Journal of the International Neuropsychological Society (2011), **17**, 1058–1066.

doi:10.1017/S1355617711001068

Apathy and Depression: Separate Factors in Parkinson's Disease

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(RECEIVED July 20, 2010; FINAL REVISION June 15, 2011; ACCEPTED July 6, 2011)

Abstract

The objective of this study was to test the hypothesis that apathy and depression are dissociable in Parkinson disease (PD) by conducting a confirmatory factor analysis (CFA) of items from two commonly used mood scales. A total of 161 non-demented PD patients (age = 64.1; ± 8.4 years) were administered the Apathy Scale and the Beck Depression Inventory-II. Items were hypothesized to load onto four factors: (1) an apathy factor representing loss of motivation, (2) dysphoric mood factor representing sadness and negativity, (3) loss of interest/pleasure factor representing the features common to both apathy and depression, and (4) a somatic factor representing bodily complaints. Results indicated a good fit for the overall CFA model, χ^2 (128, N = 146) = 194.9; $p<.01$. RMSEA was .060 ($p = .16$). The four-factor model was significantly better than all alternative nested models at $p < .001$, including an overarching single factor model, representing "depression." Results support the concept that apathy and depression are discrete constructs. We suggest a "factor based" scoring of the Apathy Scale and Beck Depression Inventory-II that disentangles symptoms related to apathy, depression, overlapping symptoms, and somatic complaints. Such scoring may be important in providing useful information regarding differential treatment options. (*JINS*, 2011, *17*, 1058–1066)

Keywords: Parkinson's disease, Apathy, Depression, Confirmatory factor analysis, Apathy Scale

INTRODUCTION

Parkinson disease (PD) is one of the most common neurodegenerative disorders of late life. While tremor, muscular rigidity, postural instability, and bradykinesia (i.e., slowness of movement) are the hallmark motor features of the disorder, neuropsychiatric symptoms are highly prevalent, and can be among the most disturbing, disabling, and complex aspects of PD. One such neuropsychiatric symptom is apathy. Apathy refers to negative/deficit symptoms such as blunted emotions, loss of interest, and lack of productivity. Two decades ago, researchers hypothesized that apathy could be present in neurological disorders as either a single symptom or as a full psychiatric syndrome. A key study in the early 1990s proposed diagnostic criteria for a syndrome of apathy (Marin, 1991). It was emphasized that lack of motivation in a syndrome of apathy is primary, and not secondary to intellectual impairment, emotional distress (e.g., depression), or impaired consciousness (e.g., delirium). Criteria includes behavioral symptoms, such as lack of productivity; cognitive symptoms, such as lack of interest in learning new things; and emotional symptoms, such as blunted affect and lack of responsivity to positive or negative events (Marin, 1991).

Studies specifically investigating apathy in PD have blossomed over the last decade. Yet, there are still many aspects of apathy that remain unknown. For example, it is unknown whether apathy is a unique syndrome or a subcomponent of depression in PD. This has important implications both for understanding the neural substrates of mood disorders and for differential diagnosis and treatment of apathy in PD. Studies to date have suggested that depression and apathy are separable (Isella et al., 2002; Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006; Pluck & Brown, 2002). However, these studies are limited methodologically by the use of total scores on clinical inventories that are used to assess their presence and severity. This is problematic because apathy and depression scales overlap in content. Thus, a particular symptom endorsement on the Beck Depression Inventory might better represent apathy and thus be counted toward depression and vice versa. The primary aim of the present study was to address whether

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apathy and depression are separable in a way that disentangles the total score confound on two commonly used clinical scales, the Beck Depression Inventory-II (BDI-II, Beck, Steer, & Brown, 1996) and the Apathy Scale (AS, Starkstein et al., 1992). To do so, confirmatory factory analysis was used to examine individual items of the two scales.

Based on prior literature and before conducting any analyses, we proposed four discrete factors: (1) an apathy factor representing loss of motivation, (2) a dysphoric mood factor representing sad mood/negativity, (3) a loss of interest and pleasure factor representing the overlap between apathy and depression, and (4) a somatic factor representing bodily complaints. The rationale for these factors is based on several ideas about how apathy and depression can be distinguished. Studies on the phenomenology of apathy describe it as a primary lack of motivation that is not attributable to emotional distress (Marin, 1990, 1991). Depressive disorders often involve emotional distress and sad mood/dysphoria. Symptoms of worthlessness, failure, disappointment, and guilt are found in depression. Apathy, however, does not involve sad mood, but instead has "blunted" or "no" mood. Apathy does not involve negative appraisal of the self, world, or future (Brown & Pluck, 2000). A NINDS workgroup on depression in PD proposed loss of interest and anhedonia as common to both depression and apathy in PD (Marsh, McDonald, Cummings, & Ravina, 2006). Physical symptoms such as fatigue, changes in appetite/sleep patterns, and loss of libido are hypothesized to load on their own separate factor because physical symptoms are common in PD even in the absence of mood disorder.

