INFORMED CONSENT FORM- MAIN

Official title: Elucidating the Neurocircuitry of Irritability with High-Field Neuroimaging to Identify Novel Therapeutic Targets

NCT number: NCT05046184

IRB Approved date: 11/21/2024

Title of Study: Elucidating the Neurocircuitry of Irritability with High-Field Neuroimaging to Identify Novel Therapeutic Targets

Consent to be part of a Research Study
To be conducted at
The University of Texas Southwestern Medical Center

Key Information about this Study

In medicine there are many unanswered questions. A research study is when scientists try to answer a question about something that we don't know enough about. Participation in a research study may or may not directly help you or others. Participation is entirely voluntary. It is completely up to you whether or not you take part. You can also change your mind at any time, and it will not affect your ability to get medical care at UT Southwestern Medical Center.

The goal of this research is to understand how patterns of brain functioning relate to irritability which is an important yet understudied symptom in adults with psychiatric disorders such as major depressive disorder (MDD). This study will investigate irritability in people with MDD as compared to control subjects, identify patterns of brain functioning that are associated with irritability, and determine how improvements of irritability with treatment in people with MDD relate to changes in patterns of brain functioning. Ketamine is a Food and Drug Administration (FDA) approved anesthetic, a drug used to produce loss of consciousness before and during surgery. Several small studies recently found ketamine, given in lower doses than what is required for anesthesia, to be an effective and promising treatment for depression and may improve irritability. However, use of ketamine for treatment of MDD is not approved by the FDA.

If you choose to participate, you will be asked to complete 7 in-person visits, each lasting roughly 2-4 hours. During the visits you will complete interviews and questionnaires. Two of these visits will also involve an MRI scan lasting no more than 1.5 hours and will include a cognitive task. Four of the visits over a two-week period will involve administration of study medication (either ketamine or midazolam) in the blood stream through a line placed in your vein [also referred to as intravenous (IV) infusion] over a 40-minute-period. Midazolam is a benzodiazepine that is approved by the FDA for sedation and for use with other medications to induce and maintain anesthesia. Therefore, midazolam is similar to ketamine in its use to produce loss of consciousness before and during surgery, and has been used as a control medication, when given in lower doses than what is required for anesthesia, in previous studies of ketamine in people with MDD. However, use of midazolam for treatment of MDD is not approved by the FDA. Costs may arise because of your participation in the study such as costs for transportation, childcare, lost wages. There may be compensation for your study participation. Your care at UT Southwestern Medical Center will not depend on whether you participate in this study.

The main risks to you if you choose to participate are: psychological stress of answering questions, undergoing medical work-up (such as blood draw), undergoing magnetic resonance imaging (MRI) scans, and undergoing treatment with study drug (ketamine or midazolam).

Participating in this research will not benefit you. Instead of participating in this research, you may seek psychiatric evaluation at UT Southwestern or in the community as well as receive treatment for depression and irritability from providers at UT Southwestern or in the community.

If you are interested in learning more about this study, please continue to read below.

Information about this form

You may be eligible to take part in a research study. This form gives you important information about the study.

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Please tell the researchers or study staff if you are taking part in another research study.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

General Information – "Who is conducting this research?"

Principal Investigator
The Principal Investigator (PI) is the researcher directing this study; the PI is responsible for protecting your rights, safety and welfare as a participant in the research. The PI for this study Manish Jha, MBBS, Department of Psychiatry at UT Southwestern Medical Center.

Research Site
All research visits will take place at UT Southwestern Center for Depression Research and Clinical Care (CDRC), UT Southwestern Advanced Imaging Research Center (AIRC), and Clinical Research Unit (CRU). The CDRC will be where general study procedures and labs will be completed and is located at 1440 Empire Central Drive, Level 3 Mood Disorders, Dallas, Texas, 75247. The AIRC is where the MRIs will be completed and is located at 2201 Inwood Road Dallas, Texas, 75390. The CRU is where the study drug infusions will occur and is located at 5303 Harry Hines Boulevard, Dallas, Texas, 75390.

Funding
National Institute of Mental Health (NIMH), a federal agency that promotes scientific research, is funding this study. This organization is providing money to UTSW so that the researchers can conduct the study.

Purpose – "Why is this study being done?"

Irritability is an important, but understudied symptom in adults with Major Depressive Disorder (MDD). Treatment options remain limited as commonly used medications, such as antidepressants, are often ineffective and may even worsen irritability. The goal of this research is to understand how patterns of brain functioning relate to irritability which is an important yet understudied symptom in adults with psychiatric disorders such as major depressive disorder (MDD). This study will investigate irritability in people with MDD as compared to control subjects, identify patterns of brain functioning that are associated with irritability, and determine how improvements in irritability with treatment in people with MDD relate to changes in patterns of brain functioning. Ketamine is a Food and Drug Administration (FDA) approved anesthetic, a drug used to produce loss of consciousness before and during surgery. Several small studies recently found ketamine, given in lower doses than what is required for anesthesia, to be an effective and promising treatment for depression and may improve irritability. However, use of ketamine for treatment of MDD is not approved by the FDA.

You are asked to participate in this research study of ketamine treatment for adults with MDD that includes MRI neuroimaging because you have met the initial prescreening criteria.

The researchers hope to learn about brain circuits that are associated with irritability and determine how treatment-related reductions in irritability relate to changes in neurocircuit functioning in the brain. The researchers will also investigate changes in brain function with ketamine versus midazolam.

Investigational Use of Drug or Device
This study involves the use of an investigational drug called Ketamine. "Investigational" means that the drug has not yet been approved by the U.S. Food & Drug Administration (FDA) for treating major depressive disorder.

