Journal of Visualized Experiments

Optimal Fixation Position of Deep Brain Stimulation Electrodes for Parkinson’s Disease in Humans

--Manuscript Draft--

Article Type:	Invited Methods Article - JoVE Produced Video
Manuscript Number:	JoVE60959R2
Full Title:	Optimal Fixation Position of Deep Brain Stimulation Electrodes for Parkinson’s Disease in Humans
Section/Category:	JoVE Neuroscience
Keywords:	Parkinson's disease; Deep Brain Stimulation - DBS; neurosurgery; microelectrode recording - MER; automatic classifier; Machine learning
Corresponding Author:	Alfredo Rosado-Muñoz Universitat de Valencia Burjassot, Valencia SPAIN
Corresponding Author's Institution:	Universitat de Valencia
Corresponding Author E-Mail:	Alfredo.Rosado@uv.es
Order of Authors:	Alfredo Rosado-Muñoz
	Juan F. Guerrero-Martinez
	Luciano Schiaffino
	Manuel Bataller-Mompeán
	Antonio Gutiérrez
Additional Information:	
Question	**Response**
Please indicate whether this article will be Standard Access or Open Access.	Standard Access (US$2,400)
Please indicate the **city, state/province, and country** where this article will be **filmed**. Please do not use abbreviations.	Valencia city. Valencia State. SPAIN

TITLE:

Optimal Fixation Position of Deep Brain Stimulation Electrodes for Parkinson's Disease in Humans

AUTHORS AND AFFILIATIONS:
Alfredo Rosado-Muñoz[1], Juan F. Guerrero-Martinez[1], Luciano Schiaffino[2], Manuel Bataller-Mompeán[1], Antonio Gutiérrez[3]

[1]Group for Digital Design and Processing (GDDP), ETSE, Department of Electronic Engineering, University of Valencia, Valencia, Spain
[2]Laboratory of Rehabilitation Engineering, National University of Entre Ríos, Oro Verde, Argentina
[3]Functional Neurosurgery Unit, La Fe Hospital, Valencia, Spain

Corresponding Author:
Alfredo Rosado-Muñoz (alfredo.rosado@uv.es)

Email Address of Co-Authors:
Juan F. Guerrero-Martinez (juan.guerrero@uv.es)
Luciano Schiaffino (lschiaffino@ingenieria.uner.edu.ar)
Manuel Bataller-Mompeán (Manuel.Bataller@uv.es)
Antonio Gutiérrez (antoniogutierrez100@gmail.com)

KEYWORDS:
Parkinson's disease, deep brain stimulation, DBS, neurosurgery, microelectrode recording, MER, automatic classifier, machine learning

SUMMARY:
The fixation of deep brain stimulation microelectrodes for Parkinson's disease requires brain surgery. This work describes a method to determine the optimal position of the stimulation electrodes during surgery, which requires a combination of techniques.

ABSTRACT:
Certain cases of Parkinson's disease are treated with deep brain stimulation (DBS), applying electrical stimuli to the subthalamic nucleus (STN) in the brain. Stimuli are provided by inserted stimulation electrodes within the brain that supply a square voltage signal generated in a control unit (IPG) typically located in the chest. The elimination of Parkinson's symptoms depends directly on the location of the stimulation electrodes. This work describes a method used to determine the best fixation position of the stimulation electrodes during surgery. The procedure provides guidance to the surgeon and requires the use of three techniques: 1) use of a stereotactic frame and stereotactic robot, 2) medical imaging (e.g., MRI and CT), and 3) signal analysis provided by microelectrode recording. In DBS surgery, the patient is usually awake with light sedation; however, one of the main advantages of this method is that the patient is fully sedated with anesthesia to avoid any distress or nervousness. Deciding where to perform electrode fixation is a result of combining intraoperative imaging and signal analysis to detect the

the electrode position with the highest probability of blocking the PD symptoms. A software tool for signal analysis (DBScan) was developed, assisting the surgical team in determining the location for electrode fixation. In long-term postsurgical analysis, PD disorders were successfully eliminated in all operated patients.

INTRODUCTION:

Parkinson's disease (PD) is a major health problem affecting ~1–2% of people over 65 years of age worldwide[1], causing motor disorders (e.g., bradykinesia, tremor at rest, rigidity, postural instability), and non-motor disorders (e.g., sleep disorders, cognitive dysfunctions)[2,3]. The deep brain stimulation (DBS) technique consists of applying electrical stimuli to the subthalamic nucleus (STN) region of the brain. This treatment has proved to be very efficient in blocking PD motor disorders in the patient[4], allowing a better quality of life.

In order to stimulate the STN, a surgical procedure is necessary to insert one electrode in its left and one in its right region and then fix them in place. The success of the operation, measured by the improvement in the patient's quality of life after surgery, greatly depends on the optimal fixation position of the stimulating electrodes. The STN is a relatively small oval region between 4 mm and 10 mm length[5], so it is difficult to target. However, it is not only necessary to place the electrodes in the STN but also carefully select the electrode positions within it.

The optimal electrode position is given by the beta band activity. It is widely accepted that the main indicator for PD is directly related to beta band activity measured by the spectral power in the band: higher activity indicates more severe PD disorders[6,7]. Brain spectral analysis divides the brain waves into bandwidths; the beta spectral band is the frequency band ranging from 13 Hz to 30 Hz. Activity in the beta band is associated with sensorimotor processing, has been observed in various different cortical areas, and is implicated in a wide range of cognitive functions[8]. When this activity appears in the STN, it is considered to be pathological and associated to PD. Electrical stimulation provided by DBS reduces beta band activity.

The surgical procedure for DBS implantation varies upon the technological equipment available at the hospital and to the neurosurgery team in charge. First, preoperative MRI images are fused with a stereotactic volumetric frame-based CT on the day of surgery for direct anatomical targeting. Then, during surgery, with the use of a stereotactic frame and an arc-shaped device attached to it, it is possible to plot the coordinates and drive the electrode to the exact location and depth in the brain using a mechanically or electrically assisted submillimeter displacement electrode driver. Prior to the placement of the stimulation electrodes, the intraoperative physiological verification of the STN is necessary. For this, a cannula with microelectrodes for signal recording (MER) are inserted at a distance calculated according to the MRI and within planned trajectory and, with the patient awake, some motor activities are performed while the brain signal activity is monitored in order to fine tune the position in view of the brain activity. According to the surgeon and the commonly accepted brain pattern criteria[4], the final fixation position is decided. The MER are then extracted, and the stimulation electrodes are inserted and fixed to the specified position. One of the main features of the proposed protocol is that, unlike other methods, the patient is completely sedated and less anxious or uncomfortable.

