INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Neurologie

Katrin Petermann, dipl.Ing, MSc
Zentrum für Parkinson und Bewegungsstörungen

Deep Brain Stimulation: when to go directional?

R version and packages used to generate this report:

R version: R version 4.2.1 (2022-06-23 ucrt)

Base packages: stats, graphics, grDevices, utils, datasets, methods, base

Other packages: dplyr 1.0.9, ggpol 0.0.7, pROC 1.18.0, biostatUZH 1.8.0, survival 3.3-1, lmerTest 3.1-3, lme4 1.1-29, Matrix 1.4-1, lattice 0.20-45, tableone 0.13.2, cowplot 1.1.1, xtable 1.8-4, ggsignif 0.6.3, MASS 7.3-57, kableExtra 1.3.4, ggpubr 0.4.0, ggplot2 3.3.6, knitr 1.39

This document was generated on August 04, 2022 at 14:13.

Deep-Brain-Stimulation: when to go directional?

Debove I[af], MD, Petermann K[af], dipl.Ing. MSc, Nowacki A[b], MD, Nguyen TAK[bc], ScD, Tinkhauser G[a], MD PhD, Michelis JP[a], MD, Müllner J[a], MD, Amstutz D[a], MSc, Bargiotas P[d], MD, Fichtner J[be], MD, Schlaeppi JA[b], MD, Krack P[a], MD, Schüpbach M[a], MD, Pollo C[b], MD, Lachenmayer ML[a], MD

[a]Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[b]Department of Neurosurgery, Inselspital, Bern University Hospital, University of Bern, Switzerland
[c]ARTORG Center for Biomedical Engineering Research, University of Bern, Switzerland
[d]Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus
[e]Cantonal medical service, Department of Health of the canton of Bern, Switzerland
[f]These authors contributed equally: Ines Debove, Katrin Petermann.

Corresponding Author:
Ines Debove, MD
Department of Neurology
Inselspital
Bern University Hospital
Freiburgstrasse 10
3010 Bern, Switzerland
Phone: +41 31 632 21 11
Fax: +41 31 632 03 21
E-mail: ines.debove@insel.ch

Keywords:
Parkinson's disease
Subthalamic nucleus
Deep Brain Stimulation
Directional electrodes
Current Steering

Abstract

Background: Directional deep brain stimulation (DBS) allows for steering of the stimulation field, but it is currently unclear in which cases directional current steering might offer an advantage. Furthermore, extensive and time–consuming testing of all segmented contacts is necessary to identify the possible benefit of steering.

Objective: The goal of the study was to investigate in a standardized, systematic manner whether directional DBS of the subthalamic nucleus (STN) provides an increased *Therapeutic Window* compared to ring level stimulation and to predict which contacts should be selected for directional testing.

Methods: 52 Parkinson's disease patients implanted in the STN with a directional DBS system (Boston Scientific model DB-2202) underwent a standardized monopolar programming session 5-9 months after implantation. Individual contacts were tested for a potential advantage of directional stimulation. Subsequently obtained results were used to build a prediction model for the selection of ring levels that would benefit from directional stimulation.

Results: According to our standardized protocol, 35% of the contacts and 66% of patients had a larger *Therapeutic Window* on directional stimulation compared to ring-mode, whereas on average no difference in *Therapeutic Window* between ring-level and best directional contact could be determined. The segmented contacts that should further be explored could be predicted with a sensitivity of 79% and a specificity of 57%.

Discussion: According to our analysis, we recommend performing additional directional testing in ring-level contacts with a *Therapeutic Window* of less than 2.0 mA. Using this algorithm, the time spent on DBS programming can be significantly reduced.

Introduction

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, undesired 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 postmarket study in PD patients have shown that directional stimulation can increase the *Therapeutic Window* of stimulation [8, 9, 10]. However, identifying and exploiting the advantages of steering would require the testing of every possible configuration of stimulation parameters of the segmented contacts of different levels.
This is not possible in clinical practice due to the overwhelming number of existing options [11, 12] and limited time resources. It remains unclear in which specific circumstances directional stimulation can provide advantages [13]. Therefore, we retrospectively analyzed standard monopolar contact reviews in PD patients implanted with directional DBS leads in the STN to determine in which cases directional stimulation can offer a relevant increase of the *Therapeutic Window* .

