Review Article

Target Selection Recommendations Based on Impact of Deep Brain Stimulation Surgeries on Nonmotor Symptoms of Parkinson's Disease

Xiao-Hong Wang[1], Lin Zhang[2], Laura Sperry[2], John Olichney[2,3], Sarah Tomaszewski Farias[2], Kiarash Shahlaie[2,3,4], Norika Malhado Chang[2], Ying Liu[5], Su-Ping Wang[1], Cui Wang[1]

[1]Department of Neurology, Dalian Municipal Central Hospital, Dalian, Liaoning 116033, China
[2]Department of Neurology, University of California Davis, Sacramento, CA, USA
[3]Center for Neuroscience, University of California Davis, Davis, CA, USA
[4]Department of Neurological Surgery, University of California Davis, Sacramento, CA, USA
[5]Department of Neurology, University of Colorado Denver School of Medicine, Denver, CO, USA

Abstract

Objective: This review examines the evidence that deep brain stimulation (DBS) has extensive impact on nonmotor symptoms (NMSs) of patients with Parkinson's disease (PD).

Data Sources: We retrieved information from the PubMed database up to September, 2015, using various search terms and their combinations including PD, NMSs, DBS, globus pallidus internus (GPi), subthalamic nucleus (STN), and ventral intermediate thalamic nucleus.

Study Selection: We included data from peer-reviewed journals on impacts of DBS on neuropsychological profiles, sensory function, autonomic symptoms, weight changes, and sleep disturbances. For psychological symptoms and cognitive impairment, we tried to use more reliable proofs: Random, control, multicenter, large sample sizes, and long period follow-up clinical studies. We categorized the NMSs into four groups: those that would improve definitively following DBS; those that are not significantly affected by DBS; those that remain controversial on their surgical benefit; and those that can be worsened by DBS.

Results: In general, it seems to be an overall beneficial effect of DBS on NMSs, such as sensory, sleep, gastrointestinal, sweating, cardiovascular, odor, urological symptoms, and sexual dysfunction, GPi-DBS may produce similar results; Both STN and Gpi-DBS are safe with regard to cognition and psychology over long-term follow-up, though verbal fluency decline is related to DBS; The impact of DBS on behavioral addictions and dysphagia is still uncertain.

Conclusions: As the motor effects of STN-DBS and GPi-DBS are similar, NMSs may determine the target choice in surgery of future patients.

Key words: Deep Brain Stimulation; Globus Pallidus Internus; Nonmotor Symptoms; Parkinson's Disease; Subthalamic Nucleus

Introduction

Medications have improved the prognosis of Parkinson's disease (PD), but also have problematic adverse effects, particularly levodopa-induced motor fluctuations and dyskinesia. These complications can be observed in 40% after 5 years and 80% after 10 years following the diagnosis of PD.[1] During the past 20 years, deep brain stimulation (DBS) has become an important therapeutic option for patients with those motor complications. The main targets for DBS treating PD are subthalamic nucleus (STN) and globus pallidus internus (GPi). It has been shown that DBS significantly improves tremor, rigidity, and bradykinesia and may reduce the occurrences of the complications of dopaminergic medications. As a result, oral medication needs are usually reduced following STN-DBS surgery.[2,3] Animal experiments showed that stimulation of the STN has a protective effect on substantia nigra pars compacta neurons.[4]

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Address for correspondence: Dr. Xiao-Hong Wang, Department of Neurology, Dalian Municipal Central Hospital, Dalian, Liaoning 116033, China
E-Mail: xhwang75@163.com

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Aside from the motor benefits of DBS, nonmotor symptoms (NMSs) can also be affected by DBS. Data from neuroanatomy, electrophysiology, neuroimaging, and clinical observation have shown that the dopaminergic system has more profound impact on cognitive, motivational, and emotional functions than previously understood.[5-7] The majority of patients with PD experience significant NMSs, depending on the stages of their clinical presentation.[8,9] The influence of NMSs on the quality of life can be as prominent as motor dysfunction and complications of medications, especially in patients with advanced PD.[9] Moreover, many patients report depression, sleep disturbances, pain, apathy, and memory impairment as the key symptoms affecting their lives, ahead of motor symptoms.[9,10] Management of NMSs is difficult because the mechanisms of NMSs in PD are not well understood. These symptoms tend to be insensitive to dopaminergic medications, and sometimes worsen with medication therapy.[11] The previous studies[12-15] are controversial with some authors suggesting that DBS triggers or worsens behavioral disorders, whereas others report improvement of neuropsychiatric symptoms. Therefore, a comprehensive understanding of the effects of DBS on NMSs is necessary.

