001	[− 1.10, − 0.28]	0.83	1.21				
Depression	6.45	1.32	4.89	< 0.001	[3.83, 9.07]	0.88	1.14				
Current psychosis	1.64	1.11	1.48	0.14	[− 0.56, 3.84]	0.95	1.06				
MDS-UPDRS III	0.06	0.04	1.37	0.17	[− 0.03, 0.15]	0.66	1.51				
Trails B	− 0.14	0.06	− 2.34	0.02	[− 0.27, − 0.02]	0.61	1.63				

SE = standard error; CI = confidence interval; VIF = variance inflation factor; Trails B = Trail Making Test Part B; MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III; depression = not depressed versus depressed using Beck Depression Inventory-II cutoff of > 13; current psychosis = no psychosis verses psychosis

Because depression and apathy are overlapping constructs, the regression analyses were re-run without the BDI-II. Doing so did not yield substantially different models.

Discussion

Consistent with prior literature [12], our findings suggest that for individuals with PD and without dementia, those with significantly elevated apathy are more likely to be less educated and have greater motor and neuropsychiatric symptomatology, compared to those without significantly elevated apathy. Specifically, apathetic participants were more likely to present with psychosis, significantly elevated depression, behavioral dysregulation, and worse cognition. Executive functioning, education, and depression were the strongest correlates of apathy.

In our cohort, depression had the most robust association with apathy. Participants with significantly elevated depression had a ninefold increased risk of significantly elevated apathy, which is far greater than previously reported [12, 23]. This overlap may be in part due to shared pathology. For example, disruptions of frontostriatal circuitry via insufficient dopamine transmission [45] and the mediating role of serotonin [9] have been associated with both depression and apathy [9, 45]. The fact that apathy is a symptom of depression, and consequently queried on both the AS and BDI-II may further explain the overlap [11]. Still, despite the strong correlation between these syndromes, it is notable that about half of our apathetic participants did not have significantly elevated symptoms of depression. This supports the notion that although related, depression and apathy are distinct constructs.

Brain regions implicated in depression and apathy in PD have been linked to deficits in executive functioning in this population as well (e.g., anterior cingulate cortex) [9, 15]. In the present study, TMT-B, a test of executive dysfunction sensitive to decline in PD [46, 47], was the only cognitive predictor retained in the regression models. Significant differences between the apathetic and non-apathetic group were also seen on other tests with heavier executive demands, including letter fluency, WAIS-IV MR, and HVLT-R total learning. This suggests that executive functioning is uniquely associated with apathy. Both apathy and executive dysfunction appear to be related to connections between the anterior cingulate cortex, lateral prefrontal cortex, dorsal caudate nucleus of the basal ganglia, and basal forebrain [1, 9, 11, 12]. Of the three neurotransmitters associated with these regions (i.e., dopamine, acetylcholine, and norepinephrine), cholinergic system dysfunction has been implicated as a primary contributor to both apathy and cognitive impairment in PD [1, 11, 48].

In our cohort, every year of education decreased the likelihood of significantly elevated apathy by 34%. This finding is consistent with previous studies [12–15, 21], though the reason for this relationship is currently unknown. One possibility is that education may be serving as a proxy of overall socioeconomic status, which has been suggested to negatively correlate with mood symptomatology in the general population [49]. This may be related to the availability and quality of both personal (e.g., coping mechanisms) and community (e.g., healthcare services) resources [49].

Although only depression, education, and TMT-B contributed significantly to one or both regression models, even the nonsignificant predictors appear to be important correlates of apathy in PD. For example, we found a positive relationship between motor impairment and apathy. This might be considered a function of age and more advanced disease [12, 14]; however, neither age nor disease duration were significantly associated with apathy in the present study. It may instead be that dopaminergic transmission reduction, caused by PD-related nigrostriatal pathway dysfunction, adversely impacts frontosubcortical systems, which in turn produces both motor symptoms and apathy [15].

The association between apathy and sex in PD is unclear, though some studies have suggested that males may be more vulnerable than females [12]. In our study, the apathetic group included a larger percentage of males than the non-apathetic group. Although the p value ($p = 0.0502$) was just above the threshold for statistical significance, the effect size (Cramer's $V = 0.18$) was the largest of demographic factors and third largest of all variables tested, supporting a hypothesis that there is a true, but subtle, relationship between sex and apathy in PD. Regarding dopaminergic medication, we did not observe a significant relationship between apathy and LED, which is a contrast to Skorvanek and colleagues [18]. Unlike their methodology, we excluded variables with non-significant means comparisons from our regression analyses, which may explain this discrepancy.

Apathy measures

The AS and FrSBe Apathy subscale, both commonly used to assess apathy in PD [30], were significantly correlated. This further validates the utility of the AS for assessing apathy in the present study and PD in general. The correlation between the AS and MDS-UPDRS item 1.5 (apathy item) was weaker and results actually yielded stronger correlations between the AS and measures of other frontally-mediated constructs. This may reflect poor sensitivity of the MDS-UPDRS apathy item and supports limiting its use to screening purposes only [30].

Clinical implications

Increased awareness and early detection of the demographic and clinical symptoms that raise the risk of clinically significant apathy in PD could lead to improved treatment and healthcare outcomes. Specifically, awareness that patients with lower education, depression, psychosis, greater motor impairment, and executive dysfunction are at higher risk of developing apathy may help providers improve screening and diagnosis of apathy in this population. Given shared dopaminergic underpinnings, particular attention to these correlates might also help guide refinement of dopamine-based treatment for PD in general.

Limitations and future directions

This study was a cross-sectional analysis of baseline data from an ongoing longitudinal study. Examination of the trajectory and predictors of apathy over time will prove important. Incorporating structural and functional imaging could help further elucidate underlying pathophysiology.

Although individual scores varied widely, mean AS and BDI-II totals were within normal limits, which may reduce the generalizability of these results to more severely affected populations. That said, the mild symptom severity of our sample is an important strength of the study, as few prior investigations have evaluated apathy in earlier stage PD with such a comprehensive constellation of variables. Some cell sizes were relatively small. In addition, the moderate Pearson r correlation between the BDI-II and AS could raise concern about multicollinearity. However, removal of the BDI-II from the regression analyses did not yield substantially different results.

Conclusions

To our knowledge, this is the first study examining the relative associations of multiple demographic, neuropsychiatric, motor, and a comprehensive set of cognitive variables with apathy in a well-characterized PD sample without dementia. We are aware of only one prior investigation that utilized a comparably robust design to examine the correlates of apathy in a similarly comprehensive manner [18]. However, whereas Skorvanek and colleagues [18] utilized only the Mini-Mental State Examination to assess cognition and employed a categorical approach in coding education, our study was strengthened by the inclusion of eight well-validated neuropsychological measures across cognitive domains and calculating education as a continuous variable. Our results provide support for increased attention towards education, depression, psychosis, motor impairment, and executive dysfunction when assessing apathy in this population. Additional focus in these areas could lead to better treatment, improved outcomes, and ultimately higher quality of life for individuals with PD.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards This study received local institutional review board approval and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Written informed consent was obtained from all participants prior to their inclusion in the study.

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