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A bidirectional relationship between anxiety, depression and gastrointestinal symptoms in Parkinson's disease

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ABSTRACT

Introduction: Anxiety, depression and gastrointestinal (GI) symptoms are common non-motor symptoms in Parkinson's disease (PD). Past studies provide evidence of a disrupted microbiome-gut-brain axis in PD, which is associated with certain motor and non-motor symptoms in PD. Additionally, there is evidence of a bidirectional association between mental health and gut health among individuals with GI disorders. The current study examined the bidirectional association between GI symptoms and anxiety/depression among individuals newly diagnosed with PD.

Methods: We conducted a secondary data analysis of the Parkinson's Progression Markers Initiative. This included 487 individuals newly diagnosed with PD and followed for up to 5 years. Participants completed questionnaires of anxiety, depression and GI symptoms (Scales for Outcomes in Parkinson's Disease Autonomic; SCOPA-AUT) at each annual visit. Multilevel models examined the bidirectional-lagged relationship between GI symptoms and anxiety/depression.

Results: Models provided evidence for a bidirectional relationship between GI symptoms and anxiety/depression. Specifically, more severe GI symptoms predicted more severe anxious/depressive symptoms within the same year and at the following year. There was also evidence of the inverse directionality, meaning that more severe anxiety/depression predicted more severe GI symptoms concurrently and in the following year.

Discussion: Findings provide preliminary evidence for a cyclical relationship among gut health and mental health in PD. Future studies are needed to examine if the microbiome-gut-brain axis plays a mechanistic role.

1. Introduction

Gastrointestinal (GI) dysfunction is common in Parkinson's disease (PD). Roughly 80% of individuals with PD have GI symptoms, including constipation, bowel incontinence, and gastroparesis [1]. Frequently, GI symptoms appear years prior to motor symptoms, which has raised interest in the role of the gut-environment in the pathophysiology of PD [2]. Indeed, PD pathology (alpha-synuclein and Lewy bodies) is first detected in the GI track years prior to motor symptoms [1]. The term, gut-brain axis, refers to bidirectional communication networks involving the enteric nervous system and the central nervous system. It is hypothesized that disruption of the gut-environment contributes to the progression of a variety of motor and non-motor symptoms [3]. Indeed, GI symptoms have been shown to be predictive of cognitive impairment and decreased motivation among individuals newly diagnosed with PD [4,5].

Depression and anxiety are also common non-motor symptoms in PD. The annual incidence rate of depression is estimated to be 1.9 percent among individuals with PD, compared to 0.2 percent in age-matched healthy adults [6]. Anxiety may be the most prevalent psychiatric symptom in PD. Clinically significant symptoms of anxiety are estimated in 20 to 60% of individuals with PD [7–9]. Common anxiety disorders include generalized anxiety disorder, panic disorder, and social anxiety [9]. Both depression and anxiety are associated with important clinical outcomes, including quality of life, cognitive impairment and caregiver burden [10–13].

The relationship between psychiatric symptoms and disruption of the GI environment is well documented in various GI disorders. More

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severe symptoms of anxiety and depression are reported among individuals with functional dyspepsia, non-erosive reflux disease, and irritable bowel syndrome relative to healthy control individuals [14]. Further support for a relationship between psychiatric symptoms and GI disruption comes from studies showing that microbiome composition is altered among individuals with generalized anxiety disorder (GAD) or major depression disorder (MDD) [15–17]. Specifically, individuals with GAD or MDD demonstrated reduced microbial richness and biodiversity relative to healthy controls. However, conflicting findings have also been reported [18].

It is important to highlight the gut-brain axis is proposed to represent bidirectional communication [19]. Therefore, the directionality of the relationship between gut-health and mental-health may also be bidirectional. Briefly, it is hypothesized that stress is associated with altered hypothalmus-pituitary-adrenal (HPA) axis activity [19]. This may lead to subsequent gut-level changes, including an imbalance of pro- and anti-inflammatory cytokines, altered microbial composition, and structural changes in the intestinal wall. These gut-level abnormalities may then promote disruption of the blood-brain barrier, neuroinflammation and neurologic disruption that, ultimately, further increase susceptibility for anxiety and depressive disorders.

Although a potential association between the GI environment and psychiatric symptoms has been proposed, vis-à-vis the gut-brain axis [2,20], this topic has received minimal investigation among individuals with PD [5]. The current study sought to investigate the longitudinal and directional associations between depression, anxiety and GI symptoms.

