Published in final edited form as:

Int J Geriatr Psychiatry. 2013 October ; 28(10): 1054–1060. doi:10.1002/gps.3927.

A Latent Class Analysis of Psychological Disturbance in Parkinson's Disease

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Abstract

Objective—Psychological symptoms are common in Parkinson's disease (PD). Psychological symptoms do not respond to psychotropic medications as well in patients with PD as in patients with psychiatric illnesses who do not have PD. Evidence that PD patients can be classified into distinct psychological symptom subgroups is conflicting. This study sought to examine potential psychological heterogeneity in PD with a broader range of instruments than has been used in previous studies.

Methods—A comprehensive battery of psychological measures assessing dysphoria, apathy, anhedonia, anxiety, and negative affect was administered to 95 PD patients without global cognitive impairment. Latent class analysis was used to identify subgroups of patients based on continuous variables derived from the psychological battery. Multinomial regression was used to examine predictors of classification.

Results—The latent class analysis identified three subgroups with incremental levels of psychopathology across most symptom domains. One exception was a greater level of affective flattening in the “psychologically healthy” group compared to the “moderate symptoms” group. Greater motor dysfunction and less education were associated with greater severity of psychological symptoms.

Conclusions—These results support high psychological co-morbidity in PD, which complicates the treatment of individual symptoms. In addition, emotional blunting and anhedonia may be less indicative of widespread psychological distress than anxiety, dysphoria, and cognitive aspects of apathy. Clinicians should be aware that PD patients with greater motor dysfunction and less education are at greater risk not only for depression, but also for a variety of other psychological symptoms that may not be routinely assessed.

Keywords

Depression; anxiety; apathy; anhedonia; dysphoria

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The authors report no conflicts of interest.

Introduction

Parkinson's disease (PD) is associated with a host of psychological symptoms that reduce quality of life. Common symptoms include apathy in up to 70% (Leentjens *et al.*, 2008), depression in 40% (Reijnders *et al.*, 2008), and anxiety in 30–40% (Pontone *et al.*, 2009) of patients. In large part, these symptoms represent direct effects of the disease process on the brain, rather than reactions to having chronic disease. Psychological symptoms in PD may reflect dopaminergic degeneration in non-motor circuits, Lewy body formation in non-motor brain regions, and/or abnormalities in neurotransmitter systems other than the dopamine system (e.g., norepinephrine, serotonin). Unfortunately, there is insufficient evidence for the efficacy of the vast majority of psychotropic agents in PD, as many psychological symptoms do not respond to psychotropic medications as well in patients with PD as in patients with psychiatric illnesses who do not have PD (Seppi *et al.*, 2011).

Recently, investigators have examined profiles of common psychological symptoms in PD using latent class analysis (LCA) (Brown *et al.*, 2011; Starkstein *et al.*, 2011; Mavandadi *et al.*, 2009). This analysis attempts to empirically identify subgroups (i.e., classes) of individuals characterized by low intraclass and high interclass variability. In contrast to cluster-based methods, LCA provides formal statistics to evaluate model fit and determine the optimal number of classes. For example, Brown and colleagues (2011) used LCA to identify a prominent subgroup of PD patients with anxious-depression. These authors argued that anxiety and depression may not represent distinct unitary conditions in this population. Unfortunately, LCA investigations of psychological symptoms in PD have been limited by the small number of psychological measures used in each. For example, the LCA study that assessed the broadest range of psychological symptoms in PD employed single instruments to index only depression, anxiety and apathy (Mavandadi *et al.*, 2009).

The present study sought to more fully examine psychological heterogeneity in PD using LCA. Separate instruments were used to index apathy subtypes (i.e., emotional, cognitive, behavioral), anhedonia subtypes (i.e., anticipatory and consummatory), anxiety subtypes (i.e., acute and chronic), dysphoria, and negative affect. Further, relationships between resultant classes and demographic and disease variables were explored using multinomial regression.

