Emerging Targets for Stimulation-Refractory Movement Disorders

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Abstract: Deep brain stimulation has proven an effective addition to the optimized medical management of some primary movement disorders. Sustained symptomatic improvement has been demonstrated for Parkinson's disease, forms of dystonia, and essential tremor. However, despite dramatic improvements in the tremor, rigidity, bradykinesia, and dyskinesias of Parkinson's disease, DBS of the STN and GPi have provided inconsistent relief of gate abnormalities and freezing. Similarly, DBS of the Vim has proven effective for distal tremors resulting from a variety of etiologies, but has limited efficacy for tremors with proximal spread. Accumulating clinical, neurophysiologic, and neuroanatomic evidence supports the pedunculopontine nucleus as a modulator of postural control and gait initiation. Further, both historical and contemporary preclinical and clinical data support the zona incerta and prelemniscal radiations as targets within the greater subthalamic area for tremor containing proximal spread. On the basis of these observations, there is considerable interest in PPN DBS for control of gate abnormalities in PD, and in ZI and PRL DBS as a means for modulation of pronounced tremor with axial involvement. The clinical evidence for consideration of the PPN and ZI/PRL as alternate stimulation targets for treatment of refractory movement disorder manifestations is reviewed.

Keywords: Deep brain stimulation, tremor, gait freezing, patient selection, targeting, zona incerta, prelemniscal radiations, pedunculopontine nucleus.

INTRODUCTION

Parkinson's disease carries both a variety of motor manifestations and a high prevalence compared to other primary movement disorders [1, 2]. These features make PD a model disease for the study of alternate therapies and targets for movement disorder treatment. One of the major motor symptoms of PD is a fine resting tremor that may ultimately progress to contain postural and action components with pronounced axial involvement. The latter may also be observed in either advanced forms of essential tremor or can be the result of other pathologies (e.g. multiple sclerosis, cerebellar lesions). Dopamine agonists, precursors, breakdown inhibitors, and cholinesterase inhibitors temporarily reverse or slow symptomatic progression of these motor findings. However, approximately 10% of PD patients present with symptoms (e.g. freezing, postural instability) that often respond poorly to current dopaminergic medical therapies [3, 4]. The has been postulated to result from pathologic changes to non-dopaminergic pathways [5, 6]. However, even the majority of PD patients which present with DOPA responsive symptomology often eventually become medically refractory. This is due to a combination of disease progression, development of dose-limiting toxicities (e.g. dyskinesias, hallucinations), and tolerance to prolonged medical treatment. The eventual inability to control both DOPA-responsive and non-DOPA responsive symptoms has a significant impact on both quality of life measures and cost of care as functional capacity and ambulation become progressively impaired [7, 8]. Therefore, both scenarios warrant consideration of a surgical neuromodulatory intervention, deep brain stimulation.

STN-DBS has proven an effective adjunctive treatment for medically refractory PD patients, especially when tremor predominant. However, gate instability is often either refractory to DBS or initial improvement may diminish even when in an optimized 'on' state [9]. Therefore, exploration of alternate targets is necessary both to achieve improved functional gains as well as to better understand movement disorder pathophysiology. An accumulating body of data supports rigorous clinical evaluation of the pedunculopontine nucleus as a modifiers of gait freezing and postural instability, while targets within the 'greater subthalamic area' (e.g. zona incerta, prelemniscal radiations) appear effective for advanced tremor with proximal involvement. This review will explore the evidence for use of these targets.

PRELIMINARY CLINICAL EXPERIENCES

The Pedunculopontine Nucleus

Multiple lines of evidence have coalesced around the PPN as a participant in neural networks responsible for modulation of gait. Post-mortem human histopathological studies studies have demonstrated reductions in both neuronal cell number and density in a variety of neurodegenerative conditions, including: Parksinson's disease, progressive supranuclear palsy, and Alzheimer's disease [10-13]. Studies assessing the complex anatomic connectivity of the PPN, as well as the functional implications of this connectivity, have spanned both multiple modalities and species. Cytoarchitectural/immunohistochemical [14-19] and anterograde/ retrograde tracing studies [20-22] have allowed identification of anatomically and neurochemically distinct ascending/ descending inputs/outputs as well as distinct cholinergic and

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dopaminergic neuronal subpopulations that are shared between species [23, 24]. Further, recent diffusion tensor imaging tractography studies have shown significant homology between the functional connectivity of the PPN in primates and lower mammals [25]. These findings have also been generalizable to healthy human controls [26-28].

