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In vivo impedance spectroscopy of deep brain stimulation electrodes

Scott F. Lempka^{1,2}, Svjetlana Miocinovic^{1,2}, Matthew D. Johnson¹, Jerrold L. Vitek³, and Cameron C. McIntyre^{1,2}

¹ Department of Biomedical Engineering, Cleveland Clinic Foundation, Cleveland, OH

² Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH

³ Department of Neurosciences, Cleveland Clinic Foundation, Cleveland, OH

Abstract

Deep brain stimulation (DBS) represents a powerful clinical technology, but a systematic characterization of the electrical interactions between the electrode and the brain are lacking. The goal of this study was to examine the *in vivo* changes in DBS electrode impedance that occur after implantation and during clinically-relevant stimulation. Clinical DBS devices typically apply high-frequency voltage-controlled stimulation, and as a result the injected current is directly regulated by the impedance of the electrode-tissue interface. We monitored the impedance of scaled-down clinical DBS electrodes implanted in the thalamus and subthalamic nucleus of a rhesus macaque using electrode impedance spectroscopy (EIS) measurements ranging from 0.5 Hz to 10 kHz. To further characterize our measurements, equivalent circuit models of the electrode-tissue interface were used to quantify the role of various interface components in producing the observed electrode impedance. Following implantation, DBS electrode impedance increased and a semicircular arc was observed in the high frequency range of the EIS measurements, commonly referred to as the tissue component of the impedance. Clinically-relevant stimulation produced a rapid decrease in electrode impedance with extensive changes in the tissue component. These post-operative and stimulation-induced changes in impedance could play an important role in the observed functional effects of voltage-controlled DBS and should be considered during clinical stimulation parameter selection and chronic animal research studies.

Keywords

non-human primate; thalamus; subthalamic nucleus; constant phase element; voltage-controlled stimulation

Introduction

Deep brain stimulation (DBS) is an established therapy for the treatment of movement disorders (Limousin and Martinez-Torres, 2008; Ostrem and Starr, 2008), and shows promise for the treatment of several neuropsychiatric disorders (Ackermans *et al.*, 2008; Lujan *et al.*, 2008). Commercial DBS systems apply high-frequency (~100–185 Hz) voltage-controlled (~1–3 V) stimulus pulses (~60–90 μ s) to the brain to achieve their therapeutic effect. The use of voltage-controlled stimulation results in voltage distributions generated in the brain that depend upon

the impedance of the electrode-tissue interface (Gimsa *et al.*, 2005; Wei and Grill, 2005; Butson *et al.*, 2006; Miocinovic *et al.*, 2009). In turn, DBS electrode impedance can affect the actual stimulus applied to the tissue medium and the corresponding volume of tissue activated by the stimulation (Butson *et al.*, 2006; Miocinovic *et al.*, 2009). The goal of this study was to examine the *in vivo* changes in DBS electrode impedance that occur after electrode implantation and during clinically-relevant stimulation.

In the days and weeks after surgical implantation of an electrode into peripheral or central nervous system tissue, electrode impedances typically increase (Grill and Mortimer, 1994; Johnson *et al.*, 2005; Williams *et al.*, 2007). These changes have been attributed to the nervous system's foreign body reaction, which involves the attachment of proteins and cells directly to the electrode and the development of an encapsulation layer around the implanted device (Xu *et al.*, 1997; Haberler *et al.*, 2000; Szarowski *et al.*, 2003; Moss *et al.*, 2004; Biran *et al.*, 2005). After several weeks, the foreign body reaction and the electrode-tissue impedance typically stabilize (Grill and Mortimer, 1994), but this stability can be perturbed with electrical stimulation (Johnson *et al.*, 2005; Otto *et al.*, 2006). Clinical measurements have also shown reversible decreases in DBS electrode impedance following electrical stimulation (Hemm *et al.*, 2004). However, the electrode-tissue interface has a substantial frequency dependence that can be more completely monitored with electrode impedance spectroscopy (EIS) (Buitengeweg *et al.*, 1998; Johnson *et al.*, 2005; Otto *et al.*, 2006; Frampton *et al.*, 2007; Williams *et al.*, 2007).

Changes in DBS electrode impedance observed under clinically-relevant conditions represent an opportunity to characterize the electrode-brain interface. Moreover, DBS impedance fluctuations may be responsible for some clinical observations relevant to patient programming. For example, most clinical centers find it is necessary to wait 3–4 weeks after electrode implantation before beginning the process of therapeutic stimulation parameter selection (Deuschl *et al.*, 2006). Another common clinical observation is the appearance of unwanted side effects (e.g. muscle contractions, dyskinesias, and paresthesias) within the first few hours of stimulation at settings that were initially therapeutic (Volkmann *et al.*, 2002). Understanding how and why these effects occur could assist in the definition of new or alternative programming paradigms to improve the DBS patient experience.

The purpose of this study was to provide a detailed description of the impedance of chronically-implanted DBS electrodes and develop a theoretical understanding of the factors that influence these observed impedances. DBS leads with four electrode contacts were implanted in the subthalamic nucleus and thalamus of a rhesus macaque and used to study the *in vivo* impedance spectra of the electrode-tissue interface over time. Equivalent circuit models were then fit to the measured impedance data to characterize the factors affecting the electrode impedance. Preliminary portions of this work have been presented in abstract form (Lempka *et al.*, 2007; Lempka *et al.*, 2008).

Methods

Electrode impedance spectroscopy

Electrode impedance spectroscopy (EIS) was used to provide a comprehensive description of the DBS electrode impedance. Impedance measurements were performed with a two-electrode cell configuration using an Autolab potentiostat (PG-STAT12, Eco Chemie, Utrecht, The Netherlands) with a built-in frequency response analyzer (FRA2, Brinkmann Instruments, Westbury, NY). A 25 mV (rms) sine wave was applied to measure impedances over a frequency range from 0.5 Hz to 10 kHz. The 25 mV signal was chosen to provide increased signal strength while still operating in a linear measurement range. The impedance was measured using either a single-sine or a multi-sine technique. In the single-sine technique, a 25 mV sinusoid was

applied at a specific frequency and the resulting impedance measured. For this technique, the frequency range examined was 1 Hz to 10 kHz with 41 frequency points spaced logarithmically. For more rapid impedance measurements, a multi-sine technique was often utilized in which 15 sine waves were applied simultaneously at 15 different frequencies. A desired base frequency was selected and multiples of this frequency were calculated (frequencies = base frequency * (1, 3, 5, 7, 9, 13, 19, 25, 33, 41, 51, 61, 73, 87, 99)). The results presented in this study used base frequencies of 0.5, 1, 10, and 100 Hz. Each sinusoid had an amplitude of 25 mV and random phase to minimize the overall excursion of the applied voltage signal. The electrode impedance at a specific frequency was calculated in the frequency domain by dividing the applied voltage signal by the measured current output.

In vitro impedance measurements

In vitro EIS measurements were performed with an individual DBS electrode contact as the working electrode and the counter electrode was a coiled Ag|AgCl wire. The DBS electrodes were scaled-down versions of clinical electrodes suitable for implantation in the monkey brain and were fabricated by the Advanced Bionics Corporation (Valencia, CA). The electrodes had a 45 mm polyurethane shaft with four cylindrical platinum/iridium contacts located near the distal end of the lead shaft. Each electrode was 0.75 mm in diameter and 0.5 mm height with 0.5 mm insulation separating the individual contacts. *In vitro* measurements were performed in a 250 mL beaker containing 0.9% NaCl that was placed inside a copper Faraday cage to help minimize noise. *In vitro* EIS measurements showed the standard constant phase element (CPE) behavior of solid metal electrodes in which the impedance data followed a straight line on the impedance plot with a phase angle less than unity (data not shown) (McAdams *et al.*, 1995). *In vitro* measurements were also used to estimate the shunt capacitance of the DBS electrode and coupling capacitances between the individual contacts. The shunt capacitance was estimated by submerging the shaft of the DBS lead in saline while keeping the contacts exposed to air. The coupling capacitance between pairs of DBS contacts was estimated by measuring the impedance between the lead wires. The total stray capacitance of the electrode was then calculated by adding these parallel capacitances (i.e. $C_{\text{stray}} = C_{\text{shunt}} + C_{\text{coupling}}$). The total stray capacitance was typically 20 pF and this value was used in the model analysis described below.

In vitro EIS measurements were also used to examine the effect of protein adsorption on possible changes to the DBS electrode impedance. For this particular experiment, a DBS electrode was submerged in 0.1 M phosphate buffered saline (pH=7.4) containing 0.2 mg/mL bovine serum albumin (Sigma-Aldrich, St. Louis, MO, Product No. A-7906), equal to the albumin concentration in cerebrospinal fluid. EIS measurements were performed periodically for two weeks using the two-electrode cell configuration described above.

In vivo impedance measurements

For this study, *in vivo* impedance measurements were performed on chronically implanted electrode leads in the brain of a rhesus macaque monkey (*Macaca mulatta*; 8 years old; weighing 6 kg) (figure 1). The first electrode lead was implanted in the ventral thalamus of the left hemisphere and a second electrode lead was implanted in the subthalamic nucleus (STN) of the right hemisphere using previously described implant procedures (Elder *et al.*, 2005; Miocinovic *et al.*, 2007; Miocinovic *et al.*, 2009). All surgical and recording protocols were approved by the Cleveland Clinic Institutional Animal Care and Use Committee and complied with United States Public Health Service policy on the humane care and use of laboratory animals.

In vivo EIS measurements were performed with a single DBS electrode contact as the working electrode and the counter electrode was a Ag|AgCl coiled wire placed in the contralateral access

chamber and submerged in 0.9% NaCl (figure 2). The surface area of the Ag|AgCl counter electrode was much larger than the individual DBS contacts and was removed and cleaned at the end of each experiment to ensure the EIS measurements were dominated by the DBS electrode-tissue interface. The animal's chair was grounded to help minimize the effects of surrounding noise. During the experimental procedures, the animal was lightly sedated with acepromazine (1 mg/kg) to help minimize movement and pressure exerted on the head implant. The animal also received 4 mg of prednisolone 7 days a week to treat an endogenous intestinal disorder.

EIS measurements were performed before electrode implantation, immediately following implantation, and periodically after implantation. These measurements provided a means to detect the temporal profile of proteins and cells adhering to the electrode, which appeared as a semicircular arc in the high frequency range of the impedance spectra (e.g. 0.1–10 kHz) (Buitenweg *et al.*, 1998; Williams *et al.*, 2007). Changes in the properties of the electrode-electrolyte interface could also be observed as changes in the magnitude and phase of the low frequency range of the impedance spectra (e.g. 0.5–100 Hz).

Stimulation applied through a DBS contact has been shown to alter the electrode impedance (Hemm *et al.*, 2004). To examine the specific effects of stimulation on electrode impedance, voltage-controlled stimulation was applied through a DBS contact using an Itrel II implantable pulse generator (Medtronic, Minneapolis, MN) with the contralateral titanium access chamber as the return electrode. A clinically-relevant stimulus train of –1.0 V amplitude 90 μ s pulses delivered at a frequency of 135 Hz was used for this study. *In vivo* EIS measurements were performed before and after stimulation to examine the effect of DBS on the electrode impedance.

Equivalent circuit models

Equivalent circuit models were used to quantify the factors influencing the DBS electrode impedance. The circuit models were fit to measured impedance data to examine changes that occur after electrode implantation and during stimulation. Multiple impedance models were examined to identify the model components that were important for reproducing the observed impedance data. Overall, each individual model had one section representing the impedance of the electrode-electrolyte interface and a second section representing the impedance of the tissue layer near the electrode resulting from the adhesion or accumulation of cells and proteins (figure 3(A)–(D)). In the first model (model A), the impedance of the electrode-electrolyte interface was represented as an ideal capacitor. The tissue layer impedance consisted of the classical Lapicque model with a resistance in series with a parallel combination of a resistor and capacitor (McAdams and Jossinet, 1995; Foster and Schwan, 1996). In the remaining three models (models B–D), the electrode-electrolyte interface was represented by a constant phase element (CPE) according the following equation:

$$Z_{CPE} = \frac{K}{(j\omega)^\alpha} \quad (1)$$

where K was a magnitude scaling factor and α was a phase factor defined for $0 < \alpha < 1$. The CPE accounted for the non-ideal capacitive behavior of the electrode-electrolyte interface for solid metal electrodes that is believed to arise from specific adsorption and surface roughness effects (McAdams *et al.*, 1995). To represent the impedance of the tissue layer around the electrode, model B had the same Lapicque model as described above for model A. In model C, this impedance was represented by an encapsulation resistance in series with cellular and extracellular compartments. The cellular compartment contained a specific membrane conductance ($g_m = 0.3 \text{ mS/cm}^2$) and membrane capacitance ($c_m = 1 \text{ } \mu\text{F/cm}^2$) multiplied by a cell

membrane area scaling term (A_m). This cellular compartment represented the membrane conductance and capacitance of glial cells and macrophages that typically accumulate around the electrode over time. The extracellular compartment was composed of a single resistor representing the resistance to ionic current flow through the extracellular space. This model has previously been used to understand the composition of the electrode-tissue interface in chronic microelectrode recording applications (Johnson *et al.*, 2005; Otto *et al.*, 2006; Williams *et al.*, 2007). In the fourth impedance model (model D), the tissue layer impedance was represented by a modified Lapicque model of a resistance (R_∞) in series with a parallel combination of a resistance (ΔR) and a CPE (figure 3(D)) (McAdams and Jossinet, 1995). R_∞ represents the tissue layer resistance measured at an infinite stimulation frequency while R represents the difference between the tissue layer resistance measured at DC (R_0) and R_∞ (i.e. $\Delta R = R_0 - R_\infty$). Each of the four models used in this study contained a capacitor representing the stray capacitance of the electrode. This capacitance was connected in parallel to the electrode and tissue components of each model. This stray capacitance represented a combination of the shunt and coupling capacitances of the DBS electrode and was set to a fixed value of 20 pF. This capacitor is not shown in the circuit diagrams.

Parameter estimation

Parameter estimates were calculated with a direct-search method using the *PATTERNSEARCH* function available in Matlab (Mathworks, Natick, MA). Model fits were performed by minimizing the following objective function:

$$J = \sum_{j=1}^N \left(\frac{\left(Z'_j - \dot{Z}'_j \right)^2}{\left(\dot{Z}'_j \right)^2} + \frac{\left(Z''_j - \dot{Z}''_j \right)^2}{\left(\dot{Z}''_j \right)^2} \right) \quad (2)$$

where j indicates a particular frequency at which the impedance was measured, N represents the total number of frequencies, Z'_j represents the real part of the measured impedance at the specific frequency and $\dot{Z}'_j$ the corresponding model estimate, and Z''_j represents the imaginary part of the measured impedance at the specific frequency and $\dot{Z}''_j$ the corresponding model estimate. According to equation (2), function weighting was used to estimate the model parameters. Function weighting was selected over other possible weighting methods, such as modulus weighting, because function weighting is less likely to lead to biased parameter estimates (Macdonald, 1992). For each data set, five sets of initial parameter values were randomly chosen throughout the entire parameter space and the set of optimized parameter values that produced the minimum error was selected. The use of a direct-search method and multiple initial starting points helped improve the probability of finding the global minimum.

Model analysis was applied to the measured impedance data to identify significant changes in the model parameters following electrode implantation and during stimulation. Statistically-significant changes in the model parameters were detected with the Wilcoxon matched-pairs signed-ranks test, a nonparametric procedure applied to hypothesis testing in which there are two dependent samples (e.g. parameter values before stimulation and after stimulation). Significance was set to $p < 0.05$.

Results

Model analysis

The model complexity necessary to accurately reproduce the measured impedance spectra was examined by comparing four impedance models (figure 3). Each model had two major sections; an electrode component representing the electrode-electrolyte interface and a tissue component representing the tissue layer around the electrode formed by the adhesion and accumulation of proteins and cells. Each model was fit to experimentally recorded impedance data and the model error was calculated using equation (2) (figure 3(E)–(F)). On average, model D returned the lowest total model error (figure 3(F)) by providing the lowest model error in both the low frequency range that described the electrode-electrode interface and the high frequency range that described the surrounding tissue layer (data not shown). Therefore, model D was used for the remaining analysis in this paper.

Changes in electrode impedance after implantation

DBS electrode impedance was examined as a function of time after implantation by performing EIS measurements periodically after implantation. Figure 4 displays a typical data set where substantial changes in the impedance spectra can be seen in the days following implantation. Changes occurred in both the magnitude and phase of the electrode-electrolyte interface, as well as development of a semicircular arc in the high frequency range of the impedance measurements (i.e. 0.1–10 kHz). This semicircular arc, typically referred to as the tissue component, became apparent within the first five days and began to stabilize within the first few weeks after implantation (figure 4).

We compared the impedance data measured 24 hours and approximately two weeks after implantation using model D (figure 5). Parameter values were determined for impedances measured from the four contacts of the DBS electrode implanted in the thalamus and the four contacts of the DBS electrode implanted in the STN ($n=8$). All of the model parameters showed a statistically-significant change except for R_∞ (figure 5(B)).

The model analysis showed a decrease in the magnitude and phase of the electrode-electrolyte interface impedance two weeks after implantation ($p=0.008$ for K_e and $p=0.023$ for α_e). However, the most significant changes in the model parameters were encountered in the impedance of the tissue layer surrounding the electrode in which K_t , α_t , and ΔR all increased ($p=0.008$). On average, the magnitude of the tissue layer capacitance (K_t) increased more than 67 times its initial value while ΔR increased more than 11 times its initial value two weeks after implantation.

Stimulation-induced changes in electrode impedance

The effect of clinically-relevant stimulation on DBS electrode impedance was examined using a train of charge-balanced biphasic stimulus waveforms. The stimuli were generated using a Medtronic pulse generator (Itrel II, Minneapolis, MN) and had the following parameters: -1.0 V amplitude, $90 \mu s$ pulse width, and 135 Hz frequency. Stimulation was applied for a total of 60 minutes and EIS measurements were performed before and after stimulation (figure 6(A)).

Model analysis showed stimulation caused statistically-significant changes in both the electrode and tissue components of the impedance model (figure 6(B)). The electrode-electrolyte interface impedance exhibited an increase in both magnitude and phase (K_e and α_e , $p=0.031$). However, stimulation caused the most substantial changes in the impedance of the tissue layer surrounding the electrode. These impedance changes were dominated by a large decrease in both the capacitive (K_t and α_t) and resistive (ΔR) components of the tissue parameters ($p=0.031$) that appeared as a large decrease in the size of the semicircular arc in

the high frequency range of the impedance spectra (figure 6). Specifically, K_i exhibited an 81% decrease while ΔR showed a 70% decrease in magnitude.

Although stimulation caused a large decrease in the electrode impedance, these changes were reversible and the electrode impedance began increasing immediately after stimulation was stopped (data not shown). Typically, small changes were observed minutes after the end of stimulation and a complete recovery to pre-stimulation impedances often occurred within days. These rapid and reversible changes in the electrode impedance demonstrate the dynamic nature of the foreign body reaction.

Discussion

The goal of this study was to investigate changes in DBS electrode impedance that occur after electrode implantation and clinically-relevant stimulation. We utilized EIS as a non-invasive and rapid technique to characterize impedance changes over a wide range of frequencies to better understand the electrode-tissue interface. EIS provides more information than the standard impedance measurement at 1kHz and has been used extensively to study the composition of the electrode-tissue interface in various microelectrode applications (Buitengeweg *et al.*, 1998; Keese *et al.*, 2004; Johnson *et al.*, 2005; Otto *et al.*, 2006; Frampton *et al.*, 2007; Williams *et al.*, 2007). Our results show that: 1) DBS electrode impedance significantly increased during the first few weeks after electrode implantation, and 2) application of clinically-relevant stimulation significantly and reversibly decreased the electrode impedance. These results have important clinical implications for the use of voltage-controlled stimulators since the current delivered to the tissue is inversely proportional to the electrode impedance.

Characterizing DBS electrode impedance

Equivalent circuit models were used to interpret the impedance spectra measured from the implanted DBS electrodes. Multiple impedance models were investigated to assess the model complexity necessary to accurately reproduce the experimental measurements. Each of the four models examined in this study had two major sections: one representing the impedance of the electrode-electrolyte interface and the other representing the impedance of the tissue layer formed around the electrode due to the adhesion and accumulation of proteins and cells (figure 3(A)–(D)). Comparison of the four models, showed model D produced the lowest model error (figure 3(F)).

Model A relied on an ideal capacitor to represent the electrode-electrolyte interface and produced the highest errors. The error in the other three models was substantially reduced by incorporating a constant phase element (CPE) to represent the impedance of the electrode-electrolyte interface. A CPE is an empirically-derived model of the electrode-electrolyte interface that accounts for the non-ideal capacitive properties of solid metal electrodes (McAdams *et al.*, 1995).

Models B and C differed in their respective tissue components. Model B consisted of a classical Lapicque model composed of a resistance (R_∞) in series with a parallel combination of a capacitance and resistance (ΔR) (McAdams and Jossinet, 1995). R_∞ represented the tissue resistance at an infinite stimulus frequency and ΔR represented the difference between the tissue resistance at DC and R_∞ . The tissue component of model C had an encapsulation resistance in series with a cellular and extracellular component. The physical interpretation of the encapsulation or sealing resistance is protein adsorption onto the electrode contact and/or an adjacent layer of connective tissue (Johnson *et al.*, 2005), while the cellular component represents the membrane conductance and capacitance of cells near the electrode (Otto *et al.*, 2006; Williams *et al.*, 2007). A specific membrane conductance (g_m) and membrane

capacitance (c_m) are multiplied by a scaling term, A_m . Thus A_m provides an estimate of the total area of cellular membrane that affects the electrode impedance. This cellular component is in parallel to an extracellular resistance that represents pathways for ions to travel in the extracellular space. Models B and C often exhibited fitting errors that were similar; however, one advantage of model C is the implied physical meaning of its parameters. This type of model may be more advantageous for microelectrode applications where the dimensions of the neural and glial cells are of a similar order of magnitude as the electrode contact. However, physical interpretation of these parameters is limited by the assumptions required in formulating this model such as the use of a purely resistive encapsulation layer, the membrane capacitance of cells near the electrode are the only capacitive component of the tissue (i.e. the extracellular pathway is purely resistive), and the conductivity and capacitance of the cell membranes are constant.

We used model D for the statistical analyses done in this study. Model D is not dependent upon the assumptions described above for model C, but physical interpretation of the model results is not as clear. Model D relied on a CPE to model the impedance of the electrode-electrolyte interface and a second CPE to represent the tissue capacitance. Thus the tissue component of model D represented a modified Lapicque model that was first proposed by Cole (Cole, 1940; McAdams and Jossinet, 1995). Incorporation of a CPE representing the capacitive behavior of the tissue allowed for model D to produce increased accuracy in fitting the experimentally measured impedance data (figure 3(F)).

We used the model analysis to quantify the effect of the foreign body reaction on the implanted electrode impedance. All of the model parameters (except R_∞) underwent a statistically-significant change during the first two weeks after implantation (figure 5(B)) that included a decrease in both the impedance magnitude and phase of the electrode component (K_e and α_e). These changes show potential modification to the behavior of the electrode-electrolyte interface caused by the adsorption of various ions, proteins, and cells to the electrode (Contu *et al.*, 2002; Frampton *et al.*, 2007). These changes in the electrode-electrolyte interface impedance could also be due to changes in the ionic composition of the cerebrospinal fluid near the electrode during vasogenic and cellular edema (Unterberg *et al.*, 2004). The largest changes were the increases in the model parameters representing the impedance of the tissue layer surrounding the electrode (K_t , α_t , and ΔR). The drastic increase in both the magnitude of the tissue layer capacitance, K_t , and the resistance, ΔR , suggests the migration of various glial cells to the electrode site as a part of the foreign body reaction. This conclusion was further supported by the time course of these impedance changes that closely paralleled the time course for establishing the chronic foreign body reaction that is characterized by the formation of foreign body giant cells and granulation tissue around the implanted device (Anderson *et al.*, 2008). Direct adhesion of cells and the development of an encapsulation layer around electrodes implanted in the central nervous system has been documented for both cortical microelectrode (Szarowski *et al.*, 2003; Biran *et al.*, 2005) and DBS applications (Haberler *et al.*, 2000; Moss *et al.*, 2004; Nielsen *et al.*, 2007).

Before cells can adhere to the electrode, proteins need to adsorb to the electrode surface. Therefore, it is possible the impedance changes measured *in vivo* could largely be attributed to the adsorption of proteins to the electrode surface and not the accumulation of cells near the electrode (Gimsa *et al.*, 2005). In order to examine this possibility, a DBS lead was submerged in 0.2 mg/mL albumin and EIS measurements were performed periodically during the following two weeks. Impedance measurements of all four contacts showed only minor changes during this time and no development of a semicircular arc in the high frequency range (data not shown). These results suggest the semicircular arc in the EIS measurements of a chronically-implanted DBS electrode was due to the accumulation of cells around the electrode contact.

Electrical stimulation caused a significant decrease in the tissue component (i.e. high frequency range) of the impedance spectra and small changes in the magnitude and phase of the electrode-electrolyte interface impedance (figure 6). The largest changes were in the magnitude of the tissue capacitance (K_t) and ΔR . While it is difficult to interpret the exact physical basis for these results, one possible explanation is that stimulation applied through the electrode polarizes the surface causing the attached proteins and cells to desorb. This “cleaning” of the electrode surface could produce a corresponding decrease in the electrode impedance. This phenomenon has been observed for both *in vitro* and *in vivo* applications (Keese *et al.*, 2004; Johnson *et al.*, 2005). Keese *et al.* (2004) observed electroporation of cultured cells adhered to the electrode after application of high frequency (40 kHz) voltage pulses and a corresponding decrease in the electrode impedance to levels similar to the bare electrode impedance. Johnson *et al.* (2005) applied DC voltage signals to help improve the chronic recording capabilities of cortical microelectrodes and showed a substantial decrease in both the electrode and tissue impedance parameters. The described cleaning of the electrode surface is further supported by the observation that stimulation applied through one contact did not cause impedance changes to adjacent contacts (data not shown). These results suggest that the measured impedance is dominated by the properties of the tissue within $\sim 100\ \mu\text{m}$ of the electrode contact and not the properties of the bulk brain tissue.

The impedance spectra of the DBS electrodes did not show significant changes in R_∞ either after implantation or after electrical stimulation (figures 5(B) and 6(C)) that would correspond to resistive shifts of the entire impedance spectra along the horizontal axis. These small resistive shifts are in contrast to the impedance changes observed for microelectrodes in which large increases in R_∞ have been documented after implantation, along with large decreases in R_∞ after applying electrical stimulation (Johnson *et al.*, 2005; Otto *et al.*, 2006). This lack of significant change in R_∞ for the DBS electrodes could be attributed to the relatively large contact size. The large DBS electrode size provides an increased number of pathways for current to flow. In turn, DBS electrodes may have a lower access resistance and a lower sensitivity to the adsorption of various proteins directly on the electrode that could produce large changes in R_∞ . This conclusion was further supported by the *in vitro* experiment described above in which the DBS electrode impedance showed little resistive shifts when placed in a solution containing in 0.2 mg/mL albumin (data not shown).

Model limitations

The equivalent circuit models used in this study provided accurate fits to the experimentally measured impedance spectra in a non-human primate, however, these models have notable limitations. The most significant limitation was the use of models composed of linear circuit elements. EIS measurements were performed with a small amplitude voltage sinusoid to ensure that the electrode was operating under linear conditions and permitted the electrode impedance to be determined at multiple frequencies using Ohm’s law. However, under stimulating conditions, the DBS electrode likely exhibits nonlinear behavior that would make these linear circuit elements invalid. Because of this limitation, the main purpose of the EIS measurements and model analysis performed in this study was to examine interval changes in the composition of the electrode-tissue interface for individual electrodes under multiple experimental conditions. However, this limitation is justified because of the extreme difficulties of attempting to examine these changes for individual electrodes using histological techniques in which the animal would need to be sacrificed and/or the electrode removed.

