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Received: 24 November 2022 | Accepted: 21 May 2023

DOI: 10.1111/ene.15890

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Development of anxiety in early Parkinson's disease: A clinical and biomarker study

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Abstract

Background: Anxiety affects approximately 40% of Parkinson's disease (PD) patients. However, little is known about its predictors and development over time.

Objective: To identify the clinical factors and biomarkers associated with development of anxiety in patients with newly diagnosed PD, and to test which risk factors predict increases in anxiety over time.

Methods: Data from the Parkinson's Progression Markers Initiative (PPMI) were utilized. The primary outcome was the State–Trait Anxiety Inventory (STAI). Covariates were demographics, motor and non-motor symptoms, cognitive functions, dopamine transporter imaging data, and cerebrospinal fluid (CSF) biomarkers. We examined the association of risk factors at baseline and over 4 years with changes in anxiety scores over time.

Results: A total of 252 patients met the inclusion criteria (mean age: 61.36 years, SD 9.53). At year 4, 42 patients had developed anxiety. Baseline predictors of increase in anxiety scores were greater autonomic dysfunction, dysexecutive function, CSF t-tau levels, excessive daytime sleepiness, and lower olfactory function scores but not motor scores. Over 4 years, change in anxiety scores correlated with deterioration in overall cognitive function, excessive daytime sleepiness, as well as depression and disability, and to a lesser degree worsening of Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor scores and caudate dopaminergic uptake changes.

Conclusions: These findings suggest that development of anxiety in PD is not primarily based on a dopaminergic deficit in the basal ganglia but related to non-dopaminergic or extrastriatal pathology. Early dysexecutive function predicts development of anxiety but increase in anxiety levels correlates most strongly with more global cognitive decline.

KEYWORDS
anxiety, biomarkers, clinical features, early stage, Parkinson's disease, prospective study

INTRODUCTION

Anxiety is one of the most prevalent and subjectively troublesome symptoms of Parkinson's disease (PD), being ranked as the second most important research priority after balance and falls in a consensus meeting commissioned by Parkinson's UK [1]. Treatment of anxiety is often challenging with no evidence-based pharmacological treatment recommendations available and understanding of

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its pathological basis still limited. Anxiety can be a feature of off-periods and can therefore improve with dopaminergic medication. It has also been reported that those with predominant anxiety are younger and more likely to have motor fluctuations [2]. It has therefore been postulated that anxiety in PD is at least partly related to mesencephalic dopaminergic loss [3]. However, dopaminergic treatment is often unhelpful in anxiety not related to off-periods. There is clinical heterogeneity, and a significant proportion of PD patients have anxiety associated with depression [4, 5]. Psychosocial factors or abnormal learning may also contribute to anxiety in patients with PD, and changes in other neurotransmitters, such as orexin-A [6] and in extrastriatal brain regions, have also been implicated [7, 8]. Furthermore, there is some evidence that anxiety in PD and non-PD populations can be associated with cognitive decline [9, 10]. In order to understand the factors predicting and accompanying the development of anxiety in patients with PD, we examined the clinical and biomarker predictors and correlates of change in anxiety scores in a cohort of patients with early PD over 4 years.

PATIENTS AND METHODS

Study design and participants

This study derived data from the Parkinson's Progression Markers Initiative (PPMI) database. The PPMI is an ongoing, observational, longitudinal study that aims to identify progression biomarkers for PD. The program started in 2010 and involved participants of six cohorts from 33 sites in the USA, Europe, Israel, and Australia. In this study, only de novo PD subjects ($n = 489$) were included. All participants were enrolled between 1 July 2010 and 31 May 2013.

