Automated deep brain stimulation programming based on electrode location: a randomised, crossover trial using a data-driven algorithm

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Summary

Background Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is highly effective in controlling motor symptoms in patients with Parkinson's disease. However, correct selection of stimulation parameters is pivotal to treatment success and currently follows a time-consuming and demanding trial-and-error process. We aimed to assess treatment effects of stimulation parameters suggested by a recently published algorithm (StimFit) based on neuroimaging data.

Methods This double-blind, randomised, crossover, non-inferiority trial was carried out at Charité – Universitätsmedizin, Berlin, Germany, and enrolled patients with Parkinson's disease treated with directional octopolar electrodes targeted at the STN. All patients had undergone DBS programming according to our centre's standard of care (SoC) treatment before study recruitment. Based on perioperative imaging data, DBS electrodes were reconstructed and StimFit was applied to suggest optimal stimulation settings. Patients underwent motor assessments using the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) during OFF-medication and in OFF-stimulation and ON-stimulation states under both conditions, StimFit and SoC parameter settings. Patients were randomly assigned (1:1) to receive either StimFit-programmed DBS first and SoC-programmed DBS second, or SoC-programmed DBS first and StimFit-programmed DBS second. The allocation schedule was generated using a computerised random number generator. Both the rater and patients were masked to the sequence of SoC and StimFit stimulation conditions. All patients who participated in the study were included in the analysis. The primary endpoint of this study was the absolute mean difference between MDS-UPDRS-III scores under StimFit and SoC stimulation, with a non-inferiority margin of 5 points. The study was registered at the German Register for Clinical Trials (DRKS00023115), and is complete.

Findings Between July 10, 2020, and Oct 28, 2021, 35 patients were enrolled in the study; 18 received StimFit followed by SoC stimulation, and 17 received SoC followed by StimFit stimulation. Mean MDS-UPDRS-III scores improved from 47·3 (SD 17·1) at OFF-stimulation baseline to 24·7 (SD 12·4) and 26·3 (SD 12·4) under SoC and StimFit stimulation, respectively. Mean difference between motor scores was –1·6 (SD 7·1; 95% CI –4·0 to 0·9; superiority test $p_{superiority}$=0·20; n=35), establishing non-inferiority of StimFit stimulation at a margin of –5 points (non-inferiority test $p_{non\text{-}inferiority}$=0·0038). In six patients (17%), initial programming of StimFit settings resulted in acute side-effects and amplitudes were reduced until side-effects disappeared.

Interpretation Automated data-driven algorithms can predict stimulation parameters that lead to motor symptom control comparable to SoC treatment. This approach could significantly decrease the time necessary to obtain optimal treatment parameters.

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Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well established treatment option for advanced Parkinson's disease, improving motor symptoms and quality of life and allowing dopaminergic medication to be reduced.[1] Yet, treatment success depends on the correct selection of stimulation parameters, which includes adaptation of amplitude, stimulation frequency, pulse width, and the relative distribution of electric current across contacts. Currently, strategies to optimise these parameters are exclusively based on clinical testing and require highly trained medical personnel to iteratively adjust DBS settings in response to therapeutic or adverse effects.[2] Typically, this process is initiated by a monopolar review for contact selection and amplitude adjustment, the two most important parameters for effective DBS.[3] Variation of stimulation frequency and pulse width usually has limited impact on clinical outcome[4] and therefore

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Research in context

Evidence before this study

We searched PubMed for clinical trials published up to July 28, 2022, combining the terms ("deep brain stimulation", "programming") AND ("automated" OR "assisted" OR "guided" OR "software") including publications with abstracts in English or German. We identified four studies that prospectively assessed the therapeutic benefit of deep brain stimulation (DBS) parameters derived from neuroimaging metrics. All studies were conducted in patients with Parkinson's disease treated with subthalamic nucleus (STN) DBS, and a double-blind crossover design was used to compare image-guided programming with standard of care (SoC). Reduced programming time and comparable motor symptom control for image-guided DBS was reported in all studies. However, three studies lack statistical power and do not provide an a priori definition of a non-inferiority margin. The margin in the fourth study should be considered too liberal, leading to inconclusive findings of non-inferiority of image-guided DBS on the one hand and statistical superiority of SoC on the other hand. Crucially, all studies used a commercially available software that provides visual feedback of stimulation sites in relation to patient anatomy but does not specify clear optimisation objectives or suggest optimal stimulation parameters. More elaborate automated or data-driven algorithms have been developed but not yet been systematically tested in prospective applications.

Added value of this study

To our knowledge, this is the largest randomised trial assessing the therapeutic benefit of DBS settings derived from neuroimaging metrics. Moreover, this is the first time a data-driven model to suggest optimal stimulation parameters was prospectively applied in a randomised, double-blind, crossover clinical trial. Leveraging the recent advances in the field of DBS neuroimaging, this approach allows identification of individual stimulation parameters, which maximise predicted motor symptom control, while accounting for potential stimulation-induced side-effects in a fully automated manner. In a cohort of 35 patients treated with STN-DBS, we established non-inferiority of motor symptom control under these stimulation settings compared with SoC treatment, with no statistically significant difference between both conditions. Furthermore, we identified differential effects with regard to specific motor symptoms. These findings provide prospective evidence for distinct symptom-specific stimulation targets and suggest that automated DBS parameter selection tailored to patients' individual symptom profiles could further improve therapeutic benefit.

Implications of all the available evidence

Individualised adaptation of stimulation parameters is essential to optimise DBS treatment benefit. Current optimisation strategies are based on clinical trial-and-error, a process which is not only time-consuming and exhausting for both patients and medical personnel, but can also easily lead to selection of suboptimal stimulation parameters. This problem was amplified with the introduction of directional electrodes and limits the potential benefit of more complex electrode designs. Multiple retrospective studies have linked electrode location and stimulation parameters to clinical outcome. This has shed light onto the anatomical structures involved in therapeutic neuromodulation, but despite the urgent need, translational applications remain sparse. First prospective trials have reported clinical advantages in using anatomical visualisation software to guide DBS parameter selection. The current study expands these findings by providing strong evidence that neuroimaging data can be used to identify beneficial stimulation settings in an automated manner. This could potentially be translated to other diseases and provides much needed prospective validation in the field. Data-driven algorithms could assist future programming strategies and pave the way for more complex electrode designs to further optimise treatment benefit.

current clinical programming strategies suggest that these parameters should be kept at default values (commonly 130 Hz, 60 µs) during initial programming and refined at later stages according to patients' symptomatic profile and treatment response.[2] Nevertheless, this procedure is highly time-consuming and impeded by multiple factors including a delayed response to parameter adjustments, symptom fluctuations, and patient fatigue. Hence, only a fraction of the vast number of parameter combinations can be evaluated in this manner, imposing the risk of selecting suboptimal settings. This problem has been aggravated by the introduction of directional electrodes, which allow for a more flexible shaping of the electric field but come at the cost of further inflating the number of possible stimulation settings.[5]

