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Predicting the Benefit of Current Steering in Subthalamic Deep Brain Stimulation in Parkinson's Disease

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Predicting the Benefit of Current Steering in Subthalamic Deep Brain Stimulation in Parkinson's Disease

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Abstract

Background: Directional deep brain stimulation (DBS) allows for steering of the stimulation field. Currently, it is unclear which patients profit from directional current steering.

Objective/Hypothesis: The goal of the study was to investigate in a standardized, systematic manner whether directional DBS of the STN provides an increased *Therapeutic Window* , and to predict which contacts should be selected for directional testing.

Methods: 52 Parkinson's disease (PD) patients implanted in the subthalamic nucleus (STN) with a directional DBS system (Boston Scientific model DB-2202) underwent a standardized programming session 5-9 months after implantation. The recorded *Effect Threshold* , *Side Effect Threshold* and *Therapeutic Window* were tested for potential benefit of current steering and used to build a prediction model for the selection of the contacts profiting from horizontal steering.

Results: According to our standardized protocol, 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 was noticed. We were able to predict which contacts should be retested in a directional manner with a sensitivity of 79% and a specificity of 57%.

Conclusion: Our results confirm the directionality of the system. According to our analysis, additional directional testing should be done in ring-level contacts with a *Therapeutic Window* <2.0mA.

Introduction

DBS of the STN is an effective treatment for levodopa-responsive PD with motor complications [5, 7]. However, the efficacy of STN-DBS may be limited by stimulation-induced side effects that emerge when the volume of tissue activated expands into adjacent structures [1, 9].
Directional electrodes represent a technical innovation in DBS, as these contacts allow for a directional alignment of the stimulation field [2, 11], while conventional DBS systems with cylindrical ring contacts generate a concentric stimulation field [8]. Postoperative pilot STN-DBS studies and a prospective postmarket study in PD patients have shown that directional stimulation can expand the therapeutic window of stimulation [3, 17, 14]. 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. Since in clinical practice this is not possible due to the overwhelming number of existing possibilities [18, 6] and limited time resources, and moreover, directional stimulation does not offer advantages in all cases, we retrospectively analyzed standard monopolar contact reviews in PD patients with directional DBS leads in the STN to determine in which cases directional stimulation can offer a relevant extension of the therapeutic window.

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

Material and Methods

Patients

Our consecutive cohort comprises 52 PD patients from the University Hospital of Berne, Switzerland for whom a general consent has been obtained. We included every patient who underwent bilateral STN-DBS surgery between 2015 and 2018, all of them 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. The selection criteria for neurosurgery and surgical procedures have been described previously.
Ethics approval KEK-BE: 287/2015

Stimulation programming / testing

4–9 months (25 $\pm$ 5 weeks) after implantation, patients underwent a programming session following the procedure of a standard monopolar contact review [17, 19] 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 and side effects were assessed by increasing stimulation amplitude in 0.5mA steps, starting from 1.0mA and up to a maximum of 8.0mA, with fixed frequency and pulse width (130Hz, 60µs). *Effect Threshold* (ET), *Side Effect Threshold* (SET) and *Therapeutic Window* (TW) 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 during the programming session. In case there was no rigidity detectable at baseline, the hemisphere was removed from 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 [1, 16].
Therapeutic Window was defined as the difference between *Effect Threshold* and *Side Effect Threshold* ($TW = SET - ET$). If the *Side Effect Threshold* occurred before the *Effect Threshold* , *Therapeutic Window* was set to 0.

Statistical Analysis

Automated contact rating and statistical analysis were performed using R version 4.2.1 (2022-06-23 ucrt) [12]. 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 to be tested*. *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 [13]. 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% confidence intervals.

Results

Patients

Preoperative patient characteristics are shown in table 1.

Monopolar Review

The monopolar review could not be done in 11 out of 208 ring levels: 3 contacts (2 Patients) testing not finished because of fatigue, 4 contacts (1 Patient) because of Gegenhalten, 2 contacts (1 Patient) because stimulation could not be turned off due to unbearable muscle cramps in OFF-state, 2 contacts (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.
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

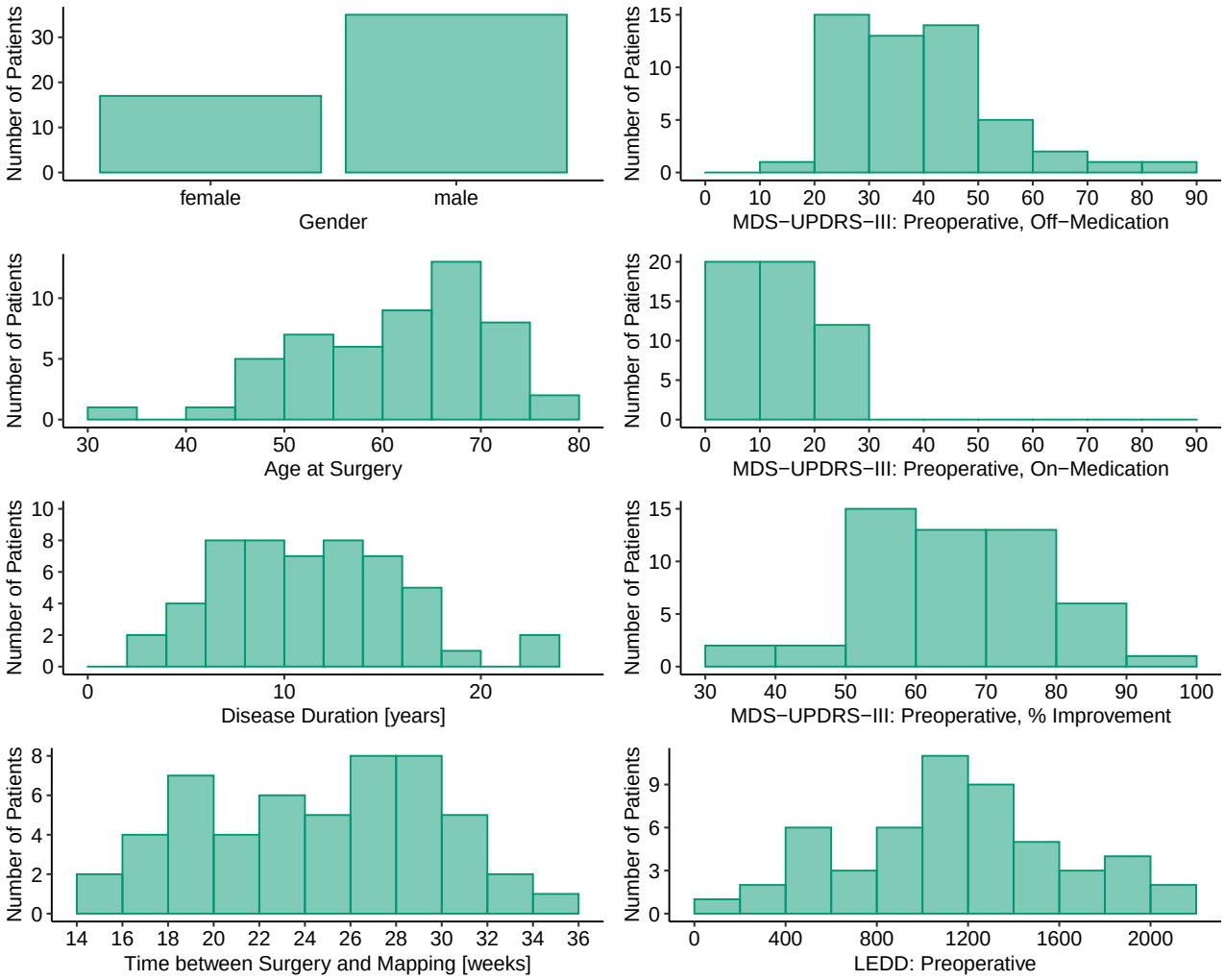

Figure 1: Patient characteristics for a total of 52 patients. For LEDD and MDS-UPDRS-III the postoperative values were measured one year after surgery.

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

ring levels and the directional contacts is shown in Figure 2. We see a clear difference in *Therapeutic Window* between the three segments, however on average the *Therapeutic Window* is not larger on the best directional contact when compared to ring level. Even so, 53 out of 153 ring levels (35%) in 31 out of 47 patients (66%) had a larger TW on the best directional contact.

Prediction Model

In order to identify a variable that could predict which of the directional contacts could provide a relevant increase of the *Therapeutic Window* , the *Therapeutic Window* of the ring level were compared with those of the corresponding directional contacts. For this, directional contacts with an increase in *Therapeutic Window* of at least 25% were considered to be worth testing. *Effect Threshold* , *Side Effect Threshold* , and *Therapeutic Window* of the ring level were considered as possible predictors of whether a contact should be tested in the directional mode. Figure 3 shows the results of the monopolar reviews divided into two categories, whether or not the directional contact was considered as worth to be tested. The aim was to find a marker 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 *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 combination 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).
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 to be tested*. Figure 4 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 $\leq$1.5mA. For our data, this means, that if we retest all patients with a *Therapeutic Window*

