The effects of deep brain stimulation on sleep in Parkinson's disease

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***Abstract*:** Sleep dysfunction is a common nonmotor symptom experienced by patients with Parkinson's disease (PD). Symptoms, including excessive daytime sleepiness, sleep fragmentation, rapid eye movement (REM) sleep behavior disorder and others, can significantly affect quality of life and daytime functioning in these patients. Recent studies have evaluated the effects of deep brain stimulation (DBS) at various targets on sleep in patients with advanced PD. Several of these studies have provided evidence that subthalamic nucleus DBS improves subjective and objective measures of sleep, including sleep efficiency, nocturnal mobility, and wake after sleep onset (minutes spent awake after initial sleep onset). Although fewer studies have investigated the effects of bilateral internal globus pallidus and thalamic ventral intermedius DBS on sleep, pallidal stimulation does appear to improve subjective sleep quality. Stimulation of the pedunculopontine nucleus has recently been proposed for selected patients with advanced PD to treat severe gait and postural dysfunction. Owing to the role of the pedunculopontine nucleus in modulating behavioral state, the impact of stimulation at this target on sleep has also been evaluated in a small number of patients, showing that pedunculopontine nucleus DBS increases REM sleep. In this review, we discuss the effects of stimulation at these various targets on sleep in patients with PD. Studying the effects of DBS on sleep can enhance our understanding of the pathophysiology of sleep disorders, provide strategies for optimizing clinical benefit from DBS, and may eventually guide novel therapies for sleep dysfunction.

***Keywords*:** deep brain stimulation, globus pallidus, Parkinson's disease, pedunculopontine nucleus, sleep, subthalamic nucleus, ventral intermediate nucleus of the thalamus

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by bradykinesia, rigidity, rest tremor, and postural instability. In addition to these motor symptoms, patients also experience nonmotor symptoms including hyposmia, constipation, cognitive dysfunction, mood changes, and sleep dysfunction [Barone *et al.* 2009; Simuni and Sethi, 2008; Martinez-Martin *et al.* 2007; Paulson and Stern, 2004]. These symptoms are often more disabling and resistant to treatment than the motor symptoms of the disease [Qin *et al.* 2009]. Alterations in sleep are particularly common, affecting 74–98% of patients with PD [Lees *et al.* 1988; Nausieda *et al.* 1982]. Sleep disturbances in PD include insomnia [Schrag *et al.* 2002], sleep fragmentation with early morning wakening [Tandberg *et al.* 1998], excessive daytime sleepiness [Brodsky *et al.* 2003; Kumar *et al.* 2002; Rye *et al.* 2000], difficulty rolling over in bed [Schrag *et al.* 2002], nocturia [Barone *et al.* 2009], nightmares, periodic limb movements of sleep, and rapid eye movement (REM) sleep behavior disorder [Kumar *et al.* 2002; Pappert *et al.* 1999; Schenck *et al.* 1996]. Objective evaluation using polysomnography (PSG) of patients with PD has shown decreased total sleep time, reduced slow wave and REM sleep, and poor sleep efficiency compared with controls [Shpirer *et al.* 2006; Rye and Bliwise, 2004; Apps *et al.* 1985].

Although currently available medications for PD effectively manage motor symptoms in early disease, the motor fluctuations that often emerge in later disease have necessitated development of alternative therapies such as deep

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brain stimulation (DBS). DBS has revolutionized therapy for patients who no longer respond optimally to medical therapy. The increasing recognition of how nonmotor symptoms adversely affect quality of life in PD has prompted further study into the effect of available treatments on these symptoms. Potential advantages of DBS over medical therapies for sleep dysfunction in patients with neurologic diseases are that stimulation is delivered continuously throughout the night and the electrical stimulation parameters can be modified based on clinical response. In this review, we discuss evidence for the use of DBS at various targets for treatment of PD. First we briefly describe the effects of stimulation on motor symptoms, followed by a discussion of the available data on the influence of DBS on sleep in patients with advanced PD.

Subthalamic nucleus deep brain stimulation

Bilateral stimulation of the subthalamic nucleus (STN) has been shown to be superior to best medical therapy for the management of motor symptoms in PD, although there is a greater risk of serious adverse events [Walker *et al.* 2009; Deuschl *et al.* 2006; Ford *et al.* 2004; Herzog *et al.* 2003; Romito *et al.* 2002; Deep-Brain Stimulation for Parkinson's Disease Study Group 2001; Kumar *et al.* 1998]. This improvement in motor symptoms in the 'off' medication state persists for at least up to 5–6 years [Moro *et al.* 2010b; Krack *et al.* 2003], and both unilateral and bilateral STN DBS have been shown to reduce motor fluctuations and improve measures of quality of life and activities of daily living [Walker *et al.* 2009; Deuschl *et al.* 2006; Rodriguez-Oroz *et al.* 2005; Kleiner-Fisman *et al.* 2003; Krack *et al.* 2003; Romito *et al.* 2002; Kumar *et al.* 1998]. In general, the symptoms that are most likely to improve with STN stimulation are those that are responsive to levodopa [Deuschl *et al.* 2003].