We downloaded data on 25 June 2020. Only patients who did not have anxiety at baseline and had data available for 4 years of follow-up were included in this study. The inclusion criteria were age over 30 years; at least two features of resting tremor, bradykinesia, and rigidity; a PD diagnosis for 2 years or less at the time of screening; Hoehn and Yahr stage I or II; not expected to require PD medication for at least 6 months from baseline; and imaging-confirmed dopamine transporter (DAT) deficits. The exclusion criteria were taking PD medications such as levodopa or dopamine agonists at baseline or within 60 days of baseline; and taking any drugs which may affect DAT single-photon emission computed tomography (SPECT) imaging or lumbar puncture [11]. The PPMI study was approved by the institutional review board at each site, and participants provided written informed consent to participate.

Clinical and biomarker features

Investigated baseline variables included demographic features (age and gender); depression as measured by the Geriatric Depression Scale (GDS); cognitive functions overall as measured by the Montreal Cognitive Assessment (MoCA) and more specifically with the Semantic Fluency Test (SFT; total score of animal, fruit, and vegetable) for executive function and to assess semantic memory, the Letter-Number Sequencing (LNS) test for executive function and working memory, the Hopkins Verbal Learning Test (HVLT; immediate recall and delayed recall) for memory, and the 15-item Benton Judgment of Line Orientation Test (BJLOT) for visuospatial function; rapid eye movement (REM) sleep behavior disorder measured using the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ); daytime sleepiness measured using the Epworth Sleepiness Scale (ESS); impulsive-compulsive behaviors measured by the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP); autonomic function on the Scale for Outcomes in Parkinson's Disease autonomic scale (SCOPA aut); olfactory function measured by the University of Pennsylvania Smell Identification Test (UPSIT); disability of daily living as measured by the Schwab & England Activities of Daily Living Scale; and Parkinson's disease severity measured by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale Parts I, II, and III (MDS-UPDRS-I, -II, and -III). Biomarkers included were CSF α-synuclein, amyloid-beta 1–42 (Aβ1–42), total tau (t-tau), and phosphorylated tau (p-tau), and imaging data included were caudate and putaminal uptake on an iodine 123-labeled ioflupane DAT SPECT scan. An asymmetry index was calculated as: |(left side uptake − right side uptake)/mean (left side uptake + right side uptake) × 100|. Four-year follow-up data were available for all variables except CSF biomarkers.

Outcome

The main outcome measure was the total score of the State–Trait Anxiety Inventory (STAI), over a 4-year follow-up period. The STAI consists of two subscales, the State subscale and the Trait subscale, with a total score for each subscale ranging from 20 to 80. The State subscale measures the current state of anxiety whereas the Trait subscale evaluates relatively stable aspects of "anxiety proneness" [12]. The total score is a sum of the two subscores. It has been reported that the STAI had a good internal consistency among de novo PD patients [13], and a good convergent validity with other commonly used anxiety rating scales, such as the Hospital Anxiety and Depression Scale (HADS) and the Hamilton Anxiety Scale (HAM-A) [14].

Statistical analysis

Associations between baseline risk factors and change in anxiety (STAI total) scores over 4 years were first examined in univariate regression analyses. Stepwise regression with a p value of <0.2 was used to select candidate risk factors for the multivariable analyses, with a variance inflation factor to test the collinearity of covariates. Amongst collinear variables, those with a smaller effect size or those that were not significantly associated with outcome in univariate analyses were excluded. All risk factors

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were chosen a priori based on the literature and their possible relevance to development of anxiety in PD [15]. Change of anxiety score was calculated as STAI total score at year 4 minus STAI total score at baseline. We also examined the correlation of changes in STAI total scores with changes in the severity of other clinical and DAT imaging variables using linear regression. To test whether the results differ with longer follow-up time, sensitivity analyses were also conducted with participants who had data on anxiety up to year 7 ($n=178$). In addition, to further eliminate confounding bias due to medications, post hoc analyses excluding patients who took anxiolytics and antidepressants at baseline ($n=57$) were conducted.

All statistical tests were two-sided, and a p value <0.05 was considered statistically significant. Analyses were implemented in Stata version 17.0 (StataCorp).

