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Letter to Editor

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Exploring relationships between state and trait anxiety and depression in patients with Parkinson's disease and controls: a cross-sectional analysis

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease comprised of motor and non-motor symptoms, including depression and anxiety. The relationship between depression, anxiety, and motor symptoms is not well understood. Additionally, there are few direct comparisons of anxiety and depression between people with PD (PwP) and those without PD. The present study determined differences in state and trait anxiety between those with and without PD, examined the impact of depression on anxiety in both groups, and explored the relationship between depression, anxiety, and motor symptoms among PwP. Data from 42 PwP and 56 non-PD comparison participants were obtained from a non-randomized, non-treatment longitudinal observational study. Anxiety [State-Trait Anxiety Inventory (STAI)], depression (Geriatric Depression Screen), and motor symptoms (Movement Disorder Society - Unified Parkinson's Disease Rating Scale part III) were assessed. There were no statistically significant differences between PwP and non-PD comparisons for anxiety or depression. Depression was associated with elevated STAI scores ($P < 0.001$) regardless of PD status. Depressed PwP displayed greater motor symptom burden compared to non-depressed PwP (median [IQR]: 25.00 [21.00, 38.50] *vs.* 20.00 [16.00, 23.00]; $P =$

0.064). There were statistically significant differences in both state and trait anxiety when participants were grouped by depression and PD status. While anxiety does not appear to be correlated with motor symptoms in people with PD, depression may be associated with greater motor symptom burden. Further study is needed to explore the relationship between depression, anxiety, and motor impairment in PwP.

Keywords: Depression, anxiety, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, projected to affect 1,238,000 adults in the United States by 2030[1]. Increasingly, two components of PD are recognized: characteristic motor symptoms - tremor, rigidity, bradykinesia, and postural instability - and non-motor symptoms including neuropsychological features, changes in olfaction, gastrointestinal dysfunction, and dysautonomia[2]. While much attention has been devoted to the study and treatment of motor symptoms, anxiety and depression remain under-recognized, under-studied, and under-treated[3].

Depression and anxiety co-occur in approximately 41% of people with PD (PwP)[4]. Furthermore, PwP with anxiety exhibit higher rates of depression as compared to PwP without anxiety[5], and depression has been proposed to mediate the PD-specific effects on anxiety[6]. There is mixed evidence regarding the relationship between motor symptoms and anxiety. Anxiety can precede the development of motor symptoms by several years[7], while the experience of motor fluctuations appears to increase vulnerability to anxiety[8]. Previous models have proposed neurological changes due to PD pathology, and psychosocial factors increase vulnerability to anxiety over a perceived threat and cause a subsequent increase in symptoms and avoidance behavior[6]. Additionally, anxiety appears to be both a core feature of PD and intimately tied to declines in physical functioning, motor fluctuations[8], and avoidance behavior[9]. This may suggest different types of anxiety - persistent anxiety and situation-specific anxiety, or alternatively, state anxiety and trait anxiety[10]. Trait anxiety is related to an individual's persistent characteristics or disposition and can be understood as "anxiety-proneness"[11]. In contrast, state anxiety arises with specific situations or circumstances and fluctuates over time[11]. For PwP, state anxiety may be more closely related to disease-specific factors, such as disease severity and duration[12], and manifest in fear of falling[9]. In contrast, trait anxiety may be more closely related to psychosocial risk factors, many of which are not PD-specific[12].

If disease-specific factors, such as motor symptoms, contribute to episodic anxiety, a difference in state anxiety would be expected between PwP and non-PD comparisons. Given the known comorbidity of anxiety and depression in this population[4,5], reported anxiety and motor symptoms may differ between depressed and non-depressed PwP and non-PD comparisons. To date, the comparison of state and trait anxiety between PwP and those without PD has been confined to untreated patients in the early stages of PD[13]. While this study found greater state and trait anxiety among PwP compared to controls[13], these conclusions need to be validated in those who are receiving dopaminergic therapy. The present study determined differences in state and trait anxiety between people with and without PD, examined the impact of depression on anxiety in both groups, and explored the relationship between depression, anxiety, and motor symptoms among PwP.

