Neuroanatomical considerations for optimizing thalamic deep brain stimulation in Tourette syndrome

*Takashi Morishita, MD, PhD,¹ Yuki Sakai, MD, PhD,^{2,6} Hitoshi Iida, MD, PhD,³
Saki Yoshimura, PhD,¹ Atsushi Ishii, MD, PhD,⁴ Shinsuke Fujioka, MD, PhD,⁵
Saori C. Tanaka, PhD,² and Tooru Inoue, MD, PhD¹

¹Department of Neurosurgery, Fukuoka University Faculty of Medicine, Fukuoka; ²ATR Brain Information Communication Research Laboratory Group, Kyoto; ³Department of Psychiatry, Fukuoka University Faculty of Medicine, Fukuoka; ⁴Department of Pediatrics, Fukuoka University Faculty of Medicine, Fukuoka; ⁵Department of Neurology, Fukuoka University Faculty of Medicine, Fukuoka; and ⁶Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

OBJECTIVE Deep brain stimulation (DBS) of the centromedian thalamic nucleus has been reportedly used to treat severe Tourette syndrome, yielding promising outcomes. However, it remains unclear how DBS electrode position and stimulation parameters modulate the specific area and related networks. The authors aimed to evaluate the relationships between the anatomical location of stimulation fields and clinical responses, including therapeutic and side effects.

METHODS The authors collected data from 8 patients with Tourette syndrome who were treated with DBS. The authors selected the active contact following threshold tests of acute side effects and gradually increased the stimulation intensity within the therapeutic window such that acute and chronic side effects could be avoided at each programming session. The patients were carefully interviewed, and stimulation-induced side effects were recorded. Clinical outcomes were evaluated using the Yale Global Tic Severity Scale, the Yale-Brown Obsessive-Compulsive Scale, and the Hamilton Depression Rating Scale. The DBS lead location was evaluated in the normalized brain space by using a 3D atlas. The volume of tissue activated was determined, and the associated normative connective analyses were performed to link the stimulation field with the therapeutic and side effects.

RESULTS The mean follow-up period was 10.9 ± 3.9 months. All clinical scales showed significant improvement. Whereas the volume of tissue activated associated with therapeutic effects covers the centromedian and ventrolateral nuclei and showed an association with motor networks, those associated with paresthesia and dizziness were associated with stimulation of the ventralis caudalis and red nucleus, respectively. Depressed mood was associated with the spread of stimulation current to the mediodorsal nucleus and showed an association with limbic networks.

CONCLUSIONS This study addresses the importance of accurate implantation of DBS electrodes for obtaining standardized clinical outcomes and suggests that meticulous programming with careful monitoring of clinical symptoms may improve outcomes.

<https://thejns.org/doi/abs/10.3171/2021.2.JNS204026>

KEYWORDS Tourette syndrome; deep brain stimulation; thalamus; adverse events; normative connectome; functional neurosurgery

TOURETTE syndrome (TS) is a neuropsychiatric disorder characterized by involuntary tic movements and psychiatric comorbidities. Although symptoms are likely to be subtle and tend to subside spontaneously in childhood, some patients suffer from severe, debilitating

involuntary movements throughout their life. Common treatment options for TS include medical and behavioral therapies, and deep brain stimulation (DBS) may be indicated for severe cases. Since the first report on the successful application of DBS therapy for TS,¹ reports on its

ABBREVIATIONS ANT = advanced normalization tools; CM = centromedian; DBS = deep brain stimulation; FGATIR = fast gray matter acquisition T1 inversion recovery; GPI = globus pallidus interna; HAM-D = Hamilton Depression Rating Scale; MD = mediodorsal; MNI = Montreal Neurological Institute; PD = Parkinson disease; PW = pulse width; RN = red nucleus; TS = Tourette syndrome; T1WI = T1-weighted imaging; VL = ventrolateral; VTA = volume of tissue activated; YBOCS = Yale-Brown Obsessive-Compulsive Scale; YGTSS = Yale Global Tic Severity Scale.

SUBMITTED November 12, 2020. **ACCEPTED** February 11, 2021.

INCLUDE WHEN CITING Published online August 6, 2021; DOI: 10.3171/2021.2.JNS204026.

* T.M. and Y.S. equally contributed equally to this study.

TABLE 1. Demographic data in 8 patients with TS

Case No.	Sex	Age (yrs) at Onset	Age (yrs) at Dx	Age (yrs) at Surgery	Medications Tried Prior to DBS
1	M	7	22	39	Haloperidol, aripiprazole, clonazepam, bromazepam
2	M	14	16	26	Risperidone, aripiprazole, fluvoxamine, atomoxetine
3	F	5	10	26	Aripiprazole, haloperidol, risperidone, fluvoxamine, pimozide, clonazepam, olanzapine, chlorpromazine
4	M	5	12	18	Aripiprazole, haloperidol, risperidone
5	M	8	8	12	Aripiprazole, fluvoxamine, biperiden
6	M	7	8	17	Aripiprazole, haloperidol, risperidone, fluvoxamine
7	M	5	14	19	Aripiprazole, haloperidol, risperidone
8	M	9	10	18	Aripiprazole, clonazepam, etizorham
Mean $\pm$ SD	7 M, 1 F	7.5 $\pm$ 3.0	12.5 $\pm$ 4.8	21.9 $\pm$ 8.3	

Dx = diagnosis.

clinical efficacy have been repeatedly published.^{2,3} Previous studies concerning DBS for severe TS have reported mixed results, although overall clinical outcomes were favorable.²⁻⁴ Additionally, a recent long-term follow-up study showed a loss of benefit after several years of continuous thalamic stimulation.⁵

Several DBS targets including the centromedian (CM) thalamic nucleus, globus pallidus interna (GPi), and anterior limb of the internal capsule have been proposed for the treatment of TS, and stimulation of these targets is reportedly equally effective.^{2,3} The heterogeneity of the therapeutic effects is, however, potentially associated with the patient selection criteria, surgical technique, and DBS programming used. A potential factor associated with DBS failure is lead misplacement,⁶ and a recent study reported that the incidence of DBS lead misplacement in a Parkinson disease (PD) cohort was higher than 15%.⁷ Even though the incidence of lead misplacement in a TS cohort has not been reported, we suspect its occurrence in some patients with TS refractory to DBS in the reported cohorts.

