Official Title: Neurobiology of a Mutation in Glycine Metabolism in Psychotic Disorders

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Principal Investigator: Deborah L. Levy, Ph.D.

Site Principal Investigator: Deborah L. Levy, Ph.D.

Description of Subject Population: 4 members of a family in which two members have a mutation in glycine metabolism and two members do not.

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Why is this research study being done?

Dr. Levy and colleagues at McLean Hospital are investigating the effects of a specific genetic mutation on brain structure and metabolism.

Three magnetic resonance imaging techniques

1) Diagnostic Magnetic Resonance Imaging, 2) Diffusion Tensor Imaging at 3T (3T MRI & DTI) and 3) Magnetic Resonance Spectroscopy at 4T (4T MRS) are brain imaging techniques use magnetic fields and radio waves to give detailed anatomical and chemical pictures of the brain, but involve no radiation. These techniques allow us to measure the levels of chemicals in the brain that help brain cells communicate with each other. Some of these chemicals are glutamate, GABA, glycine, and glutamine. The purpose of this study is to examine the effects of a specific genetic mutation in glycine metabolism on brain levels of these chemicals. You have been asked to take part in this study because you have a specific mutation in glycine metabolism or are genetically related to someone who does. There may be up to 4 individuals enrolled in this study. The findings from these 4 individuals will be compared with large groups of adults diagnosed with bipolar disorder, schizophrenia, schizoaffective disorder, delusional disorder as well as from healthy adults. A condition of your participation in this study is that you also participate in other imaging studies and you will be asked to sign the consent forms for these studies as well. These other studies include Proton Magnetic Resonance Imaging and Spectroscopy Studies of Brain Chemistry in Bipolar Disorder, Schizophrenia, and Related

Disorders and Proton Magnetic Resonance Spectroscopy Studies of Glutathione and Gamma-aminobutyric Acid in Bipolar Disorder, Schizophrenia and Related Disorders, both of which are directed by Dr. Dost Ongur. These procedures will be done at McLean Hospital.

Magnetic Resonance Imaging and Spectroscopy
Magnetic resonance imaging and spectroscopy will also be used to measure brain glycine levels before and for 2 hours after a single oral dose of glycine. You will be asked to drink a mixture that contains up to about 30 grams of glycine and lemon juice. Glycine is an amino acid that exists naturally in the body. The typical diet contains about 2 grams of glycine/day. High-protein foods, such as fish, meat, beans, and dairy products, contain glycine. This procedure will measure how the brains of different people absorb and breakdown glycine. You have been asked to take part in this study because you have a specific mutation in glycine metabolism or are genetically related to someone who does. There may be up to 4 individuals enrolled in this study. The findings from these 4 individuals will be compared with large groups of healthy adult men. A condition of your participation in this study is that you also participate in another imaging study and you will be asked to sign the consent form for this study as well. The other study is Acute Glycine Pharmacodynamic Study, directed by Dr. Marc J. Kaufman. This procedure will be done at McLean Hospital.

Neuropsychological Tests
An additional procedure involves some neuropsychological tests that test things memory, attention, and planning. There may be up to 4 individuals enrolled in this study. The findings from these 4 individuals will be compared with large groups of adults diagnosed with bipolar disorder, schizophrenia, schizoaffective disorder, delusional disorder as well as from healthy adults.

Dr. Levy and colleagues at McLean Hospital are also investigating whether daily treatment with glycine will improve the beneficial effects of standard psychiatric drug treatment. There may be up to 2 individuals enrolled in this study. The findings from these 2 individuals will be compared while on glycine and on placebo (no active substance).

These studies are funded by the National Institute of Mental Health and the Brain and Behavior Research Foundation.

How long will I take part in this research study?
The imaging procedures at McLean will take place on several days. On one day, you will have a health screen involving a physical exam, urine toxicology screen, a pregnancy test (if necessary), an EKG, a movement examination, and routine medical blood tests (5 cc of blood, less than 1 teaspoon) and urinalysis. These procedures, along with the consenting procedures, will take about 3 hours.

