Dynamic Interplay of Cognitive Functioning and Depressive Symptoms in Patients With Parkinson's Disease

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Study Registration. The DeNoPa study was conducted according to the Declaration of Helsinki and all participants provided informed written consent. Approval was received from the ethical standards committee on human experimentation for all experiments with human participants (approval no. FF89/2008). The study is registered at the German Register for Clinical Trials (DRKS00000540) according to the World Health Organization Trial Registration Data Set.

Open Practices and Data Sharing. Annotated analyses scripts and data to reproduce the main results are provided in an online repository (https://osf.io/ax9nk/).

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Abstract

Objective: We examine the trajectories of and the dynamic interplay between cognitive functioning and depressive symptoms in patients with Parkinson's disease (PD) in comparison to healthy controls (HC) from an intraindividual perspective.

Method: The DeNoPa study is a single-center, observational, longitudinal study with biennial follow-ups over 8 years. The present analyses are based on 123 PD (79 male) and 107 HC (64 male) with a mean age of 64.1 years ($SD = 8.3$). PD and HC completed a battery of neuropsychological tests and scales assessing depressive symptoms. We used a random-intercept cross-lagged panel model to study their trajectories and the dynamic interplay.

Results: Cognitive abilities of PD were on average $d = -0.67$ worse at baseline and $d = -1.22$ at 8-years follow-up in comparison to HC. Depressive symptoms in PD showed a large variability and followed a U-shaped trajectory. From an intraindividual perspective, greater impairments in cognitive abilities were subsequently associated with increased depressive symptoms ($b = -0.60$, $p = .03$), whereas the effect in the opposite direction was not significant.

Conclusions: We found indication that a decline on a global composite scale of cognition can be seen as precursor of depressive symptoms in patients with PD. To counter cognitive losses and the subsequent mood deterioration, patient education and early cognitive (and behavioral) enrichment seem promising candidates for treatment.

Keywords: Parkinson's Disease, Longitudinal Study, Cognitive Functioning, Depressive Symptoms, random-intercept cross-lagged panel

Key Points

Question: What is the dynamic interplay between cognitive functioning and depressive symptoms in patients with Parkinson's disease?

Findings: From an intraindividual perspective, a decrease in cognitive functioning was subsequently associated with increased depressive symptoms, but not vice versa.

Importance: To counter cognitive losses and the subsequent mood deterioration, patient education and early cognitive (and behavioral) enrichment seem promising candidates for treatment.

Next Steps: Intensive longitudinal data collection using smartphones may allow for a more fine-grained assessment and modeling of the dynamic interplay of non-motor symptoms in patients with Parkinson's disease.

Dynamic Interplay of Cognitive Functioning and Depressive Symptoms in Patients With

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease with an increasing prevalence with age, that is, approx. 1% of the population over 70 years and 2% over 80 years have PD (Pringsheim et al., 2014). The prevalence of PD is expected to increase due to improvement in medical treatment and increasing life expectancy, with estimates of up to 4% of the population by the year 2050 (Rocca, 2018). PD is most commonly known as a movement disorder and accordingly the focus in the diagnosis of PD is on motor symptoms (e.g., tremor, rigidity, bradykinesia). However, non-motor symptoms including cognition, depression, and anxiety are also common and severely affect patients' quality of life (Jones et al., 2015). Recently, there have been significant advances in biomarker research (Ferreira et al., 2020) and the underlying neurophysiological pathways of PD are now better understood (e.g., the systemic spreading of alpha-synuclein aggregates; Wang et al., 2019). From the perspective of clinical practice, research on the course of non-motor symptoms and their dynamic interplay is important to possibly establish different pheno- or progression types of the disease, to identify windows for intervention, and to balance the different therapeutic strategies.

Cognitive Functioning in Patients With Parkinson's Disease

More than 40% of patients with PD suffer from mild cognitive impairment (MCI) within five years of diagnosis with a high risk of dementia in later stages of the disease (Broeders et al., 2013; Monastero et al., 2018; Pedersen et al., 2017). PD-MCI is defined by a gradual decline in cognitive abilities without significant restrictions in everyday life (for details see the diagnostic criteria in the Guidelines of the Movement Disorder Society Task Force, Litvan et al., 2012). The annual conversion rates to dementia of patients with PD with MCI are approx. 12%, which is

higher than the annual progression rates from MCI to dementia of 6-10% in the general

population (Pedersen et al., 2017; Petersen et al., 2009).

Although the majority of studies examined cognitive impairment of patients with PD

cross-sectionally, there are more than twenty longitudinal studies that allow studying the course

of cognitive decline (for an overview see Muslimović et al., 2007; Roheger et al., 2018). Some

studies report a more pronounced impairment in specific cognitive abilities such as memory

(Aarsland et al., 2010; Pfeiffer et al., 2014; Yarnall et al., 2014) or visuo-spatial or language

ability (Aarsland et al., 2017; "dual syndrome hypothesis", see also Kehagia et al., 2013). "[…]

However, often the impairment is not restricted to a specific cognitive domain, but covers several

domains (Muslimović et al., 2005; Hoogland et al., 2018). The evidence for subtypes with

specific cognitive impairments (e.g., memory or language) is inconsistent, which is partly due to

methodological issues including the heterogeneity of the measurement instruments, the small

sample sizes combined with selection effects, and different time points at which the patients with

PD are examined in the course of the disease. Muslimović et al. (2007) combined the evidence of

25 longitudinal studies with 901 initially non-demented patients with PD in a comprehensive

meta-analysis and examined the cognitive decline with progressing disease across eight cognitive

domains using a random-effects model. They found impairments across all cognitive domains

2.5 years after baseline, with the most significant decline in global cognitive ability ($d = .40$).

The view that PD affects many different cognitive abilities corroborates the contemporary view

that PD is a multisystem, multipeptide neurodegeneration (Aarsland et al., 2017).

