



## CLINICAL REVIEW

# The relationship between sleep and cognition in Parkinson's disease: A meta-analysis



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## SUMMARY

It is well established that sleep disorders have neuropsychological consequences in otherwise healthy people. Studies of night-time sleep problems and cognition in Parkinson's disease (PD), however, paint a mixed picture, with many reporting no relationship between sleep problems and neuropsychological performance. This review aimed to meta-analyse this research and to examine the factors underlying these mixed results. A literature search was conducted of published and unpublished studies, resulting in 16 papers that met inclusion criteria. Data were analysed in the domains of: global cognitive function; memory (general, long-term verbal recognition, long-term verbal recall); and executive function (general, shifting, updating, inhibition, generativity, fluid reasoning).

There was a significant effect of sleep on global cognitive function, long-term verbal recall, long-term verbal recognition, shifting, updating, generativity, and fluid reasoning.

Although there are effects on memory and executive function associated with poor sleep in PD, the effects were driven by a small number of studies. Numerous methodological issues were identified. Further studies are needed reliably to determine whether disturbed sleep impacts on cognition via mechanisms of hypoxia, hypercapnia, sleep fragmentation, chronic sleep debt or decreased REM and/or slow wave sleep in PD, as this may have important clinical implications.

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## Introduction

Parkinson's disease (PD) is classified as a movement disorder, but non-motor symptoms are common and have a profound effect on patient experience and quality of life [1]. Up to a decade before the first motor symptoms emerge, patients often experience significant sleep disruption [2]. Sleep quality is strongly correlated with health related quality of life [3] and the impact of PD treatment (levodopa and dopamine agonists) on the sleep–wake cycle is an area of debate, with treatment effects varying between patients and compounds [4,5].

Sleep disorders affect up to 98% of PD patients [6]. A range of sleep disturbances are common in PD, including insomnia, sleep

fragmentation, sleep related breathing disorders (SRBD), hallucinations, nightmares, narcolepsy, REM sleep behaviour disorder (RBD) and non-REM parasomnias [7]. Similar to other neurodegenerative diseases (e.g. Alzheimer's disease) [8], significant sleep problems occur in PD, alongside significant cognitive dysfunction. This is noteworthy as cognitive impairment greatly increases disease burden [9]. Moreover, sleep problems have been shown to contribute to neuropsychological deficits in otherwise healthy people [10–12]. The cognitive changes observed in early to moderate PD are primarily deficits in executive function (EF) and memory [13–15]. These are the same domains affected in those with SRBD [16] and in insomnia [17]. SRBD causes sleep fragmentation and hypoxia, leading to daytime tiredness and cognitive deficits [18]. Daytime tiredness has an effect on attention and motivation, affecting neuropsychological test performance [10], and ability to manage daytime activities [19]. Diminished slow wave sleep (SWS) is thought to interfere with the capacity to learn new information [20] and to lead to specific deficits in spatial learning [21].

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### Abbreviations

EF	executive function
ESS	Epworth sleepiness scale
FAB	frontal assessment battery
FTD	frontotemporal dementia
H&Y	Hoehn and Yahr score
ISCS	inappropriate sleep composite score
MCI	mild cognitive impairment
MMSE	mini mental state examination
MSA	multiple system atrophy
OSA	obstructive sleep apnoea
PD	Parkinson's disease
PDSS	Parkinson's disease sleep scale

PSG	polysomnography
PSP	progressive supranuclear palsy
PSQI	Pittsburgh sleep quality inventory
RBD	rapid eye movement sleep behaviour disorder
REM	rapid eye movement
RLS	restless legs syndrome
SCOPA-cog	scales for outcomes in Parkinson's disease cognitive scale
SCOPA-sleep	scales for outcomes in Parkinson's disease sleep scale
SRBD	sleep related breathing disorders
SSS	Stanford sleepiness scale
SWS	slow wave sleep
UPDRS	united Parkinson's disease rating scale

### Glossary

Generativity:	speed and efficiency of access to long-term memory
Inhibition:	the ability to override prepotent or automatic responses
Updating:	updating and monitoring of working memory representations
Fluid reasoning:	concept formation and novel problem solving tasks
Shifting:	switching back and forth between different tasks or mental sets

Proceedings databases to 19/12/2013 was conducted, restricted to papers in English, supplemented by hand searches of reference lists from included and seminal papers.

Fig. 1 list search terms which produced a total of 2283 papers. Following exclusion of duplicates and irrelevant reports, judging by title and abstract screening, 43 papers were retained for full-text evaluation. Two reviewers (M.E.P., R.S.B.) independently evaluated all papers retained for full-text screening. Studies were evaluated by a priori inclusion criteria (described below). Disagreements, of which there were very few, were resolved through discussion.

#### Study eligibility criteria

##### Inclusion criteria:

- 1) participants must be adults diagnosed with idiopathic PD;
- 2) sleep must be measured in a reliable manner: PSG, validated questionnaire, clinical interview, actigraphy (or a combination of these);
- 3) cognition must be measured using validated neuropsychological tests;
- 4) relationship between sleep and cognition must be reported statistically; and,
- 5) samples must be independent (for prospective studies, we used baseline data; when multiple studies were published by the same authors, we confirmed independence of samples with the authors or used the study with the largest N).

##### Exclusion criteria:

- 1) atypical PD or Parkinsonian syndromes;
- 2) sleep measured by a single item score or sub-scale from non-motor symptom scale; and,
- 3) cognition measured by subjective report.

#### Outcomes

For each study, the primary outcome was neuropsychological test scores. For two studies [22,23] the outcome was the proportion of each group (RBD+, RBD-) that fell below pre-specified cut-off scores on the mini mental state examination (MMSE) and the frontal assessment battery (FAB).

We categorised the neuropsychological tests described in each paper according to memory theory employed in Wallace and Bucks

Given that sleep problems are almost universal in PD, and that they are associated with cognitive impairment even when experienced in isolation, this suggests that the neuropsychological deficits in mild to moderate PD may be compounded by chronic sleep debt or consistently fragmented sleep. That is, cognitive impairment may not only arise directly through the pathology of PD, but also indirectly via the mechanism of chronic sleep disruption. Studies of night-time sleep problems and cognition in PD, however, paint a mixed picture, with many reporting no relationship between sleep problems and neuropsychological performance. Critical appraisal of this literature, taking account of sample size and methodology is needed, as no such synthesis has been conducted.

This meta-analysis systematically examined the relationship between sleep and cognition in PD. The objectives of this study were: 1) to identify whether there are specific cognitive deficits associated with sleep problems (insomnia, sleep fragmentation, SRBD, hallucinations, nightmares, narcolepsy, RBD, and non-REM parasomnias) in PD and 2) which neuropsychological tests are sensitive to sleep-associated cognitive impairment in PD. We analysed, separately, measures of global cognitive function, EF and memory. Additionally, we analysed the sub-domains of memory: long-term verbal recall and long-term verbal recognition and the sub-domains of EF: shifting, updating, inhibition, generativity and fluid reasoning.

### Method

#### Search strategy

Electronic search of Medline, PsychInfo, PubMed, Proquest: Theses and Dissertations and Web of Science: Conference

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