Multitarget deep brain stimulation for clinically complex movement disorders

Tariq Parker, MRCS, Ashley L. B. Raghu, BSc(Hons), James J. FitzGerald, FRCS(SN), Alexander L. Green, FRCS(SN), and Tipu Z. Aziz, FMedSci

Oxford Functional Neurosurgery, Nuffield Department of Surgical Sciences, University of Oxford, United Kingdom

Deep brain stimulation (DBS) of single-target nuclei has produced remarkable functional outcomes in a number of movement disorders such as Parkinson's disease, essential tremor, and dystonia. While these benefits are well established, DBS efficacy and strategy for unusual, unclassified movement disorder syndromes is less clear. A strategy of dual pallidal and thalamic electrode placement is a rational approach in such cases where there is profound, medically refractory functional impairment. The authors report a series of such cases: midbrain cavernoma hemorrhage with olivary hypertrophy, spinocerebellar ataxia-like disorder of probable genetic origin, Holmes tremor secondary to brainstem stroke, and hemiballismus due to traumatic thalamic hemorrhage, all treated by dual pallidal and thalamic DBS. All patients demonstrated robust benefit from DBS, maintained in long-term follow-up. This series demonstrates the flexibility and efficacy, but also the limitations, of dual thalamo-pallidal stimulation for managing axial and limb symptoms of tremors, dystonia, chorea, and hemiballismus in patients with complex movement disorders.

<https://thejns.org/doi/abs/10.3171/2019.11.JNS192224>

KEYWORDS deep brain stimulation; dystonia; essential tremor; thalamus; globus pallidus; functional neurosurgery

DEEP brain stimulation (DBS) surgery for the treatment of movement disorders usually employs stimulation at a single site in one or both hemispheres. However, multitarget surgery is a recognized strategy for attempting greater functional improvement in clinically complex/atypical presentations of various movement disorders.^{18,24,25} This strategy, and target selection, is pursued largely through experience and clinical judgment given the paucity of published cases. We present a series of neurosurgical patients with challenging movement disorders who benefitted from dual pallidal and thalamic DBS (Fig. 1).

Case Reports

Case 1

A 35-year-old woman with a history of migraine presented with an uncharacteristically severe headache. Imaging revealed a midbrain hemorrhage secondary to a cavernoma, with features of hypertrophic olivary degeneration.

Her condition progressed to developing speech difficulties, left-sided one-and-a-half syndrome, and a bilateral mixed movement disorder with dystonic posturing and palatal myoclonus. Her tremor was predominantly right-sided, postural and resting, but with significant kinetic and intention tremor in the right arm. She was later referred to the functional neurosurgery department and implanted with bilateral DBS electrodes targeting the globus pallidus interna (GPi) and ventralis intermedius nucleus of the thalamus (VIM). Thalamic stimulation alone improved her tremor by approximately 50%, with benefits observed in her speech and diplopia, as well as the severity of her migraines. Unfortunately, this was accompanied by a deterioration in her dystonia. Pallidal stimulation was introduced at 4 months, which subsequently improved her right foot posturing. At the 16-month follow-up evaluation, despite minimal improvements in her activities of daily living (ADLs; Bain and Findley Clinical Tremor Rating Scale [TRS]² score change: 74 [preoperative] to 70), large

ABBREVIATIONS ADL = activity of daily living; DBS = deep brain stimulation; GPi = globus pallidus interna; HT = Holmes tremor; TRS = Tremor Rating Scale; VIM = ventralis intermedius nucleus of the thalamus; VOP/ZI = ventralis oralis posterior of the thalamus/zona incerta.

SUBMITTED August 16, 2019. **ACCEPTED** November 1, 2019.

INCLUDE WHEN CITING Published online January 3, 2020; DOI: 10.3171/2019.11.JNS192224.

FIG. 1. Representative postoperative axial fused CT-MRI scan showing typical electrode placements in a patient treated with bilateral pallido-thalamic DBS. Figure is available in color online only.

improvements in her symptoms, including palatal tremor, were reported (Table 1), attributed to surgery and achieved with minimal side effects. At her 4-year postoperative assessment, the patient discontinued routine follow-up due to minimal changes in her symptomatology and overall satisfaction with DBS therapy.

