

Sleep and other non-motor parameters in patients with Parkinson's Disease



UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Simoné Colloppen

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Declaration

I, Simone Colloopen, declare that this Dissertation is my own, unaided work. It is being submitted for the degree of Master of Science at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at any other University.



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Abstract

Background: Parkinson's Disease (PD) is a progressive neurodegenerative disease that leads to both motor and non-motor manifestations. Early research focused mainly on the motor symptoms in PD as they were the most apparent during early manifestations, while non-motor symptoms were generally neglected. However, over the past decade, non-motor symptoms in PD have gained more recognition for their negative impact on the quality of life (QOL) in patients with PD. The non-motor symptoms in PD consist of sleep disturbances, cognitive impairment advancing to dementia, autonomic dysfunctions, sensory disorders, and neuropsychiatric symptoms. Among these, sleep disturbances have a high prevalence of 74-94% in PD and may severely impact the QOL, mental and physical health and behaviour of patients with PD. Common therapeutic strategies for PD consist of antiparkinsonian drugs. However, during the mid to late stages of the disease, a surgical intervention using deep brain stimulation (DBS) is performed in patients who have a decreased sensitivity to available medication or patients with drug induced complications.

Study Aims and Objectives: This study aims to compare subjective and objective sleep measures in patients with PD following DBS with PD patients who have not undergone DBS (non-DBS) as well as to determine the relationship between sleep parameters and other PD-related non-motor and motor symptoms such as cognitive function, depression, fatigue, pain, physical activity and light exposure.

Methods: Twenty-two patients with PD were recruited and divided into two groups; DBS ($n = 7$) and non-DBS ($n = 15$). All patients completed the sleep and general health questionnaires that also assessed other PD-related non-motor symptoms. Nineteen of the patients wore both the wrist and hip-mounted activity monitors. Eight patients completed polysomnography. Sleep parameters assessed included: sleep quality, sleep efficiency, total sleep time, latency, and wake after sleep onset (WASO). Unified Parkinson's Disease rating scale scores and Hoehn and Yahr stages were also obtained from all patients.

Results: Overall, subjective sleep measures comparing DBS and non-DBS groups showed that the DBS group had greater excessive daytime dysfunction ($p = 0.044$) and fatigue ($p = 0.017$). There were no significant differences seen in PSQI global scores, or its components except the DBS group exhibited greater PSQI daytime sleepiness compared to the non-DBS group ($p = 0.016$). The DBS group also presented with a significantly higher prevalence of RLS compared to the non-DBS group ($n = 29\%$ vs $n = 13\%$) ($p = 0.0087$), however the non-DBS group had

more severe RLS according to the International Restless Legs Study Group Severity Scale scores. There were no significant differences seen in the objective sleep parameters (actigraphy and PSG) and physical activity patterns between the two groups except NREM stage 3 was higher in the non-DBS group ($p = 0.029$). Among the PD-related non-motor symptoms in PD, the DBS group showed higher BDI II scores compared to the non-DBS group ($p = 0.0143$). No significant differences were seen for pain, cognitive dysfunction, physical activity, and light exposure between the two groups, however both groups spent an increased amount of time of 83% in sedentary behaviour. Negative correlations were observed between wrist actigraphy sleep efficiency and pain ($r = -0.647$, $p = 0.011$) and wrist actigraphy total sleep time and pain ($r = -0.793$, $p = 0.001$). A positive correlation was observed between hip actigraphy sleep latency and moderate physical activity ($r = 0.576$, $p = 0.011$). None of the other relationships between sleep parameters and other PD-related non-motor symptoms and physical activity were significant.

Conclusion: In conclusion, the non-DBS group had better sleep quality compared to the DBS group, which was supported by the non-DBS group having better subjective sleep measures compared to the DBS group. This was further corroborated by the non-DBS group scoring higher in slow wave sleep as well as pain and moderate physical were also associated with sleep, suggesting that these relationships may affect sleep in PD.

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Abbreviations

AASM	American sleep academy of sleep medicine
BDI II	Beck's Depression Inventory II
CHRLS-q	Cambridge-Hopkins questionnaire for restless leg syndrome questionnaire
DBS	Deep brain stimulation
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
EEG	Electrocephalography
EEG	Electrocephalography
EMG	Electromyography
EOG	Electrooculography
ESS	Epworth sleepiness scale
FSS	Fatigue severity scale
GABA	Gamma aminobutyric acid
GPI	Globus pallidus interna
IRLSS	International restless legs severity scale
LED	Levodopa equivalent dosage
LOC	left outer canthus
MCRF	Magnocellular reticular formation
MD-UPDRS	Unified Parkinson's Disease Rating Scale
NREM	Non-rapid eye movement
PD	Parkinson's Disease
PDQ-39	Parkinson's Disease Questionnaire -39
PDSS	Parkinson's Disease sleep scale
PLMS	Periodic limb movement sleep disorder
PPN	Pedunculo pontine nucleus
PSG	Polysomnography
PSQI	Pittsburgh sleep quality index
QOL	Quality of life
RBD	Rapid eye movement sleep behaviour disorder
REM	Rapid eye movement
RLS	Restless leg syndrome
ROC	right outer canthus

SCN	Suprachiasmatic nucleus
SF-MFQ	Short-form McGill pain questionnaire
SLD	Sublateraldorsal nucleus
SNpr	Substantia Nigra
STN	Subthalamic nucleus
STN-DBS	Deep brain stimulation in the subthalamic nucleus
SWS	Slow wave sleep
VLPO	Ventrolateral pre-optic area
VTa	Ventral tegmental area
WASO	Wake after sleep onset
WHO-5	World Health Organisation -5 wellbeing index

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Chapter 1: Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disease that leads to both motor and non-motor manifestations (Sharma et al., 2018). The motor symptoms commonly associated with PD include tremors, rigidity, bradykinesia, and postural instability. Early research focused mainly on these motor symptoms in PD as they were the most apparent early manifestations, while non-motor symptoms were generally neglected (Chahine et al., 2017, Sharma et al., 2018). However, over the past decade, non-motor symptoms in PD have gained more recognition for their negative impact on the quality of life (QOL) in patients with PD. The non-motor symptoms in PD consist of sleep disturbances, cognitive impairment advancing to dementia, fatigue, pain, autonomic dysfunctions, sensory disorders, and neuropsychiatric symptoms (such as depression) (Eugster et al., 2016, French and Muthusamy, 2016). Among these, sleep disturbances have a high prevalence of 74-94% in PD and may severely impact the QOL, mental and physical health, and behaviour of patients with PD (Amara et al., 2012, Chahine et al., 2017, Sharma et al., 2018). Other non-symptoms in PD also have an increased prevalence such cognitive impairment (30-80%), pain (60-80%) and depression (40-50%) (Marsh, 2013, Martinez-Martin et al., 2018, Roheger et al., 2018). Physical activity and light exposure are also decreased in PD (van Nimwegen et al., 2011, Lee et al., 2014). All these factors have shown to influence sleep and the QOL of patients with PD.

Common therapeutic strategies for PD consist of antiparkinsonian drugs. However, during the mid-to late-stages of the disease, a surgical intervention using deep brain stimulation (DBS) is performed in patients who have a decreased sensitivity to available medication or patients with drug-induced complications (Zhang and Xie, 2019). DBS is a surgical procedure that involves the implantation of electrodes in specific brain regions with the purpose of treating the motor symptoms such as tremors and medication-induced dyskinesia (Sharma et al., 2018). However, the effects of DBS on non-motor symptoms have received less attention (Sharma et al., 2018, Zhang and Xie, 2019). Current studies suggest that DBS therapy can impact sleep disturbances in PD as well as other PD-related non-motor symptoms such as cognitive impairment, pain and depression (Massano and Garrett, 2012, Kurtis et al., 2017, Sharma et al., 2018).

For the purpose of my literature review, I will focus on previous studies investigating how sleep is affected in PD (including subjective and objective sleep measures) as well as other non-motor symptoms such as cognitive function, depression, fatigue, pain, light exposure, and physical activity. I will briefly discuss studies relating to the relationship between sleep parameters and other PD-related non-motor symptoms. Lastly, I will also review the literature

investigating sleep and circadian parameters as well as pain, cognitive impairment, depression and physical activity in patients with PD following deep DBS and with PD patients who have not undergone DBS.

1.1. Parkinson's Disease

The prevalence of PD is reported to be 1-3% of the global population with an average onset age of 60 years old (DeMaagd and Philip, 2015, Bargiotas et al., 2017, Ball et al., 2019). According to the International Parkinson and Movement Disorder Society, an estimated 9.4 million people worldwide were living with PD in 2020, with the United States of America (USA) having the highest number of cases (930 000 cases) (Maserejian et al., 2020). However, the population of those living with PD in sub-Saharan Africa is small, with a prevalence of 7 to 20/100 000 people (Blanckenberg et al., 2013, Williams et al., 2018). These low statistics could be due to a relatively youthful population (with less than 5% of the sub-Saharan African population being above the age of 65 years); in addition many PD cases being unidentified due to a lack of health care facilities or the assumption that neurological disorders are part of aging and, lastly, epidemiological studies are scarce (Williams et al., 2018).

While the exact aetiology of PD remains unknown, the disease is known to be multifactorial with genetic and environmental factors contributing to its development (Ball et al., 2019). Parkinson's Disease is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, which causes a decrease of dopamine in the striatum (Lotharius and Brundin, 2002, Suzuki et al., 2012). Usually, after a loss of approximately 50-80% of dopaminergic neurons, patients experience the motor symptoms associated with PD. The rate of degeneration of these dopaminergic neurons varies and may depend on genetic or environmental influences on its aetiology (Kalia and Lang, 2015). Parkinson's Disease affects the extrapyramidal system, which contains two types of dopamine receptors, D₁ (excitatory receptor) and D₂ (inhibitory receptor) that affect motor activity (DeMaagd and Philip, 2015). Furthermore, the basal ganglia forms part of the extrapyramidal system, which involves the globus pallidus interna (GPi) and the pars reticulata portion of the substantia nigra (SNpr) (DeMaagd and Philip, 2015). These brain structures form part of larger pathways located in the cortex and thalamus. In PD, the loss of dopamine causes an increased activity in the GPi/SNpr pathways and an increase of gamma aminobutyric acid (GABA), resulting in an inhibition of the thalamus

(DeMaagd and Philip, 2015). This in turn causes a decreased activation of the frontal cortex which ultimately results in a decreased motor activity (DeMaagd and Philip, 2015).

The causes of non-motor symptoms in PD are complex, involving both dopaminergic and non-dopaminergic systems (Jellinger, 2017). The serotonergic, noradrenergic, and cholinergic systems that may also potentially be involved in the pathophysiology of PD, have also been hypothesized to play a role in the development of the non-motor symptoms (Suzuki et al., 2012, Sharma et al., 2018). The distribution of alpha-synuclein in pre-synaptic terminals, neurons, neurites glia precede the development of Lewy bodies and may be linked to the pathology of non-motor symptoms in PD (Ferrer et al., 2011, Jellinger, 2009, Jellinger, 2017). The accumulation of alpha-synuclein and the dopaminergic neuronal loss may impact several subcortical nuclei such as nucleus basalis Meynert (found in the cholinergic system), locus coeruleus (located in the noradrenergic system), dorsal raphe nucleus and the dorsal vagus nerve (located in the serotonergic system). These nuclei project to the striatal, limbic, and neocortical regions of the brain, therefore the loss of innervation from these nuclei may contribute to the cause of non-motor symptoms in PD (Bohnen and Albin, 2011, Vermeiren and De Deyn, 2017, Guttman et al., 2007, Greene, 2014, Jellinger, 2017). Non-motor symptoms, particularly in early PD, are also associated with a dopamine deficiency in the striatum caused by an early expression of protein such as Lewy bodies, molecular changes in the substantia nigra, and the dysfunction of related frontostriatal pathways (Ferrer et al., 2011, Palmeri et al., 2017). Lastly, another contribution to the potential development of non-motor symptoms in PD is the degeneration of dopaminergic and serotonergic axons (Grosch et al., 2016). However, further research is required to determine the exact pathophysiology of the motor and non-motor symptoms. In addition, an important feature in the pathology of PD includes the accumulation of misfolded forms of ubiquitin proteins called Lewy bodies (DeMaagd and Philip, 2015). These Lewy bodies are associated with neurodegeneration in PD and produce various lesion patterns as the disease progresses to different stages (DeMaagd and Philip, 2015). Overall, PD is a complex neurodegenerative disease as highlighted by the various molecular pathways which may contribute to its neuropathophysiology (DeMaagd and Philip, 2015).

PD has been categorized into six pathological stages (Braak et al., 2003). During stages 1-2 of the disease, known as the pre-symptomatic stages of PD, Lewy bodies are restricted to the medulla oblongata, pontine tegmentum, and olfactory bulb, anterior olfactory nucleus (Braak

et al., 2003). As PD progresses to stages 3-4, patients may develop clinical symptoms. The substantia nigra, forebrain, and midbrain nuclei become affected at this stage (Braak et al., 2003). Progression of PD to stages 5-6 includes pathologies to the temporal mesocortex and mature neocortex, which includes sensory associated areas and limbic structures. During this stage cognition is affected and begins to decline (Braak et al., 2003), however studies have suggested that during early stages of PD, mild cognitive impairment was also observed (Hu et al., 2014, Santangelo et al., 2015).

PD is commonly diagnosed using the UK Parkinson's Disease brain bank clinical criteria and is dependent on the presence of motor deficits including bradykinesia, rigidity, and tremor manifesting unilaterally or asymmetrically however, these motor deficits can be preceded by the premotor or prodromal phase (Kalia and Lang, 2015, Schapira et al., 2017). The progression of motor and non-motor symptoms in PD can be described as follows, during the prodromal phase, non-motor symptoms develop, specifically rapid eye movement sleep behaviour disorder (RBD), which studies have shown may develop years before the development of the cardinal motor symptoms of PD (Swick, 2012, Kalia and Lang, 2015, Schapira et al., 2017). The duration of the prodromal phase varies from patient to patient as well as the order of manifestation of these non-motor and motor symptoms in PD (Schapira et al., 2017). Non-motor symptoms further advance after the diagnosis of PD and continue developing as the disease progresses, as seen in (Figure 1.1). During the late stages of the disease, axial motor symptoms such as postural instability, falls and freezing of gait tend to develop (Kalia and Lang, 2015). PD is infamous for being heterogenous with either rapid or/and slow forms of progression (Armstrong and Okun, 2020). After a diagnosis of PD, motor symptoms progress rapidly, while non-motor symptoms progress at a much slower rate but cause a greater disability contributing to a poor QOL in patients with PD (Kalia and Lang, 2015).

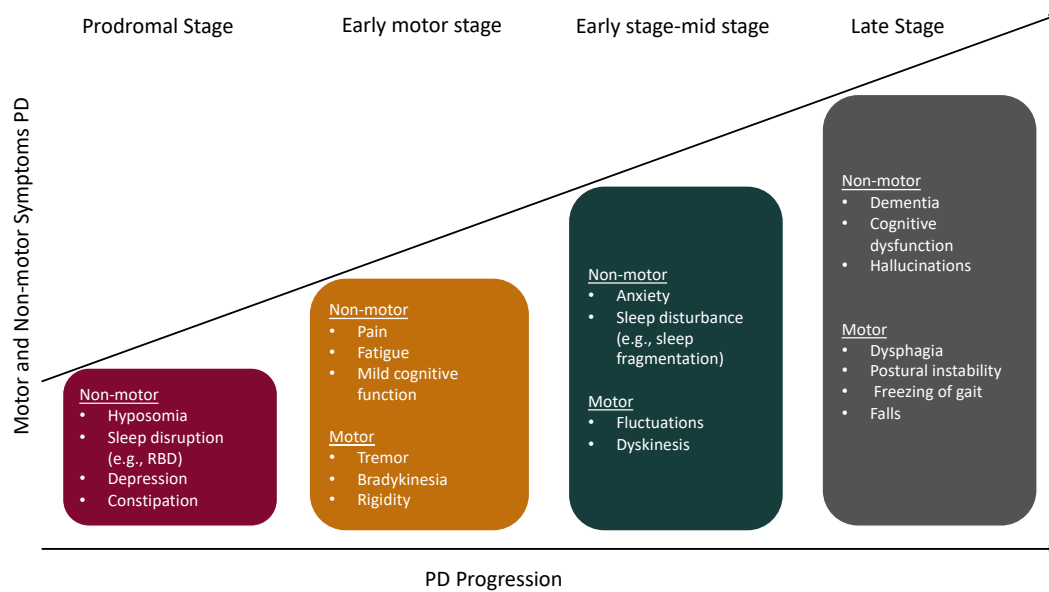


Figure 1.1: A schematic representation of the potential onset and the gradual progression of non-motor and motor symptoms in Parkinson's Disease (PD). Non-motor symptoms may gradually develop during the prodromal phase before the onset of motor symptoms.. RBD: rapid-eye movement sleep behaviour disorder. This diagram is an adaptation from Kalia and Lang, (2015).

The conventional approach for treating PD begins with a pharmacologic dopamine replacement therapy (Church, 2021) and it is usually the first line of treatment for PD. This therapy consists of either carbidopa/levodopa, or a dopamine agonist taken orally daily. Complementary medicine and integrative medicine are also used either along with or as an alternative to the dopamine replacement to improve brain health and overall QOL in patients with PD (Bega et al., 2014, Hall and Church, 2020, Church, 2021).

Deep brain stimulation (DBS) is a surgical intervention used to treat PD, especially in patients experiencing long-term adverse effects from carbidopa/levodopa therapy (Church, 2021). Since the late 1990s, DBS has been clinically used and accepted to treat PD (Zhang and Xie, 2019). It is a surgical procedure that involves the implantation of electrodes in specific brain regions (Sharma et al., 2018). DBS can be performed bilaterally and the two most commonly targeted regions in the brain are the subthalamic nucleus (STN) and the GPi (Sharma et al., 2018). The electrodes are connected to a neurostimulator, which provides electrical impulses to the targeted regions of the brain and regulates brain circuits (Sharma et al., 2018). However,

DBS requires a stringent presurgical evaluation which is recommended to assess patient candidacy to optimize the surgical outcome for DBS in patients with PD. This is due to the various motor symptoms having different responses to the DBS surgery (Sharma et al., 2020). A multidisciplinary team assesses the candidacy of patients for DBS, which includes assessing the patient's neurocognitive and psychiatric profile, neuro-imaging, on-off levodopa challenges, risk and benefit of surgery, and lastly, the patient's current level of function (Sharma et al., 2020).

Deep brain stimulation (DBS) has been shown to significantly improve a patient's primary motor symptoms and QOL as well as reduce their need for medications (Sharma et al., 2018, Zhang and Xie, 2019). The effects of DBS on non-motor symptoms have received less attention (Sharma et al., 2018, Zhang and Xie, 2019). However, current studies suggest that DBS therapy can impact different aspects of non-motor symptoms in PD, specifically one of the most common symptoms, sleep disturbances (Sharma et al., 2018).

1.2. Sleep

Sleep is a complex and fundamental biological process that plays an important role in brain function and systemic physiology which is vital for the normal functioning of the human body (Medic et al., 2017, Perez-Pozuelo et al., 2020). It has many functions such as clearing the brain of wastes, the regulation of immune responses and it plays a role in cognition and performance, hence it is agreed that sleep does not only take part in one single physiological role but in several physiological roles (Zielinski et al., 2016).

Sleep is generally divided into two parts, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Carley and Farabi, 2016). According to the American Academy of Sleep Medicine (AASM), sleep is classified into four individual stages, which consist of NREM sleep stage 1, NREM sleep stage 2, NREM sleep stage 3, and REM sleep (Moser et al., 2009).

The gold-standard used to identify the different sleep stages and objectively measure overall sleep is polysomnography (PSG). This non-invasive technique employs a combination of surface electrodes that consist of electroencephalography (EEG), electrooculography (EOG), and

electromyography (EMG) (Marino et al., 2013). The level of muscle activity and features of the EEG determine the different sleep stages which can be seen graphically in a PSG. Generally, in a healthy individual, NREM 3 sleep consists of EEG delta rhythms (0.5-4 Hz), during REM sleep EEG theta (4-7 Hz) rhythms are dominant, EEG alpha rhythms (10-13 Hz) are found during quiet wakefulness and normal consciousness features mostly EEG beta rhythms (13-16 Hz) (Zielinski et al., 2016). During NREM sleep stage 1, sleep is light with a slowness of eye movements and muscle activity (Memar and Faradji, 2018). Once NREM sleep stage 2 commences, eyes generally stop moving and brain waves become slower (Memar and Faradji, 2018). NREM sleep stage 3 is known as deep sleep or slow-wave sleep. During NREM sleep stage 3, there are almost no eye movements and muscle activity (Memar and Faradji, 2018). In REM sleep, there is rapid eye movement and an increased breathing rate (Memar and Faradji, 2018). In a healthy individual, the sleep cycle will undergo a cyclic sequence of the four sleep stages, starting with NREM sleep stage 1, proceeding to NREM sleep stage 2 followed by slow wave sleep (NREM sleep stage 3) and lastly REM sleep (French and Muthusamy, 2016). The individual will then resume back to NREM sleep stage 1 and the cycle continues (French and Muthusamy, 2016). Throughout the night, REM sleep and NREM sleep alternate in an ultradian pattern consisting of 3-5 cycles each night (French and Muthusamy, 2016, Zielinski et al., 2016). The first half of the night is made up of primarily NREM sleep with mostly NREM 3 (slow wave sleep) and the second half of the night, consists mostly of REM sleep and NREM sleep stage 2 (Walker, 2005).

Another tool used to objectively measure sleep is actigraphy. The American Academy of Sleep Medicine (AASM) indicated that actigraphy is a useful tool in studying sleep (Martin and Hakim, 2011). It is a small device used to continuously record activity and detect sleep-wake patterns (Martin and Hakim, 2011). Actigraphy can be used to estimate sleep parameters with the use of specialized algorithms (i.e., Cole-Krippe algorithm) (Martin and Hakim, 2011). It also provides a graphical overview of wakefulness and sleep patterns over a period of time (Smith et al., 2018). However, it does not provide details regarding the sleep architecture. The benefits of using actigraphy include that it is cheaper, non-invasive, more ambulatory, and less cumbersome to the patient than PSG and does not require a specialist setup and can be used over extended periods. Actigraphs have been used in several clinical studies to objectively assess sleep parameters in patients with PD (Sadeh and Acebo, 2002, Ancoli-Israel et al., 2003, Smith et al., 2018, Fekedulegn et al., 2020).

1.3. Understanding the sleep-wake cycle

The neural circuitry involved in the regulation of sleep and wakefulness is distinct for each behavioral state, yet they are both interdependent (Carley and Farabi, 2016). The primary mechanism of sleep is the sleep-wake cycle which is regulated by two processes known as the homeostatic sleep drive and circadian arousal drive. A network of subcortical structures and pathways provides support for the activation of the cortex, which is vital for the maintenance of wakefulness (Carley and Farabi, 2016) (Figure 1.2.). The ascending arousal system, responsible for wakefulness is composed of fundamental cell populations in their respective brain regions which include, dopaminergic (located in the ventral periaqueductal grey matter and the dorsal and median raphe nucleus), cholinergic, noradrenergic (located in the pedunculopontine and laterodorsal tegmental nucleus), serotonergic (located in the locus coeruleus) and histaminergic neurons (located in the tuberomammillary nucleus) (Schwartz and Roth, 2008, Carley and Farabi, 2016).

For the initiation and maintenance of sleep, the activity from the ascending arousal system is suppressed (Figure 1.3). This is carried out by inhibitory neurons, namely, the sleep-active γ -aminobutyric acid (GABA)-ergic and galaninergic neurons, of the ventrolateral pre-optic area (VLPO), which remains active throughout the duration of sleep (Schwartz and Roth, 2008, Carley and Farabi, 2016, Wennberg et al., 2017). The exact molecular mechanisms that activate the VLPO and initiate sleep onset are still unclear, however, substantial scientific evidence may indicate that extracellular adenosine may have a major role. During a period of wakefulness, adenosine in the basal forebrain accumulates, however, during sleep, the level of adenosine reduces (Carley and Farabi, 2016, French and Muthusamy, 2016). In the VLPO, adenosine receptors are expressed, and in vivo adenosine has been shown to activate the VLPO neurons, therefore disinhibiting the (GABA)-ergic neurons, hence making it a suitable candidate to initiate and maintain sleep (Schwartz and Roth, 2008, Carley and Farabi, 2016, French and Muthusamy, 2016), hence, adenosine may act as a homeostatic regulator (Carley and Farabi, 2016).

Furthermore, additional molecules may also play a vital role in the signaling and regulation of sleep initiation and maintenance. A study has shown that the monoaminergic arousal centers are inhibited by the activity of the VLPO, therefore creating the concept of the “flip-flop” switch model that controls the two behavioral states (wakefulness and sleep) (Saper et al.,

2001). Hence, the activity of the neurons involved in arousal or sleep, either dominates or suppresses one another, creating two stable pathways for either sleep or wakefulness (Schwartz and Roth, 2008, Carley and Farabi, 2016).