2. Methods

This current study utilized data from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). The PPMI is a longitudinal multisite study of untreated and newly diagnosed PD patients. Participants were followed for up to 5 years (baseline and 5 annual follow-ups). A secondary data analysis of 487 newly diagnosed PD patients was conducted. Data was downloaded from the repository on February 2019. This secondary data analysis was approved by the institutional review board at California State University San Bernardino (IRB-201975).

2.1. Gastrointestinal and motor symptoms assessment

Gastrointestinal symptoms were assessed by the Scales for Outcomes in Parkinson's Disease Autonomic (SCOPA-AUT) questionnaire at each annual assessment. The SCOPA-AUT is a well-validated self-report consisting of 23 items assessing autonomic dysfunction in individuals with PD. The SCOPA-AUT examines the frequency of gastrointestinal, urinary, cardiovascular, thermoregulatory, and pupillomotor symptoms. Items 5–7 assessed GI symptoms (constipation, hard stools and involuntary loss of stools). These items were summed together to create a GI composite score [4].

Motor severity was assessed with the Unified Disease Rating Scale-part III (UPDRS-III). The UPDRS-III is a clinician rated measure of motor symptoms (e.g. tremor, slowness, rigidity) in PD patients. Higher scores indicate greater motor severity.

2.2. Anxiety and depression

The State-Trait Anxiety Inventory (STAI) is a self-report scale to measure the presence of current anxiety symptoms and the proneness to anxiety. For the current study, we are interested in long-standing/enduring symptoms of anxiety, as opposed to momentary/situational anxiety. Therefore, we utilized the Trait Anxiety sub-scale [11]. Responses are measured on a 4-point Likert scale and higher scores indicate more frequent anxiety.

The Geriatric Depression Scale- Short Form (GDS-SF), is a 15-item self-report measure of depression in older adults. Items assess the presence or absence of depressive symptoms within the past week. Higher scores indicate more severe depression. A 4/5 cut-off score indicative of possible depression has been recommended among individuals with PD [21].

Each questionnaire was completed at the annual visits. Both the GDS-SF and STAI are recommended by the Movement Disorder Society for use with PD samples [22,23].

2.3. Statistical analyses

Multilevel models (MLM) were used to examine the cross-lagged relationship between GI symptoms and mood symptoms. Full-information, maximum-likelihood parameter estimation was used to account for missing data.

First, we examined if current and lagged GI symptoms predicted mood symptoms. Dependent variables included depression, and trait anxiety. Separate models were conducted for each dependent variable. Independent variables included age, gender, education, motor severity (UPDRS-III), occasion (e.g. baseline, 1st annual follow-up … 5th annual follow-up), current GI symptoms, and lagged GI symptoms (i.e., GI symptoms at the previous year). Current and lagged GI symptoms were entered simultaneously to examine if the lagged variable uniquely predicted the dependent variable (i.e. does change in GI symptoms from the previous year predict current mood symptoms).

Additional MLM analyses were computed to examine the alternative directionality (i.e. do past and current mood symptoms predict GI symptoms). GI symptoms were entered as the dependent variable in all analyses. Depression and trait anxiety were entered as independent variables in separate models. Both current mood symptoms, and lagged mood symptoms were entered into models. Additional predictors included age, education, gender, occasion and motor severity.

3. Results

Demographic and clinical characteristics are displayed in Table 1.

3.1. Current and lagged GI symptoms predict anxiety and depression

MLM analyses examined the longitudinal relationship between anxiety and GI symptoms (Table 2). Results revealed that anxiety was predicted by both current GI symptoms and GI symptoms in the previous year. Specifically, more severe GI symptoms were associated with more

Table 1
Demographic and Clinical Characteristics at Baseline Standard deviations are listed in parentheses. IQR = Inter-Quartile Range; UPDRS = Unified Parkinson's Disease Rating Scale-part III; GI = Gastrointestinal; STAI = State-Trait Anxiety Inventory; GDS-SF = Geriatric Depression Scale-Short Form *Measured as the sum of items 5–7 from the Scales for Outcomes in Parkinson's Disease Autonomic; **Clinical depression based on the recommended 4/5 cut-off for individuals with Parkinson's disease [21].

