Characterizing the Neural Substrates of Irritability in Women: an Experimental Neuroendocrine Model

NCT number NCT04051320
Document Date 11/05/2020

IRBIS ORIS
University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

Consent Form Version Date: November 5, 2020
IRB Study # 19-0401
Title of Study: Characterizing the neural substrates or irritability in women: an experimental neuroendocrine model
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CONCISE SUMMARY

The purpose of this research study is to determine the role of hormones (estrogen and progesterone) in postpartum depression (feelings of sadness and anxiety that can be extreme and might interfere with a woman's ability to care for herself or her family around the time of childbirth). It remains unclear why changes in estrogen and progesterone cause postpartum depression in some women and not others. You are being asked to participate because you are a woman between the ages of 21 and 45 in good medical health, taking no medication (including birth control pills), with regular menses. You also have given birth before, and you either had an episode of postpartum depression or no history of depression in the past.

Participants will undergo a two visit screening process prior to the start of the study. The first screening visit will include a psychiatric interview, and questionnaires. The second screening visit includes a blood draw, an OBGYN exam, and a physical if the participants do not have a recent exam. Once screening is complete, participants will complete an 8-week hormone "challenge" that will require two brain scans, behavioral tests, bi-weekly study visits, completing daily questionnaires, taking estrogen, progesterone and a placebo orally, and having a monthly Lupron injection. Each visit will last between 30 minutes and 3 hours, with the average visit lasting 45 minutes. One month following completion of the hormone challenge participants will be asked to complete a follow-up visit to answer some questionnaires. The total study duration is 12 weeks or 3 months.

The risks of taking hormones are described in this document. Some risks include: bloating, cramps, breast tenderness, nausea, headaches, and fatigue. During the study you may learn about your sensitivity to changes in estrogen and progesterone levels, which may be useful if you plan to have children in the future.

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

What are some general things you should know about research studies?
You are being asked to take part in a research study. To join the study is voluntary.
You may refuse to join, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with

the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The purpose of this research study is to determine the role of hormones (estrogen and progesterone) in postpartum depression (feelings of sadness and anxiety that can be extreme and might interfere with a woman's ability to care for herself or her family around the time of childbirth). We will investigate the role of these hormones in mood by using a hormonal "challenge." The hormonal challenge involves three phases. During phase one, you will receive Lupron, a medicine that will temporarily turn off your ovaries during the study. Lupron does this by reducing the levels of estrogen and progesterone in your blood. During phase two, you will continue to receive Lupron and you will take pills that contain estrogen and progesterone or placebo (a pill that looks like the hormone pills, but contains no medication). At some point during phase two, the estrogen and progesterone pills will be switched for placebo (we will not tell you when this happens), and the levels of both hormones will drop rapidly. As your hormones drop, you may experience symptoms of depression, including sadness and less interest in your daily activities. During phase three, you will stop taking all study medications, and we expect your mood and hormone levels to return to normal. You will receive two scans of your brain during the study and be asked to complete several behavioral tests. The brain scans and behavioral tests will help us understand how changing hormone levels impact your brain function and mood symptoms. During both brain scans we will monitor your heartrate with a finger pulse oximeter.

Background:

Previous studies have shown that estrogen and progesterone play a role in postpartum depression. It remains unclear why changes in estrogen and progesterone may contribute to postpartum depression in some women and not others. You are being asked to participate because you are a woman between the ages of 21 and 45 in good medical health, taking no medication (including of birth control pills), with regular menses. You also have given birth before, and you either had an episode of postpartum depression or have no history of depression in the past.

Are there any reasons you should not be in this study?

