Multitarget, dual-electrode deep brain stimulation of the thalamus and subthalamic area for treatment of Holmes’ tremor

Clinical article

KAZUTAKA KOBAYASHI, M.D., PH.D.,1 YOICHI KATAYAMA, M.D., PH.D.,1
HIDEKI OSHIMA, M.D., PH.D.,1 MITSURU WATANABE, M.D., PH.D.,1
KOICHIRO SUMI, M.D., PH.D.,1 TOSHIKI OBUCHI, M.D., PH.D.,1
CHIKASHI FUKAYA, M.D., PH.D.,2 AND TAKAMITSU YAMAMOTO, M.D., PH.D.2

1Division of Neurosurgery and 2Division of Applied System Neuroscience, Department of Neurological Surgery, Nihon University School of Medicine, Tokyo, Japan

Object. Holmes’ tremor (HT) is generally considered to be a symptomatic tremor associated with lesions of the cerebellum, midbrain, or thalamus. Deep brain stimulation (DBS) therapy for essential tremor and parkinsonian tremor has proved quite successful. In contrast, surgical treatment outcomes for HT have often been disappointing. The use of 2 ipsilateral DBS electrodes implanted in parallel within the thalamus for severe essential tremor has been reported. Since dual-lead stimulation within a single target can cover a wider area than single-lead stimulation, it produces greater effects. On the other hand, DBS of the subthalamic area (SA) was recently reported to be effective for refractory tremor.

Methods. The authors implanted 2 DBS electrodes (one at the nucleus ventralis oralis/nucleus ventralis intermedius and the other at the SA) in 4 patients with HT. For more than 2 years after implantation, each patient’s tremor was evaluated using a tremor rating scale under the following 4 conditions of stimulation: “on” for both thalamus and SA DBS; “off” for both thalamus and SA DBS; “on” for thalamus and “off” for SA DBS; and “on” for SA and “off” for thalamus DBS.

Results. The tremor in all patients was improved for more than 2 years (mean 25.8 ± 3.5 months). Stimulation with 2 electrodes exerted greater effect on the tremor than did 1-electrode stimulation. Interestingly, in all patients progressive effects were observed, and in one patient treated with DBS for 1 year, tremor did not appear even while stimulation was temporarily switched off, suggesting irreversible improvement effects.

The presence of both resting and intentional/action tremor implies combined destruction of the pallidothalamic and cerebellothalamic pathways in HT. A larger stimulation area may thus be required for HT patients. Multitarget, dual-lead stimulation permits coverage of the wide area needed to suppress the tremor without adverse effects of stimulation. Some reorganization of the neural network may be involved in the development of HT because the tremor appears several months after the primary insult. The mechanism underlying the absence of tremor while stimulation was temporarily off remains unclear, but the DBS may have normalized the abnormal neural network.

Conclusions. The authors successfully treated patients with severe HT by using dual-electrode DBS over a long period. Such DBS may offer an effective and safe treatment modality for intractable HT.

Key Words • Holmes’ tremor • deep brain stimulation • thalamus • subthalamic area • functional neurosurgery

Holmes’ tremor (HT) is generally regarded as a type of tremor associated with lesions of the cerebellum, midbrain, or thalamus. In 1904, Holmes reported “rubral tremor,” which consisted of a combination of resting, postural, and intentional tremor associated with a lesion of the rubrospinal tract. A new name for such tremors, “Holmes’ tremor,” was suggested by the Movement Disorder Society as a substitute for less satisfactory classifications such as rubral tremor, midbrain tremor, or mixed extrapyramidal tremor. The tremor is defined by the following criteria proposed by the Movement Disorder Society: 1) the presence of both resting and intentional tremor, 2) a slow frequency, usually below 4.5 Hz, and 3) a variable delay between lesion occurrence and first appearance of the tremor.

Only a few case reports have described effective management involving medical treatment. Because of the low success rate of medical treatment, some patients are referred for surgery. The ventrolateral nucleus of the thalamus is the commonly chosen target for deep brain stimulation (DBS).
stimulation (DBS) to alleviate essential and parkinsonian tremor. Thalamic DBS has therefore often been applied for the surgical treatment of HT. However, the outcomes of surgical treatment for HT have often been disappointing.

