Informed Consent Form

Title: Deep Brain Stimulation for Treatment Resistant Depression: Exploration of Local Field Potentials (LFP) with the Medtronic Activa PC+S "Brain Radio" System

NCT Number: NCT01984710

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Consent to be a Research Subject

Project Title: Deep Brain Stimulation for Treatment Resistant Depression: Exploration of Local Field Potentials (LFP) with the Medtronic Activa PC+S "Brain Radio" System

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Study Supporter: **National Institutes of Health**

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CONTACT INFORMATION
If you have any questions about your rights as a research subject, please call Emory University IRB at [redacted].

If you have any question concerning this study or if you experience any unusual symptoms, health problems or a research-related injury, contact:

Sinead Quinn or Reed Gilbert (Research Coordinators), Psychiatry at [redacted]
Dr. Patricio Riva Posse, Psychiatry at [redacted]
Dr. Robert Gross, Neurosurgery at [redacted]

You can also page Dr. Gross or Dr. Riva Posse by calling the Emory Clinic page operator at [redacted]

INTRODUCTION AND PURPOSE
You are being asked to volunteer for a research study. The goal of this study is to monitor brain electrical activity while you receive deep brain stimulation for treatment resistant depression (TRD). You are being asked to volunteer because you have depression that is resistant to treatment. Your depression has not improved with antidepressants, psychotherapy and/or electroconvulsive therapy (ECT). Electrical stimulation of an area of the brain known as the subcallosal cingulate (SCC) might help people with treatment resistant depression. This is known as deep brain stimulation or DBS. DBS involves a surgical procedure during which electrodes are placed in your brain. The DBS electrodes will stimulate the SCC in your brain. The electrodes get electricity from a battery pack placed under the skin in your chest. DBS for depression is an experimental treatment. The Food and Drug Administration (FDA) has not approved DBS for depression. The FDA has not approved the DBS device used in this study (trade name Activa PC+S, Medtronic, Inc.). The ActivaPC+S device is also known as "Brain Radio" because it allows us to measure brain electrical activity. The FDA calls this is a "significant risk" device. We do have permission from the FDA to use the ActivaPC+S in this study.

The goal of this study is to use the Activa PC+S to measure changes in the electrical patterns in your brain during SCC DBS to treat your depression. The electrical signals we will measure are known as Latent Field Potentials or LFP. We want to learn about TRD by measuring changes in LFPs while you get DBS. The battery in the ActivaPC+S device will last about 3 years. We will measure LFP as long as the battery works. When the battery dies we will replace the Brain Radio with an ActivaPC device. We will not be able to measure LFP after the ActivaPC is implanted. The FDA approved the ActivaPC device for Parkinson's disease, tremor and dystonia. The ActivaPC device is NOT FDA approved for depression. We will continue to monitor your depression as you receive SCC DBS for 10 years. Ten (10) patients will be in this study. This study will be conducted at Emory University Hospital under the supervision of Drs. Helen Mayberg, Robert Gross, and Patricio Riva-Posse.

Your participation is completely voluntary. **Please read this consent form carefully. Please ask as many questions as you have about this study.** The following information may help you decide whether you wish to participate. It is very important that you read and understand the following pages. Before you agree to take part in this study, we recommend that you take this form home and discuss it with your family and your psychiatrist. We will answer their questions as well.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CRITERIA FOR PARTICIPATION

To be in this study you must have treatment resistant depression. You must have failed several treatments for depression. You must be healthy enough to have general anesthesia and brain surgery. You must be under the care of a psychiatrist. You must be willing to allow the study team to share information with your psychiatrist and for your psychiatrist to share information with us. You must live in the Atlanta metro region or be willing to move here for the first 8 months of the study.

You cannot be in this study if you have Bipolar disorder. You cannot be in this study if you have other serious mental illness such as schizophrenia or addiction. You cannot participate if it is not safe for you to have general anesthesia or brain surgery. You cannot participate if you are not able to have a magnetic resonance imaging (MRI) scan of your head. You cannot participate if you are pregnant or planning to become pregnant during the study. You cannot participate if you have a life threatening medical illness. You cannot participate if you have a cardiac pacemaker or other implanted electrical device. You cannot participate in this study if you do not live in Atlanta or are not willing to move here for 8 months.

You or your third party payer (i.e. your insurance) will be responsible for ALL clinical costs related to the study including but not limited to the implantation surgery, battery replacements, clinical follow-up appointments and labs. We will work with you and your insurance company prior to receiving the surgery to address coverage of clinical expenses. The manufacturer, Medtronic, Inc., will provide the DBS electrodes and Activa PC+S device without cost. You or your third party payer will be responsible for the cost of the ActivaPC replacement device.

PROCEDURES

This study will be carried out in several stages over 10 years. These stages will include:

- **Pre-surgery evaluation**
- **Surgery**
- **1 month post-operative period**
- **Acute stimulation testing**
- **A 24 week (approximately six month) active stimulation phase**
- **A 1 week discontinuation after 6 months of chronic DBS**
- **A 2.5-year continuation phase with LFP recordings (until battery dies).**
- **An approximate 7-year naturalistic follow-up phase with DBS but without LFP recordings.**

These stages are described in detail below.

Pre-surgery Evaluation (at least four weeks prior to surgery):

To make sure that you qualify for this study, you will go through a comprehensive evaluation.

