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ICF Aim 1,2, 5 HIC 2000020347

Cover page

NCT04236986

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Imaging Microglial Activation in PTSD with PET

Principal Investigator: Kelly Cosgrove, Ph.D., 2 Church Street South, Suite 511, New Haven, CT 06519

Funding Source: Cosgrove Departmental Funds, the National Center for PTSD PET contract, Cosgrove R01

Version: .19 (IRES.13)

All Participants

Aims 1,2, and 5 (Target Enrollment 40 Healthy Controls, 40 PTSD)

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to examine the effects inflammation on the brain and vascular system. The proposed study will fill a major gap in our understanding of neuronal inflammation in individuals with PTSD and other psychiatric disorders. This information may help in the development of better treatments for various populations. You have been asked to take part because you either have PTSD or are a Healthy Control who has experienced a traumatic event.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to take part in Aim 1(Option 1) of this study, you will have one MRI (magnetic resonance imaging) scan and one [^{11}C]PBR28 PET brain scan. If you participate in Aim 1, you have the option to participate in Aim 2 (Option 2) of this study where you will have an additional PB28 scan and we may use lipopolysaccharide (LPS), also known as endotoxin, a substance produced by bacteria to activate your immune system. When

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endotoxin is injected into a person, the immune system "believes" that bacteria have entered the body, and an immune response happens. Your immune system acts as if you have been infected, although you actually have not been infected. In some respects this is similar to a vaccine. Vaccines also activate the immune system without causing an infection. From prior studies we know that endotoxin causes symptoms similar to the flu, such as chills, body aches, headache, and tiredness. Sometimes it can cause nausea. The effects of endotoxin are very short-lived compared to having the flu; these symptoms will only last 2-4 hours. We want to measure what happens in the brain when people feel like that. You also have the option to participate in Aim 5 (Option 3) if you participated in Aim 2. In Aim 5 you may have up to 2 additional PBR28 scans within 21 days of Aim 2.

Study personnel will inform you which aims of the study we would like you to enroll in by initialing below. Please initial below as well to acknowledge which aim(s) you are agreeing to participate in.

Option 1 (Aim 1): One single PBR28 scan

Participant Initials_____Study Personnel Initials_____

Option 2 (Aim 2): an additional PBR28 scan with administration of endotoxin

Participant Initials_____Study Personnel Initials_____

Option 3 (Aim 5): up to an additional 2 PBR28 scans if you complete Option 2

Participants Initials_____Study Personnel Initials_____

Description of Procedures

Screening

If you agree to participate in this study and indicate this by signing this consent form, you will undergo screening at the 2 Church Street South, Connecticut Mental Health Center (CMHC), and the Yale University PET Center. Screening involves an interview with a member of the research team, a physical and neurological exam, drawing of blood samples for testing, and an electrocardiogram. Women will have a pregnancy test at screening and at the beginning of each PET and MRI scan day . You will be asked questions about psychiatric or medical problems you may have had including medication allergies. All this information will determine if you are eligible to participate in the study. Any new significant findings will be provided to you. If you are eligible, you will be scheduled for the study days as illustrated above. If you participate, you must agree not to take any drugs that will affect your mind for one week before and during the PET study, please discuss all medical prescriptions you may be on with study personnel prior to participation in the study. We will discuss this during screening. We also ask that you not take medications such as aspirin, acetaminophen (Tylenol), ibuprofen (Advil, Motrin), naproxen (Aleve), or celecoxib (Celebrex) for 3 days before the PET scans, including corticosteroids and immunosuppressant drugs. No subject will be asked to stop taking medication to participate in the study and no currently prescribed medications should be stopped without consultation with your physician. If you need to use any prescription or over-the-counter medications during this study, we ask that you tell us. If you take any medication without speaking to us first, this may disqualify you from the study.

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MRI

For the second visit (duration 1 hour), you will have a Magnetic Resonance Imaging scan at The Anlyan Center (TAC) on 300 Cedar Street, a member of the research team will accompany you to the MRRC for the duration of the MRI scan. The MRI will help us identify the different regions of your brain on the PET scan. MRI is a routine way to get pictures of inside of the body. We will review whether you carry on you any metallic objects. These objects will be held for you in a locked cabinet. You will be asked to lie still in the MRI scanner for about 20 minutes. The scanner looks like a deep tunnel. You will not be able to see out of it, but you will be able to hear us and be heard if you wish to say anything. You will hear a drumming noise when it is taking pictures of your brain. If you feel uncomfortable during the scan, we can end the scan at any time you wish to do so.