On another day there will be a structural MRI (at 3.0 T), which takes 15 minutes, and a spectroscopy a MRI at 4.0 T, which takes one hour. The neuropsychological evaluation will take about 2 hours.

These procedures will be carried out on consecutive days on two occasions, before the glycine-placebo and open-label glycine trial, and at the end of the open-label glycine trial.

On a different day, there will be the glycine administration and spectroscopy scans using a 4T scanner. The pre-glycine (or baseline) scan takes one hour. After the glycine drink, the scan will last 2 hours. This procedure will be carried out before the glycine-placebo and open-label glycine trial only.

The glycine-placebo clinical treatment period will take 16 weeks. There will 6 weeks on glycine or placebo followed by 2 weeks of no treatment. There be another period of 6 weeks on glycine or placebo. If you received placebo during the first 6-week period, you will receive glycine during the second, and vice versa. After the second 6-week period, there be 2 weeks of no treatment.

The open label glycine treatment period will last for 6 weeks. You will be receiving glycine during this time. In the 5th week you will be flown to Boston to repeat the original scans (except for the glycine loading one) and other procedures, which will take about one week. Depending on scheduling issues, the three arms of the glycine clinical trial may occur in sequence or there may be a break in between them.

Length of the Study:

Part I:
Baseline measures will take up to 9 days including travel time
Part II:
Glycine-Placebo and Open-label Glycine Clinical Trials will take up to 16 weeks.
Part III:
Glycine Extension Study will take up to 8 weeks
Total Participation may take up to 25 weeks and 2 days including travel time.

What will happen in this research study?
Brain Imaging Scans at McLean Hospital
The MRI and MRS studies conducted at the McLean Hospital Brain Imaging Center will use scanners that have field strengths of 1.5T, 3T and 4T. This refers to the amount of magnetism used to collect the brain image. The magnetic resonance (MR) scanner looks like a large cylinder with a tube running down the center. You will be asked to lie down on your back on a foam-padded table and place your head into a special holder. The table will slide you inside the "hole" of the scanner. Soft foam rubber sponges may be placed on both sides of your head for comfort and to help keep your head from moving. Because the scanner contains a strong magnet, you will be asked to remove all metal objects from your person including, but not limited to: watches, rings, necklaces, bracelets, earrings, other body piercings, belts, loose change, wallet (with credit cards), cell phones, items of clothing containing magnetic materials (for example, underwire bras, certain types of zippers), and shoes. These items will be secured in a safe place until your scan is completed. You will be able to remain in your street clothes.

During the scanning procedure you will hear different sounds. Some of these sounds are loud and are part of the normal operation of the scanner. These noises vary with the type of scan being performed and include: sounds like a hammer hitting a piece of wood, repetitive buzzing noises, and long series of loud beeps. Some scans are silent. These sounds, or combinations of them, may be repeated several times. In both scanners, you will be given earplugs to help muffle the sounds of the scanners and you can also wear headphones. These headphones may further muffle the sounds, and they will allow you to more directly hear and speak to research staff and/or the technician. The longest session may be up to 50 minutes for the MRI scan and no more than 90 minutes for the MRS scan. You will be given breaks between scanning sessions. You can talk during the preparation time and during breaks, but you should not talk during the actual scanning process. During scans, you should try to remain as still as possible. The entire time that you will be in the scanner will be about 50 minutes or 90 minutes. When your session is over the technician will move you out of the scanner and assist you from the table. You may feel cramped inside the scanner, but in the 3T MR scanner a mirror has been placed so you can look out through the scanner "hole" into the scanning room. The technologist will be able to see and hear you at all times and you may end the procedure at any time. You will be given a squeeze-ball to hold while in both scanners. If you squeeze this ball, it will trigger an emergency alarm that will notify research staff and/or the technician that you need to be removed from the scanner.

