Published in final edited form as:

Parkinsonism Relat Disord. 2018 October ; 55: 8–14. doi:10.1016/j.parkreldis.2018.08.010.

Dopamine transporter availability reflects gastrointestinal dysautonomia in early Parkinson disease

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Abstract

Background: Constipation is a prodromal feature of Parkinson's disease (PD) and the gastrointestinal (GI) tract is implicated in the pathogenesis of PD. However, no studies have

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Author Roles

1) Analysis: A. Hypothesis, B. Design, C. Execution, D. Review and Critique;

2) Manuscript: A. Writing of the first draft, B. Review and Critique.

J.T.H.: 1A, 1B, 1C; 2A

K.P.: 1D, 2B

K.A.M.: 1D, 2B

Z.M.: 1D, 2B

A.B.: 1D, 2B

T.M.D.: 1D, 2B

A.P.: 1D, 2B

L.S.R.: 1D, 2B

G.M.P.: 1D, 2B

Financial Disclosure/Conflict of Interest Statement: The authors report no conflicts of interest, financial disclosures, or funding pertinent to this manuscript.

demonstrated ante-mortem relationships between nigrostriatal dysfunction and GI dysautonomia in PD.

Methods: The Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT) assesses dysautonomia in the multi-center Parkinson's Progression Marker Initiative (PPMI). We used linear mixed-effects models and reliable change indices (RCIs) to examine longitudinal associations between dysautonomia and dopamine transporter (DAT) striatal binding ratios (SBRs) measured by single-photon emission computerized tomography in PPMI participants over four years (n=397 at baseline).

Results: Adjusted mixed-models of longitudinal data showed that constipation—but not orthostatic hypotension or urinary dysfunction—was associated with reduced SBR in both caudate ($P<0.001$) and putamen ($P=0.040$). In both regions, SBR reductions between baseline and 4-year follow-up were significant and measurable ($P < 0.0001$), with larger decline and variances in the caudate nucleus. Four-year change in caudate—but not putaminal—SBR was significantly associated with RCI-indicated progression of GI dysautonomia ($P=0.031$), but not other types of dysautonomia. These associations remained after adjusting for the use of medications or supplements to control constipation. Consistent with prior PPMI reports, motor impairment progression was not associated with SBR reduction.

Conclusions: GI dysautonomia correlates with reductions in DAT availability; constipation is most closely associated with caudate-DAT reductions. Worsening GI-dysautonomia and reduced bowel movements may accompany advancing nigral degeneration or changes in nigrostriatal dopamine function.

Keywords

Parkinson disease; Dopamine transporter; constipation; autonomic; PPMI

Introduction

The motoric signs of Parkinson's disease (PD) commence within the context of many non-motor signs and symptoms (NMSS) that implicate multiple brain regions and several neurotransmitter systems [1]. Depression, anxiety, dysautonomia, anosmia, cognitive impairment, and sleep disturbances are several of many such phenomena and greatly impact quality of life [2]. NMSS were recently emphasized in Movement Disorder Society (MDS) diagnostic criteria for PD as well as prodromal PD, which is emphasized as being “a true stage of PD” [3]. For example, over half of patients with idiopathic REM behavior disorder (iRBD) will develop a synucleinopathy such as PD within a decade [4]. While it is widely accepted that the motor signs of PD are caused primarily by the loss of dopaminergic cells in the substantia nigra, the neural etiologies of prodromal non-motor phenomena in PD likely also involve other neurotransmitter deficits or tissue pathologies [1].

Chronic constipation, although a less specific prodromal symptom than iRBD, is an established risk factor for developing PD [5]. Post-mortem evaluations of GI tissue in PD patients demonstrate phosphorylated α -synuclein in the myenteric and submucosal nerve plexuses in the stomach, small intestine, large colon, esophagus, and submandibular gland [6,7]. Increasing evidence suggests that retrograde transmission of misfolded alpha-

synuclein along vagal efferents targeting the enteric nervous system (ENS) could comprise a disease mechanism in PD [8,9]. This would allow for synucleinopathy to seed the dorsal motor nucleus of the vagus (DMV) in the medulla and template its endogenous alpha-synuclein—allowing spread to higher brain centers, an idea initially articulated by Braak [10]. However, it has been shown that medullary pathology does not necessarily precede nigral cell loss in all PD cases [11].

