FACTORS INFLUENCING QUALITY OF LIFE IN PARKINSON'S DISEASE

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DEDICATION

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FACTORS INFLUENCING QUALITY OF LIFE IN PARKINSON'S DISEASE

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Abstract

BACKGROUND: Parkinson's Disease (PD) is a progressive neurodegenerative disease, that encompasses a broad range of motor and non-motor symptoms, each of which has the potential to negatively impact health-related quality of life. Depression, disease duration, and level of disability have been found to significantly influence quality of life in PD. However, there is a paucity of research examining the combined influences of depression, PD motor symptom severity and cognition on overall HRQoL, as well as various domains of HRQoL, in a PD population.

SUBJECTS: This study used data collected from 124 participants with PD, aged 50 to 85, who were enrolled in a larger study, and gave informed consent for the parent study, with no knowledge of the current study. Inclusion criteria consisted of a PD diagnosis and a response to levodopa treatment for at least 30 days. Participants meeting DSM-IV-TR criteria for Axis I disorders other than MDD were excluded.

METHOD: The current study utilized linear and multiple regression analyses to explore the relationships between HRQoL and depression severity, PD motor symptom severity and global cognitive ability. HRQoL was measured by the Parkinson's Disease Questionnaire – 39 Item, a PD specific disease questionnaire designed to assess HRQoL in a variety of domains. Measures included the Quick Inventory of Depressive Symptomatology-Clinician Version, the United Parkinson's Disease Rating Scale Part III, selected disease characteristics, and a battery of cognitive tests.

RESULTS: Depression severity (QIDS-C_{16}) and PD motor symptom severity (UPDRS) and global cognitive ability accounted for approximately 30% of the variance in PDQ-39 Single Index scores. Depression severity and motor symptom severity were the most significant

predictors of HRQoL (PDQ-39). The multiple regression analysis results aligned closely with separate, linear regression analyses designed to control for the redundancy in the independent and dependent variables, which showed that depression severity accounted for 18.7% of the variance in HRQoL, motor severity accounted for 12%, and that global cognitive ability accounted for 3.8%. Depression severity accounted for the greatest amount of variance in all domain scores comprising the PDQ-39 except for Mobility and Activities of Daily Living, of which PD motor symptom severity accounted for the largest amount of variance. Depression severity was significantly correlated with all PDQ-39 domains, (r_s=0.22 to 0.48), while PD symptom severity was significantly correlated (r_s=0.23 to 0.51) with Mobility, ADL, Cognition, Communication and Bodily Discomfort domains. Global cognitive functioning did not significantly predict overall HRQoL but did significantly influence the Communication domain. The PDQ-39 Single Index score was significantly correlated with measures visual learning and memory (BVMT-R) and processing speed (Trail Making Test Part A and Part B, and Symbol Search). Of all the significant Pearson correlations, Symbol Search scaled scores had the strongest correlation (r=0.29). In an ANCOVA analysis using QIDS-C_{16} scores as a covariate, verbal learning and memory (RAVLT) achieved statistical significance. When controlling for depression severity and age, no significant differences in HRQoL were found between individuals classified as bradykinetic/rigid motor subtype and those classified as tremor dominant motor subtype.

DISCUSSION: The primary aim of the study was to examine the relative influence of depressive symptoms, PD motor symptoms and cognition on HRQoL in individuals with PD. Both depression severity and motor symptom severity significantly influenced HRQoL, while global cognitive ability did not. The influence of depression severity in the sample is impressive,

given the low prevalence and severity of depression present. This suggests that although depression severity may be subclinical, early identification and management of these symptoms may positively influence HRQoL. The most frequently reported depressive symptoms included difficulties staying asleep, sad mood and low energy, which indicate that targeting these specific symptoms, even when subclinical, holds potential for improving the HRQoL of individuals with PD.

In exploring the relationship between cognition and HRQoL in PD further, Pearson correlational analyses indicated that HRQoL was significantly correlated with measures of visual and verbal learning and memory, working memory and processing speed, even though a global cognition screening measure was not predictive of overall HRQoL. In summary, the collective findings from this study support the influence of motor severity and even subclinical depression on HRQoL in PD, suggesting that interventions designed to improve mood and the capacity to complete activities of daily living may positively impact quality of life.

Keywords: Parkinson's Disease, Health-related quality of life, Depression, Motor symptoms, Cognition

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LIST OF ABBREVIATIONS

ADL – Activities of Daily Living

BDI – Beck Depression Inventory

BVMT-R – Brief Visuospatial Memory Test – Revised

DRS – Dementia Rating Scale

DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – Text Revision

HRQoL – Health-related quality of life

HRSD – Hamilton Rating Scale for Depression

HVLT-R – Hopkins Verbal Learning Test - Revised

IMP-SPECT – Iodoamphetamine Single Photon Emission Computed Tomography

MADRS – Montgomery-Asberg Depression Rating Scale

MCI – Mild Cognitive Impairment

MINI – Mini International Neuropsychiatric Interview

MMSE – Mini Mental State Examination

MoCA – Montreal Cognitive Assessment

PD – Parkinson's Disease

PDQ-39 – Parkinson's Disease Questionnaire – 39-Item

PIGD – Postural Instability Gait Disorder

QIDS-C16 – Quick Inventory of Depressive Symptomatology – Clinician Version

QoL – Quality of life

RAVLT – Rey Auditory Verbal Learning Test

RBD – Rapid eye movement sleep Behavior Disorder

SCOPA-COG – Scales for Outcomes in Parkinson's Diseaes-cognition

SF-36 – Medical Outcomes Study Short Form – 36

UPDRS – United Parkinson's Disease Rating Scale

WAIS-IV – Wechsler Adult Intelligence Scale -4th Edition

CHAPTER ONE

Introduction

Parkinson's Disease

Parkinson's Disease (PD) is a progressive neurodegenerative disease, that affects approximately 1 million people in the United States alone (Chen, 2010). The prevalence extends to approximately 5 million people when considered on a global scale. In addition, as the general population ages, the prevalence of chronic age-related disease, including PD, is expected to rise, which will result in a greater proportion of the population whose lives will be affected by disease symptomatology directly or indirectly through taking care of a loved one diagnosed with PD (Findlay, 2002). Though PD is a clinical syndrome that encompasses a broad range of motor and non-motor symptoms, each symptom of PD has the potential for burdening individuals economically, socially, and emotionally (Chen, 2010).

Quality of Life

Quality of life is an intricate and complex construct, with no universally accepted definition or criteria (Martinez-Martin, 1998). The World Health Organization has defined quality of life as "a state of complete physical, mental, and social well-being not merely the absence of disease" (World Health Organization, 1997). A sense of well-being is at the core of the concept, but quality of life can be expanded to include many other components including health, vocation, or social status (Martinez-Martin, 1998). Therefore, the term "health-related quality of life" (HRQoL) is widely utilized to differentiate these factors from other components that contribute to one's sense of well-being including freedom, income and an environment that promotes positive growth and development (Guyatt, Feeny, & Patrick, 1993). This distinction is important to make, as the term "health-related quality of life" (HRQoL) is inconsistently utilized

in clinical research. For the purposes of the current study, HRQoL will be defined as "the patient's own perception and self-evaluation regarding the effects of an illness and its consequences on her or his life" (Martinez-Martin, 1998). This definition conveys the subjective, individual, multidimensional, and self-report nature inherent in the assessment of HRQoL.

Medical examinations, laboratory testing, and clinical testing all provide invaluable information for clinicians in the management or treatment of an illness, but the patient's perception of the illness and the impact symptoms have on his or her life are often excluded as part of standard medical evaluations (Findlay, 2002). Findings from a survey of PD patients conducted in 2007 indicate that patients are significantly less satisfied with their treatment than other populations of chronically ill patients (Fargel, Grobe, Oesterle, Hastedt, & Rupp, 2007). The survey also asked responders to pick aspects of treatment from a list that elicited the greatest dissatisfaction and the greatest proportion of responders identified treatment involving movement disorder, especially tremors, sleep disturbances and depression as the most troublesome.

Incorporating assessments of HRQoL facilitates a number of goals that are compatible with current health care practices, which include outcome evaluations, patient benefits, and cost effectiveness of treatments (Martinez-Martin, 1998). In addition, the assessment of HRQoL provides tremendous insight into the impact of chronic illness on the functional capacity and well-being of individuals (Guyatt et al., 1993). Furthermore, the assessment of HRQoL also informs the clinician of a patient's satisfaction with treatment (Mitchell, Kemp, Benito-León, & Reuber, 2010).

Current Study

Parkinson's Disease is a progressive, degenerative disease that involves and impacts multiple systems in the body that can impact quality of life. Though the severity of PD can negatively impact HRQoL, many other symptoms and comorbidities hold the potential to negatively influence HRQOL in this population. A survey conducted in 2002 indicated that patient's disease severity accounted for only 17.3% of the variability in quality of life, whereas psychosocial factors explained approximately 60% of reported variability in HRQoL (Findlay, 2002). Furthermore, a systematic review conducted in 2011 examined 29 articles to identify demographic and clinical factors that predict HRQoL in PD. This review found that depression was the most frequently identified predictor of decreased HRQoL (Soh, Morris, & McGinley, 2011), a finding that corroborates the survey results from 2002.

Numerous research efforts have explored independent relationships between HRQoL and different aspects of PD. However, the current study aimed to investigate the combined impact of motoric symptoms, cognition and mood to overall HRQoL, as well as compare their respective influences on HRQoL. Furthermore, this study examined and compared the influences exerted by PD motor symptom severity, cognition and depression severity on specific domains of HRQoL.

CHAPTER TWO

Review of the Literature

Parkinson's Disease Overview

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that is comprised of both motor and non-motor symptoms. The four hallmark motor symptoms include tremor, rigidity, postural instability, and akinesia (inability to initiate movement) or bradykinesia (observable slowness of a movement's execution). A large variety of non-motor symptoms can accompany the hallmark motor symptoms that range from psychiatric and sleep to autonomic and gastrointestinal symptoms, as well as sensory disturbances (Chaudhuri, Healy, & Schapira, 2006). The prevalence of the disease is difficult to ascertain although it is estimated that PD impacts close to 1 million people in the United States alone, and an estimated 5 million people across the world (Chen, 2010).

The risk for developing PD increases with age, and the typical age of onset is in the early to mid-60s (Jankovic, 2008). However, earlier onset is certainly possible. In a population study conducted in 2005, age of onset appeared to be the greatest predictor of motor decline, as patients who were older at disease onset experienced more rapid motoric decline (Alves, Wentzel-Larsen, Aarsland, & Larsen, 2005). Several risk factors for the development of PD have been identified, including aging, environmental factors, and genetic predisposition (Schapira & Jenner, 2011). Environmental exposure to toxins from industrial and agricultural settings as well as bacteria or viral infections can influence the onset of PD. Interestingly, cigarette smoking and caffeine intake have been shown to decrease the risk of developing PD (Benito-León, Porta-Etessam, & Bermejo, 1998).

Disease Course

The course of PD can vary greatly across individuals. Initial non-motor symptoms commonly present in the early stages of the disease before the development of any motoric symptoms. Early premotor symptoms include anosmia, urinary disturbance, constipation, Rapid Eye Movement Behavior Disorder (RBD), sleep disturbances, and restless leg syndrome (Chen, 2010; Pellicano et al., 2007). Since these symptoms are not disease specific, their cause is usually not attributed to PD until the development of motoric symptoms. However, significant neurologic change in the substantia nigra resulting in diminished dopamine neurons occurs well before clinical characteristics are noticeable (Samii, Nutt, & Ransom, 2004). Once a diagnosis is made, treatment typically involves dopaminergic medication to augment dopamine in the brain, which is usually effective at treating motor symptoms. Medication is typically prescribed after the motoric symptoms cause impairment (Samii et al., 2004).

