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# Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes

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## ABSTRACT

**Objective:** Despite the clinical success of deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD), little is known about the electrical spread of the stimulation. The primary goal of this study was to integrate neuroimaging, neurophysiology and neurostimulation data sets from 10 patients with PD, unilaterally implanted with subthalamic nucleus (STN) DBS electrodes, to identify the theoretical volume of tissue activated (VTA) by clinically defined therapeutic stimulation parameters.

**Methods:** Each patient specific model was created with a series of five steps: (1) definition of the neurosurgical stereotactic coordinate system within the context of preoperative imaging data; (2) entry of intraoperative microelectrode recording locations from neurophysiologically defined thalamic, subthalamic and substantia nigra neurons into the context of the imaging data; (3) fitting a three dimensional brain atlas to the neuroanatomy and neurophysiology of the patient; (4) positioning the DBS electrode in the documented stereotactic location, verified by postoperative imaging data; and (5) calculation of the VTA using a diffusion tensor based finite element neurostimulation model.

**Results:** The patient specific models show that therapeutic benefit was achieved with direct stimulation of a wide range of anatomical structures in the subthalamic region. Interestingly, of the five patients exhibiting a greater than 40% improvement in their Unified PD Rating Scale (UPDRS), all but one had the majority of their VTA outside the atlas defined borders of the STN. Furthermore, of the five patients with less than 40% UPDRS improvement, all but one had the majority of their VTA inside the STN.

**Conclusions:** Our results are consistent with previous studies suggesting that therapeutic benefit is associated with electrode contacts near the dorsal border of the STN, and provide quantitative estimates of the electrical spread of the stimulation in a clinically relevant context.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN), and its surrounding anatomical structures, is an effective treatment for the motor symptoms associated with advanced Parkinson's disease (PD).<sup>1-4</sup> Despite the clinical success of DBS, debate continues on its therapeutic mechanisms of action, and little is known about the electrical spread of DBS in the context of clinical outcomes. Previous studies have examined the relationships between the stimulation parameter settings and the therapeutic response to DBS.<sup>5-10</sup> In addition, extensive effort has been dedicated to identifying the anatomical location of therapeutic electrode

contacts in the STN region.<sup>11-23</sup> However, only recently have methodological tools been developed that can link the scientific analysis of both anatomical and electrical models of human DBS.<sup>24-27</sup> In this study, we integrated neuroimaging, neurophysiology and neurostimulation data sets to define the therapeutic volume of tissue activated (VTA) by DBS electrodes unilaterally implanted in the STN region of 10 patients with PD.

The STN is a relatively small structure surrounded by a number of different fibre pathways and gray matter areas. When DBS is applied to the STN region, it remains unclear which neural response(s) from the surrounding anatomical structure(s) is directly responsible for the therapeutic or non-therapeutic effects of stimulation. Converging theoretical<sup>28</sup> and experimental<sup>29</sup> results suggest that therapeutic DBS in the STN region generates an excitatory effect on axons surrounding the electrode. While correlations between axonal activation and the therapeutic mechanisms of DBS remain controversial, one possible hypothesis is that high frequency stimulation overrides the underlying pathological neural activity patterns.<sup>30-33</sup> Therefore, the approach taken in this study was to quantify the volume of axonal tissue directly stimulated by clinically defined therapeutic stimulation parameters. We hypothesised that direct axonal activation from therapeutic DBS would spread outside the anatomical borders of the STN.<sup>24</sup> Previously, we developed and validated a methodology to predict and visualise the VTA during DBS on a patient specific basis.<sup>26</sup> Here we apply those methods to identify relationships between the VTA, its overlap with a three dimensional anatomical model of the STN and the degree of therapeutic benefit achieved by the stimulation.

## METHODS

### Patient population

Following the methodology described in Butson and colleagues,<sup>26</sup> we developed 10 patient specific models of DBS in the STN region. Subject selection was performed retrospectively from a database of DBS patients implanted at the Cleveland Clinic. Patients were identified that fulfilled four important criteria. Firstly, each patient had idiopathic PD, as defined by the UK Brain Bank Criteria,<sup>34</sup> and demonstrated >40% improvement in their Unified Parkinson's Disease Rating Score (UPDRS) motor examination (part III) to dopamine replacement therapy, suggesting that they would respond well

**Table 1** Clinically effective DBS parameters

Patient No	Side	Electrode model	Contact	Impedance*	Voltage (V)	PW ( $\mu$ s)	Freq (Hz)
1	Left	3387	2	High	-2.3	60	185
2	Right	3387	1	High	-2.3	60	130
3	Right	3387	2	Mid	-3	60	185
4	Left	3387	1	High	-3.5	60	130
5	Left	3387	2	High	-3.6	60	145
6	Left	3389	1	Mid	-2.5	90	185
7	Right	3389	2	High	-2.5	60	130
8	Right	3387	2	High	-3.6	60	185
9	Right	3389	2	High	-2	60	135
10	Right	3389	1	High	-1.5	60	130