NMSs include pain, dysosmia, gastrointestinal disorders, drenching sweats, cardiovascular obstacle, sleep disturbances, urinary symptoms, weight loss, medications or behavioral addiction, psychological disturbance, and cognition and verbal decline that we mentioned in this review. For easier understood by the readers, we categorized the NMSs into four groups: those that would improve definitively following DBS; those that are not significantly affected by DBS; those that remain controversial on their surgical benefit; and those that can be worsened by DBS. Three main targets, STN, GPi, and ventral intermediate thalamic nucleus (Vim), currently used in PD patients on NMSs were compared, besides motor benefits, NMSs may be another factor needed to be considered in target choice of DBS surgery in PD patients.

Nonmotor Symptoms that Improve After Deep Brain Stimulation

Pain

Seventy to eighty percent of PD patients suffer from chronic pain syndromes over the course of their disease,[16] which is much higher than in the general population. Pain severely impairs the quality of life, and in the setting of PD different types of painful symptoms may arise. Since pain mechanism is not clear, the current therapeutic strategy is mainly just symptomatic.

Levodopa has been shown to improve sensory symptoms by increasing pain threshold.[17] Similarly, clinical studies have demonstrated that STN-DBS may reduce pain intensity and lengthen pain-free intervals.[18,19] In patients with PD, dystonic pain and central pain significantly improve following DBS surgery with more modest improvement in radicular/neurotic and musculoskeletal pain.[18] Pain due to camptocormia only shows middle improvement with STN or Gpi stimulation.[20] The mean pain score at follow-up was lower than at baseline and development of new pain is similar to the prevalence of pain increases with age in the general population.[21] This is particularly significant since the central pain generally worsens with progression of PD.[22]

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 assumed that STN-DBS provides pain relief by alleviation of rigidity. It might also due to the improvements in depressive symptoms after DBS. One potential mechanism for pain relief following STN-DBS may be modulation of the lateral discriminative pain system, which is impaired in PD patients with neuropathic pain.[23] Gpi stimulation has also been suggested to improve pain and dysesthesia in advanced PD improvement of up to 74% were reported, which were sustained at 1 year follow-up.[24] The results are similar to reports of pallidotomy, suggesting that the basal ganglia play a critical role in modulating pain.[25]

Sleep disturbance

Patients with PD often experience disturbed sleep resulting from nighttime motor disabilities, such as nocturnal akinesia, tremor and rigidity, motor behavior during rapid-eye movement (REM) sleep, or periodic leg movements during sleep. Sleep disturbances in patients with PD are multifactorial. Degeneration of dopaminergic and nondopaminergic neurons in the brainstem cause specific sleep disorders, and parkinsonian motor dysfunction, dyskinesia, pain, nocturia, and dopaminergic and nondopaminergic medications may all contribute to sleep disturbances.[26] Recent studies have suggested that STN-DBS improves subjective and objective measures of sleep in patients with PD. Decreased awake state after sleep onset, increased continuous sleep time and sleep efficiency, improved nocturnal mobility, and improvement in restless legs syndrome (RLS) were seen after bilateral STN-DBS.[27-30] Because there was significant improvement in nocturnal motor symptoms and overall sleep quality while there was no effect on sleep fragmentation and excessive daytime sleepiness, Hjort *et al*. suggested that STN-DBS may act by reducing motor symptoms and does not have a significant effect on the central sleep modulation.[31] However, polysomnography showed that STN stimulation increased the durations of deep slow wave sleep and REM sleep, and the percentages of each sleep stage were not significantly different. When stimulation was absent, sleep disturbances were similar to those observed before surgery. These changes of polysomnography implied that direct effect of STN stimulation-on sleep regulatory center cannot be excluded.[32] On the other hand, STN-DBS can improve nocturia, which may contribute to the improvement of sleep quality.[33] In most of the reports, excessive daytime somnolence, PLM, and REM sleep behavior disorders did not improve with bilateral STN-DBS.[28,34] As proposed by Iranzo *et al*.,[35] 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,[36] whereas the

