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Deep brain stimulation: foundations and future trends

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1. ABSTRACT

Deep brain stimulation (DBS) has emerged as a revolutionary treatment option for essential tremor (ET), Parkinson's disease (PD), idiopathic dystonia, and severe obsessive-compulsive disorder (OCD). This article reviews the historical foundations of DBS including basal ganglia pathophysiological models, classic principles of electrical stimulation, technical components of the DBS system, treatment risks, and future directions for DBS. Chronic high frequency stimulation induces a number of functional changes from fast physiological to slower metabolic effects and ultimately leads to structural reorganization of

the brain, so-called neuroplasticity. Examples of each of these fast, slow, and long-term changes are given in the context of Parkinson's disease where these mechanisms have perhaps been the most intensely investigated. In particular, details of striatal dopamine release, expression of trophic factors, and a possible neuroprotective mechanism of DBS are highlighted. We close with a brief discussion of technical and clinical considerations for improvement. Deep brain stimulation will continue to offer a reversible and safe therapeutic option for a host of neurological conditions and remains one of the best windows into human brain physiology.

2. INTRODUCTION

Deep brain stimulation (DBS) is a paradigm for success in translational research. The modern beginning of DBS can be traced to the seminal work of Benabid, Pollak, and colleagues at the Joseph Fourier University in Grenoble in the 1980s (1), building on several decades of clinical work and biophysical discoveries (2). The US Food and Drug Administration (FDA) approved DBS treatment for essential tremor in 1997, DBS of the subthalamus for Parkinson's disease (PD) in 2002, DBS of the globus pallidus for PD and for dystonia in 2003, and DBS treatment for severe OCD in 2009, the latter two indications under humanitarian device exemptions. These indications are also approved in Europe under Conformité Européenne (CE) Mark with a recent additional approval for refractory epilepsy in 2010. DBS is being investigated for the treatment of chronic pain, Alzheimer's disease, and psychiatric disorders, such as treatment-resistant depression and Tourette syndrome. The clinical success of DBS has opened the door for other neurostimulation therapies, for example, transcranial magnetic stimulation for epilepsy and depression. It has also motivated intense analysis of the neural circuitry affected by neurological disorders such as Parkinson's disease.

3. BASAL GANGLIA PATHWAYS

3.1. Basal ganglia structures

Understanding how DBS can have such wide utility requires an understanding of the basal ganglia pathways in the brain. In fact, Parkinson's disease, essential tremor, and dystonia are often categorized as basal ganglia diseases due to this region's prominent role in their respective pathologies. The basal ganglia are neuronal nuclei located at the base of the cerebrum. They are thought to integrate and process sensorimotor input primarily from the cerebral cortex for action selection in motor and cognitive functions. The basal ganglia are comprised of four basic structures: the substantia nigra, the striatum, the globus pallidus (or simply the pallidum), and the subthalamic nucleus (Figure 1). All of these structures have mirror regions in both hemispheres of the brain.

Located in the mesencephalon, the substantia nigra is comprised of two divisions with very different functions: the pars compacta (SNc), which has primarily dopaminergic neurons, and the pars reticulata (SNr), which has primarily GABAergic neurons. The nigrostriatal neurons in the pars compacta can be further divided according to their expression of dopamine receptors. The dopaminergic SNc neurons of the direct pathway have excitatory D1 dopamine receptors that depolarize in response to dopamine whereas the neurons of the indirect pathway have inhibitory D2 dopamine receptors that hyperpolarize in response to dopamine (3). The GABAergic output neurons of the pars reticulata provide tonically active inhibitory output to the thalamus.

The striatum consists of the caudate nucleus and the putamen that are separated by a large tract of white matter called the internal capsule. Excitatory glutamatergic input from the cerebral cortex arrives at the striatum via corticostriatal spiny projection neurons (4), also known as medium spiny neurons, and GABA interneurons (5). The striatum is primarily comprised of GABAergic medium spiny neurons (MSN) that project to the globus pallidus and the substantia nigra pars reticulata (6). The major function of the striatum is to coordinate movement and action. It is also thought to be involved with other cognitive functions such as memory (7). The direct and indirect pathways of movement take separate routes from the striatum as will be discussed in the following section. The striatum is notably a site of the recently discovered phenomenon of adult neurogenesis (8).

The globus pallidus lies medial to the putamen in both hemispheres and receives inhibitory GABAergic input from the striatum through both the direct and indirect pathways. It is divided into the globus pallidus externus (GPe) which lies lateral to the globus pallidus internus (GPi). Both regions consist of tonically active GABAergic neurons. The GPe projects to the GPi and the subthalamic nucleus. The GPi receives inhibitory input from the GPe and excitatory input from the subthalamic nucleus while projecting inhibitory output to the thalamus. The GPi and the SNr receive the same inputs from the GPe and STN and have similar projections to the thalamus so they are often functionally represented together as they are in Figure 1, although in actuality they are located in separate regions of the basal ganglia.

The subthalamic nucleus (STN) lies deep to the thalamus and above the substantia nigra. The STN receives excitatory glutamatergic input from cortex and inhibitory GABAergic input from the GPe. The STN is thought to facilitate action selection and

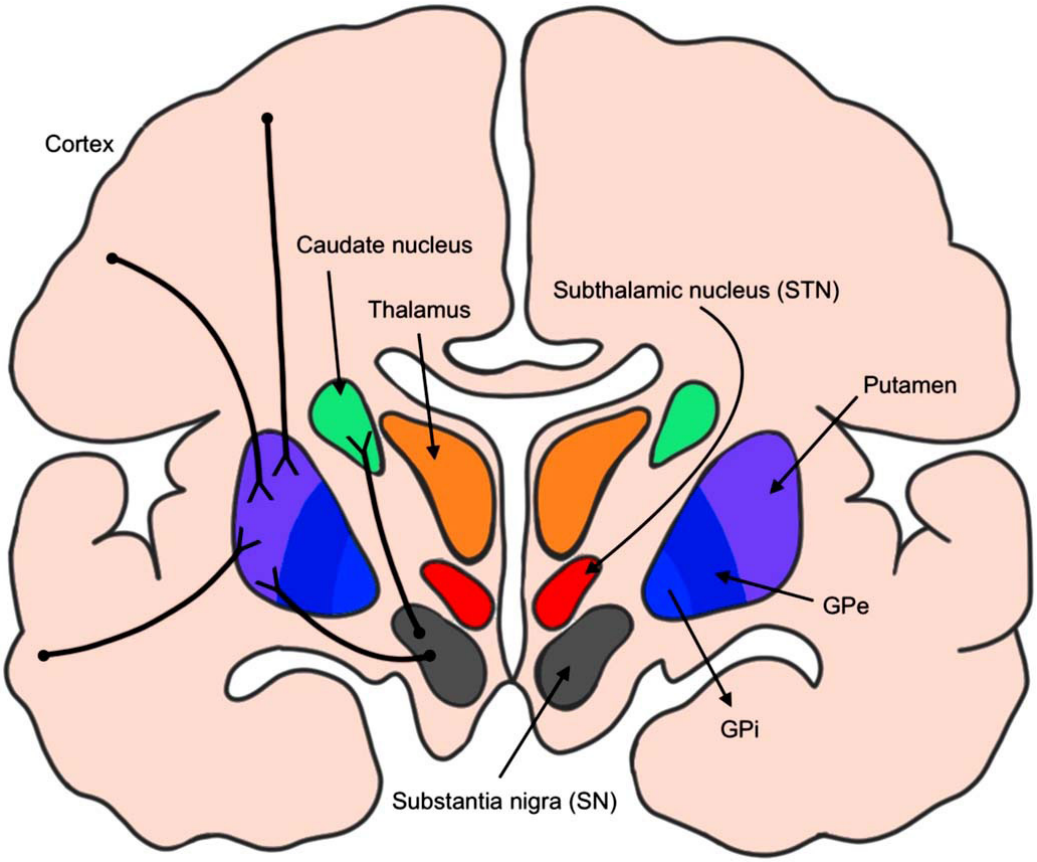

Figure 1. Basal ganglia structures. This illustration of a coronal cross-section of the brain depicts the major basal ganglia structures: (1) The substantia nigra (SN) and its innervation to the striatum. (2) The putamen and caudate nucleus which comprise the striatum. (3) The globus pallidus externus (GPe) and globus pallidus internus (GPi). (4) The subthalamic nucleus (STN). The thalamus and the cortex, which provides multiple inputs to the striatum are also labeled.

impulse control, which makes it a prime target for DBS in the treatment of PD and OCD (9). Unlike the inhibitory projections of the rest of the basal ganglia apart from the SNc, the STN has tonically excitatory glutamatergic projections going to the GPi and SNr. The inhibitory GPe and the excitatory STN both exhibit tonic synchronized activity which is postulated to constitute a feedback neural pacemaker (10).

While not directly considered part of the basal ganglia, the thalamus serves as the terminus of the basal ganglia pathways. Located inferior to the lateral ventricles in the diencephalon, the thalamus receives inhibitory GABAergic input from the GPi and SNr. The ventral anterior nucleus (VA) and the ventral lateral nucleus (VL) of the thalamus provide excitatory feedback to the cerebral cortex (11) with cerebellothalamic connections through the ventral intermediate nucleus (Vim) and pallidothalamic connections through ventral oral anterior (Voa) and ventral oral posterior (Vop) nuclei[1]. The specific regions of the basal ganglia, thalamus and cortex are connected together via distinct basal ganglia-thalamocortical loops, for example the skeletomotor circuit and the oculomotor circuit (13).

3.2. Direct and indirect pathways of movement

A balance between opposing direct and indirect pathways through the basal ganglia is thought to facilitate the coordination and execution of movement. Both pathways begin with input to the striatum from the cortex and differential input from the SNc (Figure 2a). The SNc provides excitatory input for striatal neurons expressing D1 dopamine receptors (DRD1). In the direct pathway, inhibitory GABAergic medium spiny neurons with high expression of DRD1 project directly to the GPi and SNr from the striatum (14). An increase in activity of the direct pathway causes increased inhibition of GPi inhibitory projections to the thalamus, thus resulting in disinhibition of thalamic excitatory input to the tonically excitatory activity of the cortex. This double inhibitory pathway operates such that increased firing of striatal neurons inhibits the output inhibitory neurons in the SNr and GPi from firing (15). Activation of the direct pathway is thus excitatory and acts as positive feedback for motor activity.

Whereas the direct pathway is excitatory for movement, the indirect pathway is inhibitory for movement. In contrast to its role in the direct

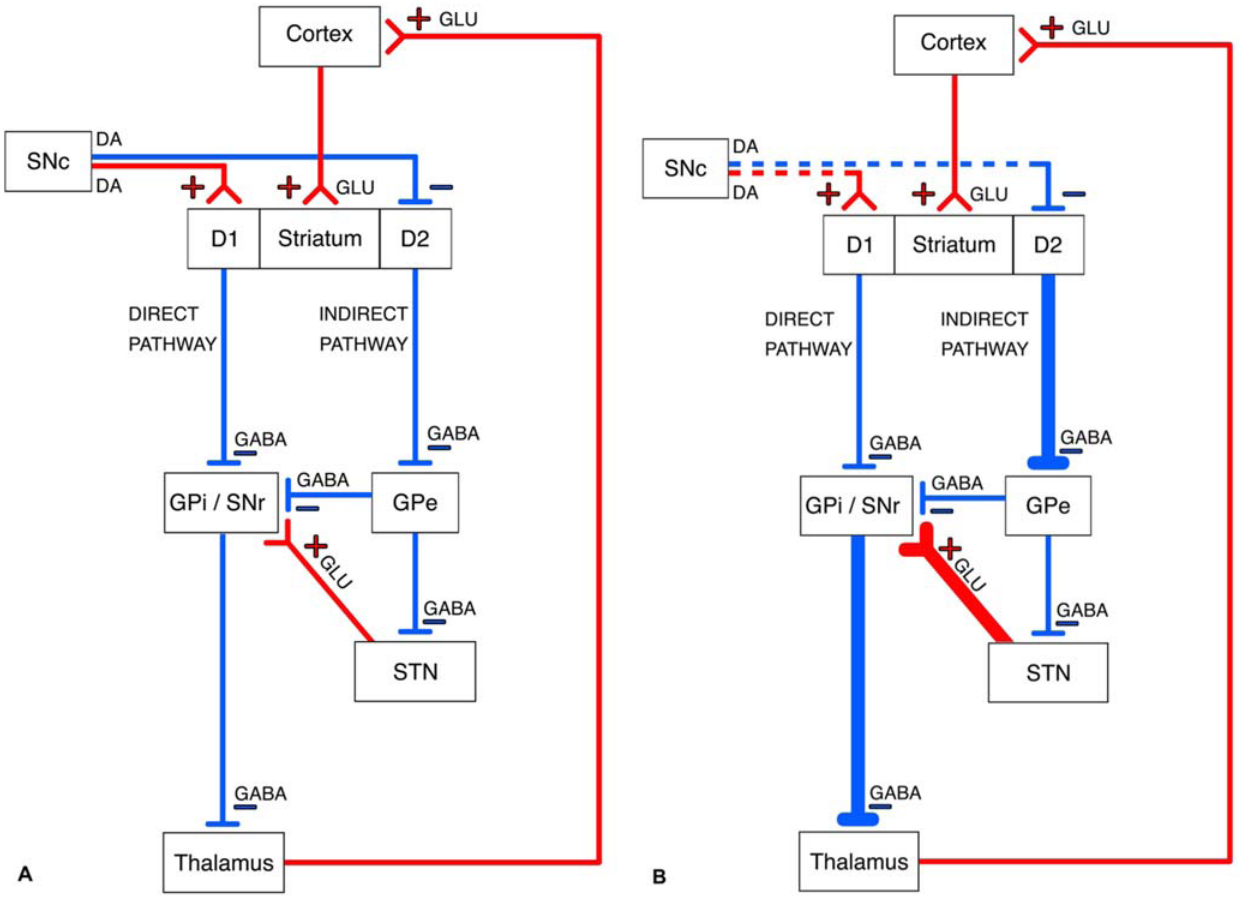

Figure 2. Basal ganglia pathways. A) The direct pathway normally receives excitatory input from the SNc dopaminergic neurons. The striatum also receives excitatory glutamatergic input from the cortex. DRD1-expressing GABAergic striatal neurons inhibit the GPi and SNr, which in turn inhibit the thalamus. Glutamatergic thalamic neurons tonically excite the cortex. The indirect pathway has inhibitory dopaminergic input from the SNc projecting to DRD2-expressing GABAergic striatal neurons that subsequently inhibit the GPe. The inhibitory GABAergic neurons of the GPE inhibit the GPi, SNr, and the STN. Glutamatergic STN neurons normally excite the GPi/SNr complex. B) In Parkinson's disease, the death of SNc neurons causes excessive indirect pathway activity. The GPe is overly inhibited and causes excessive disinhibition of excitatory STN influence on the GPi/SNr, which in turn overly inhibits thalamic input to the cortex.

pathway, the SNc provides inhibitory input to striatal medium spiny neurons expressing D2 dopamine receptors (DRD2). These GABAergic neurons exert an inhibitory effect on the GPe, which in turn has inhibitory efferents to the GPi, SNr, and the STN. An inhibition of striatal DRD2 dopamine decreases the tonically inhibitory effect of the striatal neurons on GPe, which in turn decreases inhibition of the GPi and the STN. Disinhibition of the STN increases excitatory signaling to the GPi and leads to increased inhibitory signaling from the GPi on the thalamus. The net effect is an inhibition of motor activity. Under normal conditions, such dampening of neural activity is thought to attenuate undesirable or unnecessary movement signals (16). The balance between the opposing direct and indirect pathways is thought to be maintained partly by fast-spiking GABAergic interneurons that target the striatal medium spiny neurons (17) (18).

4. CLINICAL APPLICATIONS

4.1. Essential tremor (ET)

The first approved clinical application of DBS was for the treatment of ET, a movement disorder where smooth oscillatory contractions of opposing muscles produce an involuntary action tremor. Thalamic DBS of the ventral intermediate nucleus (Vim) has been found to improve symptoms of essential tremor with long-term stability and durable reduction in tremor lasting for many years (19) (20). When compared to classic radiofrequency thalamotomy, DBS was found to be as effective with fewer surgical complications despite needing more operations for device-related technical complications (21). As a reversible therapy, DBS continues to find broad application in suppression of tremor over thalamotomy (22). A comparison of thalamotomy

and thalamic DBS for treating ET showed that DBS yielded superior tremor control with fewer adverse effects (23). Recently, however, the advent of phased array high intensity focused ultrasound (FUS) therapy has brought thalamic lesioning for ET back into vogue (24) (25) (26), and a comparison of FUS thalamotomy to thalamic DBS seems warranted.

4.2. The Dystonias

The success of DBS in treating ET prompted its evaluation for the treatment of primary dystonia, a group of related genetic conditions characterized by painful co-contraction of opposing muscles producing twisting or posturing of the face, neck, trunk or limbs. DBS treatment of intractable primary dystonia mainly targets the internal segment of the pallidum (GPi). However, the presence of focal demyelinating or neurodegenerative lesions in the pallidum that often accompanies the secondary dystonias (the so-called acquired forms) also suggested that DBS of the thalamus or STN may be equally effective (27). Sustained improvements in function and symptoms were seen up to 10 years after surgery with mild loss of therapeutic efficacy (28). An important outcome predictor in treating primary dystonia was disease duration with shorter durations correlating with better outcomes (29). Bilateral GPi DBS was found to decrease excessive motor cortex activity perhaps through increased thalamocortical inhibition (30). Studies on the effects of DBS on cognition and mood have indicated little to no deterioration (31).

4.3. Parkinson's disease (PD)

The primary etiology of Parkinson's disease is neuronal death in the substantia nigra although the cause of this degeneration is unclear (32). The death of neurons in pars compacta decreases the release of dopamine in the striatum and subsequently affects the entire basal ganglia system (33). Since dopamine normally excites the direct pathway and inhibits the indirect pathway, striatal dopamine deficiency results in abnormally high activity in the indirect pathway (Figure 2b). The striatum exerts less inhibition of the GPe, which in turn exerts less inhibition of the STN. The result is abnormally high tonic stimulation of the GPi by the STN. Ultimately, the loss of midbrain dopaminergic neurons disrupts the tonic inhibitory effect of striatal and pallidal neurons and results in decreased thalamic excitatory input to the cortex, which leads to the classic Parkinsonian triad of tremor, rigidity, and bradykinesia (34).

The cardinal motor manifestations of PD are currently managed with three main treatment modalities: pharmacological, surgical ablation and DBS (35). Pharmacological therapy aims to correct striatal dopamine deficiency through administration of L-dopa, dopamine agonists, or peripheral MAO-B inhibitors, and is always employed as first line treatment. However, prolonged oral dopamine replacement is eventually complicated by end-dose "wearing-off" effects (36) and levodopa induced dyskinesia (37). In addition to treating the primary motor manifestations of PD, DBS therapy also significantly ameliorates both of these drug induced side effects (38). In fact, the cardinal motor symptoms of PD are not currently the primary surgical indication for DBS, but rather the appearance of debilitating drug complications (39). A good pre-operative response to L-dopa has been shown to be the best predictor of optimal DBS outcomes (40).

4.4. Obsessive-compulsive disorder (OCD)

In 2009, the FDA approved DBS to treat patients with severe obsessive-compulsive disorder (OCD) unresponsive to specialized cognitive behavioral therapy and serotonin reuptake inhibitors (e.g., clomipramine). DBS of the anterior limb of the internal capsule significantly improves OCD symptoms with only minor transient adverse effects (41) (42). Over time, the preferred target for DBS has gradually shifted inferiomedially towards the nucleus accumbens in the ventral striatum (43). While the optimal target for OCD is still being refined, approximately 60% of patients undergoing DBS have responded with significant, sustained reductions in both obsessions and compulsive behavior (44). The success of DBS therapy for OCD has broadened the potential range of applications to other related psychiatric disorders such as Tourette syndrome (45).

4.5. Epilepsy

DBS has shown promise as a treatment for complex partial epilepsy inadequately controlled by anti-epileptic medications and is approved for use in Europe but not yet in the US. DBS in the medial temporal lobe resulted in a 50% reduction of interictal spikes and long-term reduction in seizure frequency (46) (47). DBS of the anterior nucleus of the thalamus or posteromedial hypothalamus also saw statistically significant improvement in seizure severity (48) (49). Typical reductions of seizure frequency can be up to 40% with maximal effect being observed 1–2 years after implantation (50) (51).

DBS treatment for epilepsy disrupts or modulates the classical memory circuit of Papez from the hippocampus to the thalamus. The anti-epileptic effect of DBS may be mediated through a long-term increase in expression of adenosine, a neuromodulator, in the hippocampus (52). However, reductions in seizures have also been observed in patients who have undergone implantation of DBS electrodes into the anterior thalamus but not yet begun stimulation (53). This observation suggests the implantation procedure itself creates a "microlesion"

that at least partially accounts for some of the initial antiepileptic effect of DBS.

4.6. Chronic pain

Although not yet approved by the FDA, evidence for the use of DBS to treat chronic pain has been accumulating in the literature for many years (54). The periventricular gray region and somatosensory the thalamus are the most frequent targets for treating nociceptive pain and neuropathic pain respectively (55). A study of patients with chronic neuropathic pain demonstrated that DBS could have long-term efficacy for certain etiologies such as amputation (56) and stroke (57). DBS for chronic pain awaits definitive sham-controlled trials to clearly document its efficacy.

5. MECHANISMS OF DBS

5.1. Fast physiological effects

One of the difficulties of investigating the mechanism of DBS lies in the complexity of applying electric current to often antagonistic and interconnected neural networks, i.e., the old and vexing problem of fibers of passage. While there is currently no unified understanding for the mechanisms of action in DBS, there is a growing body of evidence derived from experimental observations and system modeling. From a biophysical perspective, the injection of electric current induces neuronal depolarization and generates action potentials by opening voltage-gated sodium channels (58). However, there is an important distinction between local depolarizing mechanisms at the level of the neuron and the observed global effect on neural activity at the behavioral level. Experiments to identify the primary targets of DBS concluded that axons rather than cell bodies were most likely being affected by electrical stimulation (59) (60). Multicompartment cable modeling, which treats signal transmission as a relay across discrete neuron units, applied to thalamocortical relay neurons revealed a reduction of activity in the soma but an increase in axonal firing output, which was found to be synchronized with the stimuli (61). Recognizing that high-frequency stimulation (HFS) tends to preferentially depolarize axons, rather than the neuronal soma, is an important observation because it explains why DBS may preferentially stimulate target neurons at a particular location. If afferent axons are indeed the principal target of neurostimulation, predicting the effects of HFS is simplified by modeling basal ganglia pathways and their excitatory or inhibitory influences.

If the stimulated afferent axons are inhibitory, then their activation will suppress neural activity of target neurons. (62). A number of studies have shown that HFS has an inhibitory effect. Indeed, initial observations of DBS likened its effects to a reversible lesion (63). HFS applied to the GPi and SNr was found to inhibit neural firing with direct proportionality to increasing amplitude and frequency (64). These findings suggested that HFS was activating GABAergic afferents to these locations and thus depressing GPi/SNr activity. STN-DBS showed a modulatory effect with neural firing patterns in the thalamus becoming more periodic and regular (65). This study also suggests stimulation of GABAergic afferent GPe connections to the STN, resulting in decreased stimulation of the GPi. Another study of GPi inhibition by HFS suggested preferential excitation of afferent GABAergic striatal and GPe neurons to be suppressing GPi activity (66). STN-DBS has been observed to inhibit activity in the SNr and activate GPe neurons during and after stimulus, which would highly suggest that stimulation of afferent STN neurons is taking place (67). High frequency pallidal stimulation produced a decrease in firing frequency of GPi neurons correlating with an improvement in parkinsonian motor symptoms (68). This result could be explained by HFS excitation of upstream GABAergic DRD1 striatal neurons and GABAergic GPe neurons. The confirmation of GABA receptors mediating HFS-induced inhibition supports the theory that HFS is stimulating afferent GABAergic neurons (69). HFS of the STN was also observed to reduce firing activity of STN neurons and lead to a decrease in the tonically inhibitory activity of SNr neurons, thereby inducing disinhibition of motor thalamic nuclei and ultimately giving rise to an increase in motor cortical activity (70). The mechanism by which inhibition occurs is still unclear. While straightforward excitation of inhibitory neurons is possible, other studies suggest that HFS is capable of more direct inhibition by blocking axonal conduction (71).

A majority of studies found evidence for inhibitory effects of DBS, but other studies clearly observed increases in firing activity. For example, neuronal activity in the GPi was observed to increase after DBS in the STN (72). Similarly, HFS in the GPi was observed to reduce discharge frequency of thalamic neurons during stimulation, suggesting that the efferent GABAergic GPi neurons were being excited (73). Both of these results might indicate that HFS is capable of exciting efferent neurons at the site of stimulation as well as afferent neurons. A study of STN-HFS found concomitant depolarizing inward current in 58% of recorded whole-cell neurons and hyperpolarizing outward current in the remaining 42%, suggesting that both depolarization and hyperpolarization can be induced by HSF (74). Another hypothesis for the mechanism of DBS is that HFS overly stimulates the efferent neurons at a site such that they are “jammed” and unable to function normally (75). The differing observations of excitatory and inhibitory effects from DBS highlight the complexity of intersecting and sometimes antagonistic basal ganglia pathways being affected by neurostimulation (Figure 3).