METHODS

Participants

Participants included 161 non-demented patients with idiopathic PD who underwent clinical neuropsychological evaluation between 2004 and 2009 at the University of Florida's Psychology Clinic. All PD patients had been referred by the UF Movement Disorders Center. Informed consent was obtained according to university and federal guidelines. To be included, PD patients had to be between 40 and 90 years of age and meet UK Brain Bank diagnostic criteria (Hughes, Ben-Shlomo, Daniel, & Lees, 1992; Hughes, Daniel, Kilford, & Lees, 1992). These criteria are based on the presence of bradykinesia plus at least one other cardinal motor symptom: muscular rigidity, resting tremor, or postural instability. Patients must demonstrate marked improvement in response to dopaminergic therapy to differentiate idiopathic PD from Parkinson's plus syndromes. *Exclusion criteria* were co-morbid neurological illnesses, previous neurosurgical treatments (i.e., deep brain stimulation or pallidotomy), or evidence of dementia based on scores less than 130 on the Dementia Rating Scale II (DRS-II; Jurica, Leitten & Mattis, 2001). Dementia was excluded because the intent was to capture primary apathy. Including demented patients creates a confound that apathy may be secondary to cognitive impairment (Marin, 1991).

Participant information and disease characteristics are shown in Table 1. As a group, the PD patients were well educated, predominantly men (68.9%), Caucasian (95%), and ranged in age from 42 to 84 years. On average, they had been experiencing parkinsonian symptoms for 8.5 years and were in the mid-stages of their disease (i.e., Unified Parkinson's Disease Rating Scale (UPDRS) motor score = 25.5, *SD* = 8.6). Approximately one third of the patients were pre-surgical candidates for Deep Brain Stimulation (DBS). The majority of patients were tremor-predominant subtype (77%) or akinetic–rigid subtype (17.4%). Between 25 and 30% of the PD participants were taking antidepressants and/or anxiolytic medications. Importantly, rates of apathy were not significantly different between individuals who were taking antidepressants or anxiolytics and those who were not taking them ($p = .098$ for antidepressants and $p = .17$, for anxiolytics). There were no significant differences in apathy ($p = .69$) or depression ($p = .76$) between patients with tremor predominant versus akinetic rigid subtypes of PD. Additional information is shown in Table 1.

Procedure

Measures

Mood measures were the Beck Depression Inventory-II (BDI-II) and the Apathy Scale (AS). The BDI-II is a 21-item,

Table 1. Patient characteristics

Characteristic	PD patients *(N = 161)*
Age	64.1 (8.7), range 42–84
Men:women	111:50, (68.9% male)
Years of education	15.1 (2.8), range 7–22
On anti-depressants	30%
On anxiolytics	25%
On DOPA meds	98%
Levodopa equivalent dosage	813.0 (511.4), range 0–2600
Disease subtype	77% Tremor predominant 17.4% Akinetic/rigid 1.9% Postural instability/gait 3.7% Missing or not given
Months symptoms	101.8 (54.3), range 12–251
Motor score (UPDRS, on levodopa)	25.5 (8.6), range 9–47
Hoehn & Yahr stage, on levodopa	Stage 1.5 = .6%; Stage 2.0 = 57.8% Stage 2.5 = 16.1%; Stage 3.0 = 14.3% Stage 4.0 = .6%, Missing = 10.6%
DRS-II Total Score	138.8 (3.5), range 130–144
Apathy Scale	10.8 (6.3), range 0–31
Beck Depression Inventory-II	9.5 (7.2), range 0–34

Note. $N = 161$. However, 4 patients were missing UPDRS on scores ($n = 157$), 17 were missing Hoehn & Yahr staging ($n = 144$), and 6 patients did not have a subtype diagnosis ($n = 155$). Three patients (1.9%) were not taking dopaminergic medications because they were in the early stages of disease. Levodopa equivalent dosages were calculated by converting dopamine agonists into equivalent amounts of levodopa and then adding them to each patient's regular levodopa dose (i.e., Sinemet) using the formula described by Hobson and colleagues (Hobson et al., 2002).

https://doi.org/10.1017/S1355617711001068 Published online by Cambridge University Press

0–3 Likert scale that assesses symptoms of depression experienced over the last 2 weeks (Beck et al., 1996). Reliability studies of the BDI-II in PD patients have not been published yet; however, we found excellent internal consistency reliability of .89. Past literature has shown that the BDI-I has excellent reliability and validity in PD patients and a Movement Disorder Society task force recommended the BDI for assessing depression in PD (Levin, Llabre, & Weiner, 1988; Schrag et al., 2007; Visser, Leentjens, Marinus, Stiggelbout, & van Hilten, 2006).