persistence or increase of PLM might reflect the reduction of postoperative dopaminergic treatment.[35] Kedia *et al*. reported new problematic symptoms of RLS could be reversed by dopaminergic drug.[37]

GPi-DBS has been reported to improve sleep quality,[38] as well as subjective daytime sleepiness in individuals who did not have their antiparkinsonian medications reduced. It is hard to say whether it is dopaminergic medicines or Gpi-DBS itself involved in the positive effects on sleep.[39] Stimulation of Vim did not modify sleep quality or architecture.[40]

Weight loss

Studies have shown that weight loss in PD patients is a continuous and progressive process associated with loss of fat mass that commences years before a formal diagnosis is made.[41] 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,[42] and secondary dysfunction of central energy homeostasis, particularly in the autonomic nervous system.

Postoperative gain in body weight following bilateral STN-DBS was found in two studies.[43,44] Bodyweight increases most rapidly within the first 3 months after surgery, and weight gain persists slow increase in the long-term.[44] The quick initial weight gain might be explained by the transient euphoria in the immediate postoperative phase, which is often associated with increased appetite,[45] and the reduction of energy expenditure (reduced dyskinesia, rigidity, and tremor). Postoperative subthreshold eating behavior disorders (so-called emotional eating and snacking) are frequently noted in apathetic patients, which is also described in patients with depression.[46] 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.[47]

In a comparative study, weight gain is more frequent and more severe in patients who have undergone subthalamic surgery than in patients who have undergone pallidal surgery. There were no significant differences in food intake, either qualitatively or quantitatively, between the two groups. It has been 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 groups of patients. A regional effect of DBS-STN on the satiety hypothalamic centers cannot be the only hypothesis for weight variations found in PD.[48] 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.[49]

Thermoregulation and sweating disturbances

Thermoregulation is impaired in patients with PD and sweating abnormalities can be troublesome.[26] Abnormal sensations of heat or cold, impaired sweating responses, and hypothermia can all occur.[26] Severe drenching sweats occur commonly as an end-of-dose "off" phenomenon in patients with advanced disease, and these may be satisfactorily controlled with adequate dopamine replacement therapy.[50]

STN-DBS seems to improve disturbances in temperature sensations in patients with PD.[51] Cold and warm sense thresholds of patients were lower during the DBS-on mode when compared with the DBS-off mode.[51] Some incapacitating manifestations such as drenching sweats and akathisia showed a remarkably good response to chronic STN stimulation.[52] 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.[53]

Urinary symptoms

Urinary symptoms are among the most frequent NMSs of PD. They occur in 38–71% of PD patients, typically manifesting as nocturia, urgency, and frequency. The mechanisms underlying these symptoms may be earlier perception of bladder sensation resulting in detrusor over activity.[54] STN-DBS has been shown to have variable results on urinary symptoms. Some studies suggest improvement in urinary symptomatology after STN DBS,[55-57] with improvements in detrusor hyperreflexia[56] and increased bladder capacity.[57] A study on regional cerebral blood flow measured by positron emission tomography showed that STN-DBS can modulate neural activity in the thalamus and insular cortex by periaqueductal gray activity during STN-DBS on, an effect that results in enhancement of afferent urinary bladder information processing.[55] Fritsche *et al*. reported two patients that developed acute urinary retention following DBS.[58] The phenomenon may be due to suboptimal positioning of the electrodes.[58]

