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Gastrointestinal symptoms are predictive of trajectories of cognitive functioning in de novo Parkinson's disease

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Abstract

Introduction—Non-motor symptoms such as cognitive and gastrointestinal (GI) symptoms are common in Parkinson's disease (PD). In PD, GI-symptoms often present prior to motor symptoms. It is hypothesized that GI-symptoms reflect disruptions of the microbiome-gut-brain axis, which leads to altered immune functioning, chronic neuroinflammation, and subsequent neurodegeneration. Initial evidence links gut-dysbiosis to PD pathology and motor symptom severity. The present study examines the longitudinal relationship between severity of GI-symptoms and cognitive impairment in newly diagnosed PD patients.

Methods—A secondary data analysis of the Parkinson's Progression Markers Initiative (PPMI) included 423 newly diagnosed PD patients who were followed for up to 5 years. Participants underwent neuropsychological tests of processing speed, attention, visuospatial functioning, verbal learning and verbal delayed recall. Participant were classified as cognitive intact, mild cognitive impairment or Parkinson's disease dementia. Frequency of GI-symptoms were assessed with the Scales for Outcomes in Parkinson's Disease Autonomic (SCOPA-AUT). Multilevel models (MLM) examined the longitudinal relationship between GI symptoms and cognitive impairment.

Results—All cognitive outcomes were predicted by the main effect of GI symptoms, or the GI-symptom X Occasion interaction term. Specifically, more severe GI-symptoms were predictive of a less favorable trajectory of performance on tests of letter fluency, visuospatial, learning and memory. Cognitive performance was uniquely associated with GI-symptoms and unrelated to non-GI autonomic symptoms.

Conclusions—The presence of GI symptoms may serve as an early marker of cognitive impairment in PD. Future studies should examine specific mechanisms underlying the relationship between gut-dysbiosis and cognitive impairment.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.01.009.

Keywords

Parkinson’s disease; Mild cognitive impairment; Dementia; Gastrointestinal system; Microbiome

1. Introduction

Parkinson’s disease is a neurodegenerative disorder that is primarily characterized by a variety of motor and non-motor symptoms. Non-motor symptoms may include gastrointestinal (GI) symptoms and cognitive impairment.

Examples of cognitive symptoms include increased forgetfulness, bradyphrenia (slowed processing), decreased ability to multitask, and difficulties with working memory. Cognitive impairments are particularly insidious, as 80% of patients will meet criteria for Parkinson’s disease dementia (PDD) within 15–20 years [1]. However, there is considerable variability in the onset of cognitive impairment, with some individuals meeting criteria for PDD within 5 years, whereas other remain cognitively intact after 15 to 20 years [1]. Furthermore, the pattern of cognitive impairment in PD can be heterogeneous. A large cohort study found a “posterior-cortical” pattern of cognitive deficits (i.e., pentagon copying test) was predictive of PDD [2]. Other studies report a “frontal-executive” pattern of cognitive impairment was predictive of PDD [3,4]. Yet another study reported a mixed pattern of cognitive impairment (episodic memory, mental flexibility, semantic fluency and visuospatial functioning) was predictive of PDD [5]. These variable findings may be consistent with the hypothesis that multiple mechanisms contribute to cognitive impairment in PD; including but not limited to striatal dopamine loss, cholinergic disruption, comorbid Alzheimer’s or vascular pathology and neuroinflammation [6–8].

GI symptoms such as bowel incontinence, gastroparesis and constipation have received increased interest over the last decade as they can precede the development of motor symptoms by many years [9,10]. Interestingly, aggregates of alpha synuclein can be detected in the GI tract years before the onset of motor symptoms [9]. It is hypothesized that alpha synuclein deposits initially develop in the enteric nervous system (ENS) and are transmitted via the vagus nerve to the substantia nigra and other areas of the brain [10]. GI involvement in PD may further contribute to disease progression and motor symptom development through alteration of the microbiome-gut-brain axis, a system of bidirectional interactions among gut bacteria, the ENS and the brain/central nervous system (CNS) [11,12]. Communication among the elements of this system is mediated by a combination of vagal nerve signaling, release of neuroactive products from gut bacteria or enteroendocrine cells into the circulation, and modulation of neuroimmune responses. Each of these mechanisms has the potential to accelerate disease development and induce motor and non-motor symptoms, in particular by promoting neuroinflammation and consequent neurodegeneration [13].

Preliminary animal studies support the hypothesis that the gut microbiome plays a direct role in the pathogenesis of PD [9,11]. Among transgenic animals overexpressing alpha synuclein, more severe motor deficits, greater microglia activation and alpha synuclein inclusions were present if the animal had a complex microbiota composition as opposed to animals without

bacteria (i.e. those treated with antibiotics or germ free; GF) [14]. Furthermore, restoration of bacteria in GF mice or administration of bacterial products (short chain fatty acids) resulted in increased motor symptoms, with greater severity in mice receiving PD patient microbiota compared to healthy control microbiota. Recent human studies have shown that PD patients have altered microbiota composition relative to non-PD controls and that gut-microbial composition is associated with altered dopamine regulation and more severe motor symptoms [11,15,16].

Non-motor symptoms, including cognitive impairment, may also be related to disruption of the microbiome-gut-brain axis [12]. Animal studies have shown that GF mice demonstrate deficits in working memory and object recognition tasks relative to mice with normal gut composition [17,18]. Modulation of the microbiome with a prebiotic human milk oligosaccharide improved memory and learning in rodent models in a manner dependent on the vagus nerve [19]. Probiotic strains can also improve memory and learning in animal models and protect against adverse cognitive effects of a Western diet [20,21]. Additionally, mice infected with an enteric pathogen then exposed to acute stress developed memory dysfunction [17]. Interestingly, cognitive performance returned to pre-infection levels following treatment with probiotics and restoration of the gut-microbiota environment. These findings suggest that a disrupted gut-microbial environment in conjunction with elevated stress hormones may create an imbalance of pro-inflammatory vs. anti-inflammatory cytokines that induces potentially reversible cognitive impairments.

There are limited studies examining the relationship between microbiota and cognitive function in human adults. One study examined the relationship between gut microbiota, Trail Making Test (TMT) performance, and microstructural integrity indexed from R2* (an imaging technique sensitive to iron deposition) among 20 obese participants and 19 non-obese controls [22]. TMT performance was related to the abundance of specific bacterial taxa (*Actinobacteria* and *Prevotella*), which are associated with chronic inflammation [9]. Additionally, reduced microbiota diversity was related to greater amounts of iron deposition in the hypothalamus, hippocampus and caudate nucleus. Another study of 55 older adults with Alzheimer's disease (AD) or mild cognitive impairment (MCI) found the abundance of specific bacteria correlated with performance on the Mini Mental Status Exam [23]. Another study found that individuals with AD had decreased microbial diversity relative to cognitively intact controls and the abundance of various microbial taxa correlated with cerebrospinal fluid (CSF) markers of amyloid and tau [24].

Despite evidence for a relationship between the microbiome-gut-brain axis and PD pathophysiology, no studies to date have examined the relationship between GI symptoms and cognitive impairment in PD. We hypothesize that if GI symptoms are reflective of gut dysbiosis and disrupted microbiome-gut-brain signaling (which subsequently leads to neurologic compromise), then the presence of GI symptoms will predict future cognitive decline early in the course of PD.

2. Methods

The current study was a secondary data analysis of the Parkinson's Progression Markers Initiative (PPMI- www.ppmi-info.org/data). The PPMI is a longitudinal multi-site study of newly diagnosed, untreated Parkinson's disease patients. Further details of the study have been published [25]. The study was approved by the institutional review board at each site and participants provided written informed consent.

The current sample included 423 individuals newly diagnosed with Parkinson's disease, who underwent cognitive testing and were followed for up to 5 years (baseline, 1st, 2nd, 3rd, 4th and 5th annual follow-up).

2.1. Neurocognitive assessment

Participants completed neurocognitive tests at each annual assessment. Specifically, participants completed tests of global cognitive functioning (Montreal Cognitive Assessment), working memory (Letter-Number Sequencing), processing speed (Symbol Digit Modalities Test), language/semantic fluency (Animal Fluency), visuospatial functioning (Judgment of Line Orientation), learning/immediate verbal memory and delayed verbal recall (Hopkins Verbal Learning Test-Revised).

Cognitive status (cognitively intact, PD-MCI and PDD) was defined according to the Movement Disorder Society (MDS) criteria and consistent with past PPMI studies [26]. Participants were classified as MCI if they: 1) denied functional impairments related to cognitive symptoms, and 2) performed 1.5 SDs below the mean on at least two tests. PDD was classified if they 1) endorsed functional impairments related to cognitive symptoms and 2) performed 1.5 SDs below the mean on at least two tests.

2.2. Gastrointestinal and autonomic symptom assessment

Participants completed the Scales for Outcomes in Parkinson's Disease Autonomic (SCOPA-AUT) at each annual assessment. The SCOPA-AUT is a well-validated self-report questionnaire assessing the frequency of autonomic symptoms (gastrointestinal, urinary, cardiovascular, thermoregulatory, and pupillomotor) commonly experienced by individuals with Parkinson's disease [15]. Items assessing GI symptoms (constipation, hard stools and involuntary loss of stools; items 5–7) were summed together to create a GI composite score.

2.3. Statistical analyses

Multilevel models (MLM) were used to analyze the longitudinal relationship between GI symptoms and cognitive functioning. Full-information, maximum-likelihood parameter estimation was used to account for missing data. Dependent variables were normally distributed (all skewness & kurtosis values ≤ 1).

Aim 1 examined the relationship between GI symptoms and performance on separate cognitive measures. MLM analyses were computed with the cognitive domain (working memory, processing speed, language, visuospatial, learning and delayed recall) entered as the dependent variable, for a total of six analyses. Predictors included gender, age, education, occasion (baseline, 1st, 2nd, 3rd, 4th and 5th annual follow-up), GI symptoms

(main effect), and an occasion X GI symptom interaction term. The interaction term examined whether participants with more/less frequent GI symptoms had different trajectories of cognitive functioning over time (i.e. do individuals with more frequent GI symptoms experience a faster rate of cognitive decline). Random effects were modeled for all time-varying predictors, including: occasion, GI symptoms and the occasion X GI symptoms interaction term.

In order to examine if cognitive functioning is uniquely associated with GI symptoms, independently of other autonomic symptoms; the above analyses were repeated with non-GI autonomic symptoms (sum of urinary, cardiovascular, thermoregulatory, and pupillomotor symptoms) also entered into the models.

Aim 2 examined the relationship between GI symptoms and cognitive status. MLM analyses included cognitive status (cognitively intact, PD-MCI, or PDD) as the outcome. Cognitive status was treated as an ordinal variable. Predictors included gender, age, years of education, occasion (baseline, 1st, 2nd, 3rd, 4th, or 5th annual follow-up), GI symptoms and an occasion X GI symptoms interaction term.

3. Results

Table 1 provides the sample characteristics at baseline (see Supplemental Table 1 for sample characteristics at the end of the study). Regarding attrition, neuropsychological and GI symptom data was available for: 423 individuals at baseline, 367 (86.8%) at year 1, 365 (86.2%) at year 2, 361 (85%) at year 3, 338 (79.9%) at year 4, and 298 (70.4%) at year 5 for a total of 2152 cases. Supplemental Figs. 1 and 2 depict the occurrence of GI symptoms among PD and control participants (n = 195). Due to the restricted range of GI symptoms in the control group (approximately 65–75% of control participants denied any GI symptom at each time point), control participants were excluded from further analyses.

3.1. Aim 1: relationship between GI symptoms and neurocognitive tasks

Results from the MLM analyses are depicted in Table 2 (scatter plots available in Supplemental Fig. 3). The occasion X GI symptoms interaction term significantly predicted performance on tests of processing speed, visuospatial, verbal learning and verbal delayed recall. Specifically, the interaction term revealed that participants with more severe GI symptoms experienced a more detrimental trajectory of cognitive functioning, relative to their counterparts reporting less frequent GI symptoms (Fig. 1). Additionally, the main effect of GI symptoms significantly predicted performance on tests of global cognitive functioning, working memory, processing speed, verbal learning and delayed recall; meaning that across the entire study duration, more frequent GI symptoms were associated with worse cognitive performance.

