Official Title: Stress and Inflammation in the Pathophysiology of Late Life Depression

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UNIVERSITY OF PENNSYLVANIA RESEARCH SUBJECT INFORMED CONSENT - INITIAL ASSESSMENT

Protocol Title:	Stress and Inflammation in the Pathophysiology of Depression
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Center for Neuroscience of Depression and Stress:	Tommaso Girelli Email: Tommaso.girelli@pennmedicine.upenn.edu Office Phone: 215-573-0083 (Scheduling/general questions)
Emergency Contact:	If you have a study related medical emergency, please contact the study staff or call 911

Why am I being asked to volunteer?

You are being invited to participate in a research study. We are contacting you because you expressed a potential interest in participating. Your participation is voluntary, which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. We will be recruiting about 100 subjects with depression and 50 subjects with no depression who are 18-80 years old to participate.

This consent form describes what this visit is about. You will be asked to complete a psychological assessment in order to determine your eligibility to participate in the research study. If you are eligible, you will be given the option of participating in the research study, and you will be asked to sign a second consent form. If you are not eligible, you will not lose any benefits

to which you are entitled. The research team will explain the study and answer any questions you may have. If you decide to participate, you will be asked to sign this form. If you have any questions, please ask the researcher. You will be given a copy of this form for your records.

The National Institutes of Health (NIH) is funding this research study.

What is the purpose of this research study?

The purpose of the initial assessment is to determine whether you are eligible to participate in this research study.

The purpose of this entire research study is to see if depression over a person's lifetime is related to the amount of inflammation in the brain and whether the amount of inflammation affects treatment response. We also want to determine whether taking an antidepressant affects the level of inflammatory proteins in the body. This information may help us find better ways to prevent episodes of depression.

How long will I be in the study?

The screening assessment will take approximately 90 minutes of your time. The electrocardiogram (EKG) will take about 10 minutes. Your participation in this phase (the screen) will take approximately 80 minutes. If you are eligible to participate in the entire study, your participation will last approximately 6 weeks. Overall, about 100 depressed participants and 50 non-depressed participants will be enrolled over a period of 4 years.

What am I being asked to do?

You will be asked to complete an assessment that consists of a psychiatric evaluation and some brief surveys. We will also measure your vitals (temperature, respiration rate, heart rate, and blood pressure) as well as record your height and weight at this visit.

We will also administer a blood draw to test for c-reactive protein (an inflammatory protein used to measure levels of inflammation), HIV, Hepatitis B, Hepatitis C, rheumatoid factor, and autoimmune diseases. We will perform an electrocardiogram (EKG) to assess your cardiovascular health. An EKG is a test that allows physicians to assess the heart's function. During the procedure, you will be asked to remove your shirt and

lie on a table. A technician will put electrode patches on chest to measure your heartbeat.

Continuation of the study for eligible participants:

If you are eligible to continue in the study, additional information will be provided to you about the procedures involved and you will be asked to sign a second consent form. The procedures of the study include receiving 1-3 blood draws, two MRIs, and additional neuropsychological testing. You may be asked to take either escitalopram with celecoxib, a non-steroid anti-inflammatory, or escitalopram and placebo for 6 weeks. The total duration of this study will be about 6 weeks long.

What are the possible risks or discomforts?

Clinical assessment: Common side effects of participating in this evaluation may include discomfort associated with disclosing personal information.

Electrocardiogram (EKG): You may feel some discomfort similar to pulling off an adhesive bandage when the technician removes the electrodes placed on your chest during the procedure.

Blood draw:

Likely/Common:

- There is a slight risk of bruising and infection at the site of the blood draw, as well as some discomfort during the blood draw.

Risk of Breach of Confidentiality: There is a rare risk of breach of confidentiality. Breaches in confidentiality could impact future insurability and/or employability.

Future Use of Data and/or Specimens

Your information and samples will be de-identified. De-identified means that all identifiers have been removed. The information [and samples] could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information and samples only applies to the information and samples collected on this study.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

In the event that EKG clinically significant abnormalities are discovered, we will inform you of the finding and refer you to your physician. You are not expected to gain any other benefits from this portion of the study.

In the event that we discover any abnormalities in your blood work, we will let you know of this. We request permission to contact your primary care provider to share the results of your blood work for further interpretation and to have follow up procedures to determine the accuracy of these findings. Should we receive abnormal results from your blood work, we will not include you in the study until we can verify the accuracy these results through follow up testing and discussions with your primary care provider. The study will not pay for the cost of this follow blood work or provider visit.

What other choices do I have if I do not participate?

You may choose to participate in the assessment or you may choose not to participate in the assessment. Your participation is voluntary. There is no penalty if you choose not to participate in the evaluation.

Will I be paid for being in this study?

There is compensation for this portion of the study if you complete the visit up to and including the blood draw at the end of the appointment. This compensation will be $10 and it is strictly for completing the blood draw. If you are eligible to continue with the study, you will be compensated further for subsequent participation.

If you drive, we will provide you a parking voucher to make the parking free. We cannot reimburse for the cost of gas. If you take public transportation, we can provide you $5 on your Greenphire ClinCard for your travel with proof of transportation (SEPTA ticket, Uber/taxi receipt, etc.).

Will I have to pay for anything?

There will be no cost to you associated with participation in the assessment.

What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries that are a direct result of taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the Study over? Can I leave the Study before it ends?

The assessment will take approximately 90 minutes of your time. You have the right to discontinue your participation in the assessment at any time during the evaluation. You can discontinue your participation by telling the researcher that you do not want to participate any longer. There is no penalty or loss of benefits if you decide to do so. Withdrawal will not interfere with your future care.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information

will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the funding sponsor (NIH) and the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- Hospital or University representatives, to complete Hospital or University responsibilities
- University Pennsylvania's Institutional Review Board (a committee that oversees the conduct of research involving human participants.) The Institutional Review Board has reviewed and approved this study.

To help protect your confidentiality, your data will only be transported by qualified study team members, and only during actual subject participation. Once all hard copy records are collected, they will be kept in a double-locked environment. Data collected during the study will be entered and stored in a password-protected database, accessible only to engaged study members. Electronic records will not be transported via external drives or any other means. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form.

What information about me may be collected, used or shared with others?

In order to enroll you into the study, schedule appointments, contact you for follow-up, we will ask you for your name, address, telephone number, alternate telephone number, date of birth, and social security number. This information will be used only for contact and payment (if you proceed through the screen and agree to participate in the full study) and will not be linked to any of your medical data or the information you provide during the assessments. All research data will be de-identified and assigned a randomly generated research identification number. All information obtained will be kept completely confidential and will be in locked files behind locked doors. Electronic data will be encrypted and password protected.

