Interleaving Stimulation in Parkinson's Disease, Tremor, and Dystonia

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Keywords

Interleaving stimulation · Deep brain stimulation · Zona incerta

Abstract

Background/Aims: Interleaving stimulation (ILS) in deep brain stimulation (DBS) provides individualized stimulation of 2 contacts delivered in alternating order. Currently, limited information on the utility of ILS exists. The aims of this study were to determine the practical applications and outcomes of ILS DBS in Parkinson's disease (PD), tremor, and dystonia. **Methods:** We performed a single-center, unblinded, retrospective chart review of all patients with DBS attempted on ILS at our referral center assessing for rationale and outcomes. **Results:** Fifty patients (PD, $n = 27$; tremor, $n = 7$; dystonia, $n = 16$ patients) tried ILS for 2 rationales: management of adverse effects ($n = 29$) and to improve clinical efficacy ($n = 21$). A total of 19 patients demonstrated improvement with ILS for adverse effect management predominantly for the treatment of dyskinesias ($n = 12$). In the

vast majority of dyskinetic patients, a contact added into the rostral zona incerta with ILS was performed. Nine out of 21 patients demonstrated improved clinical efficacy with ILS with all 6 PD patients who tried ILS for this rationale demonstrating benefit. **Conclusions:** In PD, ILS provided benefits for dyskinesias and parkinsonism, with minimal improvement of other adverse effects. In tremor and dystonia, marginal effects in terms of mitigation of adverse effects and improvement of clinical outcomes were evident.

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Introduction

Deep brain stimulation (DBS) is an effective treatment for Parkinson's disease (PD), tremor, and dystonia [1, 2]. An advantage of DBS is that the volume of activated tissue (VAT) can be adjusted through several parameters in-

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Fig. 1. Algorithms summarizing the programming approach to manage adverse events (**a**) or improve clinical efficacy (**b**) for DBS patients at Toronto Western Hospital. Detailed information is available in the studies by Picillo et al. [3, 4].

cluding contact configuration, frequency, pulse width, and voltage/current. Despite optimal DBS programming, suboptimal benefits and stimulation-induced adverse effects may occur [3, 4].

Conventional DBS programming involves monopolar or bipolar stimulation. Interleaving stimulation (ILS) is a stimulation parameter that provides alternating sequences of stimulation on the same implant as 2 contacts can be set with different pulse widths and amplitudes independently of each other and delivered in an alternating order [5]. Conceptually, ILS may be applied in the following 2 scenarios: (1) to limit stimulation-induced adverse effects and (2) stimulation of different brain regions with individualized settings in order to alleviate specific symptoms [6]. Application of ILS is currently driven by clinician experience and knowledge of neurophysiology and neuroanatomy. The objective of this study was to determine the rationale and outcomes of ILS in clinical practice.

Materials and Methods

As is the standard at our center, all of the patients were initially treated with monopolar stimulation [3, 4]. Unwanted adverse effects or unsatisfying clinical benefits of DBS were then managed by adjusting stimulation parameters as well as changing contacts and attempting bipolar stimulation. Only upon failure of these stimulation conditions was ILS attempted. Medication adjustments and/or physical therapy are considered complementary to programming strategies and, as such, are applied after stimulation

options have been explored. The electrode tried in ILS was selected as the one contralateral to the body with signs being targeted. The second-best contact providing a clinical benefit was commonly selected as the added interleaved contact, with the exception of treatment of dyskinesias. In PD patients with dyskinesias, attempts to reduce stimulation and change activated contacts were initially made. In the event that this resulted in worsened management of parkinsonism, ILS was then implemented. Whenever possible, double monopolar stimulation was avoided to maintain battery longevity. A summary of the standard programming process is shown in Figure 1.

A systematic chart review was conducted through June 2015 by searching the electronic database at Toronto Western Hospital for all patients with DBS and ILS. This study was approved by the Research Ethics Board, the University Health Network, and the University of Toronto. Baseline information was collected as shown in Tables 1 and 2. Pre- and postoperative assessments at 6 months were performed with validated scales according to the target symptom. Collection of clinical assessments in PD patients included baseline Unified Parkinson's Disease Rating Scale (UPDRS) part III (i.e., motor section) OFF medication and after a supratherapeutic levodopa dose and postoperative scores ON medication and ON stimulation. All dopaminergic medication was calculated as an levodopa equivalent daily dose [1]. In patients with tremor, the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS) was used. Dystonic patients underwent testing including the FTMTRS, the Toronto Western Spasmodic Torticollis Rating Scale, the UPDRS part III, and the Burke-Fahn-Marsden Dystonia Rating Scale. Application of ILS was based on clinician evaluation of symptomatic improvement and mitigating stimulation-induced adverse effects. Outcomes were evaluated before and after ILS. All patient charts were reviewed to determine the rationale for attempting ILS as well as the reported efficacy and adverse effects.