\*Impedance was accounted for using electrode encapsulation models previously described in Butson and colleagues.<sup>42</sup> The high impedance model was used if the clinical impedance measured at the specified contact exceeded 1300  $\Omega$  and the mid impedance model was used for contacts that ranged between 700  $\Omega$  and 1300  $\Omega$ .  
DBS, deep brain stimulation; PW, pulse width.

to DBS therapy. Secondly, each patient achieved their clinically defined maximum therapeutic benefit via monopolar cathodic stimulation, thereby simplifying the theoretical calculations of the neural response to DBS. Thirdly, each patient was unilaterally implanted, ensuring that the measured DBS effects were the direct result of the single stimulation site. Fourthly, patients exhibited a wide range of therapeutic benefit from DBS, allowing for comparison between good and bad responders. The 10 patients were identified and the clinical/imaging data were assembled prior to the development of the patient specific computer models (table 1). In turn, we had no a priori knowledge of relationships between the anatomical location of the electrode, the VTA or the therapeutic outcomes in the selected patients. This study was approved by the Cleveland Clinic Institutional Review Board.

Prior to surgery, each patient was evaluated with the UPDRS<sup>35</sup> in both the off medication and on medication states. Subsequently, each patient underwent a unilateral, microelectrode guided, stereotactic neurosurgical procedure to implant the DBS electrode into the STN region.<sup>36</sup> Several months after surgery, once standard clinical care had defined a stable therapeutic stimulation parameter setting (table 1), each patient was again evaluated with the UPDRS under two conditions: off medication/off stimulation (OFF MEDS/OFF STIM) and off medication/on stimulation (OFF MEDS/ON STIM).

### Imaging and co-registration

Each patient underwent preoperative CT and/or MRI as part of the standard DBS surgical protocol. The CT/MRI data documented the orientation of the patient's anatomy relative to their stereotactic neurosurgical frame (Leksell model G, Elekta Corp, Stockholm, Sweden) (fig 1). The coordinate system associated with the stereotactic frame (frame space) was defined in our model system using fiducial markers in the imaging data (fig 1A). The patient specific DBS model, and all imaging data, used frame space as the unifying coordinate system. Therefore, in instances where the preoperative MRI did not include the frame fiducials, the MRI was co-registered with the preoperative CT that did have the frame fiducials. Each patient also underwent a postoperative CT to verify the DBS lead location in the brain, and this image was also co-registered to the frame space image.

Each image co-registration was performed using Analyze 7.0 (AnalyzeDirect, Lenexa, Kansas, USA). We used the ITK three dimensional registration function in Analyze, followed by manual adjustment to precisely match the positions of the anterior and posterior commissures. Co-registrations involving

two or more data sets from the same patient required only rotation and translation to yield near perfect overlaps.

The fundamental basis of location in our model system was strict adherence to the stereotactic coordinate system established by the neurosurgical frame. The major advantage of using frame space in our model system was the ability to precisely place microelectrode recording (MER) data in the context of the MRI (see below). MER data were acquired with a microelectrode placed within a microdrive unit that was attached to the frame with a specific trajectory (arc angle, ring angle and target point) defined in the stereotactic coordinate system. In turn, as the microelectrode advanced into the brain, its location could be defined as a specific point in the stereotactic coordinate system (and the patient brain as viewed in the MRI).

The anatomical images of each patient were also co-registered with a diffusion tensor MRI (DTI) atlas brain.<sup>37</sup> The DTI atlas brain represented the basis for the DBS electric field model (see below). Rotation, translation and, in some cases, scaling were all necessary to perform this co-registration. To account for pitch and yaw differences in the images, the intracommissural line of the DTI atlas brain was aligned to the intracommissural line of the patient. The DTI atlas brain was then scaled along the anterior-posterior axis to bring the anterior commissure and posterior commissure into coincidence with the patient MRI counterparts. Next, the DTI atlas brain was scaled along the dorsal-ventral and medial-lateral axes and rotated about the anterior-posterior axis, as needed. This final rotation ensured the DTI atlas brain featured the same degree of roll found in the patient's image. The transformation matrix representing the net alteration performed on the DTI atlas brain to align it with a patient's frame space image was:

[Atlas].