Depressive Symptoms in Patients With Parkinson's Disease

Clinically significant depressive symptoms occur in approximately 40% of all patients

with PD, although prevalence rates vary strongly depending on the diagnostic criteria and the

study population (Barone, 2011; Lemke, 2008). In a meta-analysis, Reijnders et al. (2008) summarized the evidence of 36 studies, taking into account the different settings and diagnostic approaches, concluding that 17% of PD patients meet the criteria for major depressive disorder, 22% for minor, and another 13% for dysthymia. Moreover, the prevalence also depends on the phase of the disease: Several studies showed that the severity of depressive symptoms increases with disease progression (e.g., Ketharanathan et al., 2014; Pankratz et al., 2008; Riedel, Klotsche, et al., 2010), whereby the exact prevalence estimates differ considerably depending on the inclusion criteria, the populations, the measures, and the cutoff values (e.g., von Glischinski et al., 2021; Goodarzi et al., 2016). In the following, we focus on depressive symptoms, that is, a continuous understanding of the underlying disease. Depressive symptoms significantly reduce the quality of life independent of the motor symptoms (Jones et al., 2015; Gallagher et al, 2010; Schrag et al., 2000), and might aggravate disability (Pontone et al., 2015, Ravina et al., 2007; Riedel, Heuser, et al., 2010; Riedel, Klotsche et al., 2010).

Motor symptoms in patients with PD are the most prominent symptoms that severely affect everyday life, which is why dopamine substitution using levodopa or dopamine agonists are established first-line treatments of motor symptoms for the majority of patients. However, any pharmacological treatment has to be evaluated in terms of its effect on motor symptoms and potentially detrimental effects on depressivity and cognitive functioning (Lemke, 2008). Studies dealing with the consequences of such a substitution on mood regulation are inconclusive (Leentjens, 2011; Ryan et al., 2019): In most studies, dopaminergic agonists have been shown to reduce the depressive symptoms (Liao et al., 2020; Schaeffer & Berg, 2017), but others have reported no effects (Choi et al., 2000), or even a worsening of the symptoms (Jaunarajs et al., 2011; Zhang et al., 2014). Ryan et al. (2019) pointed out that there are complex, structural

changes in several neurotransmitter systems in patients with PD including dopamine and serotonin, which may contribute to depressive symptoms.

Interplay Between Cognitive Functioning and Depressive Symptoms

Previous studies outlined an association between depressivity and cognitive performance in patients with PD (Aarsland et al., 2010; Pirogovsky-Turk et al., 2017). For example, Dotson et al. (2010) showed in a longitudinal study on aging that with each episode of elevated depressive symptoms the risk for all-cause dementia increases by 14%. In the case of PD, patients with dementia who had an early onset of symptoms also showed more depressive symptoms (Sanyal et al., 2014). Such findings have often been interpreted as an indication that depression may be a risk factor or a precursor symptom of dementia (Ishihara & Brayne, 2006). But the direction of effects is unclear: As with all cross-sectional, observational data or longitudinal data where the beginning of change cannot be pinpointed, three different perspectives can be taken: (1) A decline in cognitive functioning can cause the onset or amplification of depressive symptoms; (2) depressive symptoms can precede a cognitive decline or dementia; and (3) both depressive symptoms and cognitive impairment can be results of some third variable or a common underlying mechanism ("common cause model"). In fact, there is evidence for all three perspectives. Petkus et al. (2019) examined the question of directionality with longitudinal data from 362 non-demented participants from the Parkinson's Progression Markers Initiative (PPMI) with bivariate dual change score models. The authors found that over a four-year period, poorer cognitive performance across all cognitive domains predicted increased symptoms of (anxiety and) depression a year later, while the reverse direction was not significant. Accordingly, poor cognitive performance was considered a risk factor for depression. Using the same PPMI dataset (with different exclusion criteria and subsetting different cognitive tasks) Jones et al. (2019) also

studied the longitudinal relationship over four years with multilevel models. Surprisingly, they found results that completely contradict those of Petkus et al. (2019): More severe depressive symptoms were also related to worse performance on a variety of cognitive abilities. However, additional cross-lagged models demonstrated that changes in depressive symptoms preceded declines in working memory, verbal learning, memory, and global cognition, leading to the conclusion that "depressive symptoms may be a harbinger for future cognitive decline among individuals with PD" (Jones et al., 2019, p. 1111, see also Hanganu et al., 2017). And finally, neuroimaging studies also support the notion that degeneration in the various neurotransmitter systems is relevant not only for the typical motor symptoms but also for non-motor symptoms including depression (Wen et al., 2016) and cognitive dysfunction (Perez-Lloret & Barrantes, 2016).

The Present Study

In this study, we aim to better understand the disease-related development of cognitive impairment in patients with PD and to relate the decline to depressive symptoms at an individual level. Among others, the link between cognitive decline and depressive symptoms is important for monitoring of and commitment to the therapeutic intervention. Whereas dementia usually occurs relatively late in the course of the disease, MCI can be detected early on in untreated patients, even at the premotor stage (Goldman & Postum, 2014). The present work attempts to address the weaknesses of previous research in several respects: First, instead of relying on short, clinical examinations, we administered a detailed neuropsychological assessment. Second, we examine the dynamic interplay between cognitive functioning and depressive symptoms in a large sample of patients with PD in comparison to a healthy control group of elderly people matched with regard to age, sex, and educational background over the course of 8 years with

biennial follow-ups. Such a longitudinal patient-control group design allows distinguishing between age-related and disease-specific cognitive and emotional changes, respectively. Third, we use the more refined random-intercept cross-lagged panel model (RI-CLPM, Hamaker et al., 2015; Mund & Nestler, 2019) to study the intraindividual interplay between cognitive functioning and depressive symptoms longitudinally. The traditional and more prevalent CLPM has been criticized because it confounds between- and within-person effects, thus, implicitly assuming that every person varies over time around the same average trend and that there are no trait-like individual differences that endure. However, such an assumption of a homogeneous developmental pattern across individuals (e.g., Jones et al., 2019; Petkus et al., 2019) is neither warranted for cognition in patients with PD (Biundo et al., 2016), nor their depressive symptoms (Dogan et al., 2019). In contrast, the RI-CLPM decomposes the variance of the observed scores into between-person variances (i.e., the stable, time-invariant part) and within-person variance, which enables a more nuanced investigation of the dynamics of processes that take place within individuals (Hamaker, 2012).

The following research questions are answered, each with reference to possible differences between patients with PD and a matched control group:

1. What are the average trajectories of cognitive functioning and depressive symptoms? (*mean trajectories*)

2. What is the correlation between the stable part of both constructs? (*between-person associations*)

3. What are the correlations between the time-point specific parts of both constructs? (*time-point specific within-person associations*)

4. Is cognitive functioning associated with future depressive symptoms within persons or vice versa? (*within-person cross-lagged effects*)

5. How inert are the individual trajectories of cognitive abilities and depressive symptoms? (*within-person autoregressive effects*)

Method

Sample and Study Design

The data derives from the ongoing de novo Parkinson project (DeNoPa; Mollenhauer et al., 2013, 2016), a prospective and longitudinal study with patients with de novo PD and neurologically healthy controls (HC) matched with regard to age, sex, and educational background. The overall aim of this single-center, observational study with biennial follow-ups is to adequately describe the course of the development of the disease, improve early diagnosis, and identify potential progression markers. The present analyses are based on the longitudinal study of five measurement occasions at two-year intervals between 2009 and 2021. Participants had to be between 40 and 85 years old, newly diagnosed with PD featuring at least two of the criteria of resting tremor, bradykinesia, and rigidity according to UK Brain Bank Criteria, and had to fulfill de novo PD criteria. Participants with known severe vascular encephalopathy, normal-pressure hydrocephalus or signs or symptoms according to multiple system atrophy or progressive supranuclear palsy (according to consensus criteria, Gilman et al., 1998; Litvan et al., 1996) were excluded. Healthy controls had to be in the same age range, without any active known/treated condition of the central nervous system, and without a family history of idiopathic PD. Antipsychotic drugs were an exclusion criterion both for controls and patients. Controls were matched using frequency matching by age, sex, and education (see also Appendix e-1 in Mollenhauer et al., 2013).

A total of 123 PD (79 male, 44 female) and 107 HC (64 male, 43 female) with a mean

age of 64.1 (*SD* = 8.3) at baseline were included. All except one participant were German. The

distribution of the highest educational attainment was very similar across the groups and quite

common for the age distribution in the sample in Germany (see Table 1). At baseline, 19 of the

123 patients with PD (15.4%) and 6 of 107 controls (5.6%) received a concomitant medication

with antidepressants. At the last measurement occasion, 22 of 93 patients with PD (23.7%) and 4

of 84 controls (4.7%) were treated with antidepressants. At the last measurement occasion,

9 patients with PD received anticholinergic medication with Rivastigmine, which is prescribed

for patients with Parkinson-related dementia. None of the study participants received

antidopaminergic medication at baseline (i.e., de novo patients). Following the German

guidelines for the treatment of Parkinson's disease (DGN, 2021), 83 of 123 patients with PD

received a PD medication with a levodopa equivalent dosage (determined according to

Tomlinson, 2010) of *M* = 122.9 mg (*SD* = 62.3 mg) at the 2-years follow-up. At the 8-years

follow-up, 62 of 93 patients with PD received a levodopa equivalent dosage of *M* = 151.8 mg

(*SD* = 69.5 mg).

The study was conducted according to the Declaration of Helsinki and all participants

provided informed written consent. Approval was received from the ethical standards committee

on human experimentation for all experiments with human participants (approval no.

FF89/2008). The study is registered as an observational and non-interventional study at the

German Register for Clinical Trials (DRKS00000540) according to the World Health

Organization Trial Registration Data Set. That means, participants may receive advice on

medication after each study visit to be shared with their treating neurologist. Participants are not

assigned to specific interventions by the investigator (as in a clinical trial).

Measures

Both patients and controls completed a battery of neuropsychological tests. We used scores of seven psychometric tests (with a total of 14 scores, see Table 2) that were administered at all time points: *Montreal Cognitive Assessment* (MoCA; Nasreddine et al., 2005), the *Regensburger Word Fluency Test* (RWT; Aschenbrenner et al., 2001), the *Stroop Test* (Bäumler, 1985), the *Trail-Making-Test* (Tombaugh, 2004), the *Verbal Learning and Memory Test* (VLMT; Helmstaedter et al., 2001), the subtest Similarities for the *Wechsler Adult Intelligence Scale* (WIE; von Aster et al., 2006), and the subtest Digit Span of the *Wechsler Memory Scale - Revised* (WMS-R, Härting et al., 2000). We only excluded clinical screenings that had almost no variation in the HC group (i.e., Clock Drawing test, Mini-Mental State Examination, Visual Object and Space Perception Battery). The assessment covers a broad range of cognitive abilities including memory, language abilities, and executive functioning. Response times of speeded measures (TMT and Stroop) were reverse log-transformed. For outlier removal, we winsorized all raw scores (i.e., $M \pm 2.5\ SD$). To allow comparisons across measurement time points, we standardized the winsorized raw scores to the baseline measurement in the HC group. Finally, we aggregated all (winsorized and standardized) scores by measure and then equally weighted them into a single score. We used a global score instead of domain-level analyses, because clinical studies often report the simultaneous impairment of several cognitive abilities in patients with PD (Muslimović et al., 2005, 2007), whereas the evidence for domain-specific losses is inconsistent and depends on many (intertwined and partially unknown) factors. In addition, the composite score of overall cognitive ability is more reliable than the individual indicators that often capture a blend of several cognitive abilities (e.g., processing speed and broad visual perception). Finally, the assumption of a uni-dimensional model for all used cognitive ability

tests is also empirically supported, both in terms of an exploratory factor and a confirmatory

factor analysis (for additional information please see OSF repository).

    To assess the severity of depressive symptoms in both groups, the scores of two self-

report measures (*Beck's Depression Inventory*, BDI, Hautzinger et al., 1995, and the *Geriatric*

Depression Scale, GDS, Gauggel & Birkner, 1999) and a clinical rating (*Montgomery-Åsberg*

Depression Rating Scale, MADRS, Schmidtke et al., 1988) were combined. We opt for a

composite score of depressive symptoms instead of subcomponents of depression because the

diagnostic gain is often limited, which is expressed in very high factor correlations of multi-

dimensional solutions. Such a global composite score of depressive symptoms is also in line with

a common metric underlying different measurement instruments (Wahl et al., 2014) and a

higher-order subfactor of distress within the internalizing spectrum of the *Hierarchical*

Taxonomy Of Psychopathology, HiTOP, Kotov et al., 2021). Moreover, the assumption of uni-

dimensional measurement models for all scales is empirically supported with confirmatory factor

analyses at the item level (for additional information please see OSF repository). A single

composite score was used justified by the high zero-order correlations between the scales (e.g.,

correlations at baseline ranged between .68 and .80 in the overall sample, see also OSF

repository). The scales had satisfying reliability estimates (e.g., for the first measurement time

point: $\alpha_{BDI} = .89$, $\alpha_{GDS} = .84$, $\alpha_{MADRS} = .84$). To allow comparisons across measurement time

points, we used the same procedure as for the cognitive ability measures described above.

