# Sleep Disordered Breathing in Parkinson's Disease

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**Abstract**

Sleep disordered breathing (SDB) is a serious medical condition in which there are repeated reductions or cessations of breathing during sleep. Early research suggested that because Parkinson's disease (PD) patients have pulmonary abnormalities while they are awake they may be at increased risk for developing sleep disordered breathing. A large literature now demonstrates that sleep disordered

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breathing is common in Parkinson's disease patients, but no different than age-matched controls from the general population. In the general population, sleep disordered breathing often correlates with excessive daytime sleepiness, but this correlation is not typically observed within Parkinson's disease patients. However, sleep disordered breathing in Parkinson's disease has been preliminarily linked to impaired sleep-dependent memory consolidation, blunted sympathetic responses, and worsening motor function Unified Parkinson's Disease Rating Scale (UPDRS). Parkinson's disease patients who have sleep disordered breathing may benefit from positive airway pressure or mandibular advancement treatments, and an exciting avenue for future research is determining whether such treatment also positively affects disease progression and quality of life.

## 7.1 An Introduction to Sleep Disordered Breathing

Sleep disordered breathing (SDB) is a medical condition in which breathing repeatedly ceases (apnea) or is reduced (hypopnea) during sleep. This condition affects more than 40 million Americans and approximately 75 % of severe cases are undiagnosed [1, 2]. In this chapter, we first discuss SDB in the context of individuals without neurological disease. Then we turn our attention to why SDB might be particularly relevant to Parkinson's disease (PD), and we evaluate the literature with regard to two questions. First, is SDB more common in PD than in the general community? Second, in PD patients, what are the clinically relevant correlates of SDB?

### 7.1.1 Definitions, Detection, and Diagnosis

SDB is a general term that includes several distinguishable subtypes of poor breathing during sleep. Obstructive sleep apnea is characterized by the cessation of breathing due to an occluded upper airway. By contrast, in central sleep apnea there is an unstable ventilatory control system, which results in periods of absent respiration despite an open airway [3]. Complex sleep apnea syndrome is diagnosed when an individual demonstrates both central and obstructive events.

A variety of questionnaires are used in the clinical assessment of SDB (e.g., Berlin Questionnaire [4], STOP-BANG Questionnaire [5]). Some of the most important screening questions involve the frequency of snoring and bed partner reports of the patient gasping for air, because these signs indicate obstructed breathing. In addition, SDB is more likely in obese individuals [6] and in those who have an enlarged neck circumference, retrognathia, or other craniofacial morphologies that reduce airflow [7]. The gold standard for detecting SDB, however, is nocturnal polysomnographic recordings of electroencephalography, electrooculography, electromyography, respiratory effort, airflow, and oxygen saturation levels. Apneas are scored when there is a $\geq$90 % reduction in airflow for $\geq$10 s and hypopneas are scored when there is a 30–90 % reduction in airflow for $\geq$10 s accompanied by a 4 % reduction in oxygen saturation levels [8]. An apnea-hypopnea index (AHI), which is the total combined

number of apneas and hypopneas per hour of sleep, is normal when less than 5; however, an AHI from 5 to 14.9 indicates mild SDB, an AHI from 15 to 29.9 indicates moderate SDB, and an AHI greater than 30 indicates severe SDB.

### 7.1.2 Correlates of Sleep Disordered Breathing in the General Population

In the general population, the prevalence of SDB increases with age and is more prevalent in men than women [9]. Independent of these demographic factors, SDB has been linked to several poor health outcomes. First, SDB can lead to daytime sleepiness, moodiness, and poor vigilance. Such outcomes may have implications for workplace performance and vehicle accidents [10]. Second, sleep apnea has been implicated to cause poorer cognitive performance on executive control tasks [11], and may increase risk for developing mild cognitive impairment or dementia [12]. Third, SDB is strongly associated with hypertension [13], and may also predispose individuals to cardiac ischemia, congestive heart failure, cardiac arrhythmias, and cerebrovascular disease [14]. Fourth, at least in rodent models, SDB has been implicated in the loss of catecholamine neurons [15], with hypoxia contributing to a reduction in extracellular dopamine [16].

