COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 4 (2014-1)

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: *PBR28 brain PET imaging with lipopolysaccharide challenge for the study of microglia function in Alzheimer's disease*
Principal Investigator: Adam Mecca, MD, PhD, 1 Church Street, Suite 800, New Haven, CT 06510
Funding Source:

Invitation to Participate and Description of Project

You are invited to take part in a six months long research study designed to examine whether the immune system contributes to Alzheimer's dementia and to help determine how the brain reacts when the immune system is activated. In particular, we are interested in examining inflammation processes in the brain (neuroinflammatory and microglia markers). You are being enrolled in this study because you are either have Mild Cognitive impairment/Alzheimer's disease diagnosis or you are a healthy control. We will use lipopolysaccharide (LPS), also known as endotoxin, a substance produced by bacteria, to activate your immune system. When LPS 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 had 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.

We will use a type of brain scan called Positron Emission Tomography (PET), which involves injection of a tracer, a substance that is radioactive and that binds to receptors in the brain. The proposed study will fill a major gap in our understanding of Alzheimer's disease. This information may help in the development of better treatments for various populations. You have been asked to take part either as someone with Alzheimer's disease or as a healthy control.

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 this study, you will undergo a screening appointment. Before you are accepted into the study, you will be interviewed to find out if you qualify for the study. During the screening, you will have a medical evaluation including a medical history, physical examination, blood tests and urine tests, and an electrocardiogram (EKG) to ensure that you are medically healthy. You will also 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.

The blood sample will be tested for hepatitis and HIV in addition to the other required blood tests listed above for this study; this is to screen out patients who may be at increased risk of complication when exposed to lipo-polysaccharide. Results of these tests are confidential. A qualified physician will report any clinically important results of these tests to you in person. Positive hepatitis and HIV tests must be, by law, reported to the State

Department of Public Health and you will be given access to appropriate counseling and advice about the next steps to take. If any of these tests are positive, you will not be able to participate in the study. If you do not want to risk this possibility, you can refuse to have these tests done, but then you cannot participate in the study. The results of these tests will be handled according to HIPPA outlined below under the section on Confidentiality and Privacy, which among other things, explains the importance and commitment to protecting the privacy of your medical information.

The screening and baseline evaluation may occur over one or two days depending on your preference and our estimation of your ability to tolerate the long test days.

If you are eligible you will be scheduled for MRI and PET scans. If you participate you must agree not to drink any alcohol or take any drugs that will affect your mind for one week before and during the PET study. We also ask that you not take medications such as aspirin, ibuprofen (Advil, Motrin), naproxen (Aleve), or celecoxib (Celebrex) for 3 days before the PET scans. 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.

Genetic Testing

We will draw some blood samples for genetic testing at your screening. One tube will be used to measure radiotracer binding potential. Another tube may be used to look at other genes related to inflammation in the brain or response to endotoxin. The blood samples that are collected for DNA analysis will be kept until the sample is completely gone. The DNA samples will be de-identified.

MRI Scans

For the MRI scan, members of the research staff will escort you to the MRI Center at The Anlyan Center for Medical Research & Education (TAC). We will review whether you are carrying any metallic objects before approaching the magnet. These objects will be held for you in a locked cabinet to avoid having these objects fly toward the magnet when you come close to it. You will have an MRI scan of your brain. You will be lying still on a table inside the scanner. The scanner looks like a deep tunnel. You will be inside from your head to knees. 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 the scanner is taking pictures of your brain. The MRI scan takes up to 1 hour. The MRI scan serves as a map to help identify different parts of the brain on the PET scan.

We will 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 on another day prior to PET scans if that works better with your and staff schedule.

PET scans

You will be scheduled for two PBR PET scans as part of this study. However, prior to these scans, you may also complete what is called an amyloid PET scan to ascertain whether you have evidence of Alzheimer's pathology. If this scan has already been performed on a clinical basis or through another research study, then we will not need to repeat it. If it has not been completed, you will have an amyloid PET scan prior to completing the PBR PET scans. If you have the amyloid PET scan, you will have a total of three PET scans during this study.

PBR PET scan day/s

Here is your schedule on the scan day:

Step 1:

1. arterial line placement (there is no suitable reference region)

2. 1st scan – 120-min emission

Step 2:
3. LPS injection 3 hours prior to 2nd scan, fasting for 8 h prior to this injection
4. 2nd scan – 120-min emission

Steps 1 and 2 may occur over one or two days depending on your preference and our estimation of your ability to tolerate the long test days.