This matrix governed the transition from DTI atlas space to a patient's frame space and its inverse describes the opposite. Two additional transformation matrices were also generated:

[Frame]

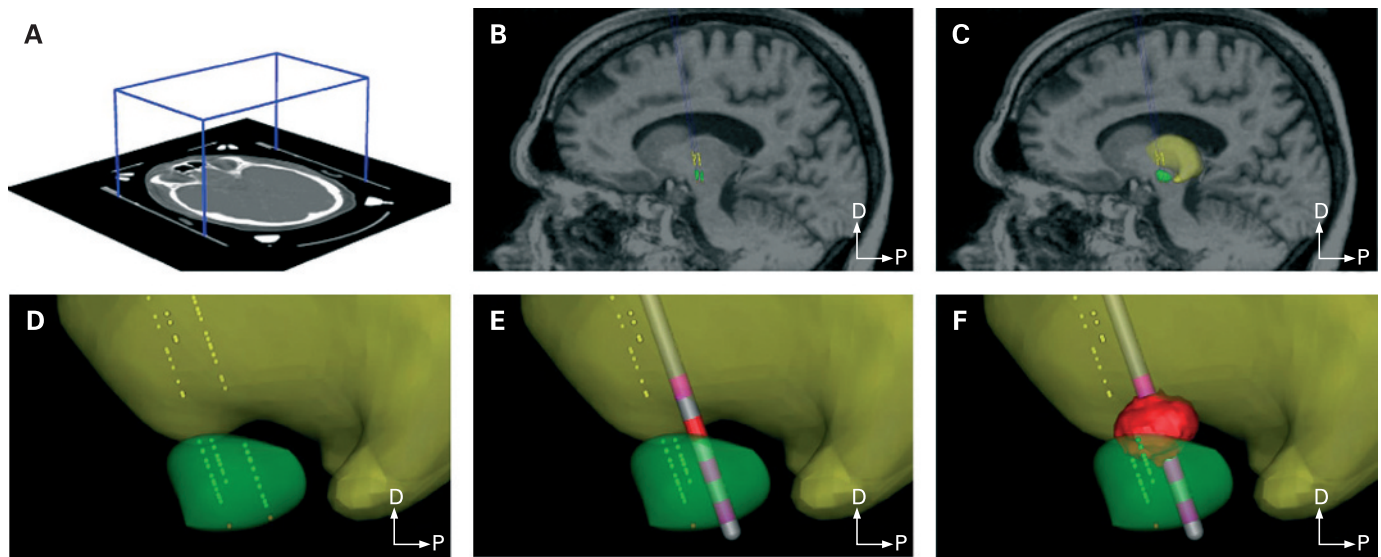
describing the exact position of the stereotactic frame relative to the co-registered imaging data and

[Origin]

a purely translational matrix cataloguing the shift from the origin of the co-registered imaging data to the origin of frame-space.

### MER data and DBS lead placement

Prior to permanent surgical implantation of the DBS electrode in the patient, MER of neuronal activity was performed in the



**Figure 1** Patient specific model of deep brain stimulation (DBS). (A) Stereotactic coordinate system was defined relative to the imaging data. (B) Microelectrode recording data were entered into the model (thalamic cells, yellow dots; subthalamic cells, green dots; substantia nigra cells, red dots). (C, D) Three dimensional brain atlas was fitted to the neuroanatomy and neurophysiology (yellow volume, thalamus; green volume, subthalamic nucleus). (E) DBS electrode was positioned in the model (pink contacts, inactive; red contact, active). (F) Volume of tissue activated (red volume) was calculated for the clinically defined therapeutic stimulation parameter settings. D, dorsal; P, posterior. Data presented for patient No 1.

operating room to further characterise the stereotactic location of the STN<sup>38,39</sup> (fig 1B–D). The patients analysed in this study had 3–6 MER trajectories each (aka tracks) (table 2). The MER data were added into a patient's model by applying their frame space transformation matrix,  $[Frame]$ , to an indicated trajectory and depth as documented in the operating room notes. An additional matrix representing a given trajectory relative to the co-registered imaging data was required as a precursor:

$[Trajectory]$ .

This process allowed for each MER data point (electrophysiologically identified cell type and stereotactic location) to be visualised within the imaging data and three dimensional brain atlas (see below) representations for the given patient (fig 1B–D).

The intended stereotactic surgical placement of the DBS electrode was added into a patient's model in the same fashion (fig 1E). The modelled DBS lead locations were verified by viewing the patient's co-registered postoperative image concurrently with their modelled DBS lead location. The radiological artefact from the implanted electrode outlined the model electrode in each patient of this study.