## 7.2 Relevance of Sleep Disordered Breathing in Parkinson's Disease

There are several reasons why SDB might be particularly important in PD patients. Mortality rates may be elevated in PD patients in the early morning hours relative to other neurological diseases [17], and some have interpreted this result as evidence for respiratory insufficiency during sleep [18]. Moreover, beyond neuropathology in the nigrostriatal pathways, PD may also be associated with neurodegeneration in other brainstem regions [19, 20], which may contribute to SDB by disrupting respiratory and autonomic functions [21].

SDB is also implicated in PD because waking pulmonary function abnormalities are associated with this disease [22]. Such abnormalities may be due to degeneration of dopaminergic neurons or to medication side effects including dyskinesias or wearing-off [23]. Pulmonary abnormalities may include upper airway obstruction as well as chest wall rigidity and hypokinesia, each of which might be expected to result in breathing abnormalities during sleep [23–26].

Another reason why SDB might be particularly important in PD patients is that one of the most common symptoms of SDB in the general population—excessive daytime sleepiness—is also a major concern in PD patients. Hobson et al. [27] found that excessive daytime sleepiness was present in 51 % of a sample of 638 PD patients, even in patients who were living independently and still driving. Though some of the excessive daytime sleepiness in PD patients may be attributable to the usage of dopaminergic medications [28], the relationship between sleepiness and medication class may be complex. Using the objective Maintenance of Wakefulness

Test (MWT) to determine alertness, Bliwise et al. [29] found that higher dosages of dopamine agonists were associated with greater daytime sleepiness (lower alertness) whereas higher dosages of levodopa were associated with lower daytime sleepiness (higher alertness). Additional research has shown that daytime sleepiness is not solely attributable to dopaminergic medications, but appears to be an integral part of the disease [30, 31].

## 7.3 Prevalence of Sleep Disordered Breathing in Parkinson's Disease

Given the prevalence of symptoms of sleep apnea in PD patients (especially daytime sleepiness) as well as possible mechanisms for its predisposition in PD (chest wall rigidity), a pertinent question is whether SDB is more common in PD patients relative to age-matched controls. There have been two approaches to address this question: one relying on questionnaires and the other relying on in-laboratory polysomnography.

### 7.3.1 Questionnaires

Chotinaiwattarakul et al. [32] found that high risk for SDB, as assessed by the Berlin Questionnaire [4], was suggested in nearly 50 % of their 134 PD patients whereas only approximately 35 % of non-blood relative controls. Similarly, Rongve et al. [33] compared 39 patients with a diagnosis of PD dementia or Lewy body dementias to 420 healthy controls using the Mayo Sleep Questionnaire. This questionnaire uses bed partner report of arrested respiratory episodes during sleep or the reported use of continuous positive airway pressure to determine probable obstructive sleep apnea. Rongve et al. [33] observed a higher rate of probable obstructive sleep apnea in their patient group (25.7 %) than in their healthy control group (15.2 %). However, not all questionnaire studies have suggested differences in SDB across PD and control groups. For example, using the Sleep Questionnaire and Assessment of Wakefulness (SQAW [34]), Happe et al. [35] found a nominally lower rate of SDB symptoms in the PD group than the control group.