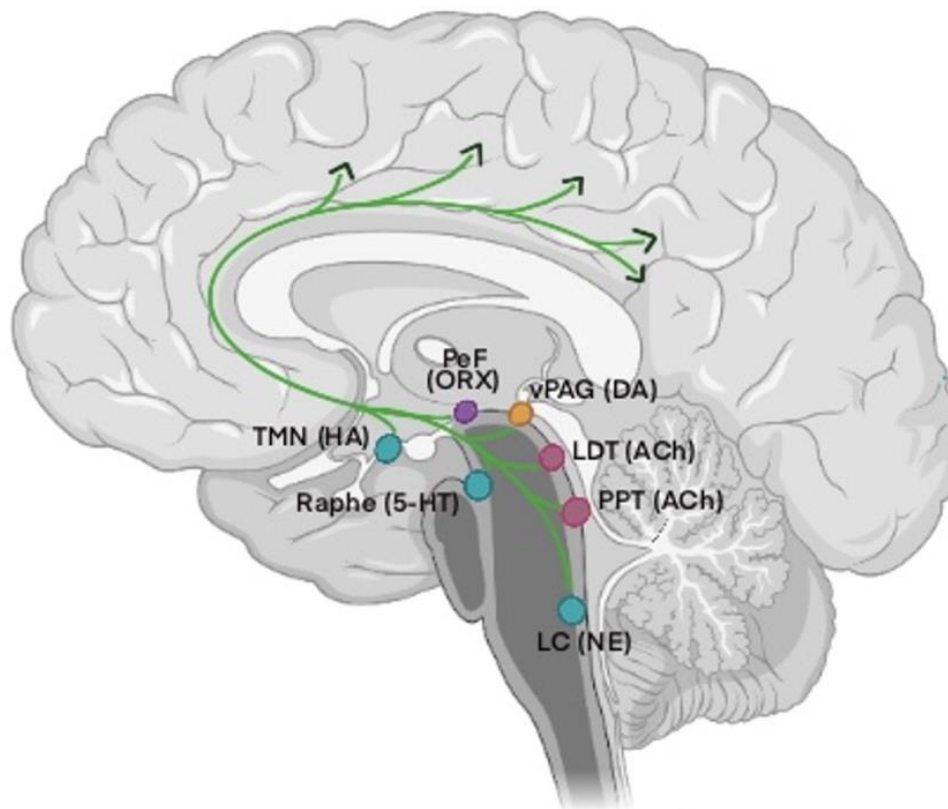


Figure 1.2: An extensive network of subcortical structures in the ascending arousal system with important pathways and major neurochemical regulating wakefulness in the sleep-wake cycle. Important neurochemicals: Ach: acetylcholine; DA: dopamine; GABA: gamma amino-butyric acid; HA: histamine; LDT: laterodorsal tegmentum; NE: norepinephrine; ORX: orexin. Important brain regions: PeF: perifornical region; PPT: pedunculo pontine tegmentum; TMN: tuberomammillary nucleus; vPAG: ventral periaqueductal gray matter; 5-HT: 5-hydroxytryptamine. This figure is an adaptation from Carley and Farabi, (2016).

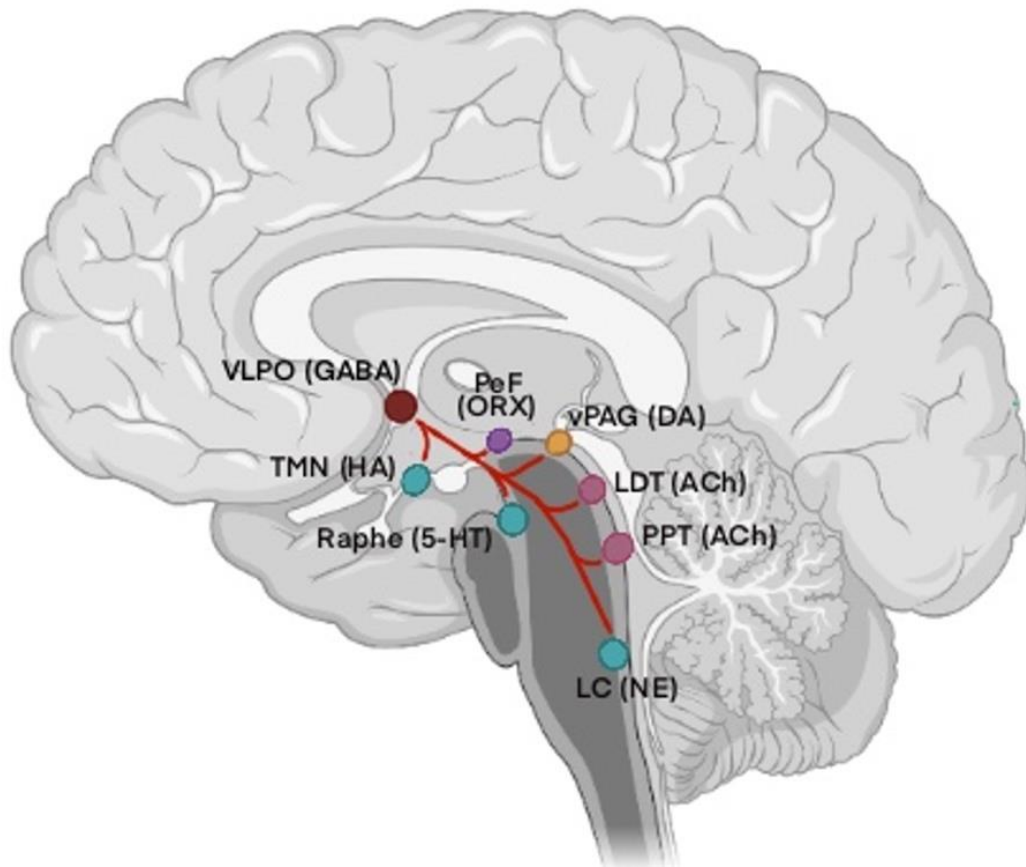


Figure 1.3: An extensive network arising from the hypothalamus inhibiting ascending arousal system with important pathways and major neurochemicals maintaining sleep in the sleep-wake cycle. Important neurochemicals: Ach: acetylcholine; DA: dopamine; GABA: gamma amino-butyric acid; HA: histamine; LDT: laterodorsal tegmentum; NE: norepinephrine; ORX: orexin. Important brain regions: PeF: perifornical region; PPT: pedunculopontine tegmentum; TMN: tuberomammillary nucleus; vPAG: ventral periaqueductal gray matter; 5-HT: 5-hydroxytryptamine; VLPO: ventral preoptic nucleus. This figure is an adaptation from (Carley and Farabi, (2016).

1.4. Sleep and sleep-wake disturbances in patients with PD

In 1817, James Parkinson described sleep disturbances and extreme exhaustion commonly known as excessive daytime sleepiness (EDS) as symptoms of PD in its final stages in his “Essay on the shaking Palsy” (Parkinson, 2002, Eugster et al., 2016). Sleep disturbances are an integral part of non-motor symptoms in PD. A few studies concluded that more than 95% of advanced PD patients suffer from a sleep disorder (Partinen, 1997, Chaudhuri et al., 2002, Melka et al., 2019, Zhang and Xie, 2019). However, recently it has been reported that sleep-

wake disturbances may be present in the early stages of PD, even before the onset of motor symptoms (Eugster et al., 2016).

The potential pathophysiological mechanism of sleep-wake disturbances in PD is complex and involves multiple factors such as neurochemical changes which are secondary to the neurodegenerative disease (Sharma et al., 2018). Projections of the dopaminergic neurons to the striatum, cortex and limbic structures have an important role in regulating the sleep-wake cycle (Sharma et al., 2018). Therefore, in PD, the loss of dopaminergic neurons from the SNpr and ventral tegmental area (VTA) results in a loss of dopamine in the mesocorticolimbic and mesostriatal pathways (Sharma et al., 2018). This causes changes in the thalamocortical rhythms which ultimately results in an impaired regulation of REM sleep, reduced slow-wave sleep (NREM stage 3), EDS and reduced sleep efficiency (Sharma et al., 2018).

Additionally, structural impairments occur in PD patients due to dopaminergic loss and pathway defects in the brainstem, which is an essential region of the brain that regulates REM sleep. Therefore, this is consistent with the observation that REM sleep disturbances are common in patients with PD (Schwartz and Roth, 2008). Thus, RBD is highly prevalent in PD patients (Zhang et al., 2017).

Antiparkinsonian drugs may also impact sleep-wake regulatory systems and circadian rhythms (Schäfer and Greulich, 2000, French and Muthusamy, 2016). Most substances present in antiparkinsonian drugs directly affect sleep-wake regulatory systems and may have adverse effects on sleep, for example insomnia is a common adverse effect of these drugs (Schäfer and Greulich, 2000). Dopaminergic substances may impact sleep through the D₁ and D₃ receptors as well as the nigrostriatal, meso-limbic and meso-cortical pathways (Schäfer and Greulich, 2000). Through indirect mechanisms, these drugs also can help to improve or worsen sleep by changing the motor symptoms such as akinesia, hyperkinesia or tremor (Schäfer and Greulich, 2000).

1.5. Circadian Dysregulation in PD

The circadian rhythm operates on a 24-hour cycle and regulates the sleep-wake cycle. The body's internal clock is located in the suprachiasmatic nucleus (SCN). The SCN acts as the central circadian pacemaker and is responsible for regulating circadian oscillations in the body (such as body temperature, sleep, and endocrine function) through autonomous rhythms (French and Muthusamy, 2016, Wennberg et al., 2017). The VLPO from the sleep-wake cycle also receives vital information with regards to the modulation of the circadian rhythm from the suprachiasmatic nucleus (the central circadian clock) (Carley and Farabi, 2016).

Functions of the SCN are linked to the hypothalamus and brainstem associated central autonomic networks that become impaired in PD however the SCN itself remains undamaged (French and Muthusamy, 2016). Therefore, the presence of these defective networks results in alterations in circadian rhythmicity and a decline in SCN activity (Willison et al., 2013, Nakamura et al., 2011). Thus, resulting in a reduction of melatonin output and disturbance in the sleep-wake cycle (Wu and Swaab, 2005, Nakamura et al., 2011). A possible mechanism for this could be the dysregulation of *Bmal1* and *Per2* gene expression, where dopamine is known to regulate the activity of the Bmal1/clock heterodimer and expression of *Per2* (Dibner et al., 2010, Vallée et al., 2020). Therefore, in PD a deficiency in dopamine can disrupt the regulation of Bmal1/clock heterodimer activity and *Per2* gene expression, thus causing a disruption of the circadian rhythm (Vallée et al., 2020). Overall, dopamine has a fundamental role in maintaining circadian rhythms and influences several interconnecting relationships between the different brain structures linked to sleep including the SCN. Hence, a decline in dopamine due to PD can result in a dysfunction of the circadian rhythm. Importantly, circadian dysfunction results in abnormal alterations in the sleep pattern that includes a reduction in sleep spindles, decreased REM sleep latency and increased arousals, reflecting poor sleep (Garcia-Borreguero et al., 2004, Gjerstad et al., 2007, Poryazova et al., 2013, Rolinski et al., 2014).

The most potent entraining factor for the SCN (also known as the central circadian pacemaker) is light (Dodson and Zee, 2010, Fonken and Nelson, 2014). Light information is delivered from the retina and travels via the retinohypothalamic tract to the SCN (Dodson and Zee, 2010).

In the general population, natural daytime light exposure at increased intensities has been shown to improve sleep quality, affect the duration of sleep and decrease sleep latency

(Boubekri et al., 2014, Blume et al., 2019). A study reporting on the phase-advancing effects of daylight indicated that for every extra hour spent outdoors, total sleep time was increased by approximately 30 minutes (Roenneberg et al., 2003). However, physical activity is often confounded with time spent outside, therefore this phase-advance must also account for physical activity. Another study that was conducted by Murray et al, suggests that outdoor moderate to vigorous physical activity during the morning may improve sleep efficiency, however physical activity outdoors during the afternoon resulted in a reduced sleep efficiency (Murray et al., 2017).

Most patients with PD spend most of their wake time sedentary (Benka Wallén et al., 2015). A consequence of assuming a sedentary lifestyle is reduced natural light exposure, which in turn leads to decreased rhythms generated by the circadian pacemaker resulting in poorer sleep quality (characterized by a change in circadian rhythmicity) (Speelman et al., 2011, Lee et al., 2014, Wams et al., 2017, Zuzuárregui and Doring, 2020) (Lee et al., 2014, Wams et al., 2017). Increased physical activity and sun exposure have both been shown to improve the quality of sleep in PD patients (Lee et al., 2014).

Melatonin is a known output of the master clock, the circadian pacemaker and is associated with physiological process such as sleep-wake cycle, hormone secretion, core body temperature, cognitive performance and mood (Li et al., 2020). The release of melatonin is regulated by the SCN. Melatonin production is closely related to light exposure, there is a continuous production of melatonin within the pineal gland, however melatonin is only released in response to darkness (during the night). It has been found there are acute suppressive effects of light on melatonin and light exposure during the day slows down or suppresses the release of melatonin (Masters et al., 2014). Hence, during the day melatonin levels are lower and associated with the lower sleep drive because the SCN suppresses the sleep drive and is firing at higher rates maintaining activity in the wake nuclei. During the night melatonin levels are elevated and associated with sleep (Li et al., 2020). It is important to note that melatonin modifies the circadian output, but it is the SCN that modifies its input to the sleep wake cycle (Li et al., 2020).

Studies have also shown that melatonin has a mutual regulatory effect with dopamine in the circadian cycle (Shen et al., 2017, Li et al., 2020). The relationship between melatonin in the CSF and motor symptoms in PD has been established (Leston et al., 2010). A study using a

24-hour melatonin profile in PD showed a significantly decreased amplitude and secretion of melatonin in PD patients compared to the healthy control group (Videnovic et al., 2014). They suggested that the dysfunction of the SCN and/or its afferent and efferent pathways such as reduced light transmission, partially resulting from the dopaminergic retinal degeneration in PD which may affect the circadian rhythm of melatonin causing a decreased amplitude of the melatonin rhythm in PD patients (Videnovic et al., 2014). Another possible mechanism could be the degeneration of the SCN itself, resulting in an impaired circadian rhythm in PD (Videnovic et al., 2014). Lastly, autonomic dysfunction may also have a role in negatively impacting the secretion of melatonin in PD, due to the disruption of the sympathetic ganglionic chain which is involved in the SCN regulation of the synthesis and release of melatonin by the pineal gland (Morris et al., 2012, Videnovic et al., 2014).

Li et al. 2020, found that plasma melatonin levels in PD patients were negatively correlated with the PSQI total score and the daytime dysfunction PSQI item and was positively correlated with item 12 of the PDSS, thus suggesting that the level of plasma melatonin in PD patients can reflect some kind of circadian dysfunction which could be the cause of the excessive daytime sleepiness. Videnovic et al. 2014, also suggested that circadian regulation has an important role in the pathophysiology of excessive sleepiness associated with PD.

1.6. Sleep disturbances in PD

The most common sleep disturbances that occur in PD include insomnia, rapid eye movement sleep behavior disorder (RBD), restless legs syndrome (RLS), periodic limb movements during sleep (PLMS), excessive daytime sleepiness (EDS), sleep fragmentation, obstructive sleep apnea and fatigue (Eugster et al., 2016). Reduced total sleep, decreased sleep efficiency and increased wakefulness after sleep onset (WASO) are also experienced by PD patients (Wetter et al., 2000). Table 1.1. shows a summary of studies focusing on common sleep disorders in PD and the UPDRS scores to determine the severity of PD.

To evaluate the quality of sleep, subjective measures using various validated sleep questionnaires are utilized. The Epworth Sleepiness Scale (ESS) is a well-validated tool, used to assess excessive daytime sleepiness and has been found to have a sensitivity of 94 % and a specificity of 100 % (Johns, 1991, Johns, 2000, Kumar et al., 2003). It provides eight everyday

scenarios and evaluates the chances of dozing off during each scenario given (Kurtis et al., 2018). It is frequently used in sleep studies in PD to determine the likelihood of a PD patient dozing off in various daily situations (Stavitsky and Cronin-Golomb, 2011, Kurtis et al., 2018). The Pittsburgh Sleep Quality Index (PSQI) is another scale that assesses self-reported sleep efficiency, sleep quality and sleep disturbances (Kurtis et al., 2018). It contains 19 items and has been used in many clinical sleep studies in PD (Kurtis et al., 2018). To screen for RLS, the Cambridge-Hopkins questionnaire for RLS is a well-validated screening tool, with an increased sensitivity and specificity for determining RLS in population-based research (Allen et al., 2009). The International Restless Legs Severity Scale (IRLSS) assesses the severity of symptoms within RLS as well as impact on quality of life. It is often used in PD studies to compare the severity of RLS (Kurtis et al., 2018). The fatigue severity scale is a commonly used self-report to assess fatigue. It is a well-validated and reliable tool used in clinical studies to measure and quantify fatigue (Valko et al., 2008).

1.6.1. Insomnia

Insomnia is a common sleep disorder in PD and is characterised by difficulty falling asleep, sleep fragmentation and early awakenings (Gjerstad et al., 2007, Loddo et al., 2017). The proposed mechanism for insomnia in PD consists of an altered neurotransmitter, by either a morphological lesion or certain medications or inflammation. This may potentially cause an imbalance between sleep-promoting and arousal-promoting brain regions, inducing a decreased function of the VLPO and increased activity of the hypocretin system (Riemann et al., 2010). Therefore, brain structures involved in wakefulness fail to switch off during the transition from wakefulness and sleep, resulting in insomnia (Riemann et al., 2010). Table 1.1 shows a longitudinal cohort study (n = 231) that used a self constructed sleep questionnaire. They found that 50-60% of PD patients have insomnia (Gjerstad et al., 2007). These patients with a mean age of 77.4 years old experienced an increase in vivid dreaming, excessive daytime sleepiness and had trouble turning in bed. Furthermore, there was no change in UPDRS scores between PD patients with insomnia and those without. Using a logistic regression model they found that insomnia was significantly associated with the duration of disease and depression in PD, (Gjerstad et al., 2007). Another study reported similar findings, in which the incidence of chronic inability to sleep increased with the duration of disease in PD (Ylikoski et al., 2015). Furthermore, a large case-control PD study (n = 124) showed that insomnia severity index was associated with UPDRS scores, Hoehn and Yahn stages and

disease duration (Yong et al., 2011). A study (n = 63) found that in PD, insomnia was related to factors such as inadequate sleep habits and REM sleep latency (Sobreira-Neto et al., 2020).

1.6.2. Rapid eye movement sleep behavior disorder

Rapid eye movement sleep behaviour disorder (RBD) is characterised by the loss of normal temporal paralysis during REM sleep and a lack of atonia present in REM sleep, thus allowing episodes of dream enactment (Kim and Jeon, 2014). During a PSG, there is immoderate chin muscle tone and limb jerking during REM sleep in patients with RBD (French and Muthusamy, 2016). RBD is commonly found in patients with PD (Kumru et al., 2007). Table 1.1 summarises a few studies showing RBD in PD such as a study consisting of 540 patients with PD, using PSG reported that 77% of these patients had RBD (Baumann- Vogel et al., 2020). Another study using PSG showed no differences between the PD RBD group and the control group, consisting of PD non-RBD patients, in sleep latency, REM latency, TST, sleep efficiency and the percentage of NREM sleep stage 1, NREM sleep stage 2, NREM sleep stage 3 and REM sleep, however they found an increase in EDS in PD patients with RBD. Furthermore was no significant difference in UPDRS III scores, however a decrease in tremor and an increase in falls was seen (Postuma et al., 2008). A study using PSG also showed no significant differences in sleep latency, REM latency, total sleep time, sleep efficiency, NREM sleep stage 1, NREM sleep stage 2, NREM sleep stage 3 and REM sleep between the PD RBD group and the control group which consisted of PD patients without RBD, however they did find that PD RBD group had a higher REM sleep with higher chin and limb movement (De Cock et al., 2007). They also found that RLS was more frequent in the PD RBD group (De Cock et al., 2007). UPDRS I and II scores were significantly higher in the PD RBD group compared to PD patients without RBD, indicating that the PD RBD group also experienced urinary, speech, swallowing and chewing problems. Furthermore, a study showed that the RBD group had a significantly higher UPDRS III score compared to the PD non-RBD control group, with a significantly lower tremor score however, there were no sleep outcomes reported (Lee et al., 2010). Using subjective measures of sleep (REM sleep behaviour disorder screening questionnaire), a study identified 47 % of patients with PD from a total of 475 to have been diagnosed with RBD. They further found that the RBD group had an increased ESS score. In addition, they also found no significant difference in UPDRS III scores between RBD patients and the control group which consisted of non-RBD PD patients (Rolinski et al., 2014) (table

1.1). Another study (n = 404) using subjective measures to assess RBD showed a prevalence of 43% of RBD in PD patients, they found an increase in awakenings and hallucinations in PD patients with RBD compared to PD patients without RBD (Poryazova et al., 2013). Furthermore, they followed up on 10 patients and found that these 10 patients did present with RBD (Poryazova et al., 2013). Interview-based RBD studies show a prevalence of 27 – 54% which is similar to PSG-based studies. Thus indicating that RBD has a high prevalence in PD using both subjective and objective measures to measure sleep and both measures can be valid tools in detecting RBD in PD.

During REM sleep, research has shown that the cells of the sublaterodorsal nucleus (SLD) are the most active. They produce atonia and REM sleep like EEG activity, indicating that they may play a vital role in producing REM sleep (Swick, 2012). Located ventral to the locus coeruleus, the SLD produces inhibitory and excitatory neurotransmitters, GABA and glutamate (Swick, 2012). In the Braak's staging of brain neuropathology in PD, as early as NREM sleep stage 2, there is evidence of pathology in the SLD, the magnocellular reticular formation (MCRF) and the perilocus coeruleus alpha (Braak et al., 2003). These structures in the brain play an important role in regulating the sleep-wake cycle, specifically controlling the two states of sleep REM/ non-REM sleep (Swick, 2012). Hence, damage to the SLD may cause a dysregulation of REM sleep and contribute to RBD. It was also suggested that the SLD may play a role in the inhibition of skeletal muscle activity during REM sleep, via a direct pathway in which the SLD signals the spinal interneurons which actively inhibits the activity of the skeletal muscles in REM sleep (Boeve et al., 2007). They proposed a potential pathophysiological mechanism causing RBD via an indirect pathway involving lesions to the SLD which causes a decreased excitation of the MCRF, resulting in a reduced inhibition of the spinal motor neurons directly or through spinal interneurons. This may contribute to a loss of muscle tone via the MCRF (Boeve et al., 2007), ultimately causing a decreased inhibition of skeletal muscle activity during REM sleep and abnormal complex motor activity (Swick, 2012). However further research is required to determine the exact pathophysiological mechanism of RBD in PD.

1.6.3. Periodic limb movement during sleep (PLMS)

Commonly associated with RLS, is the sleep-related movement disorder PLMS. PLMS is characterised by four or more clusters of repetitive involuntary movements in the lower limbs

and torso such as the rhythmic extension of the big toe, dorsiflexion of the ankle and flexion of the knee or hip (Covassin et al., 2012). These involuntary movements may occur bilaterally or unilaterally during sleep, which may awaken the individual (Covassin et al., 2012, Guo et al., 2017). PLMS have been reported to have a high prevalence in patients with PD (Leng et al., 2016). Table 1.1 shows a study (n = 20) using PSG showed decreased sleep efficiency increased PLM parameters during sleep and wakefulness in the PD group relative to the control group (Wetter et al., 2000). Another study (n = 45) using PSG showed no significant difference in PSG parameters compared to the control group which consisted of PD patients without PLMS. However, patients with PLMS scored higher for the Parkinson's disease questionnaire-39 (PDQ-39) and UPDRS compared to the PD group without PLMS, indicating the PD patients with PLMS have poorer sleep quality, lower quality of life and an increased disease severity compared to the control group (Covassin et al., 2012) (table 1.1). In addition, there is evidence proposing that PLMS and PD may share a common pathophysiology (Covassin et al., 2012). It is suggested that the nigrostriatal degeneration observed in PD may be involved in the development of PLMS (Covassin et al., 2012) however, further research is required.

1.6.4. Restless leg syndrome (RLS)

Restless leg syndrome is characterised by an urge to move the limbs due to unpleasant limb sensations, which occurs during rest and improves by moving the affected limb (Klassen and Adler, 2012, You et al., 2019). RLS is in sync with the circadian pattern, peaking during the night which disrupts the quality and quantity of nocturnal sleep (Ferini-Strambi et al., 2018).

Restless leg syndrome is a common co-morbidity associated with PD. Table 1.1 shows a study of 165 PD patients, RLS was found to be present in 12% of patients with PD and only in 2 % in the control group of 131 healthy age-and sex-matched individuals (Nomura et al., 2006). They also found that PSQI scores were higher in PD patients with RLS compared to healthy control group (Nomura et al., 2006). Krishnan et al. (2003) used subjective sleep measures (International RLS study group criteria) and reported similar findings, in which the prevalence for RLS was 8 % which was higher in the PD group compared to the control group with a RLS prevalence of 0.8% . Another study using subjective sleep measures (ESS, questionnaire based assessing the presence of RLS and a modified National sleep foundation sleep survey) that in a study population of 303 patients with PD, 21 % of patients exhibited RLS symptoms (Ondo et al., 2002). A study found that PDSS scores were lower in PD patients with RLS compared

to PD patients without RLS, however the RLS group obtained significantly worse sleep quality (You et al., 2019) (table 1.1). A case-control study did not find a significant co-morbid occurrence of PD and RLS (Calzetti et al., 2009). Overall, however, the evidence indicates that there is an increased prevalence of RLS in the PD population.

Some studies suggest that RLS and PD share a common neurotransmitter deficit (Krishnan et al., 2003, Guerreiro et al., 2010, Ferini-Strambi et al., 2018). A study reported that patients with RLS obtained a significant decline in dopamine 2 (D₂) receptors in the putamen, which is associated with the severity of RLS (Connor et al., 2009). Therefore, indicating that in both RLS and PD, the nigrostriatal dopaminergic system is affected (Peeraully and Tan, 2012).

In the PD population, RLS and PLMS may contribute to poor sleep and excessive daytime sleepiness (Klassen and Adler, 2012). A recent PD study showed that RLS is significantly correlated to poor sleep, where the patients with RLS had worse sleep quality and increased daytime sleepiness compared to those without RLS (Cederberg et al., 2020). The uncontrollable urge to move the limbs due to RLS mainly occurs during the night when an individual is resting or asleep, as a consequence leads to sleep disturbances, further exacerbating the low sleep efficiency and increasing sleep latency encountered by patients with PD (Mao et al., 2017).

Table 1.1: Studies assessing common sleep disturbances in patients with Parkinson's Disease.

Sleep disturbance	Prevalence of sleep disorder in PD (%).	Study	Total PD patients with sleep disorder (n)	Control (n)	Mean age of PD patients (years)	PSG outcomes	Other sleep outcomes	UPDRS scores
Insomnia	50.0 - 60.0	Gjerstad et al., (2007)	136	95	77.4	-	↑ Vivid dreaming or nightmares in PD patients with insomnia. ↑ EDS in PD patients with insomnia. ↑ Problems turning in bed in PD patients with insomnia.	No significant difference found in UPDRS scores between PD patients with insomnia and without insomnia.
REM sleep behaviour disorder (RBD)	~ 58.0	Postuma et al., (2008)	21	15	68.0	No differences between RBD group and control group consisting of PD patients without RBD in sleep latency, REM latency, TST, sleep efficiency and % of N1, N2, N3 and REM.	↑ EDS in PD patients with RBD.	No significant difference found in UPDRS scores between PD patients with RBD and without RBD however patients with RBD had a decrease in tremor and an increase in falls compared to the PD patients without RBD

Table 1.1 (continued): Studies assessing common sleep disturbances in patients with Parkinson's Disease.