As PD progresses, motor symptoms become more disabling in the advanced stages. Severe motor impairments can render an individual bedridden or immobile. In addition, cognitive impairment is common in PD, ranging from mild cognitive impairment (MCI) to dementia (Jankovic, 2008). Older age of PD onset has been shown to increase the rate of cognitive decline. Individuals in the advanced stages of PD can experience significant, if not complete loss, of autonomy. Though not all individuals with PD require constant care, struggles with daily activities are common and therefore, caregivers can be greatly involved.

Motor Symptoms

Parkinson's disease symptomatology can be dichotomized into motor and non-motor symptoms. Motor symptoms include tremor, rigidity, postural instability and akinesia or bradykinesia. Bradykinesia refers to slowed movement (Giovannoni, van Schalkwyk, Fritz, &

Lees, 1999) and can impact an individual's rate of completing daily activities. Akinesia refers to the inability to initiate movement and is considered one of the most disabling symptoms of PD (Bloem, Hausdorff, Visser, & Giladi, 2004) as it can render an individual temporarily unable to walk and can result in higher fall rates. Resting tremor is the most commonly experienced symptom. Resting tremor typically originates in the hand, but can also occur in the lips, chin or jaw and lower extremities, though are uncommon in the neck or head (Jankovic, 2008). These resting tremors can disappear when a patient is engaged in an action or during sleep. Along with resting tremor, many individuals with PD experience rigidity when flexing or extending a limb or when rotating a wrist or ankle. At later stages of the disease, patients begin to experience postural instability, a symptom that can be described as a loss of balance or feeling unstable while walking.

Despite a common constellation of motor symptoms in PD, not all individuals have all motor symptoms and the disease can progress differently across individuals (Samii et al., 2004). As such, a number of studies have attempted to classify or define various motor presentations into subtypes (Marras & Lang, 2013). The traditional motor subtyping includes tremor dominant versus non-tremor dominant [either postural instability gait disorder (PIGD) or akinetic-rigid] and early versus late onset. The terminology for PIGD and akinetic-rigid vary across studies, although the definitions are similar and therefore grouped together when findings were aggregated across published studies (Marras & Lang, 2013). The United Parkinson's Disease Rating Scale (UPDRS) (Goetz, 2003) is commonly utilized to document PD symptoms and classify motor types.

Items from the UPDRS can be used to classify tremor dominant (arm tremor, rest tremor of face, arms or legs, action tremors) and non-tremor dominant (postural instability, gait,

freezing, and falls) subtypes. Once the respective UPDRS items are summed, the tremor dominant sum is divided by the non-tremor dominant sum and if the resulting ratio is less than or equal to 1.0, that individual is classified as PIGD. If the resulting ratio is greater than 1.5 then the individual is classified as tremor dominant subtype. Should the ratio fall in between 1.0 and 1.5 then an indeterminate subtype or "mixed" or "indeterminate" is often the resulting classification (Jankovic et al., 1990). An important distinction needs to be made regarding the traditional motor subtypes. These various clusters of symptoms may present at various disease stages, meaning that the presentation can change over the course of time. An individual who is assessed close to the onset of PD may appear to be classifiable as one subtype though the progression of the disease may alter the dominance of symptoms (Foltynie, Brayne, & Barker, 2002).

The traditional motor subtyping method is strongly supported with biological evidence as several studies have shown differences between tremor dominant and bradykinetic subtypes (Foltynie et al., 2002; Marras & Lang, 2013; Mito et al., 2006; Rajput, Voll, Rajput, Robinson, & Rajput, 2009). Individuals classified as tremor dominant at an early stage of PD experience a slower rate of disease progression (Foltynie et al., 2002). Another study found significantly increased levels of dopamine in the globus pallidus and striatum in a group of tremor dominant cases (Rajput et al., 2009). Neuroimaging findings include different patterns of regional cerebral blood flow, as assessed by iodoamphetamine single photon emission computed tomography (IMP-SPECT), between PIGD and tremor dominant subtypes (Mito et al., 2006) as well as using fluorodeoxyglucose positron emission tomography to identify distinct metabolic networks that underlie tremor and akinesia (Marras & Lang, 2013). These findings support traditional motor

subtypes as distinct, neurobiological profiles of motor symptoms in PD although further research is needed to expand the understanding of biological correlates of motor subtypes.

Non-Motor Symptoms

The spectrum of PD non-motor symptoms is broad and encompasses psychiatric symptoms, sleep disorders, autonomic and gastrointestinal symptoms (Chaudhuri et al., 2006). Several of these occur within all individuals with PD, yet others may not ever be part of the clinical presentation. In addition, many non-motor symptoms can develop during different times of the disease, further complicating treatment. Although autonomic and gastrointestinal symptoms can present in PD, they are beyond the scope of the current study and are therefore, will not be discussed here.

Sleep disturbance and insomnia are experienced by a majority of individuals with PD and include difficulty falling and staying asleep, as well as waking up too early (Gjerstad, Wentzel-Larsen, Aarsland, & Larsen, 2007). A potential contributor to sleep disturbance in this population is Rapid Eye Movement Behavior Disorder (RBD) where individuals' act out their dreams during REM sleep. In a study conducted at the Mayo Sleep Disorders Center, researchers reported of 25 patients who experienced RBD symptoms, 13 reported onset prior to PD symptoms, 2 had simultaneous onset and RBD and motor symptoms, and 10 patients experienced RBD symptoms after the onset of PD (Olson, Boeve, & Silber, 2000).

Psychiatric symptoms experienced by individuals with PD can include depression, anxiety, apathy, and hallucinations (Chaudhuri et al., 2006). One of the most prevalent psychiatric symptoms afflicting individuals with PD is depression, and though exact rates are unknown, depression prevalence among individuals with PD is estimated to be between 10% to 48% (Burn, 2002). One possible reason for the discrepancy is that depressive disorders are

commonly missed given the large overlap between depressive and PD symptoms (Ravina, Camicioli, Como, & Marsh, 2007). Apathy is also frequently seen in PD. A study conducted in 2002 reported that PD patients with higher apathy performed significantly worse than patients with lower apathy on tests of executive functioning (Pluck & Brown, 2002). Visual hallucinations are estimated to occur in one third of individuals with PD (Diederich, Goetz, & Stebbins, 2005) although typically do not disturb the patient in earlier stages of the disease. As the illness progresses, paranoia and delusions can become more frequent.

Cognitive impairment in PD is a progressive non-motor symptom that can be seen even early in the disease process (Poletti, Emre, & Bonuccelli, 2011). Cognitive impairment in PD is well documented, with approximately 40% of eventually developing dementia (Chaudhuri et al., 2006). An intermediate stage exists between normal cognition and dementia where cognitive impairment exists beyond what is expected for age, but does not interfere with daily activities (Petersen et al., 1999). The diagnostic criteria for this stage of Mild Cognitive Impairment (MCI) (Litvan et al., 2012) include the presence of cognitive concern, cognitive impairment in 1 or more domains as assessed with a neuropsychological examination, normal functional activities and the absence of dementia (Poletti et al., 2011). Individuals whose motor presentation can be subtyped as PIGD are at increased risk for developing MCI compared to those with a tremor dominant motor presentation (Poletti et al., 2011).

The authors of the Scales for Outcomes in Parkinson's Disease-cognition (SCOPA-COG) (Marinus et al., 2003) completed a review of cognitive functioning in PD and reported the cognitive domains most frequently reported to be affected by PD. Specifically, attention functions were frequently reported to be impaired but general thinking and reasoning of individuals with PD were found to be within normal limits. In the domain of memory and

learning, free recall tended to be impaired whereas cued recall and recognition remained intact for both verbal and visual memory. In the domain of executive functioning, individuals with PD experienced difficulty with internally guided behavior although performed within normal limits with externally guided behavior. Set shifting may also be impacted by PD, particularly early in the disease course. Verbal fluency and alternating tasks are also often impaired in individuals with PD. Finally, the review identified that patients with PD experience visuospatial deficits, particularly on tasks requiring perception abilities such as visual discrimination or determining spatial relationships (Cummings, 1988).

In examining the impact of the severity PD symptoms on cognition, a study conducted in 2007 enrolled 400 patients with PD to form a clinic based sample (Verbaan et al., 2007). Each patient was evaluated for cognition as well as motor and non-motor domains. The SCOPA-COG (Marinus et al., 2003) was utilized to assess cognition and measured multiple domains including memory, attention, executive functioning, and visuospatial functioning (Verbaan et al., 2007). Patients were categorized according to disease severity utilizing Hoehn and Yahr staging. A control group was established with patients who were staged at 0, indicating a lack of disability. The results of the study indicated that the largest performance difference between controls and patients occurred in the executive function and memory domains (Verbaan et al., 2007).

Another interesting study examined the relationship between the laterality of motor symptom onset and cognitive functioning (Cooper et al., 2009). This cross sectional study divided 117 Parkinson's disease patients into right and left sided groups based on motor performance on the UPDRS Part III. All patients were administered a comprehensive neuropsychological test battery from which composite scores in the domains of verbal fluency, verbal memory, executive function, and visuoperceptual skills were calculated. The authors

reported a significant association between right-sided motor impairment and verbal memory, visuoperceptual skills and verbal fluency but not executive function while left-sided motor impairment was not significantly associated with any composite cognitive domain. This finding contrasts the results of a study conducted in 2012 which reported no differences in performance on cognitive measures between left and right sided groups (Dewey et al., 2012).

As PD progresses, greater global cognitive deficits are frequently observed in the attention and executive functioning domains, as well as memory and visuospatial domains (Svenningsson, Westman, Ballard, & Aarsland, 2012). A significant number of individuals with PD progress to develop dementia (Aarsland et al., 2007) and the progressive cognitive decline appears to be independent of non-motor aspects of the illness (Kehagia, Barker, & Robbins, 2010). The development of dementia is considered a crucial element in determining life expectancy and can carry significant caregiver burden as the individual becomes more dependent on loved ones (Kehagia, Barker, & Robbins, 2012).

The Impact of Parkinson's Disease Symptomatology on Quality of Life

With the plethora of motor and non-motor symptoms comprising this chronic, neurodegenerative disease, research efforts have examined the interaction between the various constellations of symptoms and impact on health-related quality of life. This avenue of research is valuable, as there is evidence indicating that PD exerts a greater impact on physical and mental HRQoL than other neurological or chronic conditions such as diabetes, congestive heart failure and stroke (Gage, Hendricks, Zhang, & Kazis, 2003). In addition, findings from studies are often inconclusive or conflict with one another, therefore illuminating the need for additional research to clarify the relationships between this complex illness and its toll on HRQoL. Beyond identifying clear relationships between symptoms and their association with quality of life,

exploring which symptoms and clinical features can predict change in HRQoL would be of benefit to clinicians and patients. Such knowledge would assist clinicians in targeting symptoms and prioritizing respective treatment courses that demonstrate improvement in a patient's HRQoL.

Motor Symptoms' Impact On Quality of Life

A recent systematic review conducted in 2011 sought to critically evaluate studies that have examined factors contributing to HRQoL in PD (Soh et al., 2011). The range of factors included in the review spanned motor and non-motor symptoms, although the results that pertained to non-motor symptoms will be discussed elsewhere in this manuscript. In regards to clinical factors, this review reported that disease severity, disability, disease duration and motor impairment as measured by the UPDRS were all predictors of HRQoL. In examining motor symptoms specifically, gait impairments predicted overall HRQoL with the highest frequency of the studies included in the review while tremor, rigidity and dyskinesia were not consistent predictors of overall quality of life.

Another study investigated factors associated with the decline in HRQoL in PD. That study employed the Medical Outcomes Study Short Form – 36 (SF-36)(J E Ware, Snow, Kosinski, & Gandek, 1993) to measure of HRQoL and was considered the primary outcome measure (Marras et al., 2008). The SF-36 was not designed to assess elements of a specific disease, but rather assesses general physical and mental health, as well as limitations in physical, occupational and social functioning due to health problems (John E Ware, Gandek, & Project, 1998). Other measures utilized in the study included the UPDRS Part II & Part III, Mini Mental Status Examination (MMSE), Hamilton Rating Scale for Depression (HRSD) and the Schwab and England Disability scale. The results of the study indicated that worse HRSD and Schwab

and England Disability scores, and lower self-rating of intellectual functioning by the participant (item 1 of the UPDRS) were associated with greater decline in physical quality of life. Furthermore, the PIGD score was significantly associated with change in the General Health subscale of the SF-36.

Utilizing the traditional motor subtyping system, several studies have examined the relationship between HRQoL and motor subtype. A study conducted in 2000 aimed to determine which factors of PD were related to quality of life (Schrag, Jahanshahi, & Quinn, 2000). This study utilized the PDQ-39, the Beck Depression Inventory, the Hoehn and Yahr Scale, the Schwab and England Disability Scale, the UPDRS-III and the Mini-Mental State Examination (MMSE). The study reported that high levels of depression severity, cognitive difficulties, postural instability, and a history of falls or gait difficulties resulted in significantly lower PDQ-39 Single Index scores than participants without these features. In addition, patients classified with the akinetic rigid subtype of PD had worse QoL scores than those patients classified with the tremor dominant subtype. Interestingly, the authors reported that depression was the greatest determinant of quality of life in patients with PD, followed by disability, postural instability and lastly cognitive impairment.

To explore the relationship between motor subtype and quality further, a study conducted in 2010 specifically examined the impact of motor symptom subtype on activities of daily living (Hariz & Forsgren, 2011). That study classified 99 patients as PIGD, tremor dominant or indeterminate who were compared to 31 healthy controls. In order to assess and measure quality of life, that study employed both the PDQ-39 and the SF-36. Patients classified as tremor dominant reported that PD had less of an impact on their daily life compared to those classified as PIGD and indeterminate. On the PDQ-39, the PIGD group reported lower quality of life in

the domains of Mobility, Activities of Daily Living, and Communication than the tremor dominant group and indeterminate groups. The PIGD group also reported worse scores in the Bodily comfort domain compared to the tremor dominant group. Finally, when the PDQ-39 Summary Index scores were examined, individuals classified as PIGD reported worse quality of life than individuals in the other groups.

Non-Motor Symptoms On Quality of Life

A significant amount of research effort has been expended to explore the impact of various non-motor symptoms of PD on an individual's HRQoL. In fact, evidence has suggested that the non-motor cluster of symptoms negatively impact quality of life to a greater extent than motor symptoms (Chrischilles, Rubenstein, Voelker, Wallace, & Rodnitzky, 2002; Martinez-Martin, Rodriguez-Blazquez, Kurtis, & Chaudhuri, 2011; Winter et al., 2011). Despite the impressive number of studies that have explored this topic, a clear understanding of the relationship between these symptoms and the impact on quality of life remains unknown. A recent systematic review reported that depression was the most frequently identified predictive factor of HRQoL, followed by anxiety and fatigue (Soh et al., 2011). This systemic review also identified disease severity and disability, disease duration and motor impairment as predictive clinical factors of HRQoL.

To further examine the relationship between non-motor symptoms of PD and HRQoL, a study conducted in 2011 found a close association between the number of non-motor symptoms and poorer HRQoL (Martinez-Martin et al., 2011). In addition, this study supported an association between non-motor symptom frequency and severity and HRQoL, which indicated that individuals with PD experienced worsening HRQoL as their non-motor symptoms increased both in severity and frequency. An important note made by the authors of this study involved the

question of whether "motor" domains of the PDQ-39 purely measure the impact of motor symptoms. Instead, the authors posit that these domains (Mobility & Activities of Daily Living) are potentially influenced by non-motor symptoms. An example would be item 2 on the PDQ-39, which asks the responder whether he or she has had "difficulty in looking after your home." This question could be answered affirmatively for many reasons aside from motor impairment including depression, lack of motivation, or cognitive difficulties. The ambiguity surrounding the underlying influence driving responses on the activities of daily living domain on the PDQ-39 demands further examination, in order to gain a clearer understanding as to the source of impairment in activities of daily living for patients with Parkinson's Disease.

Another question that pertains to the impact of non-motor symptoms on HRQoL revolves around the degree to which PD has progressed and the present stage of the disease course. There are data from clinical, neuroimaging, and pathologic studies that suggested the presence of non-motor symptoms predate motor features by many years (Tolosa, Wenning, & Poewe, 2006). Further, the presence and severity of non-motor symptoms fluctuate and vary as PD progresses (Müller, Assmus, Herlofson, Larsen, & Tysnes, 2013). To investigate this temporal relationship between PD symptom progression and HRQoL, a study assessed a population based cohort with very early PD which was followed longitudinally every 6 months for three years (Müller et al., 2013). The results indicated that non-motor symptoms such as sensory complaints, cognition, depression, fatigue, apathy, and daytime sleepiness were more important for physical and mental HRQoL than motor symptoms in early stages of PD. Non-motor symptoms explained 46.8% of the variance, whereas motor variables accounted for 31.56%, in physical HRQoL. Non-motor symptoms also accounted for 44.1% of the variance, in contrast to motor variables accounting for

19.5% in mental HRQoL. These findings collectively reflect the clinical importance of documenting and incorporating non-motor symptoms into treatment planning.

As non-motor symptoms as a whole have been found to contribute to HRQoL to a greater extent, further exploration of specific non-motor symptoms found to significantly contribute to HRQoL is provided further below.

Depression. Depression has been the most frequently reported predictor of HRQoL in PD (Soh et al., 2011) although further investigation is warranted to better understand the relationship between depression and PD. Importantly, overlapping symptoms between the two diagnoses complicate this relationship. For example, psychomotor agitation, fatigue, or loss of appetite are all common symptoms of depression, which can also be symptoms of PD in a euthymic individual (Schrag, 2006). In addition, current Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (American Psychiatric Association, 2013) diagnostic criteria state that depressive symptoms must not be attributable to another medical condition. Further complications arise in the interaction between depression, cognitive impairment and PD, which will be discussed later.

In further examining the relationship between depression and HRQoL, a study conducted in 2011 compared the prevalence of depression in elderly PD patients to a control group consisting of elderly patients with other chronic diseases including diabetes mellitus, hypertension, and ischemic heart disease (Arun, Bharath, Pal, & Singh, 2011). The authors reported a significantly higher prevalence of depression as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) in individuals with PD (54.3 %) than controls (23.3%). This finding must be interpreted with caution, as the authors specified that the study sample was recruited through a hospital setting, which may have influenced the depression severity

experienced by participants. When severity was examined, the authors reported that 41.3% of the PD group suffered from severe depression as measured by the Beck Depression Inventory (BDI)(Beck, 1961) compared to 16.7% in the control group. The study also examined the degree of disability and quality of life and found that individuals with PD reported greater disability in all six domains of the World Health Organization Disability Assessment Schedule – 2nd Edition (WHODAS-II), which included cognition, mobility, self-care, social interaction, life activities, and participation in community activities.

In 2000, a study that aimed to identify factors that determined quality of life in a population based PD sample found that depression was the strongest predictor (Schrag et al., 2000). That study employed the BDI to measure depression severity in the sample and the PDQ-39 to measure quality of life. Additionally, disability as measured by the Schwab and England score followed depression. These two variables accounted for 64% of the variance in reported QoL scores. In 2002, another study examined factors correlated with quality of life in patients with PD (Cubo et al., 2002). This study utilized the UPDRS (Parts I, II, & III), the Schwab and England, Hoehn and Yahr Stage, the PDQ-39 and MMSE. Depression was measured with the Geriatric Depression Scale. Through completing a stepwise multiple regression analysis, the authors found that depression, UPDRS I and II scores, and educational background accounted for 61% of the variability of PDQ-39 scores. In 2005, a study that examined factors associated with poor HRQoL in PD in a clinic-based sample reported that the most predictive factor was the MADRS score. Specifically, the MADRS score, UPDRS Part IVB and the Hoehn and Yahr staging scores, explained 79% of the variance in QoL.

Cognitive Function. Cognitive functioning holds significant implications for HRQoL, especially with the frequency of mild cognitive impairment and dementia in PD (Svenningsson

et al., 2012). The progression of cognitive difficulties in PD varies greatly, with some patients who develop dementia a few years following their diagnosis to others who remain cognitively intact for a decade or more (Aarsland et al., 2007). Even during the MCI stage, the impact of cognitive decline results in an increase of health care costs and negatively affects activities of daily living that contribute to an individual's independence (Svenningsson et al., 2012).

In 2008, a study aiming to explore the relationship between cognitive performance and HRQoL in non-demented patients reported that visual attention, memory, visuospatial abilities and executive functions were cognitive domains associated with HRQoL (Klepac, Trkulja, Relja, & Babić, 2008). The data from this study strongly suggested that better performance in these domains were independently associated with better HRQoL. A significant limitation of this study was its cross-sectional design, which limited any ability to test the causal nature of the association.

A study conducted in 2014 broadly examined the influence of motor and non-motor symptoms on HRQoL in individuals newly diagnosed with PD (Duncan et al., 2014). Utilizing the PDQ-39 to measure HRQoL and the MMSE and MoCA as measures of cognitive functioning, the researchers reported that lower cognitive scores were not associated with reduced summary index scores on the PDQ-39. The authors posited several possible explanations for this finding, the first being that the MMSE and MoCA lack sensitivity in detecting functionally significant cognitive impairment. Another possibility was that this sample of newly diagnosed individuals lacked significant cognitive impairment. A final possibility offered by the authors of the study involved the potential influence of undiagnosed depressive symptoms, which can influence the awareness of, and therefore the reporting of, subjective memory difficulties.

As depression can exert its own influence on cognition, it is important to address the confluence present in a population diagnosed with a neurodegenerative disorder with a unique cognitive profile and a propensity to experience depression. In a effort to explore this topic, a study in 2002 compared the pattern of cognitive deficits present in a cohort of depressed and non-depressed PD patients in comparison to depressed patients without PD and healthy controls (Norman, Tröster, Fields, & Brooks, 2002). The study utilized the Mattis Dementia Rating Scale (DRS), an individually administered neurocognitive measure designed to assess cognitive ability in older adults with brain dysfunction (Mattis, 1988). The DRS is comprised of five subtests including: Attention, Initiation/Perseveration, Construction, Conceptualization and memory.