Cardiovascular disturbance

Cardiac autonomic disturbances including orthostatic hypotension are common problems in advanced PD patients. Levodopa and most antiparkinsonian medications may exacerbate orthostatic hypotension.[59,60] The autonomic changes that occur following STN-DBS may improve orthostatic hypotension by increasing heart rate, improving baroreceptor sensitivity, and increasing peripheral vasoconstriction.[61] 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.[62] Priori *et al*. also demonstrated an alteration in visual evoked potential, somatosensory evoked potential, sympathetic skin response, and plasma renin level with DBS.[63] Thornton *et al*. showed similar response in humans with an increase in heart rate and mean arterial pressure on STN stimulation, while GPi stimulation showed no change in cardiovascular parameters.[64,65]

Dysosmia

Olfactory dysfunction is an early symptom in PD, often presenting before the motor signs.[66] Dopamine replacement therapy does not improve olfactory function.[67] Patients treated with bilateral STN-DBS showed no significant alterations in odor detection threshold (DT) scores in the stimulator-on and -off conditions, whereas odor identification threshold (IT) scores were significantly improved in the stimulation-on relative to the stimulation-off condition,[68,69] 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 pathological impairment of the olfactory bulb and anterior olfactory nucleus.[70] Because these structures are damaged in early stages of PD,[71] 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 but also to higher-level cognitive functioning.[70] 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 did not improve olfactory dysfunction anymore.[69] 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,[69] and striatal dopamine metabolism is related to olfactory identification,[72,73] which indicates that STN-DBS may regulate abnormal excitability to improve olfactory identification.[74] The prefrontal lobe and cingulate gyrus are closely related to mood and are easily influenced by odor.[75] Since DBS may improve somatic and psychiatric symptoms, it may increase the olfactory sensitivity of PD patients either.

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

Sexual dysfunction

In general, studies on sexual dysfunction in PD patients have been relatively sparse. Dopamine agonists and levodopa can increase sexual wellbeing.[76] Age, severity of disease, and depression seem to be the most important predictors of sexual wellbeing in PD.[77] Castelli *et al*. conducted a questionnaire survey of 31 patients with PD, investigated 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 <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.[78] 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.[79]

Gastrointestinal symptoms

Gastrointestinal dysfunction such as dysphagia, reflux, and constipation are common in patients with advanced PD. In fact, aspiration pneumonia secondary to dysphagia is a leading cause of death in PD.[80] 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.[81] The ideal strategy for the management of gastrointestinal dysfunction remains uncertain.

A limited amount of literature exists on the potential effects of DBS on gastrointestinal symptoms in PD. A study evaluating gastric empty by ^{13}C-acetate breath test showed that STN-DBS can improve gastric emptying.[82] Zibetti *et al*. reported bilateral STN-DBS improves salivation, swallow, and constipation,[83] but has no clinically significant effect on deglutition.[84] A study using video fluoroscopy found improvements in some aspects of pharyngeal swallowing following STN-DBS.[85] 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).[85] Recently, Troche *et al*.[86] reviewed 9 studies specifically addressing the effects of DBS on swallowing they concluded that none of these studies demonstrates clinically significant effects of DBS on swallowing function.

Nonmotor Symptoms that are not Affected by Deep Brain Stimulation

Psychological symptoms

In the immediate postoperative state, patients with PD commonly experience a transient period of euphoria, characterized by disinhibition, hyperactivity, and increased motivation.[13] Transient acute depressive moods that coincide with DBS parameter changes have also been described, and are reversible with decrease in current intensity.[87]

At a relative early stage, STN-DBS can improve some psychological symptoms, such as mood, anxiety, apathy, and fatigue.[14,15] However, with time, these effects become diminished. Compared with the preoperative state, neither worsening nor improving in mood and psychosocial functions were seen 3–11 years[43,88-90] following electrode implantation [Table 1]. Psychiatric problems have been reported by several groups, usually occurring several months after surgery due to preexisting psychiatric illness, surgery-related stress, changes in medication, alterations in social life that are associated with improvements in motor function, or the mismatch between the final outcome of treatment and the patient's expectations.[91] There is some

Table 1: Longitudinal follow-up studies on the effects of DBS on psychological symptoms in PD patients

