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Imaging-based programming of subthalamic nucleus deep brain stimulation in Parkinson's disease

Josefine Waldthaler [a, b, *], Miriam Bopp [b, c], Nele Kühn [a], Bugrahan Bacara [a], Merle Keuler [a], Marko Gjorgjevski [c], Barbara Carl [c, d], Lars Timmermann [a, b], Christopher Nimsky [b, c], David J. Pedrosa [a, b]

[a] Department of Neurology, University of Marburg, Germany
[b] CMBB - Center for Mind, Brain and Behavior, University of Marburg, Germany
[c] Department of Neurosurgery, University of Marburg, Germany
[d] Department of Neurosurgery, Helios Dr. Horst Schmidt Kliniken, Wiesbaden, Germany

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ABSTRACT

Background: The need for imaging-guided optimization of Deep Brain Stimulation (DBS) parameters is increasing with recent developments of sophisticated lead designs offering highly individualized, but time-consuming and complex programming.
Objective: The objective of this study was to compare changes in motor symptoms of Parkinson's Disease (PD) and the corresponding volume of the electrostatic field (VEsF) achieved by DBS programming using GUIDE XT™, a commercially available software for visualization of DBS leads within the patient-specific anatomy from fusions of preoperative magnetic resonance imaging (MRI) and postoperative computed tomography (CT) scans, versus standard-of-care clinical programming.
Methods: Clinical evaluation was performed to identify the optimal set of parameters based on clinical effects in 29 patients with PD and bilateral directional leads for Subthalamic Nucleus (STN) DBS. A second DBS program was generated in GUIDE XT™ based on a VEsF optimally located within the dorsolateral STN. Reduction of motor symptoms (Movement Disorders Society Unified Parkinson's Disease Rating Scale, MDS-UPDRS) and the overlap of the corresponding VEsF of both programs were compared.
Results: Clinical and imaging-guided programming resulted in a significant reduction in the MDS-UPDRS scores compared to off-state. Motor symptom control with GUIDE XT™-derived DBS program was non-inferior to standard clinical programming. The overlap of the two VEsF did not correlate with the difference in motor symptom reduction by the programs.
Conclusions: Imaging-guided programming of directional DBS leads using GUIDE XT™ is possible without computational background and leads to non-inferior motor symptom control compared with clinical programming. DBS programs based on patient-specific imaging data may thus serve as starting point for clinical testing and may promote more efficient DBS programming.

1. Introduction

Chronic deep brain stimulation (DBS) has emerged as an established and effective treatment for patients with advanced Parkinson's disease (PD). The preferential target is the sensorimotor portion of the subthalamic nucleus (STN) which is often located within its dorsolateral part [1]. Yet, the existence and location of a potential anatomical „sweet spot" within the STN remains a much debated question [2]. Effective symptom control has been associated with active contacts being located around the dorsolateral border of the STN, indicating that not stimulation of the nucleus itself, but of adjacent white matter tracts might be accountable for symptom relief [3].

Despite accurate lead placement in the anatomical target, identification of optimal stimulation settings requires in-depth evaluation of all available contacts of the DBS lead and often even individualized settings for pulse frequency or width. Programming

* Corresponding author. Department of Neurology, University of Marburg, Marburg, Germany.
E-mail address: josefine.waldthaler@staff.uni-marburg.de (J. Waldthaler).

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sessions may hence extend to several hours of time and be therefore exhausting for patients and clinicians, likewise. Furthermore, the evaluation of therapeutic and side effects of stimulation relies on high levels of training and experience of the performing clinician, making computer-based support highly desirable.

The need for further aid when it comes to DBS programming has been accentuated with modern DBS systems. While traditionally DBS leads consisted of four circular contacts, more sophisticated designs introduced lately to clinical routine allow further shaping of the electrical field achieving an increased therapeutic window [4,5]. This extension of the parameter space resulted, however, in an exponential increase of duration of clinical programming due to the almost uncountable potential parameter combinations. There have been considerable efforts to develop tools using imaging data to ascertain where stimulation might be most effective [6]. Nevertheless, these advances have been restricted to a small number of highly specialized centers with a strong computational background and, so far, such tools have not been implemented into or approved for clinical use. At the same time, efforts are being undertaken to develop user-friendly software which may foster a more pointed search strategy for personalized stimulation settings.

In this study, we used a commercially available software tool (GUIDE XT™, Boston Scientific Corp., Valencia, California, USA) to visualize DBS leads and to simulate potentially effective stimulation settings, that is those resulting in a volume of the electrostatic field (VEsF, which might be considered an imaging proxy for the volume of tissue activated, VTA) located in or within the immediate vicinity of the STN. Non-inferiority of motor symptom control achieved with the GUIDE XT™-derived DBS program was tested against standard-of-care DBS clinical programming. In addition to comparing results for clinical outcomes, we provide a benchmark for the effectiveness of lead rotation estimation using this software, as well as insight into differences in the VEsF achieved with imaging-guided versus clinically derived DBS programming.

2. Material and methods

The study was approved by the local ethics committee at the University of Marburg (reference number 21/19). In accordance with the Declaration of Helsinki, all patients gave informed written consent. In total, 29 PD patients who underwent DBS-surgery within a year prior to study inclusion were recruited. Clinical data are provided in Table 1 and an overview of the study's workflow is depicted in Fig. 1.

2.1. Sample size calculation

A sample size calculation was performed based on a pilot study by Pourfar and colleagues [16]. In that study, mean improvement in UPDRS III from OFF-state was 17.8 ± 34.0% with clinical programming, respectively 20.8 ± 39.1% with programming using Graphical User Interface for DBS Evaluation (GUIDE), a previous version of GUIDE XT™. Based on a mean difference of UPDRS improvement of 3.0 ± 22.5%. Between the programs, a sample size of 28 patients was estimated, assuming a one-sided type I error of 2.5% and 90% power [17].

