Neurocognitive Functioning in Parkinsons Disease Patients: Assessing the Unique Contributions of Depression and Fatigue While Controlling for Disease Severity

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NEUROCOGNITIVE FUNCTIONING IN PARKINSON'S DISEASE PATIENTS:
ASSESSING THE UNIQUE CONTRIBUTIONS OF DEPRESSION AND
FATIGUE WHILE CONTROLLING FOR DISEASE SEVERITY

by

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Abstract

Background: While individuals diagnosed with Parkinson's disease (PD) often experience cognitive deficits, depression, and fatigue, the relationships among these non-motor sequelae throughout the progression of the disease are unclear.

Objective: To examine the relationships among disease severity, depression, and fatigue and investigate the independent contributions of depression and fatigue to a composite measure of cognitive functioning, when controlling for disease severity in PD patients.

Methods: A mixed retrospective and prospective sample of PD patients completed a comprehensive neuropsychological battery, as well as self-report measures of depression and fatigue. Cognitive functioning was represented by a summary statistic, or cognitive impairment index (CII). A hierarchal linear regression model, controlling for disease severity, examined the unique contributions of depression and fatigue on cognitive functioning. A Pearson correlation examined the relationship between depression and fatigue.

Results: At step one, disease severity significantly contributed to the model, $F(1, 41) = 48.06$, $p < .001$, accounting for 52.8% of the variance in cognitive functioning. Introduction of depression and fatigue explained an additional 7.2% of the variance and this change in R^2 was significant $F(2,39) = 4.68$, $p < 0.05$. Only depression continued to be a significant contributor beyond disease severity, $t = 2.21$, $\beta = 0.24$, $p < 0.05$ and the change in the model was significant, $F(1, 40) = 4.88$, $p < 0.05$, R^2 change $= 0.05$

Conclusions: Findings suggest that depression is uniquely associated with cognitive functioning observed in PD patients independent of disease severity or level of fatigue. Interventions targeted towards depression may improve cognitive functioning.

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Table of Contents

Introduction

Parkinson's disease (PD) is a chronic and debilitating degenerative disorder that disproportionately affects adults over the age of 60 years (Abrantes et al., 2012), although it is estimated that approximately four percent of those diagnosed experienced onset before the age of 50. Through the progression of PD, motor and non-motor sequelae advance in accord with the course of the disease (Macphee & Stewart, 2012). As part of this process, cognitive decline continues through disease progression (Wood et al., 2016). Additionally, depression and fatigue, which are associated with cognitive functioning (Goldman, Stebbins, Leung, Tilley, & Goetz, 2014; Gómez-Esteban et al., 2009; Starkstein, Mayberg, Leiguarda, Preziosi, & Robinson, 1992; Tröster, Stalp, Paolo, Fields, & Koller, 1995; Wang, Zhang, Li, Wen, & Xu, 2014), also are likely to worsen as the disease progression (Dissanayaka et al., 2011; Friedman et al., 2016). Due to the frequent co-occurrence of these symptoms, it is critical to refine our understanding of how depression and fatigue combine to contribute to cognitive functioning when controlling for disease severity.

Cognitive Symptoms of PD

One of the most prevalent and consequential non-motor symptoms observed among individuals with PD is cognitive impairment (Lehrner et al., 2014). While the pattern of cognitive deficits varies across individuals, a typical PD phenotypic presentation includes the greatest deficits in frontal-type dysfunction (e.g., executive dysfunction), mild to moderate impairment in attention and memory, and very few deficits in visuospatial functioning (Vingerhoets, Verleden, Santens, Miatton, & De Reuck, 2003). Those with PD are at a much higher risk (two to six times more) of developing dementia (PDD), as compared to the general

population (Biundo, Weis, & Antonini, 2016; Löhle, Storch, & Reichmann, 2009). Similarly, prior to the development of dementia, individuals with PD have a 20%-50% chance of developing Mild Cognitive Impairment (MCI; Litvan et al., 2011). Four subtypes of PD-MCI have been identified, including a) non-amnestic single domain, b) amnestic single domain, c) non-amnestic multiple domain, and d) amnestic multiple domains (Lawrence, Gasson, & Loftus, 2016). Using a cutoff of 1.5*SD* reduction in a single category, the most common subtype among the PD population includes non-amnestic single domain (Wood et al., 2016). According to a four-year study of those recently diagnosed with PD-MCI, approximately 21% will convert to PDD over that time period (Wood et al., 2016). Identifying factors contributing to milder forms of cognitive impairment could be beneficial in slowing the progression to dementia.