This study will help find out what effects, good and/or bad, this study drug has on people who use it and on its effect on major depressive disorder. The safety of this drug in humans has been tested in prior research studies; however, some side effects may not yet be known.

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.

Information about Study Participants – "Who is participating in this research?"

You are being asked to be a participant in this study because you have met the prescreening qualifications and have depression. Additional screening procedures will be completed following the signing of this consent form to confirm your eligibility for the research study. This research study will be fully explained to you by a member of the study team. Feel free to ask all the questions you want before you make a decision about whether or not to participate. Any new information that develops during this research study that might make you change your mind about participating will be given to you promptly.

How many people are expected to take part in this study?
This study will enroll approximately 60 healthy adults and 140 people with MDD between the ages of 18 and 65.

Information about Study Procedures – "What will be done if you decide to be in the research?"

While you are taking part in this study, you will be asked to attend approximately 7 visits with the researchers or study staff over a period of 5 weeks.

Screening – After you sign this consent to participate, exams, tests, and/or procedures may be done as described below to find out if you can continue in the study; this is called screening. We may be able to use the results of exams, tests, and/or procedures you completed before enrolling in this study. You will be told which results we will obtain, and which procedures will not have to be repeated. All study procedures are described below and are for research purposes only.

Screening Procedures (2 hours and 30 minutes)

- *Physical examination:* A study physician will conduct a physical exam which includes your height, weight, listening to your heart and lungs, obtaining your temperature, pulse and blood pressure, as well as collecting your medical history. The physical exam will not include a pelvic, rectal, or breast exam.
- *Blood draw*: Blood will be taken from a vein in your arm. You may get a bruise or irritation at the place where the needle goes into your skin. Some participants may faint and, in rare cases, can get an

infection. The total amount of blood that will be taken from each person will depend on how long you stay in the study. If you complete the study, it will be approximately 3 tablespoons (45ml). Sometimes you will need to repeat a blood test. Your blood will be used to check your general health.

- *Self-report questionnaires*: You will be given different questionnaires to answer questions about how you are feeling, your mood, your health, and demographic information. These questions will give the study sponsor important information about how you are doing in the study, so it is important to complete these questions as your study doctor/staff instructs you.
- *Clinician Interviews*: Interviews with your study doctor/other qualified site staff members will be done throughout the study to assess your depressive symptoms, mood, and feelings.
- *ECG (Electrocardiogram*): Sticky patches placed on your chest that are connected to a machine that shows the electrical activity of your heart. Hot and cold drinks and food should be avoided 30 minutes before an ECG measurement whenever possible.
- *Pregnancy Test:* If you can become pregnant, a pregnancy test will also be done before you receive treatment.
- *Urine Sample*: Your urine will be collected to test for possible drug abuse.
- *Review of medications:* You will talk with the study doctor/staff about any medicines you take.
- The study team may also ask you for access to your mental health records, alcohol and/or substance abuse records, and psychotherapy notes to assist with making a psychiatric diagnosis.

The results of the screening exams, tests, and/or procedures will be reviewed to determine whether you will be allowed to continue in the study. If you are not allowed to continue in the study, the researcher will discuss the reasons with you.

Assignment to Study Groups
When it is determined that you are eligible for the study, you will be assigned by chance (like flipping a coin) to one of 2 study groups:

- Ketamine (0.5 mg/kg) or
- Placebo containing Midazolam (0.02 mg/kg)

You will have a one in 2 chance of being in the placebo group. A placebo is a harmless substance that looks like the other study drug.

Neither you nor the researchers will know whether you are receiving the study drug or placebo. In the event of an emergency, there is a way for the researcher to find out which you are receiving.

Study Procedures - as a participant, you will undergo the following procedures:

Baseline Visit (Approximately 4 hours 30 minutes)
If you are eligible for this research study, you will be asked to complete a baseline visit within 3 weeks of the screening visit.

- *Clinician Interviews*: Interviews with your study doctor/other qualified site staff members will be completed to assess your depressive symptoms, mood, and feelings.
- *Self-report questionnaires*: You will be given different questionnaires to answer questions about how you are feeling, your mood, and your health. These questions will give the study sponsor important information about how you are doing in the study, so it is important to complete these questions as your study doctor/staff instructs you.
- *Pregnancy Test:* If you can become pregnant, a pregnancy test will also be done before you receive treatment.
- *Urine Sample*: Your urine will be collected to test for possible drug abuse.

- *Vitals:* The study team will collect your vital signs including pulse, blood pressure, and respirations.
- *Review of medications:* You will talk with the study doctor/staff about any medicines you take or changes you may have made to your medications.
- *Magnetic Resonance Imaging (MRI) Scan:* You will have an MRI of your head for brain imaging data. For this procedure, you will lie still inside a large, doughnut-shaped magnet, also called the MRI scanner. The MRI technician can see and hear you during the procedure. You will also be given a squeeze ball to use for communication. You will be inside the MRI scanner for approximately 75 minutes. You will be asked to complete a cognitive test both out-of-scanner and within the scanner that is explained in further detail below. You will lie inside the scanner and rest and perform the task, which will be fully explained to you before scanning. The MRI scanner produces loud noises so you will be provided with earplugs or headphones. The MRI technician and/or designated study team member will wrap a breathing belt around your waist to measure your breathing rate throughout the scan. They will also attach a heart rate monitor and electrodes for ECG to better understand your physiology while in scanner. You will be given button boxes that you will utilize for tasks. You may choose to stop the scan at any time for any reason and will not have to explain why and will not lose any reimbursement.