Materials and Methods

Participants

Participants included 95 patients recruited from the outpatient Neurology clinic of the University of Florida Center for Movement Disorders and Neurorestoration. The study was approved by the local Institutional Review Board. All patients provided written informed consent before participating. Inclusion criterion was a diagnosis of idiopathic PD based on United Kingdom Brain Bank diagnostic criteria. Exclusion criteria were: (1) co-morbid neurological illness (e.g., stroke, Alzheimer's disease); (2) history of significant brain trauma due to injury or surgery (including deep brain stimulation); (3) history of severe psychiatric disturbance (e.g., schizophrenia, rapid-cycling bipolar disorder); and (4) global cognitive impairment, defined as a score less than 26 on the Mini-Mental State Exam (MMSE). Sample characteristics are shown in Table 1. On average, participants were 66 years old, well educated, and exhibited moderate disease severity. The majority of patients were non-Hispanic White (91%). Four patients were African American, three patients were Hispanic, one patient was Asian American, and one patient was Native American. About one-third (32%) of patients were taking antidepressants at the time of assessment.

Measures

Motor symptom severity was assessed with the Unified Parkinson's Disease Rating Scale, motor portion (UPDRS-III) while patients were on their antiparkinsonian medications. Disease stage was quantified with the Hoehn & Yahr Scale while patients were on their antiparkinsonian medications. Cognitive status was assessed with the MMSE. Disease duration and education were quantified by patient self-report. Psychological symptoms were assessed with the following well-validated self-report or structured interview measures:

Apathy Scale (AS). The AS is a self-report questionnaire of 14 items rated on a 4-point scale. Scores range from 0 to 42, with scores ≥ 14 indicating clinically relevant apathy. The AS was not used in the empirical classification of groups. Along with a structured interview for DSM-IV-TR depression diagnoses, the AS was used to externally validate the empirical classification.

Lille Apathy Rating Scale (LARS). The LARS is a semi-structured questionnaire of 14 items rated on a 4-point scale separated into 9 subscales. Subscores are computed by averaging scores on the 9 subscales within four empirically-derived domains (i.e., Intellectual Curiosity, Emotion, Action Initiation, Self Awareness). Subscores range from -4 to $+4$.

Snaith-Hamilton Pleasure Scale (SHPS). The SHPS is a self-report questionnaire of 14 items rated on a 4-point scale. Scores using the continuous scoring method range from 14 to 56.

Temporal Experience of Pleasure Scale (TEPS). The TEPS is a self-report questionnaire of 18 items rated on a 4-point scale. Consummatory Pleasure subscale scores are computed by summing scores on 8 items and range from 8 to 48. Anticipatory Pleasure subscale scores are computed by summing scores on 10 items and range from 10 to 60.

Positive and Negative Affect Schedule (PANAS). The PANAS is a self-report questionnaire comprising 20 affect adjectives rated on a 5-point scale. The Negative Affect subscale scores are computed by summing responses to 10 negative adjectives, and scores range from 10 to 50.

State-Trait Anxiety Inventory (STAI). The STAI is a self-report questionnaire of 40 statements rated on a 4-point scale. State and Trait subscale scores are computed by summing scores on the 20 state anxiety and 20 trait anxiety items, respectively. Subscale scores range from 20 to 80. Cut-off scores as low as 30 have been reported (Glozman 2004).

Beck Depression Inventory-II (BDI-II). The BDI-II is a self-report questionnaire of 21 items rated on a 4-point scale. In order to minimize overlap between the BDI-II and other scales, a dysphoria subscore was used based on previous work (Kirsch-Darrow *et al.*, 2011). This subscore is computed by summing 11 items indexing dysphoric mood based on factor analysis. Dysphoria subscores range from 0 to 33.

Statistical Analysis

Data were analyzed in Mplus 6.11. Latent Class Analysis (LCA), a type of mixture modeling, was used to identify latent subgroups based on continuous variables derived from the psychological battery. Scores on the 11 psychological measures listed in Table 1 were included in the LCA. Demographic, disease, and cognitive variables were not included in the LCA, nor were AS scores or DSM-IV-TR depression diagnoses. Model fit was evaluated with the following commonly-used statistics: Akaike information criterion (AIC), sample-size adjusted Bayes Information Criterion (BIC), and Entropy. Smaller values of AIC and

BIC, and larger values of Entropy, particularly above .9, indicate better model fit (Muthen & Muthen, 1998).

To characterize the classes, differences in symptom severity were assessed in SPSS version 20 with univariate analyses of variance (ANOVA) and post-hoc testing using Tukey's honest significant difference. Differences in demographics were also examined. Classification was externally validated with categorical variables representing clinically relevant apathy and depression (i.e., AS scores ≥ 14 , DSM-IV-TR depression diagnoses).