As expected, individuals with PD (both depressed and non-depressed) performed more poorly on the DRS in terms of overall scores, compared to depressed-only patients and healthy controls (Norman et al., 2002). Interestingly, the data showed a significant difference between the depressed and non-depressed PD groups on the Memory subtest of the DRS. Individuals with PD who were depressed performed significantly worse than those individuals with PD who were not depressed. These two groups did not differ in terms of performance on the Conceptualization and Initiation/Perseveration subtests. The authors' interpreted the study data to indicate that depression is primarily responsible for memory impairment in PD, whereas PD itself tends to influence overall cognitive abilities (Norman et al., 2002).

Summary

In summary, PD non-motor symptoms have been found to influence HRQoL to a greater extent than motor symptoms (Chrischilles et al., 2002; Martinez-Martin et al., 2011; Müller et al., 2013; Winter et al., 2011). Of the non-motor symptoms, depression is the most frequently

cited significant predictor of lower QoL (Soh et al., 2011). Individuals with PD are more likely to be depressed than individuals with other non-neurological chronic diseases (Arun et al., 2011).

In examining motor symptoms, gait impairments predicted overall HRQoL while tremor, rigidity and dyskinesia were not consistent predictors of overall quality of life (Soh et al., 2011). Multiple studies have determined that individuals classified as akinetic-rigid reported worse scores on measures of HRQoL than their tremor dominant counterparts (Muslimovic, Post, Speelman, Schmand, & de Haan, 2008; Schrag et al., 2000). In addition, one study reported that those classified as PIGD reported lower quality of life in the PDQ-39 domains of Mobility, Activities of Daily Living, Bodily Discomfort and Communication than individuals classified as tremor dominant (Hariz & Forsgren, 2011). With regard to cognition, HRQoL has been shown to be associated with visual attention, memory, visuospatial abilities and executive functions (Klepac et al., 2008). Stronger performances are associated with higher HRQoL.

Depression, motor severity and cognitive ability have each been examined independently in relation to HRQoL but no study to date has combined these variables to determine their respective predictive influence on HRQoL in PD. Exploring the combined predictive strength of these variables is of clinical significance, in order to comprehensively understand factors contributing to HRQoL in PD.

Aims and Hypotheses

Aim One: To explore the respective influence of motor severity, mood, and cognitive ability on health-related quality of life in Parkinson's Disease.

Hypothesis One: Depression severity, motor symptom severity and global cognitive ability will each contribute to reduced overall health-related quality of life with depressive symptoms accounting for the greatest amount of variance.

Hypothesis Two: Depression severity will significantly predict quality of life in the Emotional Well-being, Stigma, and Social Support domains of the PDQ-39.

Hypothesis Three: Global cognitive ability will significantly predict of quality of life impairment in the Cognition and Communication domains of the PDQ-39.

Hypothesis Four: Motor symptom severity will significantly predict quality of life in the Mobility, Activities of Daily Living and Bodily discomfort domains of the PDQ-39.

Exploratory hypothesis: Individuals classified with bradykinetic motor subtype will report lower quality of life than individuals classified with tremor dominant motor subtype.

Aim Two: To explore the relationships between various cognitive domains and reported health-related quality of life in Parkinson's Disease.

Hypothesis Five: Measures of visual learning and memory, verbal attention, processing speed, working memory, and verbal learning and memory will be negatively correlated with reported quality of life.

CHAPTER THREE

Method

Participants

This study used data collected from 124 participants with PD, aged 50 to 85, who were enrolled in a larger study aimed at validating the new National Institute of Health Tool Box (NIH Toolbox). Informed consent was obtained from participants for the parent study, with no knowledge of the current study. Participants received financial reimbursement for their participation. The parent study included three separate visits, a screening and baseline visit, a follow up visit seven days later, and a final visit scheduled three months later. The current study only used data from the screening and baseline visit. The inclusion and exclusion criteria for the parent study are listed below.

Inclusion Criteria

1. Male and female subjects, age 50 to 85.
2. Diagnosis of PD (asymmetric features including bradykinesia plus resting tremor and/or rigidity.
3. Treated and responsive to dopaminergic therapy for at least 30 days.
4. Disease-related motor or cognitive impairment does not preclude interacting with computer program for testing.
5. English as a first language.
6. Subject is willing and able to give informed consent and is willing to commit to three testing sessions.

Exclusion Criteria

1. Other known or suspected cause of parkinsonism or any significant features suggestive of a diagnosis of atypical parkinsonism.
2. Lifetime neurobiological diagnosis other than PD.
3. Lifetime Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, Text Revision (DSM-IV-TR) Axis I psychiatric diagnosis other than major depressive disorder.
4. Current alcohol abuse or dependence within the past 6 months.
5. Any unstable or clinically significant condition that would impair the subject's ability to comply with study procedures.
6. Lifetime mental retardation, current diagnosis of delirium.

Measures

The current study employed various instruments designed to measure health-related quality of life, motor symptoms, depressive symptom severity and cognitive functioning.

Quality of life. The health-related quality of life measure utilized in the current study is the *Parkinson's Disease Questionnaire - 39*, a measure with psychometrically sound reliability, validity, and sensitivity to change as demonstrated in the literature (Jenkinson et al., 2011; Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997; Peto, Jenkinson, & Fitzpatrick, 1998). This measure is comprised of 39 questions that can be categorized into 8 domains including Mobility, Activities of Daily Living (ADL), Emotional Well-being, Stigma, Social Support, Cognition, Communication and Bodily Discomfort. Please refer Appendix A to view a copy of the instrument.

The PDQ-39 Single Index (SI) Score incorporates the responses across all eight domains into a single score summary index that characterizes the overall effect PD has on the respondent's health related quality of life. As this measure utilizes a Likert scale, a numerical value is assigned for every response, with a possible range of "Never" equaling zero to "Always" equaling 4. The PDQ-39 SI score is calculated by first summing all responses within a domain. This is followed by multiplying the number of items within a domain by four. The summed number is then divided by the multiplied number, and the resulting digit is multiplied by 100 to arrive at a percentage. This percentage is referred to as a domain score and this process is repeated for all eight domains. To arrive at a single index score, the domain summary scores are averaged by dividing their sum by eight. Appendix B provides the domain names and number of items comprising each domain.

The PDQ-39 Single Index score ranges from 0 to 100 and reflects the average percentage of all items endorsed by the respondent across the eight domains. Scores at the lower end represent positive quality of life while scores at the higher end represent lower quality of life. The single index score can be useful to ascertain the impact of an illness on quality of life, and can be examined in conjunction with the eight domain scores to clarify which quality of life aspects are impacted by the illness (Jenkinson et al., 2011). No standard cutoffs have been published to facilitate the categorization of HRQoL based on PDQ-39 SI scores although the metric does permit the comparison of scores between samples in published studies.

Motor. To assess motor symptomology, the current study employed part III of the *Unified Parkinson's Disease Rating Scale* (Goetz, 2003). A version of this instrument can be found in Appendix C. The third module of this scale is a clinician-conducted motor evaluation, where 14 different motor symptoms or movements are rated on a scale of 0 (absent) to 4

(severe). Total scores range from 0 to 56. These 14 items range from postural instability and gait to speech and facial expressions. No cutoff scores have been published that permit the classification of motor symptom severity, however this instrument includes Hoehn and Yahr staging score to indicate disease progression.

Mood. Depression was assessed using the *Quick Inventory of Depressive Symptomatology – Clinician Version* (QIDS-C_{16})(Rush et al., 2003). This objective measure assesses core, melancholic, and atypical depressive symptoms, is sensitive to change, has reliable psychometric properties and was designed to assess depressive symptom severity (Bernstein, Rush, Thomas, Woo, & Trivedi, 2006; Rush et al., 2003). The QIDS-C_{16} is administered by a clinician or an assistant who has been trained in administration procedures. The total score on the measure ranges between 0 and 27, with higher scores indicating greater depression severity. Scores in the range of 0 to 5 reflect a lack of clinically significant depressive symptomatology. Scores in the range of 6 to 10 indicate depressive symptoms that are mild in severity. Scores in the range of 11 to 15 reflect depressive symptoms of moderate severity. Scores that fall in the range of 16 to 20 indicate severe depressive symptoms, and any score over 21 indicates very severe depressive symptomatology.

Cognitive. Cognitive measures were selected to assess a variety of cognitive domains that can be affected in PD. The *Montreal Cognitive Assessment* (MoCA) is a brief cognitive screening tool with demonstrated sensitivity and specificity for detecting mild cognitive impairment (Nasreddine et al., 2005). The *Trail Making Test Part B* is a measure of visual scanning, processing speed and cognitive flexibility (*Army Individual Test Battery Manual of directions and scoring.*, 1944). The *Rey Auditory Verbal Learning Test* (RAVLT) is a measure of verbal learning and memory designed to assess verbal learning, recall and recognition memory

(Schmidt, 1996; Strauss, Sherman, & Spreen, 2006). *The Brief Visuospatial Memory Test – Revised* (BVMT-R) measures an individual's ability to learn, recall, and recognize simple figures (Benedict, 1997). From the *Wechsler Adult Intelligence Scale – 4th edition* (WAIS-IV),(Wechsler, 2008), the *Digit Symbol Coding* and *Symbol Search* subtests were used to assess psychomotor processing speed, and the *Letter-Number Sequencing* subtests was utilized to assess verbal working memory. In addition, the *Controlled Oral Word Association Test* (Strauss et al., 2006) and category fluency were administered as measures of verbal fluency.

Procedures

The data for the parent study was collected across three study visits that spanned three months. The initial baseline visit involved the screening of the potential participant to ensure that he or she met inclusionary criteria and did not meet exclusion criteria. Clinical assessments were administered at this visit, as were quality of life and cognitive measures. The subsequent two study visits occurred approximately seven days and three months later.

The initial screening visit included obtaining informed consent and HIPPA authorization, a pregnancy test and a urine drug screen. In addition, a neurologist conducted a clinical neurological examination, including the UPDRS, to establish that the participant had 2 or more of 3 cardinal features of PD, and by history had been responsive to dopaminergic medication. A psychiatric examination was also conducted at this visit in order to determine the participant's depressive status. The depressive module of the Mini Neuropsychiatric Interview (MINI) (Sheehan et al., 1997) was utilized for the diagnosis of major depressive disorder and the QIDS-C16 was utilized to assess the depressive symptomatology.

The current study utilized baseline data only for several reasons. The baseline visit consists of the most complete data. In addition, testing the current study's hypotheses requires

examination of only baseline data as it is unlikely that PD symptoms would have clinically significantly progressed within seven days or three months after baseline.

Classification of Motor Subtype. Participants were classified into two separate categories: onset tremor dominant and onset bradykinesia/rigidity. This classification was based upon the type of a participant's initial symptoms at onset as determined from a thorough chart review conducted by a movement disorders specialist in the Center for Movement Disorders at the University of Texas Southwestern Medical Center at Dallas, TX.

Data preparation. Prior to any statistical analyses, all collected data were examined for completeness. Three participants were excluded due to incomplete PDQ-39 data and a fourth participant was excluded in any analyses involving cognitive measures, due to missing data.

Data Analysis

All statistical analyses were completed using IBM SPSS Statistics for Windows Version 20.0. The parent study database was thoroughly examined for data completeness and any missing values were entered from paper source documents. Once completed, a separate SPSS database was created specifically for the current study using only the variables and data necessary to complete the following analyses.

