nature mental health

Article

https://doi.org/10.1038/s44220-024-00256-8

Dissociable effects of dopaminergic medications on depression symptom dimensions in Parkinson disease

Received: 27 July 2023

Accepted: 17 April 2024

Published online: 17 June 2024

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Depression in Parkinson disease (PD) is common, is disabling and responds poorly to standard antidepressants. Motivational symptoms of depression are particularly prevalent in PD and emerge with loss of dopaminergic innervation of the striatum. Optimizing dopaminergic treatment for PD can improve depressive symptoms. However, the differential effect of antiparkinsonian medication on symptom dimensions of depression is not known. Using data from a large (n = 412) longitudinal study of patients with newly diagnosed PD followed over 5 years, we investigated whether there are dissociable effects of dopaminergic medications on different depression symptom dimensions in PD. Previously validated 'motivation' and 'depression' dimensions were derived from the 15-item geriatric depression scale. Dopaminergic neurodegeneration was measured using repeated striatal dopamine transporter imaging. We identified dissociable associations between dopaminergic medications and different dimensions of depression in PD. Dopamine agonists were shown to be effective for treatment of motivational symptoms of depression. In contrast, monoamine oxidase-B inhibitors improved both depressive and motivation symptoms, albeit the latter effect is attenuated in patients with more severe striatal dopaminergic neurodegeneration.

Depression in Parkinson disease (PD) is common, affecting up to one-third of patients[1], and is associated with greater disability[2] and increased mortality[3] and has a greater negative impact on health-related quality of life than motor symptoms[4]. As depression in PD often occurs early in the condition and predicts increased caregiver burden[5], greater impairment in activities of daily living[6] and higher costs of care[7], effective treatment of depression in PD has the potential to achieve important health and economic benefits. However, current treatment guidelines for depression in PD advise the same approach as for depressed patients with other long-term conditions, despite evidence suggesting that standard antidepressant drugs are ineffective for these patients[8,9].

Mood changes in PD are frequently associated with motor fluctuations, or 'on/off' states, that begin as end-of-dose deterioration of the effect of dopaminergic medications and later progress to unpredictable fluctuations[10]. One study of nonmotor fluctuations in PD found that two-thirds of patients experience depressed mood exclusively during off states[11]. This raises the possibility that depression in PD may be related to dopaminergic deficit and have a specific etiology, explaining why treatment recommendations for depression may not generalize to PD[10].

Depression is a heterogeneous and etiologically complex syndrome. There are at least 256 possible unique symptom profiles that meet the Diagnostic and Statistical Manual of Mental Disorders,

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Fifth Edition, (DSM-V) criteria for a diagnosis of major depressive disorder[12]. This degree of clinical heterogeneity has stimulated efforts to define subtypes based on symptom profiles[12]. In PD, motivational symptoms of depression such as apathy (diminished initiation of and engagement in activities) and anhedonia (inability to experience pleasure and loss of motivation to act in order to seek pleasure) are particularly prevalent, occurring in 40% and 46% of patients, respectively[13]. Motivational symptoms are also particularly challenging to treat. The 'interest–activity' symptom dimension in depression that includes loss of interest, diminished activity, fatigue and difficulty making decisions has been associated with poor outcome of antidepressant treatment in large prospective clinical studies[14]. People with PD report worse apathy and anhedonia when off dopaminergic medication[10,15] and loss of dopaminergic innervation of the striatum, as measured by single photon emission computed tomography (SPECT) dopamine transporter (DAT) imaging, is associated with emergent motivational symptoms in PD[16].

Dopamine activity plays a crucial role in goal-directed behavior, signaling how much better or worse an event is than predicted (a 'reward prediction error'), as well as the valuation of reward and effort costs of actions[17–19]. The effect of dopamine signaling depends on the dynamics of its release and clearance from the synapse[20]. Short-latency phasic firing of dopaminergic neurons in the striatum is thought to encode reward prediction errors, crucial for reinforcement learning, while tonic levels of activity are thought to signal average reward valuation[21]. Understanding how dopamine signaling regulates adaptive behavior and motivation at different timescales and in different brain regions has important implications for the mechanisms underlying motivation and different depressive symptoms, and their diverse responses to different dopaminergic agents[17,20,21].

Prescription of different dopaminergic medications in PD is currently largely driven by consideration of motor symptoms and side-effect profile, including impulse control disorders that most commonly occur with dopamine agonists. However, dopaminergic medications are also known to have antidepressant effects. Double-blind randomized controlled trials have shown that dopamine agonists can improve depression and apathy in patients with PD, and pramipexole, a relatively selective D3 receptor agonist, has shown promise as a treatment in chronic and severe depression in patients without PD[22,23]. Lab-based studies in both animals and humans utilizing dopamine depletion have consistently implicated mesolimbic dopamine activity as a key modulator of motivation[24]. However, it remains unclear whether the antidepressant effects of dopamine agonists are primarily caused by improvement in motivational deficits rather than mood. Therefore, we aimed to perform the first comprehensive analysis of the dimensional symptom predictors of antidepressant effects of dopamine agonists.

Other treatments, such as monoamine oxidase inhibitors (MAO-Is), are also clinically used for both their antidepressant and antiparkinsonian effects[25]. Selective type-A monoamine oxidase (MAO-A) inhibitors, such as moclobemide, are primarily used in depression to prevent the metabolism of serotonin and noradrenaline[25]. In contrast type-B monoamine oxidase (MAO-B) inhibitors, such as rasagiline and selegiline, were developed for treatment in PD owing to their ability to inhibit dopamine metabolism, thereby increasing striatal dopamine levels[25]. However, MAO-B inhibitors such as selegiline have also been shown to improve depression in PD[26,27] and, at high doses, they are nonselective, additionally affecting serotonergic transmission, which may represent a complementary pathway to improving mood[25,28]. There remains limited understanding of the effects of MAO-Is on different symptom dimensions of depression in PD, and no study has examined how these effects change over time or their relationship with progression of neurodegeneration within dopaminergic pathways.

