RESEARCH ARTICLE

Cross-Sectional and Longitudinal Association of Clinical and Neurocognitive Factors With Apathy in Patients With Parkinson Disease

Campbell Le Heron, DPhil, Kyla-Louise Horne, PhD, Michael R. MacAskill, PhD, Leslie Livingstone, BA(Hons), Tracy R. Melzer, PhD, Daniel Myall, PhD, Toni Pitcher, PhD, John Dalrymple-Alford, PhD, Tim Anderson, PhD, and Samuel Harrison, DPhil

Correspondence
Dr. Le Heron
campbell.leheron@otago.ac.nz

Neurology® 2024;102:e209301. doi:10.1212/WNL.0000000000209301

Abstract

Background and Objectives

A robust understanding of the natural history of apathy in Parkinson disease (PD) is foundational for developing effective clinical management tools. However, large longitudinal studies are lacking while the literature is inconsistent about even cross-sectional associations. We aimed to determine the longitudinal predictors of apathy development in a large cohort of people with PD and its cross-sectional associations and trajectories over time, using sophisticated Bayesian modeling techniques.

Methods

People with PD followed up in the longitudinal New Zealand Parkinson's progression project were included. Apathy was defined using the neuropsychiatric inventory subscale ≥4, and analyses were also repeated using a less stringent cutoff of ≥1. Both MoCA and comprehensive neuropsychological testing were used as appropriate to the model. Depression was assessed using the hospital anxiety and depression scale. Cross-sectional Bayesian regressions were conducted, and a multistate predictive model was used to identify factors that predict the initial onset of apathy in nonapathetic PD, while also accounting for the competing risk of death. The relationship between apathy presence and mortality was also investigated.

Results

Three hundred forty-six people with PD followed up for up to 14 years across a total of 1,392 sessions were included. Apathy occurrence did not vary significantly across the disease course (disease duration odds ratio [OR] = 0.55, [95% CI 0.28–1.12], affecting approximately 11% or 22% of people at any time depending on the NPI cutoff used. Its presence was associated with a significantly higher risk of death after controlling for all other factors (hazard ratio [HR] = 2.92 [1.50–5.66]). Lower cognition, higher depression levels, and greater motor severity predicted apathy development in those without motivational deficits (HR [cognition] = 0.66 [0.48–0.90], HR [depression] = 1.45 [1.04–2.02], HR [motor severity] = 1.37 [1.01–1.86]). Cognition and depression were also associated with apathy cross-sectionally, along with male sex and possibly lower dopaminergic therapy level, but apathy still occurred across the full spectrum of each variable (OR [cognition] = 0.58 [0.44–0.76], OR [depression] = 1.43 [1.04–1.97], OR [female sex] = 0.45 [0.22–0.92], and OR [levodopa equivalent dose] = 0.78 [0.59–1.04].

Discussion

Apathy occurs across the PD time course and is associated with higher mortality. Depressive symptoms and cognitive impairment in particular predict its future development in those with normal motivation.

From the Department of Medicine (C.L.H., M.R.M., T.R.M., T.P., J.D.-A., T.A., S.H.), University of Otago, Christchurch; New Zealand Brain Research Institute (C.L.H., K.-L.H., M.R.M., L.L., T.R.M., D.M., T.P., J.D.-A., T.A.), Christchurch; Department of Neurology (C.L.H., T.A.), Christchurch Hospital; and Department of Psychology (C.L.H., J.D.-A.), Speech and Hearing, University of Canterbury, Christchurch, New Zealand.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

HR = hazard ratio; **LED** = levodopa equivalent dose; **MoCA** = Montreal Cognitive Assessment; **NPI** = Neuropsychiatric Inventory; **PD** = Parkinson disease.

Introduction

Although apathy is now recognized as one of the most common and debilitating nonmotor symptoms occurring in Parkinson disease (PD),[1,2] the temporal dynamics of it throughout the course of PD remains poorly described.[3] Furthermore, while many cross-sectional studies have investigated associations with apathy, at times with conflicting results, no studies have examined the predictors of de novo apathy development in a large PD sample.[1,4,5] This represents an important knowledge gap because such information is crucial for understanding the reasons apathy develops, planning management strategies, discussing the problem with patients and their families, and ultimately proactively preventing loss of motivation in people at highest risk of it.

This dearth of knowledge is underscored by inconsistencies within the scientific literature and between the literature and clinical experience.[1] Apathy can occur very early in PD and in some people will be a major presenting feature[6-8] but is still presented in many reviews as a nonmotor problem that emerges once the disease is well established.[9] The few longitudinal studies to date have produced contradictory findings on the trajectory of apathy in PD. While all patients with apathy at baseline remained apathetic 4 years later in one study,[10] other work suggests it may remit in some people.[11,12] Furthermore, these studies are all limited to some extent by small sample size, short follow-up times, and often a focus on worsening apathy symptoms rather than the development of apathy in individuals with previously normal motivation.[10-14]

By contrast, significantly more is understood about the cross-sectional associations of apathy in PD.[1,4] Nevertheless, many points remain contentious. One important issue is the relationship between apathy and cognitive impairment. In different studies, apathy has been associated with worse overall cognition generally, more specific dysfunction in particular cognitive domains (often executive), or in fact not related to the degree of cognitive impairment.[1,4,12,15,16] Such disparities leave open competing explanations of this relationship. These include a simple epiphenomenon (with apathy actually determined by specific disruption of neural circuits that underlie reward-based decision-making and normal goal directed behavior); a direct effect such as executive disruption limiting production of normal motivated behavior; or apathy relating to a more general decline in cognitive abilities as the Parkinson brain moves toward a dementia state.[1,4,17,18] While these possibilities are not mutually exclusive, the current inconsistencies between studies impedes development of an overarching etiologic understanding of apathy in PD. In a similar vein, discrepancies also exist regarding levodopa equivalent dose (LED) and apathy presence/severity, with both higher and lower LED associated with apathy in different studies.[1,19,20]

Providing answers to these issues depends on sufficiently large and representative study populations combined with appropriately selected statistical techniques to analyze them. Large longitudinal cohorts with follow-up over long periods, while theoretically providing such a forum, are often convenience samples—meaning people may have been recruited at different stages of disease, followed up for varying lengths of time, and undergone other life events during follow-up, including death.[21] Statistical models provide an important toolset to derive meaningful understanding from such complexity, allowing robust inferences about specific questions to be drawn from a population more reflective of the overall Parkinson spectrum.[22] One example inherent in any longitudinal study is how to model important competing risks that may prevent apathy development, such as death. Another is how to disentangle the influence (or otherwise) of multiple highly correlated variables, as is seen when examining associations between multiple cognitive tests and a variable of interest, such as apathy.