The Apathy Scale (AS) is a 14-item scale measuring cognitive, emotional, and behavioral symptoms of apathy (Starkstein et al., 1992). Items are rated on a 0 to 3 Likert scale. The scale is abridged from the original 18-item version developed by Marin (Marin, Biedrzycki, & Firinciogullari, 1991). The original scale was shortened by 4 items, and wording was simplified by Starkstein et al. in 1992. Although other scales can be used to assess apathy, some have questionable sensitivity/specificity (i.e., single item from the Unified Parkinson Disease Rating Scale [Kirsch-Darrow et al., 2009]), while others such as the Lille Apathy Rating Scale are too lengthy for routine screening in a typical clinical setting (Sockeel et al., 2006; Zahodne et al., 2009). The AS is routinely used in studies comparing apathy and depression and has good psychometric properties in PD (internal consistency reliability = .76, test–retest 1 week r = .90, Starkstein et al., 1992). The Movement Disorder Society task force assessed apathy and anhedonia scales and classified the AS as "recommended for use" in PD (Leentjens et al., 2008). Recently, construct validity has been established for the AS in a small sample of 28 nondemented PD patients and 19 age-matched controls who were videotaped while sitting alone with six novel toys/gadgets on a table in front of them. The apathetic PD group spent significantly less time interacting with the gadgets than the nonapathetic group. Depression, motor severity, and levodopa equivalent dosage were unrelated to time spent interacting (Ferencz et al., 2010). These findings of a relationship between apathy and behavioral initiation correspond to those reported by Marin and colleagues for the original Apathy Evaluation Scale (Marin et al., 1991).

Statistical Analysis

First, the prevalence of apathy and depression was examined in this cohort of 161 PD participants using the traditionally defined criteria. Apathy was defined using the recommended cutpoint of ≥ 14 (Starkstein et al., 1992). Depression was defined using the recommended cutpoint from the BDI-II manual of ≥ 14 (i.e., minimal depression ≤ 13, mild = 14–19, moderate = 20–28, severe ≥ 29). Leentjens and colleagues recommend using 14 as a cutpoint for the original BDI-I in PD patients (Leentjens, Verhey, Luijckx, & Troost, 2000). We also examined the frequency of pure apathy (≥ 14 AS without ≥ 14 BDI-II), pure depression (≥ 14 BDI-II without ≥ 14 AS), and mixed apathy and depression symptoms (≥ 14 on AES and BDI-II).

Next, the reliability of each item from the AS and BDI-II was examined using item-total scale correlations and Cronbach's alpha. One item was excluded due to unreliability (AS item 3). Remaining items were analyzed using confirmatory factor analysis (CFA). Table 2 shows the hypothesized loadings of each item onto the factors.

Table 2. Proposed factor loadings of each item

Apathy scale items	Beck Depression Inventory-II items
A1. *Interest in learning new things*	B1. Sadness
A2. *Any interests*	B2. Pessimism
*A3. *Concern/worry about your condition*	B3. Past failure
A4. *Put forth effort*	B4. *Loss of pleasure*
A5. *Looking for activities to do*	B5. Guilty feelings
A6. *Future plans and goals*	B6. Punishment feelings
A7. *Motivation*	B7. Self-dislike
A8. **Energy**	B8. Self-criticism
A9. *Others structure your day*	B9. Suicidal thoughts
A10. *Indifference*	B10. Crying
A11. *Lack of concern*	B11. Agitation
A12. *Need help initiating things*	B12. *Loss of interest*
A13. *Blunted emotions*	B13. *Indecisiveness*
A14. *Consider yourself apathetic*	B14. Worthlessness
	B15. **Loss of energy**
	B16. **Changes in sleeping pattern**
	B17. **Irritability**
	B18. **Changes in appetite**
	B19. **Concentration difficulty**
	B20. **Tiredness or fatigue**
	B21. **Loss of interest in sex**

Note. * = unreliable item, was excluded from the CFA; *italic* = apathy factor, underlined = dysphoric mood factor, *italic & Underlined* = overlap factor of loss of interest/pleasure, **bold** = **somatic factor**.

