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Bipolar Directional Deep Brain Stimulation in Essential and Parkinsonian Tremor

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Objective: To compare directional monopolar, bipolar, and directional bipolar thalamic deep brain stimulation (DBS) in tremor patients.

Methods: Fourteen tremor patients (7 Essential Tremor and 7 Parkinson's Disease) implanted with directional DBS electrodes in the ventral intermediate nucleus (VIM) were enrolled. Side-effect thresholds of monopolar directional stimulation (DIRECT) were compared to circular DBS as well as, in a randomized design, to those of two different bipolar stimulation settings (BIPOLAR = circular anode; BI-DIRECT = directional anode). Tremor suppression (Tremor Rating Scale, TRS) right below the side-effect threshold was also assessed.

Results: Directional DBS in the individually best direction showed higher side-effect thresholds than circular DBS ($p = 0.0063$). The thresholds were raised further using either one of the bipolar stimulation paradigms (BIPOLAR $p = 0.0029$, BI-DIRECT $p = 0.0022$). The side-effect thresholds did not differ between both bipolar settings, but side-effects were less frequent with BI-DIRECT. No difference in TRS scores with stimulation just below the side-effect threshold was found between all stimulation conditions.

Conclusions: Side-effect thresholds of monopolar directional and bipolar stimulation with both circular and directional anodes were higher compared to traditional monopolar circular stimulation in the VIM. Bipolar DBS with directional anodes evoked side-effect less frequently than bipolar and monopolar directional stimulation. All stimulation settings had comparable effects on tremor suppression just below their side-effect thresholds. Thus, directional and different bipolar settings should be explored in patients with bothersome side-effects of thalamic stimulation when monopolar stimulation settings are not satisfying. Further studies are needed to explore the efficiency of the different bipolar stimulation paradigms.

Keywords: Deep brain stimulation, essential tremor, Parkinson's disease

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INTRODUCTION

Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) and the neighboring posterior subthalamic area (PSA) is an established treatment option for medication-refractory tremor in patients with essential tremor (ET) (1,2) and tremor-dominant Parkinson's Disease (PD) (3,4). Directional DBS leads have been demonstrated to increase side-effect thresholds when shaping the electrical field in the axial plane in both the subthalamic nucleus (STN) (5–7) and in the VIM compared to circular DBS (8). While these results are promising, the changes were generally subtle and might still be insufficient for some patients. Moreover, the underlying mechanisms in terms of effects on the volume of neural activation (VNA) or selective fiber activation remain to be explored.

In a case report, we successfully combined directional and bipolar stimulation to avoid stimulation-induced dysarthria in a patient with STN-DBS (9). In this case, the anode was shifted from the implantable pulse generator (IPG) to the electrode segment with the lowest side-effect threshold with the idea to reduce cathodal current spread in that direction. In light of these results, we sought to prospectively evaluate the effects of both monopolar and bipolar directional VIM-DBS in tremor patients. Our hypothesis was that bipolar directional stimulation augments side-effect thresholds more than monopolar directional DBS, with equivalent tremor suppression.

METHODS

Patients

All patients who received unilateral or bilateral implantation of directional DBS leads into the VIM/posterior subthalamic area (PSA) at our center between July 2016 and August 2017 were consecutively screened for study participation. Indication for DBS treatment had been determined clinically after standardized multidisciplinary evaluation according to established criteria and was not part of the study procedure. Inclusion criteria were a diagnosis of ET (10) or tremor-dominant PD (11), implantation of directional DBS leads into the VIM/PSA at least 3 months before enrollment, age between 18 and 80 years, and sufficient understanding of the German language with capability to provide informed consent. Exclusion criteria were clinically-relevant neuropsychological or psychiatric comorbidity, insufficient understanding of the German language, and refusal of overnight withdrawal of dopaminergic medication in PD patients.

Protocol Approval, Registration, and Consent

This investigator-initiated study was approved by the Ethics Committee of the University of Cologne (Study-No: 17–044) and conducted in accordance with the Declaration of Helsinki. Patients gave written informed consent before study participation. The study was registered with the German Clinical Trials Register (Registration-No: DRKS00012667).