Glycine Imaging Study
For the glycine imaging study, you will drink a single dose of glycine, which will be mixed with lemon juice. Before you consume the glycine drink, magnetic resonance spectroscopy will be used to measure levels of chemicals in your brain. This scan will take about 1 hour. . After you drink the drink, the scan will be repeated over the next two hours to measure changes in the levels of brain chemicals compared with baseline.

Beginning at midnight before the scan, you will begin fasting overnight. You will not eat or drink any foods or drinks that contain caffeine or smoke tobacco cigarettes on the day of the glycine study. When you come to McLean Hospital you will be asked to: 1) provide a urine sample, which will be analyzed for the presence of drugs of abuse, and 2) have your breath tested for alcohol and carbon monoxide. If you are a woman, your urine will be tested for pregnancy. You will not be able to participate if your pregnancy test is positive.

If your breath and urine screens are negative, you will undergo a baseline scan that will take about 1 hour. After that, a catheter (IV) will be inserted into your arm and blood will be drawn to determine baseline blood serum glycine levels. Then you will drink the glycine drink (250 ml, about 8 ounces) over a 10-minute period. After you drink the glycine drink, you will be positioned in the 4.0 Tesla scanner for 2 hours to undergo repeat scans. After each scan, a small blood sample will be drawn using the catheter in your arm. The amount of blood taken from you during each sample is 5 ml. There will be up to 10 blood samples, for a total of 50 ml, or about 2 tablespoons. These blood samples will be sent to the Nathan Kline Institute in Orangeburg, NY, where they will be analyzed for glycine levels. By signing this consent form, you give permission for Dr. Raymond Sukow and the Nathan Kline Institute permission to

provide Dr. Levy and her colleagues with the results of any blood samples that were analyzed at NKI.

The glycine drink is prepared using lemon juice and dissolved glycine powder. If you know that you are allergic to either of them you must let us know in advance. You will be asked to notify your personal physician that you will be participating in a study in which you will drink a mixture of glycine powder and lemon juice to make sure that you can safely participate. Your physician will be asked to provide a written statement indicating that he/she believes that there is no medical reason why you should not be able to drink lemon juice or glycine.

Neuropsychological Tests
The neuropsychological tests assess aspects of cognitive function like memory, attention, and planning.

Glycine-Placebo and Open-label Glycine Clinical Trials
After the first set of scans and procedures, you will receive either placebo or glycine for 6 weeks each, with two weeks of no extra treatment between the two treatment periods. Neither you nor the investigators will know which substance you are taking. You will continue to take your usual medications as prescribed. Your medications will not be changed as part of your participation in this study. By signing this consent form, you give Dr. Levy permission to be notified by your psychiatrist or internist if any of your medications changes, what changes occurred and the date on which the changes occurred.

Glycine comes in the form of a powder. The placebo will look and taste like glycine. It will consist of Isomaltulose (Palatinose®), a fully digestible, low glycemic, and tooth-friendly sugar that is lactose- and gluten-free.

The McLean Hospital Pharmacy will know whether you are receiving glycine or placebo. The McLean Pharmacy will prepare the appropriate dose of glycine powder or placebo in a re-closable plastic bottle. Each bottle will be marked with a fill line, indicating how much cold water should be added to the glycine or placebo dose. Each dose will include both the bottle of glycine or placebo and individual packets of lemon crystals and Splenda. Each dose will be labeled by the pharmacy with the date, dose (breakfast, lunch, dinner) and instructions (for example, fill the bottle with cold water to the fill line, shake, pour into a glass, add lemon crystals and Splenda. May be mixed with ice in a blender. Drink over a 15-20 minute period after a meal). Each dose will be in a self-contained package with instructions. Two weeks worth of doses will be FedEx'ed to you at a time by the McLean Pharmacy. The amount of glycine or placebo in each drink will gradually be increased until you are receiving 0.8 grams/kg/d of body weight. You will take a dose of glycine or placebo three times/day, after each meal. You will be given a log and asked to fill in the date and time of day that you took each dose of glycine or placebo.