We may also perform sessions of testing of your memory, attention, and concentration. This will take approximately 1hr total. This may take place on the same day as the MRI scan or PET scans. During this visit, you may play a computer game called the Face Game. The goal of the Face Game is to win as much money as possible. You may earn money by quickly and correctly pressing one of two keys on the keyboard, each time you see a face on the screen. You will press one key if you think that the mouth on the face is long, and the other if you think it is short.

PET scan days

You will have up to 4 PET scans during this study. You may be asked to participate in a single PBR28 brain scan, or two PBR28 brain scans with an endotoxin challenge with the option to complete two additional PBR28 brain scans on subsequent days. If two PET scans cannot be done in one day or should one cancel you will be asked to return to complete the study on a different day.

For PET scan visits, you will come to the Yale University PET Center, 801 Howard Avenue, New Haven, at your pre- scheduled appointment time. A research nurse will check your vital signs and test for alcohol and drug use, and do a pregnancy test in women. A nurse or CNMT (certified nuclear medicine technologist) will place an IV (a plastic tube) in a vein in your arm to get blood samples during the study, and to inject the radiotracer during the PET scans.

An experienced physician or skilled advanced practice nurse (aprn)will insert an arterial catheter in your wrist area. The arterial catheter is about 2 inches long and looks like a regular IV tube, but it is inserted into an artery, not a vein. The blood flow in the arteries can tell us about your blood pressure. If an arterial catheter is in place, we can measure your blood pressure continuously. The other main reason to put in an arterial catheter is to be able to draw blood samples rapidly, repeatedly, and without causing you pain. Here is what happens when an arterial line is placed. First, the skin is cleaned with betadine solution (contains iodine). This skin cleansing with an antiseptic aims to reduce the microorganisms present on the skin and therefore reduce the risk of an infection. Second, the insertion area is numbed with a local anesthetic, so that you feel less pain when the catheter is inserted. You will probably just feel pressure but may also feel pain. This pain is usually like the pain you feel when an IV is placed and only rarely is it worse. Third, the catheter will be flushed regularly during your scan with a saline (a salt solution), which prevents clogging of the catheter with a blood clot. Fourth, after the catheter is removed, local pressure is applied for a minimum of 15 minutes to prevent bleeding under the skin. A pressure dressing (coban) and clear dressing (tegaderm) will then be applied and you will be asked to keep it clean and dry, avoid strenuous exercise, refrain from lifting heavy objects weighing more than 5 pounds, and to avoid repetitive movements for 48 hours, but do not submerge your hand and wrist in water for a full 72 hours. Since the catheter is in for a minimal period, there is low risk of infection.

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You will have up to 4 PET scans. Both scans take measures of inflammation in your body. Each scan takes about 2 hours. To do the PET scans we will administer a radiotracer, PBR28, one at the beginning of each scan. A radiotracer is a molecule that is labeled with a very small amount of a radioactive substance. It binds to molecules in your brain and can be detected by the PET scanner. We do not expect that you will feel anything when you receive the radiotracer. During the PET scans you will be asked to lie very still on a table. You will lie in the scanner for up to 2 hours at a time and you will have breaks in between scans. The PET scanning days will require up to 10 hours per day. If you ask, we can stop the scan at any time. The first PET scan is a baseline scan. Before your second PET scan, you may receive endotoxin. We will monitor your mood and psychosis symptoms throughout the study and more often after endotoxin administration via clinical assessments and questionnaires.

You will be asked to drink several glasses of water at the end of the scanning session to wash out the tracer. A light meal will be provided after the PET scans. After the PET scans you may leave. We ask you to abstain from physical exercise for 48 hours to avoid complications from the use of the arterial catheter. You will be provided with a telephone number you can call any time after the study if you need assistance for problems related to the study procedures. Should there be problems with the PET scanning equipment or production of the PET radiotracer, it may be necessary to schedule an additional arterial line placement and tracer injection to complete this study.

