Directional Deep Brain Stimulation Electrodes in Parkinson`s Disease: Meta-Analysis and Systematic Review of the Literature

Hvingelby V[1,2], Khalil F[3,4], Massey F[3], Hoyningen A[5,6], Xu S[3], Candelario J[3], Akram H[3], Foltynie T[3], Limousin P[3], Zrinzo L[3], Krüger MT[3,7]

[1] Department of Clinical Medicine, Nuclear Medicine and PET, Aarhus University, Aarhus, Denmark

[2] Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark

[3] UCL Functional Neurosurgery Unit, National Hospital of Neurology and Neurosurgery, London, United Kingdom

[4] Department of Neurosurgery, Addenbrookes Hospital, Cambridge, United Kingdom

[5] University of Geneva, Department of Fundamental Neuroscience, Geneva, Switzerland

[6] Cantonal Hospital St. Gallen, Department of Neurosurgery, St. Gallen, Switzerland

[7] Department of Neurosurgery, University Medical Centre Freiburg, Germany

Abstract

Background: Since their introduction in 2015, directional leads have practically replaced conventional leads for deep brain stimulation (DBS) in Parkinson's disease (PD). Yet the benefits of directional DBS (dDBS) over omnidirectional DBS (oDBS) remain unclear. This meta-analysis and systematic review compares the literature on dDBS and oDBS for PD.

Methods: PRISMA guidelines were followed. Databases searches included Pubmed, Cochrane (CENTRAL), and EmBase, using relevant keywords such as 'directional', 'segmented', 'brain stimulation' and 'neuromodulation'. Screening was based on title and abstract.

Results: Twenty-three papers reporting on 1,273 participants (1,542 leads) were included. The therapeutic window was 0.70mA wider when using dDBS (95%CI 0.13-1.26mA, p=0.02) with a lower therapeutic current (0.41mA, 95%CI 0.27-0.54mA, p=0.01), and a higher side-effect threshold (0.56mA, 95%CI 0.38-0.73mA, p<0.01). However, there was no relevant difference in mean UPDRS III change after dDBS (45.8%, 95%CI: 30.7-60.9%) compared to oDBS (39.0%, 95%CI: 36.9-41.2%, p=0.39) in the medication OFF state. Median follow-up time for dDBS and oDBS studies was 6 months and 3 months, respectively (range 3-12 for both). Use of directionality often improved dyskinesia, dysarthria, dysesthesia, and pyramidal side-effects. Directionality was used in 55% of directional leads at 3-6 months, remaining stable over time (56% at a mean of 14.1 months).

Conclusions: These findings suggest that stimulation parameters favour dDBS. However, these do not appear to have a significant impact on motor scores, and availability of long-term data is limited. Directional DBS is widely accepted, but clinical data justifying their increased complexity and cost is currently sparse.

Key messages

Directional deep brain stimulation (dDBS) leads have practically replaced conventional ones in Parkinson's disease (PD) over the last 10 years, but their overall clinical benefit was unclear. This meta-analysis confirms findings from individual studies that reported wider therapeutic windows and fewer side effect with dDBS. However, it failed to find any significant benefit in overall motor scores. This review reveals a lack of high quality dDBS studies with long term outcome and highlights the need for well-designed clinical research to justify their additional cost and time commitment.

Introduction

Deep Brain Stimulation (DBS) for Parkinson's disease (PD) was introduced in the 1990s. Its ability to allow safe simultaneous bilateral intervention, and to titrate therapy, are significant advantages over stereotactic lesioning procedures. DBS is the most widely used neurosurgical intervention for PD, and has become standard of care for other movement disorders such as Tremor and Dystonia[1, 2], with an emerging role in psychiatric diseases, epilepsy, and pain[3-5].

In 2014, two intraoperative studies, with temporarily implanted directional electrodes, demonstrated that current steering increased side-effect threshold and reduce therapeutic current[6, 7]. One year later, the first directional electrodes became commercially available. Constant voltage (CV) and constant current (CC) had similar clinical outcomes with oDBS leads[8], but current steering required a shift from CV to CC.

