Evolving Concepts in Posterior Subthalamic Area Deep Brain Stimulation for Treatment of Tremor: Surgical Neuroanatomy and Practical Considerations

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Key Words
Tremor · Deep brain stimulation · Prelemniscal radiation · Zona incerta · Posterior subthalamic area

Abstract

Background: Although thalamic deep brain stimulation (DBS) has been established as an effective therapy for refractory tremor in Parkinson’s disease and essential tremor, reports investigating the efficacy of posterior subthalamic area (PSA) DBS for severe, debilitating tremors continue to emerge. However, questions regarding the optimal anatomical target, surgical approach, programming paradigms and effectiveness compared to other targets remain. Objectives: In this report, we aimed to review the current literature to assess different stereotactic techniques, anatomical considerations, adverse effects and stimulation settings in PSA DBS. Methods: A comprehensive literature review was performed searching for articles discussing tremors and PSA stimulation. We performed a quantitative analysis comparing different DBS tremor targets. Results: Tremor improvement is consistently documented in most reports with an average reduction in tremor of 79% depending on the specific tremor syndrome. Tremor benefit in patients with multiple sclerosis (MS) tremor was significantly higher than for other stimulation targets. Transient paresthesias, imbalance, dizziness and dysthria are the most common side effects with PSA DBS. Conclusions: PSA DBS is an effective and safe treatment for tremor control and should be considered in patients with refractory tremors with associated cerebellar or dystonic features, proximal tremors and MS tremor.

Introduction

Deep brain stimulation (DBS) has emerged as an accepted and highly effective treatment of medically refractory tremor in essential tremor and Parkinson’s disease (PD). Traditionally, the ventral intermediate nucleus (VIM) of the thalamus has been considered the target for ablative procedures and DBS for most tremor syndromes. Since the 1960s, multiple reports emerged demonstrating adequate tremor control with a small destructive lesion...
aimed to interrupt the thalamic, red nucleus (Rn), zona incerta (Zi) or pallidal connections [1–3]. Lesions were designed to preserve the subthalamic nucleus (STN) in the belief that lesions of this nucleus would induce hemiballismus. In 1969, Bertrand et al. [4] stated that the simple introduction of a 1.5-mm diameter electrode in the posterior subthalamic region arrested contralateral tremor in PD patients. Subsequent studies allowed further definition of the area in question leading to extraordinary effects in PD tremor control. The area in question corresponded to the prelemniscal radiations that extend caudally as far as the mesencephalic tegmentum and ends at the level of the AC-PC line [5]. This small and exquisite region to arrest tremor is located anteriorly and slightly medially to the sensory lemniscus and posteriorly/medially to the motor fibers inferiorly as it reaches the AC-PC line. Based on these studies, it became clear that the tip of the electrode was invariably below the AC-PC line as evidenced in ventriculograms [5]. Limitations with lesioning techniques in the aforementioned region included induction of a transient or even permanent neglect of contralateral extremities in advanced PD patients. Additionally, bilateral lesions increased bradykinesias, and lesions had a negligible effect in rigidity [6]. Larger lesions were also associated with considerable and persistent side effects including weakness, apathy, tremor recurrence and ataxia [3, 5, 7].

Hasler’s seminal work in the early 1950s helped to determine that the main outflow of the medial globus pallidus was to the ventrolateral (VL) thalamus, and autopsy studies concluded that tremor was relieved by lesions in the nucleus ventralis oralis posterior of the thalamus, with better results in tremor control when compared with pallidotomy or campotomy [8, 9]. Over the following years, Cooper [10] published the results of a series of 1,000 consecutive operations on the basal ganglia and thalamus for PD with an impressive rate of success in tremor control with a low rate of complications. Shortly after, VL thalamic lesions became the accepted surgical treatment for PD and other complex tremors [10].

With the advancement of DBS techniques, a renewed interest in the posterior subthalamic area (PSA) has emerged over the past years not only for treatment of advanced PD, but also for treatment of other tremor syndromes. The term PSA is an encompassing anatomical term that includes numerous closely related structures including the caudal Zi (cZi), pallidothalamic white matter in addition to the prelemniscal radiation (Raprl). At the present time, there are no randomized clinical trials directly comparing PSA stimulation versus VIM or STN stimulation for the treatment of refractory tremors. Several contemporary reports in the literature however indicate excellent short-term outcomes with this target with minimal side effects and adequate safety. Different groups around the world employ diverse surgical techniques using a different nomenclature and targeting specific structures within the PSA. Reports regarding DBS programming vary greatly among cases with no specific programming algorithms or standard approach for surgical targeting. New information regarding efficacy, patient selections and treatment considerations continue to emerge in the literature as the number of patients treated with this technique increases. Inconsistent methodologies across groups make direct comparisons or recommendations difficult. Despite the above limitations, we aim to review the current literature to assess different stereotactic techniques for targeting the PSA, review side effects and discuss the practical considerations when targeting the PSA.

Methods

A PubMed and OVID database review was performed searching for literature discussing DBS and PSA stimulation for the treatment of tremors. Search words included DBS, zona incerta, prelemniscal radiation, tremor, and subthalamic area. We limited our search to research articles (original studies, case studies or case reports) on human subjects written in the English language. Relevant references were selected, and an additional cross-reference search was also carried out in the retrieved manuscripts. Unusual adverse events, programming details and long-term follow-up periods were extracted and individually analyzed. We included all available studies with a clear description of the anatomical targets, programming details, and the outcomes.

The selected studies were quantitated by analyzing tremor improvement in relation to stimulation target. Data was further analyzed by comparing the most common PSA targets against each other with respect to etiology. Statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, version 21.0, IBM Corporation, Armonk, N.Y., USA).