The relationship between PD and cognitive functioning is most evident as the disease progresses. Disease severity is typically measured through stage ratings on the Hoehn and Yahr scale of the United Parkinson's Disease Rating Scale or Levodopa Equivalent Dose (LED), which includes the level of dosage of anti-Parkinson's medication that an individual currently requires to control their PD specific motor symptoms (Tomlinson et al., 2010). Greater disease severity has been associated with increased cognitive deficits in memory retrieval and executive functioning (Riepe, Kassubek, Tracik, & Ebersbach, 2006).

PD and Depression

In addition to cognitive impairment, depression is a common and consequential non-motor symptom and can be considered as central to PD (Löhle et al., 2009; Macphee & Stewart, 2012). A comorbid diagnosis of depression is estimated as being present in 10%-50% of PD patients (Tandberg, Larsen, Aarsland, & Cummings, 1996). The etiology of depression within PD is theorized as potentially arising through two sources that are not mutually exclusive

(McDonald, Richard, & DeLong, 2003). The first involves a reaction to the psychosocial stress of chronic effects of the disease. The second theorized etiology involves the physical neurodegeneration of the subcortical nuclei often associated with depression that occurs as a result of PD onset or disease pathology (i.e., ventral tegmental area, hypothalamus, dorsal raphe, and locus coeruleus; Lisanby et al., 1993). Regardless of its origin, depression is a common correlate of PD and is likely to occur through the disease's progression, as PD disease severity has been associated with a higher prevalence and severity of depression (Dissanayaka et al., 2011).

PD and Fatigue

Fatigue occurs in more than half of PD patients and is viewed as another prevalent non-motor symptom (Friedman et al., 2016). Fatigue impacts many life aspects for PD patients. It has been has been associated with the advancement of PD and is the primary reason for patients' applications for work disability (Zesiewicz, Patel-Larson, Hauser, & Sullivan, 2007). Additionally, fatigue has been associated with significant decreases in quality of life (QoL) and higher levels of cognitive impairment, especially with the cognitive deficits often associated with PD (i.e., executive dysfunction; Abe, Takanishi, & Yanagihara, 2000; Friedman et al., 2016). Previous studies demonstrating a relationship between fatigue and depression suggest that the presence of depression may enhance or have a bidirectional relationship with fatigue (Skorvanek et al., 2015).

The Combined Role of Depression, Fatigue, and Disease Severity on Cognitive Impairment

Cognitive impairment or dementia in PD patients has been commonly observed as being made worse by the presence of depression (Gómez-Esteban et al., 2009; Starkstein et al., 1992; Wang et al., 2014), with increased deficits in executive functioning (Fonoff et al., 2015; Lawson

et al., 2014; Wang et al., 2014), attention (Ng, Chander, Tan, & Kandiah, 2015), subjective memory (Lehrner et al., 2014), and increased impulsivity (Fonoff et al., 2015) in patients with greater depressive symptoms. Similarly, cognitive impairment within PD patients is often concurrent with fatigue (Friedman et al., 2016). For instance, deficits in the decision-making process have been observed in PD patients with higher levels of reported fatigue, as compared to non-fatigued patients (Saez-Francas et al., 2014). In addition, overall levels of cognitive impairment are higher among fatigued PD patients (Goldman et al., 2014).