### 7.3.2 Polysomnography

Polysomnographic studies have also yielded some variable findings for prevalence rates. A summary of these studies is shown in Table 7.1. Prior to modern AHI criteria, early research compared the number of apneic episodes in small samples of PD patients and normal controls, with some findings suggesting greater apneic episodes in PD patients than controls [18, 47], and other findings suggesting no differences [48]. Using more contemporary AHI cutoff scores, 7 out of 12 studies have observed high prevalence of SDB in PD patients. These studies generally observed AHIs

**Table 7.1** Overview of polysomnographic studies that assessed the prevalence of sleep disordered breathing (SDB) in Parkinson's disease (PD)

| Reference (chronological) | PSG nights | PD group | Control group | No SDB (0–4.9) | Mild SDB (5–15) | Moderate SDB (15.1–30) | Severe SDB (>30) | Author's conclusion |
|---|---|---|---|---|---|---|---|---|
| Arnulf [30] | 1 | $N=54$ | None | 50 % | 27.8 % | 11 % | 9.3 % | Higher rate in PD |
| Maria [36] | 1 | $N=15$ | Age-matched controls ($n=15$) | 33.3 % | | 60 % | | Higher rate in PD |
| Baumann [37] | 1 | $N=10$ | None | 0 % | 80 % | 10 % | 10 % | Higher rate in PD |
| Diederich [38] | 1 | $N=49$ | AHI-matched controls ($n=49$) | 57.1 % | 20.4 % | 8.2 % | 14.3 % | Lower rate in PD |
| Shpirer [39] | 1 | $N=46$ | Age-matched controls ($n=30$) | 78.3 %[a] | 21.7 %[a] | | | AHI was higher in PD |
| Monaca [40] | 1 | $N=36$ | None | 44.4 %[a] | 44.4 %[a] | | 11.1 % | No commentary |
| Sixel-Döring [41] | 2 | $N=20$ | Progressive supranuclear palsy ($n=20$) | 45 % | 55 % | | | Common, undetected in PD |
| Norlinah [42] | 1 | $N=44$ | None | 51 % | 24.5 % | 16.3 % | 8.2 % | High SDB prevalence in PD |
| Cochen De Cock [43] | 1 | $N=100$ | In-hospital controls ($n=50$) | 73 % | 6 % | 11 % | 10 % | Lower rate in PD |
| Trotti and Bliwise [44] | 3 | $N=55$ | Sleep Heart Health Study | 56.3 % (53.7 %) | 29.1 % (28.6 %) | 10.9 % (11.7 %) | 3.6 % (6.1 %) | No difference |
| Yong [45] | 1 | $N=56$ | Age-matched controls ($n=68$) | 50.9 % (34.3 %) | 15.1 % (37.3 %) | 18.9 % (19.4 %) | 15.1 % (9 %) | No difference |
| Nomura [46] | 1 | $N=107$ | Non-PD sleep apnea controls ($n=31$) | 77.6 % | | 22.4 % | | No difference or milder in PD |

Severity of SDB is determined by the apnea-hypopnea index (AHI; number in parentheses). References are listed in chronological order. When available, data from control groups are presented in parentheses. Missing cells and collapsed cells reflect the manner in which data were reported in the original papers
Notes: [a]indicates that AHI cutoff was at 10 (rather than 5 and 15)

>5 in more than 50 % of their patient samples, and one study even observed an AHI >5 in all of their PD patients. Though this might be considered to be strong evidence for an increased prevalence of SDB in PD, there exist at least three important limitations for these studies. One limitation is that these studies may have preferentially selected PD patients for excessive daytime sleepiness or those who were referred to the sleep center for clinical purposes. Either selection criteria could be expected to bias diagnosis of SDB in the PD group. In addition, only one of these studies used more than one night of polysomnographic assessment and two of these studies had very small sample sizes ($Ns \leq 15$). None of these seven studies included a sample size that exceeded $N = 54$. Furthermore, scoring criteria for apneas and hypopneas vary widely, which is a limitation for studies that did not test (healthy) control groups with blinded scoring. Only two of the six studies that concluded an increased prevalence of SDB in PD patients supported that conclusion by demonstrating significantly greater AHI relative to an age-matched control group.

Several studies have failed to observe significantly higher SDB in PD patients (Table 7.1). For example, Trotti and Bliwise [44] measured AHI in 55 idiopathic PD patients across three nights of in-laboratory polysomnographic testing, and compared prevalence rates against those observed in the Sleep Heart Health Study [13], which is the largest epidemiological study of SDB in the general population. They found no difference in the prevalence of mild, moderate, or severe sleep apnea in their PD patients. Yong et al. [45] also observed no difference between 56 PD patients and 68 age- and sex-matched controls in an Asian population. Our most recent work—the Emory 48-h protocol [29]—also suggests no increased risk of SDB in PD patients. We had 84 idiopathic PD patients undergo at least one night of polysomnographic testing ($N = 74$ completed two nights). Most patients (59.5 %) showed a mean AHI <5, and 32.1 % of patients showed mild sleep apnea (AHI 5–14.9). Only 4.8 % and 3.6 % of patients showed moderate (AHI 15–29.9) or severe (AHI ≥30) signs of sleep apnea, respectively. When compared with prevalence estimates from the Sleep Heart Health Study [13], our results suggest that the prevalence rate of AHI is similar for mild sleep apnea, and possibly lower for moderate and severe sleep apnea, in PD patients than in the general population.

Three additional studies have suggested either lower rates, or less severe, SDB in PD patients than in controls. Cochen De Cock et al. [43] found a lower prevalence of mild or greater SDB in a sample of 100 PD patients (27 %) relative to 50 non-neurological in-hospital control patients (40 %). Diederich et al. [38] conducted a case-control study in which 49 idiopathic PD patients were matched to 49 controls based on age, gender, and AHI. They observed fewer obstructive sleep apneas and higher oxygen saturation levels in the PD patients than in the AHI-matched controls. Most recently, Nomura et al. [46] concluded that SDB in their sample of 107 PD patients was very similar to that of the elderly general population; furthermore, relative to a sample of 31 non-PD patients with obstructive sleep apnea, the PD patients who showed an AHI ≥15 had a lower respiratory arousal index and a less severe decrease in oxygen saturation.

In sum, though there are reports of a higher prevalence of SDB in PD patients than the general population, several of these studies are based on small sample sizes

and may have been confounded by selection biases (referral for sleepiness). Our interpretation of the literature is consistent with Peeraully et al.'s [49] recent review of case-control polysomnographic studies that there is no increased prevalence of SDB in PD. Nevertheless, SDB is still common in PD patients and may have important clinical implications for this population.

## 7.4 Clinical Implications of Sleep Disordered Breathing

One important clinical consideration for SDB in PD may be poorer quality of life [32]. We next consider the clinical correlates of SDB that might explain why quality of life is dampened in PD patients with probable sleep apnea.

### 7.4.1 Excessive Daytime Sleepiness

First, because excessive daytime sleepiness greatly affects quality of life in PD patients [50], and because this is a primary symptom of SDB [51], one might expect that some sleepiness in this patient group is due to SDB [37]. Some findings support this association. For example, Shpirer et al. [39] found that PD patients who had an Epworth Sleepiness Scale (ESS) score greater than 10 had a higher AHI than those with scores below 10 (see also [42, 52]). However, when measured as continuous variables, AHI and ESS did not correlate significantly [39]. Other studies have reported no significant correlation between AHI and ESS [43, 44], and we did not observe a correlation in our 48-h protocol [29].

When sleepiness has been measured objectively using the Mean Sleep Latency Test, with few exceptions [53], there is typically no correlation between AHI and mean sleep latency [30, 40]. In the 48-h protocol, we incorporated up to eight Maintenance of Wakefulness Tests (MWTs) in which PD patients were instructed to stay awake while lying in bed for 40 min [29]. In this study, we did not observe a relationship between AHI and MWT scores. Therefore, the relationship between SDB and quality of life in PD [32] does not appear to be mediated by excessive daytime sleepiness. However, the causes of sleepiness are multifactorial (e.g., the presence of dopaminergic medications), which may explain why SDB is a weaker predictor of sleepiness in PD patients.