Results

Quantitative Analysis

Tremor improvement outcomes with respect to stimulation target and etiology are presented in dot-plot form in figure 1. Patients are indicated by circles, with each circle centering on tremor reduction reported in a particular study. The size of the circle corresponds to the number of patients in each particular study. Median
tremor reduction for each stimulation site is represented by the red bar for each stimulation site. Studies used to construct tremor improvement outcomes are listed in table 1.

Due to the nonparametric nature of tremor reduction data obtained from the studies, statistical analysis was conducted using Kruskal-Wallis one-way analysis of variance, the nonparametric equivalent to the one-way ANOVA. Kruskal-Wallis analysis of tremor reduction data listed in figure 1 showed a statistically significant difference between the 4 areas of stimulation (p < 0.001). To determine the pairs of stimulation targets that contributed to this significant difference, pairwise comparison using the Mann-Whitney test with Bonferroni correction [P_{corrected} = 1 - (1 - P_{MW})^6] was performed. Pairwise significance is illustrated in figure 2, which shows a statistically significant difference between PSA and STN (p < 0.05), PSA and VIM (p < 0.001), and Zi and VIM (p < 0.01).

**Neuroanatomical Considerations**

The PSA is an anatomical term that includes several closely related structures including the cZi, the Raprl and pallidothalamic white matter tracts (fields of Forel H1, H2). The PSA borders are defined by an anterior apex that lies lateral to the hypothalamus and periaqueductal gray matter, posterior and medial to the internal capsule, anterior to the tegmental area, medial lemniscus and lateral to the Rn.

Several closely related structures in the subthalamic region are relevant to the pathophysiology of tremor. Current hypotheses regarding the mechanisms of tremor generation point to abnormal synchronization of neuronal firing in the basal ganglia-thalamocortical loop or the cerebellothalamocortical loops. A more recent hypothesis interconnects both systems suggesting that the basal ganglia can trigger tremor episodes while the cerebellothalamocortical circuit modulates tremor amplitude [11]. The Zi extends rostrally above and medial to the STN, and caudally (cZi) behind the STN and around the Raprl and medial lemniscus [12] (fig. 3). The Zi is an embryological derivative of the ventral thalamus located at the base of the dorsal thalamus, and it is an extension of the reticular thalamic nucleus [13].

The Zi forms a somatotopically arranged primal center of the diencephalon for generating direct responses including visceral, arousal, attention along with posture and locomotion ones to a given sensory (somatic and/or visceral) stimulus. Zi neurons are predominantly γ-aminobutyric acidergic and have reciprocal connections with thalamic, basal ganglia, cerebellar and mesencephalic nuclei involved in coordination and motor control [14]. The Raprl is located immediately anterior to the medial lemniscus, posterior and medial to the STN and cZi, and lateral to the Rn [5].

Additionally, other subthalamic white matter fibers involved in modulating motor input include fibers interconnecting basal ganglia such as ansa lenticularis, thalamic fasciculus, lenticular fasciculus (Forel’s fields H, H1, H2), and subthalamic fasciculus. They traverse the anterior part of the subthalamus, medial and dorsal to the STN. Ascending fibers from the cerebellum and traversing rubral fibers projecting to the thalamus are located immediately lateral to the Rn within the Raprl (periaquedural fibers). Ascending tracts of specific sensory systems such as the medial lemniscus and spinothalamic tract traverse in the posterior part of the subthalamus.
Table 1. Summary of stereotactic techniques for PSA DBS