Disease severity also complicates the relationships among depression, fatigue, and cognitive impairment in persons with PD. Evidence suggests that cognitive deterioration is an inherent product of progression of the disease (Riepe et al., 2006). A comparable amount of evidence indicates that depression and fatigue also worsen with progression of the disease (Skorvanek et al., 2015). Furthermore, increases in fatigue and depression have also been associated with declines in cognitive performance (de la Riva, Smith, Xie, & Weintraub, 2014). Based on these three trends, it is particularly challenging to differentiate the source of cognitive changes in PD patients throughout the progression of the disease. In other words, are increased cognitive deficits in PD patients due to increasing depression, higher levels of fatigue, or the progression of the disease (disease severity) when the other factors are controlled for, or some combination of the factors? This last option is the most likely one considering the strong relationship between depression and fatigue, independent of PD severity (Gołąb-Janowska et al., 2016), however, research has not empirically examined the relative contribution of depression and fatigue while controlling for disease severity in explaining cognitive impairment.

Thus, the current study examined the degree to which depression and fatigue combine to explain cognitive impairment in patients with PD when controlling for disease severity. Given

the previously demonstrated relationship between the three variables (de la Riva et al., 2014; Gołąb-Janowska et al., 2016), it was hypothesized disease severity, depression, and fatigue would be positively correlated. It was expected that disease severity would account for a significant amount of variance in cognitive impairment scores and that depression and fatigue would account for additional variance above that explained by disease severity. Given the lack of prior literature examining these relationships, no hypothesis was made regarding the relative contribution of depression and fatigue on cognitive functioning in those diagnosed with PD.

Method

Participants

This study was based on data collected at a movement disorders clinic at a mid-south

neurologic and spine institute. Participants were referred to the clinic through routine referrals by

general practitioners or other qualified healthcare providers. Data from participants who met

standard medical diagnostic criteria for Parkinson's Disease (Massano & Bhatia, 2012) and

completed the neuropsychological test battery and depression and fatigue ratings from 2011 to

October 2016 were retrieved via the clinic's electronic medical records (EMR) and included in

the analysis ($n = 30$). The remainder of the data were prospectively recruited and assessed at the

clinic. Exclusion criteria for both retrospective and prospective components of the study

included: a) concomitant neurodegenerative diseases (e.g. Alzheimer's disease), b) history of

acquired brain injury (e.g. traumatic brain injury), c) history of CNS infection (e.g. meningitis),

d) hydrocephalus, e) psychotic disorder, f) surgical procedure or treatment of the brain (e.g.

tumor removal, whole brain radiation therapy, etc.).

There were 43 participants in the final sample (24 men and 19 women) who ranged in age

from 56 to 81 ($M = 65.9$, $SD = 9.42$). The sample had completed an average of 14.27 years of

education ($SD = 2.58$) The sample was primarily Caucasian ($n = 41$, 95.3%) and also included

one African American participant. A single participant did not report race. Approximately one-

quarter ($n = 10$, 23.3%) of participants indicated a history of premorbid depression and 16.3%

had a history of an anxiety disorder ($n = 7$). Forty-four percent of the total sample were

prescribed an anti-depressant. Further, 58.15% indicated the presence of a medical comorbidity

(e.g., hypertension, diabetes, etc.; $n = 25$).

Measures

  Cognitive Impairment Index (CII). This study utilized a summary statistic, the

cognitive impairment index (CII), to represent patient performance on the neuropsychological

assessment battery. Precedent for use of a CII has been previously demonstrated in the PD

population as a valid measure of global cognition (Vingerhoets et al., 1999). Measures included

those that assess executive functioning, memory, language, visuospatial functioning, working

memory, perceptual reasoning, and verbal comprehension (**See Table 1 for complete list of**

battery). Raw scores from each assessment were converted into standardized scores based on

adjustment for age and education. Standardized scores on the different assessments included

standard scores, T-scores, scaled scores ss, or z-scores. Scores that were less than 1 *SD* below the

mean were scored as 0, scores between 1 *SD* and 1.5 S*D* below the mean were given a score or 1,

scores between 1.5 *SD* and 2 *SD* below the mean were scored as 2, and scores 2 *SD* or greater

below the mean or lower were scored as 3. CII's were calculated by dividing the sum of the

scores from individual assessments by the number of assessments administered, resulting in an

average CII, which could range from 0–3 with higher scores indicating greater cognitive

impairment.

  Depression. Depression ratings were obtained through the use of multiple measures in

order to evaluate age-appropriate symptomology [e.g., the Geriatric Depression Scale (GDS) is

most appropriate for the elderly; Yesavage et al., 1982) and due to variations in provider

practice. All measures yield a severity score that allows them to be compared. The depression

variable was scored based on the severity [non-clinical to mild (1), moderate (2), and severe (3)]

determined from each assessment and depression was treated as an ordinal variable. Measures of

depression included the Hamilton Rating Scale for Depression [HAM-D; 1 = (scores between 0 -

9), 2 = (10 - 17), 3 = (>17)], the Center for Epidemiological Studies Depression Scale- Revised

[CESD-R; Eaton, Muntaner, Smith, Tien, & Ybarra, 2004); 1= (<15), 2 = (15 - 21), and 3 = (>21); (Zich, Attkisson, & Greenfield, 1990)], and the GDS (Yesavage et al., 1982); 1 = (0 - 9), 2 = (10 - 19), and 3 = (20 - 30).

Fatigue. The Fatigue Severity Scale (FSS*)* was originally designed to measure fatigue severity in a variety of medical and neurological disorders, including Parkinson's disease (Shulman, Taback, Bean, & Weiner, 2001). The scale is composed of nine statements assessing how fatigue affects exercise, physical functioning, carrying out duties, work responsibilities, and various aspects of everyday life (work, family, or social life). Participants' fatigue is rated on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree), with higher scores indicating higher levels of fatigue (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989).

Disease Severity. Disease severity was represented by the patient's Levodopa Equivalent Dose (LED), which is based on the level of dosage of anti-Parkinson's medication that an individual currently requires to control their PD specific motor symptoms (Tomlinson et al., 2010). LED is an acceptable proxy for disease severity, as it has been previously correlated with other measures of disease severity, such as disease duration recorded on the Hoen and Yahr stage scale of the Unified Parkinson's Disease Rating Scale (Lee et al., 2010). Due the heterogeneity in L-dopa dose in clinical trials, LED can be calculated through guidelines of Tomlinson (Tomlinson et al., 2010). These guidelines allow clinicians to calculate a uniform metric by taking into account the variations in quantity of levodopa within the various forms of pharmaceutical medication. Based on the number generated through this calculation, higher LED's indicate greater disease severity.

Statistical Analyses

      Pearson Correlations and a step-wise hierarchal regression analysis were used to examine associations among the predictor variables (disease severity, fatigue, and depression) and to test whether depression and fatigue are significant predictors of cognitive functioning among PD patients when controlling for disease severity. Given the robust evidence demonstrating the relationship between disease severity and cognitive impairment, LED (disease severity) was first entered into the model. Depression and fatigue were entered simultaneously as predictor variables in the second block, examining each variable's independent contribution to cognitive impairment in PD patients while controlling for the other and disease severity.

Results

Means, standard deviations, and correlations among study variables are shown in Table 1.

A wide variation of disease severity (LED) scores was observed for the sample, ranging from 0

to 1,630 (*M*=792.3, *SD*=402.64), which is comparable to other studies utilizing the metric

(Dashtipour, Chen, Kani, Bahjri, & Ghamsary, 2015). The mean depression ratings for the

sample were in the mild depression range (*M*=1.67, median=2 [48.8%]). Fatigue ratings for the

sample trended towards the mid-point of the possible range from one to seven (*M*=4.73,

SD=1.55). As hypothesized, and in alignment with prior findings, depression ratings were

significantly correlated with fatigue and disease severity. Disease severity and depression scores

were significantly correlated with cognitive functioning scores; however, fatigue scores were not

significantly correlated with disease severity or cognitive impairment (**Table 2**).

A two-step hierarchal multiple regression analysis with cognitive impairment index

scores (CII) as the dependent variable was conducted. Given the strong empirical relationship

between disease severity and cognitive impairment, disease severity, assessed by LED scores,

was entered into step one of the model. Depression and fatigue scores were entered

simultaneously in the second step of the model.

At step one, disease severity significantly contributed to the model, $F(1, 41) = 48.06$, $p <$

.001 and accounted for 52.8% (adjusted R^2) of the variance in PD patients' cognitive impairment

scores. Adding depression and fatigue into the model explained an additional 7.2% (adjusted R^2)

of the variance and this change in R^2 was significant $F(2,39) = 4.68$, $p < .05$. With the

incorporation of all three variables, the total model predicted 60.0% of variance in PD patients'

level of cognitive impairment, $F(3, 39) = 22.02$, $p < .001$. Depression significantly contributed to

the model in addition to variance accounted for by disease severity, $t = 2.751$, $\beta = 0.30$, $p < 0.01$.

Fatigue was also a unique contributor to the final model, but in the reverse direction than hypothesized, $t = -2.03$, $\beta = -0.21$, $p = .049$. Results of the regression analysis are displayed on Table 3.

Due to the counterintuitive association between fatigue and cognitive impairment in the final model and the lack of a significant bivariate correlation between fatigue and cognitive impairment, two post-hoc stepwise regressions were performed that entered depression and fatigue scores separately at the second step of the model. When only fatigue was entered into the model as the second block entry, it did not maintain its significance as a contributing source of variance to cognitive impairment observed, $t = -1.24$, $\beta = -0.13$, $p > .05$. When only depression was entered into the model as the second step, depression continued to be a significant contributor beyond disease severity, $t = 2.21$, $\beta = 0.24$, $p < .05$ and the change in the model was significant, $F(1, 40) = 4.88$, $p < .05$, R^2 change $= .05$. Ultimately, these findings suggest fatigue was significantly associated with cognitive impairment only when variance explained by depression was accounted for within the model.

Discussion

The current study examined the relationships among disease severity, depression, and fatigue and the association between these variables and cognitive functioning in individuals diagnosed with Parkinson's disease (PD). Consistent with previous findings (Dissanayaka et al., 2011), depression ratings were positively correlated with disease severity. Depression scores and fatigue ratings were also correlated. Fatigue ratings were not correlated with disease severity.

As hypothesized, disease severity was a significant predictor of cognitive functioning, which is consistent with previous findings (Mak, Bergsland, Dwyer, Zivadinov, & Kandiah, 2014; Riepe et al., 2006; Vingerhoets et al., 2003; Wakamori et al., 2014). The degree to which disease severity was associated with the observed cognitive functioning in the current study was noteworthy, accounting for 52.3% of the variance in the cognitive impairment index scores. An examination of the correlations between disease severity and individual measures of cognitive functioning supports the relationship between disease severity and widespread cognitive domains of functioning, as participants' scores on all but three of the individual cognitive measures that contributed to the cognitive impairment index were significantly correlated with disease severity (*r*'s ranging from 0.39 to .71).

The expected association between depression and PD was borne out in the current study, as 58.14% of the sample endorsed moderate to severe depressive symptomology. Depression did in fact account a significant increase in variance of cognitive scores. Interestingly, the lack of a significant correlations between fatigue and cognitive impairment and the small, but significant, inverse association between fatigue and cognitive functioning only when controlling for the effect of depression were counter to previous findings. Prior studies have demonstrated PD patients with greater levels of fatigue exhibit poorer cognitive performance (Goldman et al.,

12

2014). The current study's findings may suggest that fatigue functions as a suppressor variable. Suppressor variables often do not measure much (if any) variance in the criterion measures, but do measure some of the variance in the predictor measures that is not included in the criterion measure. Thus, they control for 'invalid' or irrelevant variance (perhaps due to measurement artifacts) in the set of predictor variables, leading to an increase in the total R^2 value when they are included in the regression (Woolley, 1997).

Clinical Implications

The current findings regarding the strong relationship between disease severity and cognitive functioning have implications for intervention. First given the evidence for the likelihood of cognitive impairment as the disease progresses, early cognitive intervention is essential for these individuals. Cognitive remediation strategies (Sitzer, Twamley, & Jeste, 2006) should be implemented when individuals initially receive the diagnosis and when cognitive abilities are less affected by the disease. Early intervention may increase the likelihood that individuals are able to learn cognitive remediation strategies, incorporate them into their activities of daily living, and decrease problems of functionality and level of support through disease progression. Additional interventions also may include recommendations for physical activity given the neuroprotective benefits of exercise (Ahlskog, Geda, Graff-Radford, & Petersen, 2011) and exercised-based interventions (Hindle, Petrelli, Clare, & Kalbe, 2013; Murray, Sacheli, Eng, & Stoessl, 2014). For example, Cruise et al. (2011) demonstrated frontal lobe based executive functioning improvements following an exercise intervention program involving anabolic and aerobic exercise weekly for 12 weeks. Further, quality of life has been shown to be positively affected by an 8-week PoleStriding exercise program in a PD sample (Baatile, Langbein, Weaver, Maloney, & Jost, 2000).

