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Predictors of Health Status in Nondepressed and Nondemented Individuals with Parkinson's Disease

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Abstract

Recent studies have shown that self-perceived health status (HS) in Parkinson's disease (PD) is associated with motor, cognitive, or mood symptoms, with the greatest association typically occurring with mood. The purpose of this study was to determine if these associations are present in nondepressed and nondemented individuals with PD by using sensitive neuropsychological measures and statistically derived factors from mood and motor scales. The best predictors of poor HS in PD participants ($N = 32$) without dementia or depression were mood symptoms, specific to self-reported cognitive impairment and anxiety. Bivariate correlations between HS and number of correct categories on the Wisconsin Card Sorting Test and the gait–balance factor from the Unified Parkinson's Disease Rating Scale Part III were also significant or approached significance. These findings suggest that specific mood and cognitive symptoms continue to be important factors in HS in those individuals who lack clinical levels of depression or dementia.

Keywords: Parkinson's disease; Health status; Health-related quality of life; Quality of life

Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disease characterized by motor, cognitive, and mood symptoms. These symptoms include rigidity, bradykinesia, tremor, postural instability, deficits in executive functions, visuospatial ability, learning, memory, and depression (Aarsland et al., 1999; Dubois & Pillon, 1997). As might be expected, compared with age-matched controls, PD is associated with poorer perceived ability to perform a variety of physical, emotional, and social activities (Quittenbaum & Grahn, 2004), also known as self-perceived health status (HS; Den Oudsten, Van Heck, & De Vries, 2007). HS has been referred to as "quality of life (QoL)" or "health-related quality of life (HRQoL)", but can be distinguished from these terms by its focus on perceived impact of PD on activities, rather than a general assessment of QoL or a reaction or feeling (e.g., level of satisfaction) about the disease's effects, as in HRQoL (for an explanation of terminology differences, *see* Den Oudsten et al., 2007). It is important to delineate these terms, as discrepancies in the contributions to HS in PD may be due in part to the evaluation of different outcomes via the use of general or disease-specific measures.

The majority of theoretical models conceptualize HRQoL or HS as a synthesis of experiences and perceptions related to one's HS that involve several key clinical variables, including mood, motor, and cognitive functioning (Wilson & Cleary, 1995). This postulation has been supported by the consistent finding of a significant relationship between HS and depression

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in PD (Behari, Srivastava, & Pandey, 2005; Cubo et al., 2002; Karlsen, Larsen, Tandberg, & Maeland, 1999; Kuopio, Marttila, Helenius, Toivonen, & Rinne, 2000; Muslimovic, Post, Speelman, Schmand, & de Haan, 2008; Schrag, Jahanshahi, & Quinn, 2000; Slawek, Derejko, & Lass, 2005; The Global Parkinson's Disease Survey (GPDS) Steering Committee, 2002). Most studies in this area suggest that greater levels of depressive symptoms are the strongest predictors of worse HS among many potential variables, including motor symptom severity, cognition, current age, and disease duration (Behari et al., 2005; Cubo et al., 2002; Karlsen et al., 1999; Kuopio et al., 2000; Muslimovic et al., 2008; Schrag et al., 2000; Slawek et al., 2005; The Global Parkinson's Disease Survey (GPDS) Steering Committee, 2002). Moreover, when participants are categorized by mood questionnaire cut-off scores, depressed PD participants report worse HS compared with minimally or nondepressed PD participants (Schrag et al., 2000; Slawek et al., 2005).

However, it is currently unknown if mood is still associated with HS in individuals with PD who are not depressed, as most studies include both depressed and nondepressed individuals in their analyses. Furthermore, which aspects of mood are primarily associated with decreases in HS have yet to be examined. This is essential as depression is multifactorial and includes somatic symptoms (e.g., loss of energy, decrease in activities), self-reported cognitive changes (e.g., inattention, memory problems), and affective symptoms (e.g., hopelessness, sadness, anxiety), which can overlap with measures of cognition and motor function.

As with mood, motor disability assessments can include a variety of distinct motor symptoms, which may vary in severity in individuals with PD. Only a few studies to date have attempted to elucidate the relationship between these individual motor symptoms and HS, with no consensus reached as of yet. Several studies have reported that individuals with PD who exhibit greater symptoms of tremor, rigidity, or bradykinesia have poorer HS (Peto, Jenkinson, & Fitzpatrick, 1998; Slawek et al., 2005) and Schrag and colleagues (2000) found that PD patients with predominant akinetic-rigid symptoms reported more HS problems than patients with the tremor-dominant subtype of the disease (Schrag et al., 2000). However, Schrag and colleagues (2000) did not find a significant relationship between HS and akinesia scores derived from formal measures of symptom severity. Furthermore, Karlsen and colleagues (1999) found that akinesia, tremor, rigidity, nor postural instability predicted HS. Yet, in two other studies, postural abnormalities predicted worse HS in individuals with PD (Muslimovic et al., 2008; Schrag et al., 2000). One possible reason for the mixed findings regarding motor symptoms and HS in PD may be due to unstandardized or arbitrary methods of classifying symptoms, which may result in the blending of several different motor symptoms.