Additionally, the aim of DBS is to reduce the beta band activity in the STN, which will reduce beta activity in the cortex and eliminate the PD disorders. In this case, the fixation position decision for the stimulation electrode is based on the beta band activity in the STN, supported by intraoperative computed tomography (CT) images. The procedure is integrated in a developed software called DBScan that makes use of signal analysis and artificial intelligence algorithms. Some STN localization algorithms are proposed[9], but they are not integrated in the surgical procedure and, in practice, they cannot be used. This work describes the use of the DBScan tool for STN localization used during the surgical procedure.

The objective of this work is to describe the method followed during DBS implantation surgery and the novel techniques supporting the operation. The procedure is derived from the standard practices in DBS surgery[10,11], but several improvements have been made and results show that all patients obtained satisfactory results (1% had some surgery problems not directly associated to the DBS). In comparison, when using previous surgery methods, 5% of patients required repositioning or had undesired disorder blocking.

PROTOCOL:

This clinical procedure was approved by the Ethical Committee for Biomedical Research of La Fe Hospital with registration number 2015/0824 in May 17, 2016. All participants signed written informed consents. These investigations using human data were carried out following the rules of the Declaration of Helsinki and its updates.

1. Presurgery: Patient screening for DBS implantation

1.1. Detect patients with increased drug dosages required to block PD disorders.

NOTE: The main drugs used to block PD are dopamine agonist (DA) and levodopa (LD). Which one is used depends on the neurologist's criteria and the patient’s state. The degree of suppression of the beta oscillations by DA/LD therapy correlates with improvement of the hypokinetic symptoms of Parkinson’s disease[7]. However, DA/LD therapy in high doses generates adverse effects to the patient, with DBS being the only remedy left to block PD disorders. The limit of drug dosage to support the use of DBS surgery depends on the patient’s symptoms, especially when psychiatric disorders appear. Surgery is recommended when the patient presents dyskinesia, behavioral disorders, and must take a DA/LD dose of 100 mg every 2 h or less in order to block PD disorders.

1.2. Have the neurologist perform several tests (e.g., motor, sensory, speech, and psychiatric) on potential candidates and decide whether they are suitable for DBS surgery[12].

1.3. Several days before surgery, perform a T2-weighted MRI.

NOTE: **Figure 1** shows an example of an obtained T2-MRI.

1.4. Visually perform a volumetric analysis of the acquired T2-MRI images. Locate the STN region and estimate its location in a maximum of four MRI cuts (i.e., in an estimated area covering a 2.4 mm brain thickness).

NOTE: Typically, each MRI image slice corresponds to 0.6 mm of brain thickness and 650 images (cuts) per brain are obtained from the MRI. Thus, a total of 390 mm is covered.

1.5. Rebuild axial images for a 0.6 mm thickness using cranial software (e.g., Medtronic S7)[13].

1.6. Based on the MRI, define the incision trajectory to reach the STN. When planning the trajectory, consider the STN position and other physiological issues such as the presence of big veins or arteries, sulci, and other formations in the brain tissue that could cause damage to the patient.

1.7. Before surgery, ensure that the patient had an off-period medication (usually 24 h).

2. DBS surgery, phase 1: In-operating room patient preparation and incisions

2.1. Anesthetize the patient (i.e., full sedation using intravenous general anesthesia). During surgery, have an anesthesiologist monitor heart rate, blood pressure, breathing, and other vital signs to make sure patients are normal and steady[14].

2.2. Use a stereotactic frame to hold the patient's head.

NOTE: It is not necessary to use the arc-shaped part of the frame to obtain the fiducial points.

2.3. Once the patient is in position, perform the first intraoperative image acquisition using CT.

2.4. In the cranial software, click on both MRI (step 1.3) and CT images (step 2.3) and select the image fusion option to perform image fusion of overlapping MRI and CT images, including the previously estimated electrode insertion trajectories (step 1.6) to obtain the incision point coordinates in the skull.

NOTE: Image fusion is an option provided by the software to superimpose MRI and CT images, and a certain degree of transparency can be automatically adjusted. **Figure 2** shows two images from the data fusion used to determine the incision point.

2.5. Transfer the obtained positions to the stereotactic robot. Move the stereotactic robot with a fiducial end-point tool so that it can accurately point to the incision location using a laser light.

NOTE: **Figure 3** shows the patient in the operating room, the intraoperative CT, and the stereotactic robot for the fiducial point determination.

2.6. Using a cranial drill (craniotome) with an 18 mm drill bit, make two burr holes (one hole for each hemisphere) in the skull at the incision point indicated by the stereotactic robot.

2.7. Place a cannula in each hole for further MER electrode insertion.

NOTE: The same cannula will also be used to insert the stimulation electrode.

2.8. Replace the fiducial end-point tool in the robot with an electrode driver (motorized positioning microdrive), used later for insertion of micrometric step MER electrode and stimulation electrodes.

3. DBS surgery, phase 2: Microelectrode Recording (MER) insertion

3.1. Perform a second intraoperative CT to verify that the cannula is located 10 mm from the target fixation point (**Figure 4-1**).

3.2. Using cranial software, perform data fusion of CT (step 3.1) with initial MRI images (step 1.3) and define the trajectory that the MER electrodes must follow to reach the STN area (**Figure 4-2**).

NOTE: The surgical team, through visual observation, defines the target STN area and trajectory.

3.3. Cranial software provides the distance from the surface to the target point by the obtained trajectory. Thus, insert the MER electrodes through the cannula.

NOTE: Typically, MER electrodes are composed of two tracks with 2 mm between them.

3.4. Using the robot with the motorized driver, insert the MER electrodes through the defined trajectory to 10 mm from the estimated target point.

NOTE: The motorized driver displaces the electrodes the exact distance specified by the surgeon.

3.5. Perform MER signal data acquisition, recording using a portable MER system (**Table of Materials**). Acquire data over 10 s.

NOTE: Data acquisition parameters are automatically set by the equipment. Data are stored either in Alpha-Omega or EDF (i.e., European Data Format) formats.

3.6. Move MER electrodes 0.5 mm further, and acquire and record data again after 10 s. Repeat this process to 4 mm from the estimated target point. During data acquisition and recording, visually inspect the signal monitor to verify that signal patterns correspond to those in the STN, according to brain atlas data[4,9].

NOTE: In total, data from 30 depths, 2 MER electrodes per trajectory, and two trajectories are obtained and saved in a removable device.

4. DBS surgery, phase 3: Signal analysis for determination of electrode fixation position

4.1. Insert the removable device where data are stored in the computer running the DBScan tool[14].

4.2. For one trajectory, execute the DBScan[15] time and frequency signal analysis module by selecting **frequency** and pressing the **trajectory analysis** button. Next, select **time** and press **trajectory analysis** and visually inspect all results. For each MER in the trajectory, DBScan displays the basal level, the dominant frequency in the beta band, and their spectrograms as a function of depth (**Figure 5**). Repeat the procedure for the second trajectory.

NOTE: Higher beta band activity provides information about the depth location of the motor area in STN.

4.3. Execute the DBScan classification analysis module by selecting **zone estimation** and pressing the **trajectory analysis** button so that the software provides the probability of optimal STN location (higher percentage provides better position) for each depth, each MER electrode, and each trajectory (**Figure 6**).

4.4. With all information (i.e., image fusion, DBScan results, and cranial software information), decide on the best stimulation electrode location (target position) and move the MER electrodes to this position.

4.5. Perform a third intraoperative CT and verify that the MER electrodes are at the target point (**Figures 4-3**,**4-4**).

4.6. Upon confirmation of the proper position, remove the MER electrodes from the brain, leaving the cannula.

5. DBS surgery, phase 4: Fixation of DBS stimulation electrode and final verification during surgery

5.1. Using the motorized driver, insert the DBS stimulation electrode through the cannula according to the best trajectory determined in step 4.4 and place it in the target position.

5.2. Perform a fourth intraoperative CT and data fusion with MRI in order to verify the correct stimulation electrode position (**Figures 4-5**,**4-6**).

5.3. Activate the stimulation electrodes with the implantable pulse generator (IPG) to verify the absence of undesired side effects such as abnormal movements in the patient.

NOTE: The IPG device will be inserted in the patient's chest.

5.4. If a mixed electrode is used (i.e., electrode combining acquisition and stimulation leads), use cranial software to verify that beta band energy decreases when stimulation is activated. If only a stimulation electrode is used, verify that the beta band energy decreases in the cortex by regular EEG.

5.5. Once confirmation of beta band attenuation is obtained and no side effects are observed, extract the cannula and proceed to the fixation of the electrodes in the skull by lead anchoring (**Table of Materials**).

5.6. Seal the skull orifices using acrylic glue to prevent any infection in the area.

5.7. Make a 2 cm skin incision at the postauricular scalp where the lead is relayed, and a 5 cm skin incision in the chest (subclavicular) or nearby area for the IPG insertion. Fix the IPG using a silk suture, connecting the stimulation electrode leads. Close the skin using a subcutaneous absorbable suture.

NOTE: The IPG must be superficially located (i.e., no more than 10 mm deep) in order to access configuration data and recharge the battery wirelessly.

6. Postsurgery analysis

6.1. After anaesthesia effects, verify that the PD disorders have disappeared, or they are minimal in comparison with the patient's previous situation.

6.2. After one week of surgery, perform a CT 3D imaging.

6.3. Perform a data fusion of this CT with presurgical MRI (step 1.3) and also with the intraoperative CT (step 3.1) in order to verify that the stimulating electrode position is still fixed in the initially estimated area (**Figure 7**).

6.4. Evaluate the patient periodically (~6 months) to verify that PD disorders are kept blocked.

REPRESENTATIVE RESULTS:

DBS surgery is the last resort for PD patients who do not respond to drug therapy or patients having adverse side effects with drug therapy (e.g., psychiatric or behavioral disorders). After DBS implantation, the drug dose administered to the patient is reduced by two thirds of the dose before implantation. Additionally, DBS provides better quality of life, reducing tremors and psychological side effects of drugs, and also reduces the number of patient visits to the doctor.

Regarding precision in the surgery, using previous DBS surgery methods (i.e., arc-shaped stereotactic frame), the error in the electrode position typically ranges from 0.4–0.5 mm, while using the stereotactic robot, a maximum error of 0.2 mm is obtained. This makes the operation more reliable and allows the surgical team to be more confident about the implantation position. Additionally, the stereotactic robot avoids the use of bone or skin-anchored fiducials, making the procedure painless to the patient.

The use of specific signal and classification software (DBScan) provides more information about the brain location of the MER and stimulation electrodes. The software provides detailed information about the brain electrical activity, which changes depending on the brain region that electrodes are crossing before reaching the target area (i.e., STN). Additionally, not only is the brain area detected, but also the optimal place for implantation inside the STN. This software makes use of different signal analysis algorithms, together with a classifier using artificial intelligence. Traditionally, the surgical team analyzes the brain signal visually, using subjective criteria according to the person visualizing data in the monitor. However, using the DBScan software (**Figure 6**), different brain signal information is displayed, providing temporal and spectral signal analysis as a function of the electrodes' position. This provides more information and provides the surgeon with more certainty regarding the electrode fixation decision. Because beta band analysis is one of the main indicators of PD, this spectral band is rigorously analyzed. The automatic classifier makes use of all spectral and temporal features of the brain signal to provide a result.

More than 300 surgeries have been carried out at La Fe Hospital (Valencia, Spain) since the introduction of DBS surgery in the hospital. Before applying the procedure described in this work, the patient was not sedated for the surgical procedure. Approximately 150 patients were operated upon without anesthesia. Currently ~150 patients (this number is growing, as each week a new operation is done) were operated with the described procedure and complete sedation (anesthesia). Post-surgery clinical evaluation showed the complete success in the sedated patients, blocking PD effects even with a reduced dose of levodopa. In contrast, for non-sedated patients where the surgery did not include the stereotactic robot or DBScan software, ~10% showed some problems related to surgery: side effects in the motor system, remaining PD effects, psychiatric alterations, and other minor effects.

FIGURE LEGENDS:

Figure 1: T2-MRI for target detection (STN location) and trajectory planning. Using MR-3D (3T T2) imaging, the location of the STN was obtained. Then, trajectories for right and left incisions for insertion of electrodes were decided upon by the surgical team. A detailed analysis of the brain in 3D to avoid sulci and other brain structures that could be affected by the incision was required.

Figure 2: Image fusion from CT and MRI (left), and fiducial points (right). The planned trajectory was transferred to the stereotactic robot.

Figure 3: DBS surgery setup. The patient is fully sedated with anesthesia, and the head is fixed with a stereotactic frame. Intraoperative CT is used for image acquisition at different moments in surgery. A stereotactic robot with fiducial end-point tool to define fiducial points (five red balls) and reference trajectory point for incision (red laser light) was used.

Figure 4: Verification of target trajectory and electrode location. Sequence of intraoperative CT:

1. Verification of cannula position 15 mm distant to the target (CT in top left); **2**. Target STN point and trajectory definition (MRI, bottom left); **3-4**. Verification of MER electrode position in target STN (CT in top center, overlapped MRI in bottom center); **5-6**. Verification of stimulation electrode in target STN (CT in top right, overlapped MRI in bottom right). All images are posterior-anterior (P-A) views. Once the cannula is 15 mm away from the target, a trajectory (left) was created and then extended to the target (center). Then, image fusion with MRI was done (right) to verify that the trajectory and final position was accurate and reached the STN effectively. Images at the top correspond to the left-right view, and posterior-anterior for the bottom images.