Statistical Analyses for Aim One

Hypothesis One. The first hypothesis predicted that depression severity, motor symptom severity and global cognitive ability would each contribute to reduced health-related quality of life with depressive symptoms accounting for the greatest amount of variance. In order to test this hypothesis, a multiple linear regression was performed. The QIDS-C_{16} measured depression severity, the UPDRS total score measured motor symptom severity, and the MoCA measured global cognitive ability. Distributions of the variables found that PDQ-39 SI scores and QIDS-

C_{16} total scores were positively skewed. Thus, a square root transformation was applied to both variables. The UPDRS and MoCA total scores were normally distributed, and no transformation was needed. Once the transformations were applied, the modified QIDS-C_{16} total score and unmodified UPDRS and MoCA total scores were loaded as independent variables in the multiple linear regression. The transformed PDQ-39 SI score was loaded into the analysis as a dependent variable.

As the PDQ-39 measure incorporates the responder's perception of disturbance in mood, cognition and mobility, there is potential for confounds to exist between the PDQ-39 and individual measures of these constructs. Therefore, independent regression analyses were conducted with the corresponding PDQ-39 domain removed from the calculation of the PDQ-39 Single Index (SI) score. For the first regression, the Mobility domain score was removed from the calculation of the PDQ-39 SI score. This modified dependent variable was included in the regression, with the UPDRS severity score as the predictor variable.

The second independent regression analysis involved modifying the PDQ-39 SI by calculating the score without including the Emotion domain score. This modified dependent variable was included in the regression, with the QIDS-C_{16} total score as the predictor variable. The final independent regression analysis required modifying the PDQ-39 SI by calculating the score without including the Cognition domain score. This modified dependent variable was included in the regression, with the MoCA total score as the predictor variable.

Hypotheses Two, Three and Four. The second hypothesis stated that depression severity (as measured by the QIDS-C_{16}) would significantly predict quality of life in the Emotional Well-being, Stigma, and Social Support domains of the PDQ-39. The third hypothesis stated that global cognitive ability (as measured by the MoCA) would significantly

predict quality of life in the Cognition and Communication domains of the PDQ-39. The fourth hypothesis stated that motor symptom severity (as measured by the UPDRS) would significantly predict quality of life in the Mobility, Activities of Daily Living and Bodily discomfort domains of the PDQ-39.

Prior to testing this hypothesis, domain scores were calculated for each of the 8 domains of the PDQ-39, as outlined earlier in the section describing the PDQ-39. Once calculated, distributions of the domain scores were subsequently analyzed. The results indicated that all domain scores for this sample were positively skewed, with the exception of the Cognition domain scores. As such, a square root transformation was applied to all skewed domain scores. This transformation did not completely correct for the positive skew and therefore, the results from the analysis conducted for this hypothesis must be interpreted with caution.

Eight multiple regressions were completed in order to test these hypotheses. The independent variables included the QIDS-C16 total score, the MoCA total score and the UPDRS total score and remained consistent through every regression. For each of the 8 regressions, a domain score served as the dependent variable. Once completed, the resulting standardized Beta coefficients indicated which of the three independent variables exerted the greatest influence on the dependent variable.

Exploratory Hypothesis. The current study included an exploratory hypothesis that individuals classified with bradykinetic motor subtype will report lower quality of life than individuals classified with tremor dominant motor subtype. The classification of motor subtype was only available for 103 of the participants and the following analyses were conducted using this subset of the sample. Prior to testing the hypothesis, distributions of PDQ-39 SI scores, disease duration and age were examined for violation of assumptions. PDQ-39 SI scores and PD

disease duration were positively skewed and therefore, a square root transformation was applied. Age was normally distributed and therefore, no transformation was applied.

Independent samples t-tests were performed to determine if disease duration, age, and education level should be included as covariates in an analysis of variance (ANCOVA) due to the small sample size of the study. A χ^2 analysis was performed to also determine inclusion of gender as a covariate. An ANCOVA was used to examine the differences in PDQ-39 scores among individuals classified with bradykinetic motor subtype Parkinson's disease versus individuals classified with dominant motor subtype Parkinson's disease.

Statistical Analyses for Aim Two

Hypothesis Five. The fifth hypothesis stated that measures of visual learning and memory, verbal attention, processing speed, working memory, and verbal learning and memory will be positively correlated with HRQoL. For this analysis, one participant was removed due to missing cognitive data. Therefore, the analyses were conducted using data from 120 participants. Pearson correlation coefficients were calculated to examine the relationship between quality of life (PDQ-39 SI), visual learning and memory (BVMT-R Learning and Delayed Recall T-scores), verbal learning and memory (RAVLT Delayed Recall and Total Recall scores), processing speed (Trail Making Test A & B T-scores, and Symbol Search scaled score), and working memory (Digit Span and Letter-Number Sequencing scaled scores). PDQ-39 SI scores were positively skewed and therefore a square root transformation was applied.

The first correlational analysis was conducted between all cognitive scores and the PDQ-39 SI to explore the relationships between all these variables. This analysis did not control for any additional factors, and provided a view of the associations between the PDQ-39 SI and the cognitive variables, prior to controlling for other influences. As depressive symptoms are known

to influence cognition, and are present in the sample, a partial correlation analysis with the same variables was subsequently conducted using QIDS-C_{16} scores as a covariate. QIDS-C_{16} scores were positively skewed and therefore, a square root transformation was applied.

CHAPTER FOUR

Results

Demographics

The present study utilized data from 121 participants, 87 (71.9%) of whom were male and 34 (28.1%) were female. The average age of the sample was 64.85 years (SD = 10.27) and the average level of education was 15.41 years (SD = 2.28). The sample included 108 Caucasians (89.26%), 7 Hispanics, 4 African Americans and 1 Asian individual. Ethnicity was not reported in 1 individual. A summary of sample demographics is presented in Table 1.

Statistical Analyses For Aim One

Hypothesis One. The first hypothesis predicted that depression severity; motor symptom severity and global cognitive ability would each contribute to lower HRQOL with depressive symptoms accounting for the greatest amount of variance. The results of the regression analysis indicated that QIDS-C_{16}, UPDRS, and MoCA scores accounted for 30% of the variance in PDQ-39 SI scores, [R^2=0.30, adjusted R^2=0.28, F= (3,117) =16.47, p<0.01]. QIDS-C_{16} (t (117) =4.58, p<0.01, *95% Confidence Intervals [CI]:* 0.37 to 0.93) and UPDRS scores (t (117) =3.15, p<0.01, *95% CI:* 0.02 to 0.08) were both significant predictors of PDQ-39 SI scores while MoCA scores were not (t (117) =-1.18, p=0.24, *95% CI:* -0.11 to 0.03). QIDS-C_{16} scores (β=0.37, p<0.01), relative to UPDRS (β=0.27, p<0.01) or MoCA scores (β=-0.10, p=0.24), explained a greater proportion of the variance in PDQ-39 SI scores. The means, standard deviations, correlation coefficients, and p-values are presented in Table 2.

In addition to the multiple linear regression, three independent linear regressions were also performed. These independent regressions involved modifying the PDQ-39 SI score to limit potential confounds. The result from the first regression analysis (modified for Mobility)

indicated that motor symptom severity accounted for 12% of the variance in quality of life (R^2=0.12, adjusted R^2=0.12, F= (1,119) =16.85, p<0.01). The results of the second independent regression analysis (modified for Emotional Well-being) indicated that depression severity accounted for 18.7% of the variance in quality of life (R^2=0.187, adjusted R^2=0.18, F= (1,119) =27.31, p<0.01). The results of the final independent regression analysis (modified for cognition) indicated that global cognition accounted for 3.8% of the variance in quality of life (R^2=0.038, adjusted R^2=0.03, F= (1,119) =4.68, p=0.03). Figure 1 provides a collective comparison of all accounted variances across each regression.

Hypothesis Two. The second hypothesis predicted that depression severity would significantly predict quality of life in the Emotional Well-Being, Stigma, and Social Support domains of the PDQ-39. The results of the eight multiple regression analyses indicated that QIDS-C_{16}, UPDRS and MoCA scores accounted for approximately 33% of the variance in the Mobility domain (R^2=0.33, adjusted R^2=0.31, F= (3,117) =18.89, p<0.01), 35% of the variance in the ADL domain (R^2=0.35, adjusted R^2=0.34, F= (3,117) =21.30, p<0.01), 21% of the variance in the Emotional Well-being domain (R^2=0.21, adjusted R^2=0.19, F= (3,117) =10.52, p<0.01), 12% of the variance in the Stigma domain (R^2=0.12, adjusted R^2=0.10, F= (3,117) =5.19, p<0.01), 22% of the variance in the Communication domain (R^2=0.22, adjusted R^2=0.20, F= (3,117) =10.99, p<0.01), 9% of the variance in the Social Support domain (R^2=0.09, adjusted R^2=0.07, F= (3,117) =3.76, p=0.013), 13% of the variance in the Bodily Discomfort domain (R^2=0.13, adjusted R^2=0.11, F= (3,117) =5.98, p<0.01), and 23% of the variance in the Cognition domain (R^2=0.23, adjusted R^2=0.21, F= (3,117) =11.31, p<0.01). These results must be interpreted with caution as the assumptions for linear regression were unmet with these data.

The results of the 8 multiple regressions indicated that QIDS-C_{16} scores significantly predicted quality of life in the Mobility (β=0.43, p<0.01), ADL (β=0.23, p<0.01), Emotional Well-Being (β=0.43, p<0.01), Stigma (β=0.32, p<0.01), Social Support (β=0.25, p<0.01), Bodily Discomfort (β=0.24, p<0.01), Cognition (β=0.40, p<0.01) and Communication (β=0.27, p<0.01) domains of the PDQ-39. A summary of the beta values for Hypotheses Two, Three, and Four are displayed in Table 3. As the interpretability of these results is limited, a Spearman's Rank Correlation analysis was conducted in order to further explore the relationships between these variables. For this hypothesis, depression severity was significantly correlated with all PDQ-39 domain scores, as noted in Table 4.

Hypothesis Three. The third hypothesis stated that global cognitive ability (as measured by the MoCA) would significantly predict quality of life impairment in the Cognition and Communication domains of the PDQ-39. The results of the 8 multiple regressions indicated that MoCA scores, relative to QIDS-C16 and UPDRS scores significantly predicted quality of life only in the Communication (β=0.18, p=0.04) domain of the PDQ-39 (See Table 3). The Spearman's Rank Correlation analysis (See Table 4) resulted in significant correlations between the MoCA and the Mobility domain score (r_s=-0.28, p<0.01), the ADL domain score (r_s=-0.20, p=0.03), and the Communication domain score (r_s=-0.22, p=0.01).

Hypothesis Four. The fourth hypothesis stated that motor symptom severity (as measured by the UPDRS) would significantly predict quality of life in the Mobility, Activities of Daily Living and Bodily Discomfort domains of the PDQ-39. The results indicated that the UPDRS, relative to QIDS-C_{16} or MoCA scores, significantly predicted quality of life in the Mobility (β=0.36, p<0.01), ADL (β=0.43, p<0.01), Communication (β=0.23, p<0.05), and Bodily Discomfort (β=0.22, p<0.05) domains of the PDQ-39 (See Table 3). The results of the

Spearman's Rank Correlation (See Table 4) analysis yielded significant correlations between the UPDRS total score and the Mobility domain (r_s=0.40, p<0.01), ADL domain (r_s=0.51, p<0.01), Cognition domain (r_s=0.27, p<0.01), Communication domain (r_s=0.35, p<0.01), and the Bodily Discomfort domain (r_s=0.23, p=0.01).