Confirmatory factor analysis was conducted with statistical software AMOS 17.0, using maximum likelihood estimation. Before factoring, items were examined for univariate normality (e.g., skewness and kurtosis). Since most items were non-normally distributed, item parcels were created instead of factoring raw items. The rationale is that CFA has an assumption of multivariate normality. Items on psychopathology scales were skewed toward the lack of psychopathology (e.g., 0 or 1) and thus present a non-normal, positively skewed, and kurtotic distribution. Parceling helps correct for this. Furthermore, parceling creates fewer indicators, requires fewer parameters of estimation, and thus improves fit (Little, Cunningham, Shahar, & Widaman, 2002). Models were examined for fit based on the following goodness of fit criteria: minimum fit function χ^2, root mean square error of approximation (RMSEA), root mean square residual (RMR), normed fit index (NFI), comparative fit index (CFI), incremental fit index (IFI), relative fit index (RFI), and the Tucker-Lewis Index (TLI). Conventional standards were used to determine goodness of fit (e.g., ratio of χ^2 to degrees of freedom 2:1 or less, RMSEA below .05 and nonsignificant, RMR below .05, and NFI, CFI, IFI, RFI, TLI above .9. As is conventional, no single fit index is the primary indicator, but the preponderance of evidence must be in support of the fit of the model (Marcoulides & Hershberger, 1997, Chap. 8).

https://doi.org/10.1017/S1355617711001068 Published online by Cambridge University Press

A nested model approach was used to test alternatives to the full four-factor model. These included a single factor model of "depression" that subsumed all items from both scales. A two-factor model was tested that included "apathy" and "depression" factors based on each scale's content. Two alternative three-factor models (one without loss of interest/pleasure and one without somatic complaints) were tested. The resulting χ^2 statistics were tested against the hypothesized four-factor model to examine for changes in fit.

RESULTS

Frequency of Apathy and Depression Symptoms

Approximately one third of the PD sample (i.e., 54 of 161; 33.5%) had clinically significant levels of apathy (defined by $\geq$14 on the Apathy Scale). Approximately one fourth of the sample (i.e., 41 of the 161; 25.3%) had clinically significant depressive symptoms (defined by $\geq$14 BDI-II score). To examine the relationship between apathy and depression, we calculated the number of individuals who exhibited traditionally defined "pure" apathy, "pure" depression, and "mixed" apathy and depression, and neither apathy nor depression again using the clinical cutoffs for the BDI-II (i.e., $\geq$14 for depression) and Apathy Scale ($\geq$14 AS). Results indicated that 17.4% (28/161 patients) had pure apathy, 9.3% (15/161 patients) had pure depression, 16% (26/161) had mixed apathy and depression, and 57.3% (92/161) had neither apathy nor depression.

Factor Structure of Apathy and Depression in PD

A primary aim of this study was to use confirmatory factor analysis (CFA) to test the hypothesis that items from the Apathy Scale (AS) and the BDI-II loaded on four different factors: (1) an apathy factor, (2) a dysphoric mood factor, (3) a loss of interest/loss of pleasure factor representing the overlapping features of apathy and depression, and (4) a somatic factor representing bodily complaints (e.g., sleep, appetite, fatigue). Before the CFA, the items from the AS and BDI-II were screened for internal consistency reliability. This was done by examining the means, standard deviations, and item-total correlations. As is conventional for reliability analysis, negatively worded items were reverse scored. Cronbach's alpha was examined for each of the total scales, and whether deleting items improved overall alpha. For the AS, all items positively correlated with the total apathy score between .4 and .7, except for item 3. This item was reverse scored such that higher scores equaled more apathy. However, it had a negative correlation with the total score ($r = -.14$). This item states: "Are you concerned about your condition?" Negative correlation with the total apathy score indicates that as patients endorse higher apathy on this item they score lower in overall total apathy. This indicates that it is an unreliable item. Furthermore, internal consistency reliability item-total statistics indicated that deleting this item improved internal consistency reliability (i.e., Cronbach's alpha) from .831 to .855. Thus, this is a psychometrically poor item and was excluded from the CFA. In contrast, the BDI-II did not have any psychometrically poor items. All items positively correlated with the total depression score (between .36 and .68), Cronbach's alpha was .89, and alpha was not improved by deleting any items.

Next, items were checked for normality. Items on both scales tended to be skewed toward the lack of psychopathology (positively skewed and positively kurtotic). Item parcels were created by summing items into pairs. This is done pseudo-randomly by combining items randomly within hypothesized factors. Item parcels improve normality, an assumption for CFA. Because some item parcels were still non-normal, the data were transformed by taking the square root ($\sqrt{(x + 1)}$) of each item parcel to further reduce the positively skew.