Material and Methods

Patients

We included every patient who underwent bilateral STN–DBS surgery between 2015 and 2018 in the University Hospital of Berne, Switzerland and who provided general informed consent. The study was approved by the local ethics committee (Ethics approval KEK-BE: 287/2015). All patients were implanted with a directional lead (Boston Scientific DB-2202, Marlborough, MA, USA). The lead includes tripartite directional contacts on the two middle levels, while the distal and proximal levels are conventional ring contacts (Supplementary figure 1). The selection criteria for neurosurgery and surgical procedures have been described previously [6].

Stimulation programming / testing

A standardized monopolar contact review [9, 14] was performed 4–9 months (25 $\pm$ 5 weeks) after implantation. The programming session was conducted in a defined medication OFF–state (>12 hours of L-DOPA and >48 hours of dopamine agonists withdrawal). Assessments were performed by one of five trained raters. Rigidity was assessed according to the MDS-UPDRS-III scale. Effect- and side-effect thresholds were evaluated by increasing stimulation amplitude in 0.5mA steps, starting from 1mA and up

to a maximum of 8mA, with fixed frequency and pulse width (130Hz, 60µs). *Effect Threshold* , *Side Effect Threshold* and *Therapeutic Window* were documented for each ring-level and all directional contacts in a standardized manner.
Effect Threshold was defined as the lowest stimulation amplitude in mA, at which the best clinical effect on rigidity was observed. In case there was no rigidity detectable at baseline, the hemisphere was removed from the analysis.
Side Effect Threshold was defined as the stimulation amplitude in mA, at which a clinically limiting stimulation-induced side effect occurred due to current spreading into adjacent structures like pyramidal contractions [3, 15].
Therapeutic Window was defined as the difference between *Side Effect Threshold* and *Effect Threshold* ($TW = SET - ET$). If the *Side Effect Threshold* occurred before the *Effect Threshold* , *Therapeutic Window* was set to 0.
The Excel template used for standardized contact testing can be found in supplementary material.

Statistical Analysis

Automated contact rating and statistical analysis were performed using R version 4.2.1 (2022-06-23 ucrt) [16]. The code for all analyses can be found on GitHub `https://github.com/kilyth/MappingDirect_Publication`.

Analysis of Monopolar Reviews:
Left and right hemispheres in the same patient were assumed to be independent. Differences in stimulation amplitude were tested with a linear mixed-effects model (random intercepts) where the hemisphere was considered as random effect. 95% confidence intervals were computed with profile likelihood and P-values with the Satterthwaite approximation.

Prediction Model:
We compared *Therapeutic Window* of ring level and corresponding directional stimulation. Contacts with an increase in *Therapeutic Window* of at least 25% were labeled as "*worth testing*". *Effect Threshold* , *Side Effect Threshold* and *Therapeutic Window* of the ring level were considered as possible predictors if a contact 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 comprises 52 PD patients. Preoperative patient characteristics are shown in table 1.

The monopolar review could not be done in 11 out of 208 ring levels: 3 levels (2 patients) testing not finished because of fatigue, 4 levels (1 patient) due to oppositional paratonia ("Gegenhalten"), 2 levels (1 patient) because stimulation could not be turned off due to unbearable muscle cramps in OFF-state, 2 levels (1 patient) because of pain in the wrist. An additional 44 ring levels from 22 patients were removed from analysis because of no rigidity at baseline. The analysis was done on a total of 47 patients and 153 contacts.

Table 1: Patient characteristics for a total of 52 patients. For LEDD and MDS-UPDRS-III the postoperative values were measured one year after surgery. Continuous variables are summarized by mean and standard deviation (in brackets), while the categorical variable *Gender* is listed in counts and percent (in brackets).

Variables	level	Overall	% Missing
n		52	
Gender	female	17 (32.7)	0.0
	male	35 (67.3)	
Age at Surgery [years]		62.06 (9.42)	0.0
Disease Duration [years]		11.44 (4.61)	0.0
Time from surgery to examination [weeks]		24.60 (5.06)	0.0
LEDD preoperative [mg]		1155.86 (487.66)	0.0
LEDD postoperative [mg]		256.54 (361.31)	9.6
MDS-UPDRS-III (preoperative, without medication)		40.52 (13.26)	0.0
MDS-UPDRS-III (preoperative, with medication)		13.88 (7.13)	0.0
MDS-UPDRS-III (postoperative, without medication)		22.43 (8.48)	19.2
MDS-UPDRS-III (postoperative, with medication)		11.29 (5.85)	21.2

Monopolar Review

We compared the stimulation amplitudes for *Effect Threshold* , *Side Effect Threshold* and *Therapeutic Window* from each ring level to the corresponding segmented contacts. The difference in *Therapeutic Window* between the ring levels and the directional contacts is shown in Figure 2. We saw clear differences in the *Therapeutic Window* between the segments. However, on average the *Therapeutic Window* of the best directional contact was not larger than the *Therapeutic Window* of the corresponding ring level. 53 out of 153 ring levels (35%) in 31 out of 47 patients (66%) had a larger TW on the best directional contact.