Reduced HS has been demonstrated in PD patients with poor cognition (Schrag et al., 2000; Slawek et al., 2005) compared with those who are cognitively unimpaired. The ability of cognitive scores to predict HS has been questionable, as some studies find that cognition is predictive of HS (Klepac, Trkulja, Relja, & Babic, 2008; Schrag et al., 2000), whereas others have found that it is not (Cubo et al., 2002; Slawek et al., 2005), and others have found that only specific aspects of cognition are related to specific aspects of HS (Muslimovic et al., 2008). Two potential problems, however, are that there has been a great deal of variability among these past studies in terms of (a) the sensitivity of the cognitive measures used and (b) the level of cognitive functioning in the samples included. This raises the question of whether the sensitivity of the employed cognitive measures or the cognitive variability of the subject sample may account for these inconsistent findings.

One recent study conducted by Klepac and colleagues (2008) attempted to delineate specific cognitive abilities in relation to HS (HRQoL) in nondemented individuals with PD and found that better cognitive performance predicted better HS, whereas visual attention/memory and visuospatial and executive functioning were independently associated with better HS (HRQoL). This study included depressed individuals, but noted that a significant interaction indicated that the association between HS and cognitive performance was conditional on the level of depression (Klepac et al., 2008). As depression can affect cognitive performance (Klepac, Trkulja, & Relja, 2008), it may be that the discrepancies in the aforementioned studies were due to the varying levels of depression in the participant samples. Therefore, one primary aim of this study was to examine specific neuropsychological abilities known to be affected in PD, such as executive function, memory, and visuospatial ability, in a group of individuals with PD without clinical levels of depression in addition to a lack of dementia.

To the best of our knowledge, no study to date has simultaneously examined the relationship between HS and neuropsychological abilities as well as the relationship between HS and specific motor and mood symptoms in an exclusively nondemented and nondepressed sample of PD participants. Understanding HS in nondepressed and nondemented individuals is important as they comprise the majority of individuals with PD in the early stages of the disease (Brown & Marsden, 1984; Rickards, 2005). Furthermore, by selecting individuals who are cognitively intact and not depressed, we are able to elucidate the relationship between HS and specific symptoms, which may be masked by clinical levels of depression and dementia in unselected samples. Although mood and cognition may play an important role in more advanced or complicated PD, these symptoms may not play as a significant role in early PD. It is possible that motor symptoms may be more influential in HS in early and uncomplicated PD. Our study design will allow us to explore the degree to which early Parkinsonian symptoms relate to HS when non-motor symptoms (i.e., mood and global cognition) are statistically controlled. The overall purpose of this

study was to use empirically derived motor and mood indices and sensitive neuropsychological measures to examine the relationship between HS and motor, cognitive, and mood symptoms in nondemented and nondepressed individuals with PD.

Materials and Methods

Participants

Thirty-two individuals with PD were selected for this study from a larger cohort of research volunteers ($N = 67$) participating in a comprehensive study of PD and cognition. All participants were originally recruited from the Movement Disorders Clinic at the University of California, San Diego (UCSD). These individuals were selected for the present study because they (a) underwent a comprehensive neuropsychological assessment including a measure of HS (i.e., PDQ-39; $N = 44$) and (b) were determined to be nondemented and nondepressed based on inclusion criteria ($N = 32$). Twenty-three individuals from the original cohort were not included in the study, as they were not administered a complete battery of tests due to time constraints. Inclusion criteria included no evidence of clinical dementia or depression based on a score of 130 or greater on the Mattis Dementia Rating Scale (MDRS; Mattis, 1988) and a score of 11 or less on the Geriatric Depression Scale (GDS; Yesavage et al., 1982). A lack of dementia and depression was further corroborated by participants failing to meet the criteria for dementia set forth by Emre and colleagues (2007) and the criteria for depression as described by Marsh, McDonald, Cummings, and Ravina (2006). Participants with a history of major depressive disorder and/or an anxiety disorder were excluded. All but two participants were on at least one medication for their PD symptoms, and the majority of participants were on a combination of two or more medications. Participants were tested on their normal dosages of medication, which are presented in Table 1. The results reported below were not confounded by the participants' medication use as indicated by insignificant bivariate correlations of levodopa equivalents (Hobson et al., 2002) with all