During your participation, you will be asked to answer questions about your medical history including questions about your physical and mental health. Information from your medical charts will be reviewed and documented for research purposes. Results from physical exams and assessments will be part of the research record. All research data will be de-identified and assigned a randomly generated research identification number. All information obtained will be kept completely confidential and will be in locked files behind locked doors. Electronic data will be encrypted and password protected.

What may happen to my information and samples collected on this study?

The data/sample was collected knowing the identity of the subject, but identifiers were removed. All samples will only be identified by the participants' randomly generated study ID number, and the date and time of the sample collection. If we write a report or article about this study or

share the study data set with others, we will do so in such a way that you cannot be directly identified

Your samples may be used to create products, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

Whole genome sequencing will not be conducted on your samples. Whole genome sequencing involves analyzing your entire personal genetic code.

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- Do the research
- Oversee the research
- To see if the research was done right.

Will I receive the results of research testing?

Most tests done in research studies are only for research and have no clear meaning for health care. Research results will not be returned to you because they would not be relevant to your health care.

Who may use and share information about me?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

An exception to confidentiality is if you report child abuse or neglect or if you report current suicidal or homicidal ideation of concern to the research team. Any information about child abuse or imminent intent to harm yourself or others will be reported to authorities, as required by law.

If you test positive for hepatitis or human immunodeficiency virus (HIV), by law we have to report the positive test results to the City of Philadelphia Health Department and/or the PA Department of Health. Personal identifiers such as name, sex, date of birth, address, and phone number will be reported. For more information about the requirements reporting infectious diseases to the City of Philadelphia Health Department, please visit https://hip.phila.gov/ReportDisease. For more information about the requirements reporting infectious diseases to the PA Health Department, please visit http://www.health.pa.gov/Your-Department-of-Health/Offices%20and%20Bureaus/epidemiology/Pages/Reportable-Diseases.aspx#.V620aZ3D9eU.

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice

to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

If you decide not to sign this form, it will not affect

- ï Your treatment or the care given by your health provider.
- ï Your insurance payment or enrollment in any health plans.
- ï Any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- ï You authorize the use of your PHI for this research
- ï Your signature and this form will not expire as long as you wish to participate.
- ï You may later change your mind and not let the research team use or share your information

If you revoke your authorization:

- ï The research team may only use and share information already collected for the study.
- ï Your information may still be used and shared if necessary for safety reasons.
- ï You will not be allowed to continue to participate in the study.

Can we contact you by email?

We would like to contact you by email for the purposes listed below. Some of these emails may contain health information that identifies you.

ï Setting or verifying your appointment

Only the research team will have access to your email communications. We will only communicate by email to send you the information listed above. For scheduling concerns and questions about participation, please call Tommaso Girelli at 215-573-0083. If you have a medical emergency, please call 911.

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

For general questions or for scheduling, please call Tommaso Girelli at 215-573-0083. If you have concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, please call Janet Stock at 215-746-5703. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

Do you agree to be contacted for future studies by the Center for Neuromodulation of Depression and Stress?

Yes *No*

_____ _____

Initials Date

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

_____

Name of Subject (Please Print)

_____

Signature of Subject Date

Name of Person Obtaining Consent (Please Print)

Signature Date

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT FORM AND HIPAA AUTHORIZATION FORM
-
CONTROL CONSENT

Protocol Title:	Stress and Inflammation in the Pathophysiology of Depression
Principal Investigator:	Yvette Sheline, M.D. Department of Psychiatry University of Pennsylvania 3700 Hamilton Walk Philadelphia, PA 19104-4283 Email: sheline@pennmedicine.upenn.edu
Center for Neuroscience of Depression and Stress:	Tommaso Girelli Email:Tommaso.girelli@pennmedicine.upenn.edu Office Phone: 215-573-0083 (Scheduling/general questions)
Emergency Contact:	If you have a study related medical emergency, please contact the study staff or call 911

Why am I being asked to volunteer?

You are being invited to participate in a research study. We are contacting you because you may have an interest in participating. Your participation is voluntary, which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. We will be recruiting about 100 subjects with depression and 50 subjects with no depression who are 18-80 years old to participate. You are being

asked to volunteer as a participant in the control group (those with no depression).

This consent form describes what this study is about, the possible risks and benefits of being in this study, and what we will ask you to do. The research team will explain the study and answer any questions you may have. You may also discuss it with your family, friends, or doctor. You may find some of the medical language difficult to understand, so please ask the research team about anything you would like to know. If you decide to participate, you will be asked to sign this form.
The National Institute for Health (NIH) is funding this research study.

What is the purpose of this research study?

The purpose of this entire research study is to see if depression over a person's lifetime is related to the amount of inflammation in the brain and whether the amount of inflammation affects treatment response. We also want to determine whether taking an antidepressant alone or with an anti-inflammatory affects the level of inflammatory proteins in the body. This information may help us find better ways to prevent episodes of depression.

We are asking about 100 depressed and 50 non-depressed people aged 18-80 to participate in this study. We would like to investigate the effect of taking a certain type of antidepressant medication, Selective Serotonin Reuptake Inhibitors (SSRIs), and a non-steroid anti-inflammatory on the levels of cytokines, which are inflammatory proteins in the body. The specific SSRI used in this study is escitalopram. We will ask you not to take any anti-depressant drugs or celecoxib, a non-steroid anti-inflammatory drug while you are participating in this study. You may use other types of anti inflammatory drugs, such as aspirin or ibuprofen, on a per need basis only, while you are participating in this study.

We want to compare the brain structure and blood of people without depression to those who have depression.

We will ask to take pictures of your brain using a magnetic resonance imaging scanner (MRI). MRI scans are commonly used by doctors to

look at structures in the body and are generally considered safe (see risks and discomforts section below).

You will also be asked to complete two blood draws (in addition to the blood draw you had completed at your screening visit) A portion of your blood will be saved and banked for use in future data analysis.

How long will I be in the study?

If you agree to take part in this study, your involvement will include several visits over about 6 weeks. Your participation will involve:

- A series of questions about your history and neuropsychological tests. This initial visit will last up to 2 hours.
- At-home actigraphy, which will not take anytime, you will be asked to simply wear an actigraph, which is a watch-like device for the course of the study
- Completing one initial and one final MRI. For both the initial and the final MRI you will be in the scanner approximately 1 hour.
- Optional saliva swab sample, which will be used for future analysis, including DNA analysis
- Two blood draws, which should take about 5 minutes each
- A final assessment visit, which involves a physical and neuropsychological assessment. This visit will last approximately 4 hours.

