RESEARCH ARTICLE

Novel Programming Features Help Alleviate Subthalamic Nucleus Stimulation-Induced Side Effects

Viswas Dayal, PhD,[1,2*] Alexis De Roquemaurel, MD,[2] Timothy Grover, MRCSLT,[1,2] Francisca Ferreira, MD,[1] Maricel Salazar, BSN,[2] Catherine Milabo, BSN,[2] Joseph Candelario-McKeown, MSc,[2] Ludvic Zrinzo, PhD,[1,2] Harith Akram, PhD,[1,2] Patricia Limousin, PhD,[1,2] and Thomas Foltynie, PhD[1,2]

[1]*Department of Clinical and Movement Neurosciences, University College London Institute of Neurology, London, United Kingdom*
[2]*Unit of Functional Neurosurgery, National Hospital for Neurology and Neurosurgery, London, United Kingdom*

ABSTRACT: Background: Subthalamic nucleus deep brain stimulation (STN-DBS) is a widely used treatment for Parkinson's disease (PD) patients with motor complications, but can result in adverse effects (AEs) in a significant proportion of treated patients. The use of novel programming features including short pulse width (PW) and directional steering in alleviating stimulation-induced AEs has not been explored.

Objective: To determine if programming with short PW, directional steering, or the combination of these novel techniques can improve stimulation-induced dysarthria, dyskinesia, and pyramidal AEs.

Methods: Thirty-two consecutive PD patients who experienced reversible AEs of STN-DBS had optimization of their settings using either short PW, directional steering, or the combination, while ensuring equivalent control of motor symptoms. Pairwise comparisons of pre- and post-optimization adverse effect ratings were made. Patients were left on the alternative setting with the greatest benefit and followed up at 6 months. Modeling of volume of tissue activated (VTA) and charge per pulse (Qp) calculations were used to explore potential underlying mechanisms of any differences found.

Results: There were significant improvements in stimulation-induced dysarthria, dyskinesia, and pyramidal side effects after optimization. At 6 months, mean AE ratings remained significantly improved compared to pre-optimization ratings. Different patterns of shift in VTA for each AE, and Qp could be used to explain improvements using novel techniques.

Conclusions: Stimulation-induced dysarthria, dyskinesia, and pyramidal AEs induced by STN-DBS can be improved by using novel programming techniques. These represent additional tools to conventional methods that can be used to address these AEs. © 2020 The Authors. *Movement Disorders* published by Wiley Periodicals LLC. on behalf of International Parkinson and Movement Disorder Society.

Key Words: deep brain stimulation; Parkinson's disease; subthalamic nucleus; directional; pulse width; side effects

Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) is a well-established advanced treatment option for Parkinson's disease (PD).[1–3] However, despite improvements in motor fluctuations and quality of life compared to medical therapy alone, a significant proportion of patients with STN-DBS experience troublesome stimulation-induced adverse effects (AEs).[4–7] Common AEs seen at therapeutic levels of stimulation include dysarthria, stimulation-induced dyskinesia, and pyramidal effects with muscle contraction.[4,5,8–10] Programming options to deal with stimulation-related adverse effects traditionally have comprised altering stimulation from a monopolar configuration to a bipolar one, using alternative contacts,

*__Correspondence to:__ Dr. Viswas Dayal, Department of Clinical and Movement Neurosciences, University College London Institute of Neurology, Level 2, 33 Queen Square, London, WC1N 3BG, UK; E-mail: v.dayal@ucl.ac.uk

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interleaving, lowering amplitude, or using low frequency stimulation.[11,12]

In recent years, there have been two further significant developments in DBS programming: the possible use of shorter pulse widths (PW) than 60 μs and the availability of leads with segmented contacts, which enable directional steering of stimulation perpendicular to the lead.[13,14] Multiple studies have demonstrated that the therapeutic window (TW) between beneficial effects and adverse effects can be expanded by using shorter PW or directional stimulation[15–22] while retaining efficacy in treating Parkinsonian motor symptoms.[16,19] There are very few data, however, on the use of these features in alleviating stimulation-induced adverse effects in practice[23,24] Consequently, despite being commercially available for over 5 years, it is not clear what the role of these features is in STN-DBS programming and troubleshooting algorithms.[11,25]

The objective of this study was to evaluate whether using directional steering and short PW, individually or in combination, can improve stimulation-induced adverse effects of dysarthria, dyskinesia, and symptomatic pyramidal muscle contraction compared to conventional stimulation. In parallel, we used commercially available imaging software to explore potential underlying mechanisms that may mediate the appearance/resolution of adverse effects including (1) direction of stimulation and modeled volume of tissue activated (VTA), and (2) the charge per pulse (Qp) of stimulation settings.

Patients and Methods

All participants in this study had been treated with bilateral STN-DBS with Boston Vercise PC or Gevia systems (Boston Scientific, Marlborough, MA) using directional leads at the National Hospital for Neurology and Neurosurgery in the 24-month period through to July 2019. Each individual had experienced persistent stimulation-induced dysarthria, dyskinesia, or symptomatic pyramidal muscle contraction at least 3 months after surgery despite optimization of conventional settings, and therefore were invited to have a 3-day DBS optimization session using directional stimulation, short PW at 30 μs, or the combination of both these features. Routine DBS adjustments that fall within the manufacturer's CE marking, and made according to the degree and extent of symptomatic control represent part of our NHS standard of care and therefore we did not seek Ethics committee approval to systematically optimize each participant's DBS settings.

Surgery and Initial Post-Operative Programming

Patients had undergone surgery under general anesthesia without micro-electrode recordings, using the Leksell frame and our MRI-guided and MRI-verified technique.[26,27] All DBS parameters were initially programmed using a traditional monopolar review in ring mode at a PW of 60 μs and frequency of 130 Hz. The amplitude was titrated in an iterative manner over subsequent weeks alongside reduction in dopaminergic medications, to obtain optimal clinical effect.

Optimization Procedure

Patients who had persistent adverse effects that could not be rectified with a reduction in stimulation using the conventional programming configuration without compromising control of motor symptoms went on to have an extended programming session after verifying that the adverse effect was stimulation-induced and reversible. Only patients using segmented contacts in ring mode were included in the study, and the vertical level of contacts was not changed during optimization. An extended monopolar review was carried out after overnight withdrawal of dopaminergic medication. The chronically used contacts were re-assessed to determine the efficacy threshold (ET) and adverse effect threshold (ST) in ring mode at 60 μs. The contralateral STN was screened in cases of clearly unilateral symptoms, and both STNs were screened for dysarthria and in cases of bilateral dyskinesia or pyramidal symptoms. The ET was determined by repetitive testing of rigidity. Bradykinesia, tremor, and gait were also assessed and further adjustments to the ET were made if necessary taking these into account, for maximal overall improvement of symptoms. The benchmark for motor symptom control was set to the optimal level achieved during this process in the RM60 configuration. Adverse effect thresholds were recorded for the relevant adverse effect at their earliest emergence, to the nearest 0.1 mA. Each of the three segments of the ring level was then screened separately to record the equivalent thresholds. The segment with the best therapeutic window (TW) was used to derive directional settings. The same process was then repeated at 30 μs. This resulted in three alternative settings to the baseline setting of ring mode at 60 μs (RM60) for each patient: ring mode at 30 μs (RM30), best directional stimulation at 60 μs (DIR60), and best directional stimulation at 30 μs (DIR30).

Patients were then assessed on their usual medications and any further adjustments to each of the alternative settings were made to optimize clinical efficacy if necessary. It was ensured during this process that there was no deterioration in motor symptom control using the three alternative settings compared to the baseline (RM60) setting. The frequency was kept constant at 130 Hz at all settings, and no medication changes were made during the optimization period.

Assessments

Treatment efficacy was evaluated using a focused motor assessment of selected items of the UPDRS-III scale: 20, 22, 23, and 29 (rest tremor, rigidity, finger taps, and gait). All adverse effect assessments during the optimization period were done in the *on*-medication state after at least 3 hours on each stimulation condition. The order of the conditions assessed was balanced across the cohort.

In patients with stimulation-induced dysarthria, the Sentence Intelligibility Test (SIT)[28] was used to rate speech intelligibility. Perceptual characteristics of speech were also scored using a recorded 60-second monologue of the patient's speech using scales developed by Darley and colleagues,[29] rated by a speech therapist unaware of the stimulation settings for each recording.

Dyskinesia was rated using the objective sections of the Unified Dyskinesia Rating Scale (sum of parts III and IV of UDysRS) on each stimulation condition.

For pyramidal tract symptoms (characteristic involuntary muscle contractions affecting the face or limbs), the thresholds for eliciting these, as reported by the patient or observed by the clinician, were recorded on each stimulation condition. To make comparisons across the different conditions, the thresholds and TW in terms of charge per pulse (TW_Q) rather than amplitude were used.

At the end of the optimization period, a full UPDRS-III score on and off medications on the final optimized stimulation condition was recorded.

Patients were followed up at 6 months after the initial optimization. Stimulation settings were recorded and adverse effects of dysarthria and dyskinesia were objectively rated. For patients with pyramidal tract symptoms, any recurrence of these symptoms and the TW_Q were recorded.

