COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY SCHOOL OF MEDICINE (YSM) – YALE-NEW HAVEN HOSPITAL (YNHH)
YALE CENTER FOR CLINICAL RESEARCH INVESTIGATIONS (YCCI)
YALE MAGNETIC RESONANCE RESEARCH CENTER (MR-TAC)

CONNECTICUT MENTAL HEALTH CENTER (CMHC)
CLINICAL NEUROSCIENCES RESEARCH UNIT (CNRU) OF THE NATIONAL CENTER FOR POST-TRAUMATIC STRESS DISORDER (PTSD)

Study Title: Combining neurobiology and new learning: Ketamine and Prolonged exposure: A potential rapid treatment for PTSD
Principal Investigator (the person who is responsible for this research): Ilan Harpaz-Rotem, Ph.D. 300 George Street, New Haven 06511
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Research Study Summary:

- We are asking you to join a research study.
- The purpose of this research study is to look at the ability of a low dose of ketamine and one week of Prolonged Exposure (PE) therapy to reduce Post Traumatic Stress Disorder (PTSD) symptoms.
- This double-blind study will use midazolam as an active placebo medication. You will be asked to have two infusions during the course of PE therapy. You have a 1/3 chance of receiving a standard dose of ketamine, and 1/3 chance of receiving a lowered dose of ketamine, and a 1/3 chance of receiving the midazolam.
- Study procedures will include: **screening, two infusions with ketamine or midazolam drug, a 1-week course of psychotherapy, and up to 4 MRI scans. You may be asked to wear a portable physiotracker device during the screening and/or psychotherapy visits. You may also be asked to sign a separate consent form to allow the therapy sessions to be audio or video recorded.**
- **9** visits are required.
- These visits will take **up to 30** hours total.
- There are some risks from participating in this study. They include risks associated with ketamine or placebo (midazolam) administration, blood draws, MRI scanning, and discomfort associated with psychiatric interviews, questionnaires, and trauma-focused psychotherapy.
- You will not be allowed to drive or operate heavy machinery for at least 24 hours after completing the infusion (Please arrange to have someone drive you back home from the study site, or inform the study personnel, and the transportation will be provided to you.)
- This research may not have benefits to you directly. Ketamine may or may not help in reducing the severity of PTSD symptoms.
  Additionally, the information obtained through this study may help develop more effective treatments for those with PTSD.
- There are other choices available to you outside of this research. For those struggling with PTSD symptoms, several treatment options exist. Veterans may inquire about treatment at West Haven V.A. clinics, and non-veterans may be eligible for treatment at the Connecticut Mental Health Center at 34 Park St, New Haven.

- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Why is this study being offered to me?

We are asking you to take part in a research study because You have been asked to participate because you are currently suffering from PTSD, you are medically healthy, do not have any implanted metallic devices (e.g., pacemaker, orthodontic braces, or shrapnel), and have no recent heavy alcohol consumption or recreational drug use. We are looking for **120** participants to be part of this research study.

Who is paying for the study?

- National Institute of Mental Health (NIMH)
- Clinical Neuroscience Division, National Center for PTSD, Veteran's Health Administration
- Yale School of Medicine, Department of Psychiatry

What is the study about?

The purpose of this study is to examine the ability of a low dose of ketamine and one week of Prolonged Exposure (PE) therapy to reduce Post Traumatic Stress Disorder (PTSD) symptoms.

Ketamine is a medication approved by the Food and Drug Administration to be used as an anesthetic (medication used to sedate people during surgery). The dose of ketamine used in this study is lower than the dose typically used for surgery, so it is unlikely that you will fall asleep during the study. We are using ketamine to study its anxiolytic (anxiety relieving) effects.

What are you asking me to do and how long will it take?

If you agree to take part in this study, you will be asked to participate in the following procedures and to discuss your participation in this study with your primary clinician. First, you must have a screening visit. This screening period will allow us to make sure the study is suitable for you. If eligible, you will be assigned to one of the experimental groups described: (1) an active PE treatment + two infusions of a standard dose of ketamine, or (2) an active PE treatment + two infusions of a lowered dose of ketamine, or (3) an active PE treatment + two infusions of midazolam.