Cold Pressor Task

You may also be asked to participate in the cold pressor task during the study. In this task, we are investigating the body's physiological response to cold water. You will be asked to immerse your hand in a bucket of ice cold water maintained at 0-4°C. You will be told to raise your other hand when you begin to feel pain and to remove your hand from the water when you can no longer tolerate the pain. While your hand is immersed in water, you will also be asked to rate your pain on a scale from 0-100 and your heart rate and blood pressure will be monitored.

Dot Probe Task

You may be asked to participate in a computer test that assesses your ability to pay attention when presented with threatening and non-threatening images. Images will be displayed for a short period of time and you will be asked to follow a dot on the screen as quickly as possible by indicating if the dot is on the right or left side.

Genetic Testing

You are invited to allow some of your samples (called specimens) and related information to be stored (banked) for future research. Future research may look at your genes, which are the units of inheritance that are passed down from generation to generation. Genes are responsible for many things about you such as eye color, hair color, blood type and hundreds of other traits. Future genetic analysis may possibly include finding out the details of how your DNA is put together, such as whole exome or genome sequencing, or genome wide association studies (that is, looking at genes other than those associated with a specific disease). This may help researchers in the future learn more about how to prevent, find, and treat depression, bipolar disorder, psychotic disorders and PTSD. Variation in some genes is known to be related to risk for certain illnesses. We may also run the sample for polymorphism of a gene to see if you are a binder for the PBR28 tracer as there is a small portion of the population the tracer may not work on. Other genes we will be studying in your DNA may be shown at some point in the future to be related to illness. When your specimens and information are stored, we are careful to try to protect your identity from discovery by others. Your samples and information will receive a unique code (make them non-identifiable). These samples will be stored for future research de-identified for 7 years and then they will be made fully anonymous and stored indefinitely.

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Other researchers in the study team will only receive coded samples and information, and will not be able to link the code to you. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information.

Using your specimens for research will probably not help you. We do hope the research results will help people in the future.

Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.

Please sign below if you chose to participate in the genetic study. This is optional-if you choose not to allow this genetic testing you may still participate in the main study without any consequences.

The choice to take part is up to you. You may choose not to let us store and use your samples, and your participation in the rest of the study will not be affected by this decision. If you decide that your samples can be kept, you may change your mind at any time. Contact he study staff by phone at (203)737-6884 to let them know you do not want your samples used any longer. Your samples will either be destroyed, or made anonymous (the code linking them to you will be destroyed).

Authorization for genetic sampling, storing, and analysis

I agree to allow my samples and information to be stored and used for future research as described above: (initial your choice)

YES _____No_____

Risks and Inconveniences

Risks from this study include 1) risk associated with MRI, 2) risks associated with arterial and IV catheters and blood drawing, 3) risks associated with radiation, 4) risks associated with pregnancy and nursing, 5) risks of genetic testing, 6) risks associated with lipopolysaccharide, and 7) Risks associated with screening and evaluation .

1. *Risks associated with MRI:* Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of various parts of the body. The Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines. You will be watches closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them. There are some risks with an MR study for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this study because the strong

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magnets in the MR scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. You will also be asked to walk through a metal detector before entering the magnet room. Nothing metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet. We want you to read and answer very carefully the questions on the MR Safety Questionnaire related to your personal safety and tell us any information you think might be important. This MR study is for research purposes only and is not in any way a clinical examination. The scans performed in this study are not designed to find abnormalities. The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator or consulting physician will contact you, inform you of the finding, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a clinical MR exam and for that reason, they will not be made available for diagnostic purposes.

If you have worked with metal in the past, as a precaution, we may require that you receive orbital x-rays in order to rule out any foreign objects in your eyes, prior to participating in any MR scans.

2. *Risks associated with blood draws and arterial line:* Drawing blood and inserting an intravenous line (IV) into an arm vein are safe and standard medical procedures. Sometimes a bruise will occur at the puncture site and rarely a blood clot or infection will occur in the vein. You should <u>not</u> donate blood for at least 8 weeks after the study. The total volume of blood collected during this study will be up to 22 tablespoons (325 mLs), including blood drawn from your vein for the screening laboratories, and blood drawn from your vein and/or artery during the PET scan day. This amount of blood loss is safe for healthy persons.

Important: If you have a history of a bleeding disorder or are taking medication to thin your blood, you will not be allowed to participate in this study.