Release of Information: You must allow us to review your medical records, including psychiatric and medical records and hospitalizations. You must currently be under the care of a psychiatrist. You must give your psychiatrist permission to share information about your health care with us. You must allow us to share information about your participation in this study with your psychiatrist.

Psychiatric Examination: The research coordinator and a board-certified psychiatrist will interview you about your medical and psychiatric history. This will include a detailed psychiatric interview and rating of your depressive symptoms. A second psychiatric evaluation will be done to confirm diagnosis. A screening physical examination may also be performed.

Neurosurgical Examination: You will meet with the neurosurgeon (Dr. Gross) who will explain the planned surgery. The neurosurgeon will perform a detailed physical examination. A small amount of blood (about 30-40 milliliters or 3-4 tablespoons) will be drawn. This sample will be used to test for medical illnesses. The blood sample will be stored for future genetic testing. A urine sample will be collected. This sample will be used to test for medical illnesses and evidence of drug abuse. An electrocardiogram (EKG) may be performed. The neurosurgeon will review your blood and urine tests to make sure that you are medically able to undergo brain surgery.

Weekly Mood Ratings: Every week during the pre-surgery evaluation period, you will meet with the research coordinator and a study psychiatrist to rate your mood and monitor your condition. Your mood will be measured with a number of questionnaires and a computer task in which you use a sliding scale to report your mood; the research coordinator will administer some of the questionnaires and some you will fill out. The weekly meetings with psychiatrists will be videotaped. These study visits will last approximately 2 to 3 hours. You will also do a short online questionnaire at home that you access on your computer.

Several tests will be performed during the 4 weeks prior to surgery. These tests will include: (1) neuropsychological testing, (2) a magnetic resonance imaging (MRI) scan, (3) emotional response testing, (4) activity monitoring, (5) an electroencephalogram (EEG). You will meet with a psychotherapist for a psychological evaluation. The therapist will provide Behavioral Activation

therapy after the DBS surgery (this is described in more detail below). The first meeting with the therapist will take 2 hours. Neuropsychological testing is paper and pencil tests of things like memory and IQ and should last 4 hours. The MRI scan helps us target the electrodes and should take 2 hours. Emotional response testing involves sitting at computer screen and looking at pictures and should take 4 hours. Activity monitoring involves wearing a wristband and carrying pedometer and GPS devices to measure your physical activity inside and outside of your house. You will be asked to carry these devices for a whole week. The EEG involves measuring the brain electrical activity. You will sit quietly and have an electrode cap on your head while the EEG is recorded. This will take about 3 hours.

Medications: You may continue to take antidepressant and other medications during this study. However, you must stay on the same antidepressant at the same doses during the four weeks before surgery and for at least the first 32 weeks following surgery (unless your depression worsens severely or you develop side effects – see RISKS section.) We will work with you and your psychiatrist to lower the dose or stop your use of certain medications including stimulants, antipsychotic and benzodiazepines before the DBS surgery.

Surgery

You will be admitted to Emory University Hospital on the morning of surgery. Under local anesthesia a stereotactic head frame will be secured to your head. This frame will allow precise localization of the place in the brain where the electrodes will go. This frame will remain on your head throughout the first part of the surgery (described below). Once the frame is placed, an MRI scan will be obtained and used in the operating room to place the DBS electrodes.

The DBS system consists of:

- An **electrode**, which consists of insulated wires with four electrical contacts at the end.
- An **extension cable**, which connects the electrode to the power source.
- An **Implanted Pulse Generator (IPG)**, which is the power source and LFP sensor (ActivaPC+S).

The IPG is a metal “can” about 2 inches in diameter and about ½ inch thick that is inserted like a pacemaker under the skin. It contains a small battery that produces the electrical impulses needed for stimulation and the sensor that measures LFP. The extension cable is tunneled under your skin from the IPG to the electrodes under your scalp. The study team will show you the device during your pre surgical visits.

In the operating room, local anesthesia will be used to numb your scalp. Two small incisions (2 inch) will be made through your scalp, and two holes will be placed in your skull (one on each side of your head) to gain access to your brain. The neurosurgeon will then insert two small electrodes into your brain. The electrodes contain contacts attached to tiny wires that come out of the holes made in your skull. Each electrode has 4 contacts that can be stimulated. While you are awake in the operating room each contact on each electrode will be tested. During a test, a contact will get 2 minutes of stimulation. With each test you will be asked if you felt a change in your mood and in your body. Some of the tests will be "sham" tests. This means no electricity will be going into the electrode. You will not know which tests are sham and which are active. The person asking you questions will not know if the test was active or sham. We will record brain electrical activity and physical responses like heart and breathing rate during these tests. This testing will last approximately 2 hours.

After the electrodes are placed and tested, you will be put fully to sleep and the operation finished. The extension cables that connect the electrodes to the battery are tunneled under the skin behind your ear, and connected to the IPG. The IPG will be placed in your chest wall, just under the skin. This will take approximately 1 hour. Following surgery, you will have another MRI scan to check your brain and to confirm that the electrodes are in the right place. The sensor on the ActivaPC+S will be turned on so brain activity will be measured while you are in the hospital. The stimulator will be turned OFF and you will not receive stimulation for the next 4 weeks. You will have routine post-operative care including pain medication and wound care. You will meet with the neurosurgeons and psychiatrists each day you are in the hospital.

