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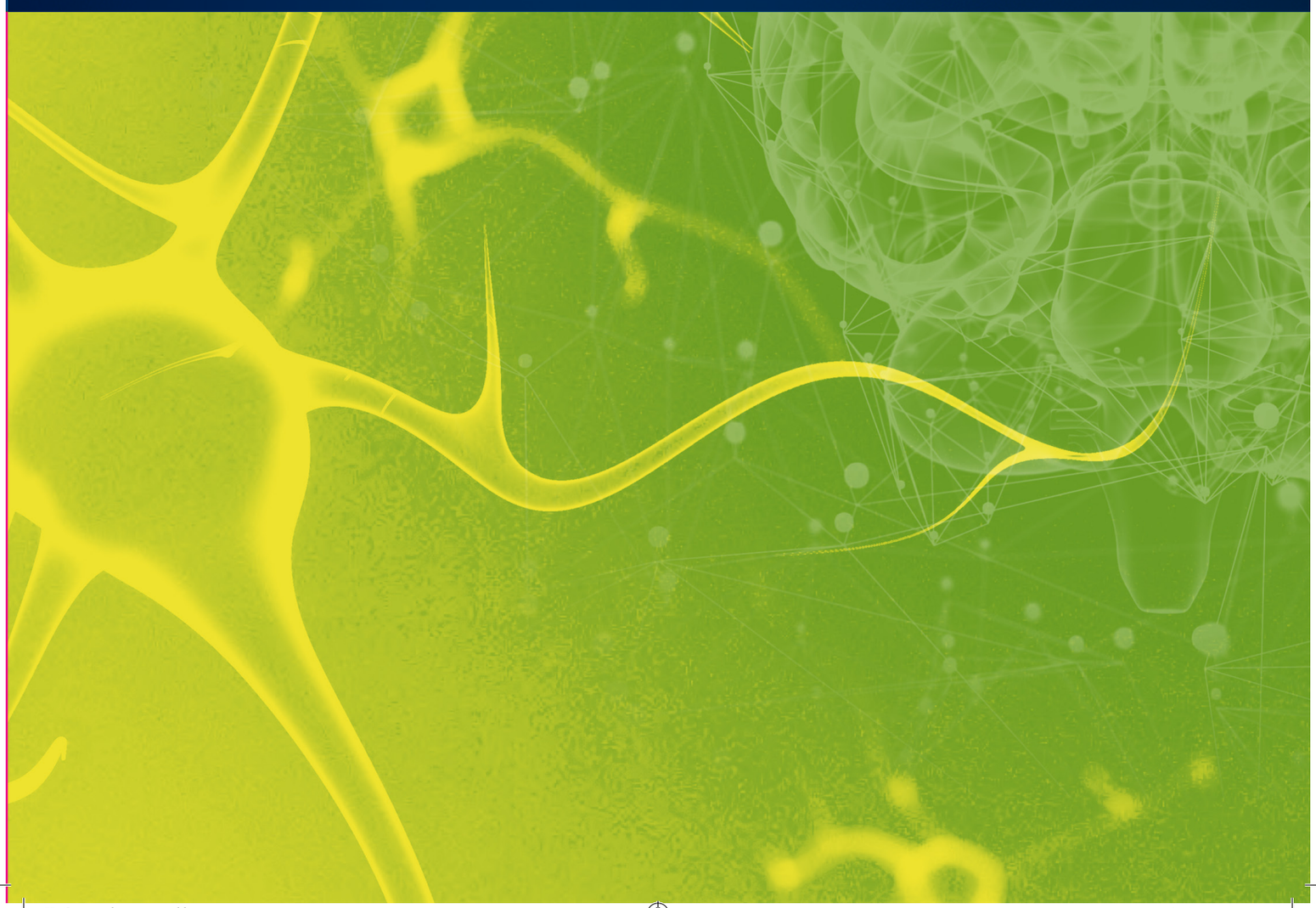
Visualization Evidence Compendium

Publications supporting the Guide™ XT workflow



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GUIDE XT™

EMPOWER DBS WITH VISUALIZATION

In Partnership with
BRAINLAB

INTRODUCTION

Visualizing the FUTURE of Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a surgical treatment which can help manage some movement disorder symptoms. DBS is typically used to treat people with advanced Parkinson's disease (PD), dystonia, and essential tremor (ET) whose symptoms are no longer controlled by medication. DBS is an established, safe, and effective treatment that improves day-to-day experiences and quality of life for these patients.

Recent innovations such as directional stimulation improve the patient experience and open new possibilities to optimize programming. Capitalizing on these advanced capabilities requires commensurate advances in programming software to maintain ease-of-use. Our Guide™ XT stimulation visualization solution and our partnership with Brainlab AG combine to evolve DBS therapy for our customers. Guide™ XT is the first system engineered to integrate directional Stimulation Field Models (SFMs) with the patient's own anatomy and lead locations to reduce programming burden. By "unblinding the brain", Guide™ XT offers Visualization aided programming for unmatched programming efficiency.

In collaboration with DBS experts, we create devices that deliver more precise and individualized treatment in Parkinson's disease and other neurological disorders. Our efforts have brought clinical centers a complete solution combing surgical planning, directional leads, pulse generators, and visualzation-aided programming, all working in harmony thanks to the core foundation of the industries only Multiple Independent Current Control (MICC) technology. This core technology in the Implantable Pulse Generator (IPG) has a dedicated power source for each electrode to accurately target and precisely control stimulation field size and shape of the Cartesia™ directional lead in the area of stimulation while avoiding areas of side effect. In Collaboration with Deep Brain Stimulation experts, we continue to push the boundaries of what is possible in Deep Brain Stimulation and work on meaningful innovations that improve patient lives around the world. As a company, we are known for always challenging the status quo and thereby changing the future trajectory in DBS.

I invite you to read this Visualization Evidence Compendium which summarizes some of the main publications currently available that support Guide XT™ as well as the Vercise™ DBS systems and their features. Examples of topics covered are Anatomical Segmentation, Lead localization, Directional lead orientation, Distortion correction and Fibertracking that are part of the Guide XT™ Workflow.

Enjoy the reading!

Kind regards,

Dr. Maulik Nunavaty

President, Neuromodulation at Boston Scientific

Note: The Guide XT Workflow includes the components of Brainlab Element AG used in Guide XT™ aided prgramming

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Fibertracking, Guide XT	**Avecillas-Chasin et al.**	**Stimulation of the Tractography-Defined Subthalamic Nucleus Regions Correlated with Clinical Outcomes**	Neurosurgery	*2019*	20
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Guide XT	**Pavese et al.**	**Traditional Trial-and-Error Versus Neuroanatomical-3D-Image Software-Assisted Deep Brain Stimulation Programming in Patients with Parkinson's Disease**	World Neurosurgery	*2019*	28

Automatic Segmentation of the Subthalamic Nucleus: A Viable Option to Support Planning and Visualization of Patient-Specific Targeting in Deep Brain Stimulation

Authors:
Reinacher P.C., Várkuti B., Krüger M.T., Piroth T., Egger K., Roelz R. and Coenen V.A.

Published:
Operative Neurosurgery 2019
17(5): 497–502.

Study type:
Cohort study, single-center, retrospective

Element supported:
Anatomical Mapping

OBJECTIVE

In this study the authors compared the automatic segmentation performed by Brainlab Elements to the anatomical boundaries defined by micro-electrode recording (MER) by quantifying the entry and exit points along the trajectory of the lead.