Imaging, Lead Localization and Orientation, and VTA Modeling

All patients underwent stereotactic MRI pre- and post-lead implantation as part of their routine surgery. Patients also had a non-stereotactic CT scan to confirm the orientation of electrodes using Brainlab Elements software (Brainlab AG, Munich, Germany: www.brainlab.com) to allow for imaging guided optimization of DBS therapy. For lead localization, the pre-implantation T1 MR-scan was co-registered with the CT scan. The lead trajectory detected on CT scan could then be visualized on the segmented pre-implantation MRI, and lead orientation was determined using the automatized analysis of the artefact generated by the anterior lead marker. Automatized segmentation of basal ganglia nuclei was performed using Brainlab Elements software. The segmentation of the STN was then systematically reviewed by a neurosurgeon and manually further refined if necessary.

Stimulation field models were constructed using a finite element model (Guide XT version 2.0, Boston Scientific, Marlborough, MA; https://www.bostonscientific.com/en-EU/products/deep-brain-stimulation-systems/Guide-DBS.html). This model was calculated assuming homogenous and isotropic tissue conductivity of 0.3 S/mm, and neural activation threshold was based on myelinated axon models 5.7 μm in diameter and oriented perpendicular to the lead orientation vector. The model also incorporated bulk tissue capacitance, an electrode electrolyte interface, and a tissue encapsulation area.[30] Models similar to the one implemented here showed good reliability in predicting corticospinal tract activation when measured on electromyogram recordings.[31] For each STN, VTAs of the baseline setting (RM60), optimized setting (one of the three alternative conditions), and segment with the lowest adverse effect threshold were modeled. The shift from the baseline to the optimized VTAs were described, in terms of the areas outside the STN involved (Supplementary Table S1).

Statistical Analysis

The primary analysis compared adverse effect measures (SIT, UDysRS, and TW_Q) at baseline to the post-optimization assessment and the 6-month follow-up assessment using pairwise comparisons.

To examine differences between the different stimulation conditions in the acute setting, a secondary analysis with repeated measures analysis of variance (ANOVA) was used, with subsequent pairwise comparisons between the four conditions.

IBM SPSS Statistics software was used (IBM SPSS for Windows, Version 25.0. IBM Corp., Armonk, NY).[32] Sphericity was verified using Mauchly's test before carrying out ANOVA analyses. All data were checked for normality, and non-parametric tests (Wilcoxon matched-pair signed-rank test and related measures Friedman's two-way ANOVA by ranks) were used for non-normal data. Statistical significance was set to 0.05, and the Bonferroni correction method was applied to adjust for multiple comparisons.

Results

Thirty-two patients with PD (10 females, mean age 60.1 ± 8.3 years, preoperative UPDRS-III 47 ± 13.5 off and 16.5 ± 7.1 on medication) participated in this study. The mean duration of STN-DBS therapy at the time of optimization was 7.9 ± 7.7 months (range = 3–32 months). Thirteen patients had dysarthria, 15 had dyskinesia, and 5 had pyramidal adverse effects.

In the optimization session, 18 STNs were identified as responsible for stimulation-induced dysarthria, 17 for dyskinesia, and 7 for pyramidal symptoms, on conventional settings (RM60). One patient presented with both dysarthria and facial muscle contraction and was included in assessment of both adverse effects. Of the 32 patients, an improvement in adverse effects during the optimization session using at least one of the alternative stimulation conditions could be achieved in all patients. However, one patient did not tolerate any of the alternative settings due to delayed onset of off symptoms and reverted to RM60 settings. The mean efficacy and adverse effect thresholds and TW on each condition from the extended monopolar review are presented in Table 1.

Adverse Effect Outcomes

In the dysarthria group, the Sentence Intelligibility Test (SIT%) at baseline was 75.5% ± 21.0% (median = 82%, range = 11–90), and was significantly improved post-optimization (mean = 95.7% ± 4.7%, median = 98%, range = 83–100; $P = 0.001$) and at the 6-month follow-up (mean = 91.3% ± 6.5%, median = 92.5%, range = 78–100; $P = 0.005$) compared to baseline (Table 2). The mean SIT% with stimulation off was 89.8% ± 9.6%; median 93% (67–99).

In the dyskinesia group, the UDysRS (III + IV) at baseline was 16.9 ± 6.8, and was significantly improved post-optimization (mean = 1.9 ± 3.2; t [14] = 7.77, $P < 0.001$) and at the 6-month follow-up (mean 1.0 ± 1.7; t [13] = 7.9, $P < 0.001$) compared to baseline. The mean dyskinesia score off stimulation was 0.2 ± 0.6.

In the pyramidal adverse effect group, the TW_Q at baseline was −22.3 ± 9.0 nC and was significantly improved post-optimization (mean = 67.3 ± 54.1; t [6] = −4.28; $P = 0.005$) and at 6 months (mean = 32.6 ± 41.1; t [6] = −3.39, $P = 0.015$). One patient had a mild recurrence of pyramidal symptoms at the follow-up visit, and this corresponded to a negative TW_Q in one STN.