METHODS

Data source and study participants

Participants were recruited for a non-randomized, natural history, non-treatment longitudinal observational study from the Movement Disorders Clinic at the institution where the research was

conducted, described in detail elsewhere[14], and approved by that institution's Institutional Review Board (#15-987). All participants were between 55 and 90 years old; had a study partner with whom they have regular contact and who can assess their behavioral, functional, and cognitive abilities; scored ≥ 12 on the Montreal Cognitive Assessment (MOCA) at the screening visit; could walk at least 30 feet; and were willing and able to complete all required study procedures for the study. As the primary aim of the parent study was to evaluate the structural and functional connectivity, individuals were excluded if they had deep brain stimulation or could not undergo MRI for any reason. Participants were divided into two groups - those with a PD diagnosis and community-dwelling older adults without a PD diagnosis, hereafter referred to as the non-PD comparison group. All participants with PD were required to have a PD diagnosis from a movement disorder-trained physician based on the UK brain bank criteria[15] and to utilize dopaminergic therapy for the duration of the study. Non-PD comparison group participants did not have a diagnosis of PD or other neurologic diagnoses and were required to live independently. Individuals were excluded from the study if they had any significant unstable medical illness or if there was evidence of screening lab abnormalities related to cognitive performance or structural lesions unrelated to study diagnosis found on baseline MRI. Data from the screening and baseline visits were used for the present study.

Measures

The primary outcomes were state and trait anxiety as assessed by the State-Trait Anxiety Inventory (STAI)[10]. The selection of items for the neuropsychological battery, including the STAI, was based on the harmonization of data with other large data sets of PwP, particularly the Parkinson Progression Marker Initiative (PPMI)[16]. The statements for the Trait scale ask participants to consider how they generally feel, while the State scale asks participants to consider how they feel at a particular moment. Each domain was analyzed separately as a continuous variable.

Secondary outcomes for the present study included the 30-item Geriatric Depression Scale (GDS)[17] and the Movement Disorders Society revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part III[18]. For the present study, a total GDS score of 10 or more was considered "depressed"[17]. The MDS-UPDRS part III was used as the motor function assessment tool for the PD participants and was conducted by a trained neurologist.

Demographic information, social history, and medical history were gathered through interviews with the participants and their study partner. The MOCA was administered to all participants by a trained interviewer and scored with an education correction (an additional point was applied for participants who had completed less than 12 years of education)[19]. A higher score indicates greater cognitive function, with a maximum score of 30[19]. The comorbidities assessed in the original study[14] were counted and categorized as a general indicator of health. PD participants completed all measures and the intake interview while their motor symptoms were controlled by medication ("on" state), with assessments beginning 45 min after prior dose of PD medications.

Statistical analysis

Continuous demographic variables and outcome measures were assessed using an independent samples *t*-test for normally distributed variables, the Mann-Whitney U test for comparisons between 2 groups, and the Kruskal-Wallis test for comparisons between 3 or more groups. Categorical variables and outcomes were assessed using a chi-square test. To assess the relationship between motor symptoms and anxiety, Spearman's Rank Order correlation was calculated between UPDRS Part III total scores and State anxiety and between UPDRS Part III total scores and Trait anxiety. Missing data were omitted on a comparison-wise basis. STAI scores were available for 88 participants. GDS scores were available for 96 participants. All analyses were conducted in R[20] at $\alpha > 0.05$, using the Tidyverse[21] package for data management and the

Tableone[22] package for creation of tables.

RESULTS

Sample demographics

Of the 98 participants, 42 documented a PD diagnosis [Table 1]. PD and non-PD participants were similar across most demographic variables. Notably, there was a greater proportion of male participants among those with PD (69% *vs.* 45.3%, respectively; Table 1). A greater proportion of those with PD reported 41 or more hours spent with a care partner per week (88.1% *vs.* 52.8%; Table 1). Most PD participants were classified as Hoehn and Yahr Stage 2 (84.6%; Table 1), with a mean disease duration of 8.69 years (SD: 4.48; Table 1).

