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Publications featuring the Vercise™ DBS Systems

Deep Brain Stimulation (DBS) Clinical Compendium

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The Rationale Driving the Evolution of Deep Brain Stimulation to Constant-Current Devices

Bronstein, J. M., Tagliati, M., McIntyre, C., Chen, R., Cheung, T., Hargreaves, E. L., Israel, Z., Moffitt, M., Montgomery, E. B., Stypulkowski, P., Shils, J., Denison, T., Vitek, J., Volkmann, J., Wertheimer, J., and Okun, M. S.

Published: Neuromodulation: Technology at the Neural Interface. 2015;18:85-89.

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Figure created by Boston Scientific based on published data. One or more authors report funding from Boston Scientific as a financial disclosure.

BACKGROUND

A panel of experts conducted a literature review regarding the development and use of newly available constant-current Deep Brain Stimulation (DBS) systems (vs. pre-existing constant-voltage systems) capable of targeting regions of the brain with enhanced specificity to help improve management of symptoms associated with movement and/or psychiatric-based neurological disorders.

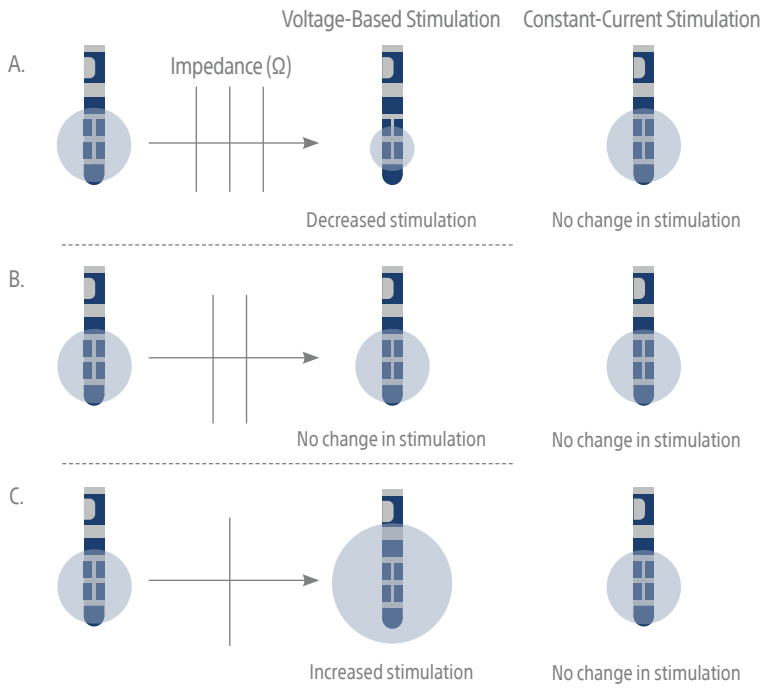
INTRODUCTION

- The success of DBS outcomes may depend on the precise density and location of a stimulation field targeting a specific area of the brain
- Parameters governing a stimulation field can be finely tuned according to the needs of each patient, thereby enabling greater optimization of clinical benefits while minimizing side effects
- Until recently, the only available and approved DBS devices for use in brain disorders were constant-voltage stimulators
- Modern DBS devices offer the ability to program the patient using a constant-current paradigm

IMPEDANCE AND DBS

Impedance changes can interfere with the delivery of stimulation to the brain using DBS by altering the stimulation energy necessary to affect a given volume of tissue:

- **Voltage-based stimulation:** the impedance around an electrode directly affects the amount of current capable of being delivered to tissues
- **Constant-current stimulation:** constant-current devices can modulate output voltage to provide stimulation irrespective of impedance fluctuation



Impact of Impedance Changes on Neuronal Activation. The theoretical effect (per Ohm's law) of changes over time in impedance of the stimulating contact with a voltage-controlled system is presented. If impedance increases and the voltage remains the same, then less current will be delivered, which in turn reduces the expected stimulation volume (A). If impedance does not change and the voltage remains the same, then there is no expected change in stimulation (B). If impedance decreases and the voltage remains the same, then more current will be delivered, which in turn increases the expected stimulation volume (C).

CLINICAL RELEVANCE OF IMPEDANCE

Available Data Suggests

- Impedance changes immediately after DBS implant
- Amount of stimulation will vary during initial activation and programming (even keeping the same voltage setting)
- Impedance can change several months post-implant, but it remains unclear whether these changes are clinically relevant

CONCLUSIONS

- Impedance can be highly variable across different patients and can change over time within each patient
- The science underlying the application of DBS supports the clinical use of constant-current systems
- Going forward, most newly manufactured DBS devices will likely be engineered utilizing constant-current approaches for use in managing symptoms associated with movement and psychiatric disorders

Brain Impedance Variation of Directional Leads Implanted in Subthalamic Nuclei of Parkinsonian Patients

Eleopra, R., Rinaldo, S., Devigili, G., Lettieri, C., Mondani, M., D'Auria, S., Piacentino, M., and Pilleri, M.

Published: Clinical Neurophysiology. 2019;130:1562-1569.

Study Type: Observational, retrospective

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Figures created by Boston Scientific based on published data. One or more authors report funding from Boston Scientific as a financial disclosure.

BACKGROUND

In this observational retrospective study, the authors aimed to quantify impedance variations over time in Parkinson's disease (PD) patients implanted with directional electrodes.

METHODS

- 11 consecutive PD patients (4 female) with bilateral implantation of directional Deep Brain Stimulation (DBS) leads into the subthalamic nucleus (STN) were retrospectively evaluated
- Bilateral Vercise Cartesia™ directional leads and Vercise™ PC Implantable Pulse Generator (IPG) were implanted simultaneously in all patients
- Impedance values were collected at the following times:
  - Before DBS activation, in the operating room (OR), and after 5 and 40 days post-surgery
  - After DBS activation, and at 1, 6, and 12 months
- Impedances were tested using a Boston Scientific clinician programmer
- Impedances were collected for directional contacts and for ring contacts at each follow-up visit
- Contacts were labeled as 'active' if they were selected in the stimulation configuration and did not change during the period of the study; otherwise, they were labeled as 'inactive'

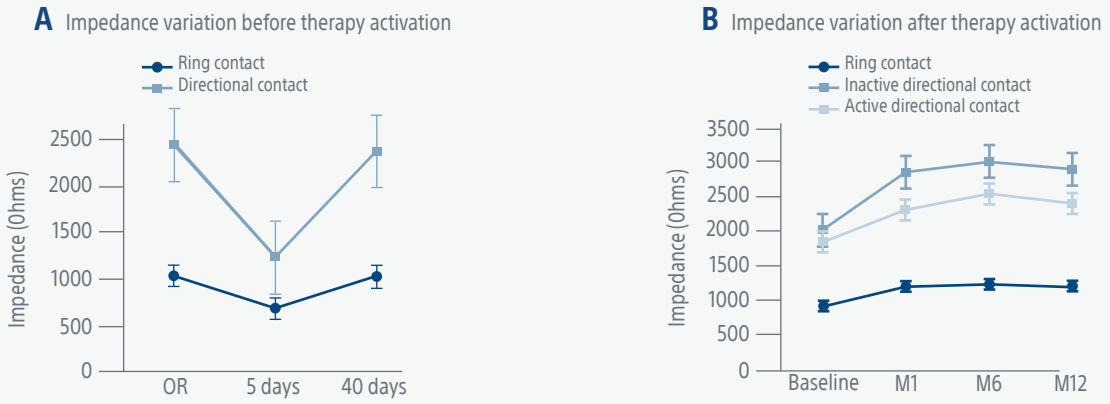
RESULTS

Pre-Activation Phase

- The mean impedance values for all contacts (directional and ring) significantly decreased from the OR (2540 ± 2519 Ω and 1056 ± 757 Ω for directional and ring, respectively), with a subsequent increase at day 40 (2386 ± 800 Ω and 1049 ± 271 Ω) (FIG. A)

Post-Activation Phase

- The mean impedance at baseline, before the system was activated, was 942 ± 289 Ω for the ring (inactive) contacts, 2036 ± 881 Ω for the directional inactive contacts, and 1870 ± 575 Ω for the directional active contacts, with a significant difference between the ring and directional contacts ($p < 0.0002$) (FIG. B)
- Directional contacts (active or inactive) have a significantly higher impedance than ring contacts (inactive)
- Independent of contact activation and contact type (ring or directional), the mean impedance values showed a significant increase during the first month, followed by a subsequent lasting stabilization
- Directional active contacts had lower impedance values than directional inactive contacts



Impedance evolution. A. Impedance evolution of the ring and directional contacts during the early postoperative phase, in the operating room, 5 and 40 days after surgery; all measurements were performed before the stimulation was activated. B. Chronic impedance evolution of the ring contacts (always inactive) and directional contact (inactive or active) at 1, 6, and 12 months after DBS therapy initiation.

CONCLUSIONS

- A directional electrode combined with an IPG with independent current sources for each electrode is the ideal combination to compensate for impedance fluctuations and allow reliable current steering
- Active therapeutic directional contacts reduced the electrode impedance over time compared with inactive directional contacts

Multiple Independent Current Control (MICC)

Multiple Source Current Steering – A Novel Deep Brain Stimulation Concept for Customized Programming in a Parkinson's Disease Patient

Barbe, M.T., Maarouf, M., Alesch, F., and Timmermann, L.

Published: Parkinsonism and Related Disorders. 2014;20:471-473.

BACKGROUND

The authors described their experience with a novel Deep Brain Stimulation (DBS) system capable of multiple source current steering.
They evaluated how this novel programming capability contributed to more customized DBS programming in a Parkinson's disease (PD) patient treated with bilateral subthalamic nucleus (STN) DBS.

CASE DESCRIPTION

- Evaluation of a 60-year-old male patient diagnosed with PD 13 years prior
- Patient suffered from severe Parkinsonism, tremor impairments that were more dominant on the left side, and a history of depressive symptoms
- Dopaminergic drugs induced severe sleep apnea and daytime sleepiness
- OFF-time freezing episodes and severe dyskinesia limited daily activities and Quality of Life
- Patient reported normal mobility for only 4-6 hours per day
- Unified Parkinson's Disease Rating Scale (UPDRS) III score was 45 points (meds-off) one month before DBS surgery
- UPDRS III score was 10 points on medication
- Medication reached a daily levodopa dosage of 800 mg, in addition to 2.1 mg of pramipexole
- Medications improved UPDRS III scores but also resulted in severe dyskinesia
- The current medical treatment was not found to be effective in controlling the patient's symptoms, resulting in social life exclusion due to severe impairment

METHODS

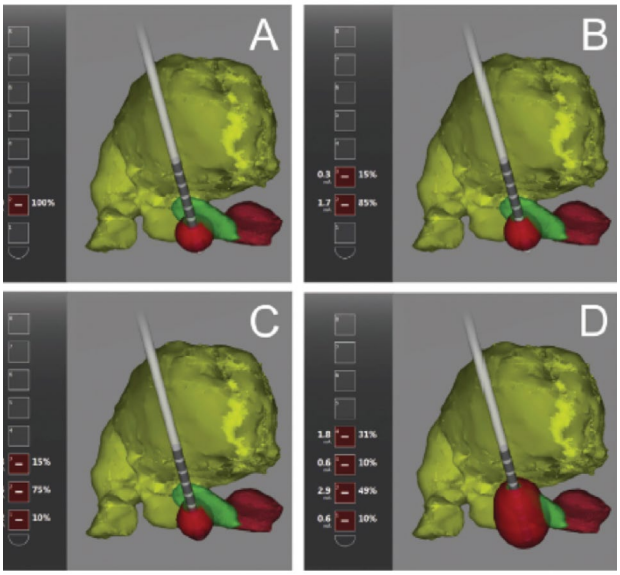
- Bilateral deep brain stimulation of the subthalamic nucleus was performed with a DBS system capable of current steering (8-contact linear leads and a Vercise™ Implantable Pulse Generator)
- Patient exhibited a good response to intraoperative test stimulation
- Microelectrode recordings detected specific STN activity, and electrode localization was confirmed by intra- and postoperative x-ray imaging
- A marked stun effect was observed in the days following implantation
- A monopolar review one week after implantation identified contact #2 on both electrodes to be optimal for suppressing motor signs
- Left hemisphere was programmed with a simple monopolar setting, while the right electrode controlling the more affected left hemibody needed more fine tuning

PROGRAMMING/OUTCOMES

- Monopolar stimulation of the right STN through contact #2 with a pulse width of 60 µs, frequency of 130 Hz, and amplitude of 2 mA, led to motor improvement
- Further increasing the amplitude on contact #2 resulted in worsening of dyskinesia and was insufficient to completely control the patient's tremor
- Patient also continued to experience some apathy and problems with mood and drive
- Stimulation field was adjusted to a "teardrop shape" by shifting the stimulation toward a more proximal contact (contact #3) and slowly increasing the amplitude
- These changes in the stimulation field resulted in improved motor symptoms without driving dyskinesia
- Apathy was reduced through monopolar stimulation of contact #1 with very low amplitude
- Activation of contact #4 further improved tremor, possibly via affection of the zona incerta
- Contact #4 also induced dyskinesia, possibly through stimulation of pallidofugal fiber tracts
- Simultaneous and independent stimulation through the 4 contacts was delivered in order to combine the optimal settings
- Overall current amplitude on the right STN lead was 5.9 mA (pulse width of 60 µs and frequency of 130 Hz remained unchanged)
- Electric field was reshaped along the 4 contacts and current was fractionalized
- Reduction in Levodopa was considerable; the dose was decreased by 70% at 3 months after surgery and by 100% after 2 years
- UPDRS motor score improved from 45 points without therapy to 15 points with DBS
- Patient reported excellent results from current steering, with clear speech, good gait, excellent postural reflex, no rest tremor, and only slight action tremor over two years after programming

CONCLUSIONS*

- This article is the first report of the use of Multiple Independent Current Control (MICC) in humans
- Pathological activity in PD patients is clustered along the STN and zona incerta; thus, customized stimulation on different contacts is reasonable
- Current steering reduced all motor symptoms while minimizing side effects
- The current steering stimulation strategy was successful in improving motor scores and providing distinct therapeutic benefits for
  dyskinesia, tremor, and apathy without causing unwanted side effects
- Previously, stimulating multiple contacts may have increased current use — consequently shortening battery life
- With the rechargeable system used in this case study, battery depletion and reduced battery life were not clinically relevant restrictions
- Future controlled, randomized, and prospective studies are required to prove superiority



Right-sided electrode location is shown in anatomical relation to the thalamus (yellow), STN (green), and red nucleus (red).

CURRENT STEERING WORKFLOW

Reconstruction of the 8-contact lead placement in a 3-dimensional atlas based on preoperative magnetic resonance imaging and postoperative computed tomography

A) Baseline – Initial Set-up

100% stimulation on contact #2 at 2.0 mA: Initial set-up led to motor improvement but resulted in worsened dyskinesia and was insufficient to completely control the patient's tremor. The patient also continued to experience some apathy and problems with mood and drive.

B) "Teardrop"

84% stimulation on contact #2, 16% on contact #3 at 2.0 mA: Improvement in motor symptoms without driving dyskinesia.

C) Stimulation on 3 contacts with Current Steering

10% on contact #1, 75% on contact #2,15% on contact #3, at 2.0 mA: Improvement of apathy in contact #1 due to the stimulation of the limbic portion of the STN.

D) Final Settings

Stimulation on all four contacts: Apathy improvement in contact #1, good overall motor outcome in contact #2, no dyskinesia or side effects in contact #3. Further right-sided electrode location is shown in anatomical relation to the improvement in tremor and dyskinesia for contact #4.

FINAL STIMULATION SETTING

Contact Number (from ventral to dorsal)	Percentage of Current Stimulation	Possible Mechanism of Action
1	10% (0.6 mA)	Authors assume that the improvement in apathy was due to stimulation of the limbic portion of the STN.
2	50% (3.0 mA)	Monopolar review identified this contact as the best single therapeutic contact, and a major part of the current is delivered through this contact for good overall motor outcome.
3	10% (0.6 mA)	Authors applied stimulation through this contact to reshape the field and maintain the clinical effect of contact #2 without driving dyskinesia side effects.
4	30% (1.7 mA)	Authors assume that the further improvement in tremor and dyskinesia was caused by stimulation of the zona incerta (tremor) and pallidofugal fiber tracts (dyskinesia) crossing the white matter located dorsal to the STN.

*Conclusions based on authors' findings in the publication

Multiple-Source Current Steering in Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease (the VANTAGE study): A Non-Randomized, Prospective, Multicenter, Open-Label Study

Timmermann, L., Jain, R., Chen, L., Maarouf, M., Barbe, M.T., Allert, N., Brücke, T., Kaiser, I., Beirer, S., Sejio, F., Suarez, E., Lozano, B., Haegelen, C., Vérin, M., Porta, M., Servello, D., Gill, S., Whone, A., Van Dyck, N., and Alesch, F.

Published: Lancet Neurology. 2015;14:693–701.

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. All figures created by Boston Scientific based on published data. One or more authors report funding from Boston Scientific as a financial disclosure. Boston Scientific was the primary sponsor of this study.

BACKGROUND

The authors published the results of the VANTAGE study, evaluating patient outcomes including the effectiveness and safety of bilateral stimulation of the subthalamic nucleus (STN) using the implantable Vercise™ Deep Brain Stimulation (DBS) System for the treatment of levodopa-responsive, severe-to-moderate idiopathic Parkinson's disease (PD).

STUDY DESIGN

Six DBS Centers:

- University Hospital Cologne, Cologne & Rehabilitation Center, Godeshoehe, Germany
- Wilhelminenspital Vienna & Medical University of Vienna, Vienna, Austria
- Hospital Universitario Central de Asturias, Oviedo, Spain
- Centre Hospitalier Universitait du Rennes, Rennes, France
- Istituto Di Ricovero e Cura a Carattere Scientifico, Milan, Italy
- Southmead Hospital, Bristol, UK

METHODS

- 40 participants underwent bilateral implantation in the STN using a multiple-source, constant-current, 8-contact, rechargeable DBS system
- Participants were assessed 12, 26, and 52 weeks after implantation
- All raters were systematically trained in Unified Parkinson's Disease Rating Scale (UPDRS) assessments

PRIMARY ENDPOINT

- Mean change in UPDRS III scores from baseline (meds-off state) to 26 weeks after first lead implantation (stim-on/meds-off state) were determined by site investigators who were aware of the treatment assignment

SECONDARY ENDPOINTS

- Change from baseline up to 52 weeks after lead placement in:
  - UPDRS II and III scores
  - Mean change in ON time (number of hours per day awake with good symptoms control and no troublesome dyskinesia)
  - Levodopa dose equivalency (LED)
  - Parkinson's Disease Questionnaire (PDQ-39) score
  - Schwab and England (SE) scale score
  - Changes in motor symptoms, as described by patients and treating clinicians

KEY INCLUSION CRITERIA

- Subjects between 21 and 75 years
- Diagnosed with bilateral idiopathic Parkinson's disease for at least 5 years, with at least two symptoms of resting tremor, rigidity, or bradykinesia and with motor complications not controlled with drugs
- Hoehn and Yahr score of 2 or greater
- UPDRS III score in the meds-off state of more than 30, which improved by 33% or more after a levodopa challenge

Table 1. Baseline Demographic and Clinical Characteristics

Patients (n = 40)		
Age (years) – Mean (SD)	60.2 (7.8)	(42-75)
Men	27	(68%)
Women	13	(33%)
Duration of Parkinson's disease symptoms (years) – Mean (SD)	11.7 (4.6)	(3-22)
Score on the Beck depression inventory – Mean (SD)	9.4 (6.6)	(0-39)
Score on the Mattis dementia rating scale – Mean (SD)	140.1 (3.6)	(130-144)

RESULTS

UPDRS III Scores After Surgery

- A **62.6%** (±19.8) improvement in UPDRS III scores at week 26, and sustained up to week 52 post-implant ($p < 0.0001$)
- At 5 years post-implant, a **34%** improvement ($p < 0.0001$) in UPDRS III scores

FIG 1. Primary Endpoint

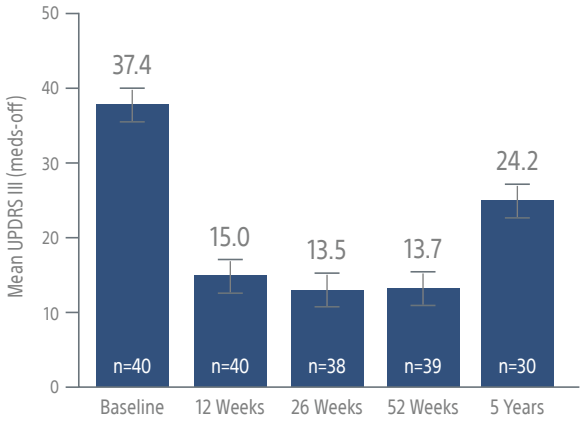


FIG. 1 created by Boston Scientific based on published data

Programming

A shift in programming was observed over time, trending toward the use of current steering on multiple contacts (FIG. 2).

At week 26 and week 52, ~70% of programs utilized current fractionalization across ≥ 2 contacts. Over the course of the study, an increased utilization of current fractionalization was observed.

FIG. 2. Increased Current Fractionalization

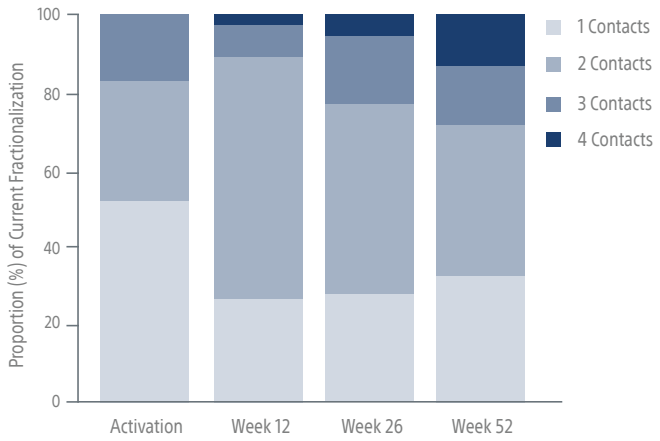


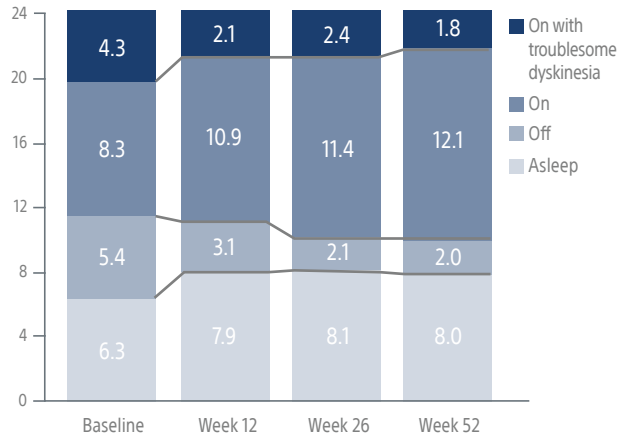
FIG. 2 created by Boston Scientific based on published data

Secondary Endpoints

Subject Motor Diary — Subjects maintained a 3-day diary prior to baseline, week 12, week 26, and week 52 post-lead placement to document their symptoms in 1-hour increments.