You will have up to two scans to gauge the activity of your brain immune system: Scans are done at baseline and 3 hours post endotoxin administrations. The timing of the additional scans will be determined by the camera and chemistry availability at the Yale PET Center. You will come to the Yale University PET Center, 801 Howard Avenue, New Haven, at your pre-scheduled appointment time. We ask that you do not eat anything after midnight the night before. Research personnel will test for alcohol and drug use, and do a urine pregnancy test if you are a woman. If you are pregnant or nursing you cannot take part in this study. A nurse or CNMT (certified nuclear medicine technologist) will place up to two IVs (plastic tubes) in a vein in your arm to get blood samples and allow for hydration with normal saline during the study and to inject the radiotracer during the PET scans.

A healthcare provider 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) so that it is sterile and protected against 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 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 and a clear dressing (tegaderm)will then be applied for a minimum of 15 minutes to prevent bleeding under the skin. You will need to keep it clean and dry. Do not exercise too much and do not lift heavy objects weighing more than 5 pounds. Avoid making the same movements for 48 hours. You may remove the pressure dressing at bedtime and the clear dressing after 48 hours, but do not put your hand and wrist in water for a full 72 hours. Since the catheter is in for a minimal period, there is a low risk of infection.

You will have 2 PET scans. During each PET scan you will be asked to lie very still on a table. Each scan takes about 2 hours. To do the PET scans we will administer a radiotracer at the beginning of each scan. For both scans we will use a radiotracer called PBR28. 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. The first PET scan is a baseline scan to measure the level of Translocator Protein (TSPO) and the activity of a cell called microglia in your brain. Microglia are the immune cells of the brain which are activated in response to inflammatory substances including the LPS which we are administering to you. When they are activated they produce more of the TSPO protein. Our hypothesis is that in Alzheimer's disease the microglia have a dysfunctional response to the stimulation. After the end of your first PET scan, you will receive endotoxin. Approximately four hours after the endotoxin you will have your second PET scan. This scan is identical to your first scan. The purpose of this second scan is to see whether the endotoxin caused any changes in the level of TSPO or the activity of microglia in your brain.

After the PET scans you will be allowed to leave. We may request that you return for additional PET scans. 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, tracer injection, and endotoxin administration to complete this study.

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. You will also receive a phone call 48 hours after the testing is done to make sure that you feel well. You will be asked a series of questions to make sure the exhaustion and length of testing as well as the administration of the medication has not caused you to become confused or disoriented. We do not anticipate this to be the case but the procedure is part of our standard "cognitive safety" protocol. We do not expect major adverse effects but we have contingency plans. If at any stage we feel there is a change in your health we may ask you to come to the research clinic or, in extreme cases, organize for you to be hospitalized.

If you are prescribed a blood pressure lowering medication by your doctor, we will ask you to bring the medication to the PET center on scanning day. We will take your blood pressure before the scan, and if it above the normal level we will ask you to take the medication to lower your blood pressure. If your blood pressure is above the normal level and you are not prescribed blood pressure lowering medication or you forgot to bring it with you, we will give you blood pressure lowering medication.

Optional Additional Blood draw during PET Scan visit for storage

During the PET scanning we would like to take more blood in small increments for banking and future testing. The blood will be obtained from one of catheters placed and will not require breaking the skin again. This part of the study is optional and it is not required to participate in the rest of the study. If you agree to this extra blood draw, four 10mL tubes of blood will be drawn. These blood samples will be deidentified and stored securely at Yale University. The samples will be used by only the investigators on this project; they will not be made available to outside researchers.

Genetic Testing

We will not store your genetic testing blood sample taken at the screening visit after we find out whether your microglia can be imaged using PET scan. In some people the radiotracer we use does not bind to the target we are studying. We screen for this prior to the scan using a genetic test. This sample from your screening visit will be destroyed after we perform this genetic test. We do not test for any other inherited condition. The result of our test is of no interest to your future health, however we have strong safeguards for privacy of genetic information. identifiers will be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies.

If you agree, we would like to draw blood and store some of your blood samples taken during PET scan visit and for future research and further investigations. This may help researchers in the future learn more about how to prevent, find and treat Alzheimer's disease. We will keep your specimens for as long as we can use them for research. Future research may look at genes other than the one we tested for during screening. A gene is the code in each cell in your body that controls the behavior of that cell. Parents pass the genes down to their children. Genes are responsible for many things about you such as eye color, hair color, blood type and hundreds of other traits. Future research may find out the details of how your DNA is put together. We may use your specimen for whole exome, genome sequencing, or genome wide association studies. That means we will look at all genes, not just those related to a specific disease. The cells may be injected into animals in some of the research.