Figure 5: Signal analysis provided by the DBScan software analyzing the beta band activity in different STN positions provided by two track MER electrodes. Signal was acquired in 0.5 mm steps for 12 mm. Basal level, beta band energy, energy ration between beta and gamma bands, and dominant frequency in the beta band are displayed (top); red arrow shows the most active regions, candidates for DBS implantation. Spectrogram of beta band energy for two different patients is shown at the bottom. In this case, track 1 (C1) provides more beta band activity than track 2.

Figure 6: DBScan software results. Signal analysis and machine learning tools were used to provide information on the optimal DBS stimulation electrode fixation position. Multiple temporal and spectral features were calculated, in addition to the classification result.

Figure 7: Image data fusion of CT 3D showing the stimulation electrode position with presurgical MRI. Data fusion showed the location of the electrodes in the initially estimated area of the STN.

DISCUSSION:

The main improvements provided by this DBS surgery method are the following: full sedation of the patient, use of a stereotactic robot for electrode insertion, and use of DBScan software for high precision fixation of the stimulation electrodes. The method provides complete confidence about the fixation location, supported by the postsurgical results showing successful blocking of PD effects.

Currently, 5% of the patients required a new DBS surgery. This was due to problems during surgery not directly associated with the electrode fixation location. The main issue was infection, because this is a prosthesis surgery and is more prone to infections. However, when this new surgical method was used, the patients fully recovered, and PD symptoms were successfully eliminated. It must be noted that all DBS surgeries, not only those using the method described here, may cause some damage in the brain areas penetrated by the cannula, from the cortex to the target position. It has been observed that 1% of the patients may show some minor effects, with symptoms varying depending on the brain area where the damage was caused.

Many DBS surgeries do not include brain signal analysis, relying solely on the use of image fusion (e.g., MRI, trajectory planning, and intraoperative CT). However, precision in the electrode fixation using solely these tools is low due to combined precision errors from the techniques used (e.g., image fusion, trajectory planning, etc.), which may lead to unsatisfactory results. The method described in this work still makes use of image fusion as an essential guidance tool, but the final microstep positioning makes use of brain signal analysis obtained from MER through DBScan software, especially beta band analysis, which provides more precision and reliability to the DBS surgery.

In total, three intraoperative CT images are acquired. Each intraoperative CT is fused with the initial MRI to settle the incision points (first CT), verify adequate position of the cannula (second CT), and verify the position of the stimulation electrode (third CT). Additionally, the second and third CTs are fused in order to verify that the stimulating electrode is located in the target position. However, it is important to note that the CT images are used for verification, but the decision about the target location of the stimulating electrode is based on the signal analysis and results provided by DBScan.

Additionally, the final position of the stimulating electrodes was verified by image fusion of a CT made one week after surgery versus the initial MRI, and versus the final intraoperative CT (step 5.2 in the protocol). Thus, the position is verified after the postoperative brain edema subsides and the intracranial gas disappears. The measurements showed that the displacement due to edema and intracranial gas modifications due to surgery was lower than 0.1 mm, which means that the total error is kept below 0.3 mm. This value is still valid for a positive effect in the patient.

One of the main conclusions of the proposed method lies in the fact that beta band power in the brain signal acquired during MER insertion is essential for optimal target position. The results provided by DBScan software are based on beta band activity, but other signal parameters are also taken into account, such as dominant frequency and spectral power.

The methods used in DBS surgery are still evolving. Currently, there are two areas of interest. First, simultaneous MER recording and electrode stimulation. Usually the DBS surgery procedure inserts MER microelectrodes for signal analysis and target estimation. Then, MER are extracted, and stimulation electrodes are inserted. If the MER and stimulation electrodes are inserted together, an initial analysis of the stimulation effect in the patient can be recorded by MER. Then, an immediate result on the brain signal could be perceived, supporting the decision of the location of electrode fixation. Second, effects of stimulation in the cortex. It is well known that beta band activity is also present in the cortex. The use of DBS decreases beta band activity in the STN, but also in the cortex. It is important to analyze the effect of DBS in the cortex, especially concerning the beta band activity.

As seen, the use of signal analysis is becoming very important in DBS surgery because it provides more accuracy in the estimation of the target position of the stimulation electrode. For instance, the signal analysis in the cortex may provide useful information. This is a future area of interest that may provide even more successful results for DBS surgeries.

ACKNOWLEDGMENTS:
We want to express our gratitude to all the surgical team at La Fe Hospital Valencia for their

support and details provided.

DISCLOSURES:

The authors have nothing to disclose.

REFERENCES:

1. Schapira, A.H., Jenner, P. Etiology and pathogenesis of Parkinson's disease. *Journal of Movement Disorders*. **26** (6), 1049-1055 (2011).

2. Dorsey, E. R. et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Journal of Neurology*. **68** (5), 384-386 (2007).

3. Peñas Domingo, E., Galvez-Sierra, M., Marín-Valero, M., Perez-Olivares, M. El libro blanco del Parkinson en España. Spanish Parkinson Federation. NIPO (online): 689-15-008-2. (2015).

4. Chaovalitwongse, W., Jeong, Y., Jeong, M.K., Danish, S., Wong, S. Pattern Recognition Approaches for Identifying Subcortical Targets during Deep Brain Stimulation Surgery. *IEEE Intelligent Systems*. **26** (5), 54–63 (2011).

5. Mavridis, I, Boviatsis, E., Anagnostopoulou, S. Anatomy of the Human Subthalamic Nucleus: A Combined Morphometric Study. *Anatomy Research International*. **2013**, 319710 (2013).

6. Tepper, A. et al. Selection of the Optimal Algorithm for Real-Time Estimation of Beta Band Power during DBS Surgeries in Patients with Parkinson's Disease. *Computational Intelligence and Neuroscience*. **2017**, 1512504 (2017).

7. Zaidel, A, Spivak, A, Grieb, B, Bergman, H, Israel, Z. Subthalamic span of β oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. *Brain*. **133** (7), 2007-2021 (2010).

8. Engel, A.K., Fries, P. Beta-band oscillations—signalling the status quo? *Current Opinion in Neurobiology*. **20** (2), 156-165 (2010).

9. Wong, S., Baltuch, G.H., Jaggi, J.L., Danish, S.F. Functional localization and visualization of the subthalamic nucleus from microelectrode recordings acquired during DBS surgery with unsupervised machine learning. *Journal of Neural Engineering*. **6** (2), 26006 (2009).

10. Abosch, A. et al. An International Survey of Deep Brain Stimulation Procedural Steps. *Stereotactic and Functional Neurosurgery*. **91**, 1-11 (2013).

