Interleaved Deep Brain Stimulation for Dyskinesia Management in Parkinson's Disease

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ABSTRACT: Background: In patients with Parkinson's disease, stimulation above the subthalamic nucleus (STN) may engage the pallidofugal fibers and directly suppress dyskinesia.
Objectives: The objective of this study was to evaluate the effect of interleaving stimulation through a dorsal deep brain stimulation contact above the STN in a cohort of PD patients and to define the volume of tissue activated with antidyskinesia effects.
Methods: We analyzed the Core Assessment Program for Surgical Interventional Therapies dyskinesia scale, Unified Parkinson's Disease Rating Scale parts III and IV, and other endpoints in 20 patients with interleaving stimulation for management of dyskinesia. Individual models of volume of tissue activated and heat maps were used to identify stimulation sites with antidyskinesia effects.

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Results: The Core Assessment Program for Surgical Interventional Therapies dyskinesia score in the on medication phase improved $70.9 \pm 20.6\%$ from baseline with noninterleaved settings ($P < 0.003$). With interleaved settings, dyskinesia improved $82.0 \pm 27.3\%$ from baseline ($P < 0.001$) and $61.6 \pm 39.3\%$ from the noninterleaved phase ($P = 0.006$). The heat map showed a concentration of volume of tissue activated dorsally to the STN during the interleaved setting with an antidyskinesia effect.
Conclusion: Interleaved deep brain stimulation using the dorsal contacts can directly suppress dyskinesia, probably because of the involvement of the pallidofugal tract, allowing more conservative medication reduction. © 2019 International Parkinson and Movement Disorder Society

Key Words: deep brain stimulation; dyskinesia; interleaving; Parkinson's disease; volume of tissue activated

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) can aggravate or induce dyskinesia.[1,2] In patients with Parkinson's disease (PD), dyskinesia improvements after STN DBS mostly result from reduction in dopaminergic therapy.[3] Stimulation superior to the STN, a region enriched with pallidofugal fibers, can directly suppress dyskinesias.[4,5]

Interleaving stimulation (ILS) is a programming technique in which 2 independent settings are programmed on the same electrode using different contacts, amplitudes, and pulse widths. These independent settings are delivered in an interleaved pattern, typically at 125 Hz.[6] ILS allows the activation of multiple areas after conventional stimulation (noninterleaved) fails to achieve the desired results.[6-9]

The aim of this study was to assess the effect of alternating stimulation from dorsal lead contacts above the STN with the presumed engagement of pallidofugal fibers for the specific suppression of dyskinesia, with a conventional STN contact to address the cardinal symptoms of PD.

Methods

Patient Selection

Patients were selected during DBS programming visits and by a review of health records. We included patients with STN DBS (unilateral or bilateral) programmed with ILS for the treatment of dyskinesia. We excluded patients with other neurosurgical interventions for PD and patients without available brain images.

DBS Programming

Initial programming was based on monopolar review to address PD symptoms with minimal side effects.[10] On follow-up visits, increments in voltage were done in parallel with medication reduction.[11] In patients with bothersome dyskinesia (residual or stimulation induced), we used ILS in a monopolar configuration of the more dorsal contact contralateral to the dyskinesia or bilaterally in case of axial dyskinesia. We started with a pulse width of 60 μs and low voltages (~1.0 V according to the thresholds). Stimulation amplitude was increased until the dyskinesia was visibly suppressed or side effects occurred. In cases limited by side effects, the contact immediately below (second more dorsal) was activated or bipolar configuration was tried.

Data Collection

The main clinical endpoints were the Core Assessment Program for Surgical Interventional Therapies (CAPSIT) dyskinesia scale (ranging from 0–28),[12] the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor symptoms), and the therapy complications measured by UPDRS part IV and divided into subitems for dyskinesia and motor fluctuations.

Additional clinical endpoints were the tremor score, axial scores, levodopa equivalent daily dose,[13] total electrical energy delivered,[14] and internal pulse generator longevity.

Computational Modeling

Computational volumes of tissue activated during conventional and ILS settings were generated as previously described.[15] Briefly, all DBS leads were mapped to the left side to allow for direct comparison. The activated volumes were brought into a common space by registering each patient's T1 magnetic resonance image to the PD-25 template[16] and applying the resulting nonlinear transform to the volume of tissue activated. Stimulation location maps were generated by discretizing each transformed activation volume into a binary volume and summing each voxel in our grid across all activation volumes. The following 3 maps were generated: (1) volume of tissue activated with conventional settings, (2) volume of tissue activated with ILS, and (3) volume of tissue activated with ILS subtracting the volume of tissue activated with conventional stimulation for each patient.

Statistical Analysis

In this study, t tests were used to for parametric variables and the Wilcoxon test for nonparametric variables. We used 1-way analyses of variance for multiple comparisons and chi-square teste for the analyses of frequencies. A 2-sided P value <0.05 was adopted for statistical significance.

Results

A total of 20 patients with STN DBS were programmed using ILS settings for dyskinesia management. The demographic features are presented in Supporting Information Table 1, and the baseline characteristics are presented in Supporting Information Table 2.

Using conventional stimulation, there was a $56.0 \pm 22.0\%$ improvement in UPDRS-III scores in the *off* medication/ON stimulation condition relative to the *off* medication at baseline ($P < 0.001$), and $62.5 \pm 19.2\%$ improvement in *on* medication/ON stimulation relative to the *off* medication at baseline ($P < 0.001$; Fig. 1A). The CAPSIT dyskinesia score improved $70.9 \pm 20.6\%$ relative to baseline ($P < 0.003$; Fig. 1B), and the patients reported improvement in complications of therapy (UPDRS-IV) relative to levodopa-induced dyskinesia ($P = 0.04$), motor fluctuations ($P = 0.06$), and total score ($P = 0.02$; Fig. 1C). The levodopa equivalent daily dose after STN DBS with conventional settings was 979 ± 472 mg/day, which represents a reduction of 346.9 ± 391.3 mg/day ($27 \pm 30\%$; $P = 0.002$).

Conventional programming settings are presented in Supporting Information Table 3. During conventional treatment, 15 (75%) patients reported bothersome dyskinesia. In this group, the CAPSIT dyskinesia score was 5.3 ± 3.6, a reduction of $58.4 \pm 16.3\%$ from baseline ($P = 0.003$). In addition, 5 (25%) patients developed stimulation-induced dyskinesia in the *off* medication state during programming visits. To improve dyskinesia in these patients, an additional dorsal contact of the DBS electrode was activated using ILS. Final ILS settings are presented in Supporting Information Table 4.

Using ILS with the activation of a more dorsal contact, the CAPSIT dyskinesia score improved $61.6 \pm 39.3\%$ (2.3 ± 3.7 points) relative to the conventional settings ($P = 0.006$) and $82.0 \pm 27.3\%$ relative to baseline ($P < 0.001$; Fig. 1E). Patients also reported improvement in the UPDRS-IV in both domains, dyskinesia ($P = 0.03$) and motor fluctuation ($P = 0.04$), relative to conventional settings (Fig. 1F). There was no significant change in the UPDRS-III *on* medication/ON stimulation ($P = 0.89$); however, there was a mild worsening in the *off* medication/ON stimulation scores ($P = 0.16$; Fig. 1D). The average levodopa equivalent daily dose with ILS was 993 ± 346 mg/day, which was not significantly changed from the conventional phase ($P = 0.75$).

To clarify the source of motor worsening, we analyzed the changes in tremor and axial scores (Supporting Information Figs. 1 and 2). There was no significant change in the tremor score in *off* medication/ON stimulation between the conventional and ILS conditions ($P = 0.77$). There was a trend for deterioration of 1.35 ± 3.2 points in the axial score during the *off* medication/ON stimulation condition with ILS ($P = 0.08$).
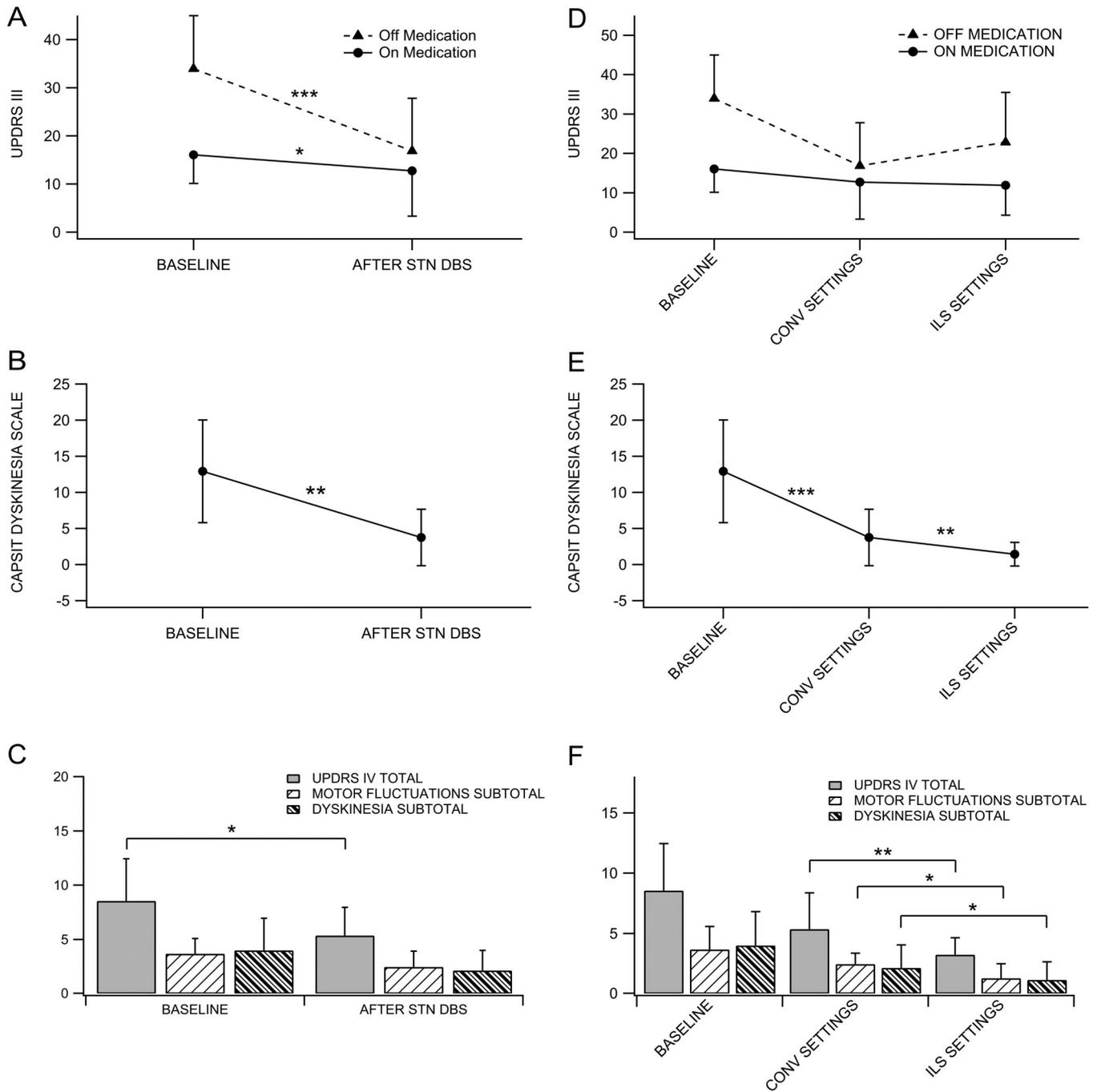
FIG. 1. Conventional settings (left). (**A**) UPDRS-III: baseline *off* medication 33.9 ± 11.0, *on* medication 16.0 ± 5.9. Conventional DBS *off* medication/ON stimulation 16.8 ± 10.9, *on* medication/ON stimulation 12.7 ± 9.4. (**B**) CAPSIT dyskinesia: baseline *on* medication 12.9 ± 7.1; conventional DBS *on* medication/ON stimulation 3.7 ± 3.9. (**C**) UPDRS-IV: baseline total score 8.5 ± 3.8, dyskinesia score 4.0 ± 2.9, and motor fluctuation score 3.6 ± 1.4. Conventional DBS total score 5.3 ± 2.5, dyskinesia score 2.1 ± 1.8, and motor fluctuation score 2.4 ± 1.4. ILS (right). (**D**) UPDRS-III: *off* medication/ON stimulation 22.8 ± 12.6, *on* medication/ON stimulation 11.8 ± 7.6. (**E**) CAPSIT dyskinesia: *on* medication/ON stimulation 1.4 ± 1.6. (**F**) UPDRS-IV: total 3.2 ± 1.4, dyskinesia 1.1 ± 1.5, and motor fluctuations 1.3 ± 1.2. Values are (mean ± standard deviation). *P < 0.05; **P < 0.01; ***P < 0.001. CAPSIT, Core Assessment Program for Surgical Interventional Therapies; DBS, deep brain stimulation; ILS, interleaving stimulation; STN, subthalamic nucleus; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; UPDRS-IV, Unified Parkinson's Disease Rating Scale part IV.

Volume of Tissue Activated

The patient-specific volume activated with conventional stimulation (STN1) were situated within or bordering the STN. The volume activated with ILS used for dyskinesia suppression (STN2) were situated above and lateral to the STN. (Supporting Information Fig. 3 represents the volume of tissue-activated models of 2 selected patients.)

The heat maps revealed a higher concentration of volume activated within or in the dorsal border of the STN during the conventional settings (STN1; Fig. 2 [conventional]). The
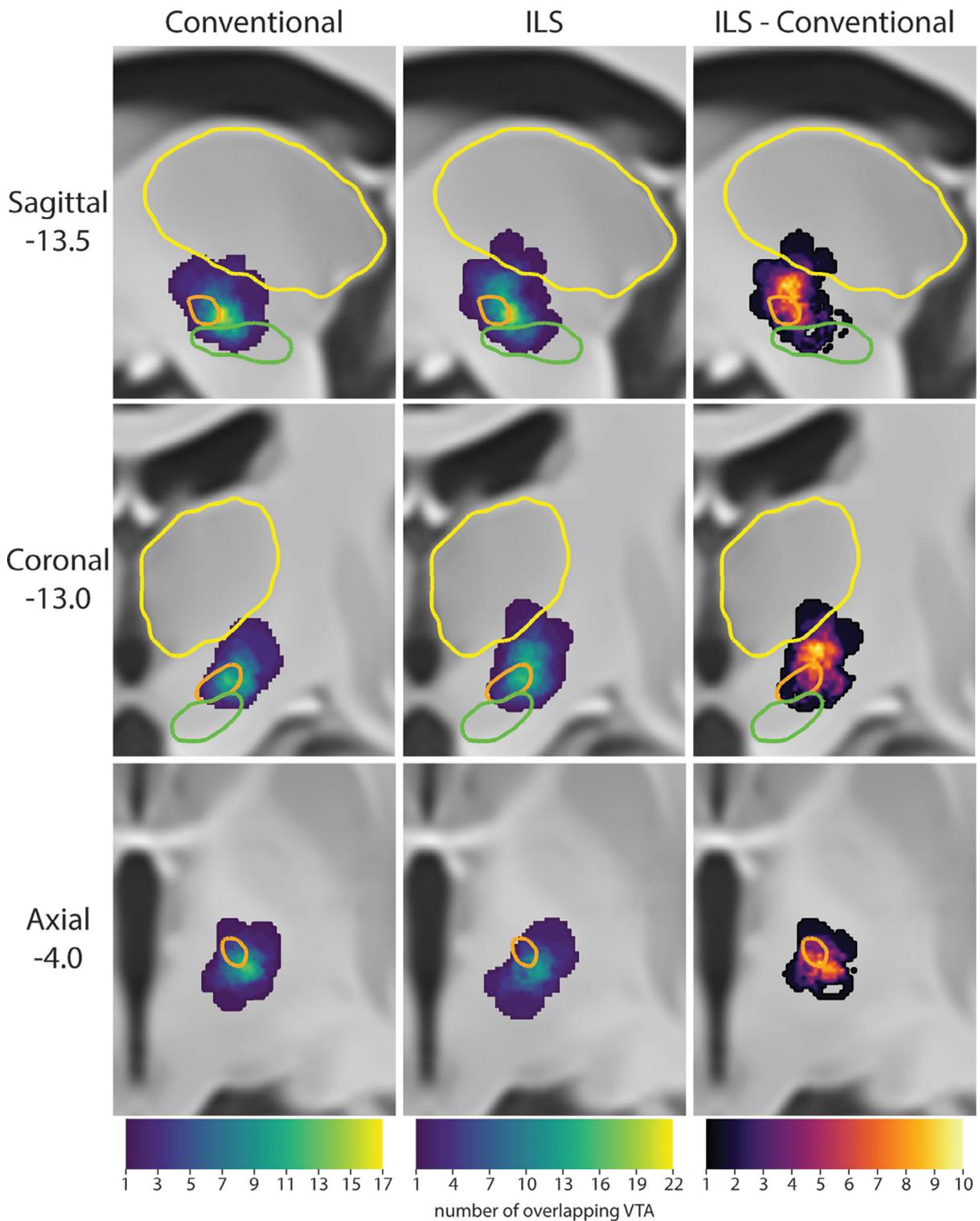
FIG. 2. Comparison of the location of activation volumes between conventional and ILS stimulation. Left: sum of volumes of tissue activated from the initial conventional programming setting. Center: sum of volumes of tissue activated from the ILS programming setting. Right: sum of the volume activated during ILS stimulation, but not during conventional stimulation. Orange = subthalamic nucleus, green = substantia nigra, yellow = thalamus. ILS, interleaving stimulation; VTA, volume of tissue activated.

volume of tissue activated with the ILS settings originated by the overlap of STN1 + STN2 were spread around the STN with no single "hot spot" (Fig. 2 [ILS]). The volume of tissue activated only during ILS were highly concentrated dorsally to the STN, suggesting that these areas were selectively stimulated by STN2 (Fig. 2).

Additional Endpoints

The total electrical energy delivered during the conventional settings was 33.5 ± 29.1 µJ. During the ILS, the total electrical energy delivered by STN1 was 42.0 ± 39.9 µJ and 27.2 ± 29.2 µJ by STN2. The average battery longevity was 4.0 ± 0.9 years.

Adverse Events

A total of 6 patients (30%) had gait deterioration after STN DBS. In 1 of these patients, the occurrence of falls was reduced by transitioning from ILS setting to low-frequency stimulation. A total of 3 patients (15%) developed dysarthrophonia. Repeated reprogramming visits were not successful in relieving the speech problems.

Discussion

In our study, we found that engaging the pallidofugal fibers through a dorsal DBS contact using the ILS paradigm resulted in more robust dyskinesia suppression (~65%) in comparison to conventional settings. This effect was independent of medication reduction. We chose to transition to ILS instead of reducing dopaminergic therapy because of the individual characteristics that raised concerns regarding mood,[17] apathy,[18,19] and axial symptoms.[20] To our knowledge, this is the first study focused on the potential of ILS engaging the pallidofugal tract as a dyskinesia-specific therapy in PD patients with STN DBS.[6-9]

Different mechanisms could potentially explain the antidyskinesia effect of the pallidofugal tract stimulation: the orthodromic activation of pallidothalamic fibers, which would inhibit the thalamus, and the antidromic stimulation of the globus pallidus internus (GPi).[21,22] Studies in nonhuman primates[23] documented the abolishment of hyperkinesia by lesions in the pallidum or pallidal outflow tract.[24] Subsequent lesioning studies in humans of the GPi, pallidal outflow tract, and pallidal receiving area of the thalamus resulted in similar suppression of dyskinesia.[25-27] The Zona incerta (Zi) also resides in this region and has been suggested as a potential antidyskinesia target.[27,28] Further studies with tractography are essential to clarify these mechanisms.

The use of the volume of tissue-activated models in our study allowed for an in vivo evaluation of the area with antidyskinesia effect. The volume of tissue activated unique to STN2, responsible for dyskinesia suppression, was above and toward the lateral aspect of the STN. In this complex area between the dorsal STN border and the ventral thalamus lie several interconnected tracts comprised in part by pallidofugal fibers en route to the thalamus (ie, the pallidothalamic tract[29]) as well as the Zi.[30] The pallidothalamic tract is formed by the lenticular fasciculus (or field H2 of Forel) and the *ansa lenticularis* of Von Monakow, both of

which merge to form the thalamic fasciculus (field H1 of Forel).[29] The thalamic fasciculus enters the ventral thalamus, carrying the bundle of fibers originated from both parts of the GPi, the ventral and the doral.[29,30]

The advantage of ILS over other configurations[4,5,31] is the use of independent parameters for each contact, allowing for a more tailored stimulation field.[9,32] This is particularly important in the compact region above the STN, which is bordered laterally by the internal capsule. Problematic side effects, particularly with gait[33] and speech,[34] have been reported with stimulation in this area. We also observed mild deterioration in axial scores in our patients, but we could not exclude the potential effect of disease progression, as there was a mean interval of 23 months between surgery and ILS in our sample.[35,36] Although a higher stimulation frequency (eg, 180 Hz)[37] may be required to control the parkinsonian tremor, the tremor score was unchanged with ILS in our sample, probably because we would immediately discontinue ILS in the case of tremor recurrence during the programming visit. A frequency-mediated effect on dyskinesia previously reported with stimulation reduction from 130 to 80 Hz is unlikely to explain our results, as most patients were switched from 140 to 125 Hz, which is still considered high frequency.[38]

We acknowledge the limitations of this small retrospective cohort, including the high risk of performance and selection bias. Also, variability in patient-specific anatomy may not be adequately accounted for using atlas-based imaging analysis. Despite these issues, we demonstrated that, at least in selected individuals, the combined stimulation of the STN and subthalamic area through ILS is feasible and effective for the treatment of residual or stimulation-induced dyskinesia.

Our results encourage the use of ILS settings not as a last resort, but as a way of refining stimulation to optimize benefit without additional side effects. As we enter a time of rapid technological advance, with the availability of directional current[39] and multiple independent current control, our ability to selectively stimulate specific fiber tracts[40,41] will further refine symptom-specific approaches. ●

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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.