Reciprocally, there is evidence that nigral pathology may exacerbate GI dysfunction. 6-hydroxydopamine-lesioned rats develop a GI phenotype featuring constipation as well as delayed gastric emptying [12], another feature of both early and advanced PD [7]. More recently, nigrovagal projections were identified in rodents, through which dopaminergic neurons in the substantia nigra activate D1 dopamine receptors on DMV neurons to regulate gastric motility [13]. Notably, neural activity in this pathway was disrupted prior to the onset of motor impairment in paraquat-treated rodents [13]. This suggests that loss of dopamine neurons might increase GI dysautonomia in PD. Importantly, this idea is distinct from the notion that local ENS or brainstem synucleinopathy effects PD-related constipation and implicates worsening GI dysfunction as a marker of dopamine depletion or nigral dysfunction. In support of this idea, nigral cell loss has been shown to correlate with reduced late-life bowel movement frequency [14]. Additionally, as α -synuclein staining has been reported in larger samples of PD patients and controls, the sensitivity of enteric α -synuclein as a PD biomarker has fallen, supporting the idea that synucleinopathies may not uniformly seed the GI tract or reliably explain constipation in these patients [15,16].

Inspired by this rapidly evolving body of literature, we hypothesized that nigral pathology is associated with GI dysfunction in early PD. We tested this hypothesis using DAT transporter neuroimaging and clinical data for 397 individuals with early PD enrolled in the Parkinson's Progression Markers Initiative (PPMI).

Methods

Study participants

Data for the present investigation were recorded through the PPMI, a multi-center observational investigation of early PD (<http://www.ppmi-info.org/data>). Documentation regarding the organization, aims, and methodology of the PPMI has been published [17]. Participating sites have obtained approval from their respective Institutional Review Boards, and written informed consent is obtained from all participants. For up-to-date information on the study, visit www.ppmi-info.org.

Major inclusion criteria for the PD cohort of the PPMI included: Bradykinesia and at least one other cardinal parkinsonian motor sign or isolated unilateral resting tremor; Hoehn & Yahr stage below three; A dopamine transporter (DAT) single-photon emission computerized tomography (SPECT) scan consistent with PD per PPMI definitions (see below); No clinical expectation to initiate PD medication until at least 6 months after baseline evaluation; Male or female aged 30 years or older at time of PD diagnosis. Major exclusion criteria included: atypical PD syndromes; use of any PD medication; a clinical

diagnosis of dementia as determined by investigator; recent (< 6 months) use of medications that may interfere with DAT-SPECT imaging.

PPMI data were downloaded for use in the present investigation on October 7, 2017. 435 PD cohort participants were identified with baseline DAT-SPECT imaging. Twenty-six of these participants lacked baseline evaluation of autonomic function through the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT) [18], reducing sample size at baseline to 409. Subsequent merging of these participant data with other metrics of interest reduced the number of participants with complete data at baseline to 397. Because the PPMI longitudinal investigation is still in progress, not all participants have full 4-year follow-up data available. Sample size at 1-year, 2-year, and 4-year follow-up was 315, 307, and 219 respectively. DAT-SPECT imaging was not performed at the 3-year evaluation.

Clinical assessments

Autonomic dysfunction was measured using a validated scale for PD, the SCOPA-AUT [18]. We analyzed the gastrointestinal (seven items), cardiovascular (three items) and urinary (six items) sections separately, as well as the total SCOPA-AUT score. This includes an additional four items measuring thermoregulation and one item for pupillomotor function; sex-specific items were not included. Each item is scored on a four-point Likert scale. Medication(s) used to reduce constipation, urinary dysfunction, or orthostatic hypotension are recorded.

Motor impairment was measured using the MDS-UPDRS motor (part III) examination. Participants in the PPMI study receive this assessment both “on” and “off” medication, if applicable. In our analyses, we used only the “off” evaluation measures to minimize medication confounds when relating DAT-SPECT results to motor impairment. Other assessments used in the present study include the Montreal Cognitive Assessment (MoCA), Geriatric Depression Scale, State-Trait Anxiety Inventory, REM behavior disorder (RBD) screening questionnaire, Epworth Sleepiness Scale and the University of Pennsylvania Smell Identification test (UPSIT; baseline only). Per PPMI protocol, results of the UPSIT are compared with a normative database to determine normosmia, hyposmia, or anosmia.