Statistical Analysis

We analyzed the relationship between cognitive functioning and depressive symptoms with a random-intercept cross-lagged panel model (RI-CLPM, Hamaker et al., 2015; Mulder & Hamaker, 2020; Mund & Nestler, 2019). The RI-CLPM decomposes the variance of the observed scores into between-person (i.e., the stable, time-invariant part) and within-person variance (i.e., fluctuations over time, for a graphical representation of the model see Figure S1 in the OSF repository). We used an extension of the RI-CLPM to the multi-group case to model both groups (HC vs. PD) simultaneously (see also Mulder & Hamaker, 2020). To answer the research questions we modeled a) the *mean trajectories* across groups and constructs. The RI-CLPM describes three associations between the constructs specifying the subsequent research questions: b) the correlations between random intercepts (*between-person associations*), c) correlations between the measurement point-specific residuals (*time-point specific within-person associations*), and d) regressions across constructs on subsequent time points (*within-person cross-lagged effects*). One advantage in contrast to the traditional cross-lagged panel model (CLPM) is that the autoregressive parameters in the RI-CLPM are not confounded with the time-invariant part of a construct (for a detailed discussion see Hamaker et al., 2015). Thus, we estimate e) the *within-person autoregressive effects*.

We used the maximum likelihood estimator with robust estimation of standard errors (MLR) and corrected test statistics. The robust versions (see also Brosseau-Liard et al., 2012; Brosseau-Liard & Savalei, 2014) of the following fit indices were considered indicators of good model fit: Comparative Fit Index (CFI) >.95, Root Mean Square Error of Approximation (RMSEA) < .06, and Standardized Root Mean Squared Residual (SRMR) < .08 (Hu & Bentler, 1999). We used Full Information Maximum Likelihood (FIML) procedure (Schafer & Graham,

2002) to handle missing data, which results in unbiased estimates under the assumption of

Missing At Random (MAR; Enders, 2010), that is, random missingness after controlling for the

effects of additional observed variables. MAR is an assumption that cannot be tested directly (in

contrast to Missing Completely At Random). As a sensitivity check, we compared the age, sex,

education, cognitive abilities, and depressive symptoms at baseline between the groups of

remainers vs. dropouts (i.e., not present at last follow-up). There were systematic differences

between both groups for age, education, and cognitive abilities. We, thus, decided to include

demographic variables that were present for all participants (i.e., age, education, and sex) as

auxiliary variables besides the variables in the analytical model to improve the model-based

handling of missing data with FIML (Graham, 2003).

Transparency and Openness

We report how the measures included in the analyses were selected and all data

transformations applied. To foster transparency, the annotated analyses scripts and data to

reproduce the main results are provided in an online repository (https://osf.io/ax9nk). All

analyses were conducted with R 4.1.0 (R Core Team, 2021), mainly with the R package lavaan

0.6-9 (Rosseel, 2012).

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Results

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Descriptive results

Table 3 gives the sample sizes, means, and standard deviations of all cognitive ability

tasks and depressive symptoms scales for each measurement time point, split by patients vs.

controls. For all the univariate and bivariate distributions as well as correlation matrices of all

measures at each time point see Figure S2 – S5 in the OSF repository. In the following, we

describe the results of the random-intercept cross-lagged panel model, which provided good fit to

the data: $\chi^2 = 104.8$, $df = 66$, $p < .01$, CFI = .979, RMSEA = .076 [$CI_{90\%}$: .047, .102],

SRMR = .065. More precisely, we report changes in the mean structure across time and group,

between-person associations, and the within-person effects.

Results of the Random-Intercept Cross-Lagged Panel Model

Mean trajectories. In line with the literature (Reijnders et al., 2008), patients with PD

reported significantly more depressive symptoms than the persons in the age-matched control

group at baseline ($d = 1.51$; all reported d-values are standardized at the standard deviation of the

control group at baseline). Although the severity of depressive symptoms decreased at the

subsequent follow-ups (indices in the following refer to months after baseline: $d_{FU24} = 1.03$ and

$d_{FU48} = 0.83$), it began to raise afterwards, ($d_{FU72} = 1.05$ and $d_{FU96} = 1.38$) indicating a U-shape

(see black lines in Figure 1). In the HC group, the average was close to zero at all time points

with no time trend. To facilitate the interpretation of the continuous, standardized depressivity

score, we also used the *Geriatric Depression Scale* (GDS-15) as a proxy to assess the severity of

depression from a categorial, clinical perspective. Weintraub et al. (2006) studied the diagnostic

accuracy of the GDS-15 in a sample of 148 outpatients with idiopathic PD and found a cutoff of

5 or higher as a good indication of a major or minor depression (sensitivity = .88;

specificity = .85, see also Goodarzi et al., 2016). According to this approximation, 36.1% of the

patients with PD could be flagged as potentially having a depressive disorder. The prevalence

rates decrease in the following honeymoon period (27.9% at 2-years follow-up and 21.1% at 4-

years follow-up), only to slightly rise afterwards (about 25% at 8 and 10-years follow-up). Thus,

it appears that the level of depression remains similar across the patient group. However, when

interpreting the values one has to take into account the dropout rates (see Table 3) and the fact

that the patients in this observational study received concomitant medication and often
psychotherapeutic intervention.

Regarding the cognitive abilities, there was a considerable and almost constant decline
for the patients with PD (d_{base} = -0.67, d_{FU24} = -0.75, d_{FU48} = -0.88, d_{FU72} = -0.94, d_{FU96} = -1.21).
For a few cases in the PD group the losses in cognitive performance were substantial (i.e., more
than 1.5 *SD* decline compared to baseline, Yarnall et al., 2014), and the figures steadily increased
with progression of the disease. Model-implied values evidenced that 17% of the PD group
crossed the -1.5 *SD* threshold at the 8-years follow-up (see Figure 1). In contrast, there were
almost no cases in the control group indicating that this change was not due to aging processes.