While you are at McLean for the scans, you will meet with the pharmacist and Dr. Levy and we will review exactly what to do to make the glycine drink, including a demonstration.

<u>Phone Calls with Dr. Levy and Dr. Bodkin or Dr. Ongur</u>

At least once every week, you will receive a phone call from Dr. Levy to discuss how you are feeling. At the end of the first week of glycine or placebo, and at the end of weeks 3, 5, 9, 11, and 13 (more often if necessary), you will also be called by a study physician (Dr. Bodkin or Dr. Ongur) to assess how you are reacting to the glycine or placebo. Your psychiatrist will also be monitoring your clinical state and side effects throughout the study. Your internist will be informed when the glycine-placebo and open-label glycine periods begin.

You will also receive a phone call from Dr. Levy each week during the two weeks following glycine or placebo to discuss how you are feeling. You may be called by a study physician (Dr. Bodkin or Dr. Ongur) to follow up on your conversation with Dr. Levy if it seems medically necessary.

Clinical Assessments

In addition, every two weeks there will be a one-hour clinical assessment using a secure skype-like connection (weeks 2, 4, 6, 8, 10, 12, 14, 16). In order to protect your confidentiality, you will not be using your usual skype credentials. Partners Collaborative Media, which is affiliated with McLean Hospital, will create generic credentials for you and will ensure that your computers and web cameras are secure. You will be provided with any additional hardware and software that are needed at no cost to you. The movement examination will also be repeated using a secure skype-like connection at the end of weeks 6 and 14. The neuropsychological tests will also be re-administered at the end of weeks 6 and 14 in the city in which you live. You will be periodically weighed and your weight recorded.

Blood Work

Before the first treatment period, at the end of each treatment period, two weeks after the end of each treatment period, there will be blood work at a local medical center. This blood work is to measure the levels of various chemicals (such as glycine) in your blood as well as the level of psychiatric medications in your blood. The amount of blood drawn on each occasion will be 113 or 114 cc (less than 4 ounces). These blood samples will be sent to the Nathan Kline Institute in Orangeburg, NY, where they will be analyzed for various amino acid levels and psychotropic medication levels. By signing this consent form, I give permission for Dr. Raymond Suckow and the Nathan Kline Institute to provide Dr. Levy and her colleagues with the results of the analyses of any blood samples that were performed at NKI. I also give permission for the Clinical Laboratories at McLean Hospital and the medical center of the city in which I live to provide Dr. Levy and her colleagues with the results of any blood tests that were performed at their facilities. Throughout the study, you will continue to take all of your other medications as usual.

Open-Label Glycine

At the end of these 16 weeks, there will be two weeks of no treatment. This will be followed by 6 weeks when you are on glycine (this 6-week period may or may not occur immediately after you finish the 16 weeks on glycine-placebo combination). The McLean Pharmacy will prepare plastic containers containing glycine powder. Each container will be marked with a fill line, indicating how much water should be added to the glycine dose. Each dose will include both the container and individual packets of lemon crystals. Each dose will be labeled by the pharmacy with the date, dose (breakfast, lunch, dinner) and instructions (for example, fill the bottle with

cold water to the fill line, shake, pour into a glass, add lemon crystals and Splenda. May be mixed with ice in a blender. Drink over a 15-20 minute period after breakfast). Each dose will be in a self-contained package with instructions. Two weeks' doses will be FedEx'ed to you at a time by the McLean Pharmacy. The amount of glycine in each drink will gradually be increased until you are receiving 0.8 grams/kg/d of body weight. You will take a dose of glycine three times/day after meals.

