Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Deep Brain Stimulation: When to Test Directional?

Ines Debove, MD,[1,] Katrin Petermann, dipl. Ing. MSc,[1] Andreas Nowacki, MD,[2] Thuy-Anh Khoa Nguyen, ScD,[2,3] Gerd Tinkhauser, MD, PhD,[1] Joan Philipp Michelis, MD,[1] Julia Muellner, MD,[1] Deborah Amstutz, MSc,[1] Panagiotis Bargiotas, MD,[1,4] Jens Fichtner, MD,[2,5] Janine Ai Schlaeppi, MD,[2] Paul Krack, MD,[1] Michael Schuepbach, MD,[1] Claudio Pollo, MD,[2] and Martin Lenard Lachenmayer, MD[1]*

Abstract: Background: Directional deep brain stimulation (DBS) allows for steering of the stimulation field, but extensive and time-consuming testing of all segmented contacts is necessary to identify the possible benefit of steering. It is therefore important to determine under which circumstances directional current steering is advantageous.

Methods: Fifty two Parkinson's disease patients implanted in the STN with a directional DBS system underwent a standardized monopolar programming session 5 to 9 months after implantation. Individual contacts were tested for a potential advantage of directional stimulation. Results were used to build a prediction model for the selection of ring levels that would benefit from directional stimulation.

Results: On average, there was no significant difference in therapeutic window between ring-level contact and best directional contact. However, according to our standardized protocol, 35% of the contacts and 66% of patients had a larger therapeutic window under directional stimulation compared to ring-mode. The segmented contacts warranting directional current steering could be predicted with a sensitivity of 79% and a specificity of 57%.

Conclusion: To reduce time required for DBS programming, we recommend additional directional contact testing initially only on ring-level contacts with a therapeutic window of less than 2.0 mA.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for levodopa-responsive Parkinson's disease (PD) with motor complications.[1,2] However, the efficacy of STN-DBS may be limited by stimulation-induced side effects that emerge when the current spreads into adjacent brain structures.[3,4]

Directional electrodes represent a technical innovation in DBS, as their segmented contacts allow for a spatially more refined shaping of the stimulation field,[5,6] while conventional DBS systems with cylindrical ring contacts generate a concentric stimulation field.[7] Postoperative pilot STN-DBS studies and a prospective post-market study in PD patients have shown that directional stimulation can increase the therapeutic window of stimulation.[8–10] However, identifying and exploiting the advantages of steering requires testing of every possible configuration of stimulation parameters for each level and segmented contact. Unfortunately, this is often not feasible in clinical practice due to the overwhelming number of existing options[11,12] and limited time resources. It remains unclear under which circumstances directional stimulation is advantageous.[13] We therefore retrospectively analyzed standardized monopolar contact reviews in PD patients implanted with directional DBS leads in the STN to determine when directional stimulation leads to a relevant increase of the therapeutic window.

[1]*Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland;* [2]*Department of Neurosurgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland;* [3]*ARTORG Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland;* [4]*Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus;* [5]*Cantonal Medical Service, Department of Health of the Canton of Bern, Bern, Switzerland*

***Correspondence to:** Dr. Ines Debove, MD, Department of Neurology, Inselspital, Bern University Hospital, Freiburgstrasse 10, 3010 Bern, Switzerland. E-mail: ines.debove@insel.ch

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Ines Debove and Katrin Petermann contributed equally.

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Material and Methods

Patients

All patients who underwent bilateral STN-DBS surgery between 2015 and 2018 at the University Hospital of Berne, Switzerland and provided general informed consent were included in the analysis. The local ethics committee approved the study (KEK-BE: 287/2015). The selection criteria for neurosurgery and surgical procedures have been described previously.[6] All patients were implanted with directional leads (Boston Scientific DB-2202, Marlborough, MA, USA). Each lead includes tripartite directional contacts on the two middle levels, while the distal and proximal levels are conventional ring contacts.