Bilateral STN DBS has been found to improve both objective PSG measures of sleep and subjective sleep quality in several studies. Arnulf and colleagues evaluated 10 patients with PD using bilateral STN DBS with PSG, and they found decreased wake after sleep onset (WASO), deceased nocturnal and early morning dystonia, and increased sleep efficiency when the stimulators were on compared to off [Arnulf *et al.* 2000b]. Another study by Iranzo and colleagues showed subjective improvement in sleep quality, improved nocturnal mobility, and increased continuous sleep time in 11 patients with PD assessed by PSG 6 months after bilateral STN DBS compared with presurgical studies. Interestingly, eight of these patients had REM sleep behavior disorder presurgically, and these symptoms persisted after STN DBS [Iranzo *et al.* 2002]. Monaca and colleagues evaluated 10 patients with PD using PSG and subjective sleep measures before and 3 months after bilateral STN DBS with the DBS off and on. They showed that stimulation significantly increased total sleep time and sleep efficiency and improved subjective sleep quality as well. In addition, the duration of slow wave sleep and REM sleep was increased, but the percentages of each sleep stage were not significantly different, and changes in sleep did not correlate significantly with motor improvement [Monaca *et al.* 2004]. Cicolin and colleagues showed significantly reduced WASO, increased sleep efficiency, and decreased REM latency in five patients with PD 3 months after bilateral STN DBS. Similar to the results of Iranzo and colleagues, there was no reported change in REM sleep behavior disorder or in periodic limb movements of sleep [Cicolin *et al.* 2004].

Other studies have examined subjective changes in sleep using a variety of measures. Hjort and colleagues used the Parkinson's Disease Sleep Scale to evaluate 10 control patients with PD and 10 patients with PD treated with bilateral STN DBS, and showed that the treatment group had a significant improvement in sleep quality after surgery while there was no improvement in the control group [Hjort *et al.* 2004]. In the longest follow up after bilateral STN DBS to date, Lyons and Pahwa reported increased total sleep time based on patient diaries at 6, 12, and 24 months after bilateral STN DBS. This change in sleep time correlated with improvement in bradykinesia scores from the Unified Parkinson's Disease Rating Scale (UPDRS) [Fahn and Elton, 1987]. Other findings included decreased early morning dystonia but no change in daytime sleepiness [Lyons and Pahwa, 2006]. Zibetti and colleagues reported improvement in sleep dysfunction in 36 patients after bilateral STN DBS based on evaluation of the UPDRS part IV (complications of therapy) [Zibetti *et al.* 2007].

While the above studies have reported the effects of bilateral STN DBS on sleep, unilateral STN DBS has also recently been advocated for the

treatment of motor symptoms in advanced PD [Okun *et al.* 2009; Walker *et al.* 2009; Alberts *et al.* 2008a; Tabbal *et al.* 2008]. Although unilateral stimulation likely has less motor efficacy than bilateral STN DBS [Samii *et al.* 2007], PD is an asymmetric disease, and its motor symptoms respond to dopaminergic therapy. In addition, unilateral STN DBS may be better tolerated than bilateral STN DBS in terms of risk for cognitive dysfunction, speech and swallowing dysfunction, and surgical adverse events [Walker *et al.* 2009; Alberts *et al.* 2008b; Bastian *et al.* 2003; Kumar *et al.* 1999]. Little is known about the effects of unilateral STN DBS on sleep dysfunction. We recently evaluated 53 consecutive patients with PD who underwent successful unilateral STN DBS contralateral to the most affected hemibody and found significant improvement in subjective sleep quality as measured by the Pittsburgh Sleep Quality Index [Buysse *et al.* 1989] at 6 months postoperatively [Amara *et al.* 2010].

In summary, unilateral and bilateral STN DBS both appear to improve subjective sleep quality. More objective studies using PSG in patients treated with bilateral STN DBS have shown improved total sleep time, sleep efficiency, and WASO but no significant change in sleep architecture (as measured by percentage of each sleep stage) or improvement in REM sleep behavior disorder or periodic limb movements of sleep.