The final optimized conditions in the dysarthria group were DIR30 (11 patients) and DIR60 (2 patients); in the dyskinesia group: DIR30 (12 patients), DIR60 (2 patients), and RM30 (1 patient); and in the pyramidal adverse effect group: DIR30 (3 patients, including one who also had dysarthria), and DIR60 (2 patients). Two patients were excluded from the analysis of follow-up data: one from the speech group was lost to follow-up, and one in the dyskinesia group needed to be reprogrammed using the dorsal-most contact in addition due to inadequate control of dyskinesia. The remaining 30 patients were on the following conditions at the 6-month follow-up: DIR30 (n = 20), DIR60 (n = 7), RM30 (n = 2), and RM60 (n = 1).

In the secondary analysis of comparisons between the four stimulation conditions during the optimization session, there were significant differences in SIT% between RM60 and each of the three alternative conditions with pairwise comparisons (vs RM30: $P = 0.019$, vs DIR60: $P = 0.015$, and vs DIR30: $P < 0.001$) but not between any of the three alternative conditions. For dyskinesia ratings, all three alternative conditions had significantly lower scores than RM60 ($P = 0.013$, $P < 0.001$ and $P < 0.001$, respectively), and the DIR30 condition also had significantly lower scores than RM30 ($P = 0.01$). For pyramidal symptoms, significant differences in TW_Q were only found between RM60 versus DIR60 ($P = 0.009$), and RM60 versus DIR30 ($P = 0.023$). Comparisons between the four conditions are presented in Fig. 1.

Representative examples of pre- and post-optimization recordings of patients with dysarthria (Supplementary Audio S1 and S2), dyskinesia (Supplementary Video S1), and pyramidal adverse effects (Supplementary Video S2) are can be viewed via the hyperlinks above.

TABLE 1. Efficacy and adverse effect thresholds and therapeutic Windows overall and in each subgroup

	RM60	RM30	DIR60	DIR30
Dysarthria (18 STNs)				
Efficacy threshold (mA)	2.8 ± 1.2	4.1 ± 1.9	2.0 ± 0.8	3.2 ± 1.4
Adverse effect threshold (mA)	2.1 ± 0.7	4.2 ± 1.5	3.0 ± 1.2	4.3 ± 1.4
Therapeutic window (mA)	−0.7 ± 0.7	0.1 ± 1.2	1.0 ± 0.9	1.1 ± 1.4
Dyskinesia (17 STNs)				
Efficacy threshold (mA)	2.6 ± 0.7	4.0 ± 1.2	2.4 ± 0.8	3.6 ± 1.4
Adverse effect threshold (mA)	2.2 ± 1.2	5.2 ± 2.6	3.8 ± 1.3	6.0 ± 3.3
Therapeutic window (mA)	−0.4 ± 1.0	1.2 ± 2.1	1.4 ± 1.5	2.4 ± 3.1
Pyramidal adverse effect (7 STNs)				
Efficacy threshold (mA)	2.7 ± 0.7	4.2 ± 1.3	2.1 ± 0.8	3.9 ± 1.4
Adverse effect threshold (mA)	2.3 ± 1.2	5.4 ± 2.7	2.9 ± 1.3	5.7 ± 3.4
Therapeutic window (mA)	−0.4 ± 1.0	1.2 ± 2.1	0.7 ± 1.5	1.8 ± 3.2
Overall (42 STNs)				
Efficacy threshold (mA)	2.7 ± 0.7	4.1 ± 1.4	2.2 ± 0.6	3.5 ± 1.7
Adverse effect threshold (mA)	2.2 ± 0.7	4.8 ± 2.9	3.3 ± 0.8	5.2 ± 2.4
Therapeutic window (mA)	−0.5 ± 0.1	0.7 ± 2.1	1.1 ± 0.5	1.8 ± 1.4

TABLE 2. Comparison of adverse effect assessments at baseline, post-optimization, and at 6 months

Adverse effect assessment	n	Baseline	Post-optimization	At 6-month follow-up	Baseline vs:	
					Post-optimization	Follow-up at 6 months
SIT %	13	82 (11–90)	98 (83–100)	92.5 (78–100)	$P = 0.001$	$P = 0.005$
UDysRS III + IV	15	16.9 ± 6.8	1.9 ± 3.2	1.0 ± 1.7	$P < 0.001$	$P < 0.001$
TW for pyramidal symptoms (TW_Q in nC)	5	−22.3 ± 9.0	67.3 ± 54.1	32.6 ± 41.1	$P = 0.005$	$P = 0.015$

Values are reported as median (range) for non-parametric data and mean ± SD for parametric data. SIT, Sentence Intelligibility Test; UDysRS III + IV, dyskinesia rating score.

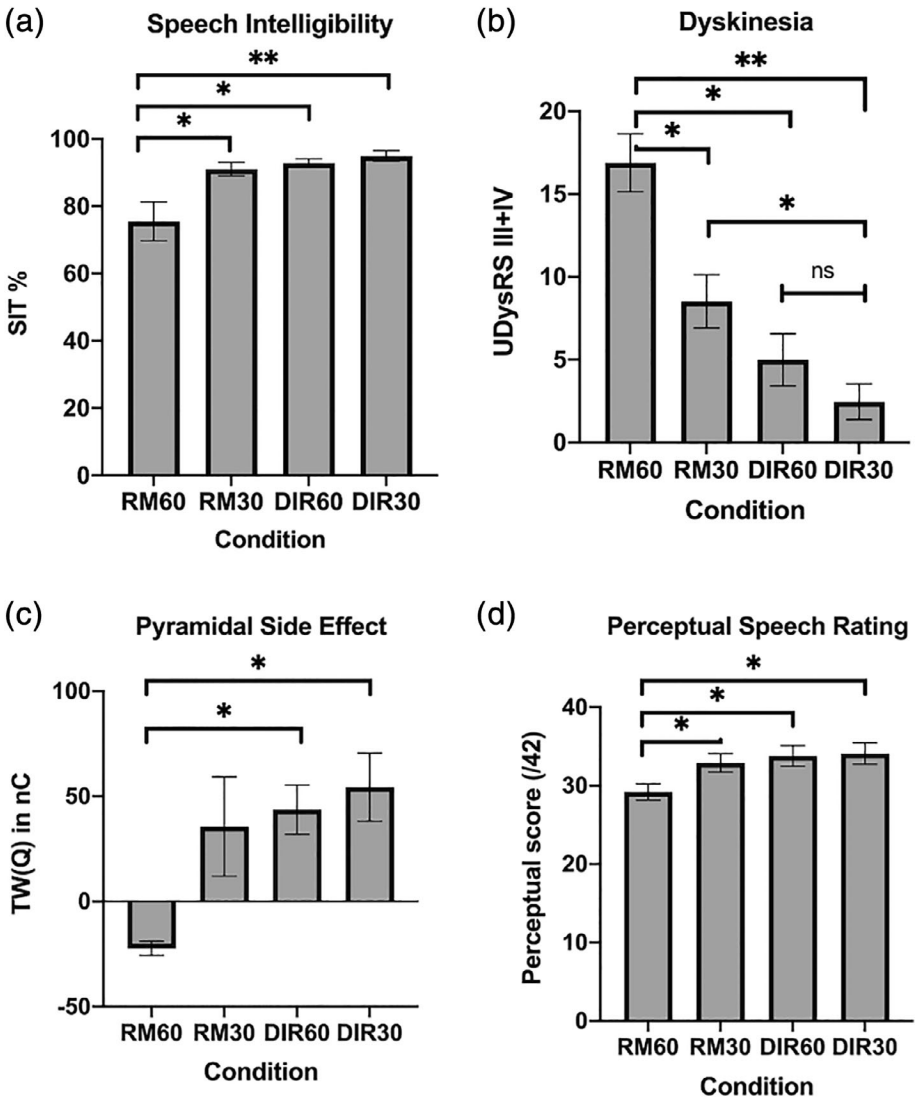

FIG 1. Adverse effect assessments on the four conditions during the optimization session. Significant differences between groups indicated by $^*P < 0.05$, $^{**}P < 0.001$, ns, not significant.

Motor Scores

The mean post-optimization UPDRS-III score was 24.6 ± 11.2 off medication and 14.1 ± 6.8 on medication. Focused motor scores for each STN optimized (composite of UPDRS-III items 20, 22, and 23) were as follows: off-medication off-stimulation: median 5 (range = 4–9); pre-optimization off-medication on-stimulation: median 2 (range = 1–4); post-optimization off-medication on-stimulation: median 2 (range = 1–4), confirming that there was no loss of therapeutic benefit for motor disability following the optimization procedure. The gait score (item 29) off-medication off-stimulation was median 2 (range = 1–4);

off-medication on-stimulation pre-optimization: median 1 (range = 1–2); off-medication on-stimulation post-optimization: median 1 (range = 0–1). A reduction (improvement) in gait scores of 1 to 2 points was seen in 10 patients in the dyskinesia group post-optimization compared to their pre-optimization assessments.

Lead Orientation and VTA Modeling

VTAs were modelled for 40 STNs. A description of the active contact location within each STN and orientation of directional segment used as detailed in the methods are presented in Supplementary Table S1. Representative examples of VTAs from each adverse effect group are shown in Figure 2.

In the dysarthria group, 11 of 17 VTAs showed a lateral/posterolateral shift after optimization from medial/posteromedial areas outside the STN at baseline. The remaining ones included anterolateral to anteromedial (2), lateral to medial (1), lateral and medial to anterior (2), and posterior to within STN (1).

In the dyskinesia group, 15 of 17 STNs showed a shift away from lateral or posterolateral areas outside the STN to more centrally within the STN, anteriorly or medially. The remaining two shifted from medial to lateral and posteromedial to central STN. Both these patients, as well as one from the former group of 15, had experienced stimulation-induced dystonic symptoms as their main adverse effect.

In the pyramidal symptom group, all seven STNs had a shift away from lateral areas outside the STN (including 1 from medial and lateral) to the central or anterior STN, or medially (2), post-optimization.

Charge per Pulse (Qp)

The mean charge per pulse (Qp) at the efficacy threshold for RM60 was 160.6 ± 55.8 nC, for RM30: 122.2 ± 45.2 nC, for DIR60: 131.3 ± 45.8, and for DIR30: 104.7 ± 43.1. There was a significant difference among the four conditions ($\chi^2[3] = 68.4$, $P < 0.001$). Pairwise comparisons showed significant differences between all pairs except RM30 versus DIR60 ($P = 0.38$) and RM30 versus DIR30 ($P = 0.067$), as shown in Figure 3.

Discussion

The results of this study provide the first systematically collected data to indicate that novel programming techniques using directional stimulation with segmented contacts and short pulse width can reproducibly improve stimulation-induced adverse effects of dysarthria, dyskinesia, and symptoms of pyramidal tract activation in patients with STN-DBS in the long term. Improvements were present acutely following optimization and were maintained at the 6-month follow-up compared to baseline assessments. Although the optimal condition out of the three alternatives for the greatest improvement in adverse effects varied for individuals, the combination of directional stimulation with short pulse width (DIR30) was the most commonly selected optimal setting in all adverse effect groups.

Modeling of the stimulation field, which was done following the optimization session, revealed different patterns of shift in the VTAs following optimization according to the major adverse effect present. In the dysarthria group, this was most commonly away from the medial area (in or outside the STN) and in a smaller number of patients, away from the lateral regions outside the STN. It is recognized that stimulation-induced dysarthria can be caused by both pyramidal tract activation affecting oromandibular muscle function and by spread of current medially, where involvement of the cerebellothalamic and pallidothalamic tracts have been implicated.[5,33–35]

In the dyskinesia and pyramidal groups, there were consistent patterns of shift away from the posterolateral and lateral regions outside the STN, respectively. The early induction of dyskinesia after electrode implantation and initiation of stimulation is usually seen as reassuring confirmation of accurate placement in the target for alleviation of PD motor symptoms. It may therefore seem counterintuitive to direct stimulation away from the segment producing this. However, it is possible that in patients who have intractable stimulation-induced dyskinesia, even at low amplitudes on ring mode settings, the current is too focused in this region, and it is evident from the VTA modelling data that often only a subtle shift in the stimulation field with directional stimulation was sufficient to resolve this. Consistent with these principles, another study reported an approach to programming using segmented contacts where directing only a small proportion of the total current to the dyskinesia-inducing contact and the remainder to other segments or different vertical levels resulted in excellent overall control of motor symptoms.[36]

The improvement in severity of adverse effects by using directional steering and spatial shaping of the stimulation field is explicable by knowledge of anatomical pathways. However, our data suggest that there appears to be an additive beneficial effect when short PW is combined with best directional stimulation. One proposed mechanism by which short PW may reduce adverse effects is by selective modulation of fibers within a stimulation field, depending on their degree of excitability.[37] However, a further consistent observation across studies on the use of short PW is that the charge per pulse (Qp) of stimulation required for an equivalent therapeutic effect is significantly lower compared to using conventional PW.[15–18] The pattern seen with Qp in the four conditions closely mirrors the magnitude of reduction in adverse effects. It is known that

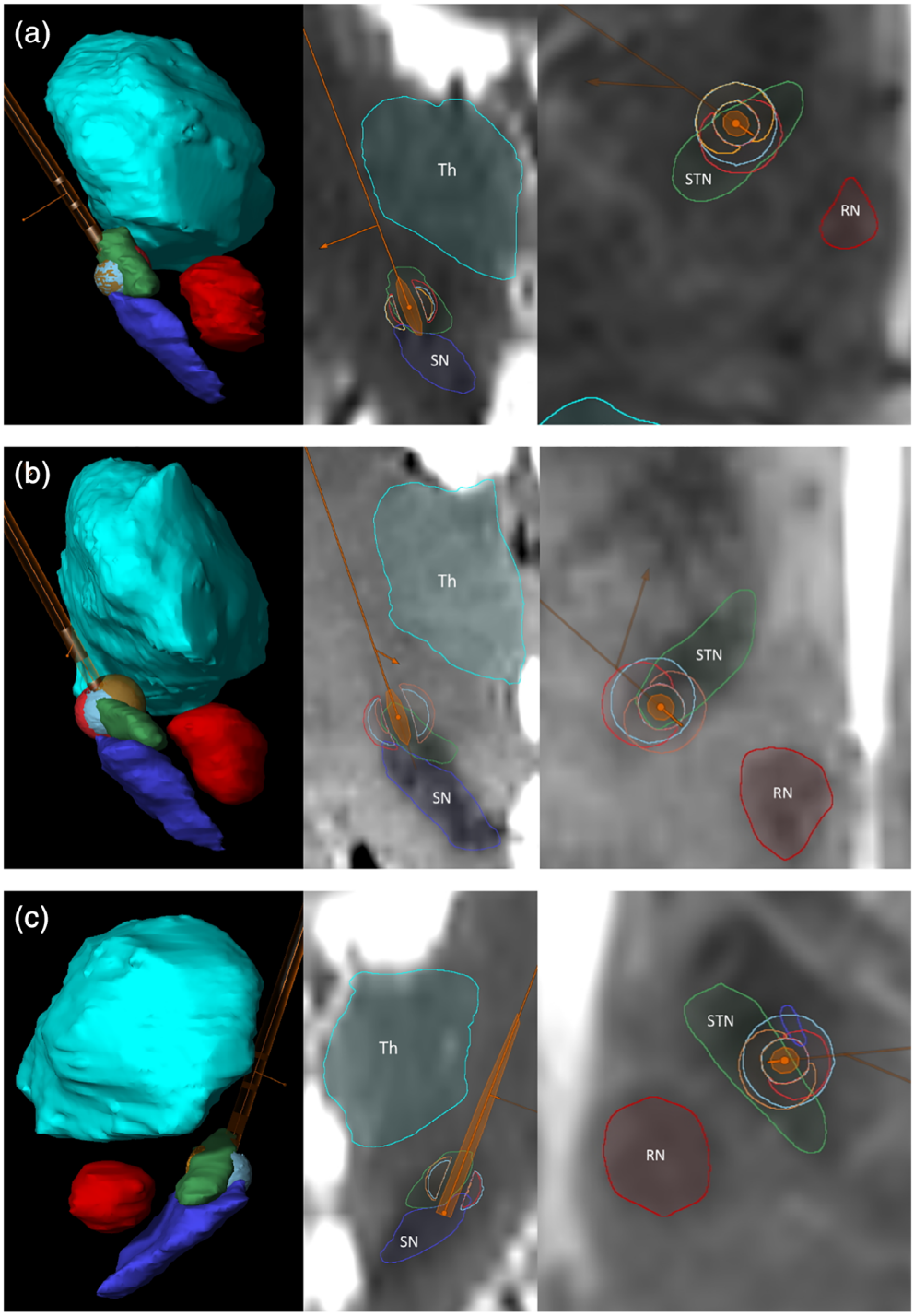

FIG 2. Representative VTA models in patients with (**A**) speech impairment (right STN), (**B**) dyskinesia (right STN), and (**C**) pyramidal adverse effects (left STN). 3D models are shown on the left; T_2-weighted MRI coronal view in the middle and axial view on the right for each patient. The baseline VTAs are indicated in light blue, optimized VTAs in yellow, and direction of segment with lowest side effect threshold in red. These images correspond to the clinical audio and video recordings included in the Supplementary Information. Nuclei: Th, thalamus (turquoise); STN, subthalamic nucleus (green); RN, red nucleus (red); SN, substantia nigra (indigo). [Color figure can be viewed at wileyonlinelibrary.com]

high amplitudes and PWs, which constitute the amount of charge per pulse, are associated with the development of adverse effects.[4,9,38] The further improvement in adverse effects seen with the use of short PW may therefore be due, at least in part, to lower electrical charge used per pulse of stimulation.

It is worth noting the distinct mechanisms of stimulation-induced side effects: current diffusion into

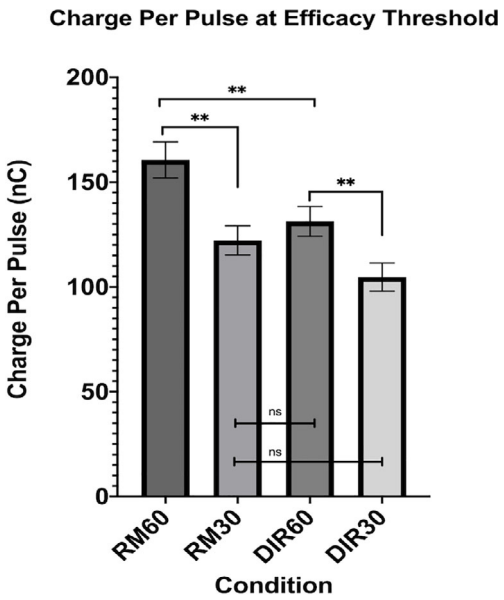

FIG 3. Charge per pulse at the efficacy threshold on the four conditions. Differences between groups indicated by *$P < 0.05$, **$P < 0.001$, ns, not significant.

adjacent structures for dysarthria and pyramidal effects, and excessive stimulation of a posterolateral subthalamic "hotspot" for dyskinesia. These are relevant when considering the predominant underlying mechanisms of alleviating these with the use of short PW, such as fiber selectivity versus a lower charge per pulse, respectively. In the case of dyskinesia, the improvement with short PW conditions (RM30 and DIR30) compared to their standard PW counterparts may be explained by injection of a lower charge per pulse.

Although several studies on the use of short pulse width and directional stimulation have shown an expanded therapeutic window with the use of these features, as well as equivalent efficacy in motor symptom control compared to conventional stimulation, the use of these novel programming techniques in alleviating stimulation-induced adverse effects has been less well studied.[15–19,22,39,40] In the current study, all patients were on 130 Hz frequency settings and were within 3 years' duration of STN-DBS therapy (with a mean duration of 7.9 months). It is possible that differences in response to novel programming strategies may relate to duration of DBS therapy due to factors such as disease progression, or possibly long term maladaptive effects of stimulation. It has also been shown that low frequency stimulation in the range of 60–100 Hz can improve adverse axial effects of STN-DBS including dysarthria.[41–43] Additionally, although we only included patients initially programmed with segmented contacts in ring mode, and did not change the vertical level of contacts (to avoid introducing additional variables in the comparisons), there are other programming strategies that include the use of superimposed directional contacts, bipolar stimulation, and multiple monopolar settings with independent current sources that may be useful in clinical routine.

Limitations of this study include its non-blinded and non-randomized design and small sample sizes, particularly in the pyramidal symptom group. This restricts interpretation of differences between the alternative stimulation conditions in particular. Although speech assessments were recorded and done without the assessor having knowledge of the stimulation condition, this was not possible in the dyskinesia or pyramidal symptom group in this study. It should also be noted that the cohort of patients in this study had clearly reproducible and reversible stimulation-induced adverse effects on conventional settings, and the results can only be generalized to such patients.

Our data show that despite optimal placement of electrodes in the intended region of the STN target, a proportion of patients develop troublesome adverse effects. Factors that may determine whether an individual develops a given adverse effect (apart from the specific electrode location) include their predisposition based on pre-existing symptoms, the specific stimulation parameters required for optimal therapeutic effect, and individual somatotopy of the STN and surrounding structures. Therefore, even with the best processes for selection of patients and meticulous pre-operative planning and surgical technique, clinicians are often faced with patients with "optimally" sited electrodes and good therapeutic benefit but accompanying adverse effects. Novel programming features using directional steering and an expanded parameter range with respect to PW give the programming clinician further tools to refine STN stimulation in these cases.

To our knowledge, this cohort represents not only the largest set of data on the use of these novel programming techniques but also the first study on the clinical use of directional stimulation in reducing stimulation-induced adverse effects, with significant and sustained results, and plausible underlying mechanisms for the observed findings. This will help inform further clinical trials and studies looking at longer term outcomes, as well as clinicians frequently faced with the challenges of dealing with treatment related adverse effects of STN-DBS. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Authors' Roles

1. Research Project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

V.D.: 1A, 1B, 1C, 2A, 2B, 3A
A.D.R.: 1C, 3B
T.G.: 1C, 3B
F.F.: 1C
M.S.: 1B, 1C
C.M.: 1C
J.C.: 1C
L.Z.: 3B
H.A.: 2C, 3B
P.L.: 2C, 3B
T.F.: 1A, 2A, 2C, 3B

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V.D. has received honoraria and travel expenses from Boston Scientific. H.A. has received honoraria and travel expenses from Boston Scientific and BrainLab. P.L. and L.Z. have received honoraria and travel expenses from Medtronic and Boston Scientific for speaking at meetings. C.M., M.S., and J.C. have received travel expenses from Medtronic, Abbott, and Boston Scientific. T.F. has received grant support from NIHR, John Black Charitable Foundation, Rosetrees Trust, Michael J. Fox Foundation, and Cure Parkinson's Trust. He has honoraria for speaking at meetings supported by Boston Scientific, BIAL and Profile Pharma. He serves on advisory boards for BIAL, Oxford Biomedica, and Peptron.

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