In this study, we use such approaches to probe the trajectories, cross-sectional associations, and longitudinal predictors of apathy in PD in a large cohort of patients followed up for up to 14 years. Our broad hypotheses are that apathy will occur throughout the course of PD, but its presence may fluctuate within individuals; that apathy will have cross-sectional associations similar to those seen in prior studies but that associations with cognitive state will be driven by performance on neuropsychological tasks underpinned by neural regions crucial for normal goal-directed behavior, such as anterior cingulate cortex; and that distinct features will predict de novo development of apathy in those with normal motivation, when accounting for the competing risk of death over time. Finally, we examined whether apathy itself independently predicts death in people with PD.

Methods

Participants

People with PD were identified from the New Zealand Parkinson's Progression Program (NZP[3]), a longitudinal study of PD running at the New Zealand Brain Research Institute in Christchurch since 2007.[21] The cohort is a convenience sample of people with PD, primarily recruited from movement disorders clinics with recruitment continuing throughout the study

duration. As such, it captures a broad cross-section of the local population, as well as being heterogeneous regarding disease stages. At enrollment, patients range from being newly diagnosed to having had PD for 20+ years (Table 1), and some have now been followed up for 14 years (eFigure 1). Patients have been reevaluated in a core group of clinical, psychological, and questionnaire measures at regular intervals (between 6 and 24 months) throughout the study.[21]

Standard Protocol Approvals, Registrations and Patient Consents

Ongoing ethical approval for the NZP3 and associated analyses has been provided by the Health and Disability Ethics Committee (HDEC - URB/09/08/037; URB/09/08/037/AM04).

Apathy Definition

We used the Neuropsychiatric Inventory (NPI) apathy subsection to classify the presence or absence of apathy, based on informant report, because it was the most frequently administered apathy assessment across the time course of the study and has been widely used to assess apathy in many conditions.[23] Although more detailed consensus criteria for the clinical diagnosis of apathy exist, we were unable to apply these because of insufficient detail within our longitudinal dataset.[24,25] We defined apathy as absent or present, based on an NPI-apathy score of 4 or greater.[1,26] We also repeated all analyses using a less stringent cutoff of 1 or greater to capture a wider breadth of apathy severity.[1] A recent study in a subsection of this population suggests the NPI provides an equivalent assessment of apathy presence to a more detailed questionnaire.[27]

Demographic and Clinical Information

Baseline demographic information included age, sex, education, and ethnicity. Core clinical information obtained at each time point included years since diagnosis, medications (including antidepressants), LED, PD motor severity assessed in the ON state (MDS-UPDRS part III, or for those assessed before 2010, and UPDRS-III with appropriate score transformation).[28] Summary statistics for the group based on their *initial assessment* within the longitudinal study is listed in Table 1.

Table Summary Statistics During Recruitment Into Study (Mean [SD])

Sample size	346
Sex (M:F)	242:104
% Apathetic	11.4%[a]
Age (y)	68.8 [7.8]
Education (y)	12.8 [2.6]
Time since diagnosis (y)	5.9 [5.4]
LED (mg)	599 [476]
UPDRS part III score	34.9 [16.6]
MoCA	24.2 [4.1]

Abbreviations: LED = levodopa equivalent dose; MoCA = Montreal Cognitive Assessment.
[a] 23.4% if using NPI ≥1 cutoff.

Questionnaires and Neuropsychological Assessments

A measure of global cognition was obtained using the Montreal Cognitive Assessment (MoCA).[29] In addition, extensive neuropsychological assessments, spanning executive, attentional, memory, language, and visuospatial domains, were also administered longitudinally, and we included a representative selection of 24 tasks across these 5 domains in our analyses (eAppendix 1).[21] Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale,[30] which was available from 2010 onward.

Data Preprocessing and Approach to Missing Data

Data were used from all individuals with a diagnosis of PD and all sessions where neuropsychiatric assessments were performed. Sessions were excluded if there was an explicitly recorded exclusion from the parent study or if there was a more than 3-month gap between the main assessment (clinical, neuropsychological) and the caregiver-administered NPI session. For variables other than the main NPI apathy measure, missing data were imputed by first taking the closest subsequent (or then previous) observation from within the same individual. For those with no observations of a given variable, we used either a single or multiple multivariate imputation strategy depending on the downstream model (eMethods for further details). Finally, variables were z scored when used by the statistical models outlined further.

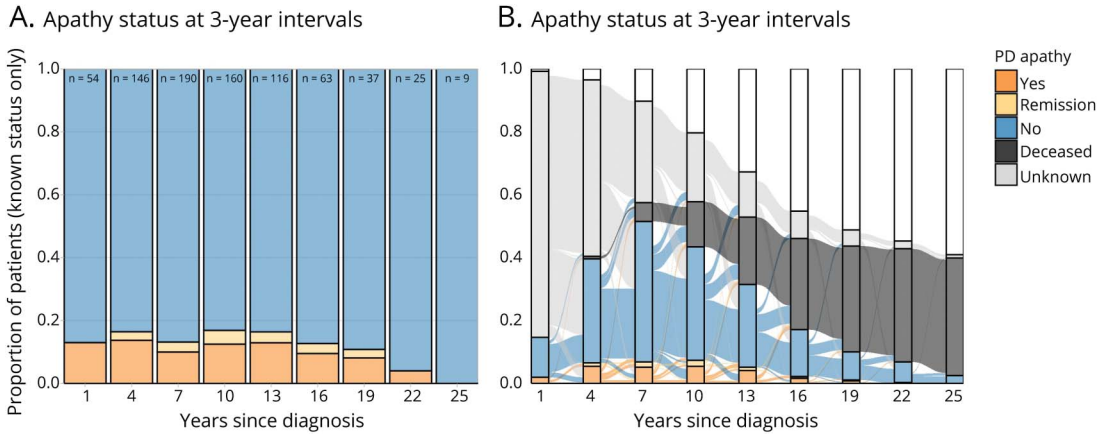
Statistical Models

We used several modeling approaches to explore the presentation of apathy across the PD course, with 2 complementary aims: first, to assess the cross-sectional associations between apathy and common clinical measures across the whole cohort; and, second, to identify any factors that predict the first onset of apathy in people with PD. Full specification of the models is available at github.com/nzbri/pd-apathy.