Deep brain stimulation of the globus pallidus internal segment

There is renewed interest in DBS of the internal segment of the globus pallidus (GPi) as a target for treatment of advanced PD [Loher *et al.* 2002; Ghika *et al.* 1998; Volkmann *et al.* 1998; Siegfried and Lippitz, 1994]. A recent randomized study found that bilateral STN and GPi DBS were essentially equivalent in terms of motor improvement and adverse events [Follett *et al.* 2010]. Other studies provided evidence that patients undergoing STN DBS have a quantitatively greater motor improvement in UPDRS, while adverse events are lower in patients treated with GPi DBS [Moro *et al.* 2010b; Anderson *et al.* 2005; Rodriguez-Oroz *et al.* 2005; Weaver *et al.* 2005; Deep-Brain Stimulation for Parkinson's Disease Study Group 2001; Krack *et al.* 1998]. Comparison of changes in mood and cognition in patients treated with unilateral STN *versus* GPi DBS showed a trend toward worsened cognition based on letter verbal fluency as well as increased anger measures on the visual analog mood scale in patients treated with STN stimulation [Okun *et al.* 2009]. Although it was not a primary outcome measure for that study, there was no difference in motor outcomes between the two targets when stimulated unilaterally [Okun *et al.* 2009].

There are relatively few studies on the effects of GPi DBS on sleep in patients with PD, and the published studies do not utilize rating instruments that are specifically designed to evaluate sleep. One study evaluated quality of life measures with the Parkinson's Disease Quality of life questionnaire [Peto *et al.* 1998], a validated 39-point rating scale, demonstrating improvement in subjective daytime sleepiness in six of 10 patients who had GPi DBS [Rodrigues *et al.* 2007]. None of these 10 patients had their anti-Parkinsonian medications reduced [Rodrigues *et al.* 2007]. Volkmann and colleagues evaluated 20 patients with the Sickness Impact Profile questionnaire before bilateral GPi DBS, and at 6 months and 3–4 years postoperatively, finding persistent improvement in subjective sleep quality [Volkmann *et al.* 2009]. Considering the limited evidence on the effects of GPi DBS on sleep, it is noteworthy that in patients with PD who underwent stereotactic lesion therapy rather than brain stimulation, 59% (13/22) treated with unilateral pallidotomy and 47% (8/17) treated with bilateral pallidotomy reported subjective improvement in sleep quality at a median 7-month follow up [Favre *et al.* 2000]. Considering the resurgence of this stimulation target for PD therapy, future studies that utilize PSG and measures of subjective sleep quality are needed to assess how GPi DBS affects sleep in patients with PD.

Deep brain stimulation of the ventral intermediate nucleus of the thalamus

Stimulation of the ventral intermediate nucleus (VIM) of the thalamus was introduced as an alternative therapy to thalamotomy for treatment of medically refractory essential tremor and Parkinsonian tremor. It is now used less often for the treatment of PD tremor because it does not have beneficial effects on bradykinesia or rigidity, nor does it allow for significant reduction of anti-Parkinsonian medications or confer persistent benefit on performance of activities of daily living [Hariz *et al.* 2008; Pahwa *et al.* 2006; Koller *et al.* 1997; Benabid *et al.* 1996]. Based on the role of the thalamus in sleep and the generation of sleep spindles by the reticular nucleus of

the thalamus [Steriade *et al.* 1993], and because of reports that bilateral thalamotomy leads to sleep disturbances and insomnia [Bricolo, 1967], Arnulf and colleagues investigated the effects of VIM DBS on sleep. They evaluated PSG in six patients (four with PD and two with essential tremor) with VIM DBS off *versus* on at the patient's stable therapeutic settings and found no difference in sleep architecture or in sleep spindles [Arnulf *et al.* 2000a].

Deep brain stimulation of the pedunculopontine nucleus

Despite the efficacy of both STN and GPi DBS in controlling many motor symptoms in advanced PD, stimulation of these targets is less effective in treating postural instability and freezing of gait [Rodriguez-Oroz *et al.* 2005; Kleiner-Fisman *et al.* 2003]. For this reason, alternate/additional stimulation sites have been explored. One such target is the pedunculopontine nucleus (PPN). The PPN is a heterogeneous group of neurons located in the dorsolateral mesopontine tegmentum and functions to promote locomotion, modulate sleep, and control postural tone [Mena-Segovia *et al.* 2004; Lee *et al.* 2000; Rye, 1997]. Lesioning of the PPN in nonhuman primates induces Parkinsonism [Matsumura and Kojima, 2001; Aziz *et al.* 1998] and degeneration of this area occurs in humans with idiopathic PD [Hirsch *et al.* 1987]. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated Parkinsonian monkey, low-frequency electrical stimulation of the PPN or pharmacologic activation of the PPN with γ-aminobutyric acid (GABA) antagonists increases motor activity and improves akinesia [Jenkinson *et al.* 2004; Nandi *et al.* 2002a, 2002b]. These data led to the hypothesis that overinhibition of PPN may promote Parkinsonian akinesia and that stimulation of PPN may provide more benefit for axial symptoms such as freezing of gait and postural instability in patients with PD [Pahapill and Lozano, 2000].