(N = 487)	Mean (SD)/ Percent	Median	IQR
Age	61.1 (9.7)	62	54–68
% Caucasian	94.9%	–	–
% Male	65.1%	–	–
Years Education	15.5 (3.1)	16	14–18
UPDRS-III	20.1 (9.2)	19	14–25
% Hoehn-Yahr Stage 1	45.6%		
% Hoehn-Yahr Stage 2	53.8%		
% Hoehn-Yahr Stage 3	0.6		
Levodopa Equivalency Dose	270.2 (213)		180–456
GI Symptoms*	1.2 (1.4)	1	0–2
STAI-Trait	32.7 (9.5)	31	26–37
GDS-SF	2.5 (2.6)	2	1–3
% Clinically Depressed at Baseline Visit**	16.0%	–	–
% Clinically Depressed at any Visit**	35.9%	–	–

Table 2
MLM: GI Symptoms Predict Anxiety.

	Anxiety	
	B	*p*
Gender	0.072	0.421
Age	−0.107	**0.016**
Education	−0.155	**0.003**
Occasion	−0.022	0.272
Motor Severity	0.136	**<0.001**
Current GI Symptoms	0.103	**0.002**
Lagged GI Symptoms	0.069	**0.035**
Model Fit		
*Δ −2LL	132.3	**<0.001**
*Δ AIC	110.3	**<0.001**
*Δ BIC	50.4	**<0.001**
Between-Person Pseudo r^2	0.171	
Within-Person Pseudo r^2	0.253	

Significant p values depicted in bold. GI = gastrointestinal. LL = Log Likelihood; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion. Gender was coded as: 0 = male, 1 = female. *Change in model indices relative to a null model with no predictors.

Table 3
MLM: GI Symptoms Predict Depression.

	GI Symptoms	
	B	*p*
Gender	−0.008	0.929
Age	<0.001	0.991
Education	−0.175	**0.001**
Occasion	−0.004	0.877
Motor Severity	0.153	**<0.001**
Current GI Symptoms	0.141	**<0.001**
Lagged GI Symptoms	0.074	**0.049**
Model Fit		
*Δ −2LL	140.3	**<0.001**
*Δ AIC	118.3	**<0.001**
*Δ BIC	58.6	**<0.001**
Between-Person Pseudo r^2	0.173	
Within-Person Pseudo r^2	0.248	

Significant p values depicted in bold. GI = gastrointestinal. LL = Log Likelihood; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion. Gender was coded as: 0 = male, 1 = female. *Change in model indices relative to a null model with no predictors.

severe anxiety at the same occasion (Fig. 1), and more severe GI symptoms predicted more severe anxiety at the subsequent year (Supplemental Fig. 1). More severe anxiety was also predicted by younger age, fewer years of education, and more severe motor symptoms.

Similar analyses examined the relationship between depression and GI symptoms (Table 3). Similar to the results above, more severe GI symptoms were associated with more severe depression at the same occasion (Fig. 2), and more severe GI symptoms predicted more severe depression at the subsequent year (Supplemental Fig. 2). Depression was also predicted by fewer years of education, and more severe motor symptoms.

3.2. Current and lagged anxiety and depression predict GI symptoms

Relative to the above findings, additional analyses examined the inverse relationship: are GI symptoms predicted by current and past depression/anxiety?

The severity of GI symptoms was significantly predicted by both current (standardized $\beta = 0.096$; $p < 0.001$) and lagged symptoms of anxiety ($\beta = 0.083$; $p < 0.001$). More severe symptoms of anxiety predicted more severe GI symptoms at the same occasion and in the following year. More severe GI symptoms were also significantly predicted by older age, male gender, more severe motor symptoms and occasion (i.e. GI symptoms become more frequent over time; Supplemental Table 1).

With regards to depression, severity of GI symptoms was predicted by both current ($\beta = 0.086$; $p < 0.001$) and lagged symptoms of depression ($\beta = 0.075$; $p < 0.001$). Specifically, depression predicted more severe GI symptoms at the same occasion and in the following year. GI symptoms were also predicted by older age, male gender, more severe motor symptoms and occasion (i.e. GI symptoms become more frequent over time; Supplemental Table 2).