METHODS

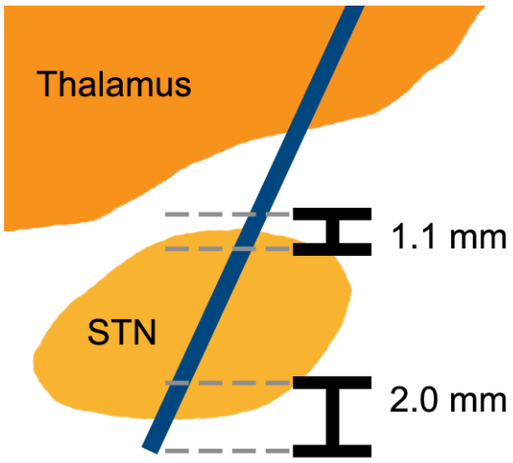
- 30 patients (median age 57, 13 female) were implanted with DBS leads in the STN for the treatment of PD (N=29) or DYT12 dystonia parkinsonism (N=1)
- Each patient received a series of MRIs including T1 with contrast, T1 without contrast, and a T2 with 1mm voxel resolution
- Each patient also received a peri-operative CT and a post-operative CT
- In each case MER was performed with the track beginning 10 mm above target and terminating 3.5 mm below
- Intraoperative macrostimulation was performed along the trajectory with testing of the contralateral motor response to
- confirm the MER defined boundaries of the STN
- MRI and post-operative CT were fused in Brainlab Elements
- MER defined entry and exit points for the STN were transformed into the stereotactic space, and compared to the dorsal and ventral borders defined by the automatic segmentation

RESULTS

MER Trajectories

- 105 out of the 175 MER trajectories penetrated the STN or passed within 0.7 mm (1/2 the diameter of the DBS lead)

77 of the trajectories exhibited an STN length of greater than 0.5 mm and this subset was used to compare entry and exit information to the automated segmentation



Accuracy of Automatic Estimation. The automated segmentation algorithm provided estimates of entry and exit points for the STN. These estimates were compared to the STN length as determined by the MER. Dorsal boundary of the STN was predicted within 1.1 mm while the ventral boundary was predicted within 2.0 mm.

Comparison to Automatic Segmentation

- Median deviation for the entry of the STN of the central, anterior, and lateral trajectories were 1.1 mm, 0.8 mm, and 1.4 mm respectively
- Median deviation for the exit of the STN of the central, anterior, and lateral trajectories were 2.1 mm, 1.7 mm, and 1.9 mm respectively
- Total mean errors were 1.1 mm for entry and 2.0 mm for exit
- The difference in entry location between the MER defined dorsal border and the automatically segmented dorsal border was not statistically significant
- The difference in exit location between the MER defined dorsal border and the automatically segmented dorsal border were statistically significant for the central and lateral trajectories, but not the anterior trajectories

AUTHORS' CONCLUSIONS

- There was a high degree of concordance between the results of automatic segmentation and MER
- This concordance was greater for entry location than for exit
- MRI based segmentation is a viable tool to aid in surgical planning and complement existing practices

Localization of Deep Brain Stimulation Electrode by Image Registration Is Software Dependent: A Comparative Study between Four Widely Used Software Programs

Authors:
Engelhardt J., Guehl D., Damon-Perriere N., Branchard O., Burbaud P. and Cuny E.

Published:
Stereotactic and Functional Neurosurgery, 2018
96(6):364-369

Study type:
Cohort study, single-center, retrospective

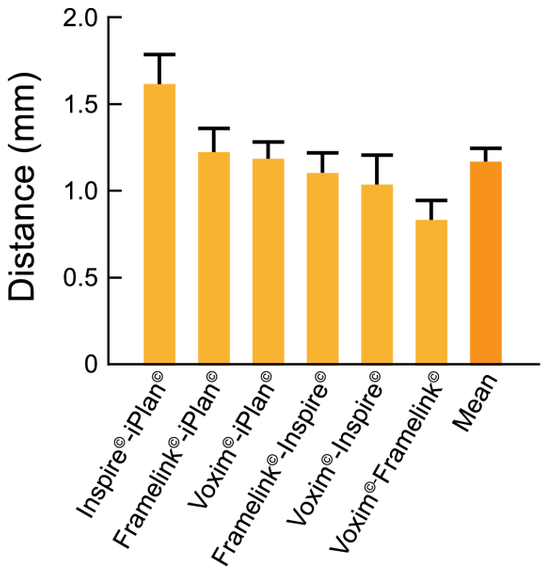
Element supported:
Lead Localization

OBJECTIVE

The authors compared four separate software packages that use different methods to localize DBS leads. They compared the final derived location of each electrode contact in common stereotactic frame space

METHODS

- 27 PD patients implanted with 53 leads (1 patient unilateral)
- On the day of surgery a 1.5T stereotactic MRI with Leksell frame was obtained
- All patients were implanted using frame based stereotactic procedure and a Renishaw operative robot with CT guidance
- CT scans were performed 3 months after surgery
- CT and MRI images were co-registered and fused with localizations calculated in stereotactic frame space and compared between the following software programs
  - VoXim neuro|mate (Renishaw Mayfield and IVS Technology)
  - Framelink v.5.4. (Medtronic)
  - Neuroinspire (Renishaw Mayfield)
  - Elements Stereotaxy with Elements Lead Localization (Brainlab)
- Manual fusions for VoXim, Framelink, and Neuroinspire were performed by same operator
- Automatic fusions were used only with Elements Lead Localization
- Euclidean distance between corresponding contacts, as well as angle between reconstructed leads were used to compare between softwares



Pairwise Distance Between Methods. The Euclidean distance between locations of contact 0 measured with different methods. No pair had a distance greater than 2.0 mm

RESULTS

- Significant differences were observed between stereotactic frame coordinates of DBS lead contacts across the four planning softwares
- Mean Distance between each pairwise comparison was 1.17 mm (95 %CI 1.09-1.25)
- Angular differences ranged from 1.29° to 2.72°

AUTHORS' CONCLUSIONS

- Mean Distance between contacts across the four methods was below the commonly accepted error tolerance impacting clinical outcomes of 2 mm
- Lead Localization remains an important step in reviewing DBS cases, particularly when directionality may be involved
- Clinical testing of different contacts should still be considered standard but may be supported by lead localization via software

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

Authors:
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(6): 1111-1116

Study type:
Bench Experiment,
Double-Blind

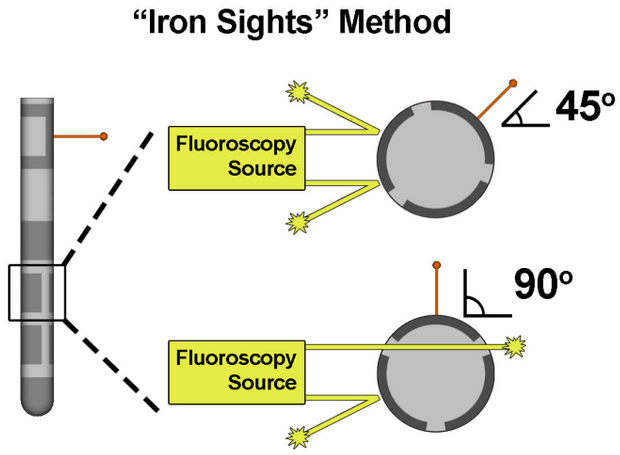
Element supported:
Lead Localization,
Orientation Estimation

OBJECTIVE

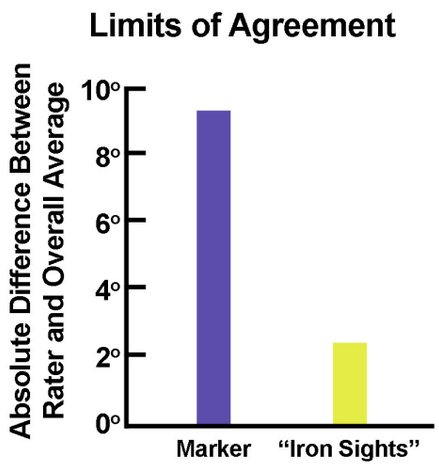
Directional DBS has the potential to increase therapeutic window size allowing for efficient treatment of Parkinson's disease (PD) symptoms by steering current away from the internal capsule and towards the sub-thalamic nucleus (STN). The exact orientation of the directional lead must be determined post-operatively if anatomical of functional imaging data is to be used to assist in programming. The objective of this study was to evaluate a rotational fluoroscopy-based method for determining the orientation of a Boston Scientific directional lead with a high degree of accuracy.

