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REVIEW

Deep brain stimulation in uncommon tremor disorders: indications, targets, and programming

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Abstract

Background In uncommon tremor disorders, clinical efficacy and optimal anatomical targets for deep brain stimulation (DBS) remain inadequately studied and insufficiently quantified.

Methods We performed a systematic review of PubMed.gov and ClinicalTrials.gov. Relevant articles were identified using the following keywords: "tremor", "Holmes tremor", "orthostatic tremor", "multiple sclerosis", "multiple sclerosis tremor", "neuropathy", "neuropathic tremor", "fragile X-associated tremor/ataxia syndrome", and "fragile X."

Results We identified a total of 263 cases treated with DBS for uncommon tremor disorders. Of these, 44 had Holmes tremor (HT), 18 orthostatic tremor (OT), 177 multiple sclerosis (MS)-associated tremor, 14 neuropathy-associated tremor, and 10 fragile X-associated tremor/ataxia syndrome (FXTAS). DBS resulted in favorable, albeit partial, clinical improvements in HT cases receiving Vim-DBS alone or in combination with additional targets. A sustained improvement was reported in OT cases treated with bilateral Vim-DBS, while the two cases treated with unilateral Vim-DBS demonstrated only a transient effect. MS-associated tremor responded to dual-target Vim-/VO-DBS, but the inability to account for the progression of MS-associated disability impeded the assessment of its long-term clinical efficacy. Neuropathy-associated tremor substantially improved with Vim-DBS. In FXTAS patients, while Vim-DBS was effective in improving tremor, equivocal results were observed in those with ataxia.

Conclusions DBS of select targets may represent an effective therapeutic strategy for uncommon tremor disorders, although the level of evidence is currently in its incipient form and based on single cases or limited case series. An international registry is, therefore, warranted to clarify selection criteria, long-term results, and optimal surgical targets.

Keywords DBS · Tremor · FXTAS · OT · Holmes · Multiple sclerosis · Neuropathy

Introduction

Tremor, defined as an involuntary, rhythmic, oscillatory movement of a body part [1] is a key semeiological feature of Parkinson disease (PD) and essential tremor (ET) [2, 3], as well as the cardinal symptom of less common but equally disabling movement disorders, namely Holmes tremor (HT), orthostatic tremor (OT), and fragile X-associated tremor/ataxia syndrome (FXTAS) [1, 4]. In addition, tremor represents a secondary yet disabling feature of immune-mediated neurological disorders such as multiple sclerosis (MS) and demyelinating peripheral neuropathies [1].

Tremulous disorders are classified basing on two axes, consisting of (a) the clinical and semeiological characteristics of tremor and (b) the underlying etiology [1]. HT is a rest, postural, and intention low-frequency (< 5 Hz) tremor [1] usually associated with an ischemic or demyelinating lesion of the cerebello-thalamo-cortical or dentate-rubro-olivary pathways, with superimposed nigrostriatal dysfunction [1, 5, 6]. OT is a 13–18 Hz tremor affecting the weight-bearing limbs and resulting in a sensation of unsteadiness

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and imbalance when standing [1, 4, 7]. Although the exact location of its generator remains unclear, available evidence suggests the involvement of the cerebellum and pons [7, 8]. MS-associated tremor is a heterogeneous syndromic entity that includes at least three different subtypes of tremor [1, 4]: a 4–5 Hz cerebellar tremor predominantly involving the upper extremities; a 3–5 Hz ataxic tremor of the head ("head titubation") and the trunk; and a 7–12 Hz mild-amplitude postural hand tremor [9]. Neuropathy-associated tremor is a posture and intention 3–6 Hz tremor predominantly involving the upper limbs [1, 10], and possibly associated with an altered peripheral sensory input, which might prevent the cerebellum ability to correct limb position and velocity during voluntary movements [11, 12]. Finally, FXTAS-associated tremor is a posture and intention tremor associated with ataxia, parkinsonism, cognitive decline, peripheral neuropathy, autonomic dysfunction, and psychiatric disorders [13, 14], and caused by a trinucleotide repeat expansion in the premutation range (CGG block lengths 55–200) in the *FMR1* gene.

While pharmacological therapies, mostly beta-blockers, benzodiazepines, and anticonvulsants represent the first line of treatment for common tremor disorders [15], uncommon tremors may be refractory to oral medications and, in selected cases, require advanced surgical treatments such as deep brain stimulation (DBS) [16, 17]. The risk/benefit profile of DBS in uncommon tremor disorders, however, remains to be clarified.

In this review, we sought to analyze the literature related to the safety and efficacy of DBS in uncommon tremor disorders, discussing clinical indications, anatomical targets, and programming strategies.

Materials and methods

We reviewed the literature for studies reporting the outcome of DBS in patients with HT, OT, MS-associated tremor, neuropathy-associated tremor, or FXTAS. Relevant articles were identified through electronic search of PubMed.gov and ClinicalTrials.gov using the following keywords: "tremor", "Holmes tremor", "orthostatic tremor", "multiple sclerosis", "multiple sclerosis tremor", "neuropathy", "neuropathic tremor", "fragile X-associated tremor/ataxia syndrome", and "fragile X." No language restrictions were applied.

We selected studies involving humans. There were no restrictions applied to gender, age, disease duration, or disease severity. The data extracted included the following: (a) DBS targets including, but not limited to, ventral intermediate (Vim) nucleus, ventro-lateral (VL), ventralis oralis anterior (VOA) and ventralis oralis posterior (VOP) nuclei, posterior subthalamic area (PSA), subthalamic nucleus (STN), globus pallidus pars interna (GPi), and zona incerta (ZI); (b) magnitude of response, according to the available presentation of clinical data; (c) follow-up duration; (d) adverse events (AEs); and (e) stimulation settings.

Results

A total of 263 cases of uncommon tremor disorders treated with DBS were identified through a systematic review of PubMed.gov and ClinicalTrials.gov. Of these, 44 had Holmes tremor (HT); 18 had orthostatic tremor (OT); 177 had multiple sclerosis (MS)-associated tremor; 14 had neuropathy-associated tremor; and 10 had fragile X-associated tremor/ataxia syndrome (FXTAS).

