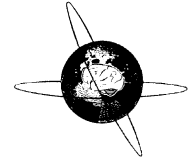




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Invited review

Selection of stimulus parameters for deep brain stimulation

Alexis M. Kuncel, Warren M. Grill*

Department of Biomedical Engineering, Duke University, Box 90281, Durham, NC 27708-0281, USA

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Abstract

Objective: To provide an analysis of stimulation parameters for deep brain stimulation (DBS).

Methods: Synthesis of theoretical and empirical findings is used to provide guidance for the selection of stimulus parameters. Finite element modeling is used to investigate the effects of contact location and electrode geometry on the electric field, and to estimate the effects of current density distribution on the limit for non-damaging stimulation.

Results: Anatomical targeting of DBS electrodes is complicated by the uncertainty of which neural elements are targeted and differences in the electric field distribution in fiber tracts and nuclei. Electrical targeting by selection of electrode geometry and stimulus waveform can alter the distribution of the electric field and control neural activation. The recommended charge density limit for DBS represents a liberal estimate for non-damaging stimulation. Short duration stimulus pulses reduce charge injection and increase the therapeutic window between therapeutic effects and side effects.

Conclusions: There are several challenges to developing rational methods of selecting stimulus parameters including a large number of degrees of freedom, the unknown effects of stimulation, and the complexity of the responses.

Significance: Understanding the fundamentals of electrical stimulation of the nervous system enables rational selection of stimulus parameters.

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Keywords: Electrical stimulation; Movement disorders; Neural prosthesis; Subthalamic nucleus; Thalamus

1. Introduction

Deep brain stimulation (DBS) is a clinically effective treatment for movement disorders, including Parkinson's disease and essential tremor and is under investigation as a treatment for epilepsy, obsessive compulsive disorder, and other neurological disorders. However, the mechanisms of action through which DBS works are unclear, and fundamental knowledge of the interactions between electrical stimulation and the neural elements of the central nervous system (CNS) is lacking. Presently there are few guidelines to inform selection of stimulus parameters, and device tuning is essentially an ad hoc empirical process, with associated difficulties of time, expense, and patient discomfort. Rationally selected stimulation parameters may allow the clinical outcome to be less sensitive to the position of the electrode, expand the dynamic range between clinical effects and side effects, use less power, and require less time-intensive tuning. In this article we

present both theoretical and empirical findings as they relate to the selection of stimulus parameters for DBS.

There are several challenges to developing rational methods of selecting stimulation parameters including a large number of degrees of freedom, the unknown effects of stimulation, and the complexity of the responses. The first challenge is that many degrees of freedom exist. There are multiple anatomical targets, 12,964 combinations of pulse width, frequency, and voltage available within the recommended charge density limit (Itrell II Model 7424 and Soletra Model 7426), and 65 combinations of electrode geometry. Another challenge is the lack of understanding of the desired effects of stimulation. It is not known what is stimulated and/or blocked during DBS treatment, nor is it known whether the stimulation has effects locally or if it acts on the entire circuit. Further, it is not known which neuronal elements must be stimulated to obtain the desired clinical effects, or which elements, when stimulated, produce unwanted side effects.

The complexity of the outcome measures also contributes to the difficulty of selecting appropriate stimulation parameters. There are multiple time-dependent effects of DBS,

* Corresponding author. Tel.: +1-919-660-5131; fax: +1-919-684-4488.

E-mail address: wmgrill@duke.edu (W.M. Grill).

and these time-dependent effects are impacted by medications. Maximum effects of stimulation on some symptoms, including bradykinesia (Krack et al., 2002), can take from hours to days to observe, while the maximum effect on other symptoms, including rigidity (Krack et al., 2002; Volkmann et al., 2002), occurs within a minute. Tremor response to subthalamic nucleus (STN) stimulation usually occurs immediately, but there may be some progressive improvements occurring over a period of weeks or months (Krack et al., 2002). Improvements for dystonia with internal globus pallidus (GPi) DBS may take several days to several months to observe (Kumar, 2002). Finding the optimal setting is also complicated by the slow return of symptoms after the stimulator is turned off. Although tremor returns within minutes, the full return of bradykinesia and rigidity can take up to an hour (Tempereli et al., 2003). In addition, some outcomes, such as the change in frequency of epileptic seizures, can be difficult to assess for tuning.

Another complication in determining optimal stimulus parameters for DBS is that optima may vary across the different symptoms, side effects, and levels of power consumption. For example, long pulse widths were found to be most effective at relieving tremor in thalamic DBS (O'Suilleabhain et al., 2003), but short pulse widths minimize charge injection and therefore increase battery life.

Previous empirical and theoretical results provide some fundamental understanding of the effects of electrical stimulation on the nervous system that can guide the selection and optimization of stimulus parameters. In this article, we review these fundamentals as well as recent data on anatomical targeting, electrical targeting, and setting the pulse width, frequency, and voltage for DBS. Understanding the fundamentals will aid in the rational selection of stimulation parameters and full development of DBS treatment.

2. Anatomical targeting

Successful treatment with DBS depends on accurately placed electrodes. Anatomical targeting involves determining where to put the electrode and where to direct the electric current, based on which neural elements, cells or fibers, are targeted for excitation. However, anatomical targeting is complicated by the uncertainty of which neural elements, nuclei (cells) or fibers, are excited in DBS.

The STN is a common target for the treatment of Parkinson's disease (PD), and targeting the STN for treatment of PD results in clinically effective outcomes (Krause et al., 2001; Kumar et al., 1998; Limousin et al., 1995). However, it is unknown whether the excitation of the neural elements in the STN and/or in the surrounding fiber tracts is responsible for the clinical improvements. The STN is a small nucleus, surrounded by several large fiber tracts, including the zona incerta (ZI) and the Fields of Forel (FF).