### 7.4.2 Cardiovascular Risk

As previously described, common correlates of SDB in healthy controls include hypertension, cardiovascular events, and higher body mass index [13, 14]. Though studies of SDB in PD are not as well powered as those in the general community, it is still surprising that the typical (aforementioned) correlates of SDB have not been observed in studies of PD patients [42, 43, 46]. Valko et al. [54] evaluated the association between heart rate variability and presence or absence of obstructive sleep

apnea syndrome in 62 PD patients and 62 age-matched controls. Their control group demonstrated several significant associations between obstructive sleep apnea syndrome and heart rate variability, particularly for the low-frequency power band and the low-frequency/high-frequency power band ratio. By contrast, heart rate variability did not correlate with SDB in the PD group. The authors suggested that there is a blunted sympathetic response to sleep breathing events in PD.

### 7.4.3 Cognition and Memory Consolidation

SDB has also often been connected to the development of dementia, mild cognitive impairment, or subtle cognitive effects in the general population [12]. It should be noted, however, that this literature has produced variable results, and in the large-scale, multicenter Apnea Positive Pressure Long-Term Efficacy Study (APPLES), few associations were observed [11]. Few studies have examined SDB in relation to cognition in idiopathic PD patients (though much work has been done for REM sleep behavior disorder [55]). Cochen De Cock et al. [43] found no correlation between SDB and Mini-Mental State Examination scores in PD patients. However, more recently, Stavitsky et al. [56] observed a positive correlation between actigraphy-defined sleep efficiency and an executive function composite. Though not necessarily implicating SDB, it is possible that some of the actigraphy-defined poor sleep efficiency might be due to breathing events due to breathing events or periodic limb movements [57].

There is an important distinction to be made between impaired cognition as assessed by neuropsychological testing (as a stable trait feature of PD), versus an emerging "memory consolidation" literature that connects cognitive test performance improvements to the sleep obtained between repeated cognitive tests (for review, see [58]). In the 48-h protocol, we gave PD patients eight digit span backward (executive function) tests across 2 days [59]. As illustrated in Fig. 7.1, PD patients taking dopaminergic medications demonstrated significant digit span backward improvements across the 48-h study. The improvement was not simply due to practice effects because no performance improvements were observed across the repeated daytime tests. Instead, performance improvements were localized to the nocturnal sleep interval (Fig. 7.1). The degree of digit span backward improvement was significantly associated with higher levels of slow-wave sleep and higher oxygen saturation *during the night that constituted the training interval*, and not during the pre-experimental night (laboratory adaptation night). PD patients who demonstrated 5 or more minutes of oxygen saturation below 90 % during the training interval night did not show significant digit span improvements. Though this (sleep) effect appears robust for repeated executive function testing, it has not been observed for motor memory testing in PD patients [60, 61]. We suggest that correcting SDB might improve the ability to acquire some new skills (as suggested by digit span backward training), which could have a positive impact on PD patients' quality of life on a day-to-day basis (cf. [32]).

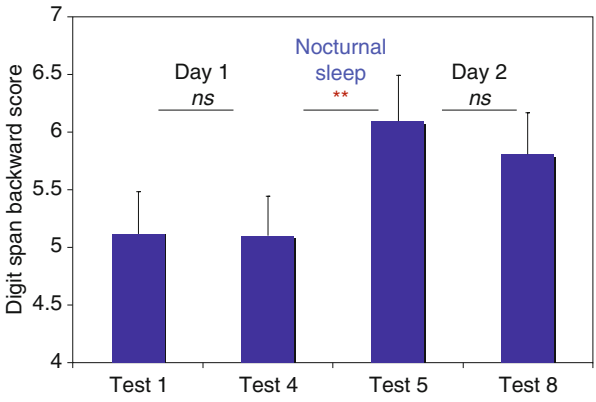


**Fig. 7.1** Improvement on the digit span backward test across an interval that included nocturnal sleep, but not daytime wake, in dopamine-treated Parkinson's disease patients [59]. ** indicates $p < .01$