Cross-Sectional Analyses

First, we used a Bayesian logistic regression (performed using the *brms* package in R)[31] to predict current apathy status from the most relevant core variables (including age, sex, time since diagnosis, education, LED, motor severity, depression, use of antidepressants, MoCA, and anxiety) accounting for the (non-independent) repeated sessions per individual. This was run on the multiply imputed data such that the posterior odds ratios include uncertainty due to missing data. Normal (0, 1) priors were used for the coefficients on the core population-level variables and were left at the *brms* defaults otherwise. This approach produces outputs broadly relatable to previous work examining cross-sectional associations of apathy in PD,

Figure 1 Trajectories of Apathy Across the PD Course



Left panel: the proportion of patients with PD with apathy did not vary significantly with time since diagnosis. Right panel: Alluvial plot showing changes in group membership at each time point since diagnosis. Some remission of apathy is evident at each time point. *Unknown* refers to time points before inclusion in the study (because most people were recruited at a time point following their diagnosis). PD = Parkinson disease.

while allowing us to examine additional questions such as whether the presence of apathy is associated with disease duration.

Next, to determine whether performance on specific cognitive tests is associated with apathy presence, we ran a second analysis that included the full battery of cognitive tests, but not MoCA. Because many of these tests are correlated, we used a cross-validated, regularized sparse regression (*glmnet* in R).[32] Because this does not by itself account for the repeated measures structure to the data, we randomly subsampled the data down to 1 session per individual and collated model parameters across 1,000 such resamplings. The main output from this model is the proportion of times each variable made a non-zero contribution to predicting apathy presence, across the resampling process. Significance was assessed through a permutation test, where the analyses were repeated but apathy status was shuffled across individuals within each resampling.[33]

Longitudinal Analysis

We used a multistate model (*msm* in R) to look for factors that predict the initial onset of apathy, while accounting for the competing risk of mortality.[34,35] In this model, patients can transition from a nonapathetic state to an apathetic one and can also die. Crucially, the probabilities of these transitions are modulated by the variables describing a patient's current symptoms and characteristics. We then used the outputs from the multistate model to estimate the risk (hazard ratio [HR]) of death associated with developing apathy, after accounting for all other variables. Finally, to provide a more nuanced view of apathy across the course of PD, we plotted exemplar trajectories of apathy in PD, as predicted by the model. These are plotted as a function of key variables such as cognition, motor status, and LED, while all other predictors are fixed to the group average values.

Data Availability

Code to fit the models and further visualizations of this dataset are freely available at github.com/nzbri/pd-apathy. Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

Results

Three hundred forty-six participants with PD, followed up for up to 14 years and with up to 25 years of PD duration, were assessed across 1,392 sessions.

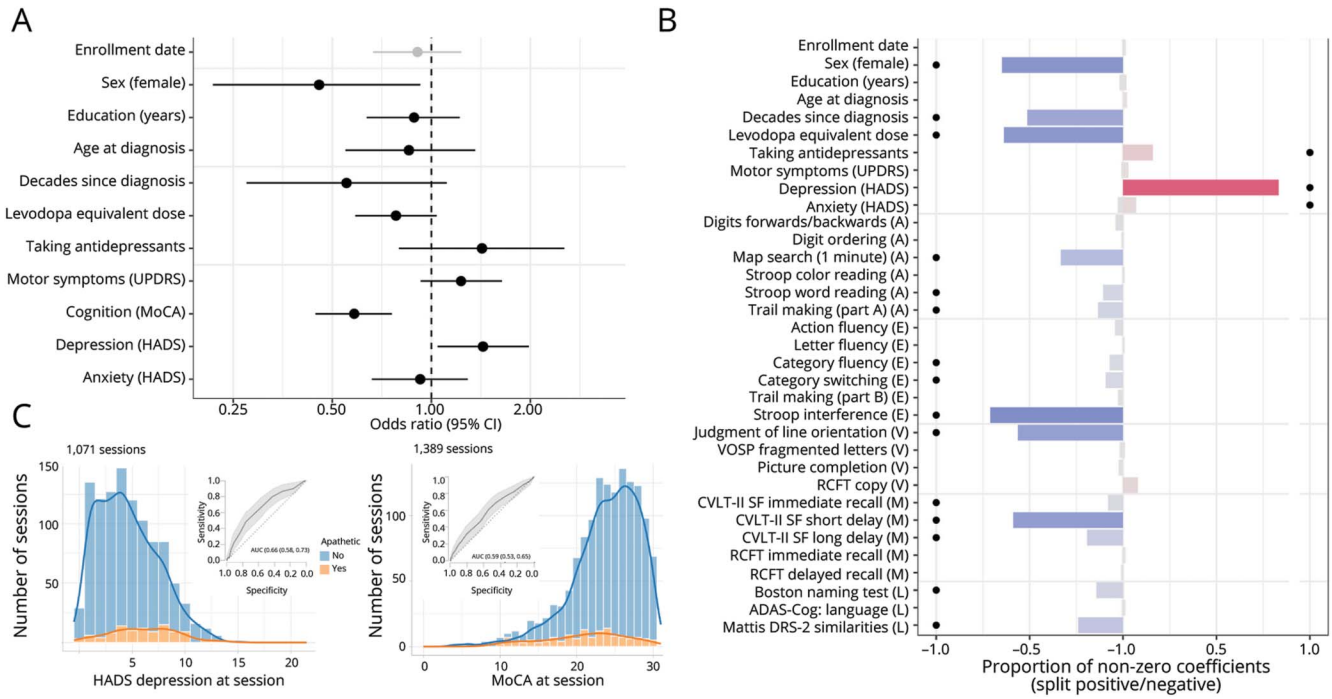
Trajectories and Prevalence

The proportion of people with PD who were apathetic did not vary significantly as a function of time since diagnosis (PE: 0.55, [95% CI 0.28–1.12] Figure 1A). At any given point, approximately 11% of people were classified as apathetic based on the NPI scale cutoff of ≥4 (22% with a less stringent cutoff of ≥1). Plotting individual trajectories demonstrates that there was some movement between groups, with approximately 19% of those previously classified as apathetic *remitting* to a nonapathetic state at the following time point (Figure 1B and eTable1). In total, 18 individuals were classified as in remission from apathy symptoms (identified as the group in yellow on Figure 1, A and B), of which only 6 individuals met the apathy classification cutoff at a subsequent time point.

Cross-Sectional Associations of Apathy in PD

In the Bayesian logistic regression, the presence of apathy was significantly associated with sex (lower risk in female individuals, odds ratio [95% CI] = 0.45 [0.22–0.92]), lower cognition (MoCA score, OR = 0.58 [0.44–0.76]), and higher levels of depression (OR = 1.43 [1.04–1.97], Figure 2A).

Figure 2 Cross-Sectional Associations With Apathy



(A) Bayesian logistic regression showing that sex, LED, MOCA, and depression were also significantly associated with apathy presence. (B) Regularized sparse regression applied to core predictor variables plus multiple different neuropsychological tests (allowing for the highly correlated nature of these.) The x-axis plots the proportion of times each variable made a non-zero contribution to predicting the presence of apathy, across the 1,000 resamplings. The black dots indicate whether the variable's relationship with apathy was statistically significant. (C) Stacked histograms of depression and MoCA scores split by apathy status, demonstrating that although these variables are associated with apathy, there remains significant overlap between the groups. Insets—an alternative way to conceptualize the effect size of these relationships is to examine the performance of a predictor in identifying apathy status, which here, while significant, is clearly not strong. LED = levodopa equivalent dose; MoCA = Montreal Cognitive Assessment.

