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Theoretical considerations of deep brain stimulation programming

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Deep brain stimulation (DBS) is an effective surgical option for medically intractable movement disorders. Adjustment of DBS parameters is the only modifiable factor that affects the clinical outcomes of DBS. It is very important to understand the basic functions of the basal ganglia and thalamus for successful DBS programming. The amplitude, frequency, and pulse width define the volume of tissue activated, the pattern of artificial action potentials, and the selectivity of activated neural elements, respectively. Based on this knowledge, it is possible to obtain the maximum clinical benefits and minimum side effects by appropriately adjusting the electrical stimulation to the target structure.

KEY WORDS: Deep brain stimulation, Electrophysiology, Basal ganglia, Movement disorders

INTRODUCTION

Deep brain stimulation (DBS) is an effective surgical option for medically intractable movement disorders, such as Parkinson's disease, dystonia, and tremor [1]. Proper diagnosis, timing of surgery and precise targeting are important factors for good clinical outcome of DBS. Unlike other surgery, clinical course of the DBS is not only determined by operation itself, but also by how electrical stimulations are performed after the operation [2-4]. In this review, DBS programming indicates adjusting parameters of electrical stimulation of DBS.

Adjustment of DBS parameter is only a modifiable factor affecting clinical outcome of DBS [2,4]. However, many clinicians have difficulties in adjusting DBS parameters. This is because DBS parameters are not adjusted in clinical term, but have to be controlled in electrical or electrophysiological language [5]. Furthermore, mechanism of action how DBS improves symptoms of movement disorders is yet to be elucidated [6,7]. Therefore, most clinicians manage their patients who underwent DBS by personal experiences or anecdotal evidences rather than by understanding mechanisms of actions [4].

It is important to understand the mechanism of DBS not only because of the desire to know, but also because of future development of neuromodulation. In the future, DBS is highly likely to be developed as a surgical treatment for several functional brain disorders, such as pain, obsessive compulsive disorder, memory impairment, addiction, and depression [7]. If more complex brain network modulation is attempted without clearing up the confusion about the effect of DBS, there is a possibility that it will only increase confusion about why DBS is effective for these diseases.

BASAL GANGLIA AND THALAMUS

In most cases, the stimulation targets of DBS are located in the basal ganglia and thalamus. Although there are some studies of new targets other than basal ganglia and thalamus, the evidence so far is insufficient to accept new targets as a promising treatment. Therefore, it is very important to find out the basic functions of the basal ganglia and thalamus, which are the principal targets of DBS.

To put it very simply, the basal ganglia regulates the thalamus with inhibitory fashions, while the thalamus facilitates the basal ganglia and the cerebral cortex [8]. This difference is due to the primary neurotransmitters used by the two organs. The output neurons of basal ganglia give off the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), and the driver neurons of thalamus uses the stimulatory neurotransmitter, glutamate [8] (Fig. 1).

Functional concept of basal ganglia includes the striatum and the subthalamic nucleus (STN), the globus pallidus externus (GPe), the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr) responsible for output, and the GPe that control the functions of the basal ganglia [9]. Neurosurgeons may be more familiar with the names caudate nucleus and putamen than the striatum. Functionally, however, the caudate nucleus and putamen play same role in the brain, and both belong to the striatum. In ad-

dition, a structure called the nucleus accumbens also belongs to the striatum [8]. Input structures of the basal ganglia are striatum and STN. In the basal ganglia, the striatum inhibits the other structures while the STN activates the other structures. Balance between the striatum (inhibitory) and the STN (stimulatory) decides actions of the basal ganglia. Even though GPi and SNr are separated from each other, both play the same role; the output structures of the basal ganglia [10]. The putamen is generally regarded to perform sensorimotor functions, so it is also referred to as sensorimotor striatum. The sensorimotor striatum is directly related to abnormal involuntary movement, such as Parkinson's disease, dystonia, and tremor, so that it would potentially be a target of neuromodulation. However, the sensorimotor striatum is too large to stimulation with a small array of electrode so that it was not used to be a stimulatory target of DBS. Unacceptably high current should be needed to modulate such a large target.

The striatum stores procedural memory, different form of memory distinct from episodic memory. Episodic memory is generated from neural network activities of the limbic circuit including the hippocampal complex, temporal lobe, and basal forebrain. In contrast, the striatum stores procedural memory by itself, independently from the limbic circuit. Therefore, people cannot consciously recognize whether they have had a procedural memory or not before they execute a process by themselves. This characteristic makes manifestation of procedural memory appear to be involuntary or automatic like special skills or habits of athletes, so called memory of the body.