Early studies have demonstrated the safety of PPN DBS in humans [Mazzone *et al.* 2005; Plaha and Gill, 2005], but its efficacy in improving postural instability and gait is controversial. Stefani and colleagues showed that PPN DBS was not as effective as STN DBS in improving UPDRS part III scores in the 'off' medication state. However, PPN DBS plus STN DBS improve motor symptoms in the medication 'on' condition to a greater extent than either target alone, particularly when evaluating axial symptoms and gait (UPDRS items 27–30) [Stefani *et al.* 2007]. Subsequently, the authors reported that four of these same patients with bilateral STN and PPN DBS had more improvement in stride length with low-frequency (60 Hz) stimulation of the STN than with stimulation of the PPN [Moreau *et al.* 2009]. These findings led them to conclude that PPN should not be a primary stimulation site, but could supplement DBS at other targets [Stefani *et al.* 2007]. Moro and colleagues found no significant improvement in UPDRS motor scores with unilateral PPN DBS, but did report a subjective decrease in falls as measured by UPDRS part II [Moro *et al.* 2010a]. Ferraye and colleagues studied bilateral PPN DBS in six patients who were previously treated with bilateral STN DBS and reported no clear effect on gait or UPDRS from this intervention, with the exception that some patients experienced a subjective decrease in falls related to freezing [Ferraye *et al.* 2010]. Owing to the small size of the PPN, there remains some uncertainty as to whether the DBS electrodes are actually within the nucleus [Yelnik, 2007; Zrinzo *et al.* 2007] and what stimulation effects there may be on surrounding structures.

In addition to promoting locomotion, the PPN is thought to regulate transitions between behavioral states, such as promoting the cortical activation that characterizes both REM sleep and wakefulness [Pahapill and Lozano, 2000; Rye, 1997]. Investigators have therefore evaluated patients with PD who have undergone PPN DBS for gait dysfunction with PSG and demonstrated alterations in sleep architecture. Lim and colleagues investigated PSG changes in three patients with PD and two patients with progressive supranuclear palsy (PSP) treated with unilateral PPN DBS on *versus* off [Lim *et al.* 2009]. The three patients with PD were stimulated at a frequency of 70 Hz, while the patients with PSP were stimulated at either 5 or 30 Hz. Regardless of the underlying disorder, PPN DBS caused a significant increase in the total duration of REM sleep and in the percentage of total sleep time spent in REM (REM percent). Two of these patients had REM sleep behavior disorder, and similar to reports of STN DBS, symptoms of REM sleep behavior disorder persisted in these patients whether PPN DBS was on or off.

Romigi and colleagues studied one patient with bilateral STN and PPN DBS and reported that while bilateral STN DBS alone and low-frequency (25 Hz) PPN DBS alone both improved sleep efficiency and WASO to a similar degree, only stimulation of the bilateral PPN increased the percentage of REM sleep [Romigi *et al.* 2008]. Subsequently, this group reported data from the same patient and three other patients who were evaluated with subjective sleep measures (Pittsburgh Sleep Quality Index [Buysse *et al.* 1989], Epworth Sleepiness Scale [Johns, 1991], and the Parkinson's Disease Sleep Scale [Chaudhuri *et al.* 2002]) during three different stimulation conditions. Each parameter was maintained for 2 weeks prior to evaluation. The three conditions were: STN-on, PPN-off; STN-on, PPN-on; and STN-on, PPN-cyclic-on (on only at night). The authors state that there was an improvement in daytime sleepiness with PPN-on and improvement in nocturnal restlessness, psychosis, and daytime sleepiness with PPN-cyclic-on. They also describe increased REM during PPN DBS in another patient studied using PSG [Alessandro *et al.* 2010]. While these reports by Alessandro and colleagues are consistent with the findings of Lim and colleagues [Lim *et al.* 2009], interpretation is difficult because of the small number of patients and because the quantitative sleep data were not shown [Alessandro *et al.* 2010].