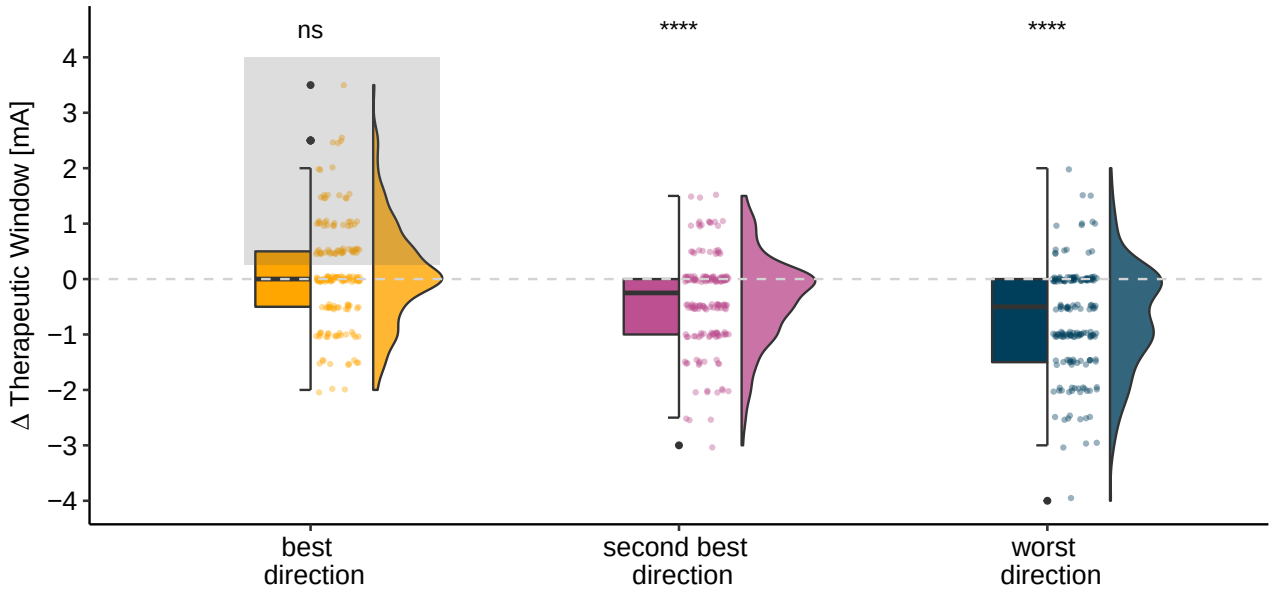

Figure 2: Differences in *Therapeutic Window* between ring level and corresponding directional contacts. Each point corresponds to the test results of a single contact. Matching boxplots and distributions are shown to the left and right of the data points. The shaded area highlights all the contacts that are labeled as worth to be tested.

smaller or equal to 1.5mA, we will catch the patients who profit from a directional testing with a sensitivity of 0.79 and a specificity of 0.57. 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

To the best of our knowledge, despite smaller pilot studies [3, 14] as well as a recently published larger prospective postmarket study [14], this is the largest PD cohort with a standardized systematic automated rating and analysis of directional STN-DBS. Although in our study, 66% of the patients (31 out of 47), respectively 35% of the contacts (53 out of 153), showed a TW that was at least 25% larger with directional stimulation compared to ring-mode stimulation, we could not confirm a systematic larger therapeutic window with directional stimulation, as described in previous studies [3, 17, 14].
However, taking advantage of steering would mean to consider every possible configuration of stimulation parameters like vertical steering and combining segmented contacts of different levels. In clinical practice, this is not possible, due to the overwhelming number of existing [18, 6] possibilities and limited time resources.
Limitations of our study include the unblinded clinical rating of rigidity and screening for side effect thresholds for horizontal and monopolar steering. Our analysis is based on acute patient evaluation, therefore a detailed investigation of chronic stimulation parameters and their clinical outcome is beyond the scope of the study but needs to be explored in the future.
Including probabilistic sweet spots based on the spatial location of the DBS directional leads together with computed modeling of the Volume of Tissue Activated [10, 4] or the spatial distribution of local field potentials in the

