Performance on the Dementia Rating Scale-2 and deep brain stimulation screening: A

retrospective review

by

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DECLARATION

I, Dané Ludik (20578319), hereby declare that this mini-dissertation **("Performance on the Dementia Rating Scale-2 and deep brain stimulation screening: A retrospective review")** is my own work except where I used or quoted another source, which has been acknowledged and referenced. I further declare that the work that I am submitting has not been submitted before for another degree or to any other university or tertiary institution for examination.

Dané Ludik

On the 8th day of November 2021

ETHICS STATEMENT

I, Dané Ludik (u20578319), obtained the applicable research ethics approval for the research titled **"Performance on the Dementia Rating Scale-2 and deep brain stimulation screening: A retrospective review"** on 27 August 2020 (reference number: HUM040/0720) from the Postgraduate Research Ethics Committee of the Faculty of Humanities at the University of Pretoria.

ABSTRACT

Deep brain stimulation (DBS) is considered as a neurotherapeutic treatment option for Parkinson's disease (PD) patients' with medically intractable motor symptoms. With the increasing implementation of DBS surgery in South Africa, research on the neuropsychological prescreening criteria would be beneficial when considering DBS candidacy suitability. International and national screening procedures often use the Dementia Rating Scale-2 (DRS-2) global cognitive functioning score as one of the determinants for cognitive stratification and DBS candidacy determination. Understanding the potential predictors of DRS-2 global cognitive functioning as measured by the Total Dementia Rating Scale score (TDRS) can aid in adapting the screening process by considering other cognitive markers, efficaciously treating and managing psychiatric symptoms influencing cognitive functioning, and determining which candidates can be considered for follow-up reassessment. The aim of this exploratory study was to determine the sociodemographic, cognitive, and psychiatric correlates of global cognitive functioning on the DRS-2 in a South African cohort with PD presenting for DBS presurgical screening. A quantitative research design was employed and a total of 144 participant protocols were reviewed and analysed using correlation analysis, t-tests and regression analysis. Data from the DRS-2, the Beck Depression Inventory, the Beck Anxiety Inventory , and the sociodemographic questionnaire were included in the analyses. The results showed that education level and age correlated significantly with the TDRS score. Significant predictors of the TDRS score were DRS-2 cognitive subscales, where Initiation/Perseveration (I/P) (verbal fluency) accounted for the highest variance. Depression was also a significant predictor of the TDRS score. This exploratory study contributes to research on prescreening of DBS PD patients in South Africa and highlights the importance of considering several factors when using the DRS-2 on a local cohort for the purpose of DBS candidacy determination.

Keywords: Deep brain stimulation; Parkinson's disease; Dementia Rating Scale-2; prescreening; South Africa

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LIST OF ABBREVIATIONS

For the purpose of clarity, consistency and transparency, a number of abbreviations repeatedly referred to throughout this dissertation are clarified below:

PD: Parkinson's disease

DRS-2: Dementia Rating Scale – 2

TDRS: Dementia Rating Scale Score (global cognitive functioning)

DBS: Deep brain stimulation

BDI: Beck Depression Inventory

BAI: Beck Anxiety Inventory

CHAPTER 1: INTRODUCTION

1.1 Overview

Deep brain stimulation (DBS) is an effective neurotherapeutic treatment option for patients with Parkinson's disease (PD) who present with medically intractable motor symptoms (Tröster et al., 2018). Parkinson's disease is a progressive disease of the nervous system marked by tremor, muscular rigidity and bradykinesia, and is commonly diagnosed in older adults (Kalia & Lang, 2015). It is associated with degeneration of the basal ganglia of the brain and a deficiency of the neurotransmitter dopamine (Hackney, 2019). Deep brain stimulation is the most advanced form of treating PD symptoms that can no longer be adequately controlled with medications (Capelle et al., 2011). Deep brain stimulation is a neurosurgical procedure involving the placement of a medical device called a neurostimulator, which sends electrical impulses, through implanted electrodes, to specific target areas in the brain for treatment of movement disorders (Kobayashi et al., 2019).

As a neuromodulatory intervention, DBS can effectively treat a variety of PD symptoms, including tremor, rigidity, stiffness, slowed movement and gait (Horn et al., 2017). While DBS is the most advanced form of treating PD, it is not an option for all individuals, since PD symptoms can be worsened or side effects can develop after receiving DBS (Follett et al., 2010). To determine suitability for DBS, PD candidates are subjected to a careful and thorough screening process by a multidisciplinary team (Krack et al., 2003).

The purpose of each step of the screening process is to recognise and identify the proportion of candidates unsuitable for surgery (Krack et al., 2003). A well-known screening tool, the DRS-2 has been shown to satisfactorily detect cognitive status in degenerative disorders affecting subcortical structures. Two forms of the DRS (the DRS-2 and the DRS-2: Alternate Form) allow for a better characterisation of declining cognitive status and in the evaluation of treatment efficacy (Schmidt et al., 2005). Research has indicated that the DRS-2 is particularly useful in distinguishing presurgical DBS cognitive risks (Matteau et al., 2011).

It is therefore important to understand the multiple factors contributing to global cognitive status on the DRS-2, as it is the recommended cognitive screening measure in the DBS selection process.

Favourable post-surgical outcomes following DBS have been associated with a comprehensive screening process and appropriate selection of patients for DBS candidacy (Pollak, 2013). Cognitive dysfunction is a common non-motor manifestation associated with PD, and deficits can range from mild cognitive impairment to Parkinson's disease dementia (PDD) (Abboud et al., 2014). As an established contraindication to optimal post-surgical outcomes, compromised cognitive capacity is frequently cited as one of the exclusion criteria for DBS suitability (Abboud et al., 2014). Several non-motor factors have the potential to influence estimation of cognitive status. Depression and anxiety are common neuropsychiatric features observed in patients with PD.

Furthermore, sociodemographic factors such as age, gender, language, and education level may have significant confounding influence when considering testing in cohorts from culturally and linguistically diverse backgrounds and with different quality of education. The Dementia Rating Scale-2 (DRS-2) is a commonly used and recommended assessment tool for the evaluation of cognitive functioning in patients with PD presenting for DBS screening (Skorvanek et al., 2017). As is the case in international screening, some movement disorder centres in South Africa use the DRS-2 global cognitive functioning score as one of many determinants of cognitive stratification and DBS candidacy determination.

To the researcher's knowledge, no research has to date been published on the use of the DRS-2 in South Africa for PD-DBS screening. Given the increase in DBS surgical procedures that are being carried out at South African medical centres, exploring the correlates of DRS-2 global cognitive functioning may provide valuable insights on the screening process for a South African cohort.

1.2 Research question

The research question for this study is "Which sociodemographic, cognitive and psychiatric factors correlate with global cognitive functioning on the DRS-2 in a South African Cohort with Parkinson's disease (PD) presenting for deep brain stimulation (DBS) screening?". Secondary question: "Which specific variable/s predict changes in DRS-2 global cognitive functioning?".

1.3 Research aim

Understanding the potential contributors to DRS-2 global cognitive functioning can aid in adapting the screening process by considering other cognitive markers, efficaciously treating and managing psychiatric symptoms influencing cognitive functioning, and determining which candidates can be considered for follow-up reassessment. This exploratory study therefore, aims to determine the sociodemographic (age, gender and educational level), cognitive (DRS-2 cognitive subscales), and psychiatric correlates (anxiety and depression) of global cognitive functioning on the DRS-2 in a South African cohort with PD presenting for DBS presurgical screening. Secondary aim: To explore which factors are significant predictors of variance in DRS-2 global functioning score.

1.4 Justification for and significance of the research

While several studies have been conducted on the factors contributing to DRS-2 global cognitive functioning (Total Dementia Rating Scale-2, or TDRS), none are based on a South African cohort screening for DBS. This exploratory study contributes to a novel field of academic and translational (clinical) research that focuses on the judicious use of cognitive tests in a South African context, together with appropriate selection of cognitive assessments such as the DRS-2 for use in DBS consideration. Investigating correlates of global functioning on the DRS-2 is an important requirement to ensure that international parameters for determining DBS cognitive suitability are applicable to local cohorts.

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Understanding these potential contributors to TDRS can then aid in adapting the DBS screening process, by considering other cognitive markers, efficaciously treating and managing psychiatric symptoms influencing cognitive functioning, and determining which candidates may be considered for follow-up reassessment. Given the novelty of the research within the South African context and the increasing number of patients presenting for DBS prescreening, a local study is warranted and potentially contribute to research within the field.

Internationally, although the DRS-2 has been recommended for use in DBS prescreening, questions arise regarding its use as the key determinant of suitability. Some of the concerns include an underestimation of cognitive capability due to the different contribution of particular subscales to the TDRS score, the psychiatric impact on cognitive performance and specifically on PD cognitive outcomes, and medication effects on cognitive tasks such as fluency and memory (Sollman et al., 2016). Exploring these correlates of global cognitive functioning would potentially allow for more flexible candidacy determination, with awareness of medication-induced cognitive side effects and psychiatric management of symptoms. Recognising the importance of psychiatric contributors also allows for optimal management of psychiatric symptoms and psychiatric medication reviews, which allow for reassessment and candidacy determination after symptom stability. Additionally, the results of this study may provide a foundation for future more robust studies on the DRS-2 within the South African context.

1.5 Nature of the study

This research study is classified as quantitative, as both the data collection and the data analysis methods make use of quantitative design elements (Vogt & Johnson, 2012). The nature of the quantitative study is exploratory. A secondary retrospective review was conducted on abstracted coded data specific to PD participants and the Dementia Rating Scale-2 (DRS-2), the Beck Depression Inventory (BDI-II), the Beck Anxiety Inventory (BAI),

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and sociodemographic variables. Data from 144 participants were reviewed. The data in this study were analysed using Pearson correlations, t-tests, and regression analysis.

1.6 Structure of the dissertation

The mini-dissertation is divided into the following chapters:

• **Chapter 2: Literature review.** This chapter reviews the extensive literature on PD, the DRS-2 as a presurgical screening tool, and DBS surgery for PD patients. The theoretical underpinnings of the study are also explained.

• **Chapter 3: Methodology.** This chapter provides an in-depth description of the methodology used in the study. This includes the research design, the sampling procedures, the instruments used, the procedure followed, and, lastly, the ethical considerations.

• **Chapter 4: Results.** This chapter presents a summary of the findings obtained after the data collection and the quantitative analysis.

• **Chapter 5: Discussion and conclusion.** This chapter integrates the findings of this research study with the literature reviewed and the contextual background of the South African PD cohort. The findings will be discussed with the overall aim of the research in mind. The limitations of the study will be mentioned, and recommendations for future research will be offered.

CHAPTER 2: LITERATURE REVIEW

This chapter presents the contextual background and a review of the literature. The chapter explains the pathophysiology and cognitive impairment related to PD, followed by an explanation of measuring cognitive function in the disease. Deep brain stimulation and its presurgical considerations are discussed, together with the factors associated with performance on the DRS-2. The chapter concludes by mentioning the limitations of the DRS-2 as a cognitive screening measure for PD patients. Patients in this study cohort are characterized as a clinical PD group who are being considered for DBS surgery. The use of the DRS-2 is one of the primary outcome measures for DBS consideration (Skorvanek et al., 2017) and thus, a discussion of the DBS procedure provides a contextual background to the study.

2.1 Introduction

Parkinson's disease is considered the second-most-common neurodegenerative disease, preceded only by Alzheimer's disease (AD) (Barbosa & Charchat-Fichman, 2019). This movement disorder is believed to be triggered by weakening of dopaminergic neurons in the the pars compacta of the Substantia Nigra (Stamelou & Höglinger, 2019). Tremors, particularly of the hands and fingers, muscle stiffness, shuffling posture, slow speech, a masklike facial appearance, and cognitive impairment are considered some of the pathognomonic symptoms of PD (Tröster, 2015). Deep brain stimulation is the alternative form of treating PD symptoms that can no longer be adequately controlled with medications (Capelle et al., 2011). While DBS is an established neurotherapeutic treatment option, it is contraindicated in some individuals, since PD symptoms can be worsened or side effects can develop after receiving DBS (Accolla & Pollo, 2019; Højlund et al., 2017). To determine suitability for DBS, PD candidates are subjected to a careful and thorough screening process by a multidisciplinary team. A well-known screening tool, the DRS-2 has been shown to satisfactorily detect cognitive impairment in degenerative disorders affecting subcortical structures. It is therefore important to

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understand the multiple factors contributing to an estimation of global cognitive status on the DRS-2, as it is the recommended cognitive screening measure in the DBS consideration process (Skorvanek et al., 2017).

2.2 Pathophysiology of Parkinson's disease

Although much scientific progress has been made in understanding the pathophysiology of PD, it is still considered largely idiopathic (of unknown cause) (Greenland & Barker, 2018). Physiologically, the symptoms associated with PD are the result of the loss of a number of neurotransmitters, most notably dopamine (Jankovic & Tolosa, 2015). Symptoms worsen over time as more and more of the cells affected by the disease are lost (Accolla & Pollo, 2019). The course of the disease is highly variable, with some patients exhibiting very few symptoms as they age and others having symptoms that progress rapidly (Lewis & Spillane, 2018). Parkinson's disease is increasingly seen as a complex neurodegenerative disease with a sequence of progression (Hurley, 2015). There is strong evidence that the sequence of progression includes the dorsal motor nucleus of the vagus nerve and the olfactory bulbs and nucleus, followed by the locus coeruleus and the substantia nigra (Kalia & Lang, 2015). Cortical areas of the brain have been reported to be affected at a later stage (Greenland & Barker, 2018). Damage to these various neuronal systems accounts for the multifaceted pathophysiological changes, which cause impairments not only to the motor system, but also to the systems implicated in cognitive processing (Balestrino & Martinez-Martin, 2017).

Dopamine, like other neurotransmitters, transmits chemical messages from one nerve cell to another across a synapse, a space between the presynaptic cell and the postsynaptic receptor (Davis & Racette, 2016). Dopamine is secreted into the synapse from membrane storage vesicles in the presynaptic membrane (Cunha, 2016). Within the synapse, as dopamine travels from one cell to another, it can be broken down and rendered inactive by two enzymes, namely monoamine oxidase and catechol-O-methyl transferase (Zucca et al., 2017).

As less and less dopamine is produced by the neurons, less binding occurs on postsynaptic membrane dopamine receptors (Jankovic & Tolosa, 2015). In PD the loss occurs at a much greater rate, and both biochemical measures and imaging studies suggest that there is a significant decrease in dopamine by the time motor symptoms appear (Hurley, 2015). In this view, cell death in PD is considered an accelerated version of the cell death seen with normal ageing (Cookson, 2009). Degeneration of dopamine neurons is particularly evident in a part of the substantia nigra called the pars compacta (Lewis & Spillane, 2018). The loss of dopamine in the pars compacta significantly increases the overall excitatory drive in the basal ganglia, disrupting voluntary motor control and causing the characteristic symptoms of PD (Gasparini et al., 2013). While the motor indicators of PD have been the subject of research for decades, it is only in recent years that cognitive impairment has become recognised as a fundamental feature of PD (Davis & Racette, 2016).

2.3 Cognitive functioning in Parkinson's disease

Cognitive impairment in PD is diverse, and it can range from mild cognitive impairment (MCI) to severe dementia (Marras et al., 2014), or Parkinson's disease dementia (PDD). Cognitive impairment in PD also differs from other disorders in its pattern, affecting to a greater or lesser degree various areas of cognition (Fang et al., 2020). The typical pattern is a leading dysexecutive syndrome with visuospatial impairment, attentional shortfalls, and decelerated processing speed (Jankovic & Tan, 2020). Executive dysfunction can be present from the early stages of PD (Fang et al., 2020). It is characterised by deficits in internal control of attention, set shifting, planning, inhibitory control, dual task performance, and compromised performance on a range of decision-making and social cognition tasks (Almeida & Hamdan, 2019).

While cognitive impairment in PD occurs on a scale of severity, it is frequently categorised into two types, namely MCI and PDD, depending on the degree to which the impairment impedes activities of daily living (Marras et al., 2014). Mild cognitive impairment

refs to cognitive deterioration which does not "markedly" affect one's occupational or social functioning, while PDD interferes substantially with daily functioning (van der Steen et al., 2019). Mild cognitive impairment is diagnosed according to the prevalence, or not, of memory deficiency, that is, amnestic MCI or non-amnestic MCI, respectively, and it corresponds with the number of cognitive areas compromised (Cammisuli et al., 2019; Weil et al., 2018).

Numerous longitudinal studies have also shown that PD-MCI is a risk factor for developing PDD (Hobson & Meara, 2015). Saredakis et al. (2019) found that in patients with PD and normal cognition, within three years, 25% converted to PD-MCI and 2% converted to PDD. The authors indicated that of those with PD-MCI, 20% converted to PDD, while 28% reverted to a state of normal cognitive function. The conversion rates to MCI and dementia were higher, and the reversion rates were lower, when follow-up was ≥3 years. Consequently, MCI is identified as a major risk factor for the development of dementia in PD, alongside male gender, older age, higher severity of motor symptoms, and the occurrence of visual hallucinations (Goldman et al., 2015). In both PD-MCI and PDD, slow cognitive decline is an essential characteristic. Detecting MCI is therefore valuable, since it has prognostic importance (Weil et al., 2018). Therefore, measuring instruments used in DBS screening processes should be sensitive to detecting MCI and patterns of cognitive changes over time.

Recent literature has therefore emphasised the use of valid measures of cognitive abilities to detect the presence and the severity of cognitive deficits in PD patients (Barbosa & Charchat-Fichman, 2019). In PD, cognitive function can be assessed in an evaluation by a physician, an occupational therapist, or a speech therapist; in a research study; or by a neuropsychologist, where a thorough clinical assessment is conducted (Bakeberg et al., 2020). It is vital that methods for measuring cognitive function in PD are selected with careful thought given to the objectives of the evaluation. In order to detect compromised cognition typical of PD, these measures should cover the main cognitive areas, namely orientation, attention, executive functioning, abstract reasoning, memory, language, basic and complex perception, visuospatial abilities, praxis, and motor skills (Federico et al., 2015).

2.3.1   Assessment of cognitive function in Parkinson's disease

Neuropsychological assessments allow for a computation of scores that can be used to test the probability that a person has undergone a change in cognitive abilities, for comparative estimations to premorbid functioning or earlier assessment profiles, or to evaluate strengths, weaknesses, or deficiencies in relation to normative standards (Nicoletti et al., 2019). The study of patterns of strengths and weaknesses, or deficiencies, across cognitive, emotional, and behavioural areas has been employed in PD to address numerous diagnostic, functional, or treatment concerns (Marras et al., 2014). While less consideration has been given to the use of neuropsychological assessments in the prediction of treatment response, preoperative neuropsychological data, together with consideration of patient age and levodopa response, may facilitate prediction of risk for post-operative cognitive and psychosocial decline (Foki et al., 2017). Neuropsychological assessments have also successfully been used to identify improvement or decline in cognitive function following medical or surgical treatment, such as DBS (Foley et al., 2018). Determining cognitive functioning of PD patients through neuropsychological assessment prior to receiving surgical treatments such as DBS is vital, considering that this surgery may worsen symptoms in certain PD patients (Cernera et al., 2019).

2.4 Deep brain stimulation

As a neurosurgical procedure, DBS involves the insertion of a medical apparatus known as a neurostimulator inside the human brain (Denys et al., 2012). The neurostimulator sends electrical impulses, by means of implanted electrodes, to targeted areas in the brain to treat movement disorders (Denys et al., 2012). Deep brain stimulation was first employed for PD in 1990, and it has been shown to limit "off-time" incapacity, reduce dyskinesia, improve quality of life, and lead to a reduction in the levodopa dosage used (Shahmoon et al., 2019). Two of the most frequently targeted DBS areas in PD are the globus pallidus interna (GPi) and the subthalamic nucleus (STN) (Southwell et al., 2018). Both the GPi and the STN are primarily

suggested for persons who, despite optimisation of medical treatment, go on to endure motor fluctuations or debilitating dyskinesias, or present with medication-resilient tremors (Abboud et al., 2014). There is a lack of consensus as to which site is better, as both GPi-DBS and STN-DBS have been proven to be effective in treating PD motor symptoms (Anderson et al., 2017; Boel et al., 2016; Pujol et al., 2016; Tröster et al., 2015).

Each site, however, is known for different post-surgical outcomes. Subthalamic nucleus deep brain stimulation provides reliably greater dopaminergic medication decrease, and it has potential functional advantages in non-motor domains, while GPi-DBS improves dyskinesia inhibition and helps control symptoms (Southwell et al., 2018). However, given that DBS is not suitable for all patients, contraindications to the procedure have been extensively considered when determining suitability of surgical candidates.

2.5 Preoperative considerations for deep brain stimulation surgery

There are several clinical/neurological factors that determine suitability for DBS candidacy, for example, how a person responds to levodopa (Follett et al., 2010; Witek et al., 2020). Persons with prevalent gait and balance impairment also react poorly to DBS surgery, (Weaver et al., 2009), although PD patients with tremor dominance have greater global motor improvement (Katz et al., 2015). The presence of a specific profile of PD symptoms therefore impacts DBS success. In addition to the neurological profile, there are also several cognitive and psychiatric contraindications to DBS surgery (Boel et al., 2016).

2.5.1 Cognitive contraindications

In some cases, DBS can lead to cognitive decline; therefore, cognitive status must be established before surgery (Cernera et al., 2019). Clinical features of diminished cognition in PD entail various cognitive areas, namely executive function, visuospatial reasoning, memory, and language function (Fang et al., 2020), and supplementary features include visual hallucinations, paranoia, and fluctuations in attention (O'Brien et al., 2020). Cognitive

deficiency in PD ranges in severity from fairly mild symptoms to end-stage dementia (Davis & Racette, 2016).

Dementia is the most recurrent cognitive exclusion condition for DBS, since dementia worsens after DBS, and PD patients will not be able to experience the surgery-induced advantages of improved motor function (Markser et al., 2015). Goldberg et al. (2012) indicated that persons with executive dysfunction may have a greater chance of developing dementia. Most PD patients display some level of deficit in executive functioning (Almeida & Hamdan, 2019). The difficulty, however, lies in determining the degree to which this cognitive deficit can deteriorate following DBS (O'Brien et al., 2020). Furthermore, given the intrusive nature of brain surgery, patients are generally given anaesthesia. Consequently, some level of cognitive reserve is necessary to avert post-surgery decline (Pollak, 2013). Research has shown that ageing patients, or patients with borderline pre-surgery global cognitive profiles, are susceptible to post-surgical cognitive risk and poor quality of life outcomes (Matteau et al., 2011). Apart from considering potential cognitive contraindications, patients' psychological status is also a consideration when screening for DBS candidacy determination.

2.5.2 Psychiatric contraindications

Deep brain stimulation may have an adverse effect on PD patients with psychiatric symptoms such as depression and anxiety (Han et al., 2018). Furthermore, executive dysfunction, which is a well-known pathognomonic cognitive symptom of advanced PD, can be aggravated by psychiatric overlays (Dotson et al., 2018; Stahl, 2019). Aggravation of psychiatric symptoms after DBS has been shown to impact quality of life outcomes (Boel et al., 2016). Psychiatric correlates may influence DRS-2 performance or estimation of global cognitive functioning. Specifically, patients with depression and/or anxiety may demonstrate significantly poorer cognitive performance, particularly impaired memory (Lee et al., 2018; Yang et al., 2015), on measures such as the DRS-2 and the Mini-Mental State Examination (MMSE) when compared to non-depressed and non-anxiety counterparts (Lee et al., 2018).

2.5.2.1 Depression

The incidence of depression in PD patients is 20%–35% (Aarsland & Kramberger, 2015). Depression can manifest at any time, from the premotor stage to the late stages of the disease (Schapira et al., 2017). Generally, depression in PD patients entails apathy, anhedonia, neurovegetative symptoms, and somatic symptoms, such as concentration difficulty, fatigue, and insomnia; consequently, it may be difficult to detect clinical depression in PD patients (Torbey et al., 2015). Depression due to PD refers to depressive symptoms, which may have a direct pathophysiological relation to PD, irrespective of symptom severity (Saleem & Anwar, 2019). Depression in PD can manifest as a single episode in response to dopamine replacement therapy, or as major depressive-like episodes, even with mixed features of manic or hypomanic episodes (Starkstein & Brockman, 2017). In some cases, severe major depression may lead to suicidal behaviour (Roca et al., 2019).

Among patients treated with DBS, suicidal behaviour seems to be related to post-operative depression and/or distorted impulse regulation (Han et al., 2018). The pathogenesis of suicidal ideation has proven to be a hypodopaminergic syndrome caused by dopamine agonist withdrawal, which is linked to anxiety, depression, apathy, and anhedonia, causing suicide attempts (Aarsland & Kramberger, 2015). Shepard et al. (2019) similarly indicated that following DBS at the subthalamic nucleus, reduced dopaminergic stimulation after drug dose reduction may be related to suicide.

2.5.2.2 Anxiety

Elevated levels of anxiety and anxiety related disorders in PD patients are also considered possible contraindications to DBS (Han et al., 2018). Anxiety is a frequent non-motor symptom, usually coexisting with depression and with motor fluctuations in PD patients (Kurtis et al., 2017). Anxiety disorders occur in up to 35% of patients with PD, and they have a negative effect on motor symptoms and quality of life (Mulders et al., 2018). The types of anxiety disorders common among this population vary, although common experiences include

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generalised anxiety, panic attacks, and social phobia and agoraphobia (Mulders et al., 2018). While DBS is transformative for some PD patients, this is not the case for all patients. Unfortunately, post-operative anxiety has been reported as more frequent after STN-DBS (Accolla & Pollo, 2019; Anderson et al., 2005). It is therefore recommended that the neuropsychiatric profile of each PD patient be carefully assessed, and that it inform the decisional process when considering both STN and GPi as stimulation targets (Mosley & Marsh, 2015). Specific preoperative symptoms, such as anxiety, could tilt the balance towards either of the two targets, possibly improving DBS outcome for a given patient.

2.6 The Dementia Rating Scale-2

The Dementia Rating Scale was first developed by Mattis (1976) to assess the cognitive status of persons with brain dysfunction. More specifically, the objective of the scale was to assess cognitive functioning among patients with known cognitive impairment, particularly of the degenerative type (Mattis, 1988). The Dementia Rating Scale-2 is a well-known test of general cognition and is widely used in clinical and research settings (Hendershott et al., 2019). Compared to the Mattis-DRS, the DRS-2 offers minor changes, such as age- and education-corrected Total Scores; enhanced scoring guidelines; an expanded normative table and reformatted designs; and reference material to assist with administering the assessment (Jurica et al., 2001). The Dementia Rating Scale-2 was designed to provide an overall score of neuropsychological functioning based on performance on a variety of cognitive tasks, and it has been shown to satisfactorily detect cognitive status in degenerative disorders affecting subcortical structures (Baird, 2006).

The Dementia Rating Scale-2 consists of 36 tasks divided into five subscales, which measure the following abilities: Attention (ATT), Initiation/Perseveration (I/P), Construction (CONST), Conceptualisation (CONCEPT), and Memory (MEM) (Jurica et al., 2001). An optimal Total Score on the DRS-2 is 144, where the standard clinical cut-off is 124 (Erdődi et al., 2020). The purpose of the DRS-2 cut-off score is to distinguish cognitively impaired

individuals from cognitively intact individuals (Springate et al., 2014). Several cut-off scores have been proposed to distinguish PDD, MCI, and intact cognitive functioning. These cut-off scores range from 123 to 138 on the TDRS (Bezdicek et al., 2015; Matteau et al., 2011; Sollman et al., 2016). Despite benefits such as detecting cognitive decline, utilising cut-off scores may potentially exclude suitable candidates. For example, the influence of age and education is not adequately reflected in a single cut-off score, nor are the specific psychometric aspects of the DRS-2 subscales and their contributions reflected in the TDRS and the fluency task contributed disproportionately to the TDRS score when compared to the contributions of the other subscales, and Sollmann et al. (2016) have corroborated these findings.

In addition, PD patients' cognitive performance profiles are significantly affected by medication on/off states, as well as by medication-induced side effects (Marras et al., 2014). A study conducted by Matteau et al. (2011) showed that anticholinergics were prescribed in 27% of patients with PD-MCI and, to a less significant extent, in 13% of patients with PDD. Medication with anticholinergic activity has been linked to cognitive impairment (Ruxton et al., 2015). Also, patients with PD-MCI (33%) and PDD (47%) took benzodiazepines in larger amounts than patients with Alzheimer's-MCI (22%) and AD (19%) (Matteau et al., 2011). Long-term benzodiazepine use is significantly associated with a higher risk of decline in global cognitive functioning (Nader & Gowing, 2020). Since PD patients are on a wide variety of medication, medication-induced side effects, such as dyskinesia, are often evident, even though patients are usually on optimal doses and in a "medication on" state when assessed. Individuals with PD respond differently to the medication, and they may display different medication-induced side effects (Sollman et al., 2016). For example, of the cognitive domain subscales of the DRS-2 verbal fluency has been found to be differentially affected by these medication-induced side effects, and consideration of how fluency scores influence global cognitive functioning is an important factor in the estimation of cognitive capability. Executive functioning is also particularly susceptible to medication response (Michely et al., 2012).

Certain medication affects patients' ability to perform executive function tasks such as planning, organising, problem solving and cognitive flexibility (Michely et al., 2012).

Hence, it is important to assess factors contributing to the estimation of TDRS and to consider alternative or supplementary cognitive determinants in the presurgical PD cluster (Bezdicek et al., 2015). Despite certain limitations as a screening tool, the DRS-2 has been recommended as useful for determining cognitive status among presurgical PD candidates (Sollman et al., 2016). The DRS-2 is also recommended by the International Parkinson and Movement Disorder Society as an effective tool for measuring global cognitive performance in PD patients presenting for DBS prescreening (Skorvanek et al., 2017).

2.7 Factors associated with the Dementia Rating Scale-2 global cognitive functioning

Cognitive reserve, education, cultural background, and language are some of the factors associated with estimations of TDRS.

2.7.1   Level of education

Education has often been used a proxy for cognitive reserve (Staekenborg et al., 2020). Cognitive reserve is defined as the brain's capacity to compensate for the adverse effects of neurodegenerative processes, and therefore to preserve mental abilities despite disease progression (Sobral et al., 2015; Steffener & Stern, 2012). The literature supports the existence of a linear relationship between level of education and cognitive resilience to neurodegenerative processes (Liu et al., 2013). More specifically, persons with higher levels of education can manage age-related changes and brain pathology, through relying on alternative neural pathways, created as a result of continued engagement in complex mental tasks (Liu et al., 2013). The relationship between level of education and performance on cognitive assessments has also been widely recognised in studies conducted in a number of countries (de Freitas & Curinga, 2015; Franco-Marina et al., 2010), indicating both floor effects (low education) and ceiling effects (high education).

Education influences brain development, and thus it serves as a likely protective factor against cognitive impairment (Then et al., 2016). Erdődi et al. (2020) found that individuals with post-secondary education performed considerably better on the DRS-2 than those with only a high school diploma.

Given that performance on the DRS-2 is influenced by education (Erdődi et al., 2020; Then et al., 2016), it is important to determine if the same trends are noticeable in South Africa. Cassimjee and Motswai (2016) investigated the differences in neuropsychological functioning between a group of human immunodeficiency virus (HIV)-positive adults and older adults, and an HIV-negative matched control group. The authors indicated a significant positive correlation between global DRS-2 scores and years of education, which indicates that the DRS-2 scores in their study show the same trend in range of scores. However, their findings also indicate significantly poorer cognitive performance in the study's control group compared to the original Mattis-DRS sample. These comparisons suggest that although the normative group and the control group each showed a decline in cognitive performance with decreasing education levels, caution should be applied when using cut-off score determinants to categorise severity of impairment based on norms outside the South African context.

2.7.2 Language and culture

Chan et al. (2001) support the view that the TDRS score can be influenced by factors such as language and culture. The authors found a substantial difference between American and Chinese healthy participants, with Chinese participants obtaining lower TDRS scores, as well as lower scores on the I/P and MEM subscales. The difference in the I/P subscale was mostly attributable to the verbal fluency task, in which participants are instructed to list items that can be bought in a supermarket. The retrieval process of the Chinese participants was slower, since they were less familiar with the idea of supermarkets. The Chinese participants possibly performed poorer on the Memory subscale, since the sentence to remember carried more meaning for American participants (Chan et al., 2001).

The variables of language, ethnicity, and geographical characteristics have also been found to influence performance on verbal fluency tasks (Casals-Coll et al., 2013). Rivera et al. (2019) similarly found that in the development of norms, certain factors impact performance on verbal fluency tasks. Higher levels of education and verbal intelligence have consistently been associated with higher total fluency scores (Olabarrieta-Landa et al., 2015). Furthermore, having high vocabulary and writing and reading ability have been related to better performance in verbal fluency tests (Olabarrieta-Landa et al., 2015). Kochhann et al. (2018) found that intelligence and bilingualism are related to verbal fluency. For example, Stolwyk et al. (2015) revealed that intelligence contributed to letter fluency in young and older adults. Rivera et al. (2019) indicated that gender differences are more distinct in semantic than in letter verbal fluency tasks, and Hirnstein et al. (2014) suggested that gender stereotypes have an effect on verbal fluency tasks in adults.

In South Africa, however, the biggest issue is the intricacy and diversity of its people, with 11 official languages, fluctuating degrees of quality in education, significant differences in different cultures, socio-economic status, and fast-occurring socialisation, all against a historical backdrop of former political and socio-economic disparity (Laher & Cockcroft, 2014). Given the complexity of the challenge, there is no global assessment battery that can accommodate such differences (Laher & Cockcroft, 2013). Laher and Cockcroft (2017) indicated that virtually no assessment of cognition is culture-fair, and that there are extensive discrepancies in test ability, both within and among cultures. While education, cultural background, language, and cognitive reserve are among the factors that have been associated with performance on the DRS-2, the impact of gender, on the other hand, is less clear. Some studies show no significant effect of gender on DRS-2 performance (Chan et al., 2001; Lucas et al., 1998), while others have found this variable to be significantly correlated with scores on at least one subscale of the test (Bank et al., 2000; Lyness et al., 2006; Pedraza et al., 2010). The above studies signify the importance of taking moderating factors such as language, education, age, and gender into account when interpreting DRS-2 performance.