You will not be permitted to enter this study if you have important clinical or laboratory abnormalities including any history of the following:

- any foreign metal objects or implants in your body as determined by the safety questionnaires
- endometriosis (an illness related to abnormal tissue growth around the uterus)
- enlargement of the ovaries
- liver disease
- breast cancer
- a history of blood clots in the legs or lungs
- undiagnosed vaginal bleeding
- porphyria (a rare genetic blood disorder)
- diabetes mellitus
- malignant melanoma (a type of skin cancer)
- gallbladder or pancreatic disease
- heart or kidney disease
- cerebrovascular disease (stroke)
- cigarette smoking of more than 10 cigarettes per day
- a history of suicide attempts or psychotic episodes
- recurrent migraine headaches with aura
- history of pregnancy-related medical conditions such as excessive vomiting, high blood pressure, deep vein thrombosis, or seizures
- menstrual cycle variability of greater than 7 days different from your normal cycle length or an abnormal level of follicle stimulating hormone
- current psychiatric diagnosis

- body mass index (BMI) greater than 35
- hormonal contraceptives that are implanted (i.e. progestin IUD or implant)

In addition, you will not be permitted to participate if you have a first degree relative (immediate family) with breast cancer that occurred before menopause, or breast cancer presenting in both breasts, or if you have multiple family members (greater than three relatives) with breast cancer.

You may not take part in this study if you are pregnant or receiving any medication. If you are using a hormonal contraceptive, you must enter a washout period (i.e. stop taking the hormonal contraceptives and instead use a barrier contraceptive) for 3-4 months prior to entering the study and have 3 regular periods (periods without variability greater than 7 days from your normal cycle length) before you can begin the study procedures.

If you are experiencing any troubling medication side effect, the dose may be changed, but you must not change your medication dose without consulting the investigator. If adequate relief cannot be achieved by changing the dose, the drug will be stopped. Dropping out of the study will not interfere with any medical treatment you were receiving at UNC Hospitals.

How many people will take part in this study?
There will be approximately 39 people in this research study.

How long will your participation in this study last?
This study will include 8 visits over the course of 12 weeks. Study visits will range from 30 minutes to 3 hours, and most visits will last approximately 45 minutes. The visits that do not require Lupron injections or brain scans may take place virtually through secure video visits or at your home provided that you live within a 60 minute drive of UNC hospital.

What will happen if you take part in the study?

Clinical and Health Screening:

You will undergo a screening process to determine if you are eligible for the study. In order to protect you from adverse medication effects, you will be screened with a complete medical and psychiatric history, physical exam, and laboratory tests. During the initial visit, approximately 2 tablespoons (about 30 mls) of blood will be drawn to test your hormone levels and liver and kidney function. We will also require that you have had a gynecological exam within the last three years. If you have not had one, a gynecological exam will be completed as part of the screening process. If you are eligible for the study, the results of your medical history, physical exam, and laboratory tests will appear in your UNC Health Care medical record.

During the initial screening, you will be asked questions about your past mental health as well as questions about any symptoms you may be experiencing now. You will also be asked to complete questionnaires about your mood symptoms and trauma history. You may choose not to answer any or all of the questions for any reason.

You will complete a safety questionnaire to determine whether you have any foreign iron or steel metal objects in your body, such as a pacemaker, shrapnel, metal plate, or metal debris. If you have any such objects in your body, you cannot participate in the MRI session. Please ask the experimenter if you are unsure.

You will also receive a urine pregnancy test and urine drug screening prior to each MRI session to make sure that it is safe for you to receive the MRI and that your brain activity is not affected by drug use.

Blood Samples and Screening:

Blood samples will be taken at the start of the study and at times during the course of the protocol. All blood samples will be drawn in the following way: you will be asked to sit down and after ten minutes a small plastic tube (catheter) will be placed in an arm vein, the blood sample will be drawn, and the catheter removed. During each of your in-person MRI visits 30 ml (2 tablespoons) of your blood will be drawn. Estrogen, progesterone, and allopregnanolone levels in your blood will be assessed.

You will receive a pregnancy test before starting the study. You may not participate in this study if you are pregnant because the study drugs (Lupron, estrogen, and progesterone) may be associated with birth defects. We will ask that you use barrier contraceptive methods (diaphragm or condom or both) for the entire time you are in this study. To prevent pregnancy, we strongly recommend that you also continue barrier contraception for at least three months after the last injection of Lupron and until you have two to three regular menstrual cycles after the study has ended.