**Table 2** Microelectrode recording

Patient No	No of tracks	STN MER points in 3D STN model (%)
1	3	100
2	6	78
3	5	75
4	4	71
5	4	78
6	3	100
7	4	54
8	3	97
9	4	83
10	4	100

MER, microelectrode recording; STN, subthalamic nucleus.

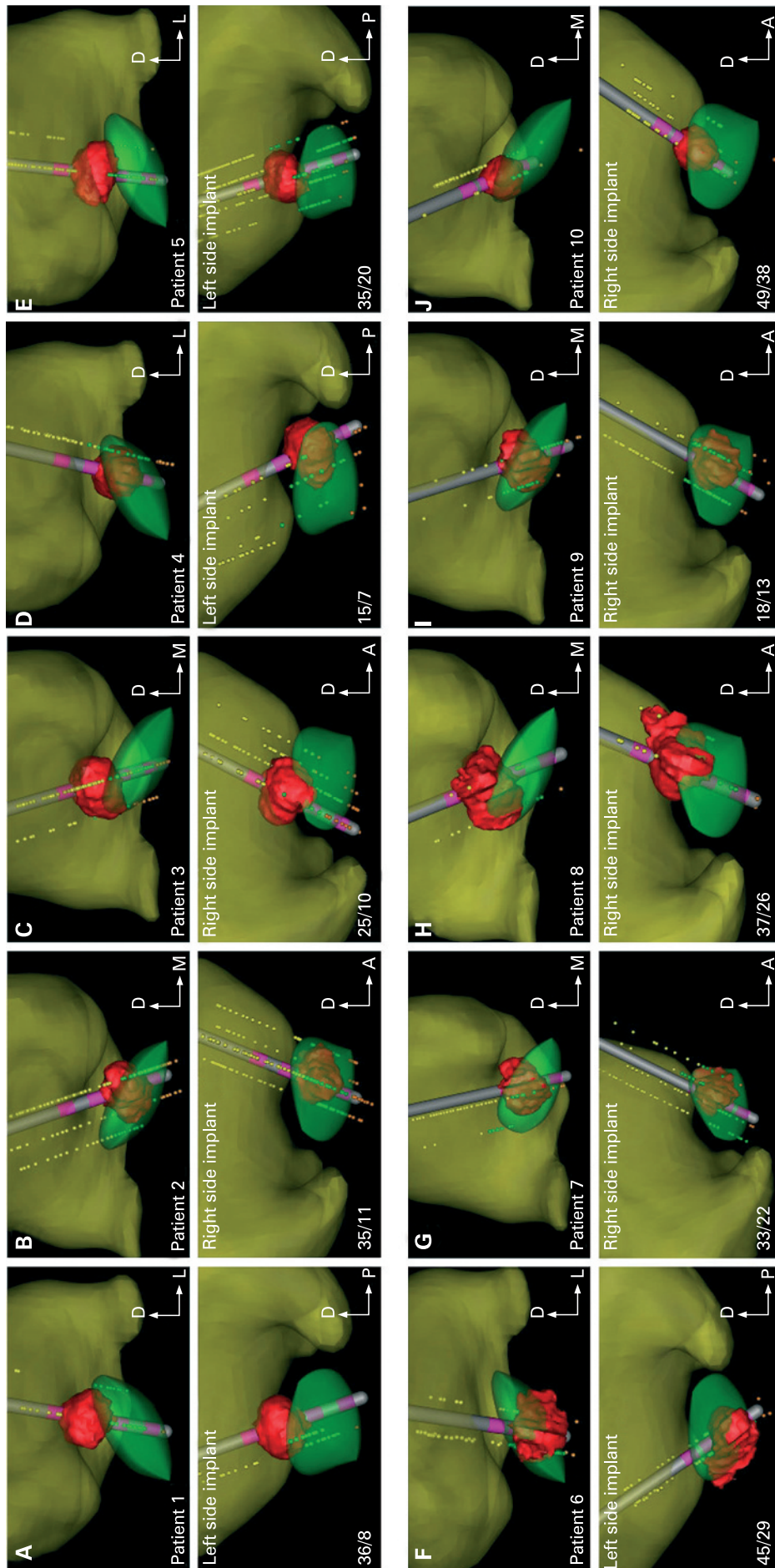
### Three dimensional brain atlas nuclei