Because the identification of each thalamic nucleus on the imaging studies has been challenging, it is difficult to determine the occurrence of lead misplacement in a patient with TS showing poor outcome. Additionally, detailed subdivisions of the thalamus associated with favorable stimulation outcome have not been identified as in the case of the GPi or subthalamic nucleus stimulation for the treatment of PD, although a multicenter analysis reported preferred stimulation points for TS.⁸ A subtle difference in the lead position and electrically stimulated areas theoretically results in the activation of different neuronal networks; however, it remains unclear how DBS electrode position and stimulation parameters modulate the specific area and related networks.

The position of DBS electrodes is conventionally reported using cartesian coordinates relative to the mid-commissural point, but recent studies have addressed the importance of considering anatomical variations while determining the optimal DBS electrode position.⁹ To analyze patient-specific electrode positions, various authors have used a common population-based standard Montreal Neurological Institute (MNI) space,^{8,10} and recent stud-

ies have reported the utility of 3D anatomical atlases and structural connectome.^{11,12} Using these neuroimaging techniques, we aimed to evaluate the relationships between the anatomical location of implanted DBS leads and clinical responses. We also evaluated stimulation-induced side effects because they interfere with optimizing stimulation settings for symptom suppression.

Methods

Study Design

We prospectively recorded the clinical course of the patients and reviewed the charts to obtain detailed information. To interpret the DBS lead positions associated with clinical benefits and stimulation-induced adverse events, we evaluated the DBS lead position in the postoperative images. This study was approved by our institutional review board, the Fukuoka University Medical Ethics Review Board, and informed consent was obtained from the participants. This study was conducted in accordance with the Declaration of Helsinki.

We included 8 patients who underwent DBS surgery at our department between May 2018 and January 2020, and all patients completed at least a 6-month follow-up. DBS therapy was indicated for patients with severe, medication-refractory symptoms who were older than 12 years of age. One patient (case 7) underwent DBS surgery because of severe cervical tic with the risk of spinal cord injury despite relatively low clinical scoring. All patients underwent multidisciplinary evaluation performed by a team consisting of a neurologist, psychiatrist, pediatrician, and neurosurgeon, as recommended by a recent guidelines paper.¹³ The demographics of patients are summarized in Table 1.

We evaluated the clinical outcomes using the Yale Global Tic Severity Scale (YGTSS),¹⁴ Yale-Brown Obsessive-Compulsive Scale (YBOCS),¹⁵ and Hamilton Depression Rating Scale (HAM-D)¹⁶ (Table 2). These evaluations were performed preoperatively and at 6 months and 1 year after surgery by a psychiatrist (H.I.) who was blinded to DBS lead location and programming. Additionally, we recorded the adverse events associated with surgery and neurostimulation. Mood changes were recorded in the

TABLE 2. Clinical outcomes in 8 patients with TS

Case No.	FU Period (mos)	YGTS Severity			YGTS Impairment			YBOCS			HAM-D		
		Baseline	6 Mos	Last FU	Baseline	6 Mos	Last FU	Baseline	6 Mos	Last FU	Baseline	6 Mos	Last FU
1	12	40	20	16	50	30	30	23	21	19	10	8	6
2	12	50	23	12	50	30	30	32	4	0	17	9	12
3	12	32	15	14	40	20	10	0	0	0	19	14	10
4	18	47	19	15	50	20	20	30	0	7	4	1	5
5	12	50	43	27	50	40	20	15	15	15	1	2	2
6	9	48	NA	23	50	NA	20	19	NA	8	11	NA	2
7	6	25	9	9	50	10	10	10	0	0	3	1	1
8	6	43	12	12	40	10	10	5	0	0	4	0	0
Mean $\pm$ SD	10.9 $\pm$ 3.9	41.9 $\pm$ 9.1	20.1 $\pm$ 11.2	15.8 $\pm$ 6.3	47.5 $\pm$ 4.6	22.9 $\pm$ 11.1	18.8 $\pm$ 8.3	16.8 $\pm$ 11.5	5.7 $\pm$ 8.7	6.1 $\pm$ 7.5	8.6 $\pm$ 6.7	5.0 $\pm$ 5.4	4.8 $\pm$ 4.4
p value	NA	NA	0.018	0.012	NA	0.017	0.010	NA	0.043	0.028	NA	0.028	0.035

FU = follow-up; NA = not applicable.

medical records on the basis of self-reported complaints of the patients.