Hormone Procedures:

Once you finish the screening, we will ask you to have an injection of Lupron into a muscle, once a month for two months. You will attend virtual video appointments every two weeks during the study when possible to minimize the risk of COVID-19 transmission. During the first two months, we will also ask you to take two different kinds of capsules that contain either estrogen and progesterone or placebo. You will not be aware of the real nature (hormones versus placebo) of the capsules you are taking, but you will know that at some point during these three months you will be started on a one- to two-month period of active medication. During this period you will receive up to 2 mg of estrogen (17-beta estradiol) and 200 mg of progesterone. All medication refills during the study will be dropped off at your home every two weeks by a member of the study team to minimize the risk of COVID-19 transmission. You will not be aware of the exact time the hormone capsules are switched over to placebo capsules. After completing the medication period lasting two months, we will continue your follow-up at the clinic for another month. At the end of the study, we will discuss the study results and their meaning with you.

Brain Imaging:

You will participate in two brain imaging sessions at the UNC Biomedical Research Imaging Center. During the COVID-19 pandemic you will be asked pre-screening questions 24 hours in advance of these visits, and on the day of the visit. You will be asked to maintain 6ft distance from others when possible and wear a surgical mask in all face-to-face visits which will be provided for you by the study team in advance. On arrival to the UNC Biomedical Research Imaging Center you will have a temperature scan prior to entering the building and will be asked to wait in one of the holding rooms. This will allow for yourself and the member of the study team to walk through the MRI center without possibility of encountering other staff members. In these sessions, magnetic resonance images (MRIs) of your brain will be taken. A MRI is a picture of your brain taken with the use of strong magnetic fields. MRIs do not use x-rays or other radiation, and there are no known risks associated with MRIs. In this study, special MRIs (called functional MRIs or fMRIs) will be taken that provide information about what areas of the brain are made active by particular kinds of stimuli. You will view "stimuli," including pictures of faces and objects such as slot machines and money. The experimenter may ask you to push a button when particular stimuli appear on the screen.

When you understand the task instructions, you will lie down on your back on a platform and your head will be positioned inside a helmet-like circular tube and the platform will be pushed inside the long tube of the MRI machine. The MRI technician will provide padding for your head and knees to make you more comfortable while lying down. If you are uncomfortable or feel pain because of lying down, please tell the technician immediately. You will be able to see outside of the helmet and outside the imaging machine by looking at a mirror. In this way, you will be able to watch the pictures or words displayed on a screen placed near your feet. If sounds are presented, you will hear them through earphones. It is expected that each imaging session will take approximately 2 hours.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. There is little chance you will benefit from being in this research study. However, you may learn about your sensitivity to changes in estrogen and progesterone levels, which may be useful if you plan to have children in the future.

What are the possible risks or discomforts involved from being in this study?

1) Mood changes – If you have never experienced an episode of depression in the past, then your risk of developing mood symptoms during this study are very low, but this risk still exists. If you experience any depression symptoms, including thoughts about death or suicide, we ask that you inform us immediately. We will assess your mood each day during the study and at your bi-weekly clinic visits. The majority of participants complete the daily mood rating every day, and if you miss a day, we will contact you to do a safety assessment over the phone. Once you have

finished taking the medication for the study, you will only need complete the mood ratings once a week.

If you experience severe mood symptoms or suicidal thoughts, then you not be allowed to continue in the study. We will provide short-term treatment with medication for depression until your symptoms improve, however **these costs will not be covered by the study**. If you do not wish not to receive standard treatment with medication for depression, you may have to be transferred to another hospital for treatment. We can only treat you at UNC if you are either in a research study or agree to receive treatment after you have completed the research study. If you receive treatment at another hospital, UNC will not cover the costs.