You will be discharged from the Emory University Hospital on the 2nd or 3rd day after surgery, unless complications occur. After surgery, the stimulator will remain OFF for one month. During that month you will have weekly study visits for mood ratings and assessments. Your mood will be measured with a number of questionnaires; the research coordinator will administer some of the questionnaires and some you will fill out. The weekly meetings with psychiatrists will be videotaped. These study visits will last approximately 2 to 3 hours. You will wear the activity monitoring devices for one week. You will continue to do the online questionnaire at home. Brain activity will be measured at regular intervals using the sensor that is part of the implanted PC+S IPG. The brain activity recordings will be downloaded from the PC+S device during the weekly visits. This is done with a wand that is held over the device and connected to a computer.

Acute Stimulation Testing Session

At the end of four weeks you will have a Computed Tomography (CT) scan to help select the electrode contacts to be used for stimulation. You will then have acute testing of the device. No surgery is required to program the DBS device. During the DBS programming, different parts of the electrodes will be turned on and off and the effects on your mood and behavior will be recorded and readouts of brain electrical activity will be taken from the Activa PC+S. We will use the research programmer, called the Nexus-D2 and a laptop to turn the electrodes on and off during these testing sessions.This testing can take place over 3 days. The acute testing sessions will be videotaped.

24-Week Active Stimulation Phase

After the acute testing, the DBS stimulator will be turned ON using the clinical programmer, called the N-Vision. You will then begin a 24-week (6 month) stimulation phase. This means you will receive continuous active stimulation. During the first three months of stimulation, you will return to the DBS laboratory once per week for your mood and overall condition to be checked, and to download readouts from the Activa PC+S. After the first three months, these visits may be spaced out to every other week. Your mood will be measured with a number of questionnaires; the research coordinator will administer some of the questionnaires and some you will fill out. The weekly meetings with psychiatrists will be videotaped. These study visits will last approximately 2 to 3 hours. You will wear the activity monitoring devices for the first 2 weeks after stimulation is turned on. Emotional Response testing, EEG and activity monitoring will be repeated after 1, 3 and 6 months of active DBS. The neuropsychological testing will be repeated after 6 months active DBS.

At the beginning of the active stimulation phase, you will begin Behavioral Activation (BA) therapy. This is psychotherapy or "talk therapy". There will be a maximum of 30 sessions over the 24-week active stimulation phase. While Behavior Activation therapy can be effective for patients with depression, we are using it here as a form of “rehabilitation” similar to physical therapy after a hip replacement. You will meet with your BA therapist approximately once a week. Therapy sessions will last for 50 to 90 minutes. All sessions will occur at the Emory Briarcliff campus. We will ask you to sign a form authorizing us to record (via audio cassette, videotape, or DVD) all therapy sessions for review of progress with the DBS team.

Stimulation Off Phase

At the end of the six-month active stimulation phase, your DBS stimulator will be temporarily turned OFF for 1 week. The LFP sensor will still be ON. The purpose of this is to determine whether the effects of DBS stimulation continue even when it is off and to measure changes in LFP patterns. Your mood will be monitored daily. You will wear the activity monitoring devices during this week. Emotional Response testing and EEG will be performed at the midpoint of the OFF week. At the end of the week, DBS will resume using the previous settings. If your mood worsens before the end of the week, the DBS stimulator will be turned back ON. We will monitor you closely until you stabilize, making adjustments to the stimulator as needed.

Three-Year Follow-up Phase

Following the 24-week (6 month) active stimulation phase and the discontinuation experiment, you will continue in the long-term phase of the study. You will continue to meet with the study team and psychiatrists. Adjustments to the stimulator and your medications can be made based on how you are doing. LFP measurements will continue to be taken from of the IPG as done in the first 6 months. If you do not live in Atlanta, you will be able to return to your home city at this time, but will need to return to Atlanta for all scheduled study visits. The frequency of visits during this phase will depend on your condition. However, you will be seen at least once a month for 3 months, then every 3 months for 1 year, then every 6 months until the end of the study. At each visit, you will meet with the study psychiatrist and the research coordinator will complete mood ratings. Your mood will be measured with a number of questionnaires; the research coordinator will administer some of the questionnaires and some you will fill out. These meetings with psychiatrists will be videotaped. These study visits will last approximately 2 to 3 hours. The status of your DBS battery will be checked at each visit and data downloaded. Based on average stimulation parameters and the planned recordings, we anticipate that the original PC+S IPG will remain active for approximately 2.5-3 years.

Battery Replacement and Long-Term Naturalistic Follow up Phase

When the battery runs low, you will be scheduled for surgery. The Activa PC+S IPG will be removed and replaced with a standard Activa PC IPG. This system provides identical stimulation to the brain but does not have a sensing device to monitor brain activity. The frequency of study visits during this phase will depend on your condition and depression symptoms, but will be at least every 6 months for in person assessments. We estimate the replacement battery will last 3 to 5 years at which point another replacement surgery can be scheduled depending on your condition and interest in continuing in the study. The costs of all battery replacement surgeries, including the ActivaPC system will be the responsibility of you or your third party payer (i.e. your insurance). We will let you know about any changes that might impact your participation in this study. Your participation in this phase could be as long as 7 years.