METHODS

- Rotational Fluoroscopy represents a promising alternative imaging modality
  - Anterior-Posterior and Lateral X-rays offer only an approximate orientation
  - CT imaging artefacts could be used to determine orientation but only for a specific range of imaging angles
  - MRI is not feasible for currently available leads because they are not MRI-opaque
- A plaster skull filled with gelatin was implanted with two Vercise CartesiaTM Directional Leads at typical DBS trajectories
- An orientation marker was affixed to the proximal end of the lead and electrodes were rotated clockwise and counter-clockwise 360° to determine how proximal rotation influenced orientation of the distal electrodes
- A series of 120 fluoroscopy frames were acquired with 2° resolution across a 240° rotational arc around the plaster skull delivering a moderate dose of radiation (2.327 mGy x cm2)
- Each of the two electrodes were randomly rotated between 1° and 360°, re-imaged as above, and then this process was repeated so 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 leads orientation
  - 'Iron Sights': At a narrow subset of known angles the gaps between the directional contacts line up and are visible on fluoroscopy appearing as bright lines (Figure) which can be used to determine which frame captures specific orientations of the lead
- Inter-rater reliability was assessed using Band-Altman plots to show the robustness of each of the two methods as a function of 'limits of agreement'



Iron Sights Method. The 'Iron Sights Method' takes advantage of a phenomenon where gaps between the directional contacts can be seen on the fluoroscopy image (top). Where 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°). The limits of agreement for the method using the marker alone were higher than for the method using this 'Iron Sights' method (±9.37° > ±2.44°).



RESULTS

- 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° counter-clockwise rotation the right lead orientation changed from -5.5° to 35.0° while the left lead changed from +5.4° to +16.0°
- Using the directional marker alone, the limits of agreement for orientation of lead could be determined within ±9.37°
- Using the 'Iron Sights' method, the limits of agreement for orientation of lead could be determined within ±2.44°
- Both methods showed high inter-rater reliability

AUTHORS' 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 post-operative imaging technique for determining orientation is required
- The incidental visualization of gaps between directional contacts on a rotational fluoroscopy provided the most accurate method to determine lead orientation
- This method is accurate over a wide range of imaging angles
- The statistics used in this study describe only the agreement between the raters and not a ground truth for lead orientation
- The radiation dose delivered by rotational fluoroscopy is moderate but represents an additional exposure if added to standard practice

DiODe: Directional Orientation Detection of Segmented Deep Brain Stimulation Leads: A Sequential Algorithm Based on CT Imaging

Authors:
Hellerbach A., Dembek T.A., Hoevels M., Holz J. A., Gierich A., Luyken K., Barbe M.T., Wirths J., Visser-Vandewalle V. and Treuer H.

Published:
Stereotactic and Functional Neurosurgery, 2018
96(5): 1-7

Study type:
Bench Experiment

Element supported:
Lead Localization, Orientation Estimation

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 the published data. One or more authors report funding from Boston Scientific as a financial disclosure.

OBJECTIVE

The use of directional leads exhibits promising clinical outcomes, however determining the orientation of the lead with respect to the patient's anatomy is essential for rapidly finding the optimal stimulation and avoid multiple re-programming for patients and consultants. The objective of this study was to develop a precise algorithm to identify the orientation angle of a Boston Scientific Vercise Cartesia™ directional lead, based on CT imaging.

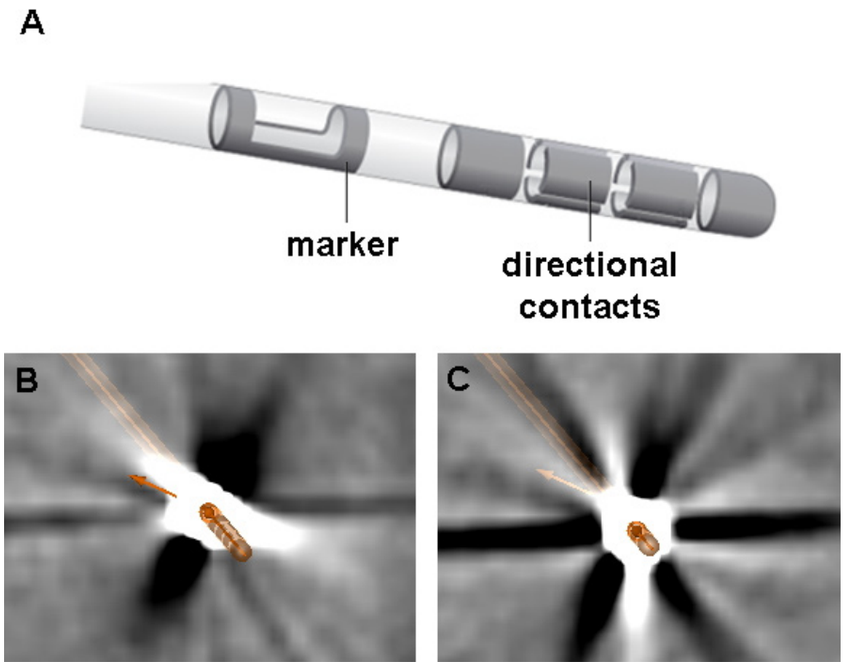
METHODS

Phantoms

- Two cylindrical agarose-gel based phantoms were used
- Each phantom was implanted with a directional lead (aligned with stylet) creating an 'ground truth' indicating the true orientation to compare with orientation determined by the algorithm described below
- A total of 60 scans were tested using the 2 cylindrical phantoms
- Scans were performed with different lead orientation, as well as different polar angulations to cover a large angular range representing a broad selection of medical case

Lead Trajectory and Marker Orientation

- Marker orientation was estimated with a two step process dependent on the CT artifacts of the different lead components
- Gross marker orientation angle was estimated using dark and bright streak artefacts from a CT scan slide containing the directional marker (Figure part B)
- This gross estimate was then used to assume an 'expected orientation of the segmented contact levels'
- A range of variations (± 30° variation in 1° increments) of this gross estimate were used to further refine the initial estimate
- The orientation of the segmented contact levels was calculated using the six dark streak artifacts on a CT scan slice containing the segmented contact level (Figure part C)
- Polar intensity of the CT was extracted in an 8.0 mm radius around the lead yielding a circular intensity profile
- A similarity index was defined using a projection of an artificially modeled CT artifact and comparing the overlap of the intensity with the actual CT artifacts
- Final lead orientation is estimated by finding the global minimum of the similarity index



Representative CT artifacts. A) Schematic representation of our Boston Scientific Cartesia™ Directional Lead showing the electrically active contacts, including the segmented directional contacts, as well as the passive directional marker. B) A representative CT scan demonstrating the characteristic butterfly artifact of the directional marker and C) the bright streaks artifact of the segmented contacts.

RESULTS

- Lead orientation was determined with a mean deviation from ground truth of - 0.6 ± 1.5° (range: - 5.4° to 4.2°)
- Precise results were obtained with a polar angle up to 60°, which yielded a higher range than previously published CT based methods
- Significant difference was observed between proximal and distal segmented levels of lead orientation and marker orientation ($p < 0.001$)

AUTHORS' CONCLUSIONS

- This study presented a highly precise and consistent method for detecting the orientation of a Boston Scientific Vericse™ Cartesia™ directional lead
- Using CT scans may reduce the number of extraneous scans because they are often standard of care for DBS procedures
- Differences between electrodes orientation angles of the 3 leads tested have been noticed, and most likely attributed to manufacturing tolerances
- Increased accuracy of lead orientation detection for higher polar angles was achieved by including segmented contact level information

Evaluation of a Novel Software Application for Magnetic Resonance Distortion Correction in Cranial Stereotactic Radiosurgery

Authors:
Calvo-Ortega J., Mateos J., Alberich A., Moragues S., Acebes J. and Casals J.

Published:
Medical Dosimetry, 2019
44(2): 136-143

Study type:
Case series, single-center, retrospective

Element supported:
Cranial Distortion Correction

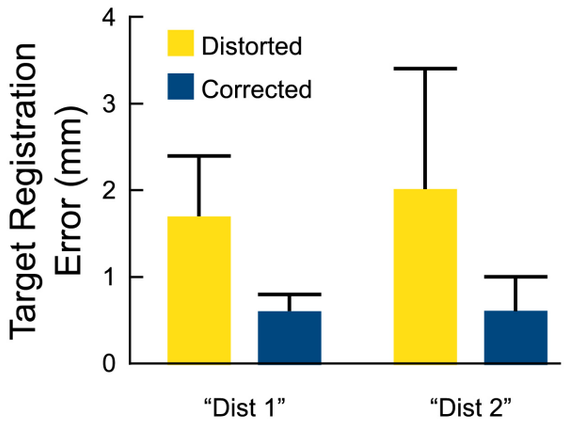
This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Figure created by Boston Scientific based on the published data. One or more authors report funding from Boston Scientific as a financial disclosure.

OBJECTIVE

Magnetic Resonance images (MRI) are susceptible to spatial distortion, both system-related and patient-induced. Distortion in cranial MRI images can displace intracranial targets in stereotactic radiosurgery and may have a significant clinical impact. This study evaluated Brainlab's Distortion Corrections software developed to overcome the spatial distortion of cranial MRI images.

METHODS

- The analysis was performed on five patients that were scheduled to be treated with cranial stereotactic radiosurgery
- The patient dataset included a computed tomography (CT) scan and an original 1.5T MRI image (MRorig)
- The original MRI was artificially distorted (MRdist) using 2 types of distortions, 'dist 1' and 'dist 2' with maximal spatial distortion of 3 mm and 5 mm respectively
- For each patient case the MRdist dataset was corrected using Brainlab's Distortion Correction software generating a corrected dataset (MRcorr).
- MRdist and MRcorr were each rigidly and independently co-registered to the CT
- Six anatomical landmarks (points on each of the two vestibules, internal auditory canals and cochleas) were selected in the CT image and selected again in the corresponding MRcorr and MRdist datasets
- CT scans were selected as the reference image (ground truth) for the definition of each selected landmark
- The CT/MR registration accuracy was assessed by measuring the Euclidian distance between the paired landmark on both modalities and was defined as the target registration error (TRE)
- TREcorr (CT/MRcorr error) represents the accuracy of the distortion correction software for the correction of the distorted MR image.
- TREdist (CT/MRdist error) represents the magnitude of the intended distortion



Mean Target Registration Errors Five MR datasets corrected for disotrion and considering six anatomical landmarks in the brain. The analysis used two artificial distortion magnitudes 'dist 1' and 'dist2'. TREs are presented as average values of the errors across each of the six anatomical landmarks between the distorted MR dataset and the CT scan of reference and between the corrected MR dataset and the CT scan of reference.

RESULTS

- A clear improvement in the CT/MR registration was found when the distortion correction software was used (Figure)
- For 'dist 1' the Distortion Correction algorithm improved TRE by 1.1 mm (TREcorr = 0.6 ± 0.2 mm vs TREdist = 1.7 ± 0.7 mm)
- For 'dist 2' the Distortion Correction algorithm improved TRE by 1.4 mm (TREcorr = 0.6 ± 0.2 mm vs TREdist = 2.0 ± 1.4 mm)
- The average value of TERcorr for each of the 5 cases were always within the voxel size of the CT scan (1x1x1mm3)

AUTHORS' CONCLUSIONS

- Brainlab's Distortion Correction software is a helpful tool that detected and adequately corrected brain MRI distortions that would be produced by the patient and the MRI scanner
- The use of a distortion correction tool is highly recommended when stereotactic radiosurgery of small cranial lesions is practiced

Postoperative Neuroimaging Analysis of DRT Deep Brain Stimulation Revision Surgery for Complicated Essential Tremor

Authors:
Coenen V.A., Várkuti B., Parpaley Y., Skodda S., Prokop T., Urbach H., Li M. and Reinacher P.C.

Published:
Acta Neurochirurgica, 2017
159(5):779-787

Study type:
Case study

Element supported:
Lead Localization,
Fibertracking,
Guide XT

OBJECTIVE

In this case study the authors describe a successful tractography assisted revision surgery to rescue an essential tremor patient who lost initial clinical benefit from DBS.

CASE DESCRIPTION

- The authors demonstrate the utility of this approach in a 72 year old male who exhibited marked truncal tremor and was treated for ET with Vim DBS
- Initial tremor suppression after traditional DBS implantation was promising, however stimulation amplitudes have to be escalated over the first few weeks
- Trunk tremor and proximal extremity tremor reoccurred; presumable after resolution of a micro-lesioning effect
- Higher stimulation amplitudes led to severe ataxia and gait disturbances, with an essential tremor rating scale (ETRS) score showing no improvement after surgery

APPROACH

Motivation

- The original DBS system was completely explanted in order to accommodate 3-tesla anatomical and 61 direction diffusion tensor imaging. Deformation correction was also performed using path-wise affine registration
- Deterministic fiber tracking was performed and the Dentatorubrothalamic tract (DRT) and surrounding structures were visualized. These fused image sets were uploaded to the planning station and used to define a new trajectory targeting the center of the DRT.
- A new octopolar linear lead and rechargeable Implantable Pulse Generator (IPG) (Boston Scientific, MA, USA) was implanted along the new trajectory. The extended contact span allowed for targeting of not only the DRT but also the classical Vim region as well as the caudal zona incerta.

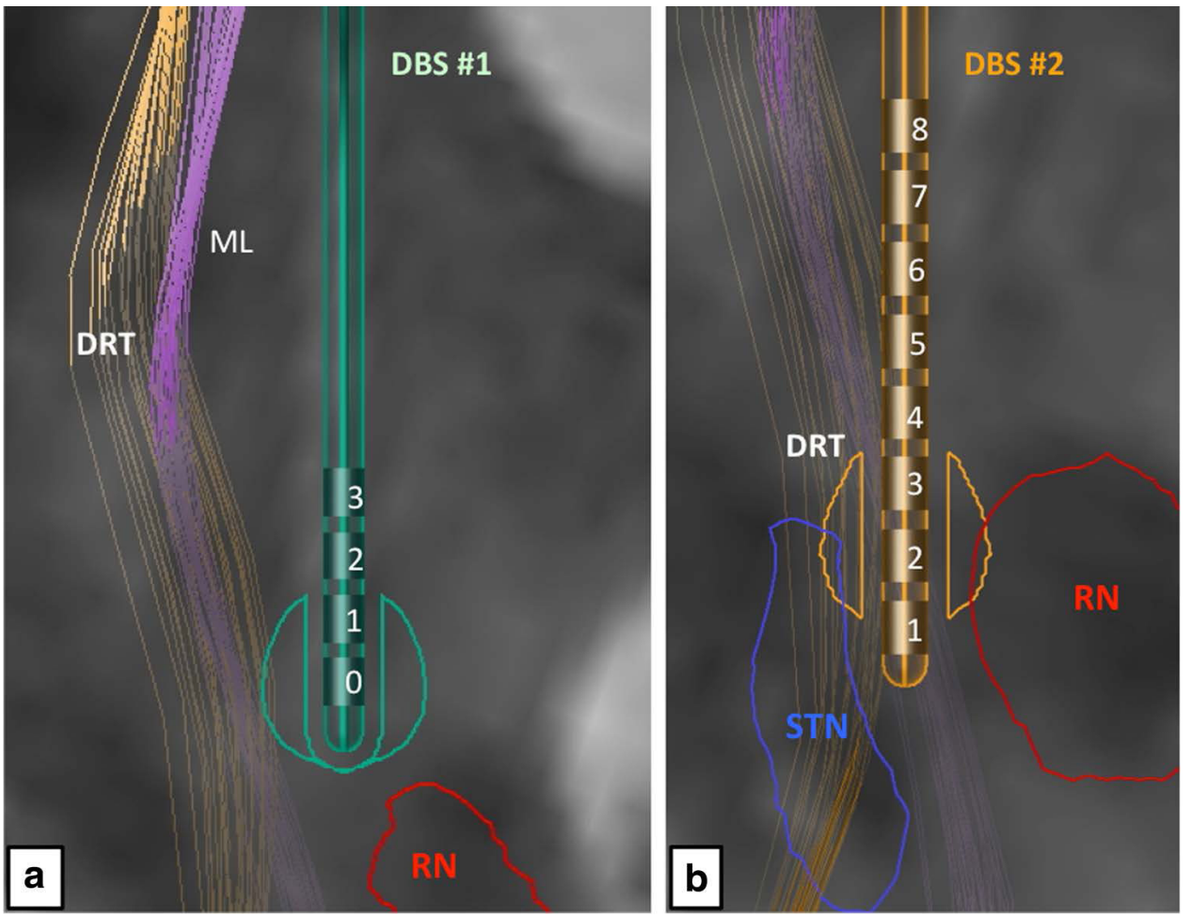


Figure 1. Simulation of (Left) Electrode Positions in Their Functional Environment. A) Initial DBS surgery and slightly eccentric position of the electric field, superficial to the red nucleus (RN) level. B) Revision surgery. The tip of the electrode is intercalated between posterior STN and RN .

Intervention

- The original DBS system explanted to accommodate 3-tesla anatomical and 61 direction diffusion tensor imaging
- Deterministic fibertracking was performed and the DRT and surrounding structures were visualized to define a new trajectory targeting the center of the DRT
- A new octopolar linear lea and rechargeable IPG was implanted along the new trajectory, with the extended contact span allowing for targeting of not only the DRT but also the classical Vim region extending to the subthalamic area until the caudal zona incerta

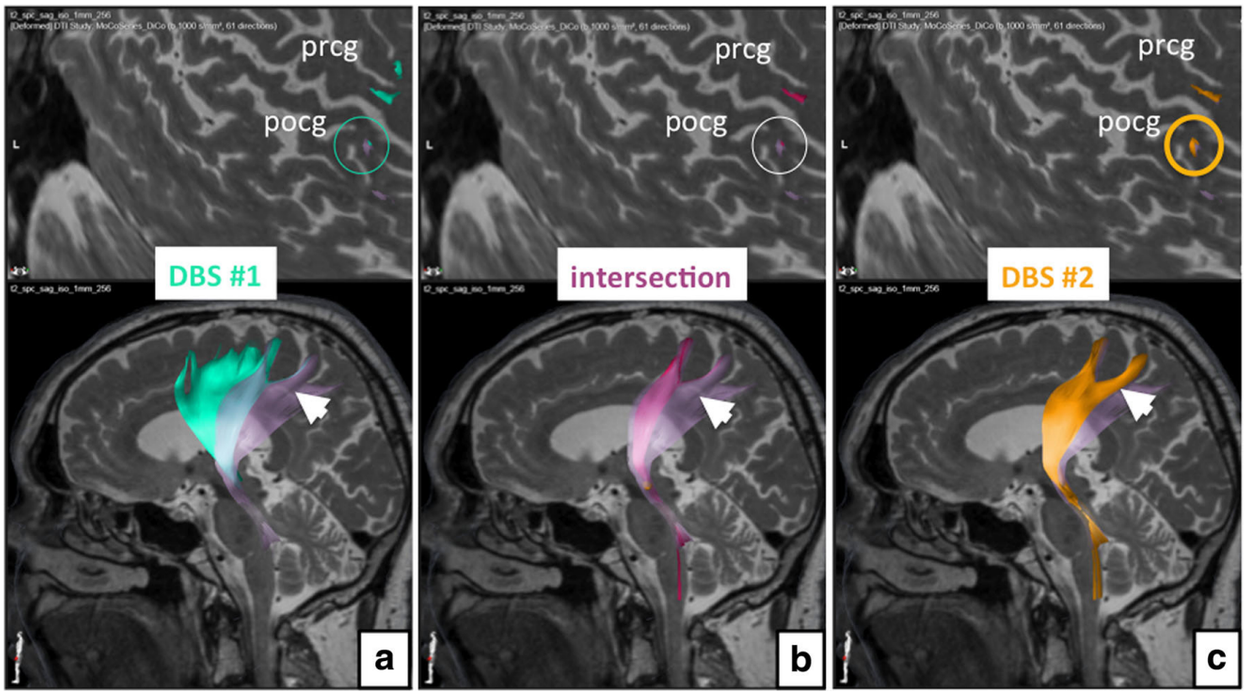


Figure 2. Analysis of the Distant Cortical Connections. A) Initial DBS conditions showing the projections from the implanted area to the cortex and C) under conditions of revised DBS. The *upper row* shows the individual curved surface or Mercator projections for the cortical region (only left side shown). B) The fiber tracts involved in both stimulation situations. Initial DBS obviously shows a less selective activation of fibers projecting to dorsal prefrontal rand supplementary motor region and a lesser focus on DRT fibers. The revision DBS for this left side shows a stronger involvement of the postcentral gyrus (pocg)

OUTCOMES

- The patient was programmed with a 30 µs pulse width, and 174 Hz with a fractionated current of 3 mA (contact 2: 80 %; contact 3: 20 %) on the left and 3.5 mA on the right hemisphere (contact 10: 40 %; contact 11: 40 %; contact 12: 20 %)
- Final lead locations, Volume of Tissue Activated (VTA), and fiber tracts were reconstructed using Brainlab Elements and Guide XT
- Post-operative CTs were fused to high resolution post-operative MRI data sets to co-localize the automatically detected lead locations with target structures
- Tremor improved dramatically with ETRS scores dropping from 51 to 20 (61 % improvement) after rescue surgery
- VTAs from the original DBS and rescue DBS lead locations were used to seed tractography, showing that the effective DBS settings captured more posterior and laterally coursing fibers of the DRT, which preferentially terminated in the post-central gyrus
- This case illustrates the utility of advanced imaging techniques to rescue a patient from suboptimal DBS, and the advantage of targeting Vim and DRT regions for complex truncal tremor
- The ability to visualize downstream effects of stimulation enabled the authors to better quantify the effect of DBS and prospectively design a surgical trajectory to achieve a more focused activation of the DRT

Stimulation of the Tractography-Defined Subthalamic Nucleus Regions Correlated with Clinical Outcomes

Authors:
Avecillas-Chasin J.M., Alonso-Frech F., Nombela C., Villanueva C. and Barcia J.A.

Published:
Neurosurgery 2019
85(2): E294-E303

Study type:
Case series, single-center, retrospective

Element supported:
Fibertracking, Guide XT

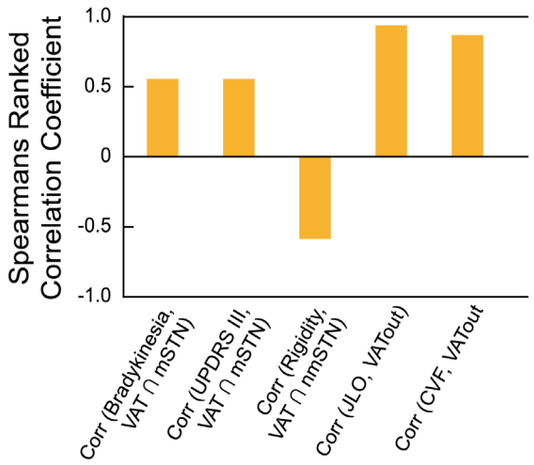
This summary was created by Boston Scientific and is intended to consolidate the paper for educational use only. Figure created by Boston Scientific based on the published data. One or more authors report funding from Boston Scientific as a financial disclosure.

OBJECTIVE

Stimulation of the different functional subdivisions of the STN remains a likely explanation for variability of STN DBS outcomes. A novel analysis was carried out to investigate the relationship between motor and neuropsychological outcomes with the overlap between the volume of activated tissue and the tractography-defined regions within the STN.

METHODS

- 13 patients diagnosed with idiopathic PD were implanted with DBS leads into the STN (2 female, 11 males; 62 years ± 7.5, mean disease duration 16.3 ± 9 years)
- Patients were evaluated 3 weeks after surgery to determine optimal clinical stimulation settings as normal standard of care and had regular follow ups every 2 to 6 months
- Both motor and non-motor symptoms were assessed using the UPDRS-III, Judgement of Line Orientation (JLO) and Categorical Verbal Fluency (CVF)
- For all patients a T1, FLAIR 3D, and DWI image was acquired on a 3T scanner
- Tractography was performed on each patient and used to segment the STN into 4 regions, based on where the fibertracks projected
  - Supplmentary motor area – samSTN
  - Primary Motor Cortex – m1STN
  - A combinsion of the two motor areas – mSTN
  - Non-motor areas – nmSTN
- Final clinical settings were modeled in GUIDE™ to obtain clinical Volumes of Tissue Activated (VATs)
- Proportion of each subsegment of the STN that overlapped with the VAT was computed by measuring the number of voxels from each segment of the STN that lay within the VAT compared to the total number of voxels in the VAT



Correlation Coefficients for Different Measures. Proportion of stimulation confined to the mSTN was significantly correlated with UPDRS-III (r = 0.55) and bradykinesia improvement (r = 0.55), while simulation confined to the nmSTN stimulation was associated with increased rigidity (r = -0.59, p = 0.01). Proportionally higher stimulation outside of the STN was correlated with improved neuropsychological outcomes as measured on the JLO (r = 0.93) and CVF (r = 0.86).

RESULTS

Clinical Results

- STN DBS resulted in significant motor improvements (UPDRS-III) by 44 % (p = 0.003)
- Bradykinesia and Rigidity were also improved by 47 % (p = 0.001) and 67% respectively (p = 0.001)
- Worsening of visuospatial functions (JLO) and categorial verbal fluency (17 % p = 0.021 and 24 % worsening p = 0.021) was also observed with stimulation

Effect of Stimulating STN Segments

- Effect of Stimulating STN Segments
- mSTN stimulation significantly correlated with UPDRS-III and bradykinesia improvement (UPDRSIII r = 0.55, p = 0.01; bradykinesia r = 0.55, p = 0.02)
- smaSTN, but not m1STN had positive correlation with bradykinesia improvement
- A higher proportion of stimulation within the nmSTN stimulation was associated increased rigidity (r = -0.59, p = 0.01)
- An increased amount of relative stimulation outside of the STN was correlated with improved neuropsychological outcomes (JLO r = 0.93, p = 0.01; CVF r = 0.86, p = 0.01)

AUTHORS' CONCLUSIONS

- Tractography-delinated motor STN (mainly smaSTN) was best correlated with improvement in UPDRS and bradykinesia
- Less stimulation within the STN seemed to correlate with beneficial neurophysiological effects
- Stimulation of areas around the STN may explain some of the differential effects of STN DBS

Reversing Cognitive–Motor Impairments in Parkinson's Disease Patients Using a Computational Modelling Approach to Deep Brain Stimulation Programming

Authors:
Frankemolle A.M.M., Wu J., Noecker A.M., Voelcker-Rehage C., Ho J.C., Vitek J.L. McIntyre C. C. and Alberts J.L.

Published:
Brain 2010
133(3): 746–761

Study type:
Case series, single-center

Element supported:
Guide XT

OBJECTIVE

In previous studies it has been shown that subthalamic nucleus Deep Brain Stimulation (STN-DBS) reduces motor impairment in patients with advanced Parkinson's disease (PD) but might be associated with cognitive decline as well. One hypothesis about the deterioration of cognitive and cognitive-motor functions is the current spread into nonmotor parts of the STN. The aim of this study was to compare the cognitive–motor performance of PD patients with bilateral STN-DBS that received either a traditional clinical programming (Clinical) or the selection of stimulation parameters was done with a patient-specific computational model (Model).

METHODS

Clinical and Cognitive Assessments

- 10 patients with advanced Parkinson's disease who had DBS surgery at least 14 months prior to study were evaluated
- Stimulation parameters were stable for at least 6 months prior to study, and patients with dysarthria or speech problems were excluded
- Cognitive assessments were done using the n-back task where participants had to repeat the nth item back in a sequentially presented list of items
  - The patients were asked to repeat either the letter presented directly before (0-back), 1 cycle before (1-back) or two cycles before (2-back)
  - Five blocks of 30 s were collected sequentially and randomized across participants
- The force-maintenance task utilized an apparatus with a six degree of freedom force-torque transducer to measure grip force (precision grip with thumb and index finger of the dominant hand)
- To further assess cognative decline a 'dual task' was performed with both n-back and force maintenance simultaneously
  - Participants performed 15 blocks of the dual-task condition

Model Programming and Comparison

- Model DBS parameters were chosen using a patient-specific DBS computer model of each hemisphere
  - The developers of the models were blinded to clinical symptoms and previous programming settings
  - Pre-operative MRI and post-operative CT images were manually co-registered to the same stereotactic coordinate system with the use of AC-PC as landmarks
  - The stereotactic location of all intraoperative microelectrode recording points were added and color-coded on its neurophysiologically defined nucleus
  - The model electrode was then palced into the coordinate space according to the intraoperatively defined stereotactic coordinates and validated with the postop CT
  - The model therapeutic STN was defined as an ellipsoid target volume containing the dorsal STN together with white matter dorsal to the STN
  - The stimulation parameter setting was defined using the theoretical predictions of the volume of tissue activated (VTA) as maximized stimulation coverage of the target volume and minimized spread outside
- Patients arrived in the meds-OFF condition at least 12 hours after their last parkinsonian medication
- UPDRS III was measured by an experienced neurologist under three DBS condition across two visits: Clinical and Model DBS as well as DBS OFF (meds ON)
- Order of clinical and model DBS testing was randomized