Table 1. Patient demographics

	PD (<i>n</i> = 27)	Tremor (<i>n</i> = 6)	Dystonia (<i>n</i> = 16)
Male/female ratio	19/8	3/3	8/8
Age at diagnosis, years	48±8.1	48.6±20.3	23.8±17.2
Age at surgery, years	58±8.5	57.8±7.9	37.8±17
Procedure	24 bilateral STN 3 unilateral left STN	5 unilateral VIM 1 bilateral VIM	15 bilateral GPi 1 left VIM+left GPi
Preoperative motor function	40±9.2/16±4.9 ^a	47±16.1 ^b	37.7±15.7 ^c 39.7±33 ^d
Postoperative motor function	17±8.5 ^e	32.6±9.6 ^b	26.1±17.6 ^c 8.3±8.2 ^d
Pre-/postoperative LEDD (SD)	1,316.2±781/ 649.5±458.1	NA	NA

Data are expressed as means ± SD unless otherwise stated. For details, see online supplemental material. LEDD, levodopa equivalent daily dose; NA, not available. ^a UPDRS III preoperative OFF/ON medication. ^b FTMTRS. ^c TWSTRS. ^d BFMDRS-M. ^e UPDRS-III postoperative ON medication ON stimulation.

Patients were implanted with Medtronic model 3387 (Medtronic Inc., Minneapolis, MN, USA). For PD the subthalamic nucleus (STN), tremor in the ventralis intermedius (VIM), and dystonia in the globus pallidus internus (GPi) were targeted. The operative techniques have been previously published [7–9]. Statistical analysis was performed using SPSS (V.22; IBM Corp., Armonk, NY, USA). A *t* test was performed for within-patient comparisons, and *p* < 0.05 was considered statistically significant.

Axial images on postoperative 1.5T MRI (GE scanner; TR = 4,516 ms, TE = 99 ms) identified the location of the lead artifact, allowing determination of the lead tip and contacts. The following analysis was conducted on postoperative T1 3-D volumetric MRI scans. First, the DBS lead of interest was manually segmented using ITK-SNAP (www.itksnap.org) [10]. The 3-D manual segmentation of the DBS lead was exported from ITK-SNAP as a binary mask. Second, using the FLIRT linear registration function in FSL (fsl.fmrib.ox.ac.uk) [11–13], we registered the patient's native space MRI to the normalized Montreal Neurological Institute (MNI) (1 mm) space. Based on visual inspection, this registration process produced more reliable results with respect to alignment of the STN mask used in our analysis [14] than the use of a nonlinear registration approach. Third, the transformation matrix computed from the registration of the patient's MRI to MNI space was applied to the 3-D binary mask of the DBS lead. The following steps were executed using custom programs written in MATLAB (MathWorks). From the 3-D binary mask of the DBS lead we extrapolated the locations of the contacts based on the physical dimensions of the DBS lead. We computed 3-D regions of interest for the dorsal most active contact, estimating whether it overlapped with an STN atlas mask derived from the ATAG elderly STN probabilistic atlas [14], which is also in MNI space (1 mm), by comparing 2 binary masks to determine whether masks occupied the same space. To mitigate overestimation of the STN volume, we constrained the probabilis-

tic STN mask using an 0.2 probability cut-off, i.e., all probability values greater than 0.2 were included in the mask. The coordinates of the centroid of contacts were provided in MNI space of a common origin (the anterior commissure) as well as in distance from the midcommissural point (MCP).

Results

ILS was performed in 50 patients (PD, *n* = 27; tremor, *n* = 7; dystonia, *n* = 16) (Table 1). The average time from the last evaluation to surgery was 29 months (range 1–115). In PD patients, STN DBS improved preoperative OFF medication scores compared to postoperative ON medication/ON stimulation UPDRS III scores by 77 ± 21.5% and dopaminergic medication was reduced by 49 ± 32% (online suppl. Table e-1; for all online suppl. material, see www.karger.com/doi/10.1159/000494983). Seven patients with tremor (essential tremor [ET; *n* = 5], multiple sclerosis [MS; *n* = 1], and PD [*n* = 1]) had VIM DBS attempted on ILS. VIM DBS improved preoperative versus postoperative FTMTRS by 21 ± 23% (online suppl. Table e-2). ILS was attempted in 16 patients implanted with GPi DBS for dystonia with heterogeneous etiologies. With the exception of patient DY5, who had VIM and GPi DBS, all of the remaining patients had bilateral GPi DBS (online suppl. Table e-3). There were 2 main reasons for attempting ILS: management of adverse effects and to improve the clinical efficacy (Fig. 2).

Table 2. PD Patient ILS responses

Pa- tient	Settings prior to ILS ^a	ILS settings ^a	Settings at the last evaluation	ILS contact: location (X, Y, Z; MNI) ^b	Time from DBS implant to ILS, months	Time on ILS	UPDRS III on MED/ on STIM pre-/ post-ILS	Response	Continued ILS settings at the last evaluation	Comments and reason for ILS discontinuation
Management of dyskinesias										
PD4	R: C+2-/3.3/60/130 L: C+9-/2.9/60/130	R: C+1-/3.2/60/125 L: C+9-/3.3/60/125; C+11-/0.5/60/125	R: C+1-/3.2/60/125 L: C+9-/3.3/60/125; C+11-/0.5/60/125	9: STN (-10, 18, 10) 11: rZI (-12, 17, 4)	8	12 months	16/15	Improve- ment	Yes	Improved dyskinesias and dysarthria
PD7	R: C+2-/2.8/60/185 L: C+7-/3.2/90/185	R: C+0-3-/1.5/60/120; C+2-/2.8/60/120 L: C+7-/3.5/90/120	R: C+0-1-/1.5/60/120; C+2-/2.8/60/120 L: C+7-/3.5/90/120	3: border rZI (14, 12, 3)	66	1 month	12/14	Improve- ment	No	Reduced dyskinesias but with tremor worsening on the right side, changed to different ILS contacts
PD8	R: C+3-/3/60/250 L: C+11-/3/60/250	R: C+2-/3.6/60/125 L: C+10-/2.2/60/125; C+11-/3.5/60/125	R: C+3-/4.3/60/180 L: C+10-/3/60/180	10: STN (-11, 12, 3) 11: rZI (-12, 11, 1)	3	1 day	28/28	Transient improve- ment	No	Dyskinesias in the clinic, but upon returning home the benefit waned
PD9	R: C+1-3-/3.1/60/180 L: C+9-/2.8/60/180	R: C+1-/3.8/60/125; C+3-/1.5/60/125 L: C+9-/3.5/60/125	R: C+1-3-/3.1/60/180 L: C+9-/2.8/60/180	1: STN (13, 15, 6) 3: rZI (16, 10, 1)	17	Program session	3/3	Improve- ment	No	Dyskinesias were reduced but the patient developed worsened parkinsonism and increase voltage caused dysarthria
PD10	R: 3+2-/3.5/60/130 L: C+11-/3/60/130	R: C+2-/2.2/60/125; C+3-/3.5/60/125 L: C+11-3.5/60/125	R: C+2-/2.2/60/125; C+3-/3.5/60/125 L: C+11-3.5/60/125	2: STN (14, 10, 7) 3: rZI (14, 9, 3)	3	7 months	24/19	Improve- ment	Yes	
PD11	R: C+1-/2.1/60/130 L: C+9-/4.1/60/130	R: C+1-/2.1/60/125; C+3-/1.5/60/125 L: C+9-/4/60/125	R: C+1-/2/60/125; C+3-/2.3/60/125 L: C+9-/4/60/125	1: STN (14, 12, 8) 3: rZI (15, 9, 2)	17	4 months	17/6	Improve- ment	Yes	
PD13	R: C+1-/3.3/60/145 L: C+0-/5/60/100	R: C+1-/3.5/60/125; C+3-/1.5/60/125 L: C+0-/5/60/100	R: C+1-/3.5/60/125; C+3-/1.5/60/125 L: C+0-/5/60/100	1: STN (17, 16, 6) 3: rZI (18, 12, 0)	59	2 months	45/35	Improve- ment	Yes	Dyskinesias completely resolved on the L side and there was a mild reduction on R side
PD21	R: C+1-/3.6/60/130 L: C+11-/4/60/130	R: C+1-/3.6/60/125 L: C+8-/1.7/60/125; C+11-/4/60/125	R: C+2-/2/60/130 L: C+11-/4.8/60/130	8: STN (-8, 18, 11) 11: rZI (-10, 10, 2)	34	2 months	15/-	Improve- ment	No	Improved dyskinesias and reduction of falls but worsened R arm pain that may be functional
PD22	R: C+11-/2.5/60/130 L: C+2-/2.1/60/130	R: C+11-/2.6/60/125 L: C+3-/3.1/60/125; C+0-/3.1/60/125	R: C+11-/3.4/60/130 L: C+3-/3/60/130	NA	13	3 days	7/-	Improve- ment	No	Dyskinesias improved but mood declined
PD23	R: C+0-/4.45/60/130 L: C+10-/2.1/60/130	R: C+0-/5.05/60/80; C+3-/1.5/60/80 L: C+10-/2.15/60/80	R: C+0-/4.5/60/60; C+3-/1.5/60/60 L: C+10-/2.1/60/60	0: out of STN (9, 21, 13) 3: rZI (12, 16, 4)	12	4 months	7/10	Improve- ment	Yes	

Table 2 (continued)