Directional Leads

Patients were implanted with directional DBS leads (Cartesia™, Boston Scientific, Marlborough), which feature eight electrodes arranged in a 1-3-3-1 design, the two middle levels consisting of tripartite directional electrodes. The leads also feature a stereotactic marker to identify lead orientation (12,13). The IPG provides independent current sources for each of the eight electrodes, so that every single electrode can be activated with an individual amount of current. Both segmented levels allow conventional circular stimulation by activating all three segments with equal amounts of current (*circular stimulation*), as well as current steering in the axial plane when shifting the current to only one or two segments (*directional stimulation*). Additionally, this system allows shifting the anode from the IPG to one or several electrodes on the lead.

Surgical Procedure, Lead Location, and Lead Orientation

DBS leads were implanted following our established stereotactic procedure of targeting the VIM and the adjacent PSA on a single trajectory (2). All patients received preoperative stereotactic CT, preoperative MRI, and postoperative CT. Correct lead placement was confirmed using the LEAD-DBS Toolbox (14). Preoperative and postoperative images were coregistered linearly and then normalized nonlinearly to MNI space using Advanced Normalization Tools with subcortical refine (15,16). Lead trajectories were then automatically detected using the PACer algorithm (17). Finally, lead orientation angles were determined from the artifacts generated by the stereotactic marker and the directional electrodes in the postoperative CT scan using the DiODe algorithm developed at our center (12,13).

Study Protocol

This double-blind study was performed with patient and rater being unaware of electrode selection as well as stimulation setting and amplitude. PD patients were examined after overnight withdrawal of dopaminergic medication. Baseline tremor severity in both PD- and ET-patients was evaluated using parts A and B of the Tremor Rating Scale (TRS) (18) after the stimulation had been turned off for at least 15 min. Only the clinically more affected side was evaluated, while stimulation for the less affected side was deactivated during all study procedures. Figure 1 provides a schematic overview of the study protocol. Our main goal was to investigate whether bipolar directional DBS [BI-DIRECT] further increases side-effect thresholds compared to monopolar directional DBS [DIRECT], while maintaining equivalent therapeutic efficacy. In order to differentiate whether possible differences between DIRECT and BI-DIRECT settings were attributable to the directional anode or to general effects of bipolar stimulation (19–21), we also tested a bipolar setting [BIPOLAR] with a non-directional anode.

Monopolar Reviews

Both levels of segmented electrodes in the investigated hemisphere, that is, the one corresponding to the clinically more affected side, were interrogated in randomized order, with circular stimulation and with increasing amplitude steps of 0.5 mA up to 6.0 mA with pulse width/frequency fixed at 60 µs/130 Hz. The blinded rater evaluated upper limb tremor suppression in the position that evoked most tremor. The more effective and efficient electrode level regarding tremor suppression was chosen for further analysis. On this level, we then conducted directional monopolar reviews for each of the three electrode segments by again increasing stimulation in 0.5 mA steps to assess the respective side-effect thresholds. The thresholds were defined as the first amplitude at which any stimulation-induced side-effect (e.g., dysarthria, dizziness, and muscle contractions) occurred,