4. Discussion

Findings revealed evidence of a bidirectional longitudinal

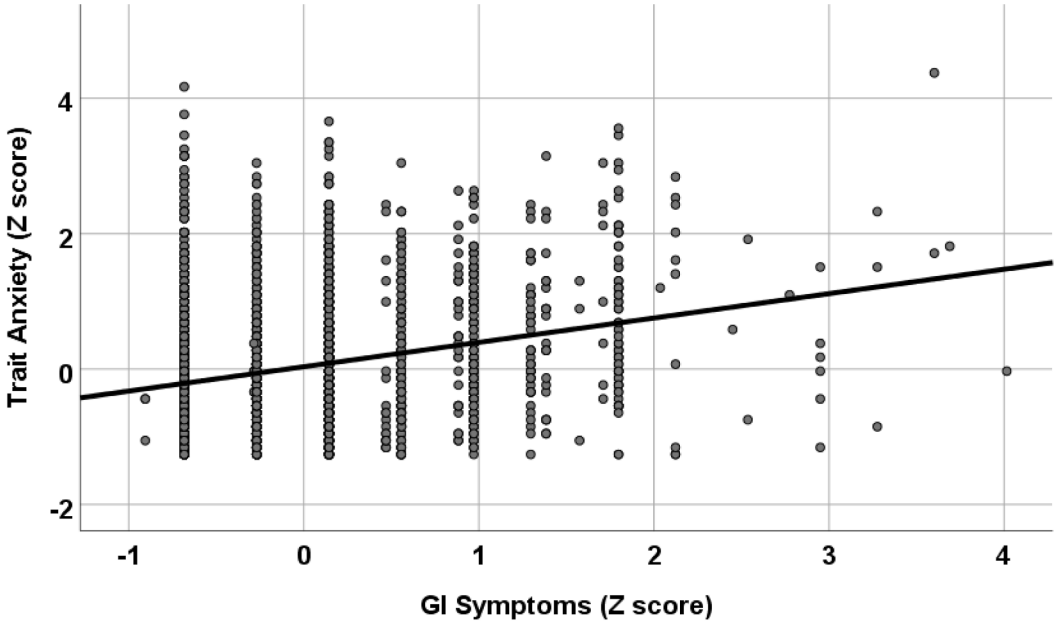

Fig. 1. Association between GI Symptoms and Anxiety. Trait anxiety represents estimated values from the full model. GI = gastrointestinal.

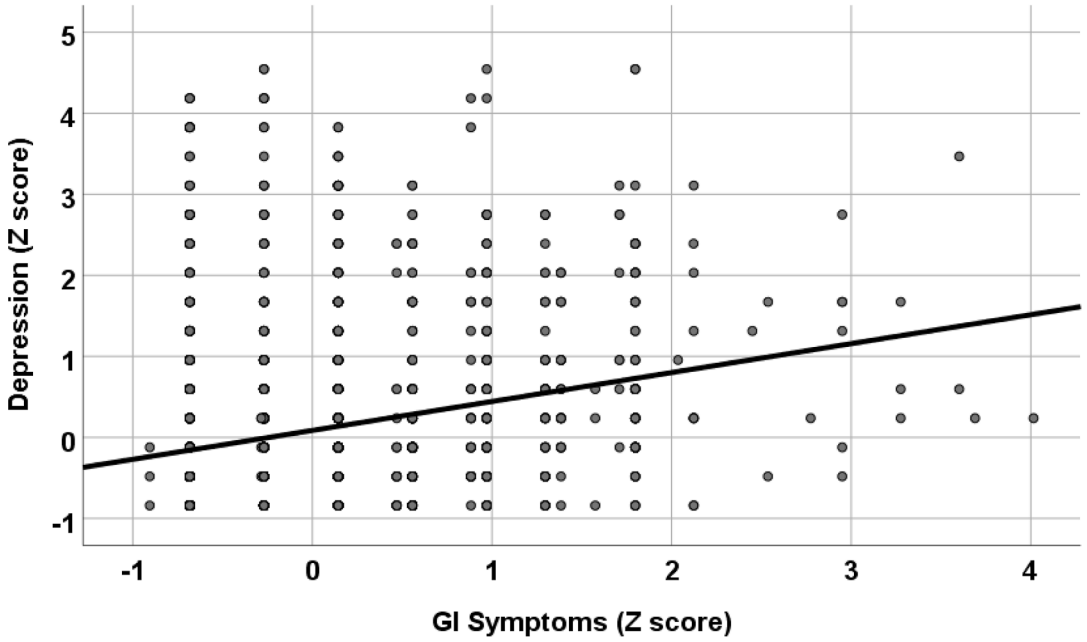

Fig. 2. Association between GI Symptoms and Depression. Depression represents estimated values from the full model. GI = gastrointestinal.

relationship between GI symptoms and mood symptoms (anxiety and depression) among individuals with PD. This suggests a possible cyclical relationship, where GI symptoms increase an individual's risk for worsening mood symptoms, which subsequently increase their risk for worsening GI symptoms.