11. Shukla, A.W., Okun, M.S. State of the Art for Deep Brain Stimulation Therapy in Movement Disorders: A Clinical and Technological Perspective. *IEEE Reviews in Biomedical Engineering*. **9**, 219-233 (2016).

12. Lang, A. E. et al. Deep brain stimulation: Preoperative issues. *Movement Disorder*. **21**, S171–S196 (2006).

13. StealthStation® S7® Treatment Guidance System Manual. Part Number 9733782, revision 14. Medtronic Navigation, Inc. Louisville, CO, USA (2012).

14. Mashour, G. A., Engelhard K. *Oxford Textbook of Neuroscience and Anaesthesiology*. Oxford University Press. Oxford, UK (2019).

15. Guerrero, J. et al. DBScan. Software Record Number: 164431. Valencia, Spain (2016).

Figure 1

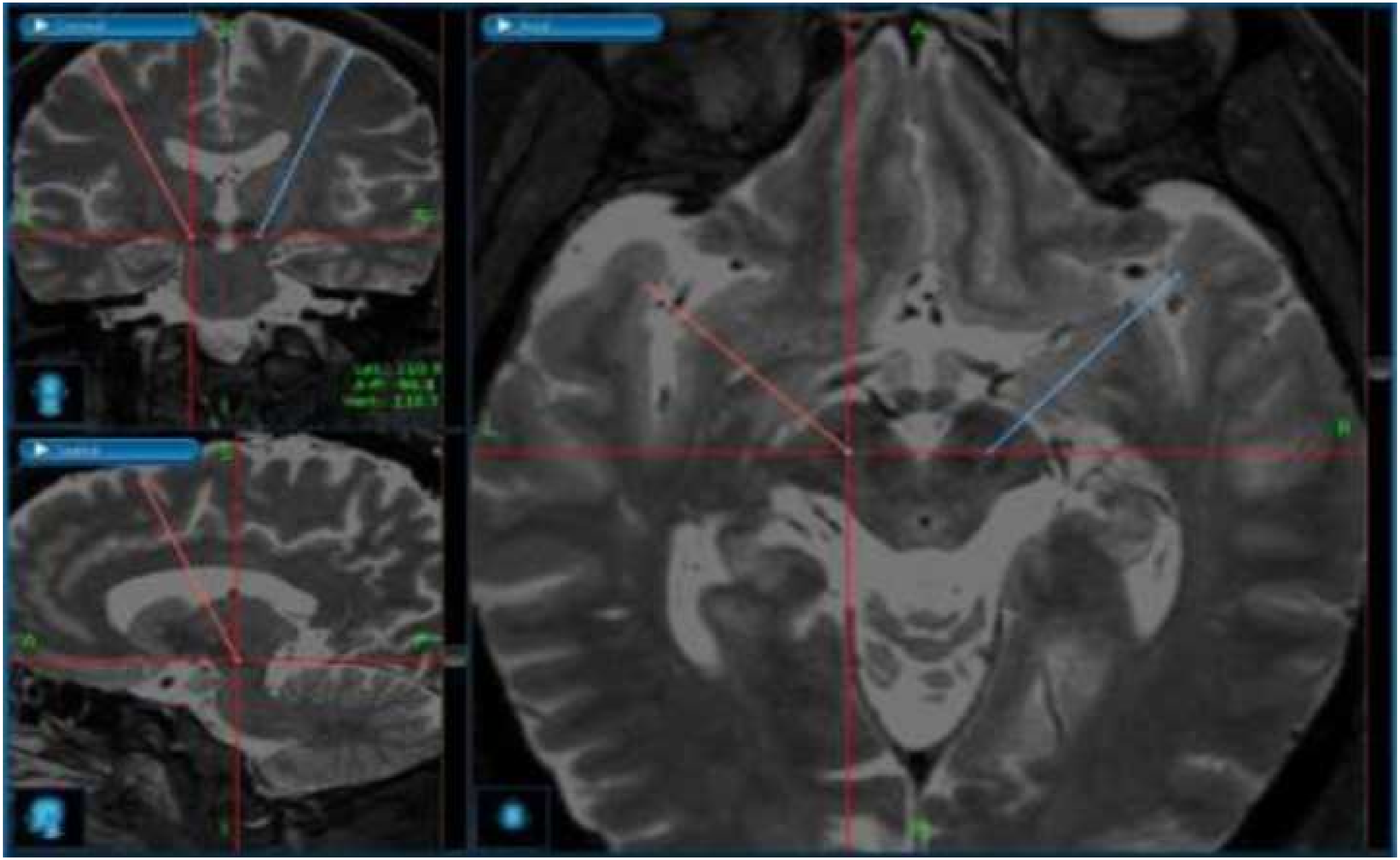


Figure 2

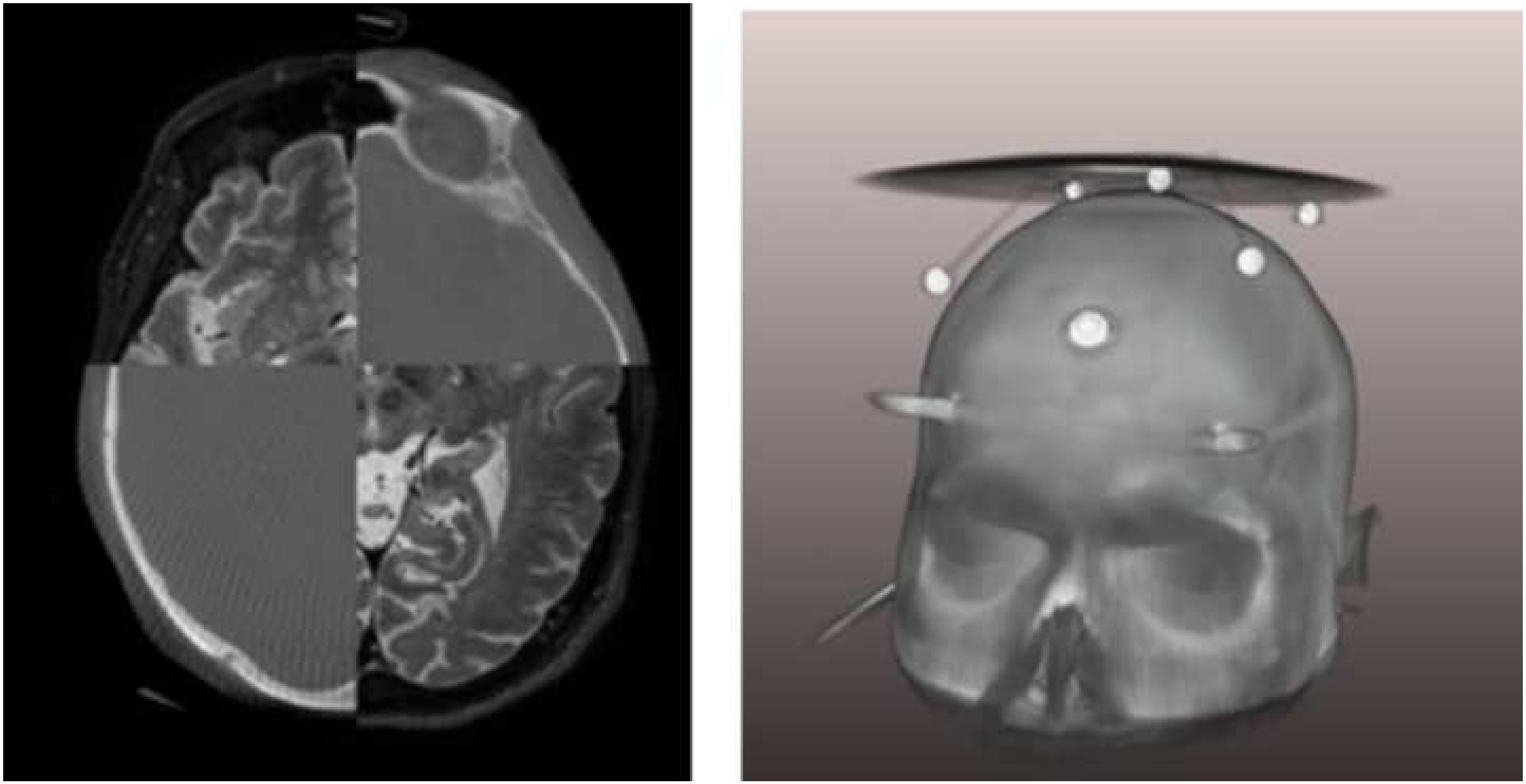


Figure 3

Figure 4

Click here to access/download;Figure;Figure4.png

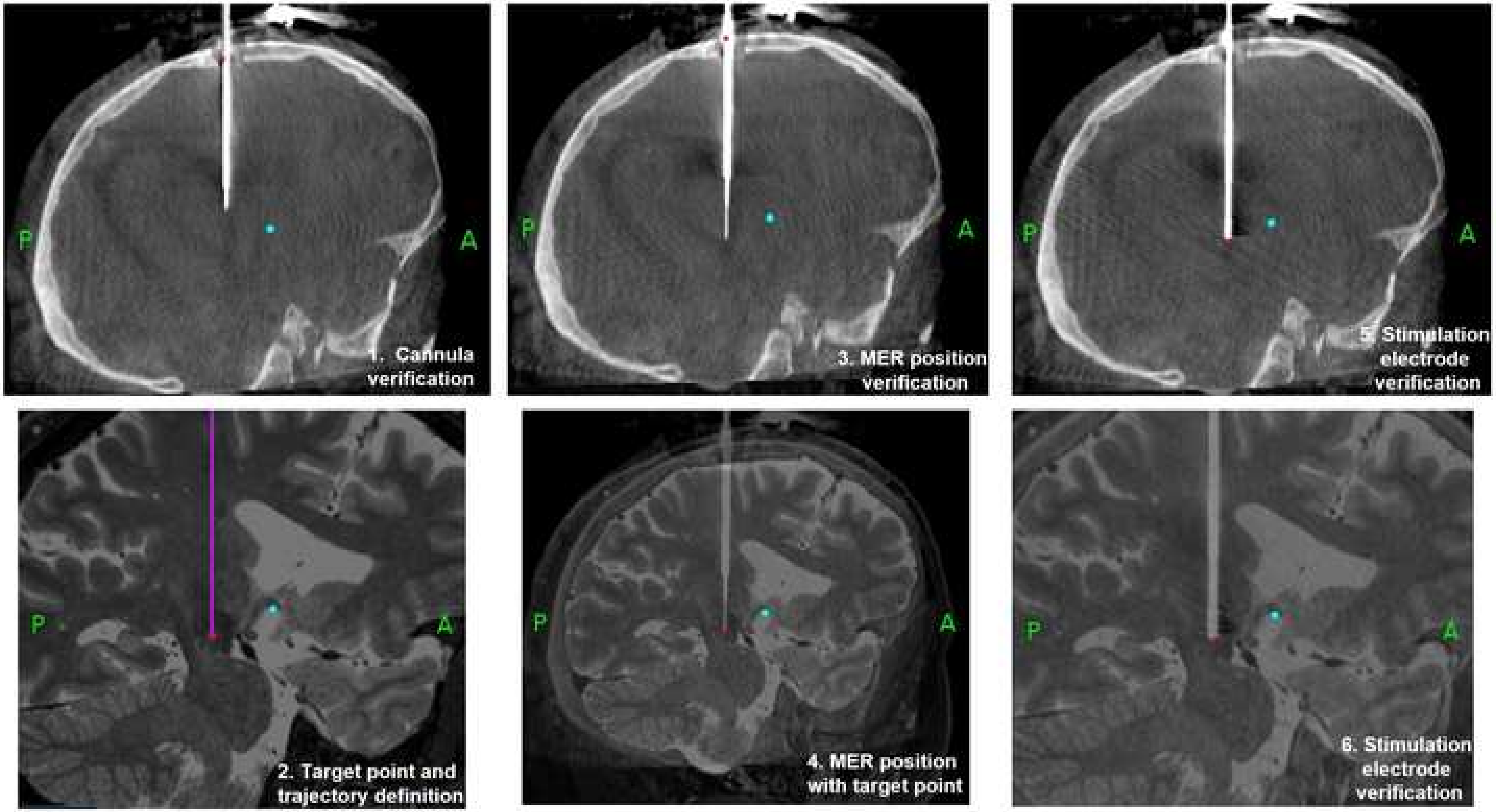


Figure 5

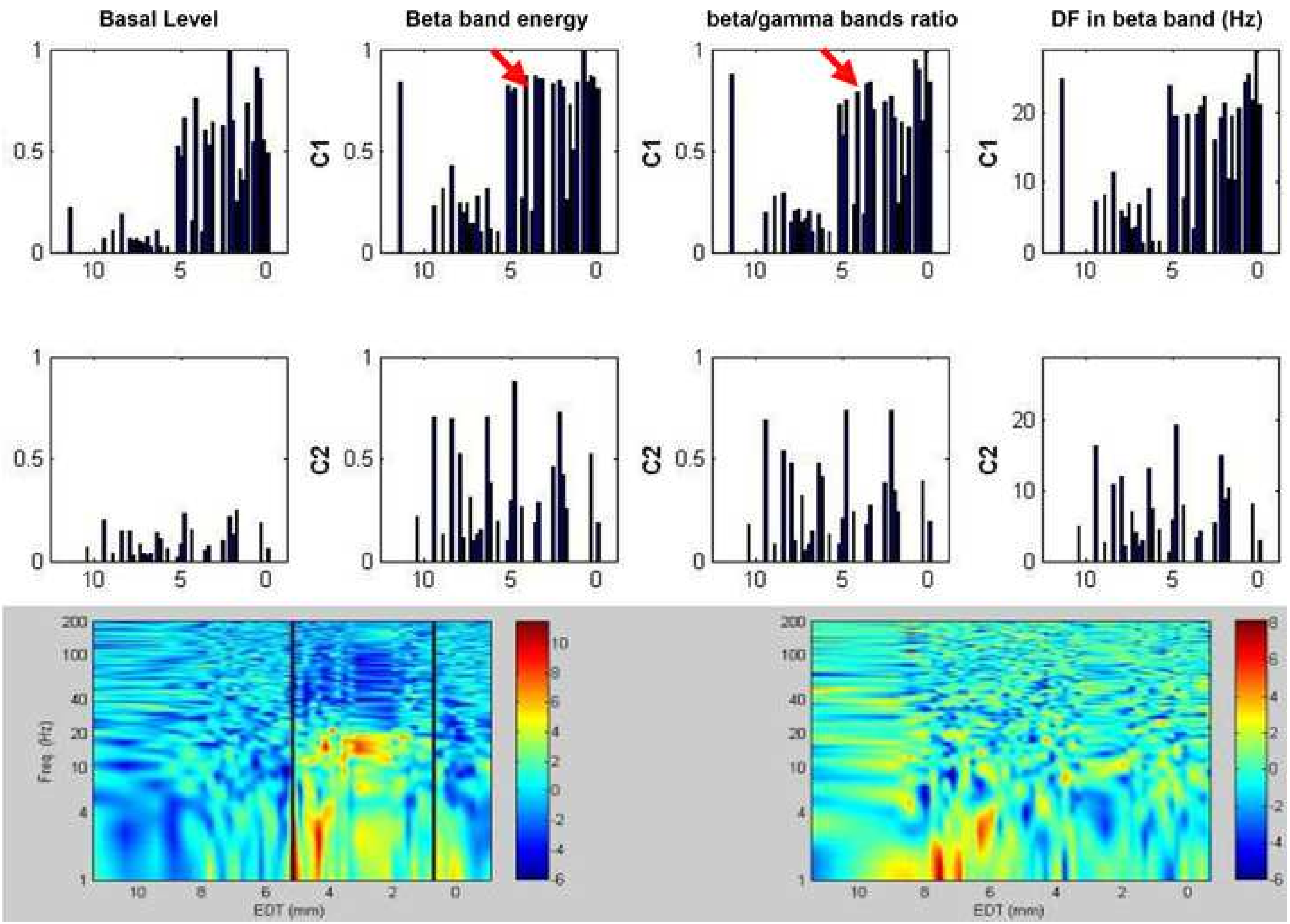

Basal Level
Beta band energy
beta/gamma bands ratio
DF in beta band (Hz)
C1
C2
Freq (Hz)
EDT (mm)
EDT (mm)