2.8 Limitations of the Dementia Rating Scale-2 as a screening tool in PD patients

The views on the limitations of the DRS-2 are somewhat controversial. Jurica et al. (2001), for example, found that the DRS-2 will not typically detect impaired cognitive ability in individuals who function in the average or higher range of intelligence, due to the fact that the DRS-2 was developed to avoid floor effects in clinically impaired populations, rather than ceiling effects in highly functioning individuals. By contrast, Skorvanek et al. (2017) indicated that the DRS-2 screening tool does have possible ceiling effects, due to the absence of normative data for individuals with less than eight years of education. Additionally, the DRS-2 measures test performance at a specific point in time, which means that fluctuating alertness and cognitive state can impact on test results (Marras et al., 2014).

Hendershott et al. (2019) indicated that while the DRS-2 can sufficiently screen for PD cognitive impairment (CI), the Montreal Cognitive Assessment (MoCA) offers consistently higher sensitivity than the DRS-2. The authors further showed that although the DRS-2 can identify domain-specific impairment, it is likely that it will lead to some patients falsely being identified as impaired, because the specificity for domain-specific impairments is low (Hendershott et al., 2019). Despite these limitations, the DRS-2 is still regarded as a highly recommended scale for screening global cognition in PD patients. Following the trend in international literature regarding screening for DBS consideration, it is important to note that other screening measures such as the MoCA have been used in South Africa on various clinical populations and the diagnostic validity of this instrument has been contested (Beath et al., 2018). Following from this, research on alternative screening measures such as the DRS-2 for DBS consideration in a local cohort is warranted.

2.9 Conclusion

As pointed out by the above studies, significant focus has been placed on the efficacy of the DRS-2 in screening global cognition, particularly cognitive deficits occurring in PD patients. There are several TDRS ranges that have been proposed as a means for stratifying cognitive

status and determining DBS candidacy. As shown in the preceding discussion, many factors, such as subscale contributions to Total Score, psychiatric, and sociodemographic factors, may contribute to deviations in estimation of Total Scores. To date, no research has been conducted on the use of the DRS-2 as a screening tool for PD-DBS candidacy in South Africa. Investigating correlates of global functioning on the DRS-2 is an important requirement to ensure that international parameters for determining DBS cognitive suitability are applicable to local cohorts.

Understanding these potential contributors to TDRS can then aid in adapting the screening process, by considering other cognitive markers, efficaciously treating and managing psychiatric symptoms influencing cognitive functioning, and determining which candidates can be considered for follow-up reassessment. Having positioned this exploratory study within the identified body of literature, the following chapter will explain the methodology employed in the research.

CHAPTER 3: METHOD

3.1 Introduction

This chapter includes a description of the sample, the research design, the data collection procedures, and the measuring instruments used. This is followed by a discussion of the data analysis methods, namely correlation analysis, regression analysis and independent sample t-tests.

3.2 Research design

This study used a quantitative research design to examine the associations between DRS-2 global cognitive functioning and performance on the DRS-2 cognitive domain subscales, levels of depression and anxiety, age, gender, and education level. Quantitative research is research that focuses on quantifying the collection and analysis of data (Creswell & Creswell, 2018). It is formed from a deductive approach, where emphasis is placed on the testing of theory, shaped by empiricist and positivist philosophies (Creswell & Creswell, 2018). The nature of this quantitative study is exploratory. Exploratory research aims to gain a better understanding of an existing problem, without necessarily providing conclusive results (Schwab & Held, 2020).

The study is a secondary retrospective review of collected clinical data. Retrospective research is defined as the analysis of existing information that was collected for non-research purposes, and it is a favoured technique in epidemiological studies, quality assessment investigations, residency training, and clinical research (Ranganathan & Aggarwal, 2018; Rastogi, 2019). The advantages of employing a retrospective review methodology are that it is less resource- and time-intensive than prospective, controlled trials; one has access to a large amount of quality data; there is increased objectivity, due to the data being collected separately from the research hypotheses and assumptions; one can examine the

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consequences of a phenomenon once they have had time to appear; and one can test hypotheses that may have been formulated before examining the data (Camm & Fox, 2018).

Hess (2004) recommends the use of retrospective reviews in exploratory research to prepare the ground for a prospective study by clarifying and focusing areas of interest and feasibility considerations. However, there are drawbacks to using this methodology. These include unrecoverable or incomplete data, which may affect formulation of the complete clinical picture; ambiguous information contained in reports, which may decrease the validity of the study; lack of a control group or premorbid data, which would allow the inference of causality; and lack of control over the quality of information that was recorded (Camm & Fox, 2018). The researcher, during the interpretive process and when generalising the findings, took cognisance of the limitations and the advantages of retrospective research, as outlined in the preceding paragraphs.

This study aimed to explore the contributing factors to DRS-2 global cognitive estimation. The DRS-2 global cognitive functioning score is frequently used in prescreening processes at international and South African movement disorder centres, as one of the determinants of suitability for DBS candidacy determination by providing an indicator of cognitive stratification of functioning.

3.3 Measuring instruments

Specific data from the DRS-2, the BDI-II, the BAI, and the sociodemographic questionnaire were retrospectively reviewed and analysed.

3.3.1 *The Dementia Rating Scale-2*

The Dementia Rating Scale-2 is used to measure cognition in older adults (Strutt et al., 2012). Five subscales provide additional information on specific cognitive abilities: ATT, I/P, CONST, CONCEPT, and MEM (Lopez & Ziemnik, 2017). The Attention subscale consists of three subdomains that contribute to the subscale score. These subdomains measure working

memory and the ability to attend to and execute verbal and visual commands of varied complexity (Jurica et al., 2001). The Initiation/Perseveration subscale consists of two subdomains, which assess verbal generative fluency, auditory articulation of vowel and consonant patterns, double alternating motor movements, and simple graphomotor skills (Lopez & Ziemnik, 2017). The Construction subscale measures the ability to copy simple visual designs, and basic writing skills. The Conceptualisation subscale assesses abstract concept formation skills and the ability to identify similarities and differences between sets of objects presented both visually and verbally. The Memory subscale measures orientation (to time, day, date, and situation), recall of verbal information after a brief delay, and verbal and visual forced-choice recognition memory (Strutt et al., 2012). This subscale has two subdomains that contribute to the subscale score.

Within each subscale, the most difficult tasks are presented first (Jurica et al., 2001). If the first one or two tasks in a subscale are performed well, subsequent tasks in the subscale are credited with correct performance and the examiner proceeds to the next subscale, a procedure that significantly shortens the total testing time (Jurica et al., 2001). Age-corrected normative tables are provided for all DRS-2 subscales, and age- and education-corrected normative data are provided for the TDRS (Jurica et al., 2001).

According to Skorvanek et al. (2017), the DRS-2 has good internal consistency (a Cronbach's alpha of 0.82), good item-total correlation for most items, and excellent test–retest reliability (0.97), with subscales having correlations of 0.61 to 0.94 with the Total Score (the lowest correlation is for the ATT subscale). The scale shows good criterion validity in distinguishing people with AD and PDD from those with MCI or healthy controls (Matteau et al., 2011). The Dementia Rating Scale-2 shows good convergent and divergent validity when compared with the Wechsler Adult Intelligence Scale, the MMSE, the Wechsler Memory Scale, the Auditory Verbal Learning Test, and Verbal Fluency; and good predictive validity for increased mortality risk in patients with and without dementia (Schmidt et al., 2006; Skorvanek et al., 2017). The DRS-2 has been found to be sensitive to change in time and after treatment

with rivastigmine in PD populations. In non-PD populations, the DRS-2 shows better sensitivity to change compared with the MMSE. Different cut-off scores have been published. Cut-off scores of 132/144 points for PDD and 139/144 and 140/144 points for PD-MCI have been suggested (Villeneuve et al., 2011).

The Dementia Rating Scale-2 has also previously been used in South Africa on older adults with HIV (Cassimjee & Motswai, 2016), which highlighted the limitations of using established neuropsychological test norms to determine neuropsychological impairment in the South African context.

3.3.2 *The Beck Depression Inventory-II*

The Beck Depression Inventory is a 21-question multiple-choice self-report inventory, and it is one of the most commonly used psychometric tests for assessing the severity of depression (García-Batista et al., 2018; Mahmoudi et al., 2019). Items are summed to create a total score, with higher scores indicating higher levels of depression. Since its publication, a number of studies have examined the validity and reliability of the BDI-II across different populations and countries (Wang & Gorenstein, 2013). Results have consistently shown good internal consistency and test–retest reliability of the BDI-II in community, adolescent, and adult clinical outpatients, as well as in adult clinical inpatients (Subica et al., 2014). Content validity of the BDI-II has improved following item replacements and rewording to reflect the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depressive disorders (Jackson-Koku, 2016). Mean correlation coefficients of 0.72 and 0.60 have been found between clinical ratings of depression and the BDI-II for psychiatric and non-psychiatric populations, respectively (Jackson-Koku, 2016). Construct validity is high for the medical symptoms measured by the questionnaire, where α is 0.92 for psychiatric outpatients and 0.93 for college students (Beck & Steer, 1987). High concurrent validities have been demonstrated between the questionnaire and other measures of depression, such as the Minnesota Multiphasic Personality Inventory-D (r = .77) (Beck & Steer, 1988). The Beck Depression Inventory shows good criterion-based validity, through the sensitive and specific way it detects

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depression, and it is known to accurately distinguish depressed and non-depressed subjects (Contreras-Valdez et al., 2015). Criterion validity of the BDI-II is also positively correlated with the Hamilton Depression Rating Scale (r = .71), with a high one-week test–retest reliability (r = .93), which suggests robustness against daily variations in mood, and an internal consistency of α = 91 (Beck et al., 1996).

The BDI-II has been translated into various languages and has been applied in numerous countries. According to a comprehensive review of the psychometric properties of the BDI-II using 118 studies conducted with 60,126 participants worldwide from 1996 to 2013, the BDI-II can be regarded as a cost-effective tool to measure the severity of depression, which is widely applicable for both research and clinical settings worldwide (Wang & Gorenstein, 2013).

In addition, although the BDI-II was originally developed and validated as a depression severity measure, it has also been used as a screening tool (Park et al., 2019). The measure's high sensitivity (85%) and specificity (88%) makes it a suitable instrument for screening, given the optimal cut-off scores (Kjaergaard et al., 2014). With improved structural, content, and concurrent validity, the BDI-II is regarded as a sound psychometric instrument, with extensive applicability for research and scientific practices, globally (Jackson-Koku, 2016).

Makhubela and Mashegoane (2016), and more recently Rousseau et al. (2020), reported that the BDI-II is a reliable and valid measure that can be used to assess the severity of depressive symptoms over time among low and middle class South African university students. Johnston (2013) conducted a study investigating the BDI-II, and its South African version, the Xhosa Beck Depression Inventory-II (XBDI-II). The author found that the BDI-II and the XBDI-II are useful diagnostic tools in a clinical setting, which provides a preliminary screening for depressive nosology. Although there are some issues with items, factorial validity, and sample sizes, the general experience and convergence of evidence found indicates that these problems will ultimately be contained to a point, but never fully, as these factors are reliant on constructs and cultural expression of nosology (Johnston, 2013). Some

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factors will hold strong, due to medical evidence of somatic symptoms, for instance, thus taking them into account is important but not an overriding factor (Makhubela & Mashegoane, 2016).

3.3.3 The Beck Anxiety Inventory

The Beck Anxiety Inventory is a self-report 21-item inventory that is used for measuring the severity of anxiety in individuals 17 years and older (Toledano-Toledano et al., 2020). According to the meta-analysis of the BAI, the measure was reported to manifest an excellent internal consistency in clinical (0.91) and non-clinical (0.91) samples and a good test–retest reliability in clinical (0.66) and non-clinical (0.65) samples (Bardhoshi et al., 2016). Each item allows the patient four choices, from "no symptom" to "severe symptom" (Oh et al., 2018). For each item, the patient is asked to report how they have felt during the past week (Lee et al., 2016).