A cyclical/bidirectional relationship between gut disruptions and psychiatric symptoms is supported in studies of GI disorders. A 12-year prospective study found evidence of a bidirectional relationship among incident functional GI disorders (e.g. irritable bowel syndrome and functional dyspepsia) and incident depression/anxiety [24]. Specifically, individuals reporting more severe anxiety were at increased risk for developing a functional GI disorder within 12 years. Additionally, individuals with functional GI disorders reported more severe anxiety and depression at the 12-year follow-up, relative to controls without a functional GI disorder.

The current findings are consistent with burgeoning research suggesting that GI symptoms may be risk factors other non-motor symptoms in early stages of PD. Our group previously demonstrated the presence of constipation was a risk factor for future cognitive decline among participants newly diagnosed with PD who were followed for five years [4]. Findings from the PRIAMO study, revealed that prodromal constipation was predictive of subjective reports of cognitive complaints and apathy among 385 PD patients who were followed for two years [5]. Unlike the current study, the Picillo et al. study did not find a significant association between prodromal constipation and depression. Discrepant findings may be due to differences in study duration (5 years vs. 2 years) or different measures of constipation/GI symptoms and depression.

Although the current study was unable to investigate underlying biological mechanisms, we hypothesize the bidirectional relationship between GI symptoms and mood symptoms is mediated by bidirectional communication along the microbiome-gut-brain axis. Emotional and physiological stress is known to alter microbiome composition and immune health [25]. Recently, there is increased interest in the alternative directionality- will changes in the gut-microbiome lead to changes within the CNS and, ultimately, changes in clinical/mental health outcomes? The overwhelming majority of the work has been conducted in animal models, but there is preliminary evidence that alteration of the microbiome can lead to improvement in depression and anxiety in humans [26]. A small trial of 22 healthy volunteers revealed that consumption of a psychobiotic (*Bifidobacterium longum* 1714 strain) resulted in reduced anxiety and cortisol, relative to a placebo group, when exposed to a socially stressful evaluation [27]. However, other groups have failed to replicate positive outcomes regarding this psychobiotic [28]. A separate study sought to alter microbiome composition via fecal microbiota transplantation [29]. 30 individuals with irritable bowel syndrome received fecal microbiota transplants and completed brief measures of anxiety and depression at 1-month and 3-months post-transplant. Although, there was no control group, individuals demonstrated decreases in both anxiety and depression at the 1-month and 3-month follow-up, and post-transplant changes in microbiome composition were detected in alpha diversity metrics and relative abundance.

To date, we are unaware of studies examining the association between anxiety, depression and measures of dysbiosis among individuals with PD. However, depression and anxiety are associated with both serum and cerebrospinal fluid markers of inflammation among individuals with PD [30,31]. Similar inflammatory markers (e.g. TNF-alpha, IL-gamma) were recently shown to be correlated with the relative abundance of *Bacteriodes* and *Verrucomicrobia* [32]. This provides support for our hypothesis that gut-dysbiosis is associated with an altered neuroinflammatory response that increases susceptibility to various clinical features, including depression and anxiety. Indeed, evidence is mounting that gut-dysbiosis is associated with a wide-range of symptoms in PD, including motor symptom severity, REM behavior sleep disorder and cognitive impairment [4,33–35]. However, findings of the association between non-motor symptoms, inflammation and dysbiosis have been correlational, and caution against causal assumptions are appropriate.

Limitations in the current study include the sample being comprised of newly diagnosed PD patients. While, this provides a unique opportunity to study early stages of the disease, findings may not generalize to the entire PD population. Similarly, the PPMI sample generally reported minimal to mild symptoms of depression and anxiety; however, 35.9% of the sample (n = 192) reported elevated symptoms of depression on at least one occasion during the 5-year study period. Future studies would benefit by examining the relationship between depression, anxiety and GI symptoms in clinically depressed/anxious PD patients. Depression and anxiety among individuals with PD may be influenced by various complications experienced by individuals with PD, including pain. Although we attempted to statistically control for differences in motor severity, other complications may influence the current findings.

Similarly, although the use of probiotics and antipsychotics are low among the PPMI cohort (2–3% of sample), iatrogenic effects may influence findings [36]. We hypothesized that change in bowel habits reflected by the GI symptom score represent a surrogate measure of gut-dysbiosis (indeed past evidence supports this; [37]), however direct measures of gut-dysbiosis were not collected as part of the larger PPMI study. Future studies would benefit from direct measurement of microbiome composition and function.

Overall, our findings provide evidence that GI symptoms and anxiety/depression are bidirectional risks factors among individuals with PD. Further, knowledge of mechanisms underlying the association between gut/immune health and mental health may potentially play an important role in detecting and treating mental health disorders in PD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2021.100104.

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