Between-person associations. The between-person variance (expressed in the variance of
the random-intercept factors) was two times larger for the patients with PD compared to HC for
the depressive symptoms and comparable in size for cognitive functioning. We observed a small
non-significant negative relation between intelligence and depressive symptoms in the HC group
(b = -0.08, p = .06). For the patients with PD, this association was significant (b = -0.24, p = .03),
indicating that at an interindividual level lower cognitive abilities were accompanied by a higher
extent of depressive symptoms, and vice versa.

Time-point specific within-person associations. The within-person variances (expressed
in the time-point specific residual variances) were more than two times larger in patients with PD
for cognitive abilities compared to the HC group, and about three times larger for the depressive
symptoms. Negative, close-to-zero associations between cognition and depressivity were found
at almost all follow-ups across groups (see Table 4).

Within person cross-lagged effects. The cross-lagged effects mark within-person effects
between cognition and depressivity at consecutive points in time. Sometimes these effects are

also referred to as spill-over effects, because they denote how the state in one domain influences the state in another. The cross-lagged effects showed that a patient's score below their usual level of cognitive abilities at a given time point after baseline was associated with higher levels of depression two years later. From an intraindividual perspective, greater impairments in cognitive abilities at a given time point (i.e., lower scores in comparison to the individual mean) were associated with increased depressive symptoms (i.e., higher scores in comparison to the individual mean) at a subsequent time point in patients with PD ($b = -0.60$, $p = .03$). However, the opposite paths from depressivity to cognition were not significant ($b = -0.03$, $p = .66$). To check whether the cross-lagged effects from cognition on depressive symptoms were different from the effects in the opposite direction, we compared the model to a model in which all cross-lagged effects in the PD group were constrained to equality. The difference in the cross-lagged effects was statistically significant ($\Delta\chi^2(1, N = 230) = 5.8$, $p = .02$). In comparison, in the HC group, none of the cross-lagged effects were significant.

Within person autoregressive effects. In the RI-CLPM the autoregressive effects do not capture rank-order stability of a trait, but they account for the additional moment-to-moment stability (i.e., inertia or carry-over) of persons' fluctuations over time (Mulder & Hamaker, 2020). The effects were significant for cognitive abilities in the PD group, demonstrating that patients with greater cognitive impairment relative to their own expected score were likely to experience the same problems relative to their own expected score at the next follow-up. Also, the within-person autoregressive effects of both cognitive abilities and depressive symptoms in the HC group were significant, which is also reflected in the low intraindividual variation (see Figure 1).

Discussion

In the present study, we compared the intraindividual developmental trajectories and the dynamic interplay of cognitive functioning and depressive symptoms of patients with PD with those of a control group that was matched according to age, sex, and educational background. Compared to other longitudinal Parkinson studies, the long study period of eight years after baseline and the implementation of a control group, that enables distinguishing between disease-related and aging-related processes, are particular strengths of this study. Using a RI-CLPM allows distinguishing within- from between-person effects, thus, to dismiss the untenable assumption that every person varies over time around the same average trend in favor of a more flexible modeling of intraindividual processes. In the following, we highlight and discuss the main findings.

First, cognitive abilities in the PD group decreased with disease progression, whereas the control group did not show any sign of decline on a global composite score assessed with a broad neuropsychological assessment. With almost a single standard deviation on average at the last follow-up (in comparison to the baseline measurement in the HC group), the losses were significant, which is in line with the literature (e.g., Yarnall et al., 2014). The trajectories of the depressive symptoms followed a U-shaped trend with an improvement 2-4 years after baseline. Thus, the average trajectory of the patients with PD is similar to the typical trajectory of motor symptoms under Levodopa medication. This period in-between has also been labeled "honeymoon" phase (Erro et al., 2016), because at this stage the motor and non-motor impairments are not yet severe, do not fluctuate, and dopaminergic therapy is still relatively continuously effective (Rascol et al., 2003).

Second, the variability in both constructs in the PD group was very large in comparison to the rather flat trajectories in the HC group: The variances were two times larger for cognitive abilities and three to four times larger for the depressive symptoms. Results of the RI-CLPM also showed that the stable, between-person differences constitute a substantial part of the observed differences. In more detail, in the PD group, between 72-79% of the total variance in cognition and 59-68% of the total variance in depressive symptoms at follow-ups could be attributed to a trait-like, time-invariant characteristic of the patient, while the remaining part reflected time-variant influences. Recently, Jones et al. (2020) pointed out that increased intraindividual variability might be predictive of incident cognitive decline among individuals with de novo PD. Thus, a separation between both sources of variances is informative. In addition to the setup of a traditional cross-lagged panel model, it is therefore necessary to introduce a random intercept factor to ensure unbiased cross-lagged estimates (Hamaker et al. 2015). The random intercept factors were significantly negatively correlated in the PD group only, indicating that at an interindividual level lower cognitive abilities were accompanied by more depressive symptoms, and vice versa. At an intraindividual level, we also observed essentially the same pattern of association for the time-specific residual associations between both constructs. In this respect, the results of the present examination show for the first time that the same associations can be detected at an intra- and an interindividual level, which was not necessarily to be expected, as has been repeatedly shown in the psychometric literature (e.g., Mund & Nestler, 2019).

Third, the main finding of this study is that cognitive losses precede an increase in depressive symptoms in the clinical group only. The effect in the opposite direction was not significant, that is, an increase in depressive symptoms is not followed by a deterioration in cognitive performance (for a similar finding see Petkus et al., 2019). The current results are not

in line with the notion that depressivity may be used as a precursor symptom of cognitive decline (Jones et al., 2019) or dementia (Ishihara & Brayne, 2006). On the contrary, the cognitive losses experienced by patients are subsequently accompanied by a marked deterioration in mood. With respect to the question of what might be the underlying mechanisms for (subsequent) depressive symptoms we have to consider several factors such as changes in brain structure and plasticity, inflammatory and neurotrophic factors as well as a decrease in resilience with age (Aarsland et al., 2012). Weintraub et al. (2019, p. 999) described the cumulative prevalence of neuropsychiatric symptoms in patients with PD as „the result of a perfect storm, with contributing factors including demographic characteristics, diffuse and multiple neurodegenerative disease pathologies, other neurobiological factors, and PD treatments themselves". The results of the present study give an indication that there may nevertheless be a temporal order in the occurrence of non-motor symptoms. To counter the cognitive losses and the following depressive symptoms, early cognitive (and behavioral) enrichment might help to mitigate these processes (Hindle et al., 2014). In addition, patient education including stress management and health promotion seems important (Chlond et al, 2016).

