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The Relationship between Sleep Disorders and Memory Dysfunction in People with Parkinson's Disease

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Abstract

The present study explored the relationship between sleep quality and memory in people with Parkinson's disease (PD). In PD sleep disorders are common, as are memory deficits. Sleep quality impacts on the mechanisms of memory and specific sleep disorders have specific effects on cognitive function. Participants were screened for common sleep problems using the Parkinson's disease sleep scale-revised (PDSS-R). Memory was assessed using the recall measure of the Hopkins Verbal Learning Test-Revised (HVLT-R) and memory for visual patterns was assessed using the Pattern Recognition Memory (PRM) test. It was found that poor sleep quality was associated with poor performance on the HVLT-R and symptoms of REM sleep behaviour disorder (RBD) were associated with poor performance on the PRM.

The Relationship between Sleep Disorders and Memory Dysfunction in People with Parkinson's Disease

Parkinson's disease (PD) is a complex neurodegenerative disorder that initially causes motor dysfunction and disrupts higher order cognitive processes (Owen, 2004). Symptoms of PD are pervasive and interrupt normal function of motor control, the autonomic nervous system, sleep cycles, perception and emotional regulation (Korczyn, 2002). There are behavioural and clinical 'markers' that indicate both healthy people who are at risk for developing PD as well as people with PD who are more likely to develop significant cognitive dysfunction (Iranzo et al., 2005). Research into such markers and their relationship to disease progression is vital. As neuroprotective treatments are developed for PD, researchers need to know who is most likely to benefit from such treatments.

PD is characterised by particular motor symptoms including: tremor, rigidity, bradykinesia (slowness of movement), hypokinesia (restricted range of movement), as well as impairments in gait and posture (Lang & Lozano, 1998). PD is a heterogeneous disorder; various combinations of these motor symptoms can be present in individual patients making differential diagnosis difficult and suggesting multiple heterogeneous pathologies underlying the disorder (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004). The motor symptoms of PD arise from loss of dopaminergic cells within the substantia nigra (Schapira, Cooper, Dexter, Clark, Jenner & Marsden, 1990), and the pattern of cell loss observed in PD is opposite to that seen in normal aging (Lang & Lozano, 1998). The exact cause of cell death is unknown, but current research suggests environmental neurotoxin exposure combined with a biological vulnerability to neurodegenerative disease (Betarbet, Sherer, MacKenzie, Osuna, Panov & Greenamyre, 2000).

Parkinson's, Cognitive Decline and Dementia

Cognitive problems are associated with PD and are present in most people with PD. A substantial proportion of people with PD go on to develop concomitant dementia (Korczyn, 2002). Development of dementia has a considerable impact on activities of daily living and quality of life, and is a significant predictor of admission to a residential care facility (Ravina et al., 2005). A longitudinal study by Levy et al. (2002) found that memory impairments in people with PD predicted the development of dementia in about one third of patients within four years of cognitive testing. According to some long term longitudinal studies, many more people with PD develop dementia than initially thought. Approximately 60-80% of PD patients develop dementia within 10-15 years of first developing motor symptoms, (McKeith, 2004). Dementia in PD differs significantly from other forms of dementia, such as Alzheimer's disease (AD). The early stage of Parkinson's Disease with Dementia (PDD) is characterised by deficits in attention, executive function and visuospatial memory, rather than the deficits in episodic memory that are the hallmark of AD, (McKeith, 2004). Consequently, PDD is often only recognised when in its advanced stages and neuroprotective treatments are no longer effective.

It is commonly thought that dementia occurs in PD because of the formation of Lewy bodies in susceptible areas of brain tissue, (Cummings, 2004). There is, however, a growing body of evidence is accumulating to suggest that this may not be the case. Braak, Rub, Jansen Steur, Del Tredici and de Vos (2005) note that Lewy bodies can be found in people with no symptoms that indicate neurological illness. Autopsy evidence reveals that some people with PDD have no Lewy bodies, but instead having significant subcortical degeneration that may have driven their cognitive decline. Although the mechanism that causes dementia to develop

in PD is currently unknown, prospective longitudinal studies have discovered three main points. First, there are subtle cognitive deficits in PD patients even before motor symptoms appear (Chaudhuri & Schapira, 2009; Vendette et al., 2007). Second, that cognitive decline usually follows the same pattern as motor deterioration (Braak, Rub, Jansen Steur, Del Tredici and de Vos, 2005). And finally, that people are affected to varying degrees; some have relatively intact cognition at advanced stages of the disease and others have significant cognitive impairment at a much earlier stage than would be predicted by their motor function (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004).

Normal Sleep and Memory

Restorative sleep refers to sleep that is sufficient in both length and quality to allow a person to feel rested upon waking (Curcio, Ferrara & De Gennaro, 2006). Healthy adults sleep for approximately 7.5 hours per night in one solid session. This begins with one cycle of non-rapid eye movement (NREM) or slow wave sleep, and then alternates between cycles of NREM and REM sleep throughout the night (Adler & Thorpy, 2005). During NREM sleep, global brain activity decreases dramatically but rises to waking levels during REM sleep, (Nofzinger, 2005). Normal REM sleep is characterised by rapid eye movements, atonia (loss of skeletal muscle tone) evidenced by EMG recordings and mixed alpha and theta activity on EEG recordings.

Restorative sleep is necessary for normal memory function, as the processes associated with memory consolidation and neural repair occur during sleep (Curcio, Ferrara & De Gennaro, 2006). Cumulative sleep deficit and sleep fragmentation have been associated with impaired memory function and decreased capacity for learning (Blunden & Beebe, 2005). Tononi and Cirelli (2003) proposed the 'synaptic homeostasis hypothesis', which describes processes occurring during slow wave sleep whereby synapses are recalibrated after

stimulation and excitation during the day. This allows learning to occur on a 'fresh slate' the next day. When sleep is restricted or disrupted, the synapses do not return to baseline levels of excitation. This limits a person's ability to encode new memory until a period of slow wave sleep restores synaptic homeostasis.

Sleep problems in PD can occur either in slow wave sleep cycles, REM sleep cycles or both. PD patients typically experience less total sleep time and more fragmented sleep than age matched controls (Friedman & Chou, 2006).

