



Universiteit
Leiden
The Netherlands

The actual use of directional steering and shorter pulse width in selected patients undergoing deep brain stimulation

Zitman, F.M.P.; Janssen, A.; Gaag, N.A. van der; Hoffmann, C.F.E.; Zutt, R.; Contarino, M.F.

Citation

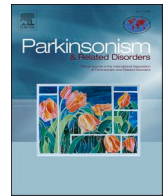
Zitman, F. M. P., Janssen, A., Gaag, N. A. van der, Hoffmann, C. F. E., Zutt, R., & Contarino, M. F. (2021). The actual use of directional steering and shorter pulse width in selected patients undergoing deep brain stimulation. *Parkinsonism & Related Disorders*, 93, 58-61. doi:10.1016/j.parkreldis.2021.11.009

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3249491>

Note: To cite this publication please use the final published version (if applicable).



The actual use of directional steering and shorter pulse width in selected patients undergoing deep brain stimulation

Femke M.P. Zitman^a, Alexander Janssen^{b,1}, Niels A. van der Gaag^{b,c}, Carel F.E. Hoffmann^b, Rodi Zutt^a, Maria Fiorella Contarino^{a,d,*}

^a Department of Neurology, Haga Teaching Hospital, The Hague, the Netherlands

^b Department of Neurosurgery, Haga Teaching Hospital, The Hague, the Netherlands

^c Department of Neurosurgery, Leiden University Medical Center, Leiden, the Netherlands

^d Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands

ARTICLE INFO

Keywords:

Deep brain stimulation
Directional steering
Low pulse width
Patient selection

ABSTRACT

Introduction: Directional deep brain stimulation (DBS) and pulse with $<60\mu\text{s}$ increase side-effects threshold, enlarging the therapeutic window. However, new systems allowing these advanced features are more expensive and often available only for a limited number of patients in some centers. It is unknown how many and which DBS patients actually need the advanced features because of an insufficient improvement with standard parameters.

Methods: We included in the analysis all patients with Parkinson's disease, dystonia and tremor who were selected to receive implantation of advanced DBS systems based on specific preoperative or intraoperative clinical features.

Results: After a median follow-up of 15 months, 54.9% of the 51 patients implanted with directional leads were using the advanced features in one or both leads ($n = 42$ leads, 42%), meaning these leads were programmed either with directional stimulation ($n = 9$, 9%), a shorter pw ($n = 20$, 20%) or both ($n = 13$, 13%). This included 92% of patients implanted in the Vim, 44% of those implanted in the STN, and 40% of those implanted in the GPi.

Conclusions: DBS systems with advanced features may be particularly indicated for selected patients based on some clinical characteristics and the chosen target. This data may help clinicians allocate resources in a more informed way.

1. Introduction

Until recently, only standard leads with four cylindrical electrodes and limited range of stimulation parameters were used for deep brain stimulation (DBS). In the last years, leads with a 1-3-3-1 configuration with split electrodes allowing for directional stimulation became available [1]. New devices also allow a wider range of stimulation parameters, including pulse width (pw) $< 60\mu\text{s}$. Early clinical studies showed that both directional stimulation [1,2] and lower pw [3,4] can increase side-effects threshold, thus enlarging the therapeutic window.

A drawback of the new systems is the more complex set-up, requiring extra time and fine-tuning. Also, advanced systems are more expensive and therefore not available in many centers, or available only for a

minor percentage of patients per center, often depending on hospital-vendors contracts.

It is hypothesized that limiting stimulation-induced side-effects are an issue only in a small number of patients, while the majority of patients would benefit sufficiently from well-placed standard leads [5,6]. Currently, there are no parameters to predict which patients would potentially benefit from advanced stimulation features and for which patients these would be superfluous.

Directional systems have been limitedly available at our hospital since 2016. Since then, the DBS team has selected the patients to receive directional systems based on clinical features that could suggest a future low threshold for limiting side-effects.

The aim of this retrospective study was to evaluate in which of these

* Corresponding author. Els Borst-Eilersplein 275-2545AA, The Hague, the Netherlands.

E-mail address: m.f.contarino@lumc.nl (M.F. Contarino).

¹ Present address: Department of Neurosurgery Department of Neurosurgery, AZ Sint-Jan Hospital Bruges-Ostend, Belgium.

selected patients the advanced stimulation features were actually used.

2. Methods

2.1. Patients and selection criteria

We included all the consecutive patients with Parkinson's disease (PD), tremor other than PD, or dystonia who received directional leads since November 2016 in the Haga/LUMC DBS center and had a minimum follow-up of 6 months. Stereotactic targets were either the subthalamic nucleus (STN), the thalamic ventral intermediate nucleus (Vim), or the internal Globus Pallidus (GPi).