The DeNoPa study makes a sensible complement to other studies of patients with PD such as PPMI: As a single-center study, DeNoPa offers a comparable and consistent neuropsychological assessment, includes a carefully selected control group as a point of comparison, enabling to detect disease-specific changes, and covers a comparatively long period of eight years to date with a comparatively low rate of attrition (not caused by death). Nonetheless, there are some limitations that need to be considered when interpreting the results: First, DeNoPa is an observational study with patients on individual medication plans. Patients are treated according to guidelines that possibly improve depressive symptoms, such as through

D4 receptor agonists that may impair cognition, as known to occur with dopamine agonists in old age. Due to the moderate sample size, the heterogeneous medication, which was also adjusted several times during the course of the disease, clear effects of PD medication on depressive symptoms and cognition could not be shown. Moreover, information on comorbid psychiatric diagnoses and psychological treatment was only partially available (i.e., for those patients who were treated as inpatients for a specific period of time). Thus, it was not possible to distinguish effects of medical or psychological intervention on depression (and cognition) from effects of aging, social support, cognitive training, etc. Second, the conducted analyses were not preregistered, so this is exploratory rather than confirmatory research (Wagenmakers et al., 2012). Combined with the—for complex latent variable modeling—still modest sample size and the researcher's degrees of freedom in processing the raw data (Simmons et al., 2011), we recommend replicating the results with another sample or conducting a specification curve (e.g., studying the effect with all reasonable specifications; Simonsohn et al., 2019). Third, in the present manuscript, we considered cognitive decline at a highly aggregated level—at the level of general cognitive ability. In principle, a more fine-grained picture would be desirable, even though the evidence for different, domain-specific impairments is sparse and inconsistent (e.g., Aarsland et al., 2017, 2021; Hoogland et al., 2018; Muslimović et al., 2005). Although our understanding of the underlying neurological mechanisms of PD has improved in the last decades (for an overview see Aarsland et al., 2021), the etiology of cognitive impairment in patients with PD is multifactorial and complex, and we still know little about the factors that contribute to or prevent domain-specific impairment. The large heterogeneity of results across studies on cognitive impairments emphasizes the need for large, prospective longitudinal studies with a comprehensive cognitive test battery. Finally, the stability and mutability of cognition and

affect are different: While changes in cognitive functioning are incremental and in the case of PD tend to signify irreversible losses, depressive symptoms are more volatile and short-term in nature. The biennial follow-ups of our study do not correspond to the time frame (of most subtypes) of depressive disorders, because the average episode duration of a treated unipolar depressive disorder was reported to be 16 weeks (Kessler et al., 2003). By implementing a smartphone-based ecological momentary assessment a finer granularity of analysis would be possible (Yim et al., 2020). Modeling approaches that allow for a separation of between-person and within-person effects (such as the presented RI-CLPM) would be ideally suited to handle such intensive, longitudinal data (e.g., Dynamic Structural Equation Modeling, Asparouhov et al., 2018). It would even be possible to gauge the effect of critical life events such as hospitalization, loss of social support, or the effect of pharmacological treatment or psychotherapy. This would, however, require large sample sizes to take into account the influence of the heterogeneous conditions and the highly individual development trajectories and to avoid capitalizing on chance.

In conclusion, well-conducted observational, longitudinal cohort studies with a broad neuropsychological assessment and carefully selected study participants (both patients and controls that are matched with regard to relevant background variables) are necessary to study the dynamic interplay between non-motor symptoms that besides motor symptoms severely affect the quality of life of patients with PD. Our study results show that, temporally, cognitive decline occurs first and depressive symptomatology increases thereafter. However, this temporal order does not necessarily imply causality (Rohrer & Murayama, 2021).

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Table 1

Demographic Data of Patients With PD and Healthy Controls at Baseline

	Patients with PD ($n = 123$)	Healthy controls ($n = 107$)	p
Mean age (*SD*) [years]	63.7 (9.5)	64.6 (6.8)	.42
Male/Female (%)	79/44 (64/36%)	64/43 (60/40%)	.49
Education (%)			.81
vocational-track Hauptschule/Volksschule	66 (54%)	57 (53%)	
intermediate-track Realschule	35 (28%)	30 (28%)	
academic-track Gymnasium	6 (5%)	3 (3%)	
university	16 (13%)	17 (16%)	

Note. P-values are based on the Welch's *t*-test for the variables age and sex, and the χ^2-test of homogeneity for the variable education.

Table 2

Overview of Cognitive Ability Tests

Measure	Task/ Indicator label
Digit Span	The subtest Digit Span of the *Wechsler Memory Scale – Revised* assesses the longest list of items a person can repeat back in correct (or reverse) order.
	WMS: total digit span (digit span forward + backward)
Montreal Cognitive Assessment	Screening instrument to detect mild cognitive impairment, including different cognitive domains: Attention, executive functions, memory, language, visuospatial skills, abstraction, and orientation.
	MoCa: Sum score
Regensburger Word Fluency Test	In 2 minutes participants have to name as many words as possible that correspond to the following instructions:
	RWTa: lexical verbal fluency (words starting with P)
	RWTb: semantic verbal fluency (animals)
	RWTc: lexical verbal fluency change (words alternating starting with G/R)
	RWTd: semantic verbal fluency change (alternating sports, fruits)
Similarities	In the subtest Similarities of the German version of the *Wechsler Adult Intelligence Scale* (WAIS-III) participants have to find an umbrella term or common characteristic of 2 items. The test measures both abstraction and language abilities.
	WIE: Sum score
Stroop[a]	Names of colors either match the color or are presented in a different color than the color named (inference).
	STROOP: Median response time of inferences
Trail Making Test[a]	Test combines visual search, speed of processing, mental flexibility, and executive functions.
	TMTa: Participants have to draw lines sequentially connecting 25 encircled numbers on a sheet of paper.
	TMTb: Task requirements are similar with the exception that the person must alternate between numbers and letters (1, A, 2, B, 3, C, etc.).
Verbal Learning and Memory Test	A test for list learning (5 times presentation of a 15 items target list) followed by distraction (single presentation of another 15 items inference list), recall after distraction and half-hour delay, and a recognition pass.
	VLMTa: Immediate recall
	VLMTb: Delayed recall after distraction
	VLMTc: Adjusted recall or recognition (indicate whether item on the target list)