To use the full therapeutic potential of modern DBS systems, data-driven algorithms could guide DBS programming by suggesting a subset of stimulation parameters.[6–8] Electrode localisation represents a promising input feature for such an approach, since numerous studies have established a link to therapeutic or adverse DBS effects across various stimulation targets and diseases.[9–12] This seems especially feasible since electrodes can be reconstructed from routinely acquired perioperative neuroimaging data, allowing for potential implementation in routine clinical practice without the need for additional data acquisition or equipment.[13] Commercial software that can provide visual feedback of stimulation and electrode location in relation to patients' individual anatomy is already available to aid clinical programming procedures, and first prospective applications indicate a potential benefit by reducing the time needed for clinical programming.[14–17] Despite these advantages, image-guided optimisation of DBS

parameters remains challenging for two reasons. First, to derive optimal stimulation settings, iterative adjustments of DBS parameters need to be conducted manually within the software. Although this allows for a much faster probing of different settings, this approach still does not solve the initial problem considering that there are more than 10^{10} combinatorial possibilities to distribute electric current in octopolar electrodes. Second, optimisation objectives are unknown. Decision making is currently based on visualisations of simplified volumetric estimates of neuronal activation (volume of tissue activated, VTA) and their overlap with anatomical regions. However, stimulation targets as well as regions of avoidance are not clearly defined.[18] Moreover, the VTA as a simplified "bottom-up" biophysical model of neuronal activation should be considered a rather vague metric to estimate the anatomical regions affected by stimulation. It is based on many pre-assumptions, most of which are unknown in the individual patient—eg, fiber diameters and their orientation relative to the electric field, which has shown to impact fiber activation in silico and in vivo.[19,20] Subsequently, VTA-based predictive modelling approaches have been shown to be vulnerable towards parameter modifications and varying statistical implementations.[21] Hence, DBS parameter selection in current image-guided programming strategies is driven (and potentially misled) by the programmers' individual understanding of the interplay between model estimations, patient anatomy, and DBS effects.

Aiming to overcome those limitations, we recently developed and retrospectively validated StimFit, a data-driven algorithm capable of suggesting optimal stimulation parameters in patients with Parkinson's disease treated with STN-DBS based on electrode location in a fully automated fashion (figure 1).[22] StimFit was trained and tested based on a large sample of over 600 different stimulation settings applied in 50 patients with Parkinson's disease.[5,7,10] Electrode reconstructions were obtained using the Lead-DBS toolbox (figure 1A) and a predictive model was implemented linking electrode locations and stimulation parameters to corresponding improvements of akinetic-rigid symptoms and tremor as well as probabilities of potential stimulation-induced side-effects (figure 1C).[13] Model predictions were based on the properties of the electric field generated by each stimulation setting. Opposed to commonly used binarised VTA models, this approach does not assume an all-or-nothing firing behaviour of the axons of passage but instead allows modelling of a probabilistic interrelation between voltage gradients (and directionalities) and clinical outcome in the target region. This way, the model is less constrained by unknown biophysical pre-assumptions and might therefore be more robust, especially in anatomically complex areas, such as the subthalamic region. We retrospectively validated the predictive model using an independent dataset, showing that the trained algorithm could predict differences in stimulation outcome caused by varying stimulation parameters in individual patients. Next, a non-linear optimisation procedure was implemented to identify the setting that would maximise therapeutic effects, while minimising probabilities of stimulation-induced side-effects in a time-efficient manner (figure 1C). It allows the clinician to predefine a maximum side-effect probability, constraining the number of possible solutions (all solutions with side-effect probabilities greater than the predefined threshold are discarded), and to define whether solutions should aim at maximising suppression of tremor or akinetic-rigid symptoms. StimFit was embedded in a graphical user interface for a clear and streamlined use (appendix p 4). The algorithm is supplied as open-source code.

See Online for appendix

For the **code** see https://github.com/JRoediger/StimFit

In the present study, we prospectively assessed the clinical effects of DBS parameter suggestions made by StimFit and compared them with the ones derived during standard of care (SoC) programming strategies.