Exploratory hypothesis. The exploratory hypothesis was that individuals categorized as bradykinetic/rigid motor subtype would report lower quality of life than individuals categorized as tremor dominant. The t-test results showed no significant differences between the bradykinetic group (n=25, M=2.33, SD=0.96) and tremor dominant group (n=76, M=2.41, SD=0.93) in disease duration (t (99) =0.37, p=0.71, CI: -0.35 to 0.51) or years of education (t (101) =1.29, p=0.20, CI: -0.28 to 1.35). However, the t-test results for age showed that individuals classified with bradykinetic motor subtype were significantly younger relative to individuals classified with tremor dominant subtype (t (101) =2.49, p=0.01, CI: 1.17 to 10.36). The χ^2 analysis found no significant difference in gender between groups (χ^2=0.00, p=1.00). Therefore, age was the only covariate included in the ANCOVA analysis. Equal variance assumptions between groups were met for all t-tests. A summary of the means and standard deviations of all variables in this analysis for both motor subtypes are presented in Table 5.

The ANCOVA results showed that individuals classified with bradykinetic motor subtype did not report a significantly lower quality of life than individuals classified with tremor dominant motor subtype (F (1, 98) =3.02, p=0.09, $\eta 2$=0.03, $Power$=0.41. A Levene's Test of Equality of Error Variances was insignificant, (F (1, 99) =0.05, p=0.82, indicating equal variances between groups was assumed. Both depression severity (QIDS-C_{16})(M=4.72, SD= 4.58) and global cognitive ability (MoCA)(M=24.48, SD= 3.15) were slightly higher in the bradykinetic/rigid group compared to depression severity (M=2.91, SD=2.54) and global

cognitive ability (*M*=23.85*, SD*=3.27*)* in the tremor dominant group. The severity of PD motor symptoms (*M*=23.78*, SD*=80.43) was higher in the tremor dominant group compared to the bradykinetic/rigid group (*M*=13.92*, SD*=8.64).

In order to further explore the lack of significant difference in HRQoL between the bradykinetic/rigid and tremor dominant motor subtype groups, an additional ANCOVA analysis was conducted. As the influence of depression severity on HRQoL in PD has been repeatedly demonstrated, an independent t-test was completed to determine if significant differences in depression severity existed between the two motor subtype groups. The independent t-test yielded a statistically significant difference in QIDS-C_{16} scores between the motor subtype groups (*t* (100) =-2.33, *p*=0.02, *CI*: -0.88 to -0.07). There was homogeneity of variances, as assessed by Levene's test for equality of variances (*p*=.265). Therefore, a second ANCOVA analysis was conducted comparing PDQ-39 SI scores between the bradykinetic/rigid and tremor dominant motor subtype groups, with QIDS-C_{16} scores and Age as covariates. The results did not differ from the previous ANCOVA analysis, and found that individuals classified with bradykinetic motor subtype did not report a significantly lower quality of life than individuals classified with tremor dominant motor subtype (*F* (1, 98) =0.89, *p*=0.35, $\eta 2$=0.01. A Levene's Test of Equality of Error Variances was insignificant, (*F* (1, 100) =2.58, *p*=0.11, indicating equal variances between groups was assumed.

Statistical Analyses for Aim Two

Hypothesis Five. The fifth hypothesis was that measures of visual learning and memory, verbal attention, processing speed, working memory, and verbal learning and memory will be negatively correlated with reported quality of life. Table 6 shows the means and standard deviations of the cognitive variables included in this analysis, and the resulting Pearson

correlation coefficients and p-values. The analysis yielded a significant negative correlation between the BVMT-R Learning T-score (r=-0.18, p=0.05) and the PDQ-39 SI. Trail Making Test Part A (r=-0.27, p<0.01), Trail Making Test Part B (r=-0.20, p=0.03), and Symbol Search (r=-0.29, p<0.01), were significantly negatively correlated with PDQ-39 SI scores, indicating that improved quality of life is associated with higher psychomotor processing speed. Letter-Number Sequencing was also significantly negatively correlated with PDQ-39 SI scores (r=-0.19, p=0.04).

The results of the partial correlation analyses (controlling for depression severity) are shown in Table 7. The BVMT-R Learning score (r=-.19, p=0.04), RAVLT Delayed Recall score (r=-.19, p=0.03), Trail Making Test Part A T score (r=-.19, p=0.04), Symbol Search scaled score (r=-.24, p=0.01) and Letter-Number Sequencing scaled score (r=-.21, p=0.03) were significantly negatively correlated with PDQ-39 SI scores, after controlling for depression severity.

CHAPTER FIVE

Discussion

The primary aim of the study was to examine the relative influence of depressive symptoms, PD motor symptoms and cognition on HRQoL in individuals with PD. The first hypothesis predicted that depression severity, motor symptom severity, and global cognitive ability, would each contribute to lower HRQOL with depressive symptoms accounting for the greatest amount of variance. The results of the multiple regression analyses supported this hypothesis, and indicated that depressive symptoms and PD motor symptoms are significant predictors of HRQoL for individuals with PD, accounting for 30% of the variance in PDQ-39 SI scores.

This finding, particularly the impact of depression on HRQoL, aligns with the findings of other studies (Behari, Srivastava, & Pandey, 2005; Dissanayaka et al., 2011; Findlay, 2002; Müller et al., 2013; Schrag et al., 2000; Sławek, Derejko, & Lass, 2005). However, these studies reported varying percentages of accounted variance in HRQoL, which can be attributed to differing depressive severity measures as well as the inclusion of additional disability measures that were unavailable for analysis in the current study. In addition, depressive symptoms explained a greater proportion of the variance in HRQoL scores than motor symptoms, which supports the notion that non-motor symptoms hold greater potential to influence HRQoL than motor symptoms.

The results of the multiple regression analysis aligned closely with linear regression analyses designed to control for the redundancy in the independent and dependent variables. Since each linear regression involved the removal of the independent variable's complementary domain of the PDQ-39, it should be kept in mind that this alters the dependent variable to some

degree. However, the results of the independent linear regressions showed that depression severity accounted for 18.7% of the variance in HRQoL, motor severity accounted for 12%, and that global cognitive ability accounted for 3.8%.

The influence of depression in this sample is impressive, as only 6 participants in the sample met DSM-IV-TR criteria for Major Depressive Disorder. In addition, the mean score on the primary measure of depression (QIDS-C_{16}) was 3.37, which falls in the "No Depression" range (Rush et al., 2003). Furthermore, possible scores on the QIDS-C_{16} range from 0 to 27, and the highest score in this study sample was 16, which defines the lowest value in the "Severe Depression" range. An item analysis conducted on the QIDS-C_{16} determined that the most frequently reported symptoms in this sample included difficulties staying asleep, sad mood, and lack of energy.

Since the incidence and severity of depression was rather low in this sample, especially for a clinical population, the finding from the current study indicates that the identification and treatment of subclinical depressive symptoms holds potential to improve the HRQoL of individuals with PD. Clinicians could greatly improve the HRQoL of patients by prioritizing the treatment of sleep difficulties, as improved sleep could in turn, ameliorate any problems patients experience with reduced energy. The specific and cumulative targeting of sad mood, sleep difficulties and reduced energy, could benefit individuals with PD through improvement in HRQoL.

In order to further elucidate the influence of depression severity, motor severity and global cognitive ability on the HRQoL of individuals with PD, a series of multiple regressions analyzed the variance explained by these three variables in all eight domains of the PDQ-39. Prior to conducting the regression analyses, the detection of a positive skew in PDQ-39 domain

scores resulted in the application of square root transformations to all domain scores except for the Cognition and Communication domain scores. It is important to note that these transformations did not completely resolve the positive skew. A potential explanation for the positive skew of domain scores lies in the overall positive quality of HRQoL of the sample. The possible range of PDQ-39 SI scores 0 to 100 and the mean score in this sample was 20 (SD=13.0), with 57 being the highest score of all participants. While no cut-off scores have been published, the fact that the highest score falls close to the median of possible ranges indicates at the group level that this sample reported experiencing moderately positive HRQoL. Therefore, the assumptions for conducting multiple regressions remained unmet, and the statistical results must be interpreted with caution.

The results of these regression analyses partially supported the hypothesis that predicted depression severity as a significant predictor of HRQoL in the Emotional Well-being, Stigma and Social Support domains of the PDQ-39. In fact, depression severity significantly influenced HRQoL in all domains of the PDQ-39, as can be seen in Table 3. The results of the multiple regression analyses also partially supported the third hypothesis, which predicted that global cognitive ability would significantly predict HRQoL in the Cognition and Communication domains of the PDQ-39. The MoCA significantly predicted HRQoL in the Communication domain but not the Cognition domain. However, the results of the Spearman's Rank Correlation analysis found statistically significant negative correlations between the MoCA and the Mobility, ADL and Communication domains. Despite achieving statistical significance, these correlations ranged between 0.2 and 0.28, indicating a poor strength of these associations.

At first glance, the results of the multiple regressions are surprising. When examining the Cognition domain item content in further detail however, questions in this domain addressed

speech difficulties and daytime sleepiness in addition to concentration problems and memory impairment. By design, the MoCA does not emphasize the assessment of speech difficulties, nor daytime sleepiness. Therefore, the differences in scope and construct of each measure are a likely explanation for the poor predictive strength of the MoCA on cognitive aspects of HRQoL.

The fourth hypothesis predicted that motor symptom severity would significantly predict HRQoL in the Mobility, ADL, and Bodily Discomfort domains of the PDQ-39. The statistical results partially supported this hypothesis, in that the UPDRS total scores significantly predicted HRQoL in the Mobility and ADL domains of the PDQ-39, but not the Bodily Discomfort domain. In part, this finding is not surprising as one would expect a measure of motor symptom severity to predict difficulties with mobility. However, these results indicated that significant reductions in HRQoL are not necessarily attributable to the physical pain or discomfort experienced from PD symptomatology, but rather the reduced ability to accomplish activities of daily living. The results from Spearman's Rank Correlation analysis determined a strong association (r_s=0.51, p<.01) between the UPDRS and the ADL domain although the Spearman's Rank Correlation coefficient for Bodily Discomfort (r_s=0.23, p=.01) attained statistical significance, the strength of the association was weak. Therefore, as PD motor symptom severity increases, so too does the importance of assessing the capacity of individuals with PD to complete activities of daily living.

Global cognitive functioning (as measured by the MoCA) was not a significant predictor of reduced HRQoL in this sample. In exploring the relationship between cognition and HRQoL in PD further, correlational analyses indicated that HRQoL was significantly correlated with BVMT-R Learning, Trail Making Test Part A, Trail Making Test Part B T-scores as well as Symbol Search scaled scores. As depression has been shown to negatively influence cognitive

function (Bunce, Batterham, Christensen, & Mackinnon, 2014), a second analysis covarying for depression severity was conducted and resulted in several significant correlations with HRQoL including the BVMT-R Learning score, RAVLT Delayed Recall score, Trails A T score, Letter-Number Sequencing scaled score and Symbol Search scaled score. Despite achieving statistical significance, the strength of these correlations remained weak, with the Symbol Search scaled score attaining the strongest *r* value (-0.24) with HRQoL.

Of all the significant Pearson correlations, Symbol Search scaled scores in particular was found to have the strongest correlation (r=0.29), although measures of processing speed tended to correlate to a greater extent than visual learning and memory and working memory. When adjusting for depression, verbal learning and memory achieved statistical significance. These correlations are an interesting finding, as it indicates that visual and verbal learning and memory, working memory, and processing speed remain significantly associated with HRQoL, even in a clinical population reporting moderately positive HRQoL. This implies an opportunity for clinical intervention, even in situations where cognitive symptoms (or other symptoms) remain relatively benign.