The unique association between depression and cognitive functioning after controlling for disease severity also has important implications for the treatment and management of PD patients with depression. Interventions directed towards depressive symptomology have the potential to decrease cognitive deficits. Given that disease severity was controlled for, these implications are likely applicable for PD patients at all stages of the disease. Further, cognitive functioning has been observed as strongly impacting quality of life/functionality (Meireles & Massano, 2013), disability status, and level of care burden (Leroi, McDonald, Pantula, & Harbishettar, 2012). Current findings suggest mental health treatment may present opportunities to have a primary and secondary positive impact on quality of life through decreased depression symptomology and subsequent improved cognitive functioning.

As noted above, the etiology of depression within PD patients is unclear (McDonald et al., 2003). Regardless of the etiology, interventions focused on decreasing depressive symptoms within PD patients should look towards a biopsychosocial approach (Schotte, Van Den Bossche, De Doncker, Claes, & Cosyns, 2006) that includes cognitive behavioral therapy (Farabaugh et al., 2010) and pharmacological intervention, both of which have been independently observed as effectively treating PD patients with depression (Connolly & Fox, 2014; Devos et al., 2008).

Future Directions

While the current study found disease severity and depression accounted for a large amount of variance (58.3%), this still suggests that other factors may play a role in cognitive functioning. A previous study examining the effects of vascular risk on cognitive functioning in PD patients suggested that presence of hypertension is strongly associated with deficits in memory and verbal fluency (Doiron, Langlois, Dupré, & Simard, 2017). Cognitive reserve (high premorbid intellectual ability), which has been demonstrated as having an effect on cognition in

14

PD patients independent of disease severity and depressive symptoms, may also be an additional factor helping to account for the unexplained variance within the current study (Koerts, Tucha, Lange, & Tucha, 2013). Additional factors known to influence cognition in individuals with PD or other neurodegenerative disorders includes genetic (Apoe e4; Mata et al., 2014), metabolic (Burté et al., 2017), and psychosocial factors (Bennett, Schneider, Tang, Arnold, & Wilson, 2006).

Limitations

There are several potential limitations in the study. All participants were functional enough to drive themselves to the appointment or had enough available social support to have a family member or friend drive them. For instance, individuals in nursing homes with higher levels of necessary care were not included. As such, it is likely that the sample contained individuals with PD-MCI rather than PDD and this might have reduce the generalizability of the findings to individuals with more severe cognitive decline. The sample also was not representative of the general population as only one (2.3%) of the participants was African-American and the mean years of education of the sample was 14.27, which is higher than the general population (McFarland, 2017).

Additionally, while the study did employ strict a priori exclusion criteria of all factors commonly associated with decreased cognitive functioning aside from PD, other medical comorbidities, such as hypertension (Obisesan, 2009) and diabetes mellitus-type 2 (Saedi, Gheini, Faiz, & Arami, 2016), that can adversely affect cognitive function were not accounted for. The use of different depression measures within the study could be a limitation because scores based on severity categories (e.g., mild, moderate, severe) rather than actual numerical scores were used. However, these measures have all been shown as being highly associated with

one another (Lyness et al., 1997; Van Dam & Earleywine, 2011; Yesavage et al., 1982), demonstrating that they are measuring a similar construct.

Findings from the current study suggest that although depression and disease severity are highly related, depression can independently produce cognitive impairment observed in PD patients. In contrast, symptoms of fatigue did not. Taken together, quality of life via cognitive functioning may be enhanced through behavioral and pharmacological intervention targeted towards depression.