Confirmatory Factor Analysis Results

One hundred forty-six participants had complete item data for both the AS and BDI-II. Fourteen patients had skipped at least one item on either scale, so their item data was incomplete and was not analyzed.[1] The remaining 146 participants' item parcels were constrained to the hypothesized four-factor solution. These factors and indicators were as follows: (1) *"Apathy/Loss of Motivation"* (five item parcel indicators, A7_A10, A9_A4, A5_A14, A11_A6, A12_A13), (2)"*Dysphoric mood"* (six item parcel indicators, B6_B8, B3_B17, B9_B2, B1_14, B5_10, B7_11), (3) *"Loss of Interest and Pleasure"* (three item parcel indicators, B4_B12, A1_A2, B13), and (4) *"Somatic Complaints"* (four item parcel indicators, B16_B18, B21_A8, B15_B20, B19).

The overall fit of the model to the data was: χ^2 (129, N = 146) = 213.3, $p < .01$ (NFI = .844, CFI = .931, IFI = .932, RFI = .815, TLI = .918). The RMSEA was .067 ($p = .04$), and the RMR was .011. The overall fit was good in terms of the ratio of χ^2 to degrees of freedom ratio being less than a ratio of 2:1, fit indices close to 1, and RMR less than .05. However, the RMSEA was significant and greater than .05. Modification indices were examined to see if there was a single parameter that would greatly improve the fit of the model. Of interest, it was a correlated uniqueness (i.e., unexplained variance) among two *"Dysphoric Mood"* indicators (B6_B8 and B7_B11) that the modification indices provided as improving fit the most. These items have to do with feelings of punishment, self-criticalness, and crying and guilt. This means that there is unexplained variance in these parcels that "clusters together." Allowing the unexplained variance of these indicators to correlate improved the model by 17.05 χ^2 points. This improved the fit to: χ^2 (128, N = 146) = 194.9, $p < .01$ (NFI = .858, CFI = .945, IFI = .946, RFI = .830, TLI = .934). The RMSEA was .060 ($p = .16$) and the RMR was .011. The χ^2 to degrees of freedom ratio is slightly lower (1.5:1 *vs.* 1.65:1 before) and fit indices are closer to 1; additionally RMSEA is nonsignificant, indicating a better fit.

[1] AMOS 17.0 software requires fully complete datasets to compute indices such as modification indices. Thus, 14 patients had to be excluded from the CFA.

https://doi.org/10.1017/S1355617711001068 Published online by Cambridge University Press

Table 3. Confirmatory factor analysis loadings and uniquenesses

Factor	Items	Loading	Uniqueness
Apathy	A7_A10	.870	.242
	A4_A9	.758	.425
	A14_A5	.646	.582
	A11_A6	.687	.528
	A12_A13	.724	.476
Dysphoric mood	B6_B8	.668	.553
	B3_B17	.770	.407
	B9_B2	.671	.549
	B1_B14	.794	.369
	B5_B10	.585	.658
	B7_B11	.868	.247
Loss of interest/pleasure	B4_B12	.761	.420
	A1_A2	.453	.795
	B13	.650	.577
Somatic	B19	.701	.508
	B15_B20	.640	.591
	B21_A8	.671	.550
	B16_B18	.630	.603

Table 3 shows these four factors, items, standardized loadings and uniquenesses.

All the loadings were high, ranging from .59 to .87. For the *Apathy/Loss of Motivation factor*, the loadings ranged from .65 to .87. The highest loadings were for items A7_A10, "Do you have motivation?," "Are you indifferent to things?," (.87) and items A4_A9, "Do you put much effort into things?," "Does someone have to tell you what to do each day?" (.76). For the *Dysphoric Mood factor*, loadings ranged from .59 to .87. The highest loadings were items B7_B11, "Self-dislike," "Agitation/Restlessness" (.87) and items B1_B14, "Sadness," "Worthlessness." The *Loss of Interest and Pleasure factor* ranged from .65 to .72, with the highest loading for items A12_A13, "Do you need a push to get started on things?," "Are you neither happy nor sad, just in between?" Finally, the *Somatic factor* ranged from .63 to .70, with the highest loading B19, "Concentration difficulty" and B21_A8 "Loss of interest in sex," "Do you have the energy for daily activities?"