MRI Tasks

During most of the MRI scan you will be lying still and passively while the scanner takes different types of images of the brain. For one part of the scan you will be asked to watch a cross on a screen for about 10 minutes and think of nothing in particular. This is called a 'resting-state' scan. For another part of the scan you will do a computerized task, lasting about 25 minutes. During this task you will be asked to play a game where you must select responses accurately and quickly. During this task, you may notice changes in how you feel and will be asked to rate your feelings at periodic intervals of the scan. You will earn money while playing this game which will be given to you after completion of the study visit. The aim of this is to see how the brain activates when anticipating and/or experiencing frustration. During the task you will be asked to rate how happy/frustrated you feel using button response pads attached to your hand. It is important to note that although this task is designed to elicit frustration that it should not cause intolerable distress. You can stop the scan at any point if the task is intolerable.

It is possible that the results of these scans might indicate a finding in which it would be informative for you to undergo further evaluation. If abnormalities are found, you may be requested to return for further imaging or evaluation. A physician will be consulted to verify whether any findings merit further investigation, in which case the investigator will contact you and inform you of these findings. The investigators, any consulting physicians, and UT Southwestern are not responsible for the cost of any examination or treatment that you may choose to undertake based on any findings resulting from your study participation.

Because this project involves the use of MRI scans, it is necessary that we make a note of your participation in the electronic medical record. That way anyone treating you will be aware of your participation and may be able to avoid any unfortunate outcomes that could arise if your research participation were unknown.

You will also undergo a clinician assessment regarding adverse events that may have occurred during the course of your study participation.

Infusion Visits 1 - 4 (Approximately 4 hours each)

Following the completion of baseline visit, you will be randomly assigned to receive ketamine or midazolam treatment. Infusion visit 1 will occur 1 to 3 days after the baseline visit, infusion visit 2 will occur 4 to 6 days after baseline visit, infusion visit 3 will occur 7 to 9 days after baseline visit, and infusion visit 4 will occur 10 to 12 days after baseline visit. All infusion procedures and monitoring will take place at the Clinical Research Unit (CRU) at UT Southwestern Medical Center. You will be asked to fast overnight before the infusion, refraining from solid food and non-clear liquids. All procedures will be performed in a private, quiet room.

- *Urine sample:* When you arrive, you will need to provide a urine sample to test for the presence of

drugs of abuse in your system (and urine pregnancy test if applicable). Next, you will be interviewed by study team and asked to complete questionnaires about your mood, beliefs, and what you think. After that, we will begin monitoring your vital signs continuously, including your blood pressure, heart rate, and breathing rate, and one IV line will be placed by trained study personnel.

- *Clinician Interviews*: Interviews with your study doctor/other qualified site staff members will be completed to assess your depressive symptoms, mood, and feelings.
- *Self-report questionnaires*: You will be given different questionnaires to answer questions about how you are feeling, your mood, and your health. These questions will give the study sponsor important information about how you are doing in the study, so it is important to complete these questions as your study doctor/staff instructs you.
- *Vitals:* The study team will collect your vital signs including pulse, blood pressure, and respirations.
- *Review of medications:* You will talk with the study doctor/staff about any medicines you take or changes you may have made to your medications.
- *Study drug infusion:* All infusion procedures and monitoring will take place at the CRU at UTSW and will occur after study procedures listed above have been completed. You will be asked to fast six to eight hours before the infusion, refraining from solid food and non-clear liquids. All procedures will be performed in a private, quiet room. When you arrive, you will need to provide a urine sample to test for the presence of drugs of abuse in your system (and urine pregnancy test if applicable). After that, we will begin monitoring your vital signs continuously, including your blood pressure, heart rate, and breathing rate, and one IV line will be placed by trained study personnel.

During this visit you will receive an intravenous infusion of 0.5 mg/kg of ketamine (total dose) or 0.02 mg/kg of midazolam (total dose) over 40 minutes. This means the medication will be administered directly into your blood stream via the IV line. A study physician will be present during the infusion. If you are unable to tolerate the infusion (i.e., you are not able to undergo the infusion of ketamine or midazolam without significant discomfort), you will be withdrawn from the study and you will be asked to complete the study exit visit at a later day. Immediately following the infusion, you will be repeatedly assessed and asked about your mood, beliefs, and what you think**.**

During the infusion procedure you will be closely monitored by a study physician. You will also be monitored for a minimum of 1 hour afterwards by study trained personnel. At the end of the intravenous infusion, you will be asked questions that check for possible side effects of the drug you are receiving. After at least a 1-hour monitoring period and a check of your vital signs, you will be discharged from the infusion clinic. You will need to have someone meet you at the clinic to accompany you home. In addition, because of the medications that you may have received, you should not drive or operate heavy machinery and you should avoid alcohol and benzodiazepines for 24 hours. You will also undergo a clinician assessment regarding adverse events that may have occurred during your study participation.

Pre-Treatment Restrictions and Guidelines

- Six to eight hours before your treatment, do not eat or drink anything, unless otherwise instructed by the treatment team.
- Ensure that your bowel and bladder are empty before your treatment.
- Contact lenses should not be worn during the procedure. Bring a container and solution to put them in if they are non-disposable. If you have dentures or partials, leave them at home or have a family member or friend keep them during your treatment. Hearing aids may be worn up to the time of your procedure. Bring a case to put them in while you are having your treatment.
- Wear comfortable, loose-fitting clothes. You may wear sweat-pants or pajama bottoms. Shirts must be short-sleeved and buttoned in the front. Staff will provide you with a hospital gown if your clothing is too restrictive.