Stress and Inflammation in the Pathophysiology of Late-Life Depression – Schedule of Assessments			
Procedures conducted with all participants			
Procedure	**In-person Screen**	**Baseline (Wk 0)**	**Wk 6**
Informed Consent	X		
Screen, History	X		
Blood Draw	X	X	X
EKG	X		
MRI		X	X
Psychiatric evaluation	X		X

Neuropsychological tests		X	X
At-home actigraphy		X	X
Optional Saliva Collection		X	X

What am I being asked to do?

Neuropsychological testing, Clinical interviewing

We will conduct neuropsychological tests to assess your attention, concentration and memory. We will also ask you questions about your medical and psychological history. Some of these questions are of a sensitive nature as they inquire about past traumas including those of a sexual nature. If you believe you would like counseling services in reference to the events inquired about in these surveys please contact a member of the research team whose contact information is noted on the cover of this document.

MRI scans

We will ask you to complete 2 MRI scans of your brain. For the MRI, you will be asked to lie still on a padded table in the scanner while images of your brain are obtained.

Blood Draw

There will be 2 blood draws. During each blood draw, we will take about 2 tablespoons of blood from your arm via a needle.

In the event that we discover any abnormalities in your blood work, we will let you know of this. We request permission to contact your primary care provider to share the results of your blood work for further interpretation and to have follow up procedures to determine the accuracy of these findings. Should we receive abnormal results from your blood work, we will not include you in the study until we can verify the accuracy these results through follow up testing and discussions with your primary care provider. The study will not pay for the cost of this follow-up blood work or provider visit.

After the blood draw, we will ask you to rest for a little while to ensure you are not dizzy. After you have rested, we will discharge you. The second blood draw will occur during the same visit as the second MRI scan.

Cheek swab/saliva sample

We can obtain information about bacteria and health from a saliva sample. Your samples may be retained for future analyses that we have not yet planned, including DNA analyses. The results of these analyses will not be given to you. This is optional.

The cheek swab saliva sample will be stored for future analyses, including DNA analysis. This is optional

Vitals

We will record your blood pressure, heart rate, respiration rate, and temperature at each study visit.

Actigraphy

You will be asked to wear an actigraph, a watch-like device that monitors your activity. This is optional, and will occur for the duration of the study.

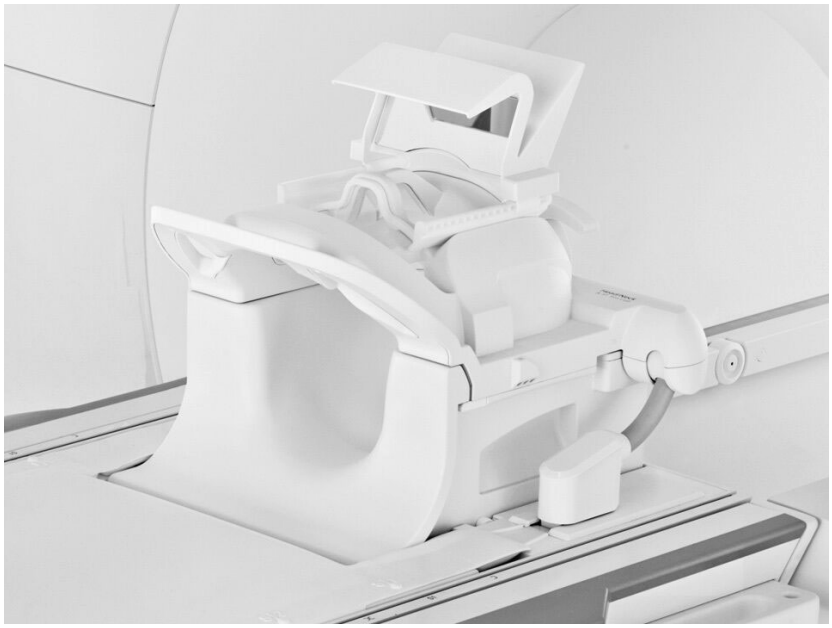
What are the possible risks or discomforts?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study. If you are injured, you should inform your treating physician that you are participating in this study.

Clinical interview and assessment: Some discomfort may be associated with the clinical assessments conducted in this study. Participants may experience emotional discomfort when answering some questions in the questionnaires or when talking about personal information. As noted above, some of these questions may be of past traumas including those of a sexual nature, therefore, if you feel you are in need of counseling services regarding these events, please notify a member of the research staff team, and they will provide you with information on counseling services. Participants may choose not to answer any of the questions.

MRI scan:

Likely/Common: You may experience claustrophobia (fear of enclosed spaces and/or anxious feelings accompanied by fast heart rate or shortness of breath) within the MRI scanner. In addition, the scanner produces a loud repetitive knocking noise during the study that some people find bothersome. If you have a problem with feeling uncomfortable while inside the scanner you may stop this study. To lessen the noise, earplugs will be provided. The picture below provides an example of a standard 64-channel head coil that will be placed on your head during the MRI scan. This coil is made for you to be able to look at the screen while being inside the MRI scanner.



Picture by Siemens Healthcare GmbH ©2020

Rare:

- Implanted medical devices and metallic foreign fragments inside your body may pose a risk if you were to enter the MRI magnet room. Devices such as Pacemakers, Internal Cardiac Defibrillators, Insulin Pumps, and other medical devices may also prevent you from safely having the MRI. Therefore, questions regarding medical and work history will be asked prior to your exam. Patients who have metallic devices in their bodies will not be permitted to be scanned using MRI. There are no known risk factors associated with MRI scans for healthy subjects.

- It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.
- Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. A negative pregnancy test will be required before a woman of child-bearing potential can participate in this study.

Blood draw:

Likely/Common:

- There is a slight risk of bruising and infection at the site of the blood draw, as well as some discomfort during the blood draw.

Actigraphy

There are no known risks of wearing an activity monitor.

Optional Saliva Collection and Saliva Cheek Swab Collection

Saliva collection is one way in which we can collect DNA. Your samples may be retained for future analyses that we have not yet planned, including DNA analyses. The results of these analyses will not be given to you. We do not anticipate risks due to the saliva collection.

Risk of Breach of Confidentiality: There is a rare risk of breach of confidentiality. Breaches in confidentiality could impact future insurability and/or employability.

Future Use of Data and/or Specimens

Your information and samples will be de-identified. De-identified means that all identifiers have been removed. The information and samples could be stored and shared for future research in this de-

identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information and samples only applies to the information and samples collected on this study.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You are not expected to get any benefit from being in this research study. We hope that in the future, other people might benefit from this study because it has the potential to greatly increase our knowledge in the treatment and prevention of depression.

What other choices do I have if I do not participate?