A decade on, directional leads paired with CC have largely replaced conventional omnidirectional leads with CV, despite their being more costly and time-consuming to programme[9]. Yet, evidence for clinical superiority of directional leads is unclear. Due to the progressive nature of PD, ongoing DBS adjustments are often necessary. However, increasing stimulation current can be limited by side effects, including pyramidal activation and dysarthria, often a result of current spread into adjacent non-target structures. Therefore, directional current steering (dDBS) is considered superior to conventional omnidirectional DBS (oDBS) since it allows for more precise stimulation. Hypothetically, target structures can be modulated with less current and minimal spread to adjacent locations, decreasing power consumption. This could lead to fewer programming sessions and battery changes, potentially improving patient satisfaction[10].

While dDBS has been commercially available for almost a decade, and has become standard hardware in most centres, no systematic assessment of its clinical outcome and stimulation parameters has yet been performed. This systematic review and meta-analysis analyses the available evidence on the use of dDBS versus oDBS for PD, focusing on clinical outcomes, stimulation parameters, and stimulation-induced side effects.

Methods

The review protocol was registered with PROSPERO (CRD42023438056) and carried out according to the Cochrane Handbook for Systematic Reviews of Interventions, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search of databases was finalised on January 9, 2024, including Pubmed, Cochrane (CENTRAL), and EmBase, with relevant keywords such as 'directional', 'segmented', 'brain stimulation', and 'neuromodulation'. Search results

were screened based on title and abstract by two authors. After inclusion, a full-text analysis was performed for rigorous assessment of inclusion and exclusion criteria (Figure 1).

Inclusion and exclusion criteria

Inclusion criteria were studies with:

1. More than one PD patient with a directional DBS lead was evaluated in directional mode and
2. At least one relevant outcome measure

Exclusion criteria were studies with/on:

1. Non-humans
2. Technical/theoretical aspects
3. Electrodes that were not commercially available
4. Only intraoperative findings
5. No new clinical data (e.g.: reviews, opinion papers, questionnaires)
6. Programming strategies without individual clinical results
7. Studies not written in English

Statistical analysis

For studies reporting group outcome data, the mean and standard deviation (SD) change, from baseline to follow-up, or from baseline to trial timepoint, were recorded or calculated. When individual values were reported, the mean and SD were calculated. If group-wise changes were reported without the SD, inferences were made according to a specific Cochrane Handbook algorithm [11]. Correlation coefficients were inferred from the combined individually reported participants. Where still not feasible, the value was recorded as missing. Within-study mean changes were calculated in percent. For clinical outcomes, mean (SD) change were pooled across all treatment arms as transitivity was assumed. When all included studies used the same outcome measure, the pooled mean (SD) were reported. Explored covariates as potential sources of heterogeneity were time to follow-up, age, disease severity, and duration. For stimulation parameters and side-effect thresholds, transitivity was not assumed, and only direct comparisons were included in the final analysis.

Variables

The main independent variable was stimulation configuration (directional vs. omnidirectional), recorded as a categorical predictor, i.e. the available configurations were assigned a label of either

omnidirectional (oDBS) or directional (dDBS). Omnidirectional stimulation meant either use of a conventional lead or a directional lead in ring mode. If specifically referring to a conventional system, this was clearly stated.

There were three main dependent variables: a) stimulation parameters, b) clinical outcomes, and c) stimulation-induced side effects.

For an outcome measure to be included in the meta-analysis, the outcome had to be reported in at least three studies, totalling at least five participants (variables a-b):

a) Reported stimulation parameters were based on:

- Side effect threshold in the best direction
- Therapeutic current
- Therapeutic window

b) Clinical outcomes were measured based on changes in:

- The Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (UPDRS III), both OFF- and ON-medication states were considered.
- Medication use was measured using levodopa equivalent daily dose (LEDD)

Further dependent variables were reported descriptively:

c) Stimulation-induced side effects related to subthalamic (STN) stimulation included:

- Dyskinesia
- Dysarthria
- Pyramidal side effects
- Dysaesthesia

d) Other aspects

- battery life
- Adverse events included lead complications requiring re-operations due to suboptimal placement with a lack of therapeutic effect or intolerable side effects, hardware-related complications requiring re-operations, or infections and haemorrhages.

e) Utilisation:

- The proportion of STN DBS patients with directional settings

Furthermore, study heterogeneity was explored by meta-regression of participant mean age, disease duration, and time to follow-up.

Results

The search returned a total of 3,147 results. After screening, a total of 23 articles were included in this review (Figure 1). These comprised 1,273 participants with 1,542 tested leads (not all studies reported the number of leads). The most popular target was the STN (n =22, 1,420 leads), followed by the globus pallidus (n=3, 10 leads), and the thalamic ventral intermediate nucleus (n=2, 15 leads). Median follow-up was 3 months (range 1 week – 2 years). Three studies compared conventional leads with directional leads, and the remainder compared omnidirectional with directional steering in directional leads. All included studies are summarized in Table 1.

Stimulation Parameters

Stimulation parameters were more favourable with dDBS than oDBS. Across all studies (n=12, 440 patients), the therapeutic window was 0.70mA wider when using dDBS (95%CI 0.13-1.26mA, p=0.02), although there was a degree of heterogeneity (Figure 2, I^2=94%). The wider therapeutic window in dDBS was driven both by a lower therapeutic current (0.41mA, 95%CI 0.27-0.54mA, p=0.001) and a higher side-effect threshold (0.56mA, 95%CI 0.38-0.73mA, p<0.01), compared to oDBS (Figure 2). The mean follow-up time point of these studies was 4.4 months (range 0-12).

Clinical outcomes

Two studies compared clinical outcomes with dDBS to oDBS through conventional leads[12, 13]. All other studies compared dDBS to oDBS in directional leads. Overall, dDBS achieved similar results compared to oDBS in both lead types. Of note, there was more heterogeneity in the response to dDBS than oDBS. In other words, for a substantial proportion of patients, the best directional setting provided less therapeutic benefit than omnidirectional stimulation.

When comparing the effect of dDBS with oDBS, there was no statistically significant difference in UPDRS Part III change in the medication OFF state [45.8% (95%CI: 30.7-60.9%) and 39.0% (95%CI: 36.9-41.2%), respectively, p=0.39] (Figure 3). The mean length of follow-up for dDBS was 6 months (range 3-12, n=139). Length of follow-up for oDBS in these studies was 3 months (range 3-6, n=229) (Supplementary Table 1).

In the medication ON state, the effect size of stimulation was similar for dDBS and oDBS (UPDRS change 3.4 vs. 5.8, p = 0.30) (Supplementary Figure 1) and did not reach significance. The mean follow-up time was 5.7 months, ranging from 7 days to 12.8 months. While the meta-analysis revealed heterogeneity between studies (Supplementary Figure 1), this was explained by differences in the examined covariates such as age and disease duration.

Only three studies[14-16] with UPDRS III outcomes also provided preoperative data on L-Dopa responsiveness (Supplementary Table 1). In these three studies, the pre-operative L-Dopa response was 61.9% (n=26 patients), and their improvement in UPDRS with dDBS in the OFF-medication state was 52.3% (SD 9.5%) at 6 months follow-up (range 2-12 months).

Reduction in LEDD with dDBS compared to oDBS was 50.6% (505mg, 95%CI 339-671mg, n=140) vs. 57.6% (586mg, 95%CI 416-756mg, n=72), after a median follow-up of 6 months (range 3-12) for dDBS and 10.5 months (range 3-12) for oDBS (Figure 4). This difference was not statistically significant (p=0.50). There were only 3 studies (n=18) that reported LEDD reduction and UPDRS-III OFF medication improvement with dDBS[14, 15, 17]. In these studies, LEDD reduction was 52.9%, and UPDRS III improvement was 55.4%.

Side-effects

Nine studies stated that directionality was used to improve side effects of STN DBS, but most did not provide quantitative data (Table 2). Of these, four studies [13, 15, 18, 19](63 patients, 123 leads) provided more detailed information on the type and management of side effects (Table 2). The mean follow-up in these studies was 6.7 months (range 3-12 months). Dyskinesia was the most reported side effect (4/4 studies), followed by dysarthria, pyramidal (2/4), and dysesthesia/paraesthesia (1/4). All four studies described improvements in stimulation-induced side effects with directional steering in most patients (Table 2). One study systematically explored how acute activation of different directional contacts correlated with different side-effects[20].

Other aspects

Five studies[12, 21-24] (2.937 patients, 837 leads) reported on surgical and device complication rates (Table 2). The most reported adverse event was lead revision due to suboptimal location[21-24].

Wu et al. examined data on 3,869 DBS patients implanted with directional (n=613) or conventional (n=3,256) leads from 283 US centres over 3 years[23]. Of these, lower reoperation rates were observed in patients with PD undergoing implantation of directional (n=386) vs. conventional (n=2127) leads (HR=0.47, 95%CI 0.30-0.74, p=0.001). Interestingly, there was no significant difference in infection or hardware malfunction rates between the two subgroups. However, the directional lead subgroup experienced a significant 56% risk reduction for reoperation “for unspecified reasons”, almost certainly relocating a suboptimal lead.

Four studies[15, 21, 24, 25] provided battery life data (301 patients, 690 leads) (Table 2). Of those, two [15, 24] reported on battery life differences between dDBS and oDBS at different time points. However, the longest follow-up period was 18 months, and no statistically significant difference in battery

consumption was reported. Karl et al[25] opined that improved battery life was a reason to use directional stimulation, but individualised data was not provided.

Utilisation

Several studies report on the utilisation of directional settings with implanted dLeads (Table 2). Across seven studies, 55% of leads (n=406/738) were on a directional setting between 3-6 months after implantation (mean 5.4 months)[13, 15, 18, 21, 24-26]. Six studies provide 12-18 month follow-up data (mean 14.1 months) with 56% of dLeads on a directional setting (n=234/426)[18, 22, 24, 25, 27, 28]. Only one study[25] reported > two-year follow-up data. Although the use of directional stimulation increased from 27% at two years to 60% at three years, missing data increased drastically over the length of follow-up (n=91 on inclusion, 26 at 2 years, 7 at three years), making it difficult to reach any meaningful conclusion.

Risk of Bias

Most of the non-controlled studies were retrospective, interrupted time series. For this reason, most clinical outcomes, including therapeutic effects and side effects, were evaluated as "at serious or critical risk of bias". Evaluation of RCTs indicated a medium risk of bias. In most studies reporting current settings and thresholds, the risk of bias was low.

Discussion

This meta-analysis and systematic literature review summarises the available evidence on the use of directional DBS compared to omnidirectional stimulation. Overall, there is good evidence that dDBS provides benefits in terms of stimulation parameters over oDBS at a group level. However, there is no objective evidence of greater therapeutic benefit on motor scores with dDBS. Although dDBS is reported to improve stimulation-induced side effects, quantitative measures are often lacking. Moreover, data on sustained benefit is lacking since the length of follow-up in these studies is relatively short.

Stimulation Parameters:

The benefits of dDBS include a wider therapeutic window (by 0.70 mA), with lower therapeutic current (by 0.41mA), and higher side effect threshold (by 0.56mA) compared to omnidirectional settings. Of note, all included studies had relatively short follow-up times, ranging from 7 days to 12 months. Given that PD is a progressive disease and a further increase in stimulation may be required over time, these

benefits may theoretically allow for therapy optimization beyond that of conventional leads at long term follow up. However, whether this potential will translate into a clinically meaningful impact is yet to be demonstrated.

