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Use of efficacy probability maps for the post-operative programming of Deep Brain Stimulation in Essential Tremor

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Abstract

Introduction—Post-operative programming of deep brain stimulation for movement disorders can be both time consuming and difficult, which can delay the optimal symptom control for the patient. Probabilistic maps of stimulation response could improve programming efficiency and optimization.

Methods—The clinically selected contacts of patients who had undergone ventral intermediate nucleus deep brain stimulation for the treatment of essential tremor at our institution were compared against contacts selected based on a probability map of symptom reduction built by populating data from a number of patients using non-rigid image registration. A subgroup of patients whose clinical contacts did not match the map-based selections prospectively underwent a tremor rating scale evaluation to compare the symptom relief achieved by the two options. Both the patient and video reviewer were blinded to the selection.

Results—54% of the map-based and clinical contacts were an exact match retrospectively and were within one contact 83% of the time. In 5 of the 8 mismatched leads that were evaluated prospectively in a double blind fashion, the map-based contact showed equivalent or better tremor improvement than the clinically active contact.

Conclusions—This study suggests that probability maps of stimulation responses can assist in selecting the clinically optimal contact and increase the efficiency of programming.

Keywords

Essential Tremor; Deep Brain Stimulation; Probability Maps

Introduction

Essential Tremor (ET) is a common movement disorder affecting between 2–14% of those over age sixty [1]. ET leads to significant morbidity and can significantly affect quality of life [2]. Medications can effectively manage mild tremor, but with disease progression medications lose their effectiveness and lead to intolerable side effects. Deep Brain

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Stimulation (DBS) of the VIM nucleus of the thalamus was approved by the FDA in 1997. It has been shown to improve tremor by over 83% and improve quality of life up to 12 years after implantation [3–5].

There have been several traditional methods described for the programming of DBS for ET [6–8]. These methods involve evaluating each of the four contacts for the threshold for both side effects and efficacy, adjusting the various parameters in a consistent pattern. This is generally done about one month post-lead implantation, which allows sufficient time for resolution of edema and the lesional effect of surgery to subside. Programming can be a time consuming process and may have to be done with little objective clinic information if there is a profound lesioning effect and hence little return of tremor [7]. Patients may then be required to return to clinic for additional extraneous programming sessions leading to a delay in tremor control and incurring additional costs in time and travel. Currently the commercially available lead has four active contacts. With the future direction of lead technology potentially involving eight plus contacts and directionally segmented leads, it will be impossible to reasonably evaluate all of the possible combinations [8]. A system needs to be developed to allow for more efficient programming.

In Parkinson's disease (PD) with Subthalamic Nucleus (STN) DBS it has been shown that with information about the location and proximity of the lead to other neuronal elements, programming response can be improved, both in terms of motor response and side effect reduction using computational models of volumes of tissue activation [9–11]. Such models have been created with respect to the anatomy for programming assistance [12, 13]. A limitation of using the anatomy to guide programming is that there is a lack of consensus on the ideal anatomical location for symptom reduction response to stimulation [14]. For example, both the dorsal part of the STN and zona incerta (ZI) are known to produce symptom relief in PD [15]. Basing programming decisions on functional outcome rather than anatomy may allow for more efficient and effective programming. Several functional atlases have been developed using intra- and post-operatively acquired electrophysiological data [16–23]. We recently demonstrated consistency with optimal contact selection by multiple neurologists using an in-house developed software tool for post-operative programming visualization. The functional maps were visualized along with the implanted electrode, the patient's anatomy and models of tissue activation [24]. Here we present the utility of our probabilistic maps in assisting with DBS post-operative programming. We performed both a retrospective study and a small double blind prospective assessment. ET was chosen due to the quicker and more discretely observable response to stimulation in terms of symptom relief.

Data and Method

With IRB approval and after a signed consent form was obtained, the study was carried out in 20 Essential Tremor patients who had Vim-DBS implants at Vanderbilt Medical Center. There were a total of 35 leads evaluated; 15 were bilateral implants and 5 were unilateral. The inclusion criterion was that the patients had to be implanted between one and three years prior to the study. This allowed at least one year for the programming neurologist (years of programming experience varied from 3 years to 15) and the patient to have

sufficient time to arrive at a stable electrode configuration and stimulation parameter settings most therapeutic to the patient.

Pre-operative MRI and CT images of the brain were acquired for each patient. A post-operative CT, which we refer to as stable CT (CT-PS), was acquired at least 3 weeks after surgery. Typical CT images were acquired at kVp = 120 V, exposure = 350 mAs and 512×512 pixels. In-plane resolution and slice thickness were respectively 0.5 mm and 0.75 mm. MRI images (TR 12.2 ms, TE 2.4 ms, 256×256×170 voxels, with typical voxel resolution of 1×1×1 mm³) were acquired using the SENSE parallel imaging technique (T1W/3D/TFE) on a Philips 3T scanner.