Mental health outcomes by PD status

Anxiety and depression were not significantly different when examined by PD diagnosis alone, although the proportion of depressed individuals in the PD group was approximately twice that of the comparison group (33.3% *vs.* 16.7%, respectively; $P = 0.098$; Supplementary Table 1). Those who were depressed (GDS ≥ 10) reported greater anxiety in both the state and trait domains, regardless of PD diagnosis ($P < 0.001$; Table 2). Among depressed participants, those with PD reported greater anxiety in both the state and trait domains than their non-PD counterparts [Table 2 and Figure 1]. Some non-depressed participants reported levels of anxiety comparable to depressed participants [Figure 1].

Motor function and mental health

Increased motor-symptom burden was observed in depressed PD participants compared to non-depressed PD participants ($P = 0.064$; Table 2). There were some non-depressed PD participants with motor dysfunction comparable to that of depressed PD participants [Supplementary Figure 1]. There were no significant correlations between anxiety and motor symptom burden [Supplementary Table 2].

DISCUSSION

The present study compared state and trait anxiety between people with PD currently using dopaminergic therapy and a non-PD comparison group and found no differences in either type of anxiety based on PD diagnosis alone. The prevalence of depression among PwP in the present study (33.3%) is comparable to other studies[23]. The lack of difference in anxiety due to PD status may be due, in part, to the general health of the comparison group - there was no statistically significant difference in personal history of anxiety or depression between PwP and non-PD comparisons [Table 1]. As the estimated prevalence of any anxiety disorder in US adults aged 60 and above is 9%, this suggests that the comparison group may not be as psychologically healthy as the general population[24]. While the distribution of gender differed between PwP and non-PD comparisons, no significant differences in mental health outcomes were observed (data not shown).

Depressed participants, regardless of their PD status, reported greater anxiety in both state and trait domains, consistent with other literature reporting an intimate and persistent link between depression and anxiety in PwP[25]. Among depressed participants, those with PD reported greater anxiety in both the state and trait domains, suggesting PD and depression may both contribute to increased anxiety in PwP[13]. No differences were noted between state and trait anxiety. A recent meta-analysis identified a strong correlation between the STAI Trait subscale and depressive symptoms[26], suggesting this instrument might be better understood as measuring negative affect broadly. Examination of the psychometric properties of the STAI using generalizability theory found both subscales were temporally stable[27], indicating a lack of discrimination between state and trait anxiety. Furthermore, while the STAI has been used in PwP[4], it has