Clinical outcome

Overall, there was no significant difference in UPDRS III improvement between dDBS and oDBS groups. Only two studies compared the outcome following implantation of directional electrodes with a historical cohort from the same centre when using conventional electrodes[12, 13] and found no significant difference in overall UPDRS III improvement between groups.

This review revealed an improvement of 39.0% (95%CI: 36.9-41.2%) (UPDRS III baseline to OFF medication / ON stimulation) for directional electrodes on a ring mode at a median follow-up time of 3 months. This increased to 45.8% (95%CI: 30.7-60.9%) when directionality was applied (at a mean of 6 months), but this improvement was not statistically significant (p=0.39). However, this should also be compared with previously published meta-analyses after implantation of conventional electrodes. None of these comparisons were performed as a randomised controlled trial, such that differences in outcome could be due to patient selection. Since the preoperative L-Dopa response is the best predictor of outcome after STN DBS, this should also be considered.

A meta-analysis of open-label studies using conventional cylindrical electrodes reported a preoperative L-Dopa response of 60.3 % with mean improvements of 52% with stimulation OFF-medication at a median of 12 months (n=25 studies, 682 patients)[29]. Information on L-Dopa response was scarce in the studies of this dDBS review. In the three studies[14-16] that provided both L-Dopa response and OFF-medication UPDRS III improvement, the L-Dopa response was similar (61.9%), and the UPDRS III improvement was also similar, with 52.3%. However, the number of patients was much lower in the dDBS group (26 vs. 682), and the mean follow-up time point was shorter; 6 months in the dDBS group, compared to 12 months in the conventional group.

More information was available on the change in LEDD. Following dDBS this was 50.6 % (SD 7.7%, n=140) at 6 months, compared with 55.9% at 12 months in the historical meta-analysis with conventional leads. Interestingly, the LEDD reduction in directional electrodes on oDBS settings was similar with 57.6% at 10.5 months.

There are numerous limitations when trying to make comparisons between older studies with conventional leads and more recent ones with dDBS. Older studies with cylindrical contacts used the old version of the UPDRS. Newer dDBS studies were generally of poorer quality with smaller patient

numbers and shorter follow-up timepoints. Moreover, most oDBS studies utilised CV, whereas dDBS employed CC, introducing another potential variable affecting clinical outcome. Nevertheless, even when taking into consideration all these criteria, there is little reassurance that directional leads provide patients with additional meaningful benefit over conventional leads.

Side-effects

The most obvious benefit of dDBS was reduction in side effects. However, this was poorly reported in most studies. Only 4 studies provided objective data demonstrating that in individual patients, directional stimulation helped reduce dyskinesia as well as dysarthria and pyramidal side effects. One study reported significant reduction of all three side effects, without loss of therapeutic benefit, that was maintained 6 months later. However, as with another study[15], this was mainly achieved via a combination of directionality and short pulse width[19]. The lack of systematic reporting and long term follow up makes it difficult to determine what proportion of patients implanted with dDBS leads would experience meaningful benefit as a result of directionality.

Lead location within the STN is fundamental to improving efficacy and reducing side effects. It remains unclear whether directionality can compensate for suboptimal lead placement and, if so, to what degree. Long-term benefits with dDBS may only be achievable in "perfectly" placed leads, and this sweet spot may differ between directional and conventional leads.

Other aspects

A lower therapeutic current means less power is consumed by the implantable pulse generator (IPG), thus allowing for longer battery life. However, studies investigating battery life did not find a major clinical benefit since there was no relevant data beyond two years. Moreover, the popularity of rechargeable IPGs reduces the importance of this factor.