Slow Wave Sleep Disorder in Parkinson's Disease

Emser, Brenner, Stober and Schmrigk (1988), compared 12 PD patients, 12 patients with Huntington's disease (HD) and 12 age-matched neurologically healthy controls in a sleep study. The patients were assessed by polysomnography and their sleep patterns were compared both within and between groups. Both PD and HD were selected as comparisons, as both diseases are known to affect the basal ganglia. Therefore, if the sleep problems present in both of these diseases are caused by shared dysfunction, then similar patterns of dysfunction should be observed on polysomnography examination. They found, however, that the PD group experienced shorter, more fragmented sleep than both HD patients and age-matched controls. Also, three of the patients in the PD group showed a complete lack of slow wave sleep. The PD group experienced a significant decrease in sleep spindle (high frequency brain waves observed in NREM sleep) density compared to both the HD group (who experienced a significant increase in sleep spindle density compared to normal patterns) and age-matched controls. Research by Neal and Keane, (1980) into the role of dopamine regulation of sleep in an animal model, suggests that the dopaminergic pathways are responsible for the regulation of both slow wave sleep and the production of sleep spindles during slow wave sleep. Given that the primary deficit of Parkinson's disease is a lack of

dopamine, slow wave sleep problems are expected to be present in a significant number of PD patients.

REM Sleep Behaviour Disorder (RBD) and Parkinson's Disease

Rapid eye movement sleep behaviour disorder (RBD) is characterised by the absence of atonia during rapid eye movement sleep, combined with the performance of complex behaviours during the REM period of sleep (Tan, Salgado & Fahn, 1996). People with this disorder tend to 'act out' their dreams and commonly become agitated or violent during sleep. RBD is associated with a group of neurodegenerative disorders called the 'synucleinopathies'; so called because of α-synuclein protein deposits which occur throughout the brain (Gagnon, Postuma, Mazza, Doyon & Montplaisir, 2006). This class of disorders includes PD, dementia with Lewy Bodies, multiple system atrophy and progressive supranuclear palsy (Boeve et al., 2001). RBD is often present as long as ten years before symptoms of a neurodegenerative disease become apparent (Vendette et al., 2007). The symptoms of RBD in PD can become less problematic as the cognitive and motor symptoms of the disease progress, as significant disability prevents people from being able to perform complex movements and prevents the manifestation of violent or dangerous behaviours (Boeve et al., 2003).

In those with RBD, EEG recordings and rapid eye movements are normal. EMG recordings, however, indicate either exaggerations of the normal phasic motor twitches or tonic increases in muscle activity (Boeve, Silber & Ferman, 2004). People with concomitant PD and RBD tend to show slowing on waking EEG examination. This is consistent with the finding that these people perform worse on cognitive tests than people with PD who do not also have RBD (Vendette et al., 2007).

The exact pathophysiology of RBD is currently unknown but animal models, neuropathological studies, lesion studies and pharmacotherapy provide important information about the disorder (Boeve et al., 2007). It has long been thought that dysfunction within the brain stem is responsible for the development of RBD. More recently, a number of other brain regions have also been implicated, including; the medullary magnocellular reticular formation (MCRF), the noradrenergic locus coeruleus (LC), the cholinergic nuclei, pedunculopontine nucleus (PPN), the laterodorsal tegemental nucleus, the substantia nigra, hypothalamus, thalamus, basal forebrain and frontal cortex (Boeve et al. 2007).

Evidence that disputes the brain stem hypothesis is proposed by Iranzo et al., (2005) who reported five cases of men who developed RBD following Voltage-gated potassium channel antibody-associated limbic encephalitis (VGKC-LE). This is an autoimmune disorder that affects the limbic system but not the brain stem. Following treatment for the autoimmune disorder, three of the five men recovered from VGKC-LE and their RBD symptoms were resolved. The two men who were treated with immunosuppressant medication who did not recover from VGKC-LE continued to experience RBD symptoms. Iranzo et al., (2005) suggested that, as both VGKC-LE and the syneucleinopathies affect the limbic system, the limbic system may be the key site implicated in RBD pathology. As the limbic system is associated with intense emotional states during wakefulness and shows activation during the REM phases of sleep, it is reasonable to suggest that intense, unpleasant dreams could be mediated by pathology within the limbic system.

Abnormalities within dopaminergic pathways are associated with all of the synucleinopathies. Simple irregularities with dopamine levels are not, however, thought to underlie the development of RBD (Boeve et al., 2003). There is currently no adequate explanation for the epidemiology of RBD, but it is now thought that a complex interaction

between noradrenergic, serotonergic, cholinergic and other neurochemical systems underlies the pathology (Boeve et al., 2007).

Although there are few (if any) rigorous medication trials for the treatment of RBD that have been published; medications, particularly Clonezepam, Melatonin and Levodopa (Adler & Thorpy, 2005) are effective treatments for this disorder. Conversely, certain medications, particularly tricyclic antidepressants and selective serotonin (SSRIs) and norephrine reuptake (NRIs) inhibitors, are known to exacerbate RBD symptoms (Boeve et al., 2007). Knowledge about the mode of action of these drugs informs about the likely processes underlying the pathology. For example, it is thought that Levodopa improves the symptoms of RBD by (i) shortening the length of REM sleep, (ii) stimulating dopamine receptors and (iii) reducing serotonin levels. These three effects of Levodopa, in combination, are thought to suppress the symptoms of RBD (Tan, Salgado & Fahn, 1996). While Clonezepam and Levodopa reduce the behavioural symptoms of RBD, neither treatment restores atonia during REM sleep cycles. There is, however, some evidence that melatonin restores atonia while ameliorating the behavioural symptoms of RBD in a significant number of patients with RBD, (Gagnon, Postuma & Montplaisir, 2006). It is thought that melatonin acts to improve RBD by restoring a normal circadian rhythm (Kunz & Bes, 1999), or by directly restoring the mechanisms responsible for REM atonia (Takeuchi, Uchimura, Hashizume, et al., 2001).

RBD is often diagnosed following a sleep episode where a person injures themselves or someone else during sleep, (Gagnon et al. 2005). Patients can, however, demonstrate complex behaviour during REM sleep without causing injury, and many people with RBD who sleep or live alone are completely unaware of their disorder. RBD also exists as a partial syndrome, where normal atonia during REM sleep cycles is lost but no complex behaviours are observed during sleep (Gagnon, Postuma & Montplaisir, 2006). In incomplete RBD,

awareness of sleep cycle abnormalities is entirely dependent on polysomnography (Boeve et al, 2007). Differential diagnosis of RBD, even when behavioural abnormalities are present often requires polysomnography as the behaviours seen in RBD can be mimicked by other non-REM sleep disorders such as sleepwalking, obstructive sleep apnea, night terrors and confusional arousals (Boeve, Silber & Ferman, 2004).