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Targeting</th>
<th>Coordinates (mean)</th>
<th>Lead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitagawa et al. [23], 2000</td>
<td>1 proximal ET 1 DT</td>
<td>3 mm below the VIM</td>
<td>Coordinates not given</td>
<td>3387</td>
</tr>
</tbody>
</table>
| Hooper et al. [33], 2001  | 1 posttraumatic extremity dystonia and KT | Junction of Zi and subthalamic regions         | x = 12 mm lateral to the midline  
y = 6 mm posterior to MCP  
z = 4 mm inferior to ICL                                         | 3387 |
| Velasco et al. [16], 2001 | 10 PD                                  | PLR                                           | Air ventriculography used to determine a standardized system – AC-PC line's length divided into 10 equal parts:  
x = 8/10 behind AC  
y = 1/10–2/10 below AC-PC line  
z = 5/10 lateral to midline                             | 3387 |
| Kitagawa et al. [37], 2005 | 8 PD                                   | Posterior subthalamic white matter            | x = 10.9±0.8 mm lateral to the midline  
y = 7.6±1.2 mm posterior to MCP  
z = 3.9±1.7 mm inferior to AC-PC line                  | 3387 |
| Murata et al. [34], 2003  | 8 ET (severe)                          | Posterior subthalamic white matter, Lateral to Rn, posteromedial to the STN  
The Schaltenbrand atlas was used as a visual guide, superimposed onto the MR-CT fused images | x = 10.9±0.8 mm lateral to the midline  
y = 7.6±1.2 mm posterior to MCP  
z = 3.9±1.7 mm inferior to AC-PC line                  | 3387 |
| Plaha et al. [36], 2004   | 4 ET – PT or IT of hands/forearm       | Just medial to the posterior dorsal third of the STN, encompassing the ascending dentate, interpositus, VIM fibers and part of the Zi  
20 leads dorsomedial/medial to STN  
27 cZi leads | cZi lead coordinates:  
x = 14.0±1.56 mm  
y = −5.8±1.49 mm  
z = −2.1±1.05 mm  
All relative to intercommissural point | 3387 or 3389 |
| Nandi and Aziz [35], 2004 | 15 MS (complex MS upper limb tremor)   | Proximal ring contacts in the Zi              | Coordinates not given  
Intraoperative neurological assessment of the response to macrostimulation-governed placement of leads | Not reported |
| Plaha et al. [38], 2006   | 35 PD – 29 bilateral implants, 6 unilaterial implants | 17 STN leads  
20 leads dorsomedial/medial to STN  
27 cZi leads | cZi lead coordinates:  
x = 14.0±1.56 mm  
y = −5.8±1.49 mm  
z = −2.1±1.05 mm  
All relative to intercommissural point | 3389 |
| Nandi and Aziz [35], 2004 | 15 MS (complex MS upper limb tremor)   | Proximal ring contacts in the VOP             | Coordinates not given  
Intraoperative neurological assessment of the response to macrostimulation-governed placement of leads | Not reported |
| Nandi and Aziz [35], 2004 | 15 MS (complex MS upper limb tremor)   | Proximal ring contacts in the VOP             | Coordinates not given  
Intraoperative neurological assessment of the response to macrostimulation-governed placement of leads | Not reported |
| Freund et al. [39], 2007  | 1 SCA type 2                           | Thalamic and subthalamic leads                | Coordinates not reported                                 | 3387 |
| Hamel et al. [19], 2007   | 11 IT of different etiologies – 5 ET 5 MS 1 SCA | VL thalamus                                   | x = 13–15 mm lateral to PC  
y = 6–7 mm anterior to PC  
z = at the intercommissural level depending on the width of the 3rd ventricle and intercommissure length | 3387 |
| Herzog et al. [40], 2007  | 10 ET 11 MS                            | VIM                                           | x = 13 mm  
y = −5.5 mm  
z = 0 mm  
Relative to the midpoint of the AC-PC line | 3387 or 3389 |
| Carrillo-Ruiz et al. [22], 2008 | 5 PD                                  | STN                                           | x = 11.69±0.66 mm lateral to midline  
y = 6.73±1.62 mm posterior to MCP  
z = 4.38±1.02 mm inferior to AC-PC | Not reported |
| Plaha et al. [14], 2008   | 5 PD 13 – HT, CT, ET, MS, DT           | Bilateral cZi                                 | x = 14.2±1.56 mm lateral to the midline  
y = 5.7±1.32 mm posterior to MCP  
z = 2.1±1.00 mm inferior to AC-PC line | 3389 |
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Targeting</th>
<th>Coordinated (mean)</th>
<th>Lead</th>
</tr>
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<tbody>
<tr>
<td>Blomstedt et al. [20], 2009</td>
<td>5 – DT, NT, CT</td>
<td>PSA</td>
<td>Patient 1 – DT: x = 9.5 mm lateral to midline, y = 4.5 mm posterior to MCP, z = 3.5 mm inferior to ICL</td>
<td>3389 and 3387</td>
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<td></td>
<td></td>
<td></td>
<td>Patient 2 – DT: x = 10 mm lateral to midline, y = 7 mm posterior to MCP, z = 5 mm inferior to ICL</td>
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<td></td>
<td></td>
<td></td>
<td>Patient 3 – writer's tremor: x = 11.5 mm lateral to midline, y = 6 mm posterior to MCP, z = 3.5 mm inferior to ICL</td>
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<td></td>
<td></td>
<td></td>
<td>Patient 4 – CT: x = 10 mm lateral to midline, y = 8 mm posterior to MCP, z = 3.5 mm inferior to ICL</td>
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<td></td>
<td></td>
<td></td>
<td>Patient 5 – NT: x = 10.5 mm lateral to midline, y = 7 mm posterior to MCP, z = 2 mm inferior to ICL</td>
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</tr>
<tr>
<td>Blomstedt et al. [41], 2010</td>
<td>21 ET</td>
<td>PSA/cZi</td>
<td>x = 11.6 ± 1.8 mm lateral to midline of third ventricle, y = 6.3 ± 1.6 mm posterior to MCP, z = 3.0 ± 2.3 mm inferior to ICL</td>
<td>3387 or 3389</td>
</tr>
<tr>
<td>Barbe et al. [42], 2011</td>
<td>21 ET</td>
<td>40 VIM leads, 26 sub-ICL leads</td>
<td>x = 12.56 ± 1.48 mm, y = −5.74 ± 1.63 mm, z = 1.04 ± 1.21 mm</td>
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<td></td>
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<td></td>
<td>Coordinates transformed with reference to length of ICL and hemispheral width, thus creating standardized brain measurements</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>x = 11.34 ± 1.55 mm, y = −7.19 ± 1.68 mm, z = −1.40 ± 1.21 mm</td>
<td></td>
</tr>
<tr>
<td>Blomstedt et al. [43], 2012</td>
<td>5 ET</td>
<td>cZi</td>
<td>Coordinates of most efficient VIM coordinate – all in relation to MCP: Patient 1: x = 15.5 mm, y = −4.9 mm, z = −1.9 mm, Patient 2: x = 13.8 mm, y = −3.9 mm, z = 1.8 mm, Patient 3: x = 14.1 mm, y = −6.7 mm, z = 2.3 mm, Patient 4: x = 14.0 mm, y = −5.6 mm, z = 0.2 mm, Patient 5: x = 12.9 mm, y = −6.7 mm, z = 0.1 mm</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blomstedt et al. [44], 2011</td>
<td>4 ET</td>
<td>STN vs. cZi</td>
<td>cZi 0: x = 11.4 mm, y = −8.0 mm, z = −6.2 mm, STN 0: x = 11.3 mm, y = −5.1 mm, z = −6.3 mm</td>
<td>3387 (1–cZi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All in relation to MCP</td>
<td></td>
</tr>
<tr>
<td>Blomstedt et al. [45], 2012</td>
<td>14 PD</td>
<td>cZi</td>
<td>Location of active cathode: x = 12.6 ± 1.4 mm lateral to midline, y = 7.0 ± 1.2 mm posterior to MCP, z = 2.0 ± 1.8 mm inferior to ICL</td>
<td>3387 or 3389</td>
</tr>
</tbody>
</table>
Numerous stereotactic surgical techniques have been introduced, and there remains no clear consensus as to the best direct or indirect approach for PSA DBS (table 1). Surgeons at individual DBS centers typically select their preferred technique(s) based on training, experience, available hardware, neuroimaging resources, capabilities of staff and facilities. Direct anatomical targeting using MRI is the preferred approach in most centers using either the Rn or STN as landmarks.

Direct planning using T2-weighted sequences targets slightly medial to the medial border of the STN and in the posterior section of the STN at the level of the maximal diameter of the Rn. Many centers employ an anatomical atlas like the Schaltenbrand stereotactic atlas as a visual guide. Velasco et al. [15] use a standardized system of predetermined coordinates based on air ventriculography in relationship to the AC-PC line. Each coordinate is expressed in one tenth of the AC-PC. Their method estimates distances in standardized units (normalized to AC-PC distance of the patient) to minimize the effect resulting from individual variations. Their approach aims to target the Raprl, which is consistently located 3 tenths behind the AC-PC midpoint, 1–2 tenths below the AC-PC.
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PC level, and 4.5–5.5 tenths to the side of the midline. Plaha et al. [14] utilize intraoperative imaging corroborating an adequate lead location in the subthalamic region. An atlas-based coordinate system to select the target, referred as indirect targeting, is also employed. The average indirect stereotactic coordinates for the Raprl are 11.63 ± 0.66 mm lateral, 6.73 ± 1.62 mm posterior and 4.38 ± 1.02 mm below the midcommissural point. Conversely, the stereotactic target for the cZi are 14.0 ± 1.56 mm lateral, 5.8 ± 1.46 mm posterior and –2.1 ± 1.05 mm below the midcommissural point [15].

Intraoperative Neurophysiological Recordings

The PSA is difficult to define in neurophysiological terms using microelectrode recordings (MER) because it contains predominantly white matter tracts rather than neuronal bodies. MER have been used to indirectly locate PSA based on the well-defined neurophysiological characteristics of both the VIM nucleus of the thalamus and STN. Neurophysiological recordings can provide useful information regarding the laterality of the MER if the unique neuronal firing patterns of the STN or Rn are encountered. Velasco et al. [16] identified the target as the area 2–3 mm below the exiting point from the inferior part of the thalamus. This observation has been corroborated by other centers, as there is a profound reduction in tremor amplitude at this level. At this level, no neuronal firing is recorded; but organized background activity from time to time in bursts of 4–6 Hz, similarly to tremor frequency, has been reported by Velasco et al. [16].

Recordings reveal marked reduction in single unit neuronal activity with low background activity without response to somatosensory stimuli or joint movement [17, 18]. These bursts of rhythmic activity resembled those recorded in the VIM and the ventralis oralis anterior of the thalamus but are less frequent and less prominent. Consistently, in most studies the most effective electrode is located 3–3.5 mm below the intercommissural line. The passage from the VL thalamus to the PSA has been reported to be associated with a reduction of MER activity, even though bursting cells and tremor-synchronous activity are present also in the PSA [19]. A pronounced microlesion effect with tremor reduction upon introduction of the electrode noticed in most patients has

Fig. 3. a Axial stereotactic representation defining PSA target location (circle) and relationship with surrounding structures. b Sagittal stereotactic image showing matching anatomical structures in the subthalamic region and topographic location of Zi and RAPRL (triangle). Cp.i.p = Internal capsule; RAPRL = prelemniscal radiation; Ni = substantia nigra; Zi = zona incerta; Lm = medial lemniscus; H2 = lenticular fasciculus.
### Table 2. Summary of PSA DBS settings and outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulation parameters (mean)</th>
<th>Side effects</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitagawa et al. [23], 2000</td>
<td>Bipolar stimulation: 3–5 V, 120–130 Hz, 50–100 μs Cathode 0, anode 1 Stimulation adjusted according to the needs of each patient</td>
<td>Slight paresthesia, palm hyperhidrosis, anorexia, and disequilibrium Side effects were transient and were eliminated by adjustments of the device parameters</td>
<td>Stimulation abolished severe postural tremor in proximal ET patient, and markedly reduced it in DT patient Improvement only observed during stimulation Dystonia reduced in DT patient, improved walking and speech Both able to use affected hands (right) effectively</td>
</tr>
<tr>
<td>Hooper et al. [33], 2001</td>
<td>Intraoperative stimulation using a Radionics stimulator: 2.5 V and 100 Hz Microthalamotomy effect provided complete suppression of movement disorder. IPG not required</td>
<td>Postoperative shoulder weakness No postoperative thalamic hemorrhage or edema</td>
<td>Tremor rating scale: 78% disability to 21% disability 16 months postoperatively Movement disorder abolished – patient was able to live independently Continued benefit at 44-month reassessment</td>
</tr>
<tr>
<td>Velasco et al. [16], 2001</td>
<td>Bipolar stimulation utilizing various contact combinations compared: 2.8±1.3 V, 130 Hz, 232±115 μs Contact 1 = upper mesencephalon between Rn and substantia nigra Contact 2 = Raprl Contact 3 = VC thalamus in 2 patients and VIM thalamus in 3</td>
<td>Paresthesias contralateral to stimulation with retraction of neck and shoulder Dysarthria, not detectable on examination Worsening of pre-existent depression and transient diplopia</td>
<td>Significant improvement on UPDRS 3, 9, and 12 months after surgery Significant, long-lasting decrease in tremor and rigidity in contralateral extremity, no change in ipsilateral tremor/rigidity Improvement in tremor was nearly complete in most patients</td>
</tr>
<tr>
<td>Murata et al. [34], 2003</td>
<td>Monopolar stimulation: 1.99 V, 130 Hz, 60 μs Contacts utilized not stated</td>
<td>Paresthesia induced with stimulation voltage applied through contacts near the medial lemniscus Limb ataxia induced via stimulation voltage applied through contacts in VIM</td>
<td>Average improvement of 81%; range = 65–100% All 5 patients with severe disturbances in writing ability experienced improvement to legible writing Voice, neck, and/or orthostatic axial tremor in 3 patients all improved with unilateral stimulation</td>
</tr>
<tr>
<td>Nandi and Aziz [35], 2004</td>
<td>Stimulation settings not stated</td>
<td>Out of 15 patients: 1 transient hemiparesis 1 episode of seizure 1 mild dysarthria 2 cases of wound infection</td>
<td>444.5 days mean follow-up 63% improvement in postural component 36% improvement in intention component</td>
</tr>
<tr>
<td>Plaha et al. [36], 2004</td>
<td>Monopolar stimulation: 1.8±0.1 V, 170.0±11.5 Hz, 108.8±14.4 μs Contacts 2 and 6 utilized</td>
<td>No procedure-, device-, or stimulation-related complications reported</td>
<td>Fahn-Tolosa-Martin tremor rating scale – overall scores 80.1% improvement from baseline Very significant improvements in upper limb tremor – both postural and action components, as well as complete arrest of head tremor in 2 patients 88.8% improvement in ADL score Tolerance to action component of tremor was not seen All patients weaned off antitremor medications</td>
</tr>
<tr>
<td>Kitagawa et al. [37], 2005</td>
<td>Monopolar stimulation: 2.3±0.4 V, 132.5±2.7 Hz, 86.3±10.6 μs All contacts tested for clinical efficacy – contact negative, case positive, contact with the best therapeutic window selected</td>
<td>Transient hand paresthesia upon device activation, lasting seconds Blurred vision with stimulation amplitude more than 3 V (1 patient)</td>
<td>24-month postoperative improvements: UPDRS-III improvement of 44.3% Contralateral tremor by 78.3% Contralateral rigidity by 92.7% Contralateral akinesia by 65.7% No effect on postural instability</td>
</tr>
<tr>
<td>Study</td>
<td>Stimulation parameters (mean)</td>
<td>Side effects</td>
<td>Results</td>
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<tr>
<td>Plaha et al. [38], 2006</td>
<td>Monopolar and bipolar stimulation utilized: 2.71 V, 149.6 Hz, 82.2 μs STN/cZi target = middle of the second contact (contact 1 or 5) Dorso-medial/medial to STN target = middle of the third contact (contact 2 or 6) Optimal contact for monopolar stimulation was usually the third contact (contact 2 or 6) and sometimes the second (contacts 1 or 5) Optimal contact for bipolar stimulation was the most proximal contact (contact 2 or 6)</td>
<td>No surgery- or device-related complications Bilateral stimulation of active contacts dorso-medial/medial to STN resulted in reversible hypophonic, slurred speech and a sense of disequilibrium. Possible encroachment on PLR.</td>
<td>High-frequency stimulation of the cZi resulted in greater improvement in contralateral motor scores than stimulation of the STN 93% improvement in the cZi group 61% improvement in the STN group 86% improvement in the group dorso-medial/medial to the STN</td>
</tr>
<tr>
<td>Freud et al. [39], 2007</td>
<td>Bilateral bipolar stimulation using square pulses: 4.2 V, 130 Hz, 90 ms impulse duration Cathode = proximal poles (contacts 3 and 7) Anode = distal poles (0–2 and 4–5)</td>
<td>No procedure-, device-, or stimulation-related complications reported</td>
<td>Patient regained functional state prior to rapid disease progression. Marked improvement in sitting, communicating, writing, painting, swallowing, etc. Postoperatively, no postural, head or chin tremor present, but some residual IT. Parenteral feeding tube removed, but continued need for urinary catheter. Condition remained stable for over 2 years postoperatively.</td>
</tr>
<tr>
<td>Hamel et al. [19], 2007</td>
<td>2.0–3.6 V, 130–145 Hz, 60 μs In general, distal electrode contacts were more effective than proximal contacts Most effective tremor suppression was achieved at or below the intercommissural plane</td>
<td>No procedure-, device-, or stimulation-related complications reported</td>
<td>Fahn-Tolosa-Martin tremor rating scale – overall 80% improvement of IT. Most effective tremor suppression (&gt;75% postoperative improvement) was achieved at or below the intercommissural plane. No specific differences between patients reported.</td>
</tr>
<tr>
<td>Herzog et al. [40], 2007</td>
<td>ET: 2.2 V, 130 Hz, 60 μs MS: 2.7 V, 148.2 Hz, 81.2 μs Each contact was utilized; stimulation of contacts below the thalamic border significantly more effective than above</td>
<td>No procedure-, device-, or stimulation-related complications reported</td>
<td>The average reduction of the preoperative tremor rating scale in all patients was 55.9 ± 4.4%, in ET patients 64.2 ± 4.4%, and in MS patients 50.4 ± 3.1% Most effective contacts clustered within the STA covering the posterior Zi and PLR. Stimulation within this region led to a mean reduction of the lateralized tremor rating scale by 15.8 points which was significantly superior to stimulation within the thalamus (p &lt; 0.05, Student’s t test).</td>
</tr>
<tr>
<td>Carrillo-Ruiz et al. [22], 2008</td>
<td>2.5–4.0 V, 90–330 μs, 130 Hz Deepest contacts were used as the cathode</td>
<td>1 patient – worsening of pre-existing emotional depression leading to 11-kg weight loss in 6 months; amplitude of stimulation had to be asymmetrically decreased for improvement 1 patient – dysarthria with slurred speech and dizziness, which was resolved with a decrease in stimulation amplitude by 1 V; this patient had the deepest placement of contacts</td>
<td>UPDRS-III improvement was analyzed with respect to each symptom: Tremor improved in 90% of patients Rigidity improved in 94% of patients Bradykinesia improved in 75% of patients. Akinetia improved in 50% of patients. Postural stability was improved in 35% of patients and was only significant at 6 months. Gait improved in 40% of patients, with only the initial 6 months being significant.</td>
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<td>Plaha et al. [14], 2008</td>
<td>PD: 2.74±0.42 V, 145.1±21.76 Hz, 93.3±18.3 μs Non-PD: 2.48±1.04 V, 147.14±25.63 Hz, 120±42.42 μs MS: 1.9 V, 40 Hz, 210 μs Active contacts were reported in coordinates</td>
<td>1 surgery-related complication – 3-month transient dysphagia due to error in frame relocation 2 patients developed transient stimulation-related disequilibrium lasting 8–10 weeks after surgery 1 MS patient experienced prolonged lethargy and reduced mobility postoperatively</td>
<td>Fahn-Tolosa-Martin tremor rating scale – baseline vs. 12-month total score improvements: PD = 94.8% PT = 88.2% ET = 75.9% HT = 70.2%, CT = 60.4% MS = 57.2% DT = improvement in both the dystonia and the tremor.</td>
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### Table 2 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulation parameters (mean)</th>
<th>Side effects</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Blomstedt et al. [20], 2009</td>
<td>DT 1: monopolar stimulation at contact 0: 2.1 V, 185 Hz, 60 μs DT 2: n.a. – pronounced, sustained microlesion effect; IPG explanted Writer’s tremor: bipolar stimulation with contact 0 negative and contact 1 positive: 2.8 V, 185 Hz, 60 μs CT: bipolar stimulation with contacts 1 and 2 negative, and 3 positive: 6.3 V, 145 Hz, 90 μs NT: bipolar stimulation with contacts 1 and 2 negative, 3 positive: 3 V, 185 Hz, 60 μs</td>
<td>No severe complications occurred Blurred vision and diplopia Pronounced microtomy effect after introduction of the electrode into PSA led to removal of 1 IPG</td>
<td>Mean improvement on stimulation after 1 year was 87% Pronounced microlesion effect in several patients – mean off stimulation improvement of 56% The 2 DT patients became free of dystonic symptoms and pain in the treated arm</td>
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<td>Blomstedt et al. [41], 2010</td>
<td>5 weeks postoperatively: 2.0 ± 0.7 V, 163.9 ± 21.8 Hz, 62.7 ± 8.6 μs 1 year postoperatively: 2.5 ± 0.8 V, 165 ± 21 Hz, 61 ± 6 μs Initially 15 (65%) patients had monopolar stimulation, which after 1 year increased to 78%</td>
<td>No hemorrhages or infections to report Transient mild expressive dysphagia in 8 patients Revision of extension cable due to strain in neck was performed in 2 patients</td>
<td>Total TETRAS reduction of 12% off stimulation (46.2 ± 10.1 to 40.6 ± 12.7) Total TETRAS further reduction of 60% on stimulation (18.7 ± 8.8) Decrease most pronounced concerning tremor of the contralateral upper extremity – reduction of 95% (6.2 ± 1.8 to 0.3 ± 0.6) Reproduced in the assessment of the contralateral hand function – tremor reduction of 87% (9.7 ± 3.6 to 1.3 ± 1.5) Part C of the TETRAS, ADL (items 15–21), improved from 12.5 ± 3.5 before surgery to 4.3 ± 4.6 (66%) on stimulation</td>
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<td>Barbe et al. [42], 2011</td>
<td>3 V, 130 Hz, 60 μs Active contacts were variable by patient, no specific contacts were reported to be superior</td>
<td>General encountered side effects = dysarthria and ataxia, controlled with optimized stimulation parameters Stimulation below ICL caused permanent contralateral paresthesia (3 electrodes), stimulation-induced dysarthria (2 electrodes)</td>
<td>Within-subject comparison with equal parameter settings revealed sub-ICL stimulation to be superior to thalamic stimulation Data analysis suggested sub-ICL stimulation may be more efficient than thalamic stimulation, but equally effective when individualized stimulation parameters are utilized</td>
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<td>Blomstedt et al. [43], 2012</td>
<td>Stimulation settings not stated</td>
<td>No procedure-, device-, or stimulation-related complications reported</td>
<td>Prior to reoperation, VIM DBS improved hand function and tremor in treated hand by 25%, whereas cZi DBS achieved 57% improvement cZi was more efficient than VIM DBS in controlling ET Patients with late failure of VIM DBS (after several years of good effect) still exhibited considerable residual tremor</td>
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<td>Blomstedt et al. [44], 2011</td>
<td>cZi: 1.4 V, 171.7 Hz, 60 μs Most effective contacts for each patient: (+0, –1), (–0), (–1), (–1) STN: 2.2 V, 173.8 Hz, 60 μs Most effective contacts for each patient: (–0), (–0), (–1), with patient 1 not reported</td>
<td>cZi leads: arm dystonia, dysarthria, paresthesia, dizziness and blurred vision STN leads: arm dystonia, dizziness, dysarthria</td>
<td>STN and cZi both proved to be potent targets for DBS in ET DBS in the cZi was more efficient, since the same degree of tremor reduction could here be achieved at lower energy consumption Three patients became tremor free in the treated hand with either STN or cZi DBS, while the fourth had a minor residual tremor after stimulation in either target</td>
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### Study Stimulation parameters (mean) Side effects Results