Lower LED trended toward an association with apathy, although this was not significant (OR = 0.78 [0.59–1.04]). There was no significant relationship between apathy and severity of motor symptoms (OR = 1.23 [0.93–1.63]). Full model parameters are available in the Supplementary material in eAppendix 2, Model Outputs.

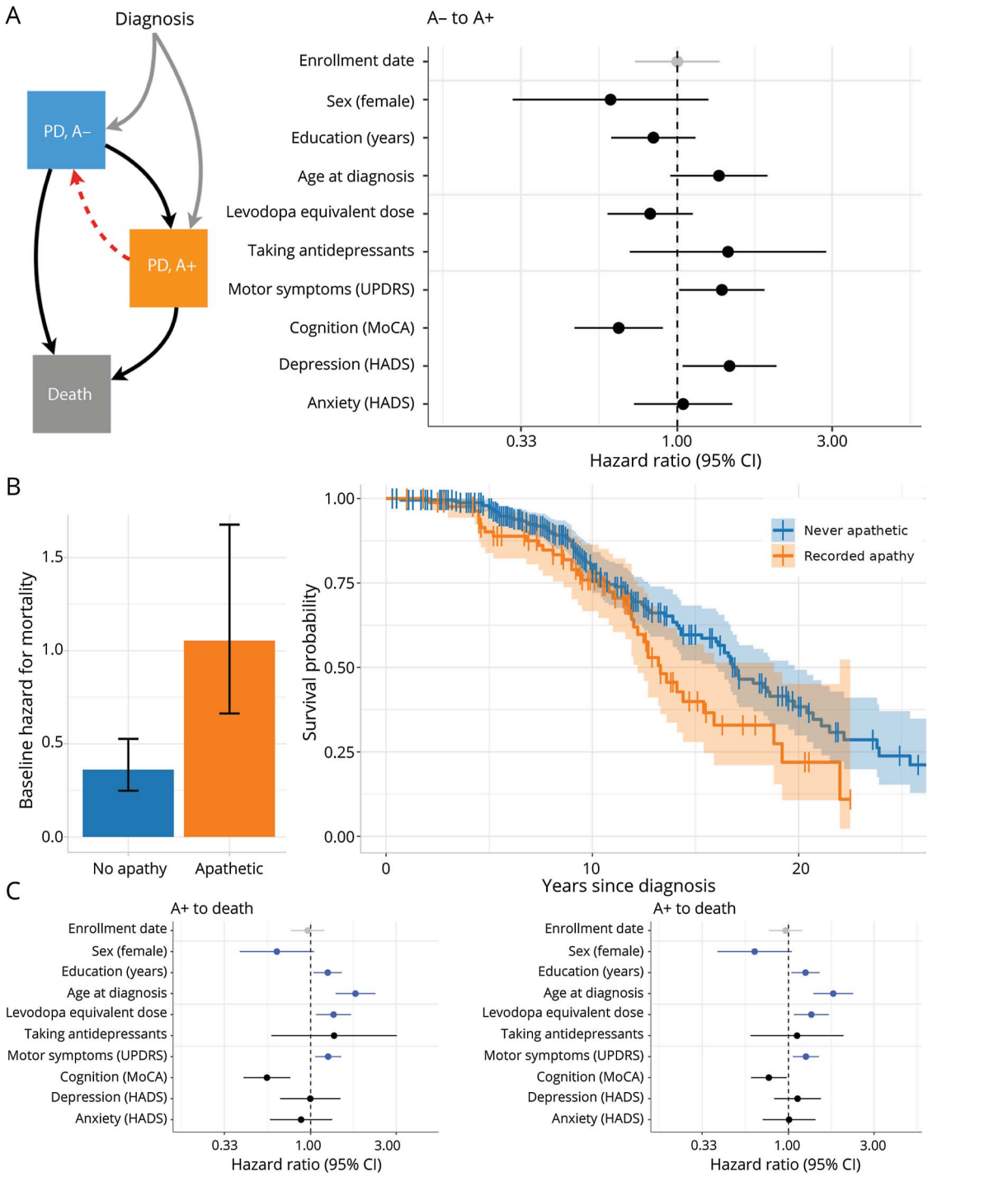
It is also important to consider the effect size of the observed associations when considering their relative importance—both for an individual patient and, more broadly, for the relationship between these variables and apathy. To illustrate this, we plot the histograms of the raw data—essentially a pictorial representation of univariate effect sizes—for 2 of the significant associations, depression and MoCA score (Figure 2C). The marked overlap in apathy and nonapathy distributions makes it clear that knowing details of these measures for a given patient still gives you little information about their apathy status. Thus, these variables, while associated with apathy, are also dissociable from it. This point is further emphasized by the poor performance, based on area under the curve of a receiver operating characteristic analysis using these variables to predict apathy status (Figure 2C—insets).

Next, we repeated the cross-sectional analysis including 24 individual neuropsychological tests instead of the MoCA, using a cross-validated, regularized sparse regression with resampling to account for the correlated nature of the data. This demonstrated very strong effects of the same variables identified in the previous model (sex and depression) and lower LED. Many of the neuropsychological tests, deriving from different cognitive domains, showed the same inverse relationship with apathy as the broader MoCA score, with the strongest associations including Stroop interference, judgment of line orientation, and CVLT immediate recall (Figure 2B and eAppendix 2 Model Outputs).