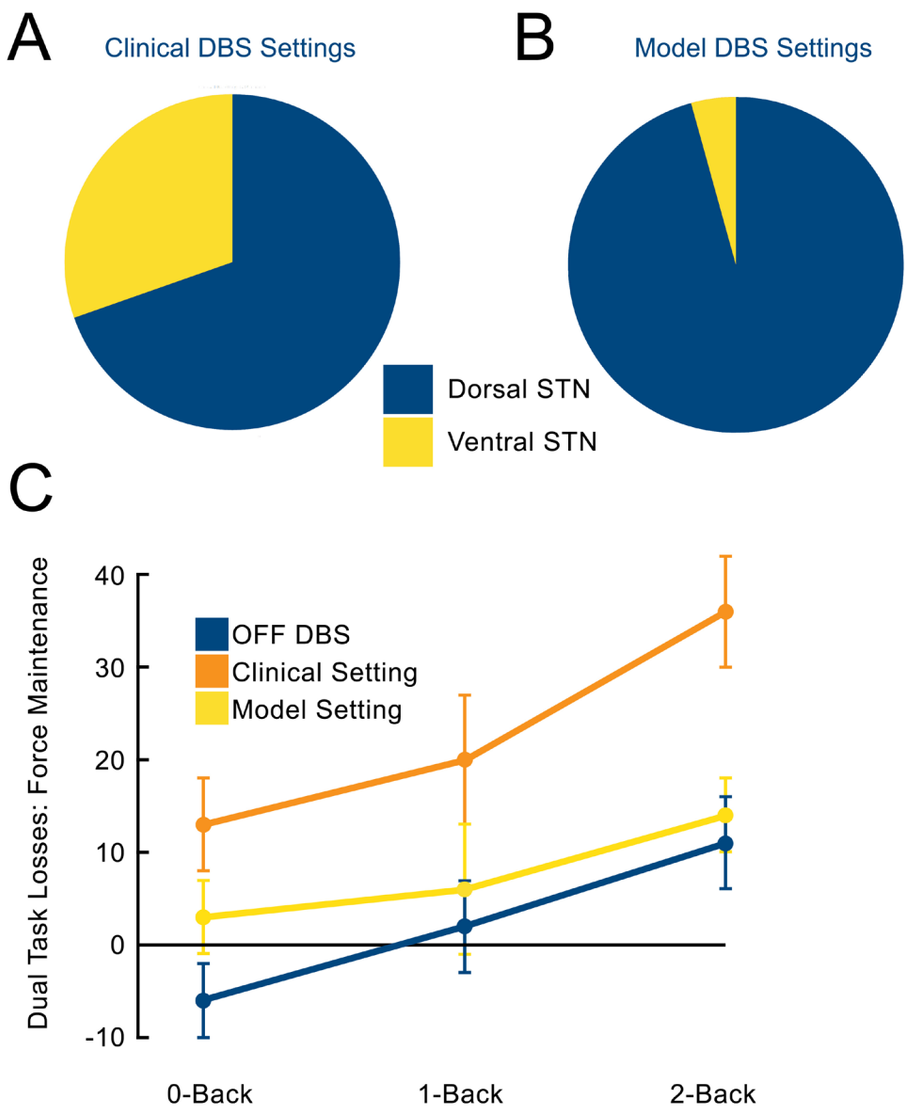
RESULTS

Clinical Outcomes and Programming

- For all patients, the UPDRS III values decreased with Clinical and Model DBS compared to the DBS OFF condition (paired sample t-test, adjusted $\alpha = 0.017$)
- Clinical and Model DBS both resulted in an average improvement of 46 % in UPDRS III score
- The total volume of VTA was not significantly different from the Clinical and Model DBS setting
- The Clinical VTA was significantly greater in the ventral portion of the STN (paired sample t-test, adjusted $\alpha = 0.017$)
- Model parameters consumed about 50 % less microwatts than the Clinical parameters (paired sample t-test: $p < 0.001$)

Cognitive Functioning

- The overall n-back performance decreased with increasing task difficulty (repeated measures ANOVA, $P < 0.001$)
- Working memory during the 2-back condition was not significantly different between Model and Clinical settings
- There was a greater performance decrease with increasing n-back difficulty for Clinical DBS than for OFF or Model (task difficulty x DBS condition repeated measures ANOVA, $P = 0.033$)
- Performance on the 2-back during Clinical DBS was significantly lower than performance at OFF in single task conditions (paired sample t-test, adjusted $\alpha = 0.017$)



Model Based Programming. A) Proportion of the VTA in the Dorsal and Ventral segments of the STN for both the 'Clinical' and 'Model' settings. The Clinical setting had an average of 31.4 mm^3 (69.6 %) inside the dorsal portion and 13.7 mm^3 (30.4 %) in the ventral portion. The Model setting had an average of 24.4 mm^3 (95.7 %) inside the dorsal portion and 1.1 mm^3 (04.3 %) in the ventral portion. B) The 'dual task losses' for the force maintenance task showing 'Clinical DBS' worsening compared to OFF-DBS, and recovery with the 'Model DBS' Setting.

Clinical Outcomes and Programming

- When performing force-tracking only, Clinical and Model DBS resulted in better performance compared to OFF
- The force variability differed between the three DBS conditions: under Clinical DBS the variability was greatest
- A significant interaction between DBS condition and task difficulty was present
- Force-tracking performance declined as task complexity increased from single to dual-task conditions while OFF DBS and under Clinical and DBS settings
  - The greatest decline was observed under Clinical DBS
- During Clinical DBS in the dual-task condition, force tracking performance declined dramatically as task difficulty increased during the 2-back condition

AUTHORS' CONCLUSIONS

- Clinical and Model based programming were equally effective in improving UPDRS-III values
- Model based programming resulted in a better performance under all dual-task conditions compared to clinical settings
- During modestly complex task conditions, the cognitive performance (working memory) was better with Model compared to Clinical DBS settings
- The results suggest that cognitive-motor declines are common during STN DBS but can be alleviated through the visualization of the targeted brain structures together with the volume of tissue activated to optimize parameter settings

Distance to White Matter Tracts is Associated with Deep Brain Stimulation Motor Outcome in Parkinson's Disease

Authors:
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Published:
Journal of Neurosurgery 2019
26: 1-10

Study type:
Cohort study, single-center, retrospective

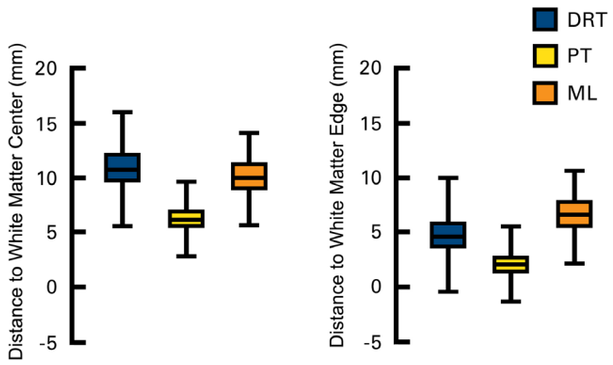
Element supported:
Fibertracking,
Guide XT

OBJECTIVE

The stimulation of white matter tracts such as the dentato-rubro-thalamic tract (DRT) may be involved in suppressing tremor, but the current spread into fibers close to the STN can also lead to unwanted side effects like dysarthria. The aim of this study was to understand the relationship between the stimulation location in white matter tracts and the effect on dysarthria and tremor suppression.

METHODS

- Over 22 months 35 PD patients underwent bilateral STN DBS surgery (including 20 tremor dominant patients) and had DTI data that met inclusion criteria for the study
- All patients were evaluated before the surgery on the UPDRS-III in the ON- and OFF-state
- Around 14 days after the surgery, the optimal DBS parameter settings were determined by trained and experienced DBS nurses that were blinded to the DTI data
- Programming was done in the OFF-state and UPDRS scores and baseline dysarthria was evaluated with stimulation OFF
- Contact-specific UPDRS scores and adverse effects were rated, ring-mode stimulation was used for patients with directional electrodes
- Overall 280 contacts were tested from 0 to 5 mA / V (60 µs, 130 Hz)
- The amplitude was not further increased in case that unpleasant side effects occurred
- For practical reasons all voltage amplitudes were transferred to milliamperes assuming an impedance of 1 kOhm
- It was assumed that the stimulation strength is proportional to the volume of tissue activated (i.e. 2 mA = 2 mm)



Mean Distance to White Matter Tracts. On average the active contacts were located closest to the center of the PT, followed by the ML, then the DRT (6.45 ± 1.39 mm, 10.32 ± 1.64, and 11.06 ± 2.05 mm respectivley). The distances to the edges of the fiber tracts differed in their order (2.30 ± 1.39 mm, 6.82 ± 1.64 mm, and 4.89 ± 2.05 mm respectivley).