- Leave valuables at home including cash, credit cards and jewelry. Leave cell phones with the person driving you home. Staff will not be responsible lost items.
- If you take prescription benzodiazepine medications, please do not take it for at least 12 hours prior to the planned infusion start time.
- If you take blood pressure medication in the mornings, then you should take it prior to your treatment unless otherwise instructed by your doctor. It is important to check your blood pressure and pulse before taking the medication in the morning. If the top number (systolic) is 90 or below, and/or the bottom number (diastolic) is 60 or below, do not take the blood pressure medication. Bring the medication with you when you come in for ketamine.
- Please arrive for your treatment at the time provided to you. Pre-treatment evaluations and assessments are required and will take time to complete. You may have your family member or the person who drove you to ketamine treatment, stay with you during this process. They will go to the waiting area when staff takes you to the procedure room. If you are going to be late or need to cancel your appointment for any reason, please call the study coordinator **as soon as possible** (contact information is found below in the Contact Information section).

Discharge Criteria and Instructions

- You will be discharged by a physician or qualified personnel when following criteria have been met:
  - Fully awake, and able to ambulate with steady gate
  - Respiration will be unlabored and patient will be able to breathe deeply and cough freely
  - Stable vital sign
  - Patient will have an escort accompany them home, and/or have a car service or other appropriate means of transportation
  - Patients are expected to remain at the clinic for at least 1 hour post infusion
- You may not drive or operate heavy machinery FOR 24 HOURS AFTER THE START OF THE INFUSION. Even if cleared for driving, if you feel sedated, confused or dizzy please avoid driving until speaking with your treatment team.
- You should have someone with you for 24 hours and access to a telephone in case you need to contact your doctor.
- There should be no access to hoarded medications or weapons of any kind. (guns, knives, etc.)
- Do not make important decisions or sign any important papers in the next 24 hours.
- You are advised to go directly home from the hospital. Restrict your activities and rest the day of treatment
- If not nauseated, then resume your normal diet. Greasy and spicy foods are not advised.
- Do not consume food or beverages containing alcohol, grapefruit juice, Seville oranges, or quinine (e.g., tonic water).
- Nausea from anesthesia medication may occur. If nausea persists, then notify your doctor.

Study Exit Visit (Approximately 4 hours)

You will return to the clinic within 1-5 days of the infusion visit 4 to complete an end of study visit. The following procedures will be completed:

- *Clinician Interviews*: Interviews with your study doctor/other qualified site staff members will be completed to assess your depressive symptoms, mood, and feelings.
- *Self-report questionnaires*: You will be given different questionnaires to answer questions about how you are feeling, your mood, and your health. These questions will give the study sponsor important information about how you are doing in the study, so it is important to complete these questions as your study doctor/staff instructs you.
- *Pregnancy Test:* If you can become pregnant, a pregnancy test will also be done before you receive

treatment.

- *Urine Sample*: Your urine will be collected to test for possible drug abuse.
- *Vitals:* The study team will collect your vital signs including pulse, blood pressure, and respirations.
- *Review of medications:* You will talk with the study doctor/staff about any medicines you take or changes you may have made to your medications.
- *Magnetic Resonance Imaging (MRI) Scan:* You will have an MRI of your head for brain imaging data. For this procedure, you will lie still inside a large, doughnut-shaped magnet, also called the MRI scanner. The MRI technician can see and hear you during the procedure. You will also be given a squeeze ball to use for communication. You will be inside the MRI scanner for approximately 75 minutes. You will be asked to complete a cognitive test both out-of-scanner and within the scanner that is explained in further detail below. You will lie inside the scanner and rest and perform the task, which will be fully explained to you before scanning. The MRI scanner produces loud noises so you will be provided with earplugs or headphones. The MRI technician and/or designated study team member will wrap a breathing belt around your waist to measure your breathing rate throughout the scan. They will also attach a heart rate monitor and electrodes for ECGto better understand your physiology while in scanner. You will be given button boxes that you will utilize for tasks. You may choose to stop the scan at any time for any reason and will not have to explain why and will not lose any reimbursement.

You will also undergo a clinician assessment regarding adverse events that may have occurred during your study participation.

Your responsibilities if you take part in this research:
If you decide to take part in this research study, you will be responsible for the following things:

- Taking the prescribed study drugs (ketamine or midazolam)
- coming into our program for research study visits
- using birth control methods as described in described in the Description of What's Involved section
- avoiding the use of (or changes if stable prior to study entry) psychotropic medications during study
- following the instructions of the principal investigator and study staff.
- telling the principal investigator or research study staff about any side effects, doctor visits, or hospitalizations that you may have because of the MRI or other procedures.
- telling the principal investigator or research staff if you believe you might be pregnant. Pregnant patients will be excluded from participation, due to potential and potentially unknown contraindications with MRI procedure.
- telling the principal investigator or research staff if you have any type of implanted electrical device (such as a cardiac pacemaker). If so, you will not be allowed to participate in this study.
- asking questions as you think of them.
- telling the principal investigator or research staff if you change your mind about staying in the study.

End of study plan:
At the end of the visit, a qualified study team member will debrief you and you will be able to ask questions. However, if you feel too uncomfortable or distressed at any point during this visit, the study procedures will be stopped, and you will be exited from the study. A study clinician will discuss your post-study participation treatment options with you. If applicable, the study team will ask if they can reach out to your mental health provider to aid in the transition of care. If you don't have a current mental health provider, a clinical referral can be provided.