In this Article, we hypothesized that there would be dissociable effects of dopaminergic medications on different depressive symptom dimensions. Considering lab-based findings of the behavioral effects of dopamine agonists, we predicted that dopamine agonist treatment would improve motivational symptoms but not other depression symptom dimensions, whereas MAO-B inhibitors may improve mood due to their concurrent serotonergic action at higher doses[29]. Our secondary hypothesis was that dopaminergic medications with mechanisms of action reliant on presynaptic dopamine neuron integrity, such as MAO-B inhibitors, would have attenuated antidepressant effects as presynaptic dopaminergic neurodegeneration progressed.

Results

Participant characteristics

In total, 412 participants with PD were included at baseline with loss to follow-up of one-quarter of participants by year 5 (Table 1). Over half of patients had commenced PD medication by the end of year 1. Levodopa, dopamine agonists and MAO-B inhibitors were comparable in the prevalence of their use in year 1, but, by year 5, levodopa was the most common class of PD medication, with over 80% of patients prescribed this drug.

Total depression symptom scores and dimension scores both increased over time. However, only 13% of patients reported a 15-item geriatric depression scale (GDS-15) score >5 at baseline (suggestive of clinical depression) and less than 10% of participants with PD were taking antidepressant medication across all years of follow-up, though the reason for antidepressant use treatment was not available.

In almost all (98.8%) patients, DAT imaging was available at baseline and in years 1, 2 and 4, with only 17 participants imaged in years 3 and 5. As reported previously in this sample, DAT specific binding ratio (SBR) in participants with PD was, on average, around half that of healthy controls, and as expected, there was evidence of a marked decline over time (mean ± standard deviation (s.d.) percentage reduction from baseline: year 1, −9.7 ± 17.4%; year 2, −16.6 ± 17.7%; year 4, −26.6 ± 18.4%)[16].

Depression symptom dimensions and medication class

We constructed longitudinal linear mixed-effects models to examine the relationship between antiparkinsonian medications and two different depression symptom dimensions within the GDS-15: a three-item 'motivation' factor[30] and a nine-item 'depression' factor[31]. Analysis revealed dissociable relationships between different antiparkinsonian medication classes and specific dimensions of depression. Dopamine agonist treatment was associated with relatively lower motivation symptoms as the disease progressed (medication-by-time interaction: $\beta = -0.06$, 95% confidence interval (CI) −0.13 to −0.01, $P = 0.039$), but this was not the case for depressive symptoms (medication-by-time interaction: $\beta = 0.01$, 95% CI −0.02 to 0.05, $P = 0.5$; main effect of medication: $\beta = -0.03$, 95% CI −0.16 to 0.11, $P = 0.7$) (Fig. 1). Both the model and empirical data indicated that dopamine agonist treatment was associated with lower motivation symptoms particularly in later years (Fig. 1). However, the overall relationship between dopamine agonist treatment and motivation symptom scores across all time points was not significant (0.15, 95% CI −0.06 to 0.36, $P = 0.2$).

In contrast, MAO-B inhibitor treatment was associated with significantly lower depression symptoms ($\beta = -0.14$, 95% CI −0.27 to −0.02, $P = 0.026$), but not motivation symptoms ($\beta = -0.08$, 95% CI −0.29 to 0.12, $P = 0.4$), on average across all years of follow-up. However, there were no significant interactions with time (motivation symptoms $\beta = -0.01$, 95% CI −0.07 to 0.04, $P = 0.6$; depression symptoms $\beta = 0.03$, 95% CI −0.01 to 0.07, $P = 0.11$) (Fig. 2).

No significant associations were observed between amantadine, levodopa or COMT inhibitor treatment and either depression or motivation symptom factor scores (Supplementary Figs. 1, 2 and 3). However, there were relatively small numbers of patients using COMT inhibitors, particularly in years 1–3 (Table 1), which limits the interpretation of this result (Table 2).

Table 1 | Characteristics of PPMI participants with PD

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
n	412	384	367	355	335	304
Age at entry	61.77 (9.76)	61.66 (9.86)	61.66 (9.86)	61.64 (9.86)	61.40 (9.96)	60.94 (9.84)
Age at diagnosis	61.22 (9.73)	61.1 (9.83)	61.1 (9.84)	61.09 (9.82)	60.86 (9.92)	60.39 (9.83)
Self-reported PD symptom duration at cohort entry (years)	6.56 (6.39)	6.64 (6.51)	6.70 (6.56)	6.65 (6.54)	6.57 (6.48)	6.6 (6.53)
Years of education	15.54 (2.99)	15.47 (2.9)	15.6 (2.87)	15.61 (2.92)	15.62 (2.90)	15.61 (2.97)
Male (%)	273/412 (66%)	255/384 (66%)	244/367 (66%)	235/355 (66%)	225/335 (67%)	205/304 (67%)
QUIP	0.29 (0.64)	0.17 (0.47)	0.29 (0.69)	0.34 (0.72)	0.39 (0.87)	0.41 (0.81)
MDS-UPDRS III	20.93 (8.80)	25.25 (10.92)	27.62 (11.39)	29.58 (12.35)	30.97 (12.20)	31.27 (12.28)
UPDRS total	32.41 (13.14)	39.59 (16.12)	43.02 (16.97)	46.33 (18.80)	48.70 (19.68)	49.96 (19.04)
MOCA	27.13 (2.28)	26.28 (2.82)	26.27 (3.14)	26.37 (3.01)	26.42 (3.57)	26.53 (3.53)
GDS-15	2.29 (2.43)	2.53 (2.92)	2.58 (2.87)	2.58 (2.79)	2.59 (2.84)	2.78 (2.80)
GDS >5	55/412 (13%)	61/384 (16%)	63/366 (17%)	58/355 (16%)	58/333 (17%)	61/303 (20%)
'Motivation' GDS-15 factor	1.02 (0.89)	1.11 (0.97)	1.16 (1.00)	1.12 (1.02)	1.19 (1.00)	1.24 (1.04)
'Depression' GDS-15 factor	0.74 (1.47)	0.86 (1.80)	0.90 (1.78)	0.88 (1.75)	0.86 (1.74)	0.96 (1.73)
% commenced on any PD medication	0/412 (0%)	225/382 (59%)	310/367 (84%)	329 (355) 92.7%	319/332 (96.1%)	293/304 (96.4%)
% commenced dopamine agonist	–	91/382 (23.8%)	136/367 (37.1%)	153/355 (43.1%)	188/332 (56.6%)	175/304 (57.6%)
% commenced levodopa	–	93/382 (24.4%)	167/367 (45.5%)	222/355 (62.5%)	252/332 (75.9%)	253/304 (83.2%)
% commenced MAO-B	–	102/382 (26.7%)	136/367 (37.1%)	148/355 (41.7%)	141/332 (42.5%)	130/304 (42.8%)
% commenced amantadine	–	27/382 (7.1%)	47/367 (12.8%)	56/355 (15.8%)	60/332 (18.1%)	59/304 (19.4%)
% commenced COMT inhibitor	–	1/382 (0.3%)	2/367 (0.6%)	10/355 (2.8%)	14/332 (4.2%)	17/304 (5.6%)
% on antidepressant	29/412 (7.0%)	29/384 (7.6%)	33/367 (9.0%)	30/355 (8.5%)	32/335 (9.6%)	26/278 (9.4%)
Number of DAT scans	408	360	341	10	280	7
Striatal DAT SBR	2.50 (0.75)	2.21 (0.66)	2.07 (0.68)	1.67 (0.54)	1.82 (0.64)	1.30 (0.67)

