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Title: Description of a Novel, Surgically Implanted Neuromodulatory Technique Known as Bilateral Epidural Prefrontal Cortical Stimulation (EPCS) for Treatment-Resistant Depression (TRD)

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Authors, please finish filling out the questionnaire below.

A. Microscopy: Does your protocol involve video microscopy, such as filming a complex dissection or microinjection technique? (Y/N)____N_____

Can you record movies/images using your own microscope camera? (Y/N)____N_____

If no, JoVE will need to record the microscope images using our scope kit (through a camera port or one of the oculars). Please list the make and model of your microscope:
_____N_____

B. Software Usage: Does your protocol include detailed, step-by-step, descriptions of software usage? (Y/N)____Y____

C. Location: Will the filming need to take place in multiple locations? (Y/N) ___Y____ If yes, how far apart are the locations? ___Charleston, SC, Minneapolis Mn, and Palo Alto, CA_____

D. Surgery: Will your filming be of a surgical procedure? (Y/N) ___Y (sham surgical procedure)_____

If yes, does the surgery move along quickly without pauses? (Y/N) ___Y (pre-existing video)____

Please indicate where during this protocol the videographer will have NO opportunity to stop and restart recording. Do this using comments after each step the bleeds into the next without pauses.

E. Which steps of your protocol will viewers benefit most from having filmed? Please list 4-6 individual steps using the step numbers listed in this document. (Please do not list entire sections.)

2.6 Using neuronavigation to determine stereotactic placement of 4 paddle leads.

2.10 Placement of the leads and checking accurate placement.

3.4 Intraoperative testing of the lead placement with patient cooperation.

4.11 Placement of pulse generators in the chest.

4.12 Testing the system after implantation, including testing impedance.

F. What is the single most difficult aspect of this procedure and what do you do to ensure success? Please list 1-2 individual steps using the step numbers listed in this document. (Please do not list entire sections.)

2.10 Now, insert the sterile paddle leads epidurally over the desired areas. The leads should be between the dura and the inner table of the skull. Then, verify the paddle lead placements using the neuronavigation and intraoperative fluoroscopy.

The above step is the single most difficult aspect of this procedure. This is because the success of the EPCS treatment relies on accurate placement of the leads. Accurate placement relies on surgical experience as well as experience with neuronavigation and intraoperative fluoroscopy tools.

1. Introduction

A. Experimental Goal: (read by voice talent at JoVE)

The overall goal of this surgery is to place 4 epidural prefrontal cortical stimulator paddles over key locations of the brain in order to treat treatment-resistant depression. **(Intro)**

B. Required Interview Statements: (Said by you on camera. Don't forget to smile!)

NOTE: Unknown who delivered which interview. Since this was filmed a few years ago, it may be best to put together the rough cut and then ask the authors to identify the interviewees during the science editing.

1.1. Senior Author 1: This method can help answer key questions in the field of interventional psychiatry, such as how to individualize cortical targeting and stimulation parameters for brain stimulation devices.

1.2. Senior Author 2: This method was conceived as a safer alternative to deep brain stimulation for transcranial magnetic stimulation.

1.3. First Author 1: The main advantage of this technique is that it has fewer surgical risks than deep brain stimulation, with a negligible risk for intracranial hemorrhage.

1.4. First Author 2: For the 41% of patients that fail to respond to two adequate trials of pharmacologic treatment, EPCS is a viable non-pharmalogical treatment.

1.5. Additional Demonstrator 1: Though this method can provide insight into depression, it can also be applied to many other disorders.

1.6. Additional Demonstrator 2: Generally, individuals new to this method will struggle with the specialized surgical experience required.

In this section, every person who speaks should read just one part, so I have put in an example of how this could be accomplished. Everybody who will be seen in the video, except the patient, should have a speaking part in the Introduction because this serves as our opportunity to flash your names and credentials on the screen while you speak.

E. Ethics title card:

1.7. Procedures involving human subjects have been approved by the Institutional Review Board (IRB) at the Medical University of South Carolina and Stanford University.