RESULTS

Of 489 subjects with newly diagnosed PD enrolled in the PPMI study, 426 completed a STAI at baseline. We excluded 112 patients who already had anxiety defined by a cut-off of 39 on the STAI State subscore [15, 16] at baseline and 62 individuals who had no available clinical anxiety score at 4-year follow-up. Table 1 lists the characteristics of the included patients. Compared with patients who had available clinical anxiety data at 4-year follow-up ($n=252$), those who did not ($n=62$) were older (mean age 64.07 vs. 61.36 years, $p=0.025$) but there were no significant differences in terms of gender ($p=0.46$) and baseline STAI total score ($p=0.99$).

Predictors for increase in anxiety scores

At 4 years of follow-up, 42 (16.7%) patients had developed clinically relevant anxiety with STAI State scores of ≥39. At baseline, the mean score of STAI total was 56.80 (SD 10.68) (STAI State subscore: 27.86 [SD 5.54] and STAI Trait subscore: 29.95 [SD 6.13]); and after 4-year follow-up, the mean score of STAI increased to 60.79 (SD 16.49) (STAI State subscore: 30.25 [SD 8.79] and STAI Trait subscore: 31.92 [SD 8.84]). The average change in score of STAI total over 4 years was 3.94 (SD 14.44). Change in STAI total scores over 4 years correlated with baseline autonomic function (SCOPA aut), excessive daytime sleepiness (EDS), and frontal lobe/working memory function scores (LNS and SFT) as well as higher baseline age, UPSIT scores, and CSF t-tau level (Table 2). In multiple regression analyses, baseline frontal lobe/working memory function (LNS and SFT), autonomic function (SCOPA aut), and CSF α-synuclein and total tau levels were the main predictors of increase in anxiety scores over 4-year follow-up (Table 3). The sensitivity analysis with a longer follow-up period and the post hoc analyses excluding patients who initiated antidepressants and anxiolytics at baseline yielded similar results (see the results of sensitivity analysis in Tables S1–S4). However, in multivariable analyses excluding patients who took antidepressants and anxiolytics at baseline, being male and having worse motor abilities were significantly associated with increased anxiety (Table S5).

Correlates of anxiety score changes

Clinical and biomarker changes that correlated with changes in anxiety scores over 4 years were changes in depression scores (GDS), excessive daytime sleepiness (ESS), cognitive scores, including MoCA, BJLOT, HVLT delayed and immediate recall (rather than frontal executive LNS and SFT) tests, as well as disability (MDS-UPDRS-II and Schwab and England Scores) scores, and to a lesser degree motor severity (MDS-UPDRS-III) and DAT caudate uptake. CSF examination was not undertaken at the 4-year follow up (Table 4). Results from post hoc analysis did not differ from the main results substantively (Table S6).

DISCUSSION

This study found that the development of anxiety in patients with early-stage PD over 4 years is predicted primarily by the presence and severity of specific non-motor features at baseline including excessive daytime sleepiness, autonomic dysfunction, olfactory scores, and frontal dysexecutive function, and linked to higher scores of CSF t-tau at baseline. There was, however, no association of increase in anxiety score with baseline severity of motor scores or striatal dopaminergic uptake on DAT imaging. Of note, over the follow-up period change in the overall cognitive scores, including memory and visuospatial function, was more closely linked to an increase in anxiety scores than the frontal-executive dysfunction and autonomic function scores. These results are in keeping with previous reports of association of anxiety in PD with poorer set-shifting [17], attention/working memory, executive functioning, memory, and language [18] and reports of a stronger association of executive dysfunction and anxiety in those with mild cognitive impairment in PD [19]. There was also a parallel, expected association of increase in anxiety scores with GDS depression scores, with excessive daytime sleepiness, and with disability as assessed by the Schwab and England and MDS-UPDRS-II scores, and to a lesser degree with deterioration of MDS-UPDRS-III motor scores or dopaminergic uptake in the caudate.