Mean (s.d.); *N* (%); QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; MOCA, Montreal Cognitive Assessment.

In the original study that validated the three-item motivation factor in an independent cohort, a score of ≥2 was identified as having high specificity for clinically relevant apathy/anhedonia in older adults (equivalent to a score of ≥14 using the Starkstein apathy scale). Consistent with the analysis described above treating the motivation factor score as a continuous outcome, logistic mixed modeling using this categorical cutoff showed that dopamine agonist use over time was also associated with a lower risk of developing clinically significant (score ≥2) apathy/anhedonia (odds ratio 0.68, 95% CI 0.49 to 0.94, $P = 0.021$) (Supplementary Table 1). No other significant interactions with time were observed for other treatments using this cutoff and other treatments (Supplementary Table 1).

Depression symptom dimensions, medication and striatal DAT binding

Mixed-effects model analysis of the relationship between striatal DAT SBR and depression symptoms across all time points revealed that the effect of MAO-B inhibitor treatment on motivation was moderated by striatal DAT SBR ($\beta = -0.23$, 95% CI −0.39 to −0.07, $P = 0.006$) (Table 3 and Fig. 3). Patients with PD with higher striatal DAT SBR appeared to experience a greater antidepressant effect of MAO-B inhibitor treatment. A logistic mixed modeling analysis also found that striatal DAT SBR moderated the effect of MAO-B inhibitor treatment in reducing the risk of developing clinically significant apathy/anhedonia (motivation factor score of ≥2). MAO-B inhibitor treatment significantly reduced the odds of developing high apathy/anhedonia specifically in patients with higher striatal DAT SBR (odds ratio 0.28, 95% CI 0.11 to 0.73, $P = 0.009$) (Supplementary Table 2).

Striatal DAT SBR did not significantly moderate the effects of dopamine agonist on individual depression symptom dimensions.

Discussion

We performed the first longitudinal analysis of how different types of dopaminergic medication for PD are associated with different symptom dimensions of depression and how these relationships are influenced by neurodegeneration of dopaminergic pathways. We found dissociable associations of PD dopaminergic medications with different dimensions of depression. Dopamine agonist treatment was associated with relatively lower motivation symptoms beyond the second year following diagnosis, but not depressed mood. In contrast, MAO-B inhibitor treatment was associated with fewer depression, but not motivation, symptoms. However, MAO-B inhibitor use did appear to improve motivation symptoms in patients with relatively preserved striatal presynaptic dopamine projections, indexed by higher striatal DAT binding. A potential explanation for this pattern is that the MAO-B inhibitor mechanism of action is dependent on presynaptic striatal dopamine neuron integrity, whereas other medication classes, such as dopamine agonists, act postsynaptically. Our results support existing evidence that striatal dopamine dysfunction plays a crucial role in motivation and highlight the need for further understanding of the effect of different dopaminergic therapies on depressive symptoms as PD pathology progresses over time[16].

Optimization of dopaminergic therapies is often the first strategy in the treatment of depression in PD[32]. However, at present, the choice of dopaminergic therapy is largely guided by motor symptoms and potential side effects[33]. Our findings suggest that depressive symptom