First author, year	Cases (*n*)	Follow-up duration	Research methods	Targets	Outcomes
McDonald 2012[14]	26	12.8 ± 8.2 months	Medicine control Prospective	Bilateral STN	Mood, anxiety, apathy, and fatigue are improved, but gregarious behavior decreased
Lhommée 2012[15]	63	12 months	Multicenter Prospective	STN	An overall improvement in psychological symptomatology, but apathetic mode aggravated
Kaiser 2008[88]	33	3 years	Prospective	Bilateral STN	No change at 3 years compared with baseline
Krack 2003[43]	49	5 years	Prospective	Bilateral STN	No significant changes in depression
Fasano 2010[89]	20	8 years	Prospective	Bilateral STN	No significant change in depression and anxiety
Rizzone 2014[90]	26	11 years	Multicenter Prospective	Bilateral STN	No significant changes in depression, but anxiety significantly improved
Follett 2010[93]	299	2 years	Multicenter Randomized Prospective	152 (GPi) 147 (STN)	Significant worsening of depression scores in STN DBS patients compared with GPi DBS patients
Odekerken 2013[94]	125	1 year	Multicenter Randomized	62 (GPi) 63 (STN)	No difference between STN DBS and GPi DBS in terms of mood
Volkmann 2009[38]	69	3 years	Multicenter Randomized Prospective Blind assessment	49 (bilateral GPi) 20 (bilateral STN)	Both GPi and STN DBS treatment have no influence on emotional behaviors

PD: Parkinson's disease; DBS: Deep brain stimulation; STN: Subthalamic nucleus; GPi: Globus pallidus internus.

evidence that changes in the limbic circuit following DBS may also contribute to psychiatric problems.[92]

STN and GPi stimulation result in similar motor benefits in both the on stimulation or off medication states.[93,94] Mood and apathy, however, may be better following STN rather than GPi-DBS.[2] A randomized trial of bilateral STN versus GPi-DBS in patients with PD demonstrated a significant worsening of depression scores in STN patients, although this had limited clinical significance.[93] In a separate multicenter, randomized trial no differences were reported in mood 1 year after STN versus GPi-DBS.[94] A similar result was reported from a 3 years follow-up study both GPi and STN-DBS had no influence on emotional behaviors [Table 1].[38]

Cognitive impairment

PD is characterized by a frontal cortical dysfunction thought to result from degeneration of cells within the substantia nigra and dysfunction within the cortical-subcortical-basal ganglia circuits.[95] Cognitive impairments in other domains (e.g., visuospatial abilities, language, and memory) are also frequently seen in PD and may be secondary to Lewy body pathology within neocortical regions. Cognitive impairment worsens with disease progression and all individuals with PD are at very high risk to develop dementia. More than 90% of PD patients have some degree of cognitive impairment[96] and the prevalence of dementia in PD was found to be slightly >40% in a population-based study.[97] Early studies of STN-DBS in PD reported declines in memory, particularly in elderly patients.[98] Two meta-analyses of cognitive outcomes of STN-DBS showed small or null effects in most cognitive domains.[99,100] Parsons *et al*. reported mild, but statistically significant, declines in the executive and verbal memory domains.[99] They found moderate declines, however, in verbal fluency (discussed further below). Appleby *et al*. reported in their meta-analysis, that 57% of studies examining cognitive outcomes showed no changes and 31% reported either significant, or non-significant underpowered, improvement.[100] In other reports, most cognitive scores remained stable at 1–11 years following STN-DBS surgery[3,15,43,89,90,101,102] [Table 2] except verbal fluency declined in some studies[15,89,90,101] (we will talk about it in another part of this review). A series of case–control studies compared the effects of DBS on cognition with the stimulator "on" and "off." Fraraccio *et al*. reported no cognitive difference between "on" and "off,"[103] whereas Pillon *et al*. reported a mild but significant improvement in psychomotor speed and working memory when the stimulator was "on."[102] These results indicate that memory problems in patients with DBS seem to reflect disease progression rather than an adverse event of the intervention.