Table 1. Demographic and medication data

	Percentage or mean (*SD*); range
Gender	56% men
Age (years)	66.6 (9.9); 46–89
Education (years)	16.9 (2.2); 12–21
Duration of PD diagnosis (years)	6.9 (5.0); 1–23
Modified Hoehn and Yahr stage 1	25.0%
Modified Hoehn and Yahr stage 1.5	0.0%
Modified Hoehn and Yahr stage 2	40.6%
Modified Hoehn and Yahr stage 2.5	28.1%
Modified Hoehn and Yahr stage 3	6.3%
History of clinical fluctuations[a,b]	46.4%
History of dyskinesias[a,b]	28.6%
History of falls[b,c]	19.4%
Sleep disturbances[a]	50.0%
L-dopa equivalents (mg/day)[d]	546.2 (404.3); 0–2101
Medication type (%)	
L-dopa	91
Dopamine agonist	69
MOA-B-inhibitor (Selegiline)	31
COMT-inhibitor (Entacapone)	22
Amantadine	19
Anticholinergic (Trihexyphenidyl)	9
CoQ10	9
Psychotropic/other	6

Notes: SD = standard deviation; L-dopa medications include levodopa–carbidopa, levodopa–carbidopa–entacapone, carbidopa, levodopa; dopamine agonist medications include pramipexole, ropinirole, pergolide; Psychotropic/other medications included Paroxetine for depression and Neurontin for pain. Those on Stalevo were considered to be on both L-dopa and a COMT-inhibitor.

[a]Four to five participants' scores were unavailable for these questions.

[b]Scores were dichotomized (feature present or not present).

[c]One participant's score was unavailable.

[d]L-dopa equivalents = regular levodopa dose × 1 + levodopa continuous release (CR) dose × 0.75 + pramipexole dose × 67 + ropinirole dose × 16.67 + pergolide dose × 100 + bromocriptine dose × 10 + [regular levodopa dose + (continuous release levodopa dose × 0.75)] × 0.25 if taking tolcapone (Hobson et al., 2002); one participant's L-dopa equivalent could not be calculated because of missing dosages.

variables used in the analyses below. Informed consent was obtained from all participants, and this study was approved by the local ethics committee.

Materials and Procedures

All participants were administered the PD Questionnaire 39-item version (PDQ-39; Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995), a well-validated measure of HS in PD (Marinus, Ramaker, van Hilten, & Stiggelbout, 2002; Peto et al., 1995, 1998), which consists of 39 questions rated by the subject on a five-item Likert-type scale (never, occasionally, sometimes, often, or always). From these questions, eight subscale scores are derived by summing the item scores for each subscale, dividing the sum by the highest possible score for that subscale and then multiplying this number by 100. Each subscale represents a specific area of HS related to mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communications, and bodily discomfort. The unweighted average of these eight subscales constitutes that Summary Index (PDQ-39 total score). Higher scores on the PDQ-39 correspond to worse HS.

The Unified Parkinson's Disease Rating Scale (UPDRS; Fahn, Elton, & the UPDRS Development Committee, 1987) was administered to assess motor symptom severity. Several motor scores, including the UPDRS Part III total score, the dichotomized duration of dyskinesias (historical) score from the UPDRS Part IV, and subscale scores derived from a previous factor analysis of the UPDRS, representing severity of gait and balance, tremor, rigidity, and bradykinesia (Stebbins, Goetz, Lang, & Cubo, 1999) were used in our analyses. (The bradykinesia score was derived by combining Factors IV and V from Stebbins and colleagues, 1999, which measures left- and right-sided bradykinesia, respectively.)

The MDRS, a well-validated measure commonly used in individuals with PD (Brown et al., 1999; Mattis, 1988), was employed as a measure of global cognitive functioning. In addition, several measures, which surveyed a range of cognitive abilities and are sensitive to specific cognitive deficits in PD, were administered (Dubois & Pillon, 1997; Henry & Crawford, 2004; Montse, Pere, Carme, Francesc, & Eduardo, 2001). We included the total words recalled on Trials 1 through 5 from the California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000), a test of verbal learning and memory; the number of correct categories achieved (CC) and number of perseverative errors (PE) on the Wisconsin Card Sorting Test (WCST; Berg, 1948; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), measures of executive function; the total number of words produced on the letter fluency (LF) and category fluency portions of the verbal fluency subtest from the Delis Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001), measures of language and executive function; and the total number of items correct on the Judgment of Line Orientation Test (JLO; Benton, Hamsher, Varney, & Spreen, 1983), a test of visuospatial ability. Standard scores for these measures are detailed in Table 2 for purposes of normative comparisons. The standard scores for the MDRS scales were derived from Montgomery and Costa (1983); the standard scores for the WCST CC were derived from Rhodes (2004); and the standard scores for the JLO were derived from Ivnik, Malec, Smith, Tangalos, and Peterson (1996). The CVLT-II, the DKEFS LF and category fluency, and the WCST PE normative scores were derived from their respective published manuals (Delis et al., 2000, 2001; Heaton et al., 1993).