The Parkinson's Disease Sleep Scale (PDSS) was devised by Chaudhuri et al., (2002) in order to screen patients with PD for some of the most common sleep complaints affecting people with PD. This scale was validated by Tse et al., (2005; PDSS-R) and revised to include an item that specifically addresses the presence of REM Sleep Behaviour Disorder (RBD) symptoms (PDSS-R, item 5: *Do you have violent behaviours such as hitting your spouse or falling out of bed when acting out dreams at night*?), and an item which addresses the presence of symptoms which indicate sleep apnea, (PDSS-R, item 7: *Are you told by others that you snore loudly and have breathing pauses (Both) during the night*?). The PDSS-R covers a wide range of sleep problems associated with PD including; difficulty falling asleep, difficulty maintaining sleep, distressing dreams, medication wearing off during sleep, motor symptoms affecting comfort during sleep, nocturia, RBD, sleep apnea and restless limb syndrome, (Chaudhuri et al., 2002; Tse et al., 2005). Although the PDSS-R yields a total score which is useful for comparing gross sleep dysfunction across participants, the PDSS-R is most useful because it provides a range of item scores which can be evaluated independently of each other to reveal specific sleep disturbances (Tse et al., 2005).

Memory in Parkinson's

Recall memory refers to the ability to deliberately recollect information presented earlier and is considered to be relatively effortful. In contrast, recognition memory refers to one's ability to identify stimuli presented earlier from a number of alternatives and requires

less cognitive resources, (Ivory, Knight, Longmore & Caradoc-Davies, 1999). Recall and recognition memory are differentially affected in various forms of dementia. Song, Kim, Yoo, Song and Lee (2008) found that both immediate and delayed recall were impaired in patients with Parkinson's disease with dementia (PDD) and mild Alzheimer's disease (AD) compared with age matched controls. Delayed recognition performance, however, remained stable across all three groups. These results suggest that recall memory and recognition memory are differentially affected by neurodegeneration, with recognition memory function being preserved in mild dementia.

Weintraub, Moberg, Culbertson, Duda and Stern (2004) suggest that there are three predominant profiles of verbal memory performance amongst people with PD. They examined participants with PD using the Hopkins Verbal Learning Test-Revised (HVLT-R); a measure of free recall, delayed recall and delayed recognition memory. Half of the participants achieved normal performance on free recall tasks and recognition. One third of participants demonstrated impaired retrieval as measured by poor recall scores, though performed well on the recognition task. The remainder of the participants demonstrated both impaired recall and recognition performance, suggesting that they experienced a deficit with encoding the material. Weintraub et al. concluded that a substantial proportion of people with Parkinson's experience memory dysfunction that can be classified as either primary encoding or primary retrieval deficits.

Impaired performance on measures of visuospatial memory is often observed in people with PD who display normal performance in other cognitive tasks. These specific deficits are usually observed in patients with specific sleep disorders common in PD, such as REM sleep behaviour disorder (RBD) (Vendette et al. 2007). Few studies have examined performance on tasks of spatial location memory in relation to sleep quality (rather than RBD specifically) in PD. Studies examining the relationship between non-restorative sleep and

visuospatial memory in healthy adults indicate that spatial memory is impaired as a result of poor quality sleep in the absence of RBD (Goder, Scharfetter, Aldenhoff & Fritzer, 2006).

Sleep and Memory in PD

Given that a substantial proportion of people with PD experience memory deficits and that the majority of people with PD experience sleep disturbances; the present study examines whether poor performance on memory tasks associated with disease progression is related to poor sleep quality. Sleep quality has a direct impact on memory in older adults (Ancoli-Israel & Ayalon, 2006), as chronic interrupted sleep limits repair of tissue in the central nervous system(Cricco, Simonsick & Foley, 2001) and synaptic recalibration (Tononi & Cirelli, 2003) and leads to sub-optimal cognitive performance.

The present study was the first study to examine the differential effects of various common types of sleep pathology on memory performance in people with PD. As sleep disorder in PD is caused by a variety of different pathologies, it was hypothesised that performance on memory tasks will vary according to the type and severity of sleep problems (Tononi & Cirelli, 2003; Vendette et al., 2007). As sleep problems become more severe as PD progresses, it was predicted that higher PDSS scores will be obtained from participants who have more advanced PD (Chaudhuri et al, 2002). People who have RBD show specific deficits in visuospatial memory so it was predicted that participants who report RBD symptoms (violent behaviours during sleep and/or distressing dreams) will also perform poorly on a measure of visuospatial memory (pattern recognition memory) (Vendette, et al., 2007). It was also predicted that overall sleep quality will correlate positively with scores on cognitive measures as sleep deprivation was expected to have a non-specific effect on cognitive performance, (Nofzinger, 2005).

Method

Participants

One hundred and six people participated in the ParkC study. A total of 42 participants were included in the analysis of this study.

Participants were recruited through Parkinson's Western Australia, as well as through a series of advertisements in the West Australian, community newspapers and radio. The present study was undertaken as part of the The Parkinson's Centre (ParkC) study investigating cognitive and motor heterogeneity in Parkinson's disease. Park C is based at Edith Cowan University's Joondalup campus and has collaborative links with the Cambridge Parkinson's Disease Research Clinic, the University of Western Australia, Curtin University of Technology and the Parkinson's Association of Western Australia. ParkC is currently establishing a prospective database in order to investigate the progression of PD in several domains: motor, cognitive, quality of life, mental health, personality, functionality, genetic predispositions and the relationship between motor and non-motor symptoms.

A diagnosis of Parkinson's disease from a Neurologist was necessary for inclusion in this study. Participants with a mini mental state examination (MMSE) score of <24 on admission to the study were excluded in order to remove potential cases of Dementia with Lewy Bodies (DLB). The sample consisted of 27 males and 15 females. Participants had a mean age of 65.1 years (SD=7.45 years). The participants were divided into two groups based on the amount of time that had elapsed since their PD diagnosis; the group defined as newly diagnosed (ND) consisted of 14 participants who had all been diagnosed within two years of admission to the ParkC study; the group who was defined as having an existing

diagnosis (ExD) consisted of 28 participants who had been diagnosed more than two years prior to their admission to the ParkC study. All participants were classified between stage 1 and 3 on the Hoehn and Yahr scale. This data was held by Parkinson's WA but was not available for release to ParkC at the time of writing.