Protocol: (read by voice talent at JoVE)

2. Preparations and Phase 1 of the Surgical Procedure

2.1. In preparation, set up complete hemodynamic monitoring of the patient [1.WID] consisting of electrocardiography, pulse oximetry, [2.MED] end-tidal carbon dioxide, and non-invasive blood pressure monitoring. [3.MED]

2.1.1. Establishing shot of the scene, with equipment being set up around the patient

2.1.2. Attaching the ECG and/or pulse oximetry leads to patient

2.1.3. Attaching CO2 sensor and/or BP monitor to patient

2.2. To begin, induce moderate sedation using intravenous fentanyl [1.MED-TXT] as well as an infusion of propofol. [2.MED-TXT]

2.2.1. Preparing injection of fentanyl (not making the injection), TEXT: 50-250 μg fentanyl / kg

2.2.2. Preparing the propofol infusion (not making it), TEXT: 25-100 μg propofol / kg / min

2.3. Next, inject 2 cc of 2% lidocaine with epinephrine locally into the periosteum, [1.MED-TXT] at the burr hole and surgical headrest pin, on the scalp. [2.CU]

2.3.1. Preparing the syringe with lidocaine + epinephrine, TEXT: 2 cc, 2% lidocaine + epinephrine

2.3.2. Cleaning the scalp to at burr hole and headrest pin to prepare skin for injection (not making injection)

2.4. Then, mark the location for the bicoronal incision [1.CU] and infiltrate the area with local anesthetic. [2.CU-TXT]

2.4.1. Marking the location of the incision

2.4.2. Preparing the syringe with local anesthetic, TEXT: 5 cc 1% lidocaine + epinephrine (1:100,000) / 0.5% bupivacaine

2.5. Next, orient the patient in a supine position with the head elevated and the neck slightly flexed. [1.MED] To limit head movements, apply a skull clamp with surgical pins. [2.MED]

2.5.1. Positioning the patient as described, focus on tilt of neck and elevation of head

2.5.2. Applying a skull clamp in a non-invasive fashion

2.6. Next, using a neuronavigation system, [1.WID] determine the stereotactic placement of the 4 paddle leads from the tagged MRI image [2.MED] and also use the surface landmarks on the patient's head. [3.CU]

2.6.1. Positioning the neuronavigation system scanner on/over patient

2.6.2. Collecting the MRI image

2.6.3. Focus on the surface landmarks on the patient's head while talent points them out

2.7. Use the linear "look ahead" function to indicate the underlying cortical area of interest and map the targeted cortical areas using a pointer wand. [1.SCREEN]

2.7.1. *Here, provide a screen capture of using the "look ahead" function in the neuronav system to find the areas of interest, using pointer wand – here we need action, so a static screen capture will not suffice*

2.8. Now, apply sterile drapes and proceed with making the first incision. Make a bicoronal incision behind the hairline and peel the flap forward. [1.LM]

2.8.1. *Please provide time codes of the relevant actions from the DVD – about 20 seconds of video*

2.9. Next, using a generic 4-mm spherical diamond drill bit, make two slit-shaped craniotomies, one over each frontal hemisphere, parallel and anterior to the coronal suture. [1.LM-TXT] After completing the holes, wax the bone edges. [2.LM]

2.9.1. *Please provide file name and time codes making the craniotomies*

TEXT: 3 cm x 0.5 cm

2.9.2. *Please provide file name and time codes of waxing the bone edge:*

2.10. Now, insert the sterile paddle leads epidurally over the desired areas. The leads should be between the dura and the inner table of the skull. [1.LM]

2.10.1. *Please provide time codes of the relevant actions from the DVD – about 20 seconds of video*

2.11. Then, verify the paddle lead placements using the neuronavigation [1.SCREEN] and intraoperative fluoroscopy. [2.LM]

2.11.1. *Provide a screen capture of the neurovnav system showing the paddle lead placement – this can be a static image, if a video isn't feasible*

2.11.2. *Provide an image of fluoroscope showing the paddle lead placement – this can be a static image, if a video isn't feasible*