Results on complications, such as infection rates or hardware malfunction, were similar to those of conventional leads. However, Wu et al.[23] found lower reoperation rates in patients with PD undergoing implantation of directional (n=386) vs. conventional (n=2,127) leads (HR = 0.47, 95%CI [0.30, 0.74], p = 0.001). The data from this large study suggests that suboptimal electrode location may play a significant role in these reoperations. The positive implication is that directional leads may allow for a greater degree of location error, reducing the rates of lead relocation. A potential negative repercussion could be higher tolerance for suboptimal lead placement with dLeads, contributing to underperformance of directional leads. For example, 6/28 PD patients required relocation of 10 leads due to a lack of therapeutic benefit that could not be overcome by directional steering[30]. Clearly, directional leads can only address a moderate degree of suboptimal lead location.

Unfortunately, data on the time required to program dDBS and oDBS leads were not routinely reported. In one study[15] the number of contact adjustments, calls, and visits to clinic were reported. While these parameters were comparable for oDBS and dDBS, this rather small study did not contain information on programming time. Future, real-world evidence is warranted, particularly in light of a recent survey conducted among European neurosurgeons, neurologists and DBS nurses that reported an increase in programming time to be the main drawback of dDBS[31].

Utilisation of directional current steering:

It may be surprising that utilisation of directional electrodes was relatively stable between 3 and 18 months after surgery (around 55%). However, this is a relatively short period in the life of a DBS patient. Moreover, it is difficult to draw conclusions from this data since the use of directional current steering is likely to depend on several factors, including, but not limited to, lead location and programming preferences.

Limitations:

The major limitation of the included studies is the short follow-up time and small number of patients. There are no well-designed randomised controlled trials (RCTs) that compare the use of directional with conventional leads, making it difficult to reach strong conclusions. Most included studies comprised small numbers of patients, and the largest randomized controlled trial, with 234 patients, only provided UPDRS III OFF medication / ON stimulation data at 3 months from baseline, when patients were all on oDBS settings (38% improvement). At 6 months, with patients on directional settings, only ON medication / ON stimulation UPDRS III data is provided[21].

Publication bias makes it more likely that authors will publish positive results and withhold negative ones. However, this should hold true for open-label studies with directional and conventional leads. Prospective, registered RCTs reduce the risk of publication bias. Multiple RCTs reporting on relevant clinical outcomes exist for STN DBS with conventional leads. However, after ten years, not a single well-designed RCT has reported on relevant clinical outcomes for STN DBS with directional leads.

Directional electrodes are more expensive than conventional leads, and more complex settings require more time to program. Ten years after their introduction it appears that the full potential of directionality is yet to be realized. There is a rising body of literature on the use of image guidance or algorithms to predict the best stimulation parameters with dDBS[32-36]. Other DBS technologies, such as sensing, have been introduced and others, such as closed loop stimulation, are in development. It may be that a combination of all these advances is required to provide a clear benefit over conventional DBS. On the

other hand, well-designed trials are essential to determine whether the clinical benefits of such technological improvements justify the soaring cost of an already expensive therapy.

Conclusion

This systematic review and meta-analysis suggests that dDBS is non-inferior to oDBS in PD. Directional settings provided a wider therapeutic window compared to omnidirectional settings and were helpful in reducing side effects, especially when used in combination with other advanced programming strategies. However, from the available short-term follow-up data, the magnitude of clinical improvement did not differ significantly between dDBS and oDBS or when compared to conventional leads. This review also revealed the paucity of well-designed long-term studies that report on the clinical outcome of DBS with directional leads in PD. Directional DBS has been widely accepted, but clinical data justifying their increased complexity, as well as financial and time cost, is sparse.

Acknowledgments

The Functional Neurosurgery Unit is supported by the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre.

REFERENCES

1. Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med. 2013;368(7):610-22. doi: 10.1056/NEJMoa1205158.
2. Moro E, LeReun C, Krauss JK, Albanese A, Lin JP, Walleser Autiero S, et al. Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis. Eur J Neurol. 2017;24(4):552-60. doi: 10.1111/ene.13255.
3. Morace R, G DIG, Quarato P, D'Aniello A, Amascia A, Grammaldo L, et al. Deep brain stimulation for intractabile epilepsy. J Neurosurg Sci. 2016;60(2):189-98.
4. Weaver F, Follett K, Hur K, Ippolito D, Stern M. Deep brain stimulation in Parkinson disease: a metaanalysis of patient outcomes. J Neurosurg. 2005;103(6):956-67. doi: 10.3171/jns.2005.103.6.0956.
5. Frizon LA, Yamamoto EA, Nagel SJ, Simonson MT, Hogue O, Machado AG. Deep Brain Stimulation for Pain in the Modern Era: A Systematic Review. Neurosurgery. 2020;86(2):191-202. doi: 10.1093/neuros/nyy552.
6. Pollo C, Kaelin-Lang A, Oertel MF, Stieglitz L, Taub E, Fuhr P, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study.
7. Contarino MF, Bour LJ, Verhagen R, Lourens MA, de Bie RM, van den Munckhof P, et al. Directional steering: A novel approach to deep brain stimulation.
8. Timmermann L, Jain R, Chen L, Maarouf M, Barbe MT, Allert N, et al. Multiple-source current steering in subthalamic nucleus deep brain stimulation for Parkinson's disease (the VANTAGE study):

a non-randomised, prospective, multicentre, open-label study. Lancet Neurol. 2015;14(7):693-701. doi: 10.1016/s1474-4422(15)00087-3.
9. Krauss P, Krüger M. Results from the EANS Survey on the Use of Directional Leads in DBS.
10. Ten Brinke T, Odekerken V, Dijk J, Munckhof PVD, Schuurman P, De Bie R. Directional deep brain stimulation: First experiences in centers across the globe.
11. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. Second edition. ed. Cochrane book series. Hoboken, New Jersey: The Cochrane Collaboration; 2019.
12. Pintér D, Járdaházi E, Balás I, Harmat M, Makó T, Juhász A, et al. Antiparkinsonian Drug Reduction After Directional Versus Omnidirectional Bilateral Subthalamic Deep Brain Stimulation.
13. Shao MM, Liss A, Park YL, DiMarzio M, Prusik J, Hobson E, et al. Early Experience With New Generation Deep Brain Stimulation Leads in Parkinson's Disease and Essential Tremor Patients.
14. Dembek TA, Reker P, Visser-Vandewalle V, Wirths J, Treuer H, Klehr M, et al. Directional DBS increases side-effect thresholds-A prospective, double-blind trial. Mov Disord. 2017;32(10):1380-8. doi: 10.1002/mds.27093.
15. Maciel R, Soh D, Munhoz RP, Poon YY, Kalia SK, Hodaie M, et al. Programming Directional Deep Brain Stimulation in Parkinson's Disease: A Randomized Prospective Trial Comparing Early versus Delayed Stimulation Steering. Stereotact Funct Neurosurg. 2021;99(6):484-90. doi: 10.1159/000517054.
16. Sabourin S, Khazen O, DiMarzio M, Staudt MD, Williams L, Gillogly M, et al. Effect of Directional Deep Brain Stimulation on Sensory Thresholds in Parkinson's Disease.
17. Asahi T, Ikeda K, Yamamoto J, Tsubono H, Sato S. Pilot Study for Considering Subthalamic Nucleus Anatomy during Stimulation Using Directional Leads.
18. Bouthour W, Béreau M, Kibleur A, Zacharia A, Tomkova Chaoui E, Fleury V, et al. Dyskinesia-inducing lead contacts optimize outcome of subthalamic stimulation in Parkinson's disease.
19. Dayal V, De Roquemaurel A, Grover T, Ferreira F, Salazar M, Milabo C, et al. Novel Programming Features Help Alleviate Subthalamic Nucleus Stimulation-Induced Side Effects.
20. Asahi T, Ikeda K, Yamamoto J, Tsubono H, Muro Y, Sato S. Bilateral Pallidal Stimulation with Directional Leads for Primary Focal Lingual Dystonia.
21. Schnitzler A, Mir P, Brodsky M, Verhagen L, Groppa S, Alvarez R, et al. Directional deep brain stimulation in subthalamic nucleus for Parkinson's disease: Results of a multicenter, prospective, blinded, crossover study.
22. Mishra A, Ramdhani RA. Directional Deep Brain Stimulation in the Treatment of Parkinson’s Disease.
23. Wu C, Potter-Nerger M, Agarwal R, Rosenberg S, Connolly A, Cheeran B, et al. Directional DBS is Associated with Fewer Surgical Revisions than Traditional DBS: A Nationwide Real-World Study.
24. Koivu M, Scheperjans F, Eerola-Rautio J, Resendiz-Nieves J, Marjamaa J, Kivisaari R, et al. The outcome of directional subthalamic deep brain stimulation in advanced Parkinson's disease.
25. Karl JA, Joyce J, Ouyang B, Verhagen Metman L. Long-Term Clinical Experience with Directional Deep Brain Stimulation Programming: A Retrospective Review.
26. Steigerwald F, Müller L, Johannes S, Matthies C, Volkmann J. Directional deep brain stimulation of the subthalamic nucleus: A pilot study using a novel neurostimulation device.
27. Zitman F, Janssen A, Vander Gaag N, Hoffmann C, Zutt R, Contarino M. The actual use of directional steering and shorter pulse width in selected patients undergoing deep brain stimulation.
28. Rammo RA, Ozinga SJ, White A, Nagel SJ, Machado AG, Pallavaram S, et al. Directional Stimulation in Parkinson's Disease and Essential Tremor: The Cleveland Clinic Experience.
29. Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord. 2006;21 Suppl 14:S290-304. doi: 10.1002/mds.20962.
30. Mishra A, Unadkat P, McBriar JD, Schulder M, Ramdhani RA. An Institutional Experience of Directional Deep Brain Stimulation and a Review of the Literature.

