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ORIGINAL ARTICLE

# Deep brain stimulation of the globus pallidus internus or ventralis intermedius nucleus of thalamus for Holmes tremor

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**Abstract** Holmes tremor (HT) is a difficult-to-treat, very disabling symptomatic condition which characteristically appears weeks to years after a brain lesion. It features a unique combination of rest, action, and postural tremors. Pharmacotherapy is mostly not effective. Chronic deep brain stimulation (DBS) of ventralis intermedius nucleus (Vim) of thalamus has been described as being the best surgical approach in singular case series; various authors observe, however, cases with partial responses only; therefore, alternatives are still needed. We report ten patients with HT unresponsive to best medical therapy who underwent DBS in our center from March 2002 to June 2012. Based in our previous experience dealing with cases of unsatisfactory Vim intraoperative tremor control and in order to optimize surgical results, presurgical target planning included two Nuclei: Vim and posteroventral Globus pallidus internus (GPi) (Espinoza et al. 2010; Espinoza et al. Stereotact Funct Neurosurg 90(suppl 1):1–202, p 61, 2012). Definitive chosen target was decided after single-cell microelectrode recording, intraoperative test stimulation, thresholds for stimulation-induced adverse effects and best clinical response compared to baseline status. Fahn-Tolosa-Marin tremor rating scale (FTM-TRS) was used to evaluate outcome. The electrode was implanted in the nucleus with the best tremor suppression achievement; on the other hand, GPi DBS was initially decided if one of the following conditions was present: (a) If Vim nucleus anatomy was grossly altered; (b) when intraoperative tremor control was unsatisfactory despite Vim high-intensity stimulation; or (c) if unaffordable side effects or even tremor worsening occurred during intraoperative macrostimulation. Seven patients received definitive Gpi DBS implantation, while three patients received Vim DBS. In all observed cases, we observed an improvement on the TRS. In two cases where Vim thalamic anatomy was altered by the pathological insult GPI was planned from the beginning, and same was true in two additional cases where the Gpi nucleus showed major alterations allowing only Vim planning. Over all cases, the average improvement in tremor was of 2.55 points on the TRS or a 64 % increase in measured results; with a minimum of 1 point (25 %) improvement in one case and a maximum of 4 points (100 % improvement) also in one case. All the results were sustained at 2 years follow-up. One case with predominant resting component, implanted in the GPi, achieved the maximum possible tremor reduction (from 4 to 0 points, meaning 100 % tremor reduction); in the nine resting cases, the average reduction was of 3 points (or 75 %). DBS demonstrated in this case series adequate tremor control in 10 patients unresponsive to medical therapy.

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Presurgical planning of two targets allowed choosing best optimal response. Gpi stimulation could be considered as an alternative target for cases in which thalamic anatomy is considerably altered or Vim intraoperative stimulation does not produce satisfactory results.

**Keywords** Holmes tremor (HT) · Deep brain stimulation (DBS) · Globus pallidum internus (Gpi) · Ventralis intermedius nucleus (Vim) · Posterior subthalamic area (PSA) · Fahn-Tolosa-Marin tremor rating scale (TRS)

## Introduction

Holmes tremor is a very disabling movement disorder, clinically defined by an unusual combination of resting, postural, and action tremor

Tremor typically appears secondary to insults in the brainstem, thalamus, or cerebellum, including ischemia, hemorrhage, trauma, metabolic disorders, infections, or neoplasms causing a structural lesion involving the red nucleus, neural fibers originated in the cerebellum and the substantia nigra [3]. Such neuropathological fiber tract disruptions affect the cerebellar dentate-thalamic tract and may also affect the nigrostriatal pathway [4–9].

There is no evidence of spontaneous remission, and satisfactory response to medical treatment is uncommon [10]. Surgery has been explored with good outcomes using either ablative procedure such as subthalamic lesions in fields of Forel, Vim thalamotomy, pallidotomy, or through Vim deep brain stimulation (DBS). Table 1 resumes available literature regarding previously employed stereotactic targets to treat HT by means of radiofrequency lesions or DBS.

Stereotactic surgical ablation of the thalamic ventralis intermedius nucleus (Vim) have been reported to markedly improved Holmes tremor in a report of Kim et al. [18] in a patient with a midbrain tumor; however, controversy continues to surround the advisability of using this procedure for proximal tremors because the placement of larger lesions carries increased risks, and the somatotopy of the proximal or truncal muscles remains obscure in the human.

Rationale behind Vim DBS is based on the concept of facing a cerebellothalamic system damage, responsible for the postural and intention (action) tremor components, all which may respond to stereotactic Vim surgery, either thalamotomy or thalamic stimulation which also remains as a mainstay in the surgical treatment of parkinsonian or essential tremors [25]. However, in our experience, and as it has been previously reported by Goto et al., Vim stimulation does not always produce satisfactory results in all patients with Holmes tremors, particularly with respect to their proximal tremor component [18]. The resting tremor component (common or classical Parkinson's disease tremor) may be explained by an additional dopaminergic nigrostriatal system dysfunction [3, 10].

Previous neuromodulation knowledge states that pallidotomy (Stereotactic surgical ablation of the GPi) can enhance motor performance, reduce akinesia, improve gait, and eliminate the neural elements responsible for levodopa-induced dyskinesias and that high-frequency GPi stimulation influences local dopamine release [3, 5, 7–9, 11, 13–16, 18–21, 23, 25–41]. Authors of several series have reported that GPi stimulation could in addition improve tremor in more than 80 to 85 % of patients with PD [23, 34–38].