At Vanderbilt, DBS surgeries are performed using a miniature stereotactic frame, the microTargeting platform® (FHC, Inc., Bowdoin, ME). The planned target was typically aimed for the ventro-lateral aspect of the thalamus not far from where the Vim is expected to be located. This allowed the surgical team to explore a wide region around this area using trajectories anterior, posterior, lateral and medial to the planned trajectory. Typical planned target coordinates were 14 mm lateral, 6 mm posterior, and 0.5 mm superior to the mid-commissural plane, but these were tailored to the individual patient during planning based on the patient's anatomy. During surgery, prior to assessing the stimulation response, micro-electrode recordings were done in 3–4 tracks parallel to the planned trajectory. Electrical semi-micro stimulation was then applied every 2–3 mm along these 3–4 tracks resulting in 12–16 stimulation response data points around the planned target. The optimal location for the placement of the final implant was based on a combination of the micro-electrode and stimulation response data. Stereotactic coordinates of the intra-operative stimulation response data were converted to X, Y, Z coordinates in the patient's CT image space (as the platform is built in the CT space) and then mapped onto the MRI space using rigid registration. In order to build probability maps for the patients in this study, positions of stimulation response data from a population of ET patients were first mapped onto an atlas MRI using non-rigid registration between the patients and the atlas MRI. From the atlas, they were projected onto individual patients in this study by non-rigid registration between the atlas MRI and the patient MRIs. Briefly, our non-rigid registration algorithm computes a deformation field that is modeled as a linear combination of radial basis functions with finite support. This results in a transformation with several thousands of degrees of freedom. Two transformations (one from the atlas to the subject and the other from the subject to the atlas) that are constrained to be inverses of each other are computed simultaneously. Details on this procedure and the algorithms that have been used can be found in [16, 25]. The validation of our algorithm for the selection of the AC and the PC can be found in [26] and for the creation of statistical maps in [27]. A probability map of efficacy (symptom relief) was built for each patient using points populated in the atlas that had produced at least 50% symptom reduction due to stimulation as observed by the neurologist intraoperatively. Briefly, this involves associating with each efficacious stimulation response point a probability density function that captures the likelihood that a region in the vicinity of the measurement point is a responsive region. The parameters of this probability density function depend on the stimulation parameters. The probability maps are created by summing and normalizing the contributions of the points. In this study, efficacy maps were built using 584 efficacious data points in 77 Vim DBS implant cases. Finally, using the CT-

PS, individual contacts in the implanted electrode were extracted so they could be overlaid on the anatomy and the maps.

For every patient, this entire process was pre-computed and packaged into a file that could simply be loaded into the post-operative module of a suite of software we have developed called CRAnialVault Explorer (CRAVE) [28]. As shown in figure 1, the module allowed the neurologists to visualize various types of information like the leads, probabilistic maps and anatomical images, and interact with them in 2D as well as in 3D. In 2D, neurologists had access to tools that allowed visualizing and interacting with the information in the coronal, axial and sagittal views simultaneously. They could navigate through slices as well as zoom into regions of interest. In 3D, they could visualize and interact with the renderings of the statistical maps and the lead. Using this software, a reviewer (FP) blinded to the clinical settings determined the optimal monopolar contact to use based on the interaction of the individual contacts on the implant with the efficacy map. This was referred to as the map-based selection and was compared to the most recent active clinical selection obtained from the patient's chart. A match was declared if the contact selected using the map was also a clinically active cathode. If the clinical contact(s) were a double or triple monopolar, or a bipolar configuration was used and the map selected contact was one of the clinical contacts, a match was declared.

Only those patients in whom the map-based contact did not produce a match with the clinically active cathode were brought back into the clinic for evaluation. The current Medtronic® system allows for multiple groups of electrode configurations to be set up so that the patient may alternatively move from one group to another to optimize therapeutic benefit. For patients with multiple groups, the group that the patient reported provided the best tremor control was used as the contact against which the map-based contact was compared. After signing a consent form, the patients underwent an IRB approved protocol. The lead under consideration was turned off and the atlas chosen contact was evaluated in a monopolar fashion using a pulse width of 60 microseconds and frequency of 130 Hz. The voltage was increased until either satisfactory tremor control or bothersome side effects were obtained. If the voltage needed to be higher than 4.0 the pulse width was then increased. The frequency was not changed. If there were limiting side effects at the optimal setting, the voltage was decreased until the side effect subsided. The stimulation was then turned off and the lead was set to either the clinical setting or map setting in a blinded fashion. To keep the patient blinded he/she was asked to select a number between 1 and 10. If an odd number was chosen the clinic setting was tried first while if an even number was chosen the map setting was tried first. The voltage was slowly increased to the final setting to limit any bothersome side effects and to protect the blind. The patient was left at this setting for 15 minutes and then underwent a WHIGET (Washington Heights-Inwood Genetic study of Essential Tremor) tremor rating scale which was video recorded [29]. The patient was then changed to the other setting with the voltage gradually increased and left at the final setting for 15 minutes. The patient then underwent a second video recorded WHIGET. The patient then reported which setting they preferred and were offered the atlas setting as a group to try at home. If bilateral leads were being evaluated, the other lead was left on with the clinical setting in place. The videos of the WHIGET evaluations for the two selections were then rated by a neurologist (CT) who was blinded to the above process.