The Beck Anxiety Inventory has been found to discriminate well between anxious and non-anxious diagnostic groups, and, as a result, it is useful as a screening measure for anxiety (Toledano-Toledano et al., 2020). According to Pang et al. (2019), the BAI demonstrates good psychometric quality. More specifically, compared to other anxiety measures, such as the Self-Rating Anxiety Scale (SAS) and the State Anxiety Inventory (S-AI), the BAI provides more information with regard to degrees of anxiety (Pang et al., 2019). Compared with the other two measures, the BAI assesses anxiety within a broader range of severity, with greater precision, so it is suitable to be used in situations where high levels of anxiety symptoms tend to occur, for example, experimental research and clinical diagnosis (Lee et al., 2016). The Beck Anxiety Inventory's brevity and simplicity make it an ideal instrument for use as a pretest for presence of anxiety disorder, which is consistent with the scientific literature (Quintão et al., 2013). The instrument shows high discriminant and convergent validity, as well as sound internal consistency across clinical and non-clinical samples, with an alpha of .94 and a Pearson test–retest correlation of .75 (Bardhoshi et al., 2016). The ease of administration and interpretation

adds to the BAI's utility for practitioners wanting to discriminate between anxiety and depression (Beck & Steer, 1990; Kabacoff et al., 1997; Oh et al., 2018).

The Beck Anxiety Inventory has also been used in South African studies. Kagee et al. (2015), for example, administered the BAI to 101 South African adults receiving HIV treatment. The results indicated that a single score may be used to indicate the overall level of anxiety of individuals receiving HIV treatment in South Africa. McGowan and Kagee (2013) similarly used the BAI, among other instruments, to investigate lifetime exposure to traumatic events and symptoms of post-traumatic stress disorder, depression, and anxiety among 1,337 students at a large residential university in South Africa. The authors had similar findings to those of other South African trauma-related studies, as well as findings from other countries, and they found the BAI to be a reliable and valid measure of overall level of anxiety. The authors further indicated that the BAI is psychometrically sound, with internal consistency as measured by the Cronbach's alpha ranging from .92 to .94 for adults and test–retest (one-week interval) reliability at .75. Concurrent validity has been established with the Hamilton Anxiety Rating Scale Revised (McGowan & Kagee, 2013).

3.3.4 Sociodemographic questionnaire

Variables such as age, gender, and education level were retrospectively reviewed and analysed.

3.4 Data collection

Neuropsychological screening protocols were collected as part of the thorough DBS screening process at a movement disorder centre in Gauteng. A secondary retrospective review was conducted on abstracted coded data collected between 2015 and 2019 specific to PD participants and the DRS-2, the BDI-II, the BAI, and sociodemographic variables. The data of 144 participants were reviewed and analysed after excluding protocols with incomplete data participants with atypical Parkinsonism. All participants were over the age of 55 years, and

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they included males and females. The participants were all medication "ON" when they were tested. Assessments were conducted in English and participants indicated proficiency in English as first or second language.

3.5 Data analysis

The data was screened for accuracy, outliers, missing values and normality. Statistical analysis was conducted when the researcher was satisfied that all assumptions underlying the appropriate use of analysis technique have been met. A 95% confidence interval was set, and Cohen's d was used as the measure of effect size for t-tests. Gender was coded as 'male' and 'female'. Due to the small sample size and clinical cohort, generalisability of the results should be applied with caution. An item analysis/reliability coefficients were not included due to the small sample size and the range of data. The data in this study were analysed using descriptive statistics, Pearson correlations, t-tests, and stepwise regression analysis. Pearson's correlation coefficient is a test statistic that measures the statistical relationship, or association, between two continuous variables (Schober et al., 2018). It is known as the best method of measuring the association between variables of interest, because it is based on the method of covariance (Schober et al., 2018). It gives information about the magnitude of the association, or correlation, as well as the direction of the relationship. A t-test is a type of inferential statistic used to determine if there is a significant difference between the means of two groups which may be related in certain features (Kim, 2015). Regression analysis is a set of statistical processes for estimating the relationships between a dependent variable (often called the "outcome variable") and one or more independent variables (often called "predictors", "covariates", or "features") (Sarstedt & Mooi, 2014).

For the purposes of this study, the TDRS score is the dependent variable, whereas anxiety, depression, age, gender, education level, and the other cognitive domain subscale scores (ATT, I/P, CONST, CONCEPT, and MEM) are the independent variables. Descriptive statistics reporting means, standard deviations, and ranges were calculated for the DRS-2,

the BDI-II, and the BAI, followed by a correlational analysis that was used to identify the significant correlates of the TDRS. Regression analysis was then conducted to explore the significant predictors of Total Scores. This allowed for determination of domain-specific cognitive and psychiatric predictors of global cognitive functioning in this PD cohort. Understanding these contributors to performance is an important aspect of the screening process, because the TDRS is frequently used as one of the primary cognitive markers of DBS candidacy determination, and the domain-specific subscales are known to be disproportionately influenced by medication on/off states and psychiatric status (Skorvanek et al., 2017).

3.6 Ethical process

The extracted data used in this study had no personal identifiers, as they were anonymised with codes, and they were confidential, in keeping with the guidelines for retrospective reviews and informed consent (Vassar & Holzmann, 2013). Ethical approval for the original retrospective review was granted on 2 June 2015 (Reference: 13349122) by the Faculty of Humanities Postgraduate Research Ethics Committee, and approval for the current review was granted on the 27th of August 2020 (Reference: HUM040/0720). Data will be stored in the Department of Psychology (HSB 11-24) and in password-protected digital files for 15 years, as per University of Pretoria policy.

3.7 Conclusion

The current research is a retrospective review of abstracted coded data specific to PD participants and scores on the DRS-2, the BDI-II, the BAI, and sociodemographic variables. The data in this study were analysed using Pearson correlations, t-tests, and regression analysis. The results of the analysis are presented in the following chapter.

CHAPTER 4: RESULTS

4.1 Introduction

In this chapter, the findings of the statistical analysis will be reported. The chapter will provide a detailed description of the participants of the study. The descriptive data from the different measuring instruments will also be reported on. Correlational analysis will highlight the bivariate relationship between the independent variables (depression, anxiety, and DRS-2 cognitive subscales) and the dependent variable (TDRS score), whereas multiple regression will provide a predictive model that takes into account the influence of all variables in predicting the relationship between the independent variables and the dependent variable.

4.2 Descriptive characteristics

Table 4.1 summarises the descriptive characteristics of the participants according to gender. Data from a total of 144 participants were reviewed. Of the participants, 59 were female, with a mean age of 65.81 years ($SD = 6.11$), and 85 were male, with a mean age of 65.67 years ($SD = 6.21$). All the participants fell within the age range of 56–78 years. The mean age of all participants was 65.73 years ($SD = 6.15$). The participants' level of education ranged from 8 to 23 years, with a mean of 13.57 years. The average level of education was 12.75 years ($SD = 1.83$) for females and 14.14 years ($SD = 2.78$) for males. The participants' illness duration ranged from 1 to 20 years, with an average of 9.02 years ($SD = 4.46$). The average illness duration for female participants was 8.92 years ($SD = 3.68$), and for males it was 9.09 years ($SD = 4.85$). The Dementia Rating Scale-2 Total Score ranged from 120 to 144 ($M = 137.35$, $SD = 4.36$). The average TDRS score for females was 138.29 ($SD = 4$), and for males it was 136.71 ($SD = 4.5$).

Table 4.1

Sociodemographic and clinical characteristics

		N	Mean	SD	Range
Age		144	65.73	6.15	56-78
	Female	59	65.81	6.11	
	Male	85	65.67	6.21	
Education		144	13.57	2.56	8-23
	Female	59	12.75	1.83	
	Male	85	14.14	2.78	
Illness duration		144	9.02	4.46	1-20
	Female	59	8.92	3.86	
	Male	85	9.09	4.85	

4.2.1 Participant descriptive statistics for assessment measures

Table 4.2 below provides a summary of the descriptive statistics for each of the assessment measures. The Dementia Rating Scale-2 (DRS-2) total score, subscale scores and task scores, the BDI-II, and the BAI were completed by 144 participants. The table below shows the means, the standard deviations, and the ranges of scores obtained by the participants on the DRS-2. For the purposes of this small data set the range of the scores are reported in Table 4.2.

Table 4.2

Descriptive statistics for the DRS-2

DRS-2	N	Mean	SD	Range
TDRS	144	137.35	4.36	120-144
ATT1	144	17.03	.69	15-18
ATT2	144	10.71	.53	9-11
ATT3	144	7.95	.22	7-8
ATT Total	144	35.72	.84	34-37
I/P1	144	27.70	3.09	16-30
I/P2	144	6.80	.51	4-7
I/P Total	144	34.51	3.11	23-37
CONST Total	144	5.77	.53	4-6
CONCEPT Total	144	37.82	1.36	32-39
MEM1	144	14.58	1.83	1-16
MEM2	144	8.77	.47	7-9
MEM Total	144	23.44	1.51	15-25

*TDRS: Total Dementia Rating Scale-2 score; ATT: Total Attention subscale; ATT1: Attention task 1; ATT2: Attention task 2; ATT3: Attention task 3; I/P: Total Initiation/perseveration subscale; I/P1: Initiation/perseveration task 1; I/P2: Initiation/perseveration task 2; CONST: Total Construction subscale; CONCEPT: Total Conceptualisation subscale; MEM: Total Memory subscale; MEM1: Memory task 1; MEM2: Memory task 2
*$p \leq .05$; **$p \leq .001$

In Table 4.3 below, participants' self-reported psychiatric profiles (mood and anxiety symptoms) are summarised.

Table 4.3

Descriptive statistics for the BDI-II and the BAI

		N	Mean	SD	Range
BDI-II Total		142	13.43	9.15	0-49
	Female	59	12.20	9.03	
	Male	83	14.30	9.18	
BAI Total		142	14.82	9.44	1-41
	Female	59	14.90	9.76	
	Male	83	14.76	9.26	

*BDI-II Total: Beck Depression Inventory II Total ; BAI Total: Beck Anxiety Inventory

Based on the observation of means for males ($M = 14.30$) and females ($M = 12.20$), it appears that males endorsed more depressive symptoms than females. When looking at the BAI means, however, females ($M = 14.90$) endorsed slightly more anxiety symptoms than males ($M = 14.76$). According to the classification in general (Beck et al., 1996), the sample endorsed depressive and anxiety symptoms that placed them in the "mild" category.

4.3 Independent samples t-test

Independent samples T-tests were used to determine gender differences in TDRS performance, age and education level. Males had a significantly higher education level than females ($t(3.66) = 129.55$, $p < .001$), and they showed higher global performance on the DRS-2 ($t(−2.11) = 115.552$, $p = .037$). " The effects sizes were small (d <.03). No significant age difference was found between male and female participants. Mean differences for age = .503, education level = 1.48 and TDRS = -1.62.

4.4 Correlational analysis

4.4.1 Correlations between sociodemographic characteristics, DRS-2 scores, and psychiatric correlates

Following a visual analysis of the scatterplots and the skewness/kurtosis range, it was extrapolated that the distribution of scores falls within range for the use of a Pearson's correlational analysis. With regard to sociodemographic characteristics, education in years and TDRS were found to be significantly correlated ($r(142) = .19$, $p = .02$). In addition, education in years correlated significantly with I/P Total ($r(142) = .18$, $p = .03$). Within the I/P subscale, education was found to have the highest correlation with the I/P1 subscale ($r(142) = .18$, $p = .03$) when compared with the other subscales. This subscale includes the verbal fluency task. Education in years and MEM Total also showed a significant association ($r(142) = -.18$, $p = .03$). Age was also found to correlate significantly with I/P Total ($r(142) = -.17$, $p = .01$), and in particular with the I/P1 subscale ($r(142) = .18$, $p = .04$).

