REVIEW ARTICLE

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Nonmotor Symptoms and Subthalamic Deep Brain Stimulation in Parkinson's Disease

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ABSTRACT

Subthalamic deep brain stimulation (STN DBS) is an established treatment for the motor symptoms in patients with advanced Parkinson's disease (PD). In addition to improvements in motor symptoms, many studies have reported changes in various nonmotor symptoms (NMSs) after STN DBS in patients with PD. Psychiatric symptoms, including depression, apathy, anxiety, and impulsivity, can worsen or improve depending on the electrical stimulation parameters, the locations of the stimulating contacts within the STN, and changes in medications after surgery. Global cognitive function is not affected by STN DBS, and there is no increase in the incidence of dementia after STN DBS compared to that after medical treatment, although clinically insignificant declines in verbal fluency have been consistently reported. Pain, especially PD-related pain, improves with STN DBS. Evidence regarding the effects of STN DBS on autonomic symptoms and sleep-related problems is limited and remains conflicting. Many symptoms of nonmotor fluctuations, which are occasionally more troublesome than motor fluctuations, improve with STN DBS. Although it is clear that NMSs are not target symptoms for STN DBS, NMSs have a strong influence on the quality of life of patients with PD, and clinicians should thus be aware of these NMSs when deciding whether to perform surgery and should pay attention to changes in these symptoms after STN DBS to ensure the optimal care for patients.

Key Words
Parkinson disease; Subthalamic deep brain stimulation; Nonmotor symptoms; Basal ganglia.

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INTRODUCTION

Subthalamic deep brain stimulation (STN DBS) is an established treatment for the motor symptoms of patients with advanced Parkinson's disease (PD). Because the prevalence and severity of nonmotor symptoms (NMSs) increase with the progression of motor symptoms in PD,[1-3] patients for whom STN DBS is considered also have many NMSs, which are sometimes more troublesome and exert a greater influence on health related quality of life (QoL) than the motor symptoms.[4,5]

Although it is clear that NMSs cannot be target symptoms for STN DBS, many studies have shown that STN DBS has beneficial effects on various NMSs in addition to eliciting improvements in motor symptoms and further improving the QoL and satisfaction with surgery.[4,6-8] In contrast, there are studies that have reported worsening of some NMSs following STN DBS.[9-11] Furthermore, in some patients, NMSs, including cognitive dysfunction and mood disorder, should be considered with motor symptoms when deciding whether to perform surgery because changes in these NMSs after surgery may have significant effects on the overall results of STN DBS.

In this regard, the authors will review the effect of STN DBS on NMSs in patients with PD and discuss its possible mechanisms.

MECHANISM OF THE EFFECT OF STN DBS IN PD

The current model of the basal ganglia (BG) indicates that the hypodopaminergic state in PD causes increased activity in the STN, which leads to increased inhibitory output from internal segment of the globus pallidus and substantia nigra pars reticulata.[12] This process results in increased inhibitory activity of the BG on the thalamic and cortical motor system, which manifests clinically as bradykinesia and rigidity. In addition to the motor system, the BG also serve as a conduit for the limbic and associative systems.[12] As in the motor system, the hypodopaminergic state of PD leads to increased inhibition from the BG onto these systems through the hyperactive STN. Dopaminergic medications and STN DBS reduce this increased activity of the STN in patients with PD, and this effect normalizes the increased inhibitory activity of the BG on the motor, limbic, and associative systems. However, when the STN becomes hypoactive due to excessive dopaminergic medications, the inhibitory activity of the BG falls below normal and patients in this state clinically present with hyperactive movement, such as that observed in levodopa-induced dyskinesias, and disinhibited behavior. Similarly, decreased activity in the STN due to STN DBS can also lead to the decreased inhibitory activity of the BG. Furthermore, because the STN is divided into sensorimotor, associative, and limbic territories that constitute the sensorimotor, associative, and limbic BG loops, respectively,[13] the effects of STN DBS on motor and NMSs are determined not only by the intensity of the electrical stimulation but also by the location of the stimulating electrode within the STN. For example, if the stimulating contact is located in the ventromedial STN, the patient will experience more prominent changes in symptoms related to limbic-associative circuits, whereas contacts located in dorsolateral STN will primarily affect motor symptoms.

Not all of the NMSs in PD are related to a dopaminergic deficit in the BG. Some NMSs, including cognitive dysfunction, mood disorders, and impulse control disorders, are thought to be related to dopaminergic deficits outside the BG[14,15] or abnormalities in other neurotransmitter systems including the serotonin and norepinephrine systems.[16,17] Autonomic dysfunction, including orthostatic hypotension and genitourinary dysfunction, have been related to the pathologies outside the brain, including the spinal cord and peripheral autonomic nerves.[18] STN DBS affects some of these NMSs but the mechanism has yet to be elucidated. Another mechanism by which STN DBS affects NMSs is through the reduction of dopaminergic medication after surgery. The adverse effects of dopaminergic medications, including nausea, vomiting, and dizziness, can improve after STN DBS with reductions in medication.[19] In contrast, because the beneficial extrastriatal nonmotor effects of dopaminergic medications cannot be replaced by STN DBS, some NMSs can emerge after STN DBS due to reductions in medications.[20]

MOOD AND BEHAVIOR

Depression

Depression is common in PD patients, and clinically significant depressive symptoms occur in 40–

50% of patients with PD[21] and constitute one of the most important factors associated with QoL in PD. Evidence indicates that the pathophysiology of depression in PD involves dysfunction of dopaminergic and noradrenergic pathways in brain regions that include the limbic areas, whereas the role of serotoninergic dysfunction is relatively limited.[22,23] Reports about changes in depressive symptoms after STN DBS have provided conflicting results that include improvements, a lack of changes, and worsening.[11,24-26] As mentioned earlier, the direct effect of properly located STN DBS should be a mild elevation of mood.[27] However, the actual change in depressive symptoms is more likely to depend on other factors including changes in medications and the severity of preoperative depressive symptoms than on the electrical stimulation. As demonstrated in a recent systemic review, depressive symptoms typically improve in the initial months after STN DBS.[28] However, in our experience, worsening of depressive symptoms can occur in the initial months and these changes are primarily related to the reduction in dopaminergic medications and can be reversed with dopaminergic medications. Reports of long-term follow-ups after STN DBS show that depressive symptoms improve or remain unchanged compared with baseline.[25,26,29]

Suicide

Much concern was been raised about mortality by suicide after STN DBS, particularly in the first postoperative year, by one retrospective case series.[30] However, a subsequent randomized controlled study found no increase in the risks of suicidal ideation or behavior after STN DBS compared with that after medical treatment, although it has been argued that this study was underpowered due to the rarity of suicide events.[31] In the literature, the rates of suicide or suicidal ideation after STN DBS have been reported to be 0.5 to 1.5%.[24,30-33] Postoperative depression, being single, and a previous history of impulse control-related behaviors (ICRB) were independent risk factors in the aforementioned case series,[30] and it was recently suggested that unmet unrealistic expectations about surgical outcome may have some role.[20] Therefore, a multidisciplinary team approach that includes a psychiatrist is recommended from the stage of patient selection.

Apathy

Apathy refers to a state of diminished goal-directed speech, motor activity and emotions. The prevalence of apathy in PD varies from 17 to 70% depending on the sample population, diagnostic criteria, and evaluation tools.[34] Although apathy usually occurs in association with cognitive dysfunction and depression, some patients develop apathy in the absence of depression and dementia. Several studies have reported increases in apathy after STN DBS.[10,25,35] Evidence shows that apathy is associated with mesolimbic dopaminergic denervation, and reductions in dopaminergic medications seem to be an important cause of apathy after STN DBS.[36] Indeed, in one study, half of the patients developed apathy associated with anxiety and depression on average 4 months after STN DBS when dopaminergic medications were markedly and abruptly decreased soon after surgery.[10] Preoperative nonmotor fluctuations (NMFs) were predictors of postoperative apathy. The introduction of piribedil, a relatively selective D2/D3 dopaminergic agonist, reversed apathy in these patients.[37] Thus, in our opinion, when a patient develops apathy in the early postoperative period, which is more likely in cases that exhibit good motor improvement with STN DBS that allows for greater reductions in medication, the adjustments in medication should be considered. However, in the long term, apathy may develop as a natural progression of PD NMSs in parallel with dementia.

Mania and impulsivity

In the immediate postoperative period, a patient may develop euphoria, hyperactivity, and disinhibition. When mild and tolerable, these changes might be regarded as normal responses to improvements in motor symptoms and relief from the fear of undergoing surgery and perioperative complications. The patient and caregiver may enjoy these symptoms. The proposed mechanisms of these symptoms reduced activity about limbic STN electrical stimulation, a transient effect of microlesioning of the STN, and a persistent long-term effect of dopaminergic medications.[20,38,39] The latter two effects diminish over time, which explains the gradual spontaneous improvements in these symptoms. However, a small proportion of patients develop hypomania, mania, and pathologically impulsive behaviors in the immediate postoperative period[40-42] that ne-

cessitate interventions including the adjustment of the electrical stimulation parameters. It currently remains unknown which patients are at risk of developing these symptoms. The location of the electrode within the STN appears to have an important role. Previous reports have found that stimulation in the more ventromedial STN, which is a limbic-associative subterritory of the STN, produces hypomanic symptoms and associated changes in cortical activations.[13,39]

ICRBs in PD consist of dopamine dysregulation syndrome, punding, and impulse control disorders (i.e., hypersexuality, binge eating, pathologic gambling, and pathologic shopping). The prevalences of dopamine dysregulation syndrome and impulse control disorders are approximately 3−4% and 6−14%, respectively.[43] ICRBs in PD are related to the use of dopaminergic medications and improve with reductions in these medications. Thus, it is expected that the symptoms of ICRBs will improve or disappear after STN DBS, which usually allows for significant reductions of dopaminergic medications. However, the results of studies are inconsistent; some have reported improvement, whereas others have reported no significant change or even the development of new ICRBs after STN DBS.[44-47] Notably, a history of ICRBs is a risk factor for suicide after STN DBS,[30] which further supports the notion that the vulnerability of the limb-associative system and the sensitivity to changes in dopaminergic medications in a subset of patients with PD are associated with a multitude of mood and behavior symptoms.

Anxiety

Anxiety in PD consists of generalized anxiety, panic attacks, and social phobia. Anxiety usually coexists with depression and can coexist with motor fluctuations as a symptom of NMFs that responds to dopaminergic medications. Studies have shown improvements in anxiety after STN DBS.[11,28] As in depression, postoperative changes in dopaminergic medications appears to have an important role. In the long-term, anxiety appears to remain unchanged compared with baseline.[28,29]

COGNITION

Cognitive dysfunction is intrinsic to PD. Dementia affects up to 80% of patients in the late stage of the disease, and detailed evaluations have revealed frontal dysfunction even in the early stage of the disease. There have been concerns about the possibility of cognitive worsening after bilateral STN DBS because the placements of the permanent stimulating electrodes itself and the insertions of the recording electrodes during surgery cause bilateral cortical and subcortical damage. Furthermore, the effects of electrical stimulation on cognitive function are still not well understood. However, although there are some reports about cognitive deterioration after STN DBS,[48,49] it is generally accepted that bilateral STN DBS is safe from a cognitive perspective.[20,50] Although it is true that declines in frontal executive function, especially verbal fluency, have consistently been reported after bilateral STN DBS compared with after medical treatment, these differences are not clinically significant in most cases.[11,50-52] Many studies have shown no significant changes in global cognitive function and no increase in the incidence of dementia after bilateral STN DBS compared with those after medical treatment, and the observed cognitive worsening after bilateral STN DBS has been attributed to the natural course of the disease rather than the adverse effects of STN DBS.[20,50] In support of this conjecture, the risk factors for cognitive decline or the development of dementia after STN DBS are not different from those for the medical treatment of PD; i.e., old age, severe axial symptoms, the presence of hallucination, impaired frontal function and attention, and the presence of mild cognitive impairment at baseline.[48,49,53]

The presence of dementia is regarded as a contraindication for STN DBS without supportive data[54] likely due to the following reasons: 1) the patient him/herself cannot give informed consent and cannot participate in the decision-making process; 2) the surgical procedure or chronic electrical stimulation may accelerate cognitive decline; 3) PD patients with dementia are in a more advanced stage of the disease than those without dementia and thus are more likely to develop end-stage problems that are resistant to medical therapy and STN DBS and may exhibit shorter survival times;[55-57] 4) these patients are at greater risk due to living with implanted electrical hardware;[58] and 5) these patients may not be able to enjoy the benefits of STN DBS subjectively, and it is impossible to measure the extent to which the patients are satisfied with DBS.

SLEEP

Sleep-related problems in PD include insomnia, excessive daytime sleepiness, REM-sleep behavior disorder (RBD), and restless legs syndrome (RLS). In studies investigating the effect of STN DBS on sleep in PD, improvements in sleep quality, increases in total sleep time and uninterrupted sleep time, increases in stage 3–4 non-REM sleep, and decreases in wakefulness after sleep onset have been reported.[59-61] These beneficial effects have been attributed to improvements in the nighttime motor disability. Another study revealed reductions in daytime sleepiness, increases in normal REM sleep, decreases in REM sleep without atonia, improvements in total sleep scale scores, and decreases in wakefulness after sleep onset.[62] The authors suggested the role of reduced dopaminergic medications, a direct effect of STN DBS on sleep, and improvements in motor symptoms as possible mechanisms.