Given the relatively brief nature and moderate severity of any mood symptoms that you may experience during this study, we do not anticipate that your mood symptoms will adversely impact your children. Nonetheless, we cannot guarantee the absence of effect, nor can we anticipate every risk that may result from your participation in this study.

2) Lupron causes the ovary to stop working for a short period of time (one month). Lupron may cause the same side effects that are seen when the ovaries stop functioning permanently (menopause). Side effects may include hot flushes (flashes), decrease in libido, headaches, nervousness, irritability, muscle aches, trouble sleeping, and a slight decrease in bone density. The decrease in bone density is reversible and should not be related to an increased risk of bone fracture because of the short time you will receive Lupron treatment. Your menstrual periods may be irregular for 2-6 months after the last Lupron injection. Skin irritation may occur at the site of injection. All side effects are reversible after the Lupron treatment is stopped, and many side effects, if they do occur, will be reversed by the estrogen and progesterone given during the study. At the dose of Lupron that we will use, the risk of developing severe side effects is small. Nevertheless, you will be monitored closely to see if side effects develop, and the medication will be stopped if side effects become intolerable.

3) Estrogen capsules (Estrace, Micronized 17-beta-estradiol) – The risk of developing side effects is small because of the dosage and period of time that you will receive estrogen treatment. The most common side effects are nausea, breast tenderness or enlargement, and fluid retention (swelling). There is a significantly increased risk of stroke following estrogen therapy in individuals with migraine with aura, as compared to individuals without aura, and as such, women with a history of recurrent migraine with aura will be excluded. Less common side effects are vomiting, depression, high blood pressure, a spotty darkening of the skin (mostly of the face), or vaginal bleeding. Any side effects that you may experience should stop after the end of the study. In the rare event that you experience spotty skin darkening, it may not disappear completely.

Estrogen use increases the risk of certain medical gallbladder problems, and it may increase the risk of certain types of cancer. However, the risk of cancer is minimal because of the dose and the short period of time estrogen is used in this study. The risk of cancer is also reduced because estrogen is given along with progesterone.

Estrogen and progesterone may also cause an increase in birth defects if they are taken during early pregnancy. Therefore, you should not become pregnant during this study. Pregnancy tests will be given during the screening phase, and you will not be allowed to participate if you are pregnant. The study will cover the cost of the pregnancy tests.

You will be followed closely to see if side effects develop, and the medication will be discontinued if you experience negative or intolerable side effects.

4) Progesterone capsules (Micronized progesterone) - Progesterone is used to treat a variety of gynecological disorders. Side effects are not common and are usually mild. These include breakthrough bleeding (menstruation earlier than expected), edema (swelling), loss or increase of weight, jaundice, rash (with or without itching), breast tenderness, diarrhea, flatulence (gas), vaginal discharge, loss or increase of sexual drive, faintness, uterine cramps, depressed mood, easily fatigued, drowsiness, lack of initiative, and skin color changes. During and shortly after the hormonal replacement you will probably experience some vaginal bleeding.

If you experience symptoms such as severe mood symptoms, nausea, hypertension (high blood pressure), vomiting or extreme fluid retention (bloating or swelling) from the medication, you will have the dose adjusted until you feel relief. If you do not feel relief, then drug treatment will be discontinued. If vaginal bleeding or any other gynecological problem occurs, we will arrange for a visit with a UNC gynecologist, which may include a

transvaginal ultrasound examination. If you experience marked discomfort during the insertion of the ultrasound probe, then the procedure will be discontinued. Otherwise, there are no additional associated risks or discomforts with the ultrasound probe. If the gynecologist finds any abnormality during the ultrasound, further testing may occur. If breakthrough bleeding occurs and is intolerable, you will be withdrawn from hormone replacement (which should precipitate a period).

5) Blood drawing - You may experience some discomfort or temporary pain at the site of the needle entry. There is a small risk of fainting and local infection.

6) MRI sessions - There are no known risks from exposure to magnetic fields and radio waves used in the MRI session. However it is not assured that harmful effects will not be recognized in the future. A known risk is that strong magnetic fields attract iron or steel metal objects posing a safety risk. Prior to this study you will be given a questionnaire to determine if you have any foreign iron or steel metal objects in your body, such as a pacemaker, shrapnel, metal plate, or metal debris. If you have such objects in your body, you cannot participate in the MRI part of the study.
If you participate in the MRI session, you will be asked to leave any metal objects in lockers provided in the waiting room of the MRI center. You will also be asked to remove any articles of clothing with metal inserts or clasps before entering the magnet room. Please ask the experimenter if you are unsure. It is possible you will feel uncomfortable or confined once inside the imaging machine. This feeling usually passes within a few minutes as the experimenters talk with you and the study begins. However, if this feeling persists, you can tell the investigators over the intercom and you will be removed immediately from the machine. On rare occasions some subjects may experience one or more of the following: momentary dizziness or nausea, a metallic taste, tingling sensations, or muscle twitches. Please tell the investigator over the intercom if any of these sensations occur. Once inside the machine, you will hear loud mechanical clanging sounds. This is part of the normal operation of the machine. You will be given earplugs to reduce the sounds. While in the scanner, you will wear a FDA approved pulse oximeter on your finger, that is typically used in standard clinical care, which should not cause any additional discomfort.

6) There may be uncommon or previously unknown risks. If you have any symptoms or unexpected side effects during this protocol, please call the study physicians or nurses right away.

7) COVID-19 Transmission – You may experience the potential risk to COVID-19 transmission during in-person study visits at the MRI center or when in contact with study team members during Lupron injections or blood draws when study staff will need to maintain less than 6ft distance. Our study team and UNC will be taking every precaution possible to protect you and the study team from COVID-19, including virtual video or telephone visits when possible, with limited in-person contact to every degree possible. During the in-person visits we will require masks at all times which will be provided to you by the study team, maintaining 6ft distance when possible, temperature checks on arrival to the UNC Biomedical Research Imaging Center, COVID-19 prescreening for yourself and staff at various timepoints including the day of the study visit, frequent cleaning with 90% alcohol or 1:10 Bleach solution, cleaning between each subject, handwashing requirements every hour for you and all staff, and before and after any contact with any subject. While the study team will be taking every pre-caution possible to protect yourself and the study staff there may still be a risk of COVID-19 transmission due to the possibility of the COVID-19 virus lingering in enclosed spaces from asymptomatic carriers. If you or a member of the study team has had direct or even secondary contact with any suspected or confirmed cases of COVID, the study team will ask to reschedule your visit until the case is confirmed negative or to quarantine for at least 14 days and monitor your symptoms. If you experience any symptoms of COVID-19 including but not limited to: cough, fever, chest pain, trouble breathing, loss of smell or taste, nausea, abdominal pain, vomiting, etc. you will be asked to notify the study team immediately, contact your Primary Care Provider and your local COVID-19 hotline to get tested for COVID-19. The study team and UNC Research are not responsible for any care or treatment of COVID-19.

<u>Addendum for Patients with a History of Gestational Diabetes, Glucose Intolerance, and Episodic Headaches</u>

1) There is no evidence that estrogen or progesterone directly causes gestational (pregnancy-related)

diabetes or diabetes mellitus. Both birth control pills and estrogen replacement can be taken by women who have had pregnancy-related diabetes or who currently have diabetes. However, it is possible that estrogen may influence how your body processes glucose. We will monitor your plasma glucose throughout the study, and if we detect increased blood sugar levels, we will ask you to stop participating in this study.

2) Lupron and estrogen treatment have been reported to aggravate migraine headaches. If you have a history of recurrent migraine headaches you may not participate in this study. Once Lupron is injected into your body its effects last for about four weeks and you may experience an increase in headache frequency while under its influence. If this does happen, we will do our best to manage the pain. If your headaches become severe enough to require repeated medication, we may decide with you to discontinue your participation in this study.