Longitudinal Predictors of Apathy

Two hundred ninety-eight people were included in the predictive model, which, across 1,168 sessions, included 48 transitions to apathy and 131 deaths. In people with PD and normal motivation, lower cognition, higher levels of depressive symptoms, and a higher UPDRS motor score, all independently predicted the future development of apathy (MoCA: HR [95% CI] = 0.66 [0.48–0.90]; depression: HR = 1.45 [1.04–2.02]; motor score: HR = 1.37 [1.01–1.86], Figure 3A). No other factors were significant predictors for transition to apathy. After controlling for all other variables, the presence of apathy was independently associated with a significantly higher risk of death (HR = 2.92 [1.50–5.66], Figure 3B). Otherwise, significant predictors of death were similar between both apathetic and non-apathetic groups and

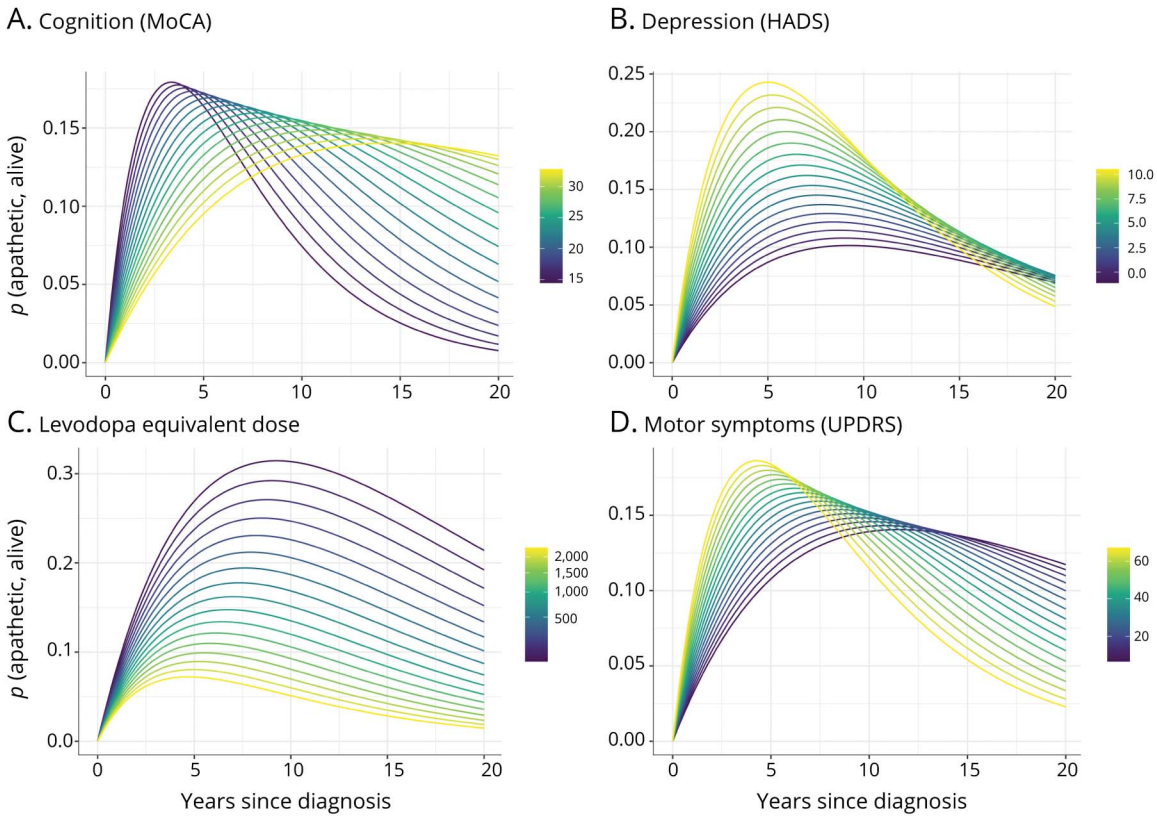
Figure 3 Multistate Model to Assess Longitudinal Predictors of Apathy Development



(A) Following PD diagnosis, lower cognition, higher levels of depression, and higher UPDRS motor score all significantly predicted transition from nonapathetic to apathetic states. (B) Apathy was associated with a significantly higher chance of death across the course of PD, after accounting for all other factors. (C) Higher education, greater age at diagnosis, higher LED, greater motor symptoms, and lower cognition were all associated with greater risk of subsequent death, irrespective of apathy status. LED = levodopa equivalent dose; PD = Parkinson disease.

included older age at diagnosis, higher UPDRS-III motor scores, higher LED, lower cognitive scores, and higher education level (see Figure 3C and, for full model outputs eAppendix 2). Although it would be of interest to examine predictors of change from apathy to no apathy status, the numbers in this study were not sufficient to confidently model this reverse transition (eFigure 2). Finally, we used the outputs from the multistate model to plot exemplar trajectories of apathy when accounting for the competing risk of death, as a function of important factors associated with its presence or general progression of PD (Figure 4). These plots provide a more nuanced view of apathy risk across the disease course

Figure 4 Exemplar Predicted Trajectories of Apathy From the Multistate Model



Although at a group level, apathy rates were similar across the disease course, they do vary significantly as a function of associated variables and the risk of death. These plots illustrate this for cognition (A), depression (B), LED (C), and motor symptoms (D), showing how each of these variables influences the chances of being alive and apathetic at each time point from diagnosis. As an example, the relationship between cognition, apathy, and death is visualized across the PD time course in (A). In the first years after diagnosis, the probability of being apathetic (and alive) is higher in those with lower baseline cognition, whereas in subsequent years, this relationship reverses (because both lower cognition and apathy are associated with a higher mortality rate). LED = levodopa equivalent dose; PD = Parkinson disease.

than the alluvial plots (Figure 1), which average across these factors at each time point.

A number of people experienced apathetic symptoms but below the NPI score of 4 threshold. Therefore, we also repeated all analyses with a more inclusive cutoff of NPI apathy score greater than or equal to 1. Using this cutoff, approximately 22% of the group were apathetic at any time point, again not varying as a function of time since diagnosis (OR = 0.60, [95% CI: 0.33–1.08], eFigure 3. The remainder of analyses remained very similar to the more stringent NPI cutoff presented above, with the exception that a significant relationship between lower LED and apathy was seen in both the cross-sectional and longitudinal models, while higher UPDRS motor score no longer predicted future development of apathy. Full results of this additional analysis are presented in eAppendix 2 Model Outputs and eFigures 4, 5, and 6.

Discussion

We used sophisticated modeling techniques to explore the longitudinal predictors and trajectories and cross-sectional associations of apathy in PD from a large population of people with PD followed up for up to 14 years. Using a multistate model that accounted for the competing risk of death as PD progressed, we identified 3 significant predictors for the development of apathy in individuals who were not currently apathetic—greater cognitive impairment, higher levels of depression, and a higher UPDRS motor score. Cognitive impairment and depression—but not motor score—were also associated with apathy cross-sectionally, but here we demonstrate that changes in these variables clearly precede the development of apathy, strengthening the case for a casual (direct or indirect) relationship. At a group level, apathy rates were similar throughout the time course of PD, although individuals demonstrated some variability in their status. Of importance, the presence of apathy at any disease stage was associated with a higher risk of death, underscoring the significance of this nonmotor feature of PD. As we discuss further, these findings provide insights into possible pathways of apathy development and identifying opportunities to intervene to prevent it occurring.

Although depression is often associated with, although dissociable from, apathy—both in PD and other conditions—this

study demonstrates that greater depressive symptoms are associated with future apathy development in previously motivated individuals.[4,5,36] There are different possibilities to explain this relationship. Current computational psychiatry conceptualizations of depression acknowledge multiple potential biological components. Some of these, particularly anhedonia, likely share mechanisms with apathy, particularly around the evaluation of rewards, and translation of this information into actions toward goals.[37] In addition, there may be specific effects of the depressed state that could lead to apathy, including devaluing outcomes of behaviors, reducing estimates of the background reward environment, and causing social isolation.[38] With time, such factors could distort cost-benefit decision-making processes that lie at the heart of normal goal-directed behavior, resulting in the apathetic phenotype.[18] Finally, in theory, it is possible that treatments associated with depression could lead to the development of apathy. In the animal literature, selective serotonin reuptake inhibitors have been shown to reduce willingness to work for rewards.[39] However, the absence of a relationship between antidepressant use and apathy in the cross-sectional analyses argues strongly against this possibility.

Similar to depression, cognitive dysfunction is also frequently associated with apathy, but again here this study demonstrates its presence predicts future apathy development. This finding could be explained by dysfunction of the normal processes underlying the production of motivated behavior.[17,18,39] Although we assessed cognition relatively crudely in the multistate analysis (using the MoCA), the results of the regularized sparse regression, whereby particular neuropsychological tests were most strongly associated with apathy cross-sectionally, provide some support to this possibility. In particular, the stroop interference task relies on neural populations within anterior cingulate cortex—a region also crucial for integrating rewards and efforts to drive behavior toward goals and strongly associated with apathy.[40-44] Similarly, in theory, impaired performance on judgment of line orientation tasks and immediate recall could reflect cholinergic dysfunction, a neurotransmitter also closely associated with aspects of normal goal-directed behavior and for which modulation can improve apathy in some patients with PD.[39,45] However, just as with depression, it may also be that lower cognition sets up a state where an individual is more likely to become apathetic—such as a less stimulating environment, poorer social connections, or reduced ability to generate potential options. Although we cannot tease these possibilities apart in this study, such changes are theoretically modifiable—through pharmacologic but also environmental and psychological manipulations, and may present an important opportunity to prevent the development of apathy in people with PD.

There was some evidence of an association between lower LED and apathy cross-sectionally, with a significant relationship demonstrated by the sparse regression—but not the logistic regression—model, and both a cross-sectional and longitudinally predictive association at the less stringent NPI cutoff of ≥1. Although a cross-sectional relationship between LED and apathy could in theory be explained by people being undertreated as a consequence of apathy, this seems less likely given that motor severity, assessed in the ON state, although predictive of future apathy development was not associated with apathy cross-sectionally in either the logistic or sparse regression models. Instead, the results suggest that people who require lower doses of dopamine to treat their motor symptoms are more likely to have apathy. A prominent hypothesis is that people with PD who develop apathy have relatively greater denervation in mesolimbic compared with nigrostriatal dopaminergic circuits.[4] Thus, titrating dopaminergic treatment to a motor response may be inadequate in this subgroup. In the future, clinical assessments could be augmented by specific behavioral or physiologic measures—such as indices of reward sensitivity—which may identify those who could benefit from additional pharmacotherapy, although this is an area that requires more work.[18,37,43]

People with PD who have apathy were at a significantly higher risk of dying, even after accounting for potential confounders such as lower cognition, age, and motor severity. To our knowledge, such a relationship has not been previously demonstrated in PD, although has been observed in association with general aging.[46] Along with clear data demonstrating the negative impact of apathy on quality of life,[2] this underscores the clinical importance of amotivation in PD. There are many potential reasons for this association with mortality. These could be relatively straightforward, such as apathetic people being less likely to seek assistance for other health problems, take medications, or exercise regularly. However, there is also an emerging concept of demoralization in the literature, which may overlap with aspects of apathy and have more direct effects on mortality.[47] We should be clear, however, that our multistate predictive model places apathy *primus inter pares*; while apathy is associated with early mortality, our cross-sectional analyses showed how apathy is also related to cognitive impairments and depression. As such, mortality is affected by all these interrelated cognitive and psychological issues.

In contrast to some other neurodegenerative conditions, such as Huntington disease,[48] group apathy rates remained stable across the course of PD, although individuals did vary in their motivational state across time. Furthermore, although stable at a group average level, exemplar plots from the multistate model demonstrate how the probability of being alive and apathetic with PD does change across the disease time course, based on the contribution of other factors that predict apathy development and death. Another consideration is whether the mechanisms underlying apathy may vary across the disease course. It is plausible that apathy occurring earlier in the course of PD is driven by dysfunction within key neuromodulatory systems such as the mesolimbic dopaminergic or noradrenergic systems—both integral for translating reward and effort information into goal-directed actions—while at later stages, dysfunction within other systems (e.g., cholinergic) and increasing degeneration within cortical brain regions crucial for goal-directed behaviors become a more significant

driver.[4] Broadly, this means that stable rates of apathy across the disease course does not imply a single mechanism, but this study is not able to disentangle these putative differences and remains a general summary of apathy across the course of PD. Future work is needed to explore these possibilities—which in themselves may point to differing treatment strategies.

We believe the results of this study should generalize to other populations of people with PD. The cross-sectional associations with apathy seen in our cohort were broadly in line with previous work; the demographic and baseline (at recruitment) clinical characteristics were also comparable with other published samples,[49] while within the multistate model, irrespective of apathy status, lower cognition, older age, higher LED, and greater motor symptoms were all associated with a higher risk of death, consistent with other studies.[50-52] The real-world nature of the dataset, recruited longitudinally as a convenience sample, allowed us to build up a picture across the spectrum of PD, but does present some challenges for data analysis—challenges we met with the application of sophisticated Bayesian frameworks. However, we cannot exclude the possibility of bias that could affect particularly apathy rates, such as people with cognitive impairment being more likely to leave the study or those who already had apathy being less likely to enroll. We also were not able to control for fatigue symptoms in this cohort because of the absence of a longitudinally collected fatigue measure. The prevalence of apathy in this study (either 11% or 22% depending on NPI cutoff score used) was lower than many previous studies. While this could be related partly to the apathy measure (NPI), it is important to note that recruitment was based on a convenience sample rather than a systematic study, and thus, the prevalence of apathy may have been underestimated, for example, if those with apathy were less likely to want to engage in a longitudinal study. However, we do not expect this to significantly influence the longitudinal analyses that probed the development of apathy in people already enrolled in the study, while cross-sectional relationships were generally aligned with previously published work, including neuroanatomical associations with apathy that were assessed in this cohort in a recently published study.[53] Reflecting the longitudinal nature of our data collection (since 2007), our assessment of apathy was based on the NPI apathy subscale, an informant-derived measure that does not allow exploration of putative components/dimensions of amotivation. However, evidence suggests the NPI remains a robust—albeit crude—measure of apathy. Nevertheless, repeating these analyses using the same models and a more in-depth apathy measure in another large, independent sample does remain an important next step that would allow exploration of how these different dimensions change across time in people with PD.