31. Krauss P, Duarte-Batista P, Hart MG, Avecillas-Chasin JM, Bercu MM, Hvingelby V, et al. Directional electrodes in deep brain stimulation: Results of a survey by the European Association of Neurosurgical Societies (EANS). Brain and Spine. 2024;4:102756. doi: https://doi.org/10.1016/j.bas.2024.102756.
32. Lange F, Steigerwald F, Malzacher T, Brandt GA, Odorfer TM, Roothans J, et al. Reduced Programming Time and Strong Symptom Control Even in Chronic Course Through Imaging-Based DBS Programming. Front Neurol. 2021;12:785529. doi: 10.3389/fneur.2021.785529.
33. Jaradat A, Nowacki A, Montalbetti M, Debove I, Petermann K, Schlaeppi JA, et al. Probabilistic Subthalamic Nucleus Stimulation Sweet Spot Integration Into a Commercial Deep Brain Stimulation Programming Software Can Predict Effective Stimulation Parameters. Neuromodulation. 2023;26(2):348-55. doi: 10.1016/j.neurom.2021.10.026.
34. Wenzel GR, Roediger J, Brücke C, Marcelino ALA, Gülke E, Pötter-Nerger M, et al. CLOVER-DBS: Algorithm-Guided Deep Brain Stimulation-Programming Based on External Sensor Feedback Evaluated in a Prospective, Randomized, Crossover, Double-Blind, Two-Center Study. J Parkinsons Dis. 2021;11(4):1887-99. doi: 10.3233/jpd-202480.
35. Roediger J, Dembek TA, Wenzel G, Butenko K, Kühn AA, Horn A. StimFit-A Data-Driven Algorithm for Automated Deep Brain Stimulation Programming. Mov Disord. 2022;37(3):574-84. doi: 10.1002/mds.28878.
36. Waldthaler J, Bopp M, Kühn N, Bacara B, Keuler M, Gjorgjevski M, et al. Imaging-based programming of subthalamic nucleus deep brain stimulation in Parkinson's disease. Brain Stimul. 2021;14(5):1109-17. doi: 10.1016/j.brs.2021.07.064.