Deep brain stimulation in movement disorders: stereotactic coregistration of two-dimensional electrical field modeling and magnetic resonance imaging

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Object. Adjusting electrical parameters used in deep brain stimulation (DBS) for dystonia remains time consuming and is currently based on clinical observation alone. The goal of this study was to visualize electrical parameters around the electrode, to correlate these parameters with the anatomy of the globus pallidus internus (GPI), and to study the relationship between the volume of stimulated tissue and the electrical parameter settings.

Methods. The authors developed a computer-assisted methodological model for visualizing electrical parameters (the isopotential and the isoelectric field magnitude), with reference to the stereotactic target, for different stimulation settings (monopolar and bipolar) applied during DBS. Electrical field values were correlated with the anatomy of the GPI, which was determined by performing stereotactic magnetic resonance imaging in one reference patient.

By using this method it is possible to compare potential and electrical field distributions for different stimulation modes. In monopolar and bipolar stimulation, the shape and distribution of the potential and electrical field are different and depend on the stimulation voltage. Distributions visualized for patient-specific parameters can be subsequently correlated with anatomical information. The application of this method to one patient demonstrated that the 0.2-V/mm isofield line fits best with the lateral GPI borders at the level of the stimulated contacts.

Conclusions. The electrical field is a crucial parameter because it is assumed to be responsible for triggering action potentials. Electrical field visualization allows the calculation of the stimulated volume for a given isoline. Its application to an entire series of patients may help determine a threshold for obtaining a therapeutic effect, which is currently unknown, and consequently may aid in optimizing parameter settings in individual patients.

Key Words • globus pallidus internus • deep brain stimulation • electrical field distribution • potential distribution • stimulated volume • dystonia • stereotactic coregistration

Since the 1990s, long-term electrical stimulation of subcortical structures has been proposed for treating movement disorders in humans. In 1996, based on the positive results of DBS in patients with parkinsonian symptoms, generalized dystonia began to be successfully treated by continuous bilateral electrical stimulation of the GPI.

The rate of improvement between centers has proved variable, however. Many factors may influence patient outcomes including the following: clinical variables such as patient selection and type of dystonia; surgical variables such as the position of electrode contacts; and electrical parameter settings such as pulse width, amplitude, and rate. Consequently, the selection of the surgical target and postoperative control of the position of the electrode are crucial to obtaining a therapeutic effect. To date, parameter adjustment procedures in patients receiving DBS for dystonia remain time consuming and are based solely on clinical observation of the patient and experience of the neurologist. This is partly because the response to stimulation is generally delayed. Many clinicians applying DBS may not be aware of the influence of the stimulation parameters on the distributions of the potential and the electrical field around the electrode. Furthermore, the anatomical structures affected by stimulation, the threshold for activation and consequently the optimal stimulation parameters for current delivery remain in question. The aim of this study was to quantify the influence of stimulation parameters in an objective way. The selection of what volume of tissue should be stimulated requires knowledge about the threshold necessary to provoke an action potential and to obtain the expected physiological effect. Therefore, the object of this study was to develop a computer-assisted method for visualizing electrical parameters around the electrode, to correlate them with the GPI anatomy, and to study the relationship between the stimulated tissue volume and electrical settings.

Clinical Material and Methods

Theoretical Model

We designed a static model (see Appendix) of the in vivo
stimulation system including the electrode (3389; Medtronic, Rueil-Malmaison, France) and pulse stimulators (IPG 7424, 7425, and 7426; Medtronic) used for bilateral DBS. The electrode has a diameter of 1.27 mm; it contains four contacts numbered 0 to 3 (0 referring to the lower contact and 3 to the upper contact), each of which is 1.5 mm in height and separated by 0.5 mm.

In our model, we considered brain tissue in the vicinity of the stimulating electrode to be homogeneous material with an isotropic resistivity and no voltage-dependent nonlinear effects. Furthermore, we applied electrostatic approximation: that is, the current was considered to be constant. Consequently, the potential (V) and the voltage gradient distribution (V/mm), that is, the electrical field, are independent of frequency and pulse width. It should be noted that both parameters depend solely on the amount of the applied voltage and the electrode configuration and not on tissue conductivity. This is based on the initial hypothesis of a constant and isotropic conductivity in the surrounding structure.

Hardware and Software

Based on this model, a computer program was developed on a Hewlett-Packard Workstation (Palo Alto, CA). This customized software calculates and displays the distributions of the potential and the electrical field magnitude around the electrode in the longitudinal and axial planes according to the stimulation parameters recorded in the patients in whom telemetry is used to monitor voltage, impedance, and contact configuration. Points around the electrode representing the same potential or electrical field magnitude are linked to one line, the IPL or the IFL, respectively. In addition, it is possible to extract the line representing a specific electrical field value from a family of IFLs and to visualize this line. The electrode orientation can be adapted by entering the coordinates of the four electrode contacts in the stereotactic space whose reference system is the surgical frame.

Study of Different Electrode Configurations

In our series of 90 surgically treated patients, we established a method for treating movement disorders based on monopolar stimulation through one contact (153 electrodes, 58% of patients) or two contacts (79 electrodes, 30% of patients). Less frequently we applied monopolar stimulation through three contacts (21 electrodes, 8% of patients) or applied bipolar stimulation (11 electrodes, 4% of patients). We studied the IFL and IPL distributions around the electrode for the reference configuration, monopolar through one contact, and for bipolar stimulation with previously established voltages. To map the position of each IFL precisely, the software was designed to consecutively extract the isofield line in 0.1-V/mm steps from the 0.1-V/mm to the 1-V/mm IFL, respectively. To improve our understanding of each image, we decided to display and compare three values: the two extreme values, 0.1 V/mm (IFL0.1) and 1 V/mm (IFL1.0), and one intermediate value, 0.2 V/mm (IFL0.2). We also investigated the IFL distribution depending on the voltage (1, 1.5, or 2 V) used in monopolar stimulation. Contact 1 negative (represented as C+1−) and bipolar (0+1−2+) stimulation.

Correlation of the Electrical Field and Anatomy of the GPI

Mean GPI Size. Typically the target in the GPI for DBS in patients with dystonia has been defined on an axial slice at the level (z coordinate) of the anterior commissure in the anterior commissure–posterior commissure plane,26 in the middle of the internal–external pallidal distance and in the third quarter between the anterior and posterior GPI border (Fig. 1). The halfway point between electrode Contact 1 and Contact 2 is placed on this surgical target. On the axial slice passing through the middle of the stimulated contact, the mean anterior–posterior distance is 16 ± 2 mm, whereas the mean internal–external distance is 4 ± 1 mm. As a consequence, the mean distances on an axial slice from the center of the contact to the internal, external, posterior, and anterior GPI borders are 2, 2, 4, and 12 mm, respectively. To visualize the position of each IFL, we coregistered the modeled field with the stereotactic MR image by using a stereotactic method.

Application of GPI Targeting. Two steps are necessary to correlate anatomical data obtained in a patient with the corresponding electrical field. First, we identify slices passing through the middle of the stimulated contacts26 on routine postoperative MR images obtained using a stereotactic Leksell frame. The coordinates expressed in the Leksell reference system, including the trajectory angles, are then transferred to the preoperative stereotactic MR images so that we may superimpose the electrical field onto an image without electrode artifacts. The slices passing through the contacts are registered afterwards and retained for the frame-based superimposition.

Secondly, we determined the three chosen electrical field values (0.1, 0.2, and 1 V/mm) in the coronal and axial directions, based on the stimulation parameters selected for the patient (1.6 V, C+1−). These data are correlated with the corresponding preoperative MR image. Furthermore, we measure the distance from the middle of the electrode artifact to the internal and external borders of the pallidum on postoperative MR images at the level of each of the four contacts. These distances are added to the longitudinal representation of the patient’s specific IFLs.
Results

Application of the Software to Different Electrode Configurations

The distributions of the IPL (Fig. 2A and D) and IFL (Fig. 2B and E) varied highly for the two electrode configurations. The affected area changed along the z axis as well as radially, depending on the stimulation mode and the number of stimulated contacts.