### 7.4.4 Motor Symptoms

SDB might also be associated with poorer quality of life because nocturnal hypoxia could potentially exacerbate certain aspects of PD neuropathology. Basic science studies have shown experimentally that sleep apnea could cause the loss of catecholamine neurons [15] or reduce extracellular dopamine [16]. Furthermore, oxidative stress has been implicated in dopamine cell degeneration, mitochondrial dysfunction, excitotoxicity, and inflammation in PD [62, 63]. Therefore, one might expect that higher AHI or indices of nocturnal hypoxia would correlate with measures of disease severity in PD. Consistent with this idea, Efthimiou et al. [47] observed more apneas in PD patients with more severe disease (Hoehn and Yahr scale). Moreover, Maria et al. [36] found significant correlations between log-transformed UPDRS motor scores and log-transformed AHI as well as median oxygen saturation levels, even after controlling for age. Cochen De Cock et al. [43] also observed a significant correlation between AHI and UPDRS motor scores, with SDB being more frequent and severe in the most disabled PD patients. One additional study [32] observed a nonsignificant trend for higher SDB risk (Berlin Questionnaire [4]) in PD patients at more severe disease stages, and another study [42] observed significant correlations for greater sleep fragmentation and more severe disease stages, but three studies have reported no significant correlations between *SDB variables* and either UPDRS or Hoehn Yahr scores [41, 42, 64].

We contend that a limitation in prior studies of the clinical correlates of SDB in PD patients is that most studies have examined polysomnography in relation to disease severity in PD patients at a single time point in the course of disease. A current direction of our research is examining the association between polysomnographic variables and change in motor disease severity over the course of disease. We recently evaluated whether change in motor disease severity (UPDRS motor subscale) in 29 idiopathic PD patients was associated with SDB variables [65]. The two time points (Time 1 [T1] and Time 2 [T2]) were separated by an average interval of 265 days, and at T2 patients underwent 2 nights of

polysomnographic recording. Variables derived from overnight polysomnography were not associated cross-sectionally with UPDRS motor scores at T1 or T2 in our data. Similar absence of significant findings with cross-sectional analyses has been observed previously [41, 64]. However, in our data poorer sleep was strongly associated with declining function in UPDRS motor scores (i.e., from T1 to T2). As illustrated in Fig. 7.2, there were strong correlations with mean oxygen saturation levels (but not AHI), particularly during REM sleep. The UPDRS-change correlations with mean oxygen saturation during REM sleep was not negated when controlling for time between UPDRS assessments, overt dream enactment, low REM sleep amounts, dopamine dosage, age, gender, education, years since diagnosis, cognitive status, or mean oxygen saturation while awake. Thus, nocturnal oxygen saturation levels may represent an important biomarker of change in disease severity.

## 7.5 Treatment Options

There are several treatment options for SDB in PD patients. First, breathing problems might be treated by normal antiparkinsonian medications to reduce rigidity [66]. SDB may also be treated using positive airway pressure therapy (e.g., CPAP), which is the most typical treatment for non-PD patients who have obstructive sleep apnea. However, controversy exists over the efficacy of CPAP treatment in PD patients, because some work has suggested that not all PD patients tolerate CPAP [67]. CPAP tolerance might be a particular limitation in PD because these patients often may not be amenable to the restrictive nature of the CPAP mask. Despite these potential issues, at least in severe cases of SDB, CPAP must be considered as a treatment option [68, 69]. In patients who are intolerant of CPAP or have milder SBD, mandibular advancement devices may be a useful second line of treatment [70].