This procedural memory is activated by input signals from cortex and thalamus, and is output through the GPi and SNr. Among them, output of sensorimotor procedural memory is in charge of the GPi, which is the one of major target of DBS. Because the STN, another input structure, is much smaller than the striatum, it have been used as another major target of DBS as the input structure of the basal ganglia. Thalamic recipient nuclei of the basal ganglia, i.e., ventral anterior (VA), ventral lateral (VL), and centromedian parafascicular (CM/PF), are the other major target of DBS as the recipient structures. An additional target called zona incerta is a region located in the passage output axons pass through, called ansa lenticularis and lenticular fasciculus, from the GPi and SNr to the thalamic recipients [11].

The VA/VL activates sensorimotor cortex, which forms the striato-pallido-thalamocortical circuit. The CM/PF facilitates the striatum, so that the striato-pallido-thalamostriatal circuit, an important feedback loop of basal ganglia, is made. When a trained motion is executed, specific forms of synchronized neural oscillation are found within these circuits. It is presumed that neurons connected to each other through synapses in these circuits sequentially acti-

Fig. 1. Basal ganglia network related to deep brain stimulation. Lines with arrowheads indicate glutamatergic fibers. The direction of the heads indicates the axonal terminal. Lines with a round head indicate projection fibers using gamma-aminobutyric acid (GABA) as their neurotransmitter. The subthalamic nucleus (STN) and striatum are the main input structures of the basal ganglia. The globus pallidus internus (GPi) is an output structure of the basal ganglia. The centromedian parafascicular (CM/PF) nucleus and ventral anterior ventral lateral (VA/VL) nucleus are thalamic structures that receive output signals from the basal ganglia and relay them to the cerebral cortex.

vate/suppress each other to execute specific movements, which in turn synchronized neural firing pattern are appeared. Importantly, specific forms of synchronized neural firing patterns were found in patients with Parkinson's disease and dystonia. Synchronized neuronal activity occurring in Parkinson's disease or dystonia is observed in different patterns. From this point of view, it can be understood that the type of abnormal movements expressed in Parkinson's disease or dystonia is a phenomenon caused by abnormal synchronization of these circuits.

MECHANISM OF ACTION OF DEEP BRAIN STIMULATION

The classic concept of mechanism of action of DBS is called "depolarization block theory," which indicates high frequency electrical stimulation at deep brain nucleus reversibly suppresses neurons around the target [12]. Actually, this classic theory had successfully explained how DBS is effective in such a several kinds of movement disorders [13]. However, a lot of clinical phenomena and experimental findings could not be interpreted using the classic theory [6]. In reality, the mechanism of action of DBS is much more complex. Shortly, a recently believed mechanism of DBS is in accordance of an increase of neural output from the target region, which overrides pathological synchronized neuronal firing by imposing a more regular signal on downstream nuclei [6,14].

Fundamentally, DBS is an extracellular electrical stimulation, so that electrophysiological properties of the extracellular stimulation to the neural tissue have to be considered [15-18]. When a single impulse of electrical stimulation is applied to a neuron, a single action potential impulse may be induced [17,18]. An important issue is whether high-frequency electrical stimulation evokes corresponding action potentials, or suppresses regional neural activities [6,15]. Both issues are seem to be mutually contradicting. High-frequency stimulation with the therapeutic range (1-4 V, 60-250 μ sec, and 60-180 Hz) found to evoke entrained action potentials corresponding to the stimulation, while simultaneously activating or suppressing neural activities near a target [6,13,19-22]. Many stimulus-related adverse effects, such as visual flashing, paresthesia, and tetanic muscle contraction, are caused by neural activation rather than suppression [23,24]. Experimental studies addressing signals from the neurons during DBS shown that the neural output from the stimulated region is increased [20-22]. Meanwhile, regional neural firing near a stimulatory electrode were found to be increased, decreased, or blocked at the same time [25].