The GDS (Yesavage et al., 1982), a well-validated measure used often with older populations and individuals with PD (Ertan, Ertan, Kiziltan, & Uygucgil, 2005), was administered as a measure of depressive symptoms. In addition to the overall score on the GDS, five individual subscales derived from a factor analysis with older adults, dysphoric mood (sadness, emptiness, dissatisfaction, unhappiness), hopelessness (helplessness, worthlessness), withdrawal-apathy-low vigor, anxiety (worry, fear), and cognitive impairment (confusion, indecision, reduced concentration) were examined (Adams, Matto, & Sanders, 2004).

Statistical Analysis

Hierarchical multiple regression was conducted to explore the association between HS and overall mood and cognitive symptoms over and beyond that of overall motor symptoms, using total scores from the UPDRS Part III, the GDS, and the MDRS as predictor variables and the PDQ-39 Summary Index as the dependent variable. Pearson correlations were employed to examine the relationship between HS (PDQ-39 Summary Index) and specific motor, cognitive, and mood symptoms (subscale scores from the UPDRS Part III and GDS, the UPDRS Part IV dyskinesia score, the WCST CC and PE, the CVLT-II, the JLO, and the DKEFS LF and category fluency). Next, each significant or significant trend bivariate correlation representing specific mood, motor, and cognitive symptoms was entered into three separate multiple regressions, in order to explore the degree of linear association among the variables and to determine if these variables were *uniquely* associated with overall HS. Three separate regressions were conducted in lieu of one in order to control for multicollinearity among GDS scores. Additionally, bivariate correlations were conducted between mood, cognitive, and motor scores and the subscales of the

Table 2. Means and standard deviations of health status, motor, cognitive, and mood test scores

	Raw score (mean [*SD*])	Standard score (*t*-score or scaled score) (mean [*SD*])
PDQ-39 Summary Index	17.5 (8.9)	–
UPDRS Part III Total Score	17.4 (8.5)	–
Gait–balance	4.8 (2.6)	–
Tremor	1.5 (1.2)	–
Rigidity	3.5 (2.7)	–
Bradykinesia	7.7 (5.1)	–
GDS total score	4.5 (3.6)	–
MDRS total score	139.0 (3.4)	52.4 (4.9)
MDRS attention	36.2 (1.2)	54.3 (7.7)
MDRS initiation/perseveration	36.2 (1.1)	52.4 (3.7)
MDRS construction	5.7 (.54)	48.1 (8.9)
MDRS conceptualization	37.4 (1.9)	50.7 (7.4)
MDRS memory	23.7 (1.6)	52.0 (7.7)
CVLT-II Trials 1–5	47.3 (12.9)	55.8 (12.5)
WCST perseverative errors	16.7 (15.2)	51.2 (12.1)
WCST categories correct	4.7 (2.1)	53.6 (11.7)
DKEFS letter fluency number correct	44.1 (14.8)	12.4 (4.3)[a]
DKEFS category fluency number correct	36.8 (10.1)	10.7 (3.6)[a]
JLO total score	25.2 (4.5)	12.8 (3.0)[a]

Notes: SD = standard deviation; PDQ-39 = Parkinson's disease questionnaire-39; UPDRS = Unified Parkinson's Disease Rating Scale; GDS = Geriatric Depression Scale; MDRS = Mattis Dementia Rating Scale; CVLT-II = California Verbal Learning Test-II; WCST = Wisconsin Card Sorting Test; DKEFS = Delis Kaplan Executive Function System; JLO = Judgment of Line Orientation Test. Gait–balance, Tremor, Rigidity, and Bradykinesia (left and right-sided combined) are UPDRS Part III factors as described in Stebbins and colleagues (1999). Normative scores for the MDRS and the MDRS subscales (attention, initiation/perseveration, construction, concentration, and memory) were derived from Montgomery and Costa (1983); normative scores for the CVLT-II were derived from Delis and colleagues (2000); normative scores for the WCST categories correct were derived from Rhodes (2004); normative scores for the WCST perseverative errors were derived from Heaton and colleagues (1993); DKEFS letter and category fluency normative scores were derived from Delis and colleagues (2001), and the normative scores for the JLO were derived from Ivnik and colleagues (1996).
[a]Scaled scores. All other standard scores are *t*-scores.

PDQ-39. All scores used in the analyses were raw scores. To control for Type I error, all statistics were considered significant at the $p < .01$ level.

Results

Table 2 displays the mean total raw scores on the PDQ-39, the UPDRS Part III and the four UPDRS Part III factors (gait–balance, tremor, rigidity, and bradykinesia), the MDRS and its five subscales (attention, initiation/perseveration, construction, conceptualization, and memory), the GDS, the CVLT-II Trials 1–5, the WCST CC and PE, the DKEFS LF and category fluency, and the JLO as well as the standard scores for each of the cognitive tests.