Methods

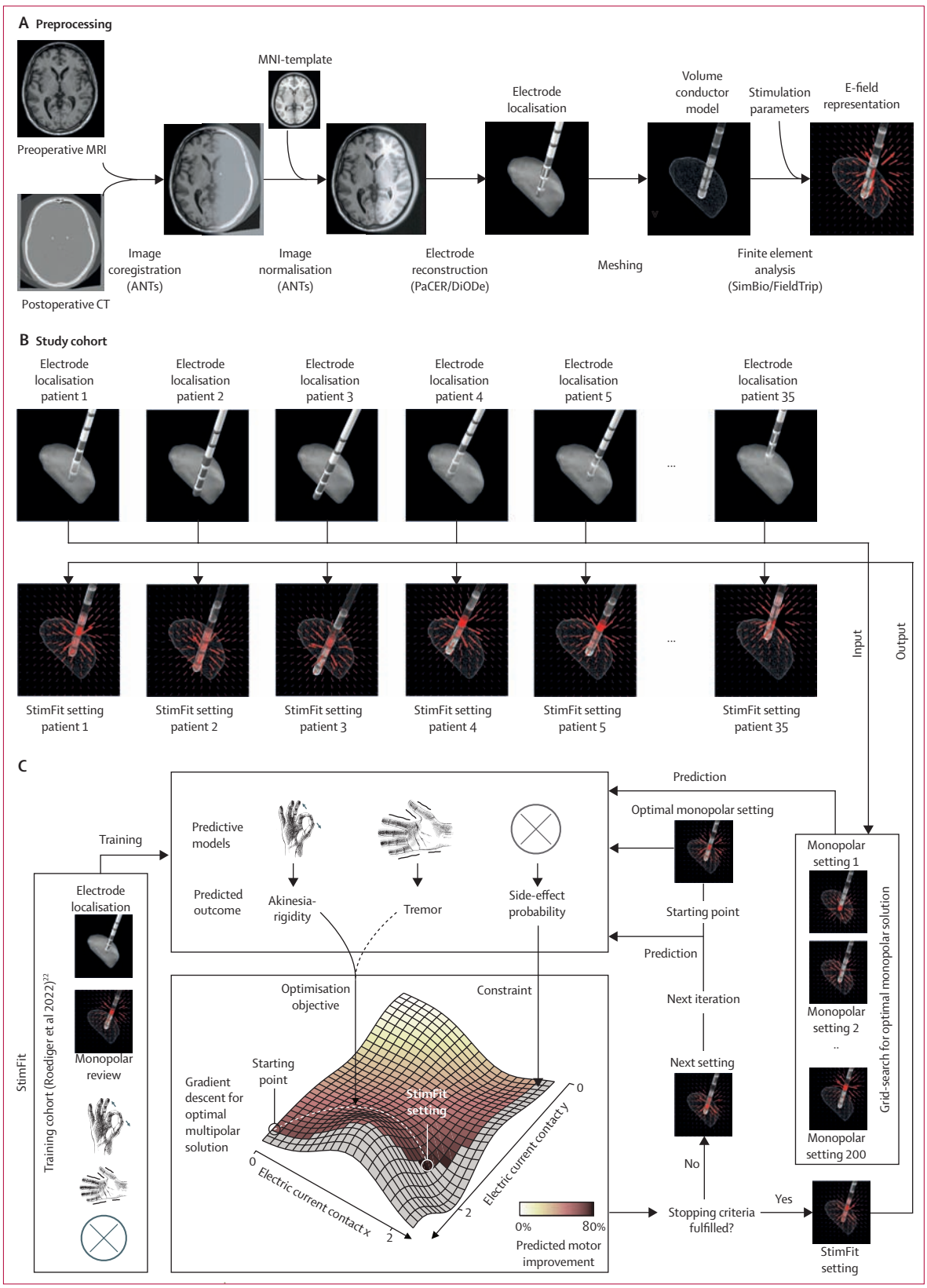
Study design and participants

This randomised, double-blind, 2×2 crossover, non-inferiority trial was designed to evaluate the clinical effects of DBS settings suggested by StimFit, a fully automated, data-driven algorithm based on neuroimaging data, and to compare results with SoC.[22] The study was carried out at Charité – Universitätsmedizin, Berlin, Germany.

Patients with Parkinson's disease who had undergone STN-DBS surgery with directional octopolar electrodes (Cartesia directional leads [Boston Scientific, Marlborough, MA, USA] or SenSight directional leads [Medtronic, Minneapolis, MN, USA) were included in the study. Inclusion criteria were a diagnosis of Parkinson's disease according to the British Parkinson's Disease Society Brain Bank without severe cognitive impairment, neuropsychiatric symptoms, or severe cerebral atrophy, and the ability to undergo overnight withdrawal of dopaminergic medication. DBS surgeries had to be carried out between 3 months and 3 years before recruitment, without any major surgical complications such as bleeding, infections of the DBS system, or reimplantation of DBS electrodes. All patients gave informed written consent. The study was approved by the ethics committee at Charité – Universitätsmedizin Campus Virchow-Klinikum (EA2/117/19).

Randomisation and masking

Patients were randomly assigned (1:1) to receive either StimFit-programmed DBS first and SoC-programmed DBS second, or SoC-programmed DBS first and StimFit-programmed DBS second. The rater as well as patients were masked to the sequence of SoC and StimFit stimulation conditions. The sequence was randomised in a 1:1 ratio without applying block stratification. An


A Preprocessing
Preoperative MRI
Postoperative CT
Image coregistration (ANTs)
MNI-template
Image normalisation (ANTs)
Electrode reconstruction (PaCER/DiODe)
Electrode localisation
Meshing
Volume conductor model
Stimulation parameters
Finite element analysis (SimBio/FieldTrip)
E-field representation
B Study cohort
Electrode localisation patient 1
Electrode localisation patient 2
Electrode localisation patient 3
Electrode localisation patient 4
Electrode localisation patient 5
Electrode localisation patient 35
StimFit setting patient 1
StimFit setting patient 2
StimFit setting patient 3
StimFit setting patient 4
StimFit setting patient 5
StimFit setting patient 35
Input
Output
C
StimFit
Training cohort (Roediger et al 2022)[22]
Training
Electrode localisation
Monopolar review
Predictive models
Predicted outcome
Akinesia-rigidity
Tremor
Side-effect probability
Optimisation objective
Constraint
Starting point
Gradient descent for optimal multipolar solution
StimFit setting
Electric current contact x
Electric current contact y
Predicted motor improvement
0%
80%
Prediction
Optimal monopolar setting
Starting point
Prediction
Next iteration
Next setting
No
Stopping criteria fulfilled?
Yes
StimFit setting
Monopolar setting 1
Monopolar setting 2
Monopolar setting 200
Grid-search for optimal monopolar solution

unmasked research assistant (A-PK) generated the allocation schedule using a computerised random number generator. The same researcher activated the stimulation settings during the study visit but was otherwise not involved in patient care, clinical ratings, or data analysis.

Procedures

SoC programming was conducted before enrolment according to the standard postoperative clinical routine at our centre. This included initial activation of DBS and medication adjustments within the first weeks after surgery in order to taper the stun effect, which attenuates over time. 3 months after system implantation, standard monopolar review of all contact levels (in ring mode) was undertaken under stable frequency and pulse width while checking for symptom remission and unwanted side-effects under increasing stimulation amplitudes. Optimal contact levels were defined as those with the lowest amplitudes necessary to achieve therapeutic benefit and large therapeutic windows until appearance of non-transient stimulation-induced side-effects (eg, muscle contractions). Segmented testing was conducted if unwanted side-effects limited clinical benefits. Assessing the therapeutic window this way provided important information used for fine-tuning DBS settings along with adjustments of dopaminergic medication over the course of several days during inpatient stays. Additionally, patients underwent multiple follow-up adjustments before study participation (appendix p 5). All DBS adjustments were conducted at specialised inpatient and outpatient facilities (at Charité – Universitätsmedizin Berlin and Beelitz Hospital for Parkinson's disease) and either carried out or supervised by movement disorders specialists with 22 (AAK) and 12 (PK) years of experience in DBS treatment.

For the StimFit setting, electrodes were reconstructed and normalised to the Montreal Neurological Institute (MNI) coordinate system based on multimodal preoperative MRI and postoperative CT using the default Lead-DBS pipeline as described in the original publication of the algorithm and depicted in figure 1A.[13,22] Algorithmic suggestions of DBS parameters were then computed using StimFit (figure 1B). Briefly, the model predicts motor improvements and side-effect probabilities of stimulation settings based on electrode reconstructions and simulations of the electric field in the target region. To identify which contact selection and stimulation amplitude would lead to the maximal therapeutic benefit, an optimiser iterated through different stimulation settings until the model converged to a final solution (figure 1C). To constrain stimulation parameters, StimFit required specifying a maximum side-effect probability, which was set to 20% (50% in the first four patients, see appendix p 3). Although StimFit allows the degree of tremor present at baseline to be individually accounted for (figure 1C), this option was not included in the study protocol. This choice was made to guarantee a clear, streamlined, and reproducible analysis solely based on imaging data rather than patient-specific adjustments with regard to individual motor symptoms. Thus, the algorithm was forced to maximise improvement for bradykinesia as the cardinal symptom for Parkinson's disease across all patients, while tremor was excluded from the optimisation procedure. The resulting stimulation parameters will be referred to as StimFit settings.