The volume included by the three chosen IFLs increased with a decreasing critical electrical field value (from 1 to 0.1 V/mm; Fig. 2C and F). The volume affected by a given IFL increased with the voltage. The shapes of the IPLs and IFLs (Figs. 2 and 3) differed between mono- and bipolar stimulation modes. Monopolar settings affected the region around the activated contacts more homogeneously, whereas the bipolar setting resulted in IFLs with irregular, wave-shaped contours.

Correlation of the Electrical Field and the GPI Anatomy

The electrical field distribution was correlated with anatomical data, based first on the mean GPI size (Fig. 3) and second on a specific three-dimensional stereotactic MR image (Fig. 4) obtained in a 17-year-old girl with primary-onset dystonia who experienced a 95.8% improvement on the Burke-Marsden-Fahn Dystonia Rating Scale following bilateral GPI stimulation.

For the correlation of the patient’s specific electrical field distribution (C−, 1−, 2−) with the anatomical information, the internal and external GPI borders were indicated by points on the longitudinal electrical field orientation (Fig. 4A). The IFLs, always remained outside the internal border and inside the external border, except at the level of the stimulated contact.

When we superimposed the axial slice of the electrical field at the level of the stimulated contact over the corresponding MR imaging slice (Fig. 4B), the IFL always extended beyond the internal border of the posterioventral portion of the GPI and overlapped the internal capsule.

The IFL always was within the GPI borders at the level of all contacts (Fig. 4A). At the level of the stimulated contacts, the IFLs generally reached the lateral GPI borders.

The IFL always remained inside the GPI very close to the electrode, especially at the middle of the stimulated Contact 1.

The posterior and anterior borders were never reached by any of the three selected critical field values.

Discussion

The exact mechanism of action of DBS remains un-
known. One approach to identifying the mechanism could be to define the critical volume of gray and/or white matter to be stimulated according to its localization and quantity. Consequently, the superimposition of electrical parameters over patient-specific anatomy is a potentially promising new method of use in clarifying this mechanism. The correlation of these data necessitates a theoretical model representing the stimulated structure and major knowledge about the mechanism of action to identify the most significant electrical parameter for stimulation and to assist in an interpretation of the results.

The existing theoretical models for neuron and nerve stimulation described in the literature rarely address DBS. Holzheimer\textsuperscript{11} presented a complex model able to simulate primary effects of spinal cord stimulation on nerve fibers. Brain studies have focused on the central nervous system\textsuperscript{21} and, more specifically, on the cerebellum\textsuperscript{22} and cerebral cortex.\textsuperscript{20} More recently, McIntyre and associates\textsuperscript{19} reported a neural model applied to DBS of the STN to estimate the stimulated volume. As with many models,\textsuperscript{13,18,20,22} these authors subdivided the environment of the stimulated structure into elements characterized by different resistivities. McIntyre and associates determined these electrical conductivities based on diffusion tensor MR imaging data obtained in one patient and correlated them with neuron cable models, taking into account axon diameter and internodal spacing. This type of model is likely to be more relevant because of its closer fit to brain structure. This approach is promising because it takes into account the heterogeneity of the brain; however, this complex model has not yet been demonstrated to be superior to a simple one, especially in clinical practice, in which individual brain anatomy is the most important parameter.

The proposed model in our study is based on the assumption that the resistivity within the GPI can be considered homogeneous. This consideration is acceptable because in the GPI neuron density is relatively low.\textsuperscript{20} If this approach proves to be contributory, a more complex model taking into account the histological structure of the region could be developed in the future.

The activation of neurons is triggered by membrane depolarization. This activation is due to a variation in the potential difference, which is influenced by several factors such as electrical and anatomical properties of neurons, distance and orientation relative to the electrode, tissue resistivities,\textsuperscript{12} stimulation pulse waveform, and configuration mode.\textsuperscript{21} The electrical field (that is, the voltage gradient parallel to the fiber) should be the main factor likely to trigger the action potential because it varies with fiber orientation relative to the electrode. Accordingly, we proposed to model the electrical field. In addition, the calculated model provides visualization of the potential distribution, illustrating the direction of the current flow and the electrical field (perpendicular to the IPLs). Current density has also been proposed as a relevant parameter to be modeled,\textsuperscript{18} but it is not directly related to the neural response to stimulation.\textsuperscript{19,21}

On the microscopic level, based on neuron cable models and microelectrode recordings, several authors have reported that action potentials are created in axons and not in cell bodies.\textsuperscript{13,28} By using whole-cell recordings in a current-clamp mode, Garcia and colleagues\textsuperscript{11} recently demonstrated that stimulation of STN neurons in the rat at therapeutically relevant frequencies suppresses spontaneous STN activity and generates instead a robust pattern of recurrent bursts of spikes. From these results we can hypothesize that stimulation works in a dual way: 1) by direct activation of neuronal and perhaps glial membranes, which become refractory to any incoming nonsynchronized signal; and 2) by stimulating exiting axons.

On the macroscopic level, there are two hypotheses for understanding the volume of the GPI that has to be stimulated to get an optimal clinical result. 1) Stimulation of a maximal volume is necessary to obtain the optimal effect (proportional effect). 2) The actual target is a network-specific target influencing remote structures and represents only a part within the stimulated volume (nonproportional effect).

Our analysis of the correlated data (electrical field and MR imaging data) is based on the proportional model. In our population of patients with primary dystonia, despite
smooth variations in the final position of the electrode within the GPI, which are caused by evolution of the target since the beginning of electrode implantation, the clinical results remain homogeneous. Hence, we can presently hypothesize that the entire target must be homogeneously stimulated—from the stimulated electrode contact to the structure boundaries. We explain this difference in the final stimulation parameters by differences in the GPI shape, extension, and perhaps neuron distribution and orientation, as well as by differences in etiological factors. Furthermore, we think that the stimulated volume is an individual factor; that is, the volume of tissue that needs to be stimulated depends on the conditions in a particular patient. The difference could also be due to a somatotopic organization within the GPI. In our study, we identified the position of several ISLs and interpreted the correlation with the GPI (Figs. 3 and 4). Our preliminary observations provided the following relationship. 1) The electrical field value of 1 V/mm probably cannot be considered sufficient because the resulting target (~1-mm width around the stimulated contact) seems to be too limited to be responsible for the clinical effect. 2) The value of 0.1 V/mm, by contrast, covers a large portion of the GPI, extending even beyond the internal and external GPI borders and overlapping the internal capsule. In this case, we would expect the occurrence of side effects. 3) The IFL_{0.2} fits best with the lateral GPI borders at the level of the stimulated contacts. This application of our computer-assisted tool to one clinical case indicates how this combination of electrical and anatomical information could be used for quantifying the electrical field that is necessary to produce the physiological effect supported by action potential triggering.

An analysis of the correlation between the three IFLs and the GPI anatomy in all our patients who displayed improvements will be presented elsewhere.

Our clinical results confirm that the anatomical volume that must be stimulated in GPI DBS to obtain a therapeutic effect overlaps the posteroverentral portion of the GPI. The discussion about the affected volume underlines the difficulty and uncertainty surrounding the construction of a visual model of tissue volume to be stimulated during electrode positioning: the target in the context of electrode implantation refers to the precise (millimetric) stereotactic target represented as a point or circle on the MR images. This targeted point does not correspond to the area to be stimulated, but to the place finally occupied by the electrode (1.27 mm in diameter and 1.5 mm in height). In the long term, the computer-assisted software that we describe could even be helpful during the targeting procedure, especially for neurosurgeons with less experience in DBS electrode placement, because it can be used to superimpose the stimulated volume for a given target onto the appropriate MR image. Furthermore, if the application of this model to all patients who experienced improvements in their dystonia reveals a common pattern, it could perhaps be used as a tool to indicate optimal stimulation parameters when starting stimulation in a given patient.