The role of PPN in gait, suggested by anatomic data, has been corroborated by multiple functional stimulation studies undertaken in feline and rat small animal studies as well as in primate studies. Lesions or functional inhibition of the pedunculopontine nucleus result in akinesia in both rats [29, 30] and primates [31, 32]. By contrast, chemical and electrical stimulation has been shown to drive locomotor activity in rat [33], feline [34-36], and primate studies [37-39]. Recently, it has been demonstrated that the effects are additive to levodopa therapy after use of the dopaminergic neuron-specific toxin MPTP in primates [40]. This supports a role for cholinergic neuronal subpopulations as participants in PPN-regulated locomotor activity. The broad consensus of data supports similarities in anatomic and functional connectivity between small animals, primates, and humans. Translational data supports the benefit of chemical- and stimulation-based activation of the PPN in small animals and primates after lesioning or functional inhibition. Together, these data have provided the background for clinical investigation of the PPN in movement disorders characterized by gait disturbances and postural instability.

Stimulation Outcomes

Only a limited number of investigators have translated the preclinical findings supporting evaluation of PPN stimulation with published reports examining safety, targeting, and outcomes. In 2005, both Mazzone *et al.* [41] and Plaha & Gill [42] published the first reports assessing human PPN implantation. Both groups assessed bilateral PPN placement with the intent of addressing 'negative' motor manifestations, each in two patients diagnosed with PD of greater than ten years' duration. Mazzone assessed clinical improvement intra-operatively in a PPN-only stimulation setting and only with selected UPDRS III items. These included: hand grip, finger tapping, and upper extremity rigidity. Greatest improvement was observed at low frequency (2V, 10Hz). The results from Plaha & Gill [42] corroborated these findings with optimal stimulation parameters of (2.5V, 20Hz; 4V, 25Hz) observed at follow-up conclusion of sixteen and forty-two days. A reduction of medication usage was observed as was global UPDRS and UPDRS II-III subsection improvement in both on- and off- medication states. The authors accounted for a possible microlesional effect in the post-operative period by using post-op stimulation-off scores as a baseline UPDRS comparator.

In subsequent work, Stefani *et al.* [43] followed a larger group (n=6) with bilateral STN-PPN electrode implantation for a period of six months. Over this period, a rigorous testing paradigm assessed functional outcomes during on- vs. off-medication states and in STN + PPN, PPN-only, and STN-only stimulation. Clinical assessment of each setting began at three months, described by the authors as the earliest post-operative time point at which PPN-only stimulation clinical outcomes scores stabilized. In both off- and on-medication states, all stimulation combinations improved both UPDRS III global and subsection scores. When 'off', STN+PPN and STN-only stimulation had a significantly greater global UPDRS III reduction than PPN-only stimulation. In the UPDRS III subsection score, a significant difference was not detected between the three stimulation combinations. When in an 'on'-state, PPN+STN DBS stimulation had a greater impact on the UPDRS III global and subsection score than either PPN or STN stimulation alone. Finally, a durable improvement in 'on-' state ADLs, as assessed by both the Schwab & England score and UPDRS II, was seen at three and six months. This improvement was greater for STN+PPN than STN-only stimulation. Together, this data extends prior pilot findings, demonstrating durable long term benefit with low frequency stimulation. The same authors, Mazzone *et al.* [44], have more recently extended their initial patient population presented above to (n=13) patients with the latter six all receiving image-guided electrode replacement, given concerns for variations in brainstem anatomy associated with increasing age, as described above.