2.2. Preoperative imaging and surgical procedure

All patients (26 at the University Hospital Marburg, three at St. Barbara Hospital Hamm) were implanted with a Boston Scientific pulse generator (Vercise Gevia™) as well as with bilateral DBS leads targeting the sensorimotor part of STN (Vercise Cartesia™ Directional Lead, Boston Scientific Neuromodulation Corporation, Valencia, CA91355, USA). These leads consist of eight contacts configured into two ring contacts at the proximal and distal pole and two three-segment contacts in-between that enable to directionally shape the VEsF.

MRI data was acquired one day before surgery on a 3T scanner. The preoperative imaging protocol including the GUIDE XT™ workflow as well as the surgical procedure have been reported in Refs. [7,8].

2.3. Postoperative imaging and detection of directionality of DBS leads

All patients received CT scans postoperatively to ascertain DBS lead localization and direction. The mean time between surgery and postoperative CT scans was 6.6 ± 4.8 months, whereas time between CT scans and the programming sessions of this study was 4.8 ± 11.7 days.

A radio-opaque marker indicated the intended anterior side of the lead so that the lead could be inserted with an intended 0°anterior/posterior orientation during surgery. To ensure optimal visualization of the characteristic lead artifact, CT gantry was angled perpendicular to the DBS leads. The Lead Orientation Detection tool (Brainlab Elements, Brainlab, Munich, Germany), which is included in the GUIDE XT™ workflow, was used to identify and adjust rotation angles from CT scans.

Additionally, DBS lead rotation, i.e., the deviation from the intended angle, was also obtained with the DiODe algorithm [9] within the framework of the open source toolbox Lead-DBS (www.lead-dbs.org) [10]. Both the Lead Orientation Detection tool and DiODe use the characteristic “star” artifacts of the two directional contact levels of the DBS lead to estimate rotation angles.

2.4. DBS programming

All patients were already treated with chronic stimulation prior to study recruitment. Twelve patients (41%) who were enrolled at their follow-up three months after surgery had not undergone a comprehensive clinical programming session before. The remaining 17 patients (59%) had taken part in at least one clinical programming session before study inclusion.

Programming sessions were performed in OFF medication state after overnight withdrawal of all dopaminergic medication for at least 12 h. The pulse width was standardized at 60 μs and stimulation frequency set to 130 Hz for both DBS programming sessions.

2.5. Clinical programming

The protocol for clinical programming was performed by trained and experienced investigators (NK, MK, BB) who were blinded for visualizations of the DBS leads and the STN as well as for the GUIDE XT™-assisted program as described below.

The first step was the assessment of the motor part of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III [11]) in the OFF-medication and OFF-DBS state after switching off DBS for at least 30 min.

Then, effects of circular stimulation at all four levels were assessed, followed by testing of each directional contact separately. Stimulation amplitude was thereby increased in 0.5 mA steps, while assessing therapeutic effects on rigidity, bradykinesia, and tremor along with side effects. Testing was stopped at 5.0 mA or when lasting (i.e., longer than 2 min) or unbearable side effects occurred. Clinical testing included upper limb rigidity, finger tapping, alternating hand movements as well as resting and postural tremor. Meaningful improvement was defined as a change of 1.5 points in the scores of rigidity, finger tapping, and hand rotation combined in the scale from 0 to 4 according to the respective items

Table 1
Demographics and clinical data of the DBS patients.

