Movement Disorders

Letter: New Observation

Tractography-based reprogramming of GPi DBS for Segmental Dystonia: A Case Report

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Yes, I am a native English speaker

Files for peer review

All files submitted by the author for peer review are listed below. Files that could not be converted to PDF are indicated; reviewers are able to access them online.

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Manuscript (1).docx	Main Document - MS Word	497.6 KB	Page 4
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Video 1.mp4	Embedded Video	40.1 MB	*Not converted to PDF*

Tractography-based reprogramming of GPi DBS for Segmental Dystonia: A Case Report

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We present a case of a 64-year-old male with a history of treatment-resistant segmental dystonia - right-sided torticollis and elevation of the right shoulder while walking. There was minimal relief with extensive medical treatment, and hence the patient was offered bilateral GPi-DBS. The IPG was programmed to achieve the best clinical response. Several combinations of contact point configurations, pulse width, frequency, and current were tried. However, the improvement observed was short-lived. Assessment in the best SoC program was documented (Video 1 Part 1, S1.1)

Stimulation of postero-ventro-lateral GPi relieves dystonia due to its connectivity with the thalamus (1-3). Hence, we decided to analyse the connectivity of GPi with the Thalamus to guide programming. T1 and diffusion-weighted sequences were acquired for probabilistic tractography and connectivity analysis in FSL (S1.2). The ventral-most contact point of both electrodes was closest to the GPi-Thalamus connectivity hotspot (Fig. 1A). When visualised in BRAINLab iPlan, the right pallidothalamic tract ranged from 1.4 mm (closest) to 3.5 mm (farthest) anterolateral to the ventral contact point. Based on calculations suggested by Mädler et al., a minimum current of 1.05 mA was required to stimulate the closest fiber, while 4.93 mA was required to stimulate the entire tract (4). On the left side, the ventral-most contact point of the electrode traversed through

the pallidothalamic tract. Thus, both the ventral contact points were stimulated in a monopolar configuration (S1.1). There was significant clinical improvement; hence, the assessment was documented at 9 months (Video 1 Part 2, S1.1).

We then compared the connectivity of the volume of tissue activated (VTA) by SoC and the tractography-based program with the thalamus (Fig. 1B-D). At first glance, the SoC and tractography-based VTA appeared similar, but the clinical outcomes were vastly different. On statistical analysis (S1.3), the connectivity of the tractography-based VTA to the thalamus was significantly higher than that of the SoC VTA on both sides (right: $t\_stat = 7.6293$; $p < 0.000001$; left: $t\_stat = 7.4316$, $p < 0.00001$). Further analysis confirmed that the connectivity of tractography-based VTA to the subthalamic nucleus was also significantly more than that of the SoC-based VTA (right: $t\_stat = -10.1147$; $p < 0.000001$; left: $t\_stat = -4.7104$, $p = 0.000011$). These differences could only have been identified through tractography and connectivity analysis, and not from clinical feedback. Thus, we suggest acquiring diffusion tensor data during pre-operative imaging and reviewing it for initial programming, in difficult cases, and to possibly integrate it into automated programming algorithms.

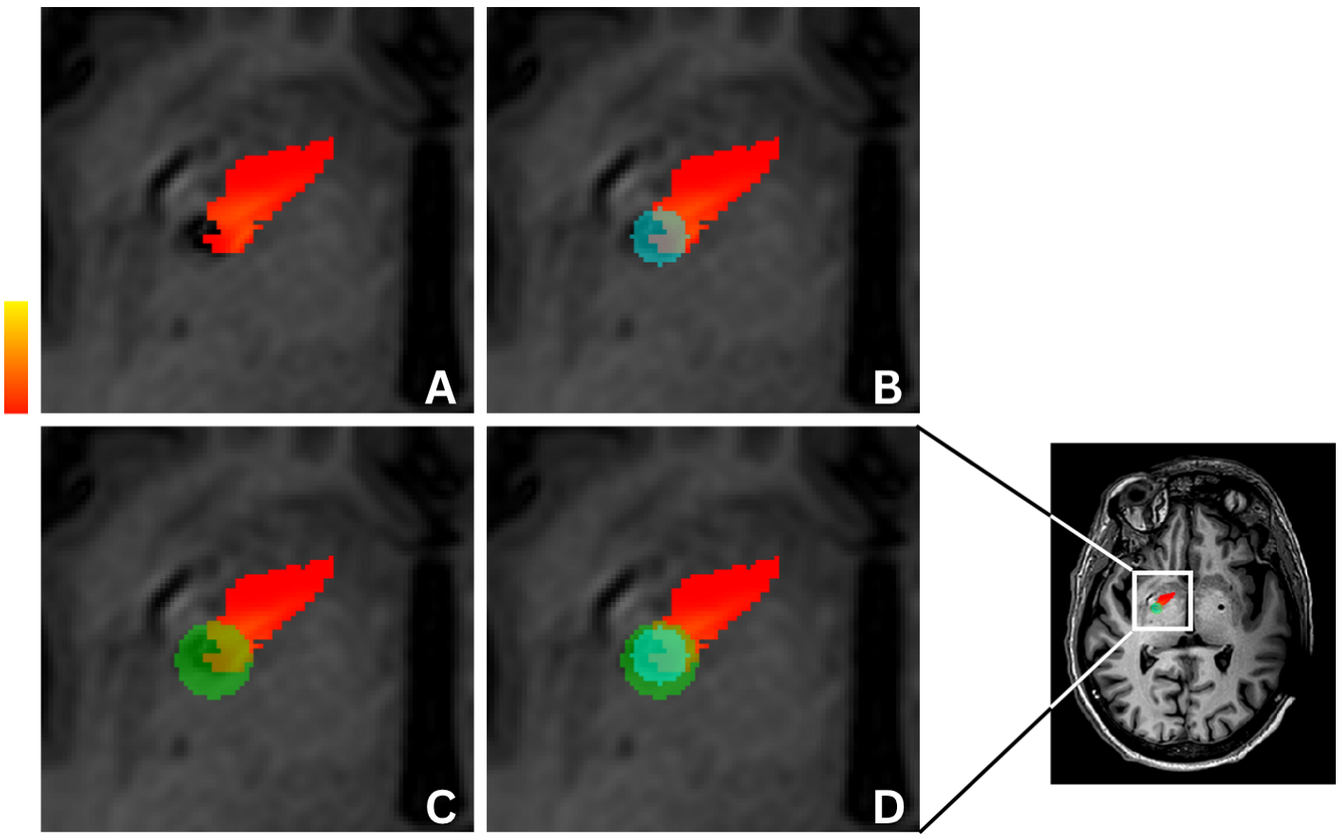

Figure 1: Comparison of the volume of GPi activated in the standard-of-care and tractography-based program, and their connectivity to the Thalamus: (A) GPi-Thalamus connectivity map; (B) Standard-of-Care program (SoC) Volume of Tissue Activated (VTA) (Green) overlaid on GPi-Thalamus connectivity map; (C) Tractography-based program VTA (Blue) overlaid on GPi-Thalamus connectivity map; and (D) SoC, and tractography-based VTA overlaid on GPi-Thalamus connectivity map.

To our knowledge, this is the first instance where the IPG, when reprogrammed exclusively based on tractography, reported significant improvement. Future work in this direction may be helpful in difficult post-DBS cases and even preoperative planning.

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Supplementary Material

1. Programming parameters and assessments -

	Best SoC-based Program		Tractography-based Program	
	Right	**Left**	**Right**	**Left**
Configuration	C (+) 1 (-19%) 2A (-21%) 2B (-23%) 2C (-22%) 3A (-5%) 3B (-5%) 3C (-5%)	C (+) 2A (-13%) 2C (-14%) 3A (-40%) 3C (-33%)	C (+) 1 (-)	C (+) 1 (-)
PW (us)	50	410	130	130
F (Hz)	60	60	60	90
I (mA)	4	2.5	4	1.5
Assesments				
BFMDRS	25		4	
DDS	3		1	
TWSTRS	51		17	

SoC - Standard of Care, PW - Pulse Width (in us), F - Frequency (in Hertz), I - Current (in milli Amperes), BFMDRS - Burke-Fahn-Marsden Dystonia Scale, DDS - Dystonia Disability Scale, TWSTRS - Toronto Western Spasmodic Torticollis Rating Scale

Table 1: Stimulation Parameters on the Best SoC-based Program and Tractography-based Program

2. Raw images (DICOM) were converted into a Neuroimaging Informatics Technology Initiative (NIfTI) format for all further analysis. DTI B0 was registered onto the high-resolution T1 image using fMRIB Software Library 6.0.7.18 (FSL) FLIRT linear registration (with 6 DOF). Thereafter, the FDT Diffusion toolkit was used to process DTI data and reconstruct tract vectors in each voxel (BEDPOSTX, number of fibers = 3, fudge=1, bi=1000, model = 1). We then made masks of GPi, thalamus, ventro-anterior nucleus, and subthalamic nucleus in FSLeyes. We then run Probabilistic Tractography using FSL FDT Diffusion Toolkit (PROBTRACKX2; default settings) with GPi as the seed and ipsilateral thalamus, ventro-anterior thalamus, and subthalamic nucleus as the classification target to construct the map of connectivity between GPi and target nuclei.

3. Statistical Analysis: We first made 3D binary masks of SoC and tractography-based VTA by finding the radius of the VTA as suggested by Mädler et al. We assumed that stimulation of a given contact point generates a perfectly spherical VTA centered at the 3D centre of the contact point. We then used fslmaths to multiply the VTA of each program with the GPi-target connectivity maps. As a product, we get voxels (that are non-zero in both the GPi-target connectivity map and the VTA) with intensity of each representing the strength of its connectivity to the target. We then ran a t-test between SoC and tractography-based VTA for each target in fslstats.