Participants who were being treated with medications were tested during 'on' times (i.e. within two hours of their last dose of medication,) as withdrawal from Levodopa is associated with poorer performance on cognitive tasks (Lewis, Slabosz, Robbins, Barker & Owen, 2005).

Materials

Materials used in the wider ParkC study consisted of a series of questionnaires, a series of orally administered cognitive tasks and a series of computer based tasks from the Cambridge Automated Neuropsychological Test Automated Battery (CANTAB): a set of tasks administered on a computer touch-screen that are designed to measure various types of memory and executive function in people with disorders of the central nervous system.

The questionnaires included were: a demographic questionnaire; a medical history questionnaire; the Epworth Sleepiness Scale (ESS; Johns, 1991); the Parkinson's Disease Sleep Scale-revised (PDSS-R; Tse et al., 2005); the Cambridge Behavioural Inventory (CBI; Nagahama et al., 2006) ; the Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986); the Depression, Anxiety and Stress Scale (DASS; Crawford & Henry, 2003); the Big Five Aspect Scale (BFAS; DeYoung, Quilty & Peterson, 2007), the Ways of Coping Inventory (WAYS; Vitaliano, Russo, Carr, Maiuro, Becker, 1985), the Metamemory Questionnaire (MMQ; Troyer & Rich, 2002), the State version of the State-Trait Anxiety Inventory (STAI; Spielberger, Gorusch, Lushene, 1970) and the Parkinson's Disease Questionnaire-39 (PDQ39; Jenkinson, Fitzpatrick, Peto, Greenhall & Hyman, 1997). As the present study was

undertaken as part of the larger ParkC study, only data on the demographic questionnaire and the PDSS-R are reported in this study.

The set of orally administered neuropsychological tests is comprised of the Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975); the Australian version of the National Adult Reading Test (AUSNART; Henriessy, 1995); the Hopkins Verbal Learning Test- Revised (HVLT-R; Benedict, Schretlen, Groninger & Brandt, 1998); a Line Bisection task (Coslett, Bowers, Fitzpatrick, Haws & Heilman, 1990); a Star Cancellation task (Wilson, Cockburn & Halligan, 1987); a Cube Analysis task (McFie & Zangwell, 1960); a Number Location Task (The Visual Object and Space Perception Battery, 1991); Verbal Fluency (FAS) and Category Fluency (Borkowski, Benton & Spreen, 1967). Only data from the HVLT-R is reported in this study, whilst the MMSE was used for selection of participants in this study.

The computer based tasks from the CANTAB administered to participants were; the Spatial Working Memory task (SWM; Robbins, James, Owen, Sahakian, Lawrence, McInnes & Rabbit, 1998); the Pattern Recognition Memory task (PRM; Robbins et al., 1998); the Spatial Location Memory task (SRM; Owen, Iddon, Hodges, Summers & Robbins, 1997) and the Stockings of Cambridge task (SOC; Robbins et al., 1998). Only data from the PRM task is reported in this study.

The Hopkins Verbal Learning Test-Revised (HVLT-R)

HVLT-R measures immediate recall, delayed recall and recognition of words from a learning list. It consists of a twelve item list which is presented to the participant with three learning trials, one delayed recall trial and one recognition trial where the participant must identify the words from the list amongst semantically related and unrelated distracters. It is a brief screening tool for memory function and is commonly used in geriatric and demented

populations (Benedict et al. 1998). The HVLT-R demonstrates good test-retest reliability when elderly participants are tested and retested on alternate forms of the test. Benedict et al. reported a Pearson's correlation coefficient of *r*= .74 for total recall trials when participants were tested on two separate occasions.

Pattern Recognition Memory (PRM)

PRM tests the ability to recognise visual patterns after a short delay. There are two blocks of trials, each consisting of a series of twelve visual patterns which are presented individually in the centre of the touch screen for three seconds. The recognition phase is a two item forced choice design where the participant must select the pattern presented in the previous series from alongside a novel distracter.

This test measures ability to learn visual information (Owen, Iddon, Hodges, Summers & Robbins, 1997). The PRM has been shown to have good test-retest reliability. Cambridge cognition reports that test retest reliability data for 100 neurologically normal participants revealed a Pearson correlation coefficient of r= .72 when participants were retested either one week or one month from first testing (Retrieved from http://www.cantab.com/cdownloads/CANTAB_reliability_study.pdf on 13/07/09).

Parkinson's Disease Sleep Scale- Revised (PDSS-R)

The PDSS-R is self-report measure developed specifically for use with people with PD. It consists of 15 items, each relating to a facet of sleep disturbance common in Parkinson's disease. Responses are scored on a ten-point visual analogue scale with a score of one indicating the best possible response and a score of ten indicating the worst possible response. Typically participants with PD have significantly higher scores on the PDSS-R than age-matched controls and those with advanced PD have significantly higher scores than

people who are in the early stages of PD (Chaudhuri et al. 2002). The PDSS-R has good test-retest reliability, with an intraclass correlation coefficient (ICC) =.94, when fifteen PD patients and fifteen control participants completed the PDSS on two occasions one week apart (Chaudhuri et al. 2002).

The Epworth Sleepiness Scale (ESS)

The ESS is a self report questionnaire designed to measure daytime sleepiness. It consists of seven items and participants are asked to indicate how likely it is that they would fall asleep in a number of different situations (e.g. while watching T.V.; while on a long car trip). It is included in this study in order to validate related item scores on the PDSS-R.

Procedure

On booking a testing session at ParkC, participants were mailed a questionnaire pack containing pencil and paper versions of all questionnaires, except for the STAI, which was administered at the end of the testing session. Participants were asked to complete all questionnaires themselves (except for the CBI) and to bring the completed pack with them to their testing appointment. Participants were instructed to ask a close friend or family member to complete the CBI. The questionnaires were checked during the testing appointment and participants were given the opportunity to complete any missing responses following their testing session.

The testing session at ParkC comprised a series of orally administered neuropsychological tests followed by a series of computer based tasks. The series of orally presented tests consisted of the MMSE, the AUSNART, the HVLT-R (learning trials), Line Bisection, Star Cancellation, Cube Analysis, Number Location, the HVLT-R (recall and recognition trials), Verbal Fluency (FAS) and Category Fluency (animals). The tests were

administered in the same order for all participants in order to minimise the length of the testing session and to subsequently minimise participant fatigue. A 20 minute break is required between the HVLT-R learning and recall/recognition trials and this break was filled with non-verbal tasks to minimise interference with information encoding.

The computer based cognitive tasks were administered using a Paceblade tablet computer situated within easy reach of the participant. All tasks operate on CANTAB eclipse software, manufactured by Cambridge Cognition. The CANTAB battery selected for this study consisted of SWM, PRM, SRM and SOC. They were conducted in this order for all participants in order to minimise frustration and fatigue. SWM and SOC are complex tasks that become progressively more difficult. PRM is an easier task and both PRM and SRM are simple tasks which include immediate feedback to the participant so they were administered as the second and third tasks in the CANTAB battery to break up the longer tasks.

Pilot studies indicated that there was no benefit in counterbalancing the order of the tests within the series of assessments.

Results

One hundred and six people participated in the ParkC study. Fifty nine people were excluded from the present study as they had completed the cognitive tasks more than 6 months prior to the PDSS. A further three participants were excluded as they were only able to complete the questionnaire portion of the testing due to health problems. One participant was excluded because his MMSE score was <24 (indicating likely dementia). A total of 42 participants were included in the analysis of this study. The characteristics of the sample are reported in table 1.

Table 1

Characteristics of participants included in present study

	M	SD
Age	65.10	7.45
Gender (%)	Male (63%), Female (37%)	
Years Since Diagnosis	5.35	3.65

Participants were divided into two groups based on the length of time following diagnosis; newly diagnosed (ND) consisted of those who were diagnosed with PD within two years of entry to the ParkC study; existing Diagnosis (ExD) consisted of those who had been diagnosed more than two years prior to entry into the ParkC study. The characteristics of the two groups are reported in table 2.

Table 2

Characteristics of the ND and ExD groups with Means and Standard Deviations of Age (years) and Years since Diagnosis

	ND (N=14)	ExD (N=28)
Age	M=64.38, (9.14)	M=65.43, (6.69)
Gender (%)	Male (77%), Female (23%)	Male (61%), Female (39%)
Years Since Diagnosis	M= 1.31 (.63)	M= 6.92 (.5)

Cronbach's alpha for the PDSS, (.73) indicated that the scale had good internal consistency. An independent samples *t* test compared the PDSS scores reported by the ND (n=14) and ExD groups (n=28). Figure 1 demonstrates the means and standard deviations of PDSS scores for the two groups. There were no significant differences in PDSS scores between the two groups, $t\ (40) = -1.56$, $p = .13$, two tailed, $d = .52$.

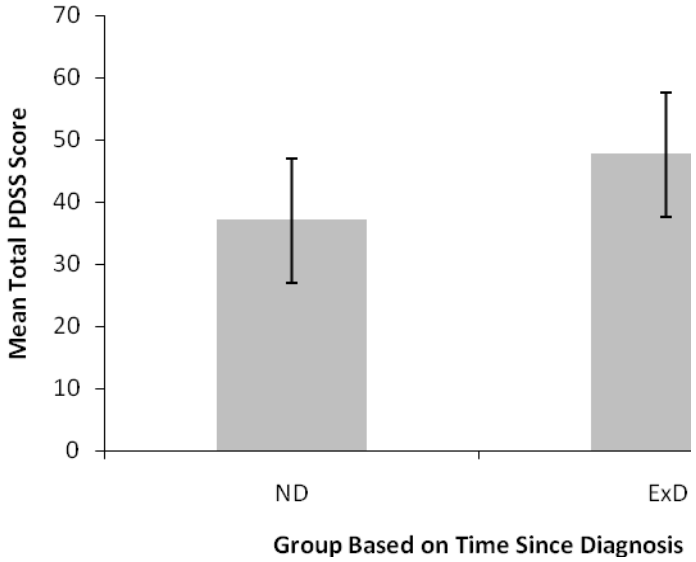

Figure 1: Mean total PDSS scores and standard deviation scores for the newly diagnosed and existing diagnosis groups with lower scores indicating less severe problems with sleep and higher scores indicating more severe problems with sleep. The maximum score on the PDSS is 150.

Independent samples *t* tests compared percentage correct scores on the PRM and the HVLT-R (recall) for the ND and ExD groups. There were no significant differences between groups for PRM scores, t (40) = 1.69, p = .099, two tailed, d = .06 or HVLT-R scores, t (40) = 1.22, p= .228, two tailed, d = .38. Means and standard deviations of test scores for the two groups are presented in figure 2.

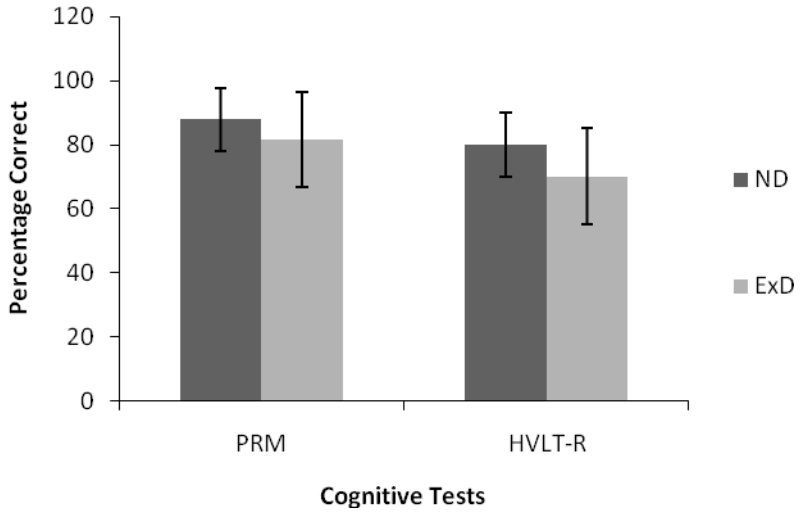

Figure 2

Mean percentage correct and standard deviations of the two cognitive measures.

As the present study is exploratory in nature and the primary measurement of sleep quality is a screening measure for a variety of common sleep problems, it is useful to examine the relationships between ESS scores, total PDSS scores, PDSS individual item scores and cognitive test scores. These correlations are presented in the following tables.