Compared with the average PDQ-39 scores (Summary Index range = 30–49) of other PD samples (Cubo et al., 2002; Peto et al., 1995; Schrag et al., 2000; Slawek et al., 2005), our participants reported an overall better HS. On average, the participants' performances on all of the MDRS subscales were greater than −1.5 *SD* from the mean. None of the participants' scores on the MDRS, DKEFS LF, or JLO were less than −1.5 *SD* from the mean, whereas five participants scored less than −1.5 *SD* from the mean on one of the other cognitive measures. Specifically, one (3%) participant's score on the WCST PE, one participant's score on the WCST CC, and another participant's score on the CVLT-II Trials 1–5 fell more than 1.5 SD below the mean; two (6%) participants' scores fell more than 1.5 SD below the mean on category fluency. None of participants scored less than −1.5 SD from the mean on more than one test.

Global Predictors of HS

Hierarchical regression, at Step 1, when the total score on the UPDRS Part III was regressed onto the Summary Index of the PDQ-39, revealed a trend toward significance ($r^2 = .13$, $F(1, 30) = 4.61$, $p = .04$). At Step 2, with the UPDRS Part III already entered, the addition of the MDRS and GDS scores revealed that there was a significant increase in the prediction of Summary Index of the PDQ-39 (r^2 change = .25, $F(2, 28) = 5.60$, $p < .01$). In regard to the individual predictors, the GDS total score was a significant predictor of the PDQ-39 Summary Index ($\beta = 0.50$, $p = .003$), whereas there was a trend toward significance

by the UPDRS Part III ($\beta = 0.35$, $p = .03$). The MDRS was not a significant independent predictor of HS ($\beta = 0.03$, $p = .85$). These results indicate that non-motor symptoms (i.e., mood) account for a significant amount of the variance over and above motor symptoms.

Specific Motor, Cognitive, and Mood Predictors of HS

To examine whether individual motor, cognitive, and mood symptoms predicted HS in individuals with PD, bivariate correlations between the PDQ-39 Summary Index and the five GDS factors, the specific symptoms from the UPDRS Part III, and the six neuropsychological test scores and indices were conducted. The GDS cognitive impairment factor was significantly correlated with the PDQ-39 Summary Index ($r = 0.55$, $p = .001$), whereas a trend toward significance was demonstrated by the relationship between the PDQ-39 and the GDS subscales of anxiety ($r = 0.35$, $p = .05$) and withdrawal-apathy-low vigor ($r = 0.37$, $p = .04$). The correlations between the PDQ-39 Summary Index and the GDS subscales of dysphoric mood ($r = 0.21$, $p = .24$) and hopelessness ($r = 0.02$, $p = .93$) were nonsignificant.

The correlations between the UPDRS Part III subscale of gait–balance and the PDQ-39 Summary Index approached statistical significance ($r = 0.42$, $p = .02$), whereas tremor, bradykinesia, rigidity, and dyskinesia were not significantly associated with HS (all absolute r-values <0.28 and all p-values $>.13$). In regard to cognition, the number of categories achieved on the WCST was significantly correlated with the PDQ-39 Summary Index ($r = -0.44$, $p = .01$). The associations between the PDQ-39 Summary Index and the WCST PE, JLO, CVLT-II Trials 1–5, and the DKEFS LF and category fluency were all nonsignificant (all absolute r-values <0.12, all p-values $>.17$). Intercorrelations among the motor, cognitive, and mood measures and indices are presented in Table 3.

Three multiple regression analyses were performed to examine specific symptom predictors of HS using the most theoretically relevant and statistically significant variables from the univariate analyses. The gait–balance subscale from the UPDRS, the WCST CC, and the cognitive impairment, anxiety, or withdrawal-apathy-low vigor subscale of the GDS, each entered separately, were entered as predictors and PDQ-39 Summary Index was entered as the dependent variable. The three regressions were all significant (all $p < .01$). However, only the GDS factor of self-perceived cognitive impairment was independently associated with HS (Table 4), whereas anxiety approached statistical significance as a predictor of HS ($p = .02$). The WCST CC was not an independent predictor of HS ($p = .06$) and gait–balance was not independently predictive of HS in any of the regression analyses.