Putting in the plastic tube into the artery in the wrist area may cause bruising, and potentially infection. The arterial puncture may also cause spasm or clotting of the artery with a temporary decrease in blood flow, hematoma (a solid swelling of blood within the tissues), bleeding, or inflammation. If this occurs, signs and symptoms will dissipate over time, usually 24 to 72 hours after the event. In rare instances blocking of the artery, poor healing, infection, at the catheter insertion site may occur. Insertion of arterial catheters for sampling blood may be associated with mild-to-moderate pain or bruising at the puncture site. To minimize these risks, an experienced physician or aprn will insert the arterial line and a trained nurse will oversee subject care.

For two days following placement of the arterial line, you should check your wrist/arm daily. If you experience any excessive pain, tenderness, swelling, redness, drainage, skin color changes, numbness, pins and needles, or decreased strength in the arm that had the catheter, you should immediately call your study team or the PET Center Physicians Dr. David Matuskey at 203-370-1403 (pg) or Dr. Ming-Kai Chen 203-766-4241 (pg) (You will need to punch in your tel. number with area code followed by the, "#," sign).

You may experience a rare allergic reaction to the medicine used to numb your skin prior to placement of the

arterial catheter. If you have had a bad reaction to lidocaine, Novocain, or other anesthetic agents used to numb the skin in the past, please tell us about this experience before you go through the arterial line placement.

Severe allergic reactions can be life threatening. You will also be asked to abstain from using aspirin and other anti-inflammatory drugs (such as Motrin or Aleve) for 7-10 days before arterial line placement and 7-10 days after arterial line removal.

3. *Risks associated with radiation:* This research study involves exposure to radiation from positron emission tomography (PET). Please note that this radiation exposure is **not** necessary for your medical care and is for research purposes only.

The targeted amount of radiation you will receive during the PET scan session in this study is from up to two injections of PBR28 and from transmission scans or low dose CT scans of your head on either our HRRT camera or mCT camera. Although each organ will receive a different dose, the amount of radiation exposure you will receive from this study if you participate in is as follows:

Option 1- one injection of PBR28 =**0.437 rem on HRRT camera or .482 on mCT camera**

Option 2- two injections of PBR28= **.874 rem on HRRT camera or .964 on mCT camera**

Option 3-up to four injections of PBR28=**1.74 rem on HRRT camera or 1.93 on mCT camera**

This value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. This amount of radiation exposure is below the occupational guideline of 5 rem followed by Yale Radiation Safety Committee for research subjects. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. If you participate in all scans you receive about 6.43 years of background radiation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful and may cause cancer at any dose- even low doses such as those received during this research. **Should the scan cancel due to problems with the tracer or camera, and additional scan may be scheduled. If this happens post injection of radiotracer, this would add an additional 0.437rem(HRRT) or .482(mCT) to your total exposure, not to exceed 1.93 rem total for all participation.**

Please tell your study doctor if you have taken part in other research studies at Yale or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. You should consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body. Before you take part in any future studies that use radiation, you should also tell those study doctors about your participation in this study.

4. *Risks associated with pregnancy and breastfeeding:* WOMEN PLEASE NOTE: You should not participate in this study if you are currently pregnant, if you might become pregnant during the study or if you are breastfeeding, because we do not know how radiation may affect a fetus or whether it is present in breast milk.

You will be tested for pregnancy as part of the routine lab tests and at the beginning of each PET scan day. If the test is positive you will not be included in the study. Before starting the study, we will ask you to avoid becoming pregnant and ask what precautions you plan to take. If you change your mind about becoming pregnant or how you will avoid becoming pregnant, we ask that you tell us immediately.

5. *Risks associated with genetic (DNA) testing:* There is a risk that your information could be misused. The chance of this happening is very small. We have protections in place to lower this risk. There can also be a risk in uncovering genetic information about inherited traits. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Vary rarely, health or genetic information could be misused by employers, health insurance companies, and others. There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers (except those with fewer than 15 employees) to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Since the results of these genetic tests may allow prediction of risk of illness in some cases, we will keep the results confidential. Only scientists working on this research project will know the results; under certain circumstances the Yale Human Investigation Committee (HIC), may access this information. We will not make any of our lab results available to you, nor will we add them to your medical record. If you want to know your risk for genetic diseases, we will refer you to a genetics counselor. Sometimes, knowledge of genetic information may be a risk of discrimination in insurance coverage, jobs, or education opportunities. There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers, except those with fewer than 15 employees, to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