https://doi.org/10.1038/s44220-024-00256-8

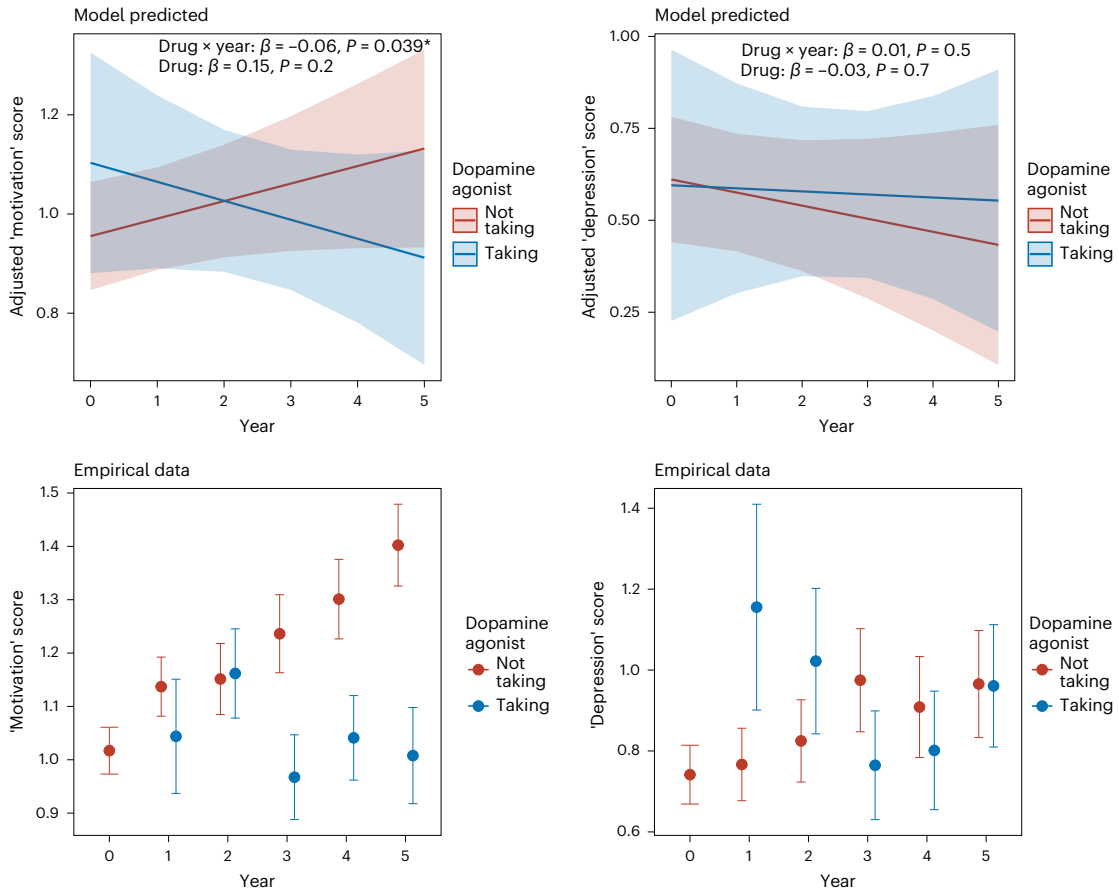

Fig. 1 | Relationship between different depression symptoms dimensions and dopamine agonist treatment over time. Top row: adjusted linear mixed-effects model of the predicted relationship between dopamine agonist treatment and 'motivation' factor score (top left) and 'depression' factor score (top right) over time (n = 412, categorized as taking (blue) and not taking (red) dopamine agonists across six time points). Shown as the mean estimate (red and blue lines) ±95% CIs (red and blue shading). Bottom row: empirical data showing (symptom factor score means and standard errors) the same pattern as the modeled estimates between dopamine agonist treatment and 'motivation' factor score (bottom left) and 'depression' factor score (bottom right).

profile may also have a role to play in guiding dopaminergic treatment therapy selection. For example, dopamine agonist treatment may be an effective strategy to treat motivational symptoms beyond 2 years following diagnosis, while alternative therapies such as MAO-B inhibitors may be indicated in patients with prominent depressed mood.

Though our study was conducted in patients with PD, these results also reveal mechanistic insights and potential treatment strategies for depression in patients without PD, specifically for those with prominent motivational symptoms that are resistant to standard antidepressant medications[14]. The dopamine agonist pramipexole is currently used as a treatment for refractory depression, and our findings support the potential for further repurposing of PD dopaminergic therapies for treatment of motivational symptoms[34].

Dopamine agonists have been identified as an effective treatment of disorders of motivation in PD previously[35]. However, the role of dopaminergic therapies on motivation and mood depends on dopaminergic receptor profile, pharmacodynamics, brain region and progression of underlying PD pathology[21]. For example, an animal study comparing D1-, D2- and D3-specific agonists in rescuing motivational deficits induced by lesions to the substantia nigra found that only D3 agonists were effective[36]. D3 receptors have a narrow distribution and are primarily located within the ventral striatum, a region implicated in reward processing and the cognitive mechanisms underlying motivation. Agonism of D3 receptors has been identified as a potential treatment of apathy in PD, and further research is needed to investigate whether dopamine agonists with high affinity for D3 receptors, such as pramipexole, are more effective options for the treatment of the motivational symptoms of depression[15,24].

Improved understanding of the dynamics of dopamine neurotransmission underlying mood and motivation may also guide novel treatment strategies for depression in PD. Optogenetic studies have confirmed that phasic midbrain dopamine firing encodes reward prediction errors, which are crucial for learning, whereas tonic dopamine signals encode reward valuation and effort costs that drive motivation[18,37]. Dopaminergic therapies modulate the complex dynamics of dopamine signaling via inhibition of synaptic clearance mechanisms, post-synaptic agonism or potentiating synaptic release. Owing to the variation in metabolism, signaling and receptor distribution, manipulating dopamine can have paradoxical consequences for cognitive processing, often depending on basal levels of dopamine in different brain regions[21]. For example, dopamine synaptic clearance varies substantially across different brain regions. In the ventral striatum, rapid recycling via DAT predominates[20]. In contrast, in the prefrontal cortex, DAT recycling is minimal, and enzymatic degradation by catechol-*O*-methyltransferase (COMT) is the primary mechanism for clearance, modulating evoked dopamine release measured over minutes[17,38,39]. Though in our sample too few patients were taking COMT inhibitors to draw definitive conclusions, functional polymorphisms in COMT have been associated with motivational and mood disorders[17,40].