A second limitation was the use of spatially-lumped circuit elements to describe a spatially-distributed environment. However, the advantage of using spatially-lumped circuit elements was their ease to parameterize while still providing insight into the physical significance of the measured electrode impedance. Another limitation was the inability to guarantee parameter

uniqueness in the model optimization. Even though multiple initial parameter values were utilized to help improve the likelihood of locating the global minimum, it was not possible to guarantee the parameter values generated from the optimization methods were unique or represented the global minimum.

Experimental limitations

While the experimental conditions used in this study closely mimicked clinical DBS, there are a number of potential issues that should be recognized. The first limitation was the physical stability of the DBS electrode in the monkey chamber system. The electrode was fixed to the access chamber attached to the skull and allowed for micromotion between the skull and brain. Brain shift could therefore affect the stability of the electrode-tissue interface and the corresponding electrode impedance. However, clinical DBS electrodes are also fixed to the skull and thus generate a similar degree of brain shift relative to the DBS electrode. A second limitation was the treatment of the experimental animal with the steroid, prednisolone, which could influence the extent of the foreign body reaction to the implanted electrodes. However, similar changes in DBS electrode impedance after implantation and during stimulation were observed with other animals not receiving this drug (data not shown).

Clinical relevance of results

The results of this study show major changes in DBS electrode impedance occur after electrode implantation and during stimulation. These impedance changes could be an important issue for DBS patients implanted with voltage-controlled stimulators. Typically, patient programming is not started until 3–4 weeks after electrode implantation to ensure that disease symptoms stabilize from any micro-lesioning effects induced in the operating room and to allow time for the foreign-body reaction to stabilize (Deuschl *et al.*, 2006). If patient programming is begun within the initial 3–4 weeks after implantation, there is often a need to frequently adjust the parameter settings to maintain therapeutic benefit while minimizing unwanted side effects. The electrode impedance changes observed in this study help explain why this initial delay in patient programming is necessary as fluctuating electrode impedance directly affects the voltage distributions generated during voltage-controlled stimulation (Butson *et al.*, 2006; Yousif *et al.*, 2008; Miocinovic *et al.*, 2009).

Following the initial electrode stabilization period, stimulation parameters (amplitude, pulse width, frequency) are selected by an experienced clinical programmer, to be delivered through an electrode contact(s) that maximize therapeutic benefit while minimizing any stimulation-induced side effects. However, after a couple hours of stimulation unwanted side effects can appear (Volkmann *et al.*, 2002). The appearance of these unwanted side effects may be attributed to the changes in electrode impedance induced by the stimulation (figure 6). The overall decrease in electrode impedance that occurs due to the applied stimulation would result in a larger area of tissue being stimulated for the same stimulation parameters (Butson *et al.*, 2006). Thus, as the impedance decreases over time, supra-threshold stimulation can reach regions of the brain implicated in the appearance of various side effects (e.g. sustained muscle contractions, dyskinesias, paresthesias, etc.).

While clinically-relevant stimulation caused changes to the properties of the electrode-electrolyte interface of the DBS electrode, the most dramatic changes occurred in the tissue component of the electrode impedance (figure 6). We observed a dramatic decrease in the size of the semicircular arc in the high frequency range of the impedance spectrum (figure 6(A)). After 1 hour of stimulation, the electrode impedance qualitatively resembled the impedance of a freshly implanted electrode except for a small residual tissue component in the high frequency range of the impedance spectrum (figure 6(A)). Similar results have also been observed following stimulation through microelectrodes (Johnson *et al.*, 2005; Otto *et al.*, 2006). This

remaining semicircular arc could be attributed to several factors. It is possible that stimulation fails to clean off all of the adhered proteins and cells. The remaining tissue component observed during stimulation could be also be representative of the encapsulation sheath surrounding the electrode that may be unaffected by the stimulation. This hypothesis is supported by histological studies that have been unable to detect any measurable differences in the encapsulation sheath around stimulated and non-stimulated DBS electrode contacts or the polyurethane tubing (Haberler *et al.*, 2000;Nielsen *et al.*, 2007). This remaining tissue component shows stimulation does not reverse all of the impedance changes due to the foreign body reaction that may directly affect the voltage distribution generated during stimulation (Butson *et al.*, 2006;Yousif *et al.*, 2008;Miocinovic *et al.*, 2009).