Because this project involves the use of medications or a medical device, it is necessary that we make a note of your participation in the electronic medical record. That way anyone treating you will be aware of your

participation and may be able to avoid any unfortunate outcomes that could arise if your research participation were unknown.

For Women:
Since you are participating in a research study that involves drugs or experimental treatment with potential risks to a developing fetus, it is recommended, for your protection, that you not become pregnant for the duration of the study. You should not participate if you are breastfeeding.

A urine pregnancy test will be done before you begin the study and will be repeated at each visit for women of childbearing potential. Therefore, practicing effective birth control is important. No individual birth control is 100% effective.

Recommended methods of birth control are:

- The consistent use of an approved hormonal birth control (pill/patches, rings),
- An intrauterine device (IUD),
- Contraceptive injection (Depo-Provera),
- Double barrier methods (Diaphragm with spermicidal gel or condoms with contraceptive foam),
- Sexual abstinence (no sexual intercourse) or
- Sterilization.

Hormonal birth control, implants, and injections are only considered effective if used properly and started at least one month before you begin the study, continuing throughout the study and for one month after the end of the study. You should ask your study doctor if you should continue birth control for longer than 30 days after the end of the study. If you are unsure whether the method of birth control you use is acceptable to use while participating in this study, you should ask your study doctor before you begin the study. If you are less than one year post-menopausal, there is the potential that you could become pregnant. If you or your partner becomes pregnant, or may be pregnant, at any time during the study, or in the month following it, it is important that you tell your study doctor immediately. The trial drug may be stopped, and a referral may be made to an obstetrician/gynecologist for follow-up. If you plan to become pregnant in the year following a clinical trial, speak with your study doctor.

Should you become pregnant, regardless of the outcome, the sponsor may ask for information on your pregnancy, even if you are withdrawn from the study. Your written consent will be obtained separately in the case that this happens.

There are no known risks during pregnancy to having an MRI. There may be risks that are unknown. Current FDA guidelines state that safety has not been established for imaging the fetus.

For Men:
Since you are participating in a study that involves experimental drugs or experimental treatment with potential risks to a developing fetus, it is recommended that you use a condom and not impregnate a woman or donate sperm while you are taking the study drug, and for an additional 90 days after you stop taking the study drug. This is because levels of the study drug may be present in the sperm and/or seminal fluid even after you stop taking the study drug. You are encouraged to tell your female partner(s) and/or their doctor(s) that you are participating in a clinical trial.

Could your participation end early? There are several reasons why the researchers may need to end your participation in the study (early withdrawal). Some reasons are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.

- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is stopped.

The researchers will discuss your options for medical care when your participation in this study ends.

It is possible that this study will identify information about you that was previously unknown, such as disease status or risk. Any clinically relevant results of the research will be communicated to you. Clinically relevant means that the information indicates that you may be at risk for a serious illness known at the time of testing to be treatable and it can be confirmed. In that case, we will attempt to notify you using the contact information you have provided.

If you do not want to be notified of any of these incidental findings, please initial below.

_____ Please do not notify me of any incidental findings obtained from this research.

Risks – "What are the risks of participation in the research?"

Risks from the specific research procedures (drug(s), interventions, or procedures)
There are risks to taking part in this research study. One risk is that you may have side effects while on the study.

Side effects from this study will usually go away soon after you stop the study drug infusions. In some cases, side effects can be long lasting or may never go away.

Everyone taking part in the study will be watched carefully for any side effects. However, the study doctors don't know all the side effects that may happen. Be sure to tell your study doctor immediately, about any side effect that you have while taking part in the study.

The following section will describe the risks related to each your participation in this research study. You should talk to your study doctor about any side effects or other problems that you have while taking part in the study.

Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or fatal (could cause death). The frequency that people experience a certain side effect can range from many (likely), few (less likely) or only one or two (rarely).

Risks of restrictions to ongoing psychiatric care: Participation in this study may require you to either not take some psychiatric medications or to be stable on these medications for at least four weeks before your baseline visit, and to not change the psychiatric medication regime during the course of your participation. Please consider the risks of these restrictions and discuss with your mental health provider. You should not discontinue any psychiatric treatments just to participate in this study.

Risks of Ketamine: Previous studies examining the antidepressant effects of ketamine have documented side effects of the drug:

- Distorted visualization of colors
- Feeling suspended in space or floating
- Experiencing out-of-body sensations
- Vivid dreaming

- Psychic experiences that are bizarre or frightening, or psychic experiences that are pleasurable, joyful, or fascinating

When such reactions do occur, they are usually mild and short-lasting. The perceptual disturbances appear more commonly in those with preexisting psychosis (such as schizophrenia). Overall, these effects have been reported in 42% studies investigating the antidepressant effect of ketamine.

- Increases in blood pressure and heart rate may occur and may require medication intervention (32% trials studying the antidepressant effect of ketamine).
- Emergence reactions (emergence reactions are altered state of consciousness, which begins with emergence from anesthesia and continues through the early recovery period) have occurred in approximately 12 percent of patients.

Additional symptoms that have been reported in previous studies (23% studies investigating the antidepressant effect of ketamine) include:

- Drowsiness
- Inability to sit still
- Blurred vision
- Stomach discomfort (constipation, diarrhea, frequent need to urinate)
- Nervousness
- Weakness
- Irritability
- Increased or decreased appetite
- Dry mouth
- Trouble sleeping
- Difficulty finding words
- Conceptual disorganization
- Trouble concentrating
- Numbness
- Loss of sexual interest
- Muscle cramps
- Stuffy nose
- Clenching of teeth at night
- Sweating

Although during the screening visit you will meet with a doctor who will complete a physical exam, review your medical history, and read your ECG, there is still a small chance that the infusion will unmask or aggravate a medical condition, specifically a cardiac condition, that could potentially be life threatening.