Once a patient's model was populated with their MER data, three dimensional atlas representations of the thalamus, globus pallidus, caudate and STN were added to the model system (fig 1C, D). The three dimensional atlas nuclei were originally customised to the neuroanatomy of the DTI atlas brain.<sup>26</sup> Therefore, the three dimensional atlas nuclei were scaled and translated to fit each patient. The goal was to use the anatomical information provided in the preoperative MRI with the neurophysiological information provided by the MER tracks to achieve the best possible fit (fig 1, table 2). The initial placement of the three dimensional atlas nuclei into the patient brain was governed by the matrix describing the DTI atlas-to-patient MRI co-registration,  $[Atlas]$ . Next, the nuclei were translated such that their boundaries best encapsulated their respective cell types, as detected by MER. Translations were applied uniformly to all nuclei so that their positioning relative to one another was preserved. Once an acceptable fit was established based on the MER data, the patient's MRI was taken into consideration. Anatomy visible in the MRI (thalamus,

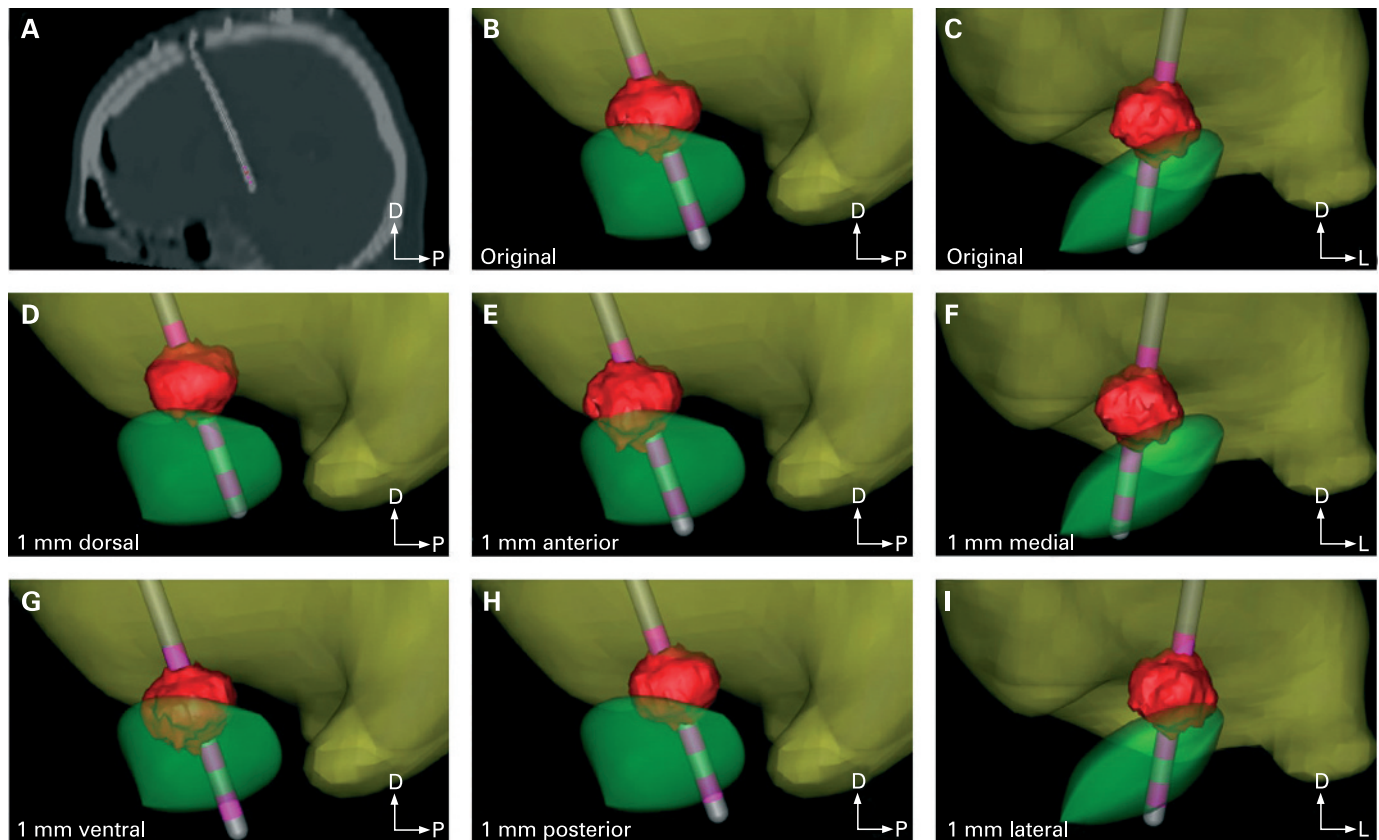
**Table 3** Clinical outcomes

Patient No	Therapeutic VTA (mm <sup>3</sup> )	VTA inside STN (%)	UPDRS improvement with DBS alone (%)	UPDRS improvement with MEDS alone (%)
1	51	16	78	47
2	57	78	69	69
3	87	11	60	76
4	65	43	53	41
5	78	5	43	40
6	116	72	36	56
7	69	79	33	52
8	96	35	30	41
9	66	83	28	45
10	30	66	22	45

DBS, deep brain stimulation; MEDS, medication; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Score; VTA, volume of tissue activated.



**Figure 2** Ten patient specific models of deep brain stimulation (DBS). Sections A–J correspond to patient Nos 1–10, respectively. Each section consists of two panels. The top panel displays a three dimensional coronal view, the bottom panel displays a three dimensional sagittal view. Each panel shows the thalamus (yellow volume), thalamic microelectrode recording (MER) data (yellow dots), subthalamic nucleus (green volume), subthalamic MER data (green dots), substantia nigra MER data (orange dots), DBS electrode and “clinically defined” therapeutic volume of tissue activated (VTA) (red volume). The lower left corner of each section lists the OFF-MEDS Unified Parkinson’s Disease Rating Score (UPDRS) motor score in the OFF-DBS/ON-DBS conditions. A, anterior; D, dorsal; L, lateral; M, medial; P, posterior.



**Figure 3** Deep brain stimulation (DBS) electrode location sensitivity analysis. (A) Postoperative CT (parasagittal slice parallel to the DBS electrode trajectory) depicting the modelled and imaged DBS electrode location. (B) Three dimensional sagittal view and (C) three dimensional coronal view of the originally modelled DBS electrode location and volume of tissue activated (VTA). (D–I) 1 mm shifts in the DBS electrode location, and for each shifted DBS electrode location the corresponding VTA calculated for the clinically defined therapeutic stimulation parameter settings. Data are presented for patient No 1.

pallidum, caudate) served as a guide to further converge the positioning of the three dimensional nuclei to the best possible manual fit. In situations where both MER and MRI data could not be maximally accommodated, MER took precedence. This decision was justified because the overriding goal was to orient atlas surfaces as accurately as possible with respect to the patient's DBS electrode, and the relative position of the MER data was the basis for the surgical DBS electrode placement. The net translational adjustment that brought the atlas nuclei in line with the patient data was recorded as:

[Nuclei].

Table 2 shows the percentage of STN MER points that were contained within the atlas defined borders of each patient's fitted STN.

### VTA generation

The Butson *et al*<sup>26</sup> human DBS modelling system was designed to provide anatomically and electrically accurate predictions of the VTA as a function of the stimulation parameter settings (fig 1F). Each patient specific DBS model included explicit representation of four important factors in calculating the neural response to DBS: (1) accurate reconstruction of the stimulus waveform generated by the implanted pulse generator,<sup>40</sup> (2) capacitance of the electrode–tissue interface which modulates the shape of the stimulus waveform transmitted into the tissue medium,<sup>41</sup> (3) high resistance sheath of encapsulation tissue surrounding the DBS electrode to appropriately account for the impedance of the electrode–tissue interface<sup>42</sup> and (4) diffusion tensor based three dimensional anisotropic and inhomogeneous tissue electrical properties that surround DBS electrodes.<sup>26</sup> We converted the diffusion tensor MRI atlas brain of Wakana and colleagues<sup>37</sup> into a set of conductivity tensors, as proposed by Tuch and colleagues.<sup>43</sup> These conductivity tensors were then mapped into the three dimensional finite element mesh, allowing for solution of the time and space dependent potential distribution generated by a DBS electrode implanted in the STN.<sup>26</sup>

**Table 4** Sensitivity analysis\*

Patient No	VTA (mm <sup>3</sup> )	VTA inside STN (mm <sup>3</sup> )	VTA outside STN (mm <sup>3</sup> )
1	51 (3)	9 (7)	42 (6)
2	58 (7)	43 (12)	14 (7)
3	85 (3)	10 (7)	75 (7)
4	67 (2)	28 (11)	39 (10)
5	78 (3)	4 (4)	74 (3)
6	114 (8)	7 (6)	37 (13)
7	69 (10)	52 (12)	17 (7)
8	96 (10)	32 (11)	64 (9)
9	68 (9)	50 (11)	17 (6)
10	30 (1)	18 (6)	12 (5)

\*Mean (SD) of the activated volume calculated from seven possible electrode locations given  $\pm 1$  mm error in electrode localisation relative to the anatomy (see fig 3).

STN, subthalamic nucleus; VTA, volume of tissue activated.

