Impact of Deep Brain Stimulation Therapy on Autonomic Disturbances and Related Symptoms of Parkinson's Disease

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Abstract

Deep brain stimulation (DBS) is an effective treatment option for patients with Parkinson's disease (PD), essential tremor and certain types of dystonia. DBS surgery is typically offered to patients that have diminishing benefits from dopamine replacement therapy with prominent motor fluctuations. Recent research has also shown that DBS can have a significant impact on non-motor symptoms (NMSs), including influencing autonomic and related symptoms. In this editorial, we will evaluate these publications and discuss the often positive impact of DBS on autonomic symptoms, weight changes, sleep disturbances and sensory function.

Keywords: Deep brain stimulation; Parkinson's disease; Autonomic function; Globus pallidus interna; Subthalamic nucleus

Abbreviations:

DBS: Deep Brain Stimulation; STN: Subthalamic Nucleus; GPi: Globus Pallidus Interna; PD: Parkinson's Disease; NMSs: Non-motor Symptoms; Vim: Ventral Intermediate Thalamic Nucleus; PLM: Periodic Leg Movements; RLS: Restless Legs Syndrome; REM: Rapid-Eye Movement Sleep; DT: Detection Threshold; IT: Identification Threshold; DRT: Dopaminergic Replacement Therapy

Introduction

During the past 20 years, DBS has become an important therapeutic option for PD patients, especially for those with motor complications of dopaminergic treatment, such as motor fluctuations and dyskinesias. It has been shown that DBS treatment significantly improves tremor, rigidity, and bradykinesia. As a result, oral medication needs are usually reduced following DBS surgery [1,2]. Aside from motor symptoms, majority of patients with PD experience significant NMSs. The influence of NMSs on quality of life can be as prominent as motor dysfunction and complications of medications, especially for those patients with advanced stages of PD [3]. Recently, Klingelhofer and colleagues reviewed the impact of deep brain stimulation on NMSs in PD, focusing on neuropsychiatric symptoms [1]. They concluded that STN and GPi DBS is a safe procedure with respect to cognitive morbidity over short- and long term follow-up in carefully selected patients.

Dysfunction of the autonomic nervous system is common in PD, and it increase with progression of disease, causing a major impact on quality of life [4]. Not only central system is thought to be due to autonomic dysfunction [5,6] but also peripheral sympathetic denervation are demonstrated involving it [7,8]. As basal ganglia is connected to areas involving in regulation of the autonomic nervous system [9] STN-DBS may affect autonomic nervous system functions. Some studies have indicated that some autonomic symptoms may improve following STN DBS. In this review, a focused literature search was performed to review the effects of DBS treatment on dysautonomia, sensation, sleep, and weight.

Thermoregulation and Sweating Disturbances

Thermoregulation is impaired in patients with PD and sweating abnormalities can be troublesome [10]. Abnormal sensations of heat or cold, impaired sweating responses, and hypothermia can all occur [10]. Severe drenching sweats occur commonly as an end-of-dose “off” phenomenon in patients with advanced disease, which may be satisfactorily controlled with adequate dopamine replacement therapy [11].

STN-DBS seems to improve disturbances in temperature sensations in patients with PD [12]. Cold and warm sense thresholds of patients were lower during the DBS-on mode when compared with the DBS-off mode [12]. Drenching sweats and akathisia showed a remarkably good response to chronic STN stimulation [13]. Imaging studies with reconstruction indicated that stimulation of, or spread of stimulation from, the caudal medial aspect of the STN and/or the caudal aspect of the ventral thalamus/zona incerta may be responsible for alleviating drenching sweats [14].

