Therapeutics and Clinical Risk Management

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REVIEW

The Application of Deep Brain Stimulation on Multiple Sclerosis Tremors and the Emerging Targets: A Mini-Review

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Abstract: Multiple sclerosis (MS) tremors, which are a common cause of disability, do not always respond to pharmacological treatment. Contrastingly, deep brain stimulation (DBS) in the thalamic or subthalamic areas (especially in the zona incerta, ZI) has prompted a response in suppressing MS tremors. In this study, we searched the relevant literature to further investigate the positive and negative effects of using DBS planted in different brain areas to suppress MS tremors. The unique effects of GABAergic agents from the ZI pertain to both the basal ganglia thalamocortical and cerebellar thalamocortical loops, in addition to the brain stem motor effector, where tremor oscillation may be transmitted. From this, the ZI is an effective target for ameliorating MS tremors through surgical treatment. Stimulation of the ZI, even bilaterally, could better control MS tremors, and with fewer side effects than targeting the thalamic area. Thus, the ZI is a promising target for regulating MS tremors. This review on MS tremor suppression will help to further understand the benefits of DBS on the ZI compared to DBS on the thalamic area in terms of managing MS tremors.

Keywords: deep brain stimulation, multiple sclerosis, tremors, different targets

Introduction

Tremors are a common symptom of multiple sclerosis, which usually present themselves at a relatively large amplitude and at a 2.5–7 hz frequency range. The tremors commonly involve the proximal and axial limbs and musculature, and mainly appear in the upper limbs, but also affect some of the lower limbs, head, face, tongue, voice, and trunk.[1–3] Tremors are complex and contain several components including postural, kinetic, or intention tremors, indicating that a combination of tremor types may coexist in one patient. The frequency of tremors varies according to what types are present. Suffering from severe tremors is one of the main reasons that can cause an MS patient to have a disability.[4] However, MS tremors are atypical and generally difficult to distinguish from ataxia, both of which are refractory to medication. Deep brain stimulation (DBS) is a technique jointly performed by neurologists, neurosurgeons, and electrophysiologists to implant electrodes into the selected target regions of the brain to alleviate tremors, but it is ineffective for ataxia. The indication for the surgery of DBS is the patient with a severe tremor in the upper limbs resulting in disability, which is refractory to medication, without ataxia that does not respond to DBS.

There are currently few papers published about MS tremors and MS tremor patients are often reported as a small subset of larger groups of patients with other etiologically generated tremors, such as essential tremors and Parkinson's tremors, among others. The number of cases is too small to compare targets with each other, and even in high-volume centers, the percentage of DBS implants for MS tremors is low, making large-scale trials unlikely in the near future. Therefore, MS tremors have not yet been described in detail.

Received: 11 December 2024
Accepted: 16 March 2025
Published: 3 April 2025

DBS in the ventral intermediate nucleus (VIM) of the thalamus is the traditional target for the surgical treatment of tremors, which various patients have benefited from, particularly patients suffering from essential tremors.[5–7] However, atypical tremors, such as MS tremors, have inconsistently responded to the DBS of the VIM. In addition, studies have also implanted electrodes in thalamic areas, such as the ventralis oralis anterior (VOA) and ventralis oralis posterior (VOP), but the reported effects are still inconsistent. One recent viewpoint[8] on DBS has changed the target area to the posterior subthalamic area (PSA), including the ZI and the preleminiscal radiation area (Raprl), which have shown promising results for MS tremor suppression. MS tremors appeared to be less responsive to DBS as Dystonic tremor and Parkinson's Tremor. In a meta-analysis of 13 studies including 129 DBS patients, stimulation improved the Hedges standardized mean tremor score by 2.15.[9] This effect size is difficult to transpose into clinical scales, as it is a pooled estimate from heterogeneous outcome measures, but the largest study of combined Vim and Vo DBS demonstrated a 29.6% tremor reduction,[10] while series of PSA DBS showed a 50–60% improvement on average.[11]

Tremors, proximal postural instability, and dysmetria compose the movement disorders found in MS patients.[12] In 2001, a study in London based on 100 MS patients found a clinically detectable tremor in 58% of participants. Thirty-seven percent of the patients had symptoms induced by tremors, in which 27% had tremor-related disabilities, and 10% were described as having an incapacitating tremor.[13] A report from Minnesota on a population study of Olmsted County provided a different outcome that clinically evident tremors were present in 26% of the 200 patients suffering from MS, in which 3% manifested in severe tremors.[12,14]

The pathophysiology of MS tremors has not yet been defined. Experimental evidence has indicated that demyelinating lesions that affect the cerebellum and its output pathways might play important roles in tremor generation.[12,13] In light of the rareness of resting tremors in MS and the relative unresponsiveness of MS tremors to L-dopa, it is thought that MS tremors may be independent of the pathology of the dopaminergic system.[12,13,15]