These findings suggest that the development and increase in anxiety in early-stage PD is closely linked not only to increases in mood disturbances but also to the development of cognitive dysfunction as well as excessive daytime sleepiness. Early dysexecutive syndrome may be a harbinger of development of anxiety with an increase in anxiety closely linked to broader subsequent cognitive impairment in other domains. Baseline t-tau levels in CSF, which are known to be associated with cognitive deterioration [20], also appear to be markers of development of anxiety, whilst reduction in dopaminergic uptake in the caudate and deterioration in motor function and disability has a more limited relationship to anxiety development. Change in other non-motor features that are thought to

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TABLE 1 Baseline characteristics of included patients ($n = 252$).

Baseline characteristic	Mean (SD) or *n* (%)	Baseline characteristic	Mean (SD) or *n* (%)
Age (years)	61.36 (9.53)	Gender (male)	171 (67.86)
15-Geriatric Depression Scale (GDS)	1.63 (1.80)	Montreal Cognitive Assessment (MoCA)	27.12 (2.26)
State–Trait Anxiety Inventory total score (STAI total)	56.80 (10.68)	Benton Judgement of Line Orientation Test (BJLOT)	26.19 (3.89)
STAI-State subscore	27.86 (5.54)	Hopkins Verbal Learning Test-immediate recall (HVLT-ir)	46.65 (10.61)
STAI-Trait subscore	29.95 (6.13)	Hopkins Verbal Learning Test-delayed recall (HVLT-dr)	45.97 (10.84)
MDS-UPDRS-I	4.79 (3.62)	Letter-Numbering Sequencing (LNS)	10.77 (2.57)
MDS-UPDRS-I[a]	4.48 (3.45)	Semantic Fluency Test (SFT)	49.52 (11.43)
MDS-UPDRS-II	5.48 (4.29)	University of Pennsylvania Smell Identification Test (UPSIT)	22.54 (7.84)
MDS-UPDRS-III	19.75 (8.68)	Questionnaire for Impulsive-Compulsive disorders in PD (QUIP)	0.18 (0.69)
Schwab and England ADL scale	93.83 (5.67)	Scale for Outcomes in PD autonomic (SCOPA aut)	8.77 (5.67)
REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)	3.69 (2.54)	Epworth Sleepiness Scale (ESS)	5.58 (3.21)
Dopamine transporter (DAT)		CSF biomarker (pg/mL)	
Mean caudate uptake	1.99 (0.53)	α-synuclein	1527.43 (631.10)
Mean putamen uptake	0.81 (0.26)	Aβ1–42	926.39 (392.98)
Caudate asymmetry	−0.01 (0.23)	t-tau	168.52 (52.98)
Putamen asymmetry	0.06 (0.45)	p-tau	14.70 (4.89)

Note: MDS-UPDRS-I[a]: total score of MDS-UPDRS-I was adjusted by deleting the score of "anxious mood". Data are shown as mean (SD) or *n* (%).

Abbreviations: ADL, activities of daily living; CSF, cerebrospinal fluid; MDS-UPDRS-I, -II, -III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part I, II, III; REM, rapid eye movement; SD, standard deviation.

be less dopaminergically determined and involve extrastriatal areas, such as sleep disturbances, autonomic dysfunction, and olfactory impairment, also appear to be associated with the development of anxiety. This suggests that development of anxiety in PD is not primarily a result of dopaminergic or striatal deficit but may be related to serotonergic or other neurotransmitter deficits. Autonomic function is thought to be related to widespread α-synuclein deposition in brain and extracerebral tissues [21], but autonomic symptoms are also classical features of anxiety disorders, without attribution to specific pathological substrates. However, of note it was particularly the pupillomotor and gastrointestinal rather than the cardiovascular subscores that correlated with later increase in anxiety scores. Excessive daytime sleepiness is not classically associated with anxiety, although it can be with depression [22], but both excessive daytime sleepiness and anxiety have been associated with low levels of the hypothalamic neurometabolite orexin [23, 24], although this has not been found uniformly [25]. The relationship with olfactory function is of interest as there is a known bidirectional relationship between anxiety and sensory, including olfactory, discrimination, and olfaction is thought to be primarily modulated by serotonin and noradrenaline rather than dopamine [26, 27].