Stimulation Programming/Testing

A standardized monopolar contact review[9,14] was performed in each patient 5–9 months (24 ± 5 weeks) after implantation. The programming session was conducted in a defined medication OFF-state (>12 h of L-DOPA and > 48 h of dopamine agonist withdrawal) and performed by one of five trained raters. Rigidity was assessed according to the MDS-UPDRS-III scale. The order of the contact review was not predetermined and varied between raters. At least 1 min was waited between the tests of the individual contacts or until rigidity had returned to the baseline level. Effect thresholds and side-effect thresholds were determined by increasing stimulation amplitude in 0.5 mA steps, starting from 1 mA and up to a maximum of 8 mA, with fixed frequency and pulse width (130 Hz, 60 μs). Effect threshold was defined as the lowest stimulation amplitude in mA, at which the best effect on rigidity was observed. In case no rigidity was detectable at baseline, the hemisphere was removed from the analysis. Side-effect threshold was defined as the stimulation amplitude in mA, at which a limiting stimulation-induced side effect occurred due to current spreading into adjacent structures (eg, pyramidal contractions).[3,15] Therapeutic window was defined as the difference between side effect threshold and effect threshold (therapeutic window = side-effect threshold—effect threshold). If the side-effect threshold occurred before the effect threshold, the therapeutic window was set to 0. Effect thresholds, side-effect thresholds and the resulting therapeutic windows were documented for each ring-level and all directional contacts.

Statistical Analysis

Automated contact rating and statistical analysis were performed using R version 4.2.0 (2022-04-22).[16] The code is available on GitHub https://github.com/kilyth/MappingDirect_Publication.

Analysis of Monopolar Reviews

Only ring levels with segmented contacts (Levels 2 and 3) were included in the analysis and left and right hemispheres were treated as independent. Differences in stimulation amplitude between ring level and directional contact were tested with a linear mixed-effects model (random intercepts) and the hemisphere was considered as a random effect. 95% confidence intervals were computed with profile likelihood and *P*-values with the Satterthwaite approximation.

Prediction Model

We compared the therapeutic window of ring level and corresponding directional stimulation. Directional contacts with an increase in the therapeutic window of clinical relevance (25%) were classified as "warranting investigation." Effect threshold, side effect threshold and therapeutic window of the ring level were used to predict whether the level should be tested in directional mode. ROC curves of the complete dataset were compared using the paired bootstrap method from the R package pROC.[17] 95% percentile bootstrap confidence intervals for ROC curves were calculated using 2000 stratified replicates. To test the predictive performance of our approach, we used a 5-fold cross-validation, where each contact was part of the test fold exactly once. With the data in the training folds, we calculated ROC curves for each predictor and chose a threshold such that the sensitivity was at least 75%. This threshold was then used to predict the label of the contacts in the test fold. The results of all test folds were combined to calculate overall sensitivity, specificity and accuracy measures and their 95% Wilson confidence intervals.

Results

Patients

Our consecutive cohort includes 52 PD patients. Preoperative patient characteristics are shown in Table 1. Out of 208 ring levels a total of 11 were excluded from the analysis because monopolar review could not be carried out for them for the following reasons: three levels (two patients) due to excessive fatigue, four levels (one patient) due to oppositional paratonia ("Gegenhalten"), two levels (one patient) due to undesirable muscle cramps in the OFF-state upon turning off the stimulation, two levels (one patient) due to pain in the wrist. Another 44 ring levels from 22 patients were excluded from the analysis as they did not show any rigidity at baseline. Overall, a complete monopolar review was carried out in a total of 47 patients and 153 ring levels.

Monopolar Review

Stimulation amplitudes for effect threshold, side-effect threshold and therapeutic window from each ring level was compared with the corresponding directional contacts. The difference between the ring levels and the directional contacts is shown in Figure 1. When taking into account the difference from one segment to another segment on the same ring level, a significant difference

TABLE 1 *Patient Characteristics for a Total of 52 Patients*

Variables N	level	Overall 52	% Missing
Gender (%)	Female	17 (32.7)	0
	Male	35 (67.3)	
Age at surgery (years)		62.06 (9.42)	0
Disease duration (years)		11.44 (4.61)	0
Time from surgery to examination (weeks)		24.60 (5.06)	0
LEDD preoperative (mg)		1155.86 (487.66)	0
LEDD postoperative (mg)		256.54 (361.31)	9.6
MDS-UPDRS-III (preoperative, without medication)		40.52 (13.26)	0
MDS-UPDRS-III (preoperative, with medication)		13.88 (7.13)	0
MDS-UPDRS-III (postoperative, without medication)		22.43 (8.48)	19.2
MDS-UPDRS-III (postoperative, with medication)		11.29 (5.85)	21.2

Continuous variables are summarized by mean and standard deviation, categorical variables are reported as absolute and relative numbers.

in the therapeutic windows was detected. However, on average the therapeutic window of the best directional contact was not larger than the therapeutic window of the corresponding ring level. Nevertheless, 53 out of 153 (35%) ring levels in 31 out of 47 (66%) patients had a larger therapeutic window on the best directional contact.