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<td>Blomstedt et al. [45], 2012</td>
<td>2.6±1.0 V, 159.7±26.4 Hz, 66.0±12.4 μs</td>
<td>1 patient suffered infection at the incision site above burr hole 4 weeks following surgery; the electrode had to be explanted with a new one implanted 3 months later 1 patient had suboptimal effect due to stimulation-induced side effects, specifically gait disturbance in the contralateral leg – likely due to inappropriate lateral placement of electrode causing stimulation of internal capsule</td>
<td>Total UPDRS-III on stimulation/off medication improved by 32.5% (p ≤ 0.001) compared to the off-medication/off-stimulation state Contralateral UPDRS-III improved by 47.7% (p ≤ 0.001) Contralateral tremor, rigidity, and bradykinesia were improved by 82.2% (p ≤ 0.001), 34.3% (p ≤ 0.05), and 26.7% (p ≤ 0.001), respectively Action tremor and tremor at rest of the hand and arm improved by 80.0% (p ≤ 0.001) and 87.1% (p ≤ 0.001), respectively Tremor at rest was totally eliminated in 10 (66.7%) and action tremor in 8 of the patients (53.3%) The 5 non-L-dopa responders improved by 82.5% (p ≤ 0.05) for tremor, 15.4% (p = n.s.) for rigidity and 28.8% (p = n.s.) for bradykinesia</td>
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<td>Kobayashi et al. [46], 2014</td>
<td>Bipolar mode used for stimulation in both leads 135 Hz, 0.21 μs Voltage of stimulation was increased until an upper limit was found with the emergence of adverse side effects Average location of the optimal cathode contact: 6.4 ± 0.5 mm posterior to MCP, 2.9 ± 0.8 mm inferior to AC–PC line, 10.9 ± 0.6 mm lateral to midline</td>
<td>Upper limit of stimulation voltage elicited paresthesia and/or muscle contractions</td>
<td>Stimulation with 2 electrodes exerted greater effect than did 1-electrode stimulation Tremor was improved in all patients for more than 2 years Multitarget, dual-lead stimulation may permit coverage of a wider area of stimulation necessary for HT patients</td>
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<td>Mehanna et al. [47], 2014</td>
<td>Patient 4 Raprl stimulation: 1–, 3+ 3.9 V, 135 Hz, 90 μs Patient 5 Raprl stimulation: C(+)–, 1– 2.5 V, 130 Hz, 90 μs</td>
<td>No procedure-, device-, or stimulation-related complications reported</td>
<td>After implanting a second DBS lead ipsilaterally to the first in the VIM, the authors found an overall clinical improvement in refractory tremor patients, which did not reach statistical significance Patient 4 (ET) improved with both the VIM and ipsilateral Raprl implants active, but not with just the Raprl contacts active Patient 5 (MS) did not improve with either both active or just Raprl The authors concluded that the secondary implants in the VOA (patients 1–3) may yield better results compared to secondary PSA implantation (patients 4 + 5), but stated future larger studies are needed</td>
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<td>Sitsapesan et al. [48], 2014</td>
<td>Patient 1: case(+), 3(−) (monopolar); 2.0 V, 90 μs, 130 Hz Patient 2: 3(+), 2(−); 2.5 V, 90 μs, 130 Hz Patient 3: 9(−), 10(+); 3.0 V, 210 μs, 100 Hz Patient 4: 4(−), 6(+); 1.5 V, 90 μs, 130 Hz Patient 5: 5(−), 7(+); 2.3 V, 210 μs, 180 Hz Patient 6: 3(+), 2(−); 3.6 V, 360 μs, 130 Hz Patient 7: 0(−), 2(−); 2.6 V, 300 μs, 130 Hz Patient 8: 1(+), 3(−); 3.3 V, 156 μs, 130 Hz</td>
<td>Patient 2: exacerbation of pre-existing gait ataxia if amplitude exceeds 3.3 mA Patient 7: postural tremor appeared with arm bent and on intention; right leg heaviness and dragging of leg when walking Patient 8: transient pins and needles on changing settings</td>
<td>All 6 patients with preoperative and on stimulation assessments showed mean 69.13% reductions in tremor severity across the 5 components of the Bain scale Across all 8 patients, there was an overall reduction of tremor severity by 80.75% following stimulation All 5 tremor elements showed significant reduction in the on-stimulation condition compared with preoperative levels All patients were said to experience some degree of functional benefit. Three regained the ability to write legibly. Three others regained the ability to hold a cup of fluid</td>
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</table>
been described as a distinct marker for the PSA [20].