ID	gender	age (years)	LEDD (mg)	disease duration (years)	MDS-UDPRS III off	MDS-UPDRS III GXT	relative improvement GXT	MDS-UPDRS III CL	relative improvement CL	GXT program left STN[a]	CL program left STN[a]	GXT program right STN[a]	CL program right STN[a]
1	male	59	1040	11	29	18	−0.38	16	−0.45	7: 80%, 8: 20%	2: 100%	6: 60%, 7: 20%, 8: 20%	5: 33%, 6: 34%, 7: 33%
2	male	52	917	10	42	26	−0.38	16	−0.62	2: 24%, 3: 8%, 4: 8%, 5: 36%, 6: 12%	2: 25%, 5: 50%, 7: 2%	1: 20%, 2: 22%, 3: 47%, 4: 11%	3: 45%, 4: 45%, 6: 10%
3	female	56	1112	9	34	26	−0.24	25	−0.26	6: 20%, 7: 60%, 8: 20%	2: 100%	6: 45%, 7: 15%, 8: 40%	4: 100%
4	female	63	1107	21	33	23	−0.30	24	−0.27	1: 60%, 2: 13%, 3: 13%, 4: 13%	1: 50%, 2: 25%, 4: 25%	1: 40%, 2: 10%, 3: 32%, 4: 18%	1: 20%, 3: 80%
5	male	53	1125	8	52	39	−0.25	42	−0.19	1: 90%, 4: 10%	2: 100%	1: 100%	1: 100%
6	male	66	867	18	34	24	−0.29	29	−0.15	2: 20%, 3: 10%, 4: 20%, 5: 20%, 6: 10%, 7: 20%	2: 25%, 3: 75%	1: 30%, 3: 70%	4: 60%, 7: 40%
7	female	62	501	10	20	16	−0.20	10	−0.50	2: 50%, 3: 50%	4: 10%, 7: 90%	1: 10%, 2: 45%, 3: 45%	2: 50%, 3: 50%
8	male	49	647	8	50	42	−0.16	23	−0.54	5: 16%, 6: 16%, 7: 28%, 8: 40%	2: 14%, 3: 13%, 4: 13%, 5: 20%, 6: 20%, 7: 20%	5: 3%, 6: 14%, 7: 3%, 8: 80%	6: 20%, 7: 20%, 8: 60%
9	female	71	1086	8	47	29	−0.38	15	−0.68	1: 50%, 2: 7%, 3: 36%, 4: 7%	2: 10%, 4: 30%, 5: 15%, 7: 45%	2: 60%, 3: 15%, 4: 15%, 5: 6%, 6: 2%, 7: 2%	5: 33%, 6: 34%, 7: 33%
10	female	46	693	5	37	27	−0.27	12	−0.68	2: 10%, 3: 5%, 4: 5%, 5: 42%, 6: 19%,7: 19%	2: 5%, 5: 60%, 6: 35%	5: 28%, 6: 38%, 7: 24%, 8: 10%	3: 25%, 5: 15%, 7: 30%, 8: 30%
11	male	63	1110	24	52	13	−0.75	43	−0.17	2: 7%, 3: 9%, 4: 14&, 5: 16%, 6: 22%, 7: 32%	2: 14%, 3: 13%, 4: 13%, 5: 20%, 6: 20%, 7: 20%	5. 14%, 6: 21%, 7: 35%, 8: 30%	5: 30%, 6: 30%, 7: 30%, 8: 10%
12	male	61	1248	12	80	56	−0.30	45	−0.44	1: 100%	5: 33%, 6: 34%, 7: 33%	1: 10%, 2: 68%, 4: 22%	2: 29%, 3: 54%, 4: 17%
13	male	60	385	10	7	1	−0.86	1	−0.86	6: 20%, 7: 60%, 8: 20%	2: 50%, 3: 50%	6: 80%, 8: 20%	2: 50%, 3: 50%
14	male	54	583	5	36	13	−0.64	8	−0.78	2: 5%, 3: 5%, 4: 20%, 5: 42%, 6: 19%, 7: 19%	1: 5%, 5: 60%, 6: 35%	2: 8%, 3: 12%, 4: 30%, 5: 12%, 6: 18%, 7: 30%	5: 10%, 6: 25%, 7: 40%, 8: 25%
15	male	65	400	8	40	35	−0.13	19	−0.53	1: 40%, 3: 60%	2: 33%, 3: 34%, 4: 33%	1: 70%, 4: 30%	2: 33%, 3: 34%, 4: 33%
16	male	39	459	6	22	11	−0.50	4	−0.81	5: 7%, 6: 7%, 7: 36%, 8: 50%	3: 20%, 4: 30%, 6: 10%, 7: 10%, 8: 50%	5: 13%, 6: 23%, 7: 44%, 8: 20%	2: 10%, 3: 20%, 4: 30%, 5: 20%, 6: 10%, 7: 10%
17	male	55	1232	9	24	13	−0.46	5	−0.79	6: 40%, 7: 40%, 8: 20%	2: 25%, 3: 40%, 5: 10%, 6: 25%	2: 4%, 3: 12%, 4: 4%, 5: 16%, 6: 48%, 7: 16%	2: 10%, 3: 40%, 4: 40%, 5: 10%
18	male	65	1184	18	35	18	−0.49	19	−0.46	2: 2%, 3: 33%, 4: 34%, 5: 3%, 6: 14%, 7: 14%	2: 30%, 5: 30%, 8: 40%	2: 11%, 3: 25%, 4: 4%, 5: 16%, 6: 38%, 7: 6%	4: 40%, 5: 20%, 7: 40%
19	female	42	621	11	29	10	−0.66	5	−0.83	5: 4%, 6: 18%, 7: 18%, 8: 60%	6: 33%, 7: 33%, 8: 34%	5: 26%, 6: 7%, 7: 7%, 8: 60%	2: 50%, 5: 50%
20	female	72	685	16	24	18	−0.25	9	−0.63	5: 15%, 7: 15%, 8: 70%	4: 30%, 7: 50%, 8: 20%	6: 12%, 7: 38%, 8: 50%	3: 50%, 4: 25%, 5: 25%
21	female	58	130	12	16	10	−0.38	3	−0.81	1. 40%, 2: 12%, 3: 12%, 4: 36%	2: 31%, 3: 42%, 4: 27%	2: 10%, 3: 10%, 4: 51%, 5: 4%, 6: 21%, 7: 4%	1: 17%, 2: 20%, 3: 25%, 4: 27%, 5: 11%
22	female	58	660	20	47	22	−0.53	22	−0.53	6: 45%, 7: 45%, 8: 10%	2: 40%, 4: 60%	3: 70%, 6: 30%	1: 40%, 2: 30%, 3: 30%
23	male	56	367	6	42	18	−0.57	9	−0.79	5: 58%, 6: 1%, 7: 11%, 8: 20%	3: 10%, 4: 10%, 5: 15%, 6: 40%, 7: 25%	5: 12%, 6: 18%, 7: 30%, 8: 40%	3: 40%, 4: 40%, 6: 10%, 7: 10%
24	male	67	400	11	57	24	−0.58	18	−0.68	2: 9%, 3: 16%, 4: 5%, 5: 20%, 6: 38%, 7: 12%	2: 30%, 5: 50%, 6: 20%	2: 14%, 3: 21%, 4: 35%, 5: 6%, 6: 9%, 7: 15%	2: 25%, 3: 15%, 4: 45%, 5: 15%
25	male	71	400	2	39	12	−0.69	13	−0.67	2: 8%, 3: 17%, 4: 35%, 5: 5%, 6: 11%, 7: 24%	4: 15%, 5: 15%, 6: 30%, 7: 30%, 8: 10%	2: 8%, 3: 18%, 4: 4%, 5: 20%, 6: 41%, 7: 9%	4: 10%, 5: 40%, 6: 40%, 7: 10%
26	male	56	852	10	41	32	−0.22	25	−0.39	2: 2%, 3: 6%, 4: 12%, 5: 8%, 6: 22%, 7: 50%	6: 30%, 7: 30%, 8: 40%	5: 8%, 6: 8%, 7: 64%, 8: 20%	5: 40%, 7: 40%, 8: 20%
27	male	60	485	8	33	5	−0.85	8	−0.76	2: 3%, 3: 3%, 4: 14%, 5: 11%, 6: 11%, 7: 58%	2: 5%, 4: 45%, 5: 25%, 7: 25%	5: 18%, 6: 16%, 7:16%, 8: 50%	3: 5%, 5: 45%, 6: 30%, 7: 10%, 8: 10%
28	male	62	683	12	42	28	−0.33	30	−0.29	2: 5%, 3: 3%, 4: 12%, 5: 22%, 6: 11%, 7: 47%	1: 40%, 2: 40%, 3: 10%, 5: 10%	1: 10%, 2: 6%, 3: 24%, 4: 60%	4: 40%, 5: 40%, 6: 20%