Figure 6 Click here to access/download;Figure;Figure6.png

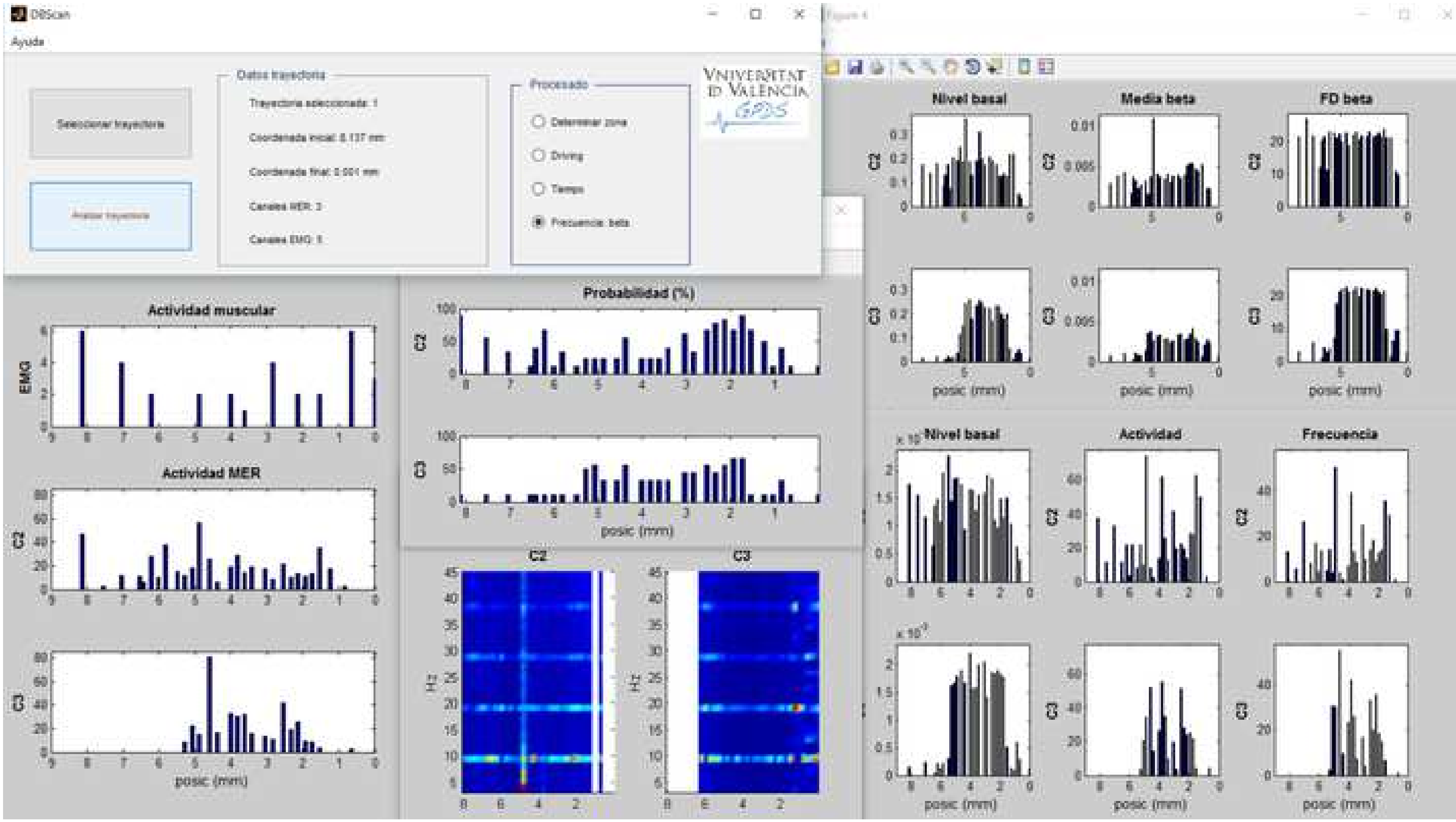
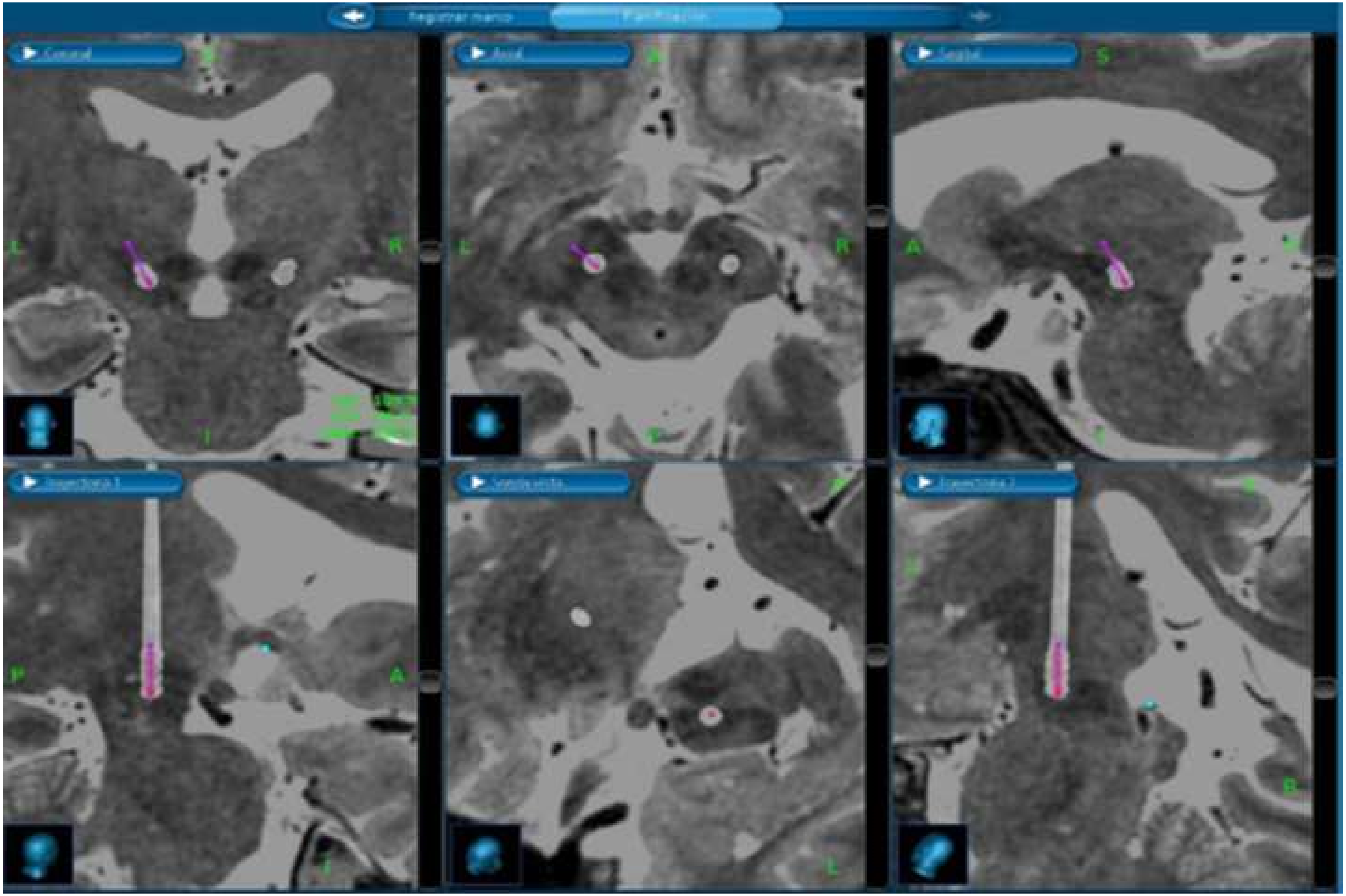


Figure 7

Click here to access/download;Figure;Figure7.png



Name of Material/Equipment	Company	Catalog Number	Comments/Description
CT - Computed Tomography	Philips	Brillance Essencial	Preoperative CT
DBS lead anchoring	Medtronic	Stimloc	Fixation system for stimulation electrode leads in the skull
DBS stimulation electrodes	Medtronic	model 3389	4 contacts
DBScan software	Univ. Valencia		Developed by authors for brain signal analysis and classification
Frameless patient registration module	Renishaw	Neurolocate	Used for fiducial points
Image Fusion and trajectory planning software	Alpha Omega	Stealthstation S7 with Framelink planning	Used for target and trajectory definition
Intraoperative CT	Medtronic	O-ARM	Used for image fusion during DBS surgery
MER electrodes	Alpha-Omega	Acute Electrode	Tungsten, glass coating, 125mm shank diameter, 2mm exposed wire, 1mm male pin, 1MW
Miroelectrode and Local Field Potential Register with automatic neuro navigation	Alpha Omega	NeuroSmart	Brain signal recorder and visualizer
Motorized electrode driver	Alpha Omega	Micromotor NeuroNav Drive	Insertion and extraction of MER and stimulation electrodes
MRI – magnetic resonance	Philips	Intera 1.5 T	Preoperative MRI
S7 Cranial software	Medtronic	S7 Cranial software	
StealthStation S7	Medtronic	StealthStation S7	

Stereotactic frame	Elekta	Leksell	Only used for head support, no skin incisions for fiducial positioning
Stereotactic robot	Renishaw	Neuro Mate	Substitute of arc-shaped stereotactic frame. Also used for electrode driver support

26th February, 2020

Dear Editor in Chief,

Please, find enclosed the revised submission for the work entitled "**Surgery procedure for optimal fixation position of Deep Brain Stimulation (DBS) electrodes for Parkinson's disease in humans"** for consideration of publication in JOVE Journal.

As already discussed with the editor, Aaron Berard, we believe that the proposed methodology fits the JOVE scope and will be of interest to readers and video watchers (once filmed). The surgical procedure takes about four hours, but we hope that we can film a summary video of the most important steps.

According to Editor and reviewers indications, we have modified the manuscript. All modified text is marked in red in the new version. The table of materials has been modified, too. The detailed reply to each of the raised issues is included in the Word document as replies to the added comments made by the reviewer.

We hope the additional information and text modification provides more information and can serve as a good support to the edited video. If you need further modifications, do not hesitate to contact us.

I look forward to hearing from you soon.

Yours sincerely,

The authors