Table 3a

Correlations between ESS scores, PDSS individual item scores (1-8), (Correlation table continued in table 3b)

	ESS	PDSS 1	PDSS 2	PDSS 3	PDSS 4	PDSS 5	PDSS 6	PDSS 7	PDSS 8
ESS	1	.255	-.083	.130	.159	.258	.066	.311*	.220
(1; Overall quality)		1	.300	.585*	.280	.081	.068	.200	.148
(2; Difficulty falling asleep)			1	.376*	.235	-.134	.026	-.257	-.084
(3; Difficulty staying asleep)				1	.416*	-0.60	.051	.054	-.089
(4; Restless leg syndrome)					1	-.123	-.131	-.061	-.151
(5; violent behaviours)						1	.689*	.222	.548*
(6; disturbing dreams)							1	.144	.568*
(7; snoring & breathing pauses)								1	.430*
(8; gasping for air)									1

*Indicates significance at p=.05 level

Table 3b

Correlations between ESS scores, PDSS total and individual item scores, PRM scores and HVLT-R scores, (continuation from table 3a)

	PDSS 9	PDSS 10	PDSS 11	PDSS 12	PDSS 13	PDSS 14	PDSS 15	PDSS total	PRM %	HVLT recall
ESS	.306	-.030	.131	.269	.214	.233 (s)	.147	.332*	-.057	-.185
1; Overall quality	.327*	.232	.254	.456*	.169	.425* (s)	.169	.628*	.268	.451*
2; Difficulty falling asleep	.141	.021	.173	.115	.072	.075 (s)	-.02	.283	.151	-.006
3; Difficulty staying asleep	.337	-.320	.140	.226	.093	.193 (s)	.122	.478*	.225	.106
4; Restless leg syndrome	.573*	.136	.394*	.419*	.098	.334* (s)	.181	.529*	.051	.136

5; Violent behaviours	.099	.154	.103	.381	.205	-.050 (s)	.118	.350*	-.369*	-.002

* indicates significance at p=.05 level; (s) denotes Spearman's Rho

Table 3c

Correlations between PDSS total and individual item scores, PRM scores and HVLT-R scores, (continuation from table 3a & 3b)

	PDSS 9	PDSS 10	PDSS 11	PDSS 12	PDSS 13	PDSS 14	PDSS 15	PDSS total	PRM %	HVLT recall
6; Distressing dreams	.165	.364*	.013	.247	.371*	-.028 (s)	.306*	.435*	-.402*	-.021
7; Snoring & breathing pauses	.056	.122	-.122	.177	.108	.152 (s)	.384*	.328*	-.086	-.138
8; waking gasping for air	.135	.359*	.003	.363*	.455*	.121 (s)	.306*	.453*	-.049	.054
9; sleep difficulty due to motor symptoms	1	.290	.559*	.558*	.385*	.434* (s)	.049	.687*	-.066	.009
10; nocturia		1	.182	.422*	.479*	.236 (s)	.438*	.558*	-.023	.180
11; painful muscle cramps			1	.436*	.248	.336* (s)	-.167	.486*	-.043	.191
12; early waking & uncomfortable posture				1	.440*	.370* (s)	.379*	.778*	-.052	.120
13; tremor on waking					1	.234 (s)	.244	.589*	-.038	.008
14; feel tired & sleepy in morning						1	.149 (s)	.564* (s)	.365* (s)	.286 (s)
15; falling asleep during day							1	.478*	.069	.088
PDSS total								1	.020	.193
PRM percentage									1	.400*
HVLT Recall										1

* indicates significance at p=.05 level; (s) denotes Spearman's rho.

There was a significant moderate positive correlation between total scores on the ESS and PDSS total scores, r (40) = .332, p = .034, indicating that people who reported poor sleep quality overall also tended to report a higher likelihood of falling asleep during the day. There was no correlation between PDSS total scores and PRM scores, r (40) = .020, p = .899, nor was there a correlation between PDSS total scores and HVLT-R scores, r (40) = .193, p = .221.

There was a significant moderate negative correlation between scores on PDSS question 5 (violent behaviours) and PRM scores, r (40) = -.369, p = .016, indicating that people who reported behaviours consistent with RBD performed worse on the PRM test than people who did not report these behaviours. There was also a moderate negative correlation between scores on PDSS question 6 (distressing dreams) and PRM scores, r (40) = -.402, p = .008, indicating that people who frequently have distressing or violent dreams performed worse on the PRM test then people who did scored lower on this item. Neither of these item scores correlated with HVLT scores. There was a moderate positive correlation between PDSS item 14 (awareness of impact of disordered sleep) and PRM scores, r (40) = .365, p = .017 indicating that people who report feel tired and sleepy on awakening performed better on the HVLT-R than those who do not report feeling tired and sleepy on awakening.

Participants who scored more than 5 on PDSS item 5 (Do you have violent behaviours such as hitting your spouse or falling out of bed when acting out dreams at night?) were classified as reporting symptoms of RBD. Those who scored less than five on the same item were classified as not reporting symptoms of RBD. Participants were classified on the basis of this item as it is the item in the scale that screens specifically for symptoms that are solely attributable to RBD. In order to examine the relationships between scores on PDSS questions 5, 6 and 14 in the subgroup of people who reported characteristics of RBD,

correlations between these three scores were conducted both for this subgroup of people (n=7) and for the wider sample of people who did not report symptoms of RBD (n=35).

PDSS items 5 and 6 did not correlate in the RBD group, $r(7) = .036$, $p = .939$ or in the No RBD group, $r(35) = .151$, $p = .388$. As responses to question 14 yielded a bimodal distribution, Spearman's correlations were calculated for these item scores; there was a large, negative, though non-significant correlation between responses on PDSS items 5 and 14, $r(7) = -.605$, $p = .150$ in the RBD group indicating that people who report significant violent behaviour during sleep tended to report feeling less tired and sleepy on awakening than people who did not report feeling tired on awakening. In the No RBD group, there was a small, negative, non-significant correlation between responses on PDSS items 5 and 14, $r(35) = -.111$, $p = .527$. All correlations are reported in table 5.

Table 5

Item score correlations for PDSS items 5, 6 and 14 for subgroups with and without reported RBD symptoms

	Item 6		Item 14	
	RBD	No RBD	RBD	NO RBD
Item 5	.036	.151	-.605 (s)	-.111 (s)
Item 6	1	1	.206 (s)	-.225 (s)
Item 14			1	1

(s) denotes Spearman's.