Case 2

A 67-year-old man was referred to the functional neurosurgery department with a “florid hyperkinetic movement disorder with atypical dystonic features” refractory to medical management. At age 11 his gait became abnormal with a “turned in” foot, and he later developed postural instability. His gait became progressively abnormal, and by his mid-20s his legs were stiff. He developed a tremor in both hands, which progressively worsened alongside a

progressive spastic paraparesis. His tremor was previously relieved by botulinum toxin injections and alcohol but was no longer responsive to either. He became reliant on walking aids, eventually becoming wheelchair-bound by age 61. Both his father and brother developed less severe tremor disorders, with his brother also exhibiting postural instability. On examination he was dysarthric and exhibited a bilateral polymorphic tremor of the head, arms, and trunk with dystonic elements, joint stiffness, and reduced sensation bilaterally below the thigh. He could not write and was dependent on his wife for all ADLs. Genetic testing was negative for *FMRI* (fragile X-associated tremor/ataxia syndrome), *SCGE* (myoclonic dystonia), *ATM* (ataxia-telangiectasia), *SCA* 1, 2, 3, 6, 7, 12, and 17 (spinocerebellar ataxia), *APT*X, and *SETX* (ataxia oculomotor apraxia 1 and 2) mutations. He underwent bilateral DBS electrode placement in the ventralis oralis posterior of the thalamus/zona incerta (VOP/ZI) and GPi with immediate clinical benefit from thalamic stimulation, regaining the ability to write, wash, and feed himself. “Dramatic improvement” was maintained for more than 2 years. His legs also improved, so that he was able to walk very short distances. However, at the 3-year follow-up deterioration was noted, particularly in the ability to write with thalamic stimulation. He presented to the clinic with a dystonic head tremor, variable postural and action tremor (particularly with the right hand), and some degree of ataxia. With pallidal leads already in situ, thalamic stimulation was withdrawn and pallidal stimulation introduced with clear improvement. At the 4-year follow-up he had regained the ability to write, feed himself, and drink from a cup (Table 2). However, he reported difficulty ambulating after cessation of VOP stimulation. Since then, he has been maintained on dual thalamo-pallidal stimulation, and at 9 years’ follow-up he describes his tremor control as “excellent.”

Case 3

A 40-year-old woman presented to the emergency department with left-sided numbness, and on examination was noted to have a right-sided ptosis, left-sided facial weakness, and ataxia. Imaging showed a hematoma in the right midbrain and cerebral peduncle, for which she was managed conservatively. Four weeks later she developed a left-sided tremor of both upper and lower limbs and was diagnosed with Holmes tremor (HT). Most of her functional difficulty occurred during ambulation, balance, and

TABLE 1. Summary of case characteristics

Case No.	Targets	Age at Surgery (yrs), Sex	Diagnosis	Preop TRS Score	Postop TRS Score	FU (yrs)
1	VIM + GPi	40, F	Mixed movement disorder secondary to brainstem cavernoma hemorrhage w/ hypertrophic olivary degeneration	30	8	1
2	VOP/ZI + GPi	67, M	Upper body mixed tremor & dystonia disorder of uncertain cause (possibly genetic, or spinocerebellar ataxia)	78	16	5
3	VIM + GPi	42, F	Lt HT secondary to brainstem hemorrhage	27	8	3
4	VOP/ZI + GPi	60, F	Lt hemiballismus & chorea secondary to head injury	32	11	4

FU = most recent follow-up appointment during which a tremor score was recorded with dual-target stimulation.

TABLE 2. TRS assessment for case 2

Time Point	Active DBS	TRS Score			
		ADLs	Head	Rt Arm	Lt Arm
Preop	NA	97	18	30	30
Postop	VOP/ZI	85	2	15	13
1 yr	VOP/ZI	65	2	13	11
2 yrs	VOP/ZI	68	2	7	7
3 yrs	VOP/ZI	85	11	18	11
4 yrs	GPI	54	3	3	10

NA = not applicable.

tasks such as cooking. She was initially treated with anticholinergics, levodopa, and clonazepam with little benefit. She was subsequently referred for surgical management and right-sided GPi and VIM DBS electrodes were placed. Three months postoperatively, her foot tremor was completely resolved, which allowed her to perform most ADLs independently. During programming, it was noted that pallidal stimulation was best for controlling her lower-limb tremor, while thalamic stimulation primarily alleviated her upper-limb tremor. Her tremor has been well controlled for 10 years, with minimal residual symptoms.

Case 4

A 60-year-old woman was referred with left-sided hemiballismus and chorea secondary to a traumatic intraparenchymal hemorrhage. Five years prior, she sustained a skull fracture and right thalamic hematoma after a fall, for which she was managed conservatively. She had minimal resultant limb weakness, but exhibited involuntary, erratic movements of her left arm and neck. She also experienced discoordination of her left leg but remained able to ambulate. Genetic testing for Huntington's chorea was negative. Trials of benzodiazepines, tetrabenazine, haloperidol, and pimozide produced modest benefit. However, medications were eventually discontinued due to symptoms of depression and drug-induced dyskinesias. On examination, there were continuous left-sided thrashing movements and dystonia of the left arm. She also displayed involuntary oromandibular movements and choreiform movements of the tongue. She then underwent implantation of right-sided VOP and GPi electrodes with substantial benefit. Unfortunately, 1 month postoperatively her system had to be removed due to infection, with an expected return of her choreiform symptoms. Six months later both pallidal and thalamic leads were re-implanted. Significant improvement was noted with both VOP and GPi leads OFF, likely due to stun effect; however, VOP stimulation was resumed without delay. Modifications to thalamic stimulation parameters were required but would, at times, result in side effects such as slurred speech at higher amplitudes (3.0 V). Therefore, at 5 months, lone pallidal stimulation was trialed, which relieved her dystonic shoulder symptoms, but she quickly returned to lone thalamic stimulation as her ballismus worsened. At 8 months she had mild left tongue chorea but demonstrated good control of her left arm despite some posturing of her left wrist. However, she was most bothered by her left shoulder still "pushing for-

ward" throughout the day, giving her constant neck ache. Dual stimulation was then initiated at the 1-year follow-up. She was very happy with the improvement from stimulation: reintroduction of pallidal stimulation had made her shoulder much calmer, and thalamic stimulation had continued to control her hemiballismus. She was independent in many ADLs and able to do much more around the home than previously. At 4 years' follow-up, benefits have been sustained: she is currently maintained on dual stimulation with substantial improvement of her chorea and ballistic movements and is much happier than before surgery.

Discussion

The VIM is generally the preferred DBS target for essential tremor, typically ameliorating tremor within seconds of stimulation.²² Hyperkinetic disorders manifest as a result of excessive disinhibition of thalamocortical projections and the VIM is believed to be a critical node in generating, relaying, or amplifying this dysfunctional oscillatory activity. In our experience, VIM stimulation reliably produces benefits for distal tremor, while the VOP is more efficacious with patients exhibiting proximal tremor. VOP has connections with the supplementary motor area and dorsolateral prefrontal cortex, whereas the VIM has strong connections with the primary motor cortex and cerebellum,⁹ suggesting important strategic differences for neuromodulation of movement disorders at these loci. Approaches to targeting these nuclei will vary depending on the individual anatomy, particularly the width of the third ventricle and laterality to the internal capsule.¹⁶ Generally, both nuclei can be identified 2–3 mm medial to the thalamo-capsular interface, with the VIM located 3–5 mm posterior, 12–14 mm lateral, and 0 mm vertical relative to the midcommissural point. In contrast, the VOP/ZI can be targeted approximately 2 mm anteromedially to the VIM, while advancing leads at a posteromedial angle until the electrode lies medial to the subthalamic nucleus posteriorly.

The therapeutic benefits of GPi stimulation on dystonia tend to manifest over weeks to months, although phasic symptoms may improve more acutely.^{12,28} The GPi is a critical inhibitory output nucleus of the direct, indirect, and hyperdirect motor pathways to the ventrolateral thalamus and brainstem. Alteration of this output during chronic DBS likely leverages neuroplasticity, driving reorganization of dysfunctional networks.²¹ Similarly, normalization of pathological network activity has been achieved with chronic dual-target DBS for HT, maintained even upon withdrawal of stimulation.¹¹

Cases 1, 2, and 4 did not present with either pure tremor or pure dystonia, instead exhibiting complex combinations of motor symptoms, for which optimal management from single-target surgery would be optimistic. Although in each case there was an argument for pallidal or thalamic stimulation, the multidisciplinary team (consisting of a movement disorder neurologist, neurosurgeon, and neuropsychologist) agreed that there was a very low preoperative probability of achieving satisfactory long-term outcomes with DBS in either target. In our experience, the response of these patients to single-target DBS (VIM/

FIG. 2. Timeline of active stimulation electrodes used in each multitarget DBS case. Figure is available in color online only.

VOP or GPi) is highly unpredictable. The severe, atypical nature of these patients' symptoms, as well as supportive literature,¹⁹ justified a dual-target approach. The team believed this strategy would remove the burden and risks of a highly likely secondary surgery, while maximizing efficiency in healthcare delivery.

The grounds for this preoperative judgment were subsequently validated as our patients demonstrated variability in their clinical response to lone thalamic/lone pallidal DBS. Symptomatic control was initially attempted with stimulation at the thalamic site (which offers the most immediate clinical benefits) for tremor-dominant patients. However, the "stun effects" from lead insertion alone have been shown to produce long-term (at least up to 6 months) alleviation of symptoms.¹³ The stun effect at the GPi, with DBS OFF, is believed to be therapeutic, akin to a micropallidotomy. Case 4 is an example of this, in which a therapeutic stun effect was observed immediately post-operatively. Lead placement in the GPi likely contributed to the patient's improvement, particularly her dystonic symptoms, despite the lead not being activated for a number of months while receiving only thalamic stimulation. However, ultimately, each of these patients benefitted most from long-term dual-stimulation DBS (Fig. 2, green) with lower stimulation settings at each lead.

Case 3 had HT, for which thalamic and pallidal tar-

gets have both previously proved therapeutic, with some evidence of synergism,^{5,6} and which resulted in a successful outcome for our patient without the necessity to trial each target individually. We recognize that dual stimulation may have adverse effects by disrupting the benefits of stimulation at one site. Indeed, this was often encountered during adjustments of DBS parameters. A systematic, iterative feedback process was used during programming (Table 3) to achieve the best anatomical coverage of symptoms while minimizing the observed side effects of stimulation (such as difficulty writing in case 2 and slurred speech in case 4). This involved locating optimal electrode contacts, with bipolar settings used preferentially to prolong battery longevity.¹ Stimulation parameters were optimized by primarily manipulating amplitude, then pulse width and frequency if necessary, to reduce the likelihood of DBS-induced side effects.³ Finally, leveraging the flexibility of choice among targets proved important in achieving the best therapeutic outcome for these patients when optimization of a single target was no longer deemed satisfactory.

The likelihood of complications will be increased with multitarget DBS, such as the lead-associated infection in case 4, and meaningful therapeutic success is not guaranteed.⁴ There is a dearth of literature on multitarget DBS for movement disorders, including reports of synergistic

TABLE 3. Sample of initial DBS programming table, demonstrating the various iterations required to individualize and optimize stimulation parameters in a single channel to target arm and leg tremor from VIM stimulation

Case*	Contacts				Rate (Hz)	Pulse Width (µsec)	Amplitude (V or mA)	Effects†	Side Effects
	0	1	2	3					
+	-				130	90	2.5	0	Paresthesias in lt leg
+	-				130	120	3.5	0	Paresthesias in lt leg
+		-			130	90	1.8	++	Mouth & facial twitching
+			-		130	90	1.4	0	Circumoral paresthesias
+				-	130	90	1.8	0	Slight facial twitching
+				-	130	90	2.4	0	None
		-	+		130	100	3.6	Arm tremor +++, leg tremor 0	Slight facial twitching
		-	+		130	120	4.1	Arm tremor +++, leg tremor 0	Slight facial twitching
			-	+	130	120	3.6	0	None
	-		+		130	90	3.5	Arm tremor +++, leg tremor +	None

* Metal case of the implantable pulse generator.

† Positive effects + (mild), ++ (moderate), or +++ (strong); 0 = no effect.

effects on symptom alleviation^{7,23,26} or efficacy on different symptoms.¹⁵ There are also reports of single-lead efficacy after dual implantation, where the optimal choice of target is unclear.¹⁰ In such a scenario, single-lead surgery may lead to failure and uncertainty over whether to proceed to another surgery. Even among homogenous etiologies, clinical response to particular DBS targets can vary considerably.^{8,27} In preparation for such uncertainty, multitarget implantation at first operation is therefore plausible, increasing available permutations to establish and optimize therapy with ease and without the need for reoperation. However, staged dual stimulation, a more conservative approach, has also been successful in HT,²⁰ dystonic tremor,¹⁴ and idiopathic Parkinson's disease.¹⁷

Weighing the risk and benefits of a multitarget approach for each patient is an important and delicate exercise. Such an approach can be undertaken with a reasonable safety profile, but it relies on the requisite capacity and expertise to optimize DBS management. However, as we have demonstrated, for patients with severe, complex, or unusual movement disorders, multitarget stimulation has the potential to provide significant therapeutic benefit.

Acknowledgments

We would like to acknowledge the significant contributions of the Movement Disorder neuromodulation nurses, in particular Beth Forrow, at the John Radcliffe Hospital for their diligence and commitment to programming, evaluation, and treatment of the patients referred to Oxford Functional Neurosurgery.

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Disclosures

Dr. FitzGerald reports being a consultant to Abbott and Medtronic. Dr. Green reports being a consultant to Abbott and Herantis Pharma Plc.

Author Contributions

Conception and design: Parker. Acquisition of data: Parker, Raghu. Analysis and interpretation of data: Parker, Raghu. Drafting the article: Parker, Raghu. Critically revising the article: Parker, Raghu, Green, Aziz. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Parker. Study supervision: FitzGerald, Green, Aziz.

Correspondence

Tariq Parker: Linacre College, Oxford, United Kingdom. tq.parker18@gmail.com.