The DBS team chose to implant a directional system (Boston-Scientific Cartesia lead and Vercise PC implantable pulse generator) in the following cases (unless patients had an indication for postoperative MRI, as this system was not MRI-compatible at that time):

- 1) When the target was thalamus (based on our own previous experience and the challenging visualization of the target).
- 2) When, due to atrophy or blood vessels along the trajectory, it was deemed not safe to use microelectrorecordings (MER), which are sharper and stiffer than the DBS lead, thus, theoretically, increasing the risk of hemorrhage when in the vicinity of a blood vessel.
- 3) When a small therapeutic window was observed during intraoperative test stimulation on the hemisphere implanted first.

2.2. Surgery

Surgery was performed as previously described [7]. For PD and tremor, the surgery was performed awake and off medication; benefit and side effects were systematically investigated at every test point with items from official rating scales. When only a single trajectory was accessible, the definitive lead was used for testing along different depths. In dystonia patients, only side-effects were tested intraoperatively, and 4/7 patients were operated under general anesthesia. MER and semi-macrostimulation were performed along 2–4 trajectories when possible. The leads final position was confirmed by image fusion of preoperative stereotactic MRI scan with stereotactic intraoperative CT or postoperative CT scan.

2.3. Postoperative stimulation

All the programming clinicians used a similar strategy for parameters adjustments. A standard off-medication omnidirectional monopolar contact review was performed 9–10 days after surgery at all levels, with the middle levels on ring mode. Only when limiting side-effects prevented optimal symptom suppression, directional steering and/or pw < 60µs (advanced features) were used. Patients visited the outpatient clinic regularly thereafter to further adjust the stimulation settings and the medication when needed.

2.4. Analysis

We collected data retrospectively from patients' files. The primary endpoint was the percentage of patients using the advanced features at the last follow-up. Data were also analyzed per lead. Furthermore we explored some aspects that might predict the use of the advanced features: diagnosis, age and disease duration at surgery, target, number of MER trajectories, and the size of the best intraoperative therapeutic window.

The local ethical committee waived a formal evaluation.

3. Results

In the selected period 155 patients underwent surgery, of whom 53 (34%) received directional leads. Patients were implanted bilaterally,

except for one patient. In another patient, the right lead was not turned on due to persistent contralateral surgical benefit. Two patients had both leads explanted due to infection and were excluded from the analysis. Thus, 51 patients (100 leads) were included in the study (Table 1). Most patients had more than one year follow-up ($n = 45/53$).

At last follow-up (6–23 months after surgery), 28 patients (54.9%) were using the advanced features in one or both leads ($n = 42$ leads, 42%), meaning these leads were programmed either with directional stimulation ($n = 9$, 9%), a shorter pw ($n = 20$, 20%) or both ($n = 13$, 13%; Fig. 1A). The choice of using advanced features remained constant in the majority of patients with follow-up longer than 6 months. In total, only six leads (in 5/49 patients) which were still programmed with standard parameters at 6 months, had been changed to pw < 60µs (3 leads) or directional stimulation (2 leads) or both (1 lead) at last follow-up. In no case advanced features had been changed back to standard stimulation.

When grouping results per target, 92% of the patients with leads in the Vim were using the advanced features in at least one lead (11/12 patients, all with non-PD related tremor; the remaining patient had tremor in the context of PD). For STN and GPi the proportion was 44% and 40% respectively. In the 16 leads implanted in the Vim, the reason for using advanced features was dysarthria in 11 leads (in 3 cases in combination with muscle twitches), ataxia in 2, paresthesia in 2 (in one case in combination with muscle twitches), and muscle twitches in 1. There was no specific pattern as to whether directional stimulation or pulse width or both features were used for any specific side effect.

When considering the different diagnoses, 100% of patients with tremor other than PD (all implanted in Vim), 50% of PD patients, and 29% of dystonia patients were using the advanced features in one or both of the leads (Fig. 1B and C).

The advanced features were used on the first implanted lead in 24/50 patients (48%) with bilateral implantation. 15/23 (65%) of these patients also used the advanced features in their 2nd lead (in one the second lead was not used). Vice versa, when the advanced features were not used on the 1st lead ($n = 26/50$), these were not used in the 2nd lead either in 85% of cases (Fig. 1B and C).

Age, disease duration and size of the best intraoperative therapeutic window (1.62 mA and 1.67 respectively) were not different between

Table 1
Descriptive of the study population.