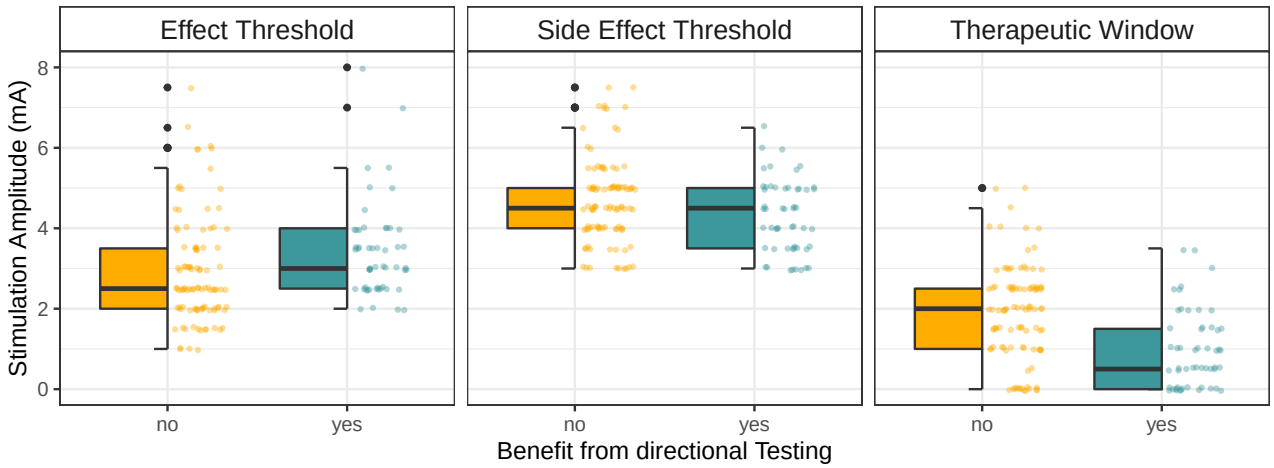

Figure 3: *Effect Threshold* , *Side Effect Threshold* and *Therapeutic Window* from the 153 ring level monopolar reviews. Contacts are labeled as *benefit from directional testing* if the directional *Therapeutic Window* is at least 25% larger than the corresponding ring level.

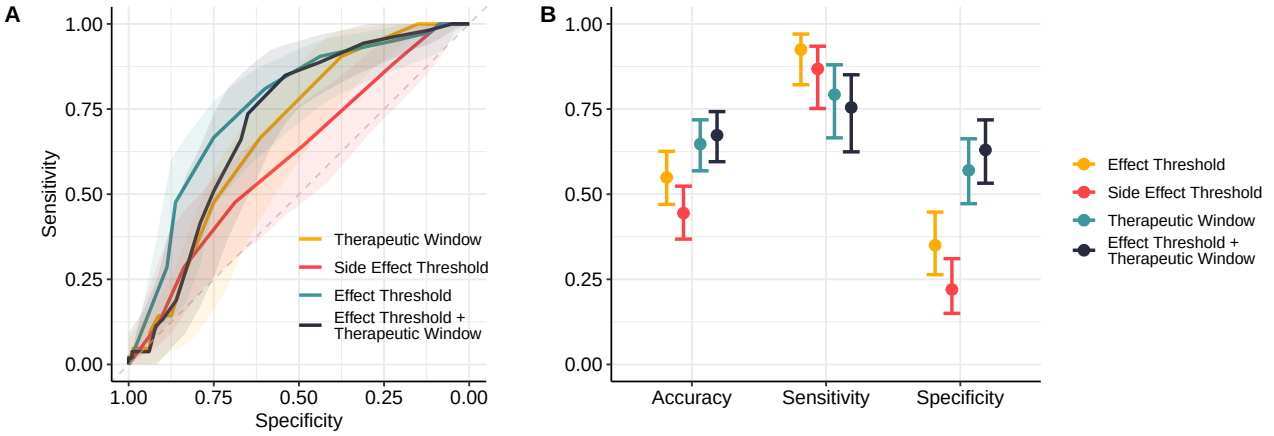

Figure 4: A: ROC curves showing sensitivity and specificity for varying thresholds for different variables (*Effect Threshold* , *Side Effect Threshold* , *Therapeutic Window* and the combination of *Therapeutic Window* and *Effect Threshold*) shaded areas indicate 95% confidence intervals. B: Results 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.

beta range [18, 6] in the programming decision making, may increase the percentage of patients stimulated in a directional mode and could help to exploit the full potential of directional DBS technology.

Conclusion

Since a suboptimal position of the stimulating electrode may cause limiting side effects, and as it has been shown that patients in this situation could further benefit from directional stimulation [10, 15], the technological achievement of steering electrodes should be available to all patients.
With systematic and thorough analyses we confirm the potential benefit of directional versus ring-mode stimulation in terms of effect threshold, side effect threshold and therapeutic window. We could show that current steering provides acute clinical benefit in a subset of patients, in whom ring-mode stimulation is limited by side-effects related to current diffusion. These findings provide an important clinical proof of concept for the potential superiority of directional DBS-leads. Future chronic studies are needed to determine in which patients and to what extent the observed differences between ring mode and directional stimulation provide a relevant clinical benefit.

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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

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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]