Apathy remains one of the most significant nonmotor symptoms associated with PD. In this study, we demonstrate clearly that it can occur at any stage of disease, and its presence is associated with a higher risk of mortality. Depressive symptoms, cognitive impairment, worse motor symptoms, and possibly lower LED, all predict its subsequent development, providing insights into mechanisms that may drive loss of motivation and identifying potential therapeutic or preventative targets for this debilitating problem.

Acknowledgment

The authors thank all the people with PD and their families who have so willingly engaged in the longitudinal study that generated these data.

Study Funding

This study was primarily supported by a Canterbury Medical Research Foundation grant (to CLH), while funding from Health Research Council of New Zealand and Neurologic Foundation, Rangahou Roro Aotearoa, Canterbury Medical Research Foundation, New Zealand Brain Research Institute, Lottery Health Research, and the University of Otago have supported the longitudinal New Zealand Parkinson's Progression Program since 2007.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* August 18, 2023. Accepted in final form February 13, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Peter Hedera, MD, PhD.

Appendix Authors

Name	Location	Contribution
Campbell Le Heron, DPhil	Department of Medicine, University of Otago, Christchurch; New Zealand Brain Research Institute, Christchurch; Department of Neurology, Christchurch Hospital; Department of Psychology, Speech and Hearing, University of Canterbury, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Kyla-Louise Horne, PhD	New Zealand Brain Research Institute, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Michael R. MacAskill, PhD	Department of Medicine, University of Otago, Christchurch; New Zealand Brain Research Institute, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Leslie Livingstone, BA(Hons)	New Zealand Brain Research Institute, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Tracy R. Melzer, PhD	Department of Medicine, University of Otago, Christchurch; New Zealand Brain Research Institute, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Daniel Myall, PhD	New Zealand Brain Research Institute, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Toni Pitcher, PhD	Department of Medicine, University of Otago, Christchurch; New Zealand Brain Research Institute, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
John Dalrymple-Alford, PhD	Department of Medicine, University of Otago, Christchurch; New Zealand Brain Research Institute, Christchurch; Department of Psychology, Speech and Hearing, University of Canterbury, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Tim Anderson, PhD	Department of Medicine, University of Otago, Christchurch; New Zealand Brain Research Institute, Christchurch; Department of Neurology, Christchurch Hospital, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Samuel Harrison, DPhil	Department of Medicine, University of Otago, Christchurch, New Zealand	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data

References

1. den Brok MGHE, van Dalen JW, van Gool WA, Moll van Charante EP, de Bie RMA, Richard E. Apathy in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord.* 2015;30(6):759-769. doi:10.1002/mds.26208
2. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord.* 2009;24(11):1641-1649. doi:10.1002/mds.22643
3. Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. *Lancet Neurol.* 2018;17(6):559-568. doi:10.1016/S1474-4422(18)30127-3
4. Pagonabarraga J, Kulisevsky J, Strafella AP, Krack P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *Lancet Neurol.* 2015;14(5):518-531. doi:10.1016/S1474-4422(15)00019-8
5. Pedersen KF, Larsen JP, Alves G, Aarsland D. Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. *Parkinsonism Relat Disord.* 2009;15(4):295-299. doi:10.1016/j.parkreldis.2008.07.006
6. Aarsland D, Brønnick K, Alves G, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2009;80(8):928-930. doi:10.1136/jnnp.2008.166959
7. Santangelo G, Barone P, Cuoco S, et al. Apathy in untreated, de novo patients with Parkinson's disease: validation study of Apathy Evaluation Scale. *J Neurol.* 2014;261(12):2319-2328. doi:10.1007/s00415-014-7498-1
8. Dujardin K, Langlois C, Plomhause L, et al. Apathy in untreated early-stage Parkinson disease: relationship with other non-motor symptoms. *Mov Disord.* 2014;29(14):1796-1801. doi:10.1002/mds.26058
9. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primer.* 2017;3(1):17013. doi:10.1038/nrdp.2017.13
10. Pedersen KF, Alves G, Aarsland D, Larsen JP. Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. *J Neurol Neurosurg Psychiatry.* 2009;80(11):1279-1282. doi:10.1136/jnnp.2008.170043
11. Santangelo G, Vitale C, Trojano L, et al. Relationship between apathy and cognitive dysfunctions in de novo untreated Parkinson's disease: a prospective longitudinal study. *Eur J Neurol.* 2015;22(2):253-260. doi:10.1111/ene.12467
12. Ou R, Lin J, Liu K, et al. Evolution of apathy in early Parkinson's disease: a 4-years prospective cohort study. *Front Aging Neurosci.* 2020;12:620762. doi:10.3389/fnagi.2020.620762
13. Zahodne LB, Marsiske M, Okun MS, Rodriguez RL, Malaty I, Bowers D. Mood and motor trajectories in Parkinson's disease: multivariate latent growth curve modeling. *Neuropsychology.* 2012;26(1):71-80. doi:10.1037/a0025119
14. Wee N, Kandiah N, Acharyya S, et al. Baseline predictors of worsening apathy in Parkinson's disease: a prospective longitudinal study. *Parkinsonism Relat Disord.* 2016;23:95-98. doi:10.1016/j.parkreldis.2015.12.004
15. Dujardin K, Sockeel P, Delliaux M, Destée A, Defebvre L. Apathy may herald cognitive decline and dementia in Parkinson's disease. *Mov Disord.* 2009;24(16):2391-2397. doi:10.1002/mds.22843
16. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Katz IR, Stern MB. Dimensions of executive function in Parkinson's disease. *Dement Geriatr Cogn Disord.* 2005;20(2-3):140-144. doi:10.1159/000087043
17. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex–basal ganglia circuits. *Cereb Cortex.* 2006;16(7):916-928. doi:10.1093/cercor/bhj043
18. Le Heron C, Holroyd CB, Salamone J, Husain M. Brain mechanisms underlying apathy. *J Neurol Neurosurg Psychiatry.* 2019;90(3):302-312. doi:10.1136/jnnp-2018-318265
19. Ziropadja L, Stefanova E, Petrovic M, Stojkovic T, Kostic VS. Apathy and depression in Parkinson's disease: the Belgrade PD study report. *Parkinsonism Relat Disord.* 2012;18(4):339-342. doi:10.1016/j.parkreldis.2011.11.020
20. Skorvanek M, Rosenberger J, Gdovinova Z, et al. Apathy in elderly nondemented patients with Parkinson's disease: clinical determinants and relationship to quality of life. *J Geriatr Psychiatry Neurol.* 2013;26(4):237-243. doi:10.1177/0891988713500587
21. MacAskill MR, Pitcher TL, Melzer TR, et al. The New Zealand Parkinson's progression programme. *J R Soc N Z.* 2022;53(4):466-488. doi:10.1080/03036758.2022.2111448
22. Frässle S, Aponte EA, Bollmann S, et al. TAPAS: an open-source software package for translational neuromodeling and computational psychiatry. *Front Psychiatry.* 2021;12:680811. doi:10.3389/fpsyt.2021.680811
23. Radakovic R, Harley C, Abrahams S, Starr JM. "A systematic review of the validity and reliability of apathy scales in neurodegenerative conditions": Corrigendum. *Int Psychogeriatr.* 2015;27(6):925. doi:10.1017/S1041610214002828
24. Robert P, Lanctôt KL, Agüera-Ortiz L, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *Eur Psychiatry.* 2018;54:71-76. doi:10.1016/j.eurpsy.2018.07.008
25. Robert P, Onyike CU, Leentjens AFG, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry.* 2009;24(2):98-104. doi:10.1016/j.eurpsy.2008.09.001
26. Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, García-Sánchez C, Gironell A, Trapecio Group Study. Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. *Mov Disord.* 2008;23(13):1889-1896. doi:10.1002/mds.22246
27. Thompson N, MacAskill M, Pascoe MJ, Anderson T, Heron CL. Dimensions of apathy in Parkinson's disease. *Brain Behav.* 2023;13(6):e2862. doi:10.1002/brb3.2862
28. Goetz CG, Stebbins GT, Tilley BC. Calibration of unified Parkinson's disease rating scale scores to Movement Disorder Society-unified Parkinson's disease rating scale scores. *Mov Disord.* 2012;27(10):1239-1242. doi:10.1002/mds.25122
29. Nasreddine ZS, Phillips NA, Bédirian V, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
30. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x
31. Bürkner PC. brms: an R package for Bayesian multilevel models using stan. *J Stat Softw.* 2017;80(1):1-28. doi:10.18637/jss.v080.i01
32. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw.* 2010;33(1):1-22. doi:10.18637/jss.v033.i01
33. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc.* 1996;91(434):473-489. doi:10.2307/2291635
34. Hamilton CA, Matthews FE, Donaghy PC, et al. Progression to dementia in mild cognitive impairment with Lewy bodies or Alzheimer disease. *Neurology.* 2021;96(22):e2685–e2693. doi:10.1212/WNL.0000000000012024
35. Jackson C. Multi-state models for panel data: the msm package for R. *J Stat Softw.* 2011;38(8):1-28. doi:10.18637/jss.v038.i08
36. Starkstein SE, Ingram L, Garau ML, Mizrahi R. On the overlap between apathy and depression in dementia. *J Neurol Neurosurg Psychiatry.* 2005;76(8):1070-1074. doi:10.1136/jnnp.2004.052795
37. Costello H, Berry AJ, Reeves S, et al. Disrupted reward processing in Parkinson's disease and its relationship with dopamine state and neuropsychiatric syndromes: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2022;93(5):555-562. doi:10.1136/jnnp-2021-327762
38. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev.* 2011;35(3):537-555. doi:10.1016/j.neubiorev.2010.06.006
39. Salamone JD, Yohn SE, López-Cruz L, San Miguel N, Correa M. Activational and effort-related aspects of motivation: neural mechanisms and implications for psychopathology. *Brain.* 2016;139(Pt 5):1325-1347. doi:10.1093/brain/aww050
40. Kolling N, Behrens T, Wittmann MK, Rushworth M. Multiple signals in anterior cingulate cortex. *Curr Opin Neurobiol.* 2016;37:36-43. doi:10.1016/j.conb.2015.12.007