GPi surgery may influence the control of otherwise inaccessible axial and proximal muscles producing a marked alleviation of the proximal tremor component in some patients with HT [11, 41].

Recent literature reports Vim as the target of choice in HT; however, it is all based in single case reports since it does not exist yet a prospective randomized trial, and one important fact to address is that there are cases in which the thalamic region is severely damaged by the primary insult responsible for significant anatomical disruption, such scenario makes quite difficult to find a good therapeutic target in this area [17, 19–22, 24, 42]. Besides this specific situation, Vim DBS is not universally possible since there are cases in which Vim stimulation not only does not achieve tremor control but also worsens under direct electrical stimulation. Based on those facts, we hypothesized that Gpi DBS could be an interesting stimulation target option for HT in patients with thalamic disrupted brain anatomical connectivity or intraoperative failure of tremor control by targeting the Vim nucleus.

In this series, we report ten consecutive cases of adult patients' with severely disabling symptomatic Holmes tremor refractory to optimal medical therapy. Patients were treated surgically by means of DBS targeting Vim nucleus including an ending trajectory of the first contact in the PSA or the posteroventral region of the GPi nucleus.

## Patients and methods

Between January 2002 and February 2012, patients with a diagnosis of HT were referred to stereotactic and functional division of CIMAD (Centro Integral de Movimientos Anormales y Dolor), the Department of Neurology of the Marly Clinic, Hospital Infantil de San Jose in Bogotá, Colombia, to be considered for DBS treatment. All patients were evaluated by an interdisciplinary team made up by neurologists, neurophysiologist, and neurosurgeons among others and were referred to surgery only when the optimized drug therapy failed; Surgical treatment thought DBS was approved by the clinic's ethics committee in all drug-resistant cases clearly affecting quality of life. Pharmacological treatment included: levodopa, amantadine, clonazepam, and primidone. After

**Table 1** Summary of studies in the literature regarding Holmes tremor treatment lesions and DBS (modificated from Peker et al. [11])

| Author | Age/sex | Event | Clinical onset | Medical treatment | Surgical treatment | Follow-up |
|---|---|---|---|---|---|---|
| Shepherd [8] | 52/M | Putaminal hemorrhage | 8 months | Levodopa<br>Propanolol<br>Clonazepam | Thalamic DBS | Tremor suppression 160 HZ |
| Plaha [12] | 84/M | | Weeks | | Bilateral DBS of the caudal zona incerta nucleus | 70.2 % improvement total tremor rating scale<br>2.48 V/120 μs/147.14 Hz |
| Kudo [13] | 67/F | Midbrain cavernoma | 19 months | Benserazide/Levodopa<br>Trihexyphenidyl<br>Clonazepam | Bilateral Vim DBS | Tremor suppression<br>2.2 V/100 μs/150 Hz |
| Pahwa [14] | 45/F | Midbrain cavernoma | 3 months | Carbidopa/levodopa<br>Dopamine agonists<br>Trihexyphenidyl<br>Benzodiazepines | Vim DBS | Major improvement<br>3.7 V/90 μs/170 Hz |
| Romanelli [15] | 79/M | – | – | Levodopa<br>Primidone<br>Atenolol | Vim DBS and STN DBS | No tremor at 2 years<br>Vim 4.3 V/90 μs/185 Hz<br>STN 2 V/90 μs/145 Hz |
| Samadani [16] | 24/M | Midbrain cavernoma | 2 years | – | Vim DBS | Tremor improvement<br>2.5 V/90 μs/185 Hz |
| Diederrich [17] | 49/M | Thalamic stroke | Days | Haloperidol, trihexiphenidyl, diazepam and amantadine | Vim DBS | Much improvement |
| | 27/M | Thalamic vascular malformation vs local infection | 7 years | Trihexiphenidyl, amantadine, and propanolol | Vim DBS | Only moderate intention tremor remained/7 years |
| Nikkhah [3] | 47/F | Midbrain infarct | 6 months | Botox injection | Vim DBS | No tremor/7 months<br>2.4 V/60 μs/130 Hz |
| | 32/F | Midbrain AVM | 3 years | Clonazepam<br>Propanolol | Vim DBS | Improvement at tremor/6 months<br>3.4 V/90 μs/130 Hz |
| Goto [18] | 53/F | Hypertension hemorrhage | 18 months | Benserazide/levodopa<br>Clonazepam | Vim DBS and Pallidotomy | No tremor<br>3.4 V/90 μs/130 Hz |
| Foote [19] | 24/M | Posttraumatic | – | Carbidopa/levodopa<br>Anticholinergic<br>Benzodiazepine | Vim and VOA/VOP DBS (two leads) | 80 % benefit/12 months<br>Vim 4.1 V/90 μs/135 Hz<br>VOA/VOP 4.0 V/90 μs/185 Hz |
| | 39/M | | – | Carbidopa/levodopa<br>Anticholinergic<br>Benzodiazepine | Vim and VOA/VOP DBS (Two leads) | Major improvement/6 months<br>Vim 3.0 V/60 μs/160 Hz<br>VOA/VOP:3.1 V/60 μs/145 Hz |
| | 18/F | | – | Carbidopa/levodopa<br>Anticholinergic<br>Benzodiazepine | Vim and VOA/VOP DBS (two leads) | Significant improvement/8 months<br>Vim 3.6 V/120 μs/180 Hz<br>VOA/VOP:2.9 V/90 μs/135 Hz |
| Selcuk P [20] | 58/M | Midbrain infarct | – | – | Vim DBS | Tremor suppressed/1.5 years |
| Lim [21] | 28/M | Midbrain cavernoma | 1 month | Carbidopa/levodopa<br>Anticholinergic<br>Benzodiazepine | Vim, VOA and GPi DBS | Tremor suppressed/8 months<br>Vim 3.6 V/150 μs/185 Hz<br>VOA:3.5 V/90 μs/185 Hz<br>GPi:6.0 V/210 μs/160 Hz |

**Table 1** (continued)

| Author | Age/sex | Event | Clinical onset | Medical treatment | Surgical treatment | Follow-up |
|---|---|---|---|---|---|---|
| Selcuk P [20] | 14/F | Thalamic abscess | 4 months | Levodopa<br>Clonazepam | Vim DBS | 90 % benefit/2.5 years<br>4.8 V/90 μs/185 Hz |
| Follett [22] | 69/F | Severe traumatic brain injury | 3 years | "At least five agents" | Vim DBS bilateral | Good tremor control without stimulation-related dysarthria/extended follow-up |
| Aydin [5] | 30/M | Brain stem cavernoma | 6 months | | GPi and Vim DBS | Significant improvement |
| MC Kim [11] | 22/M | Midbrain tumor | 2 months | Levodopa<br>Clonazepam | RF lesion<br>Vim | Major improvement |
| Shepherd [8] | | Pontine tegmental hemorrhage | 9 months | Levodopa<br>Clonazepam<br>Propanolol | Vim DBS | Significant improvement |
| Miyagi [23] | 49/M | Brain stem hemorrhage | 8 months | "Various medications" | Posteroventral pallidotomy (PVP) | Significant improvement |
| Castrop [24] | 43 | Hypertensive mesencephalic hemorrhage | | Levodopa<br>Anticholinergics | Vim DBS | Good tremor suppression<br>Dystonic posturing also present remained/5 years |
| | 40 | Pontomesencephalic hemorrhage AVM | 18 months | Levodopa<br>Anticholinergics | Vim DBS | Sustained symptoms suppression/8 years |

written informed consent was obtained, ten patients underwent uni- or bilaterally DBS according to symptomatology.

Patient details including gender, age at onset, age at initial treatment, high-quality magnetic resonance imaging, history, and clinical findings were registered. Minimum follow-up time period was of 24 months. Pre- and postoperative states were assessed using the FTM-TRS which classifies severity of tremor by body part involvement and amplitude as 0 (none), 1 (slight), 2 (moderate amplitude), 3 (market amplitude) to 4 (severe amplitude) and at rest, with posture holding, with action and intention in specific motor tasks/functions (writing, drawing, and pouring with dominant and non-dominant hands), and functional disability, resulting from tremor (speaking, eating, drinking, hygiene, dressing, writing, working, and social activities). Results were giving in percentage of improvement according to FTM-TRS. The Wilcoxon matched pairs test was performed: $N=20$; $T=0$; $Z=3.92$ $p$ level=0.0001. We developed a surgical approach algorithm based on many years of previous experience dealing with resistant HT.

Two trajectories were always planned preoperative to target Vim thalamic nucleus and GPi nucleus; definitive targeted nucleus was accepted or rejected depending on stimulation effects via test microelectrodes. The electrode was implanted in the nucleus with the best tremor suppression achievement; on the other hand, GPi DBS was initially decided if one of the following conditions was present: (a) If Vim nucleus anatomy was grossly altered; (b) when intraoperative tremor control was unsatisfactory despite Vim high-intensity stimulation; or (c) if unaffordable side effects or even tremor worsening occurred during intraoperative macrostimulation.

The stereotactical procedure was performed from a prefrontal entry point. Trajectories to the targets were calculated by image fusion of the preoperative MRI and stereotactic angioCT scan by using a Riechert-Mundinger (RM) stereotactic frame (Inomed, Germany).

Standard 1.5-T MR scanning (Siemens AG, Germany) was used under TR 5150, TE 124, TSE 11, NSA 12, 2-mm slice, voxel size (0.45 0.45) FOV 24 24, Matriz 256 256, NEX 2, Window 2730, Level 1407, average image 65, phase direction: right–left, GAP 0, Echo train 27, bandwidth 31.25, and pulse sequence: FR-FSE–XL, ASSET 2.

Sagittal and coronal MRI T2 sequences were performed every 2 mm with a 1.5-T MR imager to identify the mid-sagittal plane, the AC and PC. T1-weighted normal sequences were also performed for surgery planning; Data were analyzed with a new generation stereotactic software program: Praezis plus (Precisis AG, Heidelberg, Germany). The corresponding anatomy was compared with the corresponding section schema of the Schaltenbrand-Wahren stereotactic atlas.

### Intraoperative neurophysiologic monitoring

Intraoperative neurophysiologic monitoring was performed with physiological Inomed Microrecording system (Inomed Medizintechnik GmbH; Emmendingen Germany), with a high impedance electrode (250-μm tip, and impedance 1–1.5 MΩ).

The optimal target for Vim was determined to be 7 mm posterior (6–8 mm anterior de the PC) and 14.5 mm lateral to the midpoint of the anterior to posterior commissure (AC–PC) line and on the AC–PC line. The optimal target for the posteroventral part of the GPi was determined to be 2–3 mm anterior and 20 mm lateral (19–21) to the midpoint of the AC–PC line [18].

Confirmation of adequate targeting through electrode microrecording was performed; in the case of Vim, we compared Vim activity with sensitive ventral posterolateral nucleus (VPL) activity from the posterior channel to confirming position. Intraoperative microstimulation should induce near complete tremor arrest to be considered as positive response. Stimulations started at at 0.5 mA, 60 μs and 130 Hz, and up to 6 mA until tremor control was positively achieved.

After defining the target point and if microrecordings fulfilled the localizing criteria and positive response, the final DBS electrode (3387 or 3389, Medtronic, Minneapolis, MN, USA) was implanted with a previously biplanar X-ray mark of the target point and connected to a single channel Model 7426 Soletra or dual-channel Model 7428 Kinetra Neurostimulator (Medtronic) via Model 7482 Low Profile Extensions (Medtronic) connectors tunneled subcutaneously. Satisfactory lead positioning was verified postoperatively with MRI and/or CT scan.

## Results

Five women and five men between ages 67 and 24 years (average age of 42.3 years) received permanent DBS treatment and were followed for at least 24 months. All but four patients (two presenting destruction of the Vim thalamic anatomy and two additional cases showing major alterations in the Gpi nucleus) were presurgically planned and intraoperatively stimulated in Vim and the posteroventral region of the GPi nucleus.

In all Vim cases, trajectory planning included the insertion of the first pole of the electrode in the posterior subthalamic area (PSA) by modifying entry point. Seven patients received Gpi nucleus definitive implantation (2 bilaterally and 5 unilaterally), while the remaining three received Vim nucleus DBS (one bilaterally and two unilaterally). Pre- and postoperative TRS scores were measured and compared (Table 2).

In all observed cases, we could see an improvement on the tremor rating scale. This means that there was no scenario where postoperative tremor was equal or worse compared to preoperative tremor. Over all cases, the average improvement in tremor was of 2.55 points on the TRS or a 64 % increase in measured results, with a minimum of one point (25 %) improvement in one case and a maximum of 4 points (100 % improvement) also in one case. Tremor was rated before and periodically after DBS, noticing that HT, unlike other neurological conditions, might not be progressive. Results were analyzed according to individual predominant type of tremor. One case (5 %) measured postural tremor, nine cases measured resting tremor, and ten cases measured intention tremor. The results slightly differed, while in the postural tremor case, the maximum possible tremor reduction was achieved from 4 to 0 points, meaning 100 % tremor reduction, in the 9 resting tremor cases, the average reduction was of 3 points or 75 %. The average improvement in the intention tremor group (10 cases) was of 2 points or 50 %. At a $p$ level of 0.0001, DBS significantly improved the scores of patients on the TRS. DBS was thus very useful in reducing tremor in our patient sample (Table 3).

Initial stimulation programming was done during hospitalization, and a more detailed contact testing was performed 3 to 4 weeks after hospital discharge. Such programming sessions included single contact testing from 0 to 6 V in 0.2 V increments, an analysis of clinical benefits and side effects. Employed frequencies were above 145 Hz, and pulse width ranged from 90 to 330 μs. The chosen contact was defined by best clinical response (i.e., tremor reduction) with the lowest side effect (e.g., capsule effect, dysarthria, and ataxia). We observed that responses on tremor, obtained intraoperatively with microstimulation, were well correlated with the sustained effect over time, with DBS lasting for at least a 2-year follow-up period. All patients who were operated on the Gpi improved in the TRS; Rest tremor component diminished from 4 to 0 (asymptomatic) in one patient and from 4 to 1 (slight tremor) in six patients; meanwhile, intention tremor component was from 4 to 2 (moderate amplitude) in six patients and from 4 to 3 (market amplitude) in one patient. Notably, the resting component of tremor in those patients responded quite well to GPi stimulation when it was predominant. Results were sustained at minimum follow-up of 2 years with mild voltage increase over time.

## Discussion

Previously known as rubral or midbrain tremor, HT was first described by Gordon Holmes in 1904 [43]. HT is a symptomatic tremor characterized by rest and intention tremor whose presence and preponderance varies over time and is usually accompanied by postural components, as well as other parkinsonian and cerebellar manifestations. It is usually worsened by stress, anxiety, fatigue, and particularly when attempting to

**Table 2** Individual patient data

| Pt | S | Age | MR imaging | Pre-TRS (0–4) | DBS target | Outcome TRS (0–4) | Main improvement (%) | F-up |
|---|---|---|---|---|---|---|---|---|
| 1 | M | 67 | Pontomesencephalic cavernous angioma bleeding | Postural 4 | Right Vim | 0 (none) | Postural 100 | 12 years |
| 2 | M | 47 | Centrolateral pontine bleeding from cavernous angioma | Bilateral rest 4 and intention 4 | Right Gpi | Rest 1, intention 2; mild effect in spasticity and ataxia | Rest 90<br>Int. 65 | 5 years |
| 3 | F | 42 | Right posterior cerebral artery stroke | Left rest 4 and intention 4 | Right Gpi | Rest 1, intention 2; moderate effect in spasticity and mild in ataxia | Rest 90<br>Int. 60 | 7 years |
| 4 | F | 38 | Right posterior choroidal artery stroke with thalamic infarction | Left rest 4 and intention 3 | Left Gpi | Rest 0, intention 1; mild effect on spasticity | Rest 98<br>Int. 80 | 8 years |
| 5 | M | 53 | Right caudate and anterior pallidal hemorrhage | Rest 4 and intention 4 | Right Gpi | Rest 1, intention 2 | Rest 80<br>Int. 75 | 2 years |
| 6 | F | 26 | Multiple lesions related to multiple sclerosis | Rest and intention bilateral 4 | Bilateral Vim | Right: rest 2 intention 2<br>Left: rest 2 intention 1; mild effect in spasticity | Rest 80<br>Int. 60 | 6 years |
| 7 | M | 25 | Thalamic hemorrhage | Rest 4 and intention 4 | Left Gpi | Rest 1, intention 2 | Rest 80<br>Int. 70 | 8 years |
| 8 | F | 49 | Multiples lesions related to multiple sclerosis | Rest 4 and intention 4 | Bilateral Gpi | Rest 1, intention 2 | Rest 80<br>Int. 55 | 4 years |
| 9 | F | 24 | Posterior cerebral artery stroke | Rest 3 and intention 3 | Right Gpi | Rest 0, intention 1 | Rest 100<br>Int. 75 | 2 years |
| 10 | M | 52 | Right subthalamic and mesencephalic stroke | Rest 4 and intention 4 | Right Vim | Rest 1, intention 1 | Rest 80<br>Int. 80 | 4 years |

We should state that by definition, all three tremor components were present; here, we do analyze individually predominant impairment components before and after surgery

*Pt* patient number; sex; age; MR imaging result; tremor predominant component before and outcome after DBS surgery. Targets employed are also given for every case. *TRS* tremor rating scale, *Rest* resting tremor, *Int*. intentional tremor

**Table 3** Combination of frequency, pulse width, and voltage and most effective stimulation contacts found in the course of chronic stimulation

| Pt | Age | Sex | Target | Contacts | Parameters at 2 years |
|---|---|---|---|---|---|
| 1 | 67 | M | Vim+PSA | 3−,C+ | 2.2 V, 150 μs, 160 Hz |
| 2 | 47 | M | Gpi | 0−,1+ | 5.6 V, 180 μs, 185 Hz |
| 3 | 42 | F | Gpi | 1−,2+ | 6.0 V, 330 μs, 185 Hz |
| 4 | 38 | F | Gpi | 1−,2−,C+ | 4.8 V, 60 μs, 145 Hz |
| 5 | 53 | M | Gpi | 2−,C+ | 5.2 V, 90 μs, 160 Hz |
| 6 | 26 | F | Vim+PSA | 1−,2+ | 3.5, 90 μs, 160 Hz |
| 7 | 25 | M | Gpi | 2−,C+ | 5.0 V, 150 μs, 145 Hz |
| 8 | 49 | F | Gpi | 2−,C+ | 5.0 V, 90 μs, 160 Hz |
| 9 | 24 | F | Gpi | 2−,C+ | 5.5 V, 120 μs, 190 Hz |
| 10 | 52 | M | Vim+PSA | 1−,2−,C+ | 4.0, 90 μs, 170 Hz |

Details of frequency, pulse width, and voltage combinations in every individual case to achieve the best clinical response are shown. Contacts: the most effective electrode contacts used in these series. The electrode has 4 evenly spaced contacts numbered, from ventral to dorsal 0 to 3, any one or more of which can be either positive or negative during stimulation. In addition, the positive contact can be at a distant low impedance site (the metal case of the implantable pulse generator (IPG), implanted subcutaneously in the chest), effectively delivering monopolar stimulation to the brain. E.g., 0−,3+ means contact 0 was negative, contact 3 positive; 1−,C+ means contact 1 was negative, the case positive (monopolar stimulation with contact 1)

control or inhibit tremor [6, 9]. Thus, afflicted patients find no activity, position, or situation that could reduce tremor, except for sleep. However, they often find it also difficult to maintain sleep. Moreover, many of these patients present additional neurological comorbidities, secondary to the primary disease (e.g., brain stem stroke), exhibiting additional neurological symptoms such as spastic paresis, eventually dystonia and rigidity worsen their quality of life [6, 9].

The time course is also variable, but if a causative lesion is identified, tremor appears from weeks to few years afterwards [29, 44–48]. There are no reports of spontaneous resolution of tremor, so if it is sufficiently severe and resistant to oral medication, surgical treatment is the only treatment option. The injury usually involves the circuit of Guillain-Mollaret's triangle, which is formed by dentate nucleus, red nucleus, olivary nucleus, and their interconnections. However, imaging studies have also shown lesions in the thalamus and cerebral cortex [3, 6, 9]. HT is mostly related to strokes, either ischemic or parenchymal hemorrhages, head trauma, infections, or multiple sclerosis. Metabolic changes in PET studies have been described in the thalamus but also in structures of the Guillain-Mollaret triangle [49]. Yet, it is not clear which of these changes are causative or compensatory in nature.

The mechanisms of HT are complex and not fully understood. Hence, no standardized and universally effective therapeutic approaches are available. Treatment is challenging and poor symptomatic control with medication is frequent, although some successful cases are reported. First-line medications include levodopa, anticholinergics, propanolol, and benzodiazepines. Reported second-line options are amantadine, sulpiride, and levetiracetam [10, 32, 50].

There are several case reports suggesting that stereotactic surgery is the only effective treatment in most cases. Stereotactic interventions aim mostly the Vim, either applying DBS or radiofrequency lesions. Although data from case reports or series suggest high efficacy, there are no comparative studies between targets [11, 23, 30, 32, 51].

Even though Vim is at present the most frequently chosen primary target used to treat HT, there are cases where Vim DBS may fail or lead to insufficient improvement. In this report, we explored the posteroventral GPi nucleus, as a secondary planning target motivated by cases of anatomy disruption of the thalamus which made target planning impossible or when intraoperative tremor control was not achieved after intraoperative stimulation despite various tracks testing. Conversely, two additional cases showing major alterations in the Gpi nucleus and outflow were performed choosing Vim DBS.

Phenomenologically, HT is a combination of parkinsonian rest tremor and intention, cerebellar tremor, in which both the

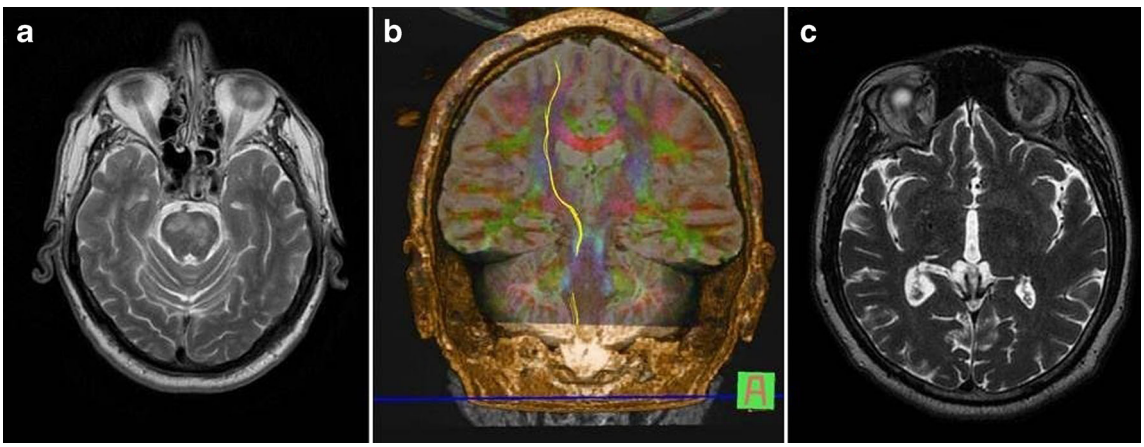


**Fig. 1** **a** Fluid-attenuated inversion recovery (FLAIR) axial MR imaging showing pontine focal lesions, secondary to stroke in a 47-year-old male patient with subsequent HT. **b** Tractography showing compromise of the dentatorubrothalamic pathway. **c** MR imaging showing left Gpi DBS

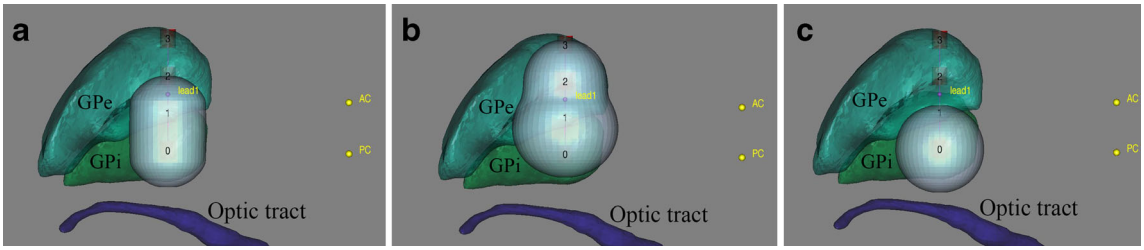


**Fig. 2** 3D representation of amount of Gpi stimulation with individually optimized parameters after MRI and CT postoperative fusion. Images show electrical stimulation parameters using software provided by Medtronic (optivise), currently under testing. **a** 1−,2−,C+; Amp 4.8 V, PW 60 μs, Rate 145 Hz; **b** 0−,C+; Amp 6.0 V, PW 330 μs, Rate 185 Hz. **c** 1−,2+. **c** Amp 3.0 V, PW 150 μs, Rate 145 Hz. **d** Bipolar stimulation

cerebellar dentate outflow (dentato-rubral and dentate-thalamic tracts) and the nigrostriatal pathways must be involved (Fig. 2). Lesions in these neurons and fiber pathways presumably lead to abnormal neuronal activity within thalamic nuclei of the ventral tier (Vim, Vop) that when relayed to cortical areas, it expresses itself as tremor [9, 31, 52].

It is conceivable that DBS electrical stimulation with high frequencies inside neural networks may achieve cessation or improvement of these abnormal thalamic oscillations. Since subthalamic and the main Gpi outflow pathways end in the thalamus, finally, this nucleus relays activity related to tremor forms to the cortex. Vim stimulation is not always feasible, because the nucleus or its connections are destroyed or distorted by the primary pathological process. In these patients, Gpi lesions have been anecdotally reported [6–8, 23, 30, 31]. Inhibitory Gpi DBS is expected to be as effective as lesions could be (Fig. 1).

The rationale behind choosing Gpi as an alternative DBS target for HT is the attempt to find a common structure where both the nigrostriatal pathway and the ganglia-thalamic outflow circuit could be stimulated.

GPi may be studied as a primary DBS target option, especially in those cases when rest tremor and distonic symptomatology is predominant. An additional consideration to stimulate the Gpi is when patients exhibit prominent dystonic or ballistic components. The decision to implant a DBS lead should be based on tremor arrest during GPi macrostimulation. Phenomenological DBS acts by delivering an electrical current, which can be modulated through modification of voltage, pulse width and frequency, creating an electrical field of variable shape, and size according to stimulation parameters (Fig. 2). Such stimulation seems to excite the neuronal fibers but to inhibit the neural cells, which

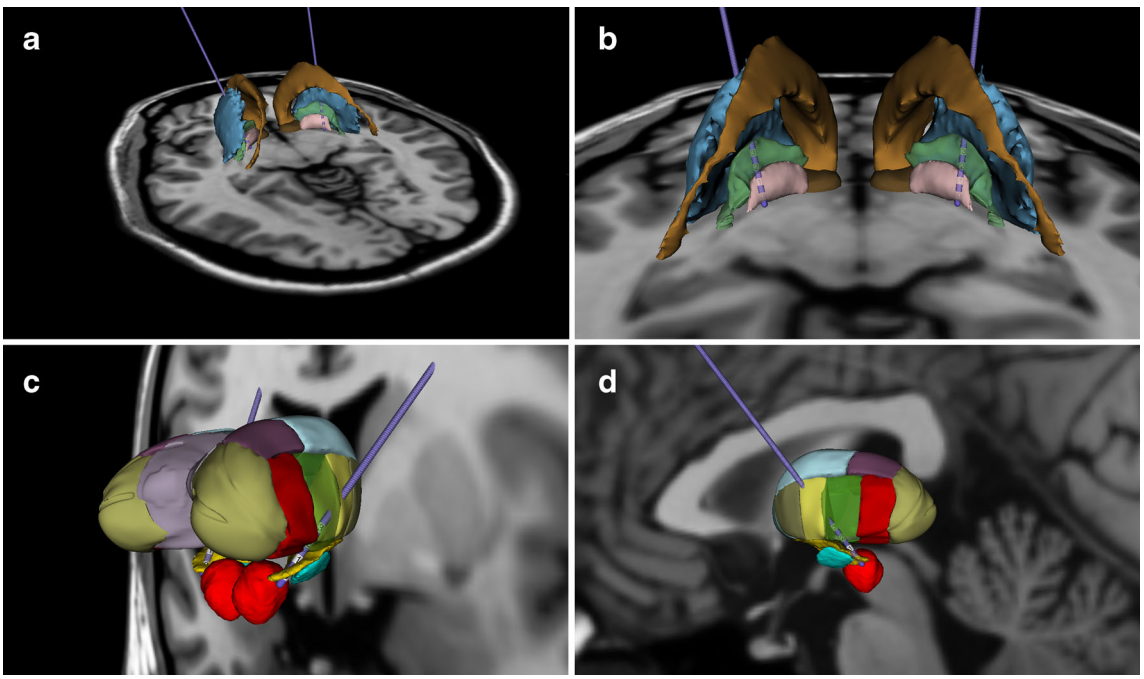


**Fig. 3** **a**, **b** Tridimensional (3D) reconstruction of a DBS electrode in the postero ventral GPI. References: Caudate (*brown*), Nuc accumbens (*dark brown*), Putamen (*blue*), GPe (*green*), and GPi (*pink*). **c**, **d** 3D of **a** coronal posterior view and **b** sagittal view of a DBS electrode placed from anterior to posterior in Vim including PSA as final basal limit. Red nuclei (*red*), subthalamicus nucleus (STN): *blue*, zona incerta (*yellow*). Thalamus: Nucleus ventralis intermedius (Vim): *semitransparent green*, ventral caudal nucleus (Vc): *red*, Pulvinar (*brown*), ventralis oralis posterior (Vop): *yellow*, lateral dorsal nucleus: *light blue*, lateral posterior nucleus: *purple*

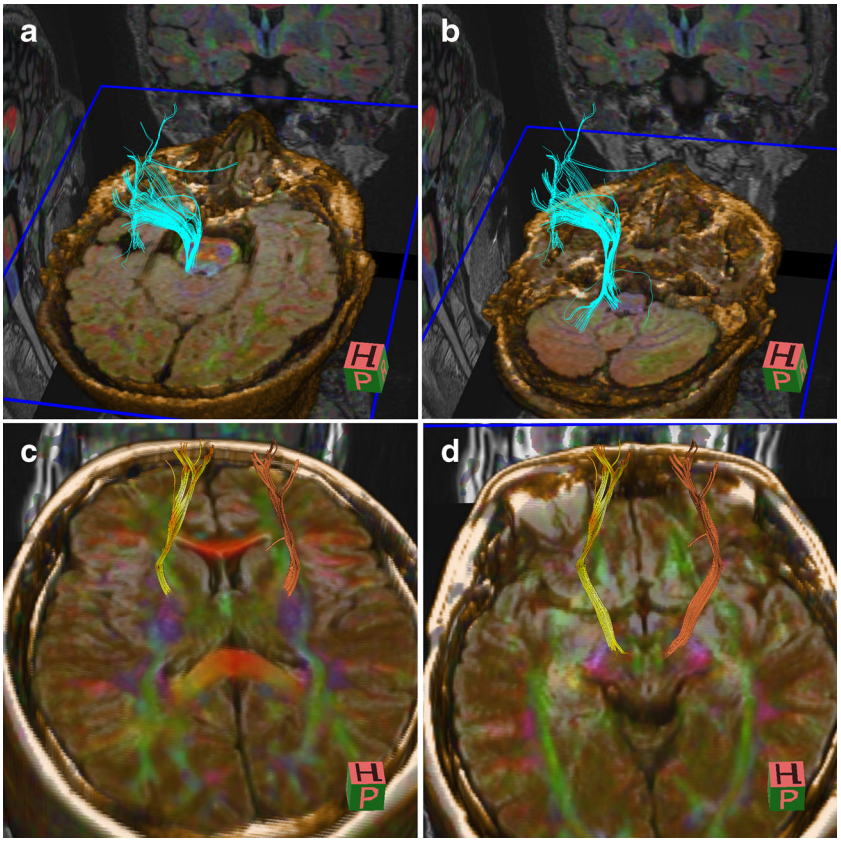


**Fig. 4** Fluid-attenuated inversion recovery (FLAIR) DTI tractography mapping showing **a**–**c** Dentatorubrothalamic interconecting fiber tracking: The linkage between the cerebellum and cerebral cortex involves a disynaptic pathway—an initial projection from the dentate nucleus to the ventrolateral thalamic nucleus and a second projection from the thalamus to the motor and premotor cortices.Workstation Siemens (Munchen-Germany 2008); Syngo MMWP VEZ 1A, DTI 12 directions, 3 NEX Siemens ESPREE Probabilistic software

translates in a decrease of the Gpi mean firing rate to a normal range [43]. Gpi DBS may mainly act by affecting afferent fibers (i.e., presynaptic information), thereby stopping the input into thalamic cells which in turn might lead to tremor suppression [43]. Furthermore, the delivered energy decreases the Gpi mean firing rate back to a normal range [33, 43].

The basal ganglia outflow pathway from the GPi exerts a direct influence on not only the thalamus but also the brain stem motor centers such as the pedunculopontine nucleus related to the mesencephalic tegmental field that controls the axial and proximal appendicular musculature via the descending reticulospinal tract (Fig. 3). Therefore, unlike thalamic surgery, which interrupts the thalamocortical output that controls distal appendicular musculature via descending corticospinal and corticobulbar tracts, GPi pallidal surgery might influence the control of otherwise inaccessible axial and proximal muscles [18].

In this report, GPi DBS was decided when Vim DBS failed to achieve tremor control. Vim nucleus may be considered as the main thalamic relay station between the cerebellum and motor cortex [9, 33, 43]. Thus, high-frequency DBS in the Vim might lead to a functional blockade of pathological circuit activity. The PSA consists of dense fiber bundles transferring information from the cerebellum to the thalamus. Rationale behind including the PSA in the Vim planned trajectory is based on the attempt to interrupt afferent (axonal) fibers, thereby blocking the cerebellothalamic pathway [9, 33, 43] (Fig. 4).

All patients described in the present report benefited from DBS, with no complications or definitive adverse effects. Seven patients were operated in the Gpi and three in the Vim nucleus. Tremor control was more often achieved in resting components (80–98 %) than that in intentional tremor (50–85 %). Mild improvement was seen in spasticity and almost none in ataxia.

In general, patients must understand that the aim of DBS relays on achieving control of tremor and that despite its benefits, it will not affect other neurological deficit that might accompany the tremor as a result of the primary neurological insult. Such is particularly important since patients very often have a poor quality of life due to non-remitting tremor and accompanying neurological comorbidities (i.e., paresis, cerebellar, or cranial nerve syndromes), which may lead to false outcome expectations.

## Conclusions

HT is a rare movement disorder caused mainly by the disruption of the cerebellorubrothalamic projection system; medical treatment strategies are largely unsuccessful: thalamic Vim stimulation is effective and safe and herein was used in three patients with good to excellent results. However, Vim DBS is not always feasible. According to the data presented herein, the Gpi emerges as a possible target for refractory Holmes tremor. Some hints could suggest that Gpi could be considered as a target: the preoperative neuroimaging showing major disruption of the thalamic anatomy, with unsatisfactory tremor control during intraoperative Vim stimulation and when there is predominant rest tremor component.

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## Comments

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The authors reported the outcome of ten patients treated with DBS for Holmes tremor. Furthermore, the group presented an algorithm to decide intraoperatively, which target should be finally stimulated. Depending on the individual anatomy referred to the damage of either the motor thalamus (Vim) and related structures or the ventro-postero-lateral pallidum (GPI) and depending on the individual response to intraoperative test stimulation, the patients received either GPI (seven cases) or Vim (three cases) electrodes. The treatment of Holmes tremor is very challenging; the number of publications dealing with DBS treatment of these patients is rare. Thus, reports of innovative approaches as described in this manuscript are important. Even though the authors analyzed their data retrospectively and derived the algorithm for target decision rather from experience and not as a hypothesis tested in a prospective clinical protocol, this approach is worth to be considered for the clinical routine in such difficult cases.