In terms of inter-factor correlations, they ranged from medium to high. The lowest correlation was between *Apathy* and *Dysphoric Mood* (r = .526) and the highest correlation was between *Dysphoric Mood* and *Loss of Interest and Pleasure* (r = .895). See Table 4 for inter-factor correlations.

Additionally, to determine the overall correlation between apathy and depression scores, total scores were correlated between the AS and BDI-2. The correlation was in the medium range (r = .61; $p < .001$).

Alternative Nested Models

A nested model approach was used to test alternatives to the four-factor model. This was performed to determine if the four-factor model has a significantly lower χ^2 (indicating a better fit) than other alternative models. The nested models were identical in structure to the original model except for the number of factors (i.e., they included the correlated uniqueness). Results are summarized in Table 5. A one-factor model, subsuming dysphoric mood, apathy, loss of interest/pleasure, and somatic into one overarching "Depression" factor was tested. This model was significantly worse than the four-factor model (one factor $\chi^2 = 433.3$, *vs.* four factor $\chi^2 = 194.9$; $p < .01$). We also tested two factors ("Apathy" and "Depression"), a three-factor solution without the Somatic factor, and a three-factor solution without the Loss of interest/pleasure factors. All of these models were significantly worse than the four-factor model ($p < .01$). Worse (higher) χ^2 indicates a greater discrepancy between the original and reproduced correlation matrix, and hence a worse fit to the data.

Thus, the four-factor model separating the constructs of apathy, depression, loss of interest/anhedonia, and somatic complaints was supported.

DISCUSSION

The present study investigated the hypothesis that apathy and depression are dissociable in PD. First, we examined the prevalence of apathy and depression in our sample. Then, we proposed discrete apathy and depression factors and conducted confirmatory factor analysis (CFA) of individual items from the Beck Depression Inventory-II and the Apathy Scale. Apathy (i.e., ≥ 14 on the AS) was present in one third of our sample (33.5%). This prevalence falls into the reported range of 23–44% in nondemented PD samples (Czernecki et al., 2002; Dujardin et al., 2007; Pedersen et al., 2009; Pluck & Brown, 2002; Zgaljardic et al., 2007). Furthermore, our results indicated 17% of patients had apathy in the absence of depression (i.e., 16% had both apathy and depression and 9% had depression without apathy). Several previous studies have also found apathy in the absence of depression in PD (Isella et al., 2002; Kirsch-Darrow et al., 2006; Oguru,

Table 4. Factor correlations

Factor	Apathy	Dysphoric mood	Loss of interest/pleasure	Somatic complaints
Apathy	–	.526	.801	.735
Dysphoric mood	.526	–	.895	.584
Loss of interest/pleasure	.801	.895	–	.870
Somatic complaints	.735	.584	.870	–

https://doi.org/10.1017/S1355617711001068 Published online by Cambridge University Press

Table 5. Goodness-of-fit statistics for confirmatory factor analysis of full four factor model and alternative nested models

Model	χ^2	*df*	$\Delta\chi^2$	Δdf	$p_{\text{difference}}$
Four factor	194.9	128	–	–	–
One factor	433.3	134	238.3	6	$p < .01$
Two factor	278.9	133	84	5	$p < .01$
Three factor, without somatic	295.2	132	100.2	4	$p < .01$
Three factor, without loss of interest	212.8	132	17.81	4	$p < .01$

Note. p values indicate the χ^2 difference between the alternative models and the four-factor model, indicating significantly worse fit for all alternative models.

Tachibana, Toda, Okuda, & Oka, 2010; Starkstein et al., 1992; Zgaljardic et al., 2007).

Next, we used CFA to test the hypothesis that items from the BDI-II and AS would fall into four factors: (1) an apathy factor representing "loss of motivation," (2) a dysphoric mood factor representing "sadness and negativity," (3) a loss of interest and anhedonia factor representing the overlapping features between apathy and depression, and (4) a somatic factor representing "bodily complaints." Results indicated the four-factor model fit the data well. It fit significantly better than a single 'general depression' factor including all apathy and depression items. It fit better than a two-factor model with all Apathy Scale items loading onto an "apathy" factor and all Beck Depression Inventory-II items loading onto a "depression" factor. Finally, it fit better than alternative three-factor models without either the: a) loss of interest/pleasure factor or b) somatic factor.

Taken together, these findings contribute to the growing body of literature suggesting a separation of these two mood states in PD (Dujardin et al., 2007; Isella et al., 2002; Kirsch-Darrow et al., 2006; Levy et al., 1998; Oguru et al., 2010; Pedersen et al., 2009; Santangelo et al., 2009; Starkstein et al., 1992 Zgaljardic et al., 2007). The findings argue *against* the idea that apathy is more accurately classified as a subcomponent of depression. Moreover, results support several concepts about the different characteristics of apathy and depression in PD. Depression includes sadness and negative thoughts about the self. One of the item clusters that loaded most highly on the dysphoric mood factor was: "Sadness," and "Worthlessness." Another that loaded highly was: "Past failure perception," and "Irritability." Additionally, symptoms of guilt and self-dislike loaded highly on the dysphoric mood factor. In contrast, apathy is free from affective evaluation and does not involve negative self or event appraisal. Apathetic individuals lack responsiveness to both negative and positive events (Brown & Pluck, 2000). Results lend support for the idea that apathy involves behavioral lack of initiation, and lack of effort. The strongest loading item parcel on the apathy factor was "Do you put much effort into things?" and "Does someone have to tell you what to do each day?"

In addition to apathy and depression factors, a somatic factor and an "overlapping symptom" factor of loss of interest and anhedonia were hypothesized. The somatic factor included physical complaints such as changes in appetite, sleep, energy, fatigue, and loss of libido. Our results supported somatic symptoms loading onto their own factor. This is logical, given that physical symptoms can occur as part of PD itself and independent of mood symptoms. The final factor, loss of interest and anhedonia, was highlighted by a National Institute of Neurological Disorders and Stroke (NINDS) PD depression workgroup as two symptoms that overlap between depression and apathy (Marsh et al., 2006). To our knowledge, this is the first study to empirically test this concept. Indeed, it was supported by our four-factor model. The workgroup cautioned that using loss of interest as one of the two core symptoms of a Major Depressive Disorder (MDD) diagnosis in PD (i.e., Criteria A1 of sad mood or Criteria A2 of markedly diminished interest or pleasure) could lead to false positive diagnosis of MDD because loss of interest might be better accounted for by a syndrome of apathy. They noted similar concerns regarding anhedonia (Marsh et al., 2006).

Using the overlapping symptoms could lead to false positive diagnosis of major or minor depressive disorder. Minor depression requires only two symptoms. One of these must be a core depression symptom and the other can be any of the MDD symptoms (DSM-IV-TR, 2000). Minor depression can easily be misdiagnosed because a patient may have loss of interest or anhedonia plus another symptom associated with PD itself (e.g., psychomotor slowing, insomnia, concentration problems). Major depressive disorder can also be misdiagnosed in the apathetic patient because appetite, sleep, psychomotor changes, concentration, and fatigue are five symptoms in common with MDD and PD.

Factor Based Scoring for BDI-II and AS

To help disentangle the assessment of apathy and depression symptoms, we propose a modified scoring of the BDI-II and AS. In addition to summing the items to derive total scores, a complementary method would combine items across scales to create subscale scores that map onto the four factors found in this study. This will provide four separate indices: "pure" apathy, "pure" depression, overlapping symptoms of loss of interest and pleasure, and somatic symptoms. Based on this study, the apathy/loss of motivation subscale contains 10 items (maximum 30 points), depression/dysphoric mood subscale contains 11 items (maximum 33 points), loss of interest and

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pleasure subscale contains 5 items (maximum 15 points), and the somatic subscale contains 7 items (maximum 21 points). We briefly examined descriptive statistics in our sample [Apathy subscale ($M = 8.0$; $SD = 5.4$; range, 0–24); Depression subscale ($M = 3.1$; $SD = 3.9$; range, 0–17); Overlapping subscale ($M = 2.6$; $SD = 2.4$; range, 0–13), Somatic subscale ($M = 6.0$; $SD = 3.4$; range, 0–19)].

LIMITATIONS

The current study has several limitations. This study did not use psychiatric interviews and DSM-IV diagnoses. This would have allowed for apathy prevalence to be assessed within the context of Dysthymia or Major Depressive Disorder (MDD). However, research has shown that patients with significant depression symptoms not meeting full criteria for MDD still experience significant disability from their mood symptoms and benefit from treatment (Judd, Paulus, Wells & Rapaport, 1996; Lyness et al., 1996). Another weakness of the present study is the lack of a large enough sample to cross-validate. Ideally, the sample can be divided in half and exploratory factor analysis can be performed first. Then, the results can be tested on the second half as a confirmatory factor analysis. Furthermore, combining the items into item pairs (e.g., parcels) is a weakness of the study. Parceling does not allow each item to independently load on factors. A stronger item could influence a weaker item in terms of loadings. Parceling was necessary in the present study because of severe non-normality of the data. For future studies, a sample with a more normal distribution of apathy scores could be created by only including patients that have apathy and depression above a certain threshold of symptoms (i.e., ≥ 14). This may be less representative of the general PD patient population, but would improve the normality of responses and avoid the need to parcel.