Phone Calls with Dr. Levy and Dr. Bodkin or Dr. Ongur
At least once every week, you will receive a phone call from Dr. Levy to discuss how you are feeling. At the end of the first week of glycine, and at the end of weeks 3 and 5, you will also be called by a study physician to assess how you are reacting to the glycine.

You will also receive a phone call from Dr. Levy each week during the two weeks following glycine to discuss how you are feeling. You may be called by a study physician (Dr. Bodkin or Dr. Ongur) to follow up on your conversation with Dr. Levy if it seems medically necessary.

Clinical Assessments
In addition, every two weeks there will be a one-hour clinical assessment using secure skype-like video conferencing. You will be periodically weighed and your weight recorded.

Repeat Scans, Electroencephalogram, Neuropsychological Tests, Clinical Assessment, and Blood Work
At the end of week 5, you will be flown to Boston to repeat the original set of brain imaging scans (but not the one involving glycine), the movement examination, clinical assessment, and the neuropsychological test assessment. The same blood work described above will be repeated. The amount of blood drawn will be 113 or 114 cc (less than 4 ounces). These blood samples will be sent to the Nathan Kline Institute in Orangeburg, NY, where they will be analyzed for various amino acid levels and psychotropic medication levels.

Participation in each part of this study is completely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care you will receive at this institution. Should you choose to withdraw, you will notify Dr. Levy or the research staff. If you withdraw in the middle of the glycine study after blood has been withdrawn, Dr. Levy or her colleagues may request that you remain in the facility until it is safe for you to travel. This restriction is for your safety. Dr. Levy and her colleagues, or the FDA can remove you from the study at any time if it is determined that this is in your best interest or the best interest of the study.

Discontinuation of the Study
Although it is unlikely that you will experience side effects warranting permanent discontinuation of the study, it may be slowed down (slower dose increases, temporary discontinuation) if you develop side effects such as GI upset, nausea, or vomiting. If you develop side effects that make you too uncomfortable or that make it medically necessary to discontinue the study, the study will be stopped.

What are the risks and possible discomforts from being in this research study?

There may be unknown risks in taking part in the study.

Confidentiality
One potential risk is a breach of your confidentiality. This could lead your employer, insurance company, or others to find out that you participated in a research study.

Steps we take to prevent this are as follows:

Appropriate precautions will be taken to preserve confidentiality and your privacy. Your private health information is maintained in a secure manner and your identity is never associated with research records, which are assigned an alpha-numeric code that is kept in a password-protected file. However, there is some risk that identifying personal information could be shared or intercepted. Risks also include compromising identifying personal information on computers and compromising study documents with identifying information. These risks will be minimized by storing your data and personal information on a password protected computer or in a locked filing cabinet in a locked office that will be accessible only to study staff.

MRI/MRS
MRI/MRS technology does not use ionizing radiation. Instead, it uses strong magnetic fields and radio waves to collect the images and data.

There are no known hazards or risks associated with MR techniques. Significant risks may exist for people with:
Cardiac pacemakers
Metal clips on blood vessels (also called stents)
Artificial heart valves
Artificial arms, hands, legs, etc.
Brain stimulator devices
Implanted drug pumps
Ear implants
Eye implants or known metal fragments in eyes
Exposure to shrapnel or metal filings (wounded in military combat, sheetmetal workers, welders, and others)
Other metallic surgical hardware in vital areas
Certain tattoos with metallic ink (please tell us if you have a tattoo)
Certain transdermal (skin) patches such as NicoDerm (nicotine for tobacco dependence), Transderm Scop (scopolamine for motion sickness), or Ortho Evra (birth control)
Metal containing IUDs

If you are unsure whether you have any of these items in your body, you should know that most would have been implanted as part of a surgical procedure. So, trying to remember any past operations may help you remember. You will be asked whether you have any implanted devices or history of exposure to shrapnel or metal filings, and if so, you will not be able to participate in this study.

Significant risks also can arise if certain materials (many types of metal objects) are brought into the scanning area, as they can be pulled into the magnet at great speed. Such items can cause serious injury if they hit you. Therefore, these types of items are not permitted in the scanning area. You will not be allowed to bring anything with you into the scanning room. The MR exams are painless, and except for pulsating sounds, you will not be aware that scanning is taking place.

3T scanners are approved by the FDA for routine clinical studies in children or adults. Although there are no known risks from these scans, there could be adverse effects that are delayed or very mild, such that they have not yet been recognized. Most people experience no ill effects from these scans, but some people do report claustrophobia (fear of being in enclosed small spaces), dizziness, mild nausea, headaches, a metallic taste in their mouth, double vision, or sensation of flashing lights. These symptoms, if present, disappear shortly after leaving the scanner.

Unlike a standard clinical MRI scanner (1.5 or 3 Tesla), one scan of the present study will be conducted in a high field (4T) MRI Scanner. This scanner is not used for routine clinical studies in children or adults, but the FDA has determined (July 14, 2003) that scanners with a magnetic field strength of less than 8 Tesla (double this scanner) or less do not represent a significant risk to adults, children, or infants aged more than 1 month. There could be adverse side effects that are delayed or very mild, such that they have not been recognized. Most people experience no ill effects from 4T scans, but some people do report claustrophobia (fear of being in enclosed small places), dizziness, and the other symptoms described in the previous paragraphs. These symptoms, if present, disappear shortly after leaving the scanner. No serious effects have been reported to date at any site operating at 4T strength.

In rare cases, a very slight, uncomfortable tingling of the back due is induced in some people undergoing certain types of scans. If you experience this sensation, you are asked to report this immediately so the scan can be stopped. Although these precautions will avoid all known risks associated with MRI, this procedure may involve risks to you that are currently unforeseeable. The sounds that you hear inside the scanner are the normal operating sounds the scanner makes while it takes pictures of your brain. While they may be annoying, their intensity is not harmful to your hearing. However, you will be given a pair of earplugs to wear to muffle the sounds. You also may be asked to wear a set of headphones, which further reduces the noise level and permits the technician to speak to you.

Women of childbearing age:
While there are also no known risks for fetuses, the safety of MRI for pregnant women, women of childbearing potential, and nursing mothers has not been established. If you are a woman of childbearing potential, you must be using an IUD, oral contraceptive, or barrier methods or must be abstinent prior to each MRI scan. In addition, you must have a negative pregnancy test prior to each MRI scan. Nursing mothers may not participate in any brain imaging procedures.

Glycine
Glycine is a dietary supplement. Side effects that have been associated with glycine include fatigue, stomachache, and vomiting (>10% of subjects in a prior study). Very rarely, (<1% of subjects), individuals who have a genetic abnormality that prevents them from metabolizing glycine normally may develop dangerously high blood glycine levels. To our knowledge, you do not have such an abnormality. Glycine is generally well tolerated without any negative effects. In research studies in which people consumed doses of glycine similar to (and even higher) than those used in this study, and for longer time periods, blood glycine levels rose, but no side effects occurred. In prior research studies we have conducted, 2/14 (14.3%) people who consumed more than 30 grams of glycine at one time developed nausea and vomiting. For that reason, the maximum glycine dose used in the glycine imaging study is 30 grams. The glycine mixture contains 300 calories per serving for a total of 900 calories per day. You may gain weight.

You may receive a bruise at the site of the catheter and your arm may be sore for a few hours after the catheter sticks. There is also the risk of infection at the site of blood withdrawal, but standard aseptic techniques will be used making this an unlikely event (<1% of subjects).

Neuropsychological Test Procedures
No adverse effects of the neuropsychological procedures are expected, but the testing may be tiring.