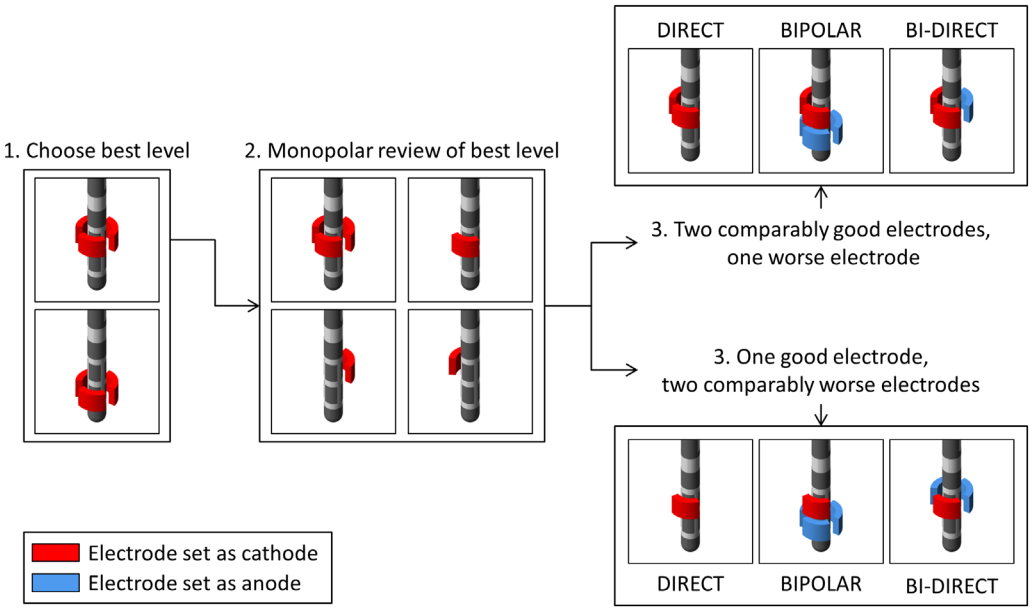

Figure 1. Study protocol. Schematic overview of the study protocol from left to right. Cathodal stimulation of an electrode is shown in red, anodal stimulation in blue. BIPOLAR, bipolar directional stimulation with circular anode; BI-DIRECT, bipolar directional stimulation with directional anode; DIRECT, monopolar directional stimulation. [Color figure can be viewed at wileyonlinelibrary.com]

except for paresthesia, which was only deemed relevant if it persisted for more than two minutes. The three electrode segments were then ranked according to their side-effect thresholds in *highest*, *lowest*, and *median*.

Comparison of Directional Monopolar, Bipolar, and Directional Bipolar Stimulation

All three conditions were derived from the monopolar reviews explained above. The electrode segment with the highest threshold for side effects was always set as the cathode. If the side-effect threshold of the electrode segment ranked *median* was closer to the one of the segment with the *highest* threshold, it was set as an additional cathode with equal current distribution between the two cathodal segments. For monopolar directional [DIRECT] stimulation, the anode was located on the IPG. For conventional BIPOLAR stimulation, a circular anode was shifted to the adjacent, therapeutically less effective segmented electrode level. For BI-DIRECT stimulation the anode was shifted to the directional electrodes within the most effective segmented level, which were not set as cathodes (also see Fig. 1).

All three conditions were investigated in randomized order with breaks of at least 15 min without stimulation in between. Side-effect thresholds of each condition were again determined using amplitude steps of 0.5 mA up to a maximum of 6.0 mA. As no side-effects occurred until 6.0 mA in the first four patients under bipolar stimulation, we adapted the study protocol so that amplitudes up to 10.0 mA were investigated in both bipolar conditions from the fifth patient onwards. After the individual side-effect threshold had been determined, patients were kept in the respective condition at an amplitude 0.5 mA below the side-effect threshold for at least 15 min. In this condition, we examined the tremor suppression using parts A and B of the TRS. TRS scores were videotaped and rated by a blinded rater not previously involved in the examinations (PR). As we investigated stimulation in one hemisphere, only TRS hemiscores were analyzed.

Statistical Analysis

Monopolar Directional DBS

Side-effect thresholds during the four different monopolar reviews (circular, anterior, posterolateral, and posteromedial) were compared using the nonparametric Friedman test with a significance threshold of $p < 0.05$. Post-hoc pairwise comparisons were conducted using the Wilcoxon signed-rank test corrected for multiple (six) comparisons using the Bonferroni method. To investigate whether directional DBS of an individual best electrode (ranked as *highest* previously) increased side-effect thresholds compared to circular DBS, we directly compared circular DBS to the pooled individually *highest* using the Wilcoxon signed-rank test.