## 7.6 Future Directions

We believe that an exciting avenue for future research will be in determining whether relatively mild levels of nocturnal hypoxia are associated with motor and nonmotor symptom progression. SDB is very common in PD (but the prevalence does not differ from the general population; Table 7.1), and nocturnal hypoxia might cause the loss of dopamine [15, 16] and result in additional cellular dysfunction [62, 63]. It therefore remains possible that even mild SDB could accelerate disease progression [65], and, conversely, that ameliorating nocturnal hypoxia in PD patients might be a viable target for improving longevity and quality of life.

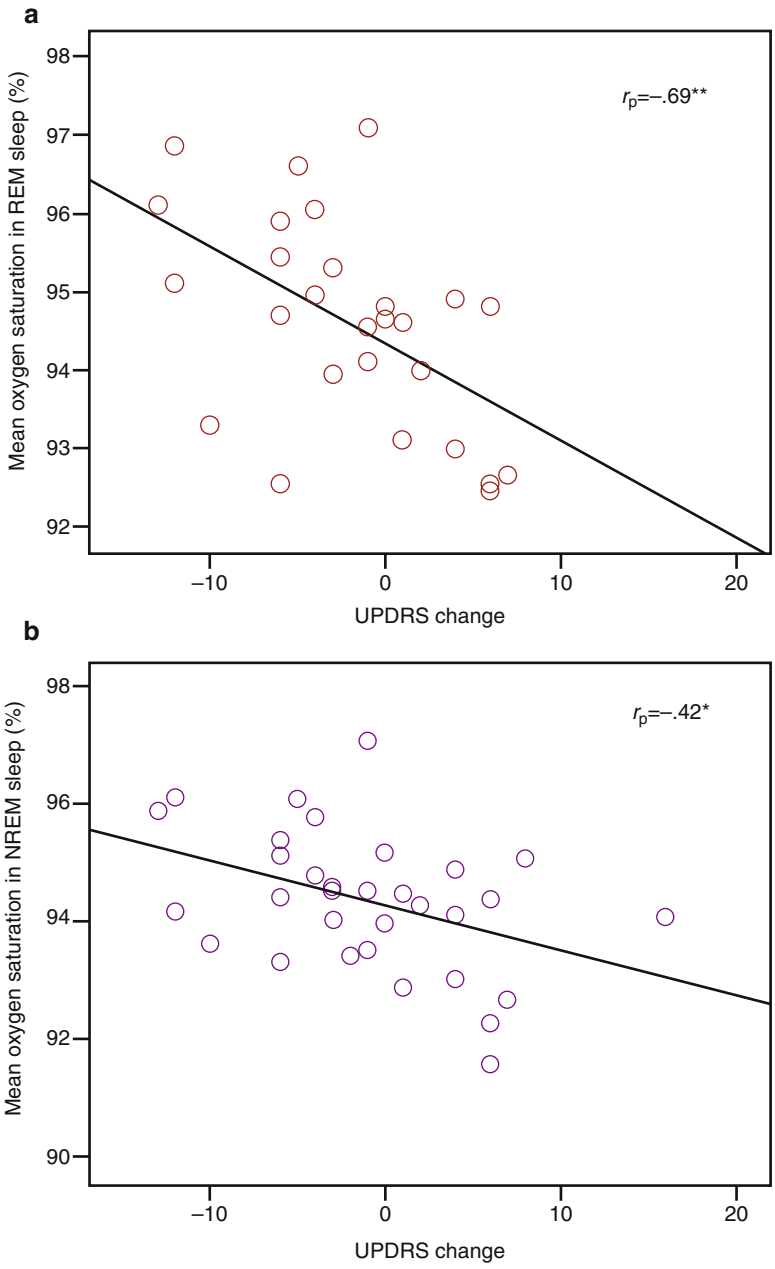


**Fig. 7.2** Change in motor symptom severity across approximately 9 months (assessed as UPDRS motor symptom score) correlates with level of oxygen saturation during REM sleep (**a**) and NREM sleep (**b**) in idiopathic Parkinson's disease patients Positive numbers indicate worsening severity of motor symptoms [65]. * indicates $p < .05$, ** indicates $p < .01$

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