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The clinical utility of methods to determine spatial extent and volume of tissue activated by deep brain stimulation

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Electrical stimulation of the nervous system is a burgeoning therapeutic technology, already in routine use for a range of neurological and psychiatric conditions, including movement disorders, epilepsy, pain, depression, and others (Gross, 2004). Its various incarnations, all undergoing continual development and refinement, comprise direct and indirect cortical stimulation, spinal cord stimulation, peripheral and cranial nerve stimulation, and deep brain stimulation (DBS) of diverse targets. Yet, despite pervasive use and a long history (Dioscorides is said to have used the electric ray to treat epilepsy in 76 AD (Kellaway, 1946)), the biophysical and physiological effects of electrical stimulation on the nervous system remain poorly understood. This detailed mechanistic knowledge, once gained, promises to free us from exhaustive and *ad hoc* investigations of stimulation parameters and targets, and rather provide us with optimal stimulation protocols, rationally selected for each disorder and each patient.

Many factors influence how electrical impulses affect the nervous system: (1) the electrical parameters of the impulse, including amplitude, waveform, duration (pulse width), frequency, pattern, and whether stimuli are voltage- or current-controlled (Kuncel and Grill, 2004); (2) the electrode geometry, including size, shape, and orientation, and whether the ‘active’ electrode and ‘indifferent’ electrode are close (i.e., ‘bipolar’ mode) or distant (i.e., so-called ‘monopolar’ mode) (Butson and McIntyre, 2006; McIntyre et al., 2004; Yousif and Liu, 2007); (3) the electrode location and orientation with respect to the neural (and glial, and perhaps even vascular) elements that comprise the stimulation target, including the cell bodies, their dendritic fields and efferent axons, and axons of passage both within and surrounding the target (Miocinovic et al., 2006); and (4) the cellular characteristics of the stimulated region, such as its relative isotropy (gray matter) or anisotropy (white matter) which affects the spread of charge (Butson et al., 2007). With all of these variables in play, determining the local effects of electrical stimulation is daunting, especially since these effects may be altered by subtle differences from patient to patient. Still greater questions pertain to the functional network changes induced by stimulation, and also to the long-term changes evoked.

Addressed in this issue by Kuncel et al. (2008) is one of the most rudimentary, but surprisingly difficult, of these questions: how far from a stimulating electrode is neural tissue activated? This is a question of fundamental importance, both for determining the mechanism of action of stimulation and for determining the optimal location of a stimulating electrode. The most

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direct means of answering this question is to interrogate the response of local neurons to electrical stimulation by using microelectrode recording. This has been done extensively in animals during stimulation with microelectrodes in various regions (see Tehovnik (1996) for review). Threshold activation current (I_{th} , the value above which neural tissue is activated) varies with the square of the distance between the electrode and the activated neuron (r^2). This relationship, described as the 'activation function', is governed by the current-distance constant, K , where $I_{th} = Kr^2$ (Asanuma and Sakata, 1967; Stoney et al., 1968). In experimental studies, the current-distance constant ranges from 100 to 4000 $\mu\text{A}/\text{mm}^2$, and depends on the properties of the neural element being stimulated, such as its size, conduction velocity and whether it is myelinated (Tehovnik, 1996). These results, it is worth noting, were derived from or calibrated to stimuli with 200 μs pulse widths. Since, empirically, longer pulse widths reduce the amount of current needed to activate a cell, longer widths lead to lower estimates of K . Lastly, it should be emphasized that, for a particular stimulation electrode in a particular location, every neuron has its own K , and these K change with changes in pulse width, pulse shape, and all of the other parameters noted above.

As a complement to microelectrode recordings of activated cells, other studies have used behavioral manifestations of stimulation to estimate K . In the more elegant of these studies (Fouriez and Wise, 1984; Yeomans et al., 1986), two stimulating microelectrodes are used to determine how far a second electrode needs to be to induce refractoriness to the stimulation pulses of the first electrode. This happens when the volumes of stimulation overlap, and knowing the inter-electrode distance when the fields overlap allows a determination of stimulation range. The span of current-distance constants determined with this technique is remarkably similar to that obtained with direct microelectrode recordings (Tehovnik, 1996).