Bipolar Directional DBS

Our two primary outcome parameters were the side-effect thresholds and the TRS hemiscores in the different stimulation settings (DIRECT, BIPOLAR, BI-DIRECT) and without stimulation (OFF). Both outcomes were analyzed separately using Friedman tests with a significance threshold of $p < 0.05$ and Wilcoxon signed-rank tests for post-hoc pairwise analysis, again corrected using the Bonferroni method for multiple comparisons (three comparisons for side-effects, six for TRS). In case no side-effects were observed inside the investigated amplitude range, we made the conservative assumption that side-effects would have occurred at 0.5 mA above the investigated limit. All results are shown as median with corrected *p*-values. All analyses were conducted with MATLAB 2016b (The MathWorks Inc., Natick, MA, USA).

RESULTS

Data Consistency and Protocol Deviations

All 14 screened patients agreed to participate in the study. Table 1 depicts the relevant demographic and clinical data.

Table 1. Patient Characteristics and Stimulation Outcome.

Patient	Sex	Age (years)	Diagnosis	Tremor-dominant side	Duration after surgery (months)	Hemi-TRS score (OFF)	DIRECT Hemi-TRS	BIPOLAR Hemi-TRS	BI-DIRECT Hemi-TRS
1	M	81	PD	right	7	18	-	-	-
2	M	52	PD	right	7	40	19	14	33
3	F	65	ET	left	4	20	6	5	4
4	M	68	PD	left	11	32	15	10	15
5	M	80	ET	left	12	29	10	13	13
6	F	77	ET	right	29	10	3	7	6
7	F	80	ET	left	10	33	-	-	-
8	M	64	ET	left	14	25	20	19	24
9	M	72	PD	right	8	10	9	10	8
10	M	54	ET	right	12	9	3	5	5
11	M	71	PD	right	18	32	6	4	4
12	M	76	PD	right	3	39	18	18	18
13	M	75	ET	left	3	11	5	6	5
14	M	71	PD	left	5	21	9	9	3
Median/ proportion	11 male, 3 female	71.5	7 PD, 7 ET	7 right, 7 left	7.5	23	9	9.5	7

Note that TRS scores under stimulation are missing in patients 1 and 7 due to exhaustion and abortion of further testing after evaluation of side-effect thresholds.
BIPOLAR, bipolar directional stimulation with circular anode; BI-DIRECT, bipolar directional stimulation with directional anode; DIRECT, monopolar directional stimulation; ET, essential tremor; PD, Parkinson's disease; TRS, Tremor Rating Scale; OFF, stimulation-OFF.

Twelve of the 14 patients completed the full protocol. In the two remaining patients (one ET, one PD), the examination had to be aborted due to exhaustion after evaluation of side-effect thresholds but before completing the TRS assessments. We thus included $n = 14$ patients for the analysis of side-effect thresholds and $n = 12$ patients for the analysis of TRS outcomes.

Lead Locations and Lead Orientation

All leads had been placed with their tip ventral to the thalamus in the posterior subthalamic area, as per routine at our center (Fig. 2). Lead orientations could be determined from the CT artifacts in 13/14 cases. In those leads, mean rotatory deviation from the patient axis was 33.42°. Two leads deviated more than 60°, so that the directional electrodes had to be reassigned to the corresponding directions anterior, posterolateral, and posteromedial.

Monopolar Directional Versus Circular Stimulation

There was no difference in side-effect thresholds for circular, anterior, posterolateral, and posteromedial stimulation ($p = 0.6882$), which also means that there was no direction generally superior to the other ones. However, side-effect thresholds of the individual best directional electrodes were higher compared to circular stimulation (median 5.0 mA vs. 4.0 mA, $p = 0.0063$) (Fig. 3a).

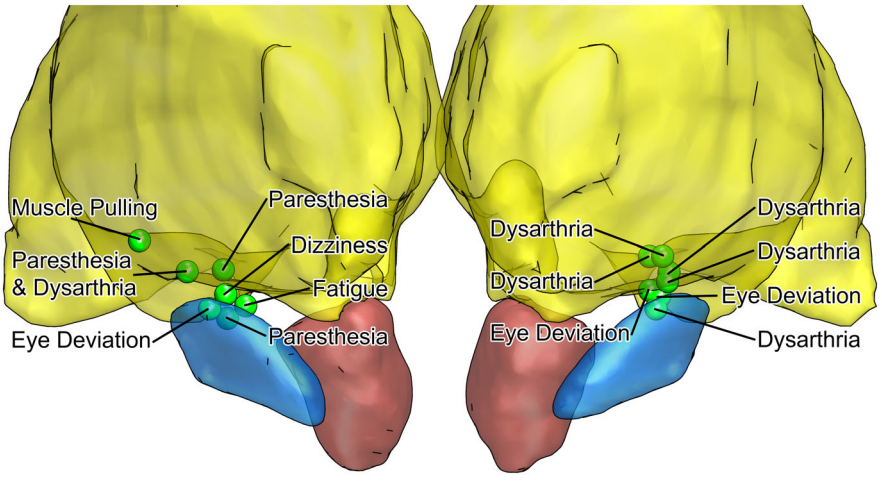

Figure 2. Lead locations. Three-dimensional view from anterior of all investigated contacts and the earliest side-effect at the respective positions together with the atlas-based thalamus (yellow), the subthalamic nucleus (blue), and the red nucleus (red). [Color figure can be viewed at wileyonlinelibrary.com]

Table 2. Individual Electrodes of All Stimulation Conditions and Side-Effects.

Pat.	Cathode	DIRECT			BIPOLAR			BI-DIRECT		
		Anode	Amplitude (mA)	Side-effect(s)	Anode	Amplitude (mA)	Side-effect(s)	Anode	Amplitude (mA)	Side-effect(s)
1	Ventral: PL	IPG	4.0	Eye deviation	Dorsal: Ring	6.0	Eye deviation	Ventral: A + PM	6.0	None
2	Ventral: PM	IPG	6.0	None	Dorsal: Ring	6.0	None	Ventral: A + PL	6.0	None
3	Ventral: PM + PL	IPG	4.0	Fatigue	Dorsal: Ring	6.0	None	Ventral: A	6.0	None
4	Ventral: PL	IPG	5.5	Dizziness	Dorsal: Ring	4.5	Discomfort	Ventral: A + PM	4.5	Discomfort
5	Dorsal: A + PL	IPG	6.0	None	Ventral: Ring	10.0	None	Dorsal: PM	10.0	None
6	Ventral: A + PL	IPG	4.5	Dysarthria	Dorsal: Ring	10.0	None	Ventral: PM	10.0	None
7	Ventral: PM + PL	IPG	5.5	Paresthesia	Dorsal: Ring	10.0	None	Ventral: A	10.0	None
8	Ventral: A	IPG	6.0	Eye deviation	Dorsal: Ring	9.0	Eye deviation	Ventral: PM + PL	10.0	None
9	Ventral: A	IPG	5.0	Eye deviation	Dorsal: Ring	10.0	None	Ventral: PM + PL	6.5	Eye deviation
10	Dorsal: A	IPG	5.5	Dysarthria	Ventral: Ring	10.0	None	Dorsal: PM + PL	10.0	None
11	Ventral: PM	IPG	5.5	Dysarthria	Dorsal: Ring	9.0	Dysarthria	Ventral: A + PL	10.0	None
12	Ventral: PM	IPG	5.5	Dysarthria	Dorsal: Ring	6.0	Dysarthria	Ventral: A + PL	10.0	None
13	Dorsal: PL	IPG	3.5	Muscle pulling	Ventral: Ring	4.5	Muscle pulling	Dorsal: A + PM	4.0	Muscle pulling
14	Dorsal: A	IPG	4.0	Dysarthria, Paresthesia	Ventral: Ring	6.0	Paresthesia	Dorsal: PM + PL	7.0	Dysarthria

Side-effects and their amplitude thresholds for conditions DIRECT (monopolar directional stimulation), BIPOLAR (bipolar stimulation with circular anode), and BI-DIRECT (bipolar stimulation with directional anode). Active cathodes/anodes for each condition are described with ventral/dorsal indicating the segmented level and A/PM/PL indicating the anterior, posteromedial, and posterolateral electrode segments, respectively.