Additional Procedures

The procedures described below will be performed on you one or more times during the study. The purpose of these tests is to better understand how DBS may work in treating depression.

These procedures include:

1. Magnetic resonance imaging (MRI)
2. Genetic research
3. Emotional monitoring and perception testing
4. Activity Monitoring
5. EEG
6. Video Taping
7. Behavioral Activation Therapy

1. MRI Scan: MRI allows detailed imaging of your brain's structure and function. An MRI technician will assist with the MRI scan. The MRI scan will take about 1 hour. During the MRI scan, you will enter a large room where the MRI scanner is located. This scanner uses a very strong magnet to generate pictures of your brain. You will be asked to remove all jewelry and other metal-containing objects. You will lie on a narrow table, which will slide into the MRI scanner. The scanner tube is approximately six feet long and 25 inches wide. You will occasionally hear loud noises while the scanner is taking pictures of your brain. You will be given earplugs to wear during the scan. You will be asked to lie very still and not move your head for about 45 to 60 minutes. Occasionally, a person in the scanner will have a claustrophobic reaction (a severe anxiety attack from being in a small space). If this occurs, you will be immediately removed from the scanner and the scan will be stopped. You will have three MRI scans during this study. One will occur during the pre-surgery evaluation period. Another will be done on the morning of surgery. The third will take place after surgery. The third MRI scan will be performed using a specialized send-receive coil, further described below under "Risks of MRI".

2. Genetic Research: We will use a small sample of the blood we collect to perform genetic research. The goal of this research is to understand who might get depressed and how they respond to treatment. By signing the consent form to participate in this study you are agreeing to allow us to perform this research. We are also asking you to allow us to store a small sample of your blood indefinitely for future genetic research. You can still be in the DBS study, even if you choose to not to be part of the genetic research. This part of the study is described at the end of this consent form.

3. Emotional response and perception testing: We will evaluate your gaze patterns and visual attention to emotional stimuli. This testing done before surgery and will be repeated one month after surgery and again after 1,3 and 6 months of active stimulation.

Eye Tracking and Pupilometry: Eye-tracking will be used to measure your visual attention. You will sit in front of a computer monitor and simply watch as pictures or sounds are presented. While you view the screen, a light beam will be used to track the position and size of the pupil and cornea over time in order to estimate position of gaze.

Psychophysiology: Galvanic Skin Response (GSR) will be measured using two sensors placed on the palm surface of the index and middle finger. Electromyography (EMG) will be measured using two pairs of sensors placed on two separate locations of the face [above the left eye brow muscle—frowning; midway between the corner of the mouth and the ear lobe (zygomaticus major muscle)—smiling].

Image and sound ratings and questions: You will rate how positive or negative a picture is and the strength of your emotional response.

4. **Activity Monitoring:** You will be asked to wear activity-tracking monitors (for example movement sensors, an activity wristband, or a GPS unit) periodically during the study. The purpose of these sensors and of monitoring your activity at home and under laboratory conditions (for example walking for several minutes around the lab) will help us measure any changes in how you move and in your general activity levels before and after your device is turned on.

5. **Videotaping:** To provide an audiovisual record of your appearance and behavior during this study, we will videotape you before, during and after surgery. We will videotape part of every study visit, in every phase of the study. Study investigators will analyze these video and audio recordings to determine if there are noticeable changes in appearance and behavior due to DBS. These videotapes will be maintained as part of your study record.

6. **Electroencephalography (EEG)**: This test involves placing sensors on your scalp and recording your brain's electrical activity while you sit quietly looking at an X on a computer screen or while viewing positive and negative emotional words. This test will provide new information as to how DBS improves symptoms of depression and the time course of changes. It will be compared with the LFP data recorded off of the Activa PC+S.

RISKS AND POTENTIAL BENEFITS

Deep Brain Stimulation is NOT FDA approved for the treatment of Major Depressive Disorder. You may not receive any benefit from your participation in this study.

This study is designed to measure changes in brain electrical activity during SCC DBS for treatment resistant depression with the ActivaPC+S device. The risks of the Activa PC+S are similar to other DBS devices without the sensing element. There may be risks, discomforts, or side effects that are not yet known.

During the study it is possible that your depression could get worse. Your mood and overall condition will be monitored very closely during this study. It is possible that your depression could worsen to the point that you become suicidal and/or require hospitalization. If this occurs, you will be carefully evaluated to determine whether it is safe for you to continue in this study.

Risks of Surgery and DBS Treatment

As with any surgery, there are risks involved from the surgery and/or the anesthesia. The neurosurgeons will discuss these with you. The complications of DBS surgery are well established and relate to surgical complications at the time of implantation (hemorrhage, seizures, stroke) and

secondary complications due to failure of the device, infection or stimulation of structures adjacent to intended target structures. The risk of death with the general anesthesia for implantation of the IPG is small (less than 1 in 20,000). You may experience pain, discomfort and/or swelling at the sites of the incisions in the head and chest, and at the sites where the pins of the stereotactic frame go. These problems generally go away within 1 week.