Note. [a] Response times were inverse log-transformed ($= 1/log(RT)$)

Table 3

Descriptive Statistics for all Subtests of Cognitive Abilities and Depressive Symptoms

	Patients with PD														
	Baseline			2 years FU			4 years FU			6 years FU			8 years FU		
	n	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*
Digit Span (Wechsler Memory Scale – Revised)	122	12.8	3.3	122	12.3	3.1	115	12.3	3.4	98	12.8	3.4	83	12.7	3.1
Montreal Cognitive Assessment	123	25.4	2.7	122	24.3	3.1	116	24.7	3.7	99	25.0	3.4	86	24.6	3.7
Regensburger Word Fluency Test (letter)	121	12.9	5.9	121	15.6	6.3	112	13.9	7.0	96	16.8	6.6	81	13.9	6.1
Regensburger Word Fluency Test (semantic)	121	30.5	8.5	121	29.8	8.7	114	30.8	9.6	96	28.5	9.5	82	29.0	9.3
Regensburger Word Fluency Test (letter change)	119	16.6	5.6	119	17.2	6.0	112	16.2	7.0	95	17.9	6.8	82	17.1	7.1
Regensburger Word Fluency Test (semantic change)	120	18.0	4.6	121	18.0	5.7	114	18.0	5.5	95	18.3	5.6	81	17.2	5.4
Similarities (Wechsler Adult Intelligence Scale)	122	23.1	5.3	120	23.7	5.5	112	23.7	5.0	98	23.5	5.1	82	22.9	5.5
Stroop Test[a]	115	95.7	26.1	118	93.7	29.7	107	94.2	31.2	91	96.4	33.1	78	95.6	32.2
Trail Making Test (numbers)[a]	119	48.1	25.6	119	47.3	22.7	113	50.0	37.9	97	48.8	29.3	83	51.6	39.9
Trail Making Test (numbers-letters)[a]	118	126.1	64.3	118	136.5	71.1	111	142.1	80.5	94	139.6	81.5	80	148.1	82.4
Verbal Learning and Memory Test (immediate recall)	118	7.4	3.5	121	7.3	3.6	114	6.5	3.6	98	7.3	3.6	80	8.6	3.8
Verbal Learning and Memory Test (delayed recall)	117	7.3	3.6	121	7.2	3.5	114	6.3	3.8	98	7.3	3.8	80	8.7	3.9
Verbal Learning and Memory Test (adjusted recall)	118	9.1	4.7	121	8.7	5.1	114	6.8	5.5	98	8.5	4.8	80	9.7	4.8
Beck Depression Inventory	120	8.7	6.0	122	7.9	5.6	112	7.6	5.7	95	7.6	5.6	82	8.0	6.2
Geriatric Depression Scale	119	3.4	2.9	122	3.0	2.7	114	2.7	2.5	98	2.9	2.8	85	3.2	3.0
Montgomery-Åsberg Depression Rating Scale	116	8.3	5.6	121	4.9	5.2	114	3.6	4.4	98	4.3	5.6	82	5.3	5.4

| | Healthy controls | | | | | | | | | | | | | | |
| | Baseline | | | 2 years FU | | | 4 years FU | | | 6 years FU | | | 8 years FU | | |
	n	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*
Digit Span (Wechsler Memory Scale – Revised)	107	13.9	3.5	105	13.5	2.9	98	13.8	3.5	91	13.7	3.2	82	13.6	3.2
Montreal Cognitive Assessment	107	26.0	2.3	105	25.6	2.5	101	26.1	2.6	94	26.6	2.4	83	25.9	2.6
Regensburger Word Fluency Test (letter)	107	15.8	6.5	105	19.0	6.8	99	17.3	6.1	91	18.3	6.7	81	16.2	6.5
Regensburger Word Fluency Test (semantic)	107	34.7	7.4	105	33.8	9.1	99	35.1	8.6	91	34.4	9.6	82	34.6	9.3
Regensburger Word Fluency Test (letter change)	106	19.2	6.0	104	20.0	6.1	99	20.4	6.4	91	20.2	6.3	81	20.1	6.2
Regensburger Word Fluency Test (semantic change)	107	20.6	4.5	105	20.7	5.3	98	21.3	5.1	91	20.5	5.4	81	20.8	5.2
Similarities (Wechsler Adult Intelligence Scale)	106	25.1	5.4	105	25.6	4.6	97	25.3	5.0	91	25.8	4.3	81	24.9	4.9
Stroop Test[a]	104	79.2	15.7	104	77.2	14.0	96	75.2	13.1	89	76.9	13.4	81	81.6	18.1
Trail Making Test (numbers)[a]	107	38.8	15.1	105	34.8	12.0	98	33.6	11.9	91	33.2	11.9	82	34.0	12.4
Trail Making Test (numbers-letters)[a]	107	101.5	50.5	105	99.4	48.0	98	94.8	49.1	91	95.3	43.3	82	110.3	65.6
Verbal Learning and Memory Test (immediate recall)	105	8.7	3.5	104	8.8	3.1	95	7.6	3.3	90	8.3	3.3	82	9.5	3.4
Verbal Learning and Memory Test (delayed recall)	105	8.2	3.5	104	8.8	3.2	96	7.4	3.5	90	7.9	3.3	82	9.3	3.7
Verbal Learning and Memory Test (adjusted recall)	103	9.9	4.6	104	9.9	3.9	96	8.5	4.5	90	9.9	4.1	82	11.1	4.1
Beck Depression Inventory	107	3.3	3.8	107	3.5	3.7	99	3.6	4.0	92	3.8	4.0	80	3.5	3.4
Geriatric Depression Scale	104	1.1	1.5	107	1.1	1.8	101	1.2	1.7	91	1.1	1.8	83	1.1	1.7
Montgomery-Åsberg Depression Rating Scale	107	3.9	4.7	104	1.9	3.7	97	1.6	3.6	90	2.2	4.1	82	2.4	3.4

Note. FU = follow-up. The data were winsorized ($M \pm 2.5*SD$), but not yet standardized to the baseline measurement of the healthy controls.
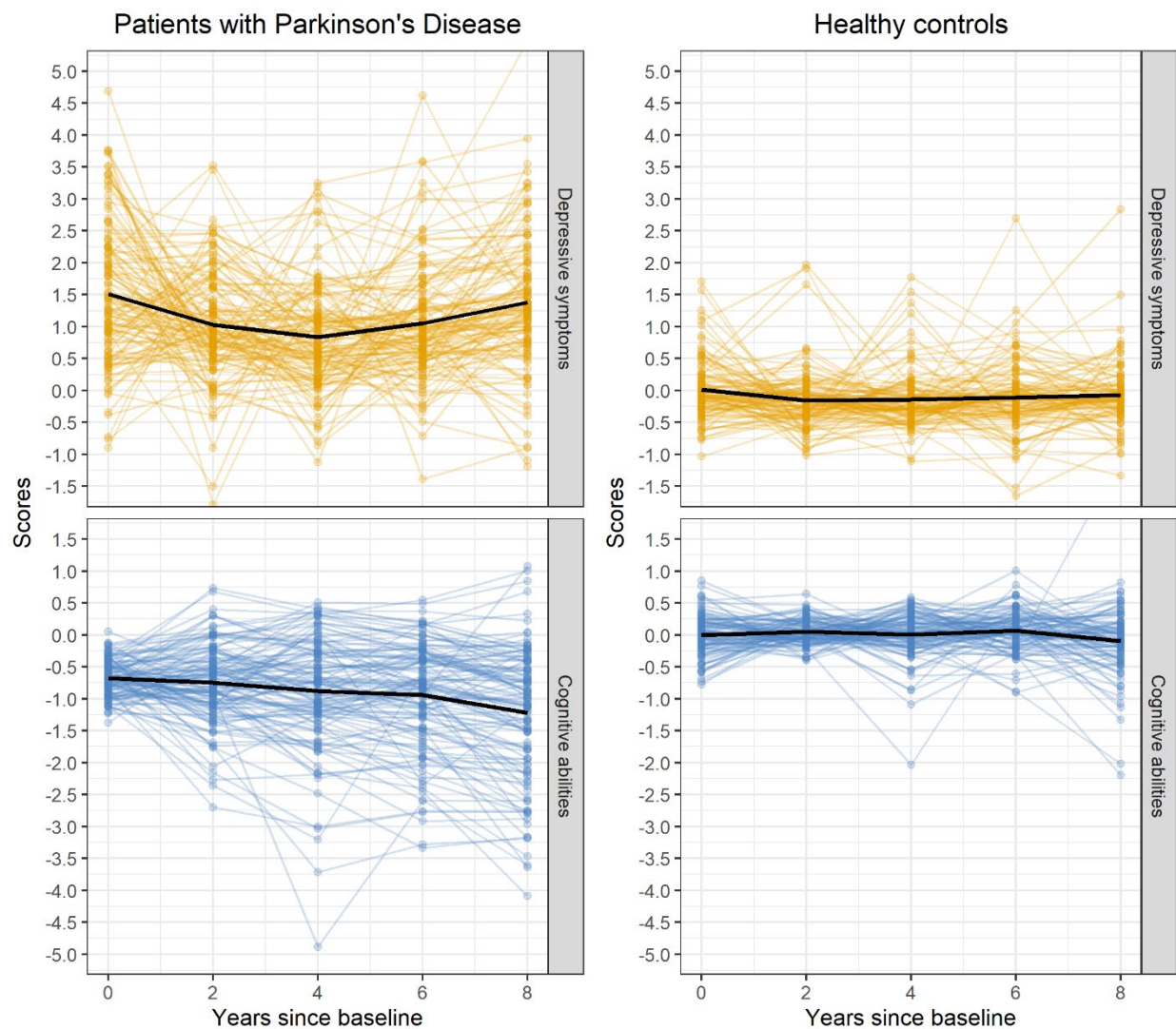
[a] Response time data [sec.] and are not yet inverse log-transformed (= $1/log(RT)$) or winsorized.

Table 4

Results of the RI-CLPM for the Interplay Between Cognitive Functioning and Depressive Symptoms

	Patients with PD			Healthy controls		
	b	*SE*	*p*	*b*	*SE*	*p*
Autoregressive effects (within persons)						
Cognitive abilities	0.82*	0.11	< .01	0.27*	0.11	.02
Depressive symptoms	0.14	0.10	.17	0.28*	0.12	.02
Cross-lagged effects (within persons)						
Cognitive abilities →						
Depressive symptoms	-0.60*	0.28	.03	-0.14	0.18	.43
Depressive symptoms →						
Cognitive abilities	-0.03	0.06	.66	0.02	0.04	.56
Time-point specific associations between cognitive abilities and depressive symptoms (within persons)						
Baseline	0.13	0.10	.22	-0.03	0.02	.18
2 years follow-up	-0.11	0.06	.08	< 0.01	0.01	.85
4 years follow-up	-0.07	0.04	.06	-0.07*	0.03	.01
6 years follow-up	-0.04	0.07	.59	-0.04	0.02	.08
8 years follow-up	-0.09	0.07	.18	-0.05	0.03	.08
Random-intercepts association (between persons)						
Covariance	-0.24*	0.11	.03	-0.08	0.04	.06

Note. b = Unstandardized parameter estimates; n(PD) = 123; n(HC) = 107. $p < .05$.

Figure 1

Intraindividual Development of Depressive Symptoms and Cognitive Functioning

Note. *n*(PD) = 123; *n*(HC) = 107. Depressive symptoms (upper panels) and cognitive abilities (lower panels) of patients with Parkinson's disease (left panels) and healthy controls (right panels). Values depicted are not observed, but model-implied.