To further explore HS in nondemented and nondepressed PD, we performed bivariate correlations between the subscales of the PDQ-39 and the variables chosen for the aforementioned regression analyses. Self-perceived cognitive impairment (GDS)

Table 3. Intercorrelations for scores on mood, motor, and neuropsychological measures

Measure/Index	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. GDS	–																		
2. UPDRS-III	.05	–																	
3. MDRS	−.22	−.30	–																
4. Dysphoria	.54	−.10	.11	–															
5. Hopelessness	.22	.05	−.42	−.24	–														
6. W-A-V[a]	.82	.15	−.22	.48	−.05	–													
7. Anxiety	.70	.03	−.17	.35	.29	.40	–												
8. Cogn. Imp.[b]	.70	.01	−.13	.08	.36	.32	.41	–											
9. Gait–balance	.14	.72	−.24	−.22	−.01	.20	−.01	.21	–										
10. Tremor	.03	.30	−.21	.10	−.16	.28	.02	−.22	.16	–									
11. Rigidity	−.20	.70	−.09	−.28	−.14	−.05	−.04	−.16	.44	.20	–								
12. Bradykinesia	.11	.86	−.28	.07	.19	.10	.08	.04	.41	.07	.38	–							
13. Dyskinesia	−.15	−.06	.06	−.43	.44	−.26	−.16	.17	.03	−.48	−.14	.09	–						
14. WCST CC	−.06	−.55	.46	.33	−.21	−.13	.04	−.22	−.46	−.12	−.32	−.48	−.17	–					
15. WCST PE	.06	.52	−.58	−.28	.30	.10	−.00	.14	.36	.09	.31	.51	.08	−.89	–				
16. CVLT-II 1–5	−.04	−.32	.31	.30	−.50	.03	−.04	−.16	−.36	−.13	−.17	−.23	−.20	.31	−.25	–			
17. Letter fluency	−.15	−.28	−.02	.08	−.13	−.06	−.17	−.17	−.08	−.12	.00	−.39	−.09	.23	−.27	.17	–		
18. Category fluency	−.17	−.44	.30	.21	−.17	−.14	.05	−.39	−.49	−.32	−.07	−.36	−.10	.51	−.43	.44	.56	–	
19. JLO	−.13	.01	.06	.00	.09	−.04	−.25	−.19	.09	−.03	−.13	.03	.34	.16	−.14	−.01	.30	.19	–

Notes: Numbers 4–8 = GDS factors; numbers 9–12 = UPDRS Part III factors; number 13 = UPDRS Part IV item; numbers 14–19 = neuropsychological measures. Absolute r-values ≥ 0.35 and $\leq 0.43 = p < .05$; absolute r-values ≥ 0.44 and $\leq 0.51 = p < .01$; absolute r–values $\geq 0.52 = p < .001$.

[a]Withdrawal-apathy-vigor factor of the GDS.

[b]Cognitive impairment Factor of the GDS.

Table 4. Regression analyses summary for mood, motor, and cognitive variables predicting the PDQ-39 Summary Index

	B	SEB	*β*	*p*-value	r^2
Regression 1					0.39
GDS anxiety	3.72	1.51	0.36	0.02	
UPDRS Part III Gait–balance	0.91	0.56	0.27	0.12	
WCST total categories correct	−1.39	0.70	−0.33	0.06	
Regression 2					0.43
GDS cognitive impairment	3.73	1.29	0.44	0.01	
UPDRS Part III gait–balance	0.73	0.55	0.22	0.19	
WCST total categories correct	−0.90	0.69	−0.26	0.20	
Regression 3					0.33
GDS withdrawal-apathy-vigor	1.56	0.89	0.28	0.09	
UPDRS Part III gait–balance	0.76	0.60	0.23	0.21	
WCST total categories correct	−1.25	0.73	−0.30	0.10	

Notes: UPDRS Part III gait–balance = Gait and balance factor derived from the Unified Parkinson's Disease Rating Scale Part III (UPDRS Part III); WCST = Wisconsin Card Sorting Test; GDS anxiety = anxiety factor derived from the Geriatric Depression Scale (GDS); GDS cognitive impairment = cognitive impairment factor derived from the GDS; GDS withdrawal-apathy-vigor = withdrawal-apathy-vigor factor derived from the GDS.

was associated with the PDQ-39 subscales of communication, stigma, and social support (all $r > 0.48$, all $p < 0.01$), but not with the cognition subscale of the PDQ-39. Likewise, the WCST CC was not associated with the cognition subscale of the PDQ-39 ($r = -0.22$, $p = .22$), but was significantly related to the PDQ-39 communication and mobility subscales ($r = -0.52$, $p < .01$; $r = -0.49$, $p < .01$, respectively). Greater levels of anxiety (GDS) were associated with poorer scores on the PDQ-39 emotional well-being subscale ($r = 0.67$, $p < .01$) and greater problems with withdrawal-apathy-low vigor (GDS) and gait–balance (UPDRS Part III) were associated with poorer mobility on the PDQ-39 ($r = 0.45$, $p < .01$; $r = 0.51$, $p < .01$, respectively).

Discussion

The purpose of this study was to identify whether general and specific mood, motor, and cognitive symptoms were associated with HS in a group of nondepressed and nondemented individuals with PD. Below we discuss separately the relationship between these factors and HS.