We may share your specimen and information with other researchers at Yale university as well. We will do our best to protect your identity. We will code your samples and your information. We will only share coded samples and information with others. They will not be able to link the code to you. We follow strict security safeguards to avoid other people knowing your identity.

Allowing us to use your specimens for research will not help you. We do hope the research results will help people in the future. There is a risk that your information could be used in ways we did not plan. 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. Researchers may find out new health information about you or your family members. Very 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.

We will use your specimens and information for research only. We will not sell them. It is possible that the research will lead to development of products that will be sold for profit. If this happens, there is no plan to share any financial gain with you. We will not return research results to you or your doctor. If we publish the research results, we will not include your name or any other personal information.

The choice to take part in blood draw and sample storage is up to you. You may choose not to let us share your genetic and other information, and your care will not be affected by this decision. If you decide that we can share your information, you may change your mind at any time. Contact the study staff by phone or mail at Alzheimer's Disease Research Unit, 1 Church Street, Suite 600 New Haven, CT 06510 Telephone:203.764.8100 Fax: 203.764.8111 to let them know you do not want your genetic and other information shared any longer. We can either destroy the information or make them anonymous. we will destroy the code linking them to you too.

Your specimens and information will only be used for research and will not be sold. There is a possibility that this research may lead to development of products that will be commercialized. If this happens, there is no plan to share any financial gain with you.

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.

__ I agree to allow my genetic and other information to be stored and used for future research as described above
__ I do not agree to allow my genetic and other information to be stored and used for future research: (initial your choice).

Optional research: Cerebrospinal Fluid (CSF) Sample collection:

If agreed to participate in this portion of the study, up to 7 days after LPS injection, CSF will be collected via a lumbar puncture, which is the procedure of taking fluid from your spine in the lower back using a thin, hollow needle. The procedure will be performed by a trained clinician at the same visit or another additional visit based on your convenience and the availability of the performing physician. Before the lumbar puncture, your lower back will be cleaned and the clinician will inject a numbing medicine. The needle will then be inserted to withdraw the CSF. We will draw approximately up to 25cc (5 teaspoons) of CSF. The entire visit for this procedure should take one hour or less. If you agree to this extra lumbar puncture these samples will be deidentified and stored securely at Yale University. The samples will be used by only the investigators on this project; they will not be made available to outside researchers.

Optional research: Cog-State Neuropsychological Testing:

The neuropsychological testing will take place in one of the Alzheimer's Disease Research Unit, Church St. Research Unit, the Analyn Center, or the Clinical Neurosciences Imaging Center during the week before LPS injection and the second visit the week after the LPS injection. These assessments are performed with an ipad. You may be asked to remember a list of several words or to perform several ipad tasks. This will take approximately 1-1.5 hr total.

Risks and Inconveniences

Possible risks from participation in this study include 1) radiation exposure, 2) risks associated with lipopolysaccharide, 3) having intravenous lines placed into your veins, 4) having arterial lines placed in your arteries, 5) MRI scanning.

1. Radiation Exposure

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.
X-rays, CT scans, PET scans, bone scans, and MUGA scans use radiation to make pictures, or images, of parts of the body. Rarely, radiation can cause a new cancer. Sometimes chemicals are put into a blood vessel to make or improve the pictures. These can cause kidney injury, especially in people who already have some kidney damage.

If you DO NOT have an amyloid PET scan

The targeted amount of radiation you will receive in this study is from up to 2 [^{11}C]PBR28 scan (each 20 millicuries or less) and from transmission scans of your head used to help obtain the PET images.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from this PET study is equal to a uniform whole-body exposure of **1.628 rem**, which is the equivalent of approximately 5.5 years of natural environmental exposure. This calculated value is known as the "effective dose equivalent" and is used to relate the dose received by each organ to a single value. This amount of radiation exposure is below the annual limit of 5 rem set by the federal government for research subjects.