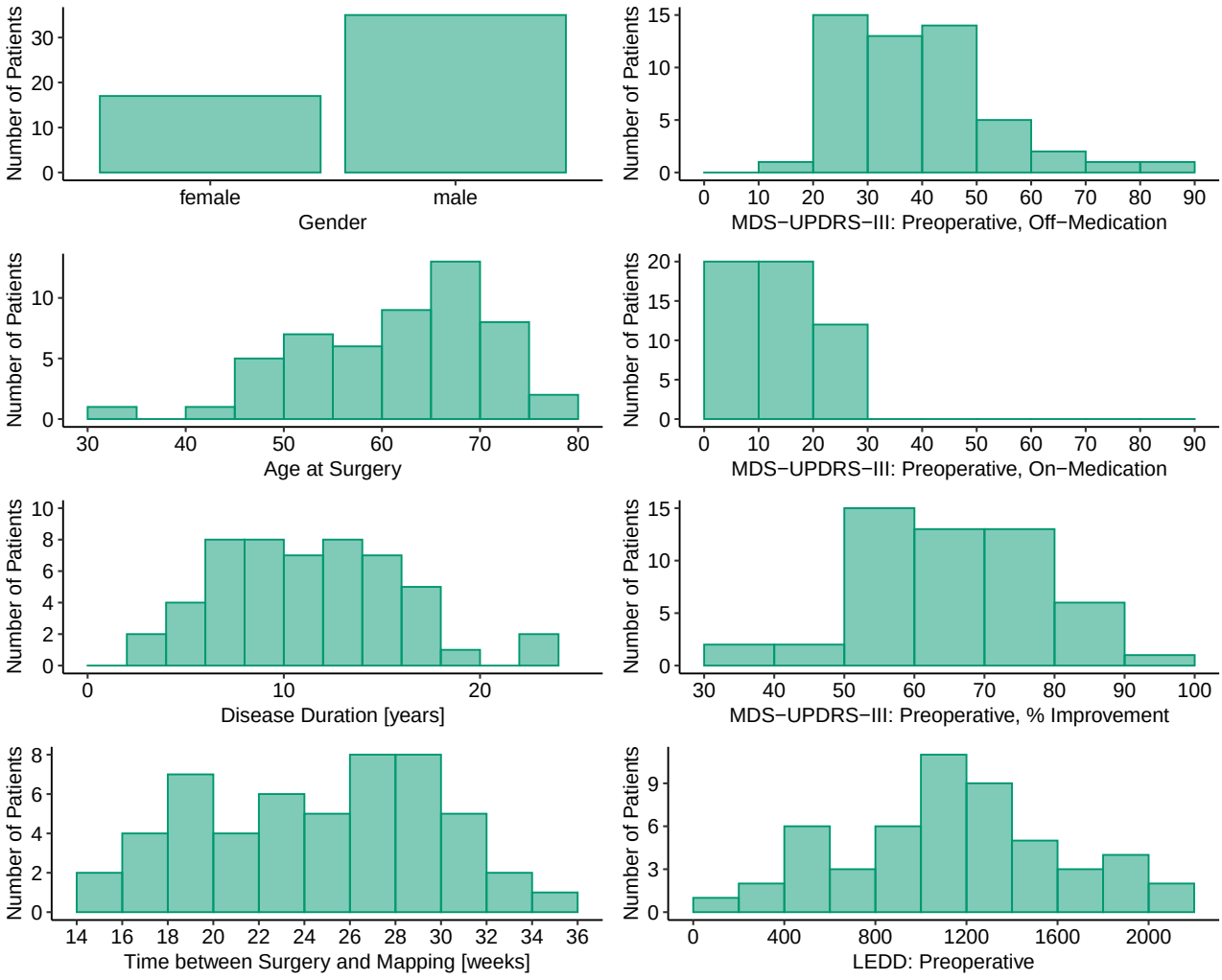

Figure 1: Patient characteristics for a total of 52 patients. For LEDD and MDS-UPDRS-III the postoperative values were measured one year after surgery.