Investigating the effects of different dopaminergic therapies on depression at the symptom dimension level provides insight into the potential utility of specific dopaminergic medications for the

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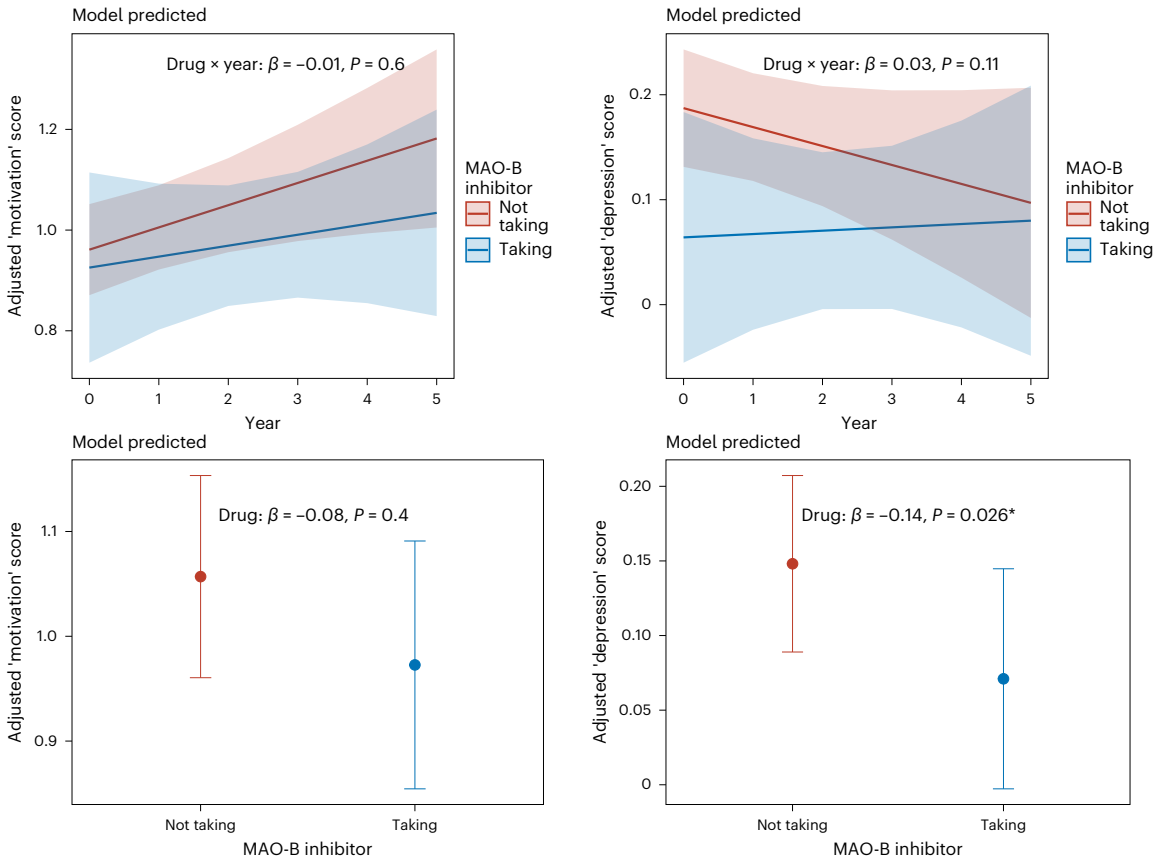

Fig. 2 | Relationship between different depression symptoms dimensions and MAO-B inhibitor treatment over time. Top row: adjusted linear mixed-effects model of predicted relationship between MAO-B inhibitor treatment and 'motivation' factor score (top left) and 'depression' factor score (top right) over time (n = 412, categorized as taking (blue) and not taking (red) MAO-B inhibitors across six time points). Shown as the mean estimate (red and blue lines) ±95% CIs (red and blue shading). Bottom row: adjusted linear mixed-effects model predicted relationship between MAO-B inhibitor treatment and 'motivation' factor score (bottom left) and 'depression' factor score (bottom right) across all time points (data presented as mean estimate ± 95% CIs).

Table 2 | Adjusted mixed-effects model results investigating the relationship between PD medication and depression symptom dimension longitudinally (drug×time) and across all time points (drug)

Medication		'Motivation' factor	'Depression' factor
Dopamine agonists	drug	0.15 (−0.06 to 0.36)	−0.03 (−0.16 to 0.11)
	drug × time	**−0.06 (−0.13 to −0.01), *P*=0.039***	0.01 (−0.02 to 0.05)
Levodopa	drug	−0.15 (−0.35 to 0.05)	0.00 (−0.12 to 0.13)
	drug × time	0.04 (−0.02 to 0.09)	0.01 (−0.03 to 0.04)
MAO-B inhibitors	drug	−0.08 (−0.29 to 0.12)	**−0.14 (−0.27 to −0.02), *P*=0.026***
	drug × time	−0.01 (−0.07 to 0.04)	0.03 (−0.01 to 0.07)
COMT inhibitors	drug	0.04 (−0.94 to 1.00)	0.48 (−0.14 to 1.1)
	drug × time	−0.01 (−0.24 to 0.22)	−0.08 (−0.23 to 0.07)
Amantadine	drug	0.11 (−0.18 to 0.39)	−0.05 (−0.23 to 0.13)
	drug × time	−0.06 (−0.15 to 0.01)	0.01 (−0.04 to 0.06)

*P < 0.05, statistically significant results in bold.

treatment of depression. However, large-scale randomized controlled trials of dopaminergic therapies for depression in PD are needed before any firm clinical recommendations can be made. Effective development of future treatments for depression in PD will depend on refining phenotypes and integrating our understanding of the evolution of depressive symptoms over time with the progression in PD pathology[41].

Limitations

The associations we observed between different classes of treatment and depression symptom dimension could be a consequence of clinician treatment selection bias. However, this is unlikely as depression symptom dimension severity did not predict treatment selection at year 1.

The PPMI cohort only includes patients recently diagnosed with PD and may not be applicable to individuals in the later stages of the condition where the spread of neurodegeneration and systems involved are probably more complex.

The associations we observed between dopaminergic medication, striatal DAT binding and the depression symptom dimension could potentially be a consequence of other PD symptoms or functional disability. However, this is unlikely as all models were adjusted for cognition, motor symptoms, disease duration and functional disability.