This is a voluntary study. You are not being treated for any condition; therefore, you do not need to seek alternate treatment if you choose not to participate.

Will I be paid for being in this study?

You will receive a total payment of $120 throughout the course of the entire study(including the $10 for the screening visit blood draw). If you choose to withdraw before the end, you will be paid incrementally in proportion to the degree of your participation and according to this schedule:

Initial assessment & consent process = $20;

Baseline MRI = $20;

Baseline Blood Draw = $10;

Final MRI and Blood Draw = $35;

Final psychological assessment = $25;

Optional Saliva Sample Collection = $10 (Total payment becomes $130 if you complete this portion)

Your payments will be given to you in the form of a Greenphire ClinCard at the end of your study participation. This is a reloadable prepaid card (similar to a debit/credit card) which allows funds to be available immediately. You can use it for in-store or online purchases by selecting the "Credit" option at check-out, or it can be cashed out by presenting to a teller at any MasterCard member bank (look for a MC logo on the bank window). Study staff will provide you with a "ClinCard Cardholder FAQ: US" document to help answer any questions you may have.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

If you drive, we will provide you a parking voucher to make the parking free. We cannot reimburse for the cost of gas. If you take public transportation (i.e. SEPTA Regional Rail or Norristown High Speed Line), we can provide up to $5 on your ClinCard per visit. If your transportation cost is greater than $5, we will still reimburse you up to $10, but we require a receipt.

Will I have to pay for anything?

You will not have any costs for participating in this research study. The administration of all procedures will be covered by the study. The scans, 2 blood draws, and any associated costs will be covered by the study.

What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

This research may involve risks that are currently unforeseeable. University of Pennsylvania investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator, Dr. Yvette Sheline at 215-573-0085.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. However, your personal participation in the study will probably last approximately 6 weeks. This study may be stopped by you or your physician at any time. It may also be stopped by the Principal Investigator, the study Sponsor, or the Food and Drug Administration (FDA) without your consent if:

- The Principal Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. There are no medical risks involved in the early termination of this study. Withdrawal will not interfere with your future care.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy.

An exception to confidentiality is if you report child abuse or neglect or if you report current suicidal or homicidal ideation of concern to the research team. Any information about child abuse or imminent intent to harm yourself or others will be reported to authorities, as required by law.

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the funding sponsor (NIH) and the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- Hospital or University representatives, to complete Hospital or University responsibilities
- University Pennsylvania's Institutional Review Board (a committee that oversees the conduct of research involving human participants.) The Institutional Review Board has reviewed and approved this study.
- Representatives from collaborating institutions

To help protect your confidentiality, your data will only be transported by qualified study team members, and only during actual subject participation. Once all hard copy records are collected, they will be kept in a double-locked environment. Data collected during the study will be entered and stored in a password-protected database, accessible only to engaged study members. Electronic records will not be transported via external drives or any other means. All biological samples will be transported by trained members of the research team directly to the appropriate facility where processing

and analysis of the samples will take place. All samples will only be identified by the participants' randomly generated study ID number, and the date and time of the sample collection. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form.
Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form.

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

What information about me may be collected, used or shared with others?

During your participation, you will be asked to provide your name, address, telephone number, email address, and your social security number (so that we may issue you a check to compensate you for participation). We will also obtain or create a medical record number (in the event that we need to order procedures and to access your medical records to collect information about your medical history). This identifiable information will be held in strict confidence and will be kept in password protected files behind locked doors. Your personally identifying information will not be linked to any of the data that is analyzed and reported. All data will be de-identified when

reported. You will also be asked to answer questions about your medical history including questions about your physical and mental health. Information from your medical charts will be reviewed and documented for research purposes. Results from physical exams and cognitive assessments will be part of the research record. All research data will be de-identified and assigned a randomly generated research identification number. All information obtained will be kept completely confidential and will be in locked files behind locked doors. Electronic data will be encrypted and password protected.

What may happen to my information and samples collected on this study?

The data/sample was collected knowing the identity of the subject, but identifiers were removed. All samples will only be identified by the participants' randomly generated study ID number, and the date and time of the sample collection. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified

Your samples may be used to create products, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

Whole genome sequencing will not be conducted on your samples. Whole genome sequencing involves analyzing your entire personal genetic code.

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- Do the research
- Oversee the research
- To see if the research was done right.

Will I receive the results of research testing?

Most tests done in research studies are only for research and have no clear meaning for health care. Research results will not be returned to you because they would not be relevant to your health care.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

If you decide not to sign this form, it will not affect

- Your treatment or the care given by your health provider.
- Your insurance payment or enrollment in any health plans.
- Any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- Your signature and this form will not expire as long as you wish to participate.
- You may later change your mind and not let the research team use or share your information

If you revoke your authorization:

- The research team may only use and share information already collected for the study.
- Your information may still be used and shared if necessary for safety reasons.
- You will not be allowed to continue to participate in the study.

Can we contact you by email?

We would like to contact you by email for the purposes listed below. Some of these emails may contain information that identifies you.

- Setting or verifying your appointment

Only the research team will have access to your email communications. We will only communicate by email to send you the information listed above.

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have).
Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

For general questions or for scheduling, please call Tommaso Girelli at 215-573-0083. If you have concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, please call Janet Stock at 215-746-5703. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

Do you agree to additional blood being collected (~4 tablespoons) for additional inflammatory analysis?

You may still participate in the study if you refuse to submit additional blood.

☐ *Yes* ☐ *No*

_____ _____

Initials Date

Do you agree to submit a **saliva cheek swab** sample as a part of this study?

You may still participate in the study if you refuse to submit a saliva cheek swab sample.

☐ *Yes* ☐ *No*

_____ _____

Initials Date

Do you agree to submit **saliva samples at each study visit** as a part of this study?

You may still participate in the study if you refuse to submit saliva samples.

☐ *Yes* ☐ *No*

_____ _____

Initials Date

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

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

_____

Name of Subject (Please Print)

_____

Signature of Subject Date

_____

Name of Person Obtaining Consent (Please Print)

_____

Signature Date

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT FORM AND HIPAA AUTHORIZATION FORM
–
STUDY GROUP

Protocol Title:	Stress and Inflammation in the Pathophysiology of Late-Life Depression
Principal Investigator:	Yvette Sheline, M.D. Department of Psychiatry University of Pennsylvania 3535 Market St., Suite 676 Philadelphia, PA 19104-4283 Email: sheline@pennmedicine.upenn.edu
Center for Neuroscience of Depression and Stress:	Tommaso Girelli Email: Tommaso.girelli@pennmedicine.upenn.eduOffice Phone: 215-573-0083 (Scheduling/general questions)
Emergency Contact:	If you have a study related medical emergency, please contact the study staff or call 911

Why am I being asked to volunteer?