Surgical Procedure

Given that we have reported our DBS procedures previously,^{17,18} we describe our method briefly herein. MRI was performed in all patients for stereotactic planning by using an MRI scanner (Ingenia 1.5 T; Philips), and the MRI sequences included volumetric T1-weighted imaging (T1WI) with contrast, and volumetric fast gray matter acquisition T1 inversion recovery (FGATIR). Using commercialized software (iPlan stereotaxy; Brainlab), we planned the trajectory of DBS lead implantation. The above-mentioned MRI sequences were automatically fused, and the cartesian coordinate system was anchored. The tentative target was initially set at 5 mm lateral and 4 mm posterior to the midcommissural point on the anterior commissure–posterior commissure plane. The trajectory was planned such that the DBS lead would not injure the blood vessels, lateral ventricle, and sulci during T1WI with contrast, and the target (presumed lead tip position at the ventral surface of the CM nucleus) was modified in each case. The CM nucleus was identified as a relatively high-intensity area on FGATIR images, as reported previously.¹⁸ The target was meticulously checked using the mammillothalamic tract and the red nucleus (RN) as landmarks (Supplementary Fig. 1). The DBS lead placement was performed under the guidance of a C-arm.

In this study, all patients underwent simultaneous bilateral implantation of DBS leads (model 3387; Medtronic) and implantation of an implantable pulse generator (Activa RC; Medtronic) on the same day. The first 4 patients underwent DBS lead implantation under local anesthesia; however, 3 of them could not tolerate the fixed head position during the awake procedure. Thus, we used general anesthesia throughout the surgical procedure for all system implantations for the remaining 4 cases (cases 5–8).

DBS Programming

Electrical stimulation was delivered immediately following DBS system implantation in the first 6 patients and 2 weeks after DBS lead implantation in the remaining 2 patients (cases 7 and 8). The initial stimulation was delivered using the monopolar setting, which activates the second most ventral contacts (contacts 1 and 9) bilaterally, with the following parameters: amplitude, 2.0 V or milliamperes; pulse width (PW), 60 microseconds; and frequency, 130 Hz.

One month following surgery, we measured the threshold levels of stimulation-induced side effects in each contact at a fixed PW of 60 μ sec and a frequency of 130 Hz. We carefully interviewed the patients at each programming session, and we increased the stimulation intensity within the therapeutic window such that acute side effects could be avoided. At each programming visit new programming parameters were saved as a new group of settings, so that patients could go back to the previous setting in case they experienced chronic stimulation-induced side effects, such as mood changes. In cases in which stimulation resulted in both tic suppression and adverse effects,

TABLE 3. The stimulation parameters at last follow-up and induced side effects in 8 patients with TS

Case No.	Time Point	Lt Side					Rt Side					Long-Term Stimulation-Induced Side Effects
		Cathode	Anode	PW (μsec)	Frequency (Hz)	Amplitude (V or mA)	Cathode	Anode	PW (μsec)	Frequency (Hz)	Amplitude (V or mA)	
1	12 mos*	0	Case	60	100	3.8 V	9	Case	60	100	3.8 V	None
		2	Case	60	100	2.5 V	11	Case	60	100	2.5 V	
2	2 mos	0	Case	120	125	3.0 V	9	Case	120	125	3.5 V	Depressed mood
	12 mos	2	Case	90	130	4.0 mA	10	Case	90	130	4.0 mA	None
	11 mos	1	Case	90	125	4.0 V	9	Case	90	125	3.9 V	Depressed mood; aggressiveness; slurred speech
3	12 mos*	1	Case	90	110	2.5 V	9	Case	90	110	2.0 V	None
		3	Case	90	110	3.0 V	11	Case	90	110	3.0 V	
	11 mos	2	Case	90	130	3.5 mA	11	Case	90	130	2.9 mA	Depressed mood & anxiety
4	18 mos	3	1	100	125	3.5 mA	11	9	100	125	3.5 mA	None
	8 mos*	0	Case	90	125	4.2 V	9	Case	90	125	4.2 V	Depressed mood & suicidal ideation
		2	Case	120	125	4.0 V	11	Case	120	125	4.0 V	
	14 mos	2	Case	100	130	4.0 mA	10	Case	100	130	4.0 mA	Depressed mood
5	12 mos*	1	Case	60	125	2.8 mA	9	Case	60	125	2.8 mA	None
		2	Case	120	125	3.0 mA	10	Case	120	125	3.0 mA	
6	9 mos*	2	Case	100	125	3.2 mA	10	Case	100	125	3.2 mA	None
		3	Case	100	125	4.0 mA	11	Case	100	125	4.0 mA	
7	6 mos*	2	Case	90	125	3.1 mA	10	Case	90	125	3.1 mA	None
		3	Case	90	125	3.0 mA	11	Case	90	125	3.0 mA	
8	6 mos	2	Case	90	130	3.8 mA	10	Case	90	130	4.2 mA	None

All side effects were reversed by reducing the stimulation intensity.

* Interleaving stimulation settings were applied.

we prioritized avoiding adverse effects. If the clinical response was insufficient, with maximum intensity at a single monopolar setting, we activated another contact to apply interleaving stimulations by using multiple contacts. The frequency of programming depends on the patients' accessibility and their clinical response.