HS and Mood

As expected, and consistent with previous studies (Behari et al., 2005; Cubo et al., 2002; Karlsen et al., 1999; Kuopio et al., 2000; Schrag et al., 2000; Slawek et al., 2005; The Global Parkinson's Disease Survey (GPDS) Steering Committee, 2002), a higher level of depressive symptoms was the best predictor of poorer HS in our sample of nondepressed and nondemented PD participants. Upon further examination, it was apparent that among motor and cognitive symptoms, increased *self-report* of cognitive impairment was the best predictor of reduced HS, with anxiety just failing to meet significance under our conservative α level. However, it is probably warranted to regard anxiety as one of the most important predictors of HS, as this was the second best predictor among other mood, cognitive, and motor symptoms.

These findings are compelling in that, mood symptoms, not motor or cognitive symptoms, are the most predictive of HS in a nondepressed PD sample. Yet, unlike studies that include depressed and demented patients, only certain symptoms that may or may not be related to mood per se are associated with HS. Symptoms of anxiety and self-reported cognitive impairment, which are usually considered ancillary to a diagnosis of mood disturbance, were associated with HS, whereas core affective symptoms (e.g., dysphoria; American Psychiatric Association, 1994) were unrelated to HS in this cohort of patients. Although this finding may seem intuitive based on our exclusion criteria for depression, it is still compelling that certain mood symptoms are important factors of HS in a seemingly affectively normal group.

Our findings suggest that anxiety may be the most important affective "mood" symptom to address as it relates to improving HS in nondepressed PD. Additionally, it was the only symptom related to the emotional well-being subscale of the PDQ-39, suggesting that anxiety may affect a specific and unique psychological aspect of HS not affected by any other PD-associated symptom. A recent study by McKinlay and colleagues (2008) found anxiety to be a significant predictor of poor HS in a sample of PD patients without dementia, suggesting that in concordance with our findings, anxiety should be a focus of assessment in early nondepressed PD patients, despite their apparent lack of psychiatric symptomatology.

Interestingly, self-perceived cognitive impairment was not related to the cognitive aspects of HS, even though several questions overlapped in content (i.e., memory and concentration problems were assessed on both the GDS and PDQ-39). This finding suggests that content overlap unlikely accounts for the relationship between self-reported cognitive impairment and HS. In contrast, subjective cognitive impairment was associated with decreases in HS related to communication, stigma, and social support. Supplementary analyses (as shown in Table 3) revealed that self-perceived cognitive impairment was unrelated to most objective measures of cognition. It may be that this is a psychological concern not based on objective cognitive problems, but rather is related to the interpersonal interactions with others.

These results raise an important issue in regard to improving HS in PD. In those individuals with PD who do not endorse problematic mood symptoms, it may still be salubrious to address and treat mood symptoms in order to improve HS in this population. Moreover, our results imply that addressing specific mood symptoms, such as those related to self-perceived cognitive impairment and anxiety, may be more efficacious to improving HS in uncomplicated PD.

HS and Motor Symptoms

Although there was a trend for overall motor symptoms to predict HS, they were not as significant in their contribution as non-motor symptoms. These results were similar to several previous studies, which failed to demonstrate at a statistically significant level that overall motor symptom severity (Behari et al., 2005; Cubo et al., 2002; Schrag et al., 2000; Slawek et al., 2005) or specific motor symptoms (Karlsen et al., 1999) predicted poorer HS in PD. It is important to note, however, that the relationship between overall HS and gait–balance just failed to meet significance at an α level of .02 and increased disturbance of gait–balance was significantly related to poor mobility aspects of HS.

The relationship between HS and the PD motor symptom of gait and balance over other types of motor symptoms has been demonstrated in several other studies. Schrag and colleagues (2000) and Slawek and colleagues (2005) found that PD participants with self-reported gait disturbance and postural instability had poorer HS than those individuals who did not acknowledge such disturbances. Likewise, several studies have demonstrated that that postural instability predicted poorer HS when examined simultaneously with non-motor symptoms, such as mood, disability, and cognitive scores (Muslimovic et al., 2008; Schrag et al., 2000). Although our study did not reveal a unique relationship between motor symptoms and HS when examined with non-motor symptoms, our results still suggest that gait and balance may play a role in HS. Furthermore, other motor symptoms, such as tremor, bradykinesia, rigidity, and dyskinesia, appear to be unrelated to HS in nondemented and nondepressed individuals with PD. The underlying factors associated with the exclusive relationship between gait–balance disturbance and HS in PD should be explored in future studies.

HS and Cognition

Cognition failed to be an independent predictor of HS when examined conjointly with mood and motor symptoms in this nondemented and nondepressed PD sample. This finding may not be entirely surprising, as the sample was selected based on intact cognitive functioning. However, our results revealed that poor HS is associated with self-perceived cognitive impairment, rather than actual, objectively measured cognitive performance. These findings suggest that it may be prudent to treat *self-perceptions* of cognitive impairment.