Holmes tremor

We identified 24 studies (17 single case reports and 7 case series), which totaled 44 patients treated with DBS for HT (Table 1).

There were 31 patients treated with Vim-DBS: 13 received unilateral Vim-DBS, 5 bilateral Vim-DBS, and 13 Vim-DBS plus an additional target (GPi $n=5$; STN $n=5$; VOA/VOP border $n=3$). Tremor improved in all cases, with a reduction $\geq 80\%$ in 10/31 patients (32.3%). The extent of improvement was not specified in 12/31 patients (38.7%). The DBS electrode was removed in 1 patient treated with unilateral Vim-DBS due to lack of efficacy. Time to follow-up varied from 3 to 52 months. AEs were reported in 4/31 patients (12.9%), consisting in 1 infection of the implantable pulse generator (IPG), 1 case of facial paresthesia, 1 case of transient dysarthria, and 1 case of ataxia, paresthesia and dystonic movements. Stimulation frequency ranged from 100 to 180 Hz, intensity from 1.7 to 4.8 V, and pulse width from 60 to 210 μs (Table 1) [18–37].

GPi-DBS was used in 14 patients with HT: 7 received unilateral GPi-DBS, 2 bilateral GPi-DBS, and 5 GPi-DBS plus Vim-DBS. Tremor improved in all cases. A reduction $\geq 80\%$ occurred in at least one component of tremor in 11/14 patients (78.6%). Follow-up spanned from 6 to 52 months. All but one study reported no occurrence of AEs, and 1 study did not report AEs. Stimulation frequency ranged from 130 to 185 Hz, intensity from 2.0 to 6.0 V, and pulse width from 90 to 210 μs (Table 1) [26, 30, 35–37].

STN-DBS was used in 6 patients with HT: 5 received unilateral STN-DBS plus Vim-DBS, and 1 STN-DBS plus Vo-DBS. Tremor improved in all cases, with a reduction $\geq 80\%$ in 1/6 patients (16.7%). The follow-up duration ranged from 24 to 72 months. All but one study reported no occurrence of AEs, and one study did not report AEs. Stimulation frequency ranged from 135 to 145 Hz, intensity was 2.0 V, and pulse width varied from 90 to 210 μs (Table 1) [21, 34, 38].

Table 1 Summary of literature data on Holmes tremor cases treated with deep brain stimulation

Author	No. of patients	Target	Follow-up	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Kudo et al.	1	Bilateral Vim	N/A	Rt. 2.2 and Left 1.7	100	120–150	Almost complete disappearance of tremor	Transient dysarthria
Pahwa et al.	1	Unilateral Vim	10 months	3.7	90	170	Improvement in postural and resting tremor	Patient developed infection over the IPG site
Romanelli et al.	1	Unilateral Vim + STN	2 years	Vim 4.3 and STN 2.0	Vim 90 and STN 90	Vim 185 and STN 145	Combined Vim-STN stimulation resolved all components of tremor	No peri- and post-operative complications were observed
Samadani et al.	1	Unilateral Vim	N/A	2.5	90	185	57% increase in dexterity, 4 points decrease in functional disability in TRS	Not reported
Nikkhah et al.	2	Unilateral Vim	7 and 6 months, respectively	2.4/3.4	60/90	130/130	Tremor resolved by 80% along with improvement in dystonic symptoms	Transient facial paresthesia
Piette et al.	1	Unilateral Vim	18 months	N/A	N/A	N/A	Tremor improvement	Not reported
Goto et al.	1	Unilateral Vim + GPi pallidotomy	24 months (Vim-DBS) and 12 months (pallidotomy)	3.4	90	160	Tremor abolished	No peri- and post-operative complications were observed
Foote et al.	3	Unilateral Vim/VOP border + unilateral VOA/VOP border	12, 6 and 8 months, respectively	Vim 4.1/3.0/3.6 VOA 4.0/3.1/2.9	Vim 90/60/120 VOA 90/60/90	Vim 185/160/185 VOA 185/145/135	Variable improvement in total TRS (38.4–66.67%)	Not reported
Lim et al.	1	Unilateral Vim/VOA + GPi	8 months	Vim 3.6, Vo 3.5 and GPi 6.0	Vim 150, Vo 90 and GPi 210	Vim 185, Vo 185 and GPi 160	Tremor suppression	Not reported
Plaha et al.	1	Bilateral ZI	12 months	2.48 (mean with other pts)	120 (mean with other pts)	147 (mean with other pts)	70.2% of tremor improvement	Dysphagia for a period of about 3 months post-surgery
Diederich et al.	2	Unilateral Vim	7 and 5 years, respectively	N/A	N/A	N/A	Substantially ameliorated postural > rest > intention component	No peri- and post-operative complications were observed
Peker et al.	1	Unilateral Vim	2.5 years	4.8	120	180	Tremor diminished by 90%	Not reported

Table 1 (continued)