## Research paper

A transformation matrix was calculated to define each patient's DBS electrode location in the context of the DTI brain atlas space:

$$[DTI] = [Atlas]^{-1} \times [Origin]^{-1} \times [Nuclei]^{-1} \times [Frame] \times [Trajectory].$$

A model solution of the voltage distribution in the brain was generated for the patient's therapeutic stimulation parameters (contact, impedance, amplitude, frequency, pulse width), and a VTA was calculated based on the second spatial derivative of the voltage<sup>26</sup> (fig 1F). The VTA can be interpreted as a region where the axons that pass through the volume will generate propagating action potentials at the stimulation frequency. The DBS model simulations were performed on an 8 processor SGI Prism (Silicon Graphics Inc, Mountain View, California, USA) with 36 GB of shared memory using BioPSE (Scientific Computing and Imaging Institute, University of Utah, Utah, USA).

## RESULTS

The 10 patients with PD analysed in this study exhibited a wide range of therapeutic benefit from unilateral DBS of the subthalamic region (table 3). The best responders exhibited UPDRS improvements from DBS that were near to or better than their UPDRS improvements from medication alone. Conversely, the worst responders exhibited UPDRS improvements from DBS that were less than their response to medication alone. Patients were selected with a range of therapeutic outcomes to provide an opportunity to identify commonalities among patients with expected and less than expected improvement from DBS. The patients were ordered from 1 to 10 with patient No 1 having the greatest improvement from DBS and patient No 10 having the least improvement. This designation was defined by the percentage improvement in their postoperative OFF MEDS UPDRS motor evaluations in the OFF DBS and ON DBS conditions.

The VTA generated by each patient's clinically defined therapeutic stimulation parameter settings was calculated and its overlap with the surrounding neuroanatomy was defined (fig 2, table 3). Our theoretical calculations predicted an average stimulation volume of 71 mm<sup>3</sup>, and each VTA was smaller than the ~200 mm<sup>3</sup> total volume of the three dimensional STN model (exact volume depended on the three dimensional brain atlas fitting). Every patient had at least some of their VTA intersect with the STN; however, every patient also had some of their VTA spread outside the borders of the STN. Interesting differences between the overlap of the VTA and STN arose when we compared the five best outcomes (patient Nos 1–5) to the five worst outcomes (patients Nos 6–10) (fig 2, table 3). Patient Nos 1–5 all exhibited a greater than 40% UPDRS improvement with unilateral DBS. Of these five patients, four had more than half of their VTA outside of the STN. Patient Nos 6–10 all exhibited a less than 40% UPDRS improvement with unilateral DBS and four of the five had more than half of their VTA inside of the STN.

The integration of multiple data sets (imaging, MER, atlas, VTA) in our study carried with it numerous registrations where the accuracy was limited by imaging resolution. Therefore, to address the impact of uncertainty in the DBS electrode location relative to the underlying neuroanatomy, we performed a sensitivity analysis on the overlap of the VTA and STN with a range of DBS electrode locations in each patient. The DBS electrode was moved by 1 mm in the anterior, posterior, dorsal, ventral, medial or lateral directions relative to its originally defined stereotactic implant location, and a new VTA was

calculated for each new electrode location (fig 3, table 4). These perturbations did not substantially change the calculated volume of stimulated tissue in each patient, nor did they alter the result that four out of the five best responders had the majority of their VTA outside of the STN, and four out of the five worst responders had the majority of their VTA inside the STN.

## DISCUSSION

The goal of this study was to integrate detailed computer modelling with clinical outcomes analysis to enhance our understanding of the effects of DBS of the subthalamic region. We developed 10 patient specific models of unilateral DBS based on neuroimaging, neurophysiology, neuroanatomy and neurostimulation data. Our results suggest that direct stimulation of the STN is only one of multiple neuroanatomical territories in the STN region that may play a role in the therapeutic benefit achieved with DBS.

Our theoretical models show that direct activation of ~70 mm<sup>3</sup> of axonal tissue dorsal, lateral and posterior to the geometric centre (or centroid) of the atlas defined STN generated therapeutic benefit from DBS (fig 3). This general area includes the sensorimotor territory of the STN that is believed to be involved in motor control, and whose physiological activity is altered in PD.<sup>38</sup> Patients with the best clinical outcomes also tended to have a higher percentage of direct stimulation of axonal tissue outside of, and dorsal to, the STN. Similar conclusions have been reached by several previous investigations examining the anatomical location of therapeutic electrode contacts,<sup>16–20</sup> while others have suggested that optimal DBS contacts were located in the dorsolateral sensorimotor STN, but not the white matter dorsal to the STN.<sup>17</sup>

Debate on the "optimal" implantation location for DBS electrodes will undoubtedly continue over the next decade as new techniques enable more detailed analysis of the anatomical, electrical and behavioural variables of DBS. The evolutionary addition of this study to the previous literature is the quantitative integration of clinical outcomes analysis and electrically accurate models of the spread of stimulation.<sup>24–26</sup> This process allowed us to critically examine the interaction between the VTA and the underlying neurophysiology and neuroanatomy.