Any psychoactive drug – a drug that affects the central nervous system – may impair judgment, thinking, or motor skills, and therefore you should not operate hazardous machinery or drive a motor vehicle until you are reasonably certain that you are capable of doing so.

Risks of midazolam**:** Potential risks associated with midazolam have been observed in 1.2-3% of cases and include:

- Headache
- Coughing
- Drowsiness
- Nausea and vomiting
- Decrease in blood pressure

- Decrease in breathing rate
- Airway obstruction
- Decrease in oxygen levels in the blood
- Difficulty breathing
- Stopping of breathing or heart function

Additional risks observed in 0.4-5.6% of cases include:

- Agitation
- Involuntary movements
- Combativeness
- hiccups
- tenderness
- Pain and redness during injection
- Unconsciousness
- Inflammation of the skin and vein
- Decrease in the blood supply to the brain (rare)

Risks and discomforts associated with MRI Scan:

- Eye Discomfort: On very rare occasions, you may feel some eye discomfort. The scanning will be stopped if this occurs. These symptoms, if present, will subside shortly after leaving the magnet.
- Claustrophobia: Please note that some subjects who are uncomfortable in small spaces have experienced claustrophobia, which is feeling discomfort in small, confined spaces, while in the MRI scanner. You may discontinue the scan at any time if you feel intolerable discomfort.
- Twitching Sensations: There is a possibility that you will experience a localized twitching sensation due to magnetic field changes during the scan. This is not unexpected and such sensations should not be painful. However, you may have the scan stopped at any time if this occurs.
- Heat Sensations: There is a risk of heating from radiofrequency imaging coils and their cables, button response boxes and their cables, and the cables from monitoring devices that record physiologic processes such as heart beats per minute or electrical activity of the brain. Please report any heating sensation immediately. You may have the scan stopped at any time if this occurs.
- Dizziness or Nausea: Dizziness and nausea will occur if you move quickly near the magnet or if your head moves within the bore of the magnet. You will be instructed on how to move through the MRI room to minimize any such dizziness and nausea.
- Frustration or Stress: The MRI task in this scan is designed to elicit frustration. The aim of this is to see how the brain activates when anticipating and/or experiencing frustration. It is important to note that his task should not cause intolerable distress. You can stop the scan at any point if the task is intolerable.

The procedure may involve risks that are currently unforeseeable. If you feel discomfort at any time, notify the operator and you can discontinue the exam at any time.

Risk of loss of private information: this risk always exists, but there are procedures in place to minimize the risk.

Psychological stress: During the clinical interviews, you may become tired or upset about the questions. If this happens, you should tell the interviewer/study personnel and he/she will stop the examination. Depending upon how you feel, you may then 1) take a rest period and resume later, 2) reschedule for a later appointment or 3) decide not to finish the exam.

Blood draw: The risks of a blood draw include pain, bruising, and the slight possibility of infection at the place where the needle goes in. Some people feel dizzy or may faint during or after a blood draw.

Potential for Abnormal Medical Findings: A limited research report will be sent to a radiologist for all scans. The scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. The investigators for this project may not be trained to perform a medical diagnosis. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. When this occurs, a physician will be consulted as to whether the findings merit further investigation, in which case the investigator will contact you and your primary care physician and inform you of the finding. The decision as to whether to proceed with further examination or treatment lies solely with you and your physician. The investigators, the consulting physician, and UTSW are not responsible for any examination or treatment that you undertake based on these findings. Because the images collected in this study may not comprise a proper clinical MRI scan, these images will not be made available for diagnostic purposes.

This MRI scan is not being done for your regular medical care. The machine settings used for this special MRI are not chosen to pick up structural changes in the brain, for example: masses or bleeds. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician and may result in additional cost to you.

Women of Childbearing Potential: Women who are or may be pregnant may not take part in this study. There are no known risks during pregnancy of having an MRI. There may be risks that are unknown related to study drug administration.

In addition to these risks, this research may hurt you in ways that are not known. The unknown risks might be minor or might be major (death).

Group Risks: Although we will not give researchers your name, we will give them basic information such as your race, ethnic group, and sex. This information helps researchers learn whether the factors that lead to health problems are the same in different groups of people. It is possible that such findings could one day help people of the same race, ethnic group, or sex as you. However, they could also be used to support harmful stereotypes or even promote discrimination.

Privacy Risks: Your name and other information that could directly identify you (such as address, date of birth or social security number) will never be placed into a scientific database. In any research study there exists the potential for loss of your private information. However, there are strict procedures in place to minimize this risk.

For more information about risks and side effects, ask one of the researchers or study staff.

There may be unforeseeable side effects that could be life threatening or fatal (could cause death). We will tell you about any significant new findings which develop during this research study which may relate to your willingness to continue taking part.

Are there Risks related to withdrawing from the study?

If you decide to withdraw from this study early, please discuss your decision with the principal investigator. The researcher may ask you to complete study withdrawal procedures at a final study visit. This visit includes the procedures described in the Study Exit Visit. There is no risk to you if you do not complete the final withdrawal procedures and you can choose not to participate in them.