Image Processing and Statistics

- Diffusion weighted Images were obtained on a 3T MR scanner
- Whole-brain fiber tracking was performed to track the dentatorubrothalamic tract (DRT), pyramidal tract (PT), and medial lemniscus (ML)
- Postoperative CT scans were registered to preoperative MRI images followed by semi-automated localization of the electrode on the CT
- The perpendicular distance from each electrode contact to white matter tracts was measured
- The difference in the distance of contacts with and without effect on tremor to the DRT was analyzed (any stimulation strength, independent samples t-test)
- The same was done for dysarthria with respect to the PT distance
- Analysis of the degree of tremor suppression correlated to the distance of the active contact to the DRT (stimulation at 2 mA, Spearman's rank correlation)

RESULTS

- In general, contacts were located closest to the center of the PT (mean 6.45 ± 1.39 mm) followed by the ML (mean 10.32 ± 1.64 mm) and DRT (mean 11.06 ± 2.05 mm)
- Estimated diameters for DRT were 11.05 mm, for PT 7.02 mm, 5.70 mm
- Mean distance from the contact to the edge of the tracts: PT = 2.30 ± 1.39 mm; ML = 6.82 ± 1.64 mm; DRT = 4.89 ± 2.05 mm
- Tremor was significantly reduced by DBS ($p < 0.001$)
- Contacts that improved tremor scores were located on average 1.13 mm closer to the center of the DRT compared to noneffective contacts
- The distance from the contacts to the center of the DRT was strongly correlated with the degree of tremor improvement ($p < 0.001$)

AUTHORS' CONCLUSIONS

- The stimulation location relative to white matter tracts is related to overall DBS outcome
- The stimulation of the DRT may be related to the DBS effect on tremor
- Visualization of fibers is a promising tool to optimize and personalize stimulation parameters in order to increase tremor improvement and minimize side effects such as dysarthria

Traditional Trial-and-Error Versus Neuroanatomical-3D-Image Software-Assisted Deep Brain Stimulation Programming in Patients with Parkinson's Disease

Authors:
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Published:
World Neurosurgery, 2019
(19): 32537-9

Study type:
Cohort Study, cross-over, prospective

Element supported:
Guide XT

OBJECTIVE

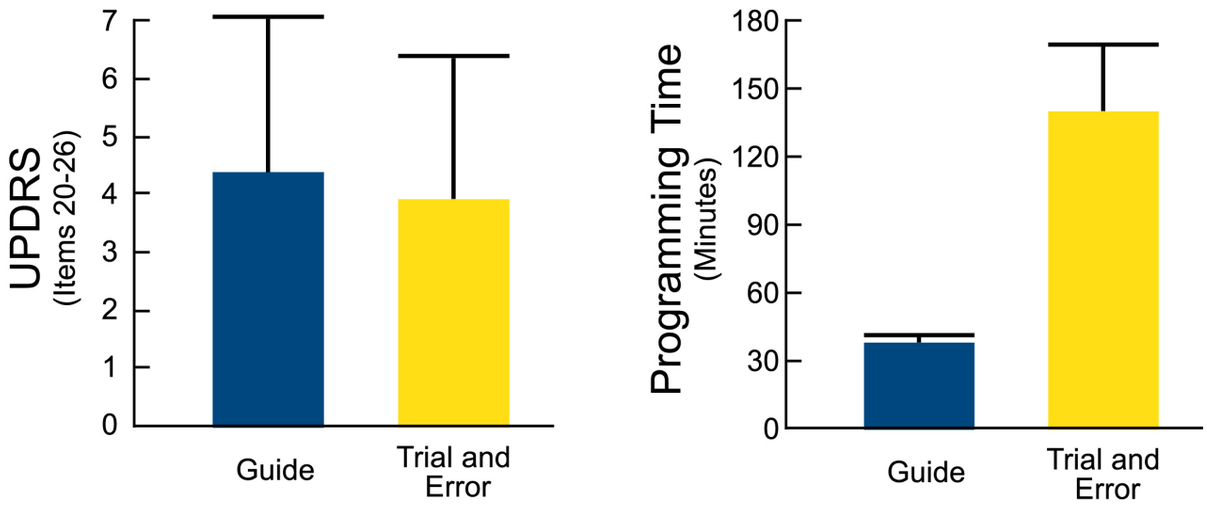
Programming of DBS systems remains a necessary and time-consuming part of the therapy, owing in part to the large number of possible stimulation configurations that must be tested. This study compares programming time and clinical outcomes for traditional trial-and-error programming and Guide™ assisted DBS programming in 10 PD patients treated with STN DBS.

METHODS

- 10 PD patients underwent bilateral DBS STN implantation (5 male, mean age 56.60 ± 10.51 years, UPDRS-OFF 57.40 ± 14.11)
- Three days after surgery each patient was programmed with both Guide™ assisted and traditional trial-and-error programming using a monopolar review
- Patients were randomized to receive one method of programming first
- After a 1-hour washout period an unblinded neurologist reset their settings
- The patients then crossed-over and were re-programmed by a third neurologist blinded to the first settings

Guide Aided Programming

- A Pre-operative MRI taken under general anesthesia was fused with the post-op CT
- The DBS leads were localized on the fused CT and a 3D reconstruction of the thalamus, STN and red nucleus using the Morel atlas was provided by the Guide™ platform
- Model DBS settings were determined by overlaying the SFM on the dorsal part of the STN
- If the clinical response was unsatisfactory, stimulation parameters were adjusted to achieve optimal clinical response
- Times to perform fusion, anatomical segmentation, and lead localization were not counted as part of the total duration for programming session



Impact of Visualization-Aided Programming. A) Non-inferiority comparing standard of care clinical programming to GuideTM-Aided programming to (3.9 ± 2.5 vs; p = 0.8219) as assessed on UPDRS-III items 20-26. B) Significant improvement of programming time for Guide-Aided programming (139.50 ± 27.73 vs 35.50 ± 3.69 minutes).

RESULTS

- Traditional trial-and-error programing outcomes were defined as 'optimal clinical response' for all patients
- The traditional programming method resulted in a mean UPDRS III (Sub-items 20-26) score of 3.9 ± 2.5
- The mean duration for the traditional programming sessions was 139.50 ± 27.73 minutes
- After the Guide™ aided approach, 7 patients required further clinical refinement
- In 5 of these patients an increase of current amplitude was sufficient and in the 2 others a selection of the contact one level above the one suggested by the model was needed
- These clinical adjustments were counted as part of the Guide™ assisted programming session
- The Guide™ assisted programming method resulted in a mean UPDRS III (Sub-items 20-26) score of 4.4 ± 2.7
- The mean duration for the Guide™ assisted programming method sessions was 35.50 ± 3.69 minutes

AUTHORS' CONCLUSIONS

- The findings show that Guide™ 3D-neuroanatomical visualization software ™ provides information helpful for programming including the final placement of the electrode and the location of the SFM
- Visualization software can be used to plan shorter and more effective programming session while achieving the same clinical outcomes
- Visualization aided programming may be of great help with directional electrodes to efficiently capitalize on the programming options and optimize clinical benefit

ACRONYMS

CT	Computed Tomography
DBS	Deep Brain Stimulation
DRT	Dentatorubrothalamic Tract
ET	Essential Tremor
ETRS	Essential Tremor Rating Scale
MER	Micro Electrode Recording
ML	Medial Lemniscus
MRI	Magnetic Resonance Imaging
PD	Parkinson's Disease
PT	Pyramidal Tract
STN	Subthalamic Nucleus
SFM*	Stimulation Field Model
UPDRS	Unified Parkinson's Disease Rating Scale
Vim	Ventral-Intermediate Nucleus of the Thalamus
VTA*	Volume of Tissue Activated
VAT*	Volume of Activated Tissue

*These terms refer to the same computational concept

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