6. *Risks associated with lipopolysaccharide:* This is a substance of the cell wall of bacteria. Endotoxin is sterile and does not cause an infection, however it tricks the body's immune system into reacting as if there were an infection. The doses used in this study will produce flu-like symptoms in most subjects. These symptoms will be mild to moderate and only last 1-3 hours. We expect that after receiving endotoxin you will feel mild depressive symptoms, such as tiredness, nervousness, reduced interest, reduced appetite, and sleepiness. These symptoms should only last for 2-3 hours and then disappear. Although very unlikely, it is possible that these symptoms last longer. If this is the case, or if you have severe depressive symptoms, we would monitor you until the symptoms improve, or refer you for appropriate treatment. Endotoxin has been given to over 2,500 human subjects over the past 20 years. Among all these subjects, only 4 experienced serious side-effects. These 4 subjects had a slowing of the heart rhythm which had to be treated, but there was no lasting harm. This happened in two subjects with higher doses of endotoxin (twice as high as in this study), in two subjects with a similar dose to that used in the current study, and only in subjects who were either dehydrated (had too little fluid in the body) or who fainted easily. In this study we will ensure that you have enough fluid in your body and that you do not have a history of fainting in the past 10 years or any history of unexplained fainting. Importantly, the dose used in this study has never before caused any dangerous effects in human subjects, and no human subject receiving endotoxin at any dose has ever died or suffered any permanent damage. Some changes in blood pressure and heart rate have been found with higher doses, though such changes are unlikely to occur at the dose used in this study. It is possible that you are more sensitive to endotoxin than most people and you could experience an unpredictable reaction. If

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you have a history of asthma you may be more likely to have a reaction. This is a potential risk with any substance that is introduced into the body, including approved medications that you can buy over the counter. In the very unlikely event that a serious side-effect occurred, it would be treated appropriately. A certified health care provider (physician or aprn)and a nurse will be present during the entire endotoxin procedure. If you have any symptoms after you go home, you can contact a member of the research staff.

A review of the literature from 2007, describes all studies wherein endotoxin was given to human subjects. All articles were reviewed for any potential adverse effect, morbidity or mortality; however, no long-term morbidity or mortality was reported in these more than 1,000 healthy volunteers. A critical review of all the cases of endotoxin administration in human subjects concludes that endotoxin has been used for well over a century and has proven to be remarkably safe. All available data support that endotoxin administration in healthy human subjects is safe.

If you are currently depressed, you may experience a worsening of depressed symptoms upon endotoxin administration. This should resolve by the time you are done with PET scanning. We will monitor your symptoms with various questions and questionnaires. If your symptoms worsen significantly and do not resolve by study end, you may be admitted to an inpatient unit (CNRU) for overnight observation. If your symptoms are severe and you are danger to self or others, we may admit you to the hospital.

The effects of endotoxin on the symptoms of psychotic conditions (e.g., hallucinations, paranoia, etc) is not known. If you do experience any worsening of symptoms related to the endotoxin challenge you should let the study staff know immediately so that they can try to treat those symptoms as soon as possible. If you experience worsening of your symptoms when you have the flu, you should let the study staff know so that we can work with you to determine whether participation in the endotoxin challenge is safe for you.

Should there be problems with the radiotracer or PET camera, you may be rescheduled for an additional endotoxin administration. In this case, you will be scheduled for no sooner than one week after your first endotoxin administration.

7) *Risks associated with screening and evaluation.* During the screening interview, we will ask about psychiatric and medical history. Certain questions may make subjects uncomfortable or anxious. Only trained and experienced research assistants will perform these interviews, which will be done in a sensitive and gentle manner.

For participants with psychotic conditions: participation in this study will not cause a delay in treating your disorders with medication. Your psychiatrist and you can decide if and when you should start medication treatment for your condition. Medication treatment should not be delayed specifically because of study participation.

Benefits

There are no direct benefits to you. You may derive subjective benefit from volunteering to take part in a study for the advancement of scientific knowledge. The findings from this study may improve knowledge of what occurs in the brain when people suffer from depression, or bipolar disorder, psychotic disorders or PTSD, which may lead to better treatments for these conditions

Economic Considerations

You will be paid $50 for the MRI, $50 for the arterial line, up to $50 for baseline assessments($40 cog testing, $10 dot probe), $150 for the endotoxin administration, $350 for each PET scan, and a $100 completion bonus for a possible total of $1900. If you play the face game, you may be compensated for how much you win during the task up to $60. You will be paid $10 for each cold pressor task that you participate in. You are free to stop the study at any point. If you decide not to complete the study, you will be paid for the procedures completed up until that point. You may receive your payments in the form of a check, credit card, or cash. The check is typically mailed to the address you provided 2-8 weeks after completion of your study participation.

Main Breakdown	# of each	Payment	Max Total Amount per item
MRI	1	50$	50$
A-Line	1-3	50$	150$
PET Scan	up to 4	350$	1400$
Completion Bonus	1	100$	100$
Endotoxin	1	150$	150$
pre-scan Baseline Assessments	1	50$	50$
Total Payment			**1900$**

Reasonable transportation and parking costs will be reimbursed. Receipts must be submitted. Please contact the study coordinator prior to your study date to discuss your transportation plans and confirm that they will be appropriate for reimbursement. We may offer to pay for scan day taxi service for participating subjects who do not have access to a car or ride home. This decision will be made at the discretion of the PI.

According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that might directly identify you. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. The research team will only give this coded information to others to carry out this research study. Research materials will be stored in locked cabinets and on password protected computers. Data from this study will be destroyed after a period of 7 years. De-identified PET data will be kept for a minimum of 7 years.

If you decide to be in this study, you may be visiting the Connecticut Mental Health Center (CMHC) as part of your study procedures, some information about your participation in this research study may become part of your CMHC medical record that identifies you. If you do not already have a medical record at CMHC, one will be made for your visit. The information that will be entered into your medical record may include the collected information listed below.

The information about your health that will be collected in this study includes:

- *Research study records*
- *Medical and laboratory records of only those services provided in connection with this Study.*
- *Records about your study visits*
- *Medical and laboratory records of only those services proved in connections with this study*
- *Information obtained during this research regarding: Physical exams Laboratory results*, and *Psychiatric testing Results of brain scans*

Information about you and your health which might identify you may be used by or given to:

- *The U.S. Department of Health and Human Services (DHHS) agencies*
- *Representatives from Yale University and the Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for insuring research compliance. These individuals are required to keep all information confidential.*
- *Those individuals at Yale who are responsible for the financial oversight of research including billings and payments*
- *The Principal Investigator, Kelly Cosgrove, PhD*
- *The U.S. Food and Drug Administration (FDA)*
- *Governmental agencies to whom certain diseases (reportable diseases) must be reported*
- *Health care providers who provide services to you in connection with this study.*
- *Those providers who are participants in the Electronic Medical Record (EMR) System.*
- *Laboratories and other individuals and organizations that analyze your health information in*

connection with this study, according to the study plan.

- *Co-Investigators and other investigators*
- *Study Coordinator and Members of the Research Team*
- *Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study: the members and staff of the Human Investigation Committee that approved this study*

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and the Connecticut Mental Health Center are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate 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 action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIMH which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). 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 you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

<u>In Case of Injury</u>

- If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

- You do not give up any of your legal rights in signing this consent form.

- If you experience a research-related injury, contact the study doctor as soon as you are able.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. If you sign this authorization, you may change your mind at any time, but the researchers may continue to use information collected before you changed your mind to complete the research.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

This authorization to use and disclose your health information will never expire unless and until you change your mind and revoke it.

If you request to withdraw from the genetic study, we will destroy all records in our research files connecting your name with your DNA sample, so that it would only be studied anonymously from that point forward.

The researchers may withdraw you from participating in the research if necessary. Conditions under which you may be withdrawn from the research include:

Worsening of depressive symptoms or symptoms of psychosis that require hospitalization or that, in the PI's assessment put you at immediate risk.

Non-compliance with the study.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Connecticut Mental Health Center, Yale University, or Yale-New Haven Hospital.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to Dr. Kelly Cosgrove at the Yale Brain Imaging Program, 2 Church Street South, Suite 511, New Haven, CT, 06519.

If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form. By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

_____

Name of Subject

_____

Signature

Date:_____

_____ _____

Signature of Principal Investigator Date

or

_____ _____

Signature of Person Obtaining Consent Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale

Privacy Officer at 203/432-5919

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Kelly Cosgrove, (203)737-6969 or study physician David Matuskey (203)737-6316. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688

APPROVED BY THE YALE UNIVERSITY IRB 11/11/2020