Current-distance constants are not easy to explore in humans. However, during neurophysiological mapping performed during the implantation of DBS electrodes, up to 5 microelectrodes are often inserted concurrently, with interelectrode distances of 2 mm (Gross et al., 2006). This fortuitous experimental situation has been leveraged to explore the mechanism of electrical stimulation's therapeutic effects, i.e. does it activate, inhibit, or in some other way affect local efferents and/or afferents (Brown et al., 2004; Dostrovsky et al., 2000)? Other approaches to examine current-distance constants might include neuroimaging studies, such as functional MRI and PET studies, though both have technical limitations precluding their use for this purpose. Computer modeling experiments have been used in recent years to explore the volume of tissue activated (VTA) by DBS electrodes (McIntyre et al., 2007). This approach usually utilizes finite element models to determine the voltage field produced on a neuron by a stimulating electrode. Neurons are represented by single or multi-compartmental models (Dayan and Abbott, 2001), which allows determination of their dynamics within the voltage field, and detailed models of three-dimensional (3D) neuroanatomy (Ascoli, 2002) can be incorporated to further enhance the model. In some cases the 3D anatomy has been made patient specific using the patient's own MRI (Butson et al., 2007; Hemm et al., 2005a; Hemm et al., 2005b). These models have undergone incremental refinement, for example with the addition of local tissue anisotropy derived from diffusion tensor imaging (Butson et al., 2007) (although this has not yet been done on a patient-specific basis), and the addition of different neural compartments to the cable model (Miocinovic et al., 2007) (e.g., synaptic afferents in addition to axonal efferents and axons in passage). The results have yielded estimations and depictions of the VTA, and have been pertinent to the debate over what the distant effects of stimulation are (activating, inhibiting, or some combination thereof). They also have been useful in examining the effects of manipulating the tremendous number of stimulation parameter combinations (e.g., there are over 800,000 practical combinations on the Soletra® 7426 (Kuncel and Grill, 2004)) on local and distant effects of DBS, something well beyond animal models or clinical research. On the other hand, these modeling approaches make assumptions about the properties of the neurons being

stimulated, and use these assumptions to generate the estimated VTA. Sensitivity analyses must then be used to evaluate the dependence of the study's conclusions on the assumed parameters.

Kuncel et al. (2008) have taken advantage of patients previously implanted with DBS systems for the treatment of tremor—consisting of electrodes in the ventral intermediate (Vim) nucleus of thalamus and internal voltage-controlled pulse generators—to examine the spatial extent of activation by DBS electrodes. Vim is the motor relay nucleus receiving cerebellar afferents and projecting to the primary motor cortex, and DBS in this target effectively suppresses tremor from Parkinson's disease, essential tremor and other etiologies (Garonzik et al., 2002). Electrodes are typically targeted to the anterior face of Vim, where it borders the ventral oral posterior (Vop) nucleus. This positions the electrode approximately 2.0 mm anterior to the posterior border of Vim with the ventral caudal (Vc) nucleus, which is the sensory relay nucleus. Stimulation within or spreading to Vc elicits paresthesia with a somatotopic distribution (Garonzik et al., 2002). Well-located DBS electrodes may evoke transient paresthesia at stimulation onset that subside within seconds. Quadripolar DBS electrodes (which in this case have 1.5 mm tall cylindrical contacts with a 1.5 mm interpolar distance) are typically implanted with an anteriorly inclined angle (in the sagittal plane) such that more proximal, rostral contacts are less likely to elicit paresthesia from spread of current to Vc.

The Grill group (Kuncel et al., 2008) capitalized on this situation to examine the activation function—the relationship between stimulation and distance—by determining the threshold for paresthesia at each successive electrode contact, which is progressively more distant from the Vc border. The equation for the current-distance relationship above was reformulated from current into voltage, since the pulse generators used deliver voltage-controlled rather than current-controlled stimulation. Thus, using Ohm's law, $I_{th}(r) = Kr^2$ becomes $V_{th}(r) = kr^2$, which states that the threshold voltage, V_{th} , at any distance r from the electrode to the neural element being stimulated is equal to the product of the amplitude-distance constant, k (the analogue of the current-distant constant), and the square of the distance. Kuncel et al. (2008) additionally modified this equation to include an offset, v , to account for the voltage required to excite a cell at $r = 0$ (i.e., at the electrode's surface), changing the equation to $V_{th}(r) = v + kr^2$. This offset is not included in the original current-distance equation, since that equation is derived by modeling the electrode as a point source of current. In that case, there is infinite current density at $r = 0$, and I_{th} is 0. But because Kuncel et al. (2008) envisage an electrode with finite extent, there is indeed a non-zero threshold value at the electrode's surface, $r = 0$ (current density in that case is whatever current the electrode delivers, divided by the electrode's surface area; it is far from infinite). As noted above, the derivation of the current-distance model assumes a uniform radial spread of current from a point source. The r^2 , in fact, comes from the equation for the surface area of a sphere, and is related to the current density at a given point (i.e., on the surface of a sphere with radius r). Consequently, the model is only approximately accurate when r is far from the electrode (when the field produced by the cylindrical electrode begins to look more or less spherical). If effects near an electrode surface are to be modeled, a more powerful representation of the preparation, like a finite element model, is more appropriate.

Kuncel et al. (2008) generalize their equation to any of a lead's four DBS contacts, c , residing at $r = y'_c$ from the Vim/Vc border. This generalization creates their equation (2): $V_{th_c}(y'_c) = v + ky'_c$. Thus, by measuring the stimulation threshold in volts for eliciting paresthesia at each contact, $V_{th_c}(y'_c)$, and by setting the threshold offset to $v = 0.1\text{ V}$ (an assumption), the authors are able to solve for k and y'_c by minimizing the function $V_{th_c} - V_{th_c}^*$, where the asterisk indicates the threshold calculated by the model (with particular values of k and y'_c 'plugged in'). In other words, the authors are finding values of k and y'_c which make the model's computed $V_{th_c}^*$ as close to the empirically measured V_{th_c} as possible. In order to properly

scale y'_c in relation to the first contact (c_0), the authors use an estimate of the angle of Vc/Vim border, and estimates of the stereotactic ring and arc angles. This is done using a model of the relationship of each DBS electrode contact to the deepest contact (c_0) based on the known angles of the electrode in stereotactic frame space (i.e. ring, arc angles and the assumed posterolateral angle of the Vim/Vc border with respect to the intercommissural line from a histological axis).