The exploratory hypothesis in the current study involved dividing the sample into two groups, either onset tremor dominant or onset bradykinesia/rigidity. This classification was based on the participant's presentation of various PD motor symptoms at the time of onset. The current study did not find a significant difference in reported HRQoL between these two groups, although other studies have found that individuals classified as akinetic-rigid report worse HRQoL than their tremor dominant counter parts (Hariz & Forsgren, 2011). One likely explanation lies in this sample's overall positive quality of life prior to being categorized into one of the two groups. Another possible explanation for this difference in results lies in the

disproportionate number of individuals classified as tremor dominant (*N*= 79) versus bradykinetic (*N*=24). A possible remedy for this problem would involve recruiting additional participants, in an attempt to normally distribute the degree of HRQoL and equally balance the two groups of motor symptom presentations.

Limitations

The current study has several limitations that must be taken into account when interpreting the results of the analyses. The demographic characteristics of this sample are not representative of the general PD population in that this group was highly educated, and predominantly Caucasian. As higher education is often associated with higher affluence, it is likely that this sample had access to additional resources including greater social and financial support, and health care, which in turn, positively influenced reported HRQoL. Furthermore, more educated patients are less likely to be depressed (Dissanayaka et al., 2011). These characteristics of the sample may have served as protective factors against worsening HRQoL. This is further supported by the fact that the sample had been diagnosed with PD for an average of 6 years. As this was not a newly diagnosed group, the findings of the study highlight the benefit in mitigating decreases in HRQoL through treatment of subclinical symptomatology.

The data analyzed in this study was transformed using square root methodology. Specifically, scores measuring quality of life, depression severity, and PD disease duration were all positively skewed prior to applying square root transformations. This transformation created an artificially normalized distribution, which permitted the various analyses to be conducted in the current study. While this methodology is statistically sound, it artificially broadened the range of scores and characteristics of a sample that was rather homogenous. Furthermore, square root transformations were applied to all domain scores of the PDQ-39, with the exception of the

Cognition domain. Despite these transformations, domain score distributions remained positively skewed, which limited the interpretability of statistical analyses that involved these variables.

The current study would have benefitted from including additional components of the UPDRS. This measure comprises of five modules including an evaluation of mood and behavior, a self-evaluation of activities of daily living, disease severity staging, and a clinician evaluation of patient activities of daily living (Goetz, 2003). As these modules assess a greater spectrum of PD related symptomatology than the motor module alone, their inclusion in the statistical analyses could expand the predictive strength of the models reported by the current study, and would also allow for a more direct comparison of findings with other published studies that utilized the entire UPDRS.

The absence of a measure of apathy is another limitation of the current study. As apathy is a symptom frequently observed in published studies examining populations with PD (Barone et al., 2009; Martinez-Martin et al., 2011; Müller et al., 2013), a measure of apathy would have facilitated the assessment of the prevalence and severity of this symptom in the study sample. Furthermore, apathy is a primary feature of depression's manifestation in individuals with PD, alongside psychomotor retardation, pessimism and suicidal ideation (Slaughter, 2001). Since the findings from this study indicate that even subclinical depressive symptomatology exerts strong effects on an individual's HRQoL, the inclusion of a measure of apathy would have allowed for deeper understanding of the influence of depressive symptomatology on HRQoL in PD.

Future Directions

The current study found that depression ubiquitously impacted HRQoL in every domain captured by the PDQ-39, even though the depression severity present in the sample was

subclinical. This highlights the need for early identification of depressive symptoms, as well as consistent monitoring of the progression of any identified depressive symptoms. Particular attention should be paid to the unique features of depression in PD, especially apathy, psychomotor retardation, and pessimism. Longitudinal research assessing this preventative approach, would be able to investigate whether the early detection and treatment of subclinical depressive symptoms successfully maintains positive HRQoL in patients with PD. Patients with PD would benefit from research efforts directed at examining the effect of anti-depressant treatments on patient HRQoL, including specific domains.

The current study also found that increased PD motor symptom severity predicted reduced HRQoL through negatively affecting an individual's capacity to complete ADLs. Future research might further investigate the predictive strength of PD motor symptom severity on individuals' reduced ability to complete daily activities. Furthermore, future studies should aim to explore whether employing interventions designed to improve autonomy in completing ADLs in turn, improve reported HRQoL.

Conclusion

The primary aim of the study was to examine the relative influence of depressive symptoms, PD motor symptoms and cognition on HRQoL in individuals with PD. Depressive symptoms (even when subclinical in severity) and PD motor symptoms are significant predictors of HRQoL in individuals with PD. For clinicians, this indicates the importance of identifying and treating even subclinical depressive symptoms. In particular, targeting and treating difficulties staying asleep, lack of energy, and sad mood in patients with PD holds significant potential to improve HRQoL in patients with PD. When treating motor symptoms, attention should also be paid to the patient's ability to attend to activities of daily living. When the

severity of PD motor symptomatology reaches the degree to which activities of daily living are negatively impacted, overall HRQoL suffers. Targeted assessments or interventions such as occupational therapy, physical therapy, and other rehabilitative interventions may enhance a patient's ability to complete activities of daily living, which in turn, improves HRQoL.

Though global cognitive ability was not identified as a significant predictor of HRQoL in this sample, Pearson correlational analyses indicated that HRQoL was significantly correlated with measures of visual and verbal learning and memory, working memory, and processing speed remain significantly associated with HRQoL, even in a clinical population reporting moderately positive HRQoL. Therefore, early screening for difficulties in these cognitive domains would benefit patients with PD, given the significant association between visual and verbal learning and memory, working memory, and processing speed with HRQoL.

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Table 1

Sample Descriptive Information (N=121)

Descriptive	*N*	*%*
Gender		
Male	87	71.9%
Female	34	28.1%
Race / Ethnicity		
Hispanic	7	5.7%
African-American	4	3.2%
Asian	1	0.8%
Caucasian	108	89.3%
Unknown	1	0.8%
	M	SD
Age	64.8	10.3
Education	15.4	2.3
Disease Duration (years)	6.4	4.7
	M	SD
PDQ-39 SI	20.0	13.0
QIDS-C_{16}	3.4	3.1
UPDRS	14.9	8.7
MoCA	23.6	3.6

PDQ-39 SI = Parkinson's Disease Questionnaire – 39 Single Index score, QIDS-C_{16} = Quick Inventory of Depressive Symptomatology – Clinician Version, UPDRS = United Parkinson's Disease Rating Scale, MoCA = Montreal Cognitive Assessment

Table 2

Correlation Coefficients, Means and Standard Deviations of Regression Variables

	PDQ-39 SI (square root)	UPDRS	MoCA	$QIDS\text{-}C_{16}$ (square root)
UPDRS	0.41*			
MoCA	-0.19*	-0.28*		
$QIDS\text{-}C_{16}$	0.46*	0.30*	-0.06	
Means	4.20	14.98	23.64	1.60
Standard Deviations	1.56	8.74	3.64	0.90

* $p < 0.05$

Table 3

Summary of Depression, Cognition and Motor Severity Standardized Beta values from regression analyses

	Mobility	ADL	Emotion	Stigma	Social	Cognition	Communication	Discomfort
QIDS-C_{16}	0.27**	0.23**	0.43**	0.32**	0.25**	0.4**	0.27**	0.24**
UPDRS	0.36**	0.43**	0.08	0.03	0.01	0.13	0.23*	0.22
MoCA	-0.16	-0.13	0.09	0.11	-0.14	-0.08	-0.18*	0.04

* $p < 0.05$, ** $p < 0.01$

QIDS-C_{16} - Quick Inventory of Depressive Symptomatology – Clinician Version, UPDRS = United Parkinson's Disease Rating Scale, MoCA = Montreal Cognitive Assessment

Table 4

Spearman's Rank Correlation Coefficients between PDQ-39 Domains and Depressive Symptoms, Motor Symptom Severity and Global Cognitive Ability

	Mobility	ADL	Emotion	Stigma	Social	Cognition	Communication	Discomfort
QIDS-C_{16}	0.42**	0.40**	0.48**	0.30**	0.22*	0.40**	0.33**	0.27*
UPDRS	0.40**	0.51**	0.15	0.07	0.08	0.27**	0.35**	0.23*
MoCA	-0.28**	-0.20*	0.04	0.10	-0.14	-0.08	-0.22*	-0.01

* $p < 0.05$, ** $p < 0.01$

QIDS-C_{16} - Quick Inventory of Depressive Symptomatology – Clinician Version, UPDRS = United Parkinson's Disease Rating Scale, MoCA = Montreal Cognitive Assessment

Table 5

Bradykinetic and tremor dominant subtype summary

Variable	Bradykinetic Subtype (*N=25)*		Tremor dominant Subtype (*N*=76)	
	Mean	SD	Mean	SD
Age	60.48	11.53	66.04	9.61
Education (years)	15.16	1.80	15.75	1.78
PD Duration (years)	6.32	5.00	6.67	4.73
PDQ-39 SI score	24.72	13.69	18.24	12.72
QIDS-C_{16}	4.72	4.58	2.91	2.54
UPDRS	13.92	8.64	14.73	8.69
MoCA	24.48	3.15	23.85	3.27

PDQ-39 SI = Parkinson's Disease Questionnaire – 39 Single Index score, QIDS-C_{16} - Quick Inventory of Depressive Symptomatology – Clinician Version, UPDRS = United Parkinson's Disease Rating Scale, MoCA = Montreal Cognitive Assessment

Table 6

Correlation Coefficients of Cognitive Variables and PDQ-39

	N	*M*	*SD*	*r*	*P-value*
Visual Learning and Memory					
BVMT Learning	120	52.32	11.47	-0.18	0.05
BVMT Delayed Recall	120	47.80	11.93	-0.17	0.07
Verbal Memory					
RAVLT Delayed Recall	120	46.56	11.99	-0.15	0.11
RAVLT 1-5 Recall	120	46.60	12.26	-0.09	0.33
Processing Speed					
Trail Making Test A	120	44.07	11.71	-0.27	0.002
Trail Making Test B	118	45.81	13.29	-0.20	0.03
WAIS-IV Symbol Search	120	9.24	2.79	-0.29	0.001
Working Memory					
WAIS-IV Digit Span	118	8.90	2.86	-0.17	0.06
WAIS-IV Letter-Number Sequencing	120	8.56	2.57	-0.19	0.04

BVMT-R = Brief Visuospatial Memory Test – Revised, RAVLT = Rey Auditory Verbal Learning Test, WAIS-IV = Wechsler Adult Intelligence Scale – 4th Edition

Table 7

Partial Correlation Coefficients of Cognitive Variables andPDQ-39 Controlling for Depression (QIDS-C_{16})

	N	*M*	*SD*	*r*	*P-value*
BVMT Learning	120	52.32	11.47	-0.19	0.04
BVMT Delayed Recall	120	47.80	11.93	-0.16	0.08
RAVLT Delayed Recall	120	46.56	11.99	-0.19	0.03
RAVLT 1-5 Recall	120	46.60	12.26	-0.11	0.24
Trail Making Test A	120	44.07	11.71	-0.19	0.04
Trail Making Test B	118	45.81	13.29	-0.16	0.08
WAIS-IV Symbol Search	120	9.24	2.79	-0.24	0.01
WAIS-IV Digit Span	118	8.90	2.86	-0.10	0.28
WAIS-IV Letter-Number Sequencing	120	8.56	2.57	-0.21	0.03