Prediction Model

To identify a variable that could predict which of the directional contacts could lead to a relevant increase in therapeutic window (25% increase), the therapeutic windows of the ring levels were compared with those of the corresponding directional contacts.

Figure 2 shows the results of the monopolar reviews divided into two categories (warranting investigation versus not warranting investigation).

The variable with the best predictive performance was the therapeutic window with an AUC of 0.76 (95% CI: from 0.67 to 0.85) that was significantly higher than the effect threshold (0.68, 95% CI: from 0.59 to 0.77, $P = 0.045$) and the side effect threshold (0.61, 95% CI: from 0.50 to 0.71, $P = 0.007$). A combined threshold of therapeutic window and effect threshold was also tested but did not lead to significantly better results than the therapeutic window alone (0.71, 95% CI: from 0.63 to 0.79, $P = 0.28$). Figure 3 A shows the calculated ROC curves of the different predictors.

Next, a 5-fold cross-validation was used to test the predictive performance of our approach. In each run, ROC curves for the three predictors were calculated. From these ROC curves, we extracted stimulation amplitudes leading to a sensitivity of at least 75% for each predictor. This stimulation amplitude was then used to predict how many of the contacts in the test-fold were correctly predicted as warranting further investigation. Figure 3 B shows the results of the 5-fold cross-validation. Interestingly the relevant threshold for the therapeutic window to reach a sensitivity of at least 75% was the same for each fold at <2.0 mA. Consequentially, by testing all levels with a therapeutic window smaller than 2.0 mA, contacts benefitting from directional stimulation could be identified with a sensitivity of 79% (95% CI: from 67% to 88%) and a specificity of 57% (95% CI: from 47% to 66%). In the case of our dataset, that means that according to that model only in 85 out of 153 ring levels (55.6%) directional monopolar review would have been performed. Out of these 85, 42 (49.4%) would have showed an increase in the therapeutic window of at least 25%, while 43 (50.6%) would have not shown a clinically relevant increase in therapeutic window.

Discussion

To the best of our knowledge, this is the largest PD cohort with a standardized systematic rating and analysis of directional STN-DBS. Although our study did not confirm a systematically larger therapeutic window with directional stimulation as described in previous studies,[6,8–10] directional stimulation showed a therapeutic window that was at least 25% larger than ring-mode stimulation in 66% of patients (31 of 47) and 35% of contacts (53 of 153), respectively. However, as mentioned, this was not statistically significant, and therefore a general effect or benefit cannot be assumed. Nevertheless, to exploit this advantage of directional stimulation, all patients would need systematic testing of all directional contacts, which is not always feasible due to the overwhelming number of existing options[11,12] and limited time resources. Using our novel statistical algorithm, we sought to determine factors that predict which ring levels warrant directional testing.

With a sensitivity of 79% and a specificity of 57%, the therapeutic window was the variable with the best predictive