Conclusions

We sought to develop a computer-assisted method for 2D modeling of electrical parameters around the electrode used for DBS in movement disorders. The final objective focused on the visualization of these parameters on 2D stereotactic MR images so that we could evaluate each patient’s condition for stimulation.
Fig. 5. Depiction of the theoretical model of the stimulation system in vivo. The conducting medium is confined within an insulating cylinder (radius 40 mm; height 80 mm) with the electrode placed along its axis. The IPG is modeled as an additional perfect conductor disk and placed at the bottom of the cylinder. A: For the bipolar mode, negative and positive contacts are located on the electrode. B: For the monopolar mode, the negative pole is on the electrode and the metal disk is positive.

The electrical field distribution is the most relevant parameter for electrical stimulation, because it is assumed to be responsible for starting bursts of action potentials. The fact that the contours of the stimulated volume are not intuitive underlines the need of such a 2D electrical parameter–anatomical coregistration. The visualization of specific IFLs should facilitate the determination of the stimulated region around the electrode. In the long term, its application to our entire population of patients with dystonia should help elucidate the mechanism of action as well as the optimal stimulation setting in individual cases. It will confirm or deny whether the identified threshold value of the electrical field at the GPI borders of approximately 0.2 V/mm really represents a common characteristic.

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Appendix

The following model has been designed and calculated in the laboratory of mathematical and theoretical physics directed by Dr. Mennessier. In the model, the conducting medium is confined within an insulating cylinder that has a radius of 40 mm and a height of 80 mm, with the electrode placed along its axis (Fig. 5). This theoretical cylinder, which has dimensions exceeding the size of the GPI, is introduced exclusively for the convenience of the numerical analysis. Its size is based on the condition that the electrical field at the border of the cylinder is infinitely small and can be neglected. The height of the cylinder was chosen by taking into consideration the mean length of the trajectory from the surface of the brain to the optic tract (the inferior face of the brain). Calculations demonstrate that this value was necessary and sufficient because superior values do not modify the final result. Possible interactions between the implanted electrodes were not taken into consideration.

The IPG is modeled as an additional perfect conductor disk placed at the bottom of the cylinder (Fig. 5). Although the real electrode dimensions were kept in the model, the radius of this disk (20 mm) was adapted to the distance between the lower electrode and the IPG. The size was chosen by comparing the magnitude for the ratios of impedances in mono- and bipolar modes in the model to the mean values measured in patients by using a radiofrequency console programmer (Medtronic, Inc., Minneapolis, MN).

The distribution of the potential $U(r, z)$ should be found as a solution of the Laplace equation. With our choice of an axial symmetrical model, the Laplace equation is reduced in cylindrical coordinates $(r, z)$ to the following:

$$\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial U}{\partial r} \right) + \frac{\partial^2 U}{\partial z^2} = 0.$$

Boundary conditions were defined corresponding to given potentials imposed at the metal contacts (depending on the specific mode of stimulation) and to zero values of the normal electrical field component ($E_n = -U/dr$) at the insulating surfaces of the central electrode and the external cylinder. The latter condition is a direct consequence of the requirement that the component of the current density normalized to the surface of an insulator is zero. Nonstimulated contacts are electrical conductors that can present a nonzero potential; the initial condition for these contacts is an unknown constant potential to be determined from the fact that the total current is zero (a double-layer effect is not considered). A finite differences method was used for the numerical analysis. An analytical description of the singularities in the electrical field distribution near the metallic edges was incorporated in the finite-difference scheme.

References

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