Using this model and empirical data from several patients, the authors arrive at an estimate of $k = 0.22 \text{ V/mm}^2$ (or $220 \text{ } \mu\text{A/mm}^2$ assuming a tissue impedance of $1000 \text{ } \Omega$, a reasonable approximation) and an estimation of y'_0 of between 1.3 and 5.1mm. These results are within the range derived from animal studies ($100\text{--}4000 \text{ } \mu\text{A/mm}^2$ (Tehovnik, 1996)). Moreover, the range of the spatial extent of activation is consistent with targeting the DBS to a point that on average is 2.0 mm anterior to Vc.

There are several assumptions and limitations with this approach. First, paresthesia is taken as a behavioral surrogate for neuronal activation. It is unknown how many neurons must be activated to produce paresthesia. However, in a location from which a single unit has been recorded, microelectrode stimulation will generate paresthesia at current thresholds of 1 - 5 μA , suggesting that very few units need to be activated to generate the percept. Second, in contrast to the animal studies, the stimulating electrode in this case was not a microelectrode. On the other hand, far-field stimulation is largely independent of the electrode size, justifying the current-distance equation's assumption of a point-source electrode (Tehovnik, 1996). Third, the authors used a pulse width of 90 μs , as compared to the 200 μs used in animal studies (Tehovnik, 1996). Since less charge is delivered at shorter pulse widths, this leads to a higher estimate of the distance constant. Consequently, if Kuncel et al.'s (2008) values were calibrated to the rest of the literature, they would be significantly lower than their determined value of $220 \text{ } \mu\text{A/mm}^2$, placing them on the lowest rung of measured current-distance constants. Fourth, the authors assumed a value for the offset voltage v —the minimum voltage threshold for evoking paresthesia—and set it to the minimum voltage that their pulse generators could deliver (0.1 V). This is likely not the actual threshold for stimulation at the electrode's surface. However, as they calculated in their mathematical model, errors in this value are probably not of great significance. Fifth, the amplitude-distance constant they derive is a unitary value, whereas previous work shows that the values for neurons, even within a single structure, may vary by an order of magnitude (i.e., there are both high- and low-threshold neurons). The calculated value likely represents a population average or minimum. Finally, Kuncel et al. (2008) use voltage-controlled rather than current-controlled stimuli, which might also affect how their current-distance constant compares to others. Because metal electrodes exhibit reactance in addition to resistance (because of their capacitive properties), the current delivered during a voltage-controlled pulse varies widely, with large current spikes at the pulse's sharp transitions (e.g., see (Wagenaar et al., 2004)). The degree to which this affects neural responses *in vivo* is unknown, though voltage-controlled pulses *in vitro* compared to charge-comparable current-controlled pulses appear to be more effective at exciting cells (Wagenaar et al., 2004). Perhaps this explains in part the lower current-distant constant reported by the authors (Kuncel et al., 2008).

Ultimately, the values determined by Kuncel et al. (2008) are reasonable in comparison to the previous animal studies, especially considering the aforementioned limitations. While the range of current-distance constants is fairly homogeneous across species (rat, cat, primate) and area (pyramidal tract, reticulospinal tract, substantia nigra) (Tehovnik, 1996), it is unclear to what degree, if any, the thalamus might differ, and this is the first study to address this structure of which we know. Moreover, this is the first study to examine the activation function in humans, which could be different than those in other species. What are the ramifications of these data, and this approach? Kuncel et al. (2008) discuss the use of this approach to determine

the distance of an implanted DBS electrode to the Vim/Vc border intraoperatively. Given the complexity and assumptions inherent to this technique, and the relative ease of targeting the Vim, it seems doubtful this will become a practical use. There may, however, be other important uses. For example, the estimation of the amplitude-distance constant from this work in humans may be transformed into an estimation of electric field strength: K (current-distance constant) $= k/R$ (amplitude-distance constant divided by tissue impedance) $= 4\pi C/\rho$, where ρ is tissue resistivity, and $C = \Delta v/\Delta r$, the voltage gradient (which is a constant when at threshold to stimulate a neuron, and every neuron will have a different value of C). This relation might provide useful comparisons for the values produced by those finite element models used to estimating the VTA in human DBS. It is still unclear, however, if these results will vary in structures or diseases that are yet to be studied. Therefore, the present approach might be used with a different behavioral surrogate for neuronal activation specific to the stimulated nucleus (e.g. tremor, rigidity, bradykinesia in subthalamic nucleus stimulation cases) to derive amplitude-distance and current-distance constants, spatial extent of activation, and ultimately electric field strengths in other targets for electrical stimulation of the central nervous system.

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