Glycine-Placebo Treatment
During the glycine-placebo treatment period and the open label-glycine treatment period: When you are taking glycine, you may experience nausea and vomiting, but this is unlikely. In research studies in which people consumed the same dose of glycine (0.8 g/kg/d) side effects were not common. If you experience any side effects, you must report them to Dr. Levy immediately (617-855-2854 or page through the McLean Hospital operator at 617-855-2000) so the dose can be lowered or the treatment period ended. If you are unable to reach Dr. Levy, you may also contact Dr. Alexander Bodkin at 617-855-3186 M-F 9-5 (can also be paged through 617-855-2000), Dr. Dost Ongur at 617-855-3922 M-F 9-5 (can also be paged through 617-855-2000), or Dr. Marc Kaufman at 617- 855-3469 M-F 9-5. Should you experience vomiting, you should go to your nearest emergency room and tell the medical staff that you are taking glycine as part of a research study.

Blood Tests
During the glycine-placebo and open-label glycine phases of the study, you will receive multiple blood tests. You are asked not to donate blood for at least one month after completion of the study.

You will be told of any significant new findings that develop during the course of this study that may relate to your willingness to continue to participate.

You may end any of these procedures at any time without penalty to current or future treatment.

What are the possible benefits from being in this research study?
There are no direct benefits to participating in this research. The information obtained in this study may to explain the effects of a mutation in glycine metabolism on brain structure, function, and metabolism. One potential benefit of participating in this research is that structural scans obtained for this research will be analyzed by a radiologist and significant findings will be reported to you. An additional potential benefit is that glycine may reduce your psychotic symptoms and improve your cognitive abilities.

What other treatments or procedures are available for my condition?
You may choose not to participate in any of these procedures and continue to receive standard psychiatric care. The treatment provided in this study, Glycine, is a nutritional supplement that may be available to you without taking part in this study.

Can I still get medical care within McLean if I don't take part in this research study, or if I stop taking part?
Yes. Your decision won't change the medical care you get within McLean now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

It is possible that we will have to ask you to drop out before you finish the study. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?
Yes. You will be paid $2,000 for completing these procedures, $1,000 for completing the baseline procedures and $1,000 for completing the glycine treatment studies and the follow-up procedures. If you do not complete the study, you will be compensated for the procedures that you did complete. All of your travel, lodging, food and local transportation expenses will also be paid.

As an identifier for internal auditing purposes, your social security number is needed because you are receiving payment for participation in this study. McLean Hospital is required to inform the IRS of any payments to you as a subject in research studies in a given calendar year totaling $600 or more. If that occurs, you will receive a 1099 form at the end of the year. No information identifying why you received payment is communicated to either the Hospitals accounting department or the government. This information is kept strictly confidential.

What will I have to pay for if I take part in this research study?
Study funds will pay for the cost of all of the research procedures, including your travel, lodging, food, and local transportation expenses while you are participating.

What happens if I am injured as a result of taking part in this research study?
We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

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

For the blood draws at Bozeman Medical Center, McLean Hospital will not be involved in mitigation of any injuries that may occur.

If I have questions or concerns about this research study, whom can I call?
You can call us with your questions, concerns or complaints. Our telephone numbers are listed below. Ask questions as often as you want.

Deborah L. Levy, Ph.D., is the person in charge of this research study. You can call her at 617-855-2854. Dr. Levy is available M-F 9-5 and can be paged 24/7 through the McLean Hospital operator by calling 617-855-2000. You can also call Dr. Alexander Bodkin at 617-855-3186 M-F 9-5, Dr. Dost Ongur at 617-855-3922 M-F 9-5 or Dr. Marc Kaufman at 617- 855-3469 M-F 9-5. Any of these people can also be reached through the McLean Hospital operator (617-855-2000) 24/7. If you have questions about the scheduling of appointments or study visits, call Dr. Levy at 617-855-2854.

If you want to speak with someone **not** directly involved in this research study, please contact the McLean Human IRB office. You can call them at 617-855-2932.