In situations where a PET scan is not successful following an injection (e.g. problems with the PET camera), you may receive one additional injection, up to a study maximum of 3 radiotracer injections. Although each organ will receive a different dose, the maximum amount of radiation exposure you will receive if you complete a third injection of [^{11}C]PBR28 is equal to **2.44 rem**, which is equivalent to approximately 8 years of natural environmental exposure**.**

If you DO have an amyloid PET scan

The targeted amount of radiation you will receive in this study is from up to 2 [^{11}C]PBR28 scan (each 20 millicuries or less), 1 [^{11}C] PIB scan (15 millicuries or less) and from transmission scans of your head used to help obtain the PET images.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from this PET study is equal to a uniform whole-body exposure of **1.888 rem**, which is the equivalent of approximately 6.2 years of natural environmental exposure. This calculated value is known as the "effective dose equivalent" and is used to relate the dose received by each organ to a single value. This amount of radiation exposure is below the annual limit of 5 rem set by the federal government for research subjects.

In situations where a PET scan is not successful following an injection (e.g. problems with the PET camera), you may receive one additional injection, up to a study maximum of 3 radiotracer injections. Although each organ will receive a different dose, the maximum amount of radiation exposure you will receive if you complete a third

injection of [^{11}C]PBR28 is equal to **2.70 rem**, which is equivalent to approximately 9 years of natural environmental exposure**.**

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 study. 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.

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.

2. Risks associated with lipopolysaccharide

This is a substance of the cell wall of bacteria. LPS 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. From prior studies we know that LPS (**at 2.5 times the dose we are using in this project)** causes symptoms similar to the flu, such as chills, body aches, headache, and tiredness. Sometimes it can cause nausea. The effects of LPS are very short-lived compared to having the flu; these symptoms will only last at most 2-4 hours.

We expect that after receiving LPS 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. LPS has been given to over 2,200 human subjects over the past twenty years. Among all these subjects, only four experienced serious side-effects. These four 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 LPS (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 their 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. Importantly, the dose used in this study has never before caused any dangerous effects in human subjects, and no human subject receiving LPS 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 LPS than most people and you could experience an unpredictable 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 physician and nurse will be present during the entire LPS 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.

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

3. Risks associated with IV line and blood draws

Mild discomfort can be expected with placement of an IV into a vein. Sometimes bruising or swelling will occur at the puncture site and on rare occasions a blood clot or infection. Very rarely fainting may occur. A total of no more than 8 ounces (half a pint) of blood will be drawn during the study. A pint of blood is the amount of a typical donation to a blood bank. You should not donate blood for at least eight weeks after the study.

4. Risks Associated with Use of an Arterial Catheter

Important: You cannot take part in the study, if you have ever had a bleeding disorder or are taking medication to thin your blood. Tell us if you have had a bad reaction to lidocaine, novocain, or other drugs used to numb the skin in the past.

The insertion of the arterial line may be painful and you can get bruises. The arterial puncture may cause a spasm. You may get a clot and your blood flow will slow down for a little while. You can get hematoma (swelling of blood within the tissues). The site can bleed or get inflamed (become red, swollen, hot, and painful). These feelings will go away after some time, usually 24 to 72 hours after the procedure. Rarely, you may experience blocking of the artery. The insertion site may not heal as fast or you may get infection. This is why a healthcare provider will insert the arterial line and a trained nurse will look after for you.

Check your wrist and arm every day for two days after the study visit with the arterial line.

Call right away your study team or the PET Center Physicians, Dr. David Matuskey at 203-370-1403 (voice mail pager) or Dr. Ming-Kai Chen 203-675-0120 (cell), if you notice any of the following:

- You feel a lot of pain;
- Your wrist or arm is tender, swollen, or red;
- You see some blood or other fluids coming out of the injection site,
- The color of your skin changes,
- Your arms feel numb,
- You feel pins and needles in your arm,
- Your arm that had the catheter does not feel as strong.

You may experience a rare allergic reaction to the medicine used to numb your skin prior to placement of the arterial catheter. Severe allergic reactions can be life threatening. Do not take aspirin and other anti-inflammatory drugs (such as Motrin or Aleve) for 7-10 days before arterial line placement and 7-10 days after the study visit.

5. MRI Scan

Magnetic resonance imaging (MRI) uses magnetic fields and radio waves to take pictures of the body. Millions of people have had MRI scans with no known safety issues. MRI uses a strong magnet, which can pull strongly on some metals. These metals must not be brought into the scan room. They could be pulled towards the magnet and cause serious injuries if they hit you. People entering the scan room must remove all metal from their body, clothing and pockets. This includes jewelry, hearing aids, watches, cell phones, keys, coins, and wallets. Some metal objects could also heat up during the MRI, burning you. Electrical devices such as pacemakers could go wrong or stop working. You must also tell us if you are wearing anything that could contain metal. For example, some medication patches have a metal backing. Some clothing can contain metal fibers that could also heat up during the MRI. We will therefore ask you to fill out an MRI safety form to check if you have anything in your body which might be dangerous in the MRI. It is very important that you fill out this form accurately and ask if you are unsure about anything.

During the MRI scan, you may feel uncomfortable or worried. When the MRI scanner is making pictures, it makes loud tapping, buzzing, and beeping noises. Without protection, this could damage your hearing. We will give you

with earplugs and/or headphones to reduce the sound to a safe level. While the scanner is making noises, we will not be able to hear you. We will give you a squeeze bulb for you to contact us.

This MR study is for research purposes only and is not in any way a health care examination of the brain. The scans performed in this study are not designed to find abnormalities. The principal 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 health care 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 principal 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 only 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 health care MR exam and for that reason, they will not be made available for health care purposes.

6. Genetic Information

There is a risk that if people other than the researchers get your genetic information, your information could be misused. We have strict privacy and confidentiality protection procedures in place to lower this risk, so the chance of this happening is very small. To help prevent this, your name will not be included with your samples or your genetic information. There can also be a risk in uncovering genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Very 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 generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

• Health insurance companies and group health plans may not request your genetic information that we get from this research.

• Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

• Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

However, this federal law does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

7. Risk of Taking Anti-Hypertensive Medication

There is a small risk that taking a medication to lower your blood pressure may cause your blood pressure to drop below the normal level. If this happens and you are asymptomatic then we will monitor you at the PET center until your blood pressure reaches a normal levels again. If you are symptomatic i.e. have some slight nausea or dizziness, then we may give you some intravenous hydration as a way of increasing your blood pressure. If low BP causes severe symptoms such as fainting or vomiting, or if the blood pressure does not improve with fluid, we will send you to the emergency department at Yale New Haven Hospital.

8. Risks with optional CSF Collection

This involves putting a needle between two spine bones to get to the fluid that surrounds the spinal cord. This can cause headache. Rarely, removing the fluid causes the brain to shift, which can cause brain injury or death

You will probably feel a brief pinch or sting when the numbing medication is given. You may feel brief pressure or pain when the spinal needle is inserted or re-positioned. During the procedure, the needle may touch one of your spinal nerves and cause a tingling feeling, like a light electrical shock running down one of your legs. The needle will not touch or damage the spinal cord.

Some people develop a headache after having a lumbar puncture. Sometimes the headache can be severe and accompanied by nausea and neck pain. These headaches generally last 24 to 48 hours and go away on their own. Pain medication may help, but you are also advised to lay flat for several hours after the procedure, which may help to ease the headache. On average, 1 to 3 out of 10 people who undergo a lumbar puncture may develop a headache. In some cases, a leak of cerebrospinal fluid may develop after a lumbar puncture. The symptom of this is a headache that will not go away after 1 to 2 days. The need for intervention for this leak is rare, but if needed will be arranged by the principal investigator, Dr. Adam Mecca. Some people may be feel nauseous and lightheaded during and/or after the procedure. If this occurs, you will be asked to continue to lie down until you are feeling better.

There are two rare but potentially very serious complications from a lumbar puncture. If you have a mass in your brain, there may be a small risk of a brain herniation, which means that the brain can shift and press on important tissues and blood vessels. After viewing you Brain MRI images, if there is any question that you have a brain mass, you will not be allowed to participate in this study. Also, very rarely, there can be bleeding between the outer membrane of the central nervous system and the skull. If you have a bleeding disorder, you will not be allowed in this study. Both of these complications can be fatal.

To reduce the possibility of any risks, the lumbar punctures will be performed by a trained and experienced physician.

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

Risks associated with confidentiality.
Although all information collected about your participation in this study will be protected by HIPAA and stored in locked cabinets and in password-protected computers, it is possible that information could be accessed by individuals who are not part of the study team. Such illegal access could have negative outcomes for the you with regards to employment, access to health insurance, and stigma. To reduce this risk, your identifiable research data, including recruitment and screening information and code keys, are stored on a secure database

Identifiers will be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent, if this might be a possibility.

Benefits

There are no direct benefits to you for participating in this study. We hope that your participation will benefit society in the future by helping us to learn more about Alzheimer's disease.