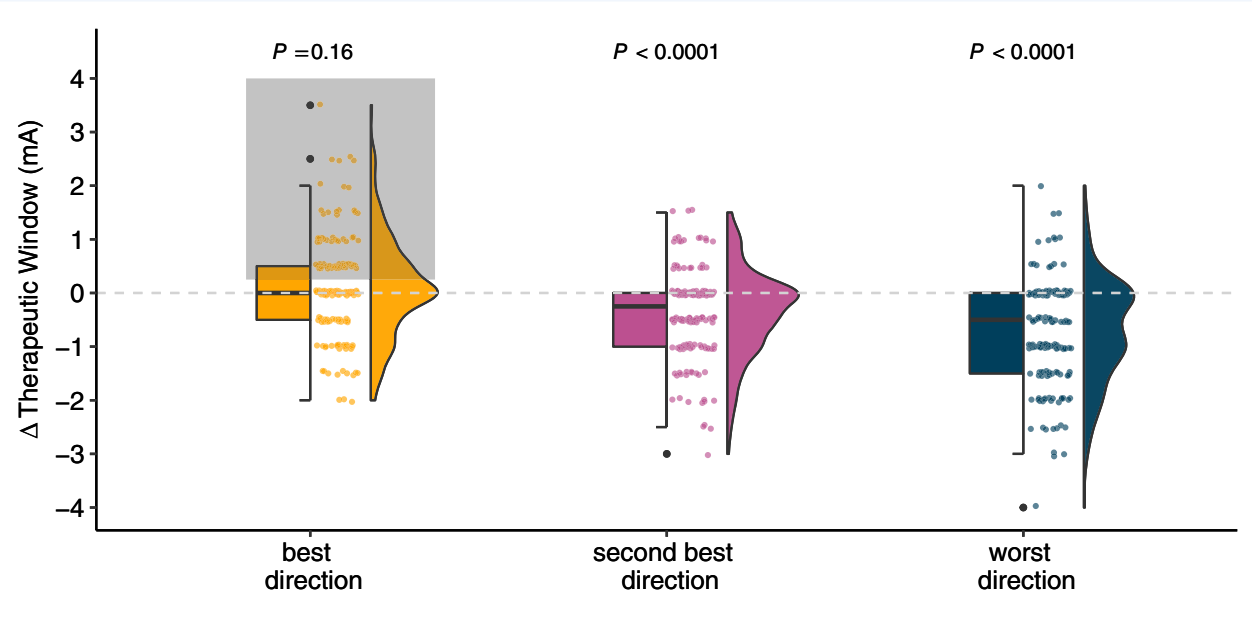

FIG 1. Differences in the therapeutic window between ring level and corresponding directional contacts. Each point corresponds to the test results of a single contact. Matching box plots and distributions are shown to the left and right of the data points. The shaded area highlights all the contacts that are labeled as "warranting investigation". *P*-values result from the mixed-effects model described in the Methods.

performance in finding contacts with a larger therapeutic window on any directional contact. Therefore, instead of extensive and time-consuming testing of all segmented contacts, we suggest that contacts with a therapeutic window at the ring level smaller than 2.0 mA should be tested directionally first. Using this algorithm, the time spent on DBS programming can be significantly reduced. However, in case chronic stimulation is limited by side effects and a larger therapeutic window cannot be identified with this procedure, extensive testing of all contacts would still be recommended given the sensitivity of this algorithm.

Limitations of our study include the unblinded clinical rating of rigidity and screening for side effect thresholds for directional monopolar stimulation. Furthermore, the model is based on the acute evaluation of the therapeutic window, which does not necessarily equate to long-term clinical benefit. For this purpose,

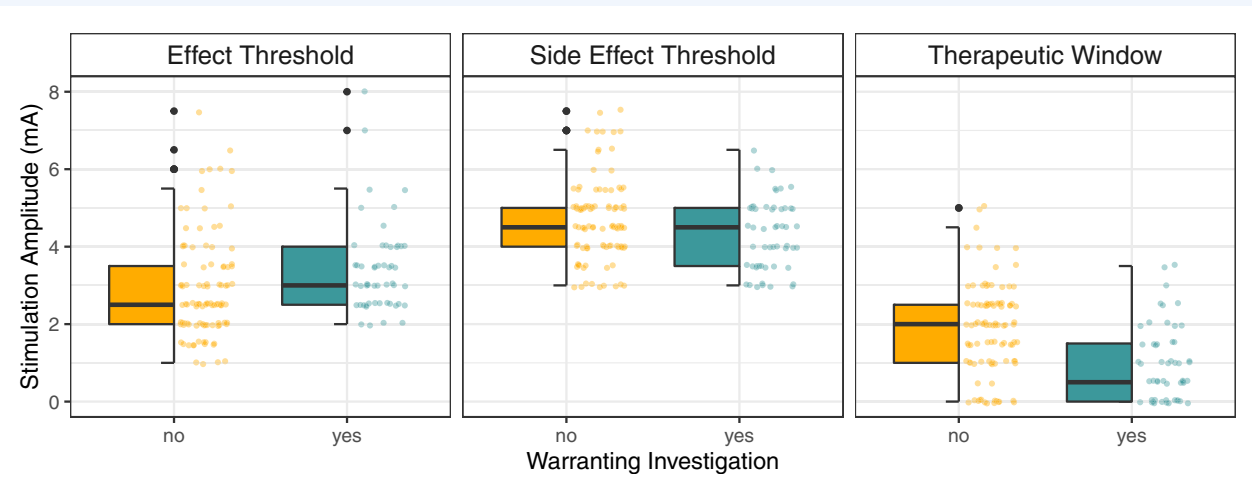

FIG 2. Effect thresholds, side-effect thresholds and therapeutic windows from the 153 ring level monopolar reviews. Contacts are labeled as "warranting investigation" if there was a relevant increase of the directional therapeutic window compared to the corresponding ring level.