DBS Lead Localization

Stereotactic CT scans were performed to determine the lead location, typically on postoperative day 9, at the point when the pneumocephalus was resolved. The CT image was fused to a preoperative scan to measure the DBS lead trajectory and contact positions relative to the midcommissural point in each case. We compared the stereotactic planning and DBS lead locations to measure the stereotactic errors. Stereotactic targeting error was calculated as the distance between the planned target point and trajectory of the implanted lead.¹⁹

All imaging data were preprocessed using the Lead-DBS software (www.lead-dbs.org).²⁰ Briefly, all (pre- and postoperative) CT and MRI scans were linearly coregistered to the preoperative T1WI using SPM software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Registration between postoperative CT and preoperative T1WI was further refined using the linear registration within the subcortical target region of interest to minimize nonlinear bias caused by the surgery.²¹ All data were normalized into the standard MNI space. This procedure

was carried out with the whole-brain nonlinear symmetric normalization (SyN) registration implemented in advanced normalization tools (ANTs; <http://stnava.github.io/ANTs/>)²² by using the "effective (low variance)" setting with subcortical refinement as implemented in Lead-DBS.²⁰ Electrode trajectories and contacts were automatically prereconstructed using the PaCER algorithm²³ and manually refined using Lead-DBS software. We also determined the lead trajectory and contact positions by using subject-independent 3D atlases of the thalamic nuclei.²⁴ We considered that contacts existed within those thalamic nuclei when spherical regions of 0.2-mm radius around contacts overlapped with each nucleus: CM, mediodorsal (MD), ventrolateral (VL), and ventroposterior nuclei. Detected electrodes and thalamic nuclei were visualized using Lead-DBS.

Volume of Tissue Activated Mapping

We calculated the volume of tissue activated (VTA) under the conditions with the optimized stimulation parameters (Table 3) and those with stimulation-induced side effects (Tables 3 and 4). All VTA calculations were conducted using Lead-DBS software.²⁵ A volume conductor model was constructed on the basis of a tetrahedral volume mesh that included the DBS electrode and surrounding tissues. Conductivities of 0.14 S/m were assigned to gray and white matter.²⁶ On the basis of the volume conductor model, the electric field distribution was

TABLE 4. Threshold levels of acute stimulation-induced side effects in 8 patients with TS

Case No.	Side	Contact 0		Contact 1		Contact 2		Contact 3	
		Threshold Level	Side Effect	Threshold Level	Side Effect	Threshold Level	Side Effect	Threshold Level	Side Effect
1	Lt	5.8 V	Dizziness	7.2 V	Dizziness	NA	None	NA	None
	Rt	3.5 V	Dizziness	6.0 V	Dizziness	8.9 V	Paresthesia in lt hand	NA	None
2	Lt	1.8 mA	Dizziness	4.0 mA	Tinnitus in lt ear	6.6 mA	Paresthesia in rt hand	NA	None
	Rt	4.0 mA	Dizziness	5.0 mA	Paresthesia in lt forearm	8.2 mA	Paresthesia in lt fingers	NA	None
3	Lt	1.8 mA	Dizziness	3.6 mA	Dizziness	6.5 mA	Dizziness	NA	None
	Rt	2.5 mA	Dizziness	2.9 mA	Dizziness	3.1 mA	Paresthesia in lt hand	4.4 mA	Dizziness
4	Lt	5.5 V	Nausea	NA	None	7.0 V	Nausea	6.7 V	Nausea
	Rt	3.2 V	Electric shock sensation in the head	4.9 V	Paresthesia in lt hand & face	6.2 V	Anxiety	7.8 V	Paresthesia in back of neck
	Lt (post-revision)	3.0 mA	Nausea	3.6 mA	Paresthesia in rt hand, squeezing sensation of the head	4.8 mA	Deep tactile sensation in rt ear	8.4 mA	Squeezing sensation of the head
5	Lt	5.1 mA	Dizziness, HA	7.4 mA	Dizziness, HA	NA	None	NA	None
	Rt	6.8 mA	Dizziness, HA	NA	None	NA	None	NA	None
6	Lt	6.0 mA	Dizziness	6.5 mA	Dizziness	NA	None	NA	None
	Rt	6.5 mA	Dizziness	NA	None	NA	None	NA	None
7	Lt	2.6 mA	Dizziness	3.6 mA	Dizziness, paresthesia in rt hand	6.2 mA	"Funny sensation" in the head	7.5 mA	Paresthesia in rt hand
	Rt	4.5 mA	Dizziness	5.9 mA	Paresthesia in both forearms	7.0 mA	Dizziness	NA	None
8	Lt	5.8 mA	Dizziness	NA	None	NA	None	NA	None
	Rt	6.0 mA	Dizziness	NA	None	NA	None	NA	None

HA = headache.

Threshold levels of stimulation-induced side effects in each contact were measured at a fixed PW of 60 μ sec and a frequency of 130 Hz.

simulated using the FieldTrip-SimBio pipeline that was integrated into Lead-DBS (<https://www.mrt.uni-jena.de/simbio/index.php/>; <http://fieldtriptoolbox.org>). The electric field distribution was thresholded for magnitudes above a commonly used value of 0.2 V/mm^{27,28} to define the extent of VTA. Following all VTA calculations, VTAs, including all areas with each effect from all subjects, were created (e.g., VTA of therapeutic effect includes all therapeutic VTA from all subjects). Considering the limited volume of data, the VTAs in the right hemisphere were nonlinearly transformed into those in the left hemisphere by using ANTs, and all VTAs were pooled across hemispheres as a left-sided VTA. Next, the overlapping regions between multiple effects (e.g., both therapeutic and mood change effects) were excluded to characterize each effect.

Normative Connectome

To characterize the brain connectome differences from very adjacent VTAs and to elucidate the brainwide mechanism of therapeutic stimulation and side effects, we used the population-averaged atlas of the macroscale human structural connectome derived from diffusion-weighted imaging data (N = 842, Human Connectome Project).²⁹ We depicted the 300 fibers from the VTAs specific to each effect by using DSI studio (<http://dsi-studio.labsolver.org>).