You can talk to them about:
- Problems and questions that you may have
- Information that you may want
- Input or suggestions that you may have
- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?
Federal law requires McLean Hospital, its health care providers and researchers to protect the privacy of health information that identifies you. This information is called Protected Health Information. In the rest of this section, we refer to this simply as "health information."

If you decide to take part in this research study, your health information may be used within McLean and may be shared with others outside of McLean, as explained below.

In addition, to protect the study participants and prevent any potential risk to the participants' privacy, Dr. Levy will apply for a Certificate of Confidentiality from the Department of Health and Human Services. To reduce the possibility that information learned from DNA/RNA studies will affect the subject's access to health insurance or employability, no research study data will be included in the subject's medical records. Further, with the Certificate of Confidentiality from DHHS, the PI cannot be forced (e.g., by court subpoena) to disclose information that may identify a study participant in any federal, state, or local criminal, administrative, legislative, or other proceeding.

We have marked with a ☒ how we plan to use and share your health information. If a box is not checked ☐, it means that type of use or sharing is not planned for in this research study.

We will also give you the **McLean Hospital Notice for Use and Sharing of Protected Health Information.** The Notice gives more details about how we use and share your health information.

- **Health Information About You That Might be Used or Shared During This Research**

  ☒ Information from your hospital or office health records within McLean or elsewhere that may be reasonably related to the conduct and oversight of the research study. This may include information about hospital admissions or visits during this study, so that we know about any possible problems or side effects. If health information is needed from your doctors or hospitals outside McLean, you will be asked to give permission for these records to be sent to researchers within McLean.

  ☒ New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study

- **Why Health Information About You Might be Used or Shared with Others**

  The reasons we might use or share your health information are:

  - To do the research described above

- To make sure we do the research according to certain standards - standards set by ethics and law, and by quality groups
- For public health, and safety - for example, if we learn information that could mean harm to you or others, we may need to report this to a public health or public safety authority, or to specific individuals as required by law
- For treatment, payment, or health care operations

- **People and Groups That May Use or Share Your Health Information**

1. People or groups within McLean

☒ Researchers and the staff involved in this research study

☒ The McLean review board that oversees the research

☒ Staff within McLean who need the information to do their jobs (such as billing, or for overseeing quality of care or research)

2. People or groups outside McLean

☒ People or groups that we hire to do certain work for us, such as data storage companies, our insurers, or our lawyers

☒ Federal and state agencies (such as the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections) and other U.S. or foreign government bodies, if required by law or involved in overseeing the research

☒ Organizations that make sure hospital standards are met

☐ The sponsor(s) of the research study, and people or groups it hires to help perform this research study

☐ Other researchers and medical centers that are part of this research study

☐ A group that oversees the data (study information) and safety of this research study

☐ Other:

Some people or groups who get your health information might not have to follow the same privacy rules that we follow. We share your health information only when we must, and we ask anyone who receives it from us to protect your privacy. However, once your information is shared outside McLean, we cannot promise that it will remain private.

- **Time Period During Which Your Health Information Might be Used or Shared With Others**

- Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

- **Your Privacy Rights**
  - You have the right **not** to sign this form permitting us to use and share your health information for research. If you don't sign this form, you can't take part in this research study. This is because we need to use the health information of everyone who takes part in this research study.
  - You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing.

    If you withdraw your permission, we will not be able to take back information that has already been used or shared with others. This includes information used or shared to carry out the research study or to be sure the research is safe and of high quality.

    If you withdraw your permission, you cannot continue to take part in this research study.
  - You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study.

    In this research study, you may only get such health information after the research is finished.
- **If Research Results Are Published or Used to Teach Others**

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifying information **will not** be used for these purposes without your specific permission.

Informed Consent and Authorization
Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

_____ _____

Study Doctor or Person Obtaining Consent Date/Time

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.

- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject Date/Time

Consent Form Version Date: 11/11/2012