Highly significant reduction was observed in both OFF time and ON time with troublesome dyskinesias through week 52 ($p < 0.0001$).

FIG. 3. Subject Motor Diary



Subject Motor Diary at baseline and weeks 12, 26, and 52 post-lead placement

FIG. 3 created by Boston Scientific based on published data

Parkinson's Disease Questionnaire (PDQ-39)

Quality of Life Assessment:

- Highly significant improvement in overall Quality of Life was reported, with a 29.0% (± 55.6) mean reduction at week 26, and a 34.5% (± 45.7) mean reduction at week 52 ($p < 0.0001$) in the PDQ-39 summary index ($p < 0.0001$)
- At 5 years post-implant, Quality of Life continued to improve following implant, as supported by PDQ-39 and SE scores

FIG. 4. Parkinson's Disease Questionnaire (PDQ-39)

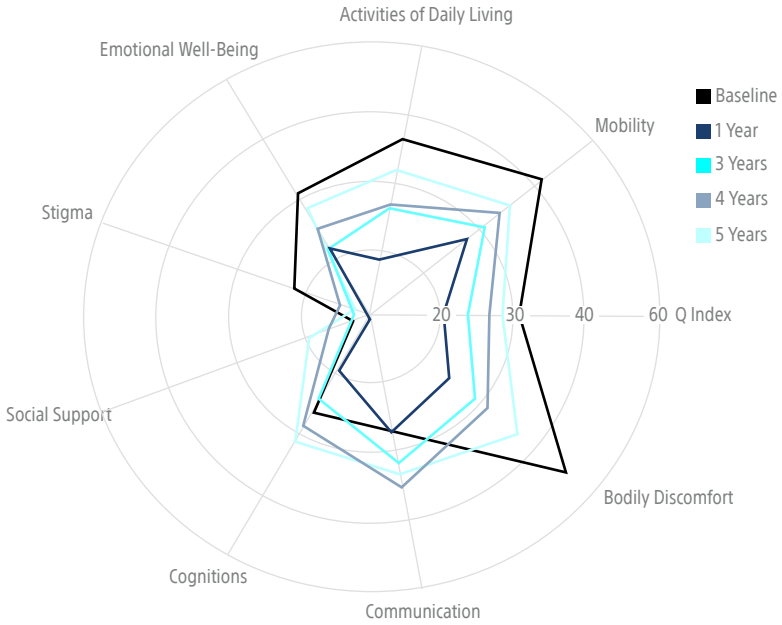


FIG. 4 created by Boston Scientific based on the published data

Global Impression of Change (GIC)

Responses of subject on impression of change following 5 years of Vercise™ DBS therapy:

- Highly significant improvement in GIC scores, as assessed by subjects and clinicians at weeks 12, 26, and 52 post-first-lead placement
- At 5 years post-lead placement, over 80% of subjects reported improved symptoms compared with baseline

FIG. 5. Global Impression of Change at 5 Years

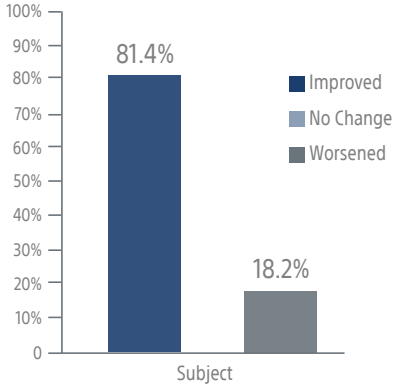


FIG. 5 created by Boston Scientific based on the published data

Levodopa Equivalents (LEDD)

Anti-Parkinson's disease medications, including both dosage and frequency, were converted to levodopa equivalent dose.

- Highly significant reduction in medication usage was observed, with a mean reduction of 53% (± 40) at week 26 and 58% (± 30) at week 52 ($p < 0.0001$)
- Significant reduction in medication usage was sustained at 5 years

Safety Evaluation up to 5 Years Post-Implant:

- A total of 176 adverse events were reported in 38 subjects
- Of these, 64 were reported as serious adverse events (SAEs)
- 5 SAEs in 2 subjects were related to the device
- 6 SAEs in 3 subjects were related to the procedure
- There were no SAEs related to stimulation

FIG. 6. Levodopa Equivalent Dose

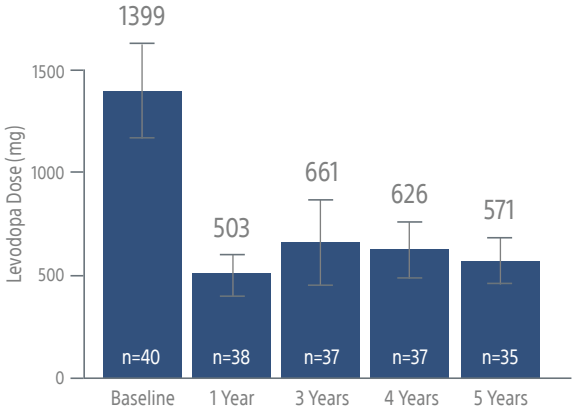


FIG. 6 created by Boston Scientific based on published data

CONCLUSIONS

- Results of the VANTAGE study demonstrated highly significant improvements in motor function ($p < 0.0001$), as assessed by UPDRS III meds-off at 6 months post-first-lead implant as compared with baseline meds-off, successfully meeting the primary endpoint
- At 5 years post-lead placement, a 34% improvement ($p < 0.0001$) in UPDRS III scores (in the stim-on/meds-off condition) was reported ($n = 30$)
- Overall improvement in Quality of Life as assessed by PDQ-39, SE scores, and reductions in medication usage, was noted up to 5 years post-lead placement
- The safety results associated with this study for up to 5 years are acceptable

Prospective, Multi-Center, International Registry of Deep Brain Stimulation for Parkinson's Disease

Vesper, J., Jain, R., Scholtes, H., Wang, A., Barbe, M.T., Paschen, S., Kühn, A., Volkmann, J., Pötter-Nerger, M., and Deuschl, G.

Published: World Society for Stereotactic and Functional Neurosurgery. 2019 Oral Presentation.

Study Type: Multi-center registry

Device Utilized: Vercise™ Deep Brain Stimulation (DBS) Systems

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BACKGROUND

Large patient data registries documenting overall improvements in Parkinson's disease (PD) symptoms and Quality of Life may facilitate new insights regarding the real-world, clinical use, and outcomes of Deep Brain Stimulation (DBS). Hence, a large-scale, ongoing registry was initiated to compile effectiveness and safety-related real-world outcomes of a DBS system capable of multiple independent current source control (MICC) in managing the symptoms of levodopa-responsive PD.

METHODS

Primary Objective

- To compile real-world clinical outcomes of an MICC-based DBS system (Vercise DBS System, Boston Scientific)

Key Study Assessments

- Parkinson's Disease Questionnaire (PDQ-39)
- Unified Parkinson's Disease Rating Scale (UPDRS) or MDS-UPDRS
- Clinical global impression of change as assessed by the subject, caregiver, and clinician
- Schwab and England (SE) scale
- EQ-5D-5L

Key Inclusion Criteria

- Subject understands study requirements and treatment procedures
- Subject provides written informed consent
- Subject meets criteria established in locally applicable Directions for Use (DFU)

Key Exclusion Criteria

- Subject meets any contraindication in applicable DFU

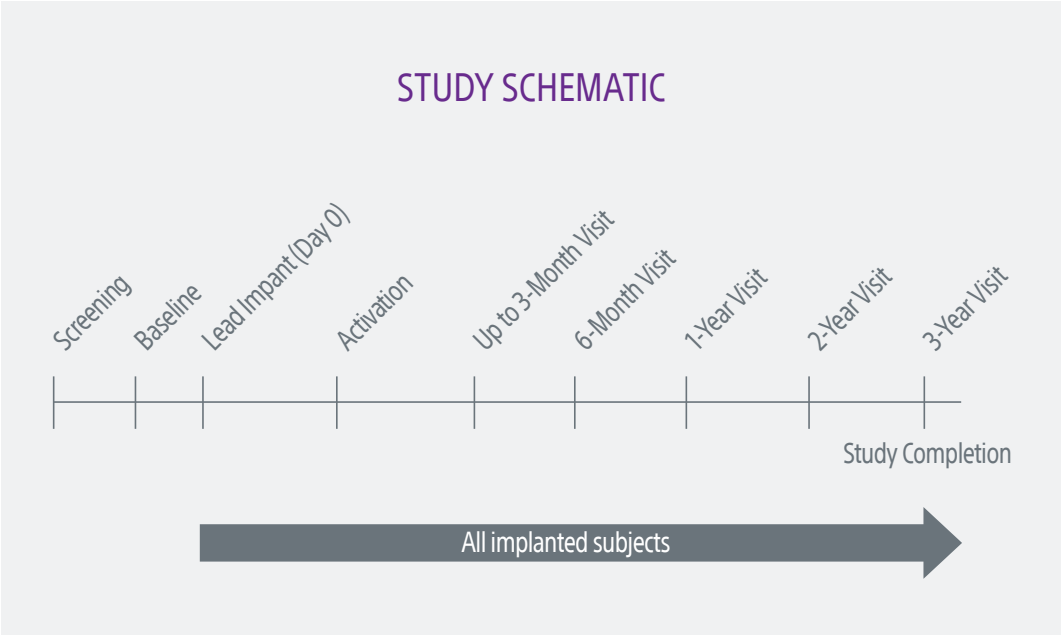
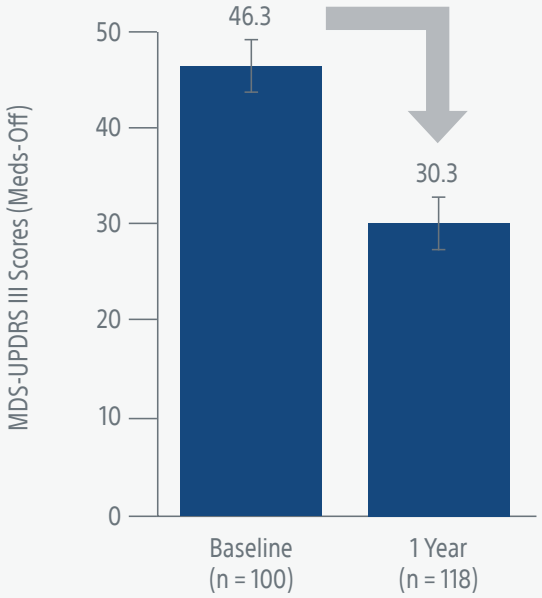


Table 1. Baseline Characteristics

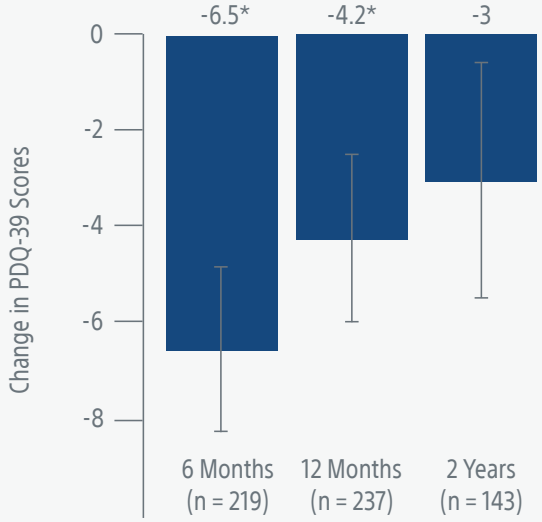
Baseline Characteristics (Subjects Enrolled: 465 / Implanted: 418 as of March 2019)	
Age (years) - Mean (SD) N	59.9 (8.62) 420
Gender – Male %	71%
PD-Related Symptoms	**Mean (SD) N**
UPDRS III Score (meds-off)	39.2 (12.2) 174
MDS-UPDRS III Score (meds-off)	44.1 (15.0) 167
Disease Duration (years)	10.2 (4.9) 420
PDQ-39 Summary Index Score	28.4 (13.7) 410

RESULTS

Improvement in MDS-UPDRS III Scores
(meds-off condition)



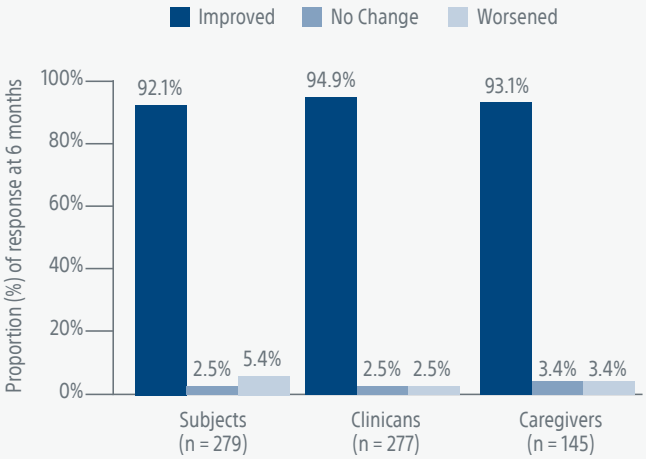
Change in PDQ-39 Summary Index
(*p < 0.0001)

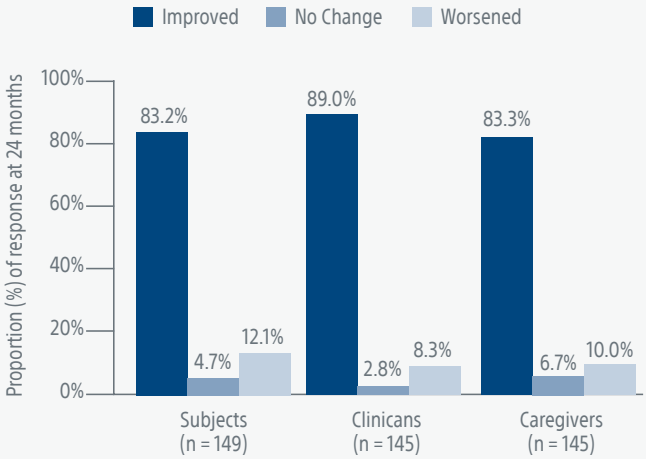


At 1-year post-implant:

- 34% improvement in motor function UDPRS III score ($p < 0.0001$)
- Improvement in Quality of Life sustained ($p < 0.0001$)
  - Mobility, Activities of Daily Living (ADL), stigma, bodily discomfort

Global Impression of Change at 6 months and 24 months,
as assessed by subjects, clinicians, and caregivers





About 90% of subjects, physicians, and caregivers noted an improvement in PD symptoms at 6 months, which was sustained up to 24-months post-implant

SAFETY EVALUATION

- The overall safety profile and patient outcomes are in accordance with several randomized clinical trials, with no major differences

CONCLUSIONS

- This registry represents the first large-scale collection of outcomes using a DBS system capable of multiple independent current source control
- Preliminary analysis demonstrated the following for 6 months and up to 24 months post-lead implantation:
  - Overall improvement in Quality of Life (PDQ-39, EQ-5D-5L, and SE scores)
  - Significant improvement in motor function, as demonstrated by change in MDS-UDPRS III scores (meds-off)
  - Over 90% of subjects, caregivers, and clinicians reported improvement in PD symptoms

Subthalamic Nucleus Deep Brain Stimulation with a Multiple Independent Constant Current-Controlled Device in Parkinson's Disease (INTREPID): a Multicentre, Double-Blind, Randomised, Sham-Controlled Study

Vitek, J., Jain, R., Chen, C., Tröster, A., Schrock, L., House, P., Giroux, M., Hebb, A., Farris, S., Whiting, D., Leichliter, T., Ostrem, J., San Luciano, M., Galifianakis, N., Verhagen Metman, L., Sani, S., Karl, J., Siddiqui, M., Tatter, S., ul Haq, I., Machado, A., Gostkowski, M., Tagliati, M., Mamelak, A., Okun, M., Foote, K., Moguel-Cobos, G., Ponce, F., Pahwa, R., Nazzarro, J., Buetefisch, C., Gross, R., Luca, C., Jagid, J., Revuelta, G., Takacs, I., Pourfar, M., Mogilner, A., Duker, A., Mandybur, G., Rosenow, J., Cooper, S., Park, M., Khandhar, S., Sedrak, M., Phibbs, F., Pilitsis, J., Uitti, R., and Starr, P.

PUBLISHED	STUDY TYPE	DEVICE
Lancet Neurology	Multi-center, prospective, double-blind, randomized (3:1), controlled trial with sham control	Vercise™ Deep Brain Stimulation (DBS) System

This summary was created by Boston Scientific and is intended to consolidate the publication for educational use only. All figures created by Boston Scientific based on published data. One or more authors report funding from Boston Scientific as a financial disclosure. Boston Scientific was the primary sponsor of this study.

BACKGROUND

The INTREPID Study assessed improvements in motor function and Quality of Life in Parkinson's disease (PD) patients following bilateral subthalamic nucleus (STN) DBS using the Vercise™ DBS System with multiple independent current sources, which allows for selective activation of individual contacts on the DBS lead, thereby permitting a defined distribution of applied current.

METHODS

Study Design

- Multi-center, prospective, double-blind, randomized (3:1) trial with sham control

Principal Investigators

- Dr. Philip Starr (University of California, San Francisco)
- Dr. Jerrold Vitek (University of Minnesota)

Primary Endpoint

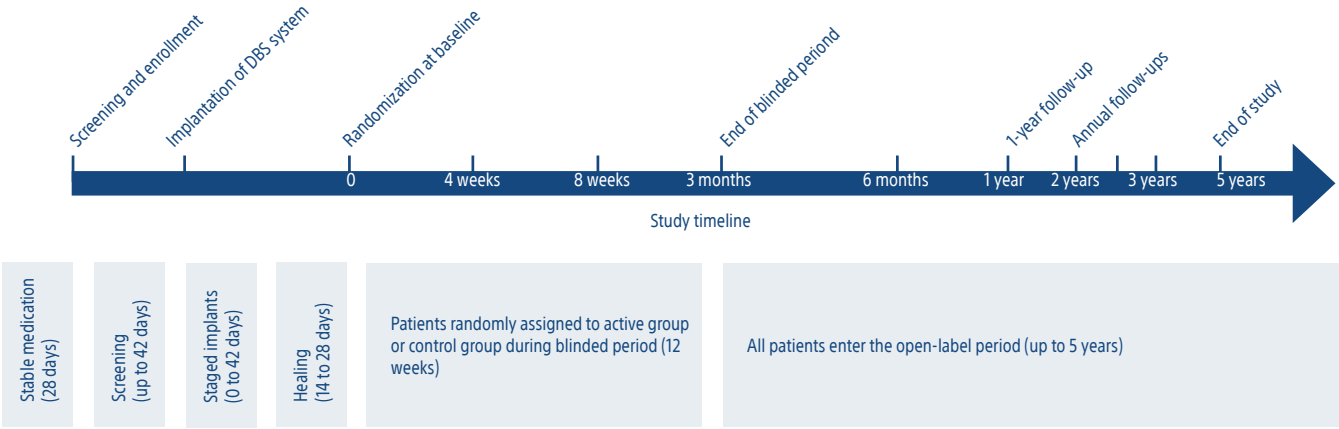
- Mean difference between active and control groups in ON time without troublesome dyskinesia, with no increase in antiparkinsonian medications (LED), from post-implant baseline to 12 weeks post-randomization

Sites and Subjects

- N = 160 randomized subjects
- 23 sites

Study Design

- Up to 5 years post-randomization



BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

CLINICAL CHARACTERISTICS/ DEMOGRAPHICS AT SCREENING	
Age (years) - Mean (SD) n	59.9 (7.95) 160
Gender – Male (n %)	72.5% (116/160)
PARKINSON'S DISEASE-RELATED SYMPTOMS	
UPDRS III Scores (meds-off) – Mean (SD) n	43.4 (9.60) 153
UPDRS III Scores (med-on) – Mean (SD) n	18.5 (8.26) 157
Disease Duration (years) - Mean (SD) n	10.1 (3.61) 160
PD diary: OFF time ON time with troublesome dyskinesias ON time without dyskinesias ON time with non-troublesome dyskinesias Asleep	 6.91 ± 2.99 hours 4.35 ± 2.63 hours 4.65 ± 2.67 hours 3.65 ± 1.90 hours 7.20 ± 1.47 hours

KEY INCLUSION/EXCLUSION CRITERIA

Key Inclusion Criteria

- Diagnosis of bilateral idiopathic PD with ≥ 5 years of motor symptoms
- Modified Hoehn and Yahr (H&Y) ≥ 2; UPDRS III score ≥ 30 (meds-off); at least 33% improvement in UPDRS III following medications
- Greater than or equal to 6 hours of poor motor function (OFF time plus ON time with troublesome dyskinesias) per day, as assessed by PD diary
- An appropriate candidate for surgical procedures required for bilateral STN DBS

Key Exclusion Criteria

- Any intracranial abnormality or medical condition that contraindicates DBS surgery
- Any significant psychiatric condition likely to compromise the subject's ability to comply with requirements of the study protocol