	Total	GPi	Vim	STN
Number of leads	100	18	23 ^a	59 ^b
Number of patients	51	9	12	30
Male (number (%))	25 (49.0%)	3 (33.3%)	9 (75.0%)	13 (43.3%)
Disease duration at surgery in years (average $\pm$ SD)	11.9 $\pm$ 9.8	18.7 $\pm$ 14.1	15.6 $\pm$ 13.0	8.6 $\pm$ 4.1
Age at surgery in years (average $\pm$ SD)	59.1 $\pm$ 12.0	50.7 $\pm$ 17.6	68.4 $\pm$ 7.4	58.3 $\pm$ 8.9
Months to last Follow-up (Median (range))	15 (6–23)	13 (7–20)	16 (7–23)	16 (6–22)
Diagnosis (Number of patients (%))	36 (69.2%)	2 (22.2%)	4 (33.3%)	30 (100%)
PD				
Dystonia	7 (15.4%)	7 (77.8%)	0	0
Tremor	8 (15.4%)	0	8 (66.7%)	0
Advanced features used at last follow-up (Number of patients (%))	28 (54.9%)	4 (44.0%)	11 (91.7%)	13 (43.3%)

Abbreviations: GPi - internal globus pallidus; PD - Parkinson's disease; STN - subthalamic nucleus; Vim - ventral intermediate nucleus of the thalamus.

^a One patient with diagnosis tremor and Vim target received a single lead (left side).

^b One patient with diagnosis Parkinson's disease and STN target received bilateral leads, but one of them (right side) remained off due to persistent postoperative benefit.

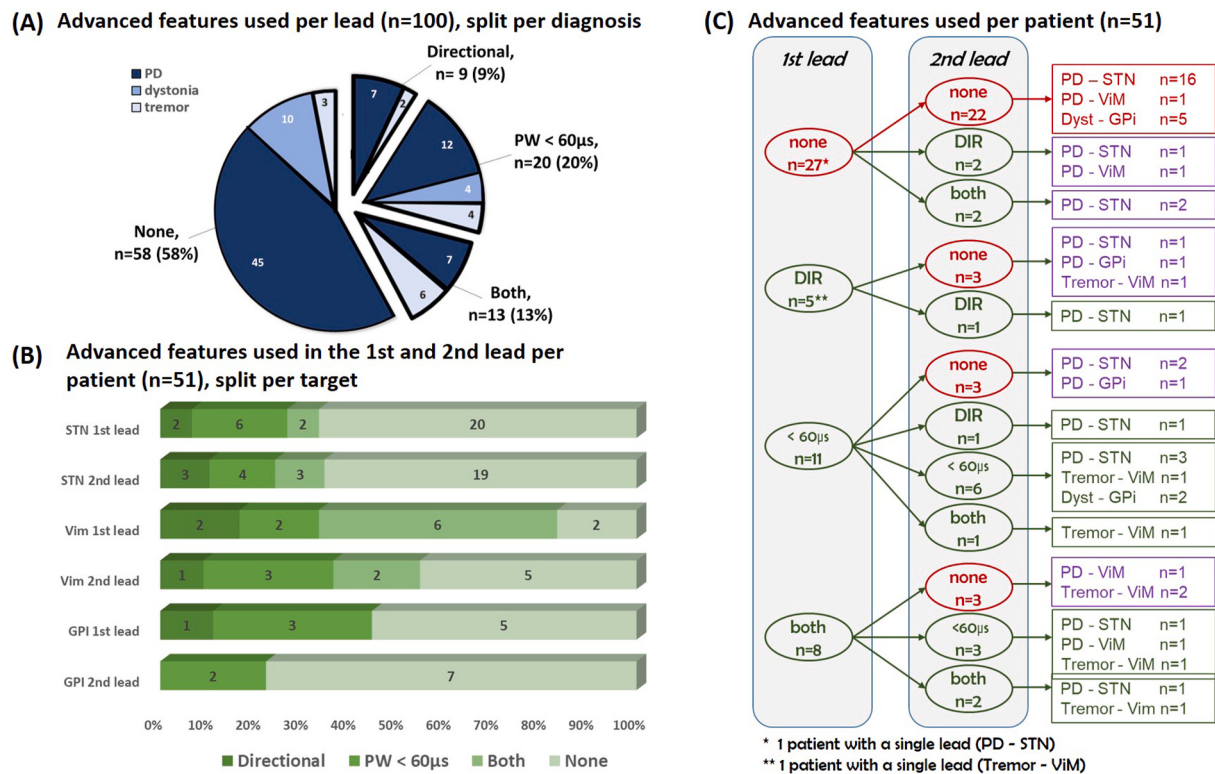


Fig. 1. Use of advanced features (A) The total number of leads categorized for the advanced features used (directional, pulse width less than 60 µs, or both) and split per diagnosis; (B) Use of advanced features per patient, split per 1st implanted and 2nd implanted lead as well as per target; (C) The combination of advanced features used per patient in the implanted 1st and 2nd leads, specified for target and diagnosis. Color code of the boxes: red = no advanced features used; purple = advanced features used in only one lead; green = advanced features used in both leads.