Psychiatric characteristics correlated significantly with the TDRS, with higher reported depression symptoms correlating with lower TDRS scores ($r(142) = -.32$, $p < .001$), followed by a significant correlation between I/P Total and BDI-II Total ($r(142) = -.24$, $p = .004$). Within I/P, the I/P1 subscale showed the highest correlation with the BDI-II ($r(142) = .23$, $p = .01$) followed by MEM Total ($r(142) = -.19$, $p = .02$) and CONST subscale ($r(142) = -.21$, $p = .01$). In addition, a strong correlation was found between the BDI-II and the BAI ($r(142) = .4$, $p < .001$). Age correlated significantly with duration of illness ($r(142) = .22$, $p = .01$) and with the BAI ($r(142) = -.21$, $p = .01$).

4.4.2 Correlations between the DRS-2 Total Scores and the DRS-2 cognitive subscale scores

All DRS-2 subscales correlated significantly with the TDRS score (see Table 4.4). The I/P subscale scores were more highly correlated with TDRS ($r(142) = .76$, $p < .001$) than the other cognitive subscales. Within I/P, the I/P1 subscale showed the highest correlation with TDRS ($r(142) = .76$, $p < .001$), followed by the I/P2 subscale ($r(142) = .31$, $p < .001$). MEM Total ($r(142) = .66$, $p < .001$) and the MEM1 subscale ($r(142) = .46$, $p < .001$) were found to have the second-highest correlations with TDRS, followed by CONST ($r(142) = .41$, $p < .001$) and CONCEPT ($r(142) = .35$, $p < .001$). The ATT subscales showed the lowest correlation with TDRS ($r(142) = .2$, $p = .02$). The correlations between the DRS-2 subscales and the subscale tasks are shown in Table 4.4.

Table 4.4

Correlations between TDRS score, subscales, and subscale tasks

DRS-2	TDRS	ATT	ATT1	ATT2	ATT3	I/P	I/P1	I/P2	CONS	CONC	MEM	MEM1	MEM2
ATT	.20*												
ATT1	.20*	.74**											
ATT2	.02	.52**	−.11										
ATT3	.28**	.35**	.20*	.06									
I/P	.80**	−.03	.02	−.10	.14								
I/P1	.76**	−.04	.02	−.01	.12	.98**							
I/P2	.31**	.09	.10	−.06	.17*	.26**	.01						
CONST	.41**	−.01	.12	−.09	.16	.21*	.19*	.11					
CONCEPT	.35**	.08	.05	.033	.18*	−.01	−.036	.11	.127				
MEM	.66**	.07	.12	−.029	.13	.36**	.34**	.15	.29**	.02			
MEM1	.46**	.01	.07	−.076	.06	.28**	.25**	.19*	.184*	−.07	.75**		
MEM2	.13	.14	.11	.124	.24**	−.07	−.077	.01	.07	.09	.32**	.00	

*TDRS: Total Dementia Rating Scale-2 score; ATT: Total Attention subscale; ATT1: Attention task 1; ATT2: Attention task 2; ATT3: Attention task 3; I/P: Total Initiation/perseveration subscale; I/P1: Initiation/perseveration task 1; I/P2: Initiation/perseveration task 2; CONST: Total Construction subscale; CONCEPT: Total Conceptualisation subscale; MEM: Total Memory subscale; MEM1: Memory task 1; MEM2: Memory task 2
*$p \leq .05$; **$p \leq .001$

4.5 Regression analysis

Multiple regression analysis was used to explore which variables were significant predictors of TDRS. This allowed for determination of sociodemographic/clinical, domain-specific cognitive, and psychiatric predictors (depression and anxiety) of global cognitive functioning on the DRS-2 in this PD cohort.

Prior to the analysis, model validity assumptions such as multicollinearity and outliers were determined using case diagnostics, standardised residual estimates, the Mahalanobis distance, Cook's distance, and average leverage estimates (Thrane, 2020). Observation of the bivariate correlations between the independent variables, the tolerance statistics, and the VIF estimates indicated that the assumptions of multicollinearity had not been violated. One case/respondent outlier was identified with a Cook's distance of >1 and a standardised residual estimate of >2. However, removing this case from the analysis did not change the output, and the case was retained in the analysis. Table 4.5 summarises the results of the multiple regression analysis.

Table 4.5

Multiple regression analysis

	Variable	B	SE B	B	T	*R2*	Δ*R2*
Model 1						.64	.64**
	Constant	98.716**	2.461		40.113		
	I/P Total	1.119**	.071	.800**	15.752		
Model 2						.80	.79**
	Constant	77.566**	2.774		27.965		
	I/P Total	.899**	.058	.643**	15.554		
	MEM Total	1.226**	.119	.425**	10.284		
Model 3						.92	.92**
	Constant	34.972**	3.392		10.309		
	I/P Total	.913**	.036	.653**	25.139		
	MEM Total	1.198**	.075	.415**	15.997		
	CONCEPT Total	1.131**	.077	.353**	14.634		
Model 4						.95	.95**
	Constant	6.104	4.394		1.389		
	I/P Total	.930**	.030	664**	31.370		
	MEM Total	1.152**	.061	.399**	18.825		
	CONCEPT Total	1.092**	.063	.341**	17.325		
	ATT Total	.864**	.102	.167**	8.446		
Model 5						.96	.96**
	Constant	4.034	3.741		1.078		
	I/P Total	.907**	.025	.648**	35.767		
	MEM Total	1.062**	.053	.368**	19.893		
	CONCEPT Total	1.040**	.054	.325**	19.26		
	ATT Total	.884**	.087	.171**	10.18		
	CONST Total	1.078**	.147	.130**	7.35		
Model 6						.96	.96**
	Constant	5.66	3.78		1.50		
	I/P Total	.897**	.025	.641**	35.27		
	MEM Total	1.054**	.053	.365**	19.93		
	CONCEPT Total	1.033**	.053	.323**	19.31		
	ATT Total	.873**	.086	.169**	10.16		
	CONST Total	1.036**	.146	.125**	7.08		
	BDI-II Total	−.017*	.008	−.036*	−2.06		

Dependent variable: DRS Total (TDRS)

*p ≤ .05; **p ≤ .001

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Following an iterative construction of the regression model, sociodemographic/clinical variables and anxiety were removed as potential explanatory variables after testing for statistical significance after each iteration. The final regression model, model 6, includes all explanatory independent variables, and the overall model was a significant predictor of the TDRS global estimate ($F(6, 135) = 434.34$, $p < .001$).

The six independent variables in model 6 account for 96% of the variance in the dependent variable. It is expected that the domain-specific cognitive subscales will account for high variance in the TDRS global estimate. The primary aim of this study was to explore which subscales and subscale tasks are the strongest predictors of TDRS score variance when including psychiatric and sociodemographic variables and disease duration. The independent variables identified in model 6 as predictors are I/P Total, MEM Total, CONCEPT Total, ATT Total, CONST Total, and BDI-II Total. All the independent variables are significant predictors, at $p < .001$, and the BDI-II is also a significant predictor, at $p = -.04$. The regression model further shows that I/P Total is the optimal predictor of TDRS global cognitive functioning, explaining 64% of the variance, followed by MEM Total (37% of the variance), CONCEPT Total (32% of the variance), ATT Total (17% of the variance), CONST Total (13% of the variance), and, lastly, BDI-II Total (4% of the variance). All the independent variables have positive Beta coefficients, except for BDI-II Total, which indicates that an increase in scores on the cognitive subscales will increase the TDRS score, while a unit change in the BDI-II total score will decrease the TDRS score.

4.6 Summary of results

This chapter presented information on the participants of this study and descriptive data from the different measuring instruments. Correlational analysis was used to focus on the relationship between depression, anxiety, and the DRS-2 subscales and the DRS-2 global estimate. Regression analysis provided a predictive model that considered the cognitive domain specific, psychiatric and sociodemographic correlates of TDRS estimates. The

following chapter provides a detailed discussion of these results in relation to the literature. Chapter 5 concludes with a bried discussion of the limitations of the study, recommendations for future research, and the practical implications of the findings.

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 Introduction

The aim of this exploratory study was to investigate the contributing factors and the significant predictors of DRS-2 global cognitive functioning in a cohort of patients with PD presenting for DBS cognitive screening. The results from the correlational analysis and the regression analysis will be discussed in the context of literature relevant to the study. The chapter closes with a summary, an explanation of the limitations of the study, recommendations for future research, and a conclusion.

5.2 Sociodemographic characteristics, performance on the DRS-2, and clinical indicators

Patients with higher levels of education obtained higher TDRS scores. These results confirm the findings reported in the literature (de Freitas & Curinga, 2015; Erdődi et al., 2020; Franco-Marina et al., 2010; Strutt et al., 2012; Then et al., 2016). The relationship between level of education and performance on cognitive assessments has been widely recognised in studies conducted in a number of countries (Bezdicek et al., 2015; Cassimjee & Motswai, 2017; de Freitas & Curinga, 2015; Franco-Marina et al., 2010). Education influences brain development, and it therefore serves as a likely protective factor against cognitive impairment, as cognitive reserve has been associated with years of formal education (Erdődi et al., 2020; Then et al., 2016). In a study comparing the MMSE and the DRS-2 in a sample of 113 highly educated older adults, the findings suggested that higher cut-offs may be warranted, and perhaps necessary, in examinees with high educational achievement (Erdődi et al., 2020). Bezdicek et al. (2015) tried to determine the validity of the Czech version of the Mattis Dementia Rating Scale 2 (czDRS-2) in screening for PD-MCI. The authors examined the effects of age, education, and gender on czDRS-2 and similarly found a statistically significant relationship between the czDRS-2 total score and education. Similar to Erdődi et al.'s (2020) findings,

Then et al. (2016) found that individuals with post-secondary education performed considerably better on the DRS-2 than those with only a high school diploma.

Cassimjee and Motswai (2016) investigated the differences in neuropsychological functioning between a group of HIV-positive adults and older adults, and an HIV-negative matched control group. The authors indicated a significant positive correlation between TDRS scores and years of education. The results suggest that cognitive reserve may explain why individuals who have higher levels of education often score within normal range on cognitive screening tests despite reporting subjective cognitive decline (Elkana et al., 2016; Guerra-Carrillo et al., 2017). Both this study cohort (education M = 13.57) and Cassimjee and Motswai's study cohort (education M = 11.53) represent participants with at least a secondary level of education, although, due to social, political, and economic inequalities in higher education, the quality of education between these cohorts may differ. Therefore, although similar to international norms, in that a positive correlation is indicated between TDRS scores and years of education, both this study and Cassimjee and Motswai's (2016) study showed a decline in cognitive performance with decreasing education levels, and caution should therefore be applied when using cut-off score determinants to categorise severity of impairment based on norms outside the South African context (Cassimjee & Motswai, 2016). Given the diversity that exists in the sociodemographic profile of the country, further research is warranted on groups with diverse education levels and language backgrounds. This is of particular interest considering that older adults presenting for testing have a generational history of diverse quality of education. This is an important factor when screening for DBS if TDRS estimates are included in the protocol for candidacy determination.

In this study, patients with higher levels of education showed better performance in executive functioning aspects, such as initiation and fluency, than patients who had less years of education. More specifically, on the DRS-2 fluency task, patients with higher levels of education showed better verbal fluency than patients who had less years of education.