Electrodes placed in the STN and the surrounding fiber tracts elicited similar clinical improvements (Fig. 1a)

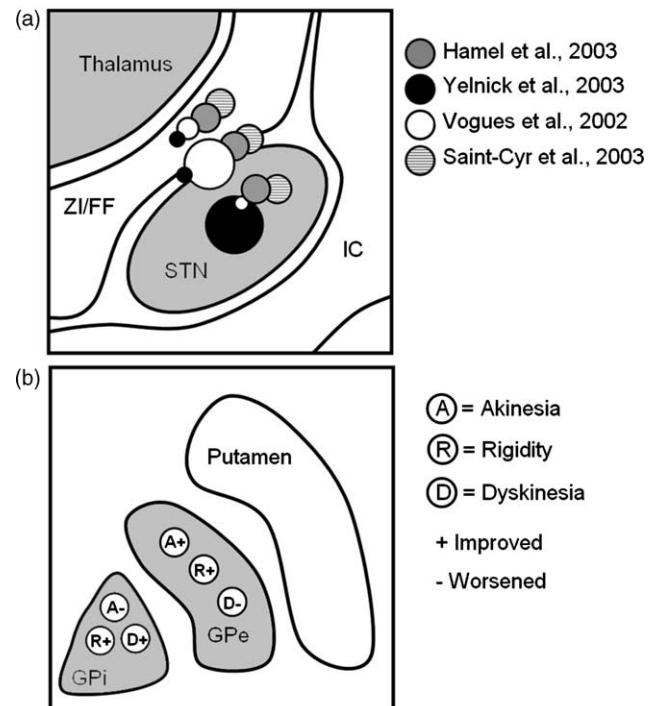


Fig. 1. Variation in anatomical targeting and clinical outcomes. (a) Active contacts placed in nuclear and fiber tract locations have resulted in similar clinical outcomes (Hamel et al., 2003; Saint-Cyr et al., 2002; Vogues et al., 2002; Yelnick et al., 2003). Subthalamic nucleus (STN) and surrounding fiber tracts (zona incerta (ZI), Fields of Forel (FF), and internal capsule (IC)) are shown with clinically effective contact location. The size of circles represents the percent of clinically effective contacts located within anatomical target. (b) Pallidum and putamen are shown. Stimulation has varying effects on different symptoms in GPi and GPe (Bejjani et al., 1997; Krack et al., 1998; Yelnick et al., 2000).

(Hamel et al., 2003; Saint-Cyr et al., 2002; Vogues et al., 2002; Yelnick et al., 2003). However, Saint-Cyr et al. (2002) found that the best efficacy and fewest adverse side effects occurred most commonly when the electrode contacts were located in the anterior-dorsal STN and/or in the FF/ZI dorsally adjacent to it. Hamel et al. (2003) found that active contacts located at the border between the STN and the area containing the ZI, FF, and STN projections required the least voltage to alleviate rigidity. Vogues et al. (2002) found that, for a similar clinical improvement, contacts located in the fiber tracts required less stimulation power (where $\text{Power} = (\text{Amplitude} \times \text{Pulse Width} \times \text{Frequency})^2 / \text{Impedance}$) than those located in the STN. Similarly, subthalamotomies that extended beyond the STN into the FF/ZI were more effective in the treatment of PD patients than lesions that did not extend beyond the STN (Patel et al., 2003). The results of these studies suggest that the fiber tracts around the STN, the activity of which may be influenced by STN DBS, play a role in mediating the motor effects of STN DBS (Vogues et al., 2002). According to previous animal studies, neural elements up to 5 mm from the cathode are affected by stimulation for stimulus amplitudes (3 mA) typically used in DBS (Ranck, 1975). Therefore, current from an electrode placed in the STN

could spread to the surrounding fiber tracts (Voges et al., 2002). If indeed clinical effects were mediated by dorsal fiber tracts, the active contacts located in the STN would therefore be effective, but less efficient than contacts located in the fiber tracts. A recent study, however, found that contacts located within the fiber tracts surrounding STN were less effective than contacts located in the dorsolateral border zone (Herzog et al., 2004). These contradictory results may be due to differences in the accuracy of the methods used to localize the electrode.

The globus pallidus (GP), or pallidum, is another target for DBS treatment of PD. Studies have found that stimulation of the GP, which is comprised of the GPi and the external globus pallidus (GPe), results in different clinical effects with electrodes placed in the GPi or the GPe (Fig. 1b) (Bejjani et al., 1997; Krack et al., 1998; Yelnik et al., 2000). Yelnik et al. (2000) found that DBS applied to the GPe or the area between the putamen and GP (13 out of 14 contacts) resulted in improved upper limb akinesia, whereas stimulation applied to the GPi (11 out of 12 contacts) resulted in worsened upper limb akinesia. Contacts located at the border of the GPe and GPi had mixed clinical effects with two contacts improving, three worsening, and one having no effect on upper limb akinesia. Rigidity was improved for contacts located throughout the GP, including the area between putamen and GP, in the GPe, in the area between the GPe and GPi, and in the GPi.

The uncertainty of what (nuclei or fiber tracts) is stimulated by DBS makes deciding on an anatomical target difficult, and it is not clear that present targets are optimal. More post-implant correlations are needed that identify contact location, motor effects, side effects, and effects of parameters of stimulation. One explanation for the difference in clinical responses between stimulation of STN and GP for the treatment of PD symptoms is the anatomical difference between the two nuclei. GP is comprised of less densely packed neurons than STN. The lower density of neurons in GP may explain why it has been found to be less successful at treating PD compared to STN, which has a high density of neurons and is successful in alleviating all three symptoms of PD (Yelnik et al., 2000). The STN and GP have different locations within the basal ganglia circuitry, which may also contribute to the different responses to DBS.

The accuracy of surgical targeting techniques is unknown, further complicating electrode placement. The final location of the electrode is not always known because the accuracy of current methods of targeting, including microelectrode recording, macroelectrode stimulation, and image-guided techniques, is unknown. Determining exactly where the DBS lead is located is difficult because anatomical images acquired from magnetic resonance imaging have distortions due to the presence of the DBS electrode (Saint-Cyr et al., 2002). No post-mortem studies have been done to validate the accuracy of different methods. Correct placement of the lead is also complicated

by anatomical variations across patients. The location of microelectrode-guided pallidal lesions for the treatment of PD varied relative to common anatomical landmarks. However, the location of the lesions was not random; all lesions were parallel to the border of the GPi and there was a common clinical benefit (Gross et al., 1999).

3. Electrical targeting

DBS requires selective and controlled effects on populations of neurons. Electrical targeting can be used to control neural activation by controlling the spread of the electric field and by selectively activating neural elements. The electric field is the first derivative of the extracellular electric potential (V_e) generated by the passage of current through the tissue. The spread of electric field depends on the location of the active contact, the electrode geometry, and the electrical properties of the surrounding tissue.

3.1. Effect of contact location on distribution of the electric field

The spatial distribution of the electric field is dependent on the electrical properties of the tissue surrounding the electrode. The gray matter of the CNS is isotropic with conductivity around 0.2 S/m (Li et al., 1968; Ranck, 1963). Cerebral white matter, composed of fiber tracts, is anisotropic and therefore has higher conductivity (1 S/m) in the direction parallel to the fibers than in the direction perpendicular to the fibers (0.1 S/m) (Nicholson, 1965). As these properties of the tissue impact the spatial distribution of the electric field, and the derivative of the electric field is the activating function ($\Delta^2 V_e$) for neuronal excitation (Rattay, 1986), the electrical properties of the tissue impact the pattern of neural stimulation (Grill, 1999). An active contact located in the white matter fiber tracts (Fig. 2b) surrounding the STN results in a greater spread of electric potential, electric field, and the activating function than an active contact located in the grey matter STN (Fig. 2c).

3.2. Effect of electrode geometry on distribution of electric field

The spatial distribution of the electric field is also impacted by varying the electrode geometry. Electrode geometries include monopolar, bipolar, tripolar, quadripolar, and quintipolar configurations. In each configuration there is a cathode, or negative electric potential (sink of current), and an anode, or positive electric potential (source of current). The pulse generator case cannot be set as a cathode, and if the case is set to be an anode, no electrode can be set as an anode. This results in 65 possible electrode configurations. Current flows from the anode to the cathode, depolarizing the neural elements nearest the cathode and hyperpolarizing neural elements nearest the anode. In monopolar stimulation (Fig. 3b), a contact on the DBS lead is selected to be the cathode and the pulse generator

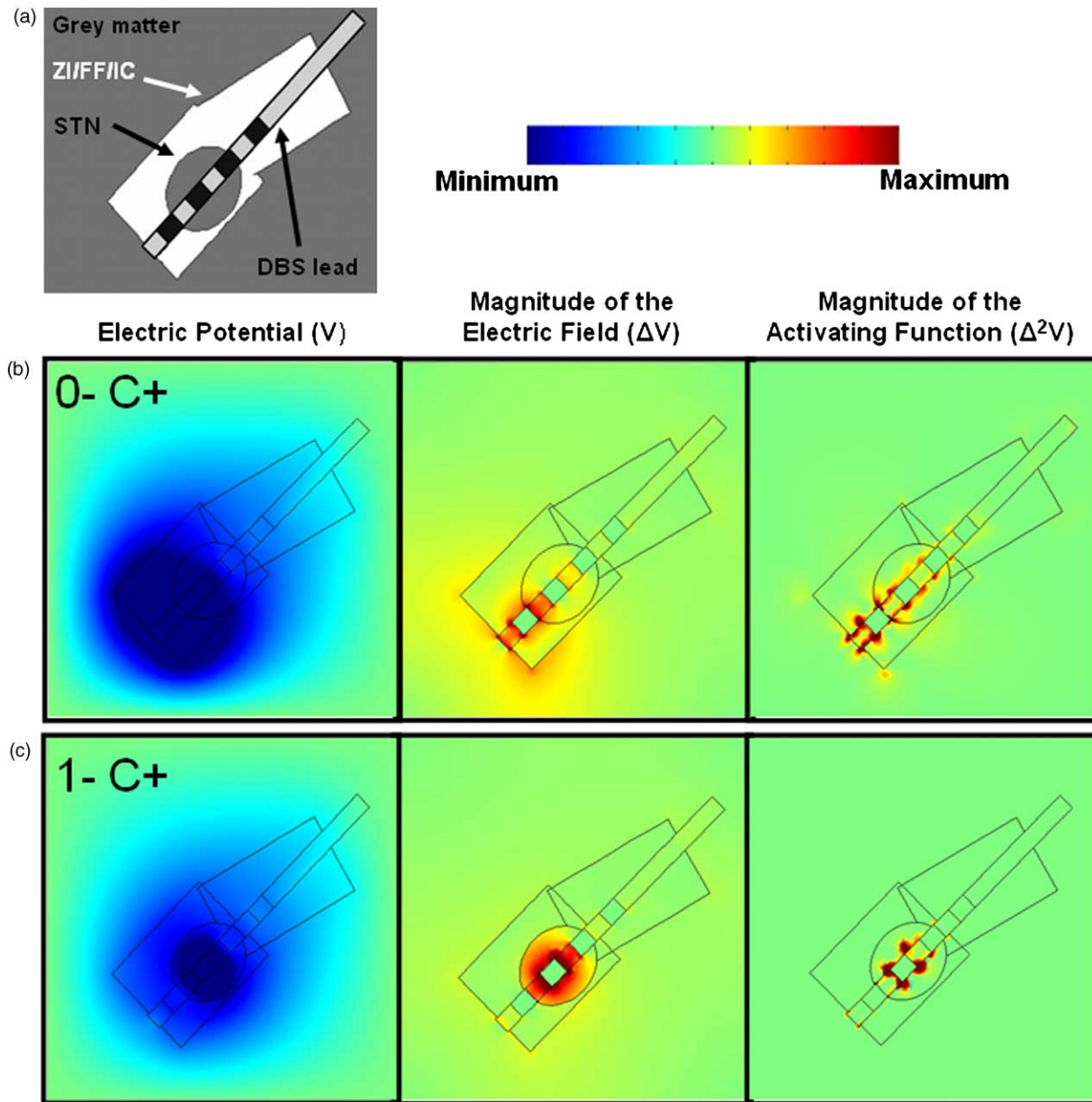


Fig. 2. (a) Model of the DBS lead with four contacts centered in the STN, surrounded by white fiber tracts (zona incerta (ZI), Fields of Forel (FF), and internal capsule (IC)) and grey matter. Distribution of (1) electric potential (V), (2) magnitude of the electric field (ΔV), and (3) magnitude of the activating function ($\Delta^2 V$) generated in the subthalamic nucleus and the surrounding fiber tracts when monopolar stimulation ($V = -1$ V) applied in (b) white matter (conductivity of 0.2 S/m) (Ranck, 1963; Li et al., 1968) through Contact 0 and (c) in grey matter (conductivities of 1 S/m in the direction parallel to the fibers and 0.1 S/m in the direction perpendicular to the fibers) (Nicholson, 1965) through Contact 1. ΔV and $\Delta^2 V$ have both positive and negative components, but the magnitudes are shown here. Positive $\Delta^2 V$ results in depolarization and negative $\Delta^2 V$ results in hyperpolarization of the surrounding neural elements. The magnitude of $\Delta^2 V$ represents the strength of the polarization on the surrounding neural elements.

case is the anode. The anode and cathode are relatively distant from each other in monopolar configurations, so there is a broader extracellular electric potential distribution (current spread) than in bipolar (Fig. 3b,c) and tripolar (Fig. 3d) configurations, where the anode and cathode are relatively close. Since there is a large electrical potential distribution, monopolar stimulation generally requires lower stimulation intensity than bipolar stimulation to achieve the same clinical benefits (Pollack et al., 1998). In bipolar stimulation, two contacts are activated, one as the cathode and one as the anode.

Since the cathode and anode are relatively close to each other, the current is more focused than in a monopolar configuration (Ranck, 1975). Bipolar electrode configurations may be less likely to elicit side effects because the current is more confined, and therefore less likely to spread into adjacent structures (Volkman et al., 2002). Bipolar and monopolar contact configurations have been found to have similar clinical benefits at low stimulus intensities, but side effects occurred more often with monopolar stimulation above 3–4 V (O'Suilleabhain et al., 2003).

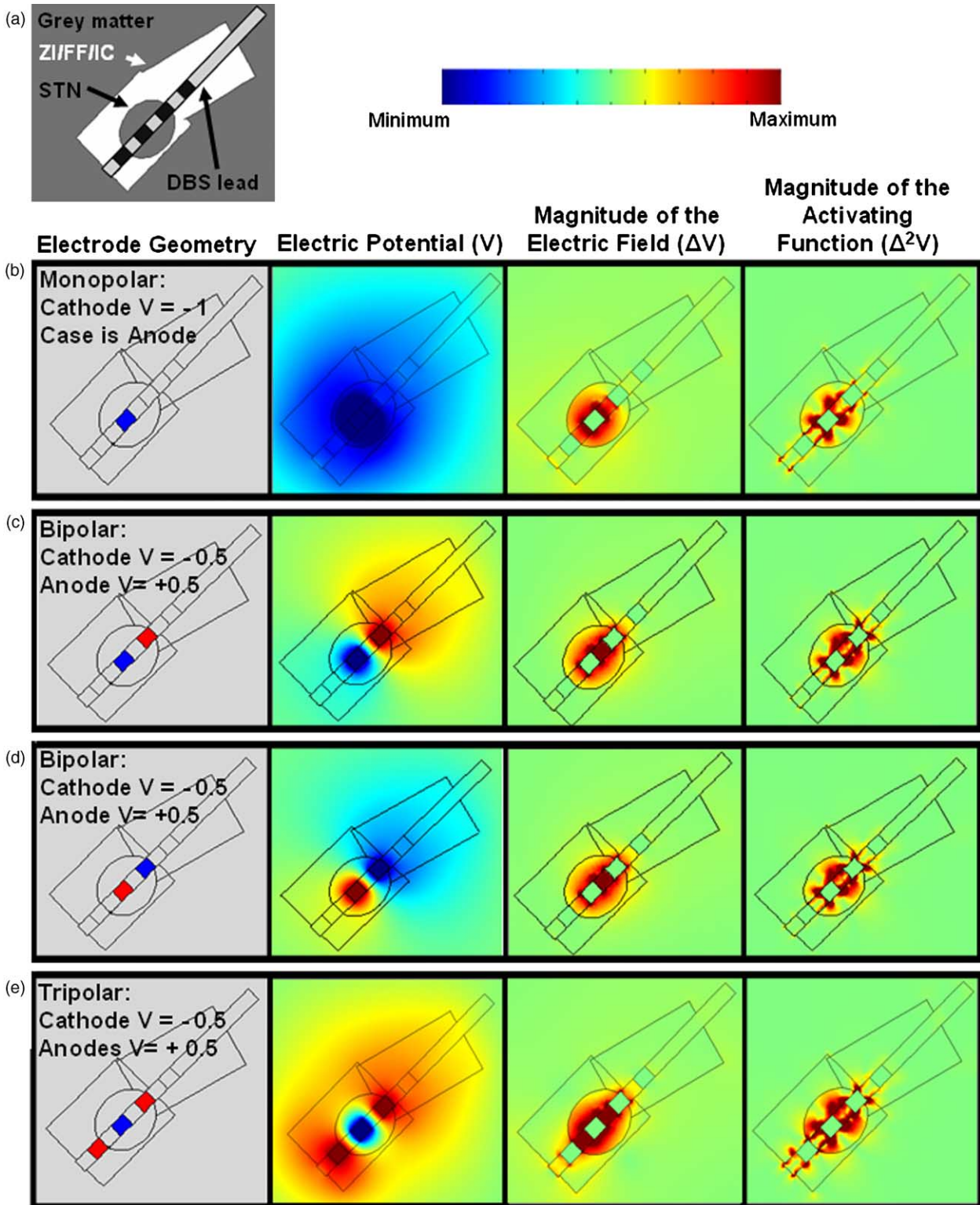


Fig. 3. (a) Model of the DBS lead with four contacts centered in the STN, surrounded by white fiber tracts (zona incerta (ZI), Fields of Forel (FF), and internal capsule (IC)) and grey matter. Distribution of (1) electric potential (V), (2) electric field (ΔV), and (3) the activating function ($\Delta^2 V$) generated in the subthalamic nucleus and the surrounding fiber tracts during (b) monopolar stimulation ($V = -1$) applied through Contact 1, (c) bipolar stimulation (Contact 1 at $V = -0.5$, Contact 2 at $V = 0.5$), (d) bipolar stimulation (Contact 1 at $V = 0.5$ V, Contact 2 at $V = -0.5$ V), and (e) tripolar stimulation (Contacts 0 and 2 at $V = 0.05$, Contact 1 at $V = -0.5$). ΔV and $\Delta^2 V$ have both positive and negative components, but the magnitudes are shown here. Positive $\Delta^2 V$ results in depolarization and negative $\Delta^2 V$ results in hyperpolarization of the surrounding neural elements. CNS gray matter has a conductivity of 0.2 S/m (Li et al., 1968; Ranck, 1963). CNS white matter has conductivities of 1 S/m in the direction parallel to the fibers and 0.1 S/m in the direction perpendicular to the fibers (Nicholson, 1965).

3.3. Control of neural activation with electrode geometry

A bipolar configuration is often chosen because it is thought to have greater selectivity as it creates less current spread; however, because the second derivative of the extracellular potential ($\Delta^2 V_e$) drives neuronal polarization, bipolar stimulation may be less selective. In bipolar stimulation (Fig. 3c,d), an extracellular electric potential, and therefore the activating function, is generated at both the anodal and cathodal contacts. Activation of neural elements may therefore occur at both the cathode and the anode in bipolar stimulation, and there may be less selectivity of neural excitation. The magnitude of the driving function for neural activation in the tissue surrounding the electrode is shown in Fig. 3. The same is true for tripolar (Fig. 3e) configurations. Modeling studies have found bipolar electrode geometry to be less selective between neural elements when compared to a monopolar configuration. With bipolar stimulation, the recruitment of fibers and cells was found to be nearly equal over the entire range of stimulus amplitudes, and varying the spacing between active electrodes had little effect on the relative selectivity of different neuronal elements (McIntyre and Grill, 2000).

4. Stimulus parameters

Along with accurately placed electrodes, successful DBS depends on properly set stimulus parameters, including pulse width, frequency, and amplitude (Su et al., 2003). Typical DBS parameter settings of voltage, pulse width, and frequency range from 1–3.5 V, 60–210 μs , and from 130–185 Hz (Moro et al., 2002; O’Suilleabhain et al., 2003; Rizzone et al., 2001; Volkmann et al., 2002). In a study comparing the efficacy of GPi and STN DBS, the final mean stimulus parameter settings used to treat PD symptoms were 3 V, 82 μs , and 152 Hz for STN DBS, and 3.2 V, 125 μs , and 162 Hz for GPi DBS (Obeso et al., 2001).

Stimulus parameters can be used to control selectively which neural elements in the surrounding tissue are excited. The stimulus parameters can also control the spatial extent of neural elements which are excited. Clinically available neurostimulators provide a finite range of voltage, frequency, and pulse width. Medtronic’s Solettra Model 7426 and Irel II Model 7424 neurostimulators use voltages ranging from 0–10.5 V in 0.115 V increments, pulse widths from 60–450 μs in 30 μs increments, and frequencies from 2–185 Hz (5–100 in increments of 5 Hz, and 2, 33, 130, 135, 145, 160, 170, and 185 Hz) (Medtronic Manual, 2002). There are a total of 25,480 (91 voltages \times 10 pulse widths \times 28 frequencies) combinations of pulse width, frequency, and voltage (Fig. 4a), but the recommended charge density limit of 30 $\mu\text{C}/\text{cm}^2$ limits the number of combinations. Charge density is calculated by dividing the product of the voltage and the pulse width by the product of

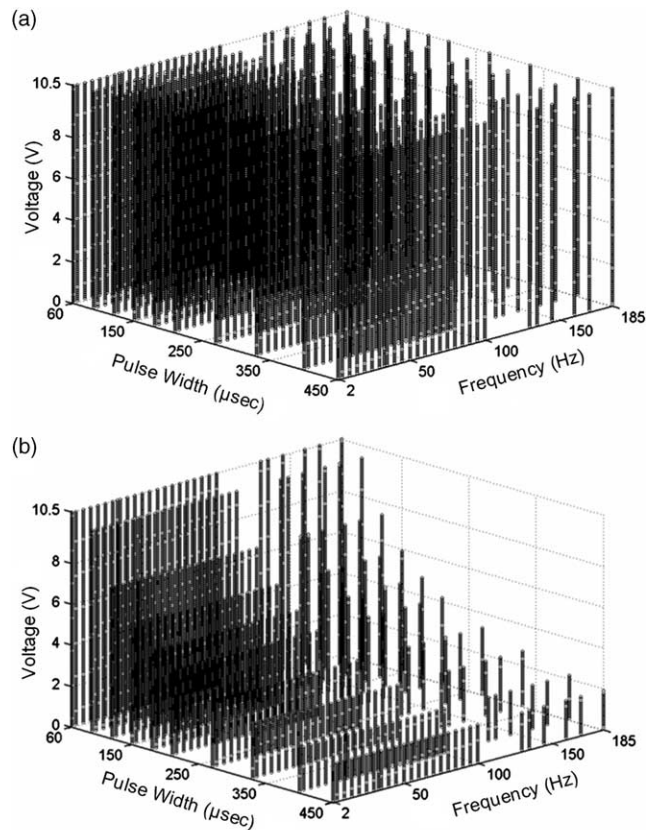


Fig. 4. (a) Large number of degrees of freedom for stimulus parameter settings. 25,480 available combinations of pulse width, frequency, and voltage in the Medtronic Solettra Model 7426 and Irel II Model 7424 neurostimulators. (b) 12,964 of these combinations fall under the manufacturer’s recommended charge density limit.

the impedance and the geometric surface area of the electrode, which is 0.06 cm^2 for the DBS contact. The impedance is estimated conservatively to be 500 Ω . Therefore, the product of voltage and pulse width must be less than 900 $\mu\text{C}/\Omega$. Even with the charge density restriction, there are 12,964 combinations of voltage, pulse width, and frequency still available (Fig. 4b).

In post-surgical management of DBS, the goal is to find an optimal combination of pulse width, frequency, and voltage. The optimal combination would best reduce symptoms, minimize side effects, and minimize power consumption. Low power consumption would increase battery life and decrease the risk of tissue damage. Finding the optimal setting is complicated because the optimal settings for reducing symptoms, minimizing side effects, and minimizing power consumption may be different. It is currently unknown which neural elements are excited in DBS, further complicating the process of finding an optimal setting. It is therefore important that we have an increased understanding of the fundamentals of electrical stimulation of the central nervous system to make rational and informed choices in setting stimulus parameters.

4.1. Strength–duration relationship

The threshold stimulus amplitude required to excite neural elements, I_{th} , decreases as pulse width increases. This relationship is shown in the strength–duration curve (Fig. 5a), and can be described by the following equation:

$$I_{th} = I_{rh}[1 + T_{ch}/PW] \quad (1) \text{ Weiss Equation}$$

Where I_{rh} is the rheobase current, defined as the minimum current needed to excite neural elements with a pulse of infinite duration, PW is pulse width, and T_{ch} is the chronaxie, defined as the threshold pulse width when the stimulus amplitude is equal to twice the rheobase current.

Chronaxie values have been measured to determine which neural elements are excited in DBS (Holsheimer et al., 2000). Using chronaxie to determine which neural element is targeted is based on findings that cells and fibers have different chronaxies; cell bodies have chronaxies in the 1–10 ms range, large myelinated fibers have chronaxies in the 30–200 μ s range, and small myelinated fibers have chronaxies in the 200–700 μ s range (Ranck, 1975). Chronaxies for tremor reduction by DBS were estimated to be approximately 65 μ s for thalamic and around 75 μ s for pallidal stimulation (Holsheimer et al., 2000), suggesting that large myelinated axons are the targeted neural elements.

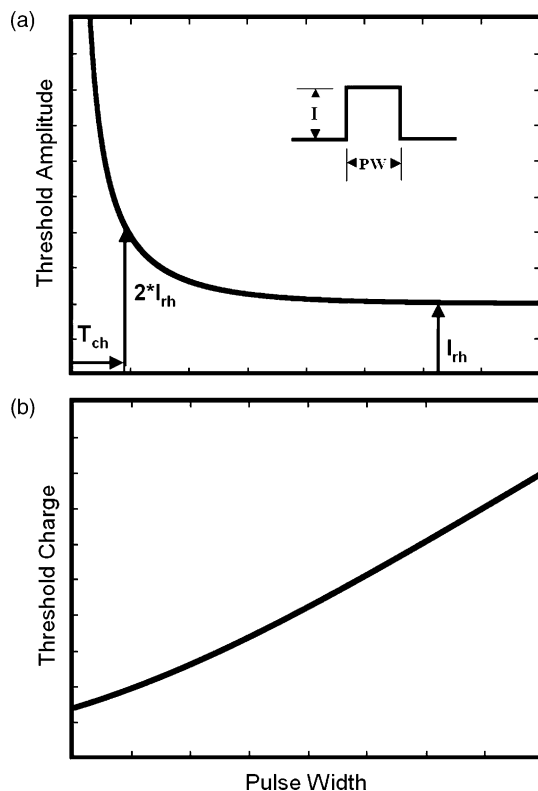


Fig. 5. The strength–duration curve (a) describes the threshold amplitude as a function of stimulus duration. Rheobase current (I_{rh}) is the minimum amount of current needed to reach threshold with a pulse of infinite duration. The pulse width at which the threshold current amplitude is equal to twice rheobase is called chronaxie (T_{ch}). The charge–duration curve (b) describes the threshold charge as a function of stimulus duration.

However, recent results indicate that chronaxie is not sensitive to the neural element stimulated, and is similar for axons of passage and local cells during extracellular stimulation (Miocinovic and Grill, 2004). This is because extracellular stimulation in the CNS results in action potential initiation in the axon even for electrodes positioned near the cell body (McIntyre and Grill, 1999; Nowak and Bullier, 1998). In DBS, neural elements are activated via extracellular stimulation, and measuring chronaxie as a method for determining the targeted neural elements in DBS may therefore not be appropriate.

The shape of the strength–duration curve suggests that the most efficient stimulation, that which requires the lowest voltage or current, occurs at longer pulse durations. However, efficiency is better measured by the amount of charge required to stimulate, and the least charge delivery occurs with the shortest duration pulses.

4.2. Charge–duration relationship

Current is a flow of electrical charge. Therefore, the total charge (Q) of an electrical stimulus (Fig. 5, inset) is calculated by taking the integral of the stimulation current over the stimulation time (Eq. (2)), or by calculating the product of the current amplitude and the pulse width (Eq. (3)).

$$i = dq/dt \rightarrow Q = \int idt \quad (2)$$

$$Q = PW \times I = PW \times (V/Z) \quad (3)$$

The relationship between the stimulus duration and the amount of charge required for excitation can be obtained directly from the strength–duration relationship (Fig. 5a) because $Q = PW \times I$. The charge–duration relationship (Fig. 5b) is described by Eq. (4).

$$Q_{th} = I_{rh}[PW + T_{ch}] \quad (4)$$

Where Q_{th} is the threshold charge, I_{rh} is the rheobase current, PW is pulse width, and T_{ch} is the chronaxie. The threshold charge to excite neural elements increases as the pulse width increases. The rise in threshold charge with increasing pulse widths is due to accommodation, the nonlinear time-dependent conductance properties of ion channels in the neural membrane. It is important to note that increasing pulse width has opposite effects on the threshold current and threshold charge. Short pulse widths require high current but low charge, and are thus more efficient at exciting neural elements.

4.3. Charge density limit for non-damaging stimulation

Charge and charge density are important stimulation parameters to consider when determining the threshold and severity of tissue damage. Charge density is defined as the charge divided by the geometric surface area of

the electrode, which is 0.06 cm^2 for the DBS contact. Medtronic provides a level of charge density above which tissue damage may occur, thus restricting the stimulus parameter combinations. The charge density limit, $30 \text{ } \mu\text{C}/\text{cm}^2$, was extracted from previous studies on charge, charge density, and tissue damage (Agnew et al., 1983; Brown et al., 1977; McCreery et al., 1988, 1990; Pudenz et al., 1975; Yuen et al., 1981). The charge and charge density combinations tested in these experiments are shown in Fig. 6, and both charge per phase and charge density were important parameters in defining a tissue damage threshold. The $30 \text{ } \mu\text{C}/\text{cm}^2$ charge density limit for DBS was determined from these data by finding the largest charge for a contact area of 0.06 cm^2 that did not result in a charge density in the damaging region.

Recent human post-mortem studies indicate that little tissue damage is associated with chronic DBS, but with stimulus parameters well under the recommended charge density limit (Burbaud et al., 2002; Haberler et al., 2000; Henderson et al., 2002). Henderson et al. (2002) found only mild cell loss, gliosis, and vacuolation in a post-mortem

analysis of a subject who was treated with bilateral STN DBS (2.4 V, $60 \text{ } \mu\text{s}$, 160 Hz, Contact 1 negative, Case positive) for two months. Haberler et al. (2000) found mild gliosis in response to the implanted lead in eight subjects with STN DBS (1–4.4 V, $60\text{--}120 \text{ } \mu\text{s}$, 130–185 Hz) for up to 70 months. Burbaud et al. (2002) reported gliosis, perivascular lymphocytic infiltrates, and iron deposits around the electrode of a subject who had received thalamic stimulation (3.5 V, $90 \text{ } \mu\text{s}$, 160 Hz) for treatment of choreic syndrome.

Several factors suggest that the basis for the recommended charge density limit for DBS, $30 \text{ } \mu\text{C}/\text{cm}^2$ is questionable. First, the data from which this limit was extracted were collected at frequencies much lower than those used in DBS, and a frequency-dependent threshold for neural damage has been found (Agnew et al., 1983). Second, although comforting, the lack of pathology in post-mortem material does not support this limit. The charge and charge density used in these studies were significantly below the recommended charge density limit of $30 \text{ } \mu\text{C}/\text{cm}^2$ and thus provide only confirmation that low charge stimulation is non-damaging.

The last confound to the recommended charge density limit for DBS is the uneven distribution of the charge density across the electrode surface. The charge distribution is non-uniform across the surface of the electrode (Bruckenstein and Miller, 1970), and charge density is greatest at the electrode-insulation interface (Fig. 7). Charge densities calculated in the derivation of the $30 \text{ } \mu\text{C}/\text{cm}^2$ limit were calculated as average values across the electrode surfaces. For an electrode 1.26 mm in diameter, with a single contact 1.5 mm in length, set to 3 V, 25.6% of the contact surface is operating at a current density above the average value of $0.0993 \text{ A}/\text{cm}^2$. Non-uniform current

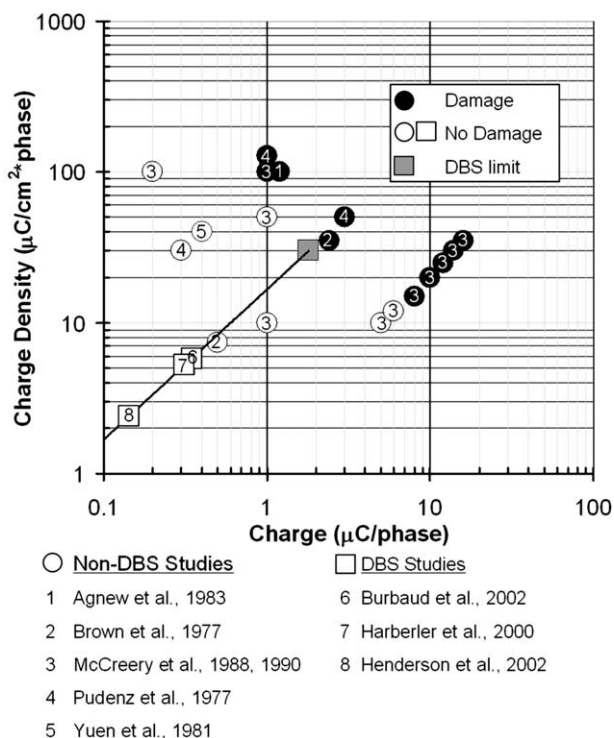


Fig. 6. The dependence of tissue damage on stimulation parameters. Combinations of charge density and charge used in several studies are shown. Charge is the product of pulse width and current (current = voltage/impedance). Circles represent non-DBS studies (Agnew et al., 1983; Brown et al., 1977; McCreery et al., 1988, 1990; Pudenz et al., 1975; Yuen et al., 1981). Solid circles represent combinations that resulted in tissue damage and hollow circles represent no tissue damage. Squares show the charge and charge density combinations reported in deep brain stimulation post-mortem studies to not have produced tissue damage (Burbaud et al., 2002; Haberler et al., 2000; Henderson et al., 2002). Charge densities that fall on the line that ends at the grey box representing the DBS limit were calculated using the contact surface area of 0.06 cm^2 .

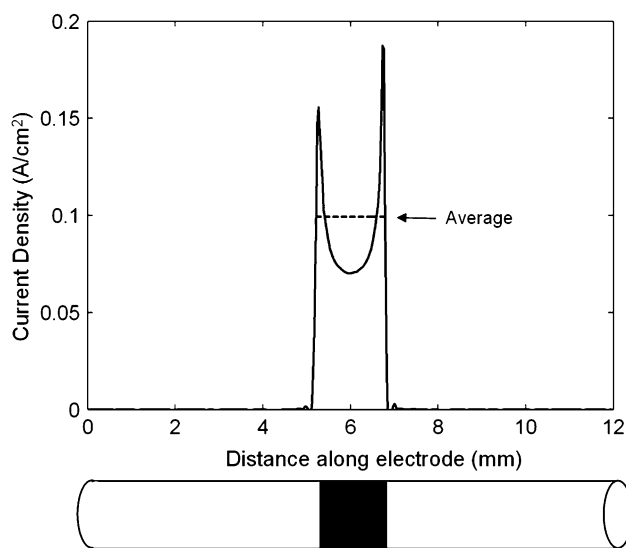


Fig. 7. Current density profile generated by an electrode, 1.5 mm in length and 1.26 mm in diameter, set to 3V. Average current density is $0.0993 \text{ A}/\text{cm}^2$, with 25.6% of the contact surface operating above the average current density.

distributions can result in charge densities exceeding the suggested limit over local regions of the electrode.

4.4. Setting the stimulus parameters

Since the mechanisms of action of DBS are unknown, there is no way to select or eliminate settings a priori. General guidelines are available to help clinicians find effective stimulus parameter settings (Krack et al., 2002; Volkmann et al., 2002); however, most of these algorithms are vague and involve turning parameters up until the effects are desirable. The average power consumption of a train of monophasic rectangular pulses can be described by the following equation:

$$P = \frac{V^2 \times F \times PW}{Z} \quad (5)$$

Where Z is impedance and V is maximum voltage. (Voges et al. (2002) calculated power using the average voltage). Increasing pulse width, frequency, and/or voltage will therefore increase power consumption. The present method of setting the stimulus parameters is not time efficient and there is no guarantee that the combination chosen by the clinician is the optimal setting.