Abbreviations: DIR – directional stimulation; GPi – internal globus pallidus; PW – pulse width; STN – subthalamic nucleus; Vim – ventral intermediate nucleus of the thalamus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

leads that used the advanced features and leads that did not.

Also the use of MER and the number of MER trajectories used was not correlated with the use of advanced features. The average number of MER trajectories was not different between the groups (on average 2.1 for leads using advanced features and 2.0 for leads not using them). When no MER were used at all, 55% of all the leads and also 55% of the leads implanted in the STN were programmed using advanced features.

4. Discussion

Our data show that 55% of the patients selected to receive advanced DBS systems in our center indeed benefitted from the advanced features in one or both leads at last follow-up.

In another naturalistic cohort, 20/59 (34%) of patients with directional DBS systems were programmed with directional settings [8]. We selected patients who could benefit from the advanced stimulation features based on clinical and intraoperative information. This could explain that a higher percentage of our patients indeed used them. Nevertheless, even in this selected population, 45% of the patients obtained a good control of the symptoms, which was considered as satisfying by the patient and the clinician, without using advanced features, suggesting that for them a standard system would have been sufficient.

The programming strategy may also influence the percentage of patients using advanced features: in our center, we only resorted to the advanced features when side effects prevented satisfying results with standard settings. In order to account for possible chronic stimulation adjustments, we only included patients who had long follow-up. In a recent multicenter survey [9], 19 physicians worldwide declared a very variable percentage of PD patients with directional leads actually using directional stimulation: in 10/17 centers this was higher than 50%, with

3 centers reporting that all their patients were using it. Interestingly, 3 centers also reported using these feature right since the beginning of DBS treatment (with no specific indication) and 3 used them in the context of clinical trials. Clinicians may be more prone to keep patients on advanced stimulation features after they participated in clinical trials, even when the clinical effect is comparable. Indeed, in the first published study on chronic directional stimulation [1], all seven patients kept directional settings after the study; similarly in a crossover study comparing ring stimulation with directional stimulation, 8/10 patients maintained directional settings [2]. In a study on patients with Vim DBS [10] the motivation to choose directional settings in 7/8 patients was to avoid side-effects in 6 cases and to improve battery lifespan in 3.

In a previous multicenter survey [5], clinicians estimated that 21% of their patients implanted with standard leads would have benefitted from directional stimulation instead. The proportion of these patients was higher for GPi (48%) or thalamus (40%) targets than for STN (12,8%). This, together with the more challenging visual targeting of the Vim and the relatively higher frequency of side effects in this target (including dysarthria, paresthesia and ataxia [11,12]) reported in the literature and observed in our own population, led us to implant Vim patients preferably with advanced systems. Interestingly, almost all patients with Vim implants benefitted indeed from the advanced features, confirming that the choice of advanced systems is warranted for this specific population.

We could not find any predictive factor for the use of advanced features, including the use of MER. A possible reason for the lack of correlation of MER tracks with the use of advanced features could be that this was mainly driven by the presence of limiting side effects, which could have occurred even when the lead was positioned in the neurophysiologically defined target.

Our study has limitations: since in this retrospective analysis results were evaluated in a clinical setting, standardized scoring of the symptoms, and thus objective comparison of the therapeutic windows with different settings was not available. It has already been demonstrated that directional stimulation and lower pw increase the therapeutic window. However, a larger therapeutic window per se may not be a sufficient reason to choose directional stimulation over standard stimulation in clinical practice if the same amount of benefit is obtained well below the side-effects threshold [6].

We have not pursued an exact correlation between the lead location and the use of the advanced features. Also the study was not powered to show correlations with predictive factors.

However, even after considering the above limitations, based on our experience we can conclude that patients implanted in the Vim may benefit more often from the advanced features than other patients and should preferably be offered DBS systems with advanced features when possible.

The potential advantages of new systems need to be weighed against the longer programming time and increased complexity. Programming strategies are continuously evolving and image-guided or neurophysiology-based approaches may change the way we select stimulation settings in the future. If actual data on battery consumption will confirm an advantage of using the new features, this could also be a criterion to favor this strategy over standard programming, even when they produce equivalent clinical benefit.