Stimulation Conditions

A detailed description of which electrodes were individually chosen in the three different stimulation conditions DIRECT, BIPOLAR, and BI-DIRECT is provided in Table 2. In 10 out of 14 patients, the ventral segmented level was deemed more effective and thus chosen for cathodal stimulation. Within the segmented level, in 10 out of 14 patients one segment was set as a cathode, while two cathodal segments were chosen in the remaining four patients.

Side-Effect Thresholds During Monopolar and Bipolar Stimulation

When stimulating up to 6 mA ($n = 14$), 12 patients exhibited side-effects in condition DIRECT, four in condition BIPOLAR, and two in condition BI-DIRECT. When stimulating up to 10.0 mA ($n = 10$), nine patients displayed side-effects in condition DIRECT, five patients in condition BIPOLAR, and three in condition BI-DIRECT (Fig. 3b). The Friedman test revealed differences in the side-effect thresholds between the conditions ($p = 0.0003$). Post-hoc analysis showed that side-effect thresholds in both bipolar conditions (BIPOLAR: median 7.75 mA; BI-DIRECT: median 8.75 mA) were higher than in monopolar stimulation (DIRECT: median 5.5 mA; DIRECT vs. BIPOLAR $p = 0.0029$; DIRECT vs. BI-DIRECT $p = 0.0022$). However, there was no statistical difference between the two bipolar conditions (BIPOLAR vs. BI-DIRECT $p = 1.0$) (Fig. 3c). The most frequent side-effects were dysarthria and paresthesia. The quality of side-effects did not change between the conditions except in one patient (Table 2).

Tremor Suppression

The Friedman test revealed differences in TRS hemiscores between the four conditions OFF, DIRECT, BIPOLAR, and BI-DIRECT ($p < 0.0001$). Post-hoc analysis revealed better scores compared to stimulation-OFF (median 23 points) for all three stimulation settings (DIRECT: median 9 points, $p = 0.0029$; BIPOLAR: median 9.5 points, $p = 0.0059$; BI-DIRECT: median 7 points, $p = 0.0029$). No differences in TRS hemiscores were found between the three stimulation settings (DIRECT vs. BIPOLAR $p >= 1$, DIRECT vs. BI-DIRECT $p >= 1$, BIPOLAR vs. BI-DIRECT $p >= 1$) (Fig. 3d).

DISCUSSION

In this prospective, double-blind study we investigated a novel concept of combined bipolar and directional stimulation in essential and parkinsonian tremor patients with VIM-DBS in order to evaluate this programming strategy as a remedy for stimulation-induced side-effects. We found that monopolar directional stimulation in the individually best direction led to an elevation of median side-effect