Though data was not presented, the authors additionally commented on observance of similar clinical improvement with either unilateral or bilateral PPN implantation. For this reason, five of the latter six patients received unilateral PPN implantation. Contemporaneously, Pereira *et al.* [45] also reported a lack of evident improvement with bilateral vs. unilateral PPN stimulation. When tracking what they felt were the only relevant measures presented on the UPDRS and subsection III questions, these authors followed average falls, near falls, and gait freezes. Corroborating above reports, data from a single patient at a two week follow-up supported optimal symptom improvement at 20Hz.

Ferraye *et al.* [46] have completed a prospective study of bilateral PPN+STN stimulation in (n=6) patients with advanced Parkinson's Disease that had previously received STN implantation. After stimulation parameter optimization, patients were randomized and received double-blinded assessment when in an on-vs. off- stimulation state between months three and six months with final follow-up at one year. Gait outcomes were assessed with a composite of specific UPDRS II and III subscores, the use of a 'walking' protocol in which freezing was assessed after provocation with appropriate stimuli. Patients also received neurocognitive and neuropsychiatric assessment. At final follow-up, the number of off-drug falls and duration of freezing episodes was reduced. No additional differences were detected between baseline and final follow-up, including: between on/off stimulation or on/off drug therapy during the double-blinded portion of the study. Isolated improvements in freezing with individual patients resulted in postulation that PPN stimulation may be optimized for patients with freezing but without other axial dysfunction impairing gait. Most recently, Moro *et al.* [47] have completed the first prospective double-blinded study assessing unilateral leads implantation into six patients with advanced PD. The authors followed UPDRS subsection scores for one year. Only falling (UPDRS II Item 13), but not other aspects of postural stability or gait, was improved at both three months and one year in both off- and on-medication states. Unique as compared to prior studies, the authors chose to stimulate at higher frequency (50-70Hz).

Targeting Approaches and Coordinates

While Mazzone and colleagues initially implanted both STN and PPN guided by intraoperative neurophysiology, Plaha *et al.* [42] used MRI-based placement of guide tubes to implant only the bilateral PPN. Both employed a transfrontal targeting approach parallel to the aqueduct of sylvius for PPN localization. Intraoperative neurophysiologic observations made by Mazzone *et al.* [41] supported the ability to distinguish between the dorsal PPN, SNpr, and the targeted lower PPN. However, an inability to: 1) detect electrical startle reflex activity with acoustic stimuli, 2) detect PPN subnuclei populations based upon expected firing patterns, or 3) observe expected PPN response to simultaneous STN stimulation were unexpected given findings in prior animal work. The lack of functional neurophysiologic targeting correlation was attributed either to disease-specific pathophysiologic changes or sample bias given the small number of overall recording tracks (n=4 tracks, 2 patients). The latter appears more likely as Weinberger *et al.* [48] have recently reported observance of expected 'bursty' firing patterns and change in firing rate with active or passive contralateral limb movement when performing human PPN microelectrode recordings.

In the following (n=13) patients reported by Mazzone and colleagues [44], the first (n=6) used intra-operative neurophysiology to guide placement [43]. The remaining patients received neuroimaging-guided electrode implantation. This was prompted by the authors' observance of inter-individual anatomic brainstem variation and targeting discrepancies between pre-operative neuroimaging and commercial stereotactic atlases. Given variations in brainstem anatomy observed to increase with age, they concluded that traditional atlas and neurophysiology-driven techniques were less optimal for brainstem nuclei localization than 'direct' stereotactic targeting strategies using intra-operative image guidance. The most recent studies, completed by Ferraye *et al.* [46] and Moro *et al.* [47], both relied on stereotactic MRI to define electrode trajectory. The former used contrast ventriculography to augment target localization while both used microelectrode recording. The mean coordinates and a summary of the approaches used in each of these studies is provided in Table **1**.