Sleep disturbance	Prevalence of sleep disorder in PD (%).	Study	Total PD patients with sleep disorder (n)	Control (n)	Mean age of PD patients (years)	PSG outcomes	Other sleep outcomes	UPDRS outcomes
REM sleep behaviour disorder (RBD)	~ 67.0	De Cock et al., (2007)	65	35	65.0	No significant differences between RDB group and control group consisting of PD patients without RBD in sleep latency, REM latency, TST, sleep efficiency and % of N1, N2, N3 and REM, however RBD group had ↑ REM sleep and a higher chin and limb muscle activity.	RLS is more frequent in RBD group.	No significant difference found in UPDRS III score between PD patients with RBD and without RBD.
	47.0	Rolinski et al., (2014)	224	251	67.5 ± 9.4	-	↑ in ESS scores for PD patients with RBD.	No significant difference found in UPDRS III score, however a higher significance was observed in UPDRS I (specifically urinary problems) and UPDRS II scores (specially speech, swallowing and chewing problems) for PD patients with RBD compared to PD patients without RBD.

Table 1.1 (continued): Studies assessing common sleep disturbances in patients with Parkinson's Disease.

Sleep disturbance	Prevalence of sleep disorder in PD (%).	Study	Total PD patients with sleep disorder (n)	Control (n)	Mean age of PD patients (years)	PSG outcomes	Other sleep outcomes	UPDRS outcomes
REM sleep behaviour disorder (RBD)	37.0	Lee et al., (2010)	164	283	63.8 ± 9.2	-	-	PD-RBD group showed a significantly higher UPDRS III score compared to the control consisting of PD patients without RBD. The PD-RBD group also had significantly higher scores in bradykinesia, axial/gait and tremor.
	~ 43.0	Poryazova et al., (2013)	404	232	69.9 ± 9	-	↑ Night time awakenings in PD patients with RBD. ↑ Hallucinations in PD patients with RBD.	-
	77.0	(Baumann-Vogel et al., 2020)	540	131	71.6	-	-	-

Table 1.1 (continued): Studies assessing common sleep disturbances in patients with Parkinson's Disease.

Sleep disturbance	Prevalence of sleep disorder in PD (%).	Study	Total PD patients with sleep disorder (n)	Control (n)	Mean age of PD patients (years)	PSG outcomes	Other sleep outcomes	UPDRS outcomes
Periodic limb movement during sleep (PLMs)	58.0	Covassin et al., (2012)	26	19	68.5 ± 8.7	No significant differences in objective sleep relative to the control group consisting of PD patients without PLMS.	↑ PDQ-39 score suggesting poor subjective sleep and QOL in PD patients with PLMS.	PD patients with PLMS obtained higher scores in UPDRS II and total UPDRS compared to the control group of PD patients without PLMS.
	-	Wetter et al., (2000)	10	10	65.2 ± 5.6	↓ sleep efficiency in PD patients with PLMS. ↑ number of awakenings in PD patients with PLMS. ↑ percentage of wake time in PD patients with PLMS.	-	No significant difference was found in UPDRS III scores between PD patients with PLMS and the healthy control group.
Restless leg syndrome (RLS)	12.0	Nomura et al., (2006)	165	131	59.7 ± 2.7	-	↑ PSQI scores in PD patients with RLS.	-
	8.0	Krishnan et al., (2003)	126 (10 PD patients with RLS, 116 PD patients without RLS)	128	63.7 ± 7.8	-	↑ Delayed sleep onset in PD patients with RLS. ↑ ESS scores in PD patients with RLS.	No significant difference found in UPDRS scores between PD patients with RLS and without.

Table 1.1 (continued): Studies assessing common sleep disturbances in patients with Parkinson's Disease.

Sleep disturbance	Prevalence of sleep disorder in PD (%).	Study	Total PD patients with sleep disorder (n)	Control (n)	Mean age of PD patients (years)	PSG outcomes	Other sleep outcomes	UPDRS outcomes
Restless leg syndrome (RLS)	22.0	You et al., (2019)	16	58	65.5±9.1	-	↑ PDSS scores PD patients without RLS compared to PD patients with RLS	No significant difference found in UPDRS III scores between PD patients with RLS and without.
	21.0	Ondo et al., (2002)	63	240	67.5±11.0	-	RLS was not associated with higher ESS scores.	-

↑ = increased; ↓ = decreased; PD = Parkinson's Disease; UPDRS = Unified Parkinson's disease rating scale; UPDRS III = Unified Parkinson's disease rating scale - section 3
 PSG = Polysomnography; TST = Total sleep time; N1 = NREM sleep Stage 1; N2 = NREM sleep Stage 2; N3 = NREM sleep Stage 3; REM = Rapid eye movement; EDS = Excessive daytime sleepiness; PSQI = Pittsburgh sleep quality index; PDQ-39= Parkinson's disease questionnaire-39; ESS = Epworth sleepiness scale; PDSS = Parkinson's disease sleep scale; QOL= Quality of life; RBD = Rapid eye movement sleep behaviour disorder; RLS = Restless leg syndrome; PLMs = Periodic limb movement during sleep.

1.6.5. Obstructive sleep Apnea

Obstructive sleep apnea (OSA) is a most common sleep-related breathing disorder that occurs from partial or total upper airway obstruction. This results in intermittent hypoxemia, arousals and sleep fragmentation (Mery et al., 2017). The prevalence of OSA significantly increases with age (Kaminska et al., 2015). It has been reported that 20-60 % of patients with Parkinson's disease have OSA (Mery et al., 2017). Neuroimaging in OSA patients show structural and functional changes in the brain, specifically in an animal model, OSA has shown to cause brain inflammation and oxidative injury in the locus coeruleus, an important area involved in the pathophysiology of PD (Kaminska et al., 2015). Although the interrelationship between PD and OSA has not been well studied. There has been emerging evidence that OSA may be associated with worsening NMS in PD, specifically cognitive function (Kaminska et al., 2015). According to a case study conducted concluded that there may be possibility of sleep improvement by DBS in PD with OSA (Dias and Antunes, 2014). However, further research must be conducted to determine the effects of DBS in PD patients with OSA.

1.6.6. Excessive daytime sleepiness (EDS)

The AASM described EDS as the inability to stay awake and alert during the day, resulting in drowsiness or rapid sleep onset. The severity of sleepiness may vary but usually occurs during sedentary and monotonous situations (Sateia, 2014, Höglund et al., 2019). EDS is a common sleep disturbance experienced by patients with PD (Knie et al., 2011). A study conducted by Kumar et al. (2003) reported that EDS had prevalence of 21% and was more common in the PD group relative to the control group (3%), they also indicated that the severity of EDS increases with PD disease severity and duration (Kumar et al., 2003).

In PD, EDS is caused by the impairment of the arousal system (French and Muthusamy, 2016). A study suggested that the pathophysiology of EDS may be due to the significant degeneration of the nigrostriatal dopaminergic system and the extrastriatal neurons located in the lower brainstem and midbrain, where both brain regions are linked to sleep-wake regulation (Knie et al., 2011).

1.6.7. Sleep fragmentation

Approximately 80% of patients with PD experience sleep fragmentation, largely contributing to a poor QOL (Claassen and Kutscher, 2011). Sleep fragmentation is described as the interruptions occurring during sleep that result in a lighter sleep stage or a wakefulness state, ultimately disrupting normal sleep architecture (Askenasy, 2001, Claassen and Kutscher, 2011). During a routine PSG, sleep fragmentation can be determined by an increased number of EEG arousals (lasting 3 seconds), increased number of stage transitions (mainly transitions to stage 1 NREM or awake), an increased WASO and an abnormal increase in the duration of stage 1 NREM sleep (Claassen and Kutscher, 2011). The causes of sleep fragmentation in PD are multifactorial and are associated with several sleep disorders such as RBD, PLMS, RLS and insomnia (Claassen and Kutscher, 2011).

1.6.8. Fatigue

Fatigue is commonly described as overwhelming exhaustion (Siciliano et al., 2018). In PD, it is one of the most disabling symptoms experienced by patients, that may manifest during the early stages of the disease and worsen as the disease progresses (Siciliano et al., 2018). Approximately 50% of patients with PD experience fatigue (Siciliano et al., 2018).

Furthermore, research has reported a correlation between fatigue and non-motor symptoms in PD, specifically cognitive function, depression, and sleep disturbances. A cross-sectional PD study concluded that fatigue is significantly associated with depression and sleep disturbances (Stocchi et al., 2014). In a study of 184 patients with PD, it was observed that 107 patients had moderate to severe fatigue (Kluger et al., 2017). There was also an association between fatigue, sleep disturbance, depression, and cognitive function, in which high fatigue scores were correlated with the presence of sleep problems, depressive symptoms, and decreased speed processing and visuospatial abilities, respectively (Kluger et al., 2017). A recent study exploring the relationship between sleep disorders and fatigue using PSG in PD, found that patients with severe fatigue had a lower percentage of REM sleep and were more likely to have RBD (Cao et al., 2021). Fatigue has also been associated with EDS (Höglund et al., 2019).

In PD, it has been hypothesized that fatigue may result from non-dopaminergic pathways or the dysfunction of extrastriatal dopaminergic projections (Kostić et al., 2016, Titova et al., 2017). Evidence supporting the non-dopaminergic pathophysiological hypothesis can be seen

by a study conducted by Pavese et al. (2010), who demonstrated a decreased binding of serotonin-transporter in the basal ganglia and limbic structures (Pavese et al., 2010), therefore causing changes to the serotonergic signaling which could potentially contribute to the dysfunction of the frontal-basal ganglia region. Therefore, impeding the integration of limbic input and motor functions, resulting in fatigue in patients with PD (Chaudhuri and Behan, 2000, Siciliano et al., 2018). Another study also found significantly elevated levels of pathological proteins, specifically alpha-synuclein oligomer, present in the cerebrospinal fluid of patients with PD and fatigue compared to the non-fatigue and control groups, indicating that alpha-synuclein oligomer could potentially contribute to the pathophysiological development of fatigue in PD (Zuo et al., 2016). In addition, the pathophysiology of sleep disturbances in PD has also been linked to the degeneration of the serotonergic pathways, therefore suggesting fatigue and sleep disturbances in PD may share a common pathophysiologic mechanism (Sharma et al., 2018, Siciliano et al., 2018).

1.7. Sleep disturbances and deep brain stimulation

Whilst many studies have shown a significant improvement in motor functions after STN-DBS in advanced stages of PD (Krack et al., 2003, Groiss et al., 2009), only during the recent years have researchers looked at the effects of DBS on sleep.

The effects of DBS on sleep disturbances in patients with PD depend on the stimulation site (Sharma et al., 2018). Studies investigating the role of DBS in sleep disturbances have largely focused on the effect on the STN, whereas studies investigating changes in sleep with stimulation of the thalamus, Globus Pallidus Interna (GPi), and pedunculopontine nucleus (PPN) are limited (Amara et al., 2011, Sharma et al., 2018). The STN is linked to sleep-regulatory centers such as the thalamus and PPN. It is also suggested that the STN has a role in sleep regulation (Sharma et al., 2018, Thompson et al., 2018). In a local field potential recorded from the STN during sleep, a significant band-power difference was noted which consists of delta, theta, beta, and alpha frequencies in all NREM sleep stages compared with REM and awake stages (Thompson et al., 2018). The mechanism of how DBS regulates sleep architecture is not fully understood, however, at this site DBS has been shown to influence the sleep-wake network, affecting sleep physiology (Sharma et al., 2018).

Research has shown an improvement in sleep post-DBS by using a subjective measure of sleep such as validated surveys (Carpenter and Andrykowski, 1998, Amara et al., 2012, Shafazand

et al., 2017, Bjerknes et al., 2020). Amara et al. (2012) evaluated changes in sleep pre- and post-STN DBS using the Pittsburgh sleep quality index (PSQI) in 53 patients. The results obtained showed a significant improvement of the global PSQI score at six months post-DBS in all patients with PD (Amara et al., 2012). They also found that patients with right-side STN DBS had a higher baseline PSQI score of (10.3 ± 3.8 to 7.8 ± 3.5) compared to patients with left-side STN DBS with a baseline PSQI score of (8.3 ± 3.7 to 7.9 ± 3.9) (Amara et al., 2012). A study conducted using the Epworth sleepiness scale (ESS) reported a significant improvement following one year post-DBS in 74 patients (Bargiotas et al., 2017).

Deep brain stimulation (DBS) has also been shown to improve objective measures of sleep. Nishida et al. (2011), conducted a sleep study that compared sleep quality in 10 patients for one week before and after DBS surgery and programming (Nishida et al., 2011). They found a significant improvement in subjective sleep quality and excessive sleepiness after DBS, using the PD sleep scale (PDSS) (Nishida et al., 2011). They also performed polysomnography (PSG) which showed a significant decrease in wake after sleep onset (WASO) and REM sleep without atonia as well as an increase in normal REM sleep (Nishida et al., 2011). The largest sleep study to date, evaluated 50 PD patients prior to STN DBS and 6 months post-STN DBS using polysomnography and actigraphy (Baumann-Vogel et al., 2017). They reported an improvement in total sleep time (Baumann-Vogel et al., 2017). According to the studies mentioned above and other sleep studies conducted, DBS improves the overall sleep quality in PD patients (Amara et al., 2012, Breen et al., 2015, Deli et al., 2015).

Deep brain stimulation in the subthalamic nucleus (STN-DBS) has also been shown to successfully improve motor symptoms and improves nocturnal mobility which also contributes to the improvement of sleep quality in PD patients (Sharma et al., 2018). However, most sleep studies subjectively measure the quality of sleep using sleep questionnaires and very few use objective measures of sleep quality such as polysomnography (PSG) (Kurtis et al., 2018, Sharma et al., 2018). Additionally, many of these sleep studies have a relatively small sample size (approximately $n=12$) (Hjort et al., 2004, Nishida et al., 2011, Tolleson et al., 2016, Zuzuárregui and Ostrem, 2020), with only a single study having a sample size of 50 participants (Baumann-Vogel et al., 2017). This could be due to the limited number of DBS surgeries performed and the strict eligibility criteria for DBS. Table 1.2. shows a summary of studies assessing the effects of DBS on sleep parameters in PD, specifically assessing objective and subjective measures.

Table 1.2: Studies assessing the effects of DBS on sleep parameters in patients with PD.

Reference	Control (n)	Study group (n)	DBS Stimulation Site	Subjective Sleep Measures	Objective Sleep Measures	Study Outcome in patients with PD
Baumann- Vogel et al., (2017)	50 (pre-DBS)	50 (post-DBS)	Bilateral STN	Zurich sleep questionnaire ESS	Actigraphy PSG	Improvement in sleep duration and sleep efficiency post-DBS . ↓ in WASO and REM latency in post DBS. No change observed in sleep fragmentation and RBD before and after DBS.
Nishida et al., (2011)	10 (pre-DBS)	10 (post-DBS)	Bilateral STN	PDSS	PSG	↓ in WASO post-DBS. ↓ in RBD and ↑ in normal REM sleep in post-DBS. Improvement in sleep quality, ESS and RLS scores post-DBS .
Amara et al., (2012)	53 (pre-DBS)	53 (post-DBS)	Unilateral STN	PSQI	-	Improvement in sleep quality 6 months post-DBS .
Breen et al., (2015)	11 (pre-DBS)	11 (post-DBS)	Bilateral STN	PDSS	-	Improvement in sleep quality 6 months post-DBS.
Bjerknes et al., (2020)	58 (pre-DBS)	49 (3 months post-DBS) 52 (12 months post-DBS)	Bilateral STN	PDSS	-	Improvement in sleep quality 3 months and 12 months post-DBS.

Table 1.2 (continued): Studies assessing the effects of DBS on sleep parameters in patients with PD.

Reference	Control (n)	Study group (n)	DBS Stimulation Site	Subjective Sleep Measures	Objective Sleep Measures	Study Outcome in patients with PD
Iranzo et al., (2002)	11 (pre-DBS)	11	Bilateral STN	PSQI ESS	PSG	Improvement of sleep quality post-DBS. ↑ in continuous sleep and nocturnal mobility post-DBS. ↓ in arousal index post-DBS. No change in RBD before and after DBS.
Tolleson et al., (2016)	5 (pre-DBS)	5	GPI	ESS PDSS Insomnia severity scale RLS severity scale	PSG	Improvement in sleep quality 6 months post-DBS. ↓ in WASO, sleep latency and REM latency post-DBS
Amara et al., (2017)	20 (DBS-off)	20 (DBS-on)	Unilateral STN Bilateral STN	PSQI ESS RDBSQ	PSG	No significant difference in sleep efficiency, sleep stage percent, arousals, limb movement and subjective sleep quality in DBS-OFF and DBS-ON (at low and high frequencies).
Chahine et al., (2011)	17	17	Bilateral STN	PDSS ESS IRLSSG scale	-	Improvement in sleep quality, ESS & RLS scores 6 months post-DBS.
Lyons and Pahwa, (2006)	89 (pre-DBS)	89 (6 months post-DBS) 83 (12 months post-DBS) 43 (24 months post-DBS)	Bilateral STN	ESS	-	UPDRS activities of daily living, motor scores, total sleep time were significantly improved at 6, 12 & 24 months post-DBS compared to pre-DBS baseline. No significant difference in ESS scores before and after DBS.

Table 1.2 (continued): Studies assessing the effects of DBS on sleep parameters in patients with PD.

Reference	Control (n)	Study group (n)	DBS Stimulation Site	Subjective Sleep Measures	Objective Sleep Measures	Study Outcome in patients with PD
Monaca et al., (2004)	10 (pre-DBS)	10 (with two conditions DBS-off & DBS-on)	Bilateral STN	PSQI	PSG	Improvement of sleep quality post DBS. ↑ in total sleep time, sleep efficiency and duration of sleep 3 months post-DBS
Kharkar et al., (2018)	40 (pre-DBS)	40 (6 months post DBS) 26 (12 months post-DBS)	Bilateral STN	PDSS ESS	-	Improvement of sleep quality and sleep maintenance 6 and 12 months post-DBS. No changes in ESS scores before and after DBS.

STN: subthalamic nucleus; DBS: deep brain stimulation; PSG: polysomnography; GPi: globus pallidus interna; PSQI: Pittsburgh sleep quality index; PDQ-39: Parkinson's disease questionnaire-39; ESS: Epworth sleepiness scale; PDSS: Parkinson's disease sleep scale; WASO: wake after sleep onset; REM: rapid eye movement; RBD: REM sleep behaviour disorder; IRLSSG: International Restless Leg study group; RLS: Restless legs syndrome; RDBSQ: REM sleep behaviour disorder screening questionnaire; ↑ = increased; ↓ = decreased.

1.8. Non-motor symptoms in PD and their relationship with sleep

In PD, sleep disturbances are strongly associated with non-motor and motor symptoms. These symptoms experienced by patients with PD also significantly influences their QOL (Wennberg et al., 2017). However, studies show there is a decrease in the severity of most non-motor and motor symptoms in PD post-DBS (Groiss et al., 2009, Klingelhoefer et al., 2014).

1.8.1. Cognitive function and mental health

Approximately 30-50% of patients may have mild cognitive dysfunction at PD diagnosis and 60-80% of patients develop dementia during the advanced stages (Huang et al., 2017, Roheger et al., 2018). The profile of cognitive dysfunction in PD is diverse, but it commonly affects the following cognitive functions, attention, memory, executive and visual-spatial abilities (Roheger et al., 2018). Evidently, studies have shown that cognitive functions have been reported to suffer from the impact of sleep disturbances in PD (Stavitsky et al., 2012, Hermann et al., 2020). A large cohort study (n = 197 PD patients) found that sleep disturbances are associated with impaired visuospatial functioning, visual learning, and memory (Specketer et al., 2019). Furthermore, sleep disturbances such as RBD could potentially contribute to cognitive dysfunction (Sobreira et al., 2019), as indicated by PD patients with RBD performing poorly in memory, visuospatial and executive function tasks compared to PD patients without RBD (Huang et al., 2017). The specific impact of sleep disturbances in PD patients on cognitive function still remain unclear, although they seem to aggravate the decline observed in PD. However further studies, investigating whether improving sleep in PD patients improves cognitive function are required. Table 1.3. shows a summary of studies that have assessed the relationship between sleep and cognitive function in patients with PD.

Table 1.3: Studies assessing the relationship between sleep and cognitive function in non-DBS patients with PD.

Study	PD patients	Sleep measures	Cognitive domain	Outcome
Stavitsky et al., (2012)	35	Actigraphy	Attention and executive function, memory and psychomotor function	Poor sleep associated with decline in attention and executive function.
Specketer et al., (2019)	192	NPI Mayo sleep questionnaire MD-UPDRS Part 1	Visuospatial functioning and visual learning and memory	Sleep disturbances are associated with visuospatial functioning and visual learning and memory.
Huang et al., (2017)	96	PDSS-2 ESS PSQI	Memory, visuospatial and executive function	Patients with RBD performed poorly in memory, visuospatial and executive function tasks.
Sobreira et al., (2019)	79	PSG ESS PSQI PDSS	Memory, visuospatial ability, executive functioning, verbal fluency	Weak correlation between visuospatial ability and ESS ($r = -0.236$; $p = 0.037$) Significant association between global cognitive performance and WASO ($r = 0.592$; $p = 0.0001$).
Hermann et al., (2020)	26	PSG PSQI PDSS-2 ESS	Attention and executive function, working memory, and semantic memory	Cognitive impairment was associated with impaired sleep quality and sleep disturbances.

RBD: REM sleep behaviour disorder; ESS: Epworth sleepiness scale; WASO: wake after sleep onset; NPI: Neuropsychiatric Inventory; MD-UPDRS: Unified Parkinson's Disease Rating Scale, Movement Disorders Society revision; PDSS: Parkinson's disease sleep scale; PSQI: Pittsburgh sleep quality index.

Understanding the mechanisms that may result in the improvement or deterioration of cognitive function in patients with PD may have potential implications for the treatment options in PD, specifically DBS. The cognitive status of patients is important when considering DBS as a potential treatment for PD. Patients who display a significant cognitive decline are considered as poor candidates for DBS due to many reasons of autonomy, co-operation and post-DBS cognitive changes (Massano and Garrett, 2012). Thus cognitive dysfunction plays a vital role in deciding which PD patients are eligible candidates for DBS (Massano and Garrett, 2012).

Research has shown an association between sleep disturbance, fatigue and depression and anxiety (Rutten et al., 2017, Kay et al., 2018). Depression is a prominent feature in patients with PD with an occurrence of approximately 40-50% (Marsh, 2013). A study found that in 50 patients with idiopathic PD, a shorter total sleep time was associated with depression severity (Kay et al., 2018). They further concluded that total sleep time may be an important predictor or consequence of depression in PD (Kay et al., 2018). Similar results were seen in another study, which found not only higher levels of depression but also increased levels of anxiety that were significantly associated with sleep disturbances in PD (Fan et al., 2016). Dopamine dysfunction could be a possible mechanism through which sleep disturbance may be associated with fatigue and depression in PD (Fu et al., 2016, Kay et al., 2018), however, further investigation is required. Some studies have reported a mild improvement in PD post-DBS (Castelli et al., 2006, Lhommée et al., 2012), however two randomized control studies showed no difference in PD six months post-DBS (Deuschl et al., 2006, Weaver et al., 2009). According, Kurtis et al. (2017) there is evidence suggesting that DBS does not worsen depression, while some studies suggest DBS results in a slight improvement in depression for patients with PD.

1.8.2. Pain

Pain is commonly classified as a non-motor symptom of PD and affects 61-81% of patients with PD (Kim et al., 2011, Martinez-Martin et al., 2018). Previous research has shown that the manifestation of pain in PD can be divided into different subtypes such as dystonic, central pain, radicular-neuropathic pain, and musculoskeletal pain (Ford, 2010). However, the exact pathophysiologic mechanism causing pain in PD is still unclear (Kim et al., 2011).

Pain and sleep have a bidirectional relationship that negatively affects one another (Finan et al., 2013). In PD studies, patients with pain have reported poorer sleep quality and more sleep disorders compared with patients without pain (Martinez-Martin et al., 2018, Rana et al., 2018). A large cohort study (n = 229) found that in PD the correlation between sleep disturbances and pain highly depends on the subtype of pain, particularly central pain, which is significantly related to an increased risk of sleep disturbances (Vila-Chã et al., 2019). Central pain has been reported to be the only subtype of pain that is not caused by musculo-skeletal pain or dystonia however, it is a direct consequence of the disease as a result of abnormal information processing (Ford, 2010). Another study (n = 144) investigating the relationship between sleep and pain in PD showed that pain was present in 52 % of PD patients, musculo-skeletal pain being the most prominent type of pain (Fu et al., 2018). They conducted a PSG and found that PD patients with pain had sleep fragmentation, seen by the decreased total sleep time (TST) and increased WASO (Fu et al., 2018), indicating that pain may influence sleep.

Modifications in the striatum and a deficiency in dopamine are hallmarks of PD (Vila-Chã et al., 2019). A review by Finan et al. strongly suggested that dopamine may have a role in the relationship between pain and sleep. Dopamine is an important neurotransmitter in maintaining and promoting arousal states and is therefore linked to the regulation of sleep and wake (Dzirasa et al., 2006, Monti and Jantos, 2008, Finan et al., 2013). In the brainstem specifically, the raphe nuclei, which houses the ascending reticular activating system and dopamine receptors are found in abundance. This is known to be an important sleep-regulating region (Lu et al., 2006). Furthermore, a deficiency in dopamine has been found to play an important role in central parkinsonian pain (Taylor et al., 2016) and in chronic pain it has been proposed that the signaling of serotonin raphe cells become dysregulated, contributing to disrupted sleep (Foo and Mason, 2003). Therefore, changes caused by pain in the dopamine signaling pathway may impact the regulation of sleep in the raphe nuclei (Finan et al., 2013). Several studies have shown that STN DBS improves pain however, the mechanism of improvement is unclear (Loher et al., 2002, Gierthmühlen et al., 2010, Kim et al., 2011, Kurtis et al., 2017).