While a few smaller studies have suggested a reduction in cognitive behavioral complications (e.g. post-operative delirium) with DBS of GPi, compared to DBS of STN,[104,105] recent long-term studies have generally found no significant difference in cognition [Table 2].[93,94,106] Similarly, Vim stimulation showed no significant effects on memory.[2]

Nonmotor Symptoms that May or May not be Affected by Deep Brain Stimulation

Medication or behavioral addictions

Addictions to dopaminergic medications or to pleasant behaviors are frequent and potentially devastating neuropsychiatric disorders observed in PD.[107] Their relationship to dopaminergic replacement therapy (DRT) is strongly suggested.[108] Since STN-DBS improves motor complications and allows for

Table 2: Longitudinal follow-up studies of the effects of DBS on cognition in PD patients

First author, year	Cases (*n*)	Follow-up duration (year)	Research methods	Targets	Outcomes
Parsons 2006[99]	612	–	Meta-analysis	STN	Small effects on all cognitive domains assessed, declines in the executive, and memory domain were statistically significant
Appleby 2007[100]	10,339	–	Meta-analysis	–	57% studies examining cognitive outcomes showed no cognitive change and 31% reported improvement
Lhommée 2012[15]	63	1	Multicenter Prospective	STN	Cognitive evaluation unchanged
Williams 2010[101]	366	1	Randomized Open-label Prospective Multicenter Medicine control	Bilateral STN	General cognitive function after DBS compared with a medically treated control group remained unchanged
Pillon 2000[102]	56	1	Prospective	Bilateral STN	STN patients had no cognitive deficit, except for lexical fluency
Krack 2003[43]	49	5	Prospective	Bilateral STN	Average scores for cognitive performance remained unchanged
Fasano 2010[89]	20	8	Prospective	Bilateral STN	Mild cognitive decline did not have clinical meaning
Rizzone 2014[90]	26	11	Multicenter Prospective	Bilateral STN	Global cognitive functions, abstract reasoning, memory and phonological verbal fluency are in the normal range, but phonological verbal fluency remarkable declined
Follett 2010[93]	299	2	Multicenter Randomized Prospective	152 (GPi) 147 (STN)	Secondary outcome: Similarly slight decrements in cognitive function in STN and GPi DBS group
Odekerken 2013[94]	125	1	Multicenter Randomized Prospective	62 (GPi) 63 (STN)	Primary outcome: No difference between STN and GPi DBS in terms of cognition
Jiang 2015[3]	10	5	Prospective	Bilateral STN	Mostly unchanged by self-comparison

PD: Parkinson's disease; DBS: Deep brain stimulation; STN: Subthalamic nucleus; GPi: Globus pallidus internus.

reductions in medication, it may be considered for treating patients with medications and behavioral addictions. However, conflicting data have emerged to suggest suppression, alleviation, worsening, or even new onset of behavioral addictions after DBS stimulation.[17,109] A prospective cohort study of 63 patients with STN-DBS surgery showed that preoperative dopamine dysregulation syndrome (DDS), behavioral addictions, or dopaminergic compulsive medication use had disappeared in all patients at the 1-year follow-up, and dopaminergic medications were reduced by 73%.[15] Another observational study of 110 patients with PD showed no new occurrences of DDS and impulse control disorders (ICDs) 1 year after STN-DBS surgery; preoperative ICDs were reduced in all patients.[110] Lim *et al*. reported a case series of 21 patients with DDS, ICDs, or pounding at some stages during their disease, had their respective symptoms persist, worsen or develop for the 1st time after 1 year postoperation, and only a minority of patients improved dramatically.[109] Hälbig *et al*.[111] and Moum *et al*.[112] reported similar findings. Djamshidian *et al*. suggested that worsening of addictions following DBS may result from biased electrode position and spread of stimulation effects into the limbic portion of the STN.[113] A large retrospective series of reported preoperative ICDs in patients treated with STN-DBS suggested that worsening of ICDs was associated with a very high dose of DRT, whereas improvement in ICDs was associated with a major decrease in DRT.[109] STN-DBS allows for a decrease in DRT, but this is not the case for GPi-DBS.[2] GPi stimulation has no significant effects on addictive behavior; in fact, some patients may experience worsening of these symptoms following surgery.[109]