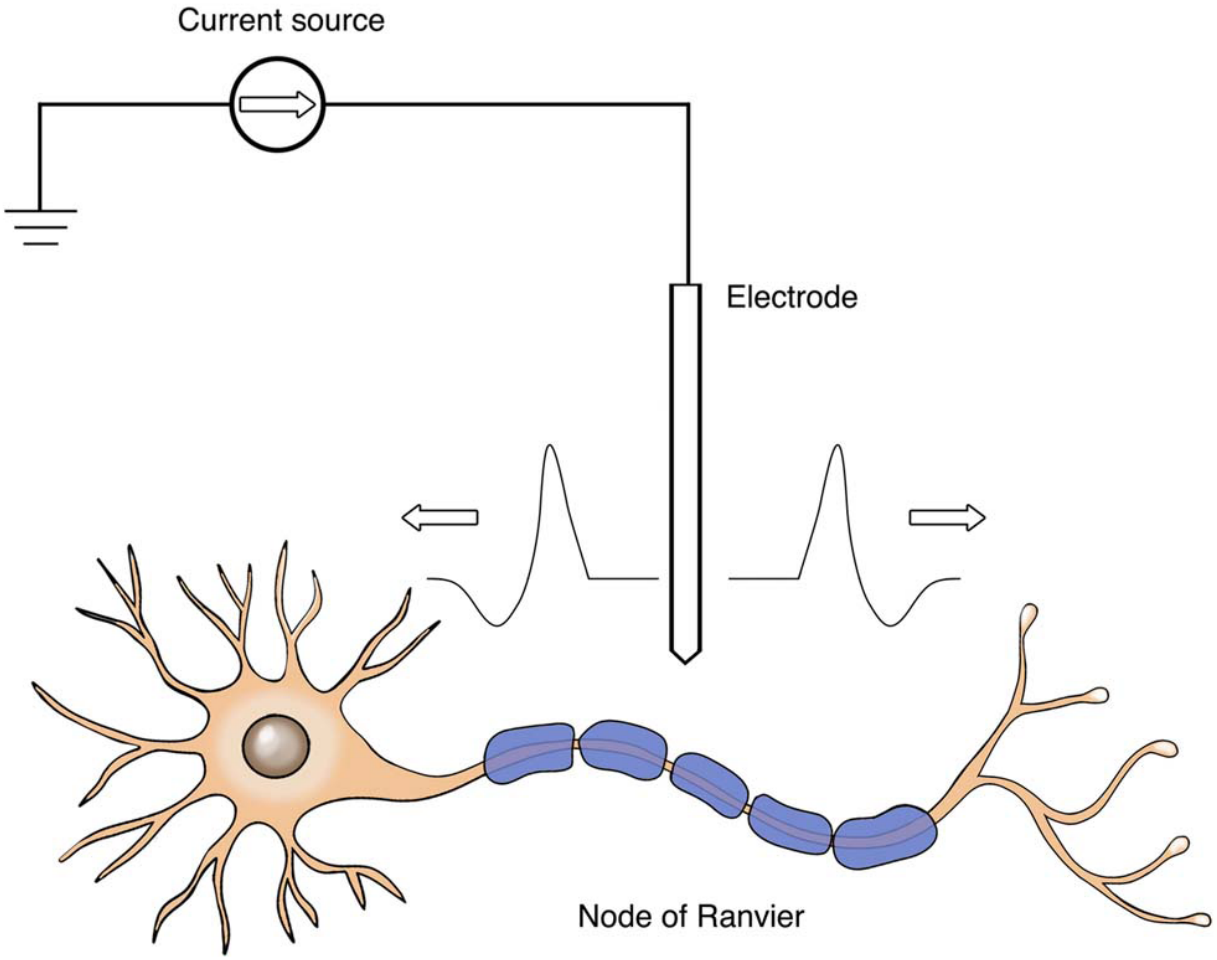

Figure 3. Current-controlled DBS electrode induces depolarization of axons. Recordings of neural activity in response to high-frequency stimulation have shown preferential activation of axons over neuronal cell bodies. This effect may be due to a greater likelihood of an electrode making contact with axons, or alternatively, to differences in biophysical properties of axons and somata. Depolarization may be induced orthodromically or antidromically as depicted.

5.2. Slow metabolic effects

In addition to rapid modulation of neural activity, a number of slow physiologic and metabolic changes caused by DBS have been reported. HFS of the STN was observed to correlate with an increase in DRD1 and a large decrease in DRD2 and DRD3 (76). Given the link between decreased DRD1 levels and motor deficits (77), this differential change in expression of D1R would be predicted to facilitate movement. DBS of the STN was also found to increase extracellular glutamate levels in the globus pallidus and GABA levels in the SNr (78), which suggests increased neuronal activity in those respective regions (79). PET scans of blood flow in patients undergoing DBS of the STN revealed reduced blood flow to the cortex and increased blood flow to the STN, GP, and thalamus (80). The observed increase in neurotransmitter levels and increased blood flow in the STN during DBS suggests that the HFS is exciting STN neuronal activity (81), rather than reducing it as previously believed (82).

5.3. A long-term neuroprotective effect?

DBS has also been shown to increase the expression of a number of neurotrophic molecules including BDNF and GDNF (83) (84), potent survival factors for midbrain dopaminergic neurons (85). Indeed in several animal models of PD, HFS of the STN has been shown to protect neurons in the substantia nigra from cell death (86) (87), but there is, as yet, still no compelling evidence for a similar neuroprotective effect of DBS in humans (88).

To summarize, the current prevailing theory for the mechanism of DBS is that it induces changes in the firing pattern of basal ganglia structures and pathways. One leading theory to reconcile conflicting excitatory and inhibitory effects observed in many studies is that DBS preferentially excites afferent axons, which can then excite or inhibit depending on the basal ganglia pathway that is being stimulated. Ultimately, DBS serves to disrupt or counteract pathological oscillatory patterns leading to improved behavioral

performance. These same changes in firing patterns induced by DBS neuromodulation may also activate down-stream differential gene expression of receptors and neurotrophic factors capable of protecting neurons from programmed cell death. Clinical evidence for a neuroprotective effect in humans will likely require meticulous stereological examination of postmortem neuropathological specimens collected from patients who have undergone DBS.

6. DBS SYSTEMS

6.1. Pulse generators

Stereotactic surgical implantation can be performed either under general anesthesia with MRI guidance (89) or under local anesthesia with microelectrode recordings. The DBS system consists of surgically implanted electrodes connected to a pulse generator that is usually placed below the clavicle like a pacemaker. The purpose of a pulse generator is to induce or inject current into tissue. The electric field generated by the flow of charge acts on membrane ion channels of nearby axons to depolarize the neuron. DBS initially used voltage-controlled pulse generators. The amount of current induced by voltage sources is determined by the electric potential difference and the total impedance across the closed electrical circuit formed by the DBS system and the patient, resulting in current that is inherently variable (90). Current-controlled pulse generators deliver a constant current independent of the system's impedance. Experimental studies comparing the two types of pulse generators confirmed that current-controlled systems have lower voltage fluctuations than voltage-controlled systems (91).

6.2. Stimulus waveforms – the Lilly pulse

The waveform of the stimulus has important ramifications. Higher frequencies of stimulus are generally observed to have a more pronounced inhibitory effect than lower frequencies. For example, low frequency stimulation of the GPi and SNr produced 25 msec inhibition compared to the 50–500 msec inhibition produced by high frequency stimulation (92). The amplitude of stimulus must be large enough to generate an effect, but small enough to prevent unwanted side effects from off-target spread of current (93). Higher amplitudes may result in a greater area of effect, but overly large current spill may cause unwanted stimulation of neurons or fibers of passage outside the desired target.

The stimulus waveform has important effects on neural tissue. Prolonged direct current has been found to cause tissue damage due to excess transfer of charge (94). If unchecked, the accumulation of residual charge can rise quickly enough to cause electrolysis of water and tissue damage. Monophasic waveforms in general have a greater risk of such damage. Consequently, all DBS systems employ a biphasic, charge-balanced waveform of opposite polarities that results in zero net charge transfer, first describe by John Lilly in 1955 (95). A potential problem with the Lilly wave is that the second pulse of opposite polarity may cancel the physiological effects of the first pulse. Consequently, biphasic waveforms may require higher amplitudes than monophasic waveforms.

There are many different variations of the biphasic waveform. The delay between the two phases can be lengthened to prevent reversal of effect although this provides more time for charge to dissipate into the tissue. The amplitudes and durations of the two phases can also be adjusted. An asymmetric biphasic waveform with a long, low amplitude cathodic phase and a short, high amplitude anodic phase was found to activate selectively the neurons closest to the electrode compared to nerve fibers (96).

Since the induced electric potential depends on the deposited charge, the total charge conveyed in a current pulse is an important factor in stimulating neurons. A short pulse width requires higher amplitudes to deliver the same amount of charge as a longer pulse width. Conversely, a broader pulse width can cause a neuron to reach threshold with a lower amplitude. Shorter pulse widths are generally preferred in order to mitigate side effects from the injection of charge into off target-tissue. Longer pulse widths tend to preferentially stimulate neuronal cell bodies (97).

6.3. Electrochemistry

The electrochemical activity at the interface between the electrode and the extracellular environment can be categorized into Faradaic and non-Faradaic transfers of charge with the difference being electronic current versus ionic current. Faradaic charge transfer involves the direct injection of charge from the electrode into the extracellular environment. A redox reaction takes place in which reduction occurs at the cathode and oxidation occurs at the anode. Since electrons are actually entering the extracellular environment from the electrode, the chemical products formed cannot be recovered simply by reversing voltage or current flow. For this reason, Faradaic reactions are irreversible. Some examples of Faradaic reactions include the electrolysis of water to release hydrogen gas and the reduction of copper ions in solution which deposits copper metal on the electrode. Redox reactions around the electrode tend to lower the extracellular pH owing to the production of H^+ ions. They also represent an impedance to the flow of charge and are thus represented as such in the equivalent circuit model (Figure 4).

Non-Faradaic charge transfer, also called capacitive charge transfer, is a redistribution of charge

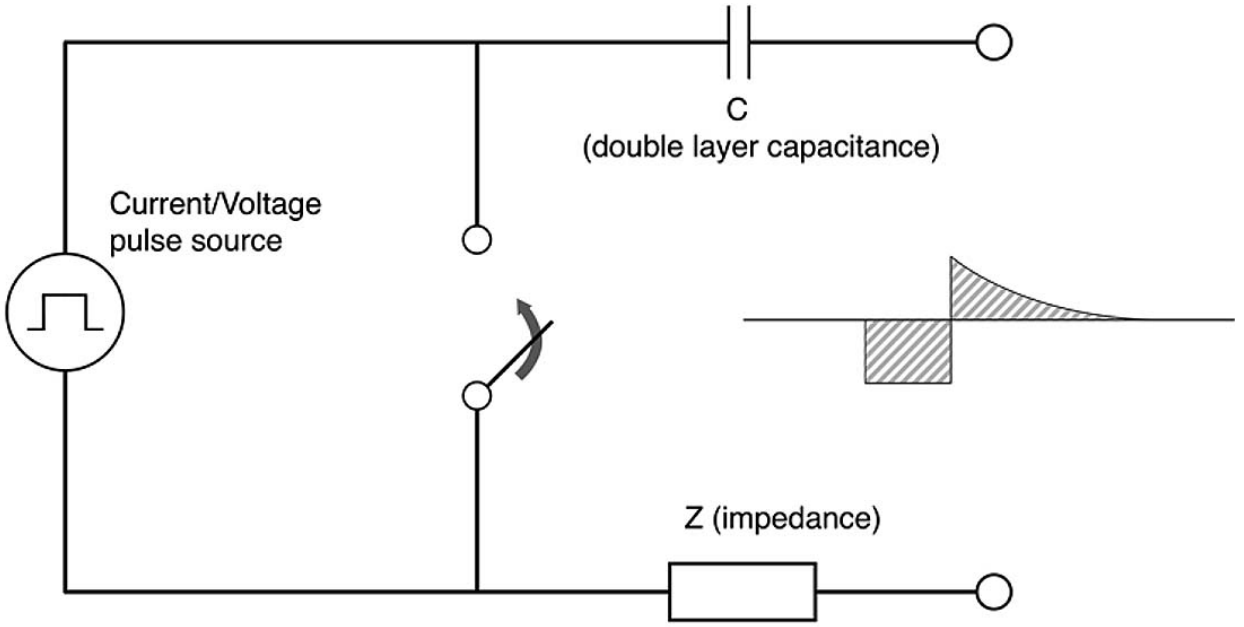

Figure 4. Simple equivalent circuit model of a DBS system. DBS systems can either be voltage-controlled in which an electric potential difference is created to induce current or current-controlled in which a current source outputs a steady level of electric current into the tissue. The double layers of charge formed at the electrode interface are represented as a capacitor. The impedance of the system is determined by the composition of neural tissue at the electrode. Glial scarring from insertion of electrodes will tend increase the impedance. The stimulus generated in DBS is a modified Lilly-pulse, a charge-balanced, biphasic wave with a fast reversal as depicted here. This waveform tends to minimize the possibility of tissue damage from excess accumulation of charge.

without electron transfer from the electrode. The charge in the electrode induces formation of a plane of opposing charge in the extracellular fluid called the inner Helmholtz layer (Figure 5). Another plane of opposing charge called the outer Helmholtz layer then forms against the first plane. These two planes can be conceptualized as the double layers of a thin plate capacitor. The voltage applied to these two planes determines their charge distribution, but there is *no charge flowing* between the plates. This separation of charge induces an electric potential field and thus a capacitance. In contrast to irreversible Faradaic reactions, non-Faradaic reactions are generally reversible since charge is not actually being transferred.

6.4. Electrodes

The configuration of DBS electrodes is an important factor in determining the amount and rate of charge that can be transferred to neural tissue. Electrodes can be used in a monopolar configuration of a cathode alone or a bipolar configuration comprised of a cathode and anode. A monopolar configuration produces larger radial current spread with less current density whereas a bipolar configuration creates a narrower field between the electrodes with greater current density (98). If a measurement is being recorded, then a third reference electrode may be used, although systems are progressing toward stimulation and recording from the same electrode (Figure 6). Greater surface area at the electrode interface allows for greater charge delivery by increasing the capacitance while decreasing the effective resistance of the electrode. Greater current amplitudes can thus be achieved at lower voltages, thereby reducing the risk of tissue damage. The non-linear impedance at the electrode interface is commonly represented as a resistor-capacitor (RC) circuit in which Faradaic charge transfer is represented by a resistor and non-Faradaic charge transfer is represented by a capacitor (Figure 4). The stimulating electrode is usually modeled as a current source. Patient outcomes with bipolar DBS systems have shown fewer adverse effects and better tremor control, leading to an increasing preference for bipolar configurations (99) (100).

7. RISKS AND LIMITATIONS OF DBS

7.1. Hardware

Hardware infection is the most commonly reported complication of DBS despite standard administration of perioperative antibiotics (101). One long-term study of 79 patients who received 124 DBS implants saw an 18.5.% complication rate such as migration, lead fractures, and infections (102). The surgical implantation of the DBS systems carries an expected but infrequent risks of hemorrhage that may lead to stroke, paralysis or cognitive impairment (103). In one study of 86 DBS patients, 6% experienced some persistent neurological sequelae but with no fatalities or severe disabilities (104).

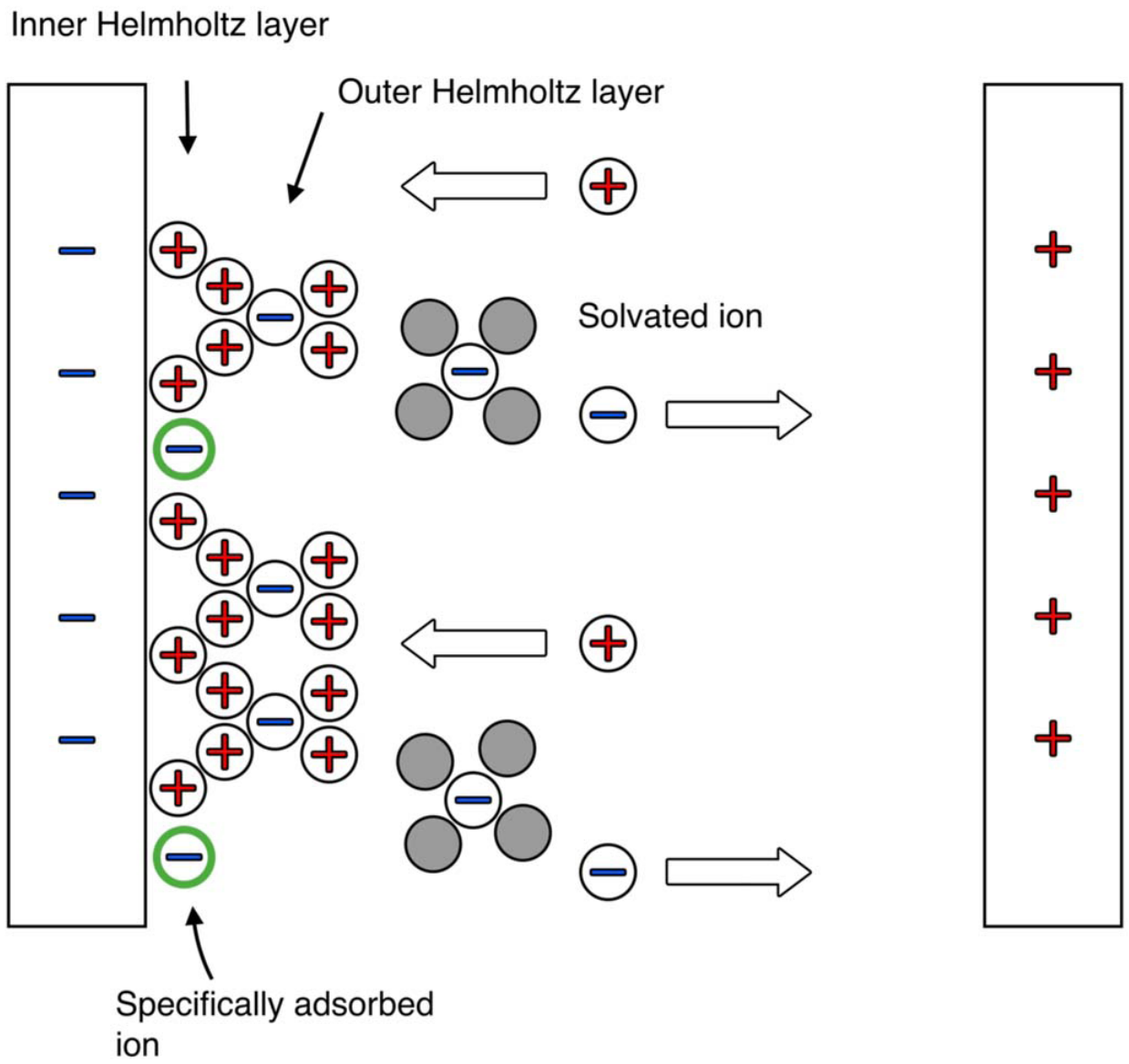

Figure 5. Double layer of charge at the electrode interface. The first layer of charge, the inner Helmholtz layer, is attracted to the oppositely charged electrode. A second layer of charge, the outer Helmholtz layer, then forms on top of the first layer of charge to create the equivalent of a double layer capacitor. The layers of charge are only depicted at one electrode whereas in actuality both electrodes in a bipolar configuration will have formation of capacitance. Other ions in solution may be solvated or adsorbed onto the metal electrode.

An important limitation of DBS is the eventual need for surgical exchange of the depleted IPG. At present, batteries last 1–3 years in treatment of dystonia (29) and 3–5 years in treatment of PD (105). The difference in lifespan can be attributed to the higher charge density of the pulse waveform for dystonia correlating with shorter battery life. Over the course of a battery's lifespan, the output voltage can decrease significantly. For example, Medtronic Soletra® batteries decreased from 3.7.V to 2.5. V in voltage-controlled DBS systems (106). Such a significant decline in output can affect the efficacy of DBS treatment toward the battery's end of life and warrants attention during clinical visits.

7.2. Neural tissue damage

Given the nature of chronic implantation of electrodes in the brain, there is a risk of tissue damage. Inflammatory and astrocytic responses to neural damage can result in a glial scar which tends to increase the electrode impedance (107). Certain electrode trajectories intersecting the caudate nucleus have been correlated with cognitive declines (108)

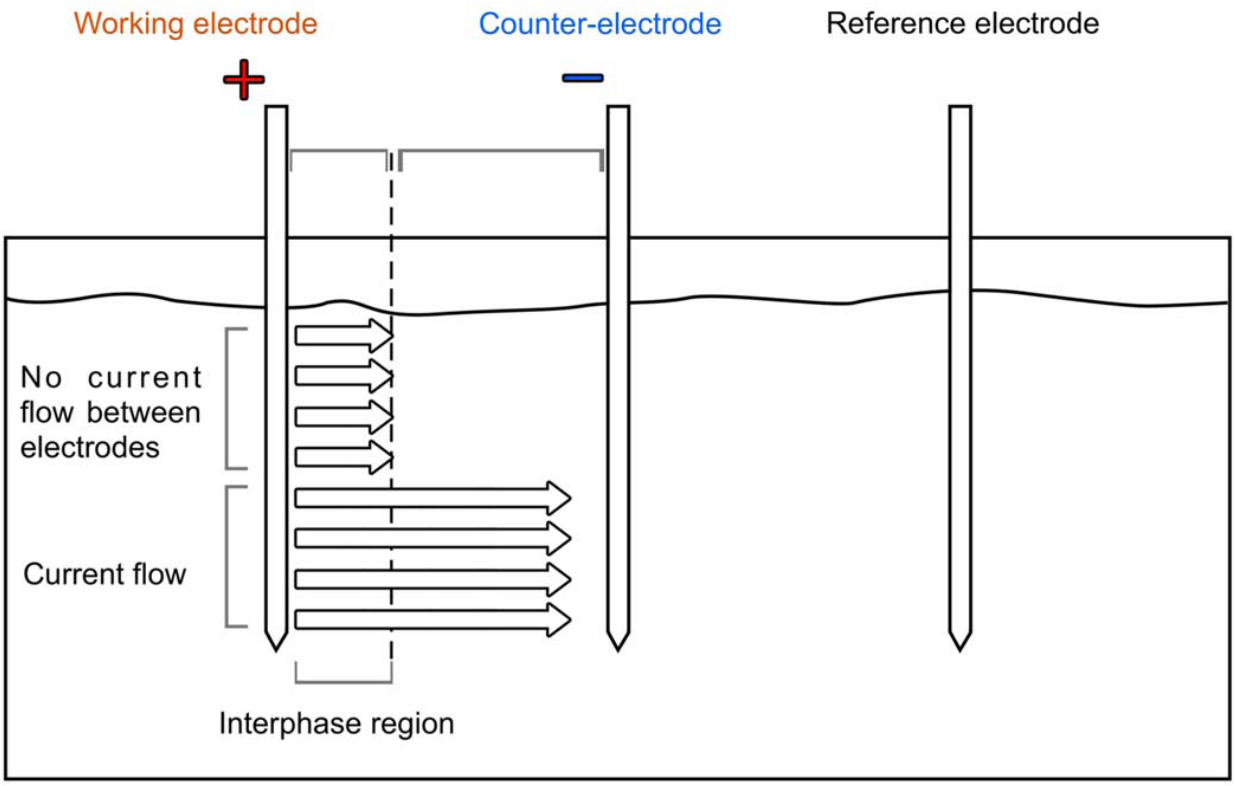

Figure 6. Monopolar/Bipolar electrode configuration. A monopolar configuration will only have one electrode with current dissipating in the vicinity of that electrode with no current flowing into another electrode. Electric current density is more diffuse and radially symmetric in monopolar configurations. In bipolar configurations, a closed-loop circuit has current flowing from the working electrode to the counterelectrode, thereby allowing a narrower volume of tissue affected. Current steering uses electrodes with multiple directional surfaces to control deliver of current more specifically.

in verbal fluency (109). However, there have been numerous studies before and after FDA approval that have not found tissue damage in periods up to 70 months (110) (111). An electron microscopy study of chronic DBS electrodes in dystonic patients did reveal the presence of macrophages and giant cells which may be a response to the polymer coat on the electrodes (112). To prevent damage, accurate placement of electrodes using patient feedback and/or MRI guidance is crucial. As with any implanted device, it is critical to avoid treatments involving electricity such diathermy, which was found to cause severe neural damage through the electrodes (113).

8. FUTURE TRENDS

8.1. Electrode improvements

The type of electrode currently used in DBS systems is highly standardized. Reducing electrode size has been a persistent goal to achieve greater specificity and precision of stimulation. Electrode designs with a low diameter-to-height ratio have been found to maximize the volume of tissue affected with greater spread of stimulation (114). The temperature near DBS electrodes is an important consideration as higher applied voltages or currents can result in tissue heating. One approach to manage temperature fluctuations has been to incorporate thermally conductive insulating material such as carbon and alumina ceramics with the electrode to act as a heat sink (115).

Current steering is an emerging technique that uses multiple directional microelectrodes to sculpt current flow in order to avoid side effects of off target current spread (116). One way to accomplish this is to have multiple conducting bands oriented at different angles on each electrode (117). Each conducting band can be independently programmed to apply current in different directions. The advantages of current steering includes greater specificity of stimulation and more flexibility of application from the same implantation site (118).

8.2. Pulse interleaving

Pulse interleaving alternates application of two different waveform profiles (e.g., different frequencies, amplitudes, and pulse widths) to the electrodes. The rationale for having two pulses is to treat two different conditions or symptoms that may require different waveforms (119). There have been some preliminary results indicating that interleaving may offer better treatment of dystonia for patients

unresponsive to conventional bipolar stimulation (120) and greater reduction of symptoms with less incidence of side effects in treating PD (121).

8.3. Adaptive closed-loop DBS systems

One continuing direction for DBS is the development of a fully closed-loop neurostimulation system that can quickly respond to changing neural activity. The main challenge is that delivery of electric current pulses to a site can obstruct the simultaneous sensing of neural signals. Efforts to overcome this obstacle have utilized front-end passive filtering and symmetric sensing for common mode rejection of interference from the stimulation pulses (122). The ultimate goal is an adaptive autonomous DBS system akin to artificial pacemakers that can tailor electric pulses to a dynamic environment. A current example would be closed-loop detection of epileptic discharge triggering delivery of abortive stimulation to epileptic foci (123).

8.4. Optogenetics

Basic mechanisms of DBS have now been investigated with a new highly-selective situation technique called optogenetics, which may essentially allow instigators to avoid the old problem of fibers of passage (124). Optogenetics can be used to map out the neural pathways affected by DBS by optically stimulating or inhibiting neurons in different target regions as was done in the motor thalamus (125). Optogenetics enables fine discrimination between stimulation or inhibition of afferent fibers versus efferent fibers as well as the neuron cell bodies (126). Application of optogenetics has already helped determine the role of the nigrostriatal pathway in motor control and its dysfunction in PD (127).

8.5. New targets and observed effects of DBS

New targets for DBS are being researched. Located caudal to the substantia nigra, the pedunculopontine nucleus (PPN) has been investigated as a DBS target for gait and posture impairment in PD. Recordings of evoked local field potentials in the PPN from STN-DBS have shown functional connections between the two structures (128). It is unclear which neural elements stimulated in or around the PPN mediate the observed improvement in postural stability (129).

The effects of DBS continue to be studied even beyond observations of inhibition or excitation. DBS of the anterior nucleus of the thalamus in rats has been observed to increase hippocampal neurogenesis (130). While this could possibly be explained by a brain repair response after insertion of an electrode (131), there is also the intriguing possibility that DBS can induce regeneration and neurorestoration (132) as seen in the denate gyrus in rats following HFS (84).

9. CONCLUSIONS

Deep brain stimulation has had a profound impact not only on how neurological disorders such as PD are treated but also in driving the investigation of the neural populations and pathways involved in their pathologies. With new tools such as optogenetics, definitively ascertaining the mechanism of action will require an understanding of the neuroanatomy involved as well as consideration of the biophysical effects of applying electric current to neural tissue. As the most successful example of neurostimulation, DBS appears poised to find even more applications and be of great benefit both as a therapy and as a stimulus for further research into the neural circuitry of the brain.

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Footnote: [1]Note that clinical and anatomical nomenclatures for the various subnuclei of the motor thalamus correspond imperfectly and can be quite confusing. For a concise view of this tangled subject see reference 12 (12).

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