On your next visit, you will meet with a clinician and begin to discuss your traumatic experiences. Soon thereafter, you will again meet for a therapy session before undergoing a magnetic resonance image scan (MRI) of your brain. During the MRI scan or immediately thereafter, you will either receive the investigational drug ketamine (standard dose = 0.5 mg/kg or lowered dose = 0.2mg/kg infused over 40 minutes through the vein) or midazolam, a medicine that is not ketamine, but does produce some cognitive effects similar to ketamine. In order to ensure that the anticipation of receiving the investigational drug ketamine is not affecting your

brain, you nor the study staff will not know which infusion you are receiving. Over the next 5 days, you will meet with your clinician for 90-minute therapy sessions. Subjects assigned to receive two infusions of ketamine or midazolam will receive the same drug each time. All subjects will receive the full course of PE therapy. After your final therapy session, we will again scan your brain using MRI. We also ask that you return for two more scans and to monitor your PTSD symptoms 30 days and 90 days after receiving treatment.

Visit 0 (Days -90 to 0) –Screening:

This study screening visit will take place either at Yale or at the West Haven VA Hospital, 950 Campbell Ave, West Haven CT 06516. You will sign a separate VA screening protocol consent form associated solely with this visit if screened at the VA.

This visit will last approximately 4 hours. During the screening period, you will be required to:

• Have the study explained to you by one the study investigators and you will be asked to sign this consent form in order to participate in the study.
• If you decide to be in this study, and you will be visiting the Yale Center for Clinical Investigation (YCCI) Church Street Research Unit (CSRU), a medical record will be made for you if do not already have one. The information that will be entered into your medical record will include the following: 1. Demographics information. 2. Medical evaluation and physical exam, 3. Psychiatric evaluation, 4. Laboratory tests, and 5. Progress notes about your participation in the study.
• Have your blood pressure and pulse (how fast your heart beats) measured and your temperature taken. The blood pressure and pulse measurements will be taken twice, while you are standing (for approximately 3 min) and while you are in a semi-reclining position.
• Have a physical examination.
• Have your height and weight measured.
• Have your medical, medication and surgical history taken. For you own safety, you must disclose all of your past and present diseases, allergies, and medical conditions of which you are aware and all drugs and medications including vitamins and supplements that you have used or are currently using.
• Have approximately 2½ tablespoons (26 mL) of blood taken for laboratory tests (including a pregnancy test if you are a female). We will test you for syphilis. We are required to report positive results to the CT Department of Health.
• Submit to a breathalyzer and provide a sample of urine for a routine examination and to screen for drugs of abuse (including alcohol use).
• Have an electrocardiogram (ECG) to determine the electrical activity of your heart.
• Complete psychological interviews by the study staff and rating scales to check if your history and medical status qualify you for this study. Some of these scales will ask about sensitive issues, such as childhood trauma, sleep quality, suicidal thoughts, and feelings of anxiety or depression.

If it is not feasible for you attend the screening due to physical distance or risk of infection from COVID-19, the psychological interview may be conducted remotely. If you remain eligible, you will then be invited to arrange for an in-person medical evaluation at the West Haven VA.

If the study doctor determines that you meet the screening criteria for participation in the study, you will be enrolled within one week of screening. We will schedule dates for your meetings with the study clinician and two MRI scans.
This visit is expected to take 3-4 hours.

Visit 1 —Life Events Scripting & PE Session 1

At your first visit, you should report to the Decision Neuroscience Lab, located on the 8th floor of 300 George St. in New Haven. A member of our research staff will meet you there.

Your first session will include completing surveys and answering questions about your PTSD symptoms. You will be asked to recall memories of past events and share them with the research staff. These memories will be recorded by a member of the research staff for use in later visits, but will remain strictly confidential and available only to research staff. You will be asked to wear a portable physiological tracking watch that will record your body's heart rate and sweat levels during this session. If it is not feasible for you attend this session due to physical distance or risk of infection from COVID-19, the interview may be conducted remotely. This visit is expected to take around 4 hours.

On the same day as the scripting session, or soon thereafter, you will then be introduced you to the clinician who will deliver the PE therapy. This PE session may take place in person at 300 George St. or the PI's therapy room at 40 Temple St, New Haven, or remotely via Zoom. This PE session, as well as all subsequent therapy sessions may be video or audio recorded. Any video recording will focus on the therapist and you will not appear in frame, but you will be audio recorded. You will be asked to sign a separate consent to audio/ video recording. You may also be asked to wear the portable physiotracking watch during this and all subsequent PE therapy sessions.

Visit 2 —1st MRI + 1st Infusion

On the day of your first MRI and first infusion, you should report to the Anlyan Center (TAC) Building, 300 Cedar St., New Haven at 8:00am. A member of the research team will meet and escort you into the facility for the MRI and infusion procedures. In order to prepare please fast (no food or drink except water) from midnight on. You should drink plenty of fluids during the day before this visit. We will give you clear juice when you arrive to your study session.

