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Symptom Dimensions of Depression and Apathy and their Relationship with Cognition in Parkinson's Disease

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Abstract

Objective—Both depression and apathy, alone and in combination, have been shown to negatively affect cognition in patients with Parkinson's disease (PD). However, the influence of specific symptom dimensions of depression and apathy on cognition is not well understood. The current study investigated the relationship between symptom dimensions of depression and apathy, based on factors identified in Kirsch-Darrow et al. (2011), and memory and executive function in PD.

Method—A sample of 138 non-demented individuals with PD (mean age = 64.51 ± 7.43 years) underwent neuropsychological testing and completed the Beck Depression Inventory, 2nd Edition and Apathy Scale. Separate hierarchical regression models examined the relationship between symptom dimensions of depression and apathy ("pure" depressive symptoms, "pure" apathy, loss of interest/pleasure [anhedonia], and somatic symptoms) and three cognitive domain composites: immediate verbal memory, delayed verbal memory, and executive function.

Results—After adjusting for general cognitive status and the influence of the other symptom dimensions, "pure" depressive symptoms were negatively associated with the delayed verbal memory composite ($p < 0.034$) and somatic symptoms were positively associated with the executive function composite ($p < 0.026$). No symptom dimensions were significantly related to the immediate verbal memory composite.

Conclusions—Findings suggest that specific mood symptoms are associated with delayed verbal memory and executive function performance in non-demented patients with PD. Further

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research is needed to better understand possible mechanisms through which specific symptom dimensions of depression and apathy are associated with cognition in PD.

Keywords

Emotion; mood; memory; executive function; neuropsychology; movement disorders

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the nigrostriatal pathway (Damier, Hirsch, Agid, & Graybiel, 1999). While the exact etiology of the disease remains unclear, this selective loss of dopaminergic neurons causes the characteristic motor symptoms, as well as a constellation of non-motor symptoms that likely precede the onset of motor symptoms (Jankovic, 2008). Neuropsychiatric symptoms are common are in PD, with one study showing that approximately 87% of patients, 5.65 (± 4.94) years after diagnosis, mostly in Hoehn and Yahr stages 2 or 3 (73% of sample), reported at least one psychiatric symptom (Kulisevsky et al., 2008). Since the degeneration of the dopaminergic neurons in the substantia nigra can differentially disrupt important emotion and cognitive brain circuits (Tekin & Cummings, 2002), the clinical presentation of these psychiatric symptoms can vary widely between patients.

Over the past decade or so, our understanding of depression and apathy in PD has flourished. Depression is characterized by low mood and/or anhedonia, along with a combination of other symptoms, such as altered sleep, altered appetite, fatigue, and concentration difficulties (American Psychiatric Association, 2013). These symptoms often overlap with other non-motor symptoms in PD (including apathy), making the diagnosis of depression in PD difficult. Apathy refers to a set of cognitive, behavioral, and emotional features that relate to reduced interest and motivation in goal-directed behaviors (Marin, Biedrzycki, & Firinciogullari, 1991). Individuals with apathy typically show flattened affect, reduced motivation, and difficulty with the initiation and perseverance of behaviors. Both of these psychiatric syndromes have been shown to negatively affect cognition in PD, with depression most consistently associated with worse delayed episodic memory and executive functioning and apathy most consistently associated with worse executive functioning (for reviews, see Poletti, De Rosa, & Bonuccelli, 2012; Santangelo et al., 2013). However, findings are variable across studies.

Interestingly, apathy often occurs as a symptom of depression. Recent research has begun to parse apart the overlap and differences between depressive and apathetic symptoms in PD. To date, only a few studies have looked at depression and apathy, alone and in combination, within the same PD sample. These studies have found cognitive deficits associated with apathy specifically related to letter fluency, verbal memory recall, visuoconstruction, executive functioning (global function, set-shifting, and abstract reasoning; Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Santangelo, Vitale, et al., 2009; Varanese, Perfetti, Ghilardi, & Di Rocco, 2011) and apathy with depression specifically related to verbal fluency, psychomotor speed, visuoconstruction, and executive functioning (global

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function and set-shifting; M. L. Cohen, Aita, Mari, & Brandt, 2015; Santangelo, Vitale, et al., 2009), with fewer to no deficits seen in depression alone. On the other hand, a separate study showed that PD participants with mild cognitive impairment (PD-MCI) reported greater symptoms of depression, but not apathy, relative to cognitively intact PD participants (Jones, Mangal, Lafo, Okun, & Bowers, 2016). In addition to these cognitive findings, a recent review of the neuroimaging literature in PD found that depression was associated with increased brain activity in prefrontal regions and decreased functional connectivity between prefrontal-limbic networks, while both positive and negative correlations were reported between apathy and metabolism or brain activity in frontal, limbic, and striatal regions (Wen, Chan, Tan, & Tan, 2016). Taken together, these results suggest that apathy may be a distinct phenomenon from depression in PD.

Previous research has typically identified depression and apathy based on total scores of clinical measures that are used to assess their presence and severity. However, these studies do not consider the overlap in content between these syndromes across clinical measures, which may contribute to discrepant findings. The Movement Disorder Society has created task forces to evaluate and critique depression and apathy rating scales in PD (Leentjens et al., 2008; Schrag et al., 2007). Basing diagnoses of depression or apathy in PD solely on the total score of a rating scale likely does not capture the full range of depressive or apathetic symptoms in PD. For example, when somatic symptoms of depression scales are endorsed by patients with PD, falsely inflated total depression scores can occur, which can lead to the diagnosis of depression even when the two core components of depression (i.e., sad mood and/or loss of interest or pleasure) are not endorsed. It has also been suggested that the latter symptom (i.e., loss of interest or pleasure) is common in both depression and apathy (Marsh et al., 2006), which can make it difficult to differentiate between the two when that symptom is endorsed. Finally, some depression scales, such as the Hospital Anxiety and Depression Scale (Snaith & Zigmond, 2000) and the Center for Epidemiologic Studies Depression Scale (Radloff, 1977), lack items that also assess for overlapping apathy symptoms (i.e., loss of interest, reduced motivation, effortful behaviors, social withdrawal) and may be more useful when used in conjunction with apathy scales, while other depression scales, such as the Hamilton Depression Scale (Hamilton, 1960) and Geriatric Depression Scale (Sheikh & Yesavage, 1986), contain overlapping apathy items.

Motivated by these critiques, Kirsch-Darrow and colleagues (2011) conducted a factor analytic study in PD patients on two commonly used measures in depression and apathy research – the Beck Depression Inventory, 2nd Edition (Beck, Steer, & Brown, 1996) and the Apathy Scale (Starkstein et al., 1992). They found that depression and apathy were dissociable in PD and identified four separate factors containing unique and overlapping symptoms: “pure” depression, “pure” apathy, anhedonia (overlapping depressive and apathetic symptoms), and somatic symptoms. Since depression and apathy can be separated into unique subcomponents in PD, these dimensions may better reflect the different neural substrates associated with each syndrome.

To date, it is unclear whether these dissociable symptom dimensions of depression and apathy identified by Kirsch-Darrow et al. (2011) are related to the cognitive dysfunction seen in PD. The purpose of the current study was to investigate the relationship between

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mood and cognition in a sample of non-demented PD subjects. Specifically, we investigated whether subcomponents of depression and apathy were uniquely related to episodic memory and executive function, as these cognitive domains are most commonly associated with these mood states in PD (Poletti et al., 2012; Santangelo et al., 2013). Given that depression is associated with fronto-subcortical dysfunction and hippocampal alterations (Sacher et al., 2012) and that hippocampal anatomic abnormalities can be observed in non-demented patients with PD (Ibarretxe-Bilbao, Junque, Marti, & Tolosa, 2011), we hypothesized that elevated depressive symptoms would be negatively associated with delayed episodic memory and executive function. Moreover, we hypothesized that, due to similar neural circuitry (i.e., frontal-striatal circuit) underlying both motivation and aspects of executive function (Bonelli & Cummings, 2007), more severe symptoms of apathy would be related to worse executive functioning. We did not expect to find relationships for anhedonic and somatic symptoms.

As gender (Heller, Dogan, Schulz, & Reetz, 2014; Miller & Cronin-Golomb, 2010), side-of-onset (Foster et al., 2011; Foster et al., 2013; Modestino, Amenechi, Reinhofer, & O'Toole, 2017), and disease subtype (Reijnders, Ehrt, Lousberg, Aarsland, & Leentjens, 2009; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007) have been shown to differently affect mood and cognition in PD, exploratory analyses investigating how these factors influenced the relationship between depression and apathy subcomponents and cognition were also conducted.

Method

Participants

A retrospective sample of 272 PD patients, between 50 to 90 years, were drawn from the INFORM database at the University of Florida Center for Movement Disorders and Neurorestoration. Participants received a diagnosis of idiopathic PD by fellowship-trained movement disorders neurologists according to the UK Brain Bank criteria (Hughes, Ben-Shlomo, Daniel, & Lees, 2001). These criteria are based on the presence of bradykinesia and at least one other cardinal motor symptom (i.e., muscular rigidity, resting tremor, or postural instability), which determined their disease subtype. Exclusionary criteria for this study included: (a) non-native English speakers (n = 8), (b) co-occurring neurological conditions (e.g., stroke, tumor; n = 16), (c) severe psychiatric disturbance (e.g., schizophrenia, bipolar disorder; n = 9), (d) history of neurosurgery (e.g., pallidotomy; n = 4), and (e) evidence of cognitive disturbance based on scores below 130 on the Dementia Rating Scale, 2nd Edition (DRS-2; Jurica, Leitten, & Mattis, 2001) and below 24 on the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975; n = 33). An additional 64 subjects were excluded from analyses due to missing data. Our final sample consisted of 138 individuals (see Table 1 for demographic data). The modified Hoehn and Yahr staging (Goetz et al., 2004) was obtained in order to describe PD severity. The scale defines broad stages of symptom PD symptom progression (from 1 to 5), with higher scores indicating greater severity. All procedures were approved by the University of Florida's Institutional Review Board and all participants provided both verbal and written consent.

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Measures

Depression—Depressive symptoms were measured using the Beck Depression Inventory, 2nd Edition (BDI-II; Beck et al., 1996), a 21-item self-report questionnaire assessing the frequency and severity of depressive symptoms over the previous two weeks. Scores on individual items range from 0–3, with total scores ranging from 0–63. In individuals with PD, scores above 14 indicate clinical significance (Visser, Leentjens, Marinus, Stiggelbout, & van Hilten, 2006).

Apathy—Apathy symptoms were measured using the Apathy Scale (AS; Starkstein et al., 1992), a 14-item self-report questionnaire assessing the severity of apathy symptoms over the previous 2–4 weeks. Scores on individual items range from 0–3, with total scores ranging from 0–42. Scores above 14 indicate clinical significance.

Cognition—Cognitive abilities were assessed with a standardized neuropsychological battery. Measures of verbal memory and executive function were used in this study. Memory tests included immediate and delayed recall scores from the Hopkins Verbal Learning Test – Revised (HVLT-R; Brandt & Benedict, 2001) and the Logical Memory subtest of the Wechsler Memory Scale, 3rd Edition (LM; Wechsler, 1997). Tests of executive functioning included the calculated interference score of the Stroop test (Golden, 1978) and Trail Making Test, Part B (TMT-B; Army Individual Test Battery, 1944). In order to reduce the number of analyses and risk for type I error, analyses of cognitive domains were restricted to tests of memory and executive functioning based on previous studies showing that these domains are the most sensitive to depression and apathy (Butterfield et al., 2010; M. L. Cohen et al., 2015; Santangelo, Vitale, et al., 2009; Varanese et al., 2011).

Descriptives of the mood questionnaires and cognitive measures are found in Table 2.

Covariates—We controlled for variables known to influence mood and cognition in PD. In PD, individuals with normal global cognitive scores have shown a broad range of performance on specific cognitive measures (Burdick et al., 2014). In addition, worse DRS-2 scores have been shown in non-demented apathetic compared to non-apathetic PD patients (Dujardin, Sockeel, Delliaux, Destee, & Defebvre, 2009). As such, we controlled for general cognitive status via DRS-2 scores. Motor severity has been shown to be correlated with apathy (Cubo, Benito-Leon, Coronell, Armesto, & Group, 2012) and cognitive performance (Riggeal et al., 2007). Using the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn, Elton, & Members of the UPDRS Development Committee, 1987), we determined motor severity via the "on" medication score from Part III (motor), where higher scores indicate greater motor severity. Additionally, we controlled for disease subtype (e.g., tremor predominant, akinetic/rigid, and gait/instability) and duration of motor symptoms (in years), as each has shown differential relationships with mood and cognition in PD (Burn et al., 2012; Foster et al., 2013; Lyros, Messinis, & Papathanasopoulos, 2008; Williams-Gray et al., 2007).

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Statistical Analysis

All analyses were conducted using SPSS 22.0 software (IBM Corp., 2013). Symptom dimensions of depression and apathy were calculated based on factors identified by Kirsch-Darrow et al. (2011). These included “pure” depression, “pure” apathy, anhedonic, and somatic symptoms. Table 3 outlines the individual items comprising each factor. Scores from the individual cognitive measures were demographically-normed using test-specific manuals or previously published norms (Heaton, Grant, & Matthews, 1991) and were converted to *z*-score metric. Composite scores reflect an average of the *z*-scores within a given cognitive domain. Cognitive domains included: 1) immediate verbal memory (immediate recall scores from the HVLT-R and LM), delayed verbal memory (delayed recall scores from the HVLT-R and LM), and executive function (scores from Stroop interference and TMT-B).

Correlational analyses were computed to determine the relationship between mood dimensions and cognitive domain performance. Separate hierarchical regression analyses were conducted for each cognitive domain. In the initial models, general cognitive status (DRS-2 total score) and disease variables (PD subtype, disease duration, and UPDRS motor score) were entered into the first block, and symptom factors from the BDI-II and AS were entered into the second block of the regression model. The symptom factors were entered simultaneously in the same regression models to examine the association of each factor while controlling for other factor scores. In the final models, the disease variables were removed due to lack of statistical significance and nearly non-existent effect sizes.

Post-hoc hierarchical regressions were run in which dependent variables were *z*-scores on the individual tests included in that cognitive domain. Exploratory analyses investigating the influence of gender (male/female), side-of-onset (left/right), and PD subtype (tremor dominant/non-tremor dominant) were also conducted for each cognitive domain. The abovementioned hierarchical regressions were run separately for each group. We used a statistical significant threshold of $\alpha \leq 0.05$ and we reported both Bonferroni corrected and uncorrected *p* values for post-hoc analyses. Effect sizes are reported as partial eta-squared (η_p^2), for which 0.01 indicates a small effect, 0.06 a medium effect, and 0.14 a large effect (J. Cohen, 1969).

Results

Participant Characteristics

As shown in Table 1, the sample had a mean age of 64.5 years and was primarily male (70.3%). The average duration of symptoms was 7.8 years and tremor was the dominant symptom (79.7%). Patients were “on” medication and in their “on” state, with an average UPDRS motor score was 26.5 (± 8.9). Over half of the sample (54.3%) was in stage 2 of the disease, based on modified Hoehn and Yahr staging. Average MMSE total score was 28.4 and average DRS-2 total score was 137.7, both of which suggest the sample was non-demented. Using the recommended clinical cutoff of 14, 8.0% of the sample had clinically elevated depression, 15.2% had clinically elevated apathy, and 18.1% had both clinically elevated depression and apathy (Table 2).

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Correlations

Table 4 depicts the relationship between mood symptoms and cognition. Neither total BDI-II score nor AS score were significantly correlated with the cognitive domains or individual cognitive tests. Somatic symptoms were positively correlated with the executive function composite ($r = 0.18$, $p = 0.036$), as well as Stroop Interference performance ($r = 0.19$, $p = 0.029$). No other symptom dimensions were correlated with cognitive performance. All cognitive domains and individual cognitive measures were significantly positively correlated, with the exception of Stroop Interference, which was only positively correlated with the executive function composite.

Hierarchical Regressions

Results are summarized in Table 5. After controlling for general cognitive status and the influence of the other symptom dimensions, “pure” depressive symptoms were significantly related to delayed verbal memory performance (parameter estimate [95% CI] = −0.058 [−0.111, −0.005], $p = 0.034$, $\eta^2_p = 0.037$) and somatic symptoms were significantly related to executive function performance (parameter estimate [95% CI] = 0.059 [0.007, 0.111], $p = 0.026$, $\eta^2_p = 0.041$). No symptom dimensions were significantly associated with the immediate verbal memory composite.

Post-hoc Analyses

No mood symptoms significantly related to any individual cognitive test when Bonferroni corrections were applied (all p values > 0.05). Follow-up analyses not adjusting for multiple comparisons revealed that “pure” depressive symptoms were significantly related to HVLT-R delayed recall performance (parameter estimate [95% CI] = −0.077 [−0.152, −0.003], $p = 0.040$, uncorrected, $\eta^2_p = 0.035$; Table 6), but not LM delayed recall. Moreover, somatic symptoms were significantly associated with Stroop Interference performance (parameter estimate [95% CI] = 0.082 [0.019, 0.146], $p = 0.012$, uncorrected, $\eta^2_p = 0.054$; Table 6), but not TMT-B performance. No mood symptoms were significantly related to the HVLT-R or LM immediate recall scores.

Exploratory Analyses

Gender—Gender differences were evident in DRS-2 total scores, immediate verbal memory, and delayed verbal memory composites, with males scoring significantly lower than females across all three measures (Supplementary Table S1). As seen in Supplementary Table S2, “pure” depressive symptoms were significantly related to delayed verbal memory performance in men (parameter estimate [95% CI] = −0.082 [−0.145, −0.020], $p = 0.010$, $\eta^2_p = 0.078$), but not in women. Likewise, anhedonic symptoms were also significantly related to delayed verbal memory performance in men (parameter estimate [95% CI] = 0.158 [0.046, 0.271], $p = 0.006$, $\eta^2_p = 0.087$), but not in women. No symptom dimensions were significantly associated with the immediate verbal memory or executive function composites in men or women.

Side-of-onset—Significant side-of-onset differences were seen in MMSE total scores, immediate verbal memory, and delayed verbal memory composites, with right onset scores

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significantly lower than left onset scores (Supplementary Table S3). “Pure” depressive symptoms were significantly associated with delayed verbal memory performance for those with left, but not right, onset PD (parameter estimate [95% CI] = −0.087 [−0.168, −0.007], p = 0.034, η^2_p = 0.107; Supplementary Table S4). No symptom dimensions were significantly associated with the immediate verbal memory or executive function composites.

PD subtype—With respect to subtype, there were no significant differences between the tremor and non-tremor dominant subtypes (Supplementary Table S5). Results of the regressions are presented in Supplementary Table S6. For the tremor dominant subtype, “pure” depressive symptoms were significantly associated with delayed verbal memory performance (parameter estimate [95% CI] = −0.080 [−0.152, −0.009], p = 0.028, η^2_p = 0.049). No symptom dimensions were significantly associated with the immediate verbal memory or executive function composites, nor were any relationships seen for the non-tremor dominant subtype.

Discussion

The present study investigated associations between symptom dimensions of depression and apathy and cognition in a sample of non-demented PD patients. Results of our primary analyses showed that, while controlling for general cognitive status and the influence of other symptom dimensions, more severe symptoms of “pure” depression were associated with worse delayed list recall and greater somatic symptoms were associated with better executive function. Both of these effects were small in size. Apathetic or anhedonic symptoms did not significantly influence neuropsychological results. This suggests that specific symptom dimensions of depression and apathy may be differentially associated with neuropsychological functioning.

Primary Findings

Similar to previous research in PD (Butterfield et al., 2010; Costa, Peppe, Carlesimo, Pasqualetti, & Caltagirone, 2006; Fernandez et al., 2009), we found an inverse relationship between “pure” depressive symptoms and memory performance. It is well-documented in non-PD samples that depression is associated with memory and executive dysfunction (for reviews, see Rock, Roiser, Riedel, & Blackwell, 2014; Snyder, 2013; Trivedi & Greer, 2014). This latter relationship was not found in the current study. Previous studies, both in PD and non-PD samples, have conceptualized depression as the total sum of items on a depression inventory. As seen by Kirsch-Darrow et al. (2011), particularly in PD, these inventories can be broken down into “pure” elements of depression, as well as elements that overlap with other emotional constructs (e.g., apathy, anhedonia). It may be that “pure” depressive symptoms are solely related to memory dysfunction and that total depressive symptoms are more sensitive to other elements of cognitive dysfunction due to the inclusion of overlapping emotional (i.e., apathy) content. Given the heterogeneity in depression symptom presentation, we may be missing important relationships between specific subsets of mood symptoms and cognition in PD when solely investigating total depressive symptoms. Depression symptom dimension work in non-PD samples suggests distinct cognitive and neurobiological correlates (Brailean et al., 2016; Dotson, Zonderman, Kraut,

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& Resnick, 2012; McLaren et al., 2017), as well as response to treatment (Vrieze et al., 2014) for specific subsets of symptoms. Given the present findings and these findings in non-PD samples, the investigation of specific mood symptom dimensions in PD is warranted in order to better understand their relationship with cognition.

Further, results of the current study found a relationship between "pure" depressive symptoms and memory performance that was driven by delayed list recall. Similar dissociations between word-list and story memory performance in PD have been reported in the literature (Lafo et al., 2015; Zahodne et al., 2011), with worse performance noted for word-lists. This discrepancy may be due to the executive demands of list-learning versus story memory tasks, such that word lists depend on self-generation in order to reorganize words into semantically-related categories, while story tasks are intrinsically organized into semantically meaningful prose. The latter facilitates subsequent retrieval, while the former only benefits when appropriate reorganization occurs during encoding (Panegyres, 2004). Interestingly, despite similar performance across cognitive composites, with 13–15% of subjects performing in the impaired range, we did not find relationships between any mood symptoms and the immediate memory and executive function composites. Other studies in both PD (Costa et al., 2006; Fernandez et al., 2009) and non-PD (Lamar, Charlton, Zhang, & Kumar, 2012) populations have found that depression is associated with worse delayed recall on word-list tasks and our results are consistent with this literature.

The failure of the apathy symptom dimension to achieve a significant relationship with executive function in the current study is interesting, as there is plenty of evidence to suggest that apathy and executive dysfunction are highly correlated in PD (Bogdanova & Cronin-Golomb, 2012; Dirnberger & Jahanshahi, 2013; Meyer et al., 2014). As our PD sample was non-demented and mostly in stage two of the modified Hoehn and Yahr PD staging, it may be that our subjects were too high functioning and not apathetic enough for executive dysfunction to be present. However, other PD studies have also included non-demented individuals who were in similar Hoehn and Yahr PD staging and found significant inverse apathy and executive function relationships (Bogdanova & Cronin-Golomb, 2012; Butterfield et al., 2010; Meyer et al., 2014; Santangelo, Vitale, et al., 2009; Varanese et al., 2011). Perhaps how apathy is conceptualized affects these results, such that "pure" apathy, as determined by the current study, is not as strongly associated with executive dysfunction, while other apathy measures that are confounded by additional mood symptoms find stronger relationships. Additional research is needed to parse this apart. Moreover, we only investigated two aspects of executive function – set-shifting and cognitive inhibition. It may be that other aspects of executive function, such as abstract reasoning or decision making, are more affected by neuropsychiatric symptoms. Future research should investigate a broader battery of executive functions, as well as investigate the relationship between mood symptoms and other meaningful outcomes in PD, such as activities of daily functioning, PD-MCI or Parkinson's disease dementia status, driving outcomes, quality of life and/or mortality. For example, past studies have provided preliminary evidence that quality of life is primarily related to symptoms of "pure" depression and mixed depression/apathy, but only minimally related to symptoms of "pure" apathy (Jones, Butterfield, et al., 2015; Jones, Marsiske, Okun, & Bowers, 2015).

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Lastly, our main analyses also found a significant positive relationship between somatic symptoms and executive functioning, particularly on the Stroop interference task, though the latter model was not significant. This finding contradicts the negative relationship that is typically reported in non-PD older adults with depression (Baune, Suslow, Arolt, & Berger, 2007; Brailean et al., 2016). As previously articulated, perhaps the PD sample in the current study was too high functioning for executive dysfunction to be present. As many of the clinical characteristics of PD are somatic in nature (e.g., sleep or appetite disturbance, bradyphrenia; Aarsland, Marsh, & Schrag, 2009), it is possible that our non-demented sample with relatively intact executive functioning accurately reported or over-reported these clinical characteristics, which led to these findings.

Exploratory Findings

The exploratory aim of this study was to examine factors known to differentially affect mood and cognition in PD, such as gender, side-of-onset, and disease subject, in order to direct future investigations on these topics. We did see that one of our main findings (i.e., “pure” depressive symptoms predicted delayed memory performance) held true for males, those with left-side onset, and those who had the tremor-dominant subtype. Two reviews of the PD literature suggest that men are more likely to have cognitive dysfunction (i.e., lower scores on global cognitive screeners, letter fluency, spatial planning), while women are more likely to report higher levels of total depression (Heller et al., 2014; Miller & Cronin-Golomb, 2010), though results were not consistent across all studies included in these reviews. It has been suggested that estrogen may have neuroprotective properties with respect to cognition and clinical characteristics in PD (Fernandez & Lapane, 2000). While men and women reported similar levels of depression and apathy in the current study, both overall and within the symptom clusters, we found a unique relationship between “pure” depressive symptoms and delayed memory performance for men, but not women, after controlling for the influence of the other mood symptom dimensions. Additional research is needed to understand the mechanisms underlying this relationship, and how it is related to the cognitive and symptomatic course of PD.

Variability in mood and cognition findings, with respect to side-of-onset differences, is reported in the literature. A recent review suggested that those with left-onset have greater difficulty on attention and memory tasks, while right-onset is associated with worse language and verbal memory functioning (Verreyt, Nys, Santens, & Vingerhoets, 2011). More recent studies have reported no cognitive or mood differences between side-of-onset groups in unmedicated PD patients (Erro et al., 2013; Pellicano et al., 2015), while another study reported worse working memory and increased anxiety in those with left-onset and greater magical thinking in those with right-onset (Modestino et al., 2017). Additional research has highlighted the importance of looking at the interaction of clinical characteristics with mood and cognition, rather than covarying out these effects, to help elucidate differences between left- and right-onset groups. For example, Foster et al. (2013) found that negative mood and disease duration interacted to significantly negatively affect global cognition in those with right-, but not left-, side onset. To the best of our knowledge, no other groups have used a symptom dimension approach to investigate cognition in left- versus right-onset PD, which may help to clarify some of the variability in findings. Clearly,

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more work is needed to understand the significance of our results in the context of the broader literature.

With respect to disease subtype, the clinical heterogeneity of PD has led to the classification of many PD subtypes, with different proposed etiologies and progressions (for review, see Marras & Lang, 2013). The current study investigated broad classifications of tremor and non-tremor dominant subtypes, as the sample was too small in the latter group to look at specific subtypes. We did not see any group differences in clinical characteristics, mood symptoms, or cognitive functioning. However, we did find that "pure" depressive symptoms negatively predicted delayed memory performance in the tremor dominant subtype. This finding is inconsistent with the literature, which suggests that those with the tremor dominant subtype are less cognitively impaired than those with non-tremor dominant subtypes. For example, studies have shown those with the tremor dominant subtype are better at tasks of procedural learning (Vakil & Herishanu-Naaman, 1998), perception (Seichepine et al., 2011), working memory (Moustafa, Bell, Eissa, & Hewedi, 2013), and reward learning (Moustafa, Krishna, Eissa, & Hewedi, 2013) than other subtypes. Regarding mood, those with non-tremor dominant subtypes report greater depression and apathy (Reijnders et al., 2009; Starkstein et al., 1998) compared to the tremor dominant subtype. Perhaps the broad classification of subtypes in these analyses, or that we investigated cognitive domains instead of specific cognitive measures, influenced results or that breaking depression and apathy down into its subcomponents allowed for more sensitive analysis of the unique relationship between mood and cognition in specific disease subtypes.

And finally, in addition to the significant relationship between "pure" depressive symptoms and delayed memory performance, we also found that as anhedonic (mixed depression/apathy) symptoms increased, better delayed memory performance was seen in males, which was a medium effect. This finding is intriguing, as it seems to contradict what is known about the inverse relationship between anhedonia and cognition (Assogna, Cravello, Caltagirone, & Spalletta, 2011; Santangelo, Morgante, et al., 2009). Methodological differences may partially explain these contradictory results, as these studies conceptualized anhedonia based on the Snaith–Hamilton Pleasure Scale (Snaith et al., 1995) and the current study used a factor analysis that identified anhedonia as overlapping depressive and apathetic symptoms.

Implications and Conclusions

The clinical implications of the current study suggest that not all patients with PD who present with significant mood symptoms manifest neuropsychological deficits. Rather, it may be that specific mood symptoms (i.e., depression) are driving cognitive difficulties or that cognitive difficulties are causing depressive symptoms. Subtyping patients with PD based on specific components of depression and apathy may aid in targeting treatment by matching underlying cognitive and brain changes in subgroups of PD with the mechanism of action of pharmacological intervention, such as antidepressants. Moreover, subtyping PD patients may also help to direct non-pharmacological interventions, such that individuals with depression or apathy may be prescribed a course of cognitive behavioral therapy (Berardelli et al., 2015), while those who present with apathy may benefit from treatment

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that focuses on behavioral activation and incorporates external cuing to counteract the motivation and initiation deficits that are commonly seen (Butterfield et al., 2017). Effective treatment of these specific mood subcomponents may help to alleviate depression- and apathy-related cognitive dysfunction and disability in PD. Conversely, if cognitive dysfunction is driving mood symptoms, treatments geared towards learning compensatory strategies, such as the Healthy Action to Benefit Independence & Thinking (HABIT™) program (Mayo Clinic Foundation), or augmenting cortical excitability via non-invasive brain stimulation (Boggio et al., 2006), may help to improve cognition, which can, in turn, reduce mood symptoms.

The underlying pathophysiology of depression- and/or apathy-related cognitive dysfunction is outside the scope of the current study. However, fronto-striatal alterations are commonly reported as the underlying mechanism of PD-related depression, apathy and cognitive dysfunction (Levy & Dubois, 2006; Mayberg & Solomon, 1995; Ravizza, Goudreau, Delgado, & Ruiz, 2012). Complex interrelationships between various neurotransmitter systems (e.g., serotonin, noradrenaline) may also underlie emotional and cognitive dysfunction in PD (Aarsland, Pahlhagen, Ballard, Ehrt, & Svenningsson, 2011; Barone, 2010), highlighting the idea that these symptoms are not the result of dysfunction in a single neurotransmitter system (e.g., dopamine). As previously mentioned, recent neuroimaging studies suggest that depression and apathy may be dissociable in PD (for review, see Wen et al., 2016), indicating that specific neural correlates underlie these neuropsychiatric syndromes. Together, these findings, in combination with findings from the current study, highlight the need for further and more sensitive inquiry into depression- and apathy-related cognitive dysfunction in PD, as a myriad of factors likely influence and are associated with these processes, and clarifying these relationships is important for advancing our understanding of PD.

The present study is not without limitations. While there is debate in the literature regarding the use of multiple comparison corrections (Rothman, 1990), and we did limit our analyses to cognitive domains shown to be sensitive to mood symptoms in PD, caution is warranted in the interpretation of post-hoc analyses due to the potential for increased Type I error. Replication of our findings in an independent sample is needed. Second, we did not group our subjects based on clinical diagnoses of depression and/or apathy. Rather, we looked at self-reported levels of depression and apathy symptom dimensions and entered these as continuous measures in our models. Across studies, differences in methodology may partially explain inconsistencies in results. Third, only 8% of our sample was clinically depressed, 15% was clinically apathetic, and 18% was both clinically depressed and apathy. Both subclinical depressive and apathetic symptoms have been shown to be related to negative brain and cognitive outcomes in both PD (Butterfield et al., 2010; Costa et al., 2006) and non-PD (Hwang et al., 2015; Spalletta, Fagioli, Caltagirone, & Piras, 2013) samples. Though our main finding in this study was statistically significant, the effect size was small. A larger sample with more severe mood and cognitive symptoms may have yielded larger effect sizes. Further, information regarding anxiety symptoms was not available for participants in our study; therefore, we were unable to determine the influence of anxiety on the present results. Additionally, we used a convenience sample of non-demented PD patients receiving outpatient clinical care and our results may not generalize to

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the general PD population. Moreover, our subjects underwent neuropsychological evaluation when they were “on” medications, which may have influenced their cognitive performance. Finally, this research is cross-sectional in nature, which does not allow the direction of this relationship to be specified. It is possible that having worse cognition may lead to greater mood symptoms or that the inverse is true – worse mood symptoms may negatively impact cognition.

In conclusion, using a symptom dimension approach, we found unique and stronger relationships for “pure” depressive and somatic symptoms with neuropsychological performance (delayed memory and executive functioning, respectively) in non-demented PD patients than other depression and apathy symptoms. Exploratory analyses suggested that the relationship between “pure” depressive symptoms and delayed memory performance varied by age, side-of-onset, and disease subtype. Given the heterogeneity of findings in the PD literature, parsing apart symptoms of depression and apathy into specific mood clusters may be a useful approach towards elucidating the cognitive and neural correlates of PD. In addition, we hope that the current study spurs additional research on the contributions of gender, side-of-onset, and disease subtype to mood and cognition in PD, as these factors may differentially influence these relationships.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson’s disease. Mov Disord. 2009; 24(15):2175–2186. [PubMed: 19768724]

Aarsland D, Pahlhagen S, Ballard CG, Ehrt U, Svenningsson P. Depression in Parkinson disease--epidemiology, mechanisms and management. Nat Rev Neurol. 2011; 8(1):35–47. [PubMed: 22198405]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5. Washington, DC: American Psychiatric Association; 2013.

Army Individual Test Battery. Manual of Directions and Scoring. Washington, DC: War Department, Adjutant General’s Office; 1944.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Assogna F, Cravello L, Caltagirone C, Spalletta G. Anhedonia in Parkinson's disease: a systematic review of the literature. Mov Disord. 2011; 26(10):1825–1834. [PubMed: 21661052]

Barone P. Neurotransmission in Parkinson's disease: beyond dopamine. Eur J Neurol. 2010; 17(3): 364–376. [PubMed: 20050885]

Baune BT, Suslow T, Arolt V, Berger K. The relationship between psychological dimensions of depressive symptoms and cognitive functioning in the elderly - the MEMO-Study. J Psychiatr Res. 2007; 41(3–4):247–254. [PubMed: 16887147]

Beck, AT., Steer, RA., Brown, GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.

Berardelli I, Pasquini M, Roselli V, Biondi M, Berardelli A, Fabbrini G. Cognitive behavioral therapy in movement disorders: A review. Mov Disord Clin Pract. 2015; 2(2):107–115.

Bogdanova Y, Cronin-Golomb A. Neurocognitive correlates of apathy and anxiety in Parkinson's disease. Parkinsons Dis. 2012; 2012:793076. [PubMed: 22203919]

Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, Fregni F. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci. 2006; 249(1):31–38. [PubMed: 16843494]

Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. Dialogues Clin Neurosci. 2007; 9(2):141–151. [PubMed: 17726913]

Brailean A, Comijs HC, Aartsen MJ, Prince M, Prina AM, Beekman A, Huisman M. Late-life depression symptom dimensions and cognitive functioning in the Longitudinal Aging Study Amsterdam (LASA). J Affect Disord. 2016; 201:171–178. [PubMed: 27235820]

Brandt, J., Benedict, RHB. Hopkins Verbal Learning Test - Revised, Professional Manual. Lutz, FL: Psychological Assessment Resources; 2001.

Burdick DJ, Cholerton B, Watson GS, Siderowf A, Trojanowski JQ, Weintraub D, … Leverenz JB. People with Parkinson's disease and normal MMSE score have a broad range of cognitive performance. Mov Disord. 2014; 29(10):1258–1264. [PubMed: 25073717]

Burn DJ, Landau S, Hindle JV, Samuel M, Wilson KC, Hurt CS, … Group P-PS. Parkinson's disease motor subtypes and mood. Mov Disord. 2012; 27(3):379–386. [PubMed: 22162098]

Butterfield LC, Cimino CR, Oelke LE, Hauser RA, Sanchez-Ramos J. The independent influence of apathy and depression on cognitive functioning in Parkinson's disease. Neuropsychology. 2010; 24(6):721–730. [PubMed: 20853956]

Butterfield LC, Cimino CR, Salazar R, Sanchez-Ramos J, Bowers D, Okun MS. The Parkinson's Active Living (PAL) Program. J Geriatr Psychiatry Neurol. 2017; 30(1):11–25. [PubMed: 28248557]

Cohen, J. Statistical Power Analysis for the Behavioural Sciences. New York, NY: Academic Press; 1969.

Cohen ML, Aita S, Mari Z, Brandt J. The Unique and Combined Effects of Apathy and Depression on Cognition in Parkinson's Disease. J Parkinsons Dis. 2015; 5(2):351–359. [PubMed: 25769262]

Costa A, Peppe A, Carlesimo GA, Pasqualetti P, Caltagirone C. Major and minor depression in Parkinson's disease: a neuropsychological investigation. Eur J Neurol. 2006; 13(9):972–980. [PubMed: 16930363]

Cubo E, Benito-Leon J, Coronell C, Armesto D, Group AS. Clinical correlates of apathy in patients recently diagnosed with Parkinson's disease: the ANIMO study. Neuroepidemiology. 2012; 38(1): 48–55. [PubMed: 22236943]

Damier P, Hirsch EC, Agid Y, Graybiel AM. The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain. 1999; 122(Pt 8):1437–1448. [PubMed: 10430830]

Dirnberger G, Jahanshahi M. Executive dysfunction in Parkinson's disease: a review. J Neuropsychol. 2013; 7(2):193–224. [PubMed: 24007368]

Dotson VM, Zonderman AB, Kraut MA, Resnick SM. Temporal relationships between depressive symptoms and white matter hyperintensities in older men and women. Int J Geriatr Psychiatry. 2012; 28(1):66–74. [PubMed: 22415749]

Dujardin K, Sockeel P, Delliaux M, Destee A, Defebvre L. Apathy may herald cognitive decline and dementia in Parkinson's disease. Mov Disord. 2009; 24(16):2391–2397. [PubMed: 19908317]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Erro R, Santangelo G, Picillo M, Vitale C, Amboni M, Longo K, … Pellecchia MT. Side of onset does not influence cognition in newly diagnosed untreated Parkinson's disease patients. Parkinsonism Relat Disord. 2013; 19(2):256–259. [PubMed: 23178144]

Fahn, S., Elton, R. Members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn, S.Marsden, CD.Calne, D., Holstein, N., editors. Recent Developments in Parkinson's Disease. Vol. 2. Plurham Park, NJ: Macmillian Healthcare Information; 1987. p. 153-163.

Fernandez HH, Lapane KL. Estrogen use among nursing home residents with a diagnosis of Parkinson's disease. Mov Disord. 2000; 15(6):1119–1124. [PubMed: 11104194]

Fernandez HH, See RH, Gary MF, Bowers D, Rodriguez RL, Jacobson Ct, Okun MS. Depressive symptoms in Parkinson disease correlate with impaired global and specific cognitive performance. J Geriatr Psychiatry Neurol. 2009; 22(4):223–227. [PubMed: 19429848]

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3):189–198. [PubMed: 1202204]

Foster PS, Drago V, Crucian GP, Sullivan WK, Rhodes RD, Shenal BV, … Heilman KM. Anxiety and depression severity are related to right but not left onset Parkinson's disease duration. J Neurol Sci. 2011; 305(1–2):131–135. [PubMed: 21420691]

Foster PS, Drago V, Mendez K, Witt JC, Crucian GP, Heilman KM. Mood disturbances and cognitive functioning in Parkinson's disease: the effects of disease duration and side of onset of motor symptoms. J Clin Exp Neuropsychol. 2013; 35(1):71–82. [PubMed: 23320400]

Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C. … Movement Disorder Society Task Force on Rating Scales for Parkinson's, D. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord. 2004; 19(9):1020–1028. [PubMed: 15372591]

Golden, CJ. Stroop Color and Word Test. Wood Dale, IL: Stoelting Company; 1978.

Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56–62. [PubMed: 14399272]

Heaton, RK., Grant, I., Matthews, CG. Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographic Corrections, Research Findings, and Clinical Applications. Odessa, FL: Psychological Assessment Resources, Inc; 1991.

Heller J, Dogan I, Schulz JB, Reetz K. Evidence for gender differences in cognition, emotion and quality of life in Parkinson's disease? Aging Dis. 2014; 5(1):63–75. [PubMed: 24490118]

Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. 1992. Neurology. 2001; 57(10 Suppl 3):S34–38. [PubMed: 11775598]

Hwang JW, Egorova N, Yang XQ, Zhang WY, Chen J, Yang XY, … Kong J. Subthreshold depression is associated with impaired resting-state functional connectivity of the cognitive control network. Transl Psychiatry. 2015; 5:e683. [PubMed: 26575224]

Ibarretxe-Bilbao N, Junque C, Marti MJ, Tolosa E. Brain structural MRI correlates of cognitive dysfunctions in Parkinson's disease. J Neurol Sci. 2011; 310(1–2):70–74. [PubMed: 21864849]

IBM Corp. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp; 2013.

Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008; 79(4):368–376. [PubMed: 18344392]

Jones JD, Butterfield LC, Song W, Lafo J, Mangal P, Okun MS, Bowers D. Anxiety and Depression Are Better Correlates of Parkinson's Disease Quality of Life Than Apathy. J Neuropsychiatry Clin Neurosci. 2015; 27(3):213–218. [PubMed: 25162776]

Jones JD, Mangal P, Lafo J, Okun MS, Bowers D. Mood Differences Among Parkinson's Disease Patients With Mild Cognitive Impairment. J Neuropsychiatry Clin Neurosci. 2016; 28(3):211–216. [PubMed: 26792098]

Jones JD, Marsiske M, Okun MS, Bowers D. Latent growth-curve analysis reveals that worsening Parkinson's disease quality of life is driven by depression. Neuropsychology. 2015; 29(4):603–609. [PubMed: 25365564]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Jurica, PJ., Leitten, CL., Mattis, S. DRS-2: Dementia Rating Scale-2: Professional Manual. Lutz, FL: Psychological Assessment Resources; 2001.

Kirsch-Darrow L, Marsiske M, Okun MS, Bauer R, Bowers D. Apathy and depression: separate factors in Parkinson's disease. J Int Neuropsychol Soc. 2011; 17(6):1058–1066. [PubMed: 22040900]

Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, Garcia-Sanchez C, Gironell A. Trapecio Group S. Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. Mov Disord. 2008; 23(13):1889–1896. [PubMed: 18709682]

Lafo JA, Jones JD, Okun MS, Bauer RM, Price CC, Bowers D. Memory Similarities Between Essential Tremor and Parkinson's Disease: A Final Common Pathway? Clin Neuropsychol. 2015; 29(7):985–1001. [PubMed: 26689342]

Lamar M, Charlton R, Zhang A, Kumar A. Differential associations between types of verbal memory and prefrontal brain structure in healthy aging and late life depression. Neuropsychologia. 2012; 50(8):1823–1829. [PubMed: 22564447]

Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE, … Goetz CG. Apathy and anhedonia rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 2008; 23(14):2004–2014. [PubMed: 18709683]

Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex. 2006; 16(7):916–928. [PubMed: 16207933]

Lyros E, Messinis L, Papathanasopoulos P. Does motor subtype influence neurocognitive performance in Parkinson's disease without dementia? Eur J Neurol. 2008; 15(3):262–267. [PubMed: 18190508]

Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991; 38(2):143–162. [PubMed: 1754629]

Marras C, Lang A. Parkinson's disease subtypes: lost in translation? J Neurol Neurosurg Psychiatry. 2013; 84(4):409–415. [PubMed: 22952329]

Marsh L, McDonald WM, Cummings J, Ravina B, Depression NNWGo, Parkinson's D. Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH Work Group. Mov Disord. 2006; 21(2):148–158. [PubMed: 16211591]

Mayberg HS, Solomon DH. Depression in Parkinson's disease: a biochemical and organic viewpoint. Adv Neurol. 1995; 65:49–60. [PubMed: 7872152]

McLaren ME, Szymkowicz SM, O'Shea A, Woods AJ, Anton SD, Dotson VM. Vertex-wise examination of depressive symptom dimensions and brain volumes in older adults. Psychiatry Res. 2017; 260:70–75. [PubMed: 28039796]

Meyer A, Zimmermann R, Gschwandtner U, Hatz F, Bousleiman H, Schwarz N, Fuhr P. Apathy in Parkinson's disease is related to executive function, gender and age but not to depression. Front Aging Neurosci. 2014; 6:350. [PubMed: 25642187]

Miller IN, Cronin-Golomb A. Gender differences in Parkinson's disease: clinical characteristics and cognition. Mov Disord. 2010; 25(16):2695–2703. [PubMed: 20925068]

Modestino EJ, Amenechi C, Reinhofer A, O'Toole P. Side-of-onset of Parkinson's disease in relation to neuropsychological measures. Brain Behav. 2017; 7(1):e00590. [PubMed: 28127512]

Moustafa AA, Bell P, Eissa AM, Hewedi DH. The effects of clinical motor variables and medication dosage on working memory in Parkinson's disease. Brain Cogn. 2013; 82(2):137–145. [PubMed: 23660434]

Moustafa AA, Krishna R, Eissa AM, Hewedi DH. Factors underlying probabilistic and deterministic stimulus-response learning performance in medicated and unmedicated patients with Parkinson's disease. Neuropsychology. 2013; 27(4):498–510. [PubMed: 23876122]

Panegyres PK. The contribution of the study of neurodegenerative disorders to the understanding of human memory. QJM. 2004; 97(9):555–567. [PubMed: 15317924]

Pellicano C, Assogna F, Cravello L, Langella R, Caltagirone C, Spalletta G, Pontieri FE. Neuropsychiatric and cognitive symptoms and body side of onset of parkinsonism in unmedicated Parkinson's disease patients. Parkinsonism Relat Disord. 2015; 21(9):1096–1100. [PubMed: 26173702]

Poletti M, De Rosa A, Bonuccelli U. Affective symptoms and cognitive functions in Parkinson's disease. J Neurol Sci. 2012; 317(1–2):97–102. [PubMed: 22503136]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977; 1(3):385–401.

Ravizza SM, Goudreau J, Delgado MR, Ruiz S. Executive function in Parkinson's disease: contributions of the dorsal frontostriatal pathways to action and motivation. Cogn Affect Behav Neurosci. 2012; 12(1):193–206. [PubMed: 22006555]

Reijnders JS, Ehrt U, Lousberg R, Aarsland D, Leentjens AF. The association between motor subtypes and psychopathology in Parkinson's disease. Parkinsonism Relat Disord. 2009; 15(5):379–382. [PubMed: 18977165]

Riggeal BD, Crucian GP, Seignourel P, Jacobson CE, Okun MS, Rodriguez R, Fernandez HH. Cognitive decline tracks motor progression and not disease duration in Parkinson patients. Neuropsychiatr Dis Treat. 2007; 3(6):955–958. [PubMed: 19300633]

Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med. 2014; 44(10):2029–2040. [PubMed: 24168753]

Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology. 1990; 1(1):43–46. [PubMed: 2081237]

Sacher J, Neumann J, Funfstuck T, Soliman A, Villringer A, Schroeter ML. Mapping the depressed brain: a meta-analysis of structural and functional alterations in major depressive disorder. J Affect Disord. 2012; 140(2):142–148. [PubMed: 21890211]

Santangelo G, Morgante L, Savica R, Marconi R, Grasso L, Antonini A, … Group PS. Anhedonia and cognitive impairment in Parkinson's disease: Italian validation of the Snaith-Hamilton Pleasure Scale and its application in the clinical routine practice during the PRIAMO study. Parkinsonism Relat Disord. 2009; 15(8):576–581. [PubMed: 19362509]

Santangelo G, Trojano L, Barone P, Errico D, Grossi D, Vitale C. Apathy in Parkinson's disease: diagnosis, neuropsychological correlates, pathophysiology and treatment. Behav Neurol. 2013; 27(4):501–513. [PubMed: 23242365]

Santangelo G, Vitale C, Trojano L, Longo K, Cozzolino A, Grossi D, Barone P. Relationship between depression and cognitive dysfunctions in Parkinson's disease without dementia. J Neurol. 2009; 256(4):632–638. [PubMed: 19370301]

Schrag A, Barone P, Brown RG, Leentjens AF, McDonald WM, Starkstein S, … Goetz CG. Depression rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 2007; 22(8):1077–1092. [PubMed: 17394234]

Seichepine DR, Neargarder S, Miller IN, Riedel TM, Gilmore GC, Cronin-Golomb A. Relation of Parkinson's disease subtypes to visual activities of daily living. J Int Neuropsychol Soc. 2011; 17(5):841–852. [PubMed: 21813030]

Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clinical Gerontologist. 1986; 5:165–173.

Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995; 167(1):99–103. [PubMed: 7551619]

Snaith, RP., Zigmond, AS. Hospital Anxiety and Depression Scale (HADS). In: Rush, AJ., editor. Handbook of Psychiatric Meaures. Washington, D. C: American Psychiatric Association; 2000. p. 547-548.

Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. Psychol Bull. 2013; 139(1):81–132. [PubMed: 22642228]

Spalletta G, Fagioli S, Caltagirone C, Piras F. Brain microstructure of subclinical apathy phenomenology in healthy individuals. Hum Brain Mapp. 2013; 34(12):3193–3203. [PubMed: 22807351]

Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 1992; 4(2):134–139. [PubMed: 1627973]

Starkstein SE, Petracca G, Chemerinski E, Teson A, Sabe L, Merello M, Leiguarda R. Depression in classic versus akinetic-rigid Parkinson's disease. Mov Disord. 1998; 13(1):29–33.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res. 2002; 53(2):647–654. [PubMed: 12169339]

Trivedi MH, Greer TL. Cognitive dysfunction in unipolar depression: implications for treatment. J Affect Disord. 2014; 152–154:19–27.

Vakil E, Herishanu-Naaman S. Declarative and procedural learning in Parkinson's disease patients having tremor or bradykinesia as the predominant symptom. Cortex. 1998; 34(4):611–620. [PubMed: 9800094]

Varanese S, Perfetti B, Ghilardi MF, Di Rocco A. Apathy, but not depression, reflects inefficient cognitive strategies in Parkinson's disease. PLoS One. 2011; 6(3):e17846. [PubMed: 21437255]

Verreyt N, Nys GM, Santens P, Vingerhoets G. Cognitive differences between patients with left-sided and right-sided Parkinson's disease. A review. Neuropsychol Rev. 2011; 21(4):405–424. [PubMed: 21956794]

Visser M, Leentjens AF, Marinus J, Stiggelbout AM, van Hilten JJ. Reliability and validity of the Beck depression inventory in patients with Parkinson's disease. Mov Disord. 2006; 21(5):668–672. [PubMed: 16450355]

Vrieze E, Demyttenaere K, Bruffaerts R, Hermans D, Pizzagalli DA, Sienaert P, … Claes S. Dimensions in major depressive disorder and their relevance for treatment outcome. J Affect Disord. 2014; 155:35–41. [PubMed: 24210628]

Wechsler, D. The Wechsler Memory Scale. 3. San Antonio, TX: Psychological Corporation; 1997.

Wen MC, Chan LL, Tan LC, Tan EK. Depression, anxiety, and apathy in Parkinson's disease: insights from neuroimaging studies. Eur J Neurol. 2016; 23(6):1001–1019. [PubMed: 27141858]

Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain. 2007; 130(Pt 7):1787–1798. [PubMed: 17535834]

Zahodne LB, Bowers D, Price CC, Bauer RM, Nisenzon A, Foote KD, Okun MS. The case for testing memory with both stories and word lists prior to dbs surgery for Parkinson's Disease. Clin Neuropsychol. 2011; 25(3):348–358. [PubMed: 21491347]

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Table 1

Sample characteristics (n = 138)

	Range	Mean (SD)
Age (years)	50–83	64.51 (7.43)
Education (years)	7–20	14.76 (2.86)
Disease duration (years)	0–21	7.82 (4.86)
UPDRS motor score (on levodopa)	9–51	26.52 (8.90)
DRS-2 total	130–144	137.68 (3.70)
MMSE total	24–30	28.37 (1.58)
	n	%
Gender		
Male	97	70.30
Female	41	29.70
Side-of-Onset		
Left	49	35.50
Right	77	55.80
Bilateral	10	7.20
Data not obtained	2	1.40
Hoehn and Yahr stage of disease		
1.5	1	0.70
2.0	75	54.30
2.5	26	18.80
3.0	23	16.70
Data not obtained	13	9.40
Disease subtype		
Tremor predominant	110	79.70
Akinetic/rigid	24	17.40
Gait/instability	4	2.90

Note. UPDRS = Unified Parkinson's Disease Rating Scale; DRS-2 = Dementia Rating Scale, 2nd Edition; MMSE = Mini-Mental State Examination.

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Table 2

Descriptives of mood questionnaires and cognitive measures

MOOD SYMPTOMS	***n* (%)**	**Range**	**Mean**	**(SD)**
BDI-II total		1.00 – 31.00	10.30	(6.63)
AS total		0.00 – 27.00	11.45	(6.07)
BDI-II > 14	11 (8.00)			
AS > 14	21 (15.20)			
Both BDI-II and AS > 14	25 (18.10)			
Symptom Dimensions				
Depression		0.00 – 16.00	3.60	(3.85)
Apathy		0.00 – 24.00	8.92	(5.14)
Anhedonia		1.00 – 10.00	4.40	(1.74)
Somatic		0.00 – 14.00	6.19	(3.09)
COGNITIVE MEASURES				
Immediate Verbal Memory composite *z*-score		−2.82 – 1.72	−0.63	(0.85)
Impaired range (−1.5*z* or less)	19 (13.80)			
HVLT-R immediate recall *z*-score		−4.00 – 2.40	−1.01	(1.11)
Impaired range (−1.5z or less)	50 (36.20)			
LM I z-score		−2.33 – 2.67	−0.24	(1.05)
Impaired range (−1.5*z* or less)	18 (13.00)			
Delayed Verbal Memory composite *z*-score		−2.67 – 1.50	−0.46	(0.95)
Impaired range (−1.5*z* or less)	20 (14.50)			
HVLT-R delayed recall *z*-score		−4.00 – 1.40	−1.05	(1.27)
Impaired range (−1.5*z* or less)	52 (37.70)			
LM II z-score		−2.67 – 2.67	0.14	(1.06)
Impaired range (−1.5*z* or less)	10 (7.20)			
Executive Function composite *z*-score		−4.00 – 1.45	−0.43	(0.90)
Impaired range (−1.5*z* or less)	19 (13.80)			
Stroop Interference *z*-score		−5.00 – 2.30	0.07	(0.97)
Impaired range (−1.5*z* or less)	8 (5.80)			
TMT, Part B z-score		−4.00 – 1.70	−0.87	(1.29)
Impaired range (−1.5*z* or less)	38 (27.50)			

Note. z-scores were calculated based on demographically adjusted (test-specific manuals or Heaton) norms. SD = standard deviation; BDI-II = Beck Depression Inventory, 2nd Edition; AS = Apathy Scale; HVLT-R = Hopkins Verbal Learning Test, Revised; LM = Wechsler Memory Scale, 3rd Edition Logical Memory; TMT = Trail Making Test.