Economic Considerations

The following payments will be offered to you:

After the completion of the screening visit	$25
After the completion of the baseline assessments	$50
After the completion of the one-week follow-up	$25
After the completion of MRI	$50
After the completion of A-line	$50
After completion for each [^{11}C]PBR28 PET scan	$700 total
After completion of [^{11}C] PiB PET scan	$250
After the administration of lipopolysaccharide	$150
After the completion of 6- month follow-up	$150
After optional Cog-state testings(before and after LPS injection)	$50
After optional CSF donation	$350

Total: $1850

You will not receive additional payment if you consent to the additional blood draw during PET scanning. You will receive payment(s) via a Bank of America pre-paid debit card. Please note that your name, address, and telephone number will be shared with Bank of America for ePayments. After your first payment milestone (initial visit), you will receive a card in the mail which you will need to activate over the phone. Any subsequent milestones payments will automatically add additional funds to your card.

If you previously received payment via a Bank of America pre-paid debit card for participation in a study at the Yale Alzheimer's Disease Research Unit, you will receive payments for this study on the card you previously received. If you no longer have that card, please let the study staff know.

Payment received as a research subject may be taxable income to you. If payment is more than $600.00 in a calendar year, the study clinic is required to report this to the Internal Revenue Service (IRS). An IRS Form 1099 (Miscellaneous Income) will be issued to you and a copy sent to the IRS

Treatment Alternatives/Alternatives

The alternative to participating in this study is to not participate.

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 identifies you and your personal health information. This may include information that might directly identify you, such as your name. Identifiers will be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies without additional informed consent. 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. The link to your personal information will be kept for 7 years post study completion, after which time the link will be destroyed and the data will become anonymous.

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.
- The following information:
    - Records about phone calls made as part of this research
    - Records about your study visits
    - Information obtained during this research regarding:
      HIV / AIDS, hepatitis infection, sexually transmitted diseases, and/or other reportable infectious diseases, physical exams, laboratory, x-ray, and other test results, diaries and questionnaires, diagnosis and treatment of a mental health condition, use of illegal drugs or the study of illegal behavior
    - Records about any study drug you received

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
- The U.S. Food and Drug Administration (FDA)
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring 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, Dr. Adam Mecca
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Food and drug administration which has approved the use of lipopolysaccharide on an investigational basis.
- Study Coordinator and Members of the Research Team

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, Alzheimer's disease research unit and Yale PET Center is 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. However, by deciding to take part in a single or double blinded treatment

study and sign this permission form, you will not be allowed to look at or copy your study related information until after the research is completed.

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

Certificate of Confidentiality

If you decide to take part in this research study, you will be required to give us information about your personal health. We have obtained a Certificate of Confidentiality (CoC) issued by the National Institutes of Health. Once granted, the researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The protection offered by the CoC does not stop us from voluntarily reporting information about suspected or known sexual, physical, or other abuse of a child or older person, or a participant's threats of violence to self or others. If any member of the research team is given such information, he or she will make a report to the appropriate authorities.

Because this research is sponsored by the Department of Health and Human Services through the National Institute of Mental Health, staff from that and other DHHS agencies may review records that identify you only for audit or program evaluation. They cannot report anything that would harm you or other research subjects.

Even when a CoC is in place, you and your family members must still continue to actively protect your own privacy. If you voluntarily give your written consent for anyone to receive information about your participation in the research, then we may not use the CoC to withhold this information.
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In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor *Dr. Adam Mecca on (203)435-6178* as soon as you are able.
Yale School of Medicine and Alzheimer's Disease Research Unit do not provide funds for the treatment of research-related injury. 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 by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. You are free to choose not to take part in the additional volunteer visits during 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. 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. The researchers may withdraw you from participating in the research if necessary.

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 Yale University, Yale Hospital Research Unit, Yale New Haven Hospital, the Alzheimer's disease research unit or with the Yale PET Center.

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 *PI, Dr. Adam Mecca, 1 Church Street, 8th Floor, New Haven, CT 06510.*

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.

Optional Research:

I would like to participate in the "optional blood draw portion during PET scan visit" of the study (initial your choice):

_____YES _____No

I would like to participate in the optional Lumbar Puncture portion of the study (initial your choice):

_____YES _____No

I would like to participate in the optional cognitive assessment by Cog-State portion of the study (initial your choice):

_____YES _____No

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. Adam Mecca, 203-764-8100* 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.