Table 1

Disease Severity , Depression, Fatigue, Cognitive Impairment, and Individual Test Correlations

	CII: M (SD)[a,b]	Mean (SD)[b]	LED[b]	Depression Rating[b]	Fatigue Severity[b]	Cognitive Impairment[a,b]
Test of Premorbid Functioning	0.29 (0.51)	98.62 (13.76)	0.16	0.3	0.37*	0.13
DKEFS Color Naming	0.63 (1.0)	8.47 (3.12)	0.28	0.44**	-0.26	0.4**
DKEFS Word Reading	0.44 (0.91)	8.84 (3.15)	0.37*	0.58**	-0.06	0.53**
DKEFS CW Interference	0.77 (1.12)	8.27 (4.02)	0.52**	0.40**	-0.05	0.73**
Letter Fluency	0.93 (1.19)	42.07 (12.60)	0.60**	0.41**	0.04	0.58**
Animals (semantic fluency)	0.44 (0.88)	48.7 (11.95)	0.25	0.13	-0.1	0.38*
Verbs (semantic fluency)	0.95 (1.21)	43.55 (13.0)	0.44**	0.14	0.15	0.56**
WAIS-IV; Similarities	0.27 (0.52)	47.33 (9.29)	0.47**	0.23	0.22	0.52**
WAIS-IV; Matrix Reasoning	0.78 (1.0)	44.48 (12.29)	0.51**	0.34*	-0.04	0.71**
WAIS-IV; Digit Span	0.44 (0.80)	45.07 (8.77)	0.51**	0.24	-0.27	0.55**
Iowa Gambling Test	0.64 (0.93)	43.05 (8.58)	0.22	0.03	0.24	0.05
HVLT Total Learning	1.19 (1.22)	38.60 (10.79)	0.43**	0.29	0.0	0.74**
HVLT Delay Recall	1.02 (1.21)	38.07 (11.42)	0.52**	0.26	0.02	0.78**
HVLT Retention	1.0 (1.34)	42.53 (15.41)	0.40*	0.08	-0.06	0.71**
HVLT Discrimination	1.17 (1.29)	37.24 (13.42)	0.50**	0.27	0.02	0.68**
WMS-IV; Logical Memory I	0.65 (0.90)	42.67 (11.48)	0.42**	0.25	0.05	0.65**
WMS-IV; Logical Memory II	0.70 (0.99)	40.68 (10.63)	0.34*	0.37*	0.15	0.69**
Logical Memory Recognition	0.64 (1.0)		0.43**	0.33	-0.1	0.59**
Judgment of Line Orientation	0.63 (1.0)	44.77 (11.76)	0.31*	0.25	-0.15	0.44**
Boston Naming Test	0.31 (0.78)	49.76 (10.34)	0.13	0.3	0.32*	0.28
Trailmaking	1.24 (1.35)	38.06 (12.33)	0.75**	0.21	-0.08	0.75**

Test A Trailmaking Test B	1.0 (1.32)	40.88 (15.21)	0.66**	0.15	-0.4	0.91**

Note. CII- Cognitive Impairment Index average rating for each individual subtest; range = 0-3.[b] Data presented as mean and standard deviation

*Sig at 0.05 level. ** Sig at 0.01 level

Table 2

Means, Standard Deviations and Correlations Among Study Variables

	Mean	*SD*	1.	2.	3.	4.
1. LED	792.63	402.64	--			
2. Depression Rating	1.67	0.64	0.40**	--		
3. Fatigue	4.74	1.56	0.17	0.31*	--	
4. Cognitive Impairment Index	0.75	0.62	0.74**	0.50**	0.0	--

Note. LED = Levodopa Equivalent Dosage

*p < 0.05 level. ** *p* < 0.01 level.

Table 3

Hierarchal Regression Analysis of Disease Severity, Depression, and Fatigue on Cognitive Impairment (N = 43)

Variable	*B*	*SE*	β
Step 1			
Disease Severity	0.001	0.00	0.74***
Step 2			
Disease Severity	0.001	0.00	0.65***
Depression	0.278	0.10	0.30**
Fatigue	-0.079	0.04	-0.21*

Note. R^2 change at Step 2 = 0.09, Adjusted R^2 at final model = 0.60, $F(3, 39) = 22.02$, $p < 0.001$
* $p < .05$. ** $p < .01$. *** $p < .001$.

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