Discussion

The present study found no differences in either severity of sleep disruption or cognitive performance in people who were recently diagnosed with PD (within 2 years) or had a less recent diagnosis (more than 2 years prior to study). There was no relationship

between PDSS total scores and either HLVT-R (recall) scores or PRM scores. A moderate, positive relationship existed between scores on PDSS item one (overall sleep quality) and HVLT-R (recall) scores, with people reporting good overall sleep quality performing better on the verbal recall task than people who reported poor sleep quality. A moderate, negative relationship was found between the two PDSS items corresponding to RBD symptoms (item 5, violent behaviours; item 6, distressing dreams) and scores on the visuospatial memory measure (PRM); with people reporting significant RBD symptoms scoring worse on the PRM task than people who did not report significant RBD symptoms. Also, a moderate positive relationship was found between scores on PDSS item 14 (tired and sleepy on waking) and PRM scores with those reporting feeling more refreshed after sleep performing worse on the PRM task. The subgroup of participants who reported symptoms most specific to RBD (measured in PDSS item 5) was the group who was driving this relationship.

There was no difference in severity of sleep disorder between the early and advanced PD groups. This finding is not consistent with previous research (Chaudhuri et al., 2002; Tse et al., 2005) that found that people with more advanced PD tend to score more highly on the PDSS than people who have early PD. This pattern reflects increasing levels of neurodegeneration combined with an increasing effect of motor dysfunction on sleep quality as PD advances (Adler & Thorpy, 2005). It is likely that this pattern was not observed in our participants as the present study only included people with Hoehn and Yahr (H&Y) scores ranging between 1 and 3 indicating mild to moderate manifestations of PD, while previous studies that have been published using the PDSS have included PD patients with H&Y scores ranging from 1 to 5.

Participants were classified as newly diagnosed (ND) or as having an existing diagnosis (ExD) based on an arbitrary cut-off of diagnosis more or less than two years prior to entry to the study. This criterion was chosen in accordance with established ParkC

methodology as access to objective motor stage data was unavailable due to cost and time constraints. The time since diagnosis criterion is problematic for several reasons; firstly, time since diagnosis does not take into account how long motor symptoms have been present. Some patients have advanced PD at the time of diagnosis whereas other patients are more proactive in seeking a diagnosis from the time they experience subtle motor symptoms. Also, PD is a heterogenous disorder and progresses at different rates in different people; some patients will retain function decades after motor symptoms first appear and others will suffer extreme disability in a much shorter period of time. These factors are not taken into account in an arbitrary classification system such as the one used in the present study and consequently, it is expected that there is a lot of qualitative overlap between participants in the two groups, limiting the chances of finding systematic differences.

The fact that there were no differences in scores indicating sleep problems in both the ND and ExD groups indicates that most variation in sleep quality occurred within these groups rather than between these groups. These results support the literature which suggests that sleep problems are present in many people very early in the course of the disease (Seugnet, Galvin, Suzuki, Gottschalk & Shaw, 2009) and in some cases before there are significant motor problems driving sleep dysfunction (Dhawan et al., 2006). The results suggest that there are people who have very early PD but who are experiencing specific sleep disturbances, especially RBD. This supports the hypothesis that there are subtypes of PD that manifest in different ways and that people with the RBD associated subtype can be identified, perhaps from the time of diagnosis (Ozekmecki, Apaydin & Kilic, 2005). Further research is needed to follow symptom progression in people with and without RBD as PD develops in order to establish the likely course of PD in different types of patients, and the differential effects of neuroprotective treatments in people affected by different types of PD.

Previous literature (Levy et al., 2002; Korczyn, 2001) reports that memory abilities worsen over time as PD develops, however, in the present study there were no differences in HVLT (recall) scores or PRM scores between the early and advanced group. Williams-Gray, Foltynie, Brayne, Robbins & Barker (2007), note that subtle cognitive problems in PD are present even before the motor symptoms in PD. This is supported by the results of the present study which found similar levels of dysfunction across each group. In particular, deficits with visuospatial memory are often seen in people with PD and concomitant RBD, even in the early stages of PD. Research by Weintraub et al. (2004) and Muslimovic, Schmand, Speelman and De Haan (2007), indicates that people who score poorly on cognitive measures such as HVLT-R and PRM are at increased risk of developing further significant cognitive dysfunction earlier than would be predicted by motor decline.

There was a moderate, significant positive correlation between overall sleep quality and scores on the HVLT-R indicating that people who reported better sleep performed better on the test of verbal recall. This relationship was not attributable to scores on any of the items pertaining to specific sleep disorders. This result indicates that simple sleep deprivation has a specific effect on verbal recall memory. This finding is consistent with previous research (Seugnet, Suzuki, Vine, Gottschalk & Shaw,2008) that suggests that sleep deprivation has a heightened effect on cognition in people who have a neurodegenerative disorder (such as PD) that involves an impairment of dopamine signalling. Seugnet et al. (2009) used a drosophilia (fly) model of PD in order to test the effects of sleep deprivation on short term memory. They found that sleep deprivation in flies with α synuclein protein deposits (simulating PD) caused a long lasting deficit in short term memory. Sleep deprivation did not have this effect in controls matched for age and breeding line. Sleep deprivation lowers cognitive resources which limits the ability to compensate for already lowered cognitive resources in those who are experiencing significant neurodegeneration. This finding is applicable to people with PD

as it goes some way to explaining why those who sleep better retain better verbal recall memory than those who experience poor sleep.

There was also a significant, moderate negative correlation between scores on PDSS items 5 and 6 (violent behaviour and distressing dreams, respectively) and PRM scores, indicating that people who reported behaviours associated with RBD performed worse on the PRM task than people who did not report such behaviours. This finding is consistent with previous research (Vendette et al., 2004 & Sinforiani, et al., 2006) who reported that people with RBD have specific deficits in visuospatial memory. RBD has been shown to be associated with both the psychotic features of PD and the development of dementia, and it is thought that visuospatial reasoning and memory deficits are early manifestations of the same pathology that gives rise to more severe cognitive deficits as PD progresses (Sinforiani et al., 2006).