Though all medication classes were incorporated into a single model, with the sample size available in PPMI it was not feasible to account for all the interactions of the various combination therapies patients were on.

Finally, depressive symptoms were analyzed as a continuous trait measure due to limited numbers of patients meeting a cut-off for clinical depression based on GDS-15 score. Future replication of our findings in a large cohort studies of PD patients with an established clinical diagnosis of depression is needed.

https://doi.org/10.1038/s44220-024-00256-8

Table 3 | Adjusted mixed-effects model results investigating the relationship between PD medication and depression symptom dimension by striatal DAT SBR

Medication		'Motivation' factor	'Depression' factor
Dopamine agonists	drug × DAT SBR	0.07 (−0.12 to 0.26)	−0.02 (−0.13 to 0.10)
Levodopa	drug × DAT SBR	−0.09 (−0.24 to 0.05)	0.00 (−0.09 to 0.09)
MAO-B inhibitors	drug × DAT SBR	**−0.23 (−0.39 to −0.07), *P*=0.006****	−0.02 (−0.12, 0.08)
COMT inhibitors	drug × DAT SBR	0.99 (−0.17 to 2.2)	0.09 (−0.62 to 0.81)
Amantadine	drug × DAT SBR	0.12 (−0.13 to 0.37)	−0.02 (−0.17 to 0.14)

**$P<0.01$, statistically significant results in bold.

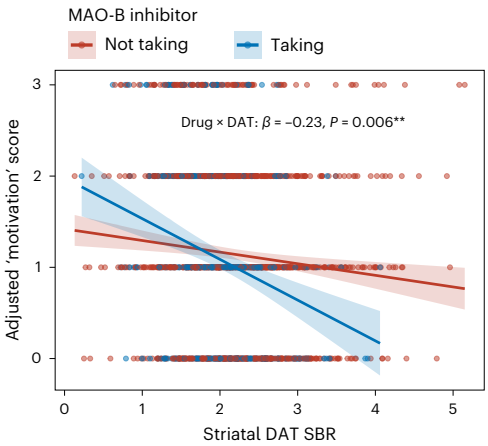

Fig. 3 | Relationship between 'motivation' factor score, MAO-B inhibitor treatment and striatal DAT binding. Adjusted linear mixed-effects model simulation showing 'motivation' factor score by striatal DAT SBR and MAO-B inhibitor treatment (n = 408, total of 1,406 scans across all six time points).

Conclusion

We identified dissociable effects of PD dopaminergic medications on different dimensions of depression. Dopamine agonists are a potentially effective treatment for motivational symptoms of depression in PD, especially beyond the second year following diagnosis. In contrast, MAO-B inhibitors may improve both depression and motivation symptoms, though the latter effect may be dependent on the severity of striatal dopaminergic neurodegeneration, potentially as a consequence of their mechanism of action depending on presynaptic dopaminergic neuron integrity. Further clinical trials of different dopaminergic treatment regimes are needed to identify clinically efficacious treatments for depression in PD.

Methods

We used data from the Parkinson's Progression Markers Initiative (PPMI) cohort, an international multicenter cohort study[42]. Launched in 2010, PPMI enrolled untreated, patients with newly diagnosed PD and age- and sex-matched healthy controls. All participants underwent a standard battery of assessments including the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the 15-item GDS (GDS-15) and SPECT DAT imaging with Ioflupane [123-I] yearly, over 5 years.

To avoid capturing chronic symptoms in the context of depression with onset before the development of PD, all participants who had received a diagnosis of major depressive disorder more than 5 years before diagnosis with PD were excluded (n = 11).

We investigated two different depression symptom dimensions within the GDS-15 previously validated in independent cohorts using factor analysis: a three-item 'motivation' factor[30] and a nine-item 'depression' factor[31]:

'Motivation' factor

GDS item 2—Have you dropped many of your activities or interests? Scale yes (1)/no (0)

GDS item 9—Do you prefer to stay at home, rather than going out and doing new things? Scale yes (1)/no (0)

GDS item 13—Do you feel full of energy? Scale yes (0)/no (1)

'Depression' factor

GDS item 1—Are you basically satisfied with your life? Scale yes (0)/no (1)

GDS item 3—Do you feel that your life is empty? Scale yes (1)/no (0)

GDS item 5—Are you in good spirits most of the time? Scale yes (0)/no (1)

GDS item 7—Do you feel happy most of the time? Scale yes (0)/no (1)

GDS item 8—Do you often feel helpless? Scale yes (1)/no (0)

GDS item 11—Do you think it is wonderful to be alive? Scale yes (0)/no (1)

GDS item 12—Do you feel pretty worthless the way you are now? Scale yes (1)/no (0)

GDS item 14—Do you feel that your situation is hopeless? Scale yes (1)/no (0)

GDS item 15—Do you think that most people are better off than you are? Scale yes (1)/no (0)

A variable recording whether patients were taking a specific medication class at each time point was created for each of the following PD medication classes: dopamine agonists, MAO-B inhibitors, levodopa, amantadine and COMT inhibitors.

Striatal DAT imaging was used as a measure of presynaptic dopaminergic neurodegeneration, indexing the established decrease in striatal DAT SBR in PD as the disease progresses, owing to a loss of presynaptic dopaminergic projections from the substantia nigra and ventral tegmental area.

Statistical analysis

We used linear mixed-effects modeling to examine the relationship between each GDS-15 factor score (dependent variable) and medication state for each class of PD medication (independent variables, all included in the same multiple regression), which were acquired contemporaneously, and how this relationship changed over the progression of illness. This involved fitting both the main effects of medication class state (across all follow-up time points) and their interactions with time. This allowed interindividual heterogeneity and unequal follow-up intervals to be accommodated by incorporating random effects. Random intercept terms at the participant level were tested.

The interaction term between medication class state and time allowed us to assess how the relationship between each GDS-15 factor and specific medication changed over time, using all available follow up GDS-15 data as the outcome.

Two sets of regressions for each GDS-15 factor were conducted: (1) unadjusted and (2) adjusted for age, sex, years of education, duration of PD, and both GDS-15 factor scores (all at baseline); plus cognition (Montreal Cognitive Assessment), impulsivity (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease), severity of motor symptoms (MDS-UPDRS part III score, 'off' medication), stage of disease/functional disability (Hoehn and Yahr scale), levodopa equivalent dose, antidepressant medication status and the other GDS-15 factor to ensure specificity (all at each contemporaneous time point).

Model fit was tested using the Akaike information criterion. Quantile–quantile plots were obtained to assess model residual distributions (Supplementary Q–Q Plots 1–3). Where model residuals did not meet a normal distribution assumption, a logarithmic transformation was applied and normality reassessed.

Secondary analysis was conducted to assess moderation of pharmacological effects by dopaminergic neurodegeneration, replacing the time interaction with an interaction with DAT SBR. The interaction term between medication class state and DAT SBR enabled analysis of how the relationship between each GDS-15 factor and specific medication changed with striatal presynaptic dopaminergic neurodegeneration.

All statistical analyses were performed in R version 4.1.2. The R package 'lme4' was used for mixed-effects modeling.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

This study used openly available data from the PPMI study at https://www.ppmi-info.org/access-data-specimens/download-data. All data produced in the present study are available upon reasonable request to the authors.

References

1. Reijnders, J. S. A. M., Ehrt, U., Weber, W. E. J., Aarsland, D. & Leentjens, A. F. G. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov. Disord.* https://doi.org/10.1002/mds.21803 (2008).
2. Barone, P. et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov. Disord.* https://doi.org/10.1002/mds.22643 (2009).
3. Hughes, T. A., Ross, H. F., Mindham, R. H. S. & Spokes, E. G. S. Mortality in Parkinson's disease and its association with dementia and depression. *Acta Neurol. Scand.* https://doi.org/10.1111/j.1600-0404.2004.00292.x (2004).
4. Müller, B., Assmus, J., Herlofson, K., Larsen, J. P. & Tysnes, O. B. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. *Parkinsonism Relat. Disord.* https://doi.org/10.1016/j.parkreldis.2013.07.010 (2013).
5. Schrag, A., Hovris, A., Morley, D., Quinn, N. & Jahanshahi, M. Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. *Parkinsonism Relat. Disord.* https://doi.org/10.1016/j.parkreldis.2005.06.011 (2006).
6. Ravina, B. et al. The impact of depressive symptoms in early Parkinson disease. *Neurology* https://doi.org/10.1212/01.wnl.0000268695.63392.10 (2007).
7. McCrone, P., Allcock, L. M. & Burn, D. J. Predicting the cost of Parkinson's disease. *Mov. Disord*. https://doi.org/10.1002/mds.21360 (2007).
8. Troeung, L., Egan, S. J. & Gasson, N. A meta-analysis of randomised placebo-controlled treatment trials for depression and anxiety in Parkinson's disease. *PLoS ONE* https://doi.org/10.1371/journal.pone.0079510 (2013).
9. Liu, J. et al. Comparative efficacy and acceptability of antidepressants in Parkinson's disease: a network meta-analysis. *PLoS ONE*. **8**, e76651 (2013).
10. van der Velden, R. M. J., Broen, M. P. G., Kuijf, M. L. & Leentjens, A. F. G. Frequency of mood and anxiety fluctuations in Parkinson's disease patients with motor fluctuations: a systematic review. *Mov. Disord.* **33**, 1521–1527 (2018).
11. Storch, A. et al. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. *Neurology* https://doi.org/10.1212/WNL.0b013e318285c0ed (2013).
12. Buch, A. M. & Liston, C. Dissecting diagnostic heterogeneity in depression by integrating neuroimaging and genetics. *Neuropsychopharmacology* **46**, 156–175 (2021).
13. Husain, M. & Roiser, J. P. Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nat. Rev. Neurosci.* **19**, 470–484 (2018).
14. Uher, R. et al. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. *Psychol. Med.* **42**, 967–980 (2012).
15. Thobois, S. et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain* **136**, 1568–1577 (2013).
16. Costello, H. et al. Longitudinal decline in striatal dopamine transporter binding in Parkinson's disease: associations with apathy and anhedonia. *J. Neurol. Neurosurg. Psychiatry* **94**, 863–870 (2023).
17. Korn, C. et al. Distinct roles for dopamine clearance mechanisms in regulating behavioral flexibility. *Mol. Psychiatry* **26**, 7188–7199 (2021).
18. Schultz, W., Dayan, P. & Montague, P. R. A neural substrate of prediction and reward. *Science* **275**, 1593–1599 (1997).
19. Eshel, N., Tian, J., Bukwich, M. & Uchida, N. Dopamine neurons share common response function for reward prediction error. *Nat. Neurosci.* **19**, 479–486 (2016).
20. Sulzer, D., Cragg, S. J. & Rice, M. E. Striatal dopamine neurotransmission: regulation of release and uptake. *Basal Ganglia* **6**, 123–148 (2016).
21. Cools, R. Chemistry of the adaptive mind: lessons from dopamine. *Neuron* **104**, 113–131 (2019).
22. Schaeffer, E. & Berg, D. Dopaminergic therapies for non-motor symptoms in Parkinson's disease. *CNS Drugs* **31**, 551–570 (2017).
23. Barone, P. et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* **9**, 573–580 (2010).
24. Chong, T. T. J. & Husain, M. in *Progress in Brain Research* Vol. 229 (eds Studer, B. & Knecht, S.) 389–426 (Elsevier, 2016).
25. Youdim, M. B. H. & Bakhle, Y. S. Monoamine oxidase: isoforms and inhibitors in Parkinson's disease and depressive illness. *Br. J. Pharmacol.* **147**, S287 (2006).
26. Korchounov, A., Winter, Y. & Rössy, W. Combined beneficial effect of rasagiline on motor function and depression in de novo PD. *Clin. Neuropharmacol.* **35**, 121 (2012).
27. Suchting, R. et al. Revisiting monoamine oxidase inhibitors for the treatment of depressive disorders: a systematic review and network meta-analysis. *J. Affect. Disord.* **282**, 1153–1160 (2021).
28. Alborghetti, M. & Nicoletti, F. Different generations of type-B monoamine oxidase inhibitors in Parkinson's disease: from bench to bedside. *Curr. Neuropharmacol.* **17**, 861–873 (2019).
29. Smith, K. M., Eyal, E. & Weintraub, D., for the ADAGIO Investigators. Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability. *JAMA Neurol.* **72**, 88–95 (2015).
30. Bertens, A. S. et al. Validity of the three apathy items of the Geriatric Depression Scale (GDS-3A) in measuring apathy in older persons. *Int. J. Geriatr. Psychiatry* **32**, 421–428 (2017).
31. Weintraub, D., Xie, S., Karlawish, J. & Siderowf, A. Differences in depression symptoms in patients with Alzheimer's and Parkinson's diseases. *Int. J. Geriatr. Psychiatry.* **22**, 1025–1030 (2007).
32. Timmer, M. H. M., Beek, M. H. C. T., van, Bloem, B. R. & Esselink, R. A. J. What a neurologist should know about depression in Parkinson's disease. *Pract. Neurol.* **17**, 359–368 (2017).
33. Pringsheim, T. et al. Dopaminergic therapy for motor symptoms in early Parkinson disease practice guideline summary: a report of the AAN Guideline Subcommittee. *Neurology* **97**, 942–957 (2021).
34. Tundo, A., de Filippis, R. & De Crescenzo, F. Pramipexole in the treatment of unipolar and bipolar depression. A systematic review and meta-analysis. *Acta Psychiatr. Scand.* **140**, 116–125 (2019).
35. Costello, H., Husain, M. & Roiser, J. P. Apathy and motivation: biological basis and drug treatment. *Annu. Rev. Pharmacol. Toxicol*. https://doi.org/10.1146/annurev-pharmtox-022423-014645 (2024).

36. Carnicella, S. et al. Implication of dopamine D3 receptor activation in the reversion of Parkinson's disease-related motivational deficits. *Transl. Psychiatry* **4**, e401 (2014).
37. Costa, K. M. & Schoenbaum, G. Dopamine. *Curr. Biol.* **32**, R817–R824 (2022).
38. Karoum, F., Chrapusta, S. J. & Egan, M. F. 3-Methoxytyramine is the major metabolite of released dopamine in the rat frontal cortex: reassessment of the effects of antipsychotics on the dynamics of dopamine release and metabolism in the frontal cortex, nucleus accumbens, and striatum by a simple two pool model. *J. Neurochem.* **63**, 972–979 (1994).
39. Tunbridge, E. M., Harrison, P. J. & Weinberger, D. R. Catechol-*O*-methyltransferase, cognition, and psychosis: Val^{158}Met and beyond. *Biol. Psychiatry* **60**, 141–151 (2006).
40. Harrison, P. J. & Tunbridge, E. M. Catechol-*O*-methyltransferase (COMT): a gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. *Neuropsychopharmacology* **33**, 3037–3045 (2008).
41. Costello, H., Roiser, J. P. & Howard, R. Antidepressant medications in dementia: evidence and potential mechanisms of treatment-resistance. *Psychol. Med.* https://doi.org/10.1017/S003329172200397X (2023).
42. Marek, K. et al. The Parkinson's progression markers initiative (PPMI)—establishing a PD biomarker cohort. *Ann. Clin. Transl. Neurol.* **5**, 1460–1477 (2018).

Acknowledgements

We thank the Michael J. Fox Foundation, the investigators and all patients living with PD that enabled the Parkinson's Progression Marker Initiative. H.C. is supported by a Wellcome Trust Clinical Training Fellowship, and R.H. is supported by the NIHR UCLH BRC. Data collection and sharing for this project was funded by the Parkinson's Progressive Marker Initiative (http://www.ppmi-info.org/), NIH R01NS052318, NIH MH108574, NIH EB015902 and Florida ADRC (P50AG047266).

Author contributions

H.C., J.P.R. and R.H. developed the study, and H.C. performed the data analysis with input from J.P.R. H.C. wrote the paper, and all authors (A.-E.S., R.H. and J.P.R.) reviewed, edited and approved the paper.

Ethics

This study involves human participants from the Parkinson's Progression Markers Initiative large openly accessible database launched in 2010 to identify markers of PD's onset and progression. All participants gave informed consent to participate before taking part (ClinicalTrials.gov NCT01141023). All applications to use the data are approved by the PPMI steering committee.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44220-024-00256-8.

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Peer review information *Nature Mental Health* thanks the anonymous reviewers for their contribution to the peer review of this work.

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Population characteristics	This study involves humans participants who volunteered for the PPMI cohort, a large openly accessible database launched in 2010 to identify markers of Parkinson's onset and progression.
Recruitment	The PPMI cohort includes recently diagnosed Parkinson's patients and may not be applicable to patients with later stage disease
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Replication	All modelling followed the design specified in the methods. This is an openly accessible cohort and code is available on request.
Randomization	Not applicable (cohort study, not randomised, relevant covariates were included modelling, see methods for details)
Blinding	Not applicable (cohort study, unblinded. Patients required diagnosis and treatment for PD prior to inclusion, therefore unblinded during data collection)

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Data collection	2010-2016, recruitment was from 21 clinical study sites (sixteen US and five European)
Outcomes	Comprehensive longitudinal schedule of clinical and imaging assessments and biosampling. Further details can be found at: http://www.ppmi-info.org/. Primary outcome was the mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in early PD patients

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