2.12. When the pointer wand coincides with the Brodmann map domain of interest on the computer screen [1.SCREEN] and it coincides with the position and orientation of the electrode paddle on the plain X-rays [2.LM] in multiple planes, the placement is correct. [3.LM]

2.12.1. *Provide a screen capture of the computer screen showing the pointer wand coincides with the Brodmann map domain – this can be a static image, if a video isn't feasible*

2.12.2. *Provide an image of x-ray in one plane showing position of electrode paddle*

2.12.3. *Provide an image of x-ray in a different plane showing position of electrode paddle*

2.13. After making final adjustments, anchor the paddle leads to the edge of the craniectomy slit openings using "dog-bone" style plates and micro-screws. The tails of the paddle leads should exit the skull at a soft angle via grooves sunk in the posterior edge of the craniectomies. [1.LM]

2.13.1. *Please provide time codes of the relevant actions from the DVD – at least 40 seconds of video*

3. Intraoperative Testing

3.1. Immediately after securing the paddle leads, [1.WID] lift the moderate propofol sedation by discontinuing the infusion [2.MED] and begin testing once the patient regains full alertness. [3.WID] [4.LM]

3.1.1. Establishing shot, show the post-operative scene, patient should act as though anesthetized – mock up as much as possible

3.1.2. Stopping the propofol sedatation, stopping infusion

3.1.3. Patient acting as though they are regaining consciousness, pantomime conversation with talents

3.1.4. video: VTS_01_1.VOB, time stamp: 22:17 – not sure how this should be used, probably not needed.

3.2. First test the bilateral anterior or midlateral leads. [1.CU] Use a patient-masked, sham-controlled parametric. [2.WID] Connect all four leads to external stimulators. [3.MED]

3.2.1. Detail view of the named leads

3.2.2. Establishing shot of the scene, talents can be preparing to connect the leads

3.2.3. Connecting the leads to the stimulator and dialing in the stimulation

3.3. Then, apply 60-Hertz stimulations at 0 to 2 Volts and at 4 to 5 Volts. Randomize the order, with the no-stimulation condition always occurring first and at least once more during the test. Apply each train of stimulations for 3 minutes. [1.SCREEN]

3.3.1. *Screen capture of programming the stimulator being set to 60 Hz with voltages as described, random order, no-stim rule and timing of stim trains*

3.4. During each stimulation train, present the patient with a series of 13 statements using a laptop. [1.WID] Phrase the statements to read like "I feel SAD," [2.MED] "I feel ANXIOUS," "I feel SETTLED emotionally," or "I feel ATTENTIVE to my surroundings." [3.SCREEN] [4.LM]

3.4.1. Setting up the laptop to be viewed by patient

3.4.2. Over the shoulder shot of patient viewing laptop, "I am SAD" statement on screen

3.4.3. *Provide a screen captures with the following three statements cycling over 15 seconds:* "I feel ANXIOUS," "I feel SETTLED emotionally," and "I feel ATTENTIVE to my surroundings."

3.4.4. video: VTS_01_02.VOB**,** time stamp: 03:00 – not sure how this should be used, probably not needed.

3.5. Then, record the subject's experience using a visual analogue scale [1.WID] ranging from complete agreement to complete disagreement. [2.MED] Also allow the patient to express any perceived changes in mood, attention, or cognition if they so desire. [3.WID] [4.LM]

3.5.1. Talents providing the patient a view of the scale

3.5.2. Patient pointing out their reaction to the laptop statement on scale, over-the-shoulder shot

3.5.3. Patient and talent(s) pantomiming a conversation about the a "change in mood"

3.5.4. Video: VTS_01_02.VOB**,** time stamp: 04:57 – not sure how this should be used, please have a look, but probably not needed

4. Phase 2 of the Surgical Procedure

4.1. Immediately after the intraoperative testing, proceed with implanting a pulse generator. [1.WID] First, discard the lead extensions [2.LM] and insert the paddle tails under the parietal galea. [3.LM]