Tentative Conclusions

These early studies have provided proof of principle data supporting the safety and feasibility of human PPN targeting. Importantly: 1) none of these early reports indicates a serious adverse event related to electrode placement; 2) adverse stimulation effects were noted to rapidly extinguish with reduction in stimulation voltage and mostly resulted in temporary paresthesia that rapidly extinguished after stimulation was initiated [43] or low frequency ipsilateral voltage-limiting oscillopsia [49]; 3) most corroborate the presence of a modest worsening of motor scores with frequencies above approximately 30-60Hz with optimal improvement at approximately 20Hz (with the notable excpetion of Moro *et al.* [47]); 4) none endorse the presence of neurocognitive or neuropsychiatric worsening during follow-up, and; and 5) initial outcome data supports further prospective study of unilateral-only PPN implantation with suggestion that benefit may be greatest with reduction in number of falls and episodes of freezing. Nevertheless, one of the greatest shared weaknesses is the predominant reliance upon UPDRS and UPDRS subsection scores to assess clinical improvement. While this clinical scale is often used in the PD literature, it was not designed to assess nuanced improvements in postural stability and gait. Direct assessment of stimulation on the frequency of these symptoms in future studies, as by Periera *et al.* [45] and Ferraye *et al.* [49], will provide a more accurate rubric for the effectiveness of PPN DBS and a better comparator when treating gate instability and freezing. This will become increasingly important as the PPN is co-assessed with alternate targets to the STN. This has occurred most recently with co-implantation of the PPN and ZI where Khan *et al.* [50] have demonstrated an additive effect to UPDRS motor sub-score improvement with co-stimulation.

Posterior Subthalamic Area Targets: The Prelemniscal Radiations & Caudal Zona Incerta

The published historical clinical experience of subthalamic lesioning procedures for treatment of refractory tremor came to encompass well over a thousand patients during the 1960s and 1970s. These largely targeted the zona incerta, prelemniscal radiations, and some examined the fields of Forel [51-55]. During the height of lesional stereotactic subthalamic surgery, the effectiveness of long-term stimulation extended to reports of treatment for torticollis (n=7) [56], MS-related tremor (n=2) [57], and post-traumatic tremor (n=1) [58]. Following this period, a relative silence within the literature lasted for almost the next two decades. This has been attributed to both skepticism of the results within the early literature as highly optimistic and a concern regarding the sometimes severe reported complication profiles [59]. Unfortunately, many of the indications being treated in the aforementioned series are still without reliably effective treatments. In light of this unmet need, widespread acceptance of DBS has spurred a new generation of non-lesional exploration and neuromodulation within these 'old' subthalamic area targets. Herein, we have attempted to roughly divide the literature based upon how the authors have defined their intended targets. However, it should be noted both that these targets exist within close anatomic approximation and that both their functional uniqueness and the capability to selectively target between them with current stimulation paradigms is a subject of contemporaneous debate [60, 61].

Zona Incerta Stimulation

The largest contemporary reports specifically targeting the subthalamic area, and more particularly the ZI, have been published by the same group [62-64]. An initial prospective study by Plaha *et al.* [62] examined implantation of leads in a group of (n=35) patients with PD in an attempt to assess optimal targeting for treatment of refractory Parkinsonian symptoms. Targeting included: STN (20 leads), adjacent dorsal/dorsomedial white matter (20 leads), or the caudal ZI (cZI; 27 leads). Over a six month follow-up period, the authors report near sequential improvement (dorsal STN, dorsal/dorsomedial white matter, cZI) in overall UPDRS III score (55%, 61%, 76%), tremor (61%, 86%, 93%), rigidity (50%, 52%, 76%), and bradykinesia (59%, 56%, 65%). As support for the generalizability of their findings, the authors cite an overall 55% UPDRS III improvement with STN

Table 1. Pedunculopontine Stimulation Targeting Approaches and Coordinates

	Indication, Pt # Uni- or Bilateral	**Targeting**		
		Modalities	Approach	Target Coordinates
Plaha & Gill (2005)	PD; n=2 Bilateral	High Res MRI with intraop MRI guide tube placement confirmation; Nieuwenhuys et al. atlas (Figs 96, 100, 101)	Tranfrontal, Parallel to AoS	**Dorsal PPN**: lateral to decussation of SCP on slice through dorsal IC and doral pons **Ventral PPN:** identified on a parallel slice 2.4mm below dorsal border
Mazzone *et al.* (2005)	PD; n=2 Bilateral	Ventriculography, IONP	Transfrontal, Parallel to AoS	Sagittal Plane: 62-65º Coronal Plane: 78-80º 13mm lateral to midline 12.5-13mm below PC
Stefani *et al.* (2007)	PD; n=6 Bilateral	IONP	Transfrontal, Parallel to floor of fourth ventricle and brainstem axis	Sagittal Plane: Not listed Coronal Plane: 80-82 º 9-13mm lateral to midline 12.5 to 13mm below PC
Pereira *et al.* (2008)	PD; n=2 Unilateral	T2 MRI DTI Stereotactic CT	Trajectory along the long axis of the brain-stem from red nucleus to IC incorporating seeded target with electrode.	Delineation of area lat to SCP on T2 MRI. Seeding of target using DTI tractography
Mazzone *et al.* (2008)	PD; n=8 Dystonic PD; n=3 PSP; n=2 Uni-/Bilateral	First Period: non-telemetric ventriculo-graphy evolving to computerized ven-triculography w/o constrast Second Period: CT with superimposition of atlas slides fitted to brainstem borders	Parallel to fhe floor of the fourth ventricle	Similar between periods: 25º in sagittal plane 11-18º in coronal plane
Ferraye *et al.* (2009)	PD; n=6 Bilateral	MRI Contrast ventriculography Imaging to define BCL and floor of 4th ventricle	Trajectory parallel to floor of 4th ventricle; adapted to conform to vessel contraints.	1.5mm posterior to PC 13mm below BCL 6mm lateral to midline
Moro *et al.* (2009)	PD; n=6 Unilateral	3D MRI T1 Inversion Recovery T2 axial sequences Microelectrode recording (passive, active evoked potentials) Spontaneous firing activity & LFP	Not described	Contact 2 in relation to PC Lateral 7.9mm AP -4.4mm Vertical -11.4mm

SCP: superior cerebellar peduncle; IC: inferior colliculus; AoS: Aqueduct of Sylvius; PD: Parkinson's disease; Intra-operative Neurophysiology: IONP; PC: posterior commisure BCL: bicommisural line; DTI: Diffusion Tensor Imaging.

stimulation compared to a range of (50-63%) [65, 66] reported elsewhere. Subsequently, the same group has attempted bilateral implantation and stimulation of the cZI for a broader set of indications [63]. Bilateral stimulation was included for (n=14) patients over a twelve month follow-up period. Etiologies included: ET (6), PD (5), MS (4), and DT & CT & HT (n=1ea). In PD patients, the UPDRS III was used to compare off med/off stim to off med/on stim. Resting and action/postural tremor were reported to improve by a mean 94.8% and 88.2% while rigidity and bradykinesia improved by 77.4% and 66.2%. Additionally, tremor reduction was noted in each of the other conditions, ET (75.9%), MS (57.2%), and HT/CT (70.4%/60.2%). The authors noted improvement in both distal and proximal ET tremor components. These findings are concordant with the results of a prior study from the same group examining electrical stimulation for treatment of ET in (n=4) patients [64]. Using the Fahn-Tolosa-Marín Tremor Rating Scale, they reported an overall 80.1% tremor reduction with A(84.2%), B (67%), and C (88.8%) subsection score improvements at a twelve month follow-up. In this earlier study, the authors were more

broadly targeting "ascending dentate – and interpositus – Vim fibers and part of the ZI".

From these series, no intra-operative complications were observed associated with electrode implantation, credited to the use of imaging-navigated placement with the use of guide tubes. Dysequilibrium and dysarthria were the most common side effects reported from stimulation. Both were reported to be transient. When comparing target locations, the authors felt that both stimulation-related side effects were related to current spread to the prelemniscal radiation, as compared to the more common report of current spread to capsular fibers [62]. In their most recent report, the authors noted peri-electrode edema (n=2) during a transient eight to ten week symptomatic period [63].