Whilst attribution of anxiety to dysfunction in specific brain areas is therefore difficult, the results suggest that pathological changes underlying cognitive impairment in PD may at least be contributors to the development of anxiety in PD, and that excessive daytime sleepiness, autonomic function, and olfactory function may result from similar underlying pathologies, or at least indicate an increased risk of later anxiety, whereas dopaminergic mechanisms and motor function have only a limited relationship with anxiety outside of off-periods.

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TABLE 2 Univariate association of baseline variables with State–Trait Anxiety Inventory (STAI) change score over the 4-year follow-up.

Baseline variable	Coefficient (95% CI)	*p* Value
Age (years)	0.214 (0.027 to 0.401)	**0.025**
Gender (male)	3.107 (−0.724 to 6.938)	0.111
Baseline STAI total score	−0.222 (−0.389 to −0.055)	**0.009**
Geriatric Depression Scale (GDS)	0.275 (−0.726 to 1.275)	0.589
Schwab and England Activities of Daily Living Scale	0.024 (−0.294 to 0.342)	0.882
MDS-UPDRS-I[a]	0.546 (0.027 to 1.064)	**0.039**
MDS-UPDRS-I	0.502 (0.007 to 0.996)	**0.047**
MDS-UPDRS-II	0.265 (−0.154 to 0.683)	0.214
MDS-UPDRS-III	0.024 (−0.185 to 0.232)	0.824
REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)	0.522 (−0.189 to 1.233)	0.149
Epworth Sleepiness Scale (ESS)	0.718 (0.163 to 1.274)	**0.011**
Montreal Cognitive Assessment (MoCA)	−0.196 (−0.993 to 0.601)	0.629
Benton Judgement of Line Orientation Test (BJLOT)	0.064 (−0.401 to 0.530)	0.786
Hopkins Verbal Learning Test-immediate recall (HVLT-ir)	−0.075 (−0.246 to 0.097)	0.394
Hopkins Verbal Learning Test-delayed recall (HVLT-dr)	−0.085 (−0.252 to 0.082)	0.316
Letter-Number Sequencing (LNS)	−1.026 (−1.722 to −0.329)	**0.004**
Semantic Fluency Test (SFT)	−0.218 (−0.374 to −0.062)	**0.006**
Scale for Outcomes in Parkinson's Disease autonomic (SCOPA aut)	0.576 (0.264 to 0.888)	**<0.001**
SCOPA aut_gastrointestinal subscale	1.286 (0.318 to 2.255)	**0.009**
SCOPA aut_urinary subscale	0.682 (0.072 to 1.292)	**0.028**
SCOPA aut_cardiovascular subscale	2.356 (−0.043 to 4.756)	0.054
SCOPA aut_thermoregulatory subscale	1.482 (0.058 to 2.906)	**0.041**
SCOPA aut_pupillomotor	6.211 (3.371 to 9.053)	**<0.001**
SCOPA aut_sexual function (men) subscale	2.150 (0.736 to 3.564)	**0.003**
SCOPA aut_sexual function (women) subscale	−1.729 (−3.777 to 0.319)	0.097
University of Pennsylvania Smell Identification Test (UPSIT)	−0.257 (−0.485 to −0.029)	**0.027**
Questionnaire for Impulsive-Compulsive disorders (QUIP)	−1.410 (−4.038 to 1.218)	0.292
Dopamine transporter (DAT)		
Mean caudate uptake	−2.531 (−6.076 to 1.014)	0.161
Mean putamen uptake	−4.665 (−11.790 to 2.460)	0.198
Caudate asymmetry	7.588 (−0.513 to 15.688)	0.066
Putamen asymmetry	3.231 (−0.901 to 7.363)	0.125
CSF biomarkers (pg/mL)		
α-Synuclein	0.001 (−0.002 to 0.004)	0.473
Aβ1–42	0.0001 (−0.005 to 0.005)	0.967
t-tau	0.038 (0.004 to 0.071)	**0.028**
p-tau	0.363 (−0.010 to 0.736)	0.056

Note: MDS-UPDRS-I[a]: total score of MDS-UPDRS-I was adjusted by deleting the score of "anxious mood". Values in bold type denote statistical significance.

Abbreviations: CSF, cerebrospinal fluid; MDS-UPDRS-I, II, III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part I, II, III; STAI, State–Trait Anxiety Inventory.

We could not perform analyses on associations of risk factors with specific anxiety subtypes, such as generalized anxiety disorder or panic disorder, as this information was not available. Change of anxiety status was conducted at two time points. It is possible that patients may experience fluctuating anxiety over time during 4-year follow-up, and anxiety status captured at baseline and at year 4 cannot reflect the fluctuation. However, excluding patients who were taking anxiolytics and antidepressants at baseline did not change the results substantively.

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TABLE 3 Multivariable association of baseline variables with State–Trait Anxiety Inventory (STAI) change score over the 4-year follow-up.

Baseline variable	Coefficient (95% CI)	*p* Value
Age (years)	−0.191 (−0.427 to 0.046)	0.114
REM Sleep Behavior Disorder Scale (RBDSQ)	−0.594 (−1.430 to 0.242)	0.163
Montreal Cognitive Assessment (MoCA)	0.848 (−0.065 to 1.761)	0.069
Semantic Fluency Test (SFT)	−0.199 (−0.378 to −0.020)	**0.029**
Letter-Number Sequencing (LNS)	−1.117 (−1.943 to −0.291)	**0.008**
Scale for Outcomes in Parkinson's Disease autonomic (SCOPA aut)	0.629 (0.259 to 0.998)	**0.001**
Benton Judgement of Line Orientation Test (BJLOT)	0.343 (−0.155 to 0.842)	0.176
University of Pennsylvania Smell Identification Test (UPSIT)	−0.231 (−0.495 to 0.034)	0.087
Caudate asymmetry	6.316 (−1.769 to 14.401)	0.125
α-Synuclein	−0.005 (−0.010 to −0.0001)	**0.047**
t-tau	0.074 (0.014 to 0.133)	**0.016**

Note: The mean variance inflation factor (VIF) for the model was 1.47. Values in bold type denote statistical significance.

Abbreviations: CI, confidence interval; REM, rapid eye movement.

TABLE 4 Univariate association of change of State–Trait Anxiety Inventory (STAI) score with change of other clinical variables over the 4-year follow-up.

Change score	Coefficient (95% CI)	*p* Value
Geriatric Depression Scale (GDS)	3.908 (3.297–4.520)	**<0.001**
Schwab and England Activities of Daily Living Scale	−0.261 (−0.439 to −0.083)	**0.004**
MDS-UPDRS-I[a]	0.863 (0.481–1.244)	**<0.001**
MDS-UPDRS-I	0.894 (0.535–1.253)	**<0.001**
MDS-UPDRS-II	0.710 (0.387–1.033)	**<0.001**
MDS-UPDRS-III	0.180 (0.019–0.341)	**0.028**
REM Sleep Behavior Disorder Scale (RBDSQ)	0.395 (−0.298 to 1.087)	0.262
Epworth Sleepiness Scale (ESS)	0.583 (0.154–1.013)	**0.008**
Montreal Cognitive Assessment (MoCA)	−1.442 (−2.062 to −0.823)	**<0.001**
Benton Judgement of Line Orientation Test (BJLOT)	−0.674 (−1.138 to −0.210)	**0.005**
Hopkins Verbal Learning Test-immediate recall (HVLT-ir)	−0.202 (−0.378 to −0.027)	**0.024**
Hopkins Verbal Learning Test-delayed recall (HVLT-dr)	−0.216 (−0.385 to −0.047)	**0.013**
Letter-Number Sequencing (LNS)	−0.342 (−1.032 to 0.348)	0.330
Semantic Fluency Test (SFT)	−0.023 (−0.220 to 0.175)	0.823
Scale for Outcomes in Parkinson's Disease autonomic (SCOPA aut)	0.253 (−0.099 to 0.605)	0.158
SCOPA aut_gastrointestinal subscale	1.082 (0.206–1.958)	**0.016**
SCOPA aut_urinary subscale	0.495 (−0.227 to 1.217)	0.178
SCOPA aut_cardiovascular subscale	1.073 (−0.817 to 2.963)	0.265
SCOPA aut_thermoregulatory subscale	−0.254 (−1.457 to 0.949)	0.678
SCOPA aut_pupillomotor	−2.068 (−4.499 to 0.362)	0.095
SCOPA aut_sexual function (men) subscale	−0.525 (−1.748 to 0.697)	0.397
SCOPA aut_sexual function (women) subscale	1.931 (−0.569 to 4.431)	0.128
Questionnaire for Impulsive-Compulsive Disorders (QUIP)	1.800 (−0.172 to 3.773)	0.073
Dopamine transporter (DAT)		
Mean caudate uptake	−6.970 (−13.458 to −0.483)	**0.035**
Mean putamen uptake	−4.281 (−15.893 to 7.332)	0.468
Caudate asymmetry	2.510 (−8.709 to 13.728)	0.660
Putamen asymmetry	−0.662 (−5.436 to 4.112)	0.785

Note: MDS-UPDRS-I[a]: total score of MDS-UPDRS-I was adjusted by deleting the score of "anxious mood". There were insufficient data available for UPSIT at 4 years; therefore, no association analysis between UPSIT changes and anxiety changes was conducted. Values in bold type denote statistical significance.

Abbreviations: CI, confidence interval; MDS-UPDRS-I, II, III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part I, II, III; REM, rapid eye movement.

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AUTHOR CONTRIBUTIONS

Hanyuying Wang: formal analysis; writing – original draft. **Yibo Zhao:** formal analysis. **Anette Schrag:** conceptualization; supervision; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

Parkinson's Progression Markers Initiative, a public–private partnership, is funded by The Michael J. Fox Foundation for Parkinson's Research and funding partners, including AbbVie, Acurex Therapeutics, Allergan, Amathus Therapeutics, ASAP Aligning Science Across Parkinson's, Avid Radiopharmaceuticals, Bial Biotech, Biogen, BioLegend, Bristol-Myers Squibb, Calico, Celgene, Cerevel, Coave Therapeutics, Dacapo Brainscience, Denali, Edmond J. Safra Philanthropic Foundation, 4D Pharma plc, GE Healthcare, Genentech, GlaxoSmithKline (GSK), Golub Capital, Handl Therapeutics, Insitro, Janssen Neuroscience, Lilly, Lundbeck, Merck, Meso Scale Discovery, Neurocine, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Vanqua Bio, Verily, Voyager Therapeutics, and Yumanity. Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study visit www.ppmmi-info.org.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

FUNDING INFORMATION

This research was funded by the European Commission Horizon2020 research and innovation programme under the grant agreement 848002. Anette Schrag was supported by the University College London Hospitals NHS Foundation Trust (UCLH) National Institute for Health and Care Research (NIHR) Biomedical Research Centre.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Parkinson's Progression Markers Initiative (PPMI). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from https://www.ppmi-info.org/ with the permission of PPMI.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang H, Zhao Y, Schrag A. Development of anxiety in early Parkinson's disease: A clinical and biomarker study. *Eur J Neurol*. 2023;30:2661-2668. doi:10.1111/ene.15890

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