You are being invited to participate in a research study. We are contacting you because you may have an interest in participating. Your participation is voluntary, which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. We will be recruiting about 100 subjects with depression and 50 subjects without depression who are 18-80 years old to participate.

This consent form describes what this study is about, the possible risks and benefits of being in this study, and what we will ask you to do. The research team will explain the study and answer any questions you may have. You may also discuss it with your family, friends, or doctor. You may find some of the medical language difficult to understand, so please ask the research team about anything you would like to know. If you decide to participate, you will be asked to sign this form. You are being asked to participate as a person with depression.

The National Institute for Health (NIH) is funding this research study.

What is the purpose of this research study?

The purpose of this entire research study is to see if depression over a person's lifetime is related to the amount of inflammation in the brain and whether the amount of inflammation affects treatment response. We also want to determine whether taking an antidepressant affects the level of inflammatory proteins in the body. This information may help us find better ways to prevent episodes of depression.

We are asking about 100 depressed and 50 non-depressed people aged 18-80 to participate in this study. We would like to investigate the effect of taking a certain type of antidepressant medication, Selective Serotonin Reuptake Inhibitors (SSRIs), in combination with a non-steroidal anti-inflammatory on the levels of cytokines, which are inflammatory proteins in the body and the number of people who stop being depressed. The SSRI used in this study is escitalopram, which is commonly used in the treatment of depression. This drug is approved by the U.S. Food and Drug Administration (FDA) to be given to people who meet criteria for major depression. We will ask participants to take a dosage of escitalopram over a period of about 6 weeks. During these 6 weeks you will come in for the same biweekly visits to receive the medication. We will also ask participants to take a dosage of Celecoxib, which can be used to treat inflammatory illness and has been shown to help treat depression when coupled with an anti-depressant. This drug is approved by the U.S. FDA to be given to people for inflammatory disease. Celecoxib is not used for the treatment of depression. Our study is hoping to show that anti-

depressant in combination with an anti-inflammatory helps people with depression more than an anti-depressant alone. We will ask participants to take a dosage of escitalopram + celecoxib over a period of about 6 weeks. Another group of participants will receive a placebo pill for about 6 weeks. A placebo is a harmless substance that does not contain treatment. Following the initial 6 weeks we will check to see if you were receiving escitalopram or placebo. If you were on placebo and you are still depressed you will offered treatment with 6 weeks of escitalopram + celecoxib.
We will ask to take pictures of your brain using a magnetic resonance imaging scanner (MRI). MRI scans are commonly used by doctors to look at structures in the body and are generally considered safe (see risks and discomforts section below).

You will also be asked to complete three-five blood draws A portion of your blood and spinal fluid will be saved and banked for use in future data analysis.

How long will I be in the study?

If you agree to take part in this study, your involvement will include several visits over about 6-12 weeks. Your participation will involve:

- A series of questions about your history and neuropsychological tests. This initial visit will last up to 1 hour.
- Completing one initial, one final MRI at 6 weeks, and an additional MRI at Open Label Week 6. For all MRI sessions you will be in the scanner approximately 1 hour.
- Completing 3-5 blood draws (2 of which to assess hematocrit levels). Individuals will have the option to provide an additional amount of blood for additional inflammatory state analyses.
- You may complete a nutrition assessment at baseline. A researcher will help you to recall all of the foods you have eaten in the past 24 hours.
- Optional saliva samples at baseline, week 1, 2, 4, and 6 both initially and during open label phase if applicable

- At-home actigraphy, which will not take any time, you will be asked to simply wear an actigraph, which is a watch-like device for the course of the study
- Optional saliva swab sample, which will be used for future analysis, including DNA analysis
- Taking a daily dose of the antidepressant escitalopram for about 6-12 weeks dependent upon which group you are initially randomized to.
- Follow-up visits to check your progress while taking escitalopram. There will be 3 follow-up visits over 6 weeks or 6 follow-up visits over the course of 12 weeks. These visits involve a psychological assessment and vitals assessment These visits last about 30 minutes each.
- A final follow-up phone call check-in will be conducted 6 months after study completion.

Stress and Inflammation in the Pathophysiology of Late-Life Depression – Schedule of Assessments							
Procedures conducted with all participants							
Procedure	**In-person Screen**	**Baseline (Wk 0)**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Optional 6 month follow-up**
Informed Consent	X	X					
Screen, History	X						X
Cardiac screening and history, EKG, nutrition screen	X						
Blood Draw	X	X		X		X	
MRI		X				X	
Neuropsychological tests		X				X	
Procedures at weekly visits:							
Drug Dispensed (Escitalopram + celecoxib or escitalopram + placebo)		X	X	X	X	X	
Psychiatric Evaluation	X	X	X	X	X	X	X
Vital Signs & Physical Assessment	X	X	X	X	X	X	X

Blood pressure monitoring (optional)	X		X			X	
Hematocrit & liver function blood test		X		X			
Saliva samples (optional)		X	X	X	X	X	
At-home actigraphy		X	X	X	X	X	

If you complete the study, your depression has not remitted, and you were on the escitalopram + placebo, we can offer you six weeks of escitalopram + celecoxib, and end your participation or we can keep you enrolled in the study and dispense escitalopram + celecoxib in the same way, where you return every one-two weeks for more and complete the appropriate assessments for which you will be compensated.

What am I being asked to do?

Neuropsychological testing, Clinical interviewing

We will conduct neuropsychological tests to assess your attention, concentration and memory. We will also ask you questions about your medical and psychological history. Some of these questions are of a sensitive nature as they inquire about past traumas including those of a sexual nature. If you believe you would like counseling services in reference to the events inquired about in these surveys please contact a member of the research team whose contact information is noted on the cover of this document.

MRI scans

We will ask you to complete 2-3 MRI scans of your brain. For the MRI, you will be asked to lie still on a padded table in the scanner while images of your brain are obtained.

Saliva Sample

You will provide saliva samples for microbiome analysis. This is optional.

Blood Draw

We will take about 2 tablespoons of blood from your arm via a needle.

If you have a CRP level 2: 3.0mg/L you may be eligible to provide additional blood for analyses. The purpose of this additional blood collection would be to evaluate an individual's inflammatory state. This additional analyses would require taking an additional ~4 tablespoons of blood.

After the blood draw, we will ask you to rest for a little while to ensure you are not dizzy. After you have rested, we will discharge you.

Administration of escitalopram and celecoxib or escitalopram and placebo

Patients will be randomized into one of two groups, those taking escitalopram and celecoxib and those taking escitalopram and a placebo. Random assignment and chance procedures means that we might use methods like flipping a coin to assign participants to a particular group. You will be asked to take the assigned medication for 6 weeks. The pills are taken orally. The researchers will not know if you are receiving the drug or the placebo.