It is also possible that an implanted electrode may move, break or become dislodged. There is also the chance of allergic reaction to the device. There is also a risk of neurotoxicity and carcinogenicity due to materials that compose the leads. The device can become infected. This could cause an infection not only in the area of the implanted device, but an infection that involves the whole body. Such an infection would require treatment with antibiotics and possibly surgery to remove the system. The risk of infection or malfunction of the DBS device and/or IPG is about 10.6%. It may be necessary to remove the DBS device. Reasons for removing the device include damage to device or infection that does not respond to antibiotics. If your depression does not improve over time or you experience a worsening in your psychiatric condition, the investigators will discuss with you the option of removing the device. Removal of the device has a very low risk of serious complications (less than 1 in 1000) but they are the same as those associated with surgical implantation of the device (see above). When the battery is depleted the device will need to be removed and replaced.

At Emory we have implanted DBS units in 28 patients for treatment resistant depression since 2007. All of the adverse events that happened in our patients were known to occur with DBS surgery. We used a different device from a different manufacturer so these numbers may not be representative of the Activa unit manufactured by Medtronic. Two patients had infections requiring the IPG and lead cables be removed and a course of IV antibiotics. One patient had the skin over the electrode on the scalp erode that required plastic surgery and IV antibiotics. The extension cables connecting the IPG to the electrodes broke in 5 patients requiring surgical replacement. One patient had a minor post op bleed and a seizure in the 24 hours after surgery. Four patients had psychiatric hospitalizations for worsening depression or suicide attempts that improved after discharge from the hospital. Three patients had the device removed and left the study. There have been no specific behavioral or psychiatric side effects such as mania, hypomania or suicide ideation that can be linked to stimulation. There have been no catastrophic bleeds, strokes or other neurological adverse events at Emory in patients with DBS for treatment resistant depression. There have been no deaths at Emory of patients with DBS for treatment resistant depression.

Worldwide, the numbers of people who have had DBS for treatment resistant depression are small so there may be risks that are not known. Including our ongoing study at Emory, there have been 4 studies published reporting on SCC DBS for treatment resistant depression. These four studies include 76 patients. The adverse events reported are those known to occur with DBS surgery. The adverse events reported in the studies of SCC DBS for TRD are the same as those listed here, with no deaths or catastrophic neurological events directly due to the DBS surgery or device. Due to the low numbers of people who have received SCC DBS for depression, the true rate of adverse events may not be known. More than 80,000 patients with Parkinson's disease have been treated with DBS so the rate of adverse events might be a better estimate of risk. The risk of serious complications from DBS surgery in patients with Parkinson's disease is estimated at 8-10%. The most serious risk is bleeding into the brain, which happens in 4-8% of patients. Bleeding into the brain can lead to stroke or death. Permanent neurological deficits, including weakness, paralysis, difficulty speaking,

impaired thinking and loss of feeling occurred in 2% of patients. DBS surgery related deaths in Parkinson's disease are less than 1% of patients.

If the rate of adverse events in this study are greater than those previously reported for DBS in other patients, the study might be stopped. This may occur even if you do not have an adverse event. An outside review committee to determine if the risks of this study outweigh the potential benefits will carefully review the data. It may be decided that the risks of continuing the study are too great and the study will be stopped and your DBS stimulator may be turned off.

Electromagnetic Interference. Medtronic DBS Neurostimulators should not be affected by normal operation of electrical equipment such as household appliances, electric machine shop tools, microwave ovens, RF transmitting systems, or microwave frequency transmitting systems. A strong magnetic field (electromagnet or permanent magnet) can switch the neurostimulator output from on to off or off to on, but does not change the programmed parameters. It is important to avoid or exercise care when approaching theft detectors, Airport/security screening devices, Large stereo speakers with magnets, Electric arc welding equipment, Electric steel furnaces, Electric induction heaters (used in industry to bend plastic), Power lines Electric substations and power generators.

Diathermy—Patients who will be exposed to diathermy (deep heat treatment). Inform anyone treating you that you CANNOT have any shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) anywhere on your body because you have an implanted neurostimulation system. Energy from diathermy can be transferred through your implanted system, can cause tissue damage and can result in severe injury or death. Diathermy can also damage parts of your neurostimulation system. This can result in loss of therapy from your neurostimulation system, and can require additional surgery to remove or replace parts of your implanted system. Personal injury or device damage can occur during diathermy treatment when the neurostimulation system is turned on or off. Diathermy is used anywhere on your body (not just where your neurostimulation system is located).

Magnetic Resonance Imaging (MRI).
Implantation of a Medtronic DBS System is contraindicated for patients who require magnetic resonance imaging (MRI) using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area. Performing MRI with this equipment can cause tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis, or death. MRIs have the potential to induce repositioning, rotation, and heating in implanted medical devices. If you need regular MRI to monitor another medical condition, you cannot participate in this study. Once implanted, if a clinical MRI is needed, you must first contact a research physician who will coordinate with the necessary party to ensure the MRI is done within DBS safety protocol.

Electroconvulsive therapy (ECT) – The safety of ECT in patients who have an implanted deep brain stimulation (DBS) system has not been established. Induced electrical currents may interfere with the intended stimulation or damage the neurostimulation system components resulting in loss of therapeutic effect, clinically significant undesirable stimulation effects, additional surgery for system removal and replacement, or neurological injury. If your depression worsens and you choose to have ECT, we will discuss with you the potential risks of applying ECT to subjects with DBS devices or whether the DBS device should be removed beforehand.

Transcranial magnetic stimulation therapy—Transcranial magnetic stimulation therapy (TMS) is contraindicated for patients with any implanted DBS System or system component.

The long-term effects of DBS are not known. There may be side effects or risk that are not yet known. You will be monitored carefully to determine if you are experiencing a bad reaction to DBS.

Risks of Battery Depletion or Interruption of Stimulation.
Depression symptoms can return if the system is not working. Temporary (hours to days) discontinuation of stimulation has not been associated with any noticeable behavioral changes. Controlled experiments of DBS discontinuation observe a slow decline that develops over several weeks with decreased motivation, interest and activities and a late change in negative mood. Abrupt changes in sadness or anxiety or sudden thoughts of suicide have not been observed. Complete battery depletion or extension lead breaks has been associated with return of depression symptoms. Battery life and system function are checked at every visit. Additional monitoring of your mood and behavior will be done during the discontinuation experiment to detect any behavioral effects.

The estimated IPG battery life using standard stimulation parameters is 36 months. Battery life may be shorter in this study due to the recordings of brain activity from the PC+S sensor, which uses extra battery power. Based on calculated use of the recording system we anticipate the battery will last approximately 32 months. The original Activa PC+S IPG will be replaced with a standard Activa PC IPG system. A minor surgical procedure will be required to replace the IPG system. The Activa PC system provides identical stimulation to the brain but cannot monitor brain activity. You will be given a test device that allows you to check if the battery is on. If it indicates that you battery is not working we will schedule a study visit to determine the cause. If the system stops working and you wish to continue in the study, the battery will be replaced surgically. The need for repeated surgeries to replace the battery is one risk of this procedure.

Risks of MRI
Pre-surgical scans. There are no known risks of MRI scanning in healthy persons. No needles will be used and no x-ray exposure will occur. People with heart pacemakers cannot enter MRI areas, because the magnetic field can interfere with the function of the pacemaker. Taking part in an experiment and being inside a scanner is an unusual experience. In some people this can cause anxiety or even claustrophobia (fear of being in confined space). Anxiety might occur in the MRI scanner, as the walls of the cylinder are close to the face. Usually, conversation and reassurance will remove such anxieties. If you still experience severe anxiety in the scanner you are free to end the session immediately.

Post-implant scan. MRI is possible with Activa PC+S or Activa PC if performed using a specialized send-receive coil. MRI performed using any other coil can cause tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis, or death. MRIs have the potential to induce repositioning, rotation, and heating in implanted medical devices. Because of these serious risks, if you need regular MRI to monitor another medical condition, you cannot participate in this study.

Risks of emotional response testing
The direct exposure to light used to track eye movement is about 0.1 to 0.3 mW/cm2. This exposure is less than you would receive walking outside into sunlight. Emotional pictures and sounds are non-threatening and not associated with risk. Measurements of EMG and ECG are non-invasive and have no risk.

Risks of EEG
There are no side effects of EEG recording. You will wear a cap on your head with the multiple EEG electrodes and these are held in place on your scalp using some gel. You will need to wash your hair after the test to remove the gel. There is no pain associated with the EEG. Some people find it to be boring, as it is necessary to stay very still and to remain awake and attentive for the entire recording session which lasts about 60 minutes.

Risks of activity monitoring and GPS logging.
There are no risks associated with wearing the heart rate, skin conductance and GPS monitors. For the GPS data, the planned analyses will only look at the distance and amount of time spent away from your home. We will not be examining where you go. If you have any concerns, you will have control of the on/off switch on the devices and you can turn it off at any time. We will set up a schedule for recording to make this as nonintrusive to your activities as possible.

Risks of Behavioral Activation Therapy
There are some potential risks and discomforts involved in this treatment. Sometimes people become upset or distressed when they are asked about their problems, such as in the interviews, when filling out questionnaires, or during therapy. You will not have to answer any questions that you are not comfortable answering, and treatment can be stopped at any time.

Other Risks
As part of the psychiatric assessments you will be asked sensitive questions (such as whether you have considered suicide and questions about sexual functioning). These questions may cause you some discomfort.

It is unknown whether the DBS treatment used in this study increases or decreases your risk of a manic or hypomanic episode. Emory studied patients with bipolar-2 depression and there was no evidence that DBS induced such episodes, but the numbers of patients studied is small. If this occurs, you will be carefully evaluated to determine whether it is safe for you to continue in this study.

The risk to an unborn fetus from the DBS treatment used for this study is not known. If you are pregnant you will not be eligible for this study. If you are a woman of child bearing potential you will have pregnancy test during initial evaluations. If you are a woman of child bearing potential you will be required to use and effective method of birth control.

On several occasions during this study you will need to have blood drawn or have an IV started. Having a blood draw and placement of an IV can cause a small amount of bruising and/or pain.

Potential Benefits
There is a possibility that your condition may improve during SCC DBS during this study. However, this is a possibility and not a certainty. **Deep Brain Simulation is not an FDA approved treatment for depression and research studies to date have been small**. Taking part in this research study may not benefit you personally. The information obtained from this study will aid in understanding depression and the effects of SCC DBS and whether the Activa PC+S sensing device can provide useful information about how SCC DBS works for depression. The information obtained from this study could potentially benefit others who suffer from depression.

VOLUNTARY WITHDRAW FROM THE STUDY
If you decide you want to withdraw from the study after the DBS device has been turned on we will meet with you to discuss this decision. If you want the device removed, we will turn it off for 4 weeks and assess your condition. If at that time you continue to want the device removed we will schedule with the neurosurgeons a time to have the device removed from your body. You will have the option of withdrawing completely from the study, or staying in touch so we can monitor your condition in the future.

ALTERNATIVE TREATMENTS
For patients with major depression who have failed cognitive behavioral therapy, medications, and ECT, other forms of treatment may still be helpful in treating depression. There may be other medications or forms of psychotherapy that may help you. There is also an FDA approved potential surgical alternative treatment called vagus nerve stimulation. Transcranial magnetic stimulation is an FDA approved treatment for depression that might help you. You should discuss other treatment alternatives with your psychiatrist before choosing to participate in this study including other clinical trials of DBS for depression. The Study Psychiatrists will also discuss potential alternatives for treatment with you and your treating psychiatrist.

CONFIDENTIALITY
People other than those doing the study may look at both medical charts and study records. Agencies and Emory departments and committees that make rules and policy about how research is done have the right to review these records. So do companies and agencies that pay for the study. The government agencies and units within Emory responsible for making sure that studies are conducted and handled correctly may look at your study records in order to do this job including the Food and Drug Administration, the Emory Office for Human Research Protections, the Emory University Institutional Review Board, the Emory Office of Research Compliance and the Office of Clinical Research. In addition, records can be opened by court order or produced in response to a subpoena or a request for production of documents. We will keep any records that we produce private to the extent we are required to do so by law. We will use a study number rather than your name on study records where we can. Your name and other facts that might point to you will not appear when we present this study or publish its results. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Medtronic, Inc., the manufacturer of the Activa PC+S system, will be provided with data collected during this study. The data that may be provided to Medtronic includes all health information collected during the study, as well as any health information in your medical records that is relevant to the study. All of

your data that is provided to Medtronic will be de-identified. Medtronic will keep your data confidential in accordance with all applicable laws and regulations. Medtronic may use your data for any purpose in accordance with applicable laws. Any reports or publications about the study or any other research will not include your name or a description of you. Information received during the study will not be used to market to you; your name will not be placed on any mailing lists or sold to anyone for marketing purposes. You agree to allow Medtronic to use your data in these ways.

Results from study tests and procedures that are performed, analyzed and/or read at or for Emory Healthcare facilities that can be used for healthcare purposes will be placed in any medical record that you have with Emory Healthcare facilities. In addition, a copy of the informed consent form and HIPAA authorization form that you sign will be placed in any Emory Healthcare medical record you may have. Persons who have access to your medical record will be able to have access to all results and documents that are placed there, and the results/documents may be used by Emory Healthcare facilities to help provide you with medical care. Certain state and federal laws and regulations that may prevent the disclosure of research data do not cover any results and documents that are kept as part of your medical record. However, laws such as HIPAA that concern medical records will govern the confidentiality of the results and other documents in the medical record.

Emory University does not have any control over results from tests and procedures performed and/or analyzed or read at non-Emory Healthcare facilities. These results are NOT routinely included in medical records at Emory Healthcare facilities, and they will not necessarily be available to Emory Healthcare providers. Emory University also does not have control over any other medical records that you may have with other healthcare providers and will not send any test or procedure results from the study to these providers. It is up to you to let these healthcare providers know that you are participating in a clinical trial.

Some tests and procedures that may be performed during this study by Emory Healthcare or other facilities or persons may not be looked at or read for any healthcare treatment or diagnostic purposes. These tests and procedures will only be looked at for research purposes and the results will not be reviewed to make decisions about your personal health or treatment. The specific types of tests or procedures, if any, that fall within this category are listed below:

- Research MRI
- Brain Radio recordings
- Genetic analysis
- Emotional monitoring and perception testing
- Activity Monitoring
- EEG
- Video Taping
- Behavioral Activation Therapy
-

This permission does not have an expiration (ending) date, but you may change your mind and revoke (take back) this permission to use your data at any time.

Certificate of Confidentiality

There is a Certificate of Confidentiality from the National Institutes of Health for this Study. The Certificate of Confidentiality helps us to keep others from learning that you participated in this study. Emory will rely on the Certificate of Confidentiality to refuse to give out study information that identifies you. For example, if Emory received a subpoena for study records, it would not give out information that identifies you.

The Certificate of Confidentiality does not stop you or someone else, like a member of your family, from giving out information about your participation in this study. For example, if you let your insurance company know that you are in this study, and you agree to give the insurance company research information, then the investigator cannot use the Certificate to withhold this information. This means you and your family also need to protect your own privacy.

The Certificate does not stop Emory from making the following disclosures about you:

- Giving state public health officials information about certain infectious diseases,
- Giving law officials information about abuse of a child, elderly person or disabled person.
- Giving out information to prevent harm to you or others.

Giving the study sponsor or funders information about the study, including information for an audit or evaluation.

NEW FINDINGS

We might learn new things during this study that you may need to know. We can also learn about things that might make you want to stop participating in the study. If so, you will be notified about any new information.