Reproductive Risks -

Concerns for sexually active men and women: Women should not become pregnant and men should not father a baby while taking part in this study because we do not know how the study drugs/procedures could affect a man's sperm (for some drugs/procedures, the concern may be that the sperm might be affected and in some cases, drugs could being carried by the semen into the vagina and cause harm) or a fetus, if a woman becomes pregnant during the study. It is important that you talk to your study doctor about avoiding pregnancy during this study. If you think you might have become pregnant or if you believe your female partner has become pregnant while you are in this study, you must tell one of the study doctors right away so that management of the pregnancy and the possibility of stopping the study can be discussed.

If you are a woman who is pregnant or could be pregnant, you cannot take part in this study because we do not know how the study drug might affect a developing fetus. We will do a pregnancy test before you start treatment to make sure you are not pregnant.

If you become pregnant during your participation in this research study, the researchers would like to collect follow-up information regarding your pregnancy.

If your partner becomes pregnant during your participation in this research study, we would like to ask permission to collect follow-up information regarding the pregnancy. Your partner will be asked to sign a separate consent form.

Risks to babies who are being breastfed: Women who are breastfeeding cannot take part in this study because we do not know what effect the drugs/procedures might have on their breast milk.

Are there risks if you also participate in other research studies?
Being in more than one research study at the same time, may increase the risk to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers.

What if a research-related injury occurs?
The researchers have taken steps to minimize the known or expected risks. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. In the event of a research-related injury or if you experience an adverse reaction, please immediately contact your study doctor. See the section “Contact Information” for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We have no plans to give you money if you are injured. The investigator can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study.

Benefits – “How could you or others benefit from your taking part in this study?”

The possible benefit of your participating in this study is temporary improvement in your symptoms of depression and irritability. There is no guarantee or promise that you will receive any benefit from this study. Your participation in this research study may yield useful information that will be helpful to the development of new treatments for irritability, and we hope the information learned from this study will benefit other people with

similar conditions in the future.

Alternative procedures or course of treatment – "What other options are there to participation in this study?"

There are other options available to you. Your other choices may include:

- Receive standard treatment for depression with oral medication
- Cognitive Behavioral Therapy (CBT)
- Neurostimulation treatment (i.e. transcranial magnetic stimulation or electroconvulsive therapy)
- Intranasal esketamine

Payments – Will there be any payments for participation?

If you agree to take part in this research study, you can earn up to a total of $750 for your time and effort. Additionally, assistance with transportation may be provided at the discretion of the study team.

You will be paid $50 for the screening visit and $100 for each of the two visits when an MRI is completed. Additionally, you can earn up to $100 for the cognitive tasks completed both outside and within MRI scanner for each of the scans. You will be paid at the completion of each visit/MRI, except the cognitive task performance-related payments will be made at the end of study participation. If you do not complete the study, you will be paid for the visits that you have completed based on the following schedule:

Study visits	**Payment**
Screening visit	$50
Baseline visit (including MRI)	$100
Cognitive task performance (1st MRI)	Up to $100
Infusion Visit 1	$75
Infusion Visit 2	$75
Infusion Visit 3	$75
Infusion Visit 4	$75
Study Exit / Early Termination Visit (including MRI)	$100
Cognitive task performance (2nd MRI)	Up to $100
Possible Total for Study:	$750

You will be issued a UT Southwestern Greenphire ClinCard, which can be used as a credit or debit card. Compensation will be credited to the card after completion of each completed study visit noted above. Your name, address, date of birth and social security number will be shared with a third-party solely for the purposes of compensation processing. All information will be stored in a secure fashion.

Please note that if you are on record as owing money to the State of Texas, such as for back child support or a delinquent student loan, the payment may be applied to that debt.

An IRS Form 1099 will be sent to you if your total payments are $600 or more in a calendar year unless it's a reimbursement.

Costs – Will taking part in this study cost anything?

The sponsor will pay UT Southwestern for the procedures that are part of the study. You will not be reimbursed for your travel or time that may be required for study visits.

Taking part in this research study may lead to added costs to you such as those related to transportation, childcare, and missed wages. Payments for study visits are to help cover such costs.

Confidentiality – How will your records be kept confidential?

Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

Certificate of Confidentiality:
To help us further protect your information, the investigators will obtain a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). This Certificate adds special protections for research information that identifies you and will help researchers protect your privacy.

With this Certificate of Confidentiality, the researchers cannot be forced to disclose information that may identify you in any judicial, administrative, legislative, or other proceeding, whether at the federal, state, or local level. There are situations, however, where we will voluntarily disclose information consistent with state or other laws, such as:

- to DHHS for audit or program evaluation purposes;
- information regarding test results for certain communicable diseases to the Texas Department of State Health Services, including, but not limited to HIV, Hepatitis, Anthrax, and Smallpox;
- if you pose imminent physical harm to yourself or others;
- if you pose immediate mental or emotional injury to yourself;
- if the researchers learn that a child has been, or may be, abused or neglected; or
- if the researchers learn that an elderly or disabled person has been, or is being, abused, neglected or exploited.

The Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your involvement in this research study. In addition, the researchers may not use the Certificate to withhold information about your participation in this research study if you have provided written consent to anyone allowing the researchers to release such information (including your employer or an insurance company). This means that you or your family must also actively protect your privacy.

A Certificate of Confidentiality does not represent an endorsement of this research project by the Department of Health & Human Services or any other Federal government agency.

How will my information be used?
With appropriate permissions, your samples and collected information may also be shared with other researchers here, around the world, and with companies.

By agreeing to participate in this study, your information could be used for future research studies or sent to other investigators for future research studies without additional consent from you. The information that

identifies you will first be removed from your information. If you do not want your information to be used for future research studies without your consent, you should not participate in this study.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study. Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your medical record. The information included in your medical record will be available to health care providers and authorized persons including your insurance company.