RESULTS

PRIMARY ENDPOINT

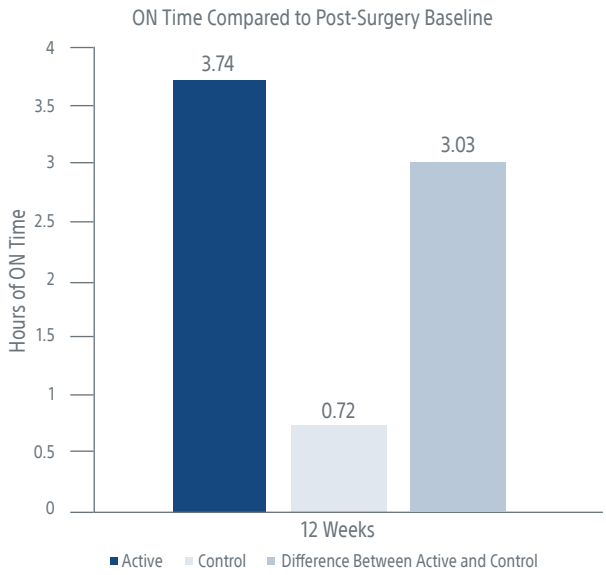
ON Time Without Troublesome Dyskinesias

At the end of the blinded phase (12 weeks):

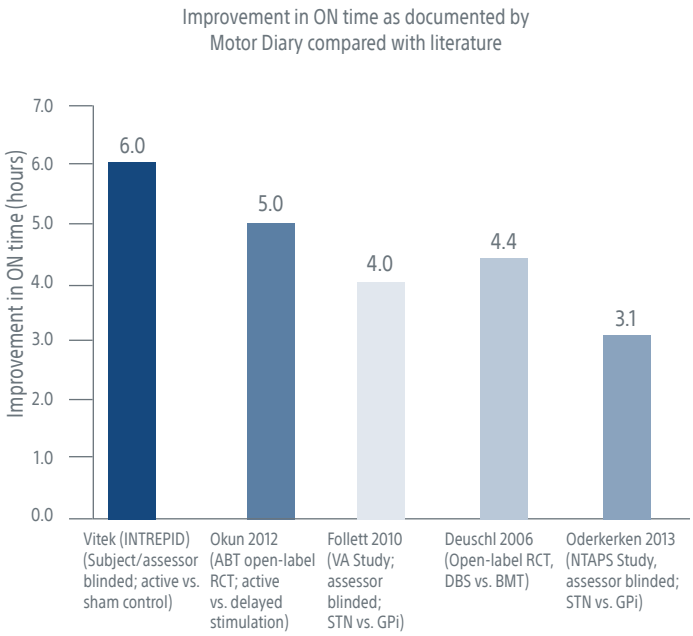
- A 3.74 ± 4.79 hour improvement in ON time was reported in the active group compared to a 0.72 ± 3.56 hour improvement in the control group compared to post-implant activation

At the end of the blinded phase (12 weeks):

- The difference in mean change from the baseline visit (post-implant) to 3 months post-randomization in increased ON time between the active and control groups was 3.03 ± 4.52 ($p < 0.001$)



IMPROVEMENT IN ON TIME AT 1 YEAR



IMPROVEMENT IN ON TIME

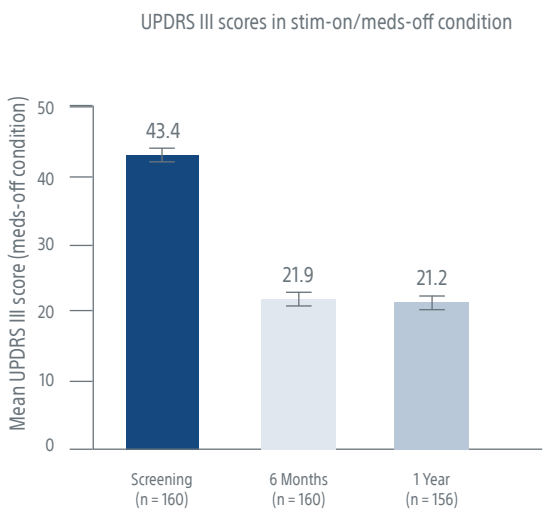
6.0 hours

- At 1 year, a 6 ± 3.8 hour increase in ON time without troublesome dyskinesias was reported compared with screening ($p < 0.001$)
- Greater improvement than other similar studies in the literature

UPDRS III SCORES (STIM-ON/MEDS-OFF)

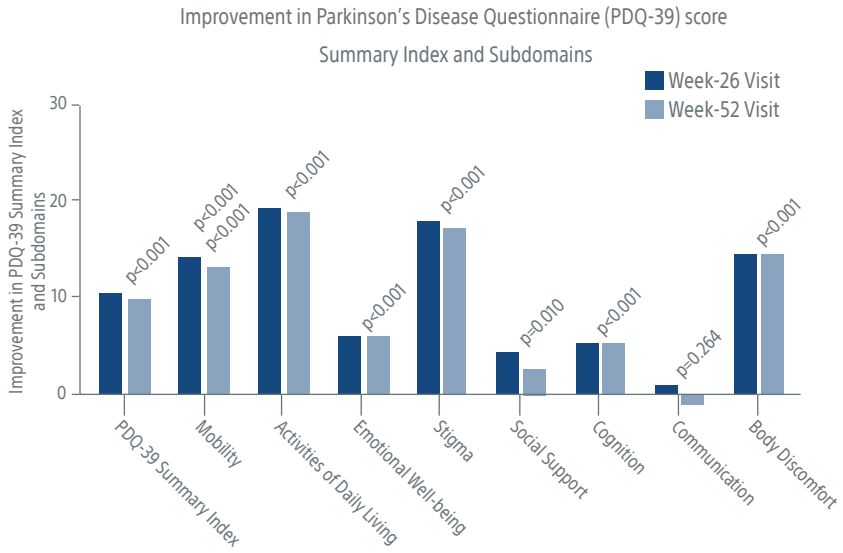
51%

Improvement in UPDRS III at 1 year (n = 160)



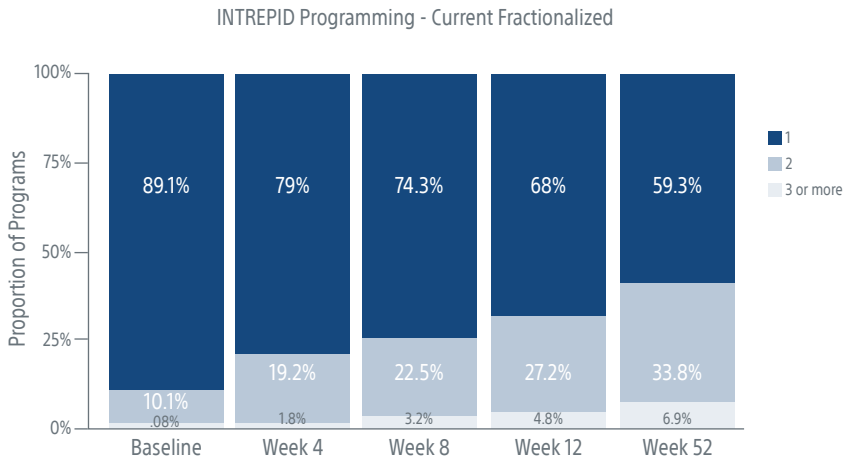
34%

Improvement in Quality of Life at 1 year



41%

of programs used more than a single contact at one year



SAFETY PROFILE

Safety profile is comparable to literature reports

Surgical complications across all patients who underwent implantation (n = 196) [regardless of whether they continued on to be randomized in the study]

EVENT	NUMBER OF EVENTS (SUBJECTS)	RATE
Infection occurring in first 6 months of surgery associated with partial/total hardware removal (SAE)	7 (7)	7/196 (3.6%)
Symptomatic perioperative intracranial hemorrhage (SAE) occurring during surgery or postsurgical hospitalization	4 (4)	4/196 (2.0%)
Symptomatic peri-lead edema (SAE)	6 (6)	6/196 (3.1%)
Return to operating room (OR) due to electronic malfunction	4 (4)	4/196 (2.0%)
Return to OR due to lead breakage/lead migration	0 (0)	0/196 (0%)
Return to OR due to hardware erosion occurring > 6 months after implantation	2 (2)	2/196 (1.0%)

- Deaths: 7 (unrelated to the study device and/or implant procedure)
- No unanticipated adverse events
- No lead breakage/lead fractures

Rate was calculated as: (number of patients with an event/total number of implanted subjects) × 100

CONCLUSIONS

- The study successfully met the primary endpoint and several secondary endpoints based on outcomes reported during the 12-week blinded period
- At 1 year, UPDRS III scores (stim-on/meds-off) improved 51%, and ON time without troublesome dyskinesias (PD-diary) increased 6 ± 3.8 hours compared with screening ($p < 0.001$), respectively
- Overall improvement in Quality of Life, medication reduction, and high satisfaction with therapy were maintained
- The overall safety profile of the DBS system was comparable to other published reports

In Silico Accuracy and Energy Efficiency of Two Steering Paradigms in Directional Deep Brain Stimulation

León Mauricio Juárez-Paz

Published: Frontiers in Neurology. 2020 Oct 30;11:593798.

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Figures created by Boston Scientific based on published data. The author is an employee of Boston Scientific.

BACKGROUND

In Deep Brain Stimulation (DBS), field shaping is utilized to obtain clinical benefits and avoid side effects. Multiple Independent Current Control (MICC) and Interleaving/Multi-Stim Set (Interleaving/MSS) are two stimulation field steering paradigms in commercially available DBS systems.

MICC (Multiple Independent Current Control) involves a multiple current source electronic architecture to activate each electrode in a DBS lead simultaneously and independently.

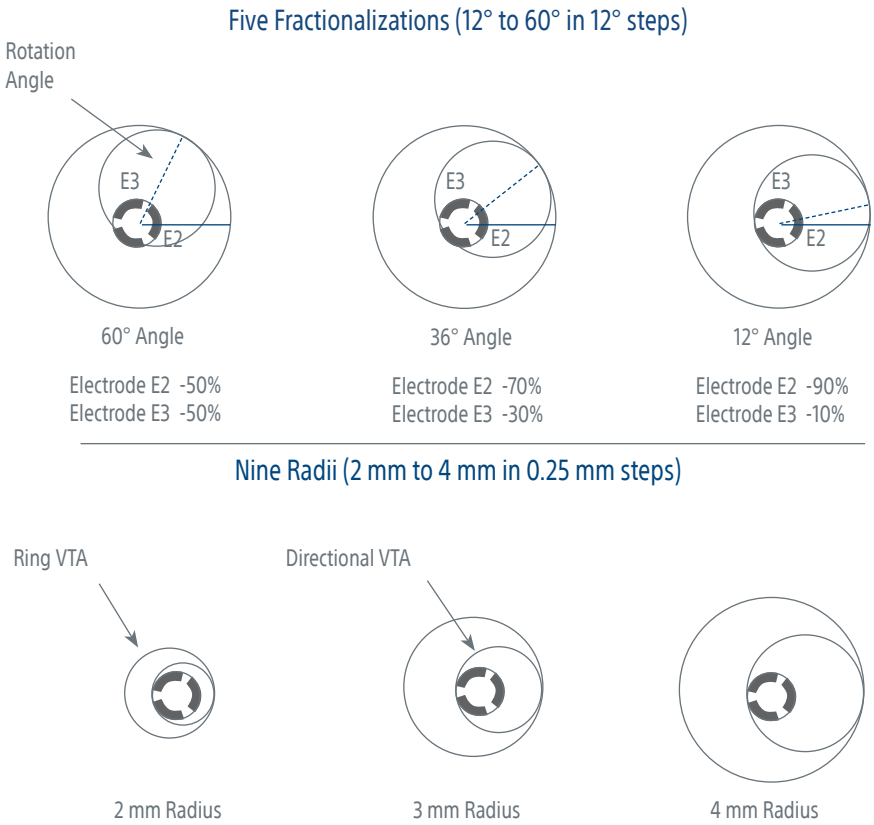
Interleaving/MSS (Multi-Stim Set) involves single electrodes activated sequentially and alternatively to stimulate different areas with defined pulse amplitudes.

METHODS

- Volume of Tissue Activated (VTA) was generated *in silico* to generate 3-dimensional representations of neural activation surrounding the DBS electrode
- Pulse amplitude distributions or "fractionalizations" were obtained by activating two electrodes with varying intensity to generate the VTAs and their associated expected rotation angle
- VTAs were generated to have nine defined target radii (from 2.00 to 4.00 mm in 0.25 mm increments) for the cross section at the vertical center of the activated electrodes

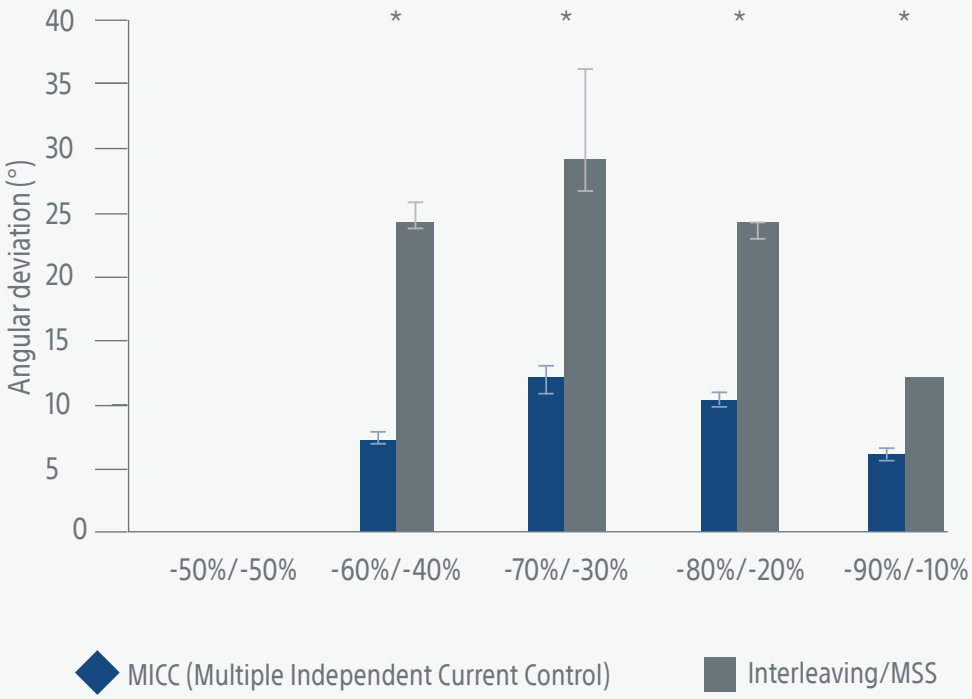
CONCLUSIONS

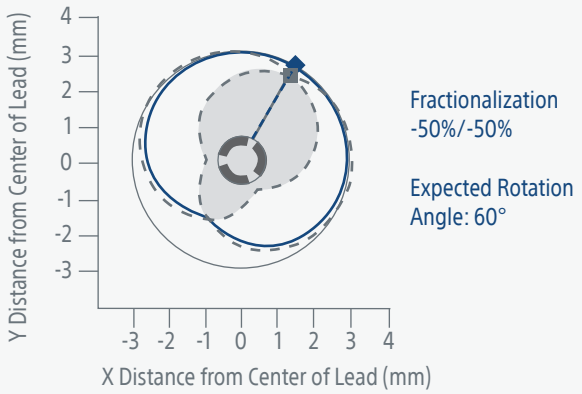
- MICC had significantly lower angle deviations ($p < 0.001$) compared to Interleaving/MSS**
- MICC had significantly lower current draw ($p < 0.001$) from battery compared Interleaving/MSS**

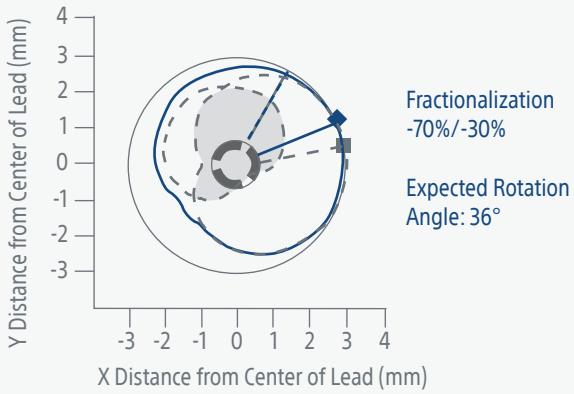


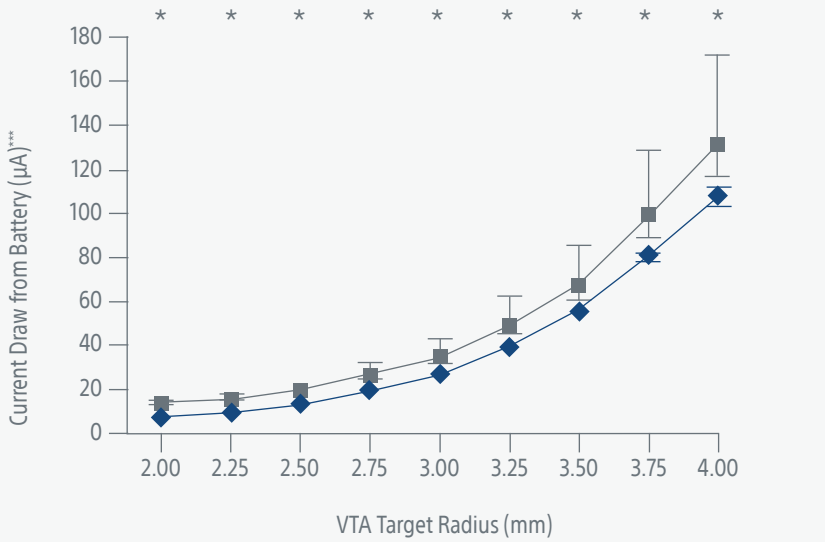
RESULTS

MICC steering was found to be significantly more accurate ($p = 0.002$) than Interleaving/MSS for all fractionalizations, except for –50/–50%.









For all analyzed fractionalizations, MICC significantly lowered ($p < 0.05$) total pulse amplitude and current draw from the battery than Interleaving/MSS to generate VTAs with a given radius. Moreover, the current draw from the battery was consistent across all analyzed fractionalizations (including activation of a single electrode and ring-mode settings) for MICC.

*Statistically significant difference

**$p < 0.001$ applies to all VTA radii and fractionalizations combinations

***Single electrode and ring-mode data not depicted

Computational modeling methods: A proprietary model was developed based on peer-reviewed literature to predict the volume of stimulation in a homogeneous isotropic medium representative of human brain tissue. Computational modeling may not necessarily be indicative of clinical performance.

Directionality

Directional Deep Brain Stimulation of the Subthalamic Nucleus: A Pilot Study Using a Novel Neurostimulation Device

Steigerwald, F., Müller, L., Johannes, S., Matthies, C., and Volkmann, J.

Published: Movement Disorders, 2016;31:1240-1243.

BACKGROUND

The authors report of a first clinical experience of directional Deep Brain Stimulation (DBS) with a novel, fully implantable neurostimulation system that combines the 8-contact Vercise Cartesia™ Directional Leads and a pulse generator capable of Multiple Independent Current Control (MICC). The retrospective analysis of monopolar review data aimed to quantify the effect of horizontal current steering on the therapeutic window of subthalamic nucleus (STN) DBS compared with conventional ring-mode stimulation.

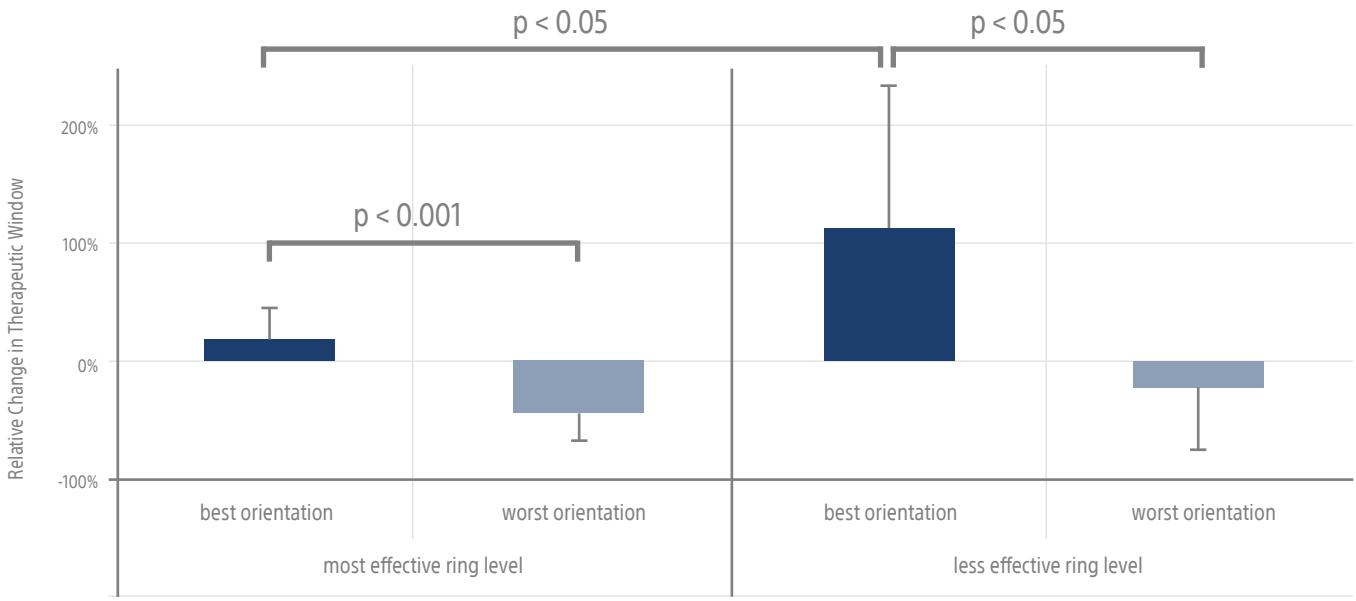
METHODS

- 7 Parkinson's disease (PD) patients (2 female; age 47-64 years; disease duration: 8-20 years; mean Unified PD Rating Scale (UPDRS) III meds-off: 42; mean UPDRS III meds-on: 19) who had been implanted with a novel directional system for bilateral subthalamic DBS underwent an extended programming session of their DBS system in the practically defined OFF state 4 to 9 days post-surgery
- Therapeutic window (TW; defined as amplitude difference between clinical efficacy and side-effect threshold in mA) was determined for the two segmented levels of each lead in ring mode, and the level with the larger TW was labeled as the "most effective ring level"
- Different stimulation directions at each level were tested by either restricting cathodal current to each of the three segments (first patient) or additionally evaluating equal current distributions between two adjacent segments (subsequent 6 patients)
- This programming results in up to six directed electrical fields with a primary field vector rotated by either 120° or 60°

RESULTS

- 154 directional and 28 ring-mode settings were assessed and TW determined for 111 and 24 settings, respectively
- After grouping the results of directional stimulation by ring level, larger TW effects of optimal current steering could more readily be observed at the less effective level than at the most effective level
- After a follow-up of 3 to 6 months, all patients remained programmed in directional mode without the need for rescue programming into ring mode to improve stimulation efficacy

FIG. 1. Directional Impact on Therapeutic Window. Bar graph depicting relative changes in the therapeutic window (%) when steering current in the best vs. worst orientation during the monopolar review. Please note: the change in therapeutic window for the best directional current steering was proportionally larger at the less effective level. On both levels, the therapeutic windows assessed for the best orientation of current steering differed significantly from those obtained for stimulation into the worst orientation, highlighting the potential clinical usefulness of directional DBS.