The effect of PPN DBS on behavioral state has also been investigated in awake subjects. Arnulf and colleagues [Arnulf *et al.* 2010] describe two patients with prior implantation of STN stimulators who subsequently had bilateral PPN area DBS. During stimulator adjustment 1 year after surgery, the authors noted that high-frequency PPN stimulation induced sleep. To further investigate this finding, they performed daytime PSG at different stimulator settings maintained for at least 5 min each with a 3-min stimulator deactivation between changes in settings. They found that low-frequency stimulation (10–25 Hz) promoted alertness in the two patients, while left, right, or bilateral high-frequency PPN stimulation (80 Hz) led to sleepiness and then behavioral sleep within 0.5–8 min in both patients. Patients attained light sleep (stage N1 and N2) but not slow wave (N3) or REM sleep. Interestingly, abrupt cessation of low-frequency stimulation in one of the patients induced sleep onset within 0.6–1.7 min and REM sleep within 3–6 min on five occasions. Sleep lasted 2.6–9 min in total, and the patient woke up spontaneously. Discontinuation of stimulation did not induce sleep in the other patient [Arnulf *et al.* 2010].

While the effects on sleep of PPN DBS in these studies may appear paradoxical, modulation of behavioral state by PPN includes promotion of both REM sleep and the maintenance of the cortical arousal during wakefulness. It is possible that low- and high-frequency stimulation differentially affect the PPN and its connections, resulting in different behavioral states. In addition, potential variations in electrode placement and disease states among patients may have important effects on the behavioral response as well. The cause of induction of REM sleep with abrupt cessation of low-frequency stimulation is not clear, although the authors do report that the patient with this effect did have more dorsal placement of the stimulator. Many of the studies discussed in this review, and in particular reports on PPN DBS, evaluate very small numbers of patients, making inference to a larger population more difficult because of the possibility of idiosyncratic responses, placebo effects, or type 2 statistical errors. Nevertheless, because of the role of the PPN in modulating sleep and wakefulness, stimulation of this novel target in patients with PD potentially provides a unique opportunity to better understand normal sleep physiology as well as the pathophysiology of sleep dysfunction in PD.

Conclusion

Sleep dysfunction has a significant impact on quality of life in patients with PD [Scaravilli *et al.* 2003]. The use of DBS for treatment of motor symptoms that no longer respond optimally to medical therapies provides an opportunity to better understand how neuromodulation affects sleep dysfunction. Recent evidence shows that DBS (particularly in the STN and possibly in the PPN) likely improves sleep quality and sleep architecture in patients with PD. In all therapeutic targets, however, evidence is derived primarily from case series and case reports and evaluation of larger numbers of patients, with appropriate controls and blinding over longer follow-up periods, is required to confirm the results. Furthermore, routine collection of sleep data through questionnaires or PSG in patients undergoing DBS could contribute to a better understanding of how DBS influences sleep. The available research discussed in this review prompts us to ask additional questions.

For example, in all targets, it has not yet been determined if unilateral and bilateral DBS affect sleep similarly, or if one approach is superior to the other. Also, because target nuclei, particularly PPN, are small anatomically, the influences of direct or indirect stimulation on surrounding nuclei and output structures should be investigated. In addition, if improvement of sleep with PPN DBS is confirmed in future studies, severe alterations in sleep and wakefulness may warrant consideration of DBS at this target in selected patients.

The mechanism of the improvement in sleep with DBS is likely multifactorial. Although it appears to be related in part to increased nocturnal mobility associated with improvement of motor symptoms, other factors that influence sleep quality such as depression and medications must also be considered. It is well established that STN DBS in particular allows for reduction of anti-Parkinsonian medications [Weaver *et al.* 2005], and this change alone could improve sleep and reduce daytime hypersomnolence in some patients. Another possibility is that DBS has a direct effect on sleep physiology that is independent of improvement in motor symptoms, mood, or medications. This may be expected, since the STN and GPi have neural connections to structures that are important in modulation of behavioral state, such as the PPN [Aravamuthan *et al.* 2007; Lu *et al.* 2006; Bevan and Bolam, 1995; Parent and Hazrati, 1995], laterodorsal tegmental nucleus [Bevan and Bolam, 1995], and dorsal raphe nucleus [Parent and Hazrati, 1995]. Despite the numerous questions yet to be answered about the effects of DBS on sleep, the potential improvements in sleep with DBS are promising and provide useful information for patients, caregivers, and physicians who assess the potential benefits and risks of this neuromodulatory therapy.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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