High-frequency DBS at the STN in primates or rats has been shown to activate the GPi [6,20,21]. Increased glutamate level in the GPi during stimulation indicates activation of the STN by DBS

[6,16,26,27]. Stimulating GPi in the therapeutic range in human or primate subjects, GABAergic output from the GPi increased by DBS, which suppressed the VA/VL nuclei of the thalamus [6,9,15,22,28]. Moreover, STN DBS was shown to increase neuronal activity in the motor cortex, antidromically [15,29,30]. Facilitation of afferent neurons via the antidromic conduction of a frequency-locked induced signal is strongly indicative that DBS facilitates rather than suppress the targeted nucleus [7,29].

DBS potentially modulates brain networks, and brain network modulation is achieved by neural signal propagation via axonal conduction [7,15,26,31-33]. Many studies have revealed abnormal patterns of synchronized neural activity across the brain network in several diseases [15,30-32,34-36]. Increased beta oscillations in STN and GPi have been reported as a relevant factor for characteristic symptoms of Parkinsonism [30,31]. This oscillatory neural activity is desynchronized by DBS, and this desynchronization is associated with symptomatic improvements [30,31,35]. Patients with dystonia also have an abnormal pattern of oscillatory activity; i.e., low-frequency oscillation in STN and GPi. GPi DBS for dystonia patients has been demonstrated to desynchronize abnormal oscillatory activity with symptomatic improvement [30,31].

DBS mimics lesioning not by suppressing targeted neurons but by activating so that producing white noise signal in the networks of targeted neurons [32]. Spontaneous spikes of the target region disappeared and were replaced by spikes evoked by a locked to stimuli of DBS [32]. DBS would therefore lead to active axons and silent somas. Since extracellular microelectrode recordings are biased toward recording action potential from cell bodies rather than axons, this would result in the appearance of decreased activity within the stimulated structure though efferent axons are excited. From a wider perspective, signal locked to DBS stimuli propagation via the orthodromic and antidromic channels finally affect the brain network [6,7,22,29].

ROLE OF EACH PARAMETER IN DEEP BRAIN STIMULATION

After implantation of DBS into a subjected target, clinicians have to determine features of electrical stimulation. Classically modifiable parameters are the amplitude, frequency and pulse width [3]. In this section, how each parameter plays its role in modifying brain functions in DBS will be described.

Amplitude

The amplitude is the main determinant for volume of tissue activated (VTA) [37].

The amplitude may be indicative of the current or the voltage of

electricity. The relationship between current and voltage is Ohm's law, i.e., V (voltage) = I (current) $\times$ R (resistance). If the resistance is constant, the voltage is linearly correlated with the current. Empirically normal range of the resistance of the brain tissue is measured between 500 and 1,500 Ω , and the mean resistance is considered to be 1,000 Ω . Therefore, electrical stimulation of 1 V is corresponded to 1 mA in general. Increasing amplitude increases VTA [17,37-40]. In the therapeutic amplitude range, the VTA margin is estimated approximately 3 mm from the surface of the electrode [17,37]. If a clinician want to stimulate more volume of brain tissue, raising the amplitude is the most intuitive and reasonable choice. However, estimating VTA in DBS may be difficult because the target structure of DBS is very complicated in terms of anatomy and electrical conductivity [17,39,40].

Active STN contacts are located at the dorsolateral border of this nucleus, where VTA may influence not only the nucleus, but also neighboring fiber bundles [3,11,15,24,41,42]. The posterolateral portion of the ventral GPi is generally believed to be the best GPi DBS target, where lies near a major output fiber tract of the GPi, the ansa lenticularis [39,43,44]. These preferred locations, which were empirically chosen, also indicate that myelinated axons are the principal target of DBS [11,16,41,42]. The white matter is not considered an ideal location for a DBS because the electrical resistance of the white matter is 2 to 3 times higher than that of the gray matter and electronically anisotropic [3,17,38,40]. When an active contact is located in the white matter, the VTA should be distorted and shrunken according to the fiber directions.

Frequency

The frequency of DBS determines the waveform of the action potential in the brain networks [20,32].

There is an endogenous neural activities constituted of specific patterns of action potential created by neurons [45]. Neurons in a VTA of DBS may be forced to produce action potentials, which are considered to be artificial neural activities. DBS creates artificial neural activities independent of endogenous neural activities. The therapeutic effect of DBS is related to patterns of facilitation of the relaying neurons of the stimulated axon (orthodromic conduction) or the afferent neurons of the targeted nucleus (antidromic conduction) [32].

Below frequency of 50 Hz, endogenous neural activity is not completely suppressed. For this reason, the endogenous neural signals and the artificial action potentials produced by DBS are coexisted, and they travel through the network at the same time. It is presumed that this characteristic makes the low-frequency DBS below 50 Hz appear to enhance the pathological signal. Endogenous neural activities are completely suppressed and are substituted by

the artificial action potentials above frequencies of 50 Hz [20].

Between 50 Hz and 150 Hz, the numbers of artificial action potentials increases as the stimulation frequency increases. Meanwhile, the number of action potentials does not increase after 150 Hz, and it may decreases after 200 Hz. This induced neural activity presents the highest response at approximately 130 Hz [20,21,32,35,46,47]. Interestingly, a clinical benefit of the DBS according to change of the frequency follows features of generation of artificial action potentials [32]. When DBS is activated at the region of pathologic signal existed, this pathologic signal will be suppressed not because DBS suppresses regional neurons but because DBS generates artificial signals that totally replace pathologic signals. This is a phenomenon corresponding to the reversible suppression of stimulated area mimicking lesioning effect described by Dr. Benabid [20,27,32,35,48-50].

In summary, frequency is a parameter that determines what type of signal the stimulated neuron will transmit to the receiver. For this reason, even if stimulation is performed at a value higher than the optimal frequency, it does not provide additional clinical benefit to the patient. Therefore, it can be said that there is an optimal value of frequencies for each patient.

Pulse width

The pulse width determines selectivity of DBS. In other words, the pulse width is the critical determinant for selecting which element of a neural component is stimulated by electrical stimulation [15,17,51].

The pulse width refers to durations of an uninterrupted electrical stimulation [52]. Usually, it is decided between 30 and 200 μ sec. To explain roles of the pulse width in DBS, it has to introduce the concept of chronaxie. The chronaxie indicates the time of electrical stimulation with twice of the intensity of the minimum current (Rheobase) that needs to induce the activation potential of a neuron. More simply, a chronaxie indicates how much time is required for a neuron to be stimulated. Chronaxies of myelinated axon has been measured as 30 to 100 μ sec whereas that of the cell body has been measured as 1 to 10 msec [15,17,18].

Which neural element is the principal target of DBS among the cell body, axon and dendrite? At lower pulse widths, myelinated axons with larger diameters are selectively stimulated. Electrophysiological studies have shown that large diameter-myelinated axon is most easily excitable element in the neuron [6,7,17,18]. On the other hand, smaller diameter axons and cell bodies are also stimulated in accordance with increasing the pulse width. It results in reduction of the selectivity of electrical stimulation, so that various types of neural elements in VTA will be activated non-selectively. Data regarding chronaxies indicate that stimulus pulse width of

DBS within the therapeutic range (60–250 μ sec) stimulate myelinated axons much more easily than the cell body [15,17,18].

A large volume of clinical studies reported that a higher pulse width narrows the therapeutic windows of DBS, indicating range between amplitudes for clinical benefits and amplitude for side effects [23,37,52,53]. As described above, DBS with lower pulse width would selectively stimulate myelinated axons. The relationship between a higher pulse width and narrowed therapeutic windows could indicate that selective stimulation of myelinated axon is associated with better therapeutic windows. Therefore, the clinical effect of DBS was found to be related to the axonal activities rather than activities of the cell body at the target [16,21,22,29,32]. It has been reported that neural signals from axons induced by DBS showed regular and predictable patterns [22,25,26]. In contrast, microelectrode recording near the DBS electrode showed irregular activities of cell bodies [25]. The stimulus-locked artificial action potential of the axon, rather than activities of the cell body, is relevant component for the symptomatic benefit of DBS [29,32]. Shortly, the pulse width mainly used in clinical practice is a low pulse width, which may selectively stimulate the myelinated axon.

STRATEGY OF DEEP BRAIN STIMULATION PROGRAMMING

Based on the theoretical knowledge described so far, it is possible to establish a DBS programming strategy based on a deductive judgment rather than an empirical one [2,4,45]. However, before establishing such a deductive strategy, it is necessary to confirm the clinical effect of each electrode during the initial stimulation after DBS. The strategy of DBS programming can be divided as monopolar review, initial programming, and follow-up programming. Strategy of follow-up programming should be considered separately for each target.