Directional Deep Brain Stimulation: A Case of Avoiding Dysarthria with Bipolar Directional Current Steering

Reker, P., Dembek, T. A., Becker, J., Visser-Vandewalle, V., and Timmermann, L.

Published: Parkinsonism and Related Disorders. 2016;31:156-158.

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Image reprinted from Reker, P., Dembek, T. A., Becker, J., Visser-Vandewalle, V., and Timmermann, L. Directional deep brain stimulation: A case of avoiding dysarthria with bipolar directional current steering. Parkinsonism and Related Disorders. 2016;31:156-158, with permission from Elsevier. One or more authors report funding from Boston Scientific as a financial disclosure.

BACKGROUND

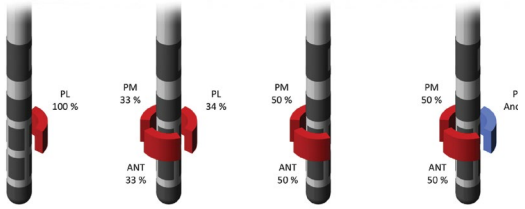
The case presented by the authors illustrates several aspects of directional Deep Brain Stimulation (DBS) by describing a case in which troublesome dysarthria was overcome with directional steering.

OVERVIEW

- A 56-year-old right-handed male diagnosed with Parkinson's disease (PD) approved for DBS surgery
- Motor fluctuations observed with good preoperative levodopa response
- Unified Parkinson's Disease Rating Scale (UPDRS) III score improved 38 points (62 to 24) in meds-on state

METHODS

- Bilateral implantation in subthalamic nucleus (STN) with directional DBS system
- Lead placement confirmed by postoperative computed tomography (CT) merged with preoperative magnetic resonance imaging (MRI)
- A detailed monopolar review was conducted on dorsal directional contact level, assessing dysarthria, bradykinesia, and rigidity
- During monopolar review, patient experienced severe stimulation-induced dysarthria from lead in left hemisphere at all contacts postoperatively and at 6-month review
- Hypomania and impulse control disorders observed on two most ventral contacts, limiting programming
- Each contact configuration was assessed with cathodic stimulation and an equal division of current between active contacts
- Greater efficacy was observed when stimulation was delivered through a combination of anterior and postero-medial contacts
- To further focus directional field in antero-medial direction, stimulation of postero-lateral contact was set as anode



STIMULATION CONDITIONS	POSTERO-LATERAL	RING MODE	POSTERO-MEDIAL + ANTERIOR	BIPOLAR STIMULATION
Rigidity	Unresolved	Unresolved	Resolved	Resolved
Bradykinesia	Moderate	Moderate	Slight	Minimal
Dysarthria Threshold	2.9 mA	3.6 mA	3.9 mA	> 5.0 mA

Stimulation conditions: Monopolar review was conducted for four different conditions. Postero-lateral stimulation resulted in unresolved rigidity and moderate bradykinesia with a threshold for dysarthria at 2.9 mA. Ring-mode stimulation resolved rigidity and resulted in moderate bradykinesia with a threshold for dysarthria at 3.6 mA. Stimulation using both the postero-medial and anterior contacts with an even current split of 50% on each contact resulted in resolved rigidity and slight bradykinesia with a threshold for dysarthria at 3.9 mA. Because postero-medial + anterior stimulation resulted in promising results, the postero-lateral contact was set as an anode to further focus stimulation into the anterio-medial direction. This stimulation configuration resolved rigidity and showed minimal bradykinesia.

RESULTS

- Postero-lateral contact showed lowest threshold for dysarthria at 2.9 mA
- Rigidity was unresolved at this amplitude, resulting in no therapeutic window
- Ring-mode stimulation at same level showed threshold for dysarthria at 3.6 mA, with resolution of rigidity and moderate bradykinesia
- Activation of postero-medial and anterior contacts showed threshold for dysarthria at 3.9 mA, with resolution of rigidity but with improved bradykinesia response
- Setting postero-lateral contact to anode further focused stimulation field, resulting in a threshold for dysarthria above 5.0 mA
- At this amplitude, resolution of rigidity and only slight bradykinesia were observed
- Using directional programming, patient successfully programmed despite no therapeutic window when ring mode alone was evaluated

Directional Local Field Potential Recordings for Symptom-Specific Optimization of Deep Brain Stimulation

Fernandez-Garcıa, C., Foffani, G., Dileone, M., Catalan-Alonso, M. J., Gonzalez-Hidalgo, M., Barcia, J. A., and Alonso Frech, F.

Published: Movement Disorders. 2017;32(4):626-628.

Study Type: Case report, single-center, open-label

Devices Used: Vercise™ Deep Brain Stimulation (DBS) Implantable Pulse Generator and Cartesia™ Directional Leads

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BACKGROUND

Directional Deep Brain Stimulation (DBS) may increase the therapeutic window by steering current toward efficacious regions and away from side-effect regions compared with traditional DBS for Parkinson's disease (PD). Because directional DBS offers expanded programming possibilities, there may also be an increase in the amount of time required to optimize a patient. Local field potential (LFP) encodes physiological information that is correlated with Parkinson's disease (PD) symptom severity. The authors investigated whether the LFP could potentially be used to optimize the selection of DBS contacts and thus reduce the programming time burden.

STUDY DESIGN

- 67-year-old woman
- Bilateral implantation in subthalamic nucleus (STN) with directional DBS system
- Investigators assessed if beta power in the LFP was related to therapeutic window on directional contacts
- Bipolar LFPs were recorded with stim-off on each of the directional contacts referenced to most dorsal cylindrical contact 5 days post-op
    - Beta power for each contact was quantified as the maximum value in the beta range
    - A detailed monopolar review was conducted on each directional contact at day 7 after implantation
    - Therapeutic window for each rigidity (TWR) and tremor (TWT) were determined
    - Correlation of beta power with TWR and TWT was calculated

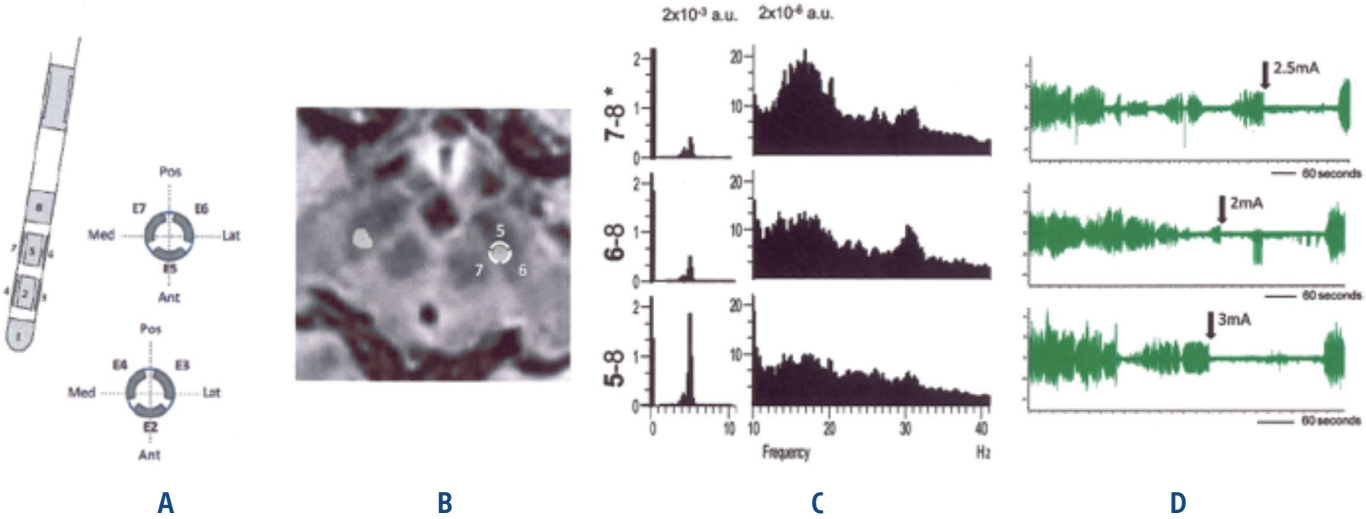


FIG. 1. (A) Left subthalamic nucleus (STN) electrode example presenting tip contact (1). Two rows of segmented contacts on lower (2-4) and upper (5-7) levels with a traditional ring electrode (8). (B) The lead location marks where the postoperative volumetric axial computed tomography (CT) meets the preoperative magnetic resonance imaging (MRI) at the mesencephalic level. The theoretical positions of anterior, postero-lateral, and postero-medial segmental electrodes are illustrated in locations 5-6-7, respectively. The X-Y-Z coordinates were 11.4-4.2-5.5 for the left electrode and 12.4-4-5.5 for the right electrode. (C) Predominant tremor (3-8 Hz) peak power spectra and LFP STN beta (12-35 Hz) band recordings. Upper ring electrode (8) with upper segmental left electrodes 5-6-7 informs the bipolar montage. (D) Current intensity needed to suppress rest tumors, as measured by an accelerometer. A derivation of 7-8 indicates highest power for beta band and best rigidity improvement. Note: Figure reproduced with permission from John Wiley and Sons as published, Fernandez-Garcia, C., et al. Movement Disorders. 2017;32(4):626-628.

RESULTS

- Both TWR and TWT differed with respect to direction of stimulation, with a maximum difference of 2.5 mA between adjacent directional contacts
- Larger TWRs were observed in the more dorsal contacts
- TWT was unchanged by current steering in the dorsal-ventral axis
- Beta power also varied with respect to dorsal-ventral location, with higher amplitude beta observed on the dorsal contacts
- TWR was correlated with beta power ($r = 0.57$, $p < 0.05$), while there was no significant correlation with TWT ($r = 0.32$, $p > 0.05$)
- Differences in therapeutic window were observed on each of the directional contacts used for stimulation
- Beta power was distributed in a similar pattern to that of the therapeutic window for rigidity and may be helpful in the future for selecting contact pairs for stimulation in adaptive DBS paradigms

Innovations in Deep Brain Stimulation Methodology

Kühn, A., and Volkmann, J.

Published: Movement Disorders. 2017;32:11-19.

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. One or more authors report funding from Boston Scientific as a financial disclosure.

BACKGROUND

This review briefly outlines the current concepts of Deep Brain Stimulation (DBS) mechanisms, defines the need for translational advances in DBS methodology, and describes the available technical solutions that may soon change the clinical practice of DBS.

INTRODUCTION

- DBS is a well-established treatment for movement disorders, although DBS mechanisms remain poorly understood
- Suboptimal clinical outcomes can occur because of complexity in delivering the therapy, including the following:
  - Improper patient selection
  - Lead misplacement
  - Patient heterogeneity
  - Poor programming
- DBS may work by influencing network activity in the brain
- Surrogates of network changes can be measured with local field potentials
- Postoperative adaptability of DBS should be used to optimize network impact, but this adds complexity to treatment

NEEDS FOR DBS

- Directional DBS
  - Current steering within horizontal plane can increase stimulation thresholds for side effects
  - The ideal stimulation system would have multiple independent current sources for each directional contact
- Novel Pulse Parameters
  - Relationship between stimulation amplitude, pulse width, and axon activation is non-linear
  - Shorter pulse widths can optimize DBS of the subthalamic nucleus (STN), reducing side effects because of the biophysics of axon activation and specific anatomy of this target
- Computational Models of DBS
  - Recent computational model efforts incorporate patient imaging, the DBS electric field, and patient-specific predictions of neural activation
  - These tools can reduce the workload on physicians to program and enable efficient use of more advanced programming options

IDENTIFICATION OF PHYSIOMARKERS

- As a marker of hypokinetic symptoms, beta power can be used to create adaptive DBS systems that respond to physiological markers of symptom severity
- Low-frequency (5-12 Hz) activity is associated with dystonic activity in dystonia patients

NOVEL STIMULATION PATTERNS

- Both coordinated reset and closed-loop DBS in laboratory settings with specific patients show promise for improving the efficacy and efficiency of DBS in the future

Directional DBS Increases Side-Effect Thresholds — A Prospective, Double-Blind Trial

Dembek, T. A., Reker, R., Visser-Vandewalle, V., Wirths, J., Treuer, H., Klehr, M., Roediger, J., Dafsari, H. S., Barbe, M. T., and Timmermann, L.

Published: Movement Disorders. 2017;32:1380-1388.

Study Type: Prospective, double-blind, single-center

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Figures created by Boston Scientific based on published data. One or more authors report funding from Boston Scientific as a financial disclosure.

BACKGROUND

In this randomized, double-blind study, the authors aimed to assess and compare associated clinical outcomes of Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD) patients using either a conventional circular stimulation or directional stimulation.

METHODS

- 10 Parkinson's patients with bilateral implantation of directional DBS leads in the STN were evaluated
- All patients were implanted with Vercise Cartesia™ Directional Leads and Vercise™ PC Implantable Pulse Generator

Monopolar Review

- A clinical evaluation of 2 segmented levels set in a circular configuration (60 µs/130 Hz) was conducted over 2 study visits
- The level with better symptom control and fewer side effects was defined as the "best" level
- A detailed exploration of the determined "best" level was then conducted after overnight dopaminergic medication withdrawal
- 3 segmented electrodes were separately tested as well as the circular configuration in a randomized order
- Stimulation amplitude was progressively increased from 0 to 5 mA in steps of 0.5 mA. The interrogation was stopped if intolerable side effects were elicited
- Side effects were assessed each 0.5 mA increments
- Upper limb motor control was assessed at each 1 mA increments (upper limb rigidity, finger tapping, and hand rotation as well as resting tremor and postural tremor)
- During monopolar review, stimulation of the hemisphere not under evaluation was turned off

Therapeutic Window

- Therapeutic window was calculated as the difference between the stimulation amplitude at the first significant improvement in symptoms and at the first intolerable side effect
- First significant improvement was defined as an improvement of 1.5 points in the scores of rigidity, finger tapping, and hand rotation combined, whereas an intolerable side effect was defined as lasting more than two minutes

Ranking

- Following a review, the blinded rater ranked the stimulation configuration from best to worst
- The ranking considered the size of the therapeutic window, the amplitude threshold, and degree of symptom suppression as well as the side-effect thresholds and the quality and severity of side effects
- The best segemented electrode and the circular configuration were then used for additional investigations

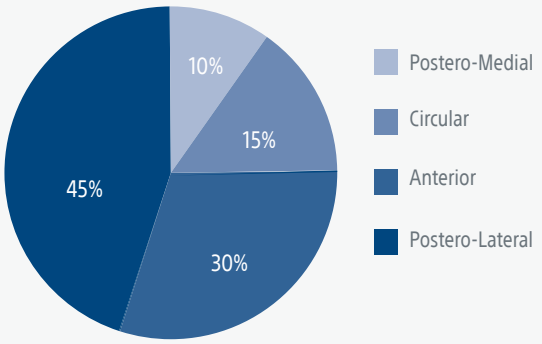
Cross-Over

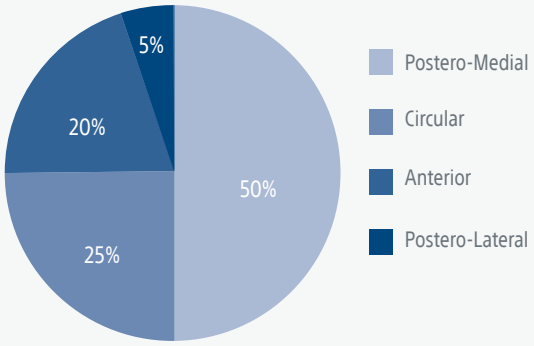
- Following the first monopolar review, patients were randomly stimulated with the circular configuration or with the best segmented electrode on the most affected hemisphere
- The stimulation amplitude was titrated to achieve the optimal symptom control with minimal side effects
- The less-affected hemisphere was activated with a circular DBS configuration, and this setting was tested overnight in the meds-off condition
- On the next day, the stimulation was adjusted to the respective alternative configuration not initially assigned (i.e., circular or best segmented electrode) and amplitude optimization was performed
- A complete Unified PD Rating Scale (UPDRS) III examination was conducted for both stimulation configurations to assess the short-term motor outcomes

RESULTS

Stimulation Configuration Ranking

- The "best" configuration was found most frequently in the postero-medial direction, followed by circular, anterior, then postero-lateral
- The postero-lateral configuration was ranked "worst" most often, followed by anterior, circular, and postero-medial



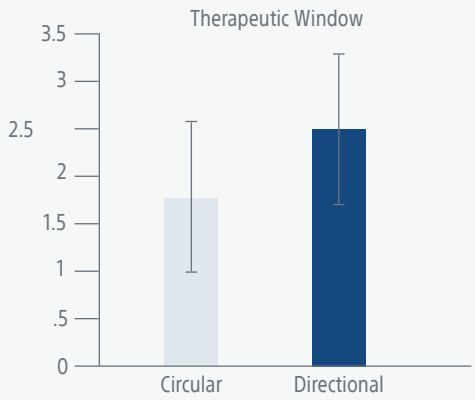


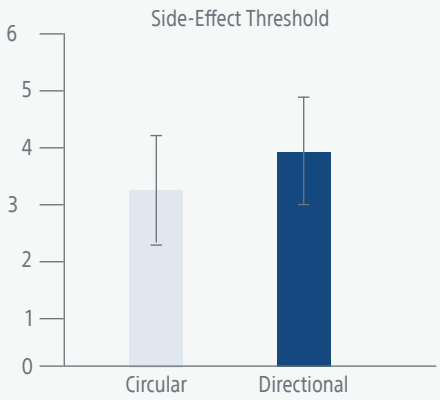
Comparison of Best-Directional Stimulation to Circular: Rankings frequencies for each contact configuration are shown, with postero-medial direction being ranked 'best' most frequently (10/20), followed by circular (5/20), anterior (4/20), then postero-lateral (1/20). The postero-lateral configuration was ranked "worst" most often (9/20), followed by anterior (6/20), circular (3/20), and postero-medial (2/20).

RESULTS

Therapeutic Window

- The best-directional DBS produced significantly larger therapeutic windows than circular DBS (median 2.0 mA vs. 1.0 mA)
- The best-directional DBS also gave significantly higher thresholds for side effects (median 4.0 mA vs. 3.0 mA)





Therapeutic windows were computed and compared between the circular stimulation and the best-directional contact. Therapeutic window was higher for the best-directional level compared to the circular configuration (2.51 ± 0.71, 1.79 ± 0.95). Side-effect thresholds were also higher for the best-directional contact than for the circular configuration (3.24 ± 1.05, 3.93 ± 0.85).

Motor Efficacy

No significant differences were observed in the improvement of rigidity and finger tapping between best-directional DBS and circular DBS (rigidity: 1.0 vs. 0.5 points, $p = 0.555$; finger tapping: 1.0 vs. 0.75 points, $p = 0.604$)

- Significant hand rotation improvement during best-directional DBS (1.25 vs. 0.75 points, $p = 0.003$)

Short-term Crossover

- There was no significant difference in motor efficacy between circular and directional DBS compared to stim-off. Mean total UPDRS III improvement score was 11.6 points ($p = 0.785$)
- Mean stimulation amplitude was not significantly different between circular and directional DBS (circular 1.5 mA, directional 1.4 mA, $p = 0.21$)

Conclusions

- This study demonstrated an enlargement of the therapeutic window as well as an increase in the side-effect threshold associated with the use of directional stimulation
- Comparable stimulation thresholds were observed between directional and circular DBS with regard to the improvement of upper limb motor symptoms, suggesting that directional DBS doesn't lower therapeutic stimulation amplitudes
- Postero-medial stimulation was ranked as the best direction in half of the reviews, whereas postero-lateral was ranked worst in most cases, likely because of activation of the internal capsule with stimulation in the lateral direction
- More advanced stimulation configurations, such as bipolar stimulation or multiple independent current stimulation, could further improve the therapeutic window

Directional Leads for Deep Brain Stimulation: Opportunities and Challenges

Schüpbach, W.M.M., Chabardes, S., Matthies, C., Pollo, C., Steigerwald, F., Timmermann, L., Visser-Vandewalle, V., Volkmann, J., and Schuurman, P.R.

Published: Movement Disorders. 2017;32:1371-1375.

Study Type: Review article

BACKGROUND

To help guide future practice, the authors summarized the thoughts and opinions of early adopters of directional Deep Brain Stimulation (DBS) systems.

INTRODUCTION

- Conventional DBS leads use circular electrodes, which provide limited control over the shape of the electric field used in DBS therapy
- Directional DBS systems use radially segmented electrodes that enable physicians to more precisely shape electric fields and to customize DBS therapy for each patient
- Commercially available leads use either a single current source or multiple independent current sources for each contact. Using multiple independent current sources enables greater specificity and consistency of field shaping than using a single current source

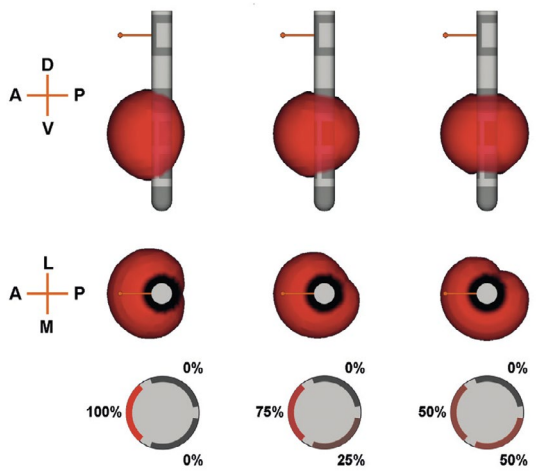


FIG. 1. **Directional Stimulation.** Using Multiple Independent Current Control (MICC) to divide current between directional contacts improves spatial specificity in activating neural tissue. The current is directed anteriorly when only the anterior contact is activated (left), 30° medially when current is divided 75%/25% between the anterior contact and the postero-medial contact (middle), and 60° medially when current is divided evenly between the two contacts (right). Because current can be fractionalized in 1% increments, the spatial specificity that can be achieved is limited only by practical implementation.