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

Apathy appears to have a prominent place in the neuropsychiatric profile of nondemented Parkinson patients. Support was found for important discriminating characteristics of apathy and depression. An additional factor based scoring of the Apathy Scale and Beck Depression Inventory-II may help disentangle symptoms related to apathy, depression, overlapping symptoms, and somatic symptoms.

Support for the dissociability of apathy and depression in Parkinson disease has broad implications, both theoretically and clinically, for the field of movement disorders. It suggests different neural mechanisms may underlie apathy and depression. Orbito-frontal-subcortical connections may underlie depression whereas mesial frontal/anterior cingulate cortex-ventral tegmental connections may underlie apathy in PD. Mayberg and colleagues found depressed PD patients had hypometabolism in the orbital-inferior frontal lobe and the caudate compared to non-depressed PD patients (Mayberg, 1994; Mayberg et al., 1990). The neurobiological substrates of apathy are unknown, but are hypothesized to involve the ACC circuit (Brown & Pluck, 2000; Isella et al., 2002). Specifically, the striato-thalamo-cortical circuit originating in the ventral tegmental area (VTA) and ending in the ACC (VTA → ventral striatum → ventral pallidum → medialdorsal thalamus → ACC). These limbic structures are involved in motivation and drive, and are important in translating motivation into action (Davidson & Irwin, 1999; Groenewegen, Wright, & Beijer, 1996; Mogenson, Jones, & Yim, 1980). Lesions in the region of the ACC and supplemental motor area produce a syndrome of extremely severe apathy called akinetic mutism. Patients make no effort to communicate or initiate activities and lie silent and motionless (Damasio & Van Hoesen, 1983). To our knowledge, one study has examined PD apathy with functional imaging. Remy and colleagues used Positron Emission Tomography (PET) and found apathy was inversely correlated with dopamine and norepinephrine binding in the ventral striatum (Remy, Doder, Lees, Turjanski, & Brooks, 2005). The ventral striatum is a key structure in the circuit described earlier. Dysfunction of the ACC circuit, perhaps neurochemically through loss of dopamine and neuropathologically through Lewy bodies, may underlie apathy in PD. Future studies are needed to elucidate differences in neural substrates between apathy and depression in PD.

Future studies are also needed to examine the relationship between apathy and cognition. Several studies have found apathy is associated with impaired executive functioning (Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Isella et al., 2002; Pedersen et al., 2009; Pluck & Brown, 2002; Santangelo et al., 2009; Starkstein et al., 1992; Zgaljardic et al., 2007). A recent study assessed patients at baseline and after an average of a 1.5 years and found that apathetic *versus* non-apathetic PD patients declined faster on the Dementia Rating Scale-2 (DRS-2), free recall, attention, cognitive inhibition, and fluency. However, the apathetic group was lower on the DRS-2 at baseline, making it difficult to attribute the change solely to apathy (Dujardin, Sockeel, Delliaux, Destee, & Defebvre, 2009).

In terms of clinical implications from the present study, our results suggest that clinicians should screen for both apathy and depression to appropriately triage and treat patients. In other neurological disorders, treatments for apathy are being examined in pharmacological areas such as amphetamines (e.g., methylphenidate), atypical antipsychotics, dopaminergic agonists, and acetylcholinesterase inhibitors (van Reekum, Stuss, & Ostrander, 2005). Some of these may hold promise for the treatment of apathy in PD. In PD patients that have undergone deep brain stimulation surgery, studies have shown that apathy can be successfully treated by reintroducing dopaminergic agonists (Thobois et al., 2010). While pharmacological research is being explored, non-pharmacological interventions such as cognitive-behavioral psychotherapy focusing on behavioral activation that re-engages the patient slowly back into activities and interests could be investigated. CBT approaches have shown promise in the treatment of PD depression

https://doi.org/10.1017/S1355617711001068 Published online by Cambridge University Press

(Dobkin, Allen, & Menza, 2007; Dobkin, Menza, & Bienfait, 2008), and may also prove beneficial for treatment of apathy.

ACKNOWLEDGMENTS

This project was completed as part of a doctoral dissertation (L.K.D.) at the University of Florida. Support was provided by NINDS (predoctoral NRSA F31-NS059142 to LKD, RO1-NS05063 to DB, and K23-NS044997 to MSO) the Michael J. Fox Foundation, and the UF National Parkinson Foundation Center of Excellence. There are no financial or other conflicts of interest regarding authors for this study.

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