Author	No. of patients	Target	Follow-up	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Bandt et al.	1	Unilateral LF + ZI	16 months	3	120	170	Almost complete resolution of tremor	No peri- and post-operative complications were observed
Acar et al.	1	Bilateral Vim	3 months	4.0	90	180	Improvement in tremor	Not reported
Aydin et al. 2013	1	Unilateral GPi + Vim	6 months	GPi3.0 and Vim 3.0	GPi 210 and Vim 90	GPi 130 and Vim 100	Resting component of tremor improved	No peri- and post-operative complications were observed
Castrop et al.	2	Unilateral Vim	8 and 7 years, respectively	N/A	N/A	N/A	Tremor suppression sustained even when during OFF stimulation	Not reported
Issar et al.	1	Bilateral Vim	N/A	Rt. 3.0 and Left 3.0	Rt. 90 and Left 90	Rt. 130 and left 130	Moderate improvement and dystonic movements persisted	Dystonic movements, paresthesia, ataxia
Follett et al.	1	Bilateral Vim	12 months	Rt. 2.5 and left 2.0	Rt. 60 and left 60	Rt. 185 and left 185	Improvement in TETRAS score from 3 to 1 on right and 3.5 to 0 on left side	No peri- and post-operative complications were observed
Grabska et al.	1	Unilateral VOA + ZI	First at 6 months then at 4 years	1.8	60	185	Postural tremor improved at 6 months and remained stable throughout the years	Four years after DBS, pt. developed an infection around the site of electrode implantation
Kobayashi et al.	4	Unilateral Vo/Vim + STN	25 months	N/A	Vo/Vim and STN 210	Vo/Vim and STN 135	Tremor improved, TRS score lower with simultaneous Vim and SA stimulation	No peri- and post-operative complications were observed
Kilbane et al.	4	Unilateral GPi (2), unilateral Vim + VOA + GPi (1), unilateral Vim + GPi (1)	36, 18, 52, 29 months	GPi 2.5/2.8/4.5/2.0	GPi 90/90/90/120	GPi 185/185/145/145	78.8% mean improvement in tremor severity using FTM tremor rating scale	No peri- and post-operative complications were observed
Espinoza-Martinez et al.	10	Unilateral GPi (5), Bilateral GPi (2), Unilateral Vim (2), Bilateral Vim (1)	> 2 years	Variable	Variable	Variable	64% mean improvement in tremor	No peri- and post-operative complications were observed

Table 1 (continued)

Author	No. of patients	Target	Follow-up	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Aydin et al. 2017	1	Unilateral GPi + Vim	6 months	Vim 3.0 and GPi 3.0	Vim 90 and GPi 210	Vim 100 and GPi 130	Tremor especially resting component improved	No peri- and post-operative complications were observed
Toda et al.	1	Vo + STN	6 years	N/A	N/A	N/A	Tremor especially resting component improved	Not reported

GPi global pallidus internus, *LF* lenticular fasciculus, *STN* subthalamic nucleus, *Vim* ventralis intermedius, *Vo* ventralis oralis, *VOA* ventralis oralis anterior, *VOP* ventralis oralis posterior, *ZI* zona incerta, *FTM* Fahn–Tolosa–Marin tremor rating scale, *IPG* implantable pulse generator, *TETRAS* the essential tremor rating assessment scale, *TRS* tremor rating scale, *N/A* not available in the respective study

Three cases were treated with ZI-DBS (1 bilateral ZI, 1 unilateral VOA/ZI, 1 unilateral lenticular fasciculus/ZI). Tremor improved in all cases, with a reduction ≥ 80% in 1/3 patients (33.4%). The follow-up duration ranged from 12 to 48 months. There was a lead infection 4 years after surgery, requiring removal of the system, and one case of transient dysphagia. Stimulation frequency ranged from 145 to 185 Hz, intensity from 1.8 to 3.0 V, and pulse width from 60 to 120 μs (Table 1) [39–41].

Orthostatic tremor

We identified 9 studies (6 single case reports and 3 case series), reporting a total of 18 patients treated with DBS for OT (Table 2).

Vim-DBS was used in 18 patients: 17 received bilateral Vim-DBS, and 1 unilateral Vim-DBS. Tremor amplitude reduction or increased latency to symptom onset after standing was reported in 15/18 patients (83.3%). One patient treated with bilateral Vim-DBS reported no improvement, and the patient receiving unilateral Vim-DBS reported only a temporary improvement, which lasted less than 6 months. Most of patients experienced a mild/moderate waning of tremor improvement over time. The follow-up duration ranged from 6 to 102 months. A total of 14 AEs was reported in 13/18 patients (72.2%), consisting in 1 skin infection over IPG, 2 surgical revisions due to cervical pain and lead dislocation, 1 generalized tonic–clonic seizure 3 days after surgery, 2 transient paresthesia, 2 gait ataxia, 1 unilateral foot dystonia, 1 case of dizziness, and 4 cases of speech difficulties. Stimulation frequency varied from 130 to 185 Hz, intensity from 1.5 to 4.0 V, and pulse width from 60 to 90 μs (Table 2) [42–50].

Multiple sclerosis-associated tremor

We identified 26 studies (3 single case reports, 22 case series, and 1 randomized clinical trial), for a total of 177 patients treated with DBS for MS-associated tremor (Table 3).

Vim-DBS was used in 146 patients: 93 received unilateral Vim-DBS, 26 bilateral Vim-DBS, 25 Vim-DBS plus an additional target (STN $n = 11$; VO $n = 13$; pre-lemniscal radiations $n = 1$), and 2 unspecified Vim laterality. Symptoms improved to some extent in 126/146 patients (83.6%). A transitory response was observed in 20/146 patients (13.7%). The follow-up duration ranged from 3 to 127 months. Several patients experienced AEs, encompassing MS exacerbation, seizures, intracerebral hematoma, gait/balance disturbance, asthenia and transient lower limb paresis, ataxia, dysarthria, paresthesias, and infections. Stimulation frequency ranged from 130 to 185 Hz, intensity from 0.5 to 8.0 V, and pulse width from 60 to 210 μs (Table 3) [25, 51–70].

Table 2 Summary of literature data on orthostatic tremor cases treated with deep brain stimulation

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Espay et al.	2	Bilateral Vim (1) and unilateral Vim (1)	18 months	First patient right 4.0 and left 4.0 Second patient 1.5	First patient right 90 and left 60 Second patient 90	First patient right 185 and left 185 Second patient 160	Improvement in patient with B/L stimulation, tremor recurrence in U/L patient after 3 months	No peri- and post-operative complications were observed
Guridi et al.	1	Bilateral Vim	4 years	Right 2.0 and left 2.0	Right 60 and left 60	Right 130 and left 160	Marked cessation of tremor	Not reported
Magarinos-Ascone et al.	1	Bilateral Vim	12 months	N/A	Right 90 and left 90	Right 185 and left 185	Reduction in tremor amplitude and patient could stand without any help or leg tremor	Not reported
Yaltho et al.	1	Bilateral Vim	6 months	Right 2.6 and left 2.1	Right 90 and left 90	Right 170 and left 135	Improvement in OT and hand tremor, manifested as improved ability to stand	Not reported
Lyons et al.	1	Bilateral Vim	30 months	Right 2.2 and left 2.7	Right 90 and left 90	Right 185 and left 185	80% improvement in OT in left leg and 50% improvement in right leg, able to stand 7 min	Infection and skin erosion around the IPG which required its removal and a new one was placed 2 months later
Contarino et al.	1	Bilateral Vim	5 years	N/A	N/A	N/A	Initially symptomatic improvement, although benefit lessened gradually to no "optimal clinical"	Persistent pain along the extension wires which required surgical replacement of non-flexible wires for flexible ones
Coleman et al.	2	Bilateral Vim	16 and 7 months, respectively	First patient (right 2.6 and left 3.0) Second patient (right 2.1 and left 1.9)	First patient (right 60 and left 60) Second patient (right 60 and left 60)	First patient (right 140 and left 140) Second patient (right 170 and left 170)	Standing time improved to 15 min in first patient and to > 4 min in second patient	All patients complained of stimulation-induced side effects such as paresthesia, dysarthria, imbalance, and light-headedness. Additionally, pt. #1 complained that his hands were clumsier and pt. #2 was hospitalized for brief generalized tonic–clonic seizures
Lehn et al.	1	Bilateral Vim	12 months	Right 2.6 and left 2.05	Right 75 and left 75	Right 130 and left 130	Improved standing time from 3 to 5 min	Not reported

Table 2 (continued)

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Merola et al.	8[a]	Bilateral Vim	Mean 38 months	N/A	N/A	N/A	Amelioration of OT symptoms and 21.6% improvement in the composite ADL/iADL	One patient developed infection leading to the removal of the entire DBS system, two patients had lead misplacement requiring surgical revision, and another patient complained of focal limb dystonia. Stimulation-induced side effects such as speech difficulties and ataxia were also reported

Vim ventralis intermedius, *ADL* activities of daily living, *iADL* instrumental activities of daily living, *IPG* implantable pulse generator, *N/A* not available in the respective study

[a]The paper reports data of 17 patients, whose 9 are already reported in other studies included in the table

ZI-DBS was used in 25 patients with MS-associated tremor: 4 received bilateral ZI-DBS, and 21 bilateral ZI-DBS plus VOP-DBS. Improvement of all the tremor components was reported for most of treated patients. Some cases gradually deteriorated across a follow-up of 12–62 months. AEs were reported in 8/25 patients (32%), consisting in 1 infection with scalp erosion leading to DBS removal, 2 other wound infections, 2 peri-operative seizure, 1 transient hemiparesis, 1 mild dysarthria, and 1 case of post-operative prolonged lethargy and reduced mobility. Stimulation frequency ranged from 40 to 105 Hz, intensity from 1.9 to 3.8 V, and pulse width from 90 to 330 μs (Table 3) [39, 71, 72].

VL thalamic DBS was used in six patients with MS-associated tremor: four received bilateral VL-DBS and 2 VL-DBS plus STN-DBS. Tremor improved in all cases, but follow-up was limited to fewer than 12 months. One study did not report AEs, and 1 study reported stimulation-induced paresthesia, dysarthria, and gait ataxia in a cohort of mixed patients, without specifying whether AEs occurred in MS patients. Stimulation frequency ranged from 130 to 145 Hz, intensity from 2.0 to 3.6 V, and pulse width was 60 μs in all cases (Table 3) [73, 74].

Neuropathy-associated tremor

We identified 9 studies (7 single case reports and 2 case series), reporting a total of 14 patients treated with DBS for tremor associated with neuropathy (Table 4).

Vim-DBS was used in 13 patients: 9 received bilateral Vim-DBS, and 4 unilateral Vim-DBS. Tremor improved in all cases. There was a complete resolution of tremor in 1/14 patient (7.1%), and a "marked" or "dramatic" tremor improvement in 2/14 patients (14.3%). Follow-up ranged from 6 months to 9 years. AEs were reported in 4/13 patients (30.8%), with 1 case of mild transient paresthesia, 1 case of dysarthria and worsening of gait ataxia, 1 case of mild dysarthria, and 1 skin erosion over IPG. Two studies reported no occurrence of AEs, and two studies did not report AEs. Stimulation frequency varied from 130 to 185 Hz, intensity from 0.6 to 4.5 V, and pulse width from 60 to 210 μs (Table 4) [12, 75–81].

One patient received unilateral PSA-DBS with a significant improvement of symptoms over a follow-up of 12 months. Intraoperative occurrence of visual phenomena, speech alterations, and paresthesia were reported. Stimulation frequency was 145 Hz, intensity 3.0 V, and pulse width 60 μs (Table 4) [82].

Fragile X-associated tremor/ataxia syndrome

We identified eight studies (seven case reports and one case series), reporting a total of ten patients treated with DBS for FXTAS (Table 5).

Table 3 Summary of literature data on multiple sclerosis-associated tremor cases treated with deep brain stimulation

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Nguyen et al.	1	Unilateral Vim	17 months	1.5–4.5	60–210	130	Both proximal and distal component of tremor improved	No peri- and post-operative complications were observed
Siegfried et al.	9	Unilateral Vim (8) and bilateral Vim (1)	N/A	N/A	N/A	N/A	Tremor activity suppressed	Not reported
Benabid et al.	4	Bilateral Vim	≥6 months	0.5–8	60	130–185	Two patients had a good or fair benefit but improvement lasted only a few months	Transient neurological deficit due to micro hematoma
Geny et al.	13	Unilateral Vim	8–26 months	N/A	60–210	130	Tremor amplitude decreased in nine (69%) and functional disability improved in 12 cases (92%)	Asthenia and transient lower limb paresis
Whittle et al.	4	Bilateral VL thalamus	N/A	N/A	N/A	N/A	Improvement in tremor and functional status	Not reported
Montgomery et al.	14	Unilateral Vim	<3–>12 months	Range 2.5–3.8	Range 90–120	Range 145–185	Improvement in tremor. Pt. developed mild tolerance to Vim-DBS	One exacerbation of multiple sclerosis that resulted in reduced mobility. One intracerebral hematoma which spontaneously resolved
Schulder et al.	5	Unilateral Vim	>6 months	N/A	N/A	N/A	All patients demonstrated reduction in tremor	No peri- and post-operative complications were observed. Two patients experienced MS exacerbations that responded to iv steroids

Table 3 (continued)

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Taha et al.	2	Bilateral Vim (1) and unilateral Vim + contralateral thalamotomy (1)	10 months	N/A	60	185	All patients demonstrated improved grade of tremor	Imbalance
Krauss et al.	2	Vim[b]	3–24 months	N/A	210	130	Symptomatic improvement in tremor	Intraoperative complications consisted of cortical venous infarction, intraventricular hemorrhage and cardiovascular problems. Stimulation-induced adverse effects consisted of dysarthria and gait disturbances, more frequent in patients with bilateral stimulation. Two cases of wire breakage[a]
Hooper et al.	10	Unilateral Vim	12 months	Mean 3.2	Mean 110	Mean 160	Significant improvement of postural tremor; less marked amelioration of kinetic tremor	Transient paresthesia. Two patients had thalamic-capsular hemorrhages at the site of electrode implant and two patients had seizures
Berk et al.	12	Unilateral Vim	First at 2 m then 1 years	N/A	N/A	N/A	Reduction in tremor at 2 months that sustained for 1 year. Trends in improved dressing, writing and personal hygiene (ADLs) were seen initially	Two wound infection treated with antibiotics. Stimulation-induced transient paresthesia was also reported. Two patients complained of transient postoperative urinary retention

Table 3 (continued)

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Nandi et al.	10	Bilateral VOP + ZI	3–24 months	N/A	N/A	N/A	Tremor was suppressed by a combination of VOP and ZI stimulation (64 and 36% improvement for postural and intention tremor, respectively)	Transient hemiparesis, mild dysarthria, two wound infection and one episode of seizure
Foote et al.	1	Unilateral Vim/VOP border + unilateral VOA/VOP border	21 months	Vim/VOP 3.6 + VOA/VOP 2.9	Vim/VOP 120 + VOA/VOP 90	Vim/VOP 185 + VOA/VOP 135	Activation of both electrodes was associated with the greatest symptom reduction	Not reported
Hamel et al.	2	Bilateral VL thalamus + STN	1 to several years	2.0–3.6	60	130–145	Suppression of intention tremor more effective with STN stimulation than VL thalamic stimulation	Adverse effects include stimulation-induced paresthesia, dysarthria and gait ataxia which were more pronounced with bilateral stimulation[a]
Herzog et al.	11	Unilateral (5) and bilateral Vim + STN (6)	6–25 months	Variable	Variable	Variable	Reduced postural tremor in the terminal phase of goal-directed movement, more pronounced with STN stimulation	Not reported
Plaha et al.	4	Bilateral ZI	Mean 12 months	1.9	210	40	Significant improvement in all components of tremor	One pt. complained of prolonged lethargy and reduced mobility postoperatively that resolved within 3 months

Table 3 (continued)

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Schuurman et al.	10	Bilateral Vim (5) and thalamotomy (5)	5 years	N/A	N/A	N/A	Tremor reduction was achieved, but after long follow-up thalamic DBS was less efficacious than thalamotomy	Patients who underwent thalamotomy reported severe gait/balance disturbances. Dysarthria and ataxia were associated with thalamic stimulation
Moore et al.	1	Unilateral Vim	1 year	4.5	120	185	Tremor improved and the patient was able to perform daily activities. But he died after 1 year	No peri- and post-operative complications were observed
Mandat et al.	5	Unilateral Vim	3 months	3.6	180	185	Tremor reduction was 40% and mean ADL score improved by 18%	No peri- and post-operative complications were observed
Torres et al.	10	Unilateral Vim (9) and bilateral Vim (1)	3 years	Range 2–3.6	Range 60–150	Range 145–185	Half of the patients had reduction in tremor scores at 1 year, 60% of them continued benefiting after 36 months	Three patients had a intraoperative seizure. One pt. developed infection that required DBS hardware removal
Thevathasan et al.	11	Unilateral VOP + ZI (6) and bilateral VOP + ZI (5)	Mean 5.2 years	Mean 3.8	Mean 216	Mean 130 or 180	Sustained improvement in tremor in 50% of limbs affected by tremor	One pt. developed scalp erosion over extension cables that necessitated the removal of DBS system. Another pt. experienced self-limited seizure post-operatively

Table 3 (continued)

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Hassan et al.	9	Unilateral thalamotomy (6) and unilateral Vim (3)	22–127 months (for Vim pts)	N/A	N/A	N/A	Improvement lasted for at least 5 years in two patients, for 1 year in the other patient	Progression of multiple sclerosis and developed complications related to it
Hosseini et al.	9	Unilateral Vim	6 months	2–3.6 (7 pts)/3.5 (1 pts)/2.7 (1 pts)	80 (7 pts)/120 (1 pts)/80 (1 pts)	130 (7 pts)/150 (1 pts)/130 (1 pts)	Kinetic and postural tremor score improved at 1 month after surgery that sustained by the end of 6 months	Aggravation of dysarthria and worsening of tremor were reported post operatively
Zakaria et al.	16	Unilateral Vim (2) and bilateral Vim (14)	Mean 11.6 months	N/A	N/A	N/A	Tremor was significantly reduced. Sub analysis of ADLs showed improvement in feeding, dressing etc.	Two patients developed infection that eventually leads to the removal and insertion of new electrodes. Another patient required replacement of the connecting leads to the battery due to malfunction with high impedance
Mehanna et al.	2	Unilateral Vim + VOA (1) and unilateral Vim + Raprl (1)	6 years	1.8 + 2.8 (Vim + VOA)/4.1 + 2.5 (Vim + Raprl)	60 + 90 (Vim + VOA)/90 + 90 (Vim + Raprl)	130	Only in Vim + VOA patient was observed an improvement with the double ON compared to stimulating the Vim alone	Not reported

Table 3 (continued)

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Oliveria et al.	11	Unilateral Vim + Vo (first randomly assigned to single lead stimulation and then dual stimulation 3 months later)	6 months	1.5–4.2	60–150	135 or 185	Mean improvement in TRS score by 29.6% with dual-lead stimulation	Two patients developed post-surgical infections that resolved with antibiotics. One case required DBS system removal. Extension wire was fractured and replaced in one patient. Self-limited intraoperative seizure, transient altered mental status and MS exacerbation were also reported

Raprl pre-lemniscal radiations, *STN* subthalamic nucleus, *Vim* ventralis intermedius, *VL* ventro-lateral, *VOA* ventralis oralis anterior, *VOP* ventralis oralis posterior, *ZI* zona incerta, *ADLs* activities of daily life, *iADL* instrumental activities of daily life, *TETRAS* the essential tremor rating assessment scale, *TRS* tremor rating scale

[a]Adverse effects were reported including all patients without the possibility to distinguish the different types of tremors

[b]Laterality has not been specified among the patients

Vim-DBS was used in eight patients: four received bilateral Vim-DBS, two unilateral Vim-DBS, one bilateral Vim-DBS plus PSA-DBS, and one bilateral Vim-DBS plus bilateral STN-DBS. Tremor improved in all cases, with a reduction ≥ 50% in 5/8 patients (62.5%). In four patients, a concomitant improvement of ataxia was reported. The follow-up duration ranged from 6 to 60 months. AEs were assessed in all studies and reported in 5/8 patients (62.5%), consisting in three cases of ataxia and speech worsening (in one case with associated cognitive decline), and two cases of slight worsening of cognition after surgery. Two studies reported no occurrence of AEs. Stimulation frequency varied from 125 to 185 Hz, intensity from 1.5 to 5.4 V, and pulse width from 60 to 150 µs (Table 5) [83–88].

Vo/ZI-DBS was used in one patient with unquantified improvement of tremor and associated ataxia. Follow-up was 30 months, during which no AEs were reported. Stimulation settings were as follows: frequency = 176 Hz; intensity = 3.0 V (right) and 3.25 V (left); and pulse width = 90 µs (Table 5) [89].

PSA-DBS was used in one patient, resulting in a 58% improvement in tremor severity with no AEs occurrence. The follow-up duration was 8 months. Stimulation frequency was 160 Hz, intensity 2.8 V, and pulse width 120 µs (Table 5) [90].

Discussion

We reviewed and summarized studies that reported the outcomes of DBS in uncommon tremor disorders, namely HT, OT, MS-associated tremor, neuropathy-associated tremor, and FXTAS. Apart from one randomized clinical trial that tested the efficacy and safety of DBS in MS [70], the majority of studies consisted of single case reports or small case series. While this relevant limitation should be recognized, suggesting the possibility that a "file drawer effect" might have influenced our results, data reported in the literature seem to suggest that DBS may be clinically useful in uncommon tremor disorders.

The majority of cases received Vim-DBS, but other surgical targets were also tested, including GPi, ZI, PSA, VOA or VOP nuclei, STN, and VL thalamus (Fig. 1). A few patients with HT and MS-associated tremor received dual-target DBS, mostly Vim-DBS in association with GPi-DBS or STN-DBS. Available data do not permit one to draw final conclusions on the best target in each subtype of tremor. Nonetheless, promising results were observed with PSA-DBS and with dual-target DBS. In fact, the most conventional Vim-DBS target was sometimes confounded by worsening pre-existent ataxia in FXTAS, MS-, and neuropathy-associated tremor. Similar complications have been reported in patients with OT, where the accuracy of Vim-DBS targeting is complicated by the somatotopic arrangement of thalamic fibers. In fact, the thalamic region corresponding to the lower limbs is located laterally and is in close proximity to the internal capsule. Such specific anatomical organization accounts for the programming's narrow therapeutic window that is frequently observed in uncommon tremor disorders. Motor and sensory stimulation-induced side effects consist of speech impairment, sensory issues, motor pulling, and possibly gait ataxia. New directional DBS systems capable of greater anatomical resolution may potentially address these difficulties, leading to an improvement in the risk/benefit profile of DBS treatment in uncommon tremor disorders.

Overall, our main findings can be summarized as follows:

Holmes tremor Vim-DBS, GPi-DBS, and STN-DBS appear to represent effective targets in HT, with a potential to modulate both cerebellar-thalamic and nigrostriatal outflows. However, given the multiple pathways involved in its pathogenesis, a combination of two targets might also be considered. In particular, positive results were observed in patients treated with Vim-DBS and GPi-DBS or with Vim-DBS and STN-DBS. The vast majority of studies reported a programming strategy based on single monopolar stimulation, with high frequency (160–180 Hz in most cases) and a pulse width of 60–90 µs (≥ 100 µs in few cases). Bipolar electrode configurations were occasionally used, mostly due to stimulation-induced side effects. Vim-DBS can be considered as a viable therapeutic option for HT patients that have failed multiple oral treatments, including levodopa, dopamine agonists, anticholinergics, and anticonvulsants [15, 91].

Orthostatic tremor Bilateral Vim-DBS demonstrated long-lasting efficacy in reducing tremor in most patients; a few cases treated with unilateral Vim-DBS reported transient and unsatisfactory results. The vast majority of studies reported a programming strategy based on single monopolar stimulation, with a frequency of 160–180 Hz (less frequently 130 Hz) and a pulse width of 60 or 90 µs. More complex programming strategies, such as bipolar configurations and interleaving, were occasionally used. Although partial efficacy in reducing OT has been demonstrated by benzodiazepines, followed by beta-blockers and anticonvulsants [7], the severity of OT symptoms usually progresses over time. This, therefore, lessens the efficacy of oral medications. Results from an international registry suggest that bilateral Vim-DBS might significantly improve the severity of symptoms in patients with incomplete response to oral medications.

Multiple sclerosis-associated tremor Dual-lead thalamic DBS (one targeting the VIM border and one targeting the ventralis oralis anterior-ventralis oralis posterior border) has the highest level of clinical trial support [70], providing a better control likely by stimulating the major pathways

Table 4 Summary of literature data on neuropathy-associated tremors treated with deep brain stimulation

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Růzicka et al.	1	Unilateral Vim	12 months	1.5	90	145	Both postural and kinetic components of tremor improved, no change in ataxia	No peri- and post-operative complications were observed
Blomstedt et al.	1	Unilateral PSA	12 months	3.0	60	185	Improvement in hand and head tremor	Intraoperative stimulation-induced side effects such as visual phenomena, speech alterations and paresthesias
Breit et al.	1	Bilateral Vim	12 months	Right 3.5 and left 4.5	210	130	Sustained tremor improvement despite worsening of neuropathy	Dysarthria and worsening of gait ataxia at high stimulation settings
McMaster et al.	1	Unilateral Vim	12 months	1.0	60	130	Tremor resolved completely and improvement in the performance of daily activities	Not reported
Bayreuther et al.	1	Bilateral Vim	6 months	Right 3.0 and left 3.0	Right 60 and left 90	Right 130 and left 130	Sustained dramatic improvement in tremor	Mild dysarthria was observed at high stimulation settings
Shields et al.	1	Bilateral Vim	19 months	Right 0.6 and left 1.5	Right 90 and left 90	Right 185 and left 185	Tremor and gait improved	No peri- and post-operative complications were observed
Weiss et al.2011	1	Bilateral Vim	12 months	Right 3.1 and left 3.5	Right 180 and left 180	Right 180 and left 180	59% improvement in FTM, 31% improved motor functionality in daily activities	Not reported
Patel et al.	5	Bilateral Vim (4) and unilateral Vim (1)	0.5–> 9 years	N/A	N/A	N/A	Tremors improved but patients developed habituation and required frequent reprogramming	Skin erosion over battery site
Cabañes-Martínez et al.	2	Bilateral Vim (1) and unilateral Vim (1)	16 and 14 years, respectively	2.2/2.5	90/120	135/135	Marked reduction of tremor along with an improvement of quality of life	Mild transient paresthesia

PSA posterior subthalamic area, *Vim* ventralis intermedius, *FTM* Fahn–Tolosa–Marin tremor rating scale, *N/A* not available in the respective study

Table 5 Summary of literature data on Fragile X-associated tremor/ataxia syndrome treated with deep brain stimulation

Author	No. of patients	Target	Follow-up (months/years)	Voltage	Pulse width (μs)	Frequency (Hz)	Outcome	Adverse events
Ferrara et al.	1	Bilateral Vim	21 months	Right 4.0 and left 4.0	Right 90 and left 90	Right 185 and left 160	56% improvement in FTM	Worsening of both gait and speech
Senova et al.	1	Unilateral Vim	6 months	2.5	60	130	73.4% improvement in FTM and 30.2% improvement in ataxia score	No peri- and post-operative complications were observed
Xie et al.	1	Unilateral Vim	24 months	4.4	150	185	Improvement in tremor and daily living function	No peri- and post-operative complications were observed
Mehanna et al.	1	Staged bilateral Vim	6 months	N/A	N/A	N/A	Tremor improvement	After unilateral DBS implant, no peri- and post-operative complications were observed. Bilateral DBS implant resulted in worsening of ataxia, cognitive decline, dysarthria and apraxia even before turning on the stimulation
Oyama et al.	1	Unilateral PSA	First at 6 months and then 8 months	2.8	120	160	57.9% sustained improvement in TRS, no change in ataxia score	No peri- and post-operative complications were observed
Weiss et al.2015	3	Bilateral Vim (2), bilateral Vim/PSA (1)	4 years	Right 1.5/4.4/4.6 Left 1.7/5.4/4.9	Right 150/90/120 Left 150/60/120	Right 125/170/150 Left 125/170/150	Mean improvement in FTM by 70% and improved ataxia (kinematic measures of gait)	Two patients developed slightly worsening of MMSE scores post-DBS
Dos Santos Ghilardi et al.	1	Bilateral VOP/ZI	30 months	Right 3.0 and left 3.25	Right 91 and left 91	Right 176 and left 176	Improvement of tremor and ataxia, functional gain in ADL	No peri- and post-operative complications were observed
Tamás et al.	1	First, bilateral Vim, then bilateral STN and at the end unilateral thalamotomy	5 years	N/A	N/A	N/A	Transient tremor cessation after Vim and STN while thalamotomy improved postural and kinetic tremor	Worsening of gait, scanning speech and nystagmus

PSA posterior subthalamic area, *STN* subthalamic nucleus, *Vim* ventralis intermedius, *VOP* ventralis oralis posterior, *ZI* zona incerta, *ADL* activities of daily life, *FTM* Fahn–Tolosa–Marin tremor rating scale, *N/A* not available in the respective study

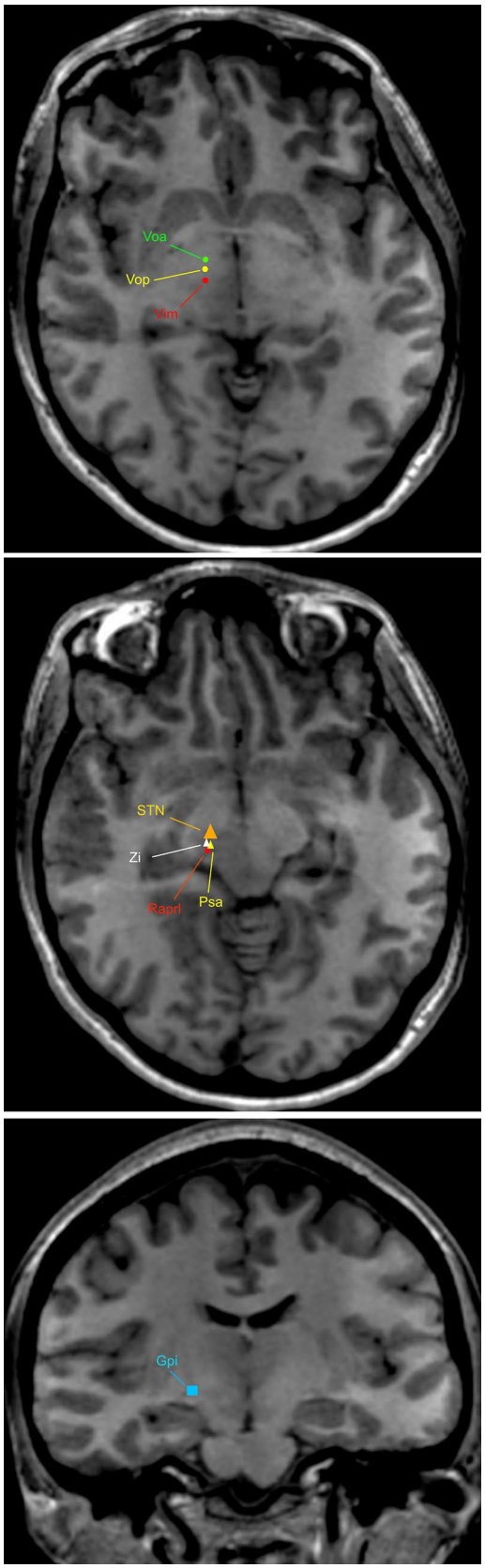

Fig. 1 Main DBS targets for uncommon tremor disorders. Holmes ▶ tremor = Vim; Voa; Vop; STN; Gpi. Orthostatic Tremor = Vim; Zi. MS-associated tremor = Vim; Voa; Vop; Zi; Raprl. FXTS = Vim; Vop; Zi; PSA. Neuropathy-associated tremor = Vim; PSA. *DBS* deep brain stimulation, *FXTAS* fragile X-associated tremor/ataxia syndrome, *MS* multiple sclerosis, *GPe* globus pallidus pars externa, *GPi* globus pallidus pars interna, *IC* internal capsule, *MS* multiple sclerosis, *PUT* putamen, *PSA* posterior subthalamic area, *Raprl* pre-lemniscal radiation, *SN* substantia nigra, *STN* subthalamic nucleus, *TH* thalamus, *Voa* ventralis oralis anterior, *Vop* ventralis oralis, *ZI* zona incerta

involved in MS-associated tremor, and cerebello-thalamocortical and pallidal pathways. Almost all studies reported the use of single monopolar stimulation, with a frequency ranging from 130 to 180 Hz and variable pulse width, ranging from 60 to 210 µs, but typically higher than other tremors. Interestingly, a very short frequency stimulation (40 Hz) was reported as efficacious in controlling the tremor of four patients. The application of DBS in MS-associated tremor is debated. Approximately 46% of MS patients have some form of tremor, severe enough to impair daily living activities in 5.8% of cases [9]. Beta-blockers and botulinum toxin injection [92, 93] should represent the first line of treatment. DBS can be considered in cases with particularly disabling symptoms, refractory to oral medications.

Neuropathy-associated tremor Vim-DBS appears to provide substantial improvement and improvement was reported in the only case treated with STN-DBS. The typical programming strategy was based on single monopolar stimulation, with a frequency of 130 or 180 Hz and a pulse width of 60 or 90 µs (in 3 cases > 100 µs). While the employment of DBS in neuropathy-associated tremor requires further confirmation by larger clinical trials, the significant impact played by tremor on functional activities in patients with immune-mediated neuropathies suggest that DBS might be a feasible therapeutic option for patients with neuropathy-associated tremor failing propranolol, primidone, and benzodiazepines [94].

Fragile X-associated tremor/ataxia syndrome Vim-DBS seems to be effective in improving tremor and sometimes also ataxia; however, a high rate of cases showed a worsening of ataxia, speech, and cognition after surgery, raising the question of the balance between the possible benefit and the potential harm deriving from DBS surgery in these patients. Most studies reported a stimulation frequency of 160–185 Hz and a pulse width of 90 µs or higher. Complex programming strategies such as bipolar or double monopolar stimulation were occasionally used, mostly due to stimulation-induced side effects. Further controlled clinical trials would help to clarify the extent of benefit achievable with Vim-DBS, as compared to oral medications, in patients with FXTAS.

Conclusions

Our review summarized the limited evidence available as well as some of the challenges associated with the use of DBS in uncommon tremor disorders. First, the inherent rarity of these conditions is, indeed, a limitation, which lends itself to certain publications being underpowered, and thus with an elevated risk of Type II errors. Second, the frequent association of uncommon tremor disorders with other movement disorders, such as ataxia, dystonia, and chorea, enhances the litany of confounders endemic to the analyses, which make disentanglement of cause-and-effect relationships challenging. Specifically, such clinical heterogeneity hampers the ability to determine the nature, and magnitude, of certain interventions and what outcomes they portend with great reliability. Third, the lack of validated scales for the objective measurements of disability and DBS-associated clinical benefits limits the generalizability of the results.

Given these limitations, particular efforts ought to be capturing the entirety of the patient's clinical picture, including identification of co-existing movement disorders. Other variables to consider may include, but are not limited to, relevant genotyping, especially in syndromes that have been not well characterized, selection of DBS target(s), and ascertainment of optimal stimulation settings. Recent and future advances in DBS technology, such as directional stimulation, lead with more contacts, and adaptive stimulation stands to improve outcomes when using DBS for uncommon tremor disorders. An international registry to gather data from DBS-treated patients with uncommon tremor disorders is warranted to clarify selection criteria, long-term results, and optimal surgical targets.

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Compliance with ethical standards

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