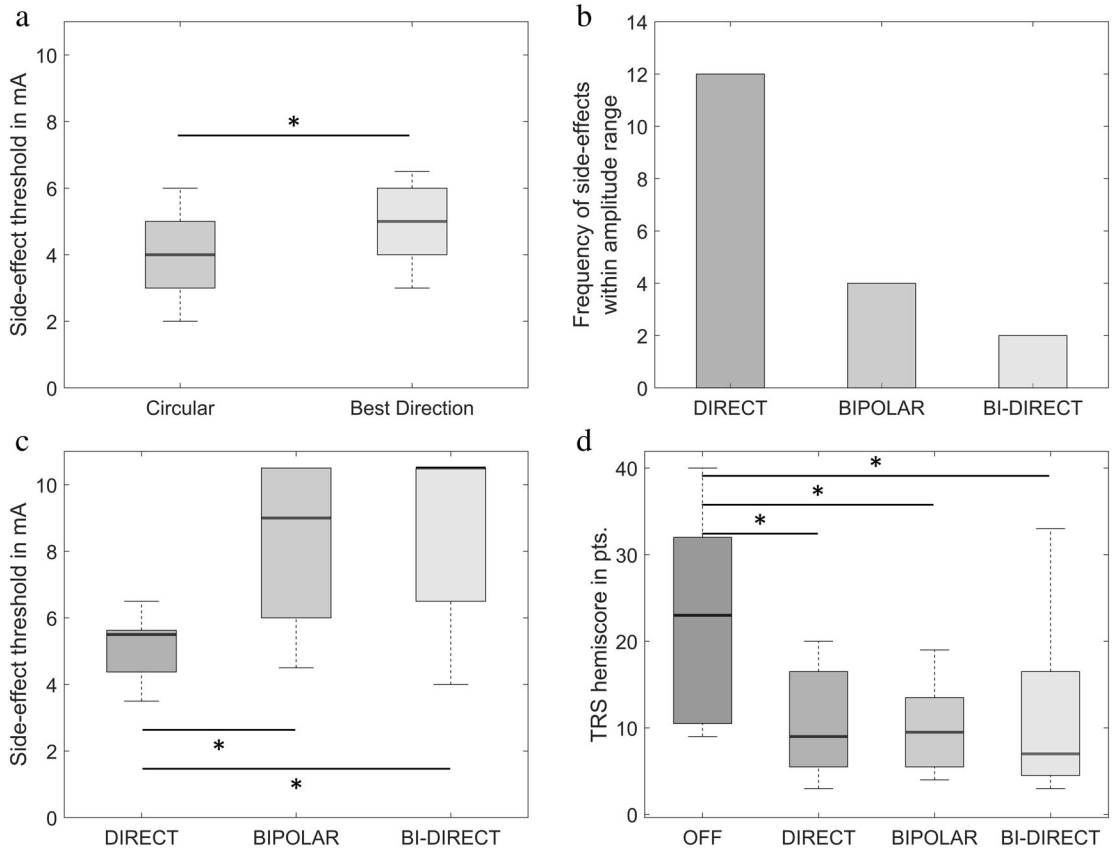

Figure 3. Results. a. Boxplot of side-effect thresholds of monopolar circular and directional stimulation in the individually best direction. b. Frequency of side-effects for stimulation up to 6 mA in the three conditions DIRECT, BIPOLAR, and BI-DIRECT. c. Boxplot of side-effect thresholds in the above-mentioned conditions. d. Boxplot of TRS hemiscores in the conditions. Boxplots represent medians, quartiles and range. Asterisks (*) indicate significance after Bonferroni-correction. BIPOLAR, bipolar directional stimulation with circular anode; BI-DIRECT, bipolar directional stimulation with directional anode; DIRECT, monopolar directional stimulation; OFF, stimulation-OFF; TRS, Tremor Rating Scale.

thresholds by 1 mA compared to circular DBS, which is in line with previous studies of STN-DBS (5–7) and with the recent retrospective evidence for advantages of directional DBS in the VIM (8). No stimulation direction (anterior, posteromedial, and posterolateral) was generally superior to circular stimulation or to other directions. This shows that there was no systematic deviation of lead location from the intended stereotactic targets and that not only one single but various adjacent structures surrounding the VIM and the PSA may cause side-effects.

Furthermore, we showed that bipolar stimulation with a conventional circular anode (BIPOLAR) and with an individualized directional anode (BI-DIRECT) allowed for again higher stimulation amplitudes without side-effects compared to monopolar directional DBS. The median side-effect threshold was highest under BI-DIRECT as the majority of patients did not experience any side-effects at stimulation amplitudes of up to 10 mA. All stimulation conditions showed comparable therapeutic effects at stimulation amplitudes of 0.5 mA below the side-effect threshold with median improvements of more than 60% in TRS hemiscores. In line with previous evidence (19), both bipolar settings were as effective in suppressing tremor as monopolar DBS, albeit at significantly higher amplitudes.