Urinary Symptoms

Urinary symptoms are among the most frequent non-motor symptoms in patients with PD. They occur in 38–71% of patients with PD, typically manifesting as nocturia, urgency, and frequency. The mechanisms of these symptoms may be earlier perception of bladder
Orthostatic Hypotension

Orthostatic hypotension is a common problem in patients with advanced PD. Levodopa and most anti-parkinsonian medications may exacerbate orthostatic hypotension [20,21]. STN-DBS may improve orthostatic hypotension by increasing heart rate, improving baroreceptor sensitivity, and increasing peripheral vasoconstriction [22,23]. Targeted electric DBS in STN can enhance sympathetic regulation; the autonomic response may be due to electrical signals being distributed to limbic components of the STN or descending sympathetic pathways in the zona incerta [24]. GPi stimulation showed no change in cardiovascular parameters [25,26].

Gastrointestinal Symptoms

Gastrointestinal dysfunction such as dysphagia, reflux and constipation is common in patients with advanced PD. In fact, aspiration pneumonia secondary to dysphagia is a leading cause of death in PD [27]. The gastrointestinal dysfunction likely results from degeneration of extranigral lesions related to neural control of gastrointestinal tract function, such as cells in the dorsal vagal nucleus and the intramural intestinal plexus [28]. The ideal strategy for the management of gastrointestinal dysfunction remains uncertain.

Bilateral STN-DBS can improve gastric emptying [29], salivation swallowing, and constipation [30]. Lengerer and colleagues reported DBS has no clinically significant effect on deglutition [31], but a study using video fluoroscopy found improvements in some aspects of pharyngeal swallowing following STN-DBS [32]. It is possible that STN-DBS modulates thalamocortical or brainstem targets to overcome the bradykinesia and hypokinesia associated with pharyngeal muscles, improving the pharyngeal stage. Stimulation of certain areas of basal ganglia and/or the entire basal ganglia circuits may contribute to selecting appropriate swallow motor plans based on proprioceptive feedback, and adapting these plans in the context of environment (what is being swallowed) [32]. Recently, Troche MS and colleagues reviewed 9 studies specifically addressing the effects of DBS on swallowing, concluding that none of these studies demonstrated clinically significant effects of DBS on swallowing function. There is no data to suggest that STN or GPi have differential effects on swallowing function [33].

Sexual Dysfunction

In general, studies on sexual dysfunction in PD patients have been relatively sparse. Dopamine agonists and levodopa can increase sexual wellbeing [34]. Age, severity of disease, and depression seem to be the most important predictors of sexual wellbeing in PD [35]. Castelli and colleagues conducted questionnaires in 31 patients with PD investigating the impact of DBS on sexual function. They found a small but significant improvement in sexual functioning in male patients with PD 1-year after bilaterally DBS surgery, particularly in those less than 60 years of age. No difference in sexual satisfaction was found in the women. They also found that changes in sexual satisfaction after surgery had no correlation with improvement in depression, anxiety, or motor function [36]. These sexual disturbances may be due to the change in activity of medial preoptic anterior hypothalamic nuclei and DBS stimulation of projections to the nucleus accumbens, both responsible for sexual functions [37].

Sleep Disturbance

Sleep disturbances in patients with PD are multifactorial. While degeneration of dopaminergic and nondopaminergic neurons in the brainstem cause specific sleep disorders, parkinsonian motor dysfunction, dyskinesias, pain, nocturia, and dopaminergic and nondopaminergic medications may all contribute to sleep disturbances [10]. Recent studies have suggested that STN-DBS improves subjective and objective measures of sleep in patients with PD. Bilateral STN-DBS decreased awake state after sleep onset, improved nocturnal mobility, RLS, nocturia, and increased continuous sleep time and sleep efficiency [38-42]. Polysomnography showed that STN stimulation increased the durations of deep slow wave sleep and REM sleep, but the proportion of time spent in each sleep stage was not significantly different. When stimulation was absent, sleep disturbances were similar to those observed before surgery [43]. These polysomnographic changes suggest a direct effect of STN stimulation on the sleep regulatory center. However, in most studies, excessive daytime somnolence, periodic limb movements of sleep, and REM sleep behavior, did not improve after bilateral STN-DBS [40,44]. As proposed by Iranzo and colleagues [45], the persistence of REM behavior disorder after surgery suggests that electrical inactivation of the STN does not restore the pedunculopontine activity which promotes muscle atonia during REM sleep [46], whereas the persistence or increase of PLM might reflect the reduction of postoperative dopaminergic treatment [45]. Kedia and colleagues reported new problematic symptoms of RLS could be reversed by dopaminergic drugs [47].