- In one group, participants will take up to 20mg daily dose of escitalopram, a commonly used anti-depressant, along with celecoxib, a non-steroidal anti-inflammatory, at 400 mg/day for 6 weeks.

- In the other group, participants will take up to 20 mg daily dose of escitalopram, a commonly used anti-depressant, along with a placebo. A placebo is a harmless, inactive substance that looks like the anti-depressant drug but contains no actual medicine.

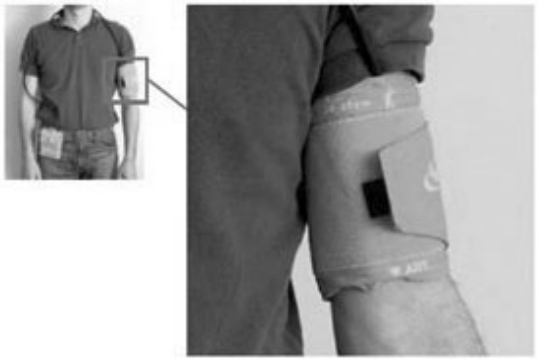
You have a 50/50 chance of being assigned to either group. The experimenters will dispense the escitalopram or placebo pills to you at each visit. You will also receive a paper with instructions on how much to take and you will receive phone calls from research staff to make sure that you understand the procedures and the dosing schedule, as well as to evaluate whether or not any drug related side

effects are occurring. The physician may adjust the dosage you receive.

When you have completed the study, the researchers will determine which group you were assigned to and they will share this information with you. Those receiving escitalopram + placebo who are still depressed at the end of the initial phase will be offered treatment with escitalopram + celecoxib following the same dosing schedule as participants who received escitalopram + celecoxib initially (200 mg in AM, 200 mg in PM). These participants will not re-complete the baseline visits, but will be asked to return for drug visits again (weeks 1, 2, and 4) as well as final visits (LP/blood draw and MRI/neurocognitive testing).

Blood Pressure Monitoring

You may be asked to participate in continuous 24-hour ambulatory blood pressure monitoring (ABPM) before the start of the study to establish a baseline, one to two weeks after the start of the study; and at the end of the study. This will involve taking home a blood pressure monitoring device for 24 hours. During a 24-hour period you will wear a blood-pressure monitoring cuff around your non-dominant arm connected to a recorder, please see picture below, which will be for example attached to your belt. The cuff will self-inflate and take your blood pressure and heart rate every 20 minutes during the day (6 am-10 pm) and every 30 minutes at night (10 pm-6 am).



We will ask you to keep a diary of your activities during this time, most importantly we need to know the times when you fall asleep and when you wake up.

Urine Samples

Urine spot samples may be collected at biweekly visits. We will look in these samples for breakdown products of fats associated with the drug effects of celecoxib. This is optional.

Liver Function Test (LFT)
Celecoxib has been associated with increased risk for people with hepatic (liver) impairment. At the baseline visit of the study, we will draw blood to perform a liver function test. If your liver is found to be impaired, you will no longer be able to participate in this study.

Hematocrit Blood Test
Celecoxib has been associated with an increased risk for bleeding in the stomach and/or small or large intestine. At the baseline/screening for the study, one or two weeks into the study, and at the end of this phase, we will test if your hematocrit levels are decreased in a blood sample. This test are important to look for possible bleeding in your digestive system. We will explain how this test works and what kind of foods, red meat or radish for example, not to eat before the test. If hematocrit levels are abnormal, you may not be able to participate in the study or if this occurs during the study we have to consider discontinuing your participation.

Cheek swab/saliva sample

We can obtain information about bacteria and health from a saliva sample. Your samples may be retained for future analyses that we have not yet planned, including DNA analyses. The results of these analyses will not be given to you. This is optional.

The cheek swab saliva sample will be stored for future analyses, including DNA analysis. This is optional

Actigraphy
You will be asked to wear an actigraph, a watch-like device that monitors your activity. This will occur for the duration of the study.

Vitals

We will record your blood pressure, heart rate, respiration rate, and temperature at each study visit.

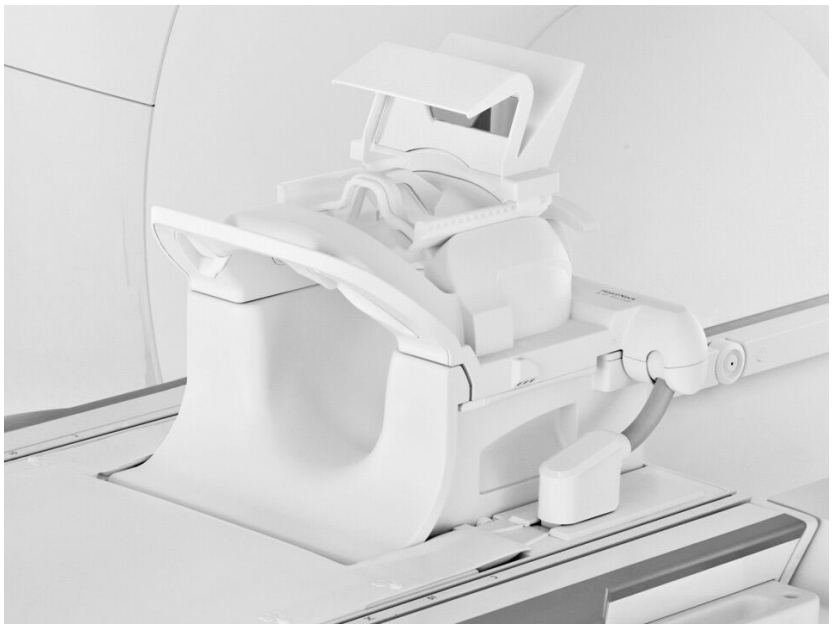
What are the possible risks or discomforts?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study. If you are injured, you should inform your treating physician that you are participating in this study.

Clinical interview and assessment: Some discomfort may be associated with the clinical assessments conducted in this study. Participants may experience emotional discomfort when answering some questions in the questionnaires or when talking about personal information. As noted above, some of these questions may be of past traumas including those of a sexual nature, therefore, if you feel you are in need of counseling services regarding these events, please notify a member of the research staff team, and they will provide you with information on counseling services. Participants may choose not to answer any of the questions.