4.1.1. Fake the preparation for implanting the pulse generator – bringing the generator to the surgery location, which can all be a mock up

4.1.2. *File and time codes of discarding lead extensions*

4.1.3. *File and time codes of inserting the paddle tails under galea*

4.2. Next, irrigate the bicoronal incision with bacitracin solution. [1.LM] Then, sprinkle the bone openings with vancomycin powder [2.LM] and fit the openings with ribbons of sterile compressed sponge. [3.LM]

4.2.1. *File and time codes of irrigating incision with solution:*

4.2.2. *File and time codes of apply Ab powder:*

4.2.3. *File and time codes of applying compressed sponge:*

4.3. Then, close the scalp using inverted, interrupted, 2-0 polyglactin sutures in the galea and [1.LM] use running 3-0 nylon in the skin. [2.LM] Then, place a sterile dressing over the area [3.LM and remove the drapes and head holder. [4.MED]

4.3.1. *Please provide time codes of placing sutures in galea*

4.3.2. *file and time codes of placing sutures in the skin*

4.3.3. *file and time code of placing dressings over the sutures*

4.3.4. Act out removing the drapes and head holder

4.4. Now, place the patient under general endotracheal anesthesia, [1.WID] as dictated by the patient's previous anesthesia history and comorbidities [2.MED] as well as the anesthesiologist's preference and expertise. [3.WID]

4.4.1. Act out preparing the anesthetic, bringing anesthetic to the scene

4.4.2. Detail of loading syringe with anesthetic

4.4.3. Pretending to deliver the anesthetic to the patient

4.5. Start with making skin incisions over the parietal scalp and below the clavicle on both sides to the depth of subcutaneous fat. The pulse generators with 2 channels are to be implanted in each side in the chest wall, 2 cm inferior to the clavicle. [1.LM]

4.5.1. *Please provide time codes of the relevant actions from the DVD – about 30 seconds of video*

4.6. Proceed in this layer to pass a hollow tunneling rod between the parietal and infraclavicular incisions. [1.LM] Then, thread the individual extension cords for each paddle through the hollow lumen of the tunneling rod [2.LM] and remove the tunneling rod. [3.LM]

4.6.1. *Please provide file and time codes of passing tunneling rod between incisions*

4.6.2. *File and time codes of threading extension cords through rod:*

4.6.3. *File and time codes of removing the tunneling rod:*

4.7. Now, connect the generators individually to two ipsilateral leads using the extension leads by tunneling the leads subcutaneously behind the ear, [1.LM] down the neck, [2.LM] and to the infraclavicular pockets. [3.LM]

4.7.1. *Please provide file and time codes of tunneling behind the ear:*

4.7.2. *File and time codes of tunneling down the neck:*

4.7.3. *File and time codes of tunneling to the infraclavicular pocket:*

4.8. Tunnel the right and left of connectors of Channel 1 to the ipsilateral anterior frontal pole. [1.LM] Tunnel the right and left connectors of Channel 2 to the ipsilateral lead over the mid-lateral prefrontal cortex. [2.LM]

4.8.1. *Please provide time codes of tunneling channel 1 connector to anterior frontal pole– about 15-20 seconds of video*

4.8.2. *Please provide time codes of channel 2 to lead tunneling over prefrontal cortex – about 15-20 seconds of video*

4.9. Then, create subcutaneous pockets below the clavicles using blunt dissection. [1.LM]

4.9.1. *Please provide time codes of the relevant actions from the DVD – about 10 seconds of video*

4.10. Now, connect the paddles to the system [1.MED] and turn it on using the associated clinician programmer device, according to the manufacturer's instructions. [2.MED]

4.10.1. Connecting the paddles to the system

4.10.2. Turning on the system and the programmer device

4.11. Once active, select each lead individually and use the "Impedance" section to test the contacts impedances. [1.SCREEN] Record these values for future reference. [2.CU] Then, turn off the system and do not reactivate it until two to three weeks post-surgery. [3.WID]

4.11.1. Provide a screen capture of using the programming device to select the leads and the impedance test option for each lead