Pa- tient	Settings prior to ILS ^a	ILS settings ^a	Settings at the last evaluation	ILS contact location (X, Y, Z; MNI) ^b	Time from DBS implant to ILS, months	Time on ILS	UPDRS III on MED/ STIM pre-/ post-ILS	Response	Continued ILS settings at the last evaluation	Comments and reason for ILS discontinuation
PD24	R: C+2-/2.5/60/130 L: C+9-11-/2/60/130	R: C+2-/2.7/60/125 L: C+10-/2.5/60/125; C+11-/0.6/60/125	R: C+2-/3.4/60/130 L: C+10-/3.5/60/130	10: STN (-12, 13, 4) 11: rZI (-12, 11, 1)	2	1 month	14/13	Improve- ment	No	Stopped interleaving due to worsened parkinsonism
PD25	L: C+1-/2.5/60/130	L: C+1-/3.5/60/80; C+2-/2/60/80	L: C+1-/4/60/80; C+2-/2/60/80	1: STN (-8, 18, 12) 2: STN (-9, 16, 9)	7	12 months	15/9	Improve- ment	Yes	
Management of other adverse effects										
PD2	R: C+1-3-/3/60/180 L: C+9-/3.75/60/180	R: C+1-/3.2/60/125; C+3-/2.8/60/125 L: 9+10-/5.5/60/125	R: C+1-3-/3.3/60/80 L: C+9-/4/60/80	1: STN (8, 14, 10) 3: STN (8, 11, 4)	14	2 months	16/17	No benefit	No	AE: dysarthria and higher stimulation resulted in diplopia
PD3	R: C+2-/3.5/60/130 L: C+9-/3.5/60/130	R: C+2-/3.5/60/125 L: C+9-/3.5/60/125; C+10-/3.5/60/125	R: C+2-/5.5/60/80 L: C+9-/5.5/60/80	9: STN (-9, 17, 8) 10: STN (-9, 16, 5)	12	1 month	20/20	No benefit	No	AE: dysarthria
PD5	R: C+2-/6/60/130 L: C+11-/6/60/130	R: C+2-/6/60/130 L: C+10-/3/60/125; C+11-/4/60/125	R: C+2-/6/60/130 L: C+10-/2.5/60/125; C+11-/3/60/125	10: STN (-8, 17, 7) 11: rZI (-8, 15, 4)	3	5 months	30/16	Improve- ment	Yes	AE: dysarthria
PD12	R: C+3-/1.5/60/130 L: C+11-/2.5/60/130	R: C+3-/1.5/60/130 L: C+10-/2.5/60/125; C+11-/2.5/60/125	R: C+3-/2.4/60/130 L: C+11-/3.5/60/130	10: STN (-12, 16, 3) 11: rZI (-13, 14, 0)	3	Program session	17/-	No benefit	No	AE: dysarthria (coming up with the words to say)
PD14	R: C+2-/3.6/60/155 L: C+6-/3.6/60/155	R: C+2-/3.6/60/125 L: C+5-/2.8/60/125; C+6-/3.6/60/125	R: C+2-/3.6/60/80 L: C+6-/3.6/60/80	5: STN (-7, 18, 11) 6: STN (-8, 16, 8)	77	Program session	21/-	No benefit	No	AE: dysarthria No benefit in speech and induced facial pulling evident
PD16	R: C+1-/2.8/60/180 L: 10+11-/4/60/180	R: C+3-/2/60/125; C+2-/2.5/60/125 L: 10+11-/3/60/125; 9+10-/3/60/125	R: C+3-/3.8/60/180 L: 10+11-/4.5/60/180	NA NA	4	3 months	27/24	No benefit	No	AE: dysarthria
PD17	R: 0+3-/3/60/130 L: C+11-/3.3/60/130	R: 0+3-/2.8/60/125; 2+3-/2.9/60/125 L: C+11-/3.3/60/130	R: 2+1-/3.6/60/130 L: 10+9-/2.5/60/130	0: STN (12, 17, 8) 2: STN (12, 13, 3) 3: rZI (13, 11, 0)	11 months	1 week	31/-	No benefit	No	AE: dystonic pain
PD26	R: C+3-/2.8/60/220 L: C+10-/3.5/90/220	R: 3+2-/4.5/60/125 L: 9+10-/5/60/125; C+10-/3.5/60/125	R: C+3-/2.8/60/220 L: C+10-/3.5/90/220	9: STN (-10, 15, 6) 10: STN (-10, 13, 3)	15	3 month	7/15	Improve- ment	No	AE: impulsivity Improvement of impulsivity but worsened tremor
PD27	R: C+3-/5.1/60/80 L: C+9-/4.1/60/80	R: C+3-/5.1/60/80 L: C+8-/4/60/80; C+11-/4.5/60/80	R: C+3-/5.2/60/80 L: C+9-/4.3/60/80	8: STN (-10, 15, 9) 11: rZI (-11, 10, 0)	7	1 day	13/-	No benefit	No	AE: dystonia

Table 2 (continued)

Pa- tient	Settings prior to ILS ^a	ILS settings ^a	Settings at the last evaluation	ILS contact: location (X, Y, Z; MNI) ^b	Time from DBS implant to ILS, months	Time on ILS	UPDRS III on MED/ on STIM pre-/ post-ILS	Response	Continued ILS settings at the last evaluation	Comments and reason for ILS discontinuation
Improvement of parkinsonism										
PD1	R: C+3-/4/60/180 L: C+10-11- /5.8/60/180	R: C+3-/4.5/60/125 L: C+9-/3/60/125; C+10-/3.5/60/125	R: C+2-/3.6/60/125; C+3-/5.4/60/125 L: C+9-/3/60/125; C+10-/3.5/60/125	9: STN (11, 15, 6) 10: STN (11, 12, 3)	22	8 months	36/28	Improve- ment	Yes	R side tremor was reduced but the tremor on the L side worsened. The patient alternates between ILS and R: C+3-/3.6/60/210, L: 11+10-/5/60/210 Reduced bradykinesia
PD6	R: C+1-/2.4/60/130 L: C+1-/1.5/60/130	R: C+1-/2.4/60/125; C+0-/2/60/125 L: C+1-/1.5/60/130	R: C+1-/2.6/60/125; C+0-/2/60/125 L: C+1-/1.5/60/130	NA	4	39 months	22/18	Improve- ment	Yes	Reduced bradykinesia
PD15	R: C+3-/3.9/60/130 L: C+4-/2.9/60/130	R: C+3-/3.9/60/70; C+0-/2.9/60/70 L: C+4-/2.8/60/70; C+5-/2.8/60/70	R: C+3-/3.7/90/100; C+0-/0.5/60/100 L: C+4-/2.5/60/125	0: SNr (12, 18, 10) 3: rZI (15, 12, 1) 4: SNr (-10, 18, 11) 5: STN (-11, 17, 8)	68	23 months	29/30	Improve- ment	Yes	Freezing of gait and speech improved; however, continuous adjustments were necessary to manage L hand dystonia
PD18	R: C+2-/4.3/60/185 L: C+9-/4.3/60/185	R: C+2-/0.5/60/125 L: C+9-/4.3/60/125; C+11-/1/60/125	R: C+2-/4.8/60/185 L: C+9-/4.8/60/185	NA	46	1 month	27/23	Improve- ment	No	Improvement of tremor and gait but worsened jaw dystonia
PD19	L: C+3-/3/60/125	A. C+3-/3/60/125; C+1-/1/60/125 and B. C+3-/3/60/125; C+2-/2/60/125	A. C+3-/3/60/125; C+2-/2/90/125	NA NA	2	1 week	22/19	A. Im- provement and B. No Benefit	Yes	Improvement in tremor but worsened dyskinesias
PD20	L: C+3-/3/60/130	L: C+2-/3/60/125; C+3-/3/60/125	L: C+1-/2.8/60/125; C+3-/2.8/60/125	2: STN (-9, 14, 5) 3: STN (-9, 13, 3)	2	8 months	11/13	Improve- ment	Yes	Marked benefit of tremor

ILS was used on one side only in all patients except in 2 cases (PD15 and PD16). ILS is in bold. ^a Contacts/voltage (V)/pulse width (μs)/frequency (Hz). ^b Coordinates as related to MNI space with a common origin to the anterior commissure. AE, adverse effect; C, case; L, left; NA, not available; R, right; SNr, substantia nigra pars reticulata.

Fig. 2. **a** Total number of patients who tried ILS, divided into 2 main rationales. **b** Patients with PD separated into the 3 rationales for attempting ILS. Overall, ILS was most efficacious for the management of dyskinesias and parkinsonism and minimally beneficial for the management of adverse effects. **c** Patients with tremor separated into the 2 rationales for attempting ILS. ILS was efficacious for the management of adverse effects in 2 out of 3 patients

and no patients had benefit for tremor. **d** Patients with dystonia separated into the 2 rationales for attempting ILS. ILS provided mixed results for the management of adverse effects improvement of dystonia. Colors delineate patients with no benefit for the indicated rationale (red), transient benefit (yellow), benefit but discontinued (green), and continued on interleaving at the last evaluation (blue). (Color version available online only.)

Management of Adverse Effects

A total of 29 patients underwent ILS for management of adverse effects. In general, ILS was attempted to reduce the VAT with the exception of treatment of dyskinesias. The selected contact inducing adverse effects was identified by increasing voltages resulting in worsened symptoms. In this cohort, 19 patients (PD, $n = 14$; tremor, $n = 2$; dystonia, $n = 3$) noted improvement of their symptoms, while 10 patients (PD, $n = 7$; tremor, $n = 1$; dystonia, $n = 2$) did not have any change with ILS. The benefit of a reduction of adverse effects was predominately driven by the response to ILS in PD patients for the management of dyskinesias.

ILS was implemented in 12 patients for the management of dyskinesias (Table 2). All patients had a reduction of dyskinesias, although half did not continue on ILS. The response to ILS for dyskinesias was commonly evident soon after the switch (online suppl. Video 1). Stimulation of the added ILS contact was increased until dyskinesias resolved. The contralateral side to the part of the body with dyskinesias was selected to attempt ILS. In the 6 patients who continued on ILS (i.e., PD4, PD10, PD11, PD13, PD23, and PD25), the average duration of ILS was 206 ± 129.2 days. Six patients with the initial benefit of reduced dyskinesias following ILS discontinued the therapy after an average of 20.8 ± 23.2 days due to

Fig. 3. DBS contact localization within STN for PD patients who transitioned to ILS for the management of dyskinesia. **a** Representative DBS contact location for PD4 on 3 planes, i.e., axial, coronal, and sagittal (black contacts are located outside of the STN and red contacts are localized within the STN). **b** Measured distances from the dorsal border of the STN to the centroid of the added ILS con-

tact from 11 out of 12 PD patients (data not available for PD22). Eleven of the 12 patients had the added contact located outside of the STN ranging from 1–7 mm dorsal to the border of the STN. One patient (PD25) had the added contact within the STN shown in red. (Color version available online only.)

either transient benefit (PD8), worsened parkinsonism (PD7, PD9, and PD24), worsened pain (PD21), or a decline in mood (PD22). In patient PD7, the most ventral contact (contact 0) was added to improve gait and the most dorsal contact (contact 3) was added to improve dyskinesias. Patient PD22 had monopolar stimulation of the dorsal contact (contact 2) changed to interleave the most ventral and most dorsal contacts (contacts 0 and 3, respectively) to improve mood and dyskinesias. Although patients who continued on ILS tended to have greater improvement in UPDRS, with an average reduction of 5 points, there was no significant difference in

UPDRS scores before and after ILS ($p = 0.09$) for this group or in comparing values for all 12 patients who tried ILS for the treatment of dyskinesias. Of the 12 PD patients who had ILS added for the treatment of dyskinesias, 10 had the active contact located dorsal to the STN in the region of the rostral zona incerta (rZI), 1 was located within the STN (PD25) based on our imaging analysis model while 1 patient (PD22) did not have imaging available (Fig. 3). The average location of the added contact in ILS for the treatment of dyskinesias referenced to the MCP was: $X = 13.9$, $Y = 0.7$, $Z = -0.9$ (online suppl. Table e-4). The average distance from the dorsal border

of the STN to the centroid of the added contact in ILS was 3.34 mm (± 2.45).

ILS was tried in 9 PD patients for the management of other stimulation-induced adverse effects such as: dysarthria ($n = 6$), impulsivity ($n = 1$), and dystonia ($n = 2$) (Table 2). Only 1 patient (PD5) out of the 6 who tried ILS for dysarthria continued with further improvement in parkinsonism. Current shaping to a more ventral contact within the STN likely accounted for the improvement in parkinsonism, and the reduction of stimulation within the rZI potentially accounted for the reduction of dysarthria observed in this patient. No benefit was obtained in the other 5 patients with dysarthria (i.e., PD2, PD3, PD12, PD14, and PD16) and 2 patients with dystonia (i.e., PD17 and PD27), with the majority of contacts located within the STN. Patients PD17 and PD27 had stimulation-induced dystonia (with a potential contribution of medication) and were therefore placed on ILS like those treated for dyskinesia. Patient PD26 tried ILS for impulsivity prior to medication adjustment and this was effective but after 3 months the tremor gradually worsened (53% worsening on the UPDRSIII compared to settings prior to ILS), necessitating discontinuation of ILS.

ILS was attempted in patients with tremor for the management of adverse effects (dysarthria and paresthesia; $n = 3$) (online suppl. Table e-5). Only 2 patients (i.e., ET4 and ET5) continued on ILS for the management of adverse effects. Among the dystonic patients, 5 (i.e., DY1, DY4, DY9, DY11, and DY16) tried ILS for the management of adverse effects (online suppl. Table e-6). Adverse effects related to capsular stimulation including dysarthria and contractions had mixed results with ILS as 3 patients (i.e., DY1, DY4, and DY9) demonstrated improvement while 2 patients (i.e., DY11 and DY16) had no benefit.

Improve Clinical Efficacy

Twenty-one patients (PD, $n = 6$; tremor, $n = 4$; dystonia, $n = 11$ patients) tried ILS to improve clinical efficacy. All 6 PD patients and 3 dystonic patients had symptomatic benefits with the switch to ILS.

Six PD patients had ILS to further reduce tremor (PD1, PD18, PD19, and PD20), bradykinesia (PD6), and freezing of gait (FOG) (PD15) (Table 2). In these patients, the average ILS trial duration was 420 ± 479 days. All of the patients benefited from ILS and 5 of them continued on ILS. Among the PD patients who tried ILS to improve tremor, stimulation of more ventral contacts was applied in 3 patients (i.e., PD1, PD19, and PD20) and 1 (PD18) had stimulation added to the most dorsal contact. Con-

tact location was determined in 2 of the patients (i.e., PD1 and PD20), indicating that the added ventral contact was within the STN. PD18 stopped ILS due to worsened jaw dystonia, although the tremor continued to be noticeably improved. PD6 demonstrated an improvement of bradykinesia without induction of dyskinesias. FOG was improved in PD15 by adding ventral contacts that were within the pars reticulata of the substantia nigra.

ILS was not effective when tried in tremor patients (i.e., ET2, ET3, MS1, and PD28) (online suppl. Table e-5). ILS was attempted for the treatment of dystonia (DY2, DY3, DY5, DY6, DY7, DY8, DY10, DY12, DY13, DY14, and DY15; $n = 11$) (online suppl. Table e-6), and only 2 patients continued on ILS (i.e., DY2 and DY7). Contacts were highly variable with no discernable pattern.

Discussion

This study illustrates our experience with ILS for the management of PD, tremor, and dystonia. ILS was attempted when conventional settings were either ineffective or produced unwanted adverse effects. The results of ILS were dependent on the disease, the DBS target, and the symptoms.

The most interesting finding was improvement of dyskinesias with ILS that was associated with addition of stimulation to more dorsal contacts in 8 out of 12 patients. In 7 of these patients, the added dorsal contact was outside of the STN within the region of the rZI [15, 16]. The rZI is located superior to the STN, inferior to the thalamus, lateral to the red nucleus, and medial to the STN. The ZI is an embryological derivative of the ventral thalamus that extends from the rostral pole of the thalamus to the rostral pole of the medial geniculate nucleus and is divided into 2 portions (rostral and caudal). The rZI lies between the STN and the thalamus while the caudal ZI (cZI) includes all portions of the nucleus posterior to the STN. The area posterior to the STN that includes the cZI is referred to as the posterior subthalamic area. Differences between the rostral and caudal portions are evident in projections as well as cell type [17, 18]. The region surrounding the ZI (including the caudal and rostral portions) includes 3 main structures involved in motor control: the cerebellothalamic tract, prelemniscal radiation, and the pallidothalamic tract [17–19].

Retrospective studies on stimulation of sites immediately dorsal to the STN for the treatment of PD have reported clinical benefits, i.e., reduced tremor, bradykinesia, and rigidity [17, 20–25]. In the only prospective stud-

ies evaluating ZI stimulation in PD, Plaha et al. [26] determined that patients with cZI or stimulation dorso-medial to the STN compared to patients with STN stimulation had greater improvement in parkinsonism. Dyskinesias were the most reduced with dorsomedial stimulation to the STN (65%) compared with cZI (56%) and STN (41%) stimulation. An advantage of ILS stimulation is that 2 regions (e.g., STN and rZI) can be costimulated. With the exception of case reports, there are no large case series of ILS for the treatment of dyskinesias [20, 27–30]. The antidyskinetic effects of rZI stimulation evident in our study and reported in the literature may involve stimulation of the rZI and/or the surrounding pallidothalamic fibers. Within the rZI, these clinical effects may resemble those of ventral GPi stimulation in PD patients, leading to a complete arrest of dyskinesias [29, 31]. Large myelinated pallidothalamic fibers are very sensitive to applied electrical fields. Therefore, low voltages applied to the rZI region may have stimulated these fibers, altering the signal-to-noise ratio, while not worsening the parkinsonism that was improved with costimulation of the STN.

Studies that have demonstrated the efficacy of ZI stimulation should be interpreted cautiously as the clinical experience is limited. Most studies were performed retrospectively and in a small number of patients. In addition, inconsistencies in the efficacy and adverse effects of ZI stimulation exist and likely reflect the inability to directly target the ZI resulting in variability of contact placement [20–23, 31, 32]. Methods for visualization of the rZI allowing direct stereotactic targeting have recently been reported [33, 34]. In addition, intraoperative microelectrode recordings may aid in direct targeting of the ZI as this region reveals a low amplitude background and a sparse cell density, as well as a lack of proprioceptive responses, which help to distinguish it from surrounding areas [24]. Furthermore, as one of the greatest limitations of increasing stimulation are unwanted adverse effects, studies aimed at assessing the response to titration of stimulation as well as immediate and potential delayed side effects need to be performed. Preliminary data indicate that dysarthria, speech articulation, postural instability, and ataxia as well as blocking beneficial effects of levodopa on bradykinesia and freezing, may be obtained with posterior subthalamic area/cZI stimulation while the adverse effects of rZI stimulation have not been fully determined [31, 35, 36].

The discontinued use of ILS for the treatment of dyskinesias was predominately due to the loss of efficacy for other symptoms previously well controlled by pre-ILS settings. This demonstrates one of the limitations of ILS,

i.e., that both activated contacts are restricted by a frequency of 125 Hz to prevent the area between the contacts from being exposed to more than 250 Hz. This is particularly relevant in our series since our patients were implanted with a Medtronic 3387 lead, which carries contacts 1.5 mm apart from each other. Further studies with a Medtronic 3389 lead (which carries contacts only 0.5 mm apart from each other) will elucidate whether ILS affects the optimal delivered frequency in light of overlapping VAT when contiguous contacts are used. The average reduction of frequency with ILS for all PD patients was 31 Hz, with a range of 0–125. Nearly half of them (14/27 patients) had a frequency that was unchanged or reduced by 5 Hz with even distributions between groups (treated for dyskinesia, 6/12; other adverse effects, 5/9; and to improve parkinsonism, 3/6 patients). Although we speculate that this small change in frequency unlikely contributed to the reduction of dyskinesias, overall it is not clear how the frequency of DBS relates to clinical efficacy. The clinical response to frequencies varies between individuals and is frequency specific [37, 38]. As the mechanism is not clear, clinical experience and expertise with regard to neurophysiological responses to stimulation guide programming [39]. In a review of the patients who discontinued ILS for dyskinesias, 4 patients had stimulation delivered through the most dorsal contact before ILS that was also located in the rZI region. In 3 of these patients stimulation was reduced and, of those, 2 experienced a reduced frequency (>180 Hz before ILS). Consequently, in these patients the beneficial results may have been due to a reduction of stimulation. It is also noteworthy that case PD22 presented a worsening mood during ILS for the management of dyskinesias without any adjustments to medications. This is in keeping with previous observations reporting apathy and depression with stimulation dorsal to the STN [28].

Overall, ILS in PD patients with STN DBS was ineffective for the treatment of other adverse effects. Theoretically, ILS was attempted to reduce adverse effects in the setting of suboptimal lead placement. ILS improved stimulation-induced adverse effects in only 2 out of 9 patients for other stimulation-induced adverse effects. Confirming previous reports [40], dysarthria was the most common stimulation-induced adverse effect ($n = 6$). Only in 1 patient (PD5) did reduced stimulation of the pre-ILS contact located within the rZI region and longitudinal current shaping to a ventral contact within the STN permit amelioration of dysarthria. The location of contacts that induced dysarthria was within the STN or the rZI, regions that may induce speech changes with stimulation

[41, 42]. Therefore, only by markedly reducing stimulation within these regions, as in PD5, was dysarthria improved. In PD26, switching to ILS produced benefits in terms of impulsivity but worsened parkinsonism, which prevented its long-term use. None of the other patients experienced any benefit with ILS (5 with dysarthria and 2 with contractions).

In patients treated with VIM DBS for tremor, ILS demonstrated mixed results for the management of adverse effects (dysarthria and paresthesia). Previous reports in ET patients with VIM DBS and ILS for the management of stimulation-induced dysarthria demonstrated efficacy in 4 of 6 patients via reshaping of the VAT [43]. This mixed result and likely cause of efficacy by current steering along the longitudinal axis is comparable to our findings, with 2 out of 3 patients demonstrating a reduction of dysarthria with ILS.

In patients with dystonia treated with GPi DBS, the results were mixed in response to treatment of adverse effects with ILS. Our study is the first to evaluate ILS for stimulation-induced adverse effects associated with GPi DBS demonstrating efficacy in 3 out of 5 patients. Future studies will need to be performed on a less heterogeneous patient population.

Overall, ILS was effective for parkinsonism, specifically tremor and bradykinesia, possibly due to current steering along contacts within the STN and a reduction of stimulation to unwanted regions that resulted in adverse effects. On the other hand, some symptoms may have improved with ILS by activation of specific contacts as exemplified by PD18, whose tremor improved after activation of the most dorsal contact likely positioned within the rZI region [44, 45]. Furthermore, in PD15, FOG improved and good control of other symptoms of parkinsonism was maintained by interleaving the most ventral contact located within substantia nigra, providing additional support for this form of stimulation in the treatment of FOG [46]. Though not commonly used at our center, ILS was recently applied for gait disturbance in 8 patients with PD and a sustained benefit was achieved for >3 months [47].

There are no reports of ILS for tremor and, in our experience, it is not effective. The lack of efficacy may be indicative of disease progression that has been reported as a cause of worsened tremor over time in patients with VIM DBS [48, 49]. Other possible explanations are that the VAT was minimally affected by shaping of stimulation with ILS.

Similar to the lack of literature on the utility of ILS for adverse effects of GPi DBS, there is a dearth of evidence

on the effects of ILS in improvement of dystonia, with the exception of a single report of 4 patients with 50% improvement in dystonia [50]. Our findings are much less impressive, with only 4 out of 11 patients having any clinical benefit and only 2 continuing on ILS.

In general, battery drainage is likely increased with ILS as 2 independent programming settings are applied. Double monopolar stimulation shortens the battery life compared to single monopolar and bipolar stimulation [51]. It is not clear how ILS compares with double monopolar stimulation on battery consumption. However, if stimulation can be reduced with ILS compared to double monopolar stimulation, then the battery life may be extended. Calculation of the total electrical energy delivered would have aided in determining the degree of electrical output and if it increased with ILS compared to settings before ILS and to double monopolar settings, even greater battery drainage, shorting the life of the battery would occur with ILS.

Interpretation of our results is strongly related to the standard strategy applied for programming DBS patients at our center. As such, ILS was applied after having tried other strategies to either manage adverse effects or improve clinical symptoms (Fig. 1). Regarding improvement of clinical efficacy, ILS was considered as an alternative to double monopolar stimulation in the case that the latter was not efficacious or not tolerated. ILS settings with identical amplitudes and pulse widths at 2 different contacts would be similar to double monopolar settings; however, pulses at each contact would be offset by 4 ms (125 Hz equal an 8-ms interpulse interval). It is unknown if the effects of 2 programs in an interleave equate to the sum of the individual fields or if the phase delay provides an enhanced synergistic outcome. The lack of efficacy of ILS in the patients we switched from double monopolar to ILS using the same contacts at the same amplitude and pulse width (e.g., DYT15) would favor the first hypothesis. However, more research is needed to better understand how ILS works.

Conclusions drawn from this study must be considered in light of inherent problems with a retrospective study design. In addition, this study had the following limitations: the patients and the examiner were not blinded, the patients were aware that stimulation adjustments were being made although they were unaware of the specific adjustments, and the programmer was also the examiner, reflecting a common clinical practice. Moreover, there were no formal validated scales performed in evaluation of dyskinesias, although validated scales were performed for other symptoms. Patient recall

was also implemented to determine the cause of discontinuation of ILS. In localizing contacts on the DBS lead and comparing them to locations with the STN, the ATAG elderly STN probabilistic atlas was used. Although use of this atlas in our study population is more appropriate than use of one derived from a younger population, individualized anatomical differences between patients and the atlas must be considered. Programs estimating the VAT individualized to each patient are currently in development by several companies and application of this technology may also be of benefit in research and clinical practice. The generalizability of our results is limited as the patients in the cohort all had suboptimal results with monopolar and bipolar stimulation and the sample size was small for tremor and heterogeneous for dystonia. Impedance was not obtained for the majority of patients in the ILS setting. Consequently, calculation of the total electrical energy delivered in comparing pre- and post-ILS settings was not possible [52, 53]. Inherent in ILS is that the frequency can only be set to a maximum of 125 Hz. Nearly half of all of the patients (i.e., 24 out of 50) had a 5-Hz frequency reduction (i.e., from 130 to 125 Hz). Although this small reduction of frequency unlikely resulted in the clinical effects, greater reductions seen in other patients may have contributed. Another limitation of ILS is that 2 contacts cannot be programmed in constant current mode but rather only in constant voltage mode as used in this study. Although a strength of our

study is that we analyzed the clinical experience in ILS usage in a large number of patients from a tertiary referral center for DBS, the attempt to establish potential guidelines with a number of patients for such a heterogeneous group is challenging.

We identified 2 reasons for attempting ILS: to mitigate adverse effects and to improve disease signs and symptoms. The most impressive finding was improvement of dyskinesias with ILS by adding a contact dorsal to the STN likely activating discrete anatomical regions within the region of the rZI. Overall, ILS appears to have limited benefits in the treatment of other stimulation-induced adverse effects potentially due to minimal adjustment of the VAT and would unlikely be effective to salvage a misplaced electrode [54].

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