DAT-SPECT imaging with DaTscan™

SPECT images of DAT radioligand binding were acquired in accordance with PPMI neuroimaging protocols and sent to the IND for uniform and standardized results generation. After pre-processing, regions of interest [17] were placed on the left and right caudate and putamen. Occipital cortex was used as the reference region. Striatal binding ratios (SBRs) were calculated as target ROI binding intensities normalized by the reference region. Visual interpretation by IND experts confirmed or rejected the presence of abnormal DAT binding.

Statistical analyses

Baseline measures for PPMI participants is presented descriptively in terms of mean and standard deviation or number and percentage as appropriate. In analyses testing significant differences between baseline and 4-year follow-up data, count data variables were analyzed

using the McNemar Chi-squared test with continuity correction. Wilcoxon Signed-rank test with continuity correction was used for continuous/ordinal variables.

Reliable change index (RCI) was also calculated for participants to assess the presence of a clinically meaningful worsening of symptoms between baseline and 4-year evaluation. This method accounts for test-retest reliability of the SCOPA-AUT and MDS-UPDRS motor exam, for which we used previously published test-retest reliability metrics [18,19]. RCI was calculated for each clinical scale in accordance with convention, with an RCI ≥ 1.96 indicating a clinically significant ($p < 0.05$) symptom progression [20].

Longitudinal data were analyzed using linear mixed-effects (LME) models, which allowed for repeated-measures data analysis accounting for intra-subject correlations. Because baseline SBRs were assumed to vary based on an underlying probability distribution, patient identifier was treated as a random effect. All other independent variables and covariates described in the manuscript were modeled as fixed effects. Preliminary analysis of model residuals suggested a non-normal residual distribution; therefore, we repeated analysis using a robust variant of LME regression to scale the weights of observations with large residual values [21]. All LME regression results reported in this manuscript are derived from robust regressions. For most analyses presented, caudate and putamen DaTscan uptakes (SBRs) were modeled as the dependent variables in parallel, separate models. P-values and 95% confidence intervals were derived from regression estimates and standard errors as previously described [22].

Results

Striatal SBR values are longitudinally associated with dysautonomia in PD

The baseline clinical characteristics PPMI enrollees are presented in Table 1. SBR was averaged across hemispheres and was on average $1.98 (\pm \text{SD: } 0.54)$ in the caudate nucleus and 0.82 ± 0.30 in the putamen. We analyzed the relationship between measures of dysautonomia and SBRs in the caudate and putamen longitudinally. β -coefficients, corresponding 95% confidence intervals, and p -values for our linear mixed-effects models are provided in Table 2. Because the gastrointestinal section (SCOPA-GI) of the SCOPA-AUT assesses both dysphagia (3 items) and constipation (4 items), which are likely pathophysiologically distinct problems with separate time courses [7,23,24], we separated these two groups of questions for LME analyses.

SCOPA-GI scores were significantly associated with reduced SBRs in both caudate ($p = 0.001$) and putamen ($p = 0.007$) in our adjusted models, but not the cardiovascular (SCOPA-CV) or urinary (SCOPA-U) scores. We separately tested the constipation and dysphagia components of the SCOPA-GI section and found constipation—but not dysphagia—to be significantly associated with reduced caudate SBR ($p < 0.001$). Worse dysphagia ($p = 0.048$) and constipation ($p = 0.040$) were both associated with lower putamen SBR. Neither the total SCOPA-AUT score average nor the SCOPA-CV or SCOPA-U sections were significantly associated with reduced putamen SBR. Consistent with prior analyses integrating PPMI DaTscan standard metric data [25], motor impairment scores were not associated with either caudate or putamen SBR. We also performed a secondary set of

analyses in which SBRs were not averaged across hemispheres but rather assigned as being contralateral or ipsilateral to the participant's predominantly affected side (Supplemental table S1). Nine patients that reported symmetric onset were excluded from this analysis. Of the remainder, 218 (56.2%) reported right-sided symptom predominance. This differentiation did not notably affect the patterns of significance observed for caudate SBR, i.e. both the contralateral and ipsilateral caudate SBRs were associated with constipation and SCOPA-GI scores ($p < 0.01$ for all comparisons). However, putaminal SBR associations with constipation became only trending (i.e., $0.05 < p < 0.10$).