Most authors agree that higher stimulation amplitudes are needed with bipolar DBS to achieve therapeutic benefit (19,21) even though the exact mechanism of bipolar stimulation remains unclear. Modeling studies suggest orientation selectivity for axons depending on spatial configuration and polarity of the active contacts as an important factor for selective stimulation of certain fiber orientations. Here, anodal DBS preferentially activated axons perpendicular to the lead, while at the same time reducing activation of axons parallel to the lead (22). Bipolar directional stimulation with a system capable of multiple independent current control might even allow for specific current steering to maximize alignment of the electric field with the targeted pathways (23). This could explain how bipolar DBS helps to avoid side effects caused by, for example, stimulation spread into the internal capsule that runs approximately parallel to the lead in VIMDBS. A clinical study showed that anodal (instead of cathodal) stimulation is effective in STN-DBS with both higher efficacy and higher side-effect thresholds (24). To our knowledge, neither comparable clinical studies in the VIM nor comparable studies for directional anodes have been published so far but they are needed to further expand our understanding of DBS mechanisms.

Importantly, the higher amplitudes necessary for tremor suppression with bipolar (directional) stimulation reduce the energy efficiency of these settings. This has recently been confirmed in a study featuring devices of the same manufacturer (25). Prolonged or permanent use of (directional) bipolar settings would therefore probably require more frequent recharging (in rechargeable IPGs) or even earlier IPG replacement (in nonrechargeable) IPGs.

As a limitation of our protocol, we did not specifically examine therapeutic anodal stimulation but employed anodes in their traditional role as the nontherapeutic electrode during bipolar stimulation. Given the multitude of stimulation conditions tested in this

trial, adding more conditions or determining the efficacy threshold needed for the calculation of the therapeutic window would have exceeded a reasonable schedule and would have possibly jeopardized reliable symptom assessment, as highlighted by the two patients who requested abortion of the study procedures due to exhaustion. Notably, we did not aim at establishing therapeutic windows for the different settings but rather at comparing their side-effect thresholds and their efficacy just below these.

The following aspects of our results deserve closer scrutiny. Fewer patients experienced side-effects in the BI-DIRECT condition than in the regular BIPOLAR condition, but side-effect thresholds did not differ significantly between the two conditions. This might be explained by our conservative statistical assumption, that patients without side-effects would have experienced them at the next amplitude increment right after the maximum investigated amplitude threshold. Thus, for BI-DIRECT, we had to assume thresholds of 6.5 mA in three and of 10.5 mA in seven patients (Table 2) even though no side-effects occurred. In general, side-effect thresholds were rather high in this cohort. Hence, differences between the bipolar conditions might be underestimated and could be more pronounced in patients with suboptimally placed leads who experience side-effects at lower stimulation amplitudes. Another limitation of our study is the small sample size. However, our results were either highly significant even after rigorous alpha-correction, or far from significant even without alpha-correction.

In conclusion, monopolar directional and bipolar directional stimulation with both circular and directional anodes can serve as programming techniques in patients with VIM-DBS to relieve stimulation-induced side-effects, while maintaining tremor control. Despite the fact that we cannot prove a potential enlargement of the therapeutic window, we propose an evaluation of these advanced paradigms in patients with bothersome and limiting stimulation-induced side-effects under standard DBS settings.

Authorship Statement

Julia K. Steffen was responsible for the study concept and design, data acquisition, data analysis, drafting of the manuscript. Paul Reker was responsible for the study concept and design, data acquisition, data analysis, drafting of the manuscript. Fiona K. Mennicken was responsible for data acquisition, data analysis, drafting of the manuscript. Till A. Dembek was responsible for the study concept and design, data analysis, drafting of the manuscript. Haidar S. Dafsari was responsible for data interpretation, critical revision of the manuscript. Gereon R. Fink was responsible for data interpretation, critical revision of the manuscript. Veerle Visser-Vandewalle was responsible for surgical intervention, critical revision of the manuscript. Michael T. Barbe was responsible for the study concept and design, critical revision of the manuscript, study supervision.

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COMMENT

This is an interesting paper that explores nuances of stimulation methods in Vim DBS. The purpose of the discussed method and protocol was reduction of side effects to allow for response improvement. Well executed.

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