Macrostimulation to determine tremor control and threshold for side effects is conducted in most centers. Speech difficulties, paresthesias or muscle spasms due to corticospinal side effects are the most common adverse effects. As motor fibers project anteriorly and laterally as they reach the AC-PC line, dysarthria or muscle spasms are commonly encountered at lower voltages with uppermost contact (based on common double oblique trajectory angle). Although not consistently studied in the literature, we advise caution for thresholds below 2.0 V utilizing a pulse width (PW) of 60 μs and a frequency of 180 Hz as programming can be compromised by the occurrence of side effects.

**DBS Programming Considerations**

There is great variability in the selected frequencies, PW, electrode selection and programming paradigms used to deliver chronic neuromodulation. The optimal programming contacts depend of several factors including specific tremor syndrome and more importantly lead location within the PSA (table 2). It is important to note that lead selection [1.5 mm (3387) versus 0.5 mm (3389) spacing between each of the 4 electrode contacts] and the patient’s individual anatomy influence the selection of programming settings for benefit and to avoid adverse effects. Unfortunately, most series do not provide specific details of the active contacts utilized, and systematic assessment is not plausible. Both monopolar and bipolar stimulation have been reported. Authors have suggested that the tremor target extends from a narrow area in the brainstem to progressively increase in size as it approaches the level of the intercommissural line [16]. The most common programming approach is to use bipolar stimulation with a PW of 60 μs and frequencies ranging from 130 to 180 Hz. This is not surprising when considering the size of the PSA proper and the close proximity to other anatomical landmarks.