Posterior Subthalamic Area Stimulation with Emphasis on the Prelimniscal Radiations

In 2001, Velasco *et al.* [67] published one of the first series in over twenty years assessing the effect of PRL stimulation on tremor. Patients (n=10) with predominately unilateral PD-related tremor received contralateral electrode implantation. Each patient had a history of tremor predominant idiopathic PD. Patient follow-up extended to twelve months. The authors reported both New York Parkinson's Disease Score (NYPDS) and UPDRS improvements when comparing pre- to post-operative scores at interval follow-ups. Persisting benefit was noted in the overall NYPDS as well as in tremor and rigidity subscores. A persistent effect ($p<0.05$) was also noted in the UPDRS score at study conclusion. Additionally, a significant reduction of L-Dopa intake was noted with 4 patients discontinuing its usage entirely between between months 4 and 6. Kitagawa *et al.* [68], have followed with a study examining unilateral electrode implantation in (n=8) tremor-predominant PD patients using the ZI/PRL target and monopolar stimulation. At a twenty-four month follow-up period, the authors reported significant improvements in overall UPDRS motor section subscore (44.3%), tremor (78.3%), rigidity (92.7%), and bradykinesia (65.7%) when comparing to 'off-stim' subscores. No intra-operative complications were reported. Finally, Carrillo-Ruiz *et al.* [69] have extended the prior work of both groups through examination of bilateral PRL targeting for treatment of tremor predominant PD in (n=5) patients. Using bipolar stimulation, nine of ten electrode arrays had at least one contact in the PRL while four of ten had both active contacts within the PRL. Multiple rating scales (e.g. UPDRS III, NYPDS, and H&Y) scores all demonstrated retained improvement from baseline to final follow-up at twelve months. UPDRS III subsection scores examining tremor, rigidity, bradykinesia, and akinesia also improved. Postural instability and gait had non-statistically significant improvements.

Studies have also examined this target region for indications other than PD. Murata *et al.* [70], have examined the posterior subthalamic white matter in (n=8) patients for treatment of medically refractory and disabling essential tremor containing both distal components as well as proximal spread. Using the same ZI/PRL target as Kitagawa *et al.* [68], each patient received unilateral electrode implantation and was followed for eight to forty-two months with a twenty-two month median. The authors reported, "Tremors, both proximal and distal, were remarkably improved in all eight patients…" when using monopolar stimulation. Scoring used a modified clinical tremor rating scale [71]. A mean 81% tremor improvement was observed when using the best contact on each electrode. Seven of these eight contacts were reported as being either in the PRL or ZI. Each of five patients with writing impairment and each of three patients with significant axial involvement (e.g. voice, neck, or trunk tremor) improved. The authors reported no decline of improvement at follow-up conclusion for any patients. Blomstedt *et al.* [72] have published data indicating benefit of posterior subthalamic area stimulation in (n=5) patients with a wide variety of indications, including: dystonic tremor (2), idiopathic writing tremor (1), cerebellar tremor (1), and neuropathic tremor (1). Patients were followed for a period of twelve months and assessed using the essential tremor rating scale. While the authors reported a mean 87% improvement in symptoms across this heterogeneous group of symptoms, they also reported a dramatic and sustained off-stimulation mean 56% improvement attributed to microlesional effect.

No intra-operative complications were reported associated with electrode implantation in the above studies. Motor deficits were observed only to have occurred beyond voltage threshold stimulation levels not used during chronic stimulation and were transient except in one patient that developed shoulder/ neck retraction [67]. Only partial effect was observed in chronic stimulation for this patient. Otherwise, mild and transient limb ataxia [70], dysarthria [67, 69], hemispastic gait [68], and diplopia or blurred vision were reported [67, 68]. Sensory side effects included hand paresthesias that disappeared within seconds of activation [68, 70]. Neuroaffective worsening included exacerbation of pre-existing depression that required an increase in medication and a decrease in voltage [67, 69].

Targeting the Zona Incerta and Prelemniscal Radiations

Table **2** summarizes the targeting locations and methods used by each of the different groups. Each of the three groups has used and refined their own targeting approach, associated with varying degrees of dependence upon pre/intra/post-operative neuroimaging and intra-operative neurophysiologic monitoring. Plaha *et al.* [60, 62-64] have used an approach that intensively uses advanced MR-based neuroimaging. Magnified T2 images are overlaid upon inverted T2-weighted images to improve the definition of nuclei borders. Guide tube and stylet placement are then confirmed with intra-operative imaging and post-operative confirmatory imaging was obtained. Velasco's group first utilized an approach based upon x-ray, ventriculography, with use of standardized coordinates derived from measurements taken from air ventriculograms [67]. This was later modified to include an increased reliance on MR-based neuroimaging, intraoperative neurophysiology (e.g. evoked potentials), and atlas-based coordinates [69]. In both studies by Murata *et al.* [70] and Kitagawa *et al.* [68] a similar hybrid approach dependent upon neuroimaging, atlas-based coordinate corroboration, and neurophysiologic monitoring were used to identify the target. Finally, Blomstedt *et al.* [72] used pre-operative sterotactic MRI/CT scans with planning software to calculate the appropriate trajectory followed by a post-operative confimatory stereotactic MRI/CT.

Table 2. Subthalamic Area Targeting Approaches and Coordinates

	Indication, Pt #	Targeting	
		Location	**Approach / Coordinates**
Plaha *et al.* (2004)	ET (n=4) Bilateral	'…medial to the posterior third of the dorsal STN, an area encompassing the ascending dentate–and interpositus–Vim fibers and part of the ZI.'	Leksell frame placement followed by axial & coronal MRI Magnified T2 images overlaid onto inverted T2 images to improve definition of deep nuclei boundaries and plan trajectory Guide tube and stylet placement to intended target Intra-op MRI to confirm appropriate placement Frame removal and lead placement Transfrontal trajectory through HoC and approximately 45º from AC-PC line
Plaha *et al.* (2006)	PD (n=35) Bi-/Unilateral (n=29, 6)	Zona Incerta WM dorsomedial/medial to STN STN	Similar to above
Plaha, Khan, and Gill (2008)	PD (n=5) Other* (n=12) Bilateral	Caudal Zona Incerta	Similar to above
Velasco *et al.* (2001)	PD (n=10) Unilateral	Prelemniscal Radiations	Pneumotaxic Guide with Air Ventriculography Target Location standardized to AC-PC line length 8/10 behind AC; 5/10 lateral to midline, and (1-2)/10 below AC-PC line. *Midline = midpoint of 3rd ventricle on AP xray
Murata *et al.* (2003)	ET (n=8) Unilateral	Prelemniscal radiation -or- posterior Zona Incerta	Pre-operative T2 MRI and high res CT with image fusion Precoronal burr hole with extraventricular trajectory Intra-operative neurophysiology with macrostimulation Macrostimulation probe removal with DBS lead placement Post-placement DBS lead confirmation with SSEP Lateral to RN: ~10mm from midline 3-4mm posterior to STN in largest slice of STN
Kitagawa *et al.* (2005)	PD; n=6 Unilateral	Prelemniscal radiation -or- posterior Zona Incerta	Similar to approach by Murata *et al* 5.5 mm posterior to MCP 3 mm inferior to AC-PC line 10.5 mm lateral to the midline 2-3mm posterior to posterior border of STN
Carillo-Ruiz *et al*. (2008)	PD; n=5 bilateral	area between the red and subthalamic nuclei, including Raprl, zona incerta, and substantia Q 'all effective stimulation arrays with the exception of one had at least one contact in Raprl'	T2 Fast Spin Echo MRI Lateral X-Ray & Ventriculography Schaltenbrand & Wahren Atlas SSEPs Merge of MR and atlas with fusion planning software Merge of MRI, ventriculography, and Atlas using standardization of AC-PC line 11.69 mm lateral to midline 6.73 mm behind MCP 4.38 mm caudal to AC-PC
Blomstedt, Fytagoridis, and Tisch (2009)	Cerebellar; n=1 Dystonic; n=2 Neuropathic; n=1 Writing; n=1 Unilateral	Posterior Subthalamic Area	Pre-operative and post-implantation MRI/stereotactic CT slightly medial to the medial border of the STN and in the posterior part of the posterior third of the STN, at the level of the maximal diameter of the red nuclei Coordinates for best contact (lateral [to midline], posterior [to MCP], caudal [to ICL]) in mm Patient 1: 9.5, 4.5, 3.5 (Contact 0) Patient 2: 10, 7, 5 (Contact 0) Patient 3: 11.5, 6, 3.5 (Contact 0) Patient 4: 10, 8, 3.5 (Contact 1) Patient 5: 10.5, 7, 2 (Contact 1)

STN: Subthalamic Nucleus; PD: Parkinson's Disease; ET: Essential Tremor; WM: White Matter; ZI: Zona Incerta; PRL/Raprl: Prelemniscal Radiation; AC-PC: Anterior Commisure-Posterior Commisure; MCP: Mid-Commisural Point; ICL: Intercommisural Line: RN: Red Nucleus: HoC: Head of Caudate
Other*: Holmes (1), cerebellar (1),essential (6), multiple sclerosis (4) and dystonic tremor(1).

CONCLUSION

Initial data agrees upon the safety of implantation and low frequency stimulation in the PPN, with development of only rare and minor transient complications. Investigators have gravitated towards use of neuroimaging-reliant targeting strategies, largely related to concerns of age-dependent variability in brainstem anatomy. While bilateral PPN+STN implantation occurred in the first three reported series, the clinical impact of combinations of PPN and STN stimulation have only more recently been assessed. While PPN-only stimulation demonstrated benefit in each study, an additive effect appears to exist with PPN+STN or PPN+ZI[50] stimulation. Further, anecdotal comments support unilateral stimulation being as effective as bilateral stimulation. The lack of an effective alternative treatment and the effect on quality of life caused by alteration of gait and postural stability underscore the importance of definitively assessing the effect of PPN stimulation. This will ideally require an appropriately powered prospective randomized controlled trial assessing unilateral vs. bilateral PPN stimulation alone and in concert with alternate targets (e.g. STN, ZI/PRL) using thoughtfully modified clinical grading scales designed to assess both gait, postural stability, and an absolute effect on fall frequency.

Both historical clinical lesioning series and clinical stimulation data support the ZI and PRL as modifiers of proximal tremor and possibly other of the more classic Parkinsonian features [61]. However, rigorous evaluation of sites within the posterior subthalamic area to achieve a best practice consensus has been confounded by the close anatomic proximity of the ZI and PRL to each other and the STN. First, their close approximation stretches the limits of current neuroimaging and neurophysiologic targeting techniques [60]. Second, isolating an effect between targets is complicated by possible concerns for adjacent current spread. These challenges have generated discussion as to whether the ZI, PRL, and STN represent functionally distinct targets when stimulated with current generation technology [73-75]. Nevertheless, the data presented provide support for the ZI and PRL as effective therapeutic targets that warrant further consideration through prospective clinical evaluation. Of interest, it remains to be seen what effect stimulation at these targets will have on neurocognitive and neuroaffective endpoints [76]. The answer to this question could result in a broadened consideration of the ZI and PRL as much for their effect on movement disorder pathology as for an alternative when STN stimulation is contraindicated [77]. Restated, the ZI or PRL may become more appealing simply based upon the presence of relative contraindications to STN stimulation. Therefore, on multiple levels, it remains to be seen whether a single 'compromise' set of coordinates may yet best treat all symptoms or whether separate targets may better ameliorate different combinations of symptoms [78]. Prospective randomized controlled trials assessing the ZI, PRL, and STN will be required to best examine the merits and shortcomings of each target.

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