Examinations were performed within 1 day after overnight withdrawal of dopaminergic medication according to the study protocol (see details in figure 2). All ratings were carried out by the same rater (JR). In the preparation phase, contact impedances were measured to confirm the integrity of the DBS system and to estimate energy efficiency of stimulation settings (see appendix p 2).[24]

Demographic and treatment data at the time of study participation included age, sex, disease duration, time since DBS surgery, and time since last adjustment of SoC settings. SoC stimulation data were retrieved from the device and included stimulation amplitude, pulse

Figure 1: **Image-based optimisation of DBS parameters**
(A) Preprocessing pipeline: preoperative MRI and postoperative CT images were coregistered and normalised to MNI space using ANTs' rigid and non-linear registration algorithms as implemented in Lead-DBS. PaCER and DiODe algorithms were applied to reconstruct electrode trajectories and rotation based on the CT artefact. Next, a three-compartment volume conductor mesh was constructed in template space. Using the SimBio/FieldTrip pipeline, finite element analyses were conducted to simulate the electric fields generated by specific stimulation settings. The pipeline was adapted from Lead-DBS. (B) Study cohort: panel showing right hemispheric electrode reconstructions and StimFit settings of patients 1 to 5 and 35 of this study cohort. Electrodes were reconstructed according to the pipeline described in panel A and provided to StimFit to predict optimal stimulation parameters (StimFit settings). (C) StimFit pipeline: the StimFit software contains predictive models (middle upper panel) for akinesia-rigidity, tremor, and side-effects, which were trained based on monopolar review data as described in Roediger et al 2022 (left panel).[22] In short, electric fields were simulated for each stimulation setting (see panel A) and electric field properties (vector magnitudes and directionalities) were used as input features for model training. To obtain suggestions for optimal stimulation settings within our study cohort, electrode locations were provided to the StimFit algorithm (input). For each electrode, 200 monopolar stimulation settings were simulated first, and corresponding electric fields were provided to the predictive models to obtain outcome predictions (grid-search, right upper panel). Monopolar solutions with maximum predicted motor improvements were then used as starting points for a gradient descent algorithm (middle lower panel). Within each iteration of the optimiser, stimulation parameters were slightly adjusted, and corresponding electric fields were simulated to predict stimulation outcome. The optimiser aimed at maximising predicted motor improvement, while being constrained by a maximum side-effect probability. This way StimFit explored complex (multipolar) stimulation settings until stopping criteria were fulfilled. For graphical representation the surface plot shows the optimisation procedure of only two contacts (x and y). In this study, however, StimFit optimisation was applied on octopolar electrodes in all patients and the number of contacts could in theory be scaled up, limited by computational power only. The resulting stimulation settings (output) were applied in our crossover design. DBS=deep brain stimulation. MNI=Montreal Neurological Institute. ANTs=Advanced Normalization Tools. PaCER=Precise and Convenient Electrode Reconstruction for Deep Brain Stimulation. DiODe=Directional Orientation Detection.

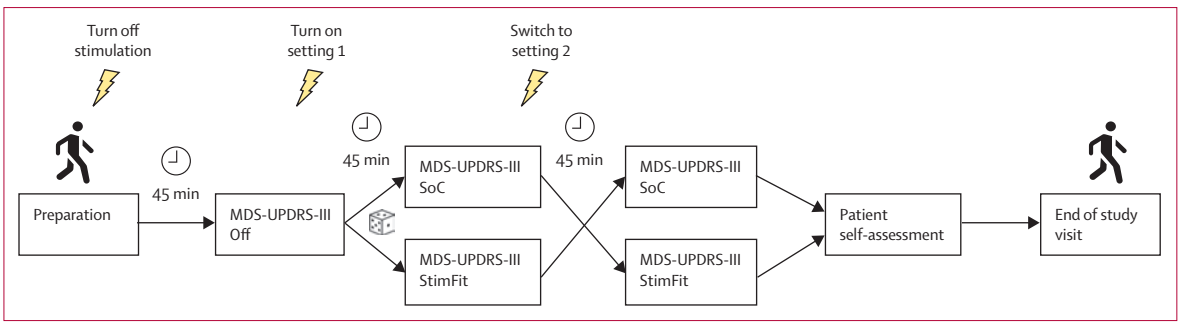


Figure 2: **Study protocol**
Patients underwent study examinations after overnight withdrawal of dopaminergic medication. StimFit settings were activated and assigned to a stimulation programme on the pulse generator. Since StimFit settings were constrained by a maximum (predicted) side-effect probability of 20%, stimulation-induced side-effects were to be expected in some cases and were resolved by reducing stimulation amplitudes until side-effects disappeared. MDS-UPDRS-III scores were assessed in OFF-stimulation conditions after a wash-out period of 45 min. Afterwards, ON-stimulation assessments were performed under both StimFit and SoC stimulation, each after approximately 45-min wash-in. The wash-in duration (length of stimulation time after onset) was chosen according to the findings of Temperli and colleagues[23] to ensure that >90% of DBS motor symptom control had been achieved by corresponding settings and carry-over effects of previous settings were negligible. After motor assessments were completed, patients were asked to self-assess both stimulation conditions on a visual analogue scale from 0 ("very unsatisfactory") to 100 ("very satisfactory") and to guess the correct order of both stimulation conditions. SoC=standard of care. MDS-UPDRS-III=part III of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale.

width, and frequency, as well as the relative distribution of electric current across contacts, contact polarities, and impedances. Dates and type of inpatient and outpatient visits related to DBS treatment were obtained retrospectively from electronic medical records at Charité and Beelitz Hospital for Parkinson's disease. Levodopa equivalent daily doses (LEDDs) were calculated based on preoperative medical records as well as medication schedules at the time of study participation.[25]

Outcomes

The primary outcome parameter was the difference between total score on the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale, part III (MDS-UPDRS-III) under SoC and StimFit stimulation conditions. Additionally, mean improvement in MDS-UPDRS-III motor score relative to OFF-stimulation was calculated for both stimulation conditions to verify effective DBS. Secondary outcome parameters were differences between MDS-UPDRS-III subscores for akinetic-rigid, tremor, and axial symptoms under both conditions. A definition of MDS-UPDRS-III items included in each of the scores is provided in the appendix (p 2). Another secondary outcome parameter was the patients' self-rating of the subjective perception of both ON-stimulation settings. Patients were asked to rate each setting according to the question: "How satisfied were you with the overall effects of the stimulation?" on a visual analogue scale (VAS) from 0 ("very unsatisfied") to 100 ("very satisfied"). Additionally, patients were asked to guess the randomisation sequence of both conditions, which was documented on a binary scale as "correct" or "incorrect". Non-transient stimulation-induced side-effects that might have occurred during initial programming of StimFit settings were documented along with the reduction of the stimulation amplitude necessary to achieve side-effect relief. Finally, energy efficiency of both settings was estimated according to the formulas for multiple independent current control published by Zhang and colleagues (details described in the appendix p 2).[24] The formulas are not applicable to bipolar stimulation settings and therefore patients with bipolar SoC settings were excluded from this subanalysis.