MRI scan:

Likely/Common: You may experience claustrophobia (fear of enclosed spaces and/or anxious feelings accompanied by fast heart rate or shortness of breath) within the MRI scanner. In addition, the scanner produces a loud repetitive knocking noise during the study that some people find bothersome. If you have a problem with feeling uncomfortable while inside the scanner you may stop this study. To lessen the noise, earplugs will be provided. The picture below provides an example of a standard 64-channel head coil that will be placed on your head during the MRI scan. This coil is made for you to be able to look at the screen while being inside the MRI scanner.



Picture by Siemens Healthcare GmbH ©2020

Rare:

- Implanted medical devices and metallic foreign fragments inside your body may pose a risk if you were to enter the MRI magnet room. Devices such as Pacemakers, Internal Cardiac Defibrillators, Insulin Pumps, and other medical devices may also prevent you from safely having the MRI. Therefore, questions regarding medical and work history will be asked prior to your exam. Patients who have metallic devices in their bodies will not be permitted to be scanned using MRI. There are no known risk factors associated with MRI scans for healthy subjects.
- It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.
- Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. A negative pregnancy test will be

required before a woman of child-bearing potential can participate in this study.

- A MRI scan requires you to be in a partially enclosed space inside the scanner. Some people may find this to be uncomfortable and claustrophobic. You need to inform the doctor ordering the scan, or the study staff, if you suffer from claustrophobia. The MRI scanner produces different types of noises during a scan. Since the noise level can be loud, you may be given special earplugs to reduce the noise. The MRI scanner has an intercom which allows the technologist to talk to you and to hear you during the scan. You will be able to hear the technologist talking to you during the scan even if you wear earplugs.

- A MRI scanner has a strong magnet which attracts certain metals. If anyone has these types of metal in their body, the MRI's strong magnetic field can cause them to move which may cause injury. The MRI will not be performed on anyone having these types of metal in their body. To prevent an injury, you will be asked questions or given a form requesting information about any metal in your body and if you work with metals. Some dyes in tattoos and permanent eyeliner contain metals which may move during the MRI scan causing the area with the tattoo to become irritated and swollen.

- No metal objects are allowed to be brought into the MRI scan room at any time, because the MRI magnet will quickly and strongly pull those items into the scanner. To prevent any injury to patients and staff and any damage to the MRI scanner, you will be asked to remove all jewelry and clothing containing metal before you enter the MRI scan room. Also, since the MRI magnet will erase credit cards, they must not be taken into the scan room. Once you are positioned in the scanner, the door to the room will be closed to prevent anyone with any metal object entering the scan room.

- Before you are scanned, you must tell the MRI technologist if there is any chance that you may be pregnant. Your pregnancy status needs to be determined. If you are pregnant, then consultation with your physician is required before having an

MRI scan. You should provide your physician with a copy of this research protocol.

Blood draw:

Likely/Common:

- There is a slight risk of bruising and infection at the ite of the blood draw, as well as some discomfort during the blood draw.

Risk of Breach of Confidentiality: There is a rare risk of breach of confidentiality. Breaches in confidentiality could impact future insurability and/or employability.

Escitalopram:

Likely/ Common:

Nausea, sleepiness, headache, dizziness, tremor, diarrhea, nervousness, dry mouth, increased sweating, insomnia, and ejaculation failure.

Less common:

Rash, agitation, decreased sex drive, vomiting, stomach upset, and fatigue.

Rare:

Constipation, loss of appetite, and vision abnormalities, which may include blurred vision and sensitivity to light.

Abrupt cessation of taking Escitalopram may cause withdrawal symptoms such as dysphoric mood, irritability, agitation, dizziness, anxiety, confusion, headache, and lethargy. To prevent this, a tapered dose will be provided following the final LP.

Celecoxib:

Celecoxib has been associated with an increased risk of cardiovascular events in people with cardiovascular disease. To minimize this risk we are excluding anyone with significant cardiovascular risk factors. We have included a consultant on the study who is an expert in the use of celecoxib.

Celecoxib has also been associated with increased risk for gastrointestinal bleeding and liver failure. For this reason, you must tell us if you have a history of ulcers or GI bleeding. We will ask you not to participate if you have impaired liver function.

Likely/Common: upset stomach, diarrhea, bloating, gas, dizziness, nervousness, headache, runny or stuffy nose, sore throat, mild skin rash.

Less common: Chest pain, weakness, shortness of breath, slurred speech, vision or balance problems, discolored stools, coughing up blood, vomit, unusual weight gain, decrease in urination frequency, jaundice, loss of appetite, discolored urine, severe skin reaction.

Rare: Heart attack, intestinal obstruction or perforation, gastrointestinal bleeding, liver or kidney failure.

Actigraphy
There are no known risks of wearing an activity monitor.

Optional Saliva Collection
We do not anticipate risks due to the saliva collection.

Future Use of Data and/or Specimens

Your information and samples will be de-identified. De-identified means that all identifiers have been removed. The information [and samples] could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information and samples only applies to the information and samples collected on this study.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

Participants who receive escitalopram during the course of the study may experience mental health benefits such as alleviation from depression. However, not all depressed participants are expected to experience benefits from being in this research study. Participants receiving celecoxib may experience additional alleviation from depression as well as a decrease in inflammatory disease.

In the future, other people might benefit from this study because it has the potential to greatly increase our knowledge in the treatment and prevention of depression.

What other choices do I have if I do not participate?

This is a voluntary study. If you choose not to participate, you may seek information about other alternatives and treatments available by discussing options with your personal physician.

Will I be paid for being in this study?

Yes, the amount you are compensated will depend on whether or not you complete all study visits. If you complete all visits without the optional 6-month follow-up, additional blood, or saliva samples you will be paid $125 in total (including the $10 received after completion of the blood draw at the screening visit). If you choose to withdraw before the end, you will be paid incrementally in proportion to the degree of your participation and according to this schedule:

Initial assessment & full study consent process = $20

Baseline MRI = $20

Baseline Blood Draw = $10; Drug visits = $5 each

Final MRI = $25;

Week 6 Blood Draw = $10;

Final cognitive & psychological assessments = $25;

Optional additional blood collection = $50 (with saliva payment becomes $195; without saliva = $175)

Optional saliva samples ($20) (without optional blood collection payment becomes $145 with this option)

Optional 6-month follow up- $20 (upon completion of follow-up)

If you initially receive escitalopram and placebo and do not remit, you will be eligible to participate in the open-label phase of the study. If you complete all study visits you will receive an additional $95. In this phase you will receive the escitalopram and celecoxib and be compensated according to this schedule:

Drug Visits- $5 each

Final cognitive and psychological assessments- $25

Final MRI- $25

Blood Draw- $10

Optional Saliva Collection- $20

Your payments will be given to you in the form of a Greenphire ClinCard at the end of your study participation. This is a reloadable prepaid card (similar to a debit/credit card) which allows funds to be available immediately. You can use it for in-store or online purchases by selecting the “Credit” option at check-out, or it can be cashed out by presenting to a teller at any MasterCard member bank (look for a MC logo on the bank window). Study staff will provide you with a “ClinCard Cardholder FAQ: US” document to help answer any questions you may have.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to

the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

If you drive, we will provide you a parking voucher to make the parking free. We cannot reimburse for the cost of gas. If you take public transportation (i.e. SEPTA Regional Rail or Norristown High Speed Line), we can provide up to $5 on the ClinCard per visit. If your transportation cost is greater than $5, we will still reimburse you up to $10, but we require a receipt.