1.9. Impact of physical activity on sleep in PD

1.9.1. Physical activity

The clinical motor features of PD (rigidity, decreased walking ability, freezing of gait, tremor and postural instability), affects daily functioning and often suggest that patients are reluctant or unable to participate in regular physical activity, therefore promoting an increase in sedentary behaviour (van Nimwegen et al., 2011). For example, a study conducted by Benka Wallén et al., in 95 patients with PD shows that approximately 75% of patients spent their awake time in sedentary behaviour, 6% of wake time was spent doing light physical activity and 6% was spent performing moderate to vigorous physical activity (Benka Wallén et al., 2015). It was noted by Van Nimwegen et al, that a reduced physical activity in PD is associated with poor walking performance, increased disability in daily activities and disease severity (van Nimwegen et al., 2011).

Research using accelerometry and subjective measures (i.e., physical activity questionnaires) found that patients with PD are approximately 30% less physically active than healthy individuals (van Nimwegen et al., 2011, Lord et al., 2013). Another study found that patients with PD spent significantly less time walking and took fewer steps daily when being compared to the healthy control group. Specifically, the patterns of activity in the PD group indicated that ambulant activity consisted mostly of shorter bouts and a decreased variability in bout length (Lord et al., 2013). These differences were most apparent in patients with mild disease severity (Lord et al., 2013). This further suggests that in PD there is a more restricted pattern of physical activity.

Several studies have shown an association between increased sedentary behaviour and poor sleep quality in older healthy adults (de Castro Toledo Guimaraes et al., 2008, Madden et al., 2014, Prusynski et al., 2021). A study comparing sleep parameters in physically active and sedentary elderly women showed that the physically active group obtained longer total sleep time (TST), a decrease in WASO and an increase in sleep quality compared to the sedentary group (de Castro Toledo Guimaraes et al., 2008).

These patterns of physical activity and sedentary behavior and their relationship with other motor and non-motor features of PD may be important to ascertain in patients whose conditions may hinder their ability to move and ultimately have an impact on their sleep. A recent study

involving patients diagnosed with PD speculated that a decrease in sleep is associated with a decrease in physical activity (Prusynski et al., 2021). Using activity monitors, they found that PD patients obtained lower levels of nighttime sleep (75 fewer minutes of sleep) and spent less minutes doing moderate to intense physical activity compare to healthy older adults (Prusynski et al., 2021). Further research is required to determine the nature of the relationship between sleep and physical activity in PD patients.

Although the exact causes behind the relationship between sedentary behaviour and poor sleep are unknown, many mechanisms have been hypothesized. Exposure to sunlight may be a contributing factor to physical activity and increased sleep quality (Dzierzewski et al., 2014), in which sunlight is known to be a vital zeitgeber of circadian rhythms (de Castro Toledo Guimaraes et al., 2008). Another possible mechanism is the association between sedentary behaviour and melatonin levels. A study conducted on rotating-shift nurses showed an inverse relationship between sedentary behaviour and melatonin levels (McPherson et al., 2011), thus indicating that an increased sedentary behaviour results in lower levels of melatonin which ultimately impacts sleep. A decrease in sleep quality and duration may result in more time spent in sedentary behaviour due to increased levels of fatigue during waking hours, making this another potential mechanism (Benka Wallén et al., 2015, Kostić et al., 2016).

Physical activity has also been shown to improve sleep in PD (Amara and Memon, 2018). For example, a study evaluated 42 PD patients who underwent resistance, aerobic, and balance training and found a significant improvement in sleep quality in the exercise group compared to the control (Nascimento et al., 2014). Another study conducted had similar results, where 22 PD patients who performed resistance training had a better sleep score relative to the control group (Silva-Batista et al., 2017). Therefore, physical activity can be used as a non-pharmacological intervention to improve sleep in PD. DBS is shown to improve motor symptoms in PD however, it does not change the physical activity behaviour in patients with PD (Daneault et al., 2015).

1.9. Rationale for the study

The findings in this literature review highlight the effects of non-motor symptoms in PD, and how these non-motor symptoms contribute to a poor QOL in patients with PD. It can be seen that sleep is a prevalent non-motor symptom and can widely affect or be affected by other and non-motor symptoms of PD as seen in the literature. The relationship between other PD-related non-motor symptoms and sleep needs to be explored further (Figure 1.4), hence determining these relationships may provide insight into the mechanisms of these sleep disturbances and help improve treatment options for patients with PD. Lastly, more research is required to better understand the effects of DBS in sleep disturbances and other non-motor and motor symptoms in PD, as it could potentially improve the QOL for patients diagnosed with PD.

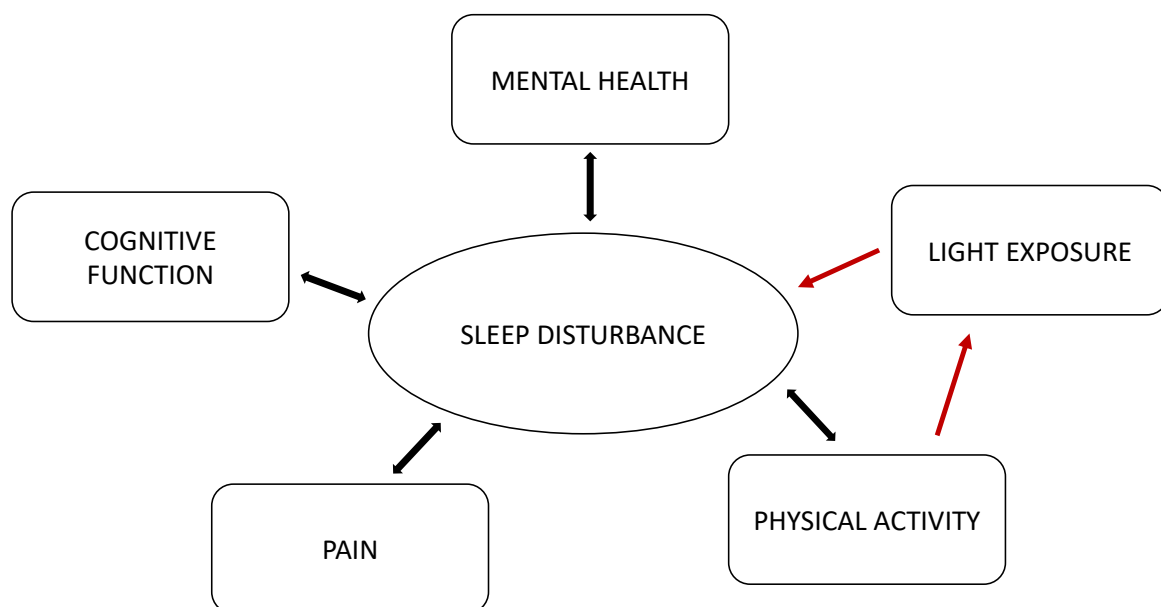


Figure1.4: Schematic diagram shows the interrelations between sleep and other non-motor and motor PD-related symptoms. Pain and sleep; cognitive function and sleep; mental health and sleep and physical activity all exhibit a bidirectional relationship. Physical activity, specifically sedentary behaviour may result in a decreased light exposure which may impact sleep in PD. Sleep can widely impact or be impacted other non-motor symptoms of PD as well as physical activity and light exposure.

1.10. Aims and study objectives

This study aims to compare sleep in patients with PD following deep DBS with PD patients who have not undergone DBS as well as to determine the relationship between sleep parameters and other PD-related non-motor symptoms such as cognitive function, depression, fatigue, pain, physical activity and light exposure.

The study objectives are to:

- Objectively measure sleep using polysomnography and actigraphy in PD patients post-DBS and PD patients who have not undergone DBS.
- Subjectively measure sleep using specific sleep questionnaires in PD patients post-DBS and PD patients who have not undergone DBS.
- Objectively assess patterns of physical activity and sedentary behavior and circadian rhythmicity in PD patients post-DBS and PD patients who have not undergone DBS.
- To characterise cognitive function, depression, fatigue, pain, physical activity and light exposure in PD patients post-DBS and PD patients who have not undergone DBS.
- Determine the relationship between sleep parameters and cognitive function as well as depression, fatigue, pain, physical activity and light exposure in PD patients post-DBS and PD patients who have not undergone DBS.

Chapter 2: Methods and materials

2.1. Ethical Approval

The methodology of this study was approved by the Human Research Ethics Committee at the University of Witwatersrand (Ethics clearance number: M200510; appendix 1). All ethical standards for human research were upheld (The Helsinki Declaration and the Singapore Statement on Research Integrity) and formal written consent was obtained from all patients.

2.2. Patients

All clinical PD patients were recruited between October 2020 and August 2021 through a private neurology practice. One hundred and forty eligible adult (≥ 18 years old) patients were contacted to participate in this study. One hundred and eighteen patients were not included for the following reasons: thirteen patients were not interested; three patients had already passed away when contacted and one hundred and two patients did not respond (Figure 2.1). Patients who did show interest in the study ($n = 22$) were contacted via email and telephone, and were provided with the study information documents (appendix 2).

The patient inclusion criteria consisted of patients who were diagnosed with PD and were willing and able to give their full consent to participate in the study. Only patients over the age of 18 were invited to participate in the study and only patients with a self-reported good proficiency in English were included. An informed signed consent was obtained by each patient and their next of kin.

This study included two groups of patients with PD: one group who had undergone DBS ($n = 7$) and another group who had not undergone DBS ($n = 15$) (Figure 2.1). The group that had not undergone DBS, acted as the control group. The two groups were age and gender matched. All DBS patients had undergone STN stimulation.

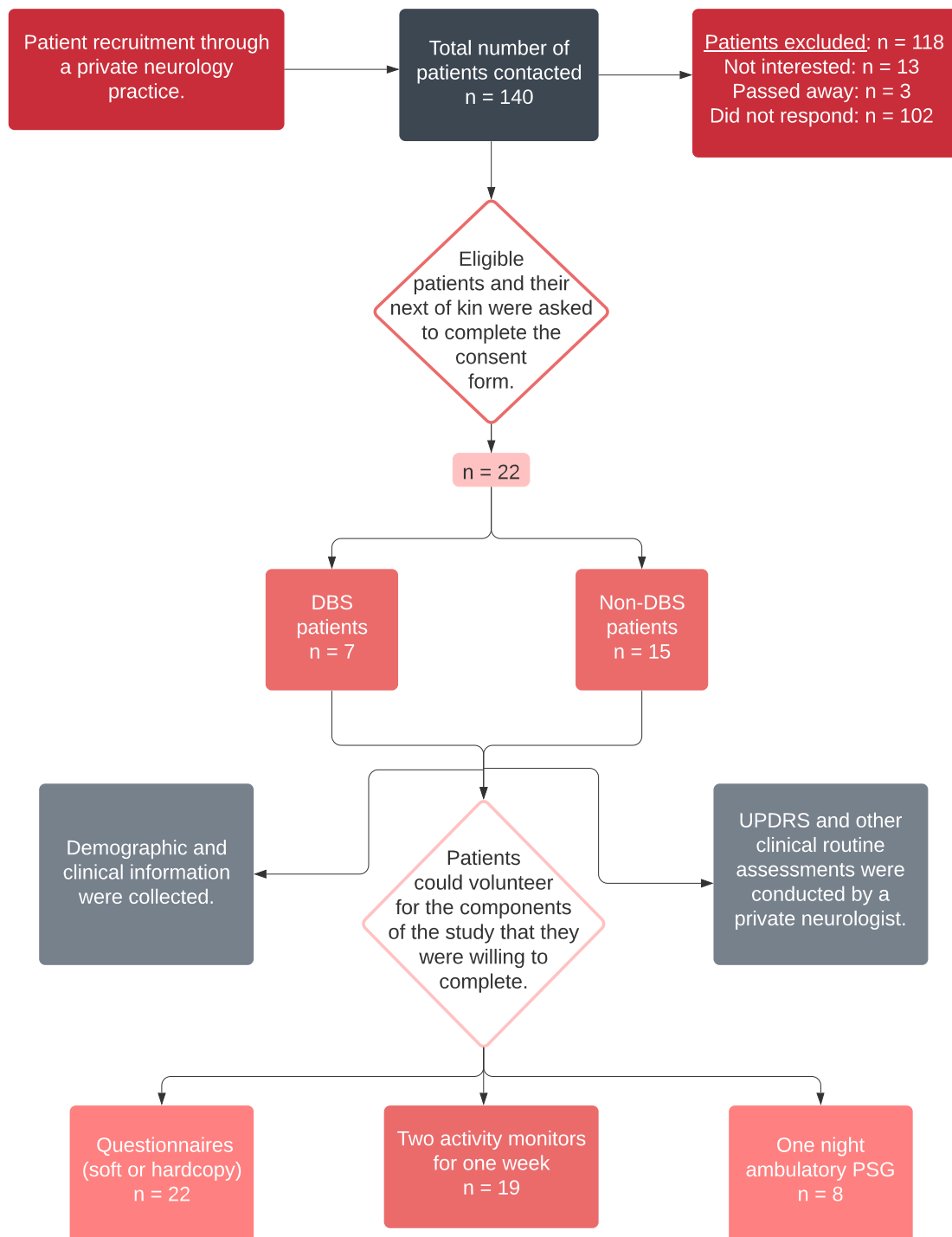


Figure 2.1. Overview of recruitment and methodology. In the same week patients received the questionnaires, both activity monitors were distributed to the patients.

2.3. Patient demographic and clinical information

Demographic characteristics (general information regarding age, sex, height and weight) and clinical information (medical history, age of onset of disease, duration of PD diagnosis,

comorbidities, medication use and dopaminergic drug dosages) was obtained through the following: General Health questionnaire (Appendix 4) and a review of medical records via the Donald Gordon Medical PD database. The neurologist provided the Movement Disorder Society- Unified Parkinson's Disease rating scale scores (MDS-UPDRS). The MDS-UPDRS is used as a rating tool to determine the severity and progression of Parkinson's Disease. It is made up of six categories: Mentation, Behaviour and mood; Activities of daily living (ADL); Motor evaluation; Complications of therapy; Modified Hoehn and Yahr scale and Schwab and England ADL (Fahn et al., 1987). To obtain the LED for each patient, the levodopa equivalent daily dose (LED) was calculated according to the standardized formulae as: $LED (mg) = [L-dopa (mg)] + [Controlled release L-dopa (mg) \times 0.75] + [pramipexole (mg) \times 100] + [ropinirole (mg) \times 20] + [piribedil (mg)] + [bromocriptine (mg) \times 10]$ (Amjad et al., 2019).

2.4. Analysis of sleep, other non-motor symptoms, physical activity and light exposure

The methodology below describes the procedures used to assess sleep, fatigue, physical activity, light exposure, pain, cognitive function, and mental health. The data collection began in November 2020 and concluded in August 2021. Data collection commenced with the administration of questionnaires. The activity monitors were distributed within ± 1 week of administering the questionnaires. The ambulatory PSG was conducted within ± 3 months of completing the questionnaire and activity monitoring. The UPDRS and other routine clinical assessments were completed within ± 6 months of the questionnaires. DBS: deep brain stimulation, PSG: polysomnography.

2.4.1. Administration of questionnaires assessing sleep, cognitive function, mental health, and pain parameters

Each patient was asked to complete a series of questionnaires either electronically or as a hardcopy, to explore their sleep, pain, fatigue, cognitive function, and emotional well-being (Table 2.1). The electronic questionnaires were distributed using RedCap (Research Electronic Data Capture) software (version 10.3.5- © 2020 powered by Vanderbilt) (Harris et al., 2009).

Table 2.1: Overview of questionnaires administered during the study

Category	Name of questionnaire	Appendix #
Sleep	Epworth Sleepiness Scale (ESS)	9
	Pittsburgh Sleep Quality Index (PSQI)	10
	Fatigue Severity Scale (FSS)	13
	Cambridge Hopkins restless leg syndrome questionnaire (CH-RLSq)	11
	International Restless Leg Syndrome Severity Scale (IRLSS)	12
Cognitive function and mental health	Parkinson's Disease Questionnaire -39 (PDQ-39)	7
	Beck's Depression Inventory II (BDI II)	5
	World Health Organisation -5 wellbeing index (WHO-5)	6
Pain	Short-form McGill pain questionnaire (SF-MPQ)	14

2.4.2. Sleep questionnaires

The Epworth Sleepiness scale (ESS) is a self-administered scale used to assess daytime sleepiness. It has been well validated by various studies and has a sensitivity of 94 % and a specificity of 100% (Johns, 1991, Johns, 2000, Kumar et al., 2003). The ESS consists of eight items. Each item has a scale from zero (would never doze) to three (high chance of dozing) with a total score ranging between 0-24. The total score was calculated by adding all eight items. A score of ≥ 10 indicates the presence of excessive daytime sleepiness (Aurora et al., 2011).

The PSQI is a self-reported questionnaire, commonly used in PD sleep studies to assess overall sleep abnormalities. It consists of 19 questions that make up seven components which are: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. Each component was scored individually from zero (no difficulty) to three (severe difficulty) (Buysse et al., 1989). We included each component of the PSQI to obtain a more descriptive subjective sleep in each patient. The scores for each of the seven components were then added to generate a global PSQI score, which ranges between zero and 21. A higher global PSQI score indicates an increased sleep impairment (Chen et al., 2018, de Almeida et al., 2019) and a global score >5 indicates poor sleep quality (de Almeida et al., 2019).

Fatigue Severity Scale (FSS) is a nine item questionnaire that assess the effect of fatigue on daily living in PD patients (Krupp et al., 1989). Each item was scored from one (completely disagree) to seven (completely agree) and the total score was determined by calculating the

mean across all the responses to the nine questions (Krupp et al., 1989). It is a reliable questionnaire with internal consistency (Valko et al., 2008). Patients with a score of four or more have significant fatigue (Herlofson and Larsen, 2002). The FSS is also able to differentiate between the frequency and severity of fatigue between healthy individuals and patients with sleep-wake disturbances (Valko et al., 2008). A mean FSS score of 3 is found in healthy individuals. In patients with sleep disturbances, the following mean scores were found, 4.78 in patients with insomnia, 4.75 in patients with narcolepsy and 4.02 in patients with restless leg (Valko et al., 2008).

To assess the presence and severity of Restless Leg Syndrome, two questionnaires were administered- the Cambridge Hopkins restless legs syndrome questionnaire (CH-RLSq) to assess whether the patient has RLS and the International restless legs severity scale (IRLS) to assess the severity of the RLS. The CH-RLSq is a validated self-completed RLS questionnaire. It contains 13 questions with an additional questionnaire for pregnant women and is one of the only RLS questionnaires that also includes questions that exclude common conditions that produce symptoms similar to those RLS (Allen et al., 2009, Allen et al., 2014), therefore increasing its accuracy for diagnosis. The first eight questions covered only diagnosis of RLS and the remaining five cover critical severity and phenotype determinations (Allen et al., 2009, Allen et al., 2014). Patients were confirmed with a definitive diagnosis of RLS if they fulfilled all the essential RLS diagnostic criteria.

The IRLS scale contains 10 questions related to the severity of RLS and the impact of RLS on daily living, by which each patient will rate all 10 questions from zero to four. The total score was calculated by adding all the answers to each question, which range between zero and 40. A total score obtained between 0-10 represents mild RLS, 11-20 represents moderate RLS, 21-30 represents severe RLS and 31-40 represents very severe RLS. The IRLS scale serves as the primary endpoint for most therapeutic studies of RLS and has become the gold-standard outcome measure for trials in RLS (Walters et al., 2014).

2.4.3. Cognitive function and mental health questionnaires

The Parkinson's Disease Questionnaire-39 (PDQ-39) is a self-reported instrument containing 39 items, which assesses how often PD patients experience difficulty associated with their PD across eight quality of life dimensions. These eight dimensions included, mobility (questions

1-10), activities of daily life (questions 11-16), emotional well-being (questions 17-22), stigma (questions 23-26), social support (questions 27-29), cognition (questions 30-33), communication (questions 34-36) and bodily discomfort (questions 37-39). Each question has a five-point ordinal scoring system (0 = never, 1 = occasionally, 2 = sometimes, 3 = often, 4 = always) and the dimension has a total score that can range from zero (never have difficulty) to 100 (always have difficulty), where higher scores reflected a poor quality of life. Each dimension score was calculated by adding all the scores from each item in the dimension, divided by the maximum possible score of all the items in the dimension, multiplied by 100. The overall score summarised by the PDQ-39 summary index was calculated by the sum of each of the dimension scores divided by eight (Jenkinson et al., 1997). A cognitive score of 11.2 and greater indicates cognitive dysfunction (Fitzpatrick et al., 2004).

The Beck's Depression Inventory II (BDI II) questionnaire is a widely used self-report instrument with 21-items, which assesses the severity of depression. The BDI is recommended by the Movement Disorders Society Task force as a validated continuous measure of depression severity in PD (Schrag et al., 2007, Kay et al., 2018). Each question has a score ranging from 0-3. A total score (level of depression) was calculated by summing the score obtained for each question of the 21 questions. This total score ranges from 0 -63 (Beck et al., 1996). A total score between 0 - 13 is considered minimum, 14 - 19 is considered mild, 20 - 28 is considered moderate and 26 - 63 is considered severe (Beck et al., 1996).

The World Health Organisation-5 wellbeing index (WHO-5 wellbeing index) contains five items that measured the subjective well-being of an individual (Topp et al., 2015). The score for each of the five statements in the questionnaire ranged from zero (none of the time) to five (all of the time), a total raw score was calculated by adding each score from each statement which ranged from zero (absence of wellbeing) to 25 (maximal wellbeing) (Topp et al., 2015). This raw score was then multiplied by four to give a final score ranging from zero (worst imaginable wellbeing) to 100 (best imaginable wellbeing) (Topp et al., 2015). The WHO-5 is a valid tool in screening for depression in patients with PD (Topp et al., 2015). A cut-off score of < 50 is used to screen depression (Topp et al., 2015).

2.4.4. Pain questionnaire

The short-form McGill pain questionnaire (SF-MPQ) includes 17 items and is used to assess pain in four domains (sensory, affective, intensity and present pain intensity). It comprised of 15 words describing different aspects of pain. The first 11 words in the questionnaire represent the sensory dimension and the last four words represent the affective dimension. Each word that described a type of pain was rated by a scale from 0-3 (Perez-Lloret et al., 2016). To obtain a score for the sensory domain, the rank values of the words chosen in the set 1-11 were added. For the affective domain, the rank values of the words chosen in the set 12-15 were added. Lastly, to obtain the overall total score for SF-MPQ, the two domains (sensory and affective) were added. There are no established cut-off points or critical scores (Hawker et al., 2011), however a higher score indicated to a higher level of pain (Perez-Lloret et al., 2016).

2.5. Home-based activity monitoring to assess sleep, physical activity, and light exposure.

All patients were provided with two activity monitors, a wristwatch tri-axial activity monitor (ActiWatch Spectrum or ActiWatch 2, Philips Respironics, Andover, Ma) and a hip-mounted activity monitor (ActiGraph GT3X+, ActiGraph, Pensacola, FL) (Figure 2.2). The patients were asked to wear both activity monitors for seven consecutive days, for 24 hours a day while removing both activity monitors for water-based activities.

The ActiWatch, either the Philips Respironics ActiWatch spectrum (4.8cm x 3.7cm x 1.5cm in dimension with a weight of 31g) or ActiWatch 2 (4.3cm x 2.3cm x 1.0cm in dimension with a weight of 16g) was worn on the non-dominant hand. The ActiWatches contain a built-in accelerometer and light sensor and were set to 1-minute epochs. ActiGraph GT3X+ are small, (3.8 cm x 3.7 cm x 1.8cm), light weight (27g) triaxial accelerometers. They were set to a medium sensitivity with a frequency 40 Hz and an epoch length of 60 seconds. The ActiGraph was worn on the non-dominant hip.

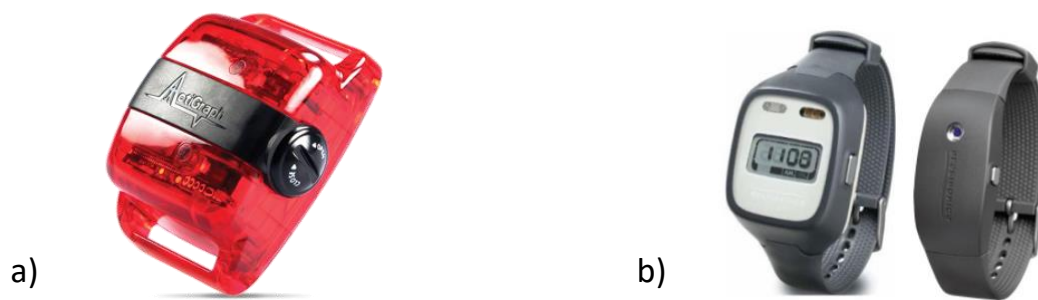


Figure 2.2. Activity monitors used in this study to measure sleep, physical activity and light exposure. a) hip-mounted ActiGraph GT3X+ b) wrist-worn Philips Respironics Spectrum and ActiWatch 2.

All the data collected during waking and sleeping hours were used and analysed to determine patterns of physical activity, sedentary behavior, light exposure, sleep, and circadian rhythmicity. Concurrent to the activity monitors, the patients were asked to complete a sleep and activity diary (Appendix 8), for seven consecutive days to corroborate the data from activity monitors. The sleep and activity diary were used to record bedtime, sleep onset latency, waking time, subjective sleep quality, daytime sleepiness, and periods of exercise during the day.

2.5.1. Data extraction and analysis using activity monitor software

The data obtained from both activity monitors were averaged across the seven days. For the Actiwatches, the Philips Respironics software (version, Koninklijke Philips N.V., 2004 - 2021) was used to download the ActiWatch data which included sleep parameters, physical activity, and light exposure (mainly white light, measured in lux). Circadian parameters were extracted from a cosinor analysis, that were run on the actigraphy data from the wristwatch tri-axial activity monitors. For the Actigraphs, the ActiLife software (version 6, Pensacola, Florida) was used to extract and analyse the sleep parameters and accelerometer data. The sleep parameters consisted of: sleep latency, sleep time, sleep efficiency, wake after sleep onset, number of awakenings and movement and fragmentation index (Stavitsky and Cronin-Golomb, 2011) and were measured using the Cole-Kripke sleep algorithm. Physical activity was measured and

analysed using the Freedson Adult (1998) algorithm, which consisted of sedentary, light, moderate, vigorous, and very vigorous activity.