Table 1. Sample demographics

	Overall *n* (%)	PD *n* (%)	Non-PD Comparison *n* (%)	*P*
n	96	42	546	
Male	53 (57.0)	29 (69.0)	24 (47.1)	0.055
Age [mean (SD)]	69.6 (6.5)	69.3 (6.6)	69.75 (6.6)	0.751
Marital status				0.844
Married	70 (75.3)	34 (81.0)	36 (70.6)	
Divorced	12 (12.9)	4 (9.5)	8 (15.7)	
Widowed	5 (5.4)	2 (4.8)	3 (5.9)	
Never married	3 (3.2)	1 (2.4)	2 (3.9)	
Domestic partnership	3 (3.2)	1 (2.4)	2 (3.9)	
Education [mean (SD)]	15.7 (2.6)	15.1 (2.6)	16.3 (2.4)	0.017
Hispanic or Latino ethnicity	7 (7.6)	4 (9.8)	3 (5.9)	0.763
Race				0.075
Asian	8 (8.8)	6 (15.0)	2 (3.9)	
White	79 (86.8)	33 (82.5)	46 (90.2)	
Black or African American	3 (3.3)	0 (0.0)	3 (5.9)	
Preferred not to answer	1 (1.1)	1 (2.5)	0 (0.0)	
Personal history of anxiety	21 (22.6)	9 (21.4)	12 (23.5)	1
Personal history of depression	20 (21.1)	7 (16.7)	13 (25.5)	0.437
MOCA - Education corrected [mean (SD)]	26.4 (2.5)	25.5 (2.6)	27.2 (2.3)	0.002
Comorbid conditions*				0.128
0	11 (11.8)	2 (4.8)	2 (4.8)	
1	16 (17.2)	9 (21.4)	9 (21.4)	
2	16 (17.2)	9 (21.4)	9 (21.4)	
3-5	38 (40.9)	19 (45.2)	19 (45.2)	
> 5	12 (12.9)	3 (7.1)	3 (7.1)	
Family history of anxiety	1 (1.1)	1 (2.4)	0 (0.0)	0.922
Family history of depression	7 (7.5)	1 (2.4)	6 (11.8)	0.189
Male CP	31 (40.3)	12 (32.4)	19 (47.5)	0.265
Relationship with CP				0.371
Partner	61 (65.6)	31 (73.8)	31 (73.8)	
Child	4 (4.3)	1 (2.4)	1 (2.4)	
Sibling	7 (7.5)	2 (4.8)	2 (4.8)	
Friend	4 (4.3)	3 (7.1)	3 (7.1)	
Preferred not to answer	14 (15.1)	4 (9.5)	4 (9.5)	
Unknown	3 (3.2)	1 (2.4)	1 (2.4)	
Time spent with CP (hours/week)				0.004
1-10	13 (14.0)	2 (4.8)	11 (21.6)	
11-20	7 (7.5)	2 (4.8)	5 (9.8)	
21-30	2 (2.2)	1 (2.4)	1 (2.0)	
31-40	7 (7.5)	0 (0.0)	7 (13.7)	
41 or more	64 (68.8)	37 (88.1)	27 (52.9)	
Disease duration† (years) [mean (SD)]	-	8.7 (4.5)	-	-
Levodopa equivalent dose† [mean (SD)]	-	809.1 (488.8)	-	-
Hoehn & Yahr stage†				
Stage 1	-	1 (2.6)	-	-

Stage 2	-	33 (84.6)	-
Stage 3	-	5 (12.8)	-

*These conditions included anxiety, autoimmune disease, bipolar disorder, subdural brain bleeding, chronic kidney disease, chronic pain, congestive heart failure, COPD, coronary artery disease, depression, diabetes type 1, diabetes type 2, epilepsy, fibromyalgia, chronic headaches, hypertension, hyperlipidemia, hypothyroidism, insomnia, myocardial infarction, treated obstructed sleep apnea, untreated obstructed sleep apnea, PTSD, stroke, vitamin deficiency, and malignancy; †PD-specific measures not evaluated in the comparison group. PD: Parkinson's disease; MOCA: Montreal Cognitive Assessment; CP: Care partner; COPD: chronic obstructive pulmonary disease; PTSD: post-traumatic stress disorder.

Table 2. Mental health outcomes by depression and PD status

	Not depressed		Depressed		*P*
	PD	Comparison	PD	Comparison	
*n**	28	45	9	14	
Anxiety (median [IQR])					
State	26.00 [22.00, 31.00]	25.00 [22.00, 30.00]	40.00 [35.75, 48.00]	35.00 [30.00, 42.00]	< 0.001
Trait	26.00 [24.00, 30.50]	27.00 [23.25, 29.75]	44.00 [38.75, 47.75]	40.00 [37.00, 47.00]	< 0.001
UPDRS Part III (median [IQR])	20.00 [16.00, 23.00]	-	25.00 [21.00, 38.50]	-	0.064

*STAI scores were missing for 9 comparison participants and 1 PD participant. PD: Parkinson's disease; STAI: State-Trait Anxiety Inventory.