Will I have to pay for anything?

You will not have any costs for participating in this research study. The administration of all procedures will be covered by the study. The scans, blood draws, and any associated costs will be covered by the study.

What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

This research may involve risks that are currently unforeseeable. University of Pennsylvania investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator, Dr. Yvette Sheline at 215-573-0083.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. However, your personal participation in the study will probably last approximately 6-12 weeks dependent on whether you receive escitalopram + placebo initially. This study may be stopped by you or your physician at any time. It may also be stopped by the Principal Investigator, the study Sponsor, or the Food and Drug Administration (FDA) without your consent if:

- The Principal Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. There are no medical risks involved in the early termination of this study. Withdrawal will not interfere with your future care.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy.

An exception to confidentiality is if you report child abuse or neglect or if you report current suicidal or homicidal ideation of concern to the research team. Any information about child abuse or imminent intent to harm yourself or others will be reported to authorities, as required by law.

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the funding sponsor (NIH) and the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- Hospital or University representatives, to complete Hospital or University responsibilities
- University Pennsylvania's Institutional Review Board (a committee that oversees the conduct of research involving human participants.) The Institutional Review Board has reviewed and approved this study.
- Representatives from collaborating institutions

To help protect your confidentiality, your data will only be transported by qualified study team members, and only during actual subject participation. Once all hard copy records are collected, they will be kept in a double-locked environment. Data collected during the study will be entered and stored in a password-protected database, accessible only to engaged study members. Electronic records will not be transported via external drives or any other means. All biological samples will be transported by trained members of the research team directly to the appropriate facility where processing and analysis of the samples will take place. All samples will only be identified by the participants' randomly generated study ID number, and the date and time of the sample collection. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form.
Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information

is de-identified, it may be used and shared for other purposes not discussed in this consent form.

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

What information about me may be collected, used or shared with others?

During your participation, you will be asked to provide your name, address, telephone number, email address, and your social security number (so that we may issue you a check to compensate you for participation). We will also obtain or create a medical record number (in the event that we need to order procedures and to access your medical records to collect information about your medical history). This identifiable information will be held in strict confidence and will be kept in password protected files behind locked doors. Your personally identifying information will not be linked to any of the data that is analyzed and reported. All data will be de-identified when reported. You will also be asked to answer questions about your medical history including questions about your physical and mental health. Information from your medical charts will be reviewed and documented for research purposes. Results from physical exams and cognitive assessments will be part of the research record. All research data will be de-identified and assigned a randomly generated research identification number. All information obtained will be kept completely confidential and will be in locked files behind locked doors. Electronic data will be encrypted and password protected.

What may happen to my information and samples collected on this study?

The data/sample was collected knowing the identity of the subject, but identifiers were removed. All samples will only be identified by the participants' randomly generated study ID number, and the date and time of the sample collection. If we write a report or article about this

study or share the study data set with others, we will do so in such a way that you cannot be directly identified

Your samples may be used to create products, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

Whole genome sequencing will not be conducted on your samples. Whole genome sequencing involves analyzing your entire personal genetic code.

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- Do the research
- Oversee the research
- To see if the research was done right.

Will I receive the results of research testing?

Most tests done in research studies are only for research and have no clear meaning for health care. Research results will not be returned to you because they would not be relevant to your health care.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization

- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

If you decide not to sign this form, it will not affect

- Your treatment or the care given by your health provider.
- Your insurance payment or enrollment in any health plans.
- Any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- Your signature and this form will not expire as long as you wish to participate.
- You may later change your mind and not let the research team use or share your information

If you revoke your authorization:

- The research team may only use and share information already collected for the study.
- Your information may still be used and shared if necessary for safety reasons.
- You will not be allowed to continue to participate in the study.

Can we contact you by email?

We would like to contact you by email for the purposes listed below. Some of these emails may contain information that identifies you.

- Setting or verifying your appointment

Only the research team will have access to your email communications. We will only communicate by email to send you the information listed above.

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have).

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

For general questions or for scheduling, please call Tommaso Girelli at 215-573-0083. If you have concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, please call Janet Stock at 215-746-5703 If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

Do you agree to submit a **saliva cheek swab** sample as a part of this study?

You may still participate in the study if you refuse to submit a saliva cheek swab sample.

☐ *Yes* ☐ *No*

_____ _____

Initials Date

Do you agree to submit **saliva samples at each study visit** as a part of this study?

You may still participate in the study if you refuse to submit saliva samples.

☐ ☐

Yes *No*

_____ _____

Initials Date

Do you agree to participate in the 6-month follow-up visit ?

You may still participate in the study if you refuse to participate in the 6 month follow-up visit.

☐ ☐

Yes *No*

_____ _____

Initials Date

If eligible, do you agree to provide the additional blood needed to conduct additional inflammatory state analyses?

You may still participate in the study if you refuse to participate in the additional blood collection.

☐ ☐

Yes *No*

_____ _____

Initials Date

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the

University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

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

_____
Name of Subject (Please Print)

_____
Signature of Subject Date

_____
Name of Person Obtaining Consent (Please Print)

_____
Signature Date

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT FORM AND HIPAA AUTHORIZATION FORM
-
CONTROL CONSENT

Protocol Title:	Stress and Inflammation in the Pathophysiology of Depression
Principal Investigator:	Yvette Sheline, M.D. Department of Psychiatry University of Pennsylvania 3700 Hamilton Walk Philadelphia, PA 19104-4283 Email: sheline@pennmedicine.upenn.edu
Center for Neuroscience of Depression and Stress:	Tommaso Girelli Email:Tommaso.girelli@pennmedicine.upenn.edu Office Phone: 215-573-0083 (Scheduling/general questions)
Emergency Contact:	If you have a study related medical emergency, please contact the study staff or call 911

Why am I being asked to volunteer?

You are being invited to participate in a research study. We are contacting you because you may have an interest in participating. Your participation is voluntary, which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. We will be recruiting about 100 subjects with depression and 50 subjects with no depression who are 18-80 years old to participate. You are being