2.6. Polysomnography (PSG) to objectively assess sleep

Ambulatory PSG was performed at the patient's home, $\pm$ 3 months after completing the sleep questionnaires and one-week of activity monitoring. The Cadwell Easy Ambulatory 2 system (Kennewick, WA 99336 USA) which consisted of the electroencephalography (EEG), electro-oculogram (EOG), chin and leg electromyography (EMG) was used to conduct the PSG. There was one night of adaptation to the set-up of the PSG equipment followed by one night of sleep monitoring for each patient (Figure 2.3).

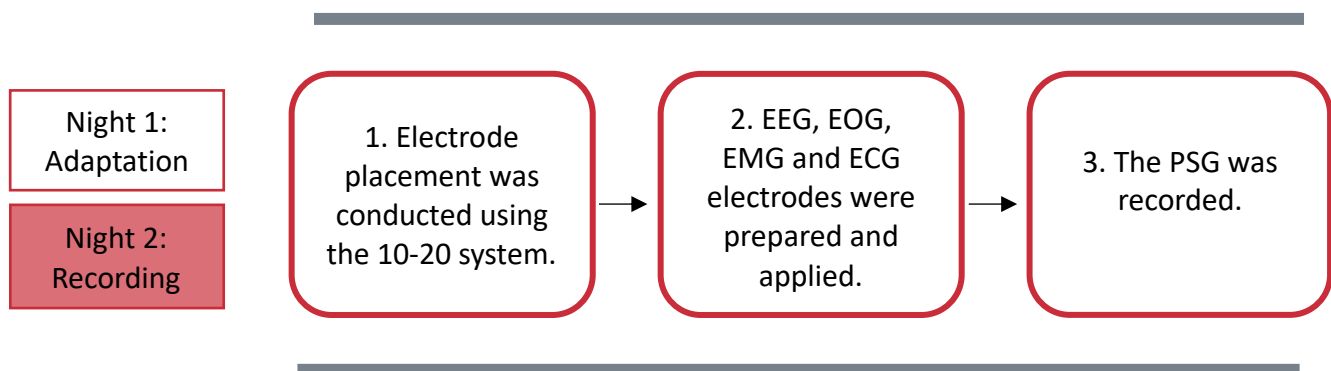


Figure 2.3. Overview of the procedures for the ambulatory Polysomnography (PSG) set-up at the patient's home. 10-20 system = International 10-20 electrode system ;EEG = electroencephalography; EOG = electro-oculogram ;EMG = electromyography ;ECG = electrocardiogram.

2.6.1. Electrode placement for PSG

This study used the International 10-20 electrode placement system to determine the placement location of the electrodes for recording sleep (Figure 2.4). To obtain the patient's head measurements for the placement of the electrodes, the four distinct skull landmarks; the nasion, inion, left pre-auricular point and right pre-auricular points, were first determined and marked (Figure 2.5) (Campbell, 2009). The electrodes were placed at 10% or 20% intervals of the distance between the skull landmarks (Figure 2.4) (Campbell, 2009). A total of 9 EEG electrodes were used and they were located at the following points: occipital electrodes which consisted of O1 and O2, central electrodes which consisted of C3, C4, frontal electrodes which consisted of F3 and F4, Fpz = ground electrode, A1 and A2 which were used as reference

electrodes. The EOG electrode placement consisted of the right outer canthus (ROC) and left outer canthus (LOC). The EMG electrode placement locations were on the chin (at the mentalis) and on the left and right legs (on the belly of the tibialis anterior muscle). The ECG electrodes were placed just below the right clavicle (collar bone) and on the fifth left intercostal space (Figure 2.6).

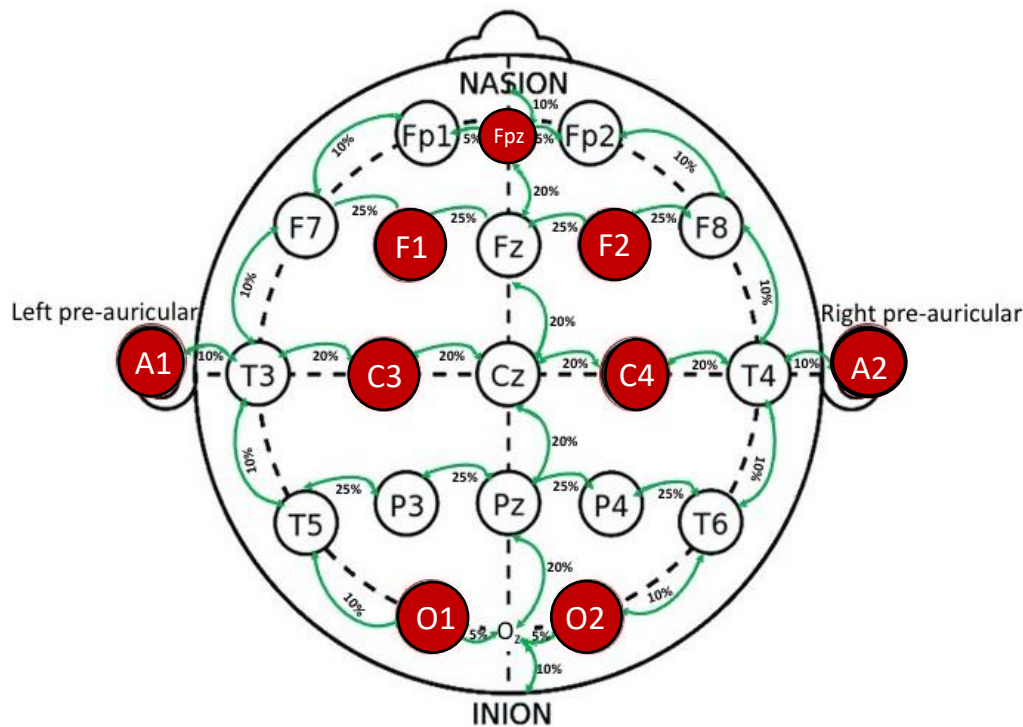


Figure 2.4. The summary of the international 10-20 electrode placement system for the ambulatory PSG. Electrodes were placed at 10% or 20% intervals of the distance between the skull landmarks. The circles highlighted in red shows the EEG electrode placements which consisted of occipital electrode = O1, occipital electrode = O2, central electrode = C3, central electrode = C4, frontal electrode = F3, frontal electrode F4, Fpz = ground electrode, A1 and A2 (Rojas et al., 2018).

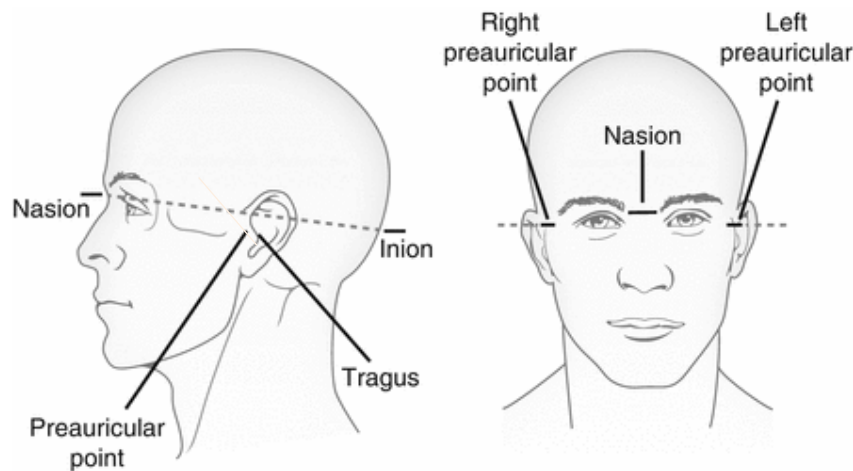


Figure 2.5. The location of the four landmarks used in the International 10-20 electrode placement- nasion, inion, left and right pre-auricular points (Sullivan and Davis, 2014).

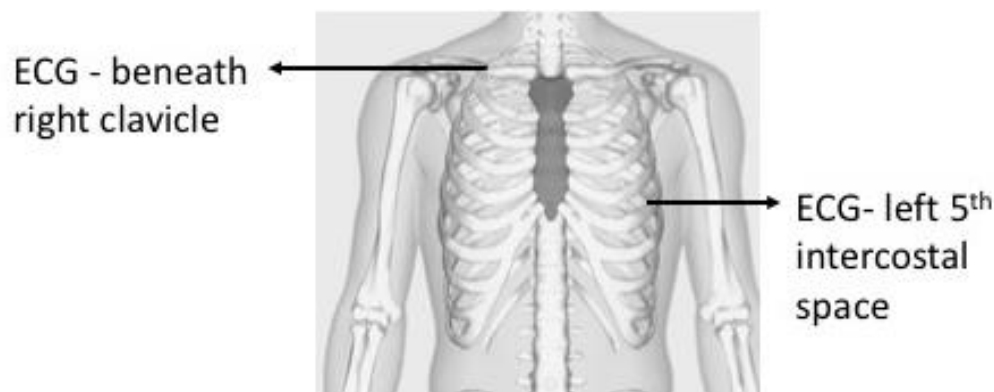


Figure 2.6. The electrocardiogram (ECG) electrode placement, one just below the right clavicle (collar bone) and one on the fifth left intercostal space for polysomnography (PSG).

2.6.2. Electrode preparation

All EEG, EOG, ECG and EMG electrode placement sites were first wiped with an alcohol swab. The EEG, EOG and chin EMG electrodes sites were then cleaned using Nuprep skin prep gel and the electrodes were filled with Ten20 electrode conductive paste and were pressed onto the clean area of the scalp or skin. A piece of gauze or micropore was then placed over the electrode. To secure the electrodes collodion was applied to the gauze and supplemented with the use of a head-net. An electrolyte gel was injected into the electrodes using a blunt needle and syringe. A disposable electrode with a snap electrode was attached for the ECG and leg EMG.

2.6.3. Recording the PSG

Ambulatory PSG was recorded using the Cadwell Easy Ambulatory 2 system, Easy II software version 2.1 (Cadwell ® Industries Inc., Kennewick, WA 99336 USA) (Figure 2.7). The filter settings that were used for the EEG and EOG were as follows; a low frequency filter 0.53 Hz, and a high frequency filter 35Hz. For the EMG filters, a low frequency filter setting of 10 Hz and a high frequency filter setting of 70 Hz was used. For the ECG filters, a low frequency filter setting of 0.53 Hz and a high frequency filter setting of 70 Hz was utilized. The impedance of all the electrodes was checked, to ensure all the electrodes presented with the correct impedance. If there were any electrodes that presented with a high impedance, more electrolyte gel was injected into the electrode to increase the conductance of the electrode and decrease any impedances.



Figure 2.7. Showing the Cadwell Easy Ambulatory system set up. The Cadwell Easy Ambulatory system consisted of a D-cell battery powered recorder and amplifier (image taken from the Wits sleep laboratory, polysomnography standard operating system).

2.6.4. PSG scoring

The PSG recordings were manually scored (according to standard criteria using the American Academy of Sleep Medicine (AASM) guidelines) to determine sleep architecture. The PSG sleep recording for each patient was scored using the Easy II software version 2.1. Each epoch

(30 second intervals) was scored as either awake, stage 1, stage 2, stage 3, or REM. All events such as eye blinks, swallowing, talking, drowsiness, coughing, head movement, muscle artefact and sneezing were marked. The amplitude and frequency of the brain waves were measured and once the scoring was completed, a report was generated.

3. Statistical Analysis

All statistical data analysis was performed using GraphPad Prism version 8 (Graph-pad Software Inc., San Diego, USA), and SPSS version 27 (IBM Corp. Armonk, NY) with a significant threshold at $p\text{-value} < 0.05$. Parametric data are expressed as mean and standard deviation ($\pm$ SD) and non-parametric data are expressed as median (interquartile range (IQR)). To assess whether groups were age and gender matched, an unpaired t-test was conducted. All graphs were prepared using GraphPad Prism version 8.

Unpaired t-tests were used to compare the subjective sleep measures in both the DBS and non-DBS groups. For the non-parametric data, the Mann-Whitney test was used to compare subject sleep measures in the DBS and non-DBS group. To assess the objective sleep measures, unpaired t-tests were used to compare the data extracted from the wrist and hip-mounted activity such as total sleep time, latency, sleep quality, sleep efficiency, WASO and duration of sleep in both groups. To determine whether the wrist and hip activity monitors were in agreement for each sleep parameter, a Kendall's (W) test was conducted. To assess the relationships of sleep and other PD-related non-motor symptoms such as cognitive function, pain, fatigue, physical activity and light exposure) correlations were performed on the combined sample (both DBS and non-DBS groups. Individual two-tailed Pearson's correlations (r) were used to assess the relationships between sleep parameters and PD-related non-motor symptoms for parametric data. The Spearman's correlation (r_s) was used to assess the relationships between pain, fatigue and the sleep parameters. To control for confounding variables such as Hoehn and Yahr stages and MDS-UPDRS scores for disease severity and LED (mg), an ANCOVA was run to determine whether these confounding variables had an effect on the difference between the DBS and non-DBS group with regards to sleep parameters, other PD-related non-motor symptoms (cognitive function, pain and depression), light exposure and physical activity.

Chapter 3: Results

3.1. Patient Demographic and Clinical Characteristics

The demographical, clinical characteristics and general health of patients are summarised in Table 3.1. Among the 22 patients analysed, 57 % and 47 % were males in the DBS and the non-DBS groups, respectively. The DBS group was age and gender matched to the non-DBS group, which also acted as the control group. The mean age for the DBS group was 70.1 years old and the mean age for the non-DBS group was 67.7 years old. The mean total Movement Disorder Society-Unified Parkinson's Disease Rating scale (MDS-UPDRS) score was not different in the DBS group compared to the non-DBS group, using unpaired t-tests ($p = 0.485$). A Fischer's Test was done to compare the Hoehn and Yahr stages amongst the two groups and a significant difference was found ($p < 0.0001$). More DBS patients presented in stage 2 while a majority of the non-DBS patients presented in stage 1 of Hoehn and Yahr stage. None of the patients presented in stages four and five of the Hoehn and Yahr. The DBS group had a significantly higher mean disease duration 14 years compared to the non-DBS group (three years) ($p=0.008$). There were no significant difference in levodopa equivalent dosage (LED) (mg) between the two groups ($p = 0.394$). Three DBS PD patients were on sleep medication and the same three patients were also on antidepressants while only one patient was on sleep medication and four patients were on antidepressants in the non-DBS group.

The WHO-5 and PDQ-39 scores were also reported in Table 3.1. There was no significant difference between the WHO-5 scores ($p = 0.544$) but the DBS group had a significantly higher PDQ-39 summary index compared to the non-DBS group ($p = 0.009$). For both groups the mean score was above 50, the threshold for the WHO-5 (≤ 50), however 80% non-DBS patients and 71 % of DBS patients obtained a WHO-5 score greater than 50 ($p = 0.720$).

Table 3.1: Summary of the demographic and clinical information of Parkinson's Disease (PD) patients with deep brain stimulation (DBS) and PD patients without DBS (non-DBS)

	DBS	Non-DBS	p-value
n	7	15	-
Gender (male: female)	4:3	7:8	>0.99
Age (years)	70.1 (10.9)	67.7 (11.3)	0.633
Disease duration (years)	14 [9 - 14]	3 [1.5 - 4]	0.008*
Total MDS-UPDRS score	30 (15.9)	25.4 (11.9)	0.485
Hoehn and Yahr stage, (n (%))			<0.0001*
Stage 1	1 (16.7)	7 (50)	
Stage 2	5 (83.3)	6 (42.9)	
Stage 3	0	1	-
Stage 4	0	0	-
Stage 5	0	0	-
LED (mg)	339.3 (213.5)	424.9 (215)	0.394
Sleep Medications, (n (%))	3 (42.9)	1 (6.7)	0.076
Other Medications, (n (%))			
Antidepressants	3 (42.9)	4 (26.7)	0.63
Blood pressure	1 (14.3)	4 (26.7)	>0.99
Cholesterol medication	3 (42.9)	1 (6.7)	0.08
Thyroid	1 (14.3)	1 (6.7)	>0.99
Pain Relief	2 (28.6)	3 (20)	>0.99
Diabetes	1 (14.3)	1 (6.7)	>0.99
Hormone replacement therapy	-	2 (13.3)	>0.99
Anticoagulants	-	2 (13.3)	>0.99
WHO-5 score	56 (22)	61.9(20.2)	0.544
PDQ-39 summary index	38.2 (14.3)	20.6 (13)	0.009*

Parametric data are shown as mean (SD); non-parametric data are shown as median [IQR]. * indicated p-value <0,05. MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale, WHO-5: World Health Organisation -5 wellbeing index, PDQ-39: Parkinson's Disease Questionnaire -39. LED: Levodopa equivalent dosage. Unpaired t-tests analysis within the study groups for age, total MDS-UPDRS score, LED, WHO-5 and PDQ-39. Mann Whitney U-tests analysis for disease duration and Fischer's test was used to analyse Hoehn & Yahr stages 1,2, and 3 (n=20).

3.2. Subjective sleep measures between DBS and non-DBS groups

All 22 patients completed the five sleep questionnaires. The scores obtained from the Epworth Sleepiness Scale (ESS), the Pittsburg Sleep Quality Index (PSQI), the Fatigue Severity Scale (FSS), Cambridge Hopkins restless leg syndrome questionnaire (CH-RLSq) and International Restless Leg Syndrome Severity Scale (IRLSS) were compared between the two study groups, DBS and non-DBS. Sample of size of participants were too small to conduct multivariant analysis.

The DBS group had a significantly higher mean Epworth sleepiness scale (ESS) score of nine (SD = 4.00) (SD = standard deviation) compared to the non-DBS group with a mean ESS score of 5.87 (SD = 3.04) (unpaired t-test, $p = 0.044$). The ESS mean for both groups was below 10 for the ESS, however 7 % of non-DBS patients and 29 % of DBS patients obtained an ESS score greater than 10 ($p = 0.491$) (Figure 3.1). Only one DBS patient with a score greater than 10 was on sleep medications. To control for Hoehn and Yahr stages, MDS-UPDRS scores and LED, an ANCOVA was run to determine whether these confounding variables had an effect on the difference in ESS scores between the DBS and non-DBS group. After adjusting for Hoehn and Yahr stage, MDS-UPDRS scores and LED only one confounding variables (LED) had a statistical significant effect on the ESS means, with a mean difference of 3.82 (95% CI, 0.78 to 6.88, $p = 0.017$) between the two groups. The adjusted mean ESS score for the DBS group of 9.47 (SE=1.90) (SE= standard error) was still significantly greater compared to the non-DBS group with an adjusted mean ESS score of 5.65 (SE = 0.81) (Table 3.3.).

The DBS group also had a significantly greater mean Fatigue severity scale score of 4.28 (SD = 1.11) compared to the non-DBS with a mean FSS score of 3.07 (SD = 1.67). The FSS mean score was greater than four in the DBS group (Figure 3.2), however 20% non-DBS patients and 43 % of DBS patients obtained a FSS score greater than 4 ($p = 0.391$).

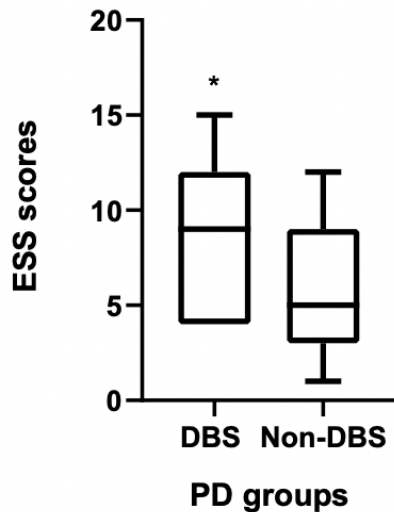


Figure 3.1. Boxplots (median, interquartile range and full range) showing Epworth sleepiness scores in patients with Parkinson's Disease who were treated with deep brain stimulation (DBS) (n=7) or not (non-DBS, n=15). Group differences were determined using unpaired t-tests. *: p-value <0.05.

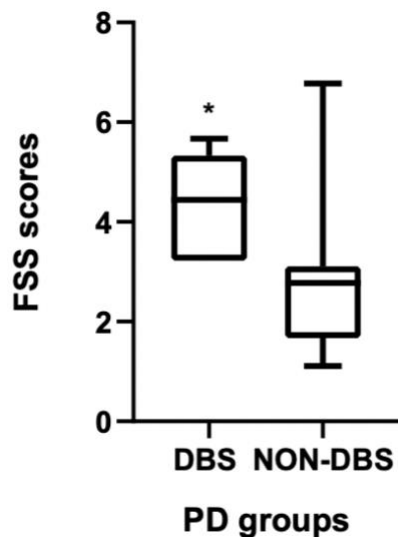


Figure 3. 2. Boxplots (median, interquartile range and full range) showing Fatigue Severity scale (FSS) scores in patients with Parkinson's Disease who were treated with deep brain stimulation (DBS) (n=7) or not (non-DBS, n=15). Group differences were determined using unpaired Mann-Whitney U-tests. *: p-value <0.05.

Although the global PSQI scores were greater than five in both groups, there were no significant differences between the global PSQI scores, nor in the individual PSQI component scores for sleep quality, sleep efficiency, sleep latency, duration of sleep, sleep disturbances and total sleep time between the DBS and non-DBS patients (Table 3.2). However, PSQI daytime dysfunction was significantly greater in the DBS with a mean of 1.57 (SD = 0.52) compared to non-DBS group with a mean of 0.67 (SD = 0.62) (p = 0.003). After adjusting for LED, this

confounding variable had a significant effect on the PSQI daytime dysfunction between the DBS group and non-DBS group with a mean difference of 0.48 (95% CI, 0.34 to 0.96, $p = 0.04$). The adjusted mean PSQI daytime dysfunction score was 1.10 (SE = 0.18) for the DBS group and it remained greater compared to the non-DBS group with a score of 0.61 (SE = 0.12). (Table 3.3). However 53 % non-DBS patients and 86 % of DBS patients obtained a PSQI global score greater than 5 ($p = 0.150$).

Table 3.2: Pittsburgh sleep quality index (PSQI) global and component scores measured in Parkinson's Disease (PD) patients with deep brain stimulation (DBS) and PD patients without DBS (non-DBS) (n=22)

	DBS (n=7)	Non-DBS (n=15)	p-value
Global Score	8.43 (3.309)	7.93 (5.175)	0.820
Sleep quality	1 [1-2]	1 [1-1]	0.711
Sleep onset latency	1.14 (0.690)	1.6 (1.056)	0.311
Sleep duration	0 [0-2]	0 [0-2]	>0.999
Sleep efficiency	0 [0-1]	1 [0-2]	0.693
Sleep medication	3 [0-3]	0 [0-1]	0.145
Sleep disturbance	2 [1-2]	1 [1-2]	0.913
Daytime dysfunction	1.57 (0.52)	0.67 (0.62)	0.003*

Parametric data are shown as mean (SD); non-parametric data are shown as median [IQR]. DBS: Deep Brain Stimulation; PD: Parkinson's Disease. Data analysed using unpaired t-tests and data analysed using unpaired Mann-Whitney U-tests. *: $p\text{-value} < 0.05$.

Table 3.3: Unadjusted and adjusted mean Epworth sleepiness scale (ESS) values and Pittsburgh sleep quality index (PSQI) daytime sleepiness for Parkinson’s disease patients with deep brain stimulation (DBS) and without (non-DBS) with the levodopa equivalent dosage (LED) (mg) as confounding variable using ANCOVA

	n	Unadjusted		Adjusted		p-value
		M	SE	M	SE	
ESS						
DBS	7	9.00	0.85	9.47	1.90	0.017*
Non-DBS	15	5.87	0.65	5.65	0.81	
PSQI daytime dysfunction						
DBS	7	1.11	0.02	1.10	0.18	0.04*
Non-DBS	15	0.61	0.11	0.62	0.12	

n-sample size, M - mean, SD - standard deviation, SE - standard error and DBS – Deep brain stimulation.

According to the Cambridge-Hopkins questionnaire, the DBS group showed a significantly higher prevalence of RLS compared to the non-DBS group (n= 29 % vs n= 13 %) (p = 0.0087), however the non-DBS group had higher scores for the IRLSS compared to the DBS group with mean scores of 17.25 in the non-DBS group and 6.5 in the DBS group.

3.3. Objective sleep measures between DBS and non-DBS groups

3.3.1. Actigraphy data assessing sleep parameters in patients with PD

From our sample of 22, only 19 PD patients participated in the actigraphy component of the study, however we could only analyse the wrist actigraphy data from 16 PD patients. This was due to the wrist ActiWatch not recording the data accurately for three PD patients. The remaining four patients chose to only participate in the sleep questionnaire component of the study. Overall there was an average wear time of 82 % and an average non-wear time of 18 % across all 19 patients over a period of seven days. There were no significant differences between the DBS and non-DBS group for either the hip or wrist measurements of sleep efficiency, sleep latency, total sleep time, WASO number of awakenings (Table 3.4). A trend was seen in the data between the wrist and hip activity monitors, therefore further analysis was performed. A Kendall’s W test was conducted to determine if there were any agreements between the sleep parameters obtained from the wrist and hip activity monitors in all the PD patients. A significant agreement was found between the wrist and hip activity monitors, sleep efficiency (W = 0.762, p = 0.027), WASO (W = 0.728, p = 0.034), number of awakenings (W

= 0.786, $p = 0.012$) and total sleep time ($W = 0.868$, $p < 0.001$). This means that we can accept that there is agreement between these sleep parameters using the wrist and hip activity monitors, however there was a non-significant agreement for sleep latency ($W = 0.549$, $p = 0.366$), therefore there was no agreement between sleep latency using wrist and hip activity monitors. Both the DBS and non-DBS reported a sleep efficiency <85% for wrist actigraphy but a sleep efficiency >85% for hip actigraphy.

Table 3.4: Sleep parameters from wrist and hip-mounted activity monitors from Parkinson's Disease (PD) patients with deep brain stimulation (DBS) and PD patients without DBS (non-DBS) measured over seven consecutive days (n=19)

	DBS (n=6)	NON-DBS (n=13)	p-value
<u>Sleep efficiency (%)</u>			
Wrist	77.07 (13.84)	82.62 (6.61)	0.287
Hip	97.65 (1.25)	97.76 (1.77)	0.899
<u>Sleep latency (min)</u>			
Wrist	11.57 [20.36-6.318]	8.73 [13.09-5.018]	0.446
Hip	0.07 [2-0]	0.86 [2.929-0.127]	0.213
<u>Total sleep time (min)</u>			
Wrist	327.8 (114.3)	454.1 (101.7)	0.055
Hip	432.8 (96.90)	517.0 (100.6)	0.105
<u>WASO (min)</u>			
Wrist	47.86 (37.93)	57.94 (24.79)	0.545
Hip	9.17 (5.431)	10.09 (7.998)	0.802
<u>Number of awakenings</u>			
Wrist	17.57 (13.19)	24.75 (7.272)	0.183
Hip	2.69 (1.203)	3.20 (2.229)	0.608

Parametric data are shown as mean (SD); non-parametric data are shown as median [IQR]. DBS: Deep Brain Stimulation; WASO: Wake after sleep onset; PD: Parkinson's Disease. Unpaired t-test used to analyse parametric data and Mann-Whitney U-test used to analyse non-parametric data.

3.3.2. Polysomnography data assessing sleep parameters in patients with PD post-DBS and who have not undergone DBS

A total of eight patients participated in the PSG component of the study. In the DBS group ($n = 4$), PD patients obtained a total sleep time of seven hours and 40 minutes, with a sleep efficiency close to 90%. Similar results were also seen in the non-DBS group ($n = 4$), where

PD patients obtained a total sleep time of seven hours and 40 minutes with a sleep efficiency of 88%. However, DBS and non-DBS group also obtained a sleep onset latency of 29 minutes and 30 minutes, respectively, which is at the threshold for insomnia (Table 3.5).

There were no significant differences seen between the DBS group and non-DBS group for all the sleep parameters except for NREM sleep stage 3, the non-DBS group obtained a significantly higher percentage of NREM stage three compared to the DBS group. To control for Hoehn and Yahr stages and MDS-UPDRS scores for disease severity, LED (mg), an ANCOVA was run to determine whether the significant difference observed in N3 (%) in unadjusted analyses still held when adjusting for severity of the disease. We found that when adjusting for MDS-UPDRS scores, a mean difference of 12.07 (95% CI, -22.61 to .54, $p = 0.032$) still remained with non-DBS patients having a significantly greater adjusted mean percentage of NREM sleep stage three of 29.79 (SE = 2.01) than DBS patients with a adjusted mean percentage of N3 of 13.46 (SE = 2.01) (Table 3.6.). There was no significant differences in the PLMS index found between the two groups, however both indices were very low that were associated with arousals. One patient was suspected to have RBD, this patient had increased EMG which (included the chin and leg) readings during their PSG.

Table 3.5: Sleep parameters from ambulatory polysomnography from Parkinson's disease (PD) patients with deep brain stimulation (DBS) and PD patients without (non-DBS) for one night (n = 8)

	DBS n = 4	Non-DBS n = 4	p-value
Bed time (PM)	21:22	21:27	0.930
Wake time (AM)	05:55	06:09	0.870
Total sleep time (min)	461.9 (18.9)	461.3 (54.6)	0.983
Sleep efficiency (%)	90.3 (3.3)	88.5 (5.3)	0.593
Sleep onset latency	29.8 [20.6-38.1]	30.3 [28-82.8]	0.686
REM latency	88.5 [36.6-114.1]	98.8 [60.1-230.8]	0.384
WASO (min)	21.3 [20.3 – 38.8]	20.3 [13.5 – 49.5]	0.886
NREM 1 (%)	22.5 (4.7)	23.8 (7.8)	0.793
NREM 1 (min)	105.3 (22.7)	107.3 (30.4)	0.910
NREM 2 (%)	44(1.6)	33 (11.4)	0.105
NREM 2 (min)	204.5 (14.7)	153.5 (64.6)	0.175
NREM 3 (%)	16.8 (3.4)	26.5 (6.6)	0.039*
NREM 3 (min)	83.8 [61.4-87-61]	121.0 [147.5-147.5]	0.029*
REM (%)	16 (3.7)	16.8 (4.1)	0.794
REM (min)	74.6 (17.0)	79.3(28.3)	0.789
Arousal index (total number of arousal/per hour)	7.5 [4.5- 9.9]	7.7 [5.1-32.43]	0.885
Total number of arousals	58 [33.5-78]	60 [39- 237.8]	0.886
Limb movement index (total number of limb movement/per hour)	45.4 (32.8)	23.3 (21.5)	0.301
Total number of limb movements	357 (258.4)	188.8 (194.4)	0.605
Limb movement index with arousals (total number of movement index with arousals/per hour)	0.7 (0.6)	0.9 (0.7)	0.338

Parametric data are shown as mean (SD); non-parametric data are shown as median [IQR]. DBS- Deep Brain Stimulation, REM- Rapid eye movement sleep, WASO- Wake after sleep onset, N1- Non-REM sleep stage 1, N2- Non-REM sleep stage 2, N3- Non-REM sleep stage 3. data analysed using unpaired t-tests and ^b data analysed using unpaired Mann-Whitney U-tests. *: *p-value* <0.05.

Table 3.6: Unadjusted and adjusted mean percentage of NREM stage 3 values for Parkinson's patients with deep brain stimulation (DBS) and PD patients without (non-DBS) with Movement Disorder Society-Unified Parkinson's Disease Rating scale (MDS-UPDRS) scores as a confounding variable using ANCOVA

	n	Unadjusted		Adjusted		p-value
		M	SE	M	SE	
DBS	7	16.75	1.20	13.46	2.01	0.032*
Non-DBS	15	26.50	2.33	29.79	2.01	

n-sample size, M - mean, SD - standard deviation, SE - standard error and DBS – Deep brain stimulation.

3.4. Characterising depression, pain, cognitive function, physical activity and light exposure in PD patients post-DBS and PD patients who have not undergone DBS

The DBS group reported significantly higher mean scores of 15.17 (SD = 3.13) for the Beck's depression inventory II (BDI II) compared to the non-DBS group with a mean score of 9.79 (SD = 4.68) (Figure 3.4), however 13 % non-DBS patients and 29 % of DBS patients obtained a BDI-II score greater than 16 ($p = 0.50$). This indicates that the DBS groups has a higher levels of depression compared to the non-DBS group. To control for Hoehn and Yahr stage and MDS-UPDRS scores for disease severity and LED (mg), an ANCOVA was run to determine whether these confounding variables had an effect on the difference in BDI II scores in the DBS and non-DBS group, only three confounding variables (age, Hoehn and Yahr stage, and MDS-UPDRS scores) had a statistical significant effect on the mean BDI II scores, with a mean difference of 4.95 (95% CI, 0.50 to 9.40, $p = 0.031$) (Table 3.7). The adjusted mean BDI II score for the DBS group was 14.87 (SE = 1.73) remained significantly higher compared to the non-DBS group with an adjusted mean score of 9.91 (SE = 1.21) (Table 3.7).

No significant differences were reported for the short-form McGill pain scores between DBS (2 [1-6]) (median [IQR]) and non-DBS groups (2 [1-8]) (Mann Whitney U-test, $p = 0.820$) (Figure 3.5). However, 13 % of non-DBS patients obtained an SF-MPQ score greater than 10, with 19 being the highest score recorded. All patients in the DBS group scored below 10 for the SF-MPQ, with 8 being the highest score recorded. There was no differences seen in the cognitive function component of the PDQ-39 between DBS (25 (16.5)) (mean (SD)) and non-DBS (20.4 (12.2)) (Unpaired t-test, $p = 0.471$) (Figure 3.6), however 73 % of non-DBS patients

and 86 % of DBS patients obtained a cognitive PDQ-39 sub-score greater than 11.29 ($p = 0.517$). No significant differences were seen for sedentary behaviour levels between the DBS (85.8 [75.8-90.1]) and non-DBS group (81.2 [75-84.1]) (Mann Whitney U-test, $p = 0.467$) (Figure 3.7), light physical activity between the DBS (14.11 [9.8-23.1]) and non-DBS group (17.48 [14.4-23.7]) (Mann Whitney U-test, $p = 0.579$) (figure 3.7) and log (light exposure) (lux) between the DBS (2.3 [1.2-7.5]) and non-DBS groups (2.2 [4.5-5.6]) (Mann Whitney U-test, $p = 0.579$) (Figure 3.8). Both groups reported a greater time spent in sedentary behaviour of 83% and only 17% of spent time doing light physical activity.

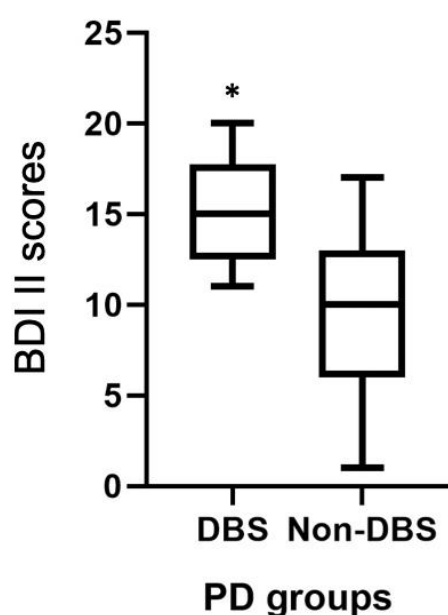


Figure 3.4. Boxplots (median, interquartile range and full range) showing Beck's depression inventory 2 (BDI II) scores in patients with Parkinson's Disease who were treated with deep brain stimulation (DBS) ($n=7$) or not (non-DBS, $n=15$). Group differences were determined using unpaired t-tests. *: p -value <0.05 .

Table 3.7: Unadjusted and adjusted mean BDI II values for DBS and non-DBS groups with Hohen and Yahr stage, Movement Disorder Society-Unified Parkinson's Disease Rating scale (MDS-UPDRS) scores and LED as covariates using ANCOVA

	n	Unadjusted		Adjusted		p-value
		M	SE	M	SE	
DBS	7	15.17	0.66	14.87	1.73	0.031*
Non-DBS	15	9.79	1.00	9.91	1.21	

n-sample size, M - mean, SD - standard deviation, SE - standard error and DBS – Deep brain stimulation.

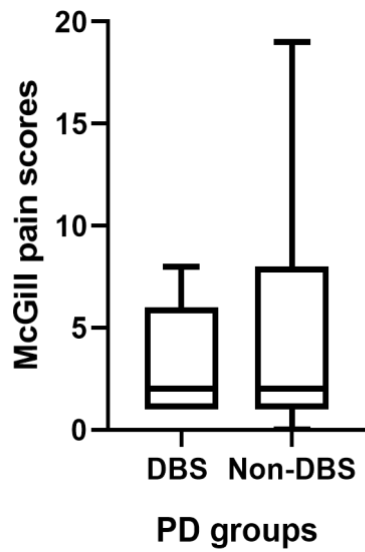


Figure 3.5. Boxplots (median, interquartile range (IQR) and full range) showing McGill pain scores in patients with Parkinson's Disease who were treated with deep brain stimulation (DBS, n=7) or not (non-DBS, n=15). Group differences were determined using unpaired t-tests. *: p-value <0.05. Group differences were determined using Mann-Whitney U-tests.

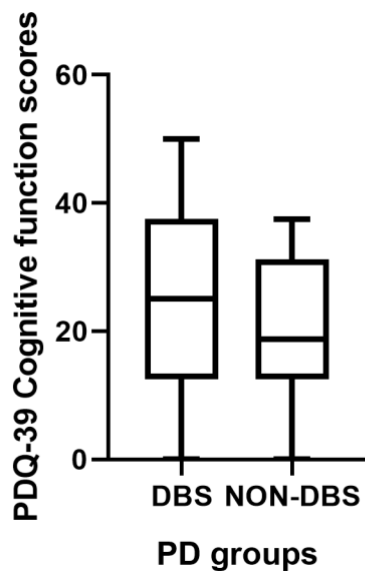


Figure 3.6. Boxplots (median, interquartile range (IQR) and full range) showing PDQ-39 cognitive function scores in patients with Parkinson's Disease who were treated with deep brain stimulation (DBS, n=7) or not (non-DBS, n=15). Group differences were determined using unpaired t-tests. *: p-value <0.05. Group differences were determined using unpaired t-tests.

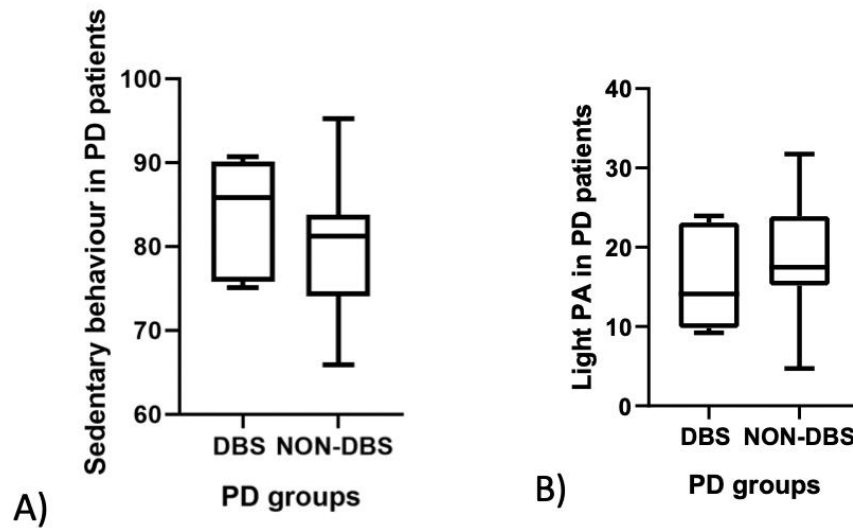


Figure 3.7. Boxplots (median, interquartile range (IQR) and full range) showing sedentary behaviour (A) and light physical activity (PA) levels (B) over seven days in patients with Parkinson's Disease who were treated with deep brain stimulation (DBS, n=7) or not (non-DBS, n=15).*: p-value <0.05. Group differences were determined using Mann-Whitney U-tests.

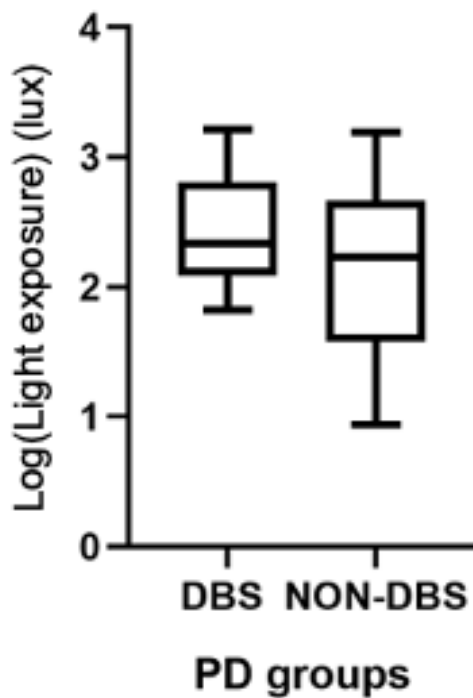


Figure 3.8. Boxplots (median, interquartile range (IQR) and full range) showing levels of daily light exposure over seven days in patients with Parkinson's Disease who were treated with deep brain stimulation (DBS, n=7) or not (non-DBS, n=15). *: p-value <0.05. Group differences were determined using Mann-Whitney U-tests.

3.5. Correlations between sleep parameters and other PD-related non-motor symptoms, physical activity and light exposure

The results of the correlation analysis between sleep parameters and other PD-related non-motor and motor symptoms are summarised in Table 3.8. Negative correlations were observed between wrist actigraphy sleep efficiency and pain (McGill pain questionnaire) ($r = -0.647$, $p = 0.011$), and wrist actigraphy total sleep time and pain ($r = -0.793$, $p = 0.001$), indicating that pain has an inverse relationship between the two sleep variables. A positive correlation was observed between hip actigraphy sleep latency and moderate physical activity ($r = 0.576$, $p = 0.010$), indicating a direct relationship between moderate physical activity and sleep latency. None of the other relationships between sleep parameters and other PD-related non-motor symptoms and physical activity were significant.

3.6. Correlations between other PD-related non-motor symptoms, physical activity and light exposure

A positive correlation was shown between depression (obtained from BDI II) and fatigue (obtained from FSS) ($r = 0.479$, $p = 0.028$) (figure 3.9) as well as light physical activity (obtained from actigraphy) and fatigue ($r = 0.629$, $p = 0.004$) (figure 3.10), indicating a positive relationship between the variables. A negative correlation was observed between sedentary behaviour and light exposure ($r = -0.458$, $p = 0.049$) as well as between sedentary behaviour and moderate physical activity ($r = -0.477$, $p = 0.039$) (both obtained from actigraphy) (figure 3.11), indicating an inverse relationship between the variables (Table 3.9).

Table 3.8. Correlation between sleep parameters, as measured by wrist and hip actigraphy, and other Parkinson's Disease-related non-motor for all patients with Parkinson's Disease (n=22)

	Cognitive Function	Pain	Depression	Fatigue	Sedentary Behaviour	Light Physical Activity	Moderate Physical Activity	Light Exposure
	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)
<u>Sleep Efficiency</u>								
Wrist	-0.129 (0.646)	*-0.647 (0.011)	0.062 (0.826)	-0.118(0.675)	-0.178 (0.526)	0.059 (0.831)	0.267 (0.335)	0.132 (0.625)
Hip	-0.123(0.627)	-0.101(0.689)	0.286 (0.249)	0.002 (0.995)	0.368 (0.133)	0.123 (0.616)	-0.457(0.057)	-0.237 (0.329)
<u>Sleep Latency</u>								
Wrist	-0.345(0.326)	0.246 (0.490)	0.251 (0.481)	0.280 (0.431)	0.006 (>0.999)	0.150 (0.593)	0.042 (0.918)	-0.286 (0.301)
Hip	0.158 (0.517)	-0.101 (0.682)	-0.162 (0.508)	-0.205 (0.400)	0.006 (0.980)	-0.297 (0.216)	*0.576 (0.010)	0.174 (0.475)
<u>Total Sleep Time</u>								
Wrist	-0.436 (0.104)	*-0.793 (0.001)	0.047 (0.868)	-0.343 (0.211)	-0.227 (0.417)	-0.424 (0.104)	0.409 (0.130)	-0.082 (0.763)
Hip	0.025 (0.920)	-0.193 (0.443)	0.253 (0.311)	-0.132 (0.601)	0.230 (0.358)	-0.319 (0.183)	0.053 (0.834)	-0.031 (0.898)
<u>WASO</u>								
Wrist	-0.262 (0.345)	0.351 (0.198)	0.063 (0.822)	-0.146 (0.604)	-0.004 (0.990)	-0.300 (0.258)	-0.176(0.531)	-0.162 (0.549)
Hip	0.145 (0.565)	-0.001 (0.971)	-0.146 (0.563)	0.025 (0.921)	-0.268 (0.282)	-0.242 (0.318)	0.329 (0.183)	0.104 (0.673)
<u>Number of awakenings</u>								
Wrist	0.215 (0.441)	-0.178 (0.526)	-0.339 (0.217)	-0.033 (0.906)	-0.055 (0.847)	0.453 (0.080)	0.161(0.568)	-0.044 (0.874)
Hip	0.076 (0.763)	-0.065 (0.797)	0.007 (0.978)	-0.057 (0.821)	-0.275 (0.270)	0.230 (0.344)	-0.070 (0.784)	0.088 (0.721)

Pearson's correlation coefficient for parametric data and Spearman's-correlation coefficient for non-parametric data. Bold text and * indicate a p-value <0.05. WASO: Wake after sleep onset.

Table 3.9. Correlation matrix between PD-related non-motor symptoms, physical activity and light exposure for all patients with Parkinson's Disease (n=22)

	Cognitive function r (p-value)	Pain r (p-value)	Depression r (p-value)	Fatigue r (p-value)	Sedentary r (p-value)	Light physical activity r (p-value)	Moderate physical activity r (p-value)	Light exposure r (p-value)
Cognitive Function	1.000							
Pain	0.357 (0.103)	1.000						
Depression	-0.037 (0.873)	-0.258 (0.260)	1.000					
Fatigue	0.189 (0.400)	0,082 (0.715)	*0.479 (0.028)	1.000				
Sedentary	0.192 (0.430)	0.032 (0.896)	0.306 (0.203)	-0.044 (0.857)	1.000			
Light Physical Activity	-0.020 (0.934)	0,110 (0.653)	0.264 (0.275)	*0,629 (0.004)	-0.033 (0.892)	1.000		
Moderate Physical Activity	-0.147 (0.547)	-0.068 (0.783)	-0.421 (0.073)	-0.178 (0.467)	*-0.477 (0.039)	-0.286 (0.235)	1.000	
Light Exposure	0.536 (0.152)	0.117 (0.632)	0,264 (0.627)	0.335 (0.161)	*-0.458 (0.049)	0.172 (0.482)	0.242 (0.318)	1.000

Pearson's correlation coefficient for parametric data and Spearman's-correlation coefficient for non-parametric data. Bold text and * indicate a p-value <0.05

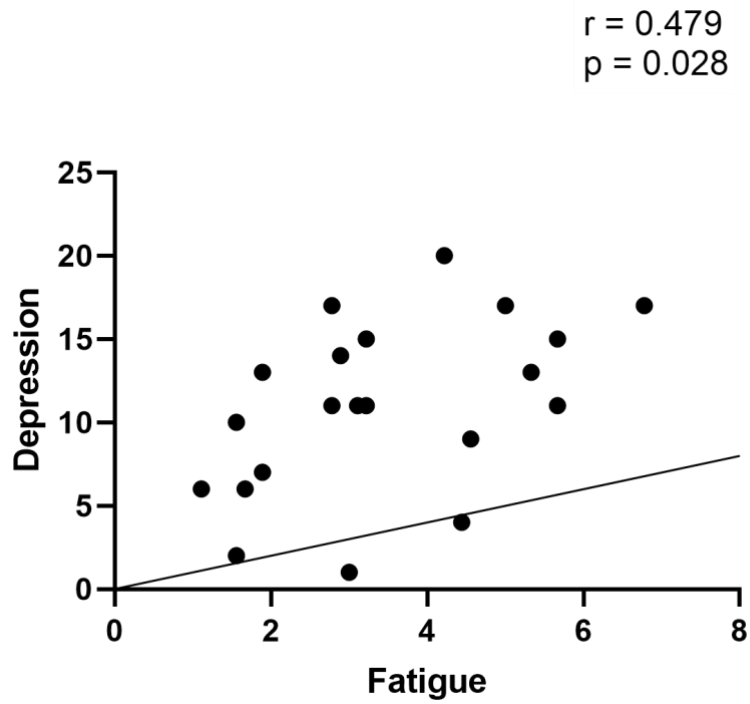


Figure 3.9: Pearson's Correlation between depression and fatigue in patients with Parkinson's disease (n=22).

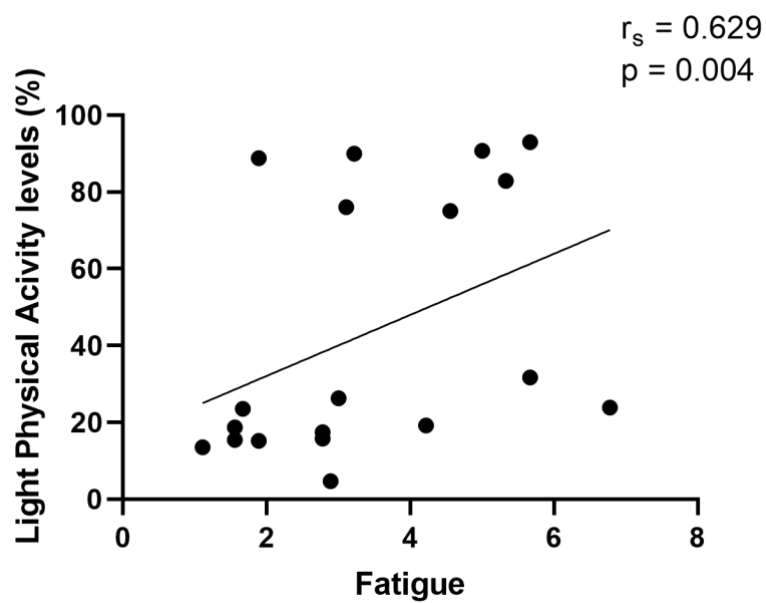


Figure 3.10: Spearman's Correlation between light physical activity levels (%) and fatigue in patients with Parkinson's disease (n = 22).

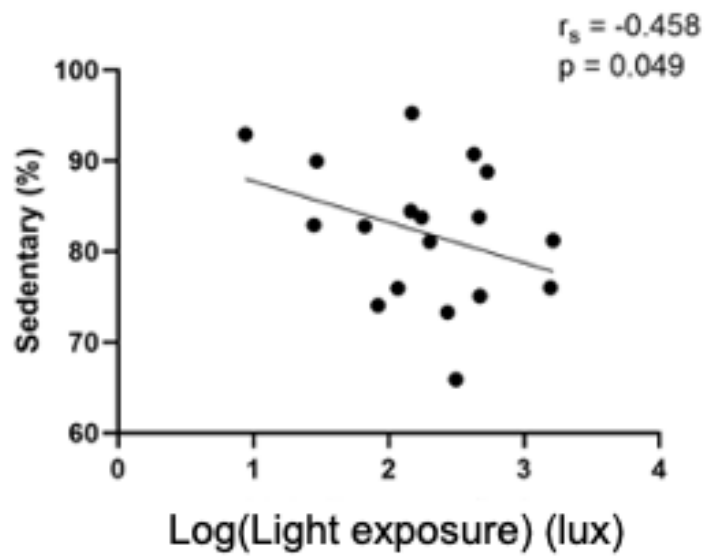


Figure 3.11: Spearman's Correlation between sedentary behaviour (%) and light exposure (lux) in patients with Parkinson's disease ($n = 22$).

Chapter 4: Discussion

This study used a cross sectional design aimed to compare sleep and circadian parameters in patients with PD following deep brain stimulation (DBS) with PD patients who have not undergone DBS, to characterize cognitive function, depression, fatigue, pain, physical activity, and light exposure in each group and to determine the relationship between sleep parameters and other PD-related non-motor symptoms. Patients who have adverse effects from antiparkinsonian drugs and have very severe symptoms undergo DBS (Zhang and Xie, 2019). . The main findings of this study are summarised as follows, for the subjective sleep measures the DBS group obtained significantly higher scores, thus indicating poorer performance, for the Epworth sleepiness scale (ESS), Fatigue severity scale (FSS) and Pittsburgh sleep quality index (PSQI) daytime sleepiness. For the rest of the subjective sleep measures there were no significant differences. For the objective measures, there were no significant differences in sleep parameters for the actigraphy and polysomnography (PSG), however the non-DBS group exhibited a greater percentage for NREM sleep stage 3 compared to the DBS group. Furthermore, the wrist actigraphy reported higher values for latency, wake after sleep onset (WASO) and number of awakenings compared to the hip actigraphy and the hip actigraphy reported higher values for sleep efficiency and total sleep time compared to wrist actigraphy. The DBS group had a greater prevalence of depression compared the non-DBS group indicated by the Beck's depression inventory II (BDI II). Both groups showed high levels of sedentary behaviour. For the correlation analysis, a negative correlation was observed between wrist actigraphy sleep efficiency and pain; the higher the pain the lower the sleep efficiency, and between wrist actigraphy total sleep time and pain; the higher the pain the lower the total sleep time. A positive correlation was seen between hip actigraphy sleep latency and moderate physical activity. Lastly, a positive correlation was seen between depression and fatigue, and fatigue and light physical activity. A negative correlation was seen between sedentary behaviour and light exposure.