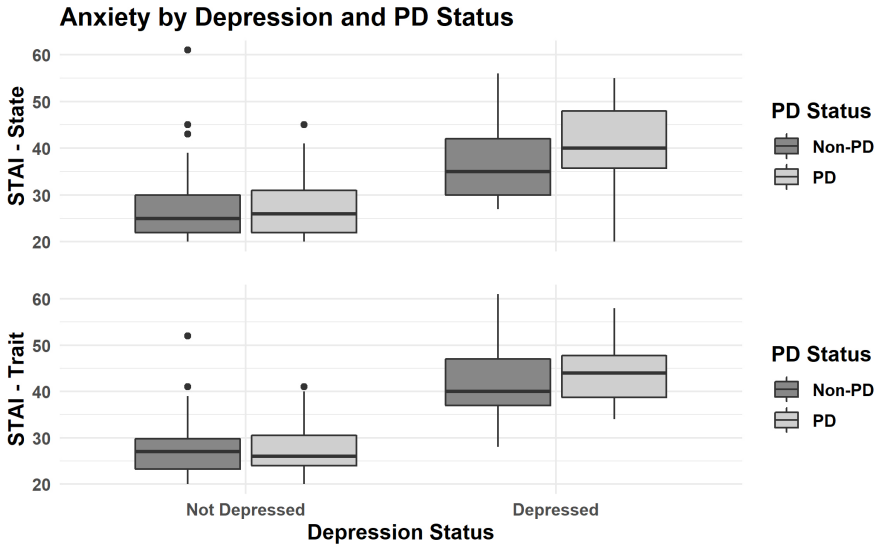

Figure 1. State and trait anxiety by depression and PD status. Participants were grouped by PD status (PD or Non-PD Comparison) and depression status, where depression was defined as total Geriatric Depression Screen ≥ 10. Only those with a depression score were included. Between groups, differences are statistically significant ($P < 0.001$). PD: Parkinson's disease.

not been validated in this population. Another approach with an instrument validated in PwP may be needed to discern differences in state (or situational) and trait (or personality-based) anxiety.

Although worsening motor function and depression have been statistically correlated in other studies[8], this relationship was not statistically supported here, possibly due to the small sample size or assessment of mood and motor symptoms only in the "on" phase. As differences in anxiety and depression symptoms have been documented between the "on" and "off" phases with a general increase in anxiety and depressive

symptoms with wearing off of medication and in the "off" phase[28], it may be necessary to explore this relationship with an assessment of motor and mood symptoms in both medication states. Of note, correlations between LEDD and state/trait anxiety were conducted and found to be non-significant (data not shown). Furthermore, while worsening motor symptom burden is one aspect of disease progression, MDS-UPDRS Part III alone may be insufficient to capture disease progression[29].

This study has several limitations, including a small sample size, missing data increasing the likelihood of type II error, and the cross-sectional nature of the present analysis. Due to the extensive demands and inclusion criteria of the parent study[14], the sample may overrepresent PwP with early- to middle-stage PD and fail to represent those at either end of the disease course. Furthermore, findings from this study may not generalize to PwP who lack a care partner. A larger, more diverse sample of PwP is necessary to validate the present findings and determine generalizability. Additionally, as depression and anxiety are known to change with disease progression and worsening motor symptoms[8], a longitudinal study could provide additional insights regarding relationships between these three aspects of PD and could better capture wearing-off effects known to increase symptoms of depression and anxiety[28].

CONCLUSION

This study explored depression, state anxiety, and trait anxiety in a population of people with early- to mid-stage PD currently utilizing dopaminergic therapy and non-PD comparisons. In contrast to previous findings, there were no differences in anxiety between those with PD and those without PD. There were, however, statistically significant differences in both state and trait anxiety when participants were grouped by depression and PD status. While anxiety does not appear to be correlated with motor symptoms, depression may be associated with greater motor symptom burden. The relationship between depression, anxiety, and motor symptoms remains unclear and further work is required.

DECLARATIONS

Authors' contributions

Conception of the research project: DeMarco EC, Longhurst J
Organization and execution of the research project: DeMarco EC
Design and execution of the statistical analysis: DeMarco EC
Review and critique of the statistical analysis: Longhurst J, Hinyard L
Writing of the first draft: DeMarco EC
Review and critique of the manuscript: Longhurst J, Hinyard L

Availability of data and materials

Data is available upon request from the Center for Neurodegeneration and Translational Neuroscience (https://nevadacntn.org/) via their Data Request Form. Analytic code will be made available upon request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This secondary data analysis study was considered non-human subjects research by Saint Louis University's Institutional Review Board.

Consent for publication

Not applicable.

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