Monopolar review and initial programming

The timing of the initiation of electrical stimulation may be different for each institution [4]. For the author's institution, the test stimulation is used to conduct 1 to 3 days after the operation, depending on the patient's postoperative clinical condition. In other institutions, electrical stimulation is started several weeks after the DBS operation when patients visit clinics. There is no consensus as to which method is correct. No matter when the stimulations are executed, the most institutions perform initial stimulation test to identify clinical responses. A regular DBS electrode consists of four contacts, and the patient's symptoms are checked while stimulating in monopolar mode from the deepest to the shallowest electrodes. This process is called "monopolar review", and it deter-

mines the therapeutic threshold and adverse effect threshold of each contact [2]. Usually, the pulse width and frequency in monopolar review were fixed at 60 μ sec and 130 Hz, respectively. The stimulation amplitudes increased sequentially from 0.5 to 4.0 V, or from 0.5 to 4.0 mA.

The goal of the initial programming of DBS is to find optimal stimulation parameters for maximal clinical benefit by increasing the stimulation amplitude slowly. When stimulation benefits could not be obtained without producing adverse effects, changing the frequency may be tried first. Patients may report which frequency is most comfortable to them. The pulse width can be changed after a preferred frequency is determined. Increasing pulse width reduces amplitude that needs to obtain best clinical benefit, but it also reduces therapeutic window of amplitude. Changes in pulse width can be regarded as a trade-off between clinical benefit and therapeutic window. After determining preferred frequency and pulse width, clinician may try to change figures of active contacts, such as numbers of active contact, and monopolar or bipolar mode.

The follow-up programming for subthalamic nucleus deep brain stimulation

The follow-up adjustment is performed in the outpatient clinic. Optimal stimulation parameters for each patient may depend on the patient's clinical condition over time. The order in which the parameters were adjusted depended on the patient's response to stimulation, with changes in the amplitude, frequency, and pulse width being made first, while changes in the active contact or stimulation mode (monopolar or bipolar) were reserved for adverse effects. The optimal stimulation benefits, an appropriate battery life (3–5 years) and the minimization of adverse effects should always be considered when determining follow-up stimulation parameters.

In the STN, somatosensory, associated, and limbic systems are segregated in a relatively small volume, and the surrounding brain tissues are very complicated, so even a small change in DBS parameters may make a large difference in symptoms [54]. Activation of adjacent structure may result in side effects such as spastic muscle contractions, gaze deviation, autonomic symptoms, gait impairment, and paresthesia [2]. These side effects can be overcome by reducing the amplitude or pulse width. Activation of unwanted circuits may result in unwanted change of brain functions such as dysarthria, depression and other psychiatric symptoms. Then clinicians have to try to change active contacts or mode of stimulation. The side effects accompanying the stimulation of the unwanted target can be adjusted by changing active contacts, but the side effects of the inevitably accompanying stimulation are often difficult to completely eliminate.

STN DBS is mainly used in patients with Parkinson's disease.

There are three circuits related to STN DBS, i.e., corticosubthalamic (Fig. 2; a), subthalamostriatal (Fig. 2; b), and subthalamopallidal (Fig. 2; c). All these three circuit use glutamate as their neurotransmitter, so that DBS of each circuit results in activation of cortex, striatum, and pallidum, respectively, with inhibition of abnormal synchronized signals [5]. Activation of corticosubthalamic circuit (Fig. 2; a) was reported as an effective route for reduce bradykinesia in an animal parkinsonian model [29]. Activation of subthalamostriatal circuit (Fig. 2; b) may activate striatum by glutamatergic output, so that reduces levodopa equivalent dose. However, it also aggravates levodopa-induced dyskinesia. In this situation, clinicians may reduce the dyskinesia by changing active

contact to modulate subthalamopallidal circuits (Fig. 2; c), which will increase pallidal output and reduce dyskinesia.

There are long-standing debates about best therapeutic target for Parkinson's disease, i.e., STN or GPi. Huge number of studies addressed this issue, and it can be said that both targets are effective for treatment of Parkinson's disease [55,56]. However, there are some noteworthy differences (Table 1). STN DBS is generally better for off-drug motor performance, and for reduction of levodopa equivalent dose [57-59]. GPi DBS is principally better for dyskinesia, and for lower psychiatric side effects. Many literatures addressed that early clinical effects were more significant in STN DBS [60-62]. However, long term follow-up studies showed equivocal outcome between two targets, or superior outcome in GPi DBS [63,64].