Decreasing SBRs and worsening constipation are measurable throughout early PD

We next investigated the relationship between dysautonomia and SBRs over time using data from 180 participants with complete data at all four timepoints (Table 3). Prior research has shown that SCOPA-GI, SCOPA-CV, and SCOPA-U scores increase with PD severity [18]; we confirmed that these metrics similarly increased with disease duration throughout 4-year PPMI follow-up ($p < 0.0001$ for all subscale score increases). The possibility of a putaminal SBR floor-effect was recently identified as a concern for DaTscan studies [26]; therefore, we also described the extent to which SBRs changed throughout the PPMI follow-up (Table 3). We found that caudate SBR variances and the reduction in mean SBR values over time were larger than those in the putamen, consistent with the possibility of a floor-effect. However, both putaminal and caudate SBRs could be demonstrated to measurably and significantly decrease throughout follow-up ($p < 0.0001$ for both).

Reduced caudate SBR is selectively associated with gastrointestinal autonomic dysfunction worsening

To consider the clinical meaningfulness of four-year changes in dysautonomia in the context of scale reliability, we investigated effect sizes relative to test-retest variability. We calculated a reliable change index (RCI) [20] for each patient using baseline and 4-year follow-up data ($n=219$) for each SCOPA-AUT domain and the MDS-UPDRS motor exam. Because most participants (204/219, 93.2%) initiated PD medications between baseline and follow-up, we adjusted for levodopa-equivalent daily dose (LEDD, average 555 ± 408 mg/day) in addition to baseline scale score and disease duration. The number of participants with significant RCIs is provided for each domain or scale in Table 4. Logistic regression indicated that reductions in caudate—but not putaminal—SBR was associated with a reliable change in SCOPA-GI ($p = 0.031$) and total SCOPA-AUT ($p = 0.049$). Neither caudate nor putaminal SBR changes were associated with reliable change in MDS-UPDRS III, SCOPA-CV, or SCOPA-U scores. As was performed for LME regressions, we also tested whether contralateral or ipsilateral SBRs were more strongly associated with SCOPA-AUT or motor impairment RCI ($n=213$). Full results are provided in supplemental table S2. Briefly, SCOPA-GI change was more strongly associated with contralateral caudate SBR (OR = 3.7; 95% CI: 1.5–9.7; $p = 0.006$) than with ipsilateral caudate SBR (OR = 2.7; 95% CI: 1.1–7.0; $p = 0.041$). Conversely, while SCOPA-AUT change was associated with ipsilateral caudate SBR (OR = 3.7; 1.4–10.6; 95% CI: $p = 0.011$), it was not significantly associated with contralateral caudate SBR (OR = 1.8; 95% CI: 0.7–4.6; $p = 0.218$).

Sixty-one participants (28%) reported using at least one medication to control constipation within the past month at their four-year evaluation. Caudate SBR change remained significantly associated with SCOPA-GI RCI when adjusting for this factor along with putaminal SBR change, disease duration, and baseline SCOPA-GI score (OR = 3.7; 95% CI: 1.3–10.7; $p = 0.015$). A list of constipation medications used is provided in supplemental information (Supplemental Table S3); polyethylene glycol and stool softeners comprised the most common choices.

Because a prior publication [27] using PPMI data cross-sectionally did not identify a relationship between DaTscan measures and MDS-UPDRS-assessed constipation at baseline, we next examined whether the association between SBRs and constipation may increase throughout the first four years after PD diagnosis ($n=219$). Consistent with this prior publication, we found non-significant correlations between caudate SBR and MDS-UPDRS constipation item score ($r = -0.12$; $p = 0.080$). Similarly, the baseline SCOPA-GI constipation section did not significantly correlate with caudate SBR values ($r = -0.13$; $p = 0.053$). The trending associations at baseline also suggest the possibility of a type II error in the prior work. Additionally, during 4-year follow-up, SCOPA-GI and constipation sub-scale variance increased from 4.4 to 6.6 and 2.2 to 3.7 respectively (see also Table 3). This, combined with the added statistical power enabled by repeated-measures analysis, suggests that the conflicting finding can also be explained simply by our utilization of longitudinal data.

Discussion

In this report, we provide evidence supporting the hypothesis that constipation is associated with decreasing striatal DAT availability throughout early PD. Our data suggest a stronger relationship between GI dysautonomia and caudate SBR than putaminal SBR; however, it is unclear to what extent this is due to the limitations conferred by the relatively smaller changes in and variance of putaminal SBRs. Additionally, our data demonstrate a pronounced association between worsening GI dysautonomia and the severity of SBR decline during four years of early PD. This is consistent with the evolving idea that enteric α -synuclein itself may not always be present in PD patients with constipation [15,16], as well as animal data suggesting that local synucleinopathy is not sufficient for sustained colonic dysmotility [28]. Such findings imply a possible role for neural dysfunction in the etiology of constipation.

Other types of dysautonomia, such as orthostatic hypotension and loss of urinary control, were not associated with decreasing SBR in our analysis. We emphasize this to show that gastric dysautonomia appears to be specifically associated with decreasing DAT availability, suggesting that the association is not merely a proxy for overall brainstem, ENS, or peripheral autonomic pathology. Additionally, it is important to contextualize this distinction in light of other current research that has described neural correlates of autonomic dysfunction in PD using other imaging modalities. Altered diffusion tensor imaging (DTI) patterns in the medulla oblongata were recently shown to correlate well with abnormal respiratory frequency and heart rate variability during REM sleep[29]. An fMRI study demonstrated that striato-thalamo-hypothalamic functional connectivity changes are

associated with total SCOPA-AUT scores [30], although this study did not examine specific sub-scales. Finally, it was recently shown that beta oscillations in the globus pallidus correlate with urinary voiding and that changes in these oscillations relate to the severity of incontinence and urinary frequency [31]. The diversity of networks and areas associated with specific autonomic functions across studies suggests that a comprehensive understanding of PD-related dysautonomia requires examination of dysfunction in multiple neural circuits and end-organ pathologies.

Progressive constipation was detailed in the original description of PD [32], but contemporaneously it remains difficult to manage clinically and to understand etiologically [7]. Despite promising evidence for nigral modulation of GI motility in rodents [12,13], it is not yet established how putative neural circuits involving the substantia nigra and the ENS may be anatomically or functionally organized in humans. It has been shown in the general population that post-mortem demonstration of neuronal loss in the dorsomedial, ventromedial, and ventrolateral—but not dorsolateral—quadrants of the substantia nigra is associated with reduced late-life bowel movement frequency [14], suggesting that constipation may be caused by loss of dopamine cells across multiple nigral regions. We are not aware of existing evidence of an ante-mortem relationship between nigral cell loss and GI dysfunction in PD; however, it is difficult to determine the extent to which a dependence of GI function on dopamine cell integrity can be inferred based on our findings. For example, although we appropriately adjusted for other clinical variables, we cannot fully control for the relevance of non-dopaminergic pathologies in GI dysfunction. It is possible that progressive neurodegeneration affecting extra-nigral foci (but temporally coincident with nigral degeneration) continues to induce GI dysfunction—as well as many other non-motor phenomena—in early PD. Nonetheless, we emphasize that such processes do not exclude a role for dopaminergic modulation of gastric function, or vice versa. For example, it is not necessarily the case that constipation in the prodromal PD phase is related to nigral pathology.

As described earlier, another PPMI-based study concluded that DaTscan SBRs were not associated with constipation based on non-significant results [27]. However, this study only utilized the single MDS-UPDRS part I constipation item in its analyses and did not examine longitudinal data. We primarily used the SCOPA-AUT, which is a more comprehensive assessment of autonomic problems in PD; additionally, SCOPA-GI scores are known to increase over time with disease severity [18]. Notably, the SCOPA-AUT was the reference clinical scale used to validate MDS-UPDRS dysautonomia items [33]. Thus, we have attempted to show that the discrepant findings likely arise from the longitudinal nature of our analysis, which reveals time-varying associations. We show that the variance of scores on each SCOPA-AUT domain increases over 4-year follow-up, which likely improves the discrimination of population-level differences when using longitudinal data. It is also expected given the heterogeneity of autonomic dysfunction severity and progression in PD. Additionally, we leverage repeated-measures analyses by modeling intra-subject correlations, increasing effective statistical power and reducing the chance of a type II error. Finally, as the SCOPA-AUT is a self-administered scale, our RCI analyses adjust for the test-retest reliability of each domain (GI, CV, and urinary) using previously published

metrics [18]. The RCI results corroborate our LME findings and directly link GI dysautonomia increase with SBR reduction magnitude.