Predictors of classification were explored in SPSS version 20 using multinomial regression with multiple imputation based on the Expectation-Maximization algorithm. The dependent variable in the regression was group classification. Independent variables were age, sex, education, disease duration, MMSE, and UPDRS-III. Some statistics from the 20 imputations could not be pooled and are therefore reported as ranges.

Results

Latent Class Analysis

Comparison of model fit statistics supported a 3-class solution, as compared to a 2-class solution ($\chi^2(12) = 92.59$; $p < .001$). A 4-class model did not converge. Fit statistics for the final 3-class model were: AIC = 5401.39; BIC = 5373.633; Entropy = 0.95. This model classified 54% of patients in Class 1 (N=51), 33% in Class 2 (N=31), and 14% in Class 3 (N=13). Standardized mean scores on the psychological measures are shown separately for the 3 classes in Figure 1. Raw scores on each of the psychological measures are shown separately for the three classes in Table 1. Visual inspection of the data revealed that Class 3 scored worse than Classes 1 and 2 on all measures and was labeled the "severe symptoms" group. Class 1 appeared to score better than Classes 2 and 3 on virtually all measures and was labeled the "psychologically healthy" group. Class 2 appeared to score in an intermediate range on virtually all measures and was labeled the "moderate symptoms" group. It should be noted that these labels were assigned based on relative differences between the classes, as cut-offs for clinically significant symptoms on each of the scales and subscales have not yet been reported. Class 2 appeared to score lower than Class 1 only on LARS Emotion, a measure of affective flattening. As shown in Figure 1, greatest separation between groups was observed for cognitive apathy (i.e., LARS Intellectual Curiosity), dysphoria (i.e., BDI-II Dysphoria), and anxiety (i.e., STAI State and Trait).

Characterizing the Classes

One-way ANOVA showed that the three classes differed significantly on all 11 psychological measures. Post hoc testing revealed that compared to Class 1, Class 2 exhibited greater cognitive apathy, negative affect, dysphoria, state anxiety and trait anxiety, but less affective flattening. Compared to Class 2, Class 3 exhibited greater cognitive apathy, affective flattening, anticipatory and consummatory anhedonia, dysphoria and trait anxiety and reduced self awareness. In addition, Class 3 exhibited more behavioral apathy and global anhedonia compared to Class 1. Classes differed in terms of education, motor symptom severity and disease stage, but not in terms of age, sex, or disease duration. Compared to Class 1, Classes 2 and 3 reported less education and were more likely to be in a more advanced disease stage. In addition, Class 3 exhibited greater motor symptom severity compared to Class 1.

External Validation of Classification

In line with this general pattern of incremental psychopathology, patients assigned to Class 3 were more likely to meet DSM-IV criteria for major or minor depression, as compared to

patients assigned to Classes 1 or 2 ($\chi^2(2) = 40.4; p < .001$). Patients assigned to Class 2 were more likely to meet DSM-IV criteria for major or minor depression, as compared to patients assigned to Class 1 ($\chi^2(1) = 13.9; p < .001$). Similarly, patients assigned to Class 3 were more likely to report clinically relevant apathy on the AS, as compared to patients assigned to Classes 1 or 2 ($\chi^2(2) = 25.8; p < .001$). Patients assigned to Class 2 were more likely to report clinically relevant apathy than patients assigned to Class 1 ($\chi^2(1) = 13.6; p < .001$).

Predictors of Classification

Univariate correlations between the psychological, demographic, disease, and cognitive variables are shown in Table 2. Multinomial regression examining the relationship between class membership and predictor variables (i.e., age, sex, education, disease duration, MMSE, UPDRS-III) produced significant models in all 20 imputed datasets (Nagelkerke R^2 ranged from .261 to .360; p 's ranged from .002 to .02). The models correctly classified 62% of patients, which is substantially higher than the 42% chance classification rate in this sample. Of the 6 variables examined, only motor severity (i.e., UPDRS-III) and education were uniquely associated with classification. Specifically, higher UPDRS-III scores (pooled $B = -.11$; pooled $p = .01$) and lower education (pooled $B = .35$; pooled $p = .02$) were associated with greater probability of classification in the “severe symptoms” group, as compared to the “psychologically healthy” group, independent of age, sex, disease duration and cognitive status.

Discussion

Results suggest high co-morbidity between symptoms of apathy, anhedonia, dysphoria, anxiety, and negative affect in individuals with PD. Rather than subgroups of patients with prominent symptoms in one symptom domain (e.g., apathy or anxiety), the model identified 3 subgroups of patients with incrementally greater levels of psychopathology in *multiple* domains that did not differ in terms of age or sex. Results also suggest that cognitive aspects of apathy, negative affect, dysphoria, and anxiety may better identify patients at risk for more global psychological dysfunction than affective flattening or anhedonia in PD. Finally, PD patients with worse motor functioning and less education were more likely to exhibit psychological disturbance.

Several studies have attempted to identify distinct subgroups of PD patients based on neuropsychiatric symptoms (Brown *et al.*, 2011; Starkstein *et al.*, 2011; Mavandadi *et al.*, 2009; Kulisevsky *et al.*, 2008; Aarsland *et al.*, 2009). Previous studies reporting separate subgroups of patients with prominent depression, apathy, and anxiety have employed cluster analysis, which is methodologically vulnerable and does not provide formal statistics to evaluate model fit and determine the optimal number of subgroups (McLachlan & Peel, 2000). Cluster analysis can be contrasted with LCA, a type of mixture cluster analysis that does not suffer from many of the limitations of traditional cluster analysis (McLachlan & Peel, 2000). Studies using LCA to examine psychological symptoms in PD have reported more symptom overlap between subgroups (Brown *et al.*, 2011) or subgroups differentiated entirely by overall symptoms severity rather than heterogeneous symptom patterns (Starkstein *et al.*, 2011; Mavandadi *et al.*, 2009). The present study extends this work by showing a similar pattern of results with a broader range of assessment instruments. The wider range of psychological domains measured in this study allowed us to demonstrate that additional psychological symptoms also co-occur in PD, including several apathy subtypes. Indeed, the “severe symptoms group” evidenced generalized distress that was evident on all psychological measures.

While the number of participants classified as exhibiting more severe levels of psychological symptoms is relatively small ($N=13$), this number represents a relatively high

proportion of the sample and underscores the importance of recognizing and treating the entire range of psychological symptoms in PD. It should be noted that these labels of “moderate” and “severe” refer to relative differences between the classes, as cut-offs for clinically significant symptoms are not available for each of the scales and subscales. Evidence that these labels reflect clinically significant differences between the classes is shown through external validation of the empirically-derived classes. Specifically, the proportion of patients meeting DSM-IV-TR criteria for depression and psychometric criteria for clinically relevant apathy increased incrementally across the three classes.

Our finding of high psychological co-morbidity in PD beyond depression and anxiety has important implications for the treatment of psychological symptoms in PD, as distressed patients are likely to have dysfunction in multiple psychological domains. Therefore, treatments shown to be efficacious in individuals with a particular psychological syndrome may not evidence the same level of efficacy in PD. For example, selective serotonin reuptake inhibitors (SSRIs) have been shown to be less efficacious among depressed individuals with comorbid anxiety, as compared to depressed individuals without anxiety (Fava *et al.*, 2008). Further, SSRIs prescribed for depression are associated with greater apathy in PD (Zahodne *et al.*, 2012).

More separation between the “psychologically healthy” and “moderate symptoms” groups was noted on cognitive apathy (i.e., LARS Intellectual Curiosity) and negative affect measures (i.e., BDI-II Dysphoria, STAI, PANAS Negative), as compared to other aspects of apathy and anhedonia measures (i.e., LARS Action Initiation, TEPS, SHPS). Indeed, these groups did not differ significantly on measures of anhedonia or behavioral apathy. Further, the “psychologically healthy” group reported greater affective flattening (i.e., higher LARS Emotion scores) than the “moderate symptoms” group, indicating that blunted affect may appear in the absence of more widespread psychological distress in PD. Taken together, these results suggest that cognitive aspects of apathy, negative affect, dysphoria, and anxiety may better indicate potential for more global psychological dysfunction than affective flattening or anhedonia in PD.

The finding that worse motor functioning and lower education were associated with higher likelihood of classification in the “severe symptoms” group extends previously-reported associations between these variables and depression to other psychological symptoms (Dissanayaka *et al.*, 2011). Clinicians should be aware that PD patients with worse motor functioning and lower education are at greater risk not only for depression, but for a variety of other psychological symptoms that may not be routinely assessed in outpatient neurological practice. The association between higher education and less psychological symptom severity may reflect opportunities to build coping skills, which may also relate to socioeconomic status. It should be noted that the multinomial regression that included age, sex, education, disease duration, MMSE, and UPDRS-III correctly assigned only 62% of patients to the classes derived from the LCA. This finding suggests that differences in psychological symptom profiles are not related only to demographic variables or disease severity. Future work should endeavor to identify other risk factors for psychological disturbance in PD in addition to motor severity and education.