Addendum for Patients with a History of Epilepsy:
There is some evidence that estrogen may increase the potential for seizures in some people. Progesterone has been shown to have the opposite effect. In the present study estrogen levels will not be higher than peak pregnancy levels. In addition, estrogen will be administered along with progesterone. Thus, the likelihood of inducing seizures in someone who has been seizure-free should be very low. However, this possibility exists. If you develop a seizure, your participation in the study will be stopped, and after assuring that you are medically stable, we will return you to the care of your primary physician for any follow up that will be required.

What are the risks to a pregnancy or to a nursing child?
You may not take part in this study if you are nursing or planning to get pregnant. You will take a pregnancy test to make sure that you are not pregnant before starting the study. Pregnant women are cannot participate because the study medications and the MRI sessions may have adverse effects on an unborn child. We request that you use barrier contraceptive methods (diaphragm or condom or both) while you are in this study. We strongly recommend that you continue barrier contraception for at least three months after the last injection of Lupron and until you have two to three regular menstrual periods after the study has ended. If you become pregnant during the study you should notify the researcher right away.

What if we learn about new findings or information during the study?
You will be given any new information gained during the study that might affect your willingness to continue your participation.

The MRI we are using in this research study is not the same quality as a MRI that you may have as part of your health care. The images from the MRI not be reviewed by a doctor who normally reads such images (such as a radiologist). As a result, you may not be informed of any unexpected findings. The results of your MRI will not be placed in your medical record. Occasionally the technologist or principal investigator may notice something abnormal on the imaging. If this does occur, the images will be reviewed by a qualified radiologist to determine if there is anything of clinical importance. If something is found to be important then you, and/or your primary care provider will be notified. Any further follow up and costs associated with the incidental finding will be your responsibility. There may be benefits to learning such results (such as early detection and treatment of a medical

condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate).

Do you wish to be informed in case of clinical/relevant unexpected findings? Please initial in the box below if you do not wish to be notified of clinical/relevant unexpected findings. If you do not initial in the box, you will be notified of any findings.

_____ I do not wish to be notified.

Will I receive any other clinical results?
Other clinically relevant results of this research will be communicated with you.

How will information about you be protected?
You will not be identified in any report or publication about this study. We may use de-identified data and/or specimens from this study in future research without additional consent.

Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of our records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of your personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Your identity will be protected by assigning you a number and omitting your name and other identifying information from scientific reports of the study. The pictures of your brain may be included in a database for future research or scientific reports, and researchers at other institutions may therefore be able to examine your brain pictures. However, your name will not be included in such a database and researchers using these databases cannot learn your identity. If you are enrolled or become enrolled in another research study, we may share your results with researchers from that study, or we may obtain information about you from them. Identifiable data and the file that links your ID with your data will be accessible only to those working on this study, including research assistants and the PI. All computer files are kept on secure computers on a secure network.

Audio recordings of your clinical interviews will be identified by your study ID only and stored on a secure computer accessible only to members of our research team. The recordings will be destroyed at the end of the study. Only your research ID number will be tape recorded along with your interview. You may request to have the audio recording turned off if you are uncomfortable with recording your interview.

Check the line that best matches your choice:
_____ OK to audio record me during the study
_____ Not OK to audio record me during the study

A copy of this consent form will be given to you.

What is a Certificate of Confidentiality?
This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers may not disclose or use information, documents or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use.

The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law,

such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

By signing this informed consent document, you agree that some of the information generated by participating in this study and/or a copy of the consent form may be included in your medical record and that this information may be viewed by other physicians or caregivers who provide healthcare services to you. This will allow the doctors caring for you to know what study medications or tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study. Additionally, the information may be shared with your medical insurance plan if the research services provided are billed to your insurance.

What will happen if you are injured by this research?
All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study.