Statistical analysis

The study was powered to assess non-inferiority of StimFit compared with SoC settings using absolute differences between corresponding MDS-UPDRS-III scores as a primary endpoint. Schrag and colleagues suggested that a difference of at least 5 points should be considered clinically significant.[26] Using a one-sided *t*-test with an alpha of 5% and power of 80%, a sample size of n=35 was needed to show non-inferiority with a margin of 5 points. The mean of differences between MDS-UPDRS-III scores under SoC and StimFit stimulation was estimated to be 0 points (SD 16·4). Estimations were based on a comparable cohort from our centre, in which algorithm-guided programming based on kinematic feedback was compared with SoC settings in a double-blind crossover design.[7] The sample size calculation was supported by the local statistics department using the TrialSize package in R.

In addition to non-inferiority, the primary outcome was tested for superiority using a two-sided *t*-test. Secondary endpoints included absolute differences in MDS-UPDRS-III subscores, patients' VAS self-ratings, and battery drain under StimFit and SoC stimulation, and were analysed using Wilcoxon signed rank tests. Patients were excluded from specific MDS-UPDRS-III subscore analyses if they did not experience the corresponding symptom at baseline (subscore in

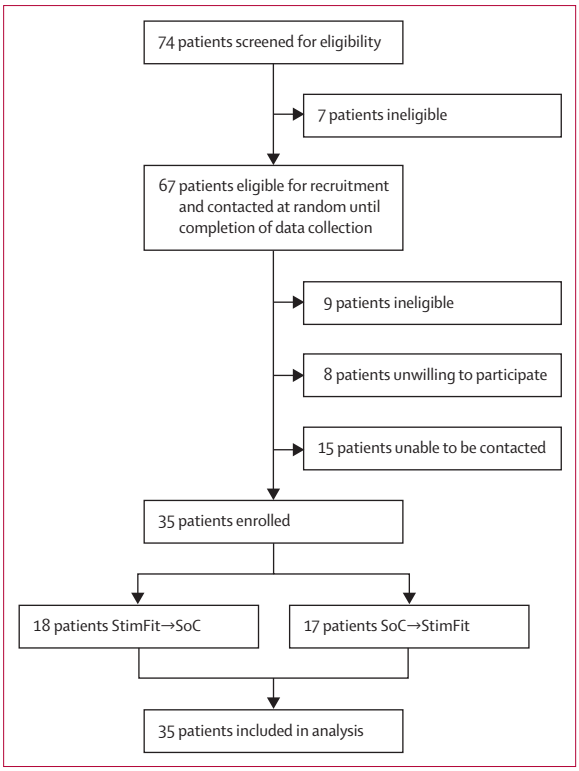


Figure 3: **Trial profile**
Trial profile depicting patient recruitment and analysis. Reasons for exclusion (total n=16) during screening of medical records (n=7) or recruitment (n=9) were the inability to undergo dopaminergic withdrawal (n=7), severe neuropsychiatric symptoms (n=3), cerebral atrophy (n=2), or cognitive impairment (n=1), as well as surgical complications such as electrode replacement (n=1) and the development of a large cyst near the electrode (n=1). One patient was reported to have died. Of note, all patients who were enrolled have completed the study. SoC=standard of care.

	Group 1: StimFit followed by SoC (n=18)	Group 2: SoC followed by StimFit (n=17)
Sex		
Male	15 (83%)	8 (47%)
Female	3 (17%)	9 (53%)
Age, years	62 (8; 46–74)	64 (8; 44–72)
Disease duration, years	13 (5; 6–28)	11 (4; 3–17)
Time since DBS surgery, months	20 (10; 6–37)	20 (12; 5–38)
Days with DBS-related treatment in inpatient and outpatient facilities since surgery*	30 (15; 6–59)	26 (16; 7–67)
Time since last adjustment of SoC settings, months	6 (4; 1–30)	7 (7; 2–18)
MDS-UPDRS-III score		
OFF medication, OFF stimulation	54 (19; 24–87)	40 (11; 11–57)
OFF medication, SoC stimulation	24 (15; 3–58)	25 (10; 3–45)
OFF medication, StimFit stimulation	28 (16; 5–56)	25 (7; 10–42)
LEDD, mg		
Before DBS surgery*	1183 (246; 875–1879)	1099 (621; 0–2755)
At timepoint of study participation	423 (220; 0–790)	567 (373; 0–1425)

Data are n (%) or mean (SD; range). SoC=standard of care. MDS-UPDRS-III=part III of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale. LEDD=levodopa equivalent daily dose. *Data were obtained retrospectively from electronic medical records at Charité – Universitätsmedizin and Beelitz Hospital for Parkinson's disease.

Table: **Demographic and treatment data**

OFF-stimulation state equal to zero). A two-sided binomial test was applied to evaluate whether patients could guess the correct order of stimulation settings above chance level. Significance levels were set to an α of 0·05, and no multiplicity adjustment was applied. Statistical analyses were conducted using MATLAB 2020a.

The study was registered at the German Register for Clinical Trials (DRKS00023115).

Role of the funding source

This study was funded by the Deutsche Forschungsgemeinschaft through the non-profit sponsors NeuroCure Clinical Research Center and TRR 295, which provided personnel as well as structural and administrative support to conduct the study but had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Screening and enrolment of patients took place between July 10, 2020, and Oct 28, 2021. Medical records of 74 patients with Parkinson's disease who had undergone bilateral STN-DBS surgery at Charité between April 1, 2018, and April 30, 2021, were screened for eligibility. Out of the remaining 67 potential study participants, 52 patients were contacted for recruitment until the intended sample size of n=35 (32 with Vercise Cartesia directional leads, three with SenSight directional leads) was achieved (figure 3). 18 patients received StimFit followed by SoC stimulation, and 17 received SoC followed by StimFit stimulation. Study visits were conducted between Oct 23, 2020, and Oct 28, 2021. All patients who participated in the study were included in the analysis. The first four patients were reinvited for study participation after a final patch to the StimFit software was applied and data from their first study visits were excluded from the analysis (details described in appendix p 3).

Patient demographics and treatment data are summarised in the table and electrode localisations are shown in the appendix (p 6). Patients underwent DBS surgery an average of 20 months (SD 11) before study participation. During this time, they received DBS-related treatment at specialised inpatient and outpatient facilities for a mean of 28 days (SD 16). For more information we

For **MATLAB** see https://www.mathworks.com/products/matlab.html

For the **German Register for Clinical Trials** see https://www.drks.de

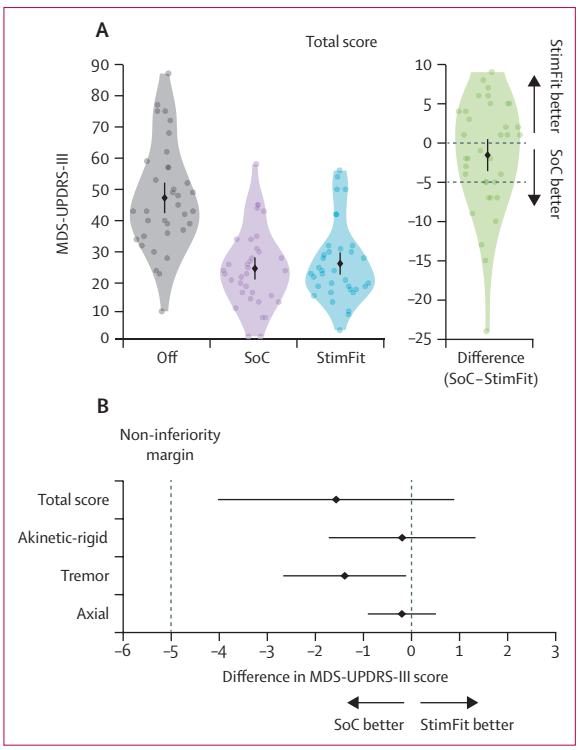


Figure 4: **Primary outcome and summary statistics**
(A) Violin plots showing total MDS-UPDRS-III scores under OFF (grey), SoC (purple), and StimFit (light blue) stimulation conditions on the left, as well as differences in motor scores between StimFit and SoC stimulation on the right (green). Mean and 95% CIs are displayed at each plot. (B) Summary statistics of the primary endpoint (total score) and symptom-specific MDS-UPDRS-III subscores. Mean absolute differences between both ON-stimulation conditions are shown together with their 95% CIs: total score: –1·6 (SD 7·1; 95% CI –4·0 to 0·9); akinesia-rigidity score: –0·2 (SD 4·4; 95% CI –1·7 to 1·3; p=0·98; n=35); tremor score: –1·4 (SD 3·3; 95% CI –2·7 to –0·1; p=0·046; n=28); and axial score: –0·2 (SD 2·0; 95% CI –0·9 to 0·5; p=0·67, n=34).The 95% CI of the total score did not include the margin of –5 points, establishing non-inferiority. SoC=standard of care. MDS-UPDRS-III=part III of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale.

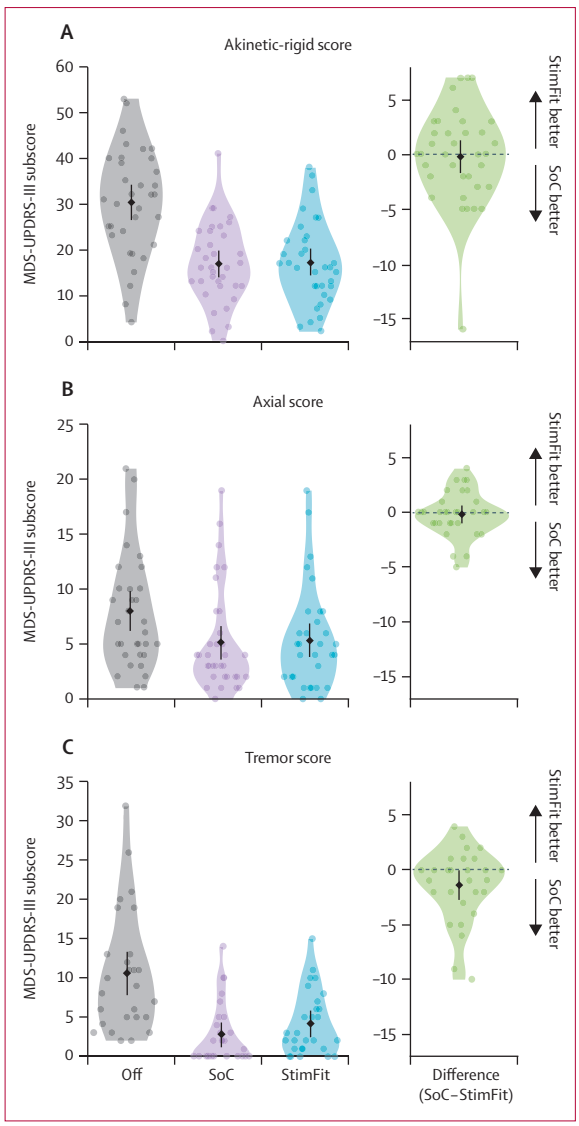


Figure 5: **Secondary outcome 1—symptom-specific motor effects**
Violin plots showing symptom-specific motor scores for akinetic-rigid (A) and axial (B) symptoms, as well as tremor (C). Each panel depicts scores under OFF (grey), SoC (purple), and StimFit (light blue) stimulation conditions on the left and differences of motor scores between StimFit and SoC stimulation on the right (green). Mean and 95% CIs are displayed at each plot. SoC=standard of care.

refer the reader to the appendix (p 5) depicting the study participants' individual DBS-related treatments at our four main movement disorders facilities.

MDS-UPDRS-III scores improved from 47·3 points (SD 17·1) at OFF-stimulation baseline to 24·7 (SD 12·4; 48% improvement) and 26·3 (SD 12·4; 43% improvement) under SoC and StimFit stimulation, respectively (figure 4A). The mean difference between motor scores was –1·6 (SD 7·1; 95% CI –4·0 to 0·9), showing no statistically significant difference between both stimulation conditions ($p_{superiority}$=0·20, n=35) when testing for superiority using a two-sided t-test. Non-inferiority of StimFit was tested by applying a one-sided t-test at the predefined non-inferiority margin of –5 points. As shown in figure 4B, the margin was smaller than the lower 95% CI (–4 points), establishing non-inferiority ($p_{non\text{-}inferiority}$=0·0038).

Analysis of MDS-UPDRS-III subscores revealed an improvement for akinesia-rigidity of 46% and 43%, tremor 70% and 62%, and axial score 36% and 35% under SoC and StimFit stimulation, respectively (figure 5). This resulted in a statistically significant difference in tremor reduction favouring SoC (p=0·046; figure 4B).

Patients' self-assessments of the overall stimulation effects showed significant differences in favour of SoC, with SoC settings on average scoring 74 points (SD 19) as compared with 55 (SD 24) under StimFit stimulation (mean difference 19 [SD 28]; 95% CI 9–29; p=0·0007; n=34; figure 6). StimFit settings were rated superior to SoC by eight patients (24%) and equal ratings were given by three patients (9%). 19 patients (56%) correctly

guessed the order of stimulation conditions, which was not significantly above chance level (p=0·50).

In six patients (17%), initial programming of StimFit settings (during the preparation phase) resulted in acute side-effects (two muscle contractions, two dysarthria, two vertigo). Stimulation amplitudes were reduced until side-effects disappeared (mean reduction 0·41 mA [SD 0·16], ranging from 0·3 to 0·7 mA). Delayed onset dyskinesias appeared in three patients (located at the head, shoulder, and leg) under StimFit stimulation. In two cases these were rated as severe and potentially interfered with motor ratings. Dyskinesias were also observed in two cases under SoC stimulation (head and shoulder) but did not affect motor assessments.

LEDDs were reduced by 57% under SoC treatment compared with presurgical medication, and SoC settings had remained unchanged for 6·7 months (SD 5·8) before study participation. Mean stimulation amplitudes were 2·6 mA (SD 1·1) and an average of 3·2 contacts (SD 1·4) were active. Bipolar settings were applied on four electrodes. One patient was treated with interleaving stimulation bilaterally. Mean pulse widths and frequencies were 60 µs (SD 3) and 134 Hz (SD 25). Mean stimulation amplitude suggested by StimFit was 2·4 mA (SD 0·3) distributed across 5·4 active contacts (SD 2·1). Battery drain was estimated to be 57 µA (SD 29) in SoC compared with 50 µA (SD 21) in StimFit settings (p=0·50, n=32). All impedance values were within normal ranges. The parameters of both stimulation conditions are provided for each patient and in a summarised form in the appendix (pp 9–11).

To obtain StimFit settings, computational time for image normalisation and electrode reconstruction using the Lead-DBS toolbox was around 45 min per patient, plus an additional 5 min to visually check the results. Other commercial or non-commercial software packages to reconstruct DBS electrodes could in theory be used as well and corresponding computational and visual inspection times might differ accordingly. Reconstructions were then provided to the StimFit algorithm. In order to predict stimulation outcome, StimFit requires patient-specific E-field templates, which are automatically generated once (taking around 45 min) when processing a patient for the first time and stored in the patient folder for later use. StimFit converged to bilateral suggestions of stimulation parameters within approximately 50 min in all patients. Of note, since SoC treatment was conducted before study recruitment, the exact times spent for clinical parameter optimisation in each patient were not available and a direct comparison between both approaches regarding the programming time necessary to achieve optimal settings was not possible.

A post-hoc analysis was done to investigate the reasons for the improved patient self-assessments with SoC as compared with StimFit. We explored the characteristics of patients who clearly rated SoC over StimFit, and found that the presence of tremor or dyskinesia under StimFit stimulation was associated with lower VAS ratings compared with SoC. Removing the effect of tremor on subjective patient ratings eliminated the difference of VAS scores between both conditions (appendix p 7).

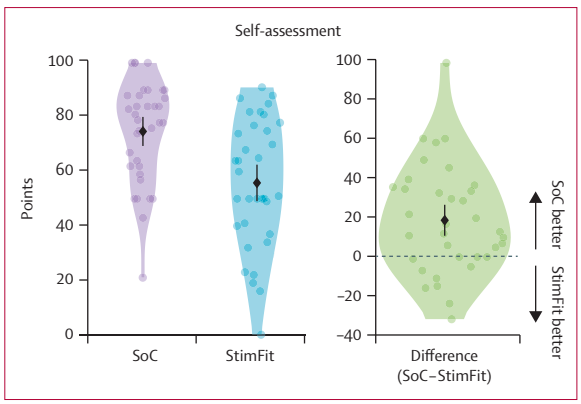


Figure 6: **Secondary outcome 2—self-assessments**
Violin plots showing results of patient ratings of both SoC (purple) and StimFit (light blue) stimulation conditions on the left as well as differences between ratings on the right (green). Mean and 95% CIs are displayed at each plot. One patient was accidentally unmasked before the first ON-stimulation assessment by looking at the patient programmer and was therefore excluded from the self-assessment analyses. SoC=standard of care.

A second post-hoc analysis was done to evaluate which anatomical regions were stimulated across the cohort with respect to the stimulation condition. This analysis showed that StimFit settings were precisely focused on the dorsolateral STN region, whereas SoC settings showed a slightly more heterogeneous distribution in and around the dorsolateral STN (appendix p 8).

Discussion

In this double-blind, crossover, randomised, non-inferiority trial, bilateral STN-DBS was applied in 35 patients with Parkinson's disease using stimulation parameters suggested by an automated algorithm (StimFit) based on electrode locations. This represents the first prospective evaluation of a data-driven algorithm capable of suggesting optimal stimulation parameters based on electrode location in a fully automated fashion. StimFit stimulation reduced motor symptoms, with a statistically non-significant mean difference of –1·6 points compared with SoC on the MDS-UPDRS-III scale, establishing non-inferiority within a predefined margin of –5 points. Importantly, both stimulation conditions resulted in significant motor improvements of 48% (SoC) and 43% (StimFit) compared with the OFF-stimulation baseline, confirming effective STN-DBS and sufficient wash-out and wash-in time between conditions in this patient group.[1] In line with this, previous long-term SoC treatment had led to reduction of dopaminergic medication (LEDD) by 57% compared with preoperative treatment in our cohort.

More and more complex electrodes, with increasing numbers of contacts, are being suggested and developed,

aiming at widening the therapeutic window of DBS.[27] However, the therapeutic potential of these technical innovations is currently limited by the small number of parameter combinations that can be explored in clinical routine with trial and error.

Despite the urgent need for guided and automated programming strategies and the rapid advances in the field of DBS neuroimaging within recent years,[9–12] prospective applications have remained sparse. Frankemolle and colleaugues used image-based models to identify stimulation settings that would minimise spread of electric current to non-motor regions of the STN and concluded that cognitive decline associated with STN-DBS could be avoided by using model-based stimulation parameters.[8] Other prospective studies concluded that software-assisted programming could markedly reduce programming time compared with standard clinical procedures.[14–17]

A strength of this study was the prospective double-blind cross-over design and the fact that it used, for the first time, a data-driven algorithm capable of suggesting optimal stimulation parameters in patients with Parkinson's disease treated with STN-DBS based on electrode location in a fully automated fashion. This approach would allow the possibilities of the latest electrode designs for complex parameter settings to be exploited without being constrained by the complexity of clinical programming procedures, and would open up avenues for further development of multisegmented DBS electrodes.

Interestingly, in our cohort, akinetic-rigid and axial subscores showed similar improvements under both stimulation conditions, while tremor responded significantly less to StimFit stimulation. Our understanding of anatomical target structures involved in therapeutic neuromodulation is currently undergoing a paradigm shift from a disease-centric to a symptom-centric view.[28] Specifically, in Parkinson's disease, multiple recent publications point towards an anatomical segregation of DBS "sweetspots" for suppression of tremor on the one hand and akinesia and rigidity on the other hand.[10] This has potential implications for personalised DBS programming procedures since optimal DBS parameters would depend on individual patients' symptom profiles. Within the StimFit software, this concept is implemented by allowing the optimisation objective (motor symptom control) to be modified to maximise the predicted therapeutic effects on tremor or akinetic-rigid symptoms on a continuous spectrum (appendix p 4). In the present study, however, we did not consider the presence of tremor in StimFit predictions, forcing the model to find optimal settings based on the cardinal features of bradykinesia and rigidity alone. The reason for this choice was that we aimed to evaluate the effects of automated DBS programming based exclusively on neuroimaging data. Although a multimodal approach, integrating—among other information—the patients' baseline symptomatology (especially the presence of tremor) could further benefit model predictions, this issue was outside the scope of this trial. The choice to exclude tremor from the optimisation objective resulted in suboptimal tremor response. This supports the hypothesis of an anatomical segregation of symptom-specific stimulation sites and emphasises the importance of taking clinical information into account in imaging-based DBS programming procedures.

The presence of tremor also affected patient VAS scores in self-assessment. Despite non-inferiority of StimFit stimulation being established for objective motor assessments, subjective patient ratings showed significant differences favouring SoC. A post-hoc analysis done to investigate potential reasons for this discrepancy found that the difference was eliminated when adjusted for the effect of tremor. It is therefore likely that an optimisation procedure tailored to the patient's symptomatic profile will also improve their subjective perception of treatment benefit. Additional integration of clinical or demographic factors as well as other data modalities (eg, local field potentials or intraoperative microelectrode recordings) might further enhance performance of future modelling approaches. It is important to highlight, however, that despite the potential advantages of unimodal or multimodal models for DBS programming, clinical supervision will still be mandatory, and manual adjustment of DBS parameters might be necessary, especially with respect to medication or dyskinesias. Strategies to adapt stimulation parameters include adjustment of stimulation amplitudes or testing a subset of DBS settings suggested by StimFit after adjusting maximum side-effect thresholds or the weight of tremor in the user interface (appendix p 4). Finally, testing stimulation parameters that cannot be derived through StimFit (eg, frequency and pulse width) could benefit individual patients.

Stimulation settings differed between StimFit and SoC with respect to numbers of contacts activated, with more multicontact configurations suggested by the algorithm (appendix pp 9–11). StimFit starts the optimisation procedure by predicting motor effects and side-effects at different amplitudes to identify favourable monopolar solutions, which are then used as starting points for a gradient descent algorithm to explore potentially superior multicathode solutions (figure 1C). The number of iterations in this optimisation procedure depends on the solver's stopping criteria, such as the changes in predicted benefit in previous iterations. Clinical programming strategies also need to apply certain stopping criteria, but due to the limited number of iterations those criteria need to be much more liberal, so that further adjustments are often only made when therapeutic outcome is clearly suboptimal, or patients are not satisfied with treatment effects. In many cases this results in monopolar, or pseudomonopolar, stimulation settings (equal distribution of electric current

across all contacts at one segmented level), which were chosen for SoC in 46% of the cases in this cohort (appendix pp 9, 11). StimFit, however, predicted superior clinical outcome for directional multicontact configurations in 93% of the cases (appendix pp 9–10). Overall, StimFit solutions show a more gradual distribution of electric current across contacts compared with SoC. Such settings could not be derived from trial-and-error programming in routine clinical practice but might bear potential therapeutic advantages, underlining the importance of data-driven optimisation strategies in modern DBS devices.[29] No statistically significant difference in battery drain between the two stimulation conditions was found in our study. This was in contrast to a reduction in estimated battery drain that has been reported for stimulation settings obtained from anatomy-guided programming.[17] Future algorithms could incorporate estimated energy efficiency as an additional variable to obtain settings with an optimised battery life-cycle.

Limitations of this study were the single-centre design and the short observational period. A prospective longitudinal study design, in which patients are randomly assigned to SoC or StimFit-assisted programming immediately after DBS surgery, is necessary to address questions regarding differences in long-term motor effects or side-effects, quality of life, programming time, and medication adjustments.[30] Of note, three patients experienced severe dyskinesias under StimFit stimulation. Dyskinesias are usually thought of as "on-target" side-effects and could therefore indicate a high efficacy of StimFit DBS. On the other hand, different approaches to medication adjustment might be needed during long-term StimFit stimulation. Moreover, only cathodal contact configurations are suggested since the algorithm has not been tested for bipolar or interleaving settings. In addition, the algorithm was trained and validated on data with a fixed pulse width of 60 µs and stimulation frequency of 130 Hz. It does not allow effects of varying frequencies, pulse shapes, or durations to be accounted for. We further noticed that the variation of stimulation amplitudes suggested by StimFit was relatively small compared with SoC. Initial amplitudes ranged between 2·3 mA and 2·5 mA across the cohort at a side-effect threshold of 20%. This might indicate that variance in electrode location and active contact configuration only had limited impact on side-effect predictions compared with stimulation amplitude and suggests that our modelling approach for side-effects should be optimised further. Furthermore, 5% of the patients who were screened for eligibility were excluded due to structural brain changes or electrode replacement (figure 3). Although this only represents a small fraction of patients, it is important to note that anatomical abnormalities could impact performance of image-based outcome predictions. Finally, StimFit was trained on a large monocentric dataset of monopolar review data. Retraining the model on fine-grained data from different centres could increase its generalisability and account for potential centre-specific or population-specific characteristics.

In conclusion, results of this prospective, randomised, double-blind, crossover trial showed that application of STN-DBS parameters suggested by a data-driven optimisation algorithm in a cohort of 35 patients with Parkinson's disease led to a significant reduction of motor impairment compared with OFF stimulation, similar to the effects obtained during SoC stimulation. This finding suggests that data-driven strategies that allow for quantitative predictions of stimulation effects, embedded in mathematical optimisation procedures, could govern future programming strategies. Additional longitudinal studies are required to confirm long-term motor benefit and to assess the impact of data-driven DBS programming on quality of life, dopaminergic medication, and programming time.

Contributors

JR, TAD, AH, and AAK conceptualised the study. Funding was acquired by JR and AAK. JR, JA, JLB, A-PK, G-HS, KF, and PK contributed to data acquisition. JR conducted the statistical analysis and data visualisation. JA and JLB verified the data and reviewed the analysis. TAD and AAK contributed to data interpretation. AAK supervised and administered the study. JR wrote the first draft and all other authors reviewed and commented on the report. All authors had full access to all the data in the study, had final responsibility for the decision to submit for publication, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

JR received speaker honoraria from Medtronic. TAD has received grants from the German Research Foundation (Cologne Clinician Scientist Program, FI 773/15-1) and received speaker honoraria from Medtronic and Boston Scientific. PK received speaker honoraria from Stadapharm. G-HS received Speaker honoraria from Medtronic, Boston Scientific, and Abbott. AH has received grants from the German Research Foundation (Emmy Noether Stipend 410169619 and Transregio CRC 424778381—TRR 295) as well as the German Aerospace Center, the National Institutes of Health (2R01 MH113929), and the Foundation for OCD Research (FFOR). AAK has received grants from the German Research Foundation (Transregio CRC 424778381—TRR 295) and the Lunbeck Foundation. AAK is on the advisory board of Boston Scientific and Medtronic and has received honoraria from Boston Scientific, Medtronic, Zambon, and Stadapharm. JA, JLB, A-PK, and KF declare no competing interests.

Data sharing

Behavioural data and data on stimulation settings are provided in the appendix (pp 10–12). Other data supporting the findings of this study are available upon reasonable request from the corresponding author but will not be made publicly available due to their containing information that could compromise the privacy of study participants.

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