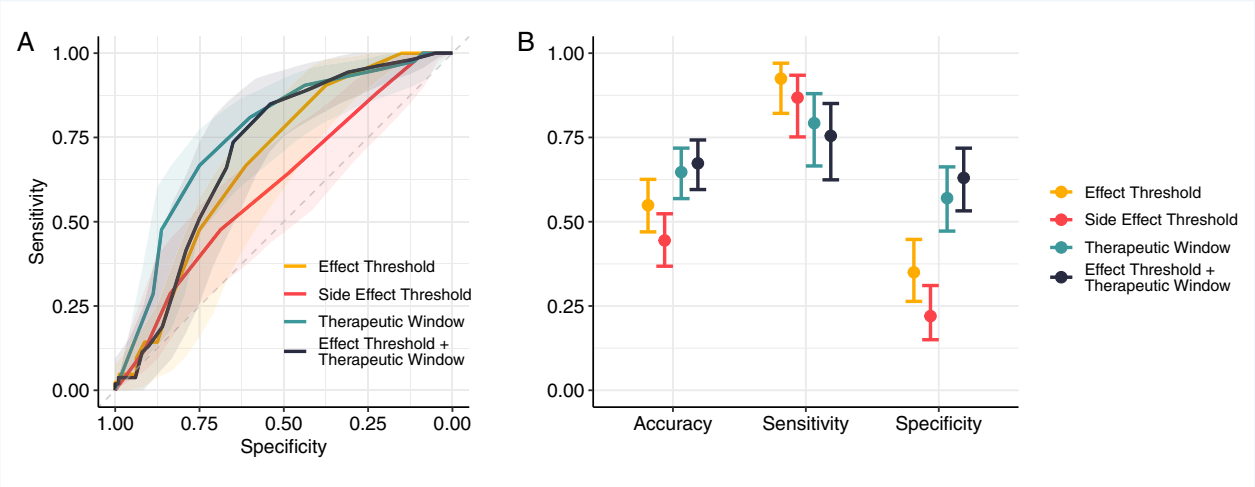

FIG 3. A: ROC curves showing sensitivity and specificity for varying thresholds for different variables (effect threshold, side-effect threshold, therapeutic window and the combination of therapeutic window and effect threshold). Shaded areas indicate 95% confidence intervals. **B:** Predictive performance for effect threshold, side-effect threshold, therapeutic window and the combination of therapeutic window and effect threshold from the 5-fold cross-validation.

a detailed investigation of chronic stimulation parameters and their clinical outcome should be performed in the future.

Regarding our model, integration of probabilistic sweet spots based on the spatial location of the DBS directional leads together with computed modeling of the Volume of Tissue Activated[16,18] and the spatial distribution of local field potentials[11,12,19] may increase the predictive power and help to exploit the full potential of directional DBS technology.

Author roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Acquisition of data; (3) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (4) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

I.D.: 1A, 1B, 1C, 2, 3A, 3C, 4A.
K.P.: 1A, 1C, 2, 3A, 3B, 3C, 4A.
A.N.: 2, 3C, 4B.
T.A.K.N.: 2, 3C, 4B.
G.T.: 3C, 4B.
J.P.M: 3C, 4B.
J.M.: 3C, 4B.
D.A.: 3C, 4B.
B.P.: 3C, 4B.
J.F.: 2, 3C, 4B.
J.A.S.: 2, 3C, 4B.
P.K.: 3C, 4B.
M.S.: 1A, 3C, 4B.
C.P.: 2, 3C, 4B.
M.L.L.: 1A, 1B, 1C, 2, 3A, 3C, 4A.

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Disclosures

Ethical Compliance Statement: The study was approved by the local ethics committee of the Canton of Bern (KEK-BE: 287/2015). All patients included into this study provided general written informed consent. On behalf of all co-authors, the first and corresponding authors confirm that all authors have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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