What is Protected Health Information (PHI)?
Protected Health Information is information about a person's health that includes information that would make it possible to figure out whose it is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for this research study. In carrying out this research, the health information we will see and use about you will include:

The researchers will also get information from your medical record from your doctor, from UT Southwestern Medical Center, and by asking you to complete the tests, procedures, questionnaires and interviews explained in the description section of this consent.

All MRI scans will be saved indefinitely after the conclusion of the study.
During the study the researchers will gather information by:

- Taking a medical history (includes current and past medications or therapies, illnesses, conditions or symptoms, family medical history, allergies, etc.)
- Doing a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature
- Completing the tests, procedures, questionnaires and interviews explained in the description section of this consent.
- Reviewing mental health records
- Reviewing alcohol and/or substance abuse records
- Reviewing psychotherapy notes

How will your PHI be shared?
Because this is a research study, we will be unable to keep your PHI completely confidential. We may share your health information with people and groups involved in overseeing this research study including:

- The Sponsor, National Institute of Health, funding the study. The sponsor includes any people, entities, groups or companies working for or with the sponsor or owned by the sponsor. The sponsor will receive written reports about your participation in the research. The sponsor may look at your health information to assure the quality of the information used in the research.
- The company, JHP Pharmaceuticals that makes the study drug used in the MDD group
- The members of the local treatment team
- The Institutional Review Board, Human Research Protection Program Office and the Compliance Office of the University of Texas Southwestern Medical Center, and other groups that oversee how research studies are carried out.
- The Research offices at the University of Texas Southwestern Medical Center.

- The Food and Drug Administration (FDA) and other U.S. and international governmental regulatory agencies involved in overseeing drug or device research.
- Representatives of domestic and foreign governmental and regulatory agencies may be granted direct access to your health information for oversight, compliance activities, and determination of approval for new medicines, devices, or procedures.

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in the research study.

Parts of your PHI may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail or fax. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

How will your PHI be protected?
In an effort to protect your privacy, the study staff will use code numbers instead of your name, to identify your health information. Initials and numbers will be used on any photocopies of your study records, and other study materials containing health information that are sent outside of the Center for Depression Research and Clinical Care (CDRC), AIRC, and CRU for review or testing. If the results of this study are reported in medical journals or at meetings, you will not be identified.

Do you have to allow the use of your health information?
You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties but you will not be allowed to participate in the study.
After you enroll in this study, you may ask the researchers to stop using your health information at any time. However, you need to say this in writing and send your letter to Manish K Jha, UT Southwestern, 1440 Empire Central Drive, Level 3 Mood Disorders, Dallas, Texas, 75247. If you tell the researchers to stop using your health information, your participation in the study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?
The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study.

During your participation in this study, you will not be able to access your medical records. This will be done to prevent the knowledge of study results from affecting the reliability of the study. Your information will be available should an emergency arise that would require your treating physician to know this information to best treat you. You will have access to your medical record and any study information that is part of that record when the study is over or earlier, if possible. The investigator is not required to release to you research information that is not part of your medical record.

How long will your PHI be used?
By signing this form, you agree to let us use and disclose your health information for purposes of the study until October 2033. This permission to use your personal health information expires on the date noted above.

Title of Study: Elucidating the Neurocircuitry of Irritability with High-Field Neuroimaging to Identify Novel Therapeutic Targets

Contact Information – Who can you contact if you have questions, concerns, comments or complaints?

If you have questions now, feel free to ask us. If you have additional questions, concerns, comments or complaints later or you wish to report a problem which may be related to this study please contact:

Primary contact:
Manish K. Jha, MBBS can be reached at 214.648.0156 or Manish.Jha@UTSouthwestern.edu.

Secondary contact:
If Dr. Jha is unavailable, please contact:

Brindley House, MA at 469.602.3679 or Ann.House@UTSouthwestern.edu

The University of Texas Southwestern Medical Center Human Research Protection Program (HRPP) oversees research on human subjects. HRPP and Institutional Review Board (IRB) representatives will answer any questions about your rights as a research subject, and take any concerns, comments or complaints you may wish to offer. You can contact the HRPP by calling the office at 214.648.3060.

Title of Study: Elucidating the Neurocircuitry of Irritability with High-Field Neuroimaging to Identify Novel Therapeutic Targets

Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research, sign this section. You will be given a copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE FOLLOWING STATEMENTS ARE TRUE:

- You have read (or been read) the information provided above.
- Your questions have been answered to your satisfaction about the research and about the collection, use and sharing of your protected health information.
- You have freely decided to participate in this research or you are voluntarily giving your consent for another person to participate in this study because you believe this person would want to take part if able to make the decision and you believe it is in this person's best interest.
- You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. Information in your medical record will be available to health care providers and authorized persons including your insurance company.
- You authorize the collection, use and sharing of your protected health information (another person's protected health information) as described in this form.

Adult Signature Section

Printed Name of Participant	Signature of Participant	Date	AM PM Time
Printed Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date	AM PM Time

Blind or Illiterate Signature Section *At the time of consent, also complete this section if consent is obtained from an individual who is unable to read and/or write but can otherwise communicate and/or comprehend English (e.g., blind, physically unable to write, etc.)*

Declaration of witness:

By signing below, I confirm I was present for the entire consent process. The method used for communication (e.g., verbal, written, etc.) with the subject was: _____ .

The specific means (e.g., verbal, written, etc.) by which the subject communicated agreement to participate was: _____.

Printed Name of Witness	Signature of Witness	Date	AM PM Time