(*continued on next page*)

Table 1 (*continued*)

ID	gender	age (years)	LEDD (mg)	disease duration (years)	MDS-UDPRS III off	MDS-UPDRS III GXT	relative improvement GXT	MDS-UPDRS III CL	relative improvement CL	GXT program left STN[a]	CL program left STN[a]	GXT program right STN[a]	CL program right STN[a]
29	male	54	234	4	13	4	−0.69	2	−0.85	5: 2%, 6: 8%, 7: 20%, 8: 70%	4: 10%, 7: 30%, 8: 60%	5: 20%, 6: 38%, 7: 12%, 8: 30%	2: 20%, 3: 40%, 5: 40%
mean	31% female, 69% male	58.4	731	10.8	36.4	21.1	−0.43	17.2	−0.57				
sd		8.1	329	5.3	14.8	12.2	0.21	12.2	0.22				

CL = clinical program, GXT = GUIDE XT™ program, LEDD = levodopa equivalent daily dosage, MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale.

[a] By convention, the contacts are numbered from ventral (1) to dorsal (8). Contacts 2/3/4, respectively 5/6/7 are the directional contacts of the middle lead levels.

of MDS-UPDRS III. After reviewing all levels and all directional contacts, the contact or the combination of contacts compromising the optimal therapeutic effect (i.e., the best clinical response and a sufficient therapeutic window) was defined as the "clinical program". The clinician who was performing the programming session was free to choose any combination of contacts based on clinical effect and experience, i.e., circular or directional stimulation on one or multiple levels.

Based on our general clinical experience and evaluation in a subset of five patients, a typical clinical programming session with review of all circular and directional contacts takes between 45 and 120 min per side depending on the patient's condition and the stimulation effects.

2.5.1. *GUIDE XT™-assisted programming*

GUIDE XT™ is a commercially available software for visualization of DBS leads. The construction of the VEsF model based on GUIDE XT™ has been described in Ref. [8]. In brief, GUIDE XT™ utilizes patient specific anatomy derived from rigidly registered of postoperative CT- and preoperative T1-weighted MRI images to provide 3D simulations of stimulation fields. Hence, patient's anatomical structures can be visualized to restrict the VEsF to the STN and spare surrounding structures involved in the generation of stimulation-induced side effects such as the internal capsule or the substantia nigra. Co-registration of MRI (T1-, and T2-weighted sequences with a voxel size of 1 mm^3) and CT data, automated brain segmentation to outline the STN, internal capsule and substantia

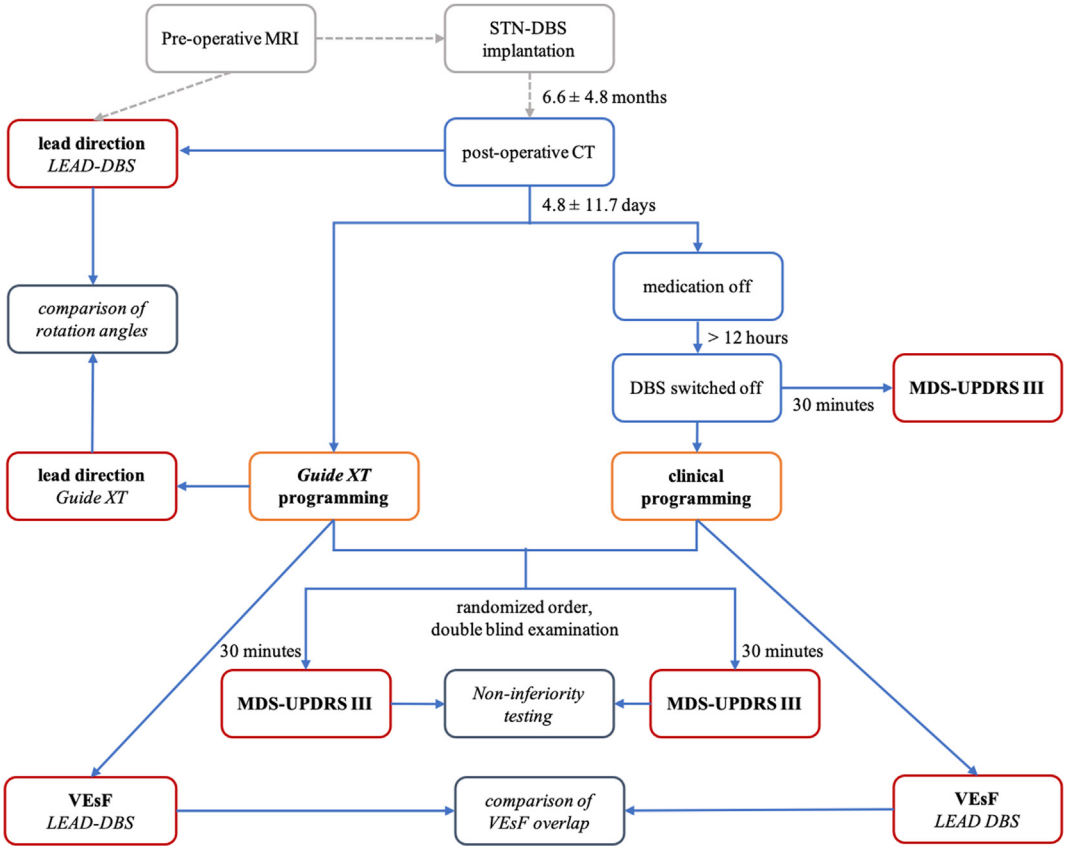

Fig. 1. Flow diagram of the study protocol. Light gray = not part of the study protocol, blue = workflow, red = outcomes, black = statistical analyses. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