4.1. Subjective and objective sleep measures in DBS and non-DBS PD patients

4.1.1. Subjective sleep measures in DBS and non-DBS PD patients

The study showed that the DBS group obtained higher scores for the ESS and the PSQI daytime dysfunction compared to the non-DBS group. This means that the DBS group experienced a higher excessive daytime sleepiness compared to the non-DBS group. Excessive daytime sleepiness is the difficulty staying awake or alert during wake periods of the day and has an

increased desire to sleep during the day (Knie et al., 2011). Although, the DBS group exhibited more excessive daytime sleepiness compared to the non-DBS group, both groups scored an average below 10, the cutoff for excessive daytime sleepiness in healthy adults, on the ESS. Therefore, the DBS group would not be classified as suffering from excessive daytime sleepiness as per the ESS. From the PSQI, the DBS group reported a daytime dysfunction score of two. A study showed that the daytime dysfunction component from the PSQI and the ESS were weakly correlated 0.34 ($p < 0.001$), suggesting the daytime dysfunction component from PSQI may measure a similar construct to the ESS (Buysse et al., 2008).

Previous research has shown that DBS improves excessive daytime sleepiness in PD patients who have undergone DBS (Chahine et al., 2011, Baumann-Vogel et al., 2017). Contrastingly, a study with 40 PD patients who underwent DBS showed no improvement in their ESS scores as a significant number of patients reported no daytime sleepiness at baseline, but at 6 and 12 months post DBS they presented with daytime sleepiness (Kharkar et al., 2018). Other studies showed no improvement in EDS after STN-DBS (Hjort et al., 2004, Lyons and Pahwa, 2006). In contrast to our finding, after administering the PSQI, Iranzo et al. (2002) showed that the daytime dysfunction component improved 6 months post-DBS, however they compared the daytime dysfunction in PD patients pre- and post-DBS.

Knie et al. (2011) indicated that the frequency of EDS may increase with disease severity and is positively correlated with disease duration. A case-control study found that after a multivariate analysis that PD patients with a higher ESS score was significantly associated with BDI scores (Yong et al., 2011). This shows that EDS can be influenced by depression. In our study the DBS group did obtain higher BDI scores compared to the non-DBS group. Supporting this finding, studies have indicated that PD patients with EDS had more severe depression than those without EDS (Kurtis et al., 2013, Xiang et al., 2019, Zhang et al., 2021). Therefore, the increase in depression in the DBS group could explain the increase in EDS in the DBS group found in our study. Physical inactivity and a sedentary lifestyle may also be a potential mechanism for the association between EDS and depression (LaGrotte et al., 2016) and an increased sedentary lifestyle was also observed in our sample of PD patients, which could further explain the increased EDS in the DBS group. However, the pathophysiological mechanism of the relationship between EDS and depression remains unclear (Xiang et al., 2019). Another study also suggested that dopaminergic medications are associated with daytime alertness (Bliwise et al., 2012). They further indicated that an increase in dopamine

agonists were associated with a reduced daytime sleepiness and an increase in levodopa were associated with increased levels of alertness (Bliwise et al., 2012). This could provide another explanation as to why the DBS group reported a higher EDS compared to the non-DBS because the DBS group has a reduction dopaminergic medication.

For the DBS group, the FSS scores were higher compared to the non-DBS group indicating that the DBS group experienced greater fatigue. Additionally, the DBS group had an average score greater than four, which is above the threshold for FSS indicating that the DBS group may have severe fatigue. This is similar to a study conducted that had a prevalence of 58% of fatigue in PD patients who underwent DBS, who had a score of four or greater on the FSS (Kluger et al., 2012). Another study suggested that DBS may not affect fatigue in PD patients as a whole cohort but on an individual level, six out of seventeen patients had an improvement in fatigue, in three patients their fatigue worsened and in 8 patients fatigue remained unchanged, however this study used a different fatigue scale, the Parkinson fatigue scale (PFS), to measure fatigue (Chou et al., 2012). The differences between these scales are the PFS focuses more on the physical aspect of PD rather than the emotional and cognitive aspects, therefore an improvement in motor function from the DBS was correlated to improved fatigue in some patients (Grace et al., 2007, Chou et al., 2012), explaining the differences observed in this study and the study by Chou and colleagues may be observed.

No statistical difference was observed in the PSQI global score including its components such as sleep efficiency, sleep onset latency, sleep duration, sleep disturbances and sleep quality between the two groups, indicating DBS may not influence PSQI scores. However, both groups obtained a global PSQI score greater than the threshold of five, which indicates poor sleep quality. A recent study conducted in patients with PD with sleep disturbances, showed higher scores for the global PSQI and its components, but also reported a Hoehn and Yahr score of two, and a disease duration of 48 months compared to the control group of PD patients without sleep disturbances (Qin et al., 2020). In contrast to this finding, studies have shown that patients with PD who have undergone DBS have an improved sleep quality (Amara et al., 2012, Monaca et al., 2004, Iranzo et al., 2002). Specifically, a study conducted by Monaca et al. (2004) showed an improvement in sleep quality in patients with PD who underwent DBS with a disease duration of 12 years, they reported a PSQI global score change from 11.7 (SD = 2.4) (SD = standard deviation) pre-operatively to 5.3 (SD = 3.5) post-operatively. Similarly, Iranzo et al. (2002), also showed an improvement in PSQI global scores by 9.4 with a pre- operative

score of 14.8 (SD = 4.5) and a post-operative 5.4 (SD = 4.6). They also found an improvement in the PSQI component scores such as sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, daytime dysfunction, post-DBS, however there were no differences found in the PSQI component score of sleep medication post-DBS. Both Monaca et al. (2004) and Iranzo et al. (2002) both measured the PSQI scores in PD patients before the DBS surgery and after the DBS, therefore the pre-DBS group was their control group. In this study, PD patients who had not undergone DBS were the control group, therefore this could explain the difference found between this study and the studies conducted by Monaca et al. (2004) and Iranzo et al. (2002). Iranzo et al. (2002) also considered a reduction in dopaminergic medications and further suggested that changes in dopaminergic medications could change postoperative sleep architecture.

The DBS group reported a higher prevalence of RLS compared to the non-DBS according to the Cambridge-Hopkins Restless legs syndrome questionnaire. Furthermore, according to the IRLSS scores the non-DBS group obtained a higher severity for RLS compared to the DBS group. The DBS group reported a higher prevalence of RLS and also obtained lower dopaminergic medication levels compared to the non-DBS group with a lower prevalence of RLS and higher dopaminergic medication levels. Prior research has suggested that a reduction in dopaminergic medication (79% or more) after DBS surgery may worsen or result in the emergence of RLS (Kedia et al., 2004). This reduction in dopaminergic medications may have unmasked RLS symptoms resulting in the emergence of RLS or the worsening of RLS symptoms (Kedia et al., 2004). Another study also observed a significant number of PD patients presenting with exacerbated RLS with a small reduction in dopaminergic medications (Kharkar et al., 2018). Contrastingly, a study hypothesized that overstimulation from the collective effects of dopaminergic medications and DBS surgery may cause changes in the excitability of the dopaminergic system resulting in the emergence of RLS (Marques et al., 2015). Therefore, the relationship between RLS in PD and true RLS remains uncertain, hence these results should be interpreted with caution. To determine the effect DBS has on RLS, our results show that the non-DBS group has a higher IRLS score indicating a higher RLS symptoms severity compared to the DBS group with a lower IRLS score and lower RLS symptoms severity. A study (n = 22) showed that DBS improved RLS in PD patients for up to two years, with a decrease in dopaminergic medications (35 %-69 %). Half of the patients had a mild improvement in RLS symptoms with a score <10 on the IRLS and approximately one third of patients had complete resolution of symptoms (Klepitskaya et al., 2018).

Overall, outcomes obtained by the subjective measure indicate that the non-DBS group had better sleep compared to the DBS group. This was indicative by the non-DBS reporting lower scores for the ESS, PSQI and FSS compared to the DBS group, however the DBS did report increased depression which may influence their subjective sleep.

4.1.2. Objective sleep measures in DBS and non-DBS PD patients

The current study did not find any statistical differences in objective sleep measures (wrist actigraphy, hip actigraphy and PSG sleep measures) between the DBS group and non-DBS group except the non-DBS group had a significantly higher N3 % stage compared to the DBS group, indicating that the non-DBS group has a longer slow wave sleep duration compared to the DBS group. However, the DBS group had a longer disease duration and higher MDS-UPDRS scores compared to the non-DBS group. Previous research indicated that older individuals with a longer PD disease duration have a significant reduced slow wave sleep (Varga et al., 2016, Boulos et al., 2019, Zhang et al., 2020). In contrast to our finding, a study showed an increase in NREM stage 3 after DBS, indicating that DBS improves slow wave sleep however this study observed pre- and post- DBS sleep measures using PSG (Baumann-Vogel et al., 2017). This study used a larger population sample of 50 PD patients, they also made additional standardized considerations for assessing sleep stages in difficult cases. This included comparing presumed sleep patterns with patterns of definite awake periods. In the absence of electromyography (EMG) atonia, if there were clear rapid eye movement patterns, and the epoch was clear enough to indicate it is not wake or non-rapid eye movement (NREM) sleep, they believed this was enough to score as rapid eye movement (REM) sleep. Lastly, if the epoch obtained poorly formed k-complexes and sleep spindles to indicate NREM sleep stage 2 and did not fulfil the criteria for wake, NREM sleep stage 1, NREM sleep stage 3 and REM sleep, they scored the epoch as NREM sleep stage 2. They also obtained an audio-video recording to obtain behavioural pattern information such as dream enacting behaviour (Baumann-Vogel et al., 2017). Another study also has similar findings to Baumann-Vogel et al. (2017) with a significantly increased slow wave sleep, with DBS switched on compared before surgery and when DBS was switched off, however they used the classic Rechtschaffen and Kales criteria (Monaca et al., 2004). Furthermore, our sample size for the DBS group was very small (n = 4) who completed the PSG component, our study used the American academy

of sleep medicine (AASM) scoring guidelines for sleep classification, during the sleep recording the DBS was switched on for the patients and the PSG was performed at the patient's home, which could relate to the differences found. In addition, there are differences found between the classic Rechtschaffen and Kales criteria and the AASM guidelines for sleep classification, the Rechtschaffen and Kales criteria considers sleep stage 4 whereas the AASM guidelines combine sleep stages 3 and 4, which they reflect as slow wave sleep, there are also differences in scoring sleep parameters due to the modifications of the sleep scoring rules (Moser et al., 2009).

Slow wave sleep is a marker of the homeostatic regulation of sleep and may be involved in maintaining sleep (Bellesi et al., 2014). An increased percentage of NREM stage 3 in the non-DBS group supports our subjective sleep measures indicating the non-DBS group may have better sleep compared to the DBS-group. Depressive symptoms may also have a direct effect on post-DBS sleep (Kharkar et al., 2018), the results obtained from this study show that the DBS group reported a significant increase in depression compared to the non-DBS group. Depression and sleep have a bidirectional relationship, a prominent symptom in individuals with depression is sleep disturbances and insomnia has been identified as a risk factor for developing depression (Fang et al., 2019).

The DBS group obtained a higher total periodic limb movement during sleep (PLMS). This finding was similar to a study conducted where PLMS was increased after DBS (Baumann-Vogel et al., 2017) which could be related to the reduction in dopaminergic medications (Baumann-Vogel et al., 2017). The non-DBS group obtained a PLMS index below 25, which is considered mild. The DBS group obtained a PLMS index greater than 25 but less than 50, indicating moderate PLMS. Both PLMS indices were below 50. PLMS index with arousals were both below 5. A study showed an increase in number of arousals in PD patients that was associated with PLMS as well as PD patients with PLMS had a decreased sleep efficiency (Wetter et al., 2000). Another study showed no change in PLMS in PD patients who underwent DBS (Cicolin et al., 2004). Iranzo et al. 2002, showed there was an increase in PLMS index after DBS surgery in PD patients. Previous studies show that DBS improves sleep efficiency and quality, however some research shows no change in PSG sleep parameters after DBS (Iranzo et al., 2002, Nishida et al., 2011, Diederich et al., 2013, Amara et al., 2017, Baumann-Vogel et al., 2017). It is important to mention that anti-parkinsonian drugs may also directly alter objective sleep parameters including PLMS (Zhang et al., 2020). The results obtained

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from our study show that the DBS group had a lower LED dosage compared to the non-DBS group.

A discrepancy was observed between the wrist and hip activity monitors show that sleep efficiency was greater than 85% for the hip activity monitors and less than 85% for wrist activity monitors. A pilot study showed a similar findings with the upper limbs worn devices reporting a higher number of awakenings and WASO compared to the lower limbs worn devices and the lower limbs worn devices reported a higher sleep efficiency and total sleep time compared to the upper limbs worn devices (Prasad and Brown, 2017). Therefore it may be suggested that the placement of actigraphy monitors has the possibility of over and underestimation of sleep scores (Prasad and Brown, 2017) and this should be taken into consideration when places activity monitoring devices. However, in this study after conducting a Kendall's (W) test, it can be seen that the data obtained from the sleep parameters (total sleep time, WASO, and number of awakenings) were in agreement with one another, however sleep latency had a non-significant and weak agreement.

4.2. Characterizing non-motor symptoms, physical activity, and light exposure in PD

The DBS group obtained higher scores for the BDI II compared to the non-DBS group, indicating that the DBS group has greater depression compared to the non-DBS group. In our study, the DBS group also exhibited a higher Hoehn and Yahr and MDS-UPDRS scores indicating that the DBS group has a higher disease severity compared to the non-DBS group. Previous research has shown that depression is associated with increased disease severity (Anguenot et al., 2002). A study conducted with 269 PD patients showed that a higher prevalence of depression was seen in the later stages of the disease (van der Hoek et al., 2011). The prevalence of depression has been explored with regards to the staging of PD, but these findings have not been consistent as depression has been reported in the early and late stages of PD (Srivastava et al., 2011, van der Hoek et al., 2011). While depression in the late stages has been linked to a monoaminergic deficit and cognitive impairment, the onset of depression in the early stages may be due to the impactful nature of the diagnosis (Braak et al., 2004). However, several studies have also illustrated a linear relationship between depression and PD staging (Rojo et al., 2003, Riedel et al., 2010). In contrast to our finding, DBS had a positive

effect on mood such as depression (Accolla and Pollo, 2019). A study (n = 22) showed an improvement in depression with the DBS switched on compared to patients with DBS switched off (McDonald et al., 2012). While others reported no change in mood post-DBS (Kaiser et al., 2008, Weaver et al., 2009, Rizzone et al., 2014). However, a study showed that depression worsen after STN-DBS, but improve in patients who underwent GPi DBS, indicating that the placement of DBS could be an important factor in treating depression in patients with PD (Follett et al., 2010).

There was no statistical significance in PDQ-39 cognitive function component between the two groups which indicates that DBS has no effect on cognitive function in our sample of PD patients who underwent DBS. Some reports show a decline in cognitive function after DBS (Parsons et al., 2006, Witt et al., 2008, Rizzone et al., 2014). In particular, Witt and colleagues studied 156 advanced PD patients and found in 60 PD patients post-DBS a decrease in frontal lobe cognitive function. To determine the effect DBS has on cognitive function, they used the Mattis dementia rating scale to assess overall cognitive function and they conducted further analysis on various cognitive domains such as verbal memory using Rey's auditory verbal learning tests, visuospatial abilities using the revised Benton visual retention test, attention and inhibition using the short version of the Stroop test. Each test was administered using parallel versions (except the Mattis dementia rating scale) to minimize test and retests effects (Witt et al., 2008). The difference in our results could be due to the sample size and the much simpler methodology used in our study.

No changes in pain were seen between the DBS group and non-DBS group using the McGill pain short-hand questionnaire to assess pain, however some studies reported positive outcome of pain after DBS (Loher et al., 2002, Kim et al., 2012). A study reported an improvement in pain after a two-year follow up post DBS in 21 patients, although some patients developed a new musculoskeletal pain (Kim et al., 2012). Kim et al. (2012) measured pain using an ordinal scale (0-10) in seven parts of the body such as the head, neck, trunk, upper and lower extremities, and for each body part the quality of pain was described by each patient and categorized using the classification proposed by Ford (2010), these pain categories include musculoskeletal, radicular/neuropathic, dystonia, central pain and akathisia (Ford, 2010, Kim et al., 2012). Overall, these differences in results could be a result of differences in sample

sizes, the methodologies used and the control groups in most particular cases studies have used pre- and post-DBS groups.

A hallmark of PD is decreased movement ability, which leads to poor physical activity and increased time spent in sedentary behaviors (Benka Wallén et al., 2015). In the current study both groups, DBS and non-DBS PD patients spent an excessive amount of time in sedentary behaviour (85% of wake time). Similarly, a study in PD patients showed that 75% of wake time was spent in sedentary behaviours (Benka Wallén et al., 2015). Another study using self-reported based questionnaire data reported that people with PD were 29% less active than the control group which consisted of older healthy adults (van Nimwegen et al., 2011). The results obtained from another study using accelerometry reported that physical activity was 27% lower in patients with PD compared to the control group consisting of healthy individuals (Lord et al., 2013). The reason for this increased sedentary behavior in patients with PD could be due to the fear of falling. A study using the Falls efficacy scale international (FES-I), the fear of falling has shown to be a predictor of physical activity in older adults (Lord et al., 2013). Among all the neurological diseases, PD has the one of the highest risks of falling, with between 45-65% of patients that will fall each year (Pelicioni et al., 2019). Risk factors for falling in PD include freezing of gait (FOG), cognitive impairment, poor balance, lower limb weakness and postural instability (Latt et al., 2009, Paul et al., 2014, Pelicioni et al., 2019). Therefore, many PD patients develop the fear of falling which prompts a sedentary lifestyle (Rahman et al., 2011). However, this increased sedentary behaviour has important clinical implications because it may predispose patients to co-morbidities such as diabetes, cardiovascular disease, and stroke. An increased sedentary lifestyle may also have negative effects on disease management because the potential positive impact physical activity may have on PD symptoms are mitigated (Benka Wallén et al., 2015).

4.3. Correlation analysis

4.3.1. Association between sleep parameters, PD-related non-motor symptoms, physical activity, and light exposure

Evidence from previous studies shows that pain and sleep are related to one another (Fu et al., 2018, Martinez-Martin et al., 2018, Finan et al., 2013, Vila-Chã et al., 2019, Rana et al., 2018). This study found pain to be strongly negatively associated with sleep efficiency and total sleep time. Similarly, a study indicated that PD patients with pain showed evidence of sleep

fragmentation which was illustrated by a decreased sleep efficiency, total sleep time, an increased WASO and sleep onset latency (Fu et al., 2018). Research suggests that sleep may be impaired due to the pain experienced, and pain may be exacerbated by the sleep disturbances, highlighting a reciprocal relationship which involves a pathophysiological mechanism that includes alterations in the dopaminergic signaling (Ohayon, 2005, Fu et al., 2018). Increased pain is also found to be common in disorders related to dysfunctions in the dopaminergic system (Jarcho et al., 2012).

A positive association was seen between sleep onset latency and moderate physical activity indicating that sleep worsens with increased moderate physical activity. However, this finding is not consistent with other studies which suggest that moderate physical activity improves sleep onset latency (Reid et al., 2010). Another study (n = 65) also showed physical activity improves sleep in PD patients (Coe et al., 2018). Sleep measures were self-reported and physical activity levels were detected using wrist-worn activity monitor (Coe et al., 2018). In our study we used a hip-mounted activity monitor to detect changes in physical activity as well as we had a smaller sample size of (n = 22). A study reported that wrist activity monitors record fewer steps compared to hip accelerometry when walking on a treadmill but record more steps than hip-activity monitor in a free-living environment (Kamada et al., 2016), possibly explaining the differences seen. A study identified that specific timing during the day in which the exercise is carried out may affect sleep onset latency, in particular another study indicated that bouts of morning exercise was found to reduce to sleep onset latency (Fairbrother et al., 2014, Alley et al., 2015). A recent study by Amara et al. (2020) assessed the effect of a 16-week exercise intervention on sleep parameters and found no change in sleep latency between the exercise group and the control group which consisted of sedentary PD patients (Amara et al., 2020). However, in our study, PD patients also had an increased sedentary behaviour of 83%.

4.3.2. Association between PD-related non-motor symptoms, physical activity, and light exposure

This study showed an association between fatigue and depression, similarly several studies also showed a correlation between fatigue and depression in PD patients (Metta et al., 2011, Kluger et al., 2012, Gołąb-Janowska et al., 2016). In addition, there was an association between fatigue and light physical activity. In contrast to this finding, patients with PD reported that fatigue

improved with exercise (Cochrane et al., 2015). A recent study with a sample of 1,029 patients with PD investigating triggers and alleviating factors for fatigue reported that 50 % of patients said that exercise improved their fatigue (Lin et al., 2021). The reason of this discrepancy could be due to our smaller sample size and different methodologies used. The study by Lin et al used the Parkinson's fatigue scale and the physical activity scale for the elderly, which is a self-reported measure of the participants activities (Lin et al., 2021) whereas our study used the Fatigue Severity Scale. Our study also found an inverse association between sedentary behaviour and light exposure. As mentioned previously decreased movement is one of the hallmarks in PD patients, therefore patients who undergo a sedentary lifestyle are exposed to reduced natural light exposure and physical activity (Benka Wallén et al., 2015).

4.4. Limitations

There were further limitations this study. Although our sample size consisted of 22 patients, only eight patients completed the PSG component, making it difficult to detect differences between the two groups in the PSG sleep parameters. A larger sample size would have provided a greater statistical power. Studies that have assessed sleep using subjective measures used larger sample sizes compared to the current dissertation and studies using objective measures to assess sleep (PSG and actigraphy) and DBS have a relatively small sample size (approximately n=12). In contrast, a single study used a sample size of 50 PD patients who underwent DBS, reported subjective and objective sleep measures in PD. Due to the small sample size we could not perform a correlation analysis on the PSG sleep outcomes and PD-related non-motor symptoms.

The current dissertation did not evaluate the patient's subjective and objective sleep parameters before the DBS surgery, thus making it challenging to make a direct comparison on the effects of DBS on sleep parameters as well as cognitive function, mental health , light exposure, pain and physical activity, however the study did assess sleep outcomes between patients who had undergone DBS compared to PD patients who had not undergone DBS to determine whether there was a difference in sleep parameters in these two populations of PD patients. Using these two populations PD patients also introduced many variables which included the different medications each patient was on. This study also did not withdraw the use of sleep medications and anti-depressants. The PD patients were also on dopaminergic medications at different dosages, therefore making it also difficult to detect true RLS among the PD patients.

The electrode positioning must be regarded as an approximation and we were also unable to switch off the DBS, therefore artifacts were caused during the sleep recording, however we did adjust for high and low filtering to account for these artifacts.

To measure cognitive impairment, the current study used the cognitive component of the PDQ-39 questionnaire, the cognitive impairment component of the PDQ-39 questionnaire was adequate for this study.

The ActiGraph system has not been calibrated for individuals with PD, therefore we used cut-offs that were calibrated for the general populations, making it challenging to assess appropriate cut-offs at different physical activity patterns using accelerometry for patients with PD. An altered gait pattern is generally present in PD, therefore these thresholds may not validly reflect the appropriate physical activity patterns (Benka Wallén et al., 2015).

4.5. Future recommendations

Further studies with a larger sample sizes, investigating and comparing the effects of the different aspects of sleep on DBS at different brain regions is recommended. This was a cross-sectional study, however longitudinal studies are required to investigate the effects of sleep in patients who have undergone DBS as well as determining the relationships between PD-other non-motor symptoms and sleep and how these relationships unfold longitudinally.

4.6. Conclusion

The results obtained in this study were conflicting, with the DBS group showing worse outcomes for most subjective sleep parameters assessed compared to the non-DBS group, however it was seen that the DBS group had a longer disease duration and an increased disease severity and depression compared to the non-DBS group. Depression has shown to influence sleep and depression was greater in the DBS group. The DBS and non-DBS groups were not significantly different in terms of age and sex distribution, however a difference was seen in disease duration between the two groups with the DBS group having a higher disease duration. The objective sleep measures (including ambulatory PSG and activity monitoring) indicated no differences in sleep between the two groups except for the non-DBS group showing an increase in slow wave sleep. Overall, the non-DBS group had better sleep quality compared to

the DBS group, this was supported by the non-DBS group having better subjective sleep measures compared to the DBS group, this was further corroborated by the non-DBS having a longer duration of slow wave sleep for objective sleep measures. The DBS group showed higher depression levels however we found no differences in pain levels, cognitive function, physical activity and ambulatory light exposure between the two groups.

Among the sleep parameters and PD-related non-motor symptoms the following were seen such as, a negative relationship between sleep efficiency and pain, a negative relationship between total sleep time and pain and a positive relationship sleep latency and moderate physical activity, indicating that pain experienced by PD patients leads to a decreased sleep efficiency and total sleep time and moderate physical activity by PD patients causes a higher sleep latency. These relationships may suggest that pain and moderate physical activity may have worsening effects on sleep in PD. Therefore it maybe suggested to improve treatment options that PD patients may try pain medications and have an increased light exposure in order to decrease their pain and better their sleep.