If you become depressed or anxious as a direct result of participating this study, the UNC Department of Psychiatry will provide outpatient medical treatment. If vaginal bleeding or any other gynecological problem occurs, we will arrange for a visit with a UNC gynecologist. The research study will not cover the costs of such outpatient exams and treatment at UNC Health Care, you will need to use your own insurance to cover these costs.

If you become sick or injured as a direct result of participating in this study, and your condition cannot be addressed with outpatient treatment, UNC Health Care will provide all needed inpatient medical treatment. UNC Health Care will not be able to reimburse you for costs of such inpatient medical treatment not covered by your insurance company. No other form of reimbursement for study-related injury or illness is offered by UNC Health Care. You do not give up any legal rights by signing this consent.

If you receive Medicare benefits, UNC Health Care is required by law to report payments made to you for treatment, complications, and injuries that arise from this study. Information that you are taking part in this study, medical treatments received, Medicare claims, and other personal information about your such as your name, social security number, and date of birth, will be provided to the Centers of Medicare and Medicaid Services and its agents and/or contractors for this purpose.

If you seek treatment outside of UNC Health Care, you will be responsible for the costs of your treatment.

What if you want to stop before your part in the study is complete?
You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?
You will receive a total of $1,000 for your participation in this study. Payment will be given through the form of a Visa Gift Card. Your card will be issued inactive and unloaded through USPS mail. Upon confirmation of receiving Visa gift card, the card will be loaded with the payment amount and you will be able to activate the card. Any payment provided for participation in this study may be subject to applicable tax withholding obligations For each of the long study visits, you will receive the following compensation:

Initial visit, psychological interview, and questionnaires (1 visit) $60.00

MRI Session 1 (1 visit)	$60.00
MRI Session 2 (1 visit)	$60.00

You will receive the remaining $820 upon completion of the study. If you are withdrawn from the study because of an adverse event, you will be compensated for the parts of the study you have completed, as shown below:

Physical/OBGYN exam (1 visit)	$60.00
Screening phase (2 weeks)	$30.00
Clinic visits following initial evaluation and screening (6)	$180.00
Repeated blood draws (3)	$150.00
Daily mood and behavioral ratings, medications ($4.76/day)	$400.00

In addition for each daily rating submitted, you will also be entered into a monthly drawing to win a $30 gift card.

You will also receive vouchers to park in the Dogwood Deck at UNC Hospitals as instructed by the research team. This should cover the cost of your parking for each of the study visits.

Your name, address, and U.S. tax payer identification number (SSN or ITIN) are required to process payments and/or to report taxable income to the IRS. You must complete a W-9 (for U.S. persons) or W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents (for non-resident aliens) in order to receive payment for participation.

U.S. person participants must complete Form W-9 in order to receive payment for participation. If payment by UNC equals or exceeds $600 per calendar year for U.S. persons, UNC will report the amount to the Internal Revenue Service on Form 1099. Nonresident alien participants must complete Form W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents in order to receive payment for participation. Payments to nonresident alien participants may be subject to tax withholding and are generally reported to the Internal Revenue Service on Form 1042-S. This information will not be linked to any of the study data and will only be used for payment purposes.

If you do not provide your SSN or ITIN, or complete the appropriate documentation noted above, we cannot issue you a payment for participation. However, you may still choose to participate in this study.

Will it cost you anything to be in this study?

If you enroll in this study, costs including transportation to the appointments at UNC as well as any incidental expenses, such as child care costs, will not be reimbursed by the study team. There will be no other costs to you for participating.

Who is sponsoring this study?

This research is funded by the National Institute of Mental Health (NIMH). This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You

can search this website at any time.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Option to Participate in Additional Studies:
You may be asked to participate in additional testing sessions, which may or may not be part of the current study. Study participation details will be explained to you at the time we contact you.

If you agree to be contacted to participate in future studies, you may initial the "YES" line. If you wish not to be contact for future studies, you may check the "NO" line.

_____ **YES** : I wish to be contacted about future studies.

_____ **NO** : I do NOT wish to be contacted about future studies.

Participant's Agreement :

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent