Deep Brain Stimulation of Caudal Zona Incerta for Parkinson’s Disease: One-Year Follow-Up and Electric Field Simulations

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ABSTRACT

Objective: To evaluate the effects of bilateral caudal zona incerta (cZi) deep brain stimulation (DBS) for Parkinson’s disease (PD) one year after surgery and to create anatomical improvement maps based on patient-specific simulation of the electric field.

Materials and Methods: We report the one-year results of bilateral cZi-DBS in 15 patients with PD. Patients were evaluated on/off medication and stimulation using the Unified Parkinson’s Disease Rating Scale (UPDRS). Main outcomes were changes in motor symptoms (UPDRS-III) and quality of life according to Parkinson’s Disease Questionnaire-39 (PDQ-39). Secondary outcomes included efficacy profile according to sub-items of UPDRS-III and simulation of the electric field distribution around the DBS lead using the finite element method. Simulations from all patients were transformed to one common magnetic resonance imaging template space for the creation of improvement maps and anatomical evaluation.

Results: Median UPDRS-III score off medication improved from 40 at baseline to 21 on stimulation at one-year follow-up (48%, p < 0.0005). PDQ-39 summary index did not change, but the subdomain activities of daily living (ADL) and stigma improved (25%, p < 0.03 and 75%, p < 0.01), whereas communication worsened (p < 0.03). For UPDRS-III sub-items, stimulation alone reduced median tremor score by 9 points, akinesia by 3, and rigidity by 2 points at one-year follow-up in comparison to baseline (90%, 25%, and 29%, respectively, p < 0.01). Visual analysis of the anatomical improvement maps based on simulated electrical fields showed no evident relation with the degree of symptom improvement and neither did statistical analysis show any significant correlation.

Conclusions: Bilateral cZi-DBS alleviates motor symptoms, especially tremor, and improves ADL and stigma in PD patients one year after surgery. Improvement maps may be a useful tool for visualizing the spread of the electric field. However, there was no clear-cut relation between anatomical location of the electric field and the degree of symptom relief.

Keywords: Deep brain stimulation, electric field simulation, improvement maps, Parkinson’s disease, quality of life, zona incerta

Conflict of Interest: Karin Wårdell is a shareholder in FluoLink AB. Patric Blomstedt is a consultant for Abbott, Boston Scientific, and Medtronic and a shareholder in Mithridaticum AB. Marwan Hariz has received honoraria for speaking at meetings by Boston Scientific. The remaining authors have no conflicts of interest to declare.

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INTRODUCTION

Deep brain stimulation (DBS) is an evidence-based therapy for advanced Parkinson’s disease (PD). Currently, the most commonly used brain targets for DBS are the subthalamic nucleus (STN), the globus pallidus internus (GPI), and the ventral intermediate nucleus (VIM) of the thalamus, chosen according to symptom profile and individual considerations.1 The posterior subthalamic area (PSA), including the caudal zona incerta (cZi), was frequently used as a target for lesion procedures in PD patients in the 1960s.2 Since the early 2000s, the PSA has been explored as a target for DBS. Several open-label non-randomized studies of PSA-DBS for PD have shown promising results on motor symptoms with none reporting severe side effects.3–9 This led to the first randomized blinded trial published in 2018, demonstrating improvement of parkinsonian symptoms and quality of life (QoL) at six months following cZi-DBS.10 The same year, Barbe et al published the first randomized double-blinded trial of PSA-DBS for essential tremor (ET), suggesting the PSA as an equally effective but more efficient target than VIM.11

However, our understanding of the PSA is limited regarding optimal electrode placement in that area, especially in relation to the effect on different symptoms. Further, it is of importance to analyze what we are stimulating, considering that the PSA is encompassing part of the dentato-rubro-thalamic tract (DRTT) and is directly adjacent to the VIM and the STN. To investigate the clinical effect in relation to the anatomy different methods have been used. Electric field simulation using the finite element method (FEM)12,13 is one commonly used method where the stimulation strength is taken into account. By transferring individual simulation results to a common space with none reporting the psychiatric side effects like what has been found following STN-DBS.3–9

The aims of the present study were to evaluate bilateral cZi-DBS one year after surgery and to develop anatomical improvement maps by analyzing the clinical effects in relation to the distribution of the electric field of stimulation.

MATERIAL AND METHODS

Patients

In a previously published randomized blinded study, we compared the six months, outcome of nine PD patients who received bilateral cZi-DBS to ten patients who received best medical treatment.10 These ten patients were subsequently implanted with bilateral cZi-DBS. The current study is an open-label evaluation of all patients with cZi-DBS one year after surgery, including an analysis of the electric field of stimulation. The same inclusion criteria as for bilateral STN-DBS were used, as previously described.10

The study was approved by the Ethical Committee of Umeå University, and written informed consent was obtained from participants according to the Declaration of Helsinki (Dnr 08-009M).

Four of the initial 19 patients could not be evaluated at one year for the following reasons: One patient had an infection with lead explantation; one patient suffered bilateral patellar fractures; one patient had severe hallucination and impulse control disorder due to overdose of dopaminergic drugs; and one patient withdrew consent. The final one-year analysis included the remaining 15 patients, of whom 4 were women. Seven had previously been part of the best medical treatment arm in the original study. The mean age at surgery was 58.6 ± 2.5 years with a mean disease duration of 6.5 ± 2.6 years.

Surgery

The surgical procedure has been described previously.10 In summary, bilateral stereotactic frame-based implantation of DBS electrodes 3389 (Medtronic, Minneapolis, MN) was performed without microelectrode recording. Trajectories and targets were planned on stereotactic T1- and T2-weighted axial magnetic resonance images (MRI, voxel size 1 × 1 × 2 mm3, 1.5 T, Philips Achieva, Philips Healthcare, The Netherlands), with the target lying slightly medial and slightly posterior to the visualized posterior tail of the STN on the axial slice showing the maximal diameter of the red nucleus (RN).11 Implantation of the electrodes and the implantable pulse generator (Kineta/Activa PC, Medtronic, Minneapolis, MN) was done in the same session. Postoperative CT scans (voxel size 0.6 × 0.6 × 1.3 mm3, Lightspeed, GE Medical Systems, Chicago, IL) were performed and fused (Stealth Cranial, Medtronic, Minneapolis, MN) with the preoperative stereotactic MRI for verification of the electrode position.

Evaluation

All patients underwent a monopolar review after surgery, where electrode contacts were screened individually using standardized parameter settings and gradually increasing amplitude. The contacts with the best effect according to the Unified Parkinson’s Disease Rating Scale’s motor part (UPDRS-III) in the absence of side effects were chosen for chronic bilateral stimulation. Medications and stimulation parameters were evaluated and optimized during the follow-up period. All adverse events were recorded.

All patients were evaluated at baseline and at one year using UPDRS-III by the same evaluator in a standardized manner on/off stimulation and on/off medication. The last evaluation prior to surgery was considered baseline for each patient. Off-medication scores were established after withholding parkinsonian medication for 12 hours. On medication scores were performed after an L-dopa dose, 150% of the patient’s normal morning dose. Both electrodes were switched off/on for 60 min before evaluation. Also, the Parkinson’s Disease Questionnaire 39 (PDQ-39) and the Unified Parkinson’s Disease Rating Scale part IV (UPDRS-IV) were administered at baseline and at one year after surgery.

Finite Element Method Modeling and Simulation

Electric field simulation was performed using the patient’s individual preoperative T1 and T2 MRI, postoperative CT, and clinical DBS settings. The degree of clinical improvement was defined based on UPDRS-III and combined with the volume of the simulated electric field for the creation of anatomical improvement maps. Figure 1 shows an overview of the total processing workflow.

Brain Tissue Modeling

An inhouse Matlab-software (ELMA Version 2.4, Department of Biomedical Engineering, Linköping University, Linköping, Sweden) was used to create a brain conductivity model.12,18 The images were first cropped to a region of interest and then segmented into gray matter, white matter, and cerebrospinal fluid based on the image intensity. Lastly, each voxel was assigned tabulated conductivity values9,20 based on the segmentation and patient stimulation parameters shown in Table 1. A peri-electrode space (PES) of 250 μm was included to model the electrode-tissue interface.
interface. The PES is assumed to consist of fibrous tissue\textsuperscript{21} and was therefore modeled as white matter.

### Table 1. Conductivity Values and Isolevels Used During Simulation of the Cohort.

<table>
<thead>
<tr>
<th>Pulse width, µsec (frequency, Hz)</th>
<th>Conductivity (S/m)</th>
<th>E-field (V/mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter</td>
<td>0.123</td>
<td>0.7</td>
</tr>
<tr>
<td>White matter</td>
<td>0.0754</td>
<td>0.2</td>
</tr>
<tr>
<td>CSF</td>
<td>0.0747</td>
<td>0.15</td>
</tr>
<tr>
<td>Blood</td>
<td>0.0747</td>
<td>0.15</td>
</tr>
<tr>
<td>CSF, cerebrospinal fluid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Electric Field Simulation

The brain conductivity model was used as input to FEM simulation in Comsol Multiphysics (v. 5.3, Comsol AB, Stockholm, Sweden). The geometry of the leads (3389) was modeled and placed in the brain model based on the lead artifact in the CT images, co-registered to the preoperative MRI\textsuperscript{22}. The clinical DBS setting one year after surgery was used as input parameters for the simulations. The electric field distribution around the active contact was computed using the equation of continuity for steady currents, details of which are available in previous work\textsuperscript{12,23}. From the resulting electric field an isosurface, according to Table 1, was applied to represent the volume of tissue affected by the active contact corresponding to stimulation of axons with a diameter of approximately 3–4 µm\textsuperscript{24}. For the bipolar cases, the electric field on the...
anodic side was scaled with a factor of 0.6 to account for anodic stimulation being less effective than cathodic stimulation.25

Improvement Maps

The patients’ cropped preoperative MR images were processed with an Advanced Normalization Tools multivariate template construction, which creates a group average brain template using non-linear transformation.26 The volumes within the isolevel (0.2 or 0.15 V/mm) were extracted as label maps, that is, 0 outside the isolevel and 1 inside, and transformed to template image space. Based on the one-year outcome on motor symptoms according to UPDRS-III, the patients were divided into response groups post hoc (see Table 2 for subscore definitions). To avoid arbitrary threshold selection of the response, a review of the literature of bilateral STN/GPI-DBS was done (in total 38 studies provided detailed information, but only selected references are provided here). The review showed a median improvement of STN/GPI-DBS of approximately 50% for total UPDRS-III, 50% for rigidity and akinesia, 75% for tremor, and 40% for axial subscores, which served as cut-off values for good responders.27–32 Poor response was based on the lower range of efficacy in previous studies and was set at <25% improvement for total UPDRS-III, rigidity, akinesia, and axial subscores and <50% for tremor. No separation of laterality was done due to bilateral stimulation during evaluation. For each response group, the label maps from the electric field were averaged, giving values ranging from 0 to 1. For visualization of each group and subscore a threshold of 0.5 was used, that is, 50%, to remove the effect of outliers.

Outcome Measures

Primary outcomes included changes in parkinsonian signs using UPDRS-III and in quality-of-life scores using the PDQ-39. Secondary outcome measures included changes in sub-scores of UPDRS-III and their relation to electric field simulations, as well as changes in dyskinesia scores according to UPDRS-IV and levodopa equivalent daily doses (LEDD) between baseline and one year.

Table 2. Unified Parkinson’s Disease Rating Scale Sub-Scores (UPDRS-III, UPDRS-IV) and LEDD at Baseline and at One-Year Evaluation.

<table>
<thead>
<tr>
<th>Sub-score</th>
<th>Maximum Score</th>
<th>Baseline</th>
<th>One Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Off med</td>
<td>On med</td>
<td>Off med</td>
</tr>
<tr>
<td></td>
<td>Off stim</td>
<td>On stim</td>
<td>Off stim</td>
</tr>
<tr>
<td>UPDRS-III (items 18–31)</td>
<td>108</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>(20)</td>
<td>(13)</td>
<td>(17)</td>
</tr>
<tr>
<td>Axial (items 18–19, 20, 22, 27–30)</td>
<td>32</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>(5)</td>
<td>(4)</td>
</tr>
<tr>
<td>Tremor (items 20–21)</td>
<td>28</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td>(5)</td>
<td>(4)</td>
</tr>
<tr>
<td>Rigidity (item 22)</td>
<td>20</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(4)</td>
<td>(4)</td>
<td>(4)</td>
</tr>
<tr>
<td>Akinesia (items 23–26)</td>
<td>32</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>(5)</td>
<td>(6)</td>
<td>(9)</td>
</tr>
<tr>
<td>Dyskinesia (items 32–35)</td>
<td>16</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>LEDD (mg)</td>
<td></td>
<td>1227</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(900)</td>
<td></td>
</tr>
</tbody>
</table>

Median (interquartile range).
LEDD, levodopa equivalent daily doses.

*p < 0.05 vs baseline off medication.
†p < 0.05 vs off medication/on stimulation at the same follow-up.
‡p < 0.05 vs off medication/off stimulation at the same follow-up.
§p < 0.05 vs baseline on medication.
¶p < 0.05 vs on medication/off stimulation at the same follow-up.

Statistical Analysis

Analysis of non-parametric values was done using Friedman’s test with double-tailed Wilcoxon signed-rank test as a post hoc analysis. A p-value <0.05 was considered statistically significant.

Voxel-Wise Statistical Test

Statistical analysis of the spatial spread of the electric field in correlation to the clinical outcome was made using a double-sided Wilcoxon’s rank-sum test. For each voxel, the cohort was divided into two groups: the patients for whom the particular voxel was inside the electric field isosurface in one group, and those for whom the voxel was outside their isosurface in the second group. For all voxels, the improvement in UPDRS-III scores was used to analyze any differences between the groups, where p < 0.05 was considered to be significant. Figure 1 shows an example of this test.

RESULTS

Clinical Outcomes

The results are presented as off-medication median scores (improvement %) unless stated otherwise. Table 2 shows the sub-scores of UPDRS-III at one-year follow-up.

Total UPDRS-III score off medication improved from 40 at baseline to 21 on stimulation at one year (48% improvement, p < 0.0005). Scores between off and on stimulation showed an improvement of 50% (p < 0.0001). Stimulation and medication combined reduced total UPDRS-III to 13, which was significantly lower compared to stimulation alone (38%, p < 0.001).
Tremor score improved by 90% (p < 0.0001), rigidity 29% (p < 0.005), and akinesia 25% (p < 0.01) on stimulation at one year compared to baseline. No significant changes were seen concerning axial scores, dyskinesia scores, or LEDD.

Table 3 shows the results of PDQ-39 where scores can range from 0 to 100, with higher scores indicating worse status. The only statistically significant changes at one year compared to baseline concerned activities of daily living (ADL), which improved from 16.7 to 12.5 points (p < 0.05) and stigma from 25 to 6.3 (p < 0.01). Communication worsened from 0 to 16.7 points (p < 0.01).

Group Analysis of Electric Field Simulations

Improvement Maps

One patient was excluded from the visual analysis due to an incompatible CT scan. The result from the remaining 14 patients is shown in Table 4. The estimated volume affected by the stimulation at one year follow-up, four patients reported a slight stimulation-induced gait disturbance and one worsening of balance. In two patients, the evaluator noted a slight dysarthria on stimulation that improved off stimulation.

Stimulation Parameters

Median stimulation parameters and mean coordinates of the active contacts in relation to the midcommissural point (MCP) are shown in Table 4. The estimated volume affected by the stimulation was 100 mm³ (interquartile range: 71, min–max: 41–283) one year after surgery.

DISCUSSION

In this study, bilateral cZi-DBS improved UPDRS-III by 48% at one year after surgery. PDQ-39 showed significant improvement in ADL and stigma, and worsening in communication. The 48% improvement in UPDRS-III in our study falls into the span of 25%–75% improvement following STN and GPI-DBS in various open-label studies.27-34 The few studies that have reported details of the UPDRS-III sub-scores postoperatively showed a similar heterogeneity in levels of improvement for tremor (25%–89%), for akinesia (28%–63%), and for rigidity (34%–75%).27-32,34

In our patients, the effect of bilateral cZi-DBS on tremor was excellent while modest for akinesia and rigidity. This contrasts with previous studies of PSA-DBS for PD, where contralateral tremor was likewise much improved (75–93%), but where considerable improvement was also reported for contralateral rigidity (45–94%) and akinesia (46–75%).3,5,36

A direct comparison between our results and these studies is difficult since the latter results are mostly reported for unilateral stimulation and due to differences in disease duration and severity, symptom distribution, targeting and the actual location of the electrode contacts, and field of stimulation.

Regarding dyskinesia, there was no significant reduction of dyskinesia according to UPDRS-IV in this study, but this might be a floor effect, considering the relative sparsity of this symptom.

In the literature, the location of the lead contacts used for stimulation has been reported in different ways, if at all, and this is also true regarding stimulation parameters. Previous attempts to identify an optimal stimulation site have mainly confirmed that this is located within the PSA.5,36 Attempts to further narrow the optimal area within the PSA have yielded little. Plaha et al reported significantly better outcome for electrodes within the PSA, compared to electrodes in, or medial to the STN, concerning contralateral UPDRS-III, tremor, and rigidity but a non-significant difference regarding akinesia.5 Castro et al found no significant difference in MCP coordinates between optimal and suboptimal outcome in the radiatio prelemniscalis (Raprl) DBS.36 This is perhaps
not surprising since the possibility to further subdivide the PSA according to outcome may be somewhat limited due to its topography and size. The PSA is a small infrathalamic area containing several fiber tracts including Forel’s fields, radiatio prelemniscalis, DRTT as well as the zona incerta proper.2,39 The cZi is the structure we use as a stereotactic target due to its close relation to structures visible on MRI (RN and STN), thereby the denomination cZi-DBS, even though the electric field is not limited to the cZi itself. The area where one can place an electrode and call it PSA-DBS is restricted to an area of a few mm in diameter. Hence, even if different groups might differ in their preferred target within the PSA, there will be considerable overlap in the final location of contacts used for stimulation, and an even larger overlap in the volume of tissue affected by the stimulation.

Electric Field Simulation and Improvement Maps
Electric field simulations were performed to analyze the effects on various motor symptoms in relation to anatomy. In our cohort, DBS reduced tremor by 90%, and FEM simulation, as well as the contact location in relation to the MCP, showed a trend toward stimulation overlapping both the fasciculus cerebello-thalamicus and Zi.39 Fytagoridis et al showed that stimulation in a more ventral position resulted in poor alleviation of ET.14 In the same fashion, the two patients with moderate/poor response on tremor in our cohort had stimulation fields located more inferior. However, looking at the contact placements in the whole cohort, good results could be achieved from several different positions within the PSA. This indicates that the targeting protocol had a high probability of achieving a good response on parkinsonian tremor.

Figure 2. Improvement maps based on improvement in total UPDRS-III and sub-scores for axial, tremor, rigidity, and akinesia. The improvement maps are overlaid on axial and coronal MRI slices and to the right a 3D representation is demonstrated where subthalamic nucleus (STN) and red nucleus (RN) are included based on manual delineation.
However, a more inferior position of active contacts could be disadvantageous.

Regarding rigidity, contact placement suggests that a medial position might be beneficial for these symptoms. However, this trend is less visual in the improvement maps, and it is important to note that only three patients had a good response on rigidity. Velasco et al suggested that a more caudal and medial localization of the electrode would affect the pallidothalamic fibers to a greater degree and therefore might explain a larger reduction of rigidity. At the same time, they did not find any correlation between symptomatic alleviation and contact location according to stereotactic coordinates.

Concerning akinesia, neither the statistical nor the visual analysis of the stimulation fields yielded any observable trends between various responders. For axial symptoms, contact placement indicates that a more superior position might be disadvantageous, but this was not supported by the analysis of the improvement maps.

The stimulation fields achieving the best effect on rigidity, akinesia, and tremor were mainly located within the PSA itself, and there was no indication that this effect was mostly achieved from an involvement of the above lying VIM or the laterally located STN. As previously mentioned, total UPDRS-III was significantly improved in the cohort, although we could not find any visible differences between patients with a good and poor response in the stimulation fields. With the hypothesis that different spatial locations can be beneficial for different symptoms, this would be a logical result. Patients with good response on the overall UPDRS-III may have different symptom profiles and thereby different choice of active contact. When all symptoms are grouped together in the total UPDRS-III, there will be an averaging effect over all locations that can generate good improvements on a particular symptom.

Quality of Life

In our patients, the improvement in QoL only reached statistical significance regarding the ADL and stigma domains but not the summary index of the PDQ-39. This may have been due to the small sample size or the reported worsening in “communication,” although the level of worsening was modest (from 0 to 16.7 points out of 100 on the PDQ-39 at one-year postop).

However, this is in accordance with our previous study showing a worsening in spontaneous speech intelligibility in three out of 11 PD patients with cZi-DBS at one year after surgery. While neuropsychological testing on the current cohort did not find a decline in verbal fluency, as seen in STN and GPI-DBS, there was a negative trend regarding phonemic and category fluency. This might, together with dysarthria, contribute to the worsened communication scores of the PDQ-39 in the present study.

Issues With Spatial Analyses and Improvement Maps

The PSA is a small area where slight changes to stimulation parameters or electrode positioning theoretically may affect different structures. Since the zona incerta can be considered as a central hub, with wide connections to various brain areas, different pathways may be stimulated with the possibility to affect different PD symptoms.

Studies that analyzed the location of the active contact have relied on an atlas and/or on coordinates of the lead in relation to the MCP. While contact location reveals some information, the amplitude of the stimulation will determine the extension of the stimulation-induced activation. Therefore, analysis of contact placement only should be used with caution. Further, to analyze the results on a group level, there is a need to transform the data to
Table 4. Median Stimulation Parameters and Mean Distance of the Active Contact in Relation to the Midcommissural Point (MCP).

<table>
<thead>
<tr>
<th>Stimulation parameters</th>
<th>Amplitude, V (IQR, min–max)</th>
<th>Pulse width, μsec (IQR, min–max)</th>
<th>Frequency, Hz (IQR, min–max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year follow-up</td>
<td>2.45 (0.6, 1.5–3.4)</td>
<td>60 (7.5, 60–90)</td>
<td>145 (30, 125–185)</td>
</tr>
<tr>
<td>MCP-coordinates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active contact, mm (mean, ±SD)</td>
<td>11.8 ± 1.2</td>
<td>−6.4 ± 1.4</td>
<td>−1.9 ± 1.7</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

a common anatomical space; either on a postmortem histology-based atlas, an MRI-based reference space, or a group-specific template. Postmortem atlases are usually limited by small sample sizes while MRI reference brains are commonly based on healthy, relatively young, individuals. This could impact the analysis since the study group has a neurodegenerative disease. A common anatomical domain based on the patients’ own MRIs could be a way of bypassing these limitations. However, most important is to use a transform that includes the entire area of interest as opposed to a landmark-based registration, like reporting in MCP coordinates, since differences among individuals cannot be defined by a linear transformation.

Several other studies have used electric field simulation as input for creating probabilistic improvement maps and in some cases also prediction analysis. This was not addressed in this study due to the low level of significance in the statistical test, but the result can be seen as a spatial visualization of the improvement in the cohort. To further elucidate the improvement of different PD symptoms, data from monopolar review would give more spatial information and smaller fields in comparison to more complicated settings like double monopolar stimulation. The downside, however, is that one only sees the acute effects of stimulation and has lower external validity than chronic stimulation parameters.

Limitations

Limitations of the present study include the small sample size and the non-blinded assessment at one year. Other limitations concern the analysis of the anatomical distributions of the electric stimulation fields: Although it was possible to create improvement maps and estimate possible optimal areas for stimulation, based on a template of the patient’s own anatomy, a statistically optimal area of stimulation could not be identified and there was no clear-cut relationship between the location of stimulation fields surrounding the PSA area and the degree of symptom relief. This might be due to limitations in the data (few number of samples, cohort heterogeneity, poor sample distribution, etc) and power of the statistical method. The lack of correlation between stimulation field location and degree of improvement may not be surprising given that this has also been observed by pioneers of ablative stereotactic surgery from the lesional era who wrote concerning thalatomy that "the lesions with good results and poor results were virtually superimposable." A common anatomical space; either on a postmortem histology-based atlas, an MRI-based reference space, or a group-specific template. Postmortem atlases are usually limited by small sample sizes while MRI reference brains are commonly based on healthy, relatively young, individuals. This could impact the analysis since the study group has a neurodegenerative disease. A common anatomical domain based on the patients’ own MRIs could be a way of bypassing these limitations. However, most important is to use a transform that includes the entire area of interest as opposed to a landmark-based registration, like reporting in MCP coordinates, since differences among individuals cannot be defined by a linear transformation.

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Several other studies have used electric field simulation as input for creating probabilistic improvement maps and in some cases also prediction analysis. This was not addressed in this study due to the low level of significance in the statistical test, but the result can be seen as a spatial visualization of the improvement in the cohort. To further elucidate the improvement of different PD symptoms, data from monopolar review would give more spatial information and smaller fields in comparison to more complicated settings like double monopolar stimulation. The downside, however, is that one only sees the acute effects of stimulation and has lower external validity than chronic stimulation parameters.

CONCLUSION

Bilateral cZi-DBS alleviated parkinsonian symptoms one year after surgery, with a prominent effect on tremor and a modest effect on akinesia and rigidity. This was reflected in QoL as a significant improvement in ADL and stigma, albeit with a slight worsening in communication. Simulation maps of the electric fields did not reveal any anatomically distinct area corresponding to a higher improvement of motor symptom. However, a visualization of the electric field may provide an intuitive understanding of the symptomatic effect in relation to the anatomy.

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Authorship Statements

Rasmus Stenmark Persson and Teresa Nordin contributed equally, through partly designing the study, data compilation, data analysis and interpretation, and drafting of the manuscript. Gun-Marie Hariz collected data and conducted analyses and interpretation. Karin Wårdell supervised the design, analysis, and interpretation of the electric field simulations. Lars Forsgren, Marwan Hariz, and Patric Blomstedt contributed through conception and design of the main study, supervision, and data interpretation. All authors have critically revised and approved the final version of the manuscript.

How to Cite This Article


REFERENCES

Person and colleagues present the clinical outcomes of caudal zona incerta (CZI) deep brain stimulation (DBS) for Parkinson's disease (PD) with the stimulation field analysis. Even though no significant differences in the stimulation fields among three cohorts with different clinical responses were identified, the value of this study is not decreased. The existence of responders and non-responders in their study may have resulted from the heterogeneous nature of PD, and this issue has been often discussed in DBS for neuropsychiatric disorders. The authors’ findings address the importance of personalized target selection for each PD patient, and further studies with the same methodology concerning controversial DBS targets for PD such as pedunculopontine nucleus may be warranted.

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The authors have been quite responsive to reviewer comments and made several changes to strengthen and clarify the manuscript. One consideration for the discussion might be to discuss how DBS targets may be more or less effective, dependent on the type of PD managed (eg, tremor dominant). The sample size is too small to address this concept, but the authors could speculate on this consideration.

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The authors evaluated the effects of bilateral caudal zona incerta (CZI) deep brain stimulation (DBS) in 15 patients with...
Parkinson’s disease (PD) one year after surgery. They also created anatomical improvement maps based on patient-specific simulation of the electric field. They reported that bilateral cZi-DBS alleviates motor symptoms, especially tremor, although no major effects on quality of life and medication reduction was found. In addition, no clear relation between the anatomical location of the electric field and the degree of symptom relief was found.

This study provides the prospective outcome of bilateral cZi DBS in a relatively small sample of PD patients. This target has been extensively investigated in the past by the same authors, particularly in the short term and with unilateral implants. Overall, their findings seem to indicate an effect less promising than hypothesized in the past.

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