There was a significant moderate positive correlation between scores on item 14 (tired & sleepy) and PRM scores, indicating that people who reported feeling tired and sleepy upon waking performed better on the PRM task than people who reported feeling rested on waking. This finding was in the opposite direction to that predicted both by theory and previous research (Curcio, Ferrara & De Gennaro, 2006). Because of the unexpected correlation between item 14 and PRM scores, the ESS was included in order to validate the responses to PDSS item 14. The ESS scores did not correlate with scores on item 14. This is likely because the ESS measures frequency of behaviour (falling asleep during the day) while PDSS item 14 measures a subjective feeling of tiredness on awakening. Clearly, there is a discrepancy between whether a person feels sleepy on awakening and whether they experience excessive daytime sleepiness as expressed by frequent daytime napping. One of the criticisms of the ESS that could also be directed at PDSS item 14 is that these items completely exclude personal and lifestyle factors that contribute to both subjective feelings of

tiredness and daytime napping (Chervin & Aldridge, 1999). These factors will exert a significant influence on behaviour and include; natural propensity to sleep during the day, occupational status, scheduled activities during the day and living alone or with family.

In order to examine whether people who reported RBD symptoms had a different pattern of responses to those who did not report RBD symptoms on PDSS items five (violent behaviours), six (distressing dreams) and 14 (tired and sleepy), the participants were classified into two groups: 'RBD' and 'No RBD'. A subgroup of participants (RBD) was identified based on their responses to item five (violent behaviours), with those who answered five or above being classified as 'likely to have RBD' in accordance with criteria described by Tse et al., 2005. Item five was selected as the criterion for classification because of greater specificity than item six; violent behaviours during REM sleep are only attributable to RBD, whereas the other major RBD related symptom (addressed by item 6; distressing dreams) could be caused by anxiety, stress, depression or Levodopa side effects (Larsen & Tandberg, 2001) . Scores on item five were then correlated with scores on item six in order to determine whether participants who scored highly on item five also scored highly on item six. No correlation between questions five and six was found in either the 'RBD' or 'No RBD' group suggesting that distressing dreams were not also a significant problem for those who reported RBD typical behaviour. This is an unexpected result, because when scores on PDSS five and six were correlated over the entire sample of scores, a strong positive correlation between violent behaviours and distressing dreams was found. This correlation was no longer observed when scores on items five and six were correlated within the two subgroups, probably due to an extreme restriction of scores on item five in both groups and a loss of power within the RBD subgroup.

Scores on item five were then correlated with scores on item 14 (tired and sleepy). There was a strong negative but non-significant correlation between scores on item five and

item 14 in the RBD group, indicating that the participants who reported more frequent violent behaviours during sleep felt less tired and sleepy on awakening than people who reported less frequent violent behaviours during sleep. As the RBD subgroup consisted of only seven participants, it is presumed that this correlation did not reach statistical significance due to a lack of power. No such relationship was found in the No RBD group. These results indicate that the group who is likely to be diagnosed with RBD are the subgroup that is driving the unexpected correlation between feeling tired and sleepy in the mornings and better performance on the PRM task. There is an extremely limited body of published literature on the awareness of sleep deficits in RBD. It is possible to speculate, however, that if the brainstem is where PD pathology originates causing the RBD early in PD progression (Tan, Salgado & Fahn, 1996), and the brainstem also plays a role in sleep regulation (Hobson, McCarley &Wyzinsky, 1975), then perhaps people with RBD have a fundamental deficit in sleep regulation that also manifests as a problem registering physical signals indicating tiredness.

Limitations

A major limitation of this study was that sleep data was based entirely on self report. Although the PDSS has been validated in samples of people with PD, no study that has used variations of the PDSS has compared data from the PDSS, structured interview and polysomnography across the sample of participants used in order to validate the scale (Chaudhuri et al., 2002; Tse et al., 2005; Dhawan et al., 2006). This is problematic as it is impossible to say what percentage of sleep disorder is identified by PDSS responses as opposed to more detailed (structured interview) or objective (polysomnography) forms of assessment.

For example, instructions for the PDSS talk about the presence of behaviours in the last month. The PDSS item measuring RBD (Item 5: *Do you have violent behaviours such as hitting your spouse or falling out of bed when acting out dreams at night*?; with a response of 0 indicating that violent behaviours are never a problem and a response of 10 indicating that they are always a problem) is inappropriate for assessing the presence and severity of RBD. This is because RBD, like many neurological problems (including seizures and migraines) tends to occur in clusters (Boeve et al., 2007). So one could experience RBD behaviours nightly for a period of weeks or months then go months or years before experiencing another cluster of RBD episodes. A participant could conceivably have experienced severe RBD behaviours in the past, but not currently be experiencing any overt symptoms. In a structured interview, however, it could be determined whether RBD symptoms had ever been experienced, and whether or not they had been apparent in more recent times. Polysomnography has the additional advantage of identifying partial syndromes even when the participant is completely unaware of any RBD symptoms. Further research is needed to examine the PDSS, structured interview and polysomnography in order to determine which method, or combination of methods, is most appropriate for quantifying the sleep problems experienced by people with PD.

A further limitation of this study is that we were unable to account for the effect of medications in our participants. One of the main classes of drugs used to treat PD, dopamine agonists, are known to cause both sleep phase disturbances and daytime sleepiness as side effects (Ondo, Dat Vuong, Khan, Atassi, Kwak & Jankovic, 2001). Many of the participants within our sample were also prescribed antidepressant medication such as Venlafaxine and Mirtzapine which are also known to cause sleep disturbances (Wilson & Argyropoulos, 2005). Unfortunately, we were unable to statistically account for differences in the type and dosage of medications used by our participants.

Implications and Directions for Future Research

The results of the present study suggest that sleep dysfunction has a measurable effect on memory in patients with PD. Different types of disordered sleep have differential effects on cognitive function, with RBD being associated with deficits in visuospatial memory and poor overall sleep quality leading to deficits in verbal recall memory. Although the PDSS is a useful and cost effective screening measure for sleep disorders in the PD population; caution is needed when interpreting the results, as sleep disorders can be insidious and reliance on patient self report may be misleading. Boeve et al., (2007) commented that treatments for the cognitive effects of PD and neuroprotective treatments have been delayed because of a research focus on the motor symptoms of PD, at the expense of research into the non-motor aspects of the disease. It is clear that cognitive dysfunction and sleep disorder are important and inter-related features of PD. Understanding the interaction between sleep and memory in PD patients will contribute important information about the pathology underlying the disease. Currently, only patients who report significant sleep problems are referred for polysomnography examination, so estimating prevalence rates of sleep disorders in PD based on objective data is impossible. Abbot et al., (2005) called for polysomnography of a random sample of all PD patients irrespective of indications of a sleep disorder in order to determine prevalence of various sleep disorders in people with PD. Although this method would be expensive and inconvenient for patients already affected by a motor disorder, it would help unravel the relationships between sleep disorders and cognitive dysfunction in people with PD.

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