Despite the reported effects of STN DBS on REM sleep in PD, previous reports have shown that RBD is not affected by STN DBS,[59,60,63,64] although there is one case report that involved the development of RBD in the immediate postoperative period.[65] A recent study of the clinically diagnosed RBD revealed that the prevalence of clinical RBD increased after STN DBS because preoperative RBD persisted and *de novo* RBD developed after STN DBS.[66]

Reports on the effects of STN DBS on RLS are scarce and inconclusive. Some have reported improvements;[67,68] however, worsening or a lack of significant change have also been reported.[59,69]

AUTONOMIC SYMPTOMS

The BG exert an inhibitory effect on micturition probably via the D1-GABAergic direct pathway.[70] It has been reported that 64–87% of early untreated PD patients suffer from lower urinary tract symptoms (LUTS) and that 27–39% of PD patients have severe LUTS.[71-75] Studies have shown that STN DBS improves LUTS, especially detrusor hyperreflexia.[76,77] The mechanism seems to involve afferent bladder information processing in the cortex in addition to the BG.[78,79]

Gastrointestinal motility is decreased in PD. One study reported that STN DBS improves gastric emptying, whereas dopaminergic medication had no effect.[80] Improvements in constipation and swallowing have also been described.[61,81] However, the clinical significance of these findings is not yet clear.

Studies of the effects of STN DBS on sweating have produced conflicting results.[27,61,82,83] However, all of these studies are limited by small numbers of included subjects. Orthostatic hypotension improvements after STN DBS have been reported in one study.[84]

PAIN AND SENSORY SYMPTOMS

Pain is a common but under-recognized and under-treated problem in PD. Studies have found that 40–85% of patients with PD suffer from pain.[85-89] Pain in PD is negatively associated with QoL. Patients with PD experience many types of pain, and these pains can be classified in several manners. Generally, pain in PD is classified into two types: PD-related pain, which is caused or aggravated by PD; and PD-unrelated pain.[87] Both types of pain are known to respond to treatment targeting the motor symptoms of PD. Pain in PD can also be classified according to the presumed etiologies as follows: dystonic, musculoskeletal, central, and radicular/neuropathic.[90]

A beneficial effect of STN DBS on pain in PD has consistently been reported in many studies.[6,91,92] The mechanisms by which pain improves with STN DBS in PD are not fully understood. Presumably, several mutually nonexclusive mechanisms underlie the improvement in pain after STN DBS including the following: improvements in pain associated with increased muscle tone, alleviation of altered pain processing in the central nervous system, effects on mood, and increased mobility due to improved motor function after STN DBS.[93] Among these putative mechanism, the central pain-modulating effect of STN DBS is notable. One study reported that dystonic pain and central pain improve substantially with STN DBS, whereas radicular/neuropathic pain and musculoskeletal pain were less responsive to STN DBS,[91,94] suggesting that the reductions in pain with STN DBS involve a central mechanism. This notion is supported by reports of the lack of correlation between improvements in pain and improvements in motor symptoms.[6,95,96] In line with this, it has long been recognized that the BG are involved in central pain processing.[97] This pain processing mechanism

is altered in patients with PD; these patients exhibit decreases in pain thresholds with corresponding changes in functional neuroimaging, and these effects are reversed by STN DBS.[98-100]

Notably, although pain improves after STN DBS, new pains develop with the progression of the disease.[94,101] These pains are primarily of musculoskeletal origin and do not readily respond to the treatment of the motor symptoms of PD. Proper evaluation and management of musculoskeletal problems is needed for patients with STN DBS, given that musculoskeletal problems were the leading cause of functional impairments at 3 years after surgery in one report.[102]

NONMOTOR FLUCTUATIONS

In addition to motor fluctuations, many patients with advanced PD experience NMFs. The prevalence of NMFs in PD ranges from 15% to 100% across studies, and in some patients, these NMFs are more troublesome than the motor fluctuations.[103-105] The most commonly experienced NMFs are the following: psychiatric and cognitive symptoms including anxiety, panic attacks, euphoria, and slowness of thinking; autonomic symptoms including sweating, facial flushing, dyspnea, and urinary frequency; and sensory symptoms including akathisia and pain.[106] NMFs tend to fluctuate with motor symptoms, and their temporal relation with the medication schedule indicate that the fluctuations between hyperdopaminergic states and hypodopaminergic states are the core mechanism underlying NMFs. Accordingly, it is expected that STN DBS would improve NMFs, and it has been reported that many, if not all, of the symptoms of NMFs improve with STN DBS.[25,107]

CONCLUSION

Many NMSs in PD improve after STN DBS, although some NMSs remain unchanged or even worsen. The exact mechanisms of these responses are yet unknown; however, evidence indicates multiple mechanisms that include the direct effect of the stimulation of the STN, reductions in dopaminergic medications and the progression of PD itself. Because NMSs strongly influence the QoL of patients with PD, clinicians should be aware of these NMSs when deciding whether to perform surgery and should pay attention to changes in these symptoms after STN DBS to ensure the optimal adjustments of the electrical stimulation parameters and medications.

Conflicts of Interest

The authors have no financial conflicts of interest.

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