GPi-DBS has been reported to improve sleep quality [48] as well as subjective daytime sleepiness in individuals who did not have their anti-Parkinsonian medications reduced. It is not known if dopaminergic medicines or GPi-DBS itself is involved in the positive effects on sleep [49]. Stimulation of Vim did not modify sleep quality or architecture [50].

Weight Loss

Weight loss in patients with PD is associated with a loss of fat mass years before a formal diagnosis is made [51]. A variety of factors have been implicated in weight loss, including increased metabolic demand from motor symptoms, decreased caloric intake from motor disability, a side effect of medication [52], and secondary dysfunction of central energy homeostasis.

Postoperative gain in body weight following bilateral STN-DBS was found in two studies [53,54]. Bodyweight increases most rapidly within the first 3 months after surgery, and weight gain slowly increases in the long term [54]. The quick initial weight gain might be explained by the transient euphoria in the immediate postoperative phase, which is often associated with increased appetite [55], and the
reduction of energy expenditure (reduced dyskinesia, rigidity, and tremor). Postoperative eating behavior disorders (so-called emotional eating and snacking) are frequently noted in apathetic patients, which is also described in patients with depression [56]. Weight variation in PD before and after DBS-STN is influenced by noradrenergic interaction between the locus coeruleus, the STN, and the hypothalamic nucleus. The locus coeruleus plays an important role in regulating energy metabolism through its noradrenergic connections with the hypothalamus. Noradrenergic degeneration is an important hallmark in PD because of neuronal loss in the locus coeruleus [57].

In a comparative study, weight gain was more frequent and more severe in patients who underwent subthalamic surgery than in patients who had pallidal surgery. There were no significant changes in food intake, either qualitatively or quantitatively, in the two groups [58]. It was concluded that an additional effect of DBS-STN on the homeostatic control centers may have contributed to the difference in weight gain between the two targets. Vim stimulation seems not to result in weight gain in patients with essential tremor, but there is inadequate evidence that this may occur in PD [59].

### Pain

Approximately 70% to 80% of patients with PD suffer from chronic pain syndromes over the course of their disease [60]. Pain severely impairs quality of life, and in the setting of PD different types of painful symptoms may arise. Since pain mechanisms are not clearly understood, the current therapeutic strategy is mainly symptomatic.

Levodopa has been shown to improve sensory symptoms by increasing pain threshold [61]. Similarly, clinical studies have demonstrated that STN-DBS may reduce pain intensity and lengthen pain-free intervals [62,63]. In patients with PD, dystonic pain and central pain significantly improve following STN-DBS surgery, with more modest improvements in radicular/neurotic and musculoskeletal pain [62]. Pain due to camptocormia only shows mild improvement with STN or GPi stimulation [64]. Post-DBS follow-up evaluations showed the mean pain score at to be lower than that at baseline and development of new pain occurred at a similar rate as that of the general aging population [65]. This is particularly significant since central pain generally worsens with progression of PD [66].

The mechanisms by which STN-DBS improves pain in PD remain unclear. Since musculoskeletal pain and dystonic pain are typically related to increased muscle tone or rigidity, it is possible that STN-DBS provides pain relief by alleviation of rigidity. It is also possible that improvements in depressive symptoms after DBS contribute to improved pain control. One potential mechanism for pain relief following STN-DBS may be the modulation of the lateral discriminative pain system, which is impaired in PD patients with neuropathic pain [67]. Stimulation of the posteroventral lateral GPi has also been suggested to improve pain and dysaesthesia in advanced PD up to 74%; the improvement in such symptoms was sustained at the one year follow up [68]. The result is similar to reports of pallidotomy, suggesting that the basal ganglia play a critical role in modulating pain [69].