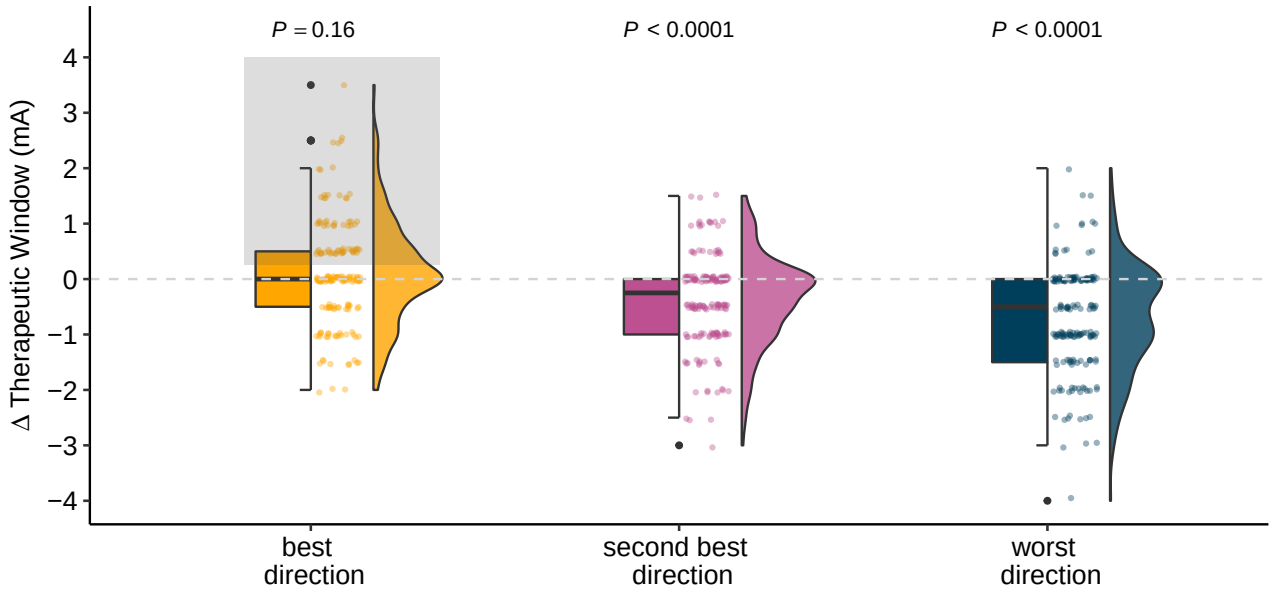

Figure 2: Differences in *Therapeutic Window* between ring level and corresponding directional contacts. Each point corresponds to the test results of a single contact. Matching boxplots and distributions are shown to the left and right of the data points. The shaded area highlights all the contacts that are labeled as "*worth testing*". P-values result from the mixed effects model described in the methods.

Prediction Model

To identify a variable that could predict which of the directional contacts could provide a relevant increase in the *Therapeutic Window* , the *Therapeutic Windows* of the ring levels were compared with those of the corresponding directional contacts. For this, directional contacts with an increase in the *Therapeutic Window* of at least 25% were considered to be "*worth testing*" Here, a percentage score was chosen instead of an absolute value, since the radius increase of the VTA is more important at low stimulation amplitudes than at higher amplitudes [18].
Effect Threshold , *Side Effect Threshold* , and *Therapeutic Window* of the ring level were considered as possible predictors of whether a level should be tested in the directional mode. Figure 3 shows the results of the monopolar reviews divided into two categories, whether the directional contact was considered "*worth testing*". The aim was to find a predictor capable of identifying contacts that could provide a relevant increase in the *Therapeutic Window* with a sensitivity of at least 75%.

The variable with the best predictive value was the *Therapeutic Window* with an AUC of 0.76 (95% CI: from 0.67 to 0.85) that was significantly higher than *Effect Threshold* (0.68, 95% CI: from 0.59 to 0.77, p = 0.046) and *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 4 A shows the calculated ROC curves of the different predictors.