Materials and Methods

PubMed and Web of science were searched for the study, mainly those published before March 2023. Inclusion criteria were articles published in English. Inevitably, some literature was not included. Clinical trial studies of MS patients who were treated by deep brain stimulation and provided results regarding tremor. Exclusion criteria studies include cross-sectional studies, case–control studies, letters to the editor, and case reports. The search strategy included the MeSH and text words as (((Brain Stimulations) OR (Deep Deep Brain Stimulations Stimulation) OR (Deep Brain Stimulations) OR (Deep Brain Brain Stimulation) OR (Deep Electrical Stimulation of the Brain)) AND (Multiple Sclerosis OR Sclerosis, Multiple) OR Sclerosis, Disseminated) OR Disseminated Sclerosis) OR MS (Multiple Sclerosis)) OR Multiple Sclerosis, Acute Fulminating). Data on the total number of participants in all included studies, first author, year of publication, target, voltage, pulse width, frequency, follow-up time, tremor assessment, function assessment and adverse effect were recorded.

Results

Targets and Programs

A total of 24 studies[3,4,7,10,12,16–34] reported patient cohorts with MS that underwent DBS surgery in the thalamic area, as either unilateral or bilateral implantations (Table 1). Ten of these studies described the "voltage", "pulse width", and "frequency" of the DBS. The patients had programming that displayed the voltages ranging from 1.0 to 8.5 v, pulse widths fluctuating widely between 60 and 150 μs, and frequency ranges of 90–190 hz, except for one patient who had an issue where one side of his or her device was never turned on. The surgical targets for DBS implantation as unilateral or bilateral that were either in the thalamic and/or the subthalamic areas, as well as in the ZI, were reported in 8 studies (Table 2).[31,35–41]

Five of these studies reported DBS with voltages ranging from 1.5 to 5 v, pulse widths fluctuating between 60 and 210 μs, and frequencies ranging from 130 to 180 Hz (except for one patient who was at 40 hz). Comparing these two groups, the variance of the voltages and the frequencies of the DBS in the thalamic area were likely more significant than those in the ZI, while the volatility of the pulse width in the ZI was more significant than that in the thalamic area. Nevertheless, the best treatment for tremor suppression demands reprogramming during the follow-up period.[4,21,29]

Table 1 Publications on DBS in the Thalamic Area

Year/ Author	N/ Gender	Target	Voltage	Pulse width	Frequency	Follow-up	Tremor assessment	Function assessment	Result	Adverse effects
1999, Schulder M, et al,[16]	6, 1M, 5F	VIM, Unilateral	Not reported	Not reported	Not reported	≥6 months (5 patients)	Bain-Finchley visual analog scale	EDSS, video recording, neuropsychological testing	5 (83%) patients had reduced tremors. 3/5 patients had improvements with daily living activities. 1 patient had improved visuospatial coordination. The EDSS did not change in any patients.	Noperi- and post-Operative complications. MS exacerbations that responded to steroids (2 patients)
1999, Jamal M, et al,[17]	2	VIM, bilateral DBS, underwent a thalamotomy procedure followed by contralateral DBS.	Not reported	Not reported	Not reported	Mean 10 months	Tremor Grade	Not reported	Tremor improvement.	Dysarthria; Disequilibrium
2000, Schuurman PR, et al,[7]	5	VIM	Not reported	Not reported	Not reported	6 months	Modified Tremor Scale	EDSS, Frenchay Activities Index	Tremor reduction, functional status had no improvement.	Dysarthria (2 patients), gait and balance disturbance (2 patients)
2001, Matsumoto J, et al,[18]	3	Ventrolateral thalamus, unilateral	Not reported	Not reported	Not reported	12 months	CTRS, QMA	FIMS, FAMS, EDSS, Box and blocks test	Tremor improvement, disability was difficult to alleviate.	No separate description.
2002, Berk C, et al,[19]	12, 5M, 7F	Thalamic, unilateral	Not reported	Not reported	Not reported	12 months	Clinical Rating Scale Of Fahn	ADL items (hygiene, social activities, writing, dressing, feeding, ability to work)	Postural tremor was reduced to 56% of the preoperative level; action tremor to 67%, overall tremor to 60%. Feeding ability was improved significantly.	Infection (1 patient), superficial wound infection (1 patient), transient paresthesia (most), transient urine retention (2 patients).
2002, Hooper J, Whittle IR, et al,[20]	15, 8M, 7F	Thalamus, unilateral	Mean 3.2 v	Mean 110 μs	Mean 160 hz	12 months	MFTRS	JTHF, Self-care section of FIM, Barthel Index	Significant benefits in tremor reduction and hand function. The scores on the FIM and Barthel Index did not improve.	Thalamocapsular hematomas (2 patients), transient upper limb paresthesia (partial), generalized tonic-clonic seizure (1 patient), *Staphylococcus* infection in the IPG site (1 patient)

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https://doi.org/10.2147/TCRM.S505015

https://doi.org/10.2147/TCRM.S505015

Table 1 (Continued).

Year/ Author	N/ Gender	Target	Voltage	Pulse width	Frequency	Follow-up	Tremor assessment	Function assessment	Result	Adverse effects
2003, Wishart HA, et al,[21]	4, 1M, 3F	Ventrolateral thalamus, bilateral	0–4.8 v	60–120 μs	90–160 hz	3–31 months	Tremor Rating 0: absent, 1: mild, 2: moderate, 3: severe.	Daily functioning	Improvement in tremor control, improvement in aspects of daily functioning.	Transient episode of right upper extremity weakness and diplopia (1 patient), transient pain and swelling around insertion site (1 patient), dysarthria and exacerbation (1 patient)
2003, Schulder M, et al,[22]	9, all F	VIM, unilateral	Not reported	Not reported	Not reported	Mean 32 months (9–54 months)	Bain-Finchley Tremor Scale	EDSS	Tremor improvement, 4 patients (44.4%) had tremor reduction at 6 months, and then MS further progressed. 1 was lost for follow-up. 1 patient had excellent tremor control, but removed for increasing fatigue, 3 patients maintained a worthwhile benefit.	No surgical complications
2003, Loher TJ, et al,[23]	2	VIM, 2 unilateral	Not reported	Not reported	Not reported	Mean 9 months (range 6–13 months)	A modified tremor scale	Not reported	The tremor improved excellently.	No surgical complications
2004, Moringlane JR, et al,[24]	1,F	Left ventrolateral thalamus (the first electrode), 2 mm more laterally to the first electrode, right thalamus (had been never activated)	Not reported	Not reported	Not reported	4 years	Finger-to-nose test	EDSS	Ataxia and intention tremors had been improved stably despite the removal of stimulation at the end of the fourth year.	Moderate dysarthria
2007, Lim DA, et al,[25]	1, M	VIM and VOA, bilateral	2–4.5 v	60–90 μs	150–160 hz	Left DBS: 19 months Right DBS: 10 months	Limited FTM Tremor Rating Scale	Not reported	Had good tremor control bilaterally.	Not reported
2009, Wayne Moore GR, et al,[26]	1, F	Ventrolateral thalamus, unilateral	4.5 v	120 μs	185 hz	Approximately 1 year	Not reported	Not reported	Tremor control was excellent.	No surgical complications

2010, Cristina V, et al,[27]	10, 4M, 6F	VIM, 9 unilateral, 1 bilateral	1.5–8.5 v	60–150 μs	130–185 hz	5–67 months	FTM Tremor Rating Scale	No reported	At 1 year, 5 patients had reduced tremors, in 3 patients the reduction was >50%. After 36 months, 3 patients continued benefiting from simulation, 2 patients had >50% improvement.	Intra-operative seizure (3 patients), infection that required DBS device removal (1 patient)
2010, Thevathasan W, et al,[28]	11, 3M, 8F	Thalamic, 6 unilateral, 5 bilateral	3.8±1.2 v	216 ±99 μs	130 ±-180 hz	≥3 years	Clinical Rating Scale	Spiral-score, able to drink, MRC, EDSS	11/18 (68.75%) upper limbs with tremor had evident permanent reduction. Early: 6 patients regained the ability to drink from a cup or beaker from a tremulous limb.	Not reported
2010, Mandat T, et al,[29]	5, 2M,3F	VIM	2–3.6 v	90–180 μs	130–185 hz	Mean 3 months	Modified Fahn Scale	Modified ADL	Mean tremor reduction was 40%. Mean ADL score improved by 18% (0–36%).	No surgical complications
2011, Hosseini H, et al,[4]	9, 2M, 7F	VIM, unilateral	2.0–3.6 v	80–100 μs	130–150 hz	6 months	FTM Tremor Rating Scale	Short- Form-36 scale	Postural tremor improved by 53%, intention tremor improved by 32%.	Aggravation of dysarthria (2 patients), progression of tremor (1 patient)
2012, Hassan A, et al,[12]	3, 2M, 1F	VIM, 2 unilateral, 1 bilateral	Not reported	Not reported	Not reported	12 years	Not reported	EDSS Tremor-disability questionnaires by telephone	2 patients were tremor-free for 5 years, 2 patients survived for 12-year f/u	Not reported
2013, Zakaria R, et al,[3]	16, 7M, 9F	VIM, 2 unilateral, 14 bilateral	Not reported	Not reported	Not reported	3–80 months	Bain scores, FTM Tremor Rating Scale	Euro–Qol 5D, Specific section of Fahn-Tolosa-Marin scale	5 patients had at least 50% tremor reduction, 11 patients had at least 30% tremor reduction. Feeding function significantly improved.	Infected by the stimulator when implanted (1patient), recurrent infections (1 patient), leads malfunctioning (1 patient)
2013, Kocabicak E, et al,[30]	1, F	VIM/VOP, bilateral	3.2v (left), 2.6 v (right)	90 μs	130 hz	6 months	FTM Tremor Rating Scale	EDSS Foot test score 9-hole peg test	Tremor reduction, eating, drinking function, and standing walking function were improved.	Not reported
2014, Mehanna R, et al,[31]	1, F	VIM, VOA, unilateral, 2 Leads	VIM, 1.8 v, VOA, 2.8 v	VIM, 60 μs, VOA, 90 μs	VIM, 130 hz, VOA, 130 hz	Not reported	Tremor Rating Scale	Not assessed	Relative improvement of contralateral upper limb score was 18.64% (double 'on' compared to double 'off ')	Not reported

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https://doi.org/10.2147/TCRM.S505015

Table 1 (Continued).

Year/ Author	N/ Gender	Target	Voltage	Pulse width	Frequency	Follow-up	Tremor assessment	Function assessment	Result	Adverse effects
2017, Oliveria SF, et al,[10]	12, 2M, 10F	Dual-lead: VIM and VO (VOA or VOP)	Not reported	Not reported	Not reported	6 months	FTM Tremor Rating Scale	Not reported	9 patients had tremor improvement, (1 patient withdrew from infection)	Superficial wound infection (1 patient), transient altered mental status and MS exacerbation (1 patient), Other adverse events including headache, fatigue, limb weakness, speech difficulty, nausea, and vomiting, among others.
2022,Joshua K. Wong, et al,[32]	11, 10M, 1F	Dual-lead: VIM and VOp	Not reported	Not reported	Not reported	3 months for single-lead stimulation, 6 months for dual-lead stimulation.	FTM Tremor Rating Scale	The motor score of the TRS	More anterior thalamic stimulation (VOP) may be important for improving the outcomes of DBS for MS tremor.	1 participant experienced worsening of tremor at 6-months post-DBS implantation (−50% worsening) and was labelled a non-responder.
2023, Claire Chagot, et al,[33]	104, 33M, 71F	VIM, 99 unilateral, 4 bilateral	Not reported	60 μs	130 hz	≥6 years	CTRS	ADL, EDSS	64% patients were improved, 29.2% of patients experienced a limited clinical improvement without functional benefit, 6.7% were not improved at all.	Surgical site infection (3 patients), transient dysarthria (3 patients), upper limb motor weakness (3 patients), cognitive impairment (1 patient), limb stiffness (1 patient), headache (1 patient), insomnia (1 patient), MS relapse (1 patient), balance impairment (1 patient)
2023, Paranathala MP, et al,[34]	7, 3M, 4F	VIM, 3 unilateral, 4 bilateral	2.0–4.3v (left), 1.0 v (right)	60 μs	130–190 hz	6–72 months	FTM Tremor Rating Scale	EuroQol-5D	A decrease in the tremor scores for all patients postoperatively, and the tremor improved over time.	No surgical complications

Abbreviations: DBS, deep brain stimulation; EDSS, Expanded Disability Status Scale; VIM, ventral intermediate nucleus; VOA, ventralis oralis anterior; VOP, ventralis oralis posterior; CTRS, Clinical Tremor Rating Scale; QMA, Quantitative Movement Analysis; FIMS, Functional Independence Measure Scale; FAMS, Functional Assessment Of MS Scale; ADL, Activity of daily living; MFTRS, Modified Fahn's Tremor Rating Scale; JTHF, Jebsen Test Of Hand Function; FIM, Functional Independence Measure; FTM Tremor Rating Scale, Fahn-Tolosa-Marin Tremor Rating Scale.

Table 2 Publications on DBS in Subthalamic Area

Year/ Author	N/ Gender	Target	Voltage	Pulse Width	Frequency	Follow-Up	Tremor Assessment	Function Assessment	Result	Adverse Effects
1980, Brice J, Mclellan L.[35]	4, F	The junction between thalamus and midbrain, all bilateral.	Not reported	Not reported	Not reported	5-6 months	Not reported	Assessment of some living ability	2 patients (50%) had striking results.	Mild deterioration of swallowing (1 patient), speech (2 patients), micturition (3 patients)
2002, Nandi D, et al[36]	1, F	ZI, unilateral	Not reported	Not reported	Not reported	12 months	No reported	She self-assessed and her closest relative assessed by Functional Limitation Profile	Good tremor control had been maintained. Total functional disability ratings were reduced.	Worsening of walking and left foot dystonia developed before 12 months.
2004, Nandi D, Aziz T.[37]	15 (21 arms), 8M, 7F	Straddle the VOP and ZI, 9 unilateral, 6 bilateral	Not reported	Not reported	Not reported	Mean of 15 months (10 patients, 14 arms)	Not reported	Not reported	Tremor improvement (postural tremor improved by 63.73%, intention tremor improved by 36%)	Transient hemiparesis (1 patient), episode of a seizure (1 patient), mild dysarthria (1 patient), wound infection (2 patients)
2007, Herzog J, et al[38]	11, 6M, 5F	Thalamus and STA, 5 unilateral, 6 bilateral	1.5-3.7 v	60-90 μs	130-180 Hz	6-25 months	FTM Tremor Rating Scale	EDSS	The average reduction of the preoperative TRS was 50.4±3.1%.	Not reported
2007, Hyam JA, et al[39]	6, 4M, 2F	1 ZI (bilateral), 1VOP/VIM-ZI (left),VIM (right), 1 VOP (left), 1 VOP-ZI (left), 1 VOP (left), VIM (right), 1 VOP (bilateral)	1.5-5 v	60-210 μs	135-180 Hz	3-5 years	A (0-10) tremor rating scale	Barthel index, ADL, EDSS	At early stage, postural tremor in 90% limbs improved, and intention tremor in 70% limbs improved. At a later stage, intention tremor in 75% limbs decreased with the weakness of the limbs.	Worsening dysarthria (1 patient)
2007, Hamel W, et al[40]	2	Ventrolateral thalamus and STA, bilateral	2-3.6 v	60 μs	130-145 Hz	At least 1 year	FTM Tremor Rating Scale	Not reported	Tremor improved substantially.	No separate descriptions

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https://doi.org/10.2147/TCRM.S505015

Table 2 (Continued).

Year/ Author	N/ Gender	Target	Voltage	Pulse Width	Frequency	Follow-Up	Tremor Assessment	Function Assessment	Result	Adverse Effects
2008, Plaha P, et al[41]	4, 1M, 3F	Caudal ZI, bilateral	Had not been shown separately, except 1 patient at 1.9 v	Had not been shown separately, except 1 patient at 210 μs	Had not been shown separately, except 1 patient at 40 Hz	Mean of 12 months	FTM Tremor Rating Scale	Not reported	Tremor improvement (postural tremor improved by 87%, intention tremor improved by 75%).	Long-term lethargy and reduced mobility (1 patient)
2014, Mehanna R, et al[31]	1, M	VIM, Raprl, unilateral, 2 leads	VIM, 4.1 v, Raprl, 2.5 v	VIM, 90 μs, 90 μs	VIM, 130 Hz, Raprl, 130 Hz	Not reported	Tremor Rating Scale	Not assessed	Relative improvement of contralateral upper limb score was 3.03% (double on compare double off)	Not reported

Abbreviations: VIM, ventral intermediate nucleus; VOA, ventralis oralis anterior; VOP, ventralis oralis posterior; ZI, zona incerta; EDSS, Expanded Disability Status Scale; STA, subthalamic area; FTM Tremor Rating Scale, Fahn-Tolosa-Marin Tremor Rating Scale; ADL, Activity of daily living.

The Follow-Up Period and Proportion of MS Tremor Suppression in the Thalamic and Subthalamic Areas

The follow-up period in most studies in Table 1 was no more than one year, where short-term tremor improvement was the main goal. The tremor improvement rates for patients with improvements were 44.4–100%, while the proportion of tremor reduction was 30–68.75%, according to studies where electrodes were planted in the thalamic area (Table 1). In Table 2, there were studies that had follow-up periods of at least one year that demonstrated good tremor control that was maintained throughout the first year. In these studies, tremors were alleviated in about 50–100% of patients/limbs, specifically posture tremors improved by 63.73–87% and intention tremors improved by 36–75%, compared to stimulation within the thalamus proper, the stimulation of the subthalamic area led to the significantly higher efficiency of tremor control.[38,40] In addition, DBS in the ZI improved all components of tremors affecting both the distal and proximal limbs, as well as the axial musculature.[41] To diminish both proximal and distal tremors, the proximal and middle electrode contacts were placed in the VOP by some researchers, and the distal contact was placed in ZI by others, where both postural and intention tremors were then improved.[36,42] A study reported by Mehanna[31] found one patient with MS that had two DBS implants in the VIM and VOA areas that had a pre-operative tremor duration of eight years who obtained a relative improvement of his or her contralateral upper limb score by 18.64% (double "on" compare double "off"). Another patient had two DBS implants in the VIM and Raprl areas and had a relative improvement of contralateral upper limb score of 3.03% (double "on" compare double "off"). The patient's pre-operative tremor duration was 30 years,[31] which demonstrated the significance of the operative opportunity, regardless of the target location.

Tremor and Functionality Assessments for MS Patients

The scales and methods of tremor assessments include the Fahn-Tolosa-Marin tremor rating scale (FTM) (9 studies) or limited FTM tremor rating scale (1 study), the Bain-Finchley tremor scale (two studies), and the Clinical Tremor Rate Scale (CTRS) (3 studies), among others. The wide variety of rating scales implies that the field lacks uniform criteria to assess MS tremors because it is difficult to assess the impact of tremors on MS. Most studies take the baseline Fahn-Tolosa-Marin scoring of tremors as a valid measure for MS tremors. However, the Bain score can be relatively simpler than the Fahn-Tolosa-Marin scoring and is also used as a valid measure for MS tremors.[3]

Similarly, there is little consensus on the criteria to evaluate a patient's functionality. The Expanded Disability Status Scale (EDSS) (11 studies) is the most commonly used method. Other scales to evaluate a patient's functionality are the Activity of Daily Living (ADL) scale, also known as ADL items or Modified ADL (respectively 2 study), the Barthel index (2 studies), and some less structured scales detailing living ability. Moreover, in spite of tremor suppression via DBS, disability in most of these patients was still difficult to alleviate. Disability alleviation was seen from the lack of changes in EDSS, except for a few patients who experienced benefits in some aspects of daily living activities.[3,19,21,22,28–30] At the same time, limb weakness, ataxia, and/or dementia can hamper the benefits that patients should have after DBS treatment.[22] Relatively few reports have focused on functional improvement since few studies have been done on DBS conducted in the subthalamic area. In 2002, Nandi described a patient with MS that experienced chronic DBS treatment in the ZI and sustained tremor control and improved functionality.[36] However, this assessment was subjective and therefore may be unreliable.

Adverse Effects

Common adverse effects of thalamic DBS included dysarthria, dysphagia, disequilibrium, infections, paresthesia, and seizures. The incidence of serious adverse effects even reached 50% after patients were treated with thalamic DBS.[10] Case reports for bilateral thalamic DBS revealed that 75% of patients with MS experienced adverse effects.[21] Most complications were minimal and transient during DBS in the ZI, even with bilateral electrodes. For patients with MS that underwent unilateral subthalamic DBS for tremor treatment, only 20% experienced adverse effects, which were transient and mild.[37] These unwanted effects were mild deterioration of swallowing, speech, and micturition.[35] After bilateral ZI DBS tremor treatment, only 25% of patients had lethargy and reduced mobility.[41]

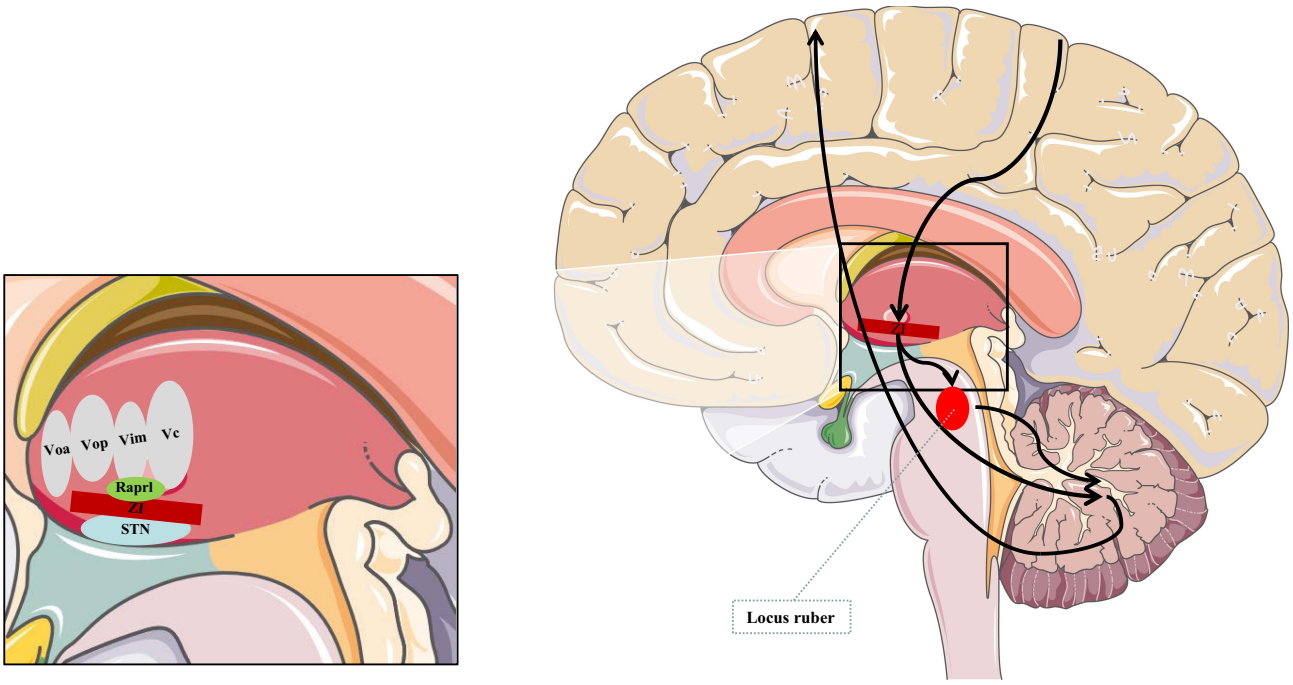

Figure 1 The location of ZI in the thalamus: in the gray matter layer between the lenticular tract and the thalamic tract, dorsomedial of the subthalamic nucleus, and laterally connected to the thalamic reticular nucleus. The extensive fiber projection from ZI formed bidirectional neural circuits with the cerebral cortex, diencephalon, brainstem, cerebellum and spinal cord, specifically associated with the nuclei of thalamus and brainstem. At the same time, rich internal neural circuits were formed between ZI in different regions of the same or both sides.Here is a cortical-brainstem-cerebellar circuit passing through the ZI area.

Therefore, ZI stimulation had a good effect on improving tremor, and there are relatively few adverse reactions in general, which may be related to unique GABAergic effect of ZI, which not only affected the brain stem motor effectors, but also connected the basal ganglia thalamocortex and cerebellocortex circuits (Figure 1).

Discussion

Deep brain stimulation has recently been used to control tremors that are unresponsive to medication in patients with multiple sclerosis. DBS has the advantages of being non-ablative and adjustable, thus making thalamic stimulation have fewer adverse effects and greater improvement in patient functionality than thalamotomy treatments.[7] However, the effects of DBS have been transient and unreliable, so it is not yet a desirable treatment method. The reasons for its transience and unreliability are: (1) Anatomical structure shifts due to the variability of demyelinating lesions make it difficult to locate the target area during the operation,[27] (2) superimposition of ataxia in MS patients impedes the benefits of DBS, (3) the progression of the underlying disease limits most patients to obtain long-lasting benefits,[12,22] (4) different targets give inconsistent outcomes, as the mechanism of MS tremors is complicated, and (5) the inconsistency of tremor and functionality assessment methods create variability and irregular judgments on the positive and negative effects of treatment. Thus, to improve the therapeutic effect of DBS, we suggest improving the treatment method process in four ways, including screening suitable patients, selecting appropriate targets, improving the location method identification, and unifying the evaluation criteria.

It is important to select patients with MS for DBS that do not have severe ataxia and have purely proximal, axial, or distal tremors that are the main cause of disability. Patients that have predominant ataxia or severe neurological dysfunction are not suitable for DBS.[20] Regardless, younger patients with MS tremors have usually had shorter disease durations and have no superimposed ataxia so they should greatly benefit from DBS treatment.[19] However, to reduce the opportunity of deterioration during the intra-operation or pro-operation periods, it is vital to select MS patients as DBS candidates that have a relatively stable state of disease, where upper extremity tremors are the disabling symptoms.[22] The general understanding is that the pre-operative condition of MS is usually stable for at least half a year.[29] Patients with MS can obtain significant functional benefits from DBS depending on careful candidate selection.[38] The assessments used to determine suitability for DBS must include

neurophysiological tests, as well as neurological and neuropsychological examinations. Furthermore, the assistance of physicians that specialize in MS to select eligible patients for DBS treatment is advisable.

Several recent systematic reviews and meta-analyses demonstrate MS-related tremor improvement after DBS.[9,43] However, there was no data on the most optimal stimulation site for MS tremors so far. The VIM or VOP areas have shown to be effective targets for distal arm tremors,[22] so they are the main center for traditional targets for surgical treatment of essential tremors or Parkinson's tremors, whose predominant tremors are in the distal extremities. As a characteristic of MS, the proximal and intentional tremors are the main cause of patient disability,[22] and are far more difficult to alleviate.[42] The pathophysiology of the MS tremor has not yet been defined. However, current hypotheses detail the MS tremor generation mechanism as the dyssynchrony of neuronal firing in the cerebellar thalamocortical loop.[41] The ZI lies dorsal and posterior to the subthalamic nucleus, joining both the basal ganglia thalamocortical circuit and the cerebellar thalamocortical circuit. Thus, MS tremors can be improved by modulating cerebellothalamic projections.[38] The unique GABAergic effect of the ZI affects both the basal ganglia thalamocortical and cerebellar thalamocortical loops, in addition to the brain stem motor effector, which may transmit tremor oscillations. From this, the ZI may be an effective surgical treatment target for all forms of tremors. The ZI is possibly able to influence proximal motor control through the pathways of connections between the ZI and the brainstem.[22,36] Although most of the evidence supported the subthalamic nucleus as a DBS key target for PD, it had been reported that stimulation of ZI had also achieved good results, even better than the subthalamic nucleus.[44] Subthalamic nucleus stimulation was often associated with psychological and psychiatric side effects. A study of 11 patients from Burrows et al[45] found that stimulation of ZI or the area near ZI reduced patients' anxiety and depression, but promoted the feeling of fear compared with subthalamic nucleus stimulation. We reviewed all the above studies and found that stimulation of the ZI, even bilaterally, can better control MS tremors, and with fewer side effects, than stimulation of the thalamic area. Thus, stimulation of the ZI is a promising target for controlling MS tremors (Figure 1).

The pre-operative and post-operative targets were sometimes inconsistent based on the intra-operative evaluation. Depending on the image-guided stereotactic neurophysiological surgery, local field potential recording during the intra-operative period can improve the target site location accuracy for DBS.[37] These recordings typically have significant consistency in the ZI but poor consistency in the thalamic region.[22] From this, electrophysiological navigation during the intra-operative period is necessary to find tremor cells.[46] However, in some patients, it is currently difficult to locate the target during the intra-operative period due to the MS-related loss of evoked potentials from distortion of the subcortical anatomy.[12,42] In order to select more suitable targets to control tremors and improve the accuracy of location targeting, it is important to undergo a detailed evaluation during the intra-operative period, including macro-electrode regulation by a physician specializing in movement disorders.

After reviewing these studies, the scales and methods of tremor and functionality assessments were diverse and lacked comparability. The Fahn-Tolosa-Marin tremor rating scale was the most commonly cited to assess tremors but was not specifically used for evaluating MS tremors. Though the Expanded Disability Status Scale was the most frequent method for assessing patients' function, the evaluation resulted in a few patients with improved function. Contrastingly, the most positive results were found in assessments of activities of daily living items. Better tremor and functional assessment measures need to be developed and then regulated to reach a consensus about MS tremor trends. In this way, the assessment will be more scientific to conduct objective, repeatable, and consensus-based evaluation methods. From this, the effect of DBS on tremor and functionality improvements in MS patients will be better revealed through multi-center research.

Furthermore, the neurological function of patients with MS has not been seen to improve satisfactorily in spite of tremor improvements in various degrees of the postoperative period. This may be related to the fact that DBS is only a symptomatic treatment that does not treat the underlying disease. Another possibility as to why there is little improvement in neurological function is that the patients have superimposed ataxia, preventing them from making improvements. On the other hand, thalamectomy with less invasive methods such as radiation surgery and focused ultrasound may further challenge the role of DBS as an invasive temporary measure. Finally, the recent suggestion that DBS might have neuroprotective effects[47] opens a new world of possibilities currently unachievable by lesioning modalities. Leveraging this unique capability will require new study designs that focus less on the targets themselves and more on how to mitigate the loss of neurons within the circuit.

However, due to the limited literature on DBS treatment for MS tremor, the included studies exhibit high heterogeneity, primarily resulting from variations in sample sizes, DBS settings, follow-up periods, and inappropriate quality assessment tools.[48] These factors reduce the clinical relevance of the research findings. To address this, studies that deviate significantly from the characteristics of most included studies should be excluded, or subgroup or sensitivity analyses should be conducted to investigate the impact of these heterogeneities on the overall results.

Conclusions

During the last 25 years, there were several attempts to treat MS patients with tremor unresponsive to pharmacotherapy. However, long-term tremor suppression in MS patients is still a challenge in the field. We analyzed studies related to MS tremor suppression and we have summarized a few points below: (1) The ZI is a promising target for MS tremor treatment that is becoming more common and more researchers need to verify the chronic efficacy and validity of DBS treatment in the ZI region, (2) it is necessary for physicians that specialize in MS to select eligible patients, (3) multiple positioning and navigation technologies can enhance the accuracy of finding target locations during the intra-operative period, and physicians that specialize in movement disorders play an important role in evaluating this locational accuracy, (4) reprogramming according to the degree of tremor severity is necessary, and (5) better tremor and functionality assessment measures for MS need to be developed and regulated to reach consensus on MS tremor treatments.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Acknowledgments

The authors want to thank the support of the fund (Zhejiang Medical Health Science and Technology Project, 2021KY1091) to complete this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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