4.11.2. Taking notes of impedance values on screen in logbook

4.11.3. Turning off the system preparing to close the incision

4.12. Now, close the incision using 3-0 interrupted polyglactin suture in the fascia [1.LM] and running 4-0 nylon suture in the skin. [2.LM] Then, apply sterile dressings, extubate the patient and take the patient to recovery. [3.LM-TXT]

4.12.1. *Please provide time codes of suturing the fascia layer:*

4.12.2. *Time codes of suturing the skin layer:*

4.12.3. *Time codes of applying dressing:*

TEXT: Post-operative procedures are outlined in the text protocol.

5. Results: Post-operative Testing

5.1. Five patients were enrolled in this trial with diagnoses like major depressive disorder and bipolar affective disorder type one. At enrollment the patients took a mean of six psychotropic drugs, at a five-year follow-up they took a mean of 4.4 drugs.

5.1.1. Table 1 – highlight the 2nd to bottom line at "At enrollment", change the highlight to the bottom ling at "at a five-year…"

Note the tables show data for FIVE patients, not six. So some changes are needed.

5.2. After seven months of active stimulation, patients showed a mean improvement on the Hamilton Rating for Depression-24 of 55%. After 60 months the improvement measured 43%. In ___ of the five patients this score didn't change by more than three points.

5.2.1. Table 2 – show as is

5.3. Scores on the Montgomery-Asberg Depression Rating Scale and the Inventory of Depressive Symptomatology, Self-Report also improved significantly from baseline.

5.3.1. Table 3 – reduce this to only show the data from preop to 5 years, the statistics columns aren't needed here

5.4. Neuropsychological testing showed no significant changes at either testing time point. Some adverse effects are outlined in the text protocol, but there were no seizures, incidents of hypomania, impulsivity, or disinhibition. Nor did any patient report new cognitive defects.

5.4.1. Table 4 – no changes needed

6. Conclusion (said by authors on camera)

6.1. Author Name: After watching this video, you should have a good understanding of how to surgically implant epidural prefrontal cortical stimulation paddle leads.

6.2. Author Name: While attempting this procedure, it's important to remember to patients should have the opportunity to familiarize themselves with the format and content of the subjective inquiries during preoperative visits.

6.3. Author Name: Following this procedure, other methods like postoperative testing can be performed in order to answer additional questions including which stimulation parameters are optimal for each patient in the long term.

6.4. Author Name: After its development, this technique paved the way for researchers in the field of interventional psychiatry to explore alternative surgical techniques to deep brain stimulation for treatment-resistant depression.

6.5. Author Name: Don't forget that surgical implantation carries risk and should only be considered for patients who have failed other standard treatment modalities.

Anybody can speak in the Conclusion section, provided that they spoke already during the introduction. You can have one person speak all five lines or mix it up however you would like.

Provided Media

Authors, Please list all images, movie files, or 3-D rendered animations that can be included in the video per editor's request. The step in the script/video where these images will be inserted should be specified. For example:

6.2 – *0123_PIname_Figure1.tif* - dual color imaging of tumor angiogenesis at 40X
6.2 – *0123_PIname_Figure2.tif* - dual color imaging of tumor angiogenesis at 100X

Formats: For static images we prefer .tiff, .eps, Illustrator, Powerpoint or Photoshop files at dimensions of at least 720X480 pixels and 300 dpi. The higher resolution, the better. Likewise any exported movie files should have at minimum these dimensions and be rendered to .mov, .mp4, or .avi files.

Insert your media filenames here.

General Preparation

It's critical for a smooth and organized shoot that all reagents are accounted for, in advance.

Any overnight or long incubation steps should be recognized and specimens/samples be prepared in advance so that prior steps can be recorded and shooting can continue with pre-prepared specimens/samples.

All tubes/flasks should be pre-labeled neatly before we arrive.

Ex. Luciferase assay done in 96 well plates should be labeled with negative/positive control wells and experimental samples are labeled accordingly.

You will receive more detailed preparation instructions are included in the email accompanying the finalized script.