Future prospective randomized trials are needed to further explore this topic and propose clinical algorithms to guide clinicians in their choices. In the meantime, in a worldwide scenario where advanced technologies are still more expensive, complex, and not overall available, observations from real-life case series such as this may help clinicians allocate resources in a more informed way.

CRediT authorship contribution statement

FMPZ: Data curation; analysis; Methodology; Visualization; Writing - first draft, final approval. AJ: Data acquisition, Data curation; final approval. NAVdG: Data acquisition, Writing - review & editing, final approval. CFEH: Data acquisition, Writing - review & editing, final approval. RZ: Data acquisition, Writing - review & editing, final approval. MFC: Conceptualization, Data acquisition, Methodology; Visualization; Resources; Writing - original draft; Writing - review & editing, final approval.

Funding

No funding was obtained for this study.

Declaration of competing interest

FMPZ: Reports none.

AJ: Reports none.

NAVdG: Reports none.

CFEH: Reports none.

RZ: Reports none.

MFC: Advisory board and speaking fees from BostonScientific; unrestricted grants, advisory board, speaking fees and consultancies from Medtronic; consultancy from CHDR, grants from AbbVie, in-kind contribution from Global Kinetics Corporation, outside the submitted work. All fees are paid to Institution.

Acknowledgements

The authors would like to thank Ms S. van der Gaag, physician assistant, and Ms G. van Holten-Noorlander and Ms P. de Maa, Parkinson Nurses at the Haga Teaching Hospital, The Hague, for clinical care of the patients.

References

- [1] F. Steigerwald, L. Muller, S. Johannes, C. Matthies, J. Volkmann, Directional deep brain stimulation of the subthalamic nucleus: a pilot study using a novel neurostimulation device, *Mov. Disord.* 31 (8) (2016) 1240–1243.
- [2] T.A. Dembek, P. Reker, V. Visser-Vandewalle, et al., Directional DBS increases side-effect thresholds-A prospective, double-blind trial, *Mov. Disord.* 32 (10) (2017) 1380–1388.
- [3] A.S. Moldovan, C.J. Hartmann, C. Trenado, et al., Less is more - pulse width dependent therapeutic window in deep brain stimulation for essential tremor, *Brain Stimul* 11 (5) (2018) 1132–1139.
- [4] V. Dayal, T. Grover, P. Limousin, et al., The effect of short pulse width settings on the therapeutic window in subthalamic nucleus deep brain stimulation for Parkinson's disease, *J. Parkinsons Dis.* 8 (2) (2018) 273–279.
- [5] M.F. Contarino, T.R. Brinke, A. Mosch, et al., How many patients would benefit from steering technology for deep brain stimulation? *Brain Stimul* 9 (1) (2016) 144–145.
- [6] F. Steigerwald, C. Matthies, J. Volkmann, Directional deep brain stimulation, *Neurotherapeutics* 16 (1) (2019) 100–104.
- [7] V.J. Geraedts, R.A.P. van Ham, J. Marinus, et al., Intraoperative test stimulation of the subthalamic nucleus aids postoperative programming of chronic stimulation settings in Parkinson's disease, *Park. Relat. Disord.* 65 (2019) 62–66.
- [8] P. Reker, J.K. Steffen, Response to letter to the editor regarding: "bipolar directional deep brain stimulation in essential and parkinsonian tremor"-A technology underutilized, *Neuromodulation* 23 (8) (2020) 1229–1230.
- [9] T.R. Ten Brinke, V.J.J. Odekerken, J.M. Dijk, P. van den Munckhof, P. R. Schuurman, R.M.A. de Bie, Directional deep brain stimulation: first experiences in centers across the globe, *Brain Stimul* 11 (4) (2018) 949–950.
- [10] P. Rebelo, A.L. Green, T.Z. Aziz, et al., Thalamic directional deep brain stimulation for tremor: spend less, get more, *Brain Stimul* 11 (3) (2018) 600–606.
- [11] M.F. Contarino, R. van Coller, A. Mosch, N.A. van der Gaag, C.F. Hoffmann, Clinical approach to delayed-onset cerebellar impairment following deep brain stimulation for tremor, *Brain* 140 (5) (2017) e27.
- [12] M. Bot, F. van Rootselaar, M.F. Contarino, et al., Deep brain stimulation for essential tremor: aligning thalamic and posterior subthalamic targets in 1 surgical trajectory, *Oper Neurosurg (Hagerstown)* 15 (2) (2018) 144–152.