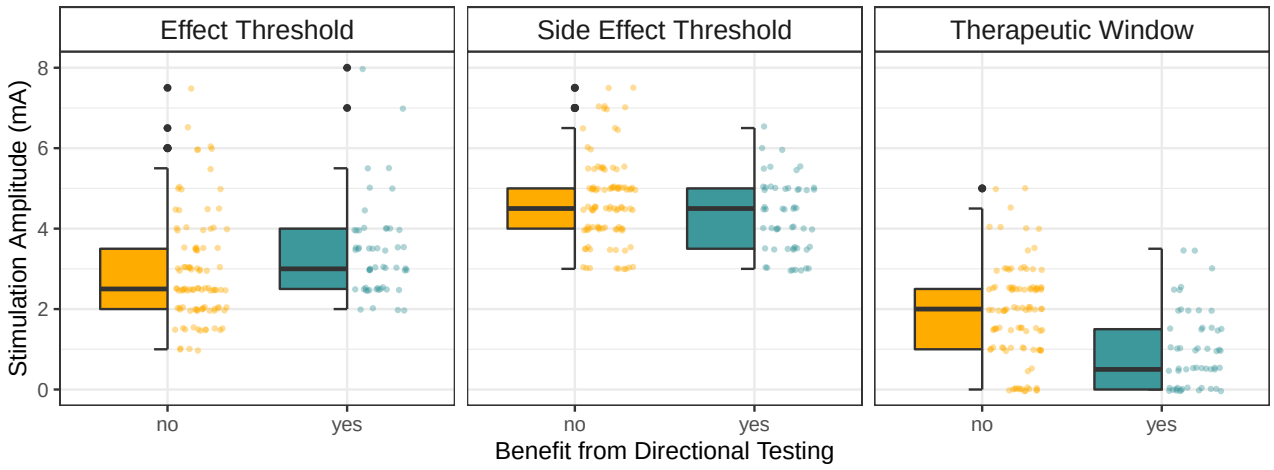

Figure 3: *Effect Thresholds* , *Side Effect Thresholds* and *Therapeutic Windows* from the 153 ring level monopolar reviews. Contacts are labeled as *benefit from directional testing* if the directional *Therapeutic Window* is at least 25% larger than the corresponding ring level.

We then used a 5-fold cross-validation 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 intensities leading to a sensitivity of at least 75% for each predicor. This stimulation intensity was then used to predict how many of the contacts in the test-fold were correctly predicted as "*worth testing*". Figure 4 B shows the results of the 5-fold cross-validation. Interestingly the relevant threshold for *Therapeutic Window* to reach a sensitivity of at least 75% is the same in each fold at $<$2.0mA. For our data, this means, that if we retest all patients with a *Therapeutic Window* smaller than 2.0mA, we will catch the patients who profit from a directional testing with a sensitivity of 79% (95% CI: from 67% to 88%) and a specificity of 57% (95% CI: from 47% to 66%). See Table 2 for all results. In our data set, out of 153 contacts, we would have done a directional monopolar review for 85 contacts. Out of these, 42 had an increase in *Therapeutic Window* of at least 25%, while 43 didn't show an increase in *Therapeutic Window* .

Discussion

In clinical practice programming of directional stimulation is challenging due to the overwhelming number of existing options [11, 12] and limited time resources. With our novel statistical algorithm, we tried to determine factors that predict which ring levels are worth to be tested directionally, i.e. have a larger *Therapeutic Window* on a directional contact compared to the ring level.

In order to identify contacts with an increase in the *Therapeutic Window* of at least 25% our prediction model suggests that ring levels with a *Therapeutic Window* on the ring level smaller than 2.0mA should be tested directionally. Considering an increase in *Therapeutic Window* of 25% as clinically meaningful, might be seen as an arbitrary number. We have chosen this value based on our clinical experience. For example, increasing the stimulation amplitude from 2.0 to 2.5mA in one patient has a higher clinical relevance than increasing it from 6.0 to 6.5mA, since in areas of high stimulation amplitudes a relevant change