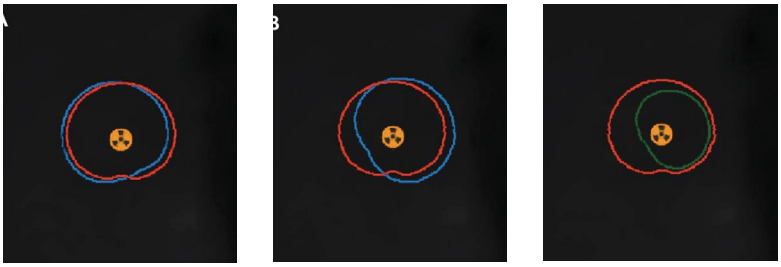


FIG. 2. **Multiple Independent Current Source vs. Single Current Source System**
Perpendicular views of a row of three segmented contacts separated by 120° around an electrode (shown in orange). Two of three contacts are activated with an intended current distribution of 50:50. (A) The red line indicates the stimulation field from a MICC system, and the blue line indicates the stimulation field from a single current source system. Impedance is 3 kΩ on one contact and 1.5 kΩ on the other. (A) Depicts a scenario where impedances are initially equal at each contact but change over time to a 3:1.5 kΩ ratio. (B) An example with an open circuit on a single contact. The blue line (left panel) illustrates the stimulation field from a single-source system when all of the current (3 mA) is sent to the other, non-open contact. The green line (right panel) shows the field with a MICC system; in this case, the amount of current sent to the non-open contact (1.5 mA) remains the same.

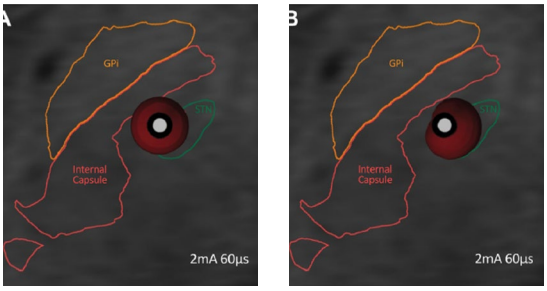


FIG. 3. Example of potential utility of a directional system. (A) Based on the location of the standard lead, the stimulation field model (SFM) shows that therapeutic stimulation of the subthalamic nucleus (STN) would be difficult without simultaneously stimulating the internal capsule. (B) Using a single contact on a novel directional lead, it is possible to steer the stimulation field model (SFM) away from the internal capsule.

Subthalamic Nucleus (STN) Internal Capsule Globus Pallidus Internus (GPi)

CLINICAL OPPORTUNITIES AND FUTURE NEEDS

- Ideally, DBS treatment should provide specific activation of the dorsolateral STN while sparing nearby fiber tracts
- Small, nearly unavoidable deviations in lead location can make this optimization difficult. Directional DBS may allow clinicians to compensate for small deviations, possibly improving outcomes and causing fewer adverse effects, while ring mode can still be used for cases that do not require fine-tuning
- Directional DBS can also enable exploration of stimulation-induced effects in the target region to better understand DBS mechanisms
- Assisting programming with anatomical and electrophysiological markers may simplify the directional DBS programming process
- Directionality has the potential to improve DBS in the STN as well as in other indications and targets
- Charge density is only explicitly controlled with a multiple independent current-controlled system

DIRECT DBS: A Prospective, Randomized, Multicenter, Double-Blinded Study on Directional DBS – Effects on Therapeutic Window

Steigerwald, F., Schuurman, P., Matthies, C., Kirsch, D., Chabardes, S., De Bie, R.M.A., Ten Brinke, T.R., Moro, E., Fraix, V., Meoni, S., Blum, D., Juarez Paz, L., Wynants, K., Van Dyck, N., and Volkmann, J.

Published: European Society for Stereotactic and Functional Neurosurgery. 2018.

Device Utilized: Vercise™ Deep Brain Stimulation (DBS) Directional Systems*

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. The authors of this study were employed by Boston Scientific. Figures created by Boston Scientific based on published data.

BACKGROUND

Historically, Deep Brain Stimulation (DBS) systems have delivered stimulation using cylindrical electrodes. In this study (DIRECT DBS), testing was performed using a directional DBS lead, which adds radially segmented electrodes designed for stimulation to be moved in the plane perpendicular to the lead. This study specifically analyzed therapeutic windows (TWs) at varying directional stimulation settings.

METHODS

12 Patients and 3 sites

Starting at the best vertical location, the four Coarse directions were blindly evaluated in a randomized order. From the best Coarse direction, 5 Fine directions were tested again blindly and in a random order.

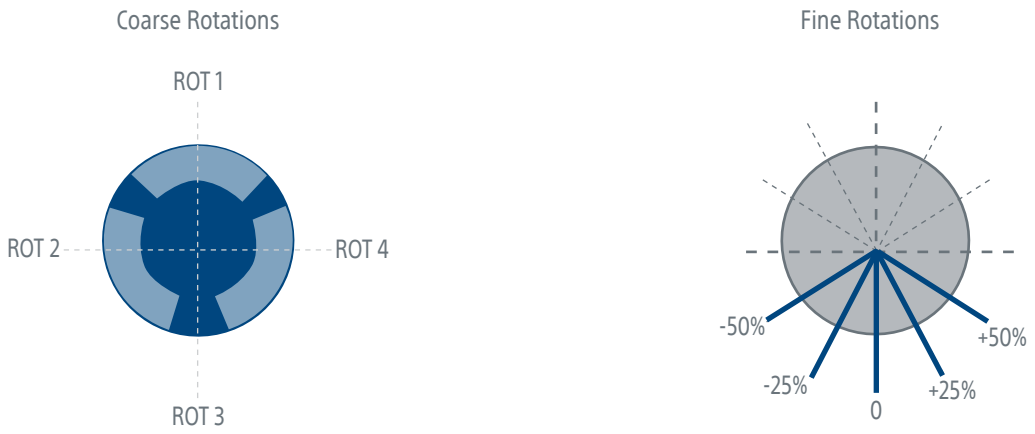


FIG 1. Depictions of Coarse (left) and Fine (right) rotational therapeutic window searches.

RESULTS

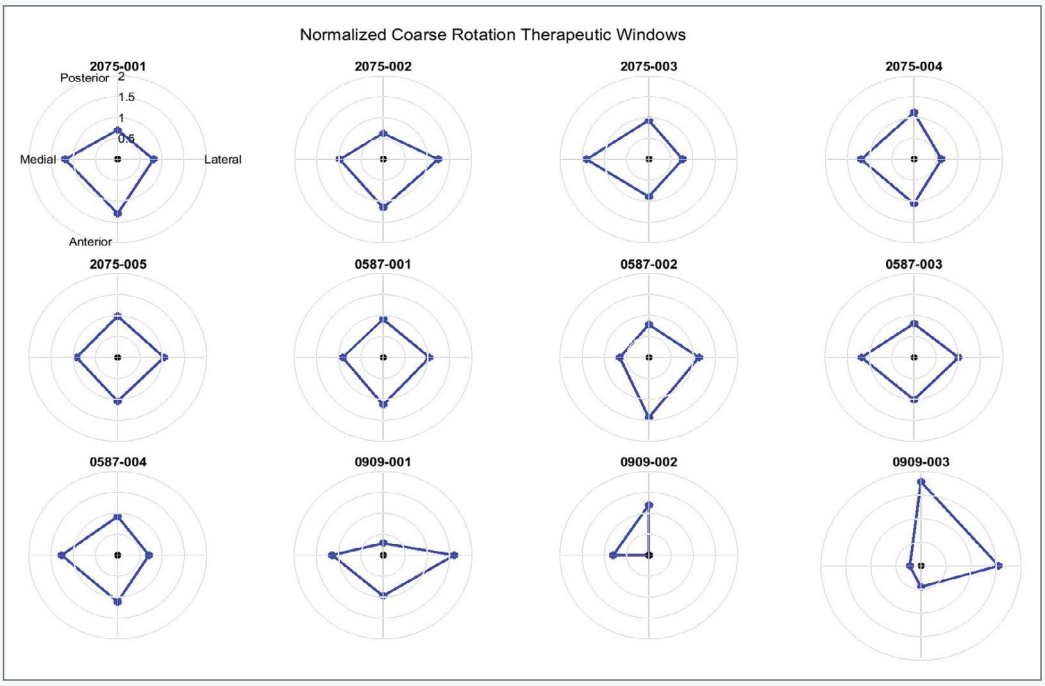


FIG 2. Therapeutic windows in the four Coarse directions (assumes that directional marker is pointed anterior) for each patient, normalized to average value.

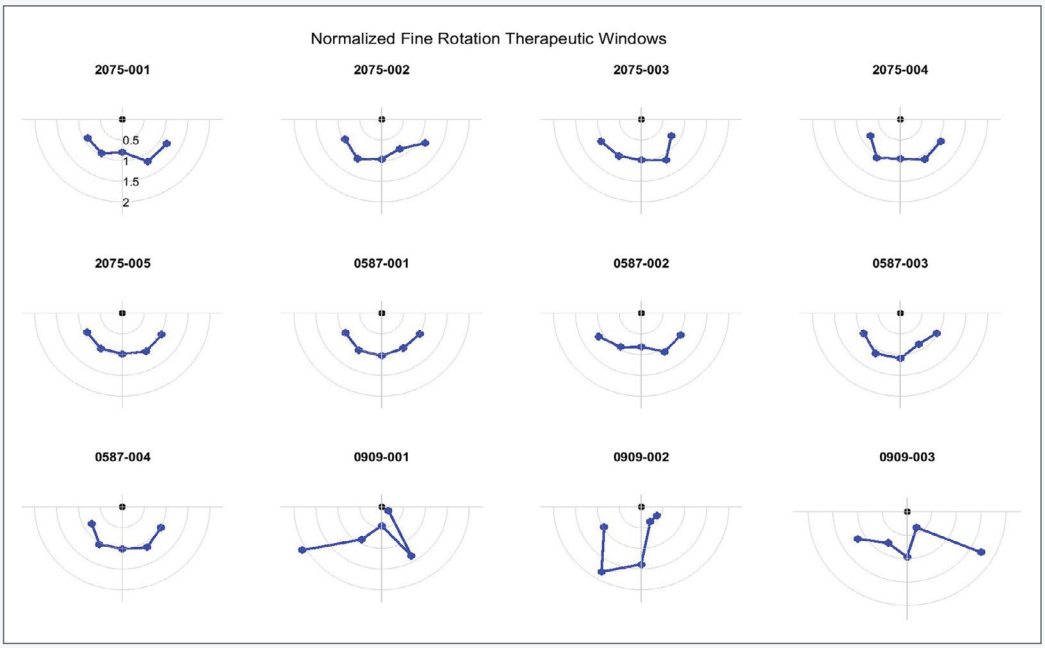
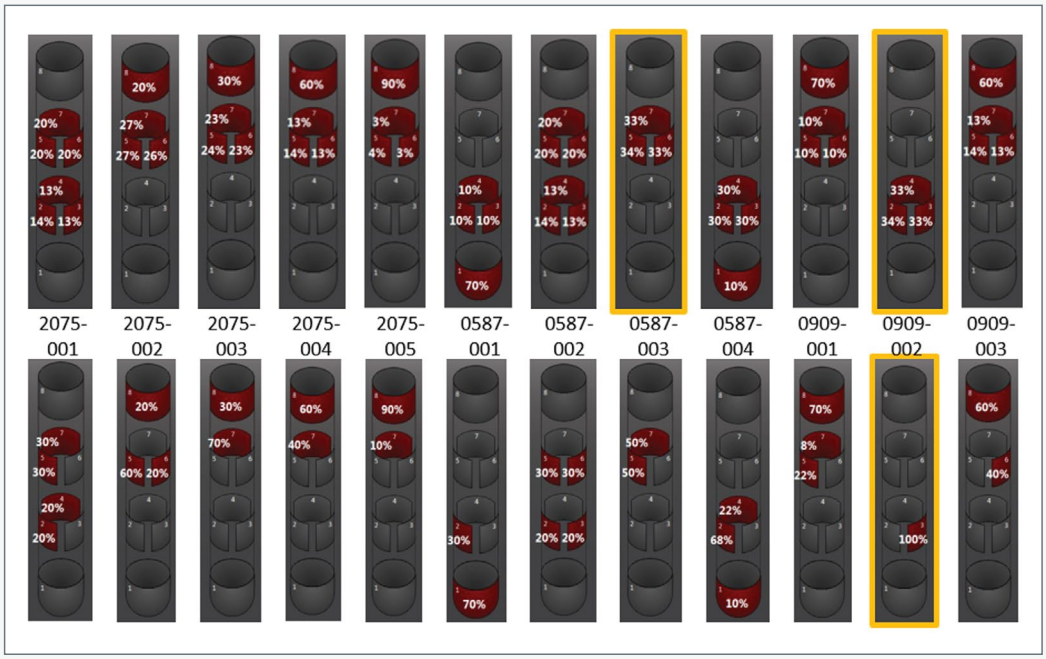


FIG 3. Therapeutic windows surrounding the best Fine direction for each patient, normalized to average value.



10/12 subjects were programmed using a virtual contact in ring mode

11/12 subjects were programmed using a virtual contact in directional mode

FIG. 4. Comparison of optimal stimulation settings for ring mode (top) and directional mode (bottom), identified in a blinded, randomized fashion. Orange outlines indicate single-row/single-contact settings.

CONCLUSIONS

- There can be marked differences in therapeutic window with different directional stimulation settings
- This holds true even with shifts as small as 25% of the current to an adjacent contact
- 10/12 of the optimal ring-mode settings needed multiple rows
- 11/12 of the optimal directional settings needed multiple contacts

*A System that includes the Vercise™ PC, Vercise Gevia™, or Vercise Genus™ IPG and Vercise Cartesia™ Directional Lead(s) forms the Vercise Directional System

Pilot Study for Considering Subthalamic Nucleus Anatomy During Stimulation Using Directional Leads

Asahi, T., Ikeda, K., Yamamoto, J., Tsubono, H., and Sato, S.

Published: Journal of Movement Disorders. 2019;12(2):97-102.

Study Type: Cohort study, single-center, retrospective

Device Utilized: Vercise Cartesia™ Directional Lead and Vercise™ PC Deep Brain Stimulation (DBS) System

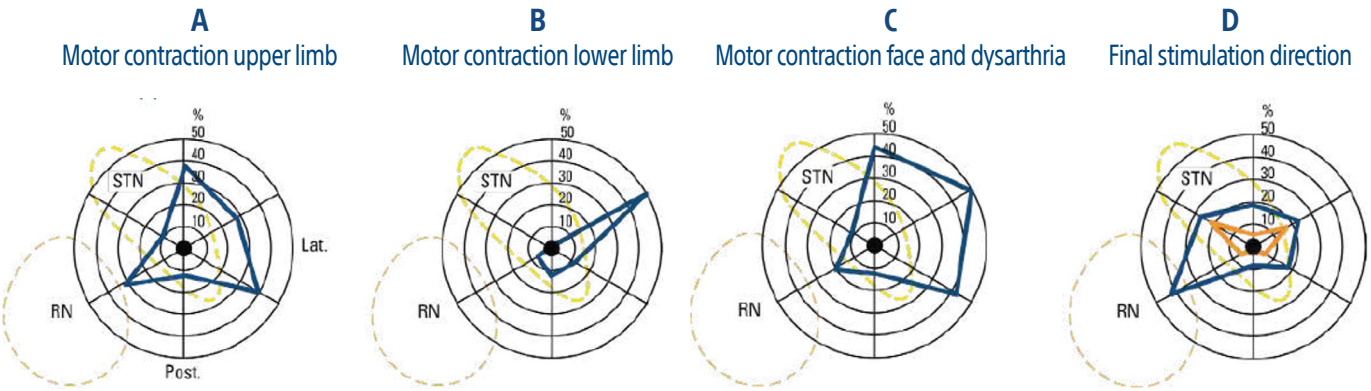
This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Figure created by Boston Scientific based on published data. One or more authors report funding from Boston Scientific as a financial disclosure.

BACKGROUND

In this study, the authors investigated the correlation between the direction of stimulation and the occurrence of adverse effects of Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD) patients.

METHODS

- 6 PD patients (mean age 66.2 years, 1 male) with bilateral implantation of directional DBS lead into the STN were enrolled in this study
- The leads were placed in order to have the centers of the two segmented levels located at the dorsal borders of the STN
- The lead position was identified by fusing a postoperative computed tomography (CT) scan with preoperative magnetic resonance imaging (MRI)
- The directional lead orientations were confirmed using radiopaque markers detected on postoperative x-ray imaging
- For the analysis, the contact directions were divided into six parts in increments of 60°
- One week after DBS surgery, the adverse-effect threshold of the directional contacts was assessed at 30 µs, 130 Hz, and a maximal stimulation amplitude of 11 mA
- The stimulation settings were adjusted to the location where maximum motor symptom improvement were observed without adverse effects



Direction of Adverse Effects and Final Stimulated Contacts. Frequency and distribution of contacts inducing motor contraction of the upper limb (A), motor contraction of the lower limb (B), and motor contraction of the face and dysarthria (C). Frequency and distribution of contacts used in the final stimulation (D). The deeper directional contacts are shown in blue, with the upper directional contacts shown in orange. The frequencies of adverse effects reported in the charts were calculated as (number of adverse effects/number of contacts in each angle) × 100.

RESULTS

- Motor symptoms (upper and lower extremities, face or voice) were frequently observed in the antero-lateral direction, which is consistent with the direction of the internal capsule (FIG. A-C)
- The final stimulation direction and the absence of adverse effects were mainly observed in the postero-medial direction
- Regarding the final stimulation level, 63% of used contacts were on the third level (segmented) from the tip, 32% were on the second level (segmented) from the tip, and only 6% were on the fourth level (ring) from the tip (FIG. D)
- Mean UPDRS part III and IV scores improved by 23.0 ± 12.3 ($p = 0.03$) and 5.2 ± 4.6
- Dyskinesia score decreased by 2.8 ± 2.3
- Levodopa equivalent daily doses decreased by 180.5 ± 173.1
- Gait and dyskinesia were controlled by a vertical steering:
    - When dyskinesia appeared, the stimulation point was moved slightly upward, toward the upper contacts
    - When patients experienced gait problems, such as freezing, the stimulation point was moved slightly downward toward the tip of the electrode

CONCLUSIONS

- Understanding the structures surrounding the STN is important for lead placement and designing stimulation strategies using directional leads
- Placing the midpoint of the directional levels in the upper border of the STN and adjusting of the vertical steering using independent current sources could be beneficial for dyskinesia suppression and gait control

Dyskinesia-Inducing Lead Contacts Optimize Outcome of Subthalamic Stimulation in Parkinson's Disease

Bouthour, W., Béreau, M., Kibleur, A., Zacharia, A., Tomkova Chaoui, E., Fleury, V., Benis, D., Momjian, S., Bally, J., Lüscher, C., Krack, P., and Burkhard, P.R.

Published: Movement Disorders. 2019;34(11):1728-1734.

Study Type: Case series, single-center, retrospective

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. One or more authors report funding from Boston Scientific as a financial disclosure.

BACKGROUND

Stimulation-induced dyskinesias (SIDs) can be observed in Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD) patients. SIDs can often be correlated with a good clinical outcome post-surgery. In this study, the authors assessed the effectiveness of dyskinesia-inducing contacts in improving patients' bradykinetic symptoms.

METHODS

- 20 patients implanted bilaterally in the STN with Vercise Cartesia™ directional leads were retrospectively analyzed
- Clinical assessments took place at least 3 months post-surgery and following a 12-hour withdrawal from dopaminergic medications
- Amplitude thresholds were recorded for rigidity (MDS-UPDRS III) and for side effects (pyramidal contraction, dysarthria, vertigo, oculomotor disturbance, and SIDs) for the following configurations:
    - Each of the 4 levels using ring-mode stimulation (2 segmented levels and 2 non-segmented levels)
    - Each of the 6 segmented contacts
    - Frequency was kept fixed at 130 Hz and pulse width at 60 µs

RESULTS

Stimulation-induced Dyskinesia

- SIDs were elicited in half of the patients (10/20)
  - 11 segmented contacts and 10 ring-mode stimulation induced SIDs
  - 6 segmented contacts produced dyskinesias that were not observed when patients were switched to ring mode using the corresponding segmented contact
  - 1 ring-mode stimulation elicited dyskinesias that were not observed on the corresponding segmented contacts

Programming Strategy

- The overall programming strategy was to program the SID-inducing contacts to obtain the best antibradykinetic effect without dyskinesia
- Multiple Independent Current Control (MICC) was used to simultaneously reduce the amount of current distribution on the SID-inducing contacts and to turn on adjacent contacts that were also effective on Parkinsonism without eliciting SIDs
- The current distribution was initially reduced by 50% on the SID-inducing contact and then progressively reduced by steps of 10% until SIDs disappeared
- On 4 contacts with a very low threshold for SIDs (≤ 1 mA), the current distribution had to be reduced to as low as 5% in order to abolish SIDs; switching off the SID-inducing contacts in those patients still worsened bradykinesia
- At 1-year follow-up, the combination of stimulating contacts was left unchanged in all patients, and only current amplitude had to be significantly increased (> 2 mA) in 2 patients

CONCLUSIONS

- The results of this study suggest that the contact(s) producing SIDs may help identify a beneficial area within the brain to stimulate
- Bradykinesia was best controlled by distributing the current among the contacts that induced SIDs vs. reducing the overall stimulation amplitude

Real World Clinical Outcomes Using a Novel Directional Lead From a Multicenter Registry of Deep Brain Stimulation for Parkinson's Disease

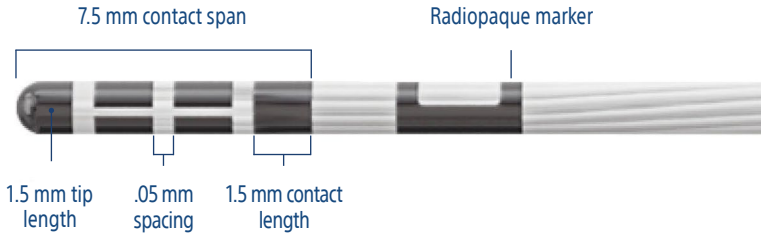
Vesper, J., Jain, R., Scholtes, H., Wang, A., Barbe, M.T., Paschen, S., Kühn, A., Volkmann, J., Pötter-Nerger, M., and Deuschl, G.

Published: World Society for Stereotactic and Functional Neurosurgery. 2019.

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. All figures created by Boston Scientific based on published data. One or more authors report funding from Boston Scientific as a financial disclosure. Boston Scientific was the primary sponsor of this study.

BACKGROUND

The authors evaluated real-world outcomes of using a directional lead with a Deep Brain Stimulation (DBS) system capable of Multiple Independent Current Control (MICC) for use in managing symptoms of levodopa-responsive Parkinson's disease (PD). Conventional DBS systems rely on ring-shaped electrodes with limited potential for controlling the shape of the electrical field or the volume of tissue activated. Directional current steering may permit a more personalized DBS approach.



The Vercise Cartesia™ DBS Directional Lead has four electrode levels, of which the two middle levels are split into three segments spanning approximately 120° (highest and lowest levels consist of ring-shaped electrodes).

METHODS

Primary Objective

- To compile real-world outcomes of an MICC-based DBS system (Vercise DBS Systems, Boston Scientific) using a directional lead (Vercise Cartesia DBS Lead, Boston Scientific)

Key Study Assessments

- Parkinson's Disease Questionnaire (PDQ-39)
- Unified Parkinson's Disease Rating Scale (UPDRS) or MDS-UPDRS
- Clinical Global Impression of Change as Assessed by Subject, Caregiver, and Clinician
- Schwab and England (SE) Scale
- EQ-5D-5L

KEY INCLUSION CRITERIA

- Subject understands study requirements and treatment procedures
- Subject provides written informed consent
- Subject meets criteria established in locally applicable Directions for Use (DFU)

KEY EXCLUSION CRITERIA

Subject meets any contraindication in applicable DFU

STUDY SCHEMATIC

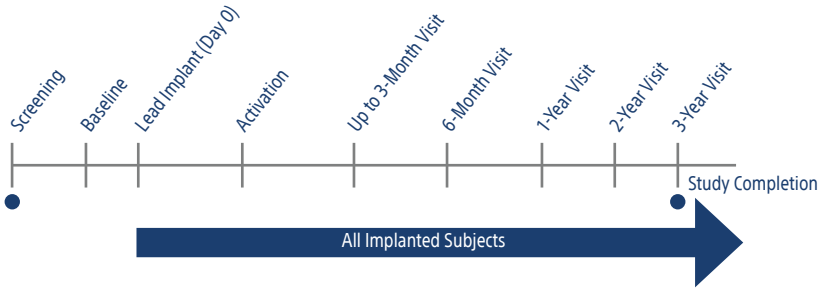


Table 1: Baseline Characteristics

Subjects Enrolled: n = 286 **Subjects Implanted as of March 2019: n = 283**	
Age (years) – Mean (SD) N	60.4 (8.2) 285
Gender – Male %	70
PD-related Symptoms	**Mean (SD) N**
UPDRS III Scores (meds-off)	38.1 (11.9) 112
MDS-UPDRS III Scores (meds-off)	9 (14.8) 130
Disease Duration (years)	10.1 (4.8) 284
PDQ-39 Summary Index Score	27.7 (13.7) 276

RESULTS

MDS-UDPRS III scores at baseline and 1 year post-implant

FIG. 1. MDS-UPDRS III Scores Converted (stim-on/meds-off)

- Improvement in motor function, as assessed by UPDRS III scores, sustained up to 1 year post-implant [34% ($p < 0.0001$)]

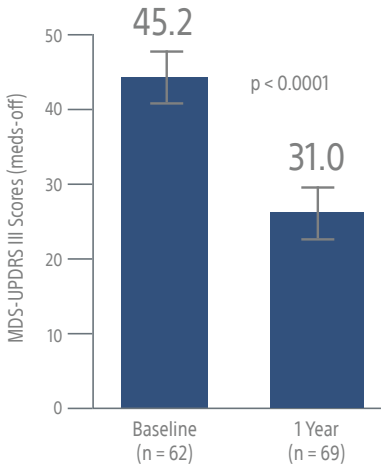


FIG. 2. Change in PDQ-39 Score

- PDQ-39 Summary Index showed improvement in Quality of Life ($p < 0.0001$) up to 1 year post-implant
- Improvements in Mobility, Activities of Daily Living (ADL), Stigma, and Bodily Discomfort domains were statistically significant ($p < 0.001$) at 6 months and were sustained at 1 year post-implant

PARKINSON'S DISEASE QUESTIONNAIRE (PDQ-39) AT 6 AND 12 MONTHS POST-IMPLANT

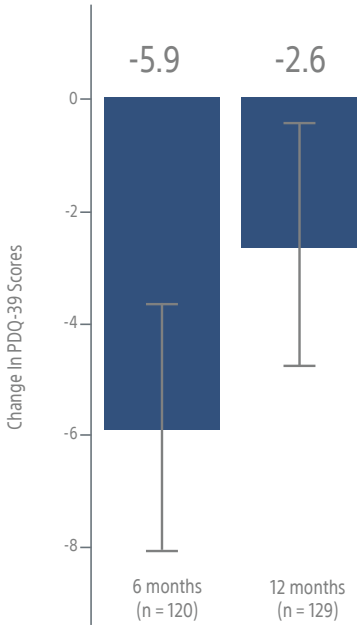
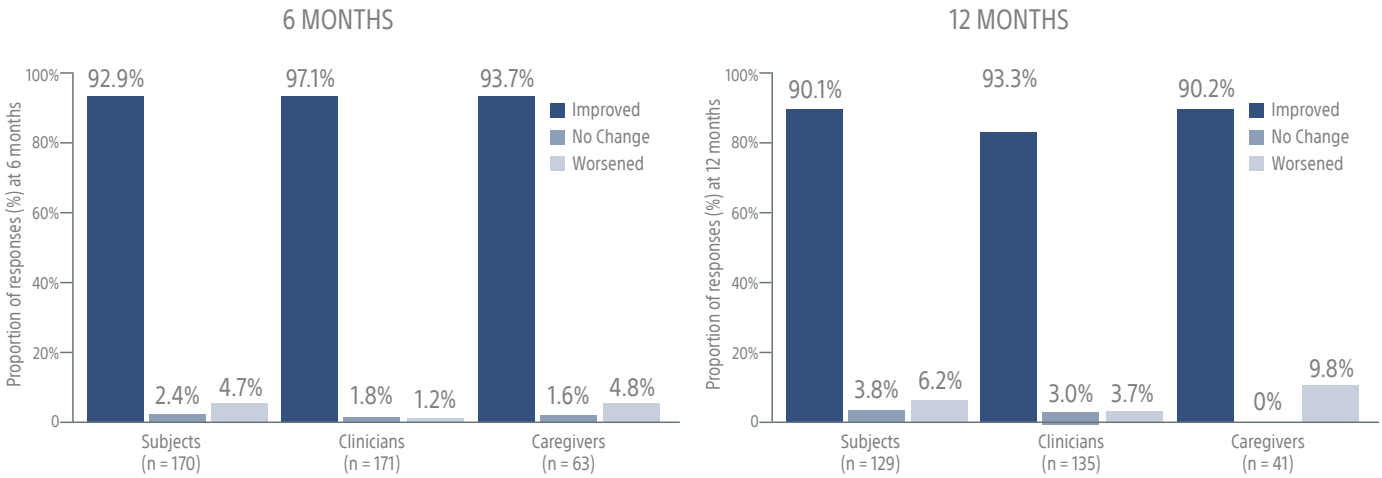


FIG. 3. Global Impression of Change (GIC) assessed by clinicians, subjects, and caregivers

- Over 90% of subjects, physicians, and caregivers noted improvement in PD symptoms at both 6 months and 12 months post-implant

GLOBAL IMPRESSION OF CHANGE (GIC) AT 6 AND 12 MONTHS POST-IMPLANT



SAFETY EVALUATION

- No unanticipated adverse events
- No lead breakages or fractures
- A total of 145 serious adverse events reported in 80 subjects

CONCLUSIONS

- This ongoing registry represents the first comprehensive, large-scale collection of real-world outcomes using a directional lead and an MICC-based DBS system
- Using directional stimulation, it may be possible to achieve a larger therapeutic window, thereby facilitating enhanced programming flexibility when optimizing for efficacy, while decreasing the likelihood of surpassing the adverse-effect threshold
- Preliminary analyses at 6 and 12 months post-lead implant demonstrated:
  - Overall improvement in Quality of Life (PDQ-39, EQ-5D-5L, and SE scores)
  - Significant improvement in motor function, as demonstrated by change in MDS-UDPRS III scores (meds-off)
  - Greater than 90% subjects, caregivers, clinicians reported improvement in PD symptoms
- Overall safety profile of directional lead is acceptable

Directional Orientation

Determining the Orientation Angle of Directional Leads for Deep Brain Stimulation Using Computed Tomography and X-ray Imaging: a Phantom Study

Sitz, A., Hoevels, M., Hellerbach, A., Gierich, A., Luyken, K., Dembek, T.A., Klehr, M., Wirths, J., Visser-Vanderwalle, V., and Treuer, H.

Published: Medical Physics. 2017;44:4463-4473.

Study Type: Laboratory experiment

Devices Utilized: Vercise Cartesia™ Directional Leads

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BACKGROUND

Typical Deep Brain Stimulation (DBS) leads cannot be steered in the horizontal plane, a limitation that can induce unintended side effects. Directional DBS can alleviate this problem but requires knowledge of lead orientation for anatomy-based or automated programming. The authors developed two algorithms to determine the orientation of a Boston Scientific directional lead with a high degree of accuracy using either a computed tomography (CT) scan or antero-posterior (AP)-lateral x-ray images.

METHODS

- The artifact created by the directional marker on the CT image can be used to determine the orientation of a lead
- Two stereoscopic x-ray images can also be used to determine the orientation using a 2D-to-3D image registration method

Phantoms

Two phantoms were utilized in this study:

- **Epoxy phantom:** A water-filled bottle with six segments of epoxy resin and a stylet was implanted with directional leads (aligned with stylets) to serve as a 'ground-truth' orientation to compare with orientation algorithms
- **Anthropomorphic phantom:** A 3D-printed bone structure resembling a human skull was filled with agarose to mimic soft tissue and was implanted with directional leads. Using multiple independent current sources enables greater specificity and consistency of field shaping than using a single current source

Lead Orientation Algorithms

- An x-ray-based and a CT-based algorithm were tested

X-ray-based Algorithm

- Lead orientation is determined by a model-based projection of the directional marker into the 2D plane of the x-ray (FIG. 1)
- X-ray images are transformed to patient's stereotactic space
- Directional markers are extracted from the images to prepare a rotated and cropped image of the directional marker for each orthogonal image
- A set of model-based projections for each orientation of the directional marker is created in the same window as the extracted image
- The set of model-based projections is compared with the extracted images to compute a similarity index based on contour of projection
- Final lead orientation is determined based on global minima of the similarity index (model projection that is most similar)

CT-based Algorithm

- Leverages presence of dark and bright streak artifacts in CT that results from the presence of the directional marker (FIG. 2)
- CT slice that contains the directional marker is manually selected
- Intensity of the CT is extracted from a 3 mm radius around the lead, yielding a circular intensity profile
- Fourier decomposition is performed on circular intensity profile to determine maxima and minima that correspond to the artifact, giving an estimate of orientation angle
- Orientation angle is adjusted to correct for aberrations based on pitch and yaw angle of lead.orientation of a lead

X-ray-based Analysis of Anthropomorphic Phantom

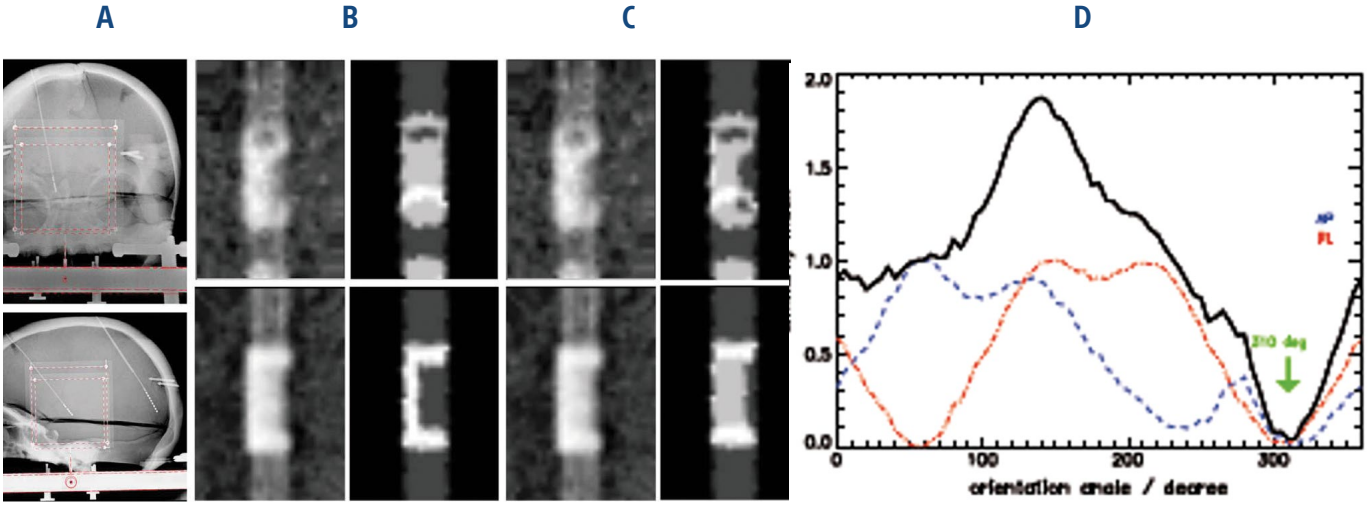


FIG. 1. Example of an anthropomorphic phantom. A. Frontal (top) and lateral (bottom) after stereotactic registration (dashed lines). B. Measured (left) and calculated (right) sub-images of the marker in frontal (top) and lateral (bottom) directions. Orientation angle of the virtual marker was assumed to be 0°. Similarity between the measured and virtual image is low. C. As in B, but after manual registration by lateral and vertical shift, and with 310° set as the orientation angle of the virtual marker. The similarity between the measured and virtual image is high. D. Similarity index of the measured and calculated images in frontal (dashed) and lateral (dot-dashed) views. The global minimum of the sum of both curves (solid) indicates the angle with the highest similarity of both image pairs together. In this example, the resulting angle was 310°. Note: Figure reproduced with permission from John Wiley and Sons as published, Sitz, A., et al. Medical Physics. 2017;44:4463-4473.

CT-based Analysis of Anthropomorphic Phantom

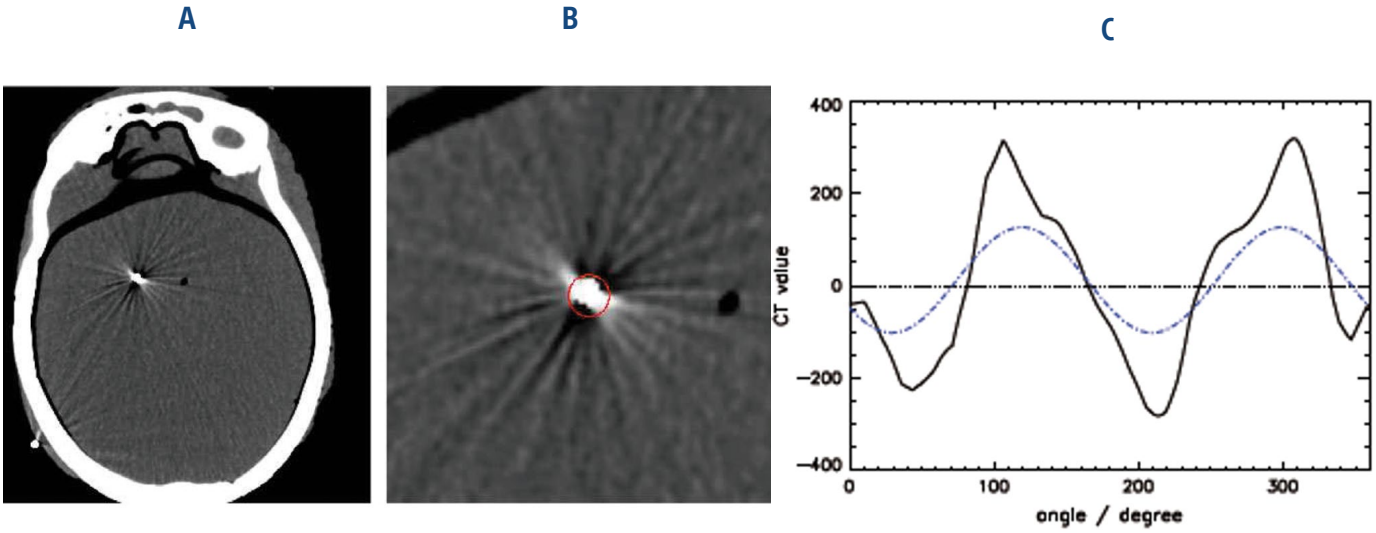


FIG. 2. CT Scan of an Anthropomorphic Phantom. A. Selected CT slice with the artifact of the directional marker (pitch angle 32.7°, yaw angle 8.6°). B. Magnified image of the artifact and sampling circle with 3 mm radius (solid line). C. Circular intensity profile (solid line) and Fourier component at a frequency of 2/360° (broken line) with maxima at 119° and 299°, resulting in possible directional lead orientation angles of 129° and 309°. Note: Figure reproduced with permission from John Wiley and Sons as published, Sitz, A., et al. Medical Physics. 2017;44:4463-4473.

PROCEDURAL METHODS

- A total of 135 CT scans and 54 x-rays were taken of the cylindrical phantoms
- Scans were taken at various directional orientations and polar angles with respect to the scanner axis
- Accuracy of each estimation method was compared to the ground-truth orientation taken from the stylets accompanying each lead in the respective phantoms
- The 3 anthropomorphic phantoms were collectively implanted with a total of 7 electrodes, and each phantom was imaged with both CT and x-ray to test the feasibility of each method in a real DBS case

RESULTS

X-ray-based Algorithm

- Lead orientation was determined with a mean deviation from ground truth of 6.9° ± 7.7°
- Significant differences between the phantoms were detected, so results were normalized to the mean of each phantom, resulting in mean deviations of 0.0° ± 5.0°
- This difference did not vary as a function of polar angle with respect to the scanner axis

CT-based Algorithm

- Lead orientation was determined with a mean deviation from ground truth of 5.3° ± 5.1°
- Significant differences between the phantoms were detected, so results were normalized to the mean of each phantom, resulting in mean deviations of 0.0° ± 2.8°
- The algorithm showed increased error at polar angles > 40°
- For the anthropomorphic phantoms, a mean deviation of 3.6° ± 7.1° was observed, again varying as a function of polar angle

AUTHORS' CONCLUSIONS

- This study presents a solution to the problem of determining the orientation of a directional DBS lead after implantation using radiographic imaging
- Both CT- and x-ray-based determination methods achieved a high level of accuracy in this phantom study
- The Fourier-based CT algorithm is a robust way to determine lead orientation based on artifacts, but it contains 180° ambiguity
- Variability introduced by the surgical technique is less than 90°, so gross estimates of the orientation should resolve this 180° ambiguity
- Loss of accuracy in the CT-based method for polar angles > 40° is a result of marker height and slice thickness
- Longer directional markers or higher-resolution CT scans may be able to take advantage of the algorithm to determine lead orientations for larger polar angles

Determining the Orientation of Directional Deep Brain Stimulation Electrodes Using 3D Rotational Fluoroscopy

Reinacher, P.C., Krüger, M.T., Coenen, V.A., Shah, M., Roelz, R., Jenkner, C., and Egger, K.

Published: American Journal of Neuroradiology. 2017;38:1111-1116.

Study Type: Double-blind, laboratory experiment

Devices Used: Vercise Cartesia™ Directional Leads

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Figures created by Boston Scientific based on published data. One or more authors report Boston Scientific as a source of financial support.

BACKGROUND

Directional Deep Brain Stimulation (DBS) has the potential to increase therapeutic window size, allowing for efficient treatment of Parkinson's disease (PD) symptoms by steering current away from internal capsule and toward the subthalamic nucleus (STN). Understanding the exact orientation of a DBS directional lead is critical for steering the electrical field in a predefined direction.

The authors of this study investigated whether 3-dimensional rotational fluoroscopy could be an optimal imaging solution for determining the precise degree of a lead's rotation and orientation.

Current Imaging Modalities

- Antero-posterior (AP) and lateral x-rays offer only an approximate orientation
- Computed tomography (CT) artifacts can be used to determine orientation but only for a specific range of imaging angles
- Magnetic resonance imaging (MRI) is not feasible because currently available leads are not MRI-opaque

METHODS

- A plaster skull filled with gelatin was implanted with two Vercise Cartesia Directional Leads at typical DBS trajectories
- An orientation marker was affixed to the proximal end of the lead, and electrodes were rotated clockwise and counterclockwise 360° to determine how proximal rotation influenced orientation of the distal electrodes
- A series of 120 fluoroscopy frames was acquired with 2° resolution across a 240° rotational arc around the plaster skull, delivering a moderate dose of radiation (2.327 mGy x cm^2)
- Each of the two electrodes were randomly rotated between 1° and 360° and imaged on the next page; this process was then repeated so that a total of 12 orientations were imaged for each lead

- Two methods were used by each of three blinded raters to determine electrode orientation
    - Marker: The distal metal orientation marker was imaged on the fluoroscopy series, and raters determined which frame captured the lead orientation
    - "Iron Sights": At very specific angles, the gaps between the directional contacts line up and are visible on fluoroscopy, appearing as bright lines (FIG. 1). Because this phenomenon occurs only at a narrow subset of known angles, the presence of these lines can be used to determine which frame captures specific orientations of lead
- Inter-rater reliability was assessed using Band-Altman plots to show the accuracy of the two methods as a function of 'limits of agreement'

"IRON SIGHTS" METHOD

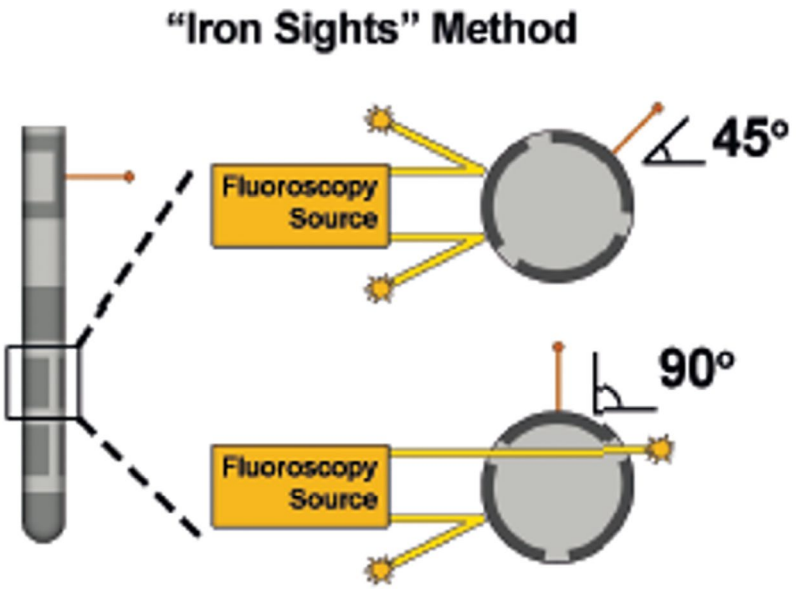
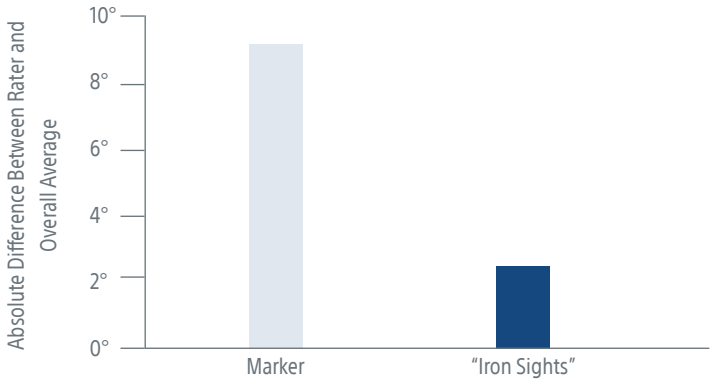


FIG 1. "Iron Sights" Method. The "Iron Sights" method takes advantage of a phenomenon in which gaps between directional contacts can be seen on the fluoroscopy image (top). When the gaps between the directional contacts are aligned orthogonal to the plane of the image, a light band can be seen, a result of the fluoro passing through the gap. This phenomenon only occurs at specific, known angles
(30°, 90°, 150°, 210°, 270°, and 330°). See the original manuscript (Reinacher et. al., 2017) for examples of this phenomenon. The limits of agreement for the method using the marker alone were higher than the limits for the "Iron Sights" method (±9.37° > ±2.44°).

LIMITS OF AGREEMENT



RESULTS

Torsion Test

- After a 360° clockwise rotation, the right lead orientation changed from +3.8° to -5.5°, while the left lead was unchanged at +5.4°
- After a 360° counterclockwise rotation, the right lead orientation changed from -5.5° to +35.0°, while the left lead changed from +5.4° to +16°

Determining Lead Orientation

- Using the directional marker alone, the limits of agreement for orientation of lead could be determined within ±9.37°
- Using the "Iron Sights" method, limits of agreement for the orientation of the lead could be determined within ±2.44°
- Both methods showed high inter-rater reliability

CONCLUSIONS

- To realize the full potential of a directional DBS system, a visually based programming system that provides models of stimulation fields overlaid with anatomy would be useful
- Such a system would require accurate knowledge of lead orientation
- Because the lead can change orientation during the fixation process, and proximal rotation is not a reliable way to influence distal orientation, a postoperative imaging technique for determining orientation is required
- The incidental visualization of gaps between directional contacts on rotational fluoroscopy provided the most accurate method to determine lead orientation
- This method is accurate over a wide range of imaging angles, unlike CT-based methods
- The statistics used in this study describe only the agreement between raters, rather than the ground truth for lead orientation
- The radiation dose delivered by rotational fluoroscopy is moderate, but represents an additional exposure if added to standard practice

Anodic Stimulation

Anodic Versus Cathodic Neurostimulation of the Subthalamic Nucleus: A Randomized-Controlled Study of Acute Clinical Effects

Dalal Kirsch, A., Hassin-Baer, S., Matthies C., Volkmann, J., and Steigerwald, F.

Published: Parkinsonism Related Disorders. 2018 May 16.

This summary was created by Boston Scientific and is intended to consolidate the paper for educational us only. Figure created by Boston Scientific based on published data. One or more authors report funding from Boston Scientific as a financial disclosure. This study was funded in part by a grant from Boston Scientific.

BACKGROUND

Cathodic stimulation has customarily been used in Deep Brain Stimulation (DBS), in part because of the limitations of traditional DBS systems. Next-generation systems allow for expanded selection of stimulation parameters, including anodic stimulation. Anodic stimulation theoretically requires amplitudes 3-6 times higher than cathodic stimulation to activate axons and similar amplitudes to activate cell bodies. The authors present the first randomized clinical assessment comparing anodic and cathodic stimulation of the subthalamic nucleus (STN) in Parkinson's disease (PD) patients.

METHODS

Enrollment

- 10 Parkinson's patients implanted with Boston Scientific Directional DBS System*
- All patients were implanted bilaterally in the STN
- All patients had good response to traditional cathodic stimulation
- Patients included tremor-dominant (n = 2), akinetic-rigid (n = 5), and equivalent (n = 3) cases

Monopolar review

- Extensive monopolar review was performed 2-3 months after surgery, before inclusion in the study
- Each contact was screened for highest efficacy and therapeutic window
- Settings were adjusted as per normal clinical practice, allowing use of horizontal and vertical current steering

STUDY DESIGN

- As part of this double-blind, randomized, cross-over design trial, participants were randomized into blocks of four to be tested either with cathodic or anodic stimulation first
- Dopaminergic medications were withdrawn overnight, and the Unified Parkinson's Disease Rating Scale (UPDRS) III score was determined in the practically defined OFF state
- After a 15-minute stimulation wash-out, stimulation polarity was reversed for anodic stimulation testing, maintaining all other simulation parameters but swapping the cathode on the contact with the anode on the implantable pulse generator (IPG)
- A blinded rater re-assessed clinical symptoms while an un-blinded programmer repeated the amplitude titration for anodic stimulation
- Thresholds for clinical effects and side effects were determined, and subjects were programmed 0.5 mA below the side-effect threshold
- After a 30-minute stimulation wash-in period, UPDRS III scores were assessed
- The subject was then crossed over to the other arm and the procedure was repeated
- Patients were allowed to stay on anodic stimulation after the study, if they preferred

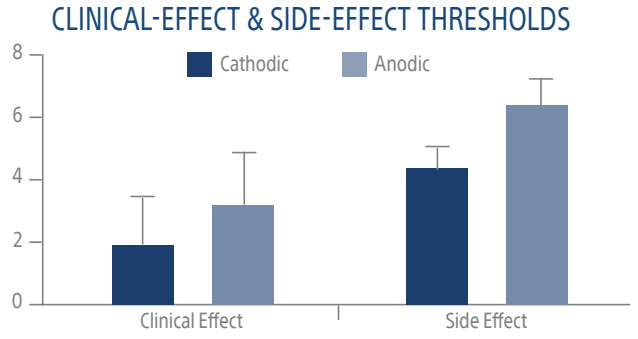
RESULTS

Effect Thresholds

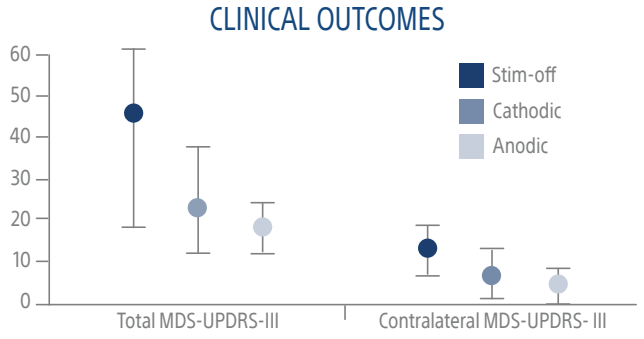
- Clinical-effect thresholds increased from 1.99 ± 1.37 mA for cathodic stimulation to 3.36 ± 1.58 mA for anodic stimulation ($p < 0.0001$)
- Side-effect thresholds also increased from 4.15 ± 1.13 mA for cathodic stimulation to 6.05 ± 1.52 mA for anodic stimulation ($p < 0.0001$)
- In 70% of electrodes, the limiting side effect for cathodic stimulation was the same as for anodic stimulation
- Therapeutic windows increased from 2.07 ± 1.14 mA for cathodic stimulation to 2.73 ± 1.43 mA for anodic stimulation after two outliers were removed ($p < 0.05$, $p = 0.065$ with outliers included)

Parkinson's Motor Sign Improvement

- All 10 patients benefitted from cathodic stimulation as per inclusion criteria (mean UPDRS III improvement 44 ± 11.4 %)
- Anodic stimulation significantly improved UPDRS III scores over the OFF state (62%)
- Anodic stimulation resulted in superior improvements over cathodic stimulation for both total UPDRS III and Contralateral UPDRS III (median UPDRS III 23 versus 17, $p < 0.005$)
- Anodic stimulation achieved a complete matching of medication effect, with a mean improvement from stimulation that was 101 ± 35.2% of the levodopa effect on UPDRS III
- Cathodic stimulation showed a mean response of 72% ± 24.5% of the levodopa effect
- Anodic stimulation was less effective at capturing tremor than cathodic stimulation (39.1% vs. 66.1%)
- Cathodic stimulation was more energy-efficient than anodic stimulation, as measured by UPDRS points gained per mA of stimulation
  (2.1 ± 1.0 vs. 1.8 ± 1.0)



Thresholds for cathodic and anodic stimulation
Clinical-effect thresholds and side-effect thresholds for both cathodic and anodic stimulation are shown. Clinical-effect thresholds increased from 1.99 ± 1.37 mA for cathodic stimulation to 3.36 ±1.58 mA for anodic stimulation ($p < 0.0001$). Side-effect thresholds also increased from 4.15 ± 1.13 mA for cathodic stimulation to 6.05 ±1.52 mA for anodic stimulation ($p < 0.0001$).



UPDRS outcomes for cathodic and anodic stimulation
Total UPDRS and Contralateral UPDRS score are also displayed. Anodic stimulation was superior to cathodic stimulation, which itself was superior to stim-off (median 17 vs. 23 vs. 45, respectively). This was also true for the UPDRS Contralateral hemibody score (median 4 vs. 7 vs. 14, respectively).

AUTHORS' CONCLUSIONS

- Anodic stimulation improved UPDRS III scores over cathodic stimulation
- Stimulation amplitudes were increased, but not by the predicted 3- to 6-fold increase
- The authors hypothesized that this improvement may be observed because anodic stimulation is preferentially activating therapeutically beneficial fibers
- The study utilized the same parameters that the patient was previously programmed on in the cathodic case, and only evaluated outcomes acutely
- Four patients opted to remain on anodic stimulation after the trial

*A System that includes the Vercise™ PC, Vercise Gevia™, or Vercise Genus™ IPG and Vercise Cartesia™ Directional Lead(s) forms the Vercise Directional System

Therapeutic Window of Deep Brain Stimulation Using Cathodic Monopolar, Bipolar, Semi-Bipolar, and Anodic Stimulation

Soh, D., Brinke, T.R., Lozano, A.M., and Fasano, A.

Published: Neuromodulation. 2019;22(4):451-455.

Study Type: Case series, open-label

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Figure created by Boston Scientific based on published data. One or more authors report funding from Boston Scientific as a financial disclosure.

BACKGROUND

In this study, the authors compared the therapeutic windows of cathodic monopolar, bipolar, anodic monopolar, and a novel "semi-bipolar" stimulation.

METHODS

- 10 Parkinson's disease (PD) patients (mean age 64.9 ± 3.6 years, 7 men) were evaluated
- Patients were bilaterally implanted with the Boston Scientific Deep Brain Stimulation (DBS) system in the subthalamic nucleus (STN)
- The mean stimulation settings were:
  - Current amplitude of 4.8 ± 1.7 mA
  - Pulse width of 55.3 ± 8.7 µs
  - Frequency of 114.0 ± 33.4 Hz
- 17/20 electrodes were initially configured as cathodic monopolar stimulation and 3/20 as bipolar stimulation
- The patients' mean Unified PD Rating Scale (UPDRS) III score (meds-on/stim-on) was 24.0 ± 10.8
- Patients were assessed off medications using the following conditions:
  - Cathodic monopolar
  - Anodic monopolar
  - Bipolar
  - Semi-bipolar (anode equally divided between the case and another contact on the lead)
- Patients were blinded to each stimulation condition, and the order of assessment was not randomized
- Battery Consumption Index (BCI) was calculated using a Boston Scientific clinical programmer

RESULTS

Therapeutic Threshold

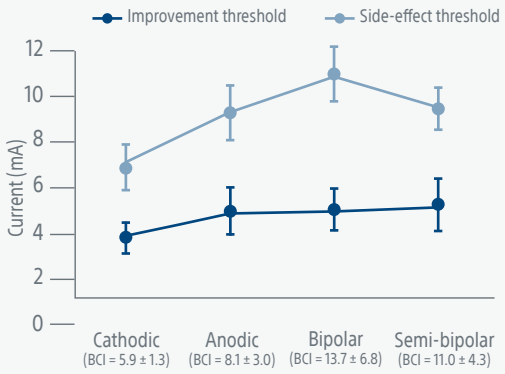
- Compared with cathodic stimulation, the therapeutic thresholds were significantly higher for anodic, bipolar, and semi-bipolar stimulation (3.8 ± 1.6 vs. 4.9 ± 2.1, 5.0 ± 1.9, and 5.2 ± 1.9 mA, p = 0.0006, 0.0002, and 0.008, respectively)
- No significant difference in therapeutic threshold was reported between anodic, bipolar, and semi-bipolar stimulation

Side-Effect Threshold

- Thresholds were significantly higher for bipolar stimulation (10.9 ± 2.5 mA) compared with cathodic (6.8 ± 2.2 mA) and anodic (9.2 ± 2.6 mA) stimulation
- Thresholds were significantly higher for anodic and semi-bipolar stimulation (9.4 ± 2.1 mA) compared with cathodic stimulation

Therapeutic Window

- The therapeutic window was significantly narrower for cathodic stimulation (2.5 ± 1.5 mA) compared to bipolar (5.4 ± 2.0 mA), semi-bipolar (4.6 ± 2.6 mA), and anodic (4.3 ± 2.3 mA) stimulation
- The therapeutic window was significantly wider for bipolar and semi-bipolar stimulation compared to anodic stimulation



Therapeutic window of the different stimulation modes. The graph shows the mean stimulation amplitude for therapeutic response of rigidity and the mean side-effect threshold under cathodic, anodic, bipolar, and semi-bipolar stimulation. The respective Battery Consumption Index (BCI) is also reported.

Battery Consumption Index

- The BCI was significantly lower for cathodic stimulation (5.9 ± 1.3) compared to bipolar (13.7 ± 6.8), semi-bipolar (11.0 ± 4.3), and anodic (8.1 ± 3.0) stimulation
- The BCI was significantly lower for anodic stimulation compared to bipolar and semi-bipolar stimulation

CONCLUSION

- Battery consumption is reduced with cathodic stimulation; therefore, cathodic stimulation may be the preferred stimulation modality followed by semi-bipolar stimulation when stimulation-induced side effects are a factor

Short Pulse Width

Short Pulse Width Widens the Therapeutic Window of Subthalamic Neurostimulation

Reich, M.M., Steigerwald, F., Sawalhe, A.D., Reese, R., Gunalan, K., Johannes, S., Nickl, R., Matthies, C., McIntyre, C.C., and Volkmann, J.

Published: Annals of Clinical and Translational Neurology. 2015;2:427-432.

Study Type: Case series, single-center, open-label

BACKGROUND

In this study, the authors sought to assess the clinical benefits of Subthalamic Deep Brain Stimulation (STN-DBS) in Parkinson's disease (PD) patients using short pulse-width (PW) stimulation (< 60 µsec). Stimulation at short PW may improve selectivity for fibers of interest and consequently may improve DBS therapeutic windows.

METHODS

- Four PD patients were enrolled in this study (two females, age 49–62 years)
- Bilateral STN-DBS implantation with Vercise™ Neurostimulation System was performed
- Between 2-4 months after surgery, DBS was programmed under meds-off state following conventional approach with PW set at 60 µsec
- After at least 1 month of stimulation, monopolar reviews were conducted using the electrode previously activated, and PW and stimulation amplitude were optimized to produce best clinical outcomes
    - Efficacy threshold was defined as the minimal stimulation amplitude to achieve complete or almost complete contralateral rigidity suppression
    - Adverse-effect threshold was defined as the minimal stimulation amplitude to elicit side effects
    - Seven PWs (20, 30, 40, 50, 60, 90, and 120 µsec) were randomly tested
    - Stimulation frequency was set at 130 Hz, and stimulation amplitude was progressively increased until adverse effects were elicited
    - Therapeutic window was defined as the difference between the efficacy threshold and the adverse-effect threshold and was assessed for each PW
    - Therapeutic windows were normalized to 60 µsec to make the results comparable between subjects
    - Based on efficacy threshold results, related chronaxies were calculated by linearizing the strength–duration curves and estimating the slope and intercept

Computational model of activation

- To support the clinical result analysis, a computational model of axon activation was created that simulates the effect of a given electric field on two different axon populations
- One pathway was composed of smaller (2 µm diameter) axons located closer (1–2 mm) to the electrode to represent the presumably therapeutic hyperdirect pathway
- A second pathway was composed of larger (5.7 µm diameter) axons located farther (4-5 mm) from the electrode to represent the internal capsule

RESULTS

- Mean Unified Parkinson's Disease Rating Scale (UPDRS III) motor score before DBS system implantation was 51 ± 11.97 and improved to 24.75 ± 8.58 points in the meds-off state
- Side-effect threshold and PW stimulation were found to be inversely related
- Compared with the therapeutic window assessed at 60 µsec (2.2 ± 1.6 mA), a 30 µsec PW increased the therapeutic window by 182 ± 128% while a 120 µsec PW decreased the therapeutic window by 46 ± 28%
- Threshold for full rigidity control was measured at 1.6 ± 0.9 mA for 60 µsec and 2.9 ± 1.4 mA for 30 µsec
- Related total charge delivered per pulse was calculated as 95 ± 51 nC/pulse for 60 µsec and 88 ± 43 nC/pulse for 30 µsec
- Based on linear regression of the strength-duration curves, the chronaxie for excitation of neural elements responsible for rigidity control was estimated to be 225 µsec and 126 µsec for muscular contractions

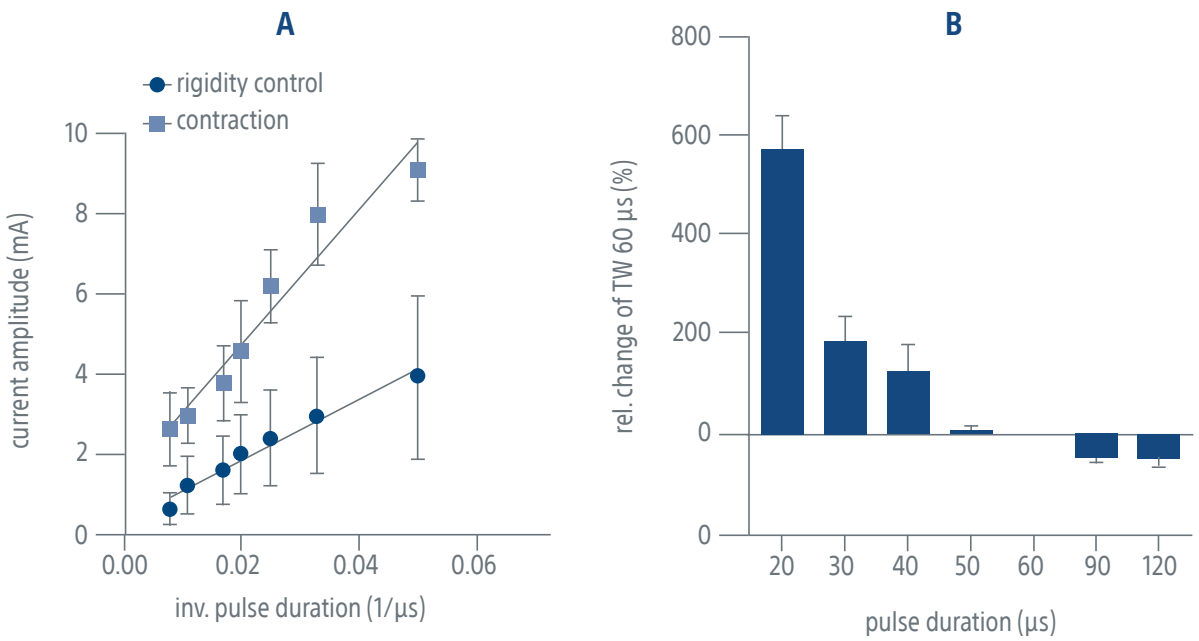


FIG 1. A. Linearized strength–duration curves for rigidity control and muscle contractions. B. Bar graph depicting the relative change in therapeutic window compared to 60 µsec pulse duration (TW 60 µsec). Error bars indicate the standard error of mean in both graphs.

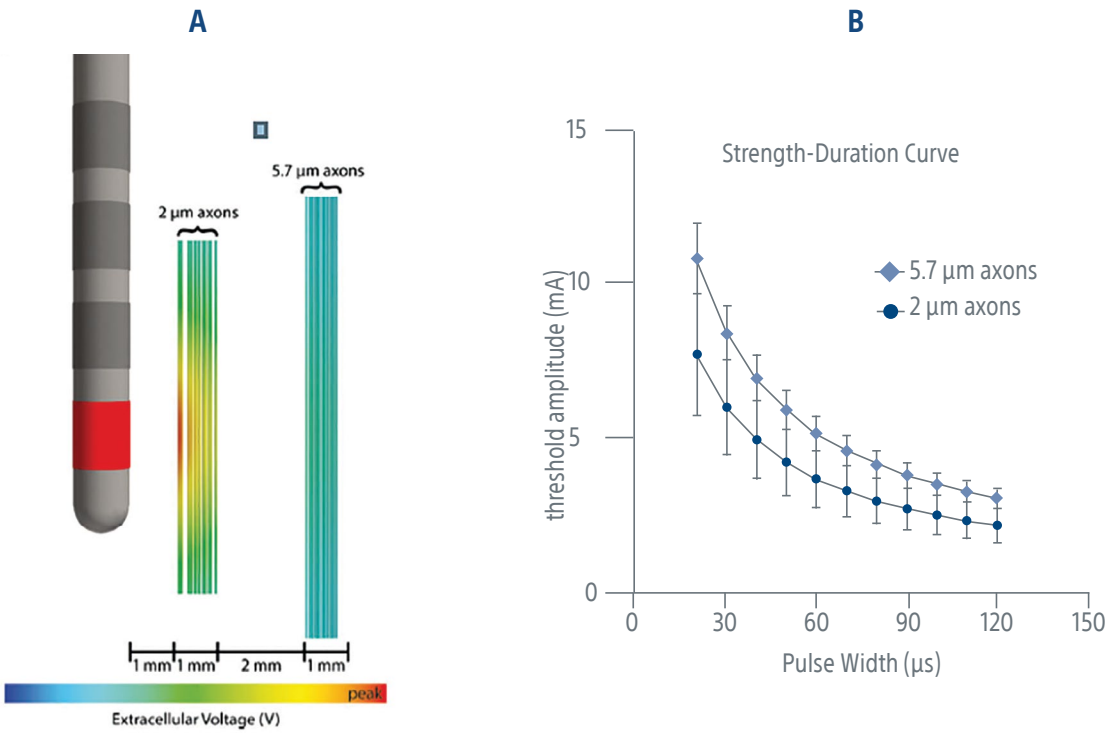


FIG 2. Model-derived strength–duration curves for action potential initiation in smaller (2 µm diameter) axons located closer (1–2 mm) to the electrode as compared to larger (5.7 µm diameter) axons located farther from (4–5 mm) the electrode. At shorter pulse durations, the two curves diverge, explaining an increased "therapeutic window" where the benefit is associated with stimulation of the nearby fibers and adverse effects are associated with the distant thick myeliniated axons.

CONCLUSIONS

- Therapeutic window was enlarged by two-fold when DBS was delivered with pulse duration of 30 µsec versus 60 µsec
- When stimulation was applied with 20 µsec pulse width, no capsular responses were obtained in 6/8 electrodes within the stimulation amplitude limit of 10 mA defined by the study
- Unsurprisingly, when reducing the PW stimulation, the stimulation amplitude needed to elicit full rigidity control (efficacy threshold) increases
- Despite the need for increased amplitude, the total charge per pulse decreased, suggesting that the PW reduction might not only increase the adverse-event threshold but also reduce battery consumption
- The suggested mechanism of action of the short PW stimulation is the preferential activation of the small fibers of the STN localized near the electrode prior to the activation of larger and further fibers in the internal capsule (responsible for side effects)
- This hypothesis is supported by the proposed computational model of axon activation

Pulse Duration Settings in Subthalamic Stimulation for Parkinson's Disease

Steigerwald, F., Timmermann, L., Kühn, A., Schnitzler, A., Reich, M. M., Dalal Kirsch, A., Barbe, M. T., Visser-Vandewalle, V., Hübl, J., van Riesen, C., Groiss, S. J., Moldovan, A., Lin, S., Carcieri, S., Manola, L., and Volkmann, J.

Published: Movement Disorders. 2018;33:165-169.

Study Type: Randomized, controlled, double-blind, multi-center

 One or more authors report funding from Boston Scientific as a financial disclosure. Boston Scientific was the primary sponsor of this study.

BACKGROUND

The CUSTOM-DBS study was designed to address the need for an evidence-based update of Deep Brain Stimulation (DBS) programming guidelines, including the expanded parameter space of novel DBS devices. The primary outcome was the use of pulse widths shorter than 60 µs to expand the window between therapeutic effects and side-effects thresholds, without compromising efficacy.

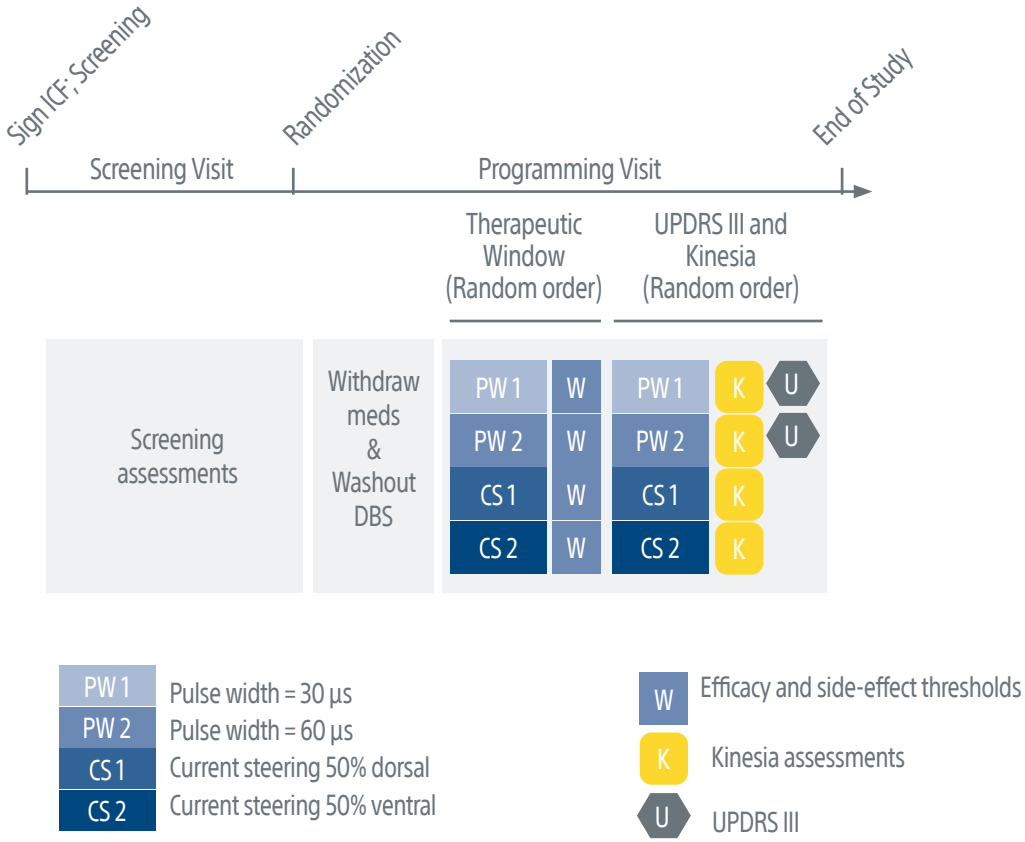
METHODS

Participants

- Parkinson's disease (PD) patients bilaterally implanted with a Vercise™ DBS System in the subthalamic nucleus (STN) for at least 3 months
- Patients had a Unified PD Rating Scale (UPDRS) III score of ≥ 30 in the preoperative meds-off state
- Following DBS, patients had ≥ 30% symptom reduction in the meds-off state
- Patients were disqualified from the study if severe tremor would interfere with assessments

Procedures

- Clinical study transpired over a single programming visit
- Test conditions were conducted in a double-blind randomized manner
- Patients were initially in a meds-off/stim-off state
- Stimulation was then turned on to the clinically more affected side of the body
- Stimulation was delivered through the best therapeutic electrode
- Frequency remained fixed at 130 Hz
- Pulse width was randomly assigned to either 30 µs or 60 µs
- At each setting, amplitude was gradually increased until a side-effect threshold was taken (defined as the minimum amplitude for any side effect persisting after 2 minutes of stimulation)

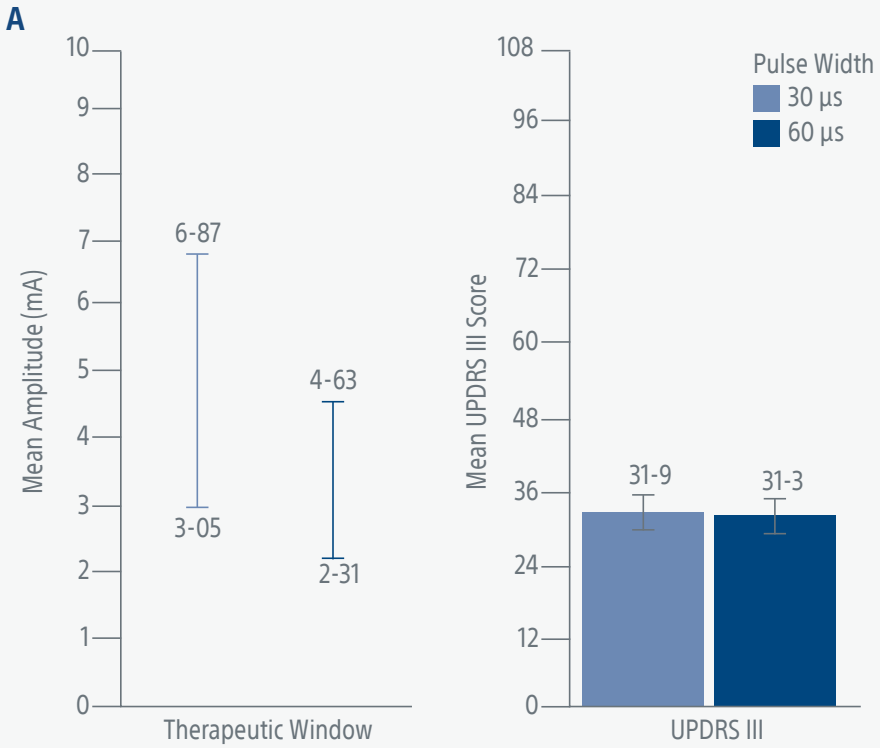


Steigerwald, F., et al. 2018

FIG 1. Study Overview.
Schematic of the CUSTOM-DBS study, a multi-center, double-blind, randomized controlled trial. At the programming visit, the therapeutic window was first measured in a randomized, double-blind assessment at four different program settings. Double-blind UPDRS III and exploratory quantitative assessments (Kinesia assessments of rest tremor, finger tapping, and rapidly alternating movement tasks; Kinesia ProView, Great Lakes Neurotechnologies) were then taken at the efficacy threshold for rigidity for each setting. In addition to test and control pulse width settings, current steering settings were also tested as exploratory endpoints.

RESULTS

- Stimulation at 30 µs resulted in a significantly larger therapeutic window than 60 µs (mean 3.82 vs. 2.32 mA; p = 0.0009)
- Efficacy at the rigidity threshold for 30 µs was non-inferior to 60 µs as measured by total UPDRS motor score (mean 31.9 vs. 31.3; p = 0.00008)
- Noninferiority of efficacy at 30 µs was further confirmed by an externally kinematic finger sensor that measures rest tremor, or rapidly alternating movements (finger taping)



Steigerwald, F., et al. 2018

FIG 2. Coprimary endpoints. A. Superiority of the therapeutic window size (left) and noninferiority of UPDRS III (right) at a short pulse width. Error bars represent ±1 standard error.

CONCLUSIONS

- This is the first double-blind assessment of the effect of a shorter pulse width. Standard programming settings used in subthalamic nucleus (STN) DBS for PD may not be optimal
- Shorter pulse width of 30 µs was superior to the standard 60 µs in terms of minimizing the likelihood of stimulation-related side effects while maintaining the same therapeutic efficacy at a lower energy cost
- Many patients might benefit from reducing pulse widths from the conventionally used 60 µs to a pulse width between 30 to 50 µs in cases where side effects do occur
- The lack of data on efficacy of chronic stimulation at a short pulse width is a limitation of the study

Battery

Does Rechargeable Neurostimulator Battery Capacity Change After Implant?

Peterson, D., Johannesen, J., and Menezes, M.

Published: NANS 2010 Poster.

Device Utilized: Zero-Volt™ Batteries

This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. The authors of this study were employed by Boston Scientific. Figure created by Boston Scientific based on published data.

BACKGROUND

Rechargeable stimulators are expected to retain battery discharge capacity throughout their functional lifetime. The authors took measurements of the discharge capacity for 109 Boston Scientific batteries that were up to 75 months old. The goal of this testing was to help better characterize the loss of discharge capacity over time.

METHODS

- The discharge capacity was measured in 109 Boston Scientific Zero-Volt explanted batteries
- Devices were not explanted due to malfunction and were confirmed fully functional via testing prior to the start of this experiment
- The implant and explant dates were determined via device registration and date of return respectively, thus able to determine the length of time the device was implanted
- The level of battery consumption was determined from the 1-year stored battery voltage profile

RESULTS

- Boston Scientific rechargeable battery is 200 mAh
- The measured discharge capacity was similar in batteries up to 75 months old and implanted up to 52 months

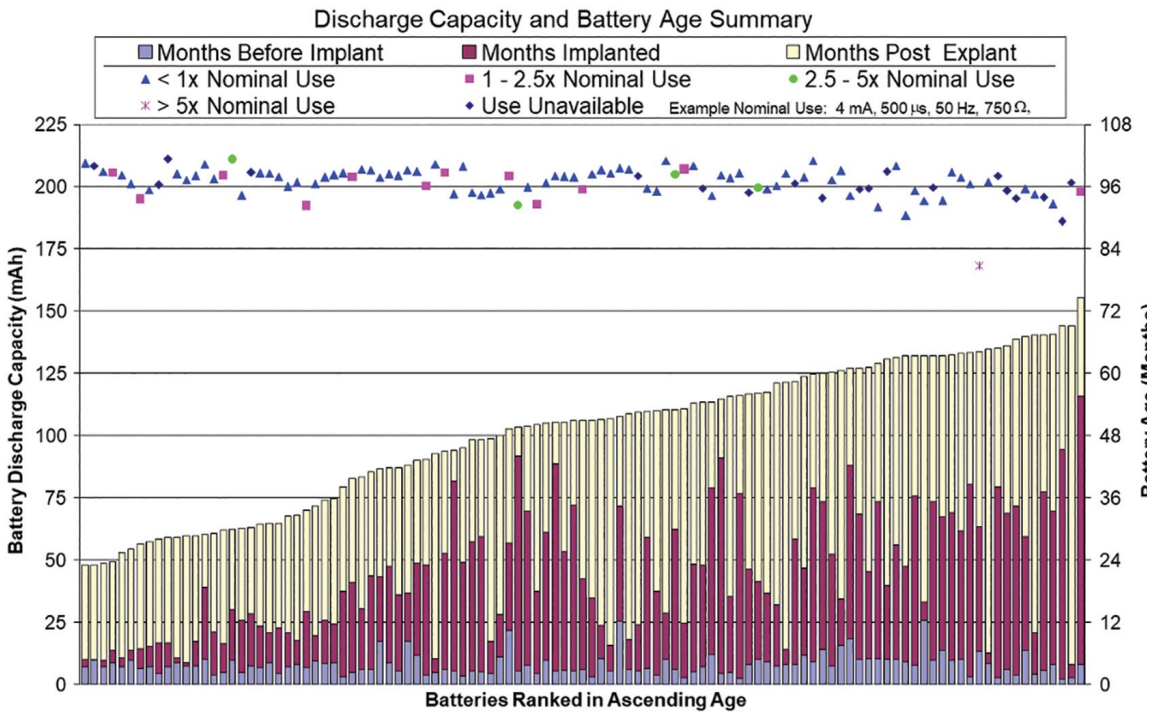


FIG 1. Summary of the discharge capacity from the Boston Scientific batteries in ascending age. The stacked bar graph illustrates the batteries' age (in months) from prior to, during, and post-implant. In addition, the corresponding energy usage was categorized and plotted.

CONCLUSION

- The Boston Scientific Batteries show an insignificant amount of loss in discharge capacity even after up to 72 months and up to 52 months of implant

Characterizing Rechargeable IPG Charge Cycle Time in DBS

Yu, X., Steinke, K., and Mustakos, R.

Published: North American Neuromodulation Society (NANS). 2013 Poster.

Device Utilized: Zero-Volt™ Batteries

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BACKGROUND

Rechargeable Deep Brain Stimulation (DBS) Implantable Pulse Generators (IPGs) have different battery capacities, which result in differing recharge intervals. Three tests were conducted to characterize the discharge cycle of Vercise™ IPGs various use models.

The use models included a standard amplitude, using typical clinical IPG parameters; a high amplitude, which doubled the current, compared to the standard settings; and a low amplitude model, which halved the current, compared to the standard settings.

METHODS

- Standard set-up consisted of a Vercise IPG with two leads attached, in a saline solution at 37°C
- Stimulation settings were 60 µs pulses at 130 Hz, providing current through two cathodic contacts, one on each lead, using the immersed case as the anode
- IPGs were interrogated with the remote control (RC) 3 times a week to simulate patient interaction

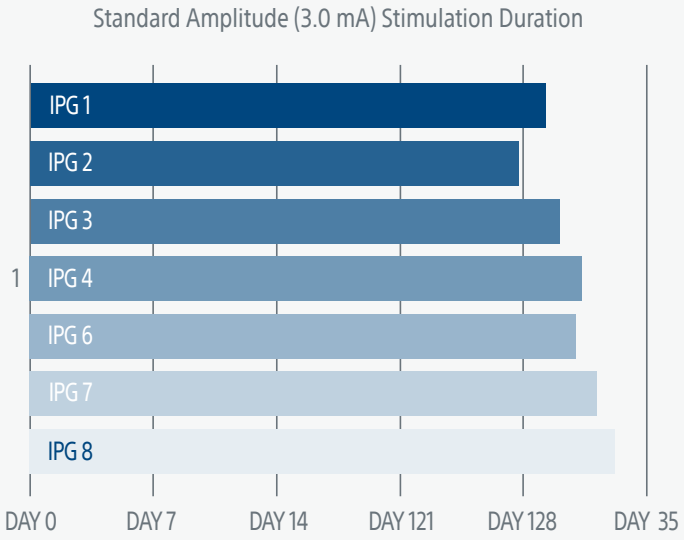
Standard Treatment Parameters
n = 7
Amplitude: **3.0** mA
Pulse Width: 60 µs
Frequency: 130 Hz

High-Amplitude Treatment Parameters
n = 7
Amplitude: **6.0** mA
Pulse Width: 60 µs
Frequency: 130 Hz

Low-Amplitude Treatment Parameters
n = 4
Amplitude: **1.5** mA
Pulse Width: 60 µs
Frequency: 130 Hz

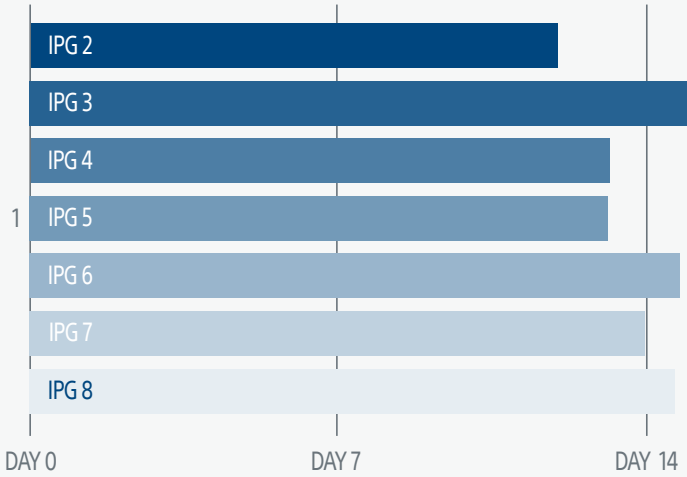
RESULTS

Standard Settings (3.0 mA)
Average Stimulation Time: 30 days 16 hours
Minimum Stimulation Time: 27 days 16 hours
Maximum Stimulation Time: 33 days 4 hours
Standard Deviation: 1 Day 16 hours



Yu, X., et al. NANS. 2013 Poster.

High Settings (6.0 mA)
Average Stimulation Time: 14 days 5 hours
Minimum Stimulation Time: 12 days
Maximum Stimulation Time: 15 days 20 hours
Standard Deviation: 1 day 8 hours



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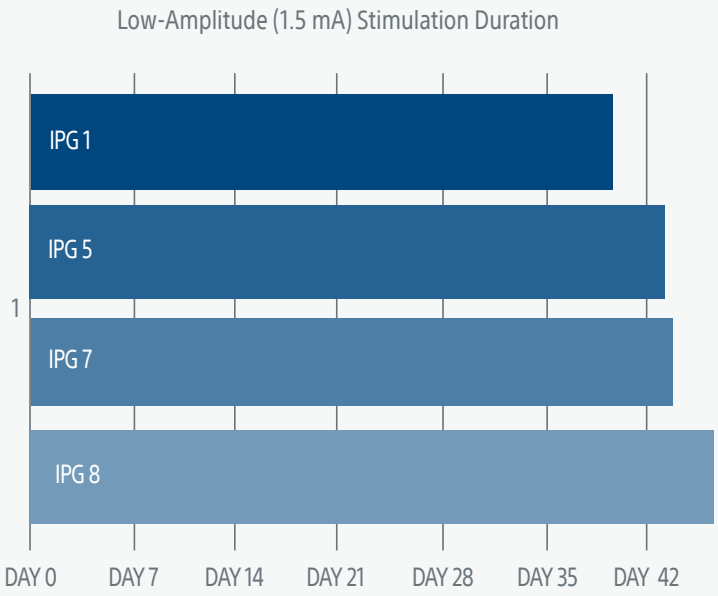
Low Settings (1.5 mA)
Average Stimulation Time: 43 days 1 hour
Minimum Stimulation Time: 39 days 8 hours
Maximum Stimulation Time: 46 days 4 hours
Standard Deviation: 2 days 10 hours



Yu, X., et al. NANS. 2013 Poster.

CONCLUSIONS

- At typical clinical parameters, Boston Scientific Vercise™ rechargeable DBS IPGs may provide up to 4 weeks of stimulation between recharging cycles
- At high amplitudes, they may provide up to 2 weeks of stimulation between charging cycles
- At low amplitudes, they may provide up to 6 weeks of stimulation between recharging cycles

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CAUTION: The law restricts these devices to sale by or on the order of a physician.

Indications, contraindications, warnings, and instructions for use can be found in the product labelling supplied with each device or at www.IFU-BSCI.com. Products shown for INFORMATION purposes only and may not be approved or for sale in certain countries. This material not intended for use in France.