Conclusion

This study utilized electrode impedance spectroscopy to characterize deep brain stimulation electrodes implanted in the brain of a rhesus macaque monkey. These electrodes were permanently implanted in regions of the brain that are common targets for deep brain stimulation applications (i.e. thalamus and subthalamic nucleus). Model analysis was used to understand the changes that occur in electrode impedance after implantation and following prolonged stimulation. We observed a major increase in the electrode impedance during the first two weeks after implantation, presumably caused by the foreign body reaction to the implanted electrode. This increase in electrode impedance was composed of changes to both the electrode and tissue components of the overall impedance. The most substantial change occurred in the tissue component of the impedance and was characterized by the development of a semicircular arc in the high frequency range of the impedance measurements. Electrical stimulation caused a decrease in the impedance within the first hour of stimulation that was characterized by a major decrease in the tissue component of the electrode impedance. Because clinical DBS systems rely on voltage-controlled stimulation, these impedance changes could play an important role during patient programming (e.g. stabilization periods, assessment times, and parameter adjustments).

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Figure 1.

Surgical planning and electrode implantation. (A) Cicerone software was used to plan the locations of the access chambers on the skull and the DBS electrodes to be implanted in the thalamus (left hemisphere) and the STN (right hemisphere). (B) Sagittal X-ray images of the two DBS electrodes after implantation. (C, E) The post-DBS-implantation CT was co-registered to the pre-operative MRI scan. The white contours were defined from the CT and represent the implanted DBS electrodes. (D, F) The approximate location of the implanted DBS electrodes with respect to specific brain nuclei was defined with an atlas scaled to match the neuroanatomy of the animal.

Figure 2.

Electrode impedance spectroscopy (EIS) of the implanted DBS electrodes. (A) A two-cell electrode configuration was used to perform the EIS measurements. The working electrode was the DBS contact of interest and the counter electrode consisted of a Ag|AgCl electrode placed in the contralateral chamber. (B) The typical impedance spectrum was linear in the low frequency range, which followed the constant phase element (CPE) behavior at electrode-electrolyte interfaces. In the higher frequency range, a semicircular arc represented the tissue component surrounding the electrode contact.

Figure 3.

Equivalent circuit models. Each model consisted of an electrode component that represented the impedance of the electrode-electrolyte interface and a tissue component that represented the impedance of the tissue layer around the electrode. Each model had a capacitor connected in parallel to account for the stray capacitance of the electrode (capacitor not shown). (A) Classical model with the electrode-electrolyte interface impedance represented by a capacitor and the tissue layer impedance represented with a Lapicque equivalent circuit model. (B) The electrode-electrolyte interface impedance is replaced by a constant phase element (CPE) to account for non-ideal capacitive properties of solid metal electrodes. (C) A model used in previous studies to understand the impedance of cortical microelectrodes in which the tissue

component has cellular and extracellular compartments. (D) The electrode-electrolyte interface impedance is represented by a CPE and the tissue layer impedance is represented by a modified Lapicque equivalent circuit model in which the tissue capacitance is modeled using a second CPE. (E) An example in which each of the four models was fit to the same impedance data. (F) Average error for each model when fitting the impedance data measured 15 days and 16 days after implantation for the DBS leads implanted in the thalamus and STN, respectively. The error bars represent the standard deviations.

Figure 4.

Evolution of DBS electrode impedance after implantation. (A) Nyquist plots of the complex impedance during the first nine days after implantation. Immediately after implantation in the brain (day 0), the DBS electrode exhibited CPE behavior. Within the first five days, there was a significant change in the DBS electrode impedance due to the foreign body reaction and a prominent semicircular arc developed in the high frequency range. The 1, 10, and 100 Hz frequency points are indicated for the impedance measurements performed on day 0 and day 9. (B) The resistive and reactive components of the measured impedance as a function of frequency during the first nine days after implantation. (C) The 1 kHz impedance during the first nine days after implantation for the same electrode shown in (A) and (B). The inset shows stabilization of the 1 kHz electrode impedance over the first 100 days after implantation.

Figure 5.

Model parameters after electrode implantation. (A) Model D was used to analyze the changes in DBS electrode impedance that occurred following implantation. (B) Impedance data measured 24 hours (gray bar) and more than 2 weeks (black bar) after implantation was used to examine potential changes in model parameters. The data presented in (B) represents the mean parameter values for the impedance measured at 8 DBS electrode contacts. The error bars represent the standard deviations. Model analysis was performed for impedance data measured 1 day and 15 days after implantation for the thalamic DBS lead and 1 day and 16 days after implantation for the STN lead. All of the model parameters, except R_∞ , showed statistically-significant changes (* for $p=0.023$ and ** for $p=0.008$).

Figure 6.

Effect of clinically-relevant stimulation on DBS electrode impedance. (A) An example of typical impedance spectra measured before stimulation and after 60 minutes of stimulation. The model fits are also shown. (B) The resistive and reactive components of the impedance data shown in (A) as a function of frequency. (C) Average of the model parameters estimated for six separate experiments performed on contacts from both the DBS electrode implanted in the thalamus and the DBS electrode implanted in the STN (n=6). The error bars represent the standard deviation. All of the model parameters, except R_∞ , showed a statistically-significant change (* for p=0.031).