BVMT-R = Brief Visuospatial Memory Test – Revised, RAVLT = Rey Auditory Verbal Learning Test, WAIS-IV = Wechsler Adult Intelligence Scale – 4th Edition

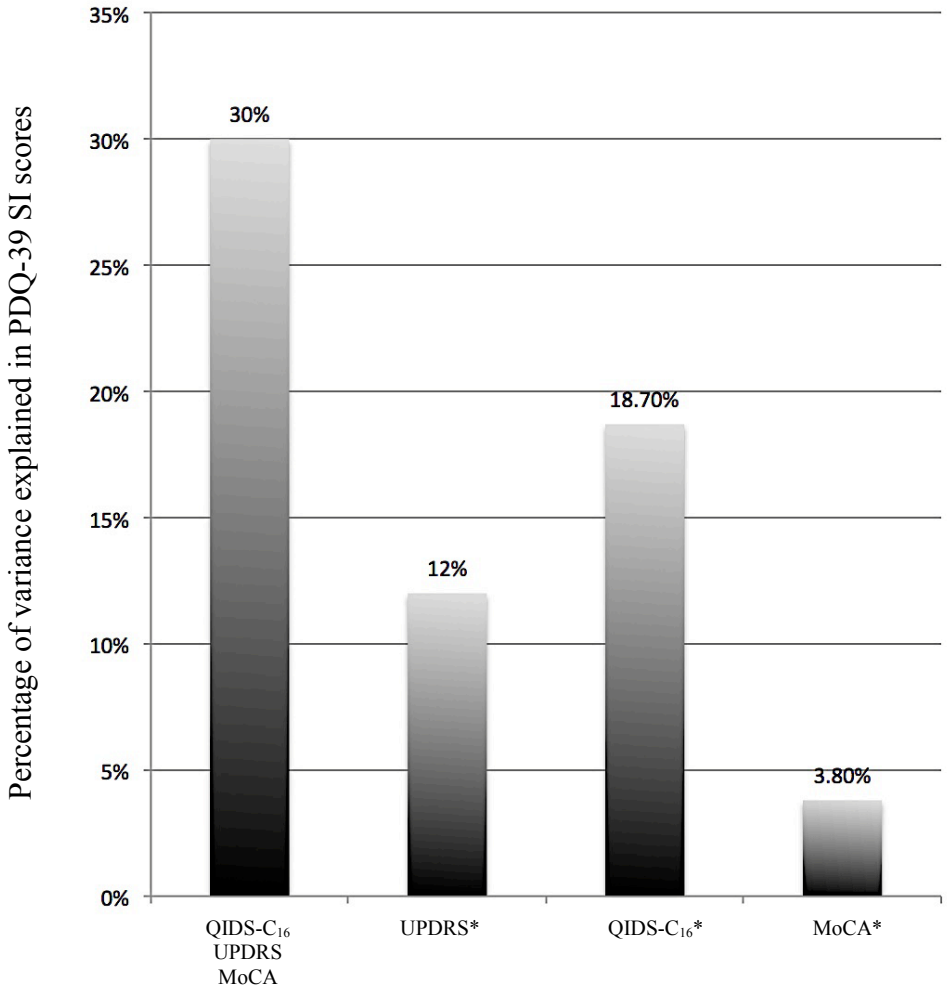

Figure 1. Summary of Regression Analyses for Hypothesis One
* Used modified PDQ-39 SI scores to reduce redundant content in independent and dependent measures.

Appendix A

The PDQ-39 Measure

DUE TO HAVING PARKINSON'S DISEASE, how often have you experienced the following, during the last month?

Due to having Parkinson's disease, how often during the last month have you		*Please tick **one box** for each question*				
		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1.	Had difficulty doing the leisure activities which you would like to do?	⑨	⑨	⑨	⑨	⑨
2.	Had difficulty looking after your home, e.g. DIY, housework, cooking?	⑨	⑨	⑨	⑨	⑨
3.	Had difficulty carrying bags of shopping?	⑨	⑨	⑨	⑨	⑨
4.	Had problems walking half a mile?	⑨	⑨	⑨	⑨	⑨
5.	Had problems walking 100 yards?	⑨	⑨	⑨	⑨	⑨
6.	Had problems getting around the house as easily as you would like?	⑨	⑨	⑨	⑨	⑨
7.	Had difficulty getting around in public?	⑨	⑨	⑨	⑨	⑨
8.	Needed someone else to accompany you when you went out?	⑨	⑨	⑨	⑨	⑨
9.	Felt frightened or worried about falling over in public?	⑨	⑨	⑨	⑨	⑨

*Please check that you have ticked **one box for each question** before going on to the next page*

Due to having Parkinson's disease, how often during the last month have you	*Please tick **one box** for each question*				
	Never	Occasionally	Sometimes	Often	Always
10. Been confined to the house more than you would like?	⑨	⑨	⑨	⑨	⑨
11. Had difficulty washing yourself?	⑨	⑨	⑨	⑨	⑨
12. Had difficulty dressing yourself?	⑨	⑨	⑨	⑨	⑨
13. Had problems doing up buttons or shoe laces?	⑨	⑨	⑨	⑨	⑨
14. Had problems writing clearly?	⑨	⑨	⑨	⑨	⑨
15. Had difficulty cutting up your food?	⑨	⑨	⑨	⑨	⑨
16. Had difficulty holding a drink without spilling it?	⑨	⑨	⑨	⑨	⑨
17. Felt depressed?	⑨	⑨	⑨	⑨	⑨
18. Felt isolated and lonely?	⑨	⑨	⑨	⑨	⑨

*Please check that you have ticked **one box for each question** before going on to the next page*

Due to having Parkinson's disease, how often <u>during the last month</u> have you	*Please tick **one box** for each question*				
	Never	**Occasionally**	**Sometimes**	**Often**	**Always**
19. Felt weepy or tearful?	⑨	⑨	⑨	⑨	⑨
20. Felt angry or bitter?	⑨	⑨	⑨	⑨	⑨
21. Felt anxious?	⑨	⑨	⑨	⑨	⑨
22. Felt worried about your future?	⑨	⑨	⑨	⑨	⑨
23. Felt you had to conceal your Parkinson's from people?	⑨	⑨	⑨	⑨	⑨
24. Avoided situations which involve eating or drinking in public?	⑨	⑨	⑨	⑨	⑨
25. Felt embarrassed in public due to having Parkinson's disease?	⑨	⑨	⑨	⑨	⑨
26. Felt worried by other people's reaction to you?	⑨	⑨	⑨	⑨	⑨
27. Had problems with your close personal relationships?	⑨	⑨	⑨	⑨	⑨

*Please check that you have ticked **one box for each question** before going on to the next page*

Due to having Parkinson's disease, how often <u>during the last month</u> have you	*Please tick **one box** for each question*				
	Never	**Occasionally**	**Sometimes**	**Often**	**Always**
28. Lacked support in the ways you need from your spouse or partner? *If you do not have a spouse or partner tick here* ☐	⑨	⑨	⑨	⑨	⑨
29. Lacked support in the ways you need from your family or close friends?	⑨	⑨	⑨	⑨	⑨
30. Unexpectedly fallen asleep during the day?	⑨	⑨	⑨	⑨	⑨
31. Had problems with your concentration, e.g. when reading or watching TV?	⑨	⑨	⑨	⑨	⑨
32. Felt your memory was bad?	⑨	⑨	⑨	⑨	⑨
33. Had distressing dreams or hallucinations?	⑨	⑨	⑨	⑨	⑨
34. Had difficulty with your speech?	⑨	⑨	⑨	⑨	⑨
35. Felt unable to communicate with people properly?	⑨	⑨	⑨	⑨	⑨
36. Felt ignored by people?	⑨	⑨	⑨	⑨	⑨

*Please check that you have ticked **one box for each question** before going on to the next page*

Due to having Parkinson's disease, how often <u>during the last month</u> have you	*Please tick **one box** for each question*				
	Never	**Occasionally**	**Sometimes**	**Often**	**Always**
37. Had painful muscle cramps or spasms?	⑨	⑨	⑨	⑨	⑨
38. Had aches and pains in your joints or body?	⑨	⑨	⑨	⑨	⑨
39. Felt unpleasantly hot or cold?	⑨	⑨	⑨	⑨	⑨

Please check that you have ticked one box for each question

Thank you for completing the questionnaire

Appendix B

The PDQ-39 Domain Summary

Domain Number	*Name of Domain*	*Number of Items*
Domain 1	Mobility	10
Domain 2	Activities of Daily Living	6
Domain 3	Emotional Well-Being	6
Domain 4	Stigma	4
Domain 5	Social Support	3
Domain 6	Cognitions	4
Domain 7	Communication	3
Domain 8	Bodily Discomfort	3

Appendix C

The United Parkinson's Disease Rating Scale – Part III

III. MOTOR EXAMINATION

18. Speech

0 = Normal
1 = Slight loss of expression, diction and/or volume
2 = Monotone, slurred but understandable; moderately impaired
3 = Marked impairment, difficult to understand
4 = Unintelligible

19. Facial Expression

0 = Normal
1 = Minimal hypomimia, could be normal "Poker Face"
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

0 = Absent
1 = Slight and infrequently present
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

0 = Absent
1 = Slight; present with action
2 = Moderate in amplitude, present with action
3 = Moderate in amplitude with posture holding as well as action
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

0 = Absent
1 = Slight or detectable only when activated by mirror or other movements
2 = Mild to moderate
3 = Marked, but full range of motion easily achieved
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)

0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement
4 = Can barely perform the task

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straight-backed chair, with arms folded across chest.)

0 = Normal
1 = Slow; or may need more than one attempt
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help
4 = Unable to arise without help

28. Posture

0 = Normal erect
1 = Not quite erect, slightly stooped posture; could be normal for older person
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side
4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion
3 = Severe disturbance of gait, requiring assistance
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

0 = Normal
1 = Retropulsion, but recovers unaided
2 = Absence of postural response; would fall if not caught by examiner
3 = Very unstable, tends to lose balance spontaneously
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)

0 = None
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude
3 = Moderate slowness, poverty or small amplitude of movement
4 = Marked slowness, poverty or small amplitude of movement.

BIOGRAPHICAL SKETCH

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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
The University of Texas at Dallas	B.A.	2008	Psychology
The University of Texas Southwestern Graduate School of Biomedical Sciences	M.R.C.	2015	Rehabilitation Counseling Psychology

Positions and Employment

2008-2009 Student Intern – UT Southwestern – Department of Psychiatry, Mood Disorders Clinic

2009-2010 Psychological Assistant I – UT Southwestern – Department of Neurology and Neurotherapeutics

2010-2015 Clinical Data Specialist – UT Southwestern – Department of Psychiatry, Neurostimulation Division

Clinical Experience

2009-2015 Administration of neurocognitive measures designed to assess cognition in a variety of clinical populations including dementia, depression, and anxiety.

2010-2015 Administration of clinical assessments designed to assess the presence and severity of depressive, anxious, manic and psychotic symptoms in depressed populations.

2014-2015 Provision of counseling and psychotherapeutic interventions in depressed and anxious populations.

Presentations and Publications

2011 McClintock SM, Tirmizi O, Chansard M, Husain MM (2011). A Systematic Review of the Neurocognitive Effects of Magnetic Seizure Therapy. International Review of Psychiatry, 23(5), 413-423.

2010 McClintock SM, Chansard M, Husain MM. Parkinson's Disease: Psychosocial Aspects. In Gellman and Turner (Editors), Encyclopedia of Behavioral Medicine (in press). New York: Springer Press.