Additionally, the current study's patients with PD, who had higher levels of education, also showed better performance on the MEM subscale than patients with less years of education. Education, a popular proxy for cognitive reserve, has been shown to have protective effects, which delay the onset of clinical symptoms, including memory decline (Lee et al., 2018). Zahodne et al. (2019) evaluated how education affects a well-studied pathway that occurs during ageing: white matter hyperintensities. The authors' findings indicated that education does, in fact, affect the relationship between white matter hyperintensity volume and memory scores. More specifically, the memory scores of individuals with higher educational attainment were less affected by increases in white matter hyperintensity volume than those with less education (Zahodne et al., 2019).

In this study, older participants showed poorer performance on executive aspects, such as initiation and fluency, particularly verbal fluency, than younger patients. Aziz et al. (2017) focused on establishing the effects of age, gender, and education on cognitive functioning in a community sample. Moreover, the authors found that age had a significant association with category fluency, while education significantly influenced both letter and category fluency. No significant associations were found between gender and fluency tasks. Similarly, in the current study no gender differences were found in performance on fluency tasks. Brabo et al. (2014) explored the frequency of occurrence of dysfluencies in individuals with PD who had a mean age of 62.3 years. They found that the higher the age, the greater the number of atypical dysfluencies. The authors further suggested that ageing is associated with increased hesitations and pauses in speech, with interjection tending to be the most common typical dysfluency.

Parkinson's disease is a neurodegenerative disorder, which leads to progressive deterioration of motor function due to loss of dopamine-producing brain cells (Bilgic et al., 2012). Hence, PD symptoms usually begin gradually and get worse over time (Goldberg et al., 2012). Reeve et al. (2014) conducted a study of over 750 elderly individuals (mean age 88.5 years) without clinically defined PD, and they found that nearly one-third of

them showed mild to severe neuronal loss within the substantia nigra, with 10% also showing Lewy body pathology. Cell loss within the substantia nigra was shown to be extensive and was estimated to occur at a rate of 9.8% per decade (Reeve et al., 2014). The authors therefore concluded that age-related decline leads to loss of neurons in this disease, hence advancing age led to substantia nigra neuronal loss and PD in some individuals (Reeve et al., 2014). Confirming Reeve et al.'s (2014) findings, this study found that older PD patients with longer disease duration are likely to present with poorer cognitive outcomes.

5.3 Psychiatric correlates and performance on the DRS-2

Participant psychiatric characteristics were found to correlate significantly with the TDRS score, with higher reported depression symptoms correlating with lower TDRS scores. Psychiatric correlates such as anxiety and depression are prevalent non-motor symptoms in PD, even in early stages, and can affect cognitive functioning (Khatri et al., 2020; Lee et al., 2018; Marsh, 2013). Reynolds et al. (2017) examined self-reported anxiety and neurocognitive function indexed by measures of executive function, categorical fluency, and attention/working memory. The Beck Anxiety Inventory and cognitive tests were administered to 77 non-demented adults with mild to moderate idiopathic PD (mean age 62.9 years). The findings indicated that higher anxiety was associated with more advanced disease stage and severity and with poorer set-shifting when using a derived metric to account for motoric slowing (Reynolds et al., 2017). Furthermore,although depression correlated with greater anxiety and disease severity, contrary to the findings of the current study, no significant correlation was found between depression and cognitive performance (Reynolds et al., 2017).

In this study, patients with PD who self-reported higher depression severity showed poorer performance on executive aspects, such as initiation and fluency, than patients who self-reported lower depression severity. Research has indicated an association between depression and fluency (Pantzar et al., 2014). Gallagher et al. (2016) studied the relationship between depressive symptoms and cognitive decline in later life. Over 7,000 community-

dwelling older adults (age ≥ 50) from the English Longitudinal Study of Ageing (ELSA) underwent clinical assessment. The authors found that depressive symptoms significantly predicted age-adjusted decline in delayed recall and verbal fluency.

Obeso et al. (2012), assessed semantic and phonemic fluency in a large sample of PD patients, to investigate the effect of clinical and sociodemographic variables on verbal fluency in the patient group. Three-hundred patients with idiopathic PD, who were consecutive referrals to the clinic, and 50 age- and education-matched healthy controls, completed the phonemic and the semantic verbal fluency tasks. The authors found that both phonemic and semantic verbal fluency were significantly impaired in the PD patients relative to the matched controls. More significantly, similar to the findings of this study, presence of depression, lower education level, and older age influenced verbal fluency measures. Regression analyses established that global measures of cognitive ability, executive function, and side of onset of motor symptoms predicted 36%–37% of the variance in phonemic and semantic verbal fluency measures (Obeso et al., 2012).

In this study, patients with PD who self-reported higher depression severity showed poorer performance on motor tasks, such as on the CONST subscale. The Construction subscale measures fine motor movement and visuo-constructional elements. Ribeiro et al. (2020) studied the executive functioning, functionality, and quality of life of institutionalised old-aged persons, to determine the potential roles of self-reported depression and satisfaction with social support on these domains. The sample comprised 36 participants (13 males and 23 females) aged between 71 and 94 years. The measures consisted of a well-established battery of neuropsychological tests, and a comparative study was performed. The authors found that participants with depressive symptoms showed impaired executive functioning. More specifically, participants with higher levels of depression struggled with cognitive flexibility, functionality in instrumental activities of daily living, and quality of life (Ribeiro et al., 2020). Similarly, in this study, PD patients with higher depression rates performed poorer on the CONST subscale. This could possibly be due to the association between depression and

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poor executive functioning, and this may partially explain why PD patients struggle with visuo-constructional tasks that require planning, cognitive flexibility, and logical sequencing (Ribeiro et al., 2020).

Participants of the current study who self-reported higher depression severity showed poorer performance on the MEM subscale than patients who self-reported lower depression severity. Patients with depression may demonstrate significantly poorer cognitive performance, particularly impaired memory (Malak et al., 2017; Yang et al., 2015), on measures such as the DRS-2, compared to their non-depressive counterparts (Lee et al., 2018). It has been suggested that this sub-threshold late-life depression may be just as disabling and detrimental to the well-being of an elderly individual as major depressive disorder (Lee et al., 2018).

Malak et al. (2017) investigated the most frequent depressive symptoms and their association with cognition in PD patients with MCI. The sample included 48 PD-MCI patients, none of whom were diagnosed with depression, and 44 controls (CG), aged between 50 and 80 years and with at least 4 years of formal education. Participants underwent clinical evaluation followed by neuropsychological assessment, where, among other instruments, the BDI-II was employed. The results indicated that BDI-II scores correlated negatively with learning and recognition memory in both groups. Episodic memory was the cognitive function showing greatest impairment. Thus, similar to this study, Malak et al. (2017) suggested that PD patients with higher depression severity performed poorer on the MEM subscale than patients with lower depression severity.

In the current study, patients with PD who self-reported higher depression severity also self-reported higher anxiety severity. Depression and anxiety are some of the most common comorbidities arising in patients with PD (Schrag & Taddei, 2017). More specifically, PD patients presenting with depression tend to have concomitant apathy and anxiety (Ng et al., 2015).

Khedr et al. (2020) studied 64 patients with PD (mean age 71.8 years) and 50 gender- and age-matched healthy control subjects for depression and anxiety. The authors found that 31.25% of patients with PD had depression, while 40.6% of patients had anxiety disorder. Similar to this study, depression was higher in females. Overlap between depression and anxiety was recorded in 23.4% of patients. This finding confirms the results of this study, which indicates that anxiety and depression often occur comorbidly in PD.

Older PD patients in this study self-reported higher anxiety severity than younger PD patients. Anxiety has been observed as a primary non-motor symptom of PD (Yohn et al., 2017), and it has a significant impact on the quality of life, the functioning, and the mortality of specifically older adults with PD (Sagna et al., 2014). Sagna et al. (2014) conducted a systematic review to examine the factors associated with the prevalence of depression and anxiety disorders among individuals with PD aged 60 years and older. Similar to the findings of this study, the authors found that autonomic symptoms, motor fluctuations, severity and frequency of symptoms, staging of the disease, and PD onset and duration were associated with the prevalence of depression and anxiety disorders among older adults suffering from PD (Sagna et al., 2014).

5.4 Cognitive domain subscale correlates of DRS-2 global functioning

Patients in this study with PD who demonstrated better performance on the cognitive domains of attentional processing, executive aspects such as initiation, perseveration, conceptualisation and fluency, constructional ability, and memory showed higher global functioning than patients who evidenced lower performance on the DRS-2 subscales. Of these subscales, I/P scores were more highly correlated with TDRS score than the other cognitive subscales. From the two subscales that tap into executive functioning (I/P and CONCEPT), behavioural initiation, perseveration, and fluency (I/P) were the highest contributors to TDRS global estimation when compared to the other cognitive domains. Within the I/P subscale,

verbal generative fluency accounted for the highest significant contribution to global estimation of functioning on the DRS-2.

Changes in cognitive function among patients with PD have been extensively documented, and they have been defined as a "frontal"-type executive dysfunction (Brabo et al., 2014). One of the main components of this executive dysfunction is the impairment in verbal fluency (Rodrigues et al., 2015). Obeso et al. (2012) assessed semantic and phonemic fluency in a large sample of PD patients. The authors reported that both phonemic and semantic verbal fluency were significantly impaired in PD patients, and that global measures of cognitive ability, executive function, and side of onset of motor symptoms predicted 36%–37% of the variance in phonemic and semantic verbal fluency measures.

In a previous study by Chan et al. (2001), using a Chinese sample, differences between elderly Chinese and American participants were found for performance on a verbal fluency task. The Americans outperformed the Chinese on a subscale requiring them to generate items found in a supermarket. The results suggest that the slower retrieval of elderly Chinese may have occurred because they are less familiar with the supermarket than their American counterparts. Overall, the findings indicate that some DRS subscales may be susceptible to cultural and language differences (Chan et al., 2001). In another study, Spanish speakers scored significantly lower than education-, age-, and gender-matched English speakers on the TDRS score, more specifically on the ATT, CONCEPT, and MEM subscales (Lyness et al., 2006). The authors suggested that this could be explained by language features and by cultural and educational differences (Lyness et al., 2006). Indeed, although the two groups were matched for years of education, their educational experience was not necessarily comparable.

Strutt et al. (2012) found that American English-speaking subjects outperformed age- and education-matched American Spanish-speaking subjects assessed with a Spanish translation of the DRS-2. The greatest difference between the two groups was found on the MEM subscale, where most errors of Spanish-speaking participants were committed on three

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specific orientation items: current president; governor and mayor; and items significantly related to their level of acculturation. These data, combined with evidence about the impact of culture on cognition in general (Park & Huang, 2010), strongly suggest the need for culture-specific norms for an accurate estimate of cognitive performance on neuropsychological tests such as the DRS-2. In another study, Lavoie et al. (2013) aimed to establish normative data for the DRS-2 to take into account the linguistic and cultural reality of the French-speaking elderly population of Quebec. The results of their study are in line with those of previous studies conducted in other cultural communities. As mentioned above, both culture and language have an impact on cognition, and it is therefore important to use normative data that are adjusted for the population to which they are applied (Lavoie et al., 2013). While the members of the cohort of this study are all South Africans, not all the participants have English as their first language. Thus, similar to Chan et al. (2001) and Lavoie et al.'s (2013) findings, the participants' results on the I/P subscale may have been influenced by cultural factors or the fact that English is not their first language. Due to the small sample size and characteristics of the sample in this study, it was not feasible to analyse statistically the differences between language groups and cognitive functioning, particularly on verbal fluency.