Results

In 19 of the 35 leads (54%) the contact selected based on the efficacy map retrospectively matched the contact that was clinically active (table 1). 11 of the 19 were in a monopolar configuration, 6 were double monopolar, 1 was triple monopolar and one was monopolar interleaving; 10 of the 35 were off by one contact with the map based contact above in 6 and below in 4 cases.

Of the 16 cases that did not match retrospectively, the map-based contact was below the clinical contact in 11 leads (one contact below in 6 cases and two contacts below in 5 cases) and above in 5 leads (one contact above in 4 cases and two contacts above in one case). Of the 16 non-matching cases, 8 were formally evaluated prospectively where both patient and the neurologist who was evaluating based on the video recordings of WHIGET were blinded to the selections. In 7 of these 8 leads, the map-based contact was below the clinical contact. In 5 of the 8 leads (63%), the map predicted contact resulted in the same or lower (better) WHIGET score than the clinical configuration when evaluated by the second (blinded) neurologist (table 2: subject 2 right, subject 4 right, subject 10 left, and subject 12 right, subject 14 right). Of the 8 cases that were re-evaluated in clinic, 4 left with the map-based selection turned on as a new group option. In most cases the map-based contact had a lower voltage and/or pulse width likely resulted in lower energy required to provide comparable tremor control as shown in Table 3

Discussion

Probabilistic maps derived from intra-operative stimulation are useful in predicting the clinically chosen contact during post-operative programming for ET. The efficacy map-based contacts matched the clinically chosen contacts 54% of the time and were within one contact 83% of the time. When the mismatched contacts were assessed prospectively in a double blinded fashion, in 5 of the 8 leads (63%) the WHIGET score for the map-based selections were better (4 cases) or the same (1 case). Most were better by 1–3 points. In the 3 cases when the map-based scores were worse; they were so by 1 point in 1 case (subject 12 left) which could be considered to be within the variability of tremor and not clinically different. In the two cases the WHIGET scores for the map-based selections were worse by more than 2 points (subject 6 left, and subject 10 right). We believe this was potentially due to limitations in the study that prevented optimization of the map-based contact where paresthesias limited increasing the stimulation voltage and also because we restricted the map-based contact selections to monopolar configuration in order to have the most robust evaluation of the efficacy map. Also, paresthesias can be transient, but due to clinical restrictions we only allowed about 5 minutes for the assessment of the map-based contact. It is possible that with a longer assessment the paresthesias may have faded and we may have been able to increase voltage to obtain better tremor control. For future studies we will complement the information provided by the efficacy maps with other maps, e.g., paresthesias or dysarthria maps. Nonetheless, using the map-based selections there appears to be a potential savings in the energy consumption given that in most cases the map-based contacts had a lower voltage and/or pulse width.. This could reduce the cost of the therapy and also decrease the number of stimulator replacement procedures for patients.

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Figure 1. CRAVE software interface that shows probabilistic efficacy map for an ET Vim-DBS patient and extraction of the DBS electrode implanted in that patient overlaid on the patient's MRI. A 3D rendering is also shown.

Lead configurations in the study and the distribution of retrospective matches between the map-based and clinically active contacts.

Table 1

Lead configuration	Number of leads	Leads where map and clinic contacts were an exact match	% exact match	Leads where map and clinic contact were off by one contact	% off by at most one contact
Monopolar	25	11	44	9	80
Double monopolar	8	6	75	1	88
Triple monopolar	1	1	100	-	-
Monopolar interleaving	1	1	100	-	-
Totals	35	19	54	10	83

Table 2

WHIGET scores for the clinically active and map-based contacts that were evaluated prospectively.

Subject ID	Side	WHIGET SCORE	
		Clinical	Map-based
2	Right	3	1
4	Right	4	2
6	Left	8	12
10	Right	4	7
10	Left	4	3
12	Right	5	5
12	Left	3	4
14	Right	9	6

Table 3

	Cathode	Anode	Voltage	PW	Hz	Total Energy
Subject #2						
Map-based(R)	8	Case	2.9	60	130	43.7
Clinical(R) Interleaved	9/10	Case	3.3/3.1	90/90	125	153.8*
Subject#4						
Map-based(R)	0	Case	1.0	60	130	5.2
Clinical(R)	1	Case	2.5	60	130	32.5
Subject #6						
Map-based(L)	1	Case	4.3	60	130	96
Clinical(L)	0	1	3.8	180	180	311.9
Subject # 10						
Map-based(L)	0	Case	2.0	60	130	20.8
Clinical(L)	1	Case	1.4	120	125	19.6
Map-Based(R)	8	Case	1.0	60	130	5.2
Clinical(R)	10	Case	2.0	60	125	20
Subject # 12						
Map-based(L)	0	Case	1.5	60	130	11.7
Clinical(L)	1	Case	3.5	90	160	117.6
Map-based(R)	8	Case	1.3	60	130	8.8
Clinical(R)	10	Case	3.2	90	160	98.3
Subject #14						
Map-based(R)	8	Case	2.5	60	130	32.5
Clinical(R)	10 and 11	Case	2.2	90	120	34.8