41. Klein-Flügge MC, Kennerley SW, Friston K, Bestmann S. Neural signatures of value comparison in human cingulate cortex during decisions requiring an effort-reward trade-off. *J Neurosci.* 2016;36(39):10002-10015. doi:10.1523/JNEUROSCI.0292-16.2016
42. Le Heron C, Apps MAJ, Husain M. The anatomy of apathy: a neurocognitive framework for amotivated behaviour. *Neuropsychologia*. 2018;118(Pt B):54-67. doi:10.1016/j.neuropsychologia.2017.07.003
43. Holroyd CB, Umemoto A. The research domain criteria framework: the case for anterior cingulate cortex. *Neurosci Biobehav Rev.* 2016;71:418-443. doi:10.1016/j.neubiorev.2016.09.021
44. Pardo JV, Pardo PJ, Janer KW, Raichle ME. The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proc Natl Acad Sci U S A.* 1990;87(1):256-259. doi:10.1073/pnas.87.1.256
45. Devos D, Moreau C, Maltête D, et al. Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial. *J Neurol Neurosurg Psychiatry*. 2014;85(6):668-674. doi:10.1136/jnnp-2013-306439
46. Eurelings LS, van Dalen JW, Ter Riet G, et al. Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: a systematic review and meta-analysis of individual participant data. *Clin Epidemiol.* 2018;10:363-379. doi:10.2147/CLEP.S150915
47. de Figueiredo JM, Zhu B, Patel A, Kohn R, Koo BB, Louis ED. From perceived stress to demoralization in Parkinson disease: a path analysis. *Front Psychiatry*. 2022;13:876445. doi:10.3389/fpsyt.2022.876445
48. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2012;24(1):53-60. doi:10.1176/appi.neuropsych.11030057
49. Hoogland J, van Wanrooij LL, Boel JA, et al. Detecting mild cognitive deficits in Parkinson's disease: comparison of neuropsychological tests. *Mov Disord.* 2018;33(11):1750-1759. doi:10.1002/mds.110
50. De Pablo-Fernández E, Lees AJ, Holton JL, Warner TT. Prognosis and neuropathologic correlation of clinical subtypes of Parkinson disease. *JAMA Neurol.* 2019;76(4):470-479. doi:10.1001/jamaneurol.2018.4377
51. Willis AW, Schootman M, Kung N, Evanoff BA, Perlmutter JS, Racette BA. Predictors of survival in patients with Parkinson disease. *Arch Neurol.* 2012;69(5):601-607. doi:10.1001/archneurol.2011.2370
52. Gonzalez MC, Dalen I, Maple-Grødem J, Tysnes OB, Alves G. Parkinson's disease clinical milestones and mortality. *NPJ Parkinson's Dis.* 2022;8(1):58. doi:10.1038/s41531-022-00320-z
53. Morris LA, Harrison SJ, Melzer TR, et al. Altered nucleus accumbens functional connectivity precedes apathy in Parkinson's disease. *Brain*. 2023;146(7):2739-2752. doi:10.1093/brain/awad113