The value of using imaging to investigate striatal presynaptic dopamine function in PD is also worth examining critically. A recent meta-analysis of the topic that included 64 studies with DAT-tracer imaging [26] supported caudate—but not putaminal—SBR as a useful correlate of disease duration and Hoehn & Yahr stage; neither was associated significantly with motor UPDRS score or age. The authors noted that dramatic compensatory changes at nigro-putaminal terminals may contribute to a floor effect that limits the utility of putaminal SBR as a biomarker, particularly for motor signs. We similarly observed that SBR reduction was not associated with meaningful increases in motor impairment (measured “off” medication). Thus, while our results are concordant with current understanding of DaTscan utility, its inherent limitations preclude us from drawing definitive conclusions regarding the importance of caudate vs. putaminal dopamine function for GI autonomic function.

In conclusion, we have presented neuroimaging data to support the hypothesis that striatal dopaminergic denervation is associated with GI dysfunction in PD. While not causal evidence, this finding is important in the context of evolving literature implicating the GI tract in the pathogenesis of PD. To our knowledge, our analysis is also the first to provide ante-mortem evidence that DAT binding reduction is a relevant correlate of GI dysautonomia in PD. Further investigation of the etiological significance of nigral degeneration in GI dysfunction is required to assess the value of constipation as a prodromal PD marker, suggest treatment strategies for managing this troublesome autonomic symptom, and clarify the evolving hypothesis of PD as a spreading proteinopathy that interferes with multiple organ systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson’s Research and funding partners, including Abbvie, Allergan, Avid Radiopharmaceuticals, Biogen, Biolegend, Bristol-Myers Squibb, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche, Sanofi Genzyme, Servier, Takeda, Teva, and UCB. Golub Capital is a philanthropic funding partner.

Financial Acknowledgements and Disclosures

J.H.: Receives tuition and stipend support through the Medical Scientist Training Program at the Johns Hopkins School of Medicine (NIH/NIGMS 5 T32 GM007309).

K.P.: No disclosures to report.

K.M.: Dr. Mills receives salary support through the NIH NCATS (KL2TR001077, PI Daniel Ford). He has received funding from Northwestern University.

Z.M.: Dr. Mari is supported by the National Parkinson’s foundation with a Center of Excellence Grant and is supported by NIH/NINDS U01 NS082133.

A.B.: No disclosures to report

T.M.D.: Dr. Dawson acknowledges the Adrienne Helis Malvin and Diana Henry Helis Medical Research Foundations and their research partnership with The Johns Hopkins Hospital, The Johns Hopkins University School of Medicine, and the Foundation's Parkinson's Disease Programs. He is supported by NIH/NINDS P50NS038377, NIH/NINDS U01NS082133, NIH/NINDS R37NS067525, NIH/NIDA P50 DA00266 and the JPB Foundation. Dr. Dawson is the Leonard and Madlyn Abramson Professor in Neurodegenerative Diseases, chair of the Dystonia Prize committee of the Bachmann Strauss Dystonia and Parkinson's Disease Foundation and the Michael J. Fox Foundation. He is on the Board of Directors of the Bachmann Strauss Dystonia and Parkinson's Disease Foundation and on the Scientific Advisory Board of CurePSP and a member of American Gene Technologies International Inc. advisory board. The terms of this arrangement are being managed by The Johns Hopkins University in accordance with its conflict of interest policies. Dr. Dawson is a founder of Valted, LLC and holds an ownership equity interest in the company. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies.

A.P.: Dr. Pantelyat is supported for this project by NIH/NINDS U01 NS082133 and P50 NS38377.

L.R.: Dr. Rosenthal has received support from NIH/NINDS P50NS038377, Marilyn and Edward Macklin Foundation, and the Michael J. Fox Foundation. She also received an honorarium from the Edmond J. Safra Foundation and Functional Neuromodulation.

G.P.: Dr. Pontone receives funding through the NIH/NIA as part of a K23 award (AG044441-01A1). He is also co-sponsored by Acadia Pharmaceuticals, Inc., for writing a book on psychosis in Parkinson's that was co-written by the National Parkinson's Foundation.

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Table 1:

Baseline clinical characteristics of PD participants in the PPMI

	Mean $\pm$ SD	Range
Age, years	63.8 $\pm$ 9.9	31 – 89
Disease duration, months	5.5 $\pm$ 6.4	0 – 35.0
MDS-UPDRS motor exam	21.0 $\pm$ 8.9	4 – 58
MoCA score[*]	26.4 $\pm$ 3.3	2 – 31
Education, years	15.6 $\pm$ 3.0	5 – 26
Dominantly affected side		
Right	218 (54.9%)	
Left	170 (42.8%)	
Symmetric	9 (2.3%)	
Striatal binding ratio (SBR)		
Right caudate	1.98 $\pm$ 0.59	0.42 – 3.98
Left caudate	1.98 $\pm$ 0.59	0.35 – 3.69
Right putamen	0.84 $\pm$ 0.36	0.14 – 2.53
Left putamen	0.81 $\pm$ 0.35	0.12 – 2.60
Caudate, averaged	1.98 $\pm$ 0.54	0.39 – 3.71
Putamen, averaged ^{**}	0.82 $\pm$ 0.30	0.24 – 2.17
Caudate, contralateral	1.83 $\pm$ 0.55	0.35 – 3.70
Caudate, ipsilateral	2.15 $\pm$ 0.58	0.42 – 3.98
Putamen, contralateral	0.69 $\pm$ 0.27	0.12 – 2.16
Putamen, ipsilateral	0.96 $\pm$ 0.38	0.22 – 2.60
SCOPA-AUT		
Total	8.3 $\pm$ 5.3	0 – 28
Gastrointestinal	2.1 $\pm$ 2.1	0 – 11
Cardiovascular	0.5 $\pm$ 0.7	0 – 6
Urinary	4.1 $\pm$ 2.8	0 – 17
Epworth sleepiness scale	5.8 $\pm$ 3.5	0 – 20
Geriatric depression scale	5.3 $\pm$ 1.5	1 – 11
State-Trait Anxiety Inventory		
State	47.2 $\pm$ 5.3	20 – 68
Trait	46.0 $\pm$ 4.2	33 – 58
Hoehn & Yahr, n (%)		
1	170 (42.8%)	
2	225 (56.7%)	
3	2 (0.5%)	
Male sex, n (%)	260 (65.5%)	
Normalized olfactory index, n (%)		
Anosmia	142 (35.8%)	
Hyposmia	218 (54.9%)	
Normosmia	37 (9.3%)	

RBD screening questionnaire	Mean $\pm$ SD	Range
Probable RBD, n (%)	100 (25.2%)	
Score	4.1 $\pm$ 2.7 (range: 0 – 12)	

* Missing MoCA results for 1 PD participant (n = 396). SD = standard deviation.

** The 9 participants reporting symmetric onset were excluded from lateralization analyses (n=388).

Table 2:

Adjusted linear mixed-effect models of DaTscan uptake and measures of dysautonomia

Independent variable	Caudate SBR		Putamen SBR	
	β -coefficient (95% CI)	<i>p</i>	β -coefficient (95% CI)	<i>p</i>
<u>SCOPA-AUT measures</u>				
Total	−0.05 (−0.11 to 0.0001)	0.051	−0.01 (−0.04 to 0.02)	0.462
SCOPA-GI	−0.07 (−0.11 to −0.03)	0.001	−0.03 (−0.06 to −0.01)	0.007
SCOPA-CV	0.003 (−0.04 to 0.05)	0.890	−0.003 (−0.03 to 0.02)	0.814
SCOPA-U	−0.02 (−0.05 to 0.01)	0.213	0.006 (−0.01 to 0.02)	0.520
Dysphagia	−0.01 (−0.05 to 0.02)	0.462	−0.02 (−0.04 to −0.0001)	0.048
Constipation	−0.06 (−0.09 to −0.03)	***	−0.02 (−0.04 to −0.001)	0.040
MDS-UPDRS part III (total motor impairment score)	−0.001 (−0.002 to 0.001)	0.353	−0.0004 (−0.001 to 0.0003)	0.266

Multivariable linear mixed-effects (LME) models included patient ID as a random-intercept variable to adjust for intra-subject correlations over multiple visits. SCOPA-AUT measures are the mean score for items in the indicated scale or sub-scale. Each SCOPA-AUT model included the following covariables: baseline SBR, MDS-UPDRS III (motor impairment score), RBD screening questionnaire score, age, disease duration, Epworth Sleepiness Scale score, Geriatric Depression Scale score, State-Trait Anxiety Inventory score (state), and Smell Identification Test score. The same covariables were used in the MDS-UPDRS III model, except that it was also adjusted by total SCOPA-AUT score.