Limitations of this study include its cross-sectional design. Future studies should examine whether subgroups of patients can be identified based on longitudinal course of psychological symptoms. Another limitation is the lack of comprehensive measures of cognition. While no patients in this study evidenced frank dementia, it would be interesting to examine relationships between the subgroups and specific cognitive abilities. Future studies should also explore potential pathophysiological overlap between psychological

symptoms in PD. This knowledge could lead to the development of new treatment approaches to address the constellation of psychological dysfunction seen in this population.

Conclusion

Psychological symptoms appeared to be co-morbid in this sample of PD patients without global cognitive impairment, which may suggest overlapping pathophysiological substrate. Emotional blunting was evident in the group of “psychologically healthy” patients, suggesting that this aspect of apathy may not be as indicative of psychological dysfunction as cognitive apathy or negative affect. Correlates of psychological dysfunction include worse motor functioning and lower education.

Acknowledgments

Sponsors: This study was carried out at the university of Florida Center for Movement Disorders and Neurorestoration with support from the National Institute on Aging (T32-AG020499), the Bryan W. Robinson Endowment for Neuroscience, the American Psychological Foundation, the American Psychological Association Divisions 20 and 40, and the National Parkinson Foundation Center of Excellence (UF).

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Key points

- Psychological symptoms are highly co-morbid in PD, suggesting possible pathophysiological overlap
- Greater motor dysfunction and low education are associated with greater psychological dysfunction in PD

Figure 1.

Standardized scores on the psychological measure shown separately for each class. UPDRS-III: Unified Parkinson's Disease Rating Scale-motor portion; MMSE: Mini-Mental State Exam; LARS: Lille Apathy Rating Scale; TEPS: Temporal Experience of Pleasure Scale; SHPS: Snaith-Hamilton Pleasure Scale; PANAS: Positive and Negative Affect Schedule; BDI-II: Beck Depression Inventory, 2nd Edition; STAI: State-Trait Anxiety Inventory.

Note. Standardized scores were computed from the present sample of 95 patients.

Standardized scores have a mean of 0 and a standard deviation of 1. Higher scores indicate greater psychopathology for all psychological instruments. TEPS scores have been inverted to facilitate comparison across measures.

Table 1

Sample characteristics

	All Patients (N=95)	Class 1 (N=51)	Class 2 (N=31)	Class 3 (N=13)	Difference Testing ^a
<i>Demographics</i>					
Age	66.2 (9.9)	67.3 (9.5)	65.3 (9.4)	64.4 (12.5)	1=2=3
Sex (% male)	68.4	68.6	74.2	53.8	1=2=3
Education	15.5 (3.0)	16.4 (2.8)	14.8 (2.8)	13.8 (3.2)	1<2=3
<i>Disease characteristics</i>					
Years with symptoms	8.7 (5.7)	8.2 (5.3)	9.2 (6.7)	9.1 (5.3)	1=2=3
UPDRS-III	29.1 (9.8)	26.1 (8.6)	31.3 (9.3)	36.3 (10.8)	1<3
Hoehn & Yahr (%)					1<2=3
1	1.3	2.1	0	0	
2	67.5	78.7	52.4	50.0	
2.5	12.5	14.9	14.3	8.3	
3	15.0	4.3	33.3	25.0	
4	37.5	2.1	0	16.7	
<i>Cognitive</i>					
MMSE	28.1 (1.5)	28.4 (1.3)	27.6 (1.8)	27.6 (1.8)	1=2=3
<i>Psychological</i>					
LARS Intellectual Curiosity	-2.0 (1.1)	-2.6 (0.7)	-1.9 (0.7)	0.0 (1.1)	1<2<3
LARS Action Initiation	-2.4 (1.5)	-2.9 (1.1)	-2.2 (1.3)	-1.1 (2.2)	1<3
LARS Emotion	-1.9 (1.3)	-1.7 (1.3)	-2.6 (0.9)	-0.8 (1.6)	2<1=3
LARS Self Awareness	-2.9 (1.3)	-3.0 (1.3)	-3.1 (1.1)	-2.1 (1.2)	1=2<3
TEPS Anticipatory	45.4 (7.8)	47.0 (7.1)	46.0 (7.1)	37.7 (7.8)	1=2<3
TEPS Consummatory	38.2 (6.9)	40.1 (5.4)	37.8 (7.5)	31.5 (6.7)	1=2<3
SHPS	23.0 (6.9)	21.4 (4.8)	24.3 (9.4)	26.7 (5.2)	1<3
PANAS Negative	20.5 (8.2)	15.4 (5.8)	25.5 (6.6)	28.9 (5.2)	1<2=3
BDI-II Dysphoria	3.3 (3.9)	0.9 (1.3)	4.6 (3.1)	9.7 (4.1)	1<2<3
STAI State	35.9 (11.1)	27.6 (5.0)	44.4 (7.0)	48.4 (8.1)	1<2=3
STAI Trait	36.0 (11.1)	27.4 (5.0)	44.0 (5.2)	52.8 (4.3)	1<2<3
Clinical Apathy ^b (% yes)					1<2<3

	All Patients (N=95)	Class 1 (N=51)	Class 2 (N=31)	Class 3 (N=13)	Difference Testing ^a
No Apathy	53.7	76.5	35.5	7.7	
Apathy	46.3	23.5	64.5	92.3	
<i>DSM-IV Depression (% yes)</i>					1<2<3
No Depression	71.6	94.1	61.3	7.7	
Minor Depression	3.2	0	3.2	15.4	
Major Depression	25.3	5.9	35.5	76.9	

^aSignificant differences between the classes were identified using one-way analyses of variance and Tukey's honest significant difference for continuous variables and chi square tests for categorical variables.

^bClinical apathy was defined as Apathy Scale score 14.

Note: Class 1: "psychologically healthy;" Class 2: "moderate symptoms;" Class 3: "severe symptoms."

Higher scores indicate greater psychopathology for all psychological instruments except TEPS.

UPDRS-III: Unified Parkinson's Disease Rating Scale-motor portion; MMSE: Mini-Mental State Exam; LARS: Lille Apathy Rating Scale; TEPS: Temporal Experience of Pleasure Scale; SHPS: Snath-Hamilton Pleasure Scale; PANAS: Positive and Negative Affect Schedule; BDI-II: Beck Depression Inventory, 2nd Edition; STAI: State-Trait Anxiety Inventory.

Table 2

Univariate correlations psychological measures and variables of interest

	Age	Female Sex ^a	Education	Disease Duration	MMSE	H&Y ^a	UPDRS-III
LARS Intellectual Curiosity	.009	-.097	-.280 *	.187	-.309 *	.226 *	.384 *
LARS Emotion	-.033	-.057	.049	-.082	.173	-.071	-.122
LARS Action Initiation	-.013	-.131	-.098	.107	-.380 *	.247 *	.332 *
LARS Self Awareness	-.165	-.091	.008	-.049	-.199 *	.091	.139
TEPS Anticipatory	.055	.380 *	-.005	.067	.046	.072	-.149
TEPS Consummatory	.050	.276 *	-.044	-.030	.082	.064	-.126
SHPS	-.136	-.237 *	-.113	.020	-.099	-.006	.017
PANAS Negative Affect	-.183	.044	-.212 *	.000	-.322 *	.223	.286 *
BDI-II Dysphoria	-.173	-.002	-.279 *	-.034	-.120	.308 *	.388 *
STAI State	-.145	-.045	-.272 *	.028	-.339 *	.284 *	.443 *
STAI Trait	-.218 *	.040	-.340 *	.048	-.204 *	.072	.347 *

* $p < .05$

^aValues represent Spearman's rho for categorical variables

Note. Higher scores indicate greater psychopathology for all psychological instruments except TEPS.

MMSE: Mini-Mental State Exam; H&Y: Hoehn & Yahr Scale; UPDRS-III: Unified Parkinson's Disease; LARS: Lille Apathy Rating Scale; TEPS: Temporal Experience of Pleasure Scale; SHPS: Snaith-Hamilton Pleasure Scale; PANAS: Positive and Negative Affect Schedule; BDI-II: Beck Depression Inventory, 2nd Edition; STAI: State-Trait Anxiety Inventory.