When compared with the typical electrical charge necessary to achieve tremor suppression with thalamic stimulation in essential tremor, Holmes tremor or dystonic tremor, a smaller amount of stimulation is required in PSA for tremor suppression. There are no reports utilizing lower frequency stimulation except in 1 patient with multiple sclerosis (MS) tremor reported by Plaha et al. [14]. Patients with nonparkinsonian tremors also re-
qured a slightly higher PW for tremor suppression. A wide range of PW has been utilized (from 60 to 330 μs) with a median of 105 μs. In 15 PD cases, PW up to 330 μs were reported. Overall, the mean improvement in tremor control with PSA DBS is approximately 79%. There is a great variability reported in outcome measures and follow-up ranging from tremor scales to subjective improvement. Intention tremor and tremor response in MS tremors are less robust with approximate 50–60% improvement. Paresthesias are the most common induced adverse effects due to stimulation of the medial lemniscus. If paresthesias are encountered, the use of bipolar stimulation to minimize spreading to the nearby medial lemniscus can be entertained. Additionally, using a more dorsal contact (located slightly more anterior and lateral based on DBS approach angles) can minimize posterior (sensory) side effects as long as tremor efficacy is not compromised.

Dysarthria, transient diplopia, disequilibrium and ataxia are also common and likely represent stimulation of the internal capsule, Rn and nearby cerebellar fibers, respectively. A small number of patients reported onset of depression possibly due to stimulation of the limbic STN or substantia nigra reticulata. In the largest series assessing side effects, Fytagoridis and Blomstedt [21] reported the occurrence of mild postoperative dysphasia, which regressed completely within 1 day to 5 weeks postoperatively in 22% of their cohort. Carrillo-Ruiz et al. [22] reported development of somnolence lasting from a few hours to 2 days after bilateral prelemniscal radiation DBS in PD. Because of the heterogeneous nature of current reports regarding programming settings, outcome measures, or postoperative lead locations, the predictive value of targeting coordinates or programming paradigms cannot be correlated with outcomes at this time.

Discussion

PSA DBS appears to be a safe and effective target for the treatment of a variety of tremor syndromes with clinical benefits comparable to other stereotactic targets. Because of the heterogeneity of reports and conditions reported, comparison of clinical benefits between PSA and thalamic stimulations is impractical. Nevertheless, despite the intrinsic limitations with reported studies, PSA DBS provides statistically superior tremor benefit compared with other targets, and further studies to validate the efficacy and candidacy for this target are warranted. Patients with secondary or symptomatic tremors commonly display additional neurological signs or features refractory to standard VIM stimulation [14, 23]. Proximal involvement, associated dysmetria and cerebellar findings, severe intention tremor, spasticity, rigidity, or dystonic features are regarded as the major source of disability and an important factor when considering surgical alternatives. Although thalamic DBS might have a role in the treatment of tremor in patients with cerebellar ataxia, reports have highlighted inconsistent responses, short-term benefit and worsening balance and gait [24, 25]. Intention tremor is clinically defined as a tremor with increasing amplitude during movements towards a target, and it is representative of cerebellar dysfunction and as such difficult to separate from other features like proximal postural instability or limb dysmetria. Although limited by the small number of patients and follow-up, PSA DBS provided functional improvement and marked tremor benefit in cerebellar tremor patients without reports of worsening cerebellar features or gait.

MS tremor is manifested on action as postural tremor and/or intention tremor (occurring during target-directed movement where tremor amplitude increases during visually guided movements towards the target) [26], and severity correlates with the degree of dysarthria, dysmetria, and dysdiadochokinesia [27]. MS tremor typically involves the proximal upper limbs with low-frequency postural tremors. Thalamic DBS has demonstrated limited benefit in MS tremors with variability in tremor reduction and loss of benefit or tolerance over time [28]. Additionally, an extended follow-up in patients with MS tremor showed transient benefit for severe tremor (median 3 months), with poor long-term prognosis [29]. PSA stimulation provides a theoretical advantage for the treatment of proximal tremors. Because the fibers and neurons are more widely dispersed in the VL and VIM than in the PSA, it may not be easy to control the neural activity related to tremor on proximal and/or distal parts of the upper and lower extremities by applying stimulation through a larger area of stimulation located in the thalamus. Superior suppression of intention tremor in the subthalamic region has been related to the fact that proximal muscle groups (paraspinal, limb girdle) used for locomotion, reaching, and axial movements are rather controlled by upper brainstem structures, whereas the predominant control of distal muscles is exerted by thalamocortical pathways [19]. Furthermore, increasing evidence shows that the cZI is responsible for the generation of axial and proximal limb movements including locomotion [30, 31]. Some authors support the idea that DBS may mainly act by affecting efferent fibers (i.e. presynaptic informa-
tion), thereby stopping the input into thalamic cells which in turn might lead to tremor suppression [32]. PSA DBS has been reported to be effective for MS tremor with a mean improvement of 57.25% with no reports of tolerance or other worsening symptoms. In addition to effects on tremor control, PSA DBS has been found to be effective in controlling rigidity and bradykinesia in PD. The limited number of cases reported limits the comparison with STN or globus pallidus internus DBS. Finally, the effect of PSA DBS on axial symptoms including vocal, head, face, tongue tremors, dysarthria, or swallowing functions is rarely reported with some authors reporting benefits in axial tremors.

Conclusions

Albeit the initial results are encouraging, comparative studies among different DBS targets are needed to determine the specific advantages and effectiveness of different targets. PSA DBS should be considered in patients with refractory tremors with associated cerebellar or dystonic features, proximal tremors and MS tremor as it provides theoretical and clinical advantages to thalamic DBS. The long-term effect of PSA stimulation is not known and validated, and objective instruments to assess complex tremor or syndrome outcomes including quality of life are also necessary.

References
Evolving Concepts in Posterior Subthalamic Area Deep Brain Stimulation