 $p < 0.001$.

Table 3:

Striatal SBRs reduce and dysautonomia worsens over 4-year follow-up

	Baseline	1-year	2-year	4-year	Baseline vs. 4-year	
	Mean (SD) or n (%)				X ² or U	P
<u>DaTscan</u>						
Caudate SBR	1.98 (0.54)	1.80 (0.49)	1.69 (0.54)	1.50 (0.53)	480	****
Putamen SBR	0.81 (0.28)	0.71 (0.25)	0.66 (0.25)	0.55 (0.22)	374	****
<u>SCOPA-AUT</u>						
Constipation score	1.2 (1.5)	1.7 (1.7)	1.8 (1.8)	2.1 (1.9)	6180	****
Constipation score 1 (n, %)	104 (58%)	120 (67%)	130 (72%)	138 (77%)	17.6	****
SCOPA-CV score	0.5 (0.8)	0.6 (0.9)	0.7 (1.2)	0.7 (1.0)	2146	***
SCOPA-CV score 1 (n, %)	61 (34%)	68 (38%)	75 (42%)	84 (47%)	8.8	0.003
SCOPA-U score	4.2 (2.8)	4.6 (2.8)	4.7 (2.9)	5.4 (3.3)	8099	****
SCOPA-U 1 (n, %)	170	171	173	173	0.44	0.505
MDS-UPDRS III motor exam	20.8 (8.3)	23.6 (11.8)	24.7 (12.3)	26.7 (15.3)	11480	****

Mean striatal binding ratios (SBR) and mean scores on the corresponding sections of the SCOPA-AUT or MDS-UPDRS exam are presented throughout follow-up. *P*-values for count data variables comparing baseline vs. 4-year data are derived from McNemar Chi-squared test with continuity correction. Wilcoxon Signed-rank test with continuity correction was used for continuous/ordinal variables.

 $p < 0.001$;

 $p < 0.0001$.

SCOPA-CV and SCOPA-U refer to the cardiovascular and urinary dysfunction sections of the SCOPA-AUT, respectively. Only items from the constipation component of the SCOPA-AUT gastrointestinal section were used for constipation score (4 items total).

Table 4:

Reduced caudate SBR in early PD over four years is associated with clinically significant worsening of gastrointestinal dysautonomia

Scale	Reliable change, n (%)	Caudate SBR change		Putamen SBR change	
		Odds ratio (95% CI)	<i>p</i>	Odds ratio (95% CI)	<i>p</i>
SCOPA-AUT (total)	63 (28.3)	2.95 (1.02 to 8.93)	0.049	0.94 (0.14 to 6.21)	0.947
SCOPA-GI	104 (47.5)	3.20 (1.14 to 9.51)	0.031	4.74 (0.76 to 31.82)	0.101
SCOPA-CV	70 (32.0)	1.71 (0.62 to 4.79)	0.301	1.00 (0.16 to 6.11)	0.999
SCOPA-U	38 (17.4)	2.54 (0.69 to 9.72)	0.164	0.56 (0.05 to 5.68)	0.629
MDS-UPDRS III (total)	131 (59.8)	1.45 (0.54 to 3.94)	0.466	2.10 (0.35 to 13.00)	0.419

In accordance with convention [24], reliable change was scored as a binary variable (0 or 1) based on whether reliable change index (RCI) exceeded 1.96 (indicating statistical significance at $p < 0.05$). Odds ratios and *p*-values are presented for four-year SBR changes in logistic regressions. SBR changes are expressed as absolute differences such that a positive odds ratio indicates higher odds of an RCI scored as 1. One regression model was constructed for each scale with reliable change in that scale as the dependent variable. The four independent variables shared by all models were (1) four-year change in caudate SBR; (2) four-year change in putamen SBR; (3) disease duration; (4) baseline section/scale score; (5) Levodopa-equivalent daily dose (mg/day). SCOPA-AUT subsections are indicated by the suffixes “GI” (gastrointestinal), “CV” (cardiovascular), and “U” (urinary).