All detected structural fibers were visualized using Lead-DBS. We evaluated the proportion of the 300 fibers that passed through each brain region defined by Harvard-Oxford cortical/subcortical atlases³⁰ combined with the cerebellum from the automated anatomical labeling atlas.³¹ All small parcels of the cerebellum defined in automated anatomical labeling were integrated into one binarized parcel. The proportion of 300 fibers was thresholded above 0.02 and visualized using a circular plot.

Statistical Analysis

To compare the pre- and post-DBS clinical scores on YGTSS, YBOCS, and HAM-D, we used the Wilcoxon signed-rank test. Statistical analyses were performed using SPSS version 21.0 (IBM Corp.), and $p < 0.05$ indicated statistical significance.

Results

Clinical Outcomes

The mean follow-up period was 10.9 ± 3.9 months, but one patient (case 6) missed a formal 6-month follow-up due to the occurrence of the COVID-19 pandemic during the study period. YGTSS severity and impairment scores improved from 41.9 ± 3.9 and 47.5 ± 4.6 at baseline to 15.8

± 6.3 ($z = -2.52$, $p = 0.012$) and 18.8 ± 8.3 ($z = -2.59$, $p = 0.010$), respectively, at the last follow-up. Furthermore, YBOCS and HAM-D scores improved from 16.8 ± 11.5 and 8.6 ± 6.7 at baseline to 6.1 ± 7.5 ($z = -2.20$, $p = 0.028$) and 4.8 ± 4.4 ($z = -2.11$, $p = 0.035$), respectively, at the last follow-up. Clinical outcomes are summarized in Table 2. It is noteworthy that one patient (case 8) experienced an enormous microlesion effect while the tic movements had disappeared for a week after surgery. The microlesion effect then gradually waned, and had almost disappeared by the time the electrical stimulation was started (2 weeks after surgery). This patient responded well to DBS therapy; YGTSS severity and impairment scores were improved from 43 and 40 to 10 and 10, respectively, at 6-month follow-up.

With regard to the stimulation-induced side effects, no permanent problems were reported. All stimulation-induced side effects, including paresthesia and depressed mood, were temporary in that patients followed the programming instruction to change the stimulation setting at home. The surgical adverse events included wound dehiscence and lead misplacement. Two patients (cases 1 and 4) experienced wound dehiscence of the scalp incision site and underwent a wound revision. One patient (case 4) underwent a left DBS lead revision due to insufficient phonic tic suppression despite the motor tic improvement.

DBS Lead Location

Coordinates of the preoperative stereotactic targeting and the measured DBS lead locations are summarized in Supplementary Table 1. The stereotactic targeting error was 1.2 ± 0.5 mm. Analysis of DBS lead positions indicated that 15 of 17 DBS leads, including a misplaced lead, penetrated the CM nucleus and that 11 leads penetrated the MD nucleus (Supplementary Table 2). The dorsal contacts of the quadripolar electrodes were located in the VL nucleus in all cases except for the initial left lead of case 4. In case 4, the tip of the misplaced DBS lead on the left was on the border between MD and CM nuclei, and 3 contacts were positioned in the MD nucleus. Two ventral contacts and 2 dorsal contacts of the revised lead in case 4 were successfully placed in the CM nucleus and VL nucleus, respectively (Supplementary Table 2 and Video 1).

VIDEO 1. Lead electrode placement in MNI space. Lead electrodes with the CM nucleus (peach), RN (red), MD nucleus (purple), and ventral lateral dorsal/ventral nucleus (yellow). The lead electrodes of each patient were displayed in different colors (case 1, orange; case 2, red; case 3, blue; case 4, purple; case 4 after the repositioning, dark purple [only in the left hemisphere]; case 5, light green; case 6, yellow; case 7, light blue; case 8, green). Click here to view.

The DBS lead contact locations in the normalized brain space are shown in Fig. 1 and Video 1.

Clinical Response According to the Stimulated Area

Contacts 2 (10 contacts) and 3 (11 contacts) were likely to be selected as the active contacts at the last visit (Table 3). Therapeutic effects were achieved by stimulation of the border between the CM and VL nuclei in our case series. Depressed mood or anxiety was reported after long-term stimulation (Table 3). Four patients commonly experienced mood changes after long-term stimulation for sev-

eral days after a programming session. The programming parameters at the last follow-up and chronic side effects are summarized in Table 3. The common acute side effects were dizziness and paresthesia in the upper extremity contralateral to the active DBS lead. Dizziness and paresthesia tended to be observed with high-intensity stimulation of the 2 ventral contacts and 2 middle contacts, respectively. These acute stimulation-induced side effects are summarized in Table 4.

Stimulated Areas and Normative Connectome

In Fig. 2, we demonstrate the VTAs related to the therapeutic stimulation and side effects. We found the VTA to be related to the clinical response in the border between CM and VL nuclei (blue area in Fig. 2A). Although the paresthesia-related region mostly overlapped the therapeutic region, it extended slightly into lateral, medial, and anterior directions (green area). The VTA related to dizziness extended into the ventral direction and overlapped with the RN (orange area). We found that long-term stimulation of the relatively medial and dorsal region entering the MD nucleus led to a depressed mood (purple area).

Using the normative connectome, we found that each VTA related to the therapeutic stimulation and side effects showed clearly different network properties (Fig. 3). Brain regions connected with each VTA are summarized using the circular plot (Fig. 4, Supplementary Fig. 2). Fibers of therapeutic stimulation were characterized by more dense connections with the precentral gyrus than were those of side effects (Fig. 4A). Dizziness-related and paresthesia-related VTAs extended fibers into relatively specific brain regions (Fig. 4B and C). In contrast, the stimulation-induced mood change was related to more spatially distributed brain regions (Fig. 4D). Specifically, we detected dizziness-related fibers in the cerebellorubral network (Figs. 3B and 4B). The paresthesia symptom was characterized by the fibers that connect the thalamus and insular cortex (Figs. 3C and 4C). We found a relatively dense connection with the thalamus in the amygdala and the orbitofrontal cortex, which are related to depressed mood (Figs. 3D and 4D).

Discussion

Our study revealed that overall outcomes were favorable and our results were consistent with those of the past reports.²⁻⁴ The results of our study showed a variety of DBS contacts (Fig. 1, Video 1) and illustrated the relationship between the DBS lead locations and clinical effects inclusive of therapeutic and side effects (Figs. 2-4).

Regarding the stereotactic planning technique, the lead trajectory is determined according to the safety issues.³² Indirect targeting using the same template coordinates is not appropriate because this technique does not consider the anatomical variations in the subcortical structures.⁹ According to the literature, DBS leads were presumed to pass through the ventralis oralis complex nucleus to the CM nucleus; however, our series showed that there were a variety of lead locations even among the responders (Fig. 1, Video 1). We consider that such differences may have led to the occurrence of difference in threshold levels of stimulation-induced side effects (Tables 3 and 4). Vari-

FIG. 1. Lead electrode placement in MNI space. Lead electrodes with the CM nucleus (*peach*), RN (*red*), MD nucleus (*purple*), and ventral lateral dorsal/ventral nucleus (*yellow*). In panel **A**, the ventral lateral dorsal/ventral nucleus shown in panel **B** was removed. The lead electrodes of each patient were displayed in different colors (case 1, *orange*; case 2, *red*; case 3, *blue*; case 4, *purple*; case 4 after the repositioning, *dark purple* [only in the left hemisphere]; case 5, *light green*; case 6, *yellow*; case 7, *light blue*; case 8, *green*). Figure is available in color online only.

ous factors associated with the surgical procedure such as brain shift and distortion of the frame are considered to misplace the lead from the planned target.¹⁹ Although we did not measure the electrode positions intraoperatively, an image-guided procedure using intraoperative CT or MRI may improve the stereotactic accuracy and precision.^{33,34}

A potential factor predicting the incidence of a favorable outcome is the microlesion effect, and this issue also underpins the importance of accurate lead implantation. Microlesion effect has been reported to be associated with the optimal lead position in other movement disorders such as PD and essential tremor.^{35,36} Similarly, we have noted a temporary but complete resolution of tic movements immediately after surgery in a patient (case 8). These findings indicate that stimulation of a specific area is associated with tic suppression. In this context, the clinical outcomes of DBS for TS may be improved with accurate and precise DBS lead implantation in the specific area. Additionally, our experience that DBS lead repositioning improved the clinical outcome (case 4) addresses the importance of im-

planting DBS leads in the optimal position to maximize the benefit.

Difficulty in DBS programming for TS exists in that an immediate response may not be observed in the clinical setting, unlike that in the case of PD or essential tremor. Practitioners programming the DBS, however, should understand the relationship between the DBS lead and the surrounding structures. A subtle difference in stimulating position can lead to various effects through different properties of the brain network because the thalamus is quite a dense structure, containing many small nuclei, that relays information between different brain regions.²⁴ The VTA and normative connectivity analyses linked our clinical findings with how electrical currents spread to the surrounding neuroanatomical structures according to the situation (Figs. 2–4).

The VTA associated with therapeutic effects covered the dorsal area of the CM nucleus and the VL nucleus, and our normative connectome analysis showed its association with the motor networks (Figs. 3A and 4A). This finding is

FIG. 2. VTAs related to therapeutic stimulation and side effects. Each VTA color represents areas associated with the following effects: *blue* = therapeutic effect, *orange* = dizziness, *green* = paresthesia, and *purple* = depressed mood. The *peach-colored* region in the right hemisphere is the CM nucleus. **A:** Front view. **B:** Medial view. **C:** Lateral view.

FIG. 3. Normative connectome from VTAs related to therapeutic stimulation and side effects. The normative connectome from VTAs related to the therapeutic stimulation (**A**), dizziness (**B**), paresthesia (**C**), and depressed mood (**D**). The *peach-colored* region is the CM nucleus. Figure is available in color online only.

FIG. 4. Proportion of structural fibers projected from VTAs related to therapeutic stimulation and side effects. The circular plot represents the proportion of projected fibers that connect the thalamus and the other brain regions that have at least one connectivity (see Supplementary Fig. 2 for all brain regions); therapeutic stimulation (A), dizziness (B), paresthesia (C), and depressed mood (D). ant = anterior; inf = inferior; mid = middle; post = posterior; sup = superior. Figure is available in color online only.

consistent with that reported by a recent study showing the relationship of tic reduction with the fibers connecting the thalamus and the motor cortex.³⁷ On the contrary, it is well known that high electrical intensity is usually required for tic suppression,⁴ and therapeutic stimulation may also modulate the limbic systems subclinically, inducing psychiatric side effects.

With regard to the immediate side effects, the spread of stimulation current to the ventroposterior nucleus and the RN may induce paresthesia and dizziness, respec-

tively. These findings were partly supported by those of normative connectome analyses. These side effects can be observed immediately when the stimulation intensity is above the threshold levels in the clinical setting, but mood changes are likely to be detected several days after increasing the stimulation intensity. The lower threshold levels of these stimulation-induced side effects may indicate lead misplacement, and clinicians should be aware that the careful evaluation of clinical response to each stimulation parameter is important to estimate the lead location.

The reported mood changes are considered to result from the suprathreshold level of electrical stimulation of the limbic network, and this finding was supported by that of the normative connectome analysis; that is, the electrically activated area associated with the mood change is connected to limbic structures such as the amygdala, potentially through the inferior thalamic peduncle (Figs. 3D and 4D). We consider that the high-intensity electrical current to the MD nucleus was associated with the side effects, and this may underpin the mechanism of loss of benefits due to reduced levels of energy following long-term thalamic DBS that was reported recently.⁵ In our study, the depressed moods were temporary because we decreased the stimulation intensity or changed active contacts when patients experienced the side effects. Clinicians should be cautious that optimal long-term DBS may induce irreversible benefits,³⁸ but long-term high-intensity stimulation of the MD nucleus may result in irreversible mood changes or loss of beneficial effects.

In summary, based on our study findings, the ideal lead placement may be achieved by penetrating the VL and anterior border of the CM nuclei. The DBS lead should not be placed too posterolaterally or too ventrally, to avoid paresthesia caused by stimulation current to the ventralis caudalis nucleus or dizziness caused by stimulation current to the RN, respectively. The centerline angle of the trajectory, however, should be steep enough to avoid a depressed mood by current spread to the MD nucleus.

Although our study has demonstrated promising clinical outcomes of DBS therapy for severe, medication-refractory TS and provides a guide for identifying stimulation areas in the thalamus that yield desirable effects, it has several limitations. First, we included medically refractory cases, but several patients were younger than 18 years and may have had spontaneous improvements of symptoms. The records of mood change in our study were based on patients' reports rather than on quantified data. With regard to the mood change, we have not investigated potential factors other than stimulation parameters, such as medication changes and/or the patient's living environment. Besides, given the difficulties of acquiring the high-quality diffusion-weighted imaging data, we decided to conduct the normative connectome analysis because the usefulness of the normative connectome has been reported,¹² although the patient-specific connectome could add some information to our analysis. To confirm our findings, multicenter studies with a higher number of patients are warranted. A registry collecting meticulous data from multiple centers may address these issues.^{3,8,39}

Conclusions

Our study addresses the importance of accurate implantation of DBS electrodes for obtaining standardized clinical outcomes and suggests that meticulous programming with careful monitoring of clinical symptoms may improve outcomes. Clinicians should attempt to detect any subtle changes in the clinical symptoms at each clinical visit for better stimulation adjustment, and in this context, the findings of our study may be useful with regard to the systematic programming paradigm. Further meticulous

evaluation of neurostimulation effects at a specific area with a large study population is warranted.

Acknowledgments

This study was partially supported by a Japan Society for the Promotion of Science (JSPS) grant-in-aid for Scientific Research (C) (grant no. 18K08956); the Central Research Institute of Fukuoka University (grant no. 201045); and a JSPS KAKENHI grant (grant no. JP16H06396).

References

1. Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J. Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. *Lancet*. 1999; 353(9154):724.
2. Baldermann JC, Schuller T, Huys D, et al. Deep brain stimulation for Tourette syndrome: a systematic review and meta-analysis. *Brain Stimul*. 2016;9(2):296–304.
3. Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, et al. Efficacy and safety of deep brain stimulation in Tourette syndrome: the International Tourette Syndrome Deep Brain Stimulation Public Database and Registry. *JAMA Neurol*. 2018;75(3):353–359.
4. Dowd RS, Pourfar M, Mogilner AY. Deep brain stimulation for Tourette syndrome: a single-center series. *J Neurosurg*. 2018;128(2):596–604.
5. Smeets AYJM, Duits AA, Leentjens AFG, et al. Thalamic deep brain stimulation for refractory Tourette syndrome: clinical evidence for increasing disbalance of therapeutic effects and side effects at long-term follow-up. *Neuromodulation*. 2018;21(2):197–202.
6. Morishita T, Foote KD, Burdick AP, et al. Identification and management of deep brain stimulation intra- and postoperative urgencies and emergencies. *Parkinsonism Relat Disord*. 2010;16(3):153–162.
7. Rolston JD, Englot DJ, Starr PA, Larson PS. An unexpectedly high rate of revisions and removals in deep brain stimulation surgery: analysis of multiple databases. *Parkinsonism Relat Disord*. 2016;33:72–77.
8. Johnson KA, Fletcher PT, Servello D, et al. Image-based analysis and long-term clinical outcomes of deep brain stimulation for Tourette syndrome: a multisite study. *J Neurol Neurosurg Psychiatry*. 2019;90(10):1078–1090.
9. Nestor KA, Jones JD, Butson CR, et al. Coordinate-based lead location does not predict Parkinson's disease deep brain stimulation outcome. *PLoS One*. 2014;9(4):e93524.
10. Witt K, Granert O, Daniels C, et al. Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial. *Brain*. 2013;136(Pt 7):2109–2119.
11. Van Essen DC, Ugurbil K, Auerbach E, et al. The Human Connectome Project: a data acquisition perspective. *Neuroimage*. 2012;62(4):2222–2231.
12. Wang Q, Akram H, Muthuraman M, et al. Normative vs. patient-specific brain connectivity in deep brain stimulation. *Neuroimage*. 2021;224:117307.
13. Pringsheim T, Okun MS, Müller-Vahl K, et al. Practice guideline recommendations summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*. 2019;92(19):896–906.
14. Storch EA, Murphy TK, Geffken GR, et al. Reliability and validity of the Yale Global Tic Severity Scale. *Psychol Assess*. 2005;17(4):486–491.
15. Storch EA, Shapira NA, Dimoulas E, et al. Yale-Brown Obsessive Compulsive Scale: the dimensional structure revisited. *Depress Anxiety*. 2005;22(1):28–35.

16. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278–296.
17. Morishita T, Higuchi MA, Saita K, et al. Changes in motor-related cortical activity following deep brain stimulation for Parkinson's disease detected by functional near infrared spectroscopy: a pilot study. *Front Hum Neurosci*. 2016;10:629.
18. Morishita T, Higuchi MA, Kobayashi H, et al. A retrospective evaluation of thalamic targeting for tremor deep brain stimulation using high-resolution anatomical imaging with supplementary fiber tractography. *J Neurol Sci*. 2019;398:148–156.
19. Zrinzo L. Pitfalls in precision stereotactic surgery. *Surg Neurol Int*. 2012;3(1)(suppl 1):S53–S61.
20. Horn A, Li N, Dembek TA, et al. Lead-DBS v2: towards a comprehensive pipeline for deep brain stimulation imaging. *Neuroimage*. 2019;184:293–316.
21. Schöneck T, Kupsch A, Kühn AA, et al. Automated optimization of subcortical cerebral MR imaging-atlas coregistration for improved postoperative electrode localization in deep brain stimulation. *AJNR Am J Neuroradiol*. 2009;30(10):1914–1921.
22. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal*. 2008;12(1):26–41.
23. Husch A, V Petersen M, Gemmar P, et al. PaCER—a fully automated method for electrode trajectory and contact reconstruction in deep brain stimulation. *Neuroimage Clin*. 2017;17:80–89.
24. Ilinsky I, Horn A, Paul-Gilloteaux P, et al. Human motor thalamus reconstructed in 3D from continuous sagittal sections with identified subcortical afferent territories. *eNeuro*. 2018;5(3):ENEURO.0060-18.2018.
25. Horn A, Reich M, Vorwerk J, et al. Connectivity predicts deep brain stimulation outcome in Parkinson disease. *Ann Neurol*. 2017;82(1):67–78.
26. Vorwerk J, Cho JH, Ramp S, et al. A guideline for head volume conductor modeling in EEG and MEG. *Neuroimage*. 2014;100:590–607.
27. Astrom M, Diczfalusy E, Martens H, Wardell K. Relationship between neural activation and electric field distribution during deep brain stimulation. *IEEE Trans Biomed Eng*. 2015;62(2):664–672.
28. Hemm S, Mennessier G, Vayssière N, et al. Co-registration of stereotactic MRI and isofieldlines during deep brain stimulation. *Brain Res Bull*. 2005;68(1-2):59–61.
29. Yeh FC, Panesar S, Fernandes D, et al. Population-averaged atlas of the macroscale human structural connectome and its network topology. *Neuroimage*. 2018;178:57–68.
30. Makris N, Goldstein JM, Kennedy D, et al. Decreased volume of left and total anterior insular lobule in schizophrenia. *Schizophr Res*. 2006;83(2-3):155–171.
31. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15(1):273–289.
32. Morishita T, Okun MS, Burdick A, et al. Cerebral venous infarction: a potentially avoidable complication of deep brain stimulation surgery. *Neuromodulation*. 2013;16(5):407–413.
33. Burchiel KJ, McCartney S, Lee A, Raslan AM. Accuracy of deep brain stimulation electrode placement using intraoperative computed tomography without microelectrode recording. *J Neurosurg*. 2013;119(2):301–306.
34. Larson PS, Starr PA, Martin AJ. Deep brain stimulation: interventional and intraoperative MRI approaches. *Prog Neurol Surg*. 2018;33:187–197.
35. Mann JM, Foote KD, Garvan CW, et al. Brain penetration effects of microelectrodes and DBS leads in STN or GPi. *J Neurol Neurosurg Psychiatry*. 2009;80(7):794–797.
36. Morishita T, Foote KD, Wu SS, et al. Brain penetration effects of microelectrodes and deep brain stimulation leads in ventral intermediate nucleus stimulation for essential tremor. *J Neurosurg*. 2010;112(3):491–496.
37. Andrade P, Heiden P, Hoevels M, et al. Modulation of fibers to motor cortex during thalamic DBS in Tourette patients correlates with tic reduction. *Brain Sci*. 2020;10(5):E302.
38. Kimura Y, Ikegaya N, Iijima K, et al. Withdrawal of deep brain stimulation in patients with Gilles de la Tourette syndrome. *Mov Disord*. 2019;34(12):1925–1926.
39. Schrock LE, Mink JW, Woods DW, et al. Tourette syndrome deep brain stimulation: a review and updated recommendations. *Mov Disord*. 2015;30(4):448–471.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Morishita, Sakai. Acquisition of data: Morishita, Iida, Yoshimura, Ishii, Fujioka. Analysis and interpretation of data: Morishita, Sakai. Drafting the article: Morishita, Sakai. Critically revising the article: Morishita, Sakai, Tanaka. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Morishita. Statistical analysis: Morishita. Administrative/technical/material support: Morishita. Study supervision: Tanaka, Inoue.

Supplemental Information

Video

Video 1. <https://vimeo.com/513067798>.

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Figures and Tables. <https://thejns.org/doi/suppl/10.3171/2021.2.JNS204026>.

Preprint Server

An earlier version of this article can be found on a preprint server. Preprint server name: medRxiv. Preprint DOI: 10.1101/2020.09.29.20200501.

Correspondence

Takashi Morishita: Fukuoka University Faculty of Medicine, Fukuoka, Japan. tmorishita@fukuoka-u.ac.jp.