### Dysosmia

Olfactory dysfunction is an early symptom in PD, often presenting before the motor symptoms [70]. DRT does not improve olfactory function [71]. Patients treated with bilateral STN-DBS showed no significant alterations in odor DT scores in the stimulator-on and off conditions, whereas odor IT scores were significantly improved in the stimulation-on relative to the stimulation off condition [72,73], which may indicate that DBS has a positive effect on the cognitive processing of olfactory information in patients with PD.

It remains unclear why the odor IT improved but the odor DT did not after DBS treatment. It is possible that odor DT is a low-level marker of olfactory function and is related to the degree of pathohological impairment of the olfactory bulb and anterior olfactory nucleus. [74] Because these structures are damaged in early stages of PD [75], stimulation may not be able to improve the function of these areas. In contrast, olfactory identification is not only related to higher-order olfactory center operations but also to higher-level cognitive functioning [74]. These cortical regions relevant to olfactory identification are only damaged in advanced PD. A previous study demonstrated that when PD patients lose all olfactory functioning, and olfactory DT increases maximally, DBS no longer improves olfactory dysfunction [73]. Fibers involved in the production, integration, and transmission of olfactory information are located in numerous cortical and subcortical regions sharing vast connections with the STN [73], and striatal dopamine metabolism is related to olfactory identification [76,77], which indicates that STN-DBS may regulate abnormal excitability to improve olfactory identification [78]. The prefrontal lobe and cingulate gyrus are closely related to mood and are easily influenced by odor [79]. Since DBS may improve somatic and psychiatric symptoms, it may also increase the olfactory sensitivity of PD patients.

No data are available on dysosmia in PD patients following GPi- and Vim-DBS.

### Conclusions

Most of the current literature on the effects of DBS on autonomic nervous system dysfunction is based on using STN as the target, with limited data on GPi and almost no evidence from Vim for PD. We summarized the impact of these three commonly used DBS targets on NMSs of PD patients in Table 1. It shows that STN-DBS may be a safe procedure with regard to pre-existing dystautonmia. In fact, STN-DBS may even have beneficial effects on non-motor symptoms such as pain, sleep, weight, gastrointestinal disturbance, sweating, orthostatic hypotension, anosmia, bladder overactivity, and sexual dysfunction. In conclusion, improvements in these non-motor symptoms may significantly improve quality of life of PD patients beyond improvements resulting from motor benefits alone. GPI DBS may produce similar results, but further clinical research is needed. As the motor effects of STN-DBS and GPi DBS are similar [48], it is possible that NMSs may determine the target of choice in the future.

| STN | GPI | Vim |
|-----|-----|-----|
| **Verbal fluency** | Declined | Possibly declined | Unknown |
| **Pain** | Improved | Improved | Adverse events |
| **Dysosmia** | Improved | Unknown | Unknown |
| **Sleep disturbance** | Some aspects improved, some aspects unchanged | Improved | Unchanged |
| **Weight loss** | Gain | Gain less | Possible none |
Table 1: Synopsis of the impact of the most commonly used DBS targets on NMSs in PD patients

| Symptom                        | Improvement Status        |
|--------------------------------|---------------------------|
| Dysphagia                      | Uncertain, possibly improved |
| Cardiovascular disturbance     | Improved, unchanged, unknown |
| Urinary symptoms               | Improved, unchanged, unknown |
| Thermoregulation               | Improved, unchanged, unknown |
| Drenching sweats               | Improved, unchanged, unknown |
| Sexual dysfunction             | Man improved, unknown     |

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