In order to examine if cognitive functioning is uniquely related to GI symptoms, the above analyses were repeated with non-GI symptoms also entered into the model (Table 3). Results revealed that participants with more severe GI symptoms experience a more detrimental trajectory of cognitive functioning. The main effect of GI symptoms significantly predicted tests of global cognitive functioning, working memory, processing speed, verbal learning

and delayed recall. Neither the main effect of non-GI symptoms, nor the occasion X non-GI interaction term significantly predicted performance in any cognitive measure.

3.2. Aim 2: relationship between GI symptoms and cognitive status

Aim 2 examined if GI symptoms were risk factors for PD-MCI or PDD over the 5-year period (Table 4). Results from the MLM analysis revealed that more frequent GI symptoms were associated with a greater occurrence of PD-MCI and PDD (Fig. 2). A greater occurrence of PD-MCI and PDD was also associated with male gender, older age, fewer years of education and a main effect of occasion. The main effect of occasion suggests the occurrence of PD-MCI and PDD was more common at later assessments.

4. Discussion

Findings from the current study provide evidence for a relationship between gut-health and cognitive functioning among individuals with PD. Specifically, more frequent GI-symptoms were predictive of worse performance across all cognitive domains and were risk factors for PD-MCI or PDD. Furthermore, cognitive functioning did not have a significant relationship with non-GI autonomic symptoms, suggesting that GI-symptoms are uniquely related to cognitive decline.

Regarding possible mechanisms underlying the relationship between cognitive functioning and GI-symptoms, we hypothesize that GI-symptoms reflect longstanding disruption of gut microbiota [11]. Unfortunately, direct measure of microbiota composition are not available in the current study; however, GI-symptoms may be a surrogate marker of microbiota dysbiosis [9,11]. Microbiota dysbiosis may subsequently lead to increased neuroinflammation and degeneration of neural systems important for cognitive functioning. We are unaware of studies examining the relationship between gut-microbial composition and cognition in PD. However, there has been limited human research among other populations. One study showed the abundance of bacterial taxa *Actinobacteria* and *Prevotella* were associated with performance on the TMT among a sample of individuals with obesity [22]. Although this study was limited to only a single measure of cognitive functioning, microbiota composition was also associated with a neuroimaging marker of iron deposition in the hypothalamus, hippocampus and caudate nucleus. Among 23 individuals with Alzheimer's disease (AD) and mild cognitive impairment (MCI), scores on the Mini-Mental Status Exam correlated with the abundance of *Faecalibacterium* [23]. In the same study, the abundance of *Faecalibacterium* also correlated with the pro-inflammatory marker serum neopterin.

PD is associated with an altered gut microbial composition relative to non-PD older adults which has been demonstrated to exacerbate alpha synuclein-mediated motor deficits [14,16]. Specifically, increases in abundance of *Lactobacillus, Bifidobacterium* and *Akkermansia*, along with decreases in *Prevotella, Faecalibacterium and Blautia*, have been reported in PD patients relative to healthy controls [11]. These microbial shifts may contribute to intestinal inflammation as evidenced by increased expression of pro-inflammatory cytokines including tumor necrosis factor-α, interferon gamma, interleukin-6 and interleukin-1β in the gut of PD patients [27]. Furthermore, CSF markers of these same pro-inflammatory cytokines are

altered in patients with PD-MCI or PDD relative to cognitively intact PD patients, supporting a link between neuroinflammation (possibly exacerbated by altered microbiome-gutbrain signals) and cognitive decline [28,29].

A recent PPMI study of newly diagnosed PD patients showed that GI symptoms are associated with striatal dopamine availability [15]. Additionally, striatal dopamine availability in the putamen and caudate were significantly associated with the presence of GI symptoms only, and not cardiovascular symptoms, urinary symptoms or motor symptoms. These findings raise the possibility that disruption of the GI system leads to disruption of frontal-striatal systems important for cognitive functioning. However, it is important to consider the inverse directionality or, perhaps more likely, the possibility of a bidirectional relationship between the enteric and central nervous system [11,12].

Altered production of amyloid and tau may be a separate mechanism underlying the relationship between GI symptoms and cognitive impairment in PD. A study of 25 individuals with AD and 25 cognitively intact controls revealed reduced gut microbiota diversity among the AD group [24]. Furthermore, genera that were more abundant in the AD group were generally correlated with CSF markers of phosphorylated tau (p-tau) and p-tau/$A\beta_{42}$. Future research examining the role of gut health on amyloid and tau production may have implications for individuals with PD, as up to 50% of individuals with PDD may have comorbid AD pathology [30].

It is possible that the relationship between gut symptoms and cognition is confounded by motor severity. This could be particularly relevant to processing speed, as slowed reaction time could be due to motor slowing rather than cognitive slowing. We believe that the relationship between gut symptoms and cognition is not fully confounded by motor symptoms due to two reasons. First, gut symptoms were significantly predictive of cognitive tests (letter number sequencing, animal fluency, judgement of line orientation, HVLT-R) that do not require motor responses and/or are untimed. Second, we conducted a supplemental analysis that examined the longitudinal relationship between gut symptoms and motor symptoms (Supplemental Table 2). Longitudinal changes in motor severity were not predicted by changes in gut-symptoms. This reduces the likelihood that longitudinal declines in motor functioning fully mediate/confound the longitudinal relationship between cognitive functioning and GI symptoms.

Regarding limitations, the current study was a secondary data analysis of the PPMI cohort. Analyses were limited in the number of cognitive tests/domains available and particularly limited in tests of executive functioning. Although, PPMI administered tests that are sometimes subsumed under the domain executive functioning (working memory, animal fluency), future research may benefit from a more comprehensive assessment of executive functioning. The PPMI is a study of newly diagnosed PD patients, therefore findings may not generalize to the entire PD populations. However, it has been hypothesized that disruption of the gut environment occurs early, even years before motor symptoms. Therefore, studies spanning the course of prodromal, early and late stages of PD are needed. Additionally, the sample was relatively intact in terms of cognitive functioning. This may reflect that participants are newly diagnosed. Additionally, the occurrence of cognitive

impairment may be artificially low due to learning effects (i.e. being administered the same tests multiple times). With this being said, the trajectory of cognitive functioning depicted in the Figures may be artificially favorable (i.e. stable cognitive abilities or possible improvements) due to learning effects. Non-PD controls were not included in analyses due to restricted range of the primary predictor (GI symptoms) and we were unable to examine if the relationship between GI symptoms is unique to PD patients. Although both GI symptoms and cognitive impairment are more common/severe in PD, the relationship between gut/immune health and cognitive health may be relevant to both PD and healthy aging populations.

On average, individuals with PD reported a single GI symptom at the time of diagnosis and two GI symptoms at the five year follow. Findings from the current study may not generalize to PD samples with more or less GI symptoms. Lastly, the current relied on a surrogate marker of the gut-brain-microbiome environment. Therefore, studies utilizing more direct measures of gut microbial composition and inflammatory markers are needed to provide support for the study hypothesis.

Overall, this study provides evidence of a relationship between GI disruption and cognitive functioning in early stages of PD. Understanding the contribution of gut/immune health to cognitive impairment is important because it may lead to better prognostic prediction and yield new targets for intervention (i.e. fecal-microbiota transplants, dietary alterations or administration of prebiotics/probiotics).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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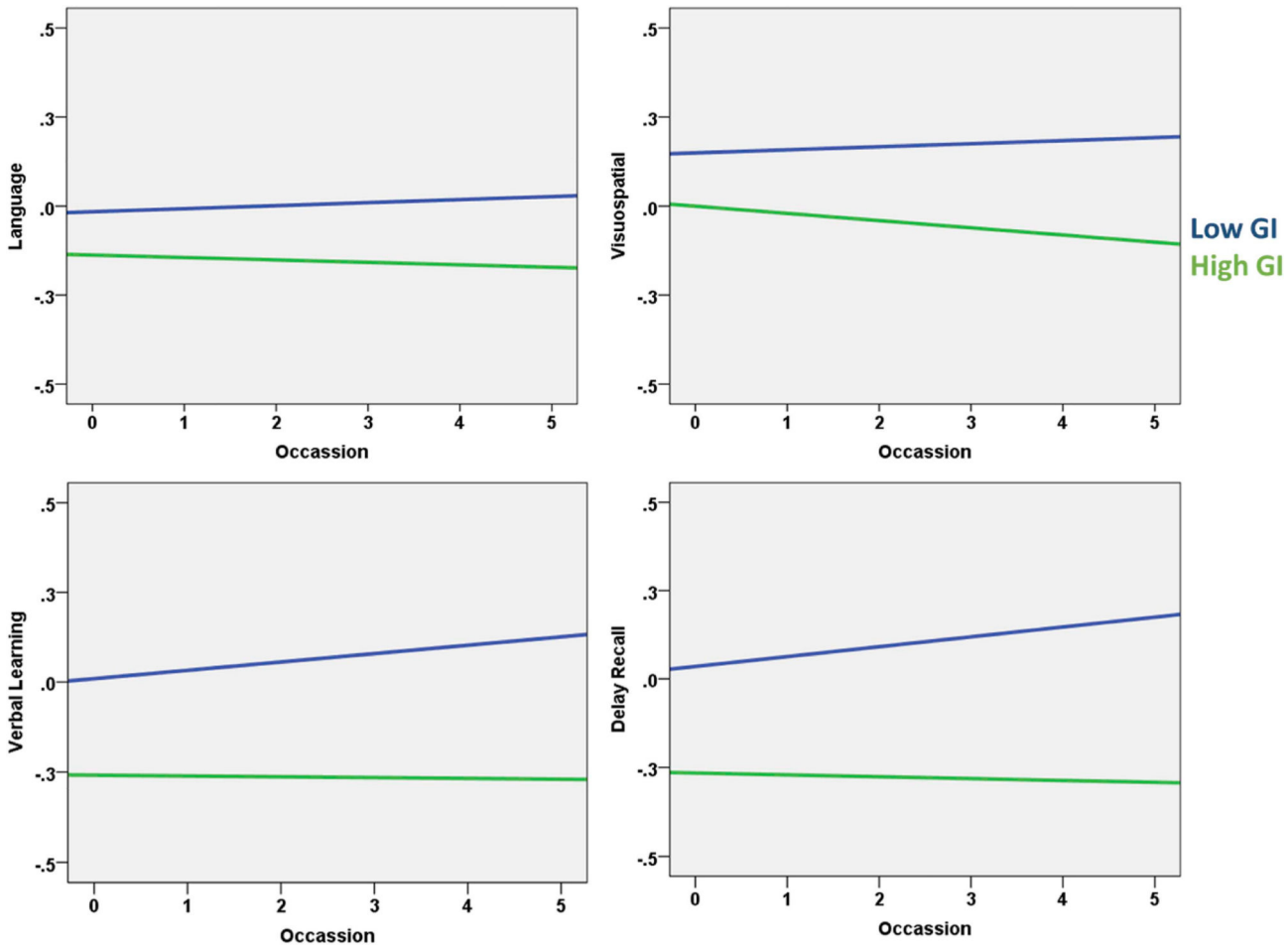

Fig. 1.

Depiction of GI Symptom X Occasion Interaction. Note: Low GI vs. High GI was based on median split. Use of this dichotomous variable is for depiction purposes only, and analyses in Aim 1 quantified GI Symptoms as a continuous variable.

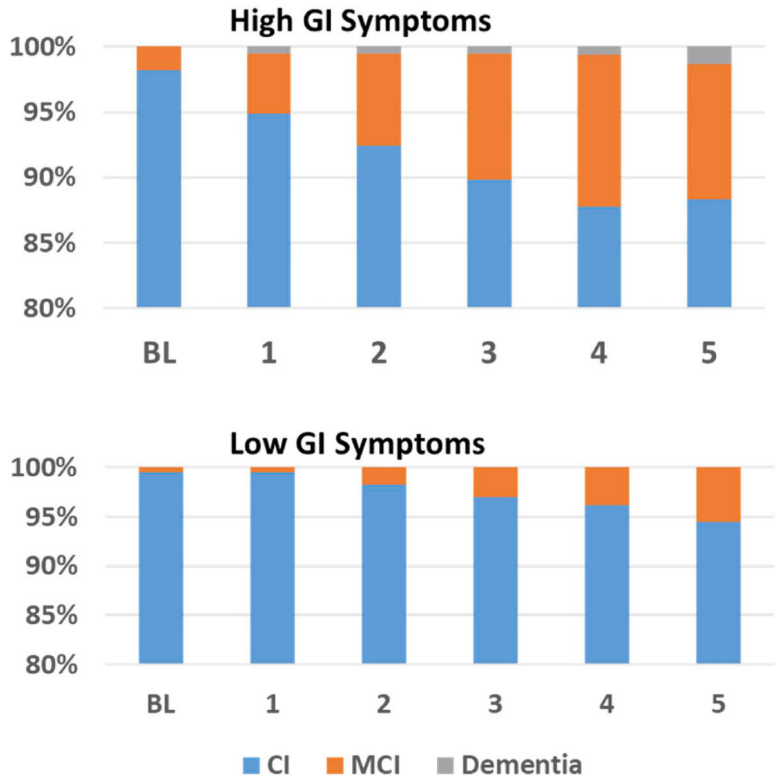

Fig. 2.

Depiction of GI Symptom Frequency and Cognitive Status. Note: Low GI vs. High GI was based on median split. Use of this dichotomous variable is for depiction purposes only, and analyses in Aim 1 quantified GI Symptoms as a continuous variable. CI = Cognitively Intact; MCI = Mild Cognitive Impairment; PDD = Parkinson's Disease Dementia.

Table 1

Baseline Sample Characteristics (N=423)

	Mean (SD)/Percent	Median	IQR
Age	61.2 (9.7)	62	54–68
Education	15.5 (3.0)	16	14–18
% Male	65.5%	–	–
% Caucasian	94.8%	–	–
UPDRS Motor	20.9 (8.9)	20	14–26
% Hoehn-Yahr Stage 1	43.7%	–	–
% Hoehn-Yahr Stage 2	55.8%	–	–
% Hoehn-Yahr Stage 3	0.5%	–	–
SCOPA-AUT	9.30 (6.9)	8	5–12
% Reporting Constipation	32.5%	–	–
% Reporting Hard Stools	52.4%	–	–
% Reporting Loss of Control of Stools	4.7%	–	–
% Reporting Any GI Symptom *	55.1%	–	–
% Taking Probiotic **	3.1%	–	–
HVLT Learning Trials	−0.17 (.95)	0.3	−0.7 – 0.6
HVLT Delay	−0.20 (.95)	0.1	−0.5 – 0.5
JOLO	0.09 (.94)	0.2	−0.2 – 0.6
LNS	0.02 (.88)	0.2	−0.5 – 0.6
Animal Fluency	−0.11 (.90)	−0.2	−0.8 – 0.4
SDMT	−0.19 (.83)	0.0	−0.6 – 0.5
% Cognitively Intact	96.0%	–	–
% MCI	4.0%	–	–

Standard deviations are listed in parentheses. Normative z-scores are presented for cognitive tests. IQR = Inter-Quartile Range; UPDRS = Unified Parkinson's Disease Rating Scale- part III; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease Autonomic; GI = Gastrointestinal; HVLT = Hopkins Verbal Learning Test; JOLO = Judgement of Line Orientation; SDMT = Symbol Digit Modalities Test; IIV = intra-individual variability; MCI = mild cognitive impairment.

*Percent of participants reporting Constipation, Hard Stools or Loss of Stools (Items 5–7) at a frequency of "Sometimes", "Regular", or "Often."

**Percent reporting taking a probiotic any time during the study duration.

Table 2

MLM: GI Symptoms Predict Cognitive Functioning

	Global Cognition		Working Memory		Processing Speed		Language		Visuospatial		Verbal Learning		Verbal Delayed Recall	
	B	***p***	***B***	***p***	***B***	***p***	***B***	***p***	***B***	***p***	***B***	***p***	***B***	***p***
Gender	0.26	**0.001**	0.10	0.188	0.31	**<0.001**	0.17	**0.032**	−0.44	**<0.001**	0.43	**<0.001**	0.41	**<0.001**
Age	−0.34	**<0.001**	−0.37	**<0.001**	−0.42	**<0.001**	−0.25	**<0.001**	−0.19	**<0.001**	−0.37	**<0.001**	−0.35	**<0.001**
Education	0.16	**<0.001**	0.19	**<0.001**	0.20	**<0.001**	0.19	**<0.001**	0.22	**<0.001**	0.20	**<0.001**	0.22	**<0.001**
Occasion	−0.06	**0.001**	−0.09	**<0.001**	−0.11	**<0.001**	−0.03	0.126	−0.05	**0.001**	−0.03	0.086	−0.04	**0.041**
GI Symptoms	−0.07	**0.014**	−0.15	**0.020**	−0.19	**0.001**	−0.09	0.161	−0.08	0.186	−0.17	**0.005**	−0.23	**<0.001**
Occasion X GI	−0.05	0.063	−0.01	0.621	−0.10	**<0.001**	−0.05	0.076	−0.07	**0.013**	−0.09	**0.001**	−0.10	**<0.001**
Model Fit Indices														
*Δ −2LL	316	**<0.001**	190	**<0.001**	337	**<0.001**	99	**<0.001**	107	**<0.001**	191	**<0.001**	189	**<0.001**
*Δ AIC	298	**<0.001**	172	**<0.001**	319	**<0.001**	81	**<0.001**	89	**<0.001**	173	**<0.001**	163	**<0.001**
*Δ BIC	247	**<0.001**	121	**<0.001**	268	**<0.001**	30	**<0.001**	38	**<0.001**	122	**<0.001**	89	**<0.001**
Between-Person Pseudo R2	0.242		0.519		0.724		0.450		0.036		0.306		0.320	
Within-Person Pseudo R2	0.269		0.132		0.228		0.096		0.041		0.120		0.106	