COSTS

All study related clinical care costs are you or your third party payer's responsibility. These costs include, but are not limited to doctors study visits (in psychiatry and neurosurgery), the initial implantation surgery, battery replacements and labs. The DBS electrodes and Activa PC+S IPG will be provided free of charge as part of the study. The replacement battery will be a standard Activa PC IPG and will be subjected to usual clinical care costs. We will work with you and your insurance company to facilitate their approval of the payment.

COMPENSATION

You will receive no compensation for being in this study. However, your parking expenses for study visits will be reimbursed.

DISCLOSURE

This study uses devices manufactured by Medtronics. Dr. Mayberg, the principle investigator of this study, has no relationship with this company outside of the contract that gives the research team and this protocol access to their Activa PC+S device, which is not FDA, approved for use to treat

depression. Dr. Mayberg is however, an inventor on patents for the use of DBS for major depression. She has licensed her rights for the specific DBS procedure to be used in this study to St. Jude Medical Neuromodulation (SJMN), which is a different company than the one that is manufactures, the devices that you will have implanted (Medtronics, Inc). Her relationship with SJMN, her interest in the procedure, and this research study has been reviewed by Emory University, and the Icahn School of Medicine at Mount Sinai has developed a management plan that she must follow.

Dr. Gross serves as a consultant to Medtronic, Inc. and receives compensation for these services. Medtronic, Inc. develops products used in this research project. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

IN CASE OF INJURY

If you get ill or injured from being in this study, Emory and the study staff will help you to get medical treatment. Emory has not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proved that your injury or illness is directly caused by the negligence of an Emory employee. "Negligence" is the failure to follow a standard duty of care.

If you become ill or injured from being in this trial, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs. If you believe that you have been injured by this research, you should contact, either Dr. Riva Posse [redacted], Dr. Gross [redacted]. You can also page Dr. Gross or Dr Riva Posse by calling the Emory Clinic page operator at [redacted]

CONTACT INFORMATION

If you have any questions about your rights as a research subject, please call Emory University IRB at [redacted].

If you have any question concerning this study or if you experience any unusual symptoms, health problems or a research-related injury, contact:

Sinead Quinn or Reed Gilbert (Research Coordinators), Psychiatry at [redacted]
Dr. Helen Mayberg, Psychiatry and Neurology at [redacted]
Dr. Robert Gross, Neurosurgery [redacted]
Dr. Patricio Riva Posse at [redacted]

You can also page Dr. Gross or Dr. Riva-Posse by calling the Emory Clinic page operator at [redacted]

IDENTIFICATION CARD

You will be sent a patient identification card after you are implanted with the Medtronic Activa PC+S Stimulation System. This small card:
* Identifies you as having an implanted medical device.
* Helps you pass through security systems like those in airports.
* Provides emergency information that allows your physician to be contacted.

I. VOLUNTARY PARTICIPATION AND WITHDRAWAL (signature page):

Your participation in this study is completely voluntary. You have the right to withdraw from the study at any time. This decision will not in any way affect your current or future medical care or any benefits to which you are otherwise entitled.

Your participation may be withdrawn if the research team for this study feels it is in your best interest, or if you fail to follow study procedures. If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, device manufacturer or Emory University from their legal and professional responsibilities.

If you have read this informed consent form and had your questions answered and would like to volunteer to participate in this research study, please sign below. We will give you a copy of this consent form to keep.

Title: Deep Brain Stimulation for Treatment Resistant Depression: Exploration of Local Field Potentials (LFP) with the Medtronic Activa PC+S "Brain Radio" System
Principal Investigator: Helen Mayberg, MD

I, _____, have been given a full explanation of the purpose of the study, the procedures to be used, the risks and benefits of my participation as well as the confidentiality of the information collected. I have received a signed copy of this consent form. I understand that I am free to withdraw from the study at any time and that such withdrawal will not affect my future treatment or medical management. I agree to inform clinical staff if anything unexpected occurs.

I voluntarily agree to participate in this study.

_____ _____
Signature of PATIENT **Date**

_____ _____
Printed name **Time**

_____ _____
Signature of WITNESS **Date**

_____ _____
Printed name **Time**

FUTURE GENETIC RESEARCH

A small sample of your blood (10-20 ml or about 1-2 tablespoons) will be stored for future genetic research. The research team plans to test how specific genes relate to brain function and behavior. To do this, the genetic information obtained from your blood will be linked with information about you such as your age, gender and symptoms of mental illness. However, the blood will be labeled with a barcode number that contains no information that can personally identify you; only Dr. Mayberg and the research nurse will hold the master key that links your personal information to the barcode on the blood tube. No information that actually identifies you will ever be used in any of the genetic testing analyses. The research team will store and use your DNA for as long as the supply lasts. Since techniques are available to make copies of your DNA, the research team could use your DNA for 10 years or more. You may choose to NOT have any of your blood **stored** for future genetic testing. You may choose to have your blood sample destroyed at any time in the future by contacting Dr. Mayberg. This will in no way affect your participation in the other parts of this study. If you AGREE to have your blood stored for future genetic research, please sign below:

“I agree that a small sample of my blood may be stored for future genetic testing. I understand that I may ask Dr. Mayberg (or any study investigator) to destroy this sample at any time.”

_____	_____
Signature of PATIENT	**Date**
_____	_____
Printed name	**Time**
_____	_____
Signature of WITNESS	**Date**
_____	_____
Printed name	**Time**