Though people perceive mood and behavioral changes as contraindications for STN-DBS surgery,[114] dopaminergic treatment abuse, and drug-induced behavioral addictions may be considered as relative indications for STN stimulation.[15,110]

Nonmotor Symptoms that Worsened by Deep Brain Stimulation

Verbal fluency

Postoperative decline on phonological and semantic verbal fluency tasks in patients with PD has been frequently reported after STN-DBS. The phenomenon is detected within a few months after surgery and gradually worsens over long-term follow-up (up to 8 years).[89,115] Controlled studies at 6-month,[116] 1-year,[117] and 3-year[118] follow-up after DBS implantation also confirmed verbal fluency impaired. In Parsons *et al*. meta-analysis, more noteworthy declines were identified in semantic and phonemic verbal fluency after STN-DBS with declines in verbal learning ability also noted; Changes in verbal fluency were not related to patient

Table 3: Synopsis of the impact of the most commonly used DBS targets on NMSs in PD patients

NMSs	STN	GPi	Vim
Psychological symptoms	Unchanged	Unchanged	Unknown
Addiction	Uncertain, possibly improved	Uncertain, possibly worsen	Unknown
Cognitive impairment	Unchanged	Unchanged	Unchanged
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
Dysphagia	Uncertain, possibly improved	Uncertain	Unknown
Cardiovascular disturbance	Improved	Unchanged	Unknown
Urinary symptoms	Improved	Unknown	Unknown
Thermoregulation	Improved	Unknown	Unknown
Drenching sweats	Improved	Unknown	Unknown
Sexual dysfunction	Man improved	Unknown	Unknown

PD: Parkinson's disease; DBS: Deep brain stimulation; STN: Subthalamic nucleus; GPi: Globus pallidus internus; Vim: Ventral intermediate thalamic nucleus; NMSs: Nonmotor symptoms.

age, disease duration, stimulation parameters, or change in dopamine mimetic dose after surgery.[99] Verbal fluency decline played an important role in total cognitive score decrease in some research,[119,120] which maybe the reason that DBS may worsen cognitive ability in the conclusions of those kind research. Interestingly, this has also been found after 3 months in the unstimulated but implanted control group[121] suggesting that a lesion within the electrode tract may be involved. It has been suggested that ideal positioning of the DBS electrode in the dorsolateral STN may provide excellent motor improvements while avoiding the effects of DBS on verbal fluency.[122]

Contemporary theories of language include involvement of subcortical structures, particularly the role of GPi in the control of lexical-semantic operations.[123] Bilateral GPi-DBS treatment results in statistically significant reductions in performance on verbal fluency measures. For unilateral GPi-DBS treatment, reductions in verbal associative fluency were significant after left-sided treatment,[124] whereas Zahodne *et al*. reported no verbal fluency impairment.[125] Comparing the impact of verbal fluency between GPi and STN treatments, Rothlind *et al*. concluded that there were few significant differences,[124] but two other studies showed that letter verbal fluency scores in STN group decreased more than GPi group.[93,106] Overall it appears that verbal fluency likely declines regardless of electrode placement and should be taken into account when surgical outcomes and surgical patient selection are considered.

Conclusions

Most of the current literature on the effects of DBS on NMSs 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 3. In general, there seems to be an overall beneficial effect of DBS on NMSs, such as sensory, sleep, gastrointestinal, sweating, cardiovascular, odor, urological symptoms, and sexual dysfunction, GPi-DBS may produce similar results, but more clinical research is needed; both STN and Gpi-DBS are generally safe with regard to cognition and psychological symptoms over long-term follow-up, though verbal fluency decline is related to DBS; the impact of DBS on behavioral addictions and dysphagia is still uncertain. Considering the effect of DBS on both motor and NMSs, surgery is a safe and highly effective therapy in selected patients. As the motor effects of STN-DBS and GPi-DBS are similar,[38] NMSs may determine the target choice in surgery of future patients.

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Conflicts of interest

There are no conflicts of interest.

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