Fig. 2. Circuits related to subthalamic nucleus (STN) deep brain stimulation (DBS). STN DBS is indicated by the lightning symbol. Circuits affected by STN DBS are shown with dotted lines. The corticosubthalamic circuit (a) is activated antidromically. The subthalamostriatal (b) and subthalamopallidal (c) circuits send increased glutamatergic output signals to the recipient structures. GPi: globus pallidus internus, GABA: gamma-aminobutyric acid, CM/PF: centromedian parafascicular, VA/VL: ventral anterior ventral lateral.

The follow-up programming for globus pallidus internus deep brain stimulation

GPi DBS has been used to treat both Parkinson's disease and dystonia. Related brain circuits are striatopallidal, pallidothalamic, and subthalamopallidal circuits. Because the pallidothalamic circuit uses GABAergic neurotransmitter, GPi DBS results in increase of GABAergic output from the GPi, so that it inhibits activity of the VA/VL and CM/PF [5].

The primary therapeutic target of GPi DBS is hyperkinesia caused by abnormal basal ganglia activities. Increasing amplitude may be correlated to suppression of hyperkinesia. Excessive stimulation of GPi DBS results in over-activation of GABAergic output (Fig. 3; b) to recipient nucleus, so that it may renders impairments in sensorimotor function such as dysarthria, and gait disturbance [65]. In this situation, reductions in the amplitude or pulse width may ameliorate these side effects [66]. The most common side effect of GPi DBS is dysarthria. In spite of the occurrence of dysarthria, patients are often accompanied by improvement of motor symptoms. And if the amplitude is lowered to eliminate dysarthria, the improvement of motor symptoms also tends to decrease.

Table 1. Comparison of STN DBS vs. GPi DBS in Parkinson's disease

Component	Preference	Note
Short-term motor score	STN	STN is better in off-drug conditions.
Long-term motor score	GPi	GPi is better in on-drug conditions.
Levodopa dose	STN	Significant reduction of dose in the STN target.
Tremor	Equivalent	STN is better in early treatment, but both are the same in the long-term.
Gait	Equivalent	Both targets are good, with slightly better effects in GPi.
Dyskinesia	GPi	GPi is obviously a better target for dyskinesia.
Cognition	GPi	GPi is considered to be better.
Mood	GPi	GPi is considered to be better.
Swallowing	GPi	No swallowing problem has been reported in GPi.

STN: subthalamic nucleus, DBS: deep brain stimulation, GPi, globus pallidus internus.

Fig. 3. Circuits related to globus pallidus internus (GPi) deep brain stimulation (DBS). The circuits affected by GPi DBS are indicated by dotted lines. The output signal of the striatopallidal circuit (a) collides antidromically. The pallidothalamic circuit (b) increases GABAergic output to the recipient thalamic nuclei. The subthalamopallidal circuit (c) may be antidromically activated. STN: subthalamic nucleus, GABA: gamma-aminobutyric acid, CM/PF: centromedian parafascicular, VA/VL: ventral anterior ventral lateral.

When the increase of amplitude is not related to improvement of hyperkinesia, the frequency is needed to be changed. Higher frequencies between 100 and 150 Hz may be beneficial in most cases, but lower frequency can be also beneficial for some patients. It was reported that chronic electrical stimulation of the GPi at 60 Hz is at least as effective as stimulation at frequencies of 130 Hz or higher, and can enhance tolerability of GPi DBS [48,49].

In contrast to dystonia, Parkinson's disease is not a hyperkinetic disorder but a hypokinetic disorder. However, similar to the STN DBS, GPi DBS reduce parkinsonian motor symptoms, such as bradykinesia, akinesia, and tremor. Axial symptoms are also a challenging component like STN DBS. This similar effect of GPi DBS may be related to antidromic activation of the striatum via striatopallidal circuit (Fig. 3; a). The most significant difference between STN and GPi DBS on Parkinson's disease is effectiveness on levodopa-induced dyskinesia. GPi DBS reduce dyskinesia by directly increase of GABAergic outflow via pallidothalamic circuit (Fig. 3; b). Therefore, increasing amplitude does not deteriorate dyskinesia in GPi DBS while dyskinesia can be worsened by increasing amplitude in STN DBS.

CONCLUSION

Successful DBS programming can be achieved by understanding

of physiology of basal ganglia and property of electricity. The amplitude, frequency, and pulse width define VTA, pattern of artificial action potential, and selectivity of neural elements activated, respectively. Based on this knowledge, it is possible to obtain the maximum clinical benefits and minimum side effects by appropriately adjusting the electrical stimulation to the target structure.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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