Yamamoto et al.39 reported the use of 2 ipsilateral DBS electrodes implanted in parallel within the thalamus for severe essential tremor. Since stimulation by this method, which involves dual-lead stimulation within a single target, can cover a wider area than single-lead stimulation, it also produces a greater effect than single-lead stimulation. On the other hand, DBS of the subthalamic area (SA) was recently found to offer an effective lead stimulation. In this report, we describe the clinical outcome of dual-lead stimulation of 2 targets—one at the thalamus (ventralis oralis [VO]/ventralis intermedius [VIM] nuclei) and the other at the SA—for HT.

Methods

Patient Population

We applied 2 DBS electrodes to the thalamus and SA in 4 patients with HT. Table 1 summarizes the clinical features of each patient. These patients were diagnosed as having symptomatic tremor associated with lesions of the cerebellum, midbrain, or thalamus,6,7 which was consistent with the criteria established by the Movement Disorder Society for establishing the diagnosis of HT.6 Tremor at rest in all the patients was severe, which was different from essential tremor. Medication therapy did not produce any evidence of a good response.

We used Items 1–9 (face, tongue, voice, head, right upper extremity, left upper extremity, trunk, right lower extremity, and left lower extremity) of the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) to assess patients’ tremors. Based on the rating scale score, we evaluated the tremor under the following conditions: face tremor at action/intention; voice tremor at action/intention; tongue, head, and trunk tremor at rest and posture; and upper- and lower-extremity tremor at rest, posture, and action/intention.

The severity of each tremor was graded according to the following 5-point rating scale: 0, none; 1, slight, can be intermittent; 2, moderate amplitude, can be intermittent; 3, marked amplitude; and 4, severe amplitude. Thus, the scores could range from 0 (normal) to 80 (most severe). Based on the rating scale score, we evaluated the tremor under the following 5-point rating scale: 0, none; 1, slight, can be intermittent; 2, moderate amplitude, can be intermittent; 3, marked amplitude; and 4, severe amplitude. Thus, the scores could range from 0 (normal) to 80 (most severe). Based on this, we implanted a DBS electrode in the SA, at which point a satisfactory effect on the tremor was observed. Subsequent patients with HT therefore underwent implantation of dual-lead electrodes in the thalamus and SA.

The surgical procedure was planned using MR images. Following administration of a local anesthetic, a Leksell G head frame (Elekta Instruments AB) was applied to the patient’s head. We then obtained MR images with 1-mm-thick tissue sections. The MRI data sets were then transferred into a StealthStation FrameLink system (Medtronic Inc.). The anterior commissure (AC) and posterior commissure (PC) were identified, and the trajectory and tentative target were planned using FrameLink software (Medtronic Inc.).

The tentative target for the thalamus (VO/VIM nuclei) was directed at the anterior one-fourth of the AC-PC line length, ahead of the PC on the level of the AC-PC line, 11 mm from the lateral wall of the third ventricle. The posterior limit of the VIM nucleus on the AC-PC line has been reported to be situated at one-sixth of the AC-PC line length, ahead of the PC.28 However, the electrode was placed more anterior to the posterior border of the VIM to avoid current spreading to the primary somatosensory thalamic relay ventralis caudalis nucleus, which tends to induce contralateral paresthesias.2 The angle of trajectory to the horizontal plane of the AC-PC line was set at 45°–50° to cover a wide area of the ventral thalamus including the VO and VIM nuclei.21,40 The SA was targeted at the posterior part of the subthalamic white matter, including the zona incerta and prelemniscal radiation, which were identified on T2-weighted images at the level of 2–3 mm inferior to the AC-PC line (Fig. 1).

<table>
<thead>
<tr>
<th>Table 1: Characteristics of patients with Holmes’ tremor*</th>
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<tr>
<td><strong>Case No.</strong></td>
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</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
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<tr>
<td>4</td>
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</tbody>
</table>

* LE = lower extremity; UE = upper extremity.

Surgical Procedures

Informed consent of all patients and their families was obtained. In the first patient (Case 1), we planned to implant a DBS electrode into the thalamus to treat the tremor, and if intraoperative thalamic stimulation with the DBS electrode had an insufficient effect on the tremor, we planned to add an electrode in the SA. Although intraoperative stimulation of the thalamus with the DBS electrode did not produce any evidence of a good response, we planned to add another electrode in the SA. Although intraoperative stimulation of the thalamus with the DBS electrode did not produce any evidence of a good response, we planned to add another electrode in the SA.

The mean total TRS score (Items 1–9) was 16.5 ± 4.2. The mean contralateral upper-extremity TRS score (possible range 0 [normal] to 12) was 11.3 ± 0.5 (Table 2).
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Extracellular unit recordings were obtained using a microelectrode to confirm the tentative targets identified on the MR images. Neuronal activity was also fed into an audio speaker. The neuronal activity was examined under various conditions such as somatic sensory stimulation and active movements. On the thalamic trajectory, intraoperative audio and oscilloscopic monitoring of the tremor frequency and neural activity was performed to detect whether the neuronal bursting and tremor had the same frequencies. In addition, cells exhibiting neuronal activity in response to somatic sensory stimulation—that is, in response to passive joint movement of the contralateral limbs without a response to skin deformation caused by stimuli—were detected as deep sensory cells located in the part of the thalamus anterior to the ventralis caudalis nucleus. On the SA trajectory, low-amplitude units or the absence of neuronal firing in the prelemniscal radiation or middle-amplitude units in the caudal zona incerta were recorded. The overall activity was reduced in the SA, usually beginning within 1 mm from the intercommissural level. After confirmation of neural activity, we performed macrostimulation by using the outer cannula of the microelectrode, with a contact point length of 1 mm, from 2–4 mm below the target to 2–4 mm above the target at 1- to 2-mm intervals to confirm the effects of stimulation on the tremor. We were concerned about brain shift due to leakage of CSF during surgery. Using an intraoperative cranial radiograph, we confirmed the position of the first electrode after implantation of the electrode. When CSF leakage–induced brain shift caused the first electrode to move posteriorly, the target of the second electrode was changed depending on the direction of the shift.

The DBS electrodes were implanted into each target trough using the same trajectory we used for the microrecording. The DBS electrodes (model 3387; Medtronic, Inc.) implanted in all patients had 4 contact points numbered 0–3 sequentially from the most distal contact (0) to the most proximal contact (3). Each contact of the electrode was 1.5 mm long, and the contacts were separated from each other by 1.5 mm. Subsequently, implantation of the stimulator was performed with the patient under general anesthesia.

Clinical Evaluations

After surgery, the locations of the implanted electrodes were confirmed on MRI (Fig. 2), and stimulation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Baseline TRS Score (preop)</th>
<th>Both-Off DBS TRS Score (% improvement)</th>
<th>Postop Time of Exam for Both-Off DBS (mos)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Contralat UE</td>
<td>Total</td>
<td>Contralat UE</td>
</tr>
<tr>
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<td>12</td>
<td>12</td>
<td>0 (100)</td>
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<tr>
<td>2</td>
<td>11</td>
<td>17</td>
<td>11 (0)</td>
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<tr>
<td>3</td>
<td>11</td>
<td>22</td>
<td>6 (45)</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>15</td>
<td>6 (45)</td>
</tr>
<tr>
<td>mean ± SD</td>
<td>11.3 ± 0.5</td>
<td>16.5 ± 4.2</td>
<td>5.8 ± 4.5</td>
</tr>
</tbody>
</table>

* The contralateral upper-extremity TRS score range is 0–12; the total TRS score range is 0–80 (Items 1–9); both-off DBS indicates that stimulation of both electrodes in the thalamus and SA was turned off.
was initiated by determining the thresholds for side effects and benefits at each contact on each electrode. We assessed the most effective combination of contacts on each electrode at a frequency of 135 Hz and a pulse width of 0.21 msec. The voltage of stimulation was increased to an upper limit at which such adverse effects as paresthesia or muscle contraction began to appear. The active contacts and the voltage of stimulation were changed depending on the disappearance of the lesioning effect over several months. When the parameters and contacts for stimulation were altered, initially the parameters and contacts for each electrode alone were established to provide the best effect on the tremor without any stimulation-induced adverse effects, and absence of adverse effects during simultaneous stimulation with both electrodes was then confirmed.

After 6 months, these parameters were not changed. At 6 months and 12 months after implantation and at the last follow-up visit (mean 25.8 ± 3.5 months [± SD]), the tremor scores were evaluated in the stimulation-on condition of both thalamus and SA DBS. At the last follow-up visit after implantation, the TRS scores were evaluated under 4 stimulation conditions: “on” for both thalamus and SA DBS (both on); “off” for both thalamus and SA DBS (both off); “on” for thalamus and “off” for SA DBS (on-thalamus); and “on” for SA and “off” for thalamus DBS (on-SA). First, the both-on condition was evaluated. Next,
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the both-off condition was evaluated at 30 minutes after turning off the stimulator. The on-thalamus and on-SA conditions were then assessed at 30-minute intervals. The same contacts and parameters of stimulation that had been applied during follow-up since 6 months postimplantation were used for each electrode. The combinations of contacts and parameters of stimulation for each electrode of the SA and thalamus were thus not changed in the 4 conditions.

Mean values are presented ± SD.

Results

Location of Selected Electrode Contacts

No surgical complications occurred. Figure 3 shows plots of the cathode contact of each electrode in each patient. A bipolar mode was selected for some combinations of contacts. Only cathode contact locations are plotted in Fig. 3 because most current strength is applied at the site of the cathode contact in the bipolar mode. In all patients, the most effective cathode contact of the SA electrode was presumed to be located in the subthalamic white matter including the zona incerta/prelemniscal radiation; briefly, the localization of the optimal cathodal contact was on average 6.4 ± 0.5 mm posterior to the midcommissural point, 2.9 ± 0.8 mm inferior to the AC-PC line, and 10.9 ± 0.6 mm lateral to the midline. The localization of the optimal cathode contact of the thalamic electrode was on average 4.5 ± 0.4 mm posterior to the midcommissural point, 2.5 ± 1.3 mm superior to the AC-PC line, and 13.3 ± 0.3 mm lateral to the midline.

Effects on Tremor

Table 3 lists the total TRS scores for each patient at baseline and in the both-on condition (stimulation of both the thalamus and SA DBS). In all patients, the tremor was improved at more than 2 years after implantation. The total TRS score at last follow-up visit in all patients was lower than the baseline (preoperative) score (mean 0.5 ± 0.6 vs 16.5 ± 4.2, respectively). A decrease in TRS score in the both-on condition over time was observed in all patients, although the parameters of stimulation were not changed after 6 months.

Table 2 summarizes the individual results for each of the 4 patients in the both-off condition. In Case 1, tremor did not appear at 30 minutes after turning off the stimulator (both-off condition) when applying the TRS following chronic stimulation at 12 months and at the last follow-up visit (31 months). The patient was also evaluated under both-off condition 2 weeks after surgery. Because the total TRS score was 12 and the contralateral upper-extremity TRS score was 12, which were the same as those determined at preoperatively, we considered that the lesioning effect did not cause the disappearance of tremor. The TRS score in Case 1 was therefore not evaluated in the remaining 3 conditions of stimulation: both-on, on-thalamus, and on-SA. In 2 of the remaining 3 patients (Cases 3 and 4), the contralateral upper-extremity TRS score at 30 minutes after turning off the stimulator (both-off condition) was still lower than the baseline (preoperative) score. In all 3 remaining patients (Cases 2–4), both the total and upper-extremity TRS scores for the 3 conditions (both-on, on-thalamus, and on-SA) were lower than for the both-off condition (Table 4).

Table 5 shows the difference in effect of thalamic stimulation, SA stimulation, and simultaneous stimulation of the thalamus and SA on the upper-extremity tremor components. Statistical analyses were not performed in these conditions because of the small number of patients. However, among the TRS values for the both-on, on-thalamus, and on-SA conditions in Cases 2–4, the score for the both-on condition tended to be lower than those for on-SA and on-thalamus, and that for the on-SA condition tended to be slightly lower than that for the on-thalamus condition.

Discussion

Target of Stimulation for HT

The best target site for treating HT remains a matter of debate. In most case reports, the thalamus was selected as a DBS target.8,10,11,28 As an exception to the use of the thalamus as a DBS target for HT, the globus pallidus internus (GPi) was selected in a single patient for whom thalamic DBS was not effective in treating tremor.23 Deep brain stimulation of the GPi demonstrated a satisfactory effect on tremor in this case. Goto and Yamada performed thalamic VIM nucleus stimulation in a patient with HT.12

![Fig. 3.](https://example.com/fig3.png) Location of the cathode contact of each electrode in the thalamus and SA used for stimulation after 6 months. Contact positions are plotted in commissure-based coordinates (midcommissural point: x = 0, y = 0, z = 0) representing a coronal view (left) and sagittal view (right). MC = midcommissure; Th = thalamus.
Although the initial effect was good, the patient’s tremor recurred after 1 year postimplantation and could not be reduced sufficiently with thalamic DBS. Ultimately, a pallidotomy was performed and resulted in complete disappearance of the tremor.

The reasons underlying the difficulty in reducing HT with DBS include the larger area involved in the mechanism of the tremor. The fact that the tremor is resting, postural, and intentional suggests a combined destruction of the pallidothalamic and cerebellothalamic pathways.1,36 In other words, the dopaminergic nigrostriatal and cerebellothalamic systems must both be involved to produce the combination of resting and kinetic tremor.6 Experimental data in monkeys 22,29 have shown that involvement of the rubro-olivo-cerebello-rubral loop results in postural tremor. Clinical and PET studies have also demonstrated that postural and resting tremors occur when the nigrostriatal system is involved.34 These observations support the notion that the mechanisms of HT differ from those invoked to explain essential tremor. Since different pathophysiological mechanisms appear to underlie these tremors, it follows that different treatment strategies may be needed. In addition, in most cases of HT, the tremor is distributed in the distal and proximal muscles. For this reason, a larger stimulation area, involving multiple pathways, may be required in HT.

It has been reported that patients with HT require higher DBS voltage levels than patients with other types of tremor.30 Diederich et al.8 reviewed cases in which DBS was used to treat HT and suggested that a beneficial effect was achieved in only in patients who underwent dual stimulation, mainly in another part of the VIM nucleus. Two studies have documented dual-lead stimulation for HT. Foote and Okun10 described the implantation of dual leads into the thalamus. Romanelli et al.36 reported implantation of one electrode into the thalamus and another electrode into the subthalamic nucleus (STN). The dual-lead stimulations in these reports provided excellent reduction of HTs. Multitarget, dual-lead stimulation enabled coverage of the wide area necessary to suppress the tremor without adverse effects of the stimulation.

**Stimulation of the SA for Tremor**

In the 1960s, a small lesion in the posterior subthalamic white matter, including the prelemniscal radiation and zona incerta, was reported to alleviate tremor.2,5,26 In the 2000s, several authors described the application of DBS to this target, indicating significant effectiveness of stimulation of the area on tremor.19,27,32,38 This area includes important afferent pathways, such as the cerebellothalamic tract and the zona incerta, related to the pathophysiology of involuntary movement. The zona incerta receives afferents from the GPi and the substantia nigra reticulata,35,37 the ascending reticular activating system,35,37 and the interpositus nucleus of the cerebellum, and it has outputs to the ventral anterior nucleus and the ventrolateral nucleus of the thalamus.3 It also sends efferents to the brainstem, the GPi, and the substantia nigra reticulata.34 Stimulation of this site is thus effective in reducing tremor. Plaha et al.32 reviewed previous reports on the coordinates of the targets for subthalamic stimulation for the treatment of tremor. According to their review, the coordinates of targets x (lateral to the midline), y (posterior to the midcommissural point), and z (inferior to the AC-PC line) are as follows: 10.9 ± 0.8 mm, 7.6 ± 1.2 mm, and 3.9 ± 1.7 mm, respectively, according to Murata et al.;27 11.5 ± 0.5 mm, 4.5 ± 0.4 mm, and 2.2 ± 0.4 mm, respectively, according to Plaha et al.;33 and 10.5 ± 1.2 mm, 5.6 ± 1.2 mm, and -3.2 mm ± SD 4.2 ± 2.5, 2.5 ± 2.1, 0.5 ± 0.6, 25.8 ± 3.5.

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**TABLE 3: Total TRS score for each patient at baseline (preoperatively) and under the both-on DBS condition at 6 and 12 months after implantation and at the last follow-up visit**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Preop Total TRS Score (% improvement)</th>
<th>6 Mos Both-On DBS*</th>
<th>12 Mos Both-On DBS*</th>
<th>Last Visit (time of evaluation)</th>
<th>Time of Last Visit (mos)</th>
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<tr>
<td>1</td>
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<td>0 (0)</td>
<td>0 (100)</td>
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</tr>
<tr>
<td>2</td>
<td>17 (82)</td>
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<td>0 (100)</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>22 (73)</td>
<td>6 (73)</td>
<td>5 (77)</td>
<td>1 (95)</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>15 (73)</td>
<td>4 (73)</td>
<td>2 (87)</td>
<td>1 (93)</td>
<td>24</td>
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<tr>
<td>mean ± SD</td>
<td>16.5 ± 4.2</td>
<td>3.5 ± 2.5</td>
<td>2.5 ± 2.1</td>
<td>0.5 ± 0.6</td>
<td>25.8 ± 3.5</td>
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</tbody>
</table>

* Both-on DBS indicates that stimulation of both electrodes in the thalamus and SA was turned on.

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**TABLE 4: Tremor Rating Scale score according to stimulation site**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>TRS Score (% improvement)</th>
<th>Both-Off DBS</th>
<th>On-VO/VIM DBS</th>
<th>On-SA DBS</th>
<th>Both-On DBS</th>
<th>Time of Exam (mos)</th>
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<tr>
<td></td>
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<td>Contralat UE</td>
<td>Total Contralat UE</td>
<td>Total</td>
<td>Contralat UE</td>
<td>Total</td>
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<tr>
<td>2</td>
<td>11 (73)</td>
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<td>4</td>
<td>6 (33)</td>
<td>10 (50)</td>
<td>3 (50)</td>
<td>4 (60)</td>
<td>4 (33)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>mean ± SD</td>
<td>7.7 ± 2.9</td>
<td>11.0 ± 1.7</td>
<td>2.7 ± 0.6</td>
<td>4.0 ± 1.0</td>
<td>2.0 ± 2.0</td>
<td>3.7 ± 3.2</td>
</tr>
</tbody>
</table>
± 1.1 mm, respectively, according to Kitagawa et al. In our patients, the coordinates of the active contacts were on average 10.9 ± 0.6 mm, 6.4 ± 0.5 mm, and −2.9 ± 0.8 mm for the x, y, and z coordinates, respectively, and were close to those reported by Kitagawa et al. and Murata et al.

Optimal Stimulation Site for the Tremor Components of HT

The optimal stimulation sites for affecting each tremor component of HT remain unclear. In our patients, no obvious differences in effects on the tremor components were observed when comparing thalamic stimulation and SA stimulation. Generally, SA stimulation tended to have a slightly better effect in terms of tremor control than thalamic stimulation. Among our cases, SA stimulation showed a better effect than thalamic stimulation in Case 2, whereas thalamic stimulation had a better effect than SA stimulation in Cases 3 and 4. Simultaneous stimulation of the thalamus and SA provided the best effect. Deep brain stimulation of the VIM nucleus was reported to be more effective for the resting and postural tremor components than for the intentional tremor component in patients with HT. On the other hand, Romanelli et al. reported that VIM nucleus DBS was effective for the intentional and postural tremor components but ineffective for the resting tremor component, and that STN DBS resolved the resting tremor component. Only one report comparing the effects of thalamic and SA stimulation on tremor has been published, and this study indicated that SA stimulation is more effective than VIM nucleus stimulation at treating intentional tremor. Since the underlying pathology involves a structural lesion, a variable combination of neural elements is damaged, giving rise to a rich variety of tremor phenomenology in HT. Further studies are thus needed to clarify the optimal stimulation sites for exerting effects on each tremor component of HT.

Progressive and Irreversible Improvement Effects on HT

In all patients, interestingly, progressive effects were observed, and the tremor measured 30 minutes after turning off the stimulator was not worse than that documented preoperatively. In Case 1, in particular, tremor did not reappear while the stimulation was temporarily turned off. The maximum effect of DBS on other types of tremor such as essential tremor appears within several seconds after turning on the stimulator, and tremor reappears quickly when the DBS is turned off. Thus, in contrast to other types of tremor, chronic stimulation of HT yields progressive and irreversible improvement effects. Similar to our cases, Diederich et al. have also reported the maintenance of a satisfactory effect on HT without stimulation in an HT patient after turning off the DBS. In addition, Foote et al. described thalamic DBS for the treatment of HT, and in all 4 of their patients tremor scores in the stimulation-off condition at 6 months after surgery were lower than those documented at baseline (preoperatively). Some reorganization of the neural network may be involved in the development of HT, because the tremor appears several months after a primary insult. The mechanisms underlying this progressive effect and the absence of tremor while the stimulation is temporarily off remain unclear; however, DBS may lead to a normalization of the abnormal neural network.

Conclusions

We successfully treated patients with severe HT by applying dual-electrode DBS to multiple targets. Such stimulation may offer an effective and safe treatment modality for intractable HT. However, this study involved only 4 patients, and further investigations are needed to substantiate this hypothesis.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. The present work was supported in part by the following grants. Dr. Kobayashi received a KAKENHI (Project No. 23791616) from the Japan Society for the Promotion of Science. Dr. Yamamoto received a Strategic Research Base Development Program for Private Universities from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT). Dr. Katayama received a Strategic Research Program for Brain Sciences from MEXT.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kobayashi. Acquisition of data: Kobayashi, Sumi, Obuchi, Oshima, Watanabe. Analysis and interpretation of data: Kobayashi, Katayama, Oshima, Fukaya, Yamamoto. Drafting the article: Kobayashi. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kobayashi. Study supervision: Katayama, Oshima.

References