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 Cognitive Functioning Independent of Non-GI Autonomic Symptoms

	Global Cognition		Working Memory		Processing Speed		Language		Visualspatial		Verbal Learning		Verbal Delayed Recall	
	B	***p***	***B***	***p***	***B***	***p***	***B***	***p***	***B***	***p***	***B***	***p***	***B***	***p***
Gender	0.26	**0.001**	0.10	0.187	0.31	**<0.001**	0.16	**0.036**	−0.44	**<0.001**	0.43	**<0.001**	0.41	**<0.001**
Age	−0.33	**<0.001**	−0.37	**<0.001**	−0.42	**<0.001**	−0.25	**<0.001**	−0.19	**<0.001**	−0.37	**<0.001**	−0.35	**<0.001**
Education	0.16	**0.001**	0.19	**<0.001**	0.19	**<0.001**	0.19	**<0.001**	0.21	**<0.001**	0.20	**<0.001**	0.22	**<0.001**
Occasion	−0.06	**0.002**	−0.09	**<0.001**	−0.11	**0.036**	−0.02	0.232	−0.05	**0.002**	−0.03	0.053	−0.04	**0.036**
Non-GI Symptoms	−0.03	0.632	0.01	0.988	−0.18	0.352	−0.05	0.615	−0.08	0.470	−0.04	0.687	−0.03	0.785
Occasion X Non-GI	−0.05	0.177	−0.02	0.545	−0.04	0.440	0.07	0.095	0.03	0.501	−0.06	0.142	−0.02	0.626
GI Symptoms	−0.08	**0.018**	−0.15	**0.033**	−0.14	**0.034**	−0.10	0.153	−0.05	0.445	−0.16	**0.016**	−0.22	**0.002**
Occasion X GI	−0.04	0.203	−0.01	−0.8859	−0.09	0.478	−0.07	**0.026**	−0.08	**0.012**	−0.07	**0.021**	−0.10	**0.002**
Model Fit Indices														
*Δ −2LL	321	**<0.001**	190	**<0.001**	307	**<0.001**	102	**<0.001**	437	**<0.001**	193	**<0.001**	189	**<0.001**
*Δ AIC	295	**<0.001**	164	**<0.001**	281	**<0.001**	76	**<0.001**	411	**<0.001**	167	**<0.001**	163	**<0.001**
*Δ BIC	222	**<0.001**	91	**<0.001**	207	**<0.001**	2.3	0.999	337	**<0.001**	93	**<0.001**	89	**<0.001**
Between-Person Pseudo R2	0.266		0.519		0.713		0.450		<0.001		0.307		0.319	
Within-Person Pseudo R2	0.270		0.132		0.196		0.096		0.281		0.119		0.106	

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 4

MLM: GI Symptoms Predict Cognitive Status

	Cognitive Status	
	B	***p***
Gender	0.26	**0.001**
Age	−0.33	**<0.001**
Education	0.16	**0.001**
Occasion	−0.06	**0.002**
GI Symptoms	−0.08	**0.018**
Occasion X GI	−0.04	0.203

Gender was coded as: 0 = male, 1 = female.

Significant p values depicted in bold. GI = gastrointestinal