Chapter 5: References

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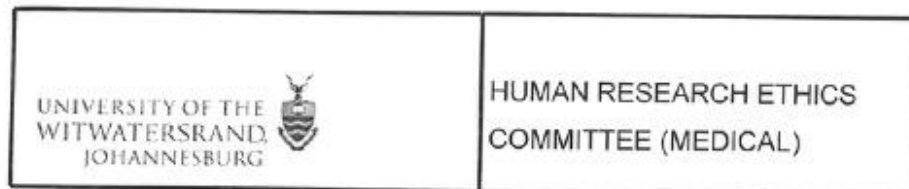
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Chapter 6: Appendix

Appendix 1: Ethical Clearance



Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Ms S Collopy; Drs K Scheuermaier & A Ferreira-Correl
School of Physiology
Medical School
University

E-mail: 1116269@students.wits.ac.za

CC: Supervisor: Dr S Kerr <Samantha.Kerr@wits.ac.za>
and <HREC-MedicalResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/08/17

REF: R14/49

PROTOCOL NO: M200510 *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Sleep and non-motor parameters in patients with Parkinson's Disease*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.



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 UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
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Ms S Collopy; Drs K Scheuermaier & A Ferreira-Correia
School of Physiology
Medical School
University

2020/09/10

Sent by e-mail to: 1116269@students.wits.ac.za

Dear Ms Collopy

Re: Protocol Ref No: M200510
Protocol Title: *Sleep and non-motor parameters in patients with Parkinson's Disease*
Principal Investigator: Ms S Collopy; Drs K Scheuermaier & A Ferreira-Correia

Thank you for your letter of 2020/08/31.

I confirm that we have noted and approve of the intention to source patients from Dr M Smith, in addition to those sourced via Dr D Anderson.

Thank you for keeping us informed.

Yours Sincerely



.....
 Mr I Burns
 For the Human Research Ethics Committee (Medical)



.....
 Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

Works2000tsin0007/Acknowledge.docx

Appendix 2: Study information document for patients with Parkinson's Disease

Study title: Sleep and other non-motor parameters in Patients with Parkinson's Disease

Good Day,

I, Simoné Colloppen, together with my MSc supervisors, Dr. Kerr, Dr. Scheuermaier and Dr. Ferreira-Correia, are researchers at the University of Witwatersrand and are interested in understanding how sleep is affected by Parkinson's Disease (PD). We are also studying how sleep changes with treatment (e.g. Deep Brain Stimulation (DBS)) and other PD symptoms (e.g. decreased physical activity).

To help us discover this, we would like to invite you to volunteer for our study. This study includes three parts; (1) completing several questionnaires (2), wearing two activity monitors for one week (3) and an overnight sleep assessment called polysomnography (PSG) (3). The data captured in this study will also contribute to an ongoing study established by Dr David Anderson at the Wits Donald Gordon Medical Centre to longitudinally capture motor and non-motor characteristic of patients with PD. In order to fully investigate the sleep component of our study, please consent to allowing us to access your clinical records in Dr David Anderson's research database.

If you agree to participate,

(1) You will be asked to complete a series of sleep questionnaires, which will ask about your general health, particularly on sleep. The questionnaires should about an hour to complete.

(2) You will be asked to wear two activity monitors (about the size of a match box) to measure daily activity and movements during your sleep for one week. The activity monitors also have light sensors, which will measure your daily light exposure. At the same time you will be asked to keep a sleep and physical activity diary. After the week you will be asked to return the activity monitors together with the sleep diary. The activity monitors will be worn on the wrist and around the waist (each location provides different information).

(3) You will be asked to participate in an overnight sleep assessment (PSG). PSG non-invasively records your brain waves, as well as eye and leg movements during sleep. During the PSG, sensors will be placed on your scalp, temples, chin, chest and leg using a mild sticky paste. The sensors will be connected to a computer, to collect your sleep data. The wires are long enough to allow free movement during sleep. The equipment is mobile thus we can conduct the sleep study in your own home. The study takes place over two consecutive nights – the first night to get used to sleeping with the setup and the second night for the recording. On both nights, I, Simonè, will come to your home and set up the equipment, which will take approximately 30 minutes, and then leave your home. The following morning, I will collect the equipment. Alternatively, the sleep assessment can be conducted at the Wits School of Physiology Sleep Laboratory.

No one will be able to see or access your data other the researchers involved in this study. Your confidentiality will be protected at all times. The results will be analyzed and published in

scientific papers and presented at a scientific conference, however your identity will remain anonymous.

We have obtained approval for this study from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand whose contact details are listed below*. Participation in this study is voluntary and you are allowed to withdraw at any time. There will be no payment, or direct personal benefit from participating in the study. However, the results of your sleep assessment can be made available to you and your neurologist if you wish. There is no penalty for refusing to take part, or for subsequent withdrawal from the study. If after reading this information sheet you decide against participating in the study, please be assured that this will not impact on you negatively in any way. If you have further questions, please do not hesitate to ask.

Yours Sincerely,

Dr. Sam Kerr
072 731 2216
samantha.kerr@wits.ac.za

Simoné Colloppen
071 331 9635
1116269@students.wits.ac.za

*If you have any doubts to your rights as a participant please feel free to contact Mr Rhulani Mkansi Rhulani.Mkansi@wits.ac.za or Ms Zanele Ndlovu zanele.ndlovu@wits.ac.za – 011 717 1252/2700/1234/2656, Medical School, Parktown, Phillip Tobias Building, 2nd Floor, Cnr York Road and Princess of Wales Terrace, Mon-Fri 08h00-17h00. Chair of the Human Research Ethics Committee.

CONSENT TO ACT AS PARTICIPANT IN RESEARCH

I, _____(full name and surname) agree to participate in the study titled: **Sleep and other non-motor parameters in patients with Parkinson's Disease.**

The procedures/questionnaires have been explained to me and I understand and appreciate their purpose, any risks involved, and the extent of my involvement. I have read and understand the attached information sheet.

I understand that the procedures form part of a research project and may not provide any direct benefit to me.

I understand that all experimental procedures have been sanctioned by the Committee for Research on Human Subjects, University of the Witwatersrand, Johannesburg.

I understand that my participation is voluntary and that I am free to withdraw my participation from the project at any time without prejudice.

Participant name and signature

Date

Investigator name and signature

Date

Appendix 3: Study title: Sleep and other non-motor parameters in Patients with Parkinson's Disease (for next of kin)

Dear (name of next of kin and his/her relationship to the patient to be entered)

I, Simoné Colloppen, together with my MSc supervisors, Dr. Kerr, Dr. Scheuermaier and Dr. Ferreira-Correia, are researchers at the University of Witwatersrand and are interested in understanding how sleep is affected by Parkinson's Disease (PD). We are investigating how sleep changes with treatment (e.g. Deep Brain Stimulation (DBS)) and other PD symptoms (e.g. cognitive function and mental health; pain, gait freezing, physical activity and light exposure).

To help us discover this, we would like to invite (name of patient) to volunteer for our study. This study includes three parts; (1) completing several questionnaires (2), wearing two activity monitors for one week (3) and an overnight sleep assessment called polysomnography (PSG) (3). The data captured in this study will also contribute to an ongoing study established by Dr David Anderson at the Wits Donald Gordon Medical Centre to longitudinally capture motor and non-motor characteristic of patients with PD. In order to fully investigate the sleep component of our study, please consent to allowing us to access (name of patient) clinical records in Dr Anderson's research database. The reason we are asking both you and him/her is because although the reasoning capacity in patients with PD is largely preserved, some patients might experience other cognitive difficulties and we want to ensure that patients are supported in the process of making a research decision.

If (name of patient) agrees to participate, (1) they will be asked to complete a series of sleep questionnaires, which will ask about his/her general health, mental health and sleep. The questionnaires will be electronically sent to the patient (via email) or given to them to take home to complete.

(2) The patient will be asked to wear two activity monitors (about the size of a match box) to measure daily activity and movements during your sleep for one week. The activity monitors also have light sensors, which will measure his/her daily light exposure. At the same time, the patient will be asked to keep a sleep and physical activity diary. After the week, the patient will be asked to return the activity monitors together with the sleep diary. The activity monitors will be worn on the wrist and around the waist (each location provides different information).

(3) The patient will be asked to participate in an overnight sleep assessment (PSG). PSG non-invasively records brain waves, as well as eye and leg movements during sleep. During the PSG, sensors will be placed on the patient's scalp, temples, chin, chest and leg using a mild sticky paste. The sensors will be connected to a computer, to collect the patient's sleep data. The wires are long enough to allow free movement during sleep. The equipment is mobile thus we can conduct the sleep study in the patient's own home. The study takes place over two consecutive nights – the first night to get used to sleeping with the setup and the second night for the recording. On both nights, I, Simone, will come to the patient's home and set up the equipment, which will take approximately 30 minutes, and then leave the patient's home. The following morning, I will collect the equipment. Alternatively, the sleep assessment can be conducted at the Wits School of Physiology Sleep Laboratory. While the Covid-19 lockdown is still in place, this component of the study will be postponed.

No one will be able to see or access the patient's data other than the researchers involved in this study. The patient's confidentiality will be protected at all times. The results will be analyzed and published in scientific papers and presented at a scientific conference, however the patient's identity will remain anonymous.

We have obtained approval for this study from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand whose contact details are listed below*. Participation in this study is voluntary and the patient is allowed to withdraw at any time. There will be no payment, or direct personal benefit from participating in the study. However, the results of the patient's sleep assessment can be made available to the patient and the patient's neurologist if you wish. There is no penalty for refusing to take part, or for subsequent withdrawal from the study. If after reading this information sheet you decide against (name of patient) participating in the study, please be assured that this will not impact on the patient negatively in any way. If you have further questions, please do not hesitate to ask.

Yours Sincerely,

Dr. Sam Kerr
072 731 2216
samantha.kerr@wits.ac.za

Simoné Colloppen
071 331 9635
1116269@students.wits.ac.za

*If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

INFORMED CONSENT NEXT OF KIN

I, _____ (full name and surname) give my consent for the participation of my (.....) (define relationship) to participate in the study titled: **Sleep and other non-motor parameters in patients with Parkinson's Disease**. I acknowledge the following:

I am aware that:

- The participation of (please insert the name of the patient) in this research study is voluntary and that he/she may withdraw from the study at any time. If he/she decides to withdraw, he/she does not need to give a reason and there will be no negative impact on the care he/she receives at the Brain and Mind Centre at Wits Donald Gordon Medical Centre.
- I am aware that he/she will not be paid for participating in the research study and it will not cost him/her anything.
- I have had the opportunity to ask questions about the study and these have been answered to my satisfaction.
- I have given Simoné Colloppen, together with her MSc supervisors, Dr. Kerr, Dr. Scheuermaier and Dr. Ferreira-Correia permission to access data from the clinical records of Mr/Ms for use for research purposes, with the assurance that his/her personal details will not be disclosed.
- I am aware that these data will be kept strictly confidential and will only be accessed by Simoné Colloppen, together with her MSc supervisors, Dr. Kerr, Dr. Scheuermaier and Dr. Ferreira-Correia.
- The procedures/questionnaires have been explained to me and the patient and I understand and appreciate their purpose, any risks involved, and the extent of the patients involvement. I have read and understand the attached information sheet.
- I understand that the procedures form part of a research project and may not provide any direct benefit to the patient.
- I understand that all experimental procedures have been sanctioned by the Committee for Research on Human Subjects, University of the Witwatersrand, Johannesburg.

I confirm that Mr/Ms _____ is willing to participate in this study.

Next of kin signature: _____ Date: _____

Next of kin full name: _____

Signature of person who sought consent: _____

Name of person who sought consent: _____

Date: _____

Investigator name and signature _____

Date : _____

Appendix 4: General Questionnaire

1. During the past month, what time have you usually gone to bed at night?

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____

3. During the past month, what time have you usually gotten up in the morning?

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the past month, how many times per night have you woken during the night?

6. Have any of your family members experienced a sleep problem:

Yes/no (circle the appropriate response)

If yes, please explain the relationship (i.e. parent, sibling, cousin) _____

and the nature of the sleep problem _____

7. Are you currently (within the last 6 months) taking any chronic medications? Please indicate the medication, dosage, what you are taking it for and the times you take the medication.

8. Do you experience any pain? Yes/No (circle appropriate answer)

a) If yes, when do you experience pain? (circle all that are appropriate)

00:00 – 06:00 / 06:00 – 12:00 / 12:00 – 18:00 / 18:00 – 00:00

b) Does the pain prevent you from falling asleep or wake you from your sleep?

Yes/No (circle appropriate answer)

c) In the past month, how would you rate the intensity of your pain?

Make a mark on the line below.

Visual analog scale

No pain | _____ | Pain as bad as it could possibly be

Appendix 5: Beck's Depression Inventory II

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
 - 0 I do not feel sad.
 - 1 I feel sad
 - 2 I am sad all the time and I can't snap out of it.
 - 3 I am so sad and unhappy that I can't stand it.
2.
 - 0 I am not particularly discouraged about the future.
 - 1 I feel discouraged about the future.
 - 2 I feel I have nothing to look forward to.
 - 3 I feel the future is hopeless and that things cannot improve.
3.
 - 0 I do not feel like a failure.
 - 1 I feel I have failed more than the average person.
 - 2 As I look back on my life, all I can see is a lot of failures.
 - 3 I feel I am a complete failure as a person.
4.
 - 0 I get as much satisfaction out of things as I used to.
 - 1 I don't enjoy things the way I used to.
 - 2 I don't get real satisfaction out of anything anymore.
 - 3 I am dissatisfied or bored with everything.
5.
 - 0 I don't feel particularly guilty
 - 1 I feel guilty a good part of the time.
 - 2 I feel quite guilty most of the time.
 - 3 I feel guilty all of the time.
6.
 - 0 I don't feel I am being punished.
 - 1 I feel I may be punished.
 - 2 I expect to be punished.
 - 3 I feel I am being punished.
7.
 - 0 I don't feel disappointed in myself.
 - 1 I am disappointed in myself.
 - 2 I am disgusted with myself.
 - 3 I hate myself.
8.
 - 0 I don't feel I am any worse than anybody else.
 - 1 I am critical of myself for my weaknesses or mistakes.
 - 2 I blame myself all the time for my faults.
 - 3 I blame myself for everything bad that happens.
9.
 - 0 I don't have any thoughts of killing myself.
 - 1 I have thoughts of killing myself, but I would not carry them out.
 - 2 I would like to kill myself.
 - 3 I would kill myself if I had the chance.
10.
 - 0 I don't cry any more than usual.
 - 1 I cry more now than I used to.
 - 2 I cry all the time now.
 - 3 I used to be able to cry, but now I can't cry even though I want to.

Appendix 6: WHO 5 well-being index

Please respond to each item by marking <u>one box per row</u> , regarding how you felt in the last two weeks.		All of the time	Most of the time	More than half the time	Less than half the time	Some of the time	At no time
WHO 1	I have felt cheerful in good spirits.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
WHO 2	I have felt calm and relaxed.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
WHO 3	I have felt active and vigorous.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
WHO 4	I woke up feeling fresh and rested.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
WHO 5	My daily life has been filled with things that interest me.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

Appendix 7: Parkinson's Disease Questionnaire

***Due to having Parkinson's disease,
how often during the last month
have you....***

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1	Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2	Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3	Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4	Had problems walking half a mile?	☐	☐	☐	☐	☐
5	Had problems walking 100 yards?	☐	☐	☐	☐	☐
6	Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7	Had difficulty getting around in public?	☐	☐	☐	☐	☐
8	Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐
9	Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐
10	Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11	Had difficulty washing yourself?	☐	☐	☐	☐	☐
12	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13	Had problems doing up your shoe laces?	☐	☐	☐	☐	☐

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

**Due to having Parkinson's disease,
how often during the last month
have you....**

Please tick one box for each question

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
14	Had problems writing clearly?	☐	☐	☐	☐	☐
15	Had difficulty cutting up your food?	☐	☐	☐	☐	☐
16	Had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17	Felt depressed?	☐	☐	☐	☐	☐
18	Felt isolated and lonely?	☐	☐	☐	☐	☐
19	Felt weepy or tearful?	☐	☐	☐	☐	☐
20	Felt angry or bitter?	☐	☐	☐	☐	☐
21	Felt anxious?	☐	☐	☐	☐	☐
22	Felt worried about your future?	☐	☐	☐	☐	☐
23	Felt you had to conceal your Parkinson's from people?	☐	☐	☐	☐	☐
24	Avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25	Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26	Felt worried by other people's reaction to you?	☐	☐	☐	☐	☐
27	Had problems with your close personal relationships?	☐	☐	☐	☐	☐
28	Lacked support in the ways you need from your spouse or partner?	☐	☐	☐	☐	☐
	<i>If you do not have a spouse or partner tick here</i>		☐			
29	Lacked support in the ways you need from your family or close friends?	☐	☐	☐	☐	☐

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

***Due to having Parkinson's disease,
how often during the last month
have you....***

Please tick one box for each question

		Never	Occasionally	Sometimes	Often	Always
30	Unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
32	Felt your memory was bad?	☐	☐	☐	☐	☐
33	Had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34	Had difficulty with your speech?	☐	☐	☐	☐	☐
35	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐
36	Felt ignored by people?	☐	☐	☐	☐	☐
37	Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38	Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39	Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

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

Appendix 8: Sleep and activity diary

Complete in the morning

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day of the week							
Time you went to bed							
Time you woke up							
How long did it take you to fall asleep?							
How many times did you wake up last night and for how long?							
Number of times							
Number of minutes							
Did anything disturb your sleep? (side effects of medication, noise, hot/cold, uncomfortable, etc)							
Rate the quality of your sleep (0, worst -10, best ever)							
What time did you attach the activity monitors before bed?							
What time did you remove the activity monitors in the morning?							

Complete in the evening

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day of the week							
Did you exercise for at least 20 minutes?							
(circle one)	Yes/ No	Yes/ No	Yes/ No	Yes/ No	Yes/ No	Yes/ No	Yes/ No
If yes, what time did you exercise? (M)orning, (A)fternoon, (E)vening. (circle one)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)
Did you consume caffeine?							
(circle one)	Yes/ No	Yes/ No	Yes/ No	Yes/ No	Yes/ No	Yes/ No	Yes/ No
If yes, what time did you consume caffeine? (M)orning, (A)fternoon, (E)vening. (circle one)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)	(M) (A) (E)
How much? (number of cups)							
Did you take a nap?							
(circle one)	Yes/ No	Yes/ No	Yes/ No	Yes/ No	Yes/ No	Yes/ No	Yes/ No
If yes, for how long? (minutes)							
Rate how sleepy you felt during the day (0, not sleepy - 10, very sleepy)							

Appendix 9: Epworth sleepiness scale (ESS)

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

- 0 = would **never** doze
- 1 = **slight chance** of dozing
- 2 = **moderate chance** of dozing
- 3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading _____	_____
Watching TV _____	_____
Sitting, inactive in a public place (e.g. a theatre or a meeting) _____	_____
As a passenger in a car for an hour without a break _____	_____
Lying down to rest in the afternoon when circumstances permit _____	_____
Sitting and talking to someone _____	_____
Sitting quietly after a lunch without alcohol _____	_____
In a car, while stopped for a few minutes in the traffic _____	_____

THANK YOU FOR YOUR COOPERATION

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Appendix 10: Pittsburgh sleep quality index (PSQI)

Subject's Initials_____ID#_____Date_____Time_____AM
PM

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

- a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

- b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

- c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

- a) Loud snoring

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

- b) Long pauses between breaths while asleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

- c) Legs twitching or jerking while you sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

Appendix 11: Cambridge-Hopkins restless leg syndrome questionnaire (CHRLS-q)

Cambridge- Hopkins Questionnaire 13 (Version 2)

Answer the questions as completely as you can. Please **mark the checkbox** for the best answer to each question.

1. Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down?	☐ Yes ☐ No
2. Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down?	☐ Yes ☐ No
If you answered YES to either question 1 or 2 continue Question 3. If you answered NO to BOTH stop here The following is about these feelings	
3. Are you more likely to have these feelings when you are resting (either sitting or lying down) or when you are physically active?	☐ Resting ☐ Active
4. Do these feelings usually start when you are resting (either sitting or lying down)?	☐ Yes ☐ No
5. If you get up or move around when you have these feelings do these feelings get any better while you actually keep moving?	☐ Yes ☐ No ☐ Don't know
6. Which times of day are these feelings in your legs most likely to occur? (Please indicate one or more than one)	☐ Morning ☐ Midday ☐ Afternoon ☐ Evening ☐ Night ☐ About equal at all times
7. Which times of day are these feelings in your legs least likely to occur? (Please indicate one or more than one)	☐ Morning ☐ Midday ☐ Afternoon ☐ Evening ☐ Night ☐ About equal at all times
8. Will simply changing leg position by itself <i>once</i> without continuing to move usually relieve these feelings?	☐ Usually relieves ☐ Does <i>not</i> usually relieve ☐ Don't know
9. Are these feelings ever due to muscle cramps?	☐ Yes ☐ No ☐ Don't know
9b. If so, are they always due to muscle cramps?	☐ Yes ☐ No ☐ Don't know
10. Do these feelings occur only when sitting or only when lying down?	☐ Neither ☐ Only when sitting ☐ Only when lying down ☐ Both when sitting and lying down
11. When you actually experience the feelings in your legs, how distressing are they?	☐ Not at all distressing ☐ A little bit ☐ Moderately

	☐ Extremely distressing
12. In the past 12 months, how often did you experience these feelings in your legs? (Please indicate one)	☐ Every day ☐ 4-5 days per wk ☐ 2-3 days per wk ☐ 1 day per wk ☐ 2 days per month ☐ 1 day per month or less ☐ Never
13. Approximately how old were you when you first noticed these feelings in your legs?(please write age)	___ Yrs
14. WOMEN: Did you first notice these feelings in your legs during pregnancy?	☐ Yes ☐ No
a. If yes have you noticed these other than related to pregnancy?	☐ Yes ☐ No
b. If so, how old were you when you first noticed these feelings in your leg outside of pregnancy?	___ Yrs

Appendix 12: International Restless leg syndrome scale (IRLS)

Assess the Severity of Restless Legs Syndrome

USING THE INTERNATIONAL RLS (IRLS) RATING SCALE

The IRLS Rating Scale was developed by the **International Restless Legs Syndrome Study Group (IRLSSG)** to assess the severity of a patient's RLS symptoms.¹ Ask your patient the 10 questions listed below and have them rate their symptoms from 0 to 4. Mark each answer and total their IRLS score. It will range from 0 to 40.

The IRLS Rating Scale was validated in a controlled study and found to have high levels of internal consistency, interexaminer reliability, and test-retest reliability.¹ The IRLSSG is an organization of professionals committed to advancing basic and clinical research on RLS. To learn more about the group, visit www.irlssg.org.

In the past week:

Score

Overall, how would you rate the RLS discomfort in your legs or arms?

4 Very severe 3 Severe 2 Moderate 1 Mild 0 None

☐

Overall, how would you rate the need to move around because of your RLS symptoms?

4 Very severe 3 Severe 2 Moderate 1 Mild 0 None

☐

Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?

4 No relief 3 Mild relief 2 Moderate relief 1 Either complete or almost complete relief 0 No RLS symptoms to be relieved

☐

How severe was your sleep disturbance from your RLS symptoms?

4 Very severe 3 Severe 2 Moderate 1 Mild 0 None

☐

How severe was your tiredness or sleepiness during the day due to your RLS symptoms?

4 Very severe 3 Severe 2 Moderate 1 Mild 0 None

☐

How severe was your RLS as a whole?

4 Very severe 3 Severe 2 Moderate 1 Mild 0 None

☐

How often did you get RLS symptoms?

4 Very often (6–7 days in 1 week). 3 Often (4–5 days in 1 week). 2 Sometimes (2–3 days in 1 week). 1 Occasionally (1 day in 1 week). 0 Never

☐

When you had RLS symptoms, how severe were they on average?

4 Very severe (8 h or more per 24 h) 3 Severe (3–8 h per 24 h) 2 Moderate (1–3 h per 24 h) 1 Mild (less than 1 h per 24 h) 0 None

☐

Overall, how severe was the impact of your RLS symptoms, on your ability to carry out your daily affairs, for example, carrying out a satisfactory family, home, social, school, or work life?

4 Very severe 3 Severe 2 Moderate 1 Mild 0 None

☐

How severe was your mood disturbance from your RLS symptoms—for example angry, depressed, sad, anxious, or irritable?

4 Very severe 3 Severe 2 Moderate 1 Mild 0 None

☐

Add the scores from above and share the total with your patient.

Mild 0 to 10

Moderate 11 to 20

Severe 21 to 30

Very Severe 31 to 40

Total Score

☐

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Reference: 1. The International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group Rating Scale for Restless Legs Syndrome. *Sleep Med.* 2003;4(2):121-132.

For information about approved uses of this scale and about RLS, contact www.IRLSSG.org. IRLS contact information and permission to use: MAPI Research Trust, Lyon, France. Email: PROinformation@mapi-trust.org

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Appendix 13: Fatigue severity scale (FSS)

Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. Essentially, the FSS consists of answering a short questionnaire that requires the subject to rate his or her own level of fatigue. The obvious problem with this measure is its subjectivity.

Here is an example FSS questionnaire containing nine statements that attempt to explore severity of fatigue symptoms. The subject is asked to read each statement and circle a number from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement.

FSS Questionnaire							
During the past week, I have found that:	Agreement Score						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

The scoring is done by calculating the average response to the questions (adding up all the answers and dividing by nine).

People with depression alone score about 4.5. But people with fatigue related to MS, SLE or CFIDS average about 6.5.

Appendix 14: Short-form McGill pain questionnaire

Short-Form McGill Pain Questionnaire

PATIENT'S NAME: _____ DATE: _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT/BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING/EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING/CRUEL	0) _____	1) _____	2) _____	3) _____

VAS	NO PAIN	 	WORST POSSIBLE PAIN
PPI			
0 NO PAIN	_____		
1 MILD	_____		
2 DISCOMFORTING	_____		
3 DISTRESSING	_____		
4 HORRIBLE	_____		
5 EXCRUCIATING	_____		

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The short-form McGill Pain Questionnaire (SF-MPQ). Descriptors 1-11 represent the sensory dimension of pain experience and 12-15 represent the affective dimension. Each descriptor is ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. The Present Pain Intensity (PPI) of the standard long-form McGill Pain Questionnaire (LF-MPQ) and the visual analogue scale (VAS) are also included to provide overall intensity scores.

Appendix 15: Turn-it-in report

Sleep and other non-motor parameters in patients with Parkinson's Disease-5.docx

ORIGINALITY REPORT

18%	15%	8%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.frontiersin.org Internet Source	1 %
2	onlinelibrary.wiley.com Internet Source	1 %
3	www.ncbi.nlm.nih.gov Internet Source	1 %
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