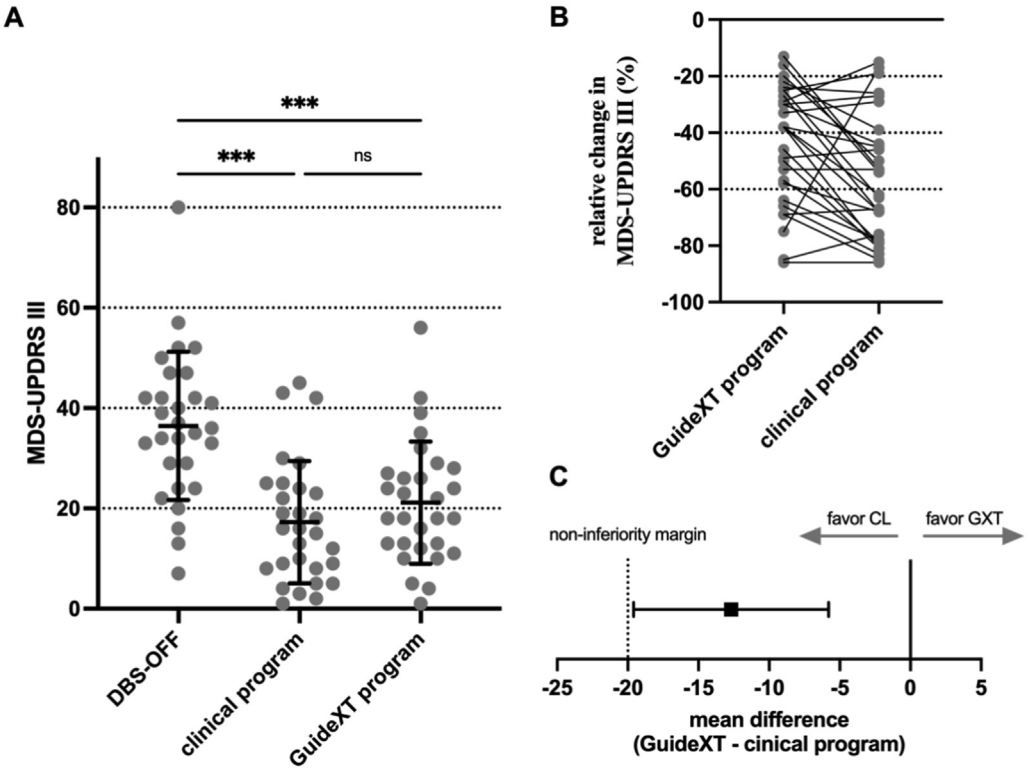

Fig. 2. A) Scatter plot of MDS-UPDRS III scores achieved with GUIDE XT™-assisted programming and clinical programming compared with OFF DBS state as reference condition. *Post-hoc* analysis revealed significant reductions of motor symptoms with both DBS programs ($p < .001$) compared to when DBS was switched-off. The vertical lines refer to mean ± standard deviation. Results of pairwise comparison are indicated as horizontal lines: ns = not significant, ***$p < .001$. **B)** Scatter plot of relative reduction in MDS-UPDRS III compared with OFF DBS state achieved with the GuideXT™ program (left) and the clinical program (right). **C)** The confidence interval of the mean difference in MDS-UPDRS III reduction between the GuideXT™ and the clinical program does not exceed the non-inferiority margin. MDS-UDPRS III = motor section of the MDS-revised Unified Parkinson's Disease Rating Scale.

nigra, as well as lead detection were executed using the respective tools of the Brainlab Elements software (Brainlab, Munich, Germany) which are part of the GUIDE XT™ workflow.

The VEsF model is composed of two parts. First, a 3D finite element mesh (FEM) is constructed and electrical properties are assigned depending upon the tissue (brain tissue, DBS lead, glial sheath, electrode-tissue interface) [12], DBS pulses are consecutively modeled and potential distributions estimated by means of a Fourier FEM solver for each node and any given set of DBS parameters [13]. The second component is a multi-compartment axon model consisting of a set of differential equations representing flows within CNS axons. Extracellular potentials resulting from the above mentioned electric field model are then imposed onto this model, which allows conclusions to be drawn about whether action potentials are likely with the selected DBS parameters or not (for further details about the VEsF modeling [12]). Repeating this process for a set of axons arrayed in 3D space at even intervals thus enable 3D contours of the VEsF.

GUIDE XT™-derived programs were created by investigators (JW, DP) who were not involved in the clinical programming sessions and blinded to its results. VEsF were simulated at an amplitude 1.5 mA, pulse width of 60 μs and frequency of 130 Hz. The contact or combination of contacts creating a VEsF that encompassed the maximum of the dorsolateral part of the STN while sparing the surrounding structures was selected as the optimal GUIDE XT™-derived program. This procedure takes approximately 60 min in total, whereby half of this time is a semi-automated process supervised by the clinician. After loading the patient's imaging data (10 min), rigid registration of MRI and CT data, automated segmentation of the STN, and lead detection takes on average 30 min. Finally, it requires approximately 20 min for a trained clinician to create and export the VEsF.

2.5.2. Clinical evaluation of DBS effects

The assessment of motor symptoms was performed by an investigator who was not involved in the DBS programming sessions. The clinical program and the GUIDE XT™-derived program were sequentially activated at 1.5 mA double-blinded and in a randomized order for a full assessment of MDS-UPDRS III with wash-out periods of at least 30 min between the two assessments. The order of the clinical and GUIDE XT™-assisted program was alternated to control for longer washout periods of medication and possible bias due to longer DBS intervals in the respective second assessment.

DBS amplitude was restricted to 1.5 mA since VEsF were simulated at the same amplitude aiming at maintaining the directional properties of the leads and to avoid a disbalance between the two sessions. In both the clinical program as well as the GUIDE XT™-assisted program, two patients (at three STN sites, respectively) experienced intolerable side effects with lower intensities. In these cases, the highest tolerable amplitude was set (range 0.5–1.2 mA).

In a subgroup of 18 patients, the threshold for side effects was determined for both programs by step-wise increment of stimulation until lasting (i.e., longer than 2 min) or unbearable side effects occurred.

2.5.3. VEsF generation in Lead-DBS

Routines in Lead-DBS software were utilized to generate the VEsF for the GUIDE XT™-derived program and the clinical program. The detailed processing pipeline has been described elsewhere [10]. In brief, postoperative CT scans were linearly co-registered to the preoperative MRI (T1-, and T2-weighted sequences). Then, images were nonlinearly normalized into standard space using advanced normalization tools as implemented in Lead-DBS. After DBS leads reconstruction and determination of lead orientation (cf. postoperative imaging and detection of directionality of DBS leads), VEsF were estimated using a finite element method [6]. Two VEsF were generated based on the DBS parameters defined as the clinical program and the GUIDE XT™-derived program and exported for further analysis.

2.6. Statistical analyses

Statistical analyses were performed in R (version 3.6.3) [14]. One-way ANOVA with condition as within-subject factor was used for comparisons of MDS-UPDRS III scores between OFF-state and the two DBS programs after testing for normality using Shapiro-Wilk test. For the primary endpoint of comparing change in MDS-UPDRS III between the clinical and the GUIDE XT™-derived programs, non-inferiority testing was performed since our main intention was to demonstrate that symptom control based on imaging-guided programming is not inferior to the standard clinical procedure. The 90% confidence interval for the difference in relative change of MDS-UPDRS III from OFF-state was calculated using a non-inferiority margin of 20%. This margin was defined based on a study by Schrag and colleagues that reported that a 20% decrease in UPDRS can be considered a minimal clinically relevant improvement [15]. We decided in favor for a relative margin instead of an absolute value because of the large variability in the absolute MDS-UPDRS III scores in our sample, ranging from seven to 82 in OFF-state. Further, the absolute margin reported by Schrag et al. may not be directly applicable here since their study used the former, not MDS-revised version of UPDRS.

Post-hoc pairwise superiority testing using paired t-tests with Bonferroni correction was employed for comparisons of OFF condition with both DBS programs.

VEsF for the GUIDE XT™-derived program and the clinical program were generated in the Lead-DBS software [10]. The overlap between these VEsF, resulted from the masks of the resulting polyhedrons and Sørensen–Dice coefficient, was estimated according to:

$$DSC = \frac{2|X \cap Y|}{|X| + |Y|}$$

Resulting Dice coefficients were correlated with the difference in MDS-UPDRS III sub-scores of the contralateral body side using Pearson's product-moment correlation.

Raleigh's z-Test was applied to test for differences in the mean direction between the lead rotation angles calculated in GUIDE XT™ and Lead-DBS. These analyses were performed using MATLAB™ version 9.3.0 (R2017b, Natick, Massachusetts: The MathWorks Inc.). A p value $< .05$ was considered statistically significant.

3. Results

3.1. Effects on motor symptoms achieved by the GUIDE XT™-assisted program and clinical program

First, MDS-UPDRS III score in all three conditions (OFF, clinical program and GUIDE XT™ program) were compared and the ANOVA revealed an overall significant effect of condition ($F(2,56) = 71.260$, $p < .0001$). Pairwise comparison indicated that significant improvements of motor symptoms were achieved with both programming procedures compared to when DBS was switched off (OFF vs. clinical program: $t = -10.9$, $p < .0001$; OFF vs. GUIDE XT™ program: $t = -8.92$, $p < .0001$) (Fig. 2). A mean reduction of 56.6 ± 22.4% from OFF-state MDS-UPDRS III was achieved with the clinical program, respectively 43.9 ± 20.8% with GUIDE XT™-derived program.

The mean difference in MDS-UPDRS III changes between the clinical and GUIDE XT™ programs was 12.7 ± 21.8% with the confidence interval ([5.8, 19.6]) entirely below the margin of 20%. Thus, non-inferiority of the program determined with GUIDE XT™ on reduction motor symptoms compared with the clinical program was confirmed. Since the upper limit of the confidence interval (19.6%) was very close to the non-inferiority margin (Fig. 1), we additionally evaluated individual patients' data in detail. In 13 patients (45%), the difference in relative MDS-UPDRS III improvement between the two programs was larger than 20% (i.e., above the cut-off for a minimal clinically relevant difference). Twelve of 13 patients experienced preferable symptom control with the clinical program, while only one had a considerably larger improvement with the Guide XT™-derived program.

The threshold for side effects was assessed in a subset of 18 patients (36 STN sites) and did not differ between the GUIDE XT™ program (2.18 ± 0.97 mA) and the clinical program (2.29 ± 0.83 mA, mean difference 0.11 ± 0.76 mA, $t = 0.852$, $p = .4$), with involuntary muscle contractions (61% with the GUIDE XT™ program, 50% with the clinical program) or isolated dysarthria (14%, with the GUIDE XT™ program, 28% with the clinical program) due to spread of stimulation to the internal capsule occurring most frequently in both stimulation settings. A summary of all side effects for both programs can be found in Supplementary Material 1.

3.2. VEsF generated by the GUIDE XT™ program and clinical program

The overlap between the VEsF generated by the GUIDE XT™ -derived and by the clinical program showed considerable variability (mean Dice-coefficient 0.52 ± 0.22) (Fig. 3A). Yet, the magnitude of overlap did not correlate with differences in the clinical effect of the programs on the respective body side measured as the difference in side-restricted MDS-UPDRS III subscores relative to the OFF-state ($r = -.194$, $r^2 = 0.038$, $p = .1$) (Fig. 3B, Supplementary Material 1 for complete descriptive data). Notably, the overlap of VEsF in the subgroup of 13 patients who experienced a clinically relevant difference in improvement between the programs (mean DICE-coefficient 0.53) did not differ from the mean overlap of the rest of the sample ($t = 0.6$, $p = .5$).

3.3. Estimation of lead direction with GUIDE XT™ and Lead-DBS

The mean deviation from the intended rotation angle was 45.9° ± 25.1 in GUIDE XT™, respectively 48.8° ± 28.5 in Lead-DBS. There was no significant difference between the lead angle estimations using GUIDE XT™ and Lead-DBS (mean difference 2.9° ± 11.3, Rayleigh test of uniformity, test statistic: 0.97 $p < .0001$) (Fig. 4).

4. Discussion

The aim of this study was to compare standard-of-care clinical DBS programming of directional leads with an individualized image-based programming approach. The detection of DBS lead positions resulted from fusions of patients' preoperative MRI and

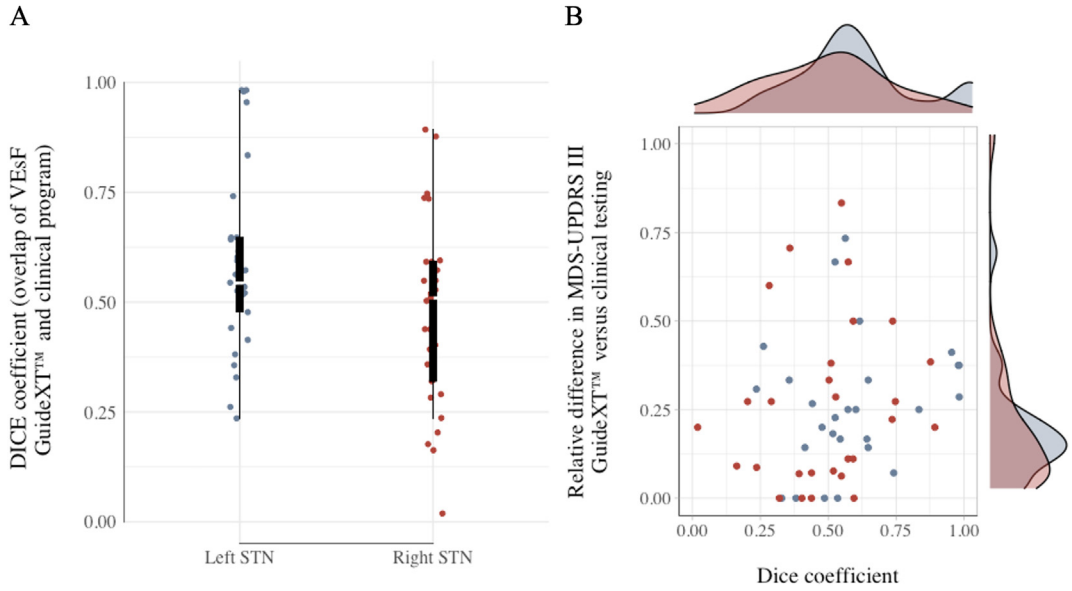

Fig. 3. A) Box plot illustrating the relative overlap of VEsF generated by the GUIDE XT™ and the clinical program as estimated in the Lead-DBS package, measured as Dice-coefficients. The overlap ranged from 18% to 98%, whereby vertical lines represent upper and lower quartiles. B) Scatter plot and frequency distributions (upper row and right column) of Dice coefficients and the difference in MDS-UPDRS III score achieved by the Guide XT™ and the clinical program. Left lead is depicted in blue, right lead in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

postoperative CT scans, enabling visualization of the VEsF within the STN. Additionally, two different approaches to detect the orientation of segmented contacts by means of postoperative CT scans were compared: the build-in GUIDE XT™ and the DiODe algorithm [9] of the Lead-DBS open source software tool.

Imaging-based DBS programming using GUIDE XT™ resulted in non-inferior motor symptom control compared to the standard-of-care procedure that is time-intensive clinical evaluation of effects of circular stimulation as well as directional current shaping. This finding is consistent with a pilot study including ten PD-patients with octopolar unidirectional DBS which demonstrated equality in motor improvement [18]. Additionally, we demonstrated that side effects and the threshold at which they occurred did not differ between the programs.

Emergence of DBS has been an important therapeutic leap step for PD-patients. Nevertheless, satisfactory results depend upon accurate lead positioning but above all on individualized stimulation settings. In modern clinical routine, time restrictions often hamper extensive testing of DBS systems [19] so that, despite the new possibilities of current steering, some patients remain on suboptimal standard settings. Moreover, in clinical routine an inertia in the implementation of changes can be observed. This is particularly problematic when patients are considered non-responders, although only standard settings have been attempted and they could benefit from an individualized approach by the hands of a specialist. In this study, we could show that imaging-based techniques may facilitate more targeted testing. Nevertheless, our data still indicates a trend towards greater motor symptom relief with clinical programming compared to the entirely image-based approach with GUIDE XT™ that we chose in the study protocol. We therefore advocate for imaging-based parameters serving as baseline settings (i.e., lead level and directionality) which may be refined based on clinical effects. By this means, the proposed approach or similar techniques may still reduce the total time needed for clinical DBS programming sessions, given the approximate time of 75 min for the entire procedure (60 min at the computer and 15 min with the patient). Particularly, the efforts required for satisfying symptom control may be reduced using imaging-based initial DBS settings. In general terms, imaging techniques may hence play a role in improving efficiency of DBS programming.

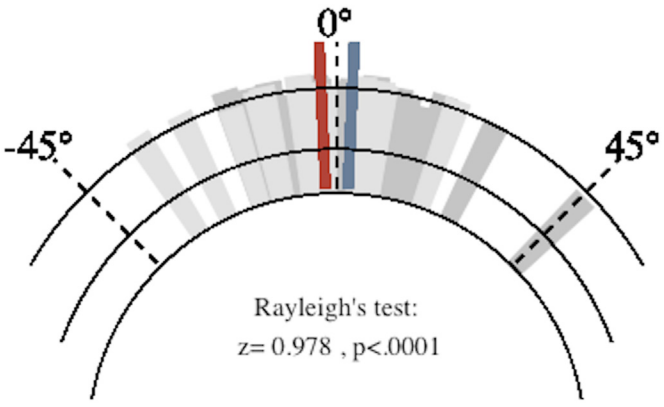

Fig. 4. Circular plot illustrating the differences in estimated lead angles between the GUIDE XT™ software and the DiDODe algorithm (implemented in Lead-DBS). Mean differences are shown in blue for the left leads (dark gray) and in red for the right leads (light gray). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Since the very beginnings of DBS, accurate imaging has been pivotal for its success. Not only is it indispensable for stereotactic planning of the often very small target structures, in clinical routine it is also without any alternative to identify malfunctioning systems. With recent development of directional leads, another important domain of imaging has emerged in determination of lead orientation. There is the possibility that leads rotate after insertion, coming to rest at very different angles to the intended 0° anterior/posterior orientation. Here, we could replicate results of Dembek et al. with extensive rotation after implantation in some cases [20]. Reasons for this are subject of debate but in clinical routine rotation adds considerable uncertainty to programming as opposed to former leads with circular contacts. Therefore, precise estimation of rotation angles is crucial for successful integration of individualized

imaging-guided programming into clinical routine. We provide evidence for comparable results between GUIDE XT™ and the protocol offered in Lead-DBS. As demonstrated by two recent studies using CT and rotation fluoroscopies, deviations from the intended orientation of DBS leads occur during surgery but seem to be stable over long periods of time postoperatively [21,22]. These results support that once-only determination of the actual individual lead orientation being sufficient and that longitudinal reassessments might not be necessary.

An unanticipated finding of our study was the difference in VEsF between the DBS programs. Despite comparable clinical outcomes and side-effect profiles, VEsF overlap for both settings at 1.5 mA was highly variable ranging from 16% to 100%. Furthermore, the magnitude of VEsF overlap was unrelated to differences in clinical improvement between the DBS programs. Aside from the possibility of effective stimulation of white matter tracts adjacent to the STN [23], these results could also be explained by the fact that satisfying motor symptom relief may be attainable by more than one DBS program, respectively at more than one area within or in the vicinity of the STN. For further debate about the existence of one "sweet spot" [24] or several locations in which DBS results in comparable outcomes, a better understanding of DBS mechanism of action is needed. Moreover, restricting our analyses on acute stimulation effects, it is too early to draw reliable conclusions in the long-term outcome base on our results.

Performing programming solely in OFF medication state may be considered a limitation of this study as motor symptom control in the long run relies on both, medication state and DBS efficacy.

That a portion of patients had taken part in comprehensive clinical programming session before their inclusion into the study may be a source of bias since these patients were already aware of the procedure and what therapeutic and side effects to expect. This might also have reduced the time needed from clinical programming in these patients.

The clinical programming session took place at least three months after surgery which is the standard of care for the first comprehensive evaluation of DBS effects at our center. In clinical practice, DBS-induced dyskinesias may be encountered particularly during the first few weeks after surgery before the lesion effect, with physicians not yet having had the time to adjust dopaminergic medication accordingly. We aimed at controlling for transient effective settings or dyskinesias during that time specifically testing patients who had reached a steady state for which three months of time appear reasonable. Therefore, potential effects of DBS-induced dyskinesia on the selection of the stimulation settings were not accounted for in this study.

Another important limitation of our study was the use of fixed stimulation amplitudes, pulse width, and frequency. As we intended to ascertain feasibility and comparability between both approaches, we decided in favor of a fixed intensity at 1.5 mA (instead of individual adaptations based on the clinical effect). We are aware of the risk of sub-therapeutic effects, at the same time we refer to current literature in which similar current densities were assessed as sufficient and clinically relevant [5,20]. Further research may ascertain whether differentiated settings may promote clinical effects and the applicability of modifications of other DBS parameters. We can only reiterate that to date selection and adjustments of stimulation settings based on the clinical examination remain the core of DBS programming and that imaging should serve as aid, i.e., starting point for searching the parameter space.

Further research will be necessary to find out whether differentiated optimizations of the settings derived from imaging or, e.g., the inclusion of continuous monitoring of motor symptoms in PD with always more present wearables could change the way DBS settings are determined in the future. Besides structural MRI and CT scans, several other neuroimaging modalities are currently investigated to aid DBS programming, including the use of local field potentials [25], functional connectivity profiles [6] or closed-loop stimulation guided by deep or cortical brain oscillations [26]. That the software used in this study is already commercially available and, more importantly, is easy to apply by clinicians without any background in neuroimaging or computational science is an advantage of the approach presented in this study compared to other advancing techniques.

In summary, imaging-guided programming of directional DBS leads using GUIDE XT™ is possible without computational background and leads to non-inferior motor symptom control compared with clinical programming. Taking patient-specific anatomy into consideration, this technique or similar approaches may promote more efficient programming of DBS, serving as a starting point for clinical testing without entirely replacing it. Given that determination of the lead direction is an indispensable presupposition for successful clinical use of directional DBS, reliable visualization of DBS leads including their rotation angle is possible with GUIDE XT™ and Lead-DBS with comparable results.

Questions remain on how to simulate VEsF more precisely and if different targets enable similar results. More insight into these details may be fundamental to shorten programming sessions of modern DBS systems or even more complex lead designs and therefore to aid clinicians and patients.

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CRediT authorship contribution statement

Josefine Waldthaler: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. **Miriam Bopp:** Software, Visualization, Writing – review & editing. **Nele Kühn:** Investigation, Data curation. **Bugrahan Bacara:** Investigation, Data curation. **Merle Keuler:** Investigation, Data curation. **Marko Gjorgjevski:** Investigation, Data curation. **Barbara Carl:** Resources, Supervision, Writing – review & editing. **Lars Timmermann:** Investigation, Data curation. **Christopher Nimsky:** Investigation, Data curation. **David J. Pedrosa:** Conceptualization, Methodology, Software, Data curation, Formal analysis, Supervision, Visualization, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.07.064.

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