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Table 3

Item content of the BDI-II and AS subscales used in the current study

Depression	Apathy	Anhedonia	Somatic
BDI-II 1: Sadness	AS 4: Put effort into things	BDI-II 4: Loss of Pleasure	BDI-II 15: Loss of Energy
BDI-II 2: Pessimism	AS 5: Looking for something to do	BDI-II 12: Loss of Interest	BDI-II 16: Changes in Sleep
BDI-II 3: Past Failure	AS 6: Plans/goals for future	BDI-II 13: Indecisiveness	BDI-II 18: Changes in Appetite
BDI-II 5: Guilty Feelings	AS 7: Motivation	AS 1: Interested in learning new things	BDI-II 19: Concentration Difficulty
BDI-II 6: Punishment Feelings	AS 9: Someone tells you what to do	AS 12: Push to get started	BDI-II 20: Tiredness/Fatigue
BDI-II 7: Self-Dislike	AS 10: Indifferent to things		BDI-II 21: Loss of Interest in Sex
BDI-II 8: Self-Criticalness	AS 11: Unconcerned about many things		AS 8: Energy for daily activities
BDI-II 9: Suicidal Thoughts/Wishes	AS 12: Need a push to get started		
BDI-II 10: Crying	AS 13: Neither happy nor sad		
BDI-II 11: Agitation	AS 14: Consider self apathetic		
BDI-II 14: Worthlessness			
BDI-II 17: Irritability			

Note: BDI-II = Beck Depression Inventory; 2nd Edition; AS = Apathy Scale

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Table 4

Correlations between mood and cognitive measures

	BDI-II total	AS total	Depression	Apathy	Anhedonia	Somatic	Immediate Memory	HVLT-R immediate	LM I	Delayed Memory	HVLT-R delay	LM II	Executive Function	Stroop INT
BDI-II total	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AS total	0.60*	--	--	--	--	--	--	--	--	--	--	--	--	--
Depression	0.89*	0.50*	--	--	--	--	--	--	--	--	--	--	--	--
Apathy	0.61*	0.94*	0.55*	--	--	--	--	--	--	--	--	--	--	--
Anhedonia	0.58*	0.53*	0.49*	0.46*	--	--	--	--	--	--	--	--	--	--
Somatic	0.78*	0.47*	0.45*	0.44*	0.35*	--	--	--	--	--	--	--	--	--
Immediate Memory	−0.09	−0.13	−0.13	−0.15	−0.09	0.06	--	--	--	--	--	--	--	--
HVLT-R immediate	−0.10	−0.09	−0.08	−0.08	−0.09	0.02	0.80*	--	--	--	--	--	--	--
LM I	−0.04	−0.12	−0.12	−0.15	−0.04	0.07	0.78*	0.25*	--	--	--	--	--	--
Delayed Memory	−0.09	−0.09	−0.13	−0.12	−0.03	0.07	0.77*	0.65*	0.57*	--	--	--	--	--
HVLT-R delay	−0.11	−0.06	−0.13	−0.08	−0.03	0.05	0.57*	0.71*	0.19*	0.84*	--	--	--	--
LM II	−0.03	−0.09	−0.08	−0.12	0.00	0.07	0.71*	0.34*	0.80*	0.78*	0.33*	--	--	--
Executive Function	0.08	−0.07	0.03	−0.03	0.01	0.18*	0.33*	0.31*	0.22*	0.33*	0.27*	0.27*	--	--
Stroop INT	0.10	−0.04	0.05	−0.03	0.08	0.19*	0.13	0.14	0.06	0.15	0.15	0.08	0.65*	--
TMT-B	0.01	−0.07	−0.02	−0.04	−0.06	0.08	0.36*	0.30*	0.27*	0.34*	0.23*	0.32*	0.82*	0.10

Note. BDI-II: Beck Depression Inventory, 2nd Edition; AS = Apathy Scale; HVLT-R = Hopkins Verbal Learning Test, Revised; LM = Wechsler Memory Scale, 3rd Edition Logical Memory; INT = Interference; TMT = Trail Making Test.

* $p < 0.05$.

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Table 5

Hierarchical regression coefficients for depression and apathy symptom dimensions and covariates on memory and executive function

	Immediate Memory				Delayed Memory				Executive Function			
	Parameter estimate	**[95% CI]**	***p***	η^2_p	**Parameter estimate**	**[95% CI]**	***p***	η^2_p	**Parameter estimate**	**[95% CI]**	***p***	η^2_p
DRS-2 total	**0.07**	**[0.03, 0.11]**	**<0.01**	**0.09**	**0.09**	**[0.05, 0.13]**	**<0.01**	**0.12**	**0.06**	**[0.02, 0.10]**	**<0.01**	**0.07**
Depression	−0.04	[−0.09, 0.01]	0.09	0.02	**−0.06**	**[−0.11, −0.01]**	**0.03**	**0.04**	−0.00	[−0.05, 0.05]	0.98	0.00
Apathy	−0.02	[−0.05, 0.02]	0.37	0.01	−0.01	[−0.05, 0.03]	0.51	0.00	−0.02	[−0.05, 0.02]	0.29	0.01
Anhedonia	0.02	[−0.08, 0.11]	0.76	0.00	0.05	[−0.06, 0.16]	0.34	0.01	0.01	[−0.08, 0.11]	0.82	0.00
Somatic	0.05	[−0.01, 0.10]	0.09	0.02	0.05	[−0.01, 0.11]	0.09	0.02	**0.06**	**[0.01, 0.11]**	**0.03**	**0.04**
						5.32						
F		4.30				0.18				3.22		
R^2		0.15								0.12		
Model *p*			<0.01				<0.01				<0.01	

Note. DRS-2 = Dementia Rating Scale, 2nd Edition. Bold data indicates significance at $p < 0.05$.

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Table 6

Regression coefficients for post-hoc analyses for depression and apathy symptom dimensions and covariates on individual measures

	DRS-2 total	Depression	Apathy	Anhedonia	Somatic	*F*	R^2	Model *p*
HVLT-immediate						1.95	0.08	0.09
Parameter Estimate	**0.06**	−0.04	−0.01	−0.01	0.04			
95% Confidence Interval	**0.01, 0.12**	−0.10, 0.03	−0.06, 0.04	−0.14, 0.12	−0.03, 0.11			
p	**0.02**	0.24	0.73	0.83	0.30			
η^2_p	**0.04**	0.01	0.00	0.00	0.01			
LM I						3.27	0.12	<0.01
Parameter Estimate	**0.08**	−0.05	−0.02	0.05	0.05			
95% Confidence Interval	**0.03, 0.13**	−0.10, 0.02	−0.07, 0.02	−0.08, 0.17	−0.02, 0.12			
p	**<0.01**	0.15	0.31	0.46	0.13			
η^2_p	**0.07**	0.02	0.01	0.01	0.02			
HVLT-delayed						2.77	0.10	0.02
Parameter Estimate	**0.08**	**−0.08**	−0.00	0.06	0.05			
95% Confidence Interval	**0.02, 0.46**	**−0.15, −0.00**	−0.06, 0.05	−0.09,0 0.21	−0.03, 0.13			
p	**<0.01**	**0.04**	0.88	0.43	0.19			
η^2_p	**0.06**	**0.04**	0.00	0.01	0.01			
LM II						4.58	0.16	<0.01
Parameter Estimate	**0.10**	−0.04	−0.02	0.06	0.04			
95% Confidence Interval	**0.05, 0.15**	−0.10, 0.02	−0.06, 0.03	−0.07, 0.18	−0.02, 0.11			
p	**<0.01**	0.17	0.48	0.36	0.21			
η^2_p	**0.12**	0.02	0.00	0.01	0.01			
Stroop INT						1.83	0.08	0.11
Parameter Estimate	0.01	−0.00	−0.04	0.05	**0.08**			
95% Confidence Interval	−0.04, 0.05	−0.06, 0.05	−0.08, 0.01	−0.07, 0.16	**0.02, 0.15**			

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	DRS-2 total	Depression	Apathy	Anhedonia	Somatic	*F*	R^2	Model *p*
p	0.82	0.88	0.09	0.42	**0.01**			
η^2_p	0.00	0.00	0.03	0.01	**0.05**			
TMT-B						2.02	0.11	0.02
Parameter Estimate	**0.10**	−0.00	−0.00	−0.03	0.03			
95% Confidence Interval	**0.04, 0.16**	−0.07, 0.07	−0.06, 0.05	−0.17, 0.12	−0.05, 0.11			
p	**<0.01**	0.98	0.93	0.72	0.44			
η^2_p	**0.09**	0.00	0.00	0.00	0.01			

Note. HVLT-R = Hopkins Verbal Learning Test, Revised; LM = Wechsler Memory Scale, 3rd Edition Logical Memory; INT = Interference; TMT-B = Trail Making Test, Part B; DRS-2 = Dementia Rating Scale, 2nd Edition. Bold data indicates significance at $p < 0.05$, uncorrected.