Although motor and mood symptoms appear to be better predictors of HS, there was evidence that higher levels of executive functioning and problem solving, as measured by the number of categories achieved on the WCST, were significantly associated with better HS (via bivariate correlations). This was in contrast to associations between HS and overall cognition (MDRS), verbal learning and memory, visuospatial ability, and verbal fluency, which were all nonsignificant. Our results suggest that decreases in HS in PD may be more specific to poorer performances in executive functioning and problem solving as opposed to other aspects of cognition. This is consistent with previous studies that have shown that early PD patients have impaired executive functioning (Dubois & Pillon, 1997) associated with great disturbance in daily functioning (Cahn et al., 1998). However, the lack of an association between HS and the participants' performance on the PE index of the WCST and the verbal fluency measures suggests that only certain areas of executive functioning may be related to HS in PD. It is also apparent that decrements in executive functioning are associated with specific aspects of HS, including poorer levels of communication and mobility, but are seemingly unrelated to cognitive aspects of HS or self-perceived cognitive impairment. This suggests that despite their similar designations, these three factors are clearly assessing different perceptions and abilities.

Our results were similar to those of Muslimovic and colleagues (2008), who found minimal contribution of cognition to HS. However, unlike our findings, Muslimovic and colleagues (2008) did not find a relationship between HS and executive functioning, but rather found that psychomotor/attention tests made a small contribution to one dimension (psychosocial) of HS. Although the tests used in Kelpac and colleagues' (2008) study were not the same as the ones we employed in our study, they

found a relationship between executive function and HS, which is consistent with our result trends. However, unlike Kelpac and colleagues' (2008) study, we did not find an association between memory and HS. Some of these conflicting findings may be due to inclusion of demented patients, as in Muslimovic and colleagues' (2008) study or because of the different neuropsychological measures employed. Therefore, further delineation of specific cognitive abilities to HS in PD is warranted. Overall, these findings, in addition to the association we found between self-assessed cognitive impairment and HS, emphasize the necessity for managing expectations of cognitive performance and the potential benefit of addressing executive function to improve HS in individuals with PD.

Limitations and Future Directions

There are several limitations to this study. First, due to the relatively small sample size, some of the analyses may have been under-powered and would benefit from replication with a larger sample. As the variance in our analyses was largely unexplained (57%), a study with a larger sample size would allow for more variables to be entered into the analyses in an attempt to explain the additional factors predictive of HS. Second, this study was cross-sectional and based on measures of association, preventing observation of change over time, and determination of causality. It is important to note that we interpreted several statistical trends and significant bivariate correlations that failed to reach significance in the regression analyses. We believe that these relationships were important to discuss, as they may have been masked by shared variance with other symptoms and our conservative α level. Replication studies will be important to confirm our conclusions. Moreover, the relationships among mood, cognition, and motor symptom severity might change with disease progression, and this question should be the focus of future research. One recent study explored this very issue and revealed that longitudinal changes in HS were related to depression, self-reported cognitive function, and degree of functional independence (Marras et al., 2008). It would be important to expand upon this study to include measures of executive function and specific mood and motor symptoms, which we found to be sensitive to HS in PD, to assess their relationship to longitudinal HS changes.

Our finding that anxiety was the best affective neuropsychiatric predictor of HS in our nondepressed and nondemented PD sample was based on the anxiety factor of the GDS. Our study did not include a validated anxiety measure for PD or employ a full psychodiagnostic interview. It would be important to determine whether such an association exists using scales that are specifically designed to examine anxiety. Nevertheless, one strength of using the GDS anxiety factor in our analyses is that it excludes somatic symptoms, which are often included in anxiety measures and can overlap with the motor symptoms associated with PD. We are currently collecting data using several tests specifically designed to measure anxiety to determine if this symptom continues to be an important factor of HS in early PD. Finally, our participants were highly educated and from a University Medical Center, which may limit the generalizability of our findings to other PD patient populations.

Conclusions

In summary, this study suggests that increases in mood symptoms, specifically self-reported cognitive impairment and anxiety, are the best predictors of poor HS in nondemented and nondepressed individuals with PD. In addition, our findings emphasize the important contribution of executive functioning to HS over other cognitive abilities and suggest that gait and balance problems may be related to poor HS in uncomplicated PD. Although individuals with PD may not experience clinical levels of depression or dementia, it is important to realize that greater reports of non-motor symptoms may still be associated with poorer HS or reduced QoL in this relatively normal functioning sample. Although we are not recommending that aggressive treatment for mood symptoms (e.g., pharmacological) be implemented with these individuals, our results do suggest that monitoring symptoms, as well as possibly employing interventions (e.g., behavioral therapy) targeting specific mood and cognitive symptoms, could be beneficial to improving HS in nondepressed and nondemented individuals with PD.

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Conflict of Interest

None declared.

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