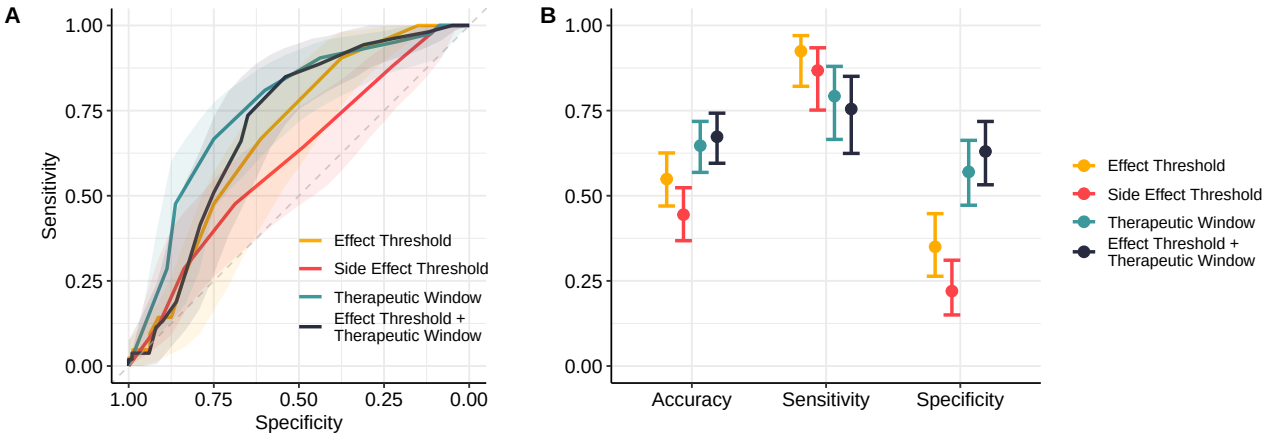

Figure 4: A: ROC curves showing sensitivity and specificity for varying thresholds for different variables (*Effect Threshold* , *Side Effect Threshold* , *Therapeutic Window* and the combination of *Therapeutic Window* and *Effect Threshold*) shaded areas indicate 95% confidence intervals. B: Results for *Effect Threshold* , *Side Effect Threshold* , *Therapeutic Window* and the combination of *Therapeutic Window* and *Effect Threshold* from the 5-fold crossvalidation. Accuracy, sensitivity and specificity for the prediction if a contact should be tested directionally.

in clinical symptoms is limited. This can be best reflected with a percentage value of this size.

In our cohort 66% of patients ((31 of 47)) and 35% of ring levels (53 of 153) respectively showed a therapeutic window that was at least 25% larger than ring-mode stimulation. However, a systematically larger *Therapeutic Window* with directional stimulation as described in previous studies [8, 9, 10] could not be confirmed. Nevertheless, to identify this potential advantage of directional stimulation, all patients in these studies needed to receive thorough testing of all directional contacts. With our algorithm and our patient cohort, only 85 out of 153 ring levels needed retesting.

To the best of our knowledge, despite smaller pilot studies [8, 9] as well as a recently published larger prospective postmarket study [10], this is the largest PD cohort with a standardized systematic rating and analysis of directional STN-DBS.

Limitations of our study include the unblinded clinical rating of rigidity and screening for *Side Effect Thresholds* for directional monopolar stimulation. Our model is based on the acute evaluation of the *Therapeutic Window* , which does not necessarily equate to long-term clinical benefit. For this purpose, a detailed investigation of chronic stimulation parameters and their clinical outcome should be performed which is beyond the scope of this study.

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 [19, 20] and the spatial distribution of local field potentials in the beta range [11, 12, 21], may increase the predictive power and help to exploit the full potential of directional DBS technology.

References

[1] Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., Daniels, C., Deutschländer, A., Dillmann, U., Eisner, W., Gruber, D., Hamel, W., Herzog, J., Hilker, R., Klebe, S., Kloß, M., Koy, J., Krause, M., Kupsch, A., Lorenz, D., Lorenzl, S., Mehdorn, H. M., Moringlane, J. R., Oertel, W., Pinsker, M. O., Reichmann, H., Reuß, A., Schneider, G.-H., Schnitzler, A., Steude, U., Sturm, V., Timmermann, L., Tronnier, V., Trottenberg, T., Wojtecki, L., Wolf, E., Poewe, W. and Voges, J. A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease. *New England Journal of Medicine* (2006). https://doi.org/10.1056/NEJMoa060281.

[2] Kleiner-Fisman, G., Herzog, J., Fisman, D. N., Tamma, F., Lyons, K. E., Pahwa, R., Lang, A. E. and Deuschl, G. Subthalamic nucleus deep brain stimulation: Summary and meta-analysis of outcomes. *Movement Disorders* (2006). https://doi.org/10.1002/mds.20962.

[3] Baizabal-Carvallo, J. F. and Jankovic, J. Movement disorders induced by deep brain stimulation. *Parkinsonism & Related Disorders* (2016). https://doi.org/10.1016/j.parkreldis.2016.01.014.

[4] Maks, C. B., Butson, C. R., Walter, B. L., Vitek, J. L. and McIntyre, C. C. Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes. *Journal of Neurology, Neurosurgery & Psychiatry* (2009). https://dx.doi.org/10.1136/jnnp.2007.126219.

[5] Contarino, M. F., Bour, L. J., Verhagen, R., Lourens, M. A., De Bie, R. M., Van Den Munckhof, P. and Schuurman, P. Directional steering: a novel approach to deep brain stimulation. *Neurology* (2014). https://doi.org/10.1212/WNL.0000000000000823.

[6] Pollo, C., Kaelin-Lang, A., Oertel, M. F., Stieglitz, L., Taub, E., Fuhr, P., Lozano, A. M., Raabe, A. and Schüpbach, M. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain* (2014). https://doi.org/10.1093/brain/awu102.

[7] Mädler, B. and Coenen, V. Explaining clinical effects of deep brain stimulation through simplified target-specific modeling of the volume of activated tissue. *American Journal of Neuroradiology* (2012). https://doi.org/10.3174/ajnr.A2906.

[8] Dembek, T. A., Reker, P., Visser-Vandewalle, V., Wirths, J., Treuer, H., Klehr, M., Roediger, J., Dafsari, H. S., Barbe, M. T. and Timmermann, L. Directional DBS increases side-effect thresholds – a prospective, double-blind trial. *Movement Disorders* (2017). https://doi.org/10.1002/mds.27093.

[9] Steigerwald, F., Müller, L., Johannes, S., Matthies, C. and Volkmann, J. Directional deep brain stimulation of the subthalamic nucleus: a pilot study using a novel neurostimulation device. *Movement Disorders* (2016). https://doi.org/10.1002/mds.26669.

[10] Schnitzler, A., Mir, P., Brodsky, M. A., Verhagen, L., Groppa, S., Alvarez, R., Evans, A., Blazquez, M., Nagel, S., Pilitsis, J. G., Pötter-Nerger, M., Tse, W., Almeida, L., Tomycz, N., Jimenez-Shahed, J.,

Libionka, W., Carrillo, F., Hartmann, C. J., Groiss, S. J., Glaser, M., Defresne, F., Karst, E., Cheeran, B. and Vesper, J. Directional deep brain stimulation for Parkinson's disease: Results of an international crossover study with randomized, double-blind primary endpoint. *Neuromodulation: Technology at the Neural Interface* (2022). https://doi.org/10.1111/ner.13407.

[11] Tinkhauser, G., Pogosyan, A., Debove, I., Nowacki, A., Shah, S. A., Seidel, K., Tan, H., Brittain, J.-S., Petermann, K., di Biase, L., Oertel, M., Pollo, C., Brown, P. and Schüpbach, M. Directional local field potentials: a tool to optimize deep brain stimulation. *Movement disorders* (2018). https://doi.org/10.1002/mds.27215.

[12] Horn, A., Neumann, W.-J., Degen, K., Schneider, G.-H. and Kühn, A. A. Toward an electrophysiological "sweet spot" for deep brain stimulation in the subthalamic nucleus. *Human brain mapping* (2017). https://doi.org/10.1002/hbm.23594.

[13] Kramme, J., Dembek, T. A., Treuer, H., Dafsari, H. S., Barbe, M. T., Wirths, J. and Visser-Vandewalle, V. Potentials and Limitations of Directional Deep Brain Stimulation: A Simulation Approach. *Stereotactic and Functional Neurosurgery* (2021). https://doi.org/10.1159/000509781.

[14] Volkmann, J., Moro, E. and Pahwa, R. Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. *Movement Disorders* (2006). https://doi.org/10.1002/mds.20961.

[15] Shields, D. C., Gorgulho, A., Behnke, E., Malkasian, D. and DeSalles, A. A. Contralateral conjugate eye deviation during deep brain stimulation of the subthalamic nucleus. *Journal of Neurosurgery* (2007). https://doi.org/10.3171/JNS-07/07/0037.

[16] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria (2022). https://www.R-project.org/.

[17] Robin, X., Turck, N., Hainard, A., Tiberti, N., Lisacek, F., Sanchez, J.-C. and Müller, M. pROC: An Open-Source Package for R and S+ to Analyze and Compare ROC Curves. *BMC Bioinformatics* (2011). https://doi.org/10.1186/1471-2105-12-77.

[18] McIntyre, C. C., Mori, S., Sherman, D. L., Thakor, N. V. and Vitek, J. L. Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. *Clinical neurophysiology* (2004). https://doi.org/10.1016/j.clinph.2003.10.033.

[19] Nguyen, T. A., Nowacki, A., Debove, I., Petermann, K., Tinkhauser, G., Wiest, R., Schüpbach, M., Krack, P. and Pollo, C. Directional stimulation of subthalamic nucleus sweet spot predicts clinical efficacy: Proof of concept. *Brain Stimulation* (2019). https://doi.org/10.1016/j.brs.2019.05.001.

[20] Dembek, T. A., Roediger, J., Horn, A., Reker, P., Oehrn, C., Dafsari, H. S., Li, N., Kühn, A. A., Fink, G. R., Visser-Vandewalle, V., Barbe, M. T. and Timmermann, L. Probabilistic sweet spots predict motor outcome for deep brain stimulation in Parkinson disease. *Annals of Neurology* (2019). https://doi.org/10.1002/ana.25567.