Given that the fundamental purpose of DBS is to modulate neural activity with electric fields, it is imperative that scientific analyses of DBS attempt to account for the variables associated with clinical stimulation parameter selection (contact, impedance, voltage, pulse width, frequency) and the resulting spread of stimulation relative to the anatomy. Our patient specific DBS modelling system uses some of the most advanced neurostimulation prediction techniques currently available. However, it should be noted that there are several limitations in this study. Firstly, we selected patients with monopolar stimulation to simplify calculations of the neural response to DBS. This selection criterion may have biased our analysis away from patients with lateral electrodes who have capsular spread limiting benefit, as these patients are typically reprogrammed to bipolar stimulation. Secondly, the co-registration of multiple images and atlas representations of the patient creates spatial variability that cannot be ignored. We attempted to minimise co-registration error by using easily identifiable landmarks such as the anterior commissure/posterior commissure and widely accepted co-registration algorithms. Thirdly, while we extended great effort to place all of our data into the stereotactic coordinate system of the patient to utilise MER data in the

most accurate way possible, one caveat was the inherent uncertainty in the intraoperative electrophysiologist's anatomical designation of the recordings. However, we used established criteria (eg, increased background activity followed by the presence of neuronal activity with discharge patterns similar to that previously described by the STN, along with the presence of sensorimotor responses) to make the MER designations used in our study.<sup>38</sup> Fourthly, outside of histological reconstruction it is impossible to know the exact size, shape and location of the STN in a given patient.<sup>44–46</sup> We relied on a three dimensional atlas model fit to match boundaries defined by the recorded neurophysiology and neuroanatomy visible on the MRI. Fifthly, due to signal to noise considerations, the DTI brain atlas used in this study was acquired with relatively large voxel sizes<sup>37</sup>; therefore, the three dimensional tissue conductivities used in the model only represent a gross estimate. Sixthly, the VTA prediction functions used in the model were derived from the activation of straight, relatively large diameter myelinated axons, and may not be representative of the response of other neuron types surrounding the electrode (local projection neurons, local interneurons, afferent inputs, etc). Given that myelinated axons are considered the most excitable neuron type to extracellular electrical stimulation,<sup>47</sup> our VTA predictions should be considered an upper limit in terms of stimulation spread.

Experimental validation of the VTA predictions is a difficult task. We are actively pursuing research studies that link our DBS models with electrophysiological recordings in humans and non-human primates.<sup>26 28 48</sup> The results of these studies show that our models can accurately predict stimulation spread into the corticospinal tract during STN DBS, and the synergistic evolution of our modelling technology and experimental analysis will allow for continuous improvement in their accuracy and validity. Nonetheless, we believe that the patient specific DBS modelling system used in this study is capable of making quantitative, clinically relevant, predictions.

Our results suggest that stimulation of axonal tissue dorsal, lateral and posterior to the centroid of the STN maximises therapeutic benefit from DBS. However, every patient's disease pathology, electrode location and behavioural response to stimulation are different. For example, patient Nos 2, 7 and 9 all had therapeutic VTAs with similar sizes and anatomical locations but their therapeutic outcomes showed substantial differences. In turn, maximising therapeutic benefit for an individual DBS patient involves more than just electrode placement and a VTA calculation, as many variables unaccounted for in this study could impact on the behavioural response to DBS. For example, it is possible that based on the patient's symptoms, one electrode location may be preferential to another, or stimulation spread into one anatomical region may be preferential to another. In turn, the interplay between the patient and clinician performing the DBS parameter selection is critical in defining the balance between therapeutic benefit and side effects. However, this clinical process is typically done without the opportunity to visualise the regional spread of stimulation and its location with respect to the surrounding anatomy. This could be an important issue in patients such as Nos 6 and 8 where the model suggests that the electrodes are in a good location but the stimulation parameter settings may not be optimal because of stimulation spread into the internal capsule. The converse is also suggested with patient No 10 where a lateral electrode location limits the allowable size of the VTA to avoid spread into the internal capsule. Therefore, the next step along this line of research is to couple patient

specific DBS model predictions with prospective clinical evaluations to develop new and improved techniques to optimise the clinical efficacy of DBS. For example, methodology from this study may find utility in augmenting DBS surgical placement planning,<sup>46 49–51</sup> and the postoperative stimulation parameter selection process.<sup>52</sup>

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**Competing interests:** CBM, CRB and CCM authored intellectual property related to the project methodology. CRB and CCM hold company shares in IntEct Medical Inc.

**Ethics approval:** This study was approved by the Cleveland Clinic Institutional Review Board.

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