4.4.1. Pulse width

Short pulse widths minimize charge, as explained by the charge–duration relationship. Reduced charge minimizes the probability of inducing tissue damage. Theoretical studies indicate that short pulse durations increase the threshold difference between activation of different diameter nerve fibers (Gorman and Mortimer, 1983) and between activation of nerve fibers lying at different distances from the electrode (Grill and Mortimer, 1995). Empirically, short pulse widths were found to increase the dynamic range between clinical benefit and adverse side effects, also referred to as the therapeutic window. Rizzzone et al. (2001) determined the pulse width/stimulus intensity relationships for reduction of wrist rigidity in patients with PD and for onset of side effects. As the pulse width was decreased, the stimulus intensity required to elicit a clinically significant improvement increased, which is explained by the strength–duration relationship (Fig. 5a). The stimulus intensity that caused side effects also increased as the pulse width was decreased, but the difference between the two amplitudes, the size of the therapeutic window, increased as the pulse width was decreased. Cumulatively, these results suggest that DBS devices should be programmed with the shortest possible pulse duration, and that future generation stimulators should include lower ranges of pulse widths.

4.4.2. Frequency

High frequency stimulation requires more power, and therefore decreases battery life (Eq. (5)) DBS has been found to be effective for reduction of tremor, akinesia,

and rigidity at frequencies greater than 50 Hz but larger stimulus amplitudes were required at low frequencies (Benabid et al., 1991; Limousin et al., 1995). Tremor suppression at the lowest current occurred between 150 and 1000 Hz, and the lowest stimulus intensity required was about 2 mA (Benabid et al., 1991). Above 1000 Hz, the efficiency of tremor suppression decreased, presumably as a result of neural refractoriness. The clinical effect of STN stimulation on akinesia and rigidity was studied with similar results (Limousin et al., 1995). Rigidity and akinesia were only reduced for frequencies above 50 Hz, the effect rose linearly with increasing frequency, and was almost maximum around 130 Hz. There was a further small, nonlinear increase in efficacy above 130 Hz, up to the maximum frequency of the Itrel II neurostimulator (185 Hz). A large range (60–1000 Hz) of frequencies is effective at relieving symptoms, and frequency is often set to 130 Hz as a compromise between power consumption and clinical efficacy (Volkmann et al., 2002).

4.4.3. Amplitude

The stimulus amplitude required to activate neural elements depends on the spatial relationship between the electrode and the nerve fiber (McNeal, 1976). As the distance between the active contact and the neural element is increased, the stimulus amplitude required to stimulate neural elements increases non-linearly. The relationship between the threshold stimulus intensity (I_{th}) and the distance between the electrode and the neuron (R) is:

$$I_{th} = I_R + kR^2 \quad (6)$$

Where I_R is the absolute threshold and the slope (current–distance constant, k) determines the threshold difference between neurons at different distances, R , from the electrode (Stoney et al., 1968). DBS studies have shown that the clinical benefits saturate above a certain voltage. Tremor, bradykinesia, and rigidity progressively improved between two and three volts and did not continue to improve beyond 3 V (Moro et al., 2002). High voltages result in increased power consumption (Eq. (5)). Voltages above 3.6 and 7.3 V are generally avoided clinically because they result in an increase in battery drain due to activation of a voltage doubler or tripler circuit within the neurostimulators. A linear increase in voltage does not correlate to a linear increase in the volume of neural elements excited, but it increases the power consumption.

4.5. Control of activation with waveforms

Selective neural stimulation through the use of novel waveforms would compensate for the variability in anatomical placement of the electrode in DBS. Preferential stimulation of either fibers or cells can be achieved using monophasic cathodic or anodic stimuli, respectively (McIntyre and Grill, 2000). However, charge-balanced

biphasic stimulus waveforms decrease the probability of electrode corrosion and tissue damage (Pudenz et al., 1975). Biphasic symmetrical stimulus waveforms result in less selectivity than monophasic waveforms (McIntyre and Grill, 2000). Novel asymmetrical charge-balanced biphasic waveforms selectively stimulate fibers and cells by taking advantage of the nonlinear conductance properties of the neural elements (McIntyre and Grill, 2000, 2002). The first pulse serves to change the excitability of the neural elements by altering the degree of sodium channel inactivation (Grill and Mortimer, 1995). The subthreshold pre-pulse depolarizes the non-target neural element and hyperpolarizes the target element. Subthreshold depolarization decreases the excitability of the non-target neural elements and subthreshold hyperpolarization increases excitability of the target elements. Use of these novel waveforms may increase the dynamic range between the desired clinical effects and undesired side effects (Grill et al., 2003).

5. Conclusions/recommendations

Currently there are several challenges to rational selection of optimal stimulation parameters for DBS treatment. These challenges include the large number of degrees of freedom in stimulus parameters and electrode geometries, the variability and uncertainty in electrode positioning, the unknown effects of stimulation, and the complexity and diversity of responses to DBS. However, fundamental understanding of electrical stimulation of the nervous system obtained through theoretical and empirical studies can guide selection of appropriate stimulus parameters.

There are presently several anatomical targets for placement of DBS electrodes, and the uncertainty concerning which neural elements are stimulated makes choosing one target difficult. The GPi and STN are targets for treatment of PD symptoms. In STN stimulation, it is unclear whether stimulation of the fiber tracts surrounding the STN or stimulation of the STN itself results in clinical benefits. Lower stimulus intensities were required for similar clinical benefits for electrodes located in or near the fiber tracts suggesting that excitation of fibers is responsible for clinical improvements. In GP stimulation, stimulation of the GPe and GPi has different effects on different symptoms, suggesting that the symptoms are alleviated by different mechanisms. More post-implant studies correlating electrode position and parameter settings with both desired and undesired responses to DBS must be completed to refine further the anatomical target.

A greater understanding of the effects of electrode geometry on the region of tissue stimulated may provide a means to make the outcomes of DBS less sensitive to electrode position. Novel electrode geometries may be used to guide the electric field to the correct anatomical target or to activate selectively neural elements. Understanding

the fundamentals of electrical stimulation of the nervous system can guide selection of voltage, pulse width, and frequency in DBS. Short pulse widths minimize the charge necessary for excitation as explained by the charge–duration relationship, and thereby increase battery life and decrease the probability of inducing tissue damage. Short pulse widths also expand the dynamic range between clinical effects and side effects. Low voltages decrease the likelihood of eliciting side effects and decrease power usage, however, sufficient voltage is required to achieve the desired clinical effects. There is a range of high frequencies that allow for effective and efficient DBS. Setting the pulse width, frequency, and voltage can be a time-consuming process for clinician to find a proper setting and there is no guarantee that the final setting is the optimal one. Less time-intensive tuning methods based on an understanding of the influence of changes in parameter settings on the effects of DBS must be developed.

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