[21] Shah, A., Nguyen, T.-A. K., Petermann, K., Khawaldeh, S., Debove, I., Shah, S. A., Torrecillos, F., Tan, H., Pogosyan, A., Lachenmayer, M. L. et al. Combining Multimodal Biomarkers to Guide Deep Brain Stimulation Programming in Parkinson Disease. *Neuromodulation: technology at the neural interface* (2022). https://doi.org/10.1016/j.neurom.2022.01.017.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not–for–profit sectors.

CRediT authorship contribution statement

Ines Debove: Conceptualization, Formal analysis, Methodology, Data curation and interpretation, Writing – original draft, Writing – review and editing, Writing of manuscript, Review and approval of the manuscript, Project administration.
Katrin Petermann: Conceptualization, Formal analysis, Methodology, Data curation and interpretation, Writing – original draft, Writing – review and editing, Writing of manuscript, Review and approval of the manuscript.
Andreas Nowacki: Data curation, Methodology review, Review and approval of the manuscript.
Thuy Anh Khoa Nguyen: Data curation, Methodology review, Review and approval of the manuscript.
Gerd Tinkhauser: Methodology review, Data interpretation, Review and approval of the manuscript.
Joan Philipp Michelis: Methodology review, Data interpretation, Review and approval of the manuscript.
Julia Müllner: Methodology review, Data interpretation, Review and approval of the manuscript.
Deborah Amstutz: Methodology review, Review and approval of the manuscript.
Bargiotas Panagiotis: Methodology review, Data interpretation, Review and approval of the manuscript.
Jens Fichtner: Data curation, Methodology review, Review and approval of the manuscript.
Janine Ai Schlaeppi: Data curation, Methodology review, Review and approval of the manuscript.
Paul Krack: Methodology review, Data interpretation, Review and approval of the manuscript.
Michael Schüpbach: Conceptualization, Methodology review, Review and approval of the manuscript.
Claudio Pollo: Patient inclusion, Critical advice, Data interpretation, Review and approval of the manuscript.
Martin Lenard Lachenmayer: Conceptualization, Methodology, Data curation and interpretation, Writing – original draft, Writing – review and editing, Writing of manuscript, Review and approval of the manuscript.

Declaration of competing interests

Ines Debove: receives a research grant from Boston Scientific, as well as reimbursement of traveling from Zambon and Boston scientific, all support outside the submitted work.
Andreas Nowacki: received travel grants from Boston scientific. He received a research grant from the Swiss Parkinson Foundation.
Thuy Anh Khoa Nguyen: has received a grant from the Swiss National Science Foundation (project PZ00P3_186142) and funding from the Swiss Parkinson Association.
Gerd Tinkhauser: is funded by the Swiss National Science Foundation (project number: PZ00P3_202166).
Jens Fichtner: has received consultant fees from BrainLab AG, Munich, Germany.
Paul Krack: reports grants from Swiss National Science Foundation, ROGER DE SPOELBERCH Foun-

dation, Bertarelli Foundation, Michael J Fox Foundation, Annemarie Opprecht Foundation, Parkinson Schweiz, research grants from Boston Scientific and Aleva, lecturing fees paid to employ institution from Boston Scientific and Bial, as well as reimbursement of travel expenses to a scientific meeting by Zambon, all support outside the submitted work.
Michael Schüpbach: is a consultant for Medtronic. MS has received personal educational funding from Biogen and Spirig HealthCare.
Claudio Pollo: has received consultant fees from Boston, Abbott and Medtronic. He is cofounder of Aleva Neurotherapeutics.
Martin Lenard Lachenmayer: reveived reimbursement of travelling expenses to scientific meeting by Medtronic and Teva Pharmaceutical Industries.

Acknowledgments

We would like to thank all the patients and the entire team of the Center for movement disorders for their participation and support in this study.

Appendix

Table 2: Same results as Figure 4 but in numbers.

	Sensitivity	(95% CI)	Specificity	(95% CI)	Accuracy	(95% CI)
Therapeutic Window	0.79	[0.67, 0.88]	0.57	[0.47, 0.66]	0.65	[0.57, 0.72]
Effect Threshold	0.92	[0.82, 0.97]	0.35	[0.26, 0.45]	0.55	[0.47, 0.63]
Side Effect Threshold	0.87	[0.75, 0.93]	0.22	[0.15, 0.31]	0.44	[0.37, 0.52]
TW and ET	0.75	[0.62, 0.85]	0.63	[0.53, 0.72]	0.67	[0.60, 0.74]