Differences in performance on verbal fluency tasks have also been associated with clinical factors. In a more recent study, Sollman et al. (2016) conducted an archival analysis of medication-on DRS-2 performance in 228 PD patients undergoing DBS presurgical workup. People with frank impairment were not included. Mean age was 64.7 (8.4) years, mean education was 14.1 (2.8) years, and mean disease duration was 9.7 (5.3) years, which is parallel to the cohort of this study. The findings suggest that all DRS-2 subscales correlated significantly with the TDRS score, however I/P scores were more highly correlated than any other subscale ($r = .803$). Within I/P, 94% of the variance was accounted for by fluency. Sollman et al.'s (2016) findings support the results of the current study, which indicated that TDRS score was disproportionately affected by I/P performance ($r = .76$), which relies strongly on semantic fluency. Verbal fluency is also known to be prone to medication on-off states,

which may result in further underestimation of capability. Herrera et al.'s (2012) study aimed to determine the effect of dopamine on the performance of PD patients' on verbal fluency tasks, focused on action-word fluency. A cohort of 20 PD patients and 20 controls were assessed using four different verbal fluency tasks: semantic (supermarket and animal words), phonological, and action fluency. PD patients were tested twice (on/off medication) and controls were tested only once. The results indicated that for the number of words, there were substantial differences between PD patients on and off medication in the phonological and action fluency tasks. More specifically, compared to controls, PD off medication produced significantly fewer words in actions and phonological. With regards to frequency, differences were found between PD patients off medication and controls for the action-word category.

In this study, MEM Total and the MEM1 subscale were found to have the second-highest correlations with TDRS score, followed by CONST Total and CONCEPT Total. ATT Total showed the lowest correlation with TDRS. The findings of this study are in line with the results of Greenaway et al. (2012) and Sollman et al.'s (2016) studies, who reported that the TDRS score significantly correlated with all subscales, however the cognitive subscales contributed differentially to TDRS in the current study with a cohort from a lower-middle income country. For example, Sollman et al. (2016) indicated that following I/P; CONST and ATT contributed significantly to the TDRS score (Sollman et al., 2016). Interestingly, the current study indicated that MEM 1 was highly correlated with TDRS and may thus reflect the language/culture aspects that Strutt el al. (2012) alluded to.

5.5 Predictors of global cognitive functioning

Following the regression analysis results showed I/P Total to be the optimal predictor of TDRS global cognitive functioning, explaining 64% of the variance, when compared to the other cognitive domain subscales. The I/P subscale consists of items that assess verbal generative fluency, auditory articulation of vowel and consonant patterns, double alternating motor movements, and simple graphomotor skills (Jurica et al., 2001). In Sollman et al.'s (2016)

archival analysis of PD patients, a sequential multiple regression model supported I/P as the optimal predictor, explaining 65% of the variance in the TDRS score, and hence is in concordance with the findings of this study. Thus, the TDRS score was disproportionately impacted by medication-on I/P performance, which relies heavily on semantic fluency. When looking at the South African context, one can argue that because I/P fluency is a significant predictor of TDRS global estimation, inclusion of other fluency tasks with normative data for the South African population may provide a more robust screening of patients.

Following I/P, MEM Total in this study accounted for 37% of the variance in TDRS. Bezdicek et al.'s (2015) study aimed to provide normative data and to determine the validity of the czDRS-2 in screening for PD-MCI. Of the czDRS-2 subscales, I/P performed best, with an AUC (area under the curve) of 79%, and, in combination with ATT and MEM, with an AUC of 74%, both have the highest discriminatory potential for PD-MCI diagnosis among the czDRS-2 subscales. Greenaway et al. (2012) indicated that the TDRS score and the MEM and I/P subscales were found to be predictive of instrumental activities of daily living (IADLs), with total scores accounting for 19% of the variance in IADL performance, on average (Greenaway et al., 2012). Thus, detecting memory impairments in PD patients screening for DBS is crucial, given the selection criteria and the invasive nature of the surgery (Pollak, 2013). More importantly, cognitive disorder/PDD is the most frequent exclusion criterion for DBS surgery, because dementia may be worsened, and patients will not derive the surgery-induced benefit of improved motor function (Pollak, 2013).

Several studies have reported that elderly patients, or those with borderline preoperative global cognitive scores, are at risk of permanent post-operative cognitive deterioration (Krack et al., 2003; Saint-Cyr et al., 2000; Vingerhoets et al., 1999) or failure of improvement in quality of life (Witt et al., 2008). Therefore, a thorough screening for cognitive deficits is mandatory. Neuropsychological evaluation with a special emphasis on memory and executive function is highly recommended (Voon et al., 2016). Several groups use the DRS-2 (range 0–144) for evaluation of overall cognitive function. It is considered an appropriate tool

in degenerative diseases involving subcortical structures, given its inclusion of tests evaluating attention and executive functions (Matteau et al., 2011). Given the invasive nature of DBS, careful and thorough consideration of several factors should be taken into account when estimating and interpreting performance on the DRS-2.

In this study CONCEPT Total explained 32% of the variance in the TDRS score. Greenaway et al. (2012) examined the utility of cognitive evaluation to predict IADLs and decisional ability in MCI. Sixty-seven individuals with single-domain amnestic MCI were administered the DRS-2 as well as the Everyday Cognition (ECog) form to assess functional ability. The authors indicated that DRS-2 CONCEPT is a key variable in decision-making ability and helps predict ability to communicate with others. Decisional ability is very important in DBS post-operative management, where patients' have to manage their long-term post-operation care in conjunction with health professionals.

Royall et al. (2007) likewise reported that the DRS-2 accounted for more than 20%, on average, of functional outcomes. In fact, DRS-2 performance explained more variance in functional ability than formal tests of attention, executive function, memory, or verbal or visuospatial function in those authors' large-scale meta-analysis. In Greenaway et al.'s (2012) study, the DRS-2 was also significantly predictive of performance on all specific IADL items examined, as well as comprehension questions related to decision-making abilities. Bambara et al. (2007) found that TDRS global functioning was significantly correlated with ability to understand and appreciate the consequences of treatment choice.

ATT Total explained 17% of the variance in TDRS in this study, which is similar to Greenaway et al.'s (2012) findings. CONST Total explained 13% of the variance in the TDRS score. The Construction subscale measures the ability to copy simple visual designs, and to sign one's own name. An optimal score of 6 can be obtained (Jurica et al., 2001). In Porto et al.'s (2007) study, the CONST subscale also showed the least amount of specificity (16.7%) when compared to the other DRS-2 subscales.

Following from the above the patients psychiatric profile indicates that BDI-II Total explains −4% of the variance in the TDRS score. Depression affects around 45% of the population of PD patients (Marsh, 2013). The pathophysiology of depression is based on the monoamine hypothesis, which states that depleted levels of serotonin, dopamine, and norepinephrine are involved in the pathophysiology of depression (Khatri et al., 2020). Malak et al. (2017) suggested that some of the depressive symptoms observed in PD patients with MCI seem to be attributable to complications of PD, while others are common to both PD and MCI, making differential diagnosis complex but crucial. Consequently, depression has been found to negatively influence DRS-2 estimation of global cognitive functioning (Khatri et al., 2020; Lee et al., 2018; Marsh, 2013).

Although depression accounts for a small variance in TDRS global functioning in this study, it is important to consider the psychiatric aspects, because of the influence of untreated depression on cognitive scores. If the DRS-2 is used as one of the criterion for DBS candidacy, then exclusion can result from untreated depression, not compromised cognition. Lastly, management/treatment of symptoms of depression can enhance patient quality of life and allow for reconsideration of DBS candidacy after symptom stability. Thus, even though the PD patients in this study have mild depression, depression was found to be a significant predictor of TDRS global functioning. It is therefore important to consider in patients with mild depressive symptoms that the TDRS score is an indication of current cognitive ability, while the neuropsychiatric profiles are an intermediate or transitional reflection of self-reported symptoms experienced over time.

5.6 Summary

The findings of the study have shown that sociodemographic (age and level of education), psychiatric (depression and anxiety), and cognitive (I/P Total, MEM Total, CONCEPT Total, ATT Total, and CONST Total) correlates are significantly associated with global cognitive performance on the DRS-2. All cognitive subscales were significant predictors of TDRS global

performance, with behavioural initiation (fluency), perseveration, and initiation accounting for the highest variance. Verbal fluency, which contributes significantly to the I/P subscale, is known to be differentially influenced by sociocultural and clinical factors, such as medication-on effects. This underlines the importance of exploratory research on DBS screening using the DRS-2 cognitive estimation for candidacy determination. Of the psychiatric correlates, depression accounted for a small percentage of the variance in TDRS performance, which suggests that even in a cohort with mild self-reported symptoms, psychiatric factors are an important consideration in cognitive estimation, and hence DBS candidacy determination when using the DRS-2 as part of the screening protocol. Several studies reported results in concordance with the results reported in this study.

For example, similar to the findings of this study, Erdődi et al. (2020), Then et al. (2016), and Cassimjee and Motswai (2016) found a statistically significant relationship between the TDRS score and education. Zahodne et al.'s (2019) findings confirmed the results of this study, namely that PD patients with higher levels of education showed better performance on memory tasks than patients with less years of education. Older patients with PD showed poorer performance on executive aspects than younger patients (Brabo et al., 2014). Gallagher et al. (2016) found that higher levels of self-reported depression were associated with declines in recall and verbal fluency.

This study found that PD patients with higher depression rates performed poorer on specific cognitive domains, such as CONST and MEM (Malak et al., 2017; Ribeiro et al., 2020), than patients with lower depression severity. It was also found that anxiety and depression occurred comorbidly in this cohort with PD (Khedr et al., 2020). Various authors have concurred that depression negatively influences DRS-2 estimation of global cognitive functioning (Khatri et al., 2020; Lee et al., 2018; Marsh, 2013). The findings of the study are consistent with those of Sollman et al. (2016), particularly on the disproportionate contribution of the I/P subscale and verbal fluency to TDRS global cognitive estimation. Thus, there are several factors that should be considered when using the DRS-2 on a local cohort for the purpose of DBS

candidacy determination. Importantly, the contribution of different cognitive subscales differ from those reported in studies on international cohorts and this should be considered when using the DRS-2 in South Africa.

5.7 Limitations of the study

- One of the limitations of this study is the use of self-report measures to measure depression and anxiety. This allows for the possibility of response bias, where participants could have exaggerated or under-reported symptoms

- The sample size was limited and specific to PD patients presenting for presurgical workup.

- The sample characteristics was limited in range and thus, caution should be applied when generalizing results to diverse groups.

- Additional cognitive measures were not included in the analysis and comparisons between DRS-2 and other fluency measures, for example, could not be carried out.

5.8 Recommendations for future studies

- Further research is warranted on local cohorts prior to establishing optimal DRS-2 cognitive estimates for determining DBS suitability.

- Recognising the importance of medication-induced effects on cognition, and neuropsychiatric contributors to TDRS profiles, allows for better management of symptoms, medication reviews, and the possibility for reassessment.

- Future research with larger samples including diverse groups of PD patients and inclusion of a control group would allow for more robust and generalizable findings.

- Future research on the DRS-2 with more robust psychometric analysis is warranted in the South African context.

- Inclusion of additional cognitive tests would allow for comparisons between DRS-2 subscales, and other potential cognitive markers. This could inform the composition of

appropriate neuropsychological assessment protocols for DBS screening in South Africa.

5.9 Conclusion

This exploratory study aimed to investigate the factors contributing to TDRS performance. More specifically, the study explored the sociodemographic, cognitive, and psychiatric correlates of TDRS global cognitive functioning in a PD cohort presenting for DBS screening. To the best of the researcher's knowledge, no South African studies have focused on the predictors of TDRS global cognitive functioning in a cohort with PD presenting for DBS screening. Furthermore, several international and South African movement disorder centres include the use of the TDRS global functioning score as one of the determinants of cognitive stratification and DBS candidacy determination. Given the limited amount of research on DBS assessment protocols and prescreening in general in South Africa, and the increasing number of patients considered for this procedure, more information on the prescreening criteria/measures used can be beneficial for establishing optimal postsurgical outcomes.

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