At the MRI center you will be brought to a prep room where two intravenous (IV) lines will be placed in your arms to allow for the infusion of the study drug (ketamine or placebo (midazolam)) and repeated blood withdrawals. About 5 tablespoons of blood will be drawn. At this time we will also attach several electrodes to the fingertips of your non-dominant hand and your chest in order to measure your sweat responses and heart rate.

After the IV lines are placed in your arms you will be brought to the magnet room for the MRI.

You will meet your therapist at the MRI center and s/he will conduct the PE session with you there and will be present during the first 30 min of the scan to make sure you are doing fine. At all times your clinician will be present in case you will need any further psychological assistance.

MRI:
Before entering the magnet room, we will make sure you are not carrying any metallic objects before approaching the magnet in order to avoid having these objects fly toward the magnet when you approach it. If you wish, these objects will be held for you in a locked cabinet in the MRRC until you complete the test. You must also complete a safety checklist before entering the magnet in order to avoid any potential risks or complications that may be associated with movement of implanted ferromagnetic (iron or steel) objects during the scanning session.

You will then lie on a firm platform inside a big tube-shaped magnet. A coil will be positioned on your head during each MRI session to help measure the amount of activity in your different parts of your brain. Neither you nor the magnet will move during the test. You will feel no unusual sensations related to the measurements. You will notice that the magnet makes a "drumming" noise when it is operating. A member of the research team will watch you closely throughout the study. It may be difficult to see them from inside the magnet, but the magnet is open at both ends, so they will be able to hear you if you need to talk to them. You will be inside the magnet for about one and half hours (1.5). During the MRI scan, you will be asked to wear headphones. As you are being scanned, a recording of the memories you described during the first visit will play over the headphones. You should pay attention to the recording as it plays. Before and during the scan, you will be given detailed instructions by the experimenter. And eyetracking camera mounted inside the MRI machine will measure your pupil size during the experiment.

Infusion Procedure:

After completing the MRI assessment, you will undergo the drug infusion procedure. The infusion will take place at the MRI center or at YCCI Church Street Research Unit (CSRU; 2 Church Street South, New Haven) or the Hospital Research Unit (HRU; 10th floor Yale New Haven Hospital, 20 York Street, New Haven). If the infusion will occur at either YCCI facility, you will be accompanied by the research staff from the MRI center to the infusion location. Prior to the infusion, you will be asked to provide a urine sample for drug testing and pregnancy testing, if applicable. You will also be asked to submit to a breathalyzer. The drug (ketamine or midazolam) will be delivered into your arm. You will receive the study medication or midazolam for approximately 40 minutes. After receiving the study medication or midazolam, you will remain at the study center for at least 4 hours after the start of the infusion, or longer if the study doctor determines that, for your safety, you will require a longer observation period. You will be monitored and given a meal.

You will be interviewed and monitored throughout the procedure by the study doctor with knowledge and experience in PTSD and will be asked questions so that the study team can determine the state of detachment or disconnectedness you may be experiencing. Before, during, and following the infusion, you will be administered a series of neuropsychiatric evaluations (questionnaires) that will assess your PTSD symptoms and symptoms of dissociation. Following this session, you will be discharged to home if there are no ongoing concerns for your health or safety. You will not be allowed to drive or operate heavy machinery for at least 24 hours after completing the infusion. You will be asked to refrain from nicotine, and alcohol use for one day prior to each MRI session.

Visits 3-6 -PE sessions 3-6

During visits 3, 4, 5, and 6, you will receive prolong exposure therapy for PTSD (the most effective treatment available for PTSD) at the Decision Neuroscience Lab on the 8th floor of 300 George St. or the PI's therapy room at 40 Temple St., New Haven (location where your first study visit occurred). These sessions will each last around 90 minutes. During the sessions, the clinician may ask you to imagine certain situations that typically cause you to feel anxious or frightened. You will be taught relaxation techniques and given strategies to handle unwanted feelings of anxiety. During these sessions, you will be asked to wear a portable physiological tracking watch

that will record your body's heart rate and sweat levels. The clinician may also assign you "homework" exercises for you to practice outside of therapy that will enhance the progress made in-session.

Additionally, you will have ketamine or midazolam administered again on Day 4. These will occur inside of the MRI machine or in the recovery room at the Anlyan Center or at the YCCI Church Street Research Unite (CSRU) or Hospital Research Unit (HRU). All of the same infusion procedures from Day 2 will be repeated. You will again be asked to provide a urine sample for drug and pregnancy testing as well as submit to a breathalyzer. The study doctor will remain present throughout the infusion and will monitor you afterwards. As before, you will not be allowed to drive or operate heavy machinery for at least 24 hours after completing the infusion.

Visit 7 -PE session 7 & 2nd MRI

This visit will begin with your final 90-minute therapy session at the Decision Neuroscience Lab on the 8th floor of 300 George St. Once the session has ended, you will be escorted to the MRI center at 300 Cedar St. by a member of the research staff. All procedures from your 1st MRI scan will be repeated. However, you will not receive any infusion during this scan, so no IV lines will be placed before entering the scanner. This visit will take about 3 hours.

Visits 8 & 9 (Days 30 & 90)—Follow up scans*:*
You will be asked to return to the MRI center at 300 Cedar St. for follow-up MRI scans. The first follow-up appointment will be scheduled approximately 30 days after visit #7. The second follow-up appointment will take place approximately 60 days after visit #8. Both follow-up visits will begin with discussion of your symptoms and experiences since treatment with a clinician. You will also fill out surveys at this time. The procedure of the MRI scans will be identical to visit #7. You will not receive any infusions during these visits. Each follow-up visit is expected to take about 3 hours. If you are unable to attend the follow-up scan sessions, a study clinician will contact you by phone to discuss symptoms and complete some surveys.

It is important for you to know that that there is a new law in Connecticut (Public Act 13-3), that may affect you if you participate in this study. The law requires hospitals to report to the Department of Mental Health and Addiction Services (DMHAS) the names of all persons who are voluntarily admitted for psychiatric care. Under the law, DMHAS will report to the Department of Emergency Services and Public Protection (DESPP) the names, addresses, birthdates and social security numbers of all persons who are voluntarily admitted and who are registered gun owners or who apply for a gun registration within six months of admission. The DESPP will revoke the gun permit, confiscate the gun and deny new permits for six months after the admission. You will be affected by this law only if
you legally own a gun or are planning to register for one in the next six months.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

What are the risks and discomforts of participating?
Although precautions will be taken to minimize risk, some risks and inconveniences remain.

Possible risks associated with the study include (listed from most likely to least likely)

1. **Risks associated with medication infusion**
2. **Risks associated with blood drawing**
3. **Risks associated with MRI scanning**

4. **Risks associated with psychiatric evaluation and clinical assessments**
5. **Risks associated with portable physiotracker**

Common:

Risks associated with medication infusion:

Risks associated with Ketamine

Ketamine is a medication approved by the Food and Drug Administration (FDA) to be used as an anesthetic (medication used to sedate people during surgery). The dose of ketamine used in this study is lower than the dose typically used for surgery, so it is unlikely that you will fall asleep during the study. We are using ketamine to study its anxiolytic (anxiety relieving) effects.

The temporary side effects associated with the infusion you receive during this study may include anxiety, giddiness, perceptual changes, and thinking disturbances. In this study we expect these effects would last for the time of administration and begin to decrease within 10-15 minutes after the infusion is stopped.

There may be longer lasting side effects including residual 'hangover' effects, such as sleepiness and impaired psychomotor and cognitive functions on the day following infusion.

Risks associated with Midazolam

This study will also use an active placebo drug called midazolam. This drug is also FDA-approved as an anesthetic, but the dose used in this study is not expected to cause you fall asleep during the study.

Serious cardiorespiratory adverse events have occurred after administration of midazolam. These have included respiratory depression, airway obstruction, anaphylaxis, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury.

We are also taking a number of precautions to help reduce the chance of having an unpleasant response to ketamine or placebo (midazolam) and to reduce the severity of any lingering medication effects. These precautions include:

1) A research nurse and medical doctor will be present throughout the study to offer support and to help clarify the progress of the test day in case the medication causes feelings of confusion. A physician will also be present for the entire ketamine or midazolam infusion to monitor your vital signs. If respiratory depression or other cardiorespiratory distress occurs, the infusion will be terminated.

2) Medications are available (Valium) to relieve distress related to the behavioral effects of ketamine.

3) We will ask you to remain at the MR center at Yale for several hours after the behavioral effects of ketamine or midazolam should have worn off.

4) We will review the test day with you to deal with your feelings and reactions to each test day before you leave.

5) We will ask you to contact us at any time if any unpleasant effects occur.

6) We will ask you not to engage in demanding work in the day following the test sessions and we will work with you to schedule your test days accordingly.

7) If you have any lingering medication effects, such as sedation, we will terminate the remaining test days and work with you until these side effects have resolved.

8) If your symptoms worsened or you developed other psychiatric symptoms, we may admit you to the hospital. This may be involuntary if you are in danger of harming yourself or others.

9) We will contact you by phone or we will assess you in person at 24 hours, 1 weeks, one month, and 3 months after you have completed the infusion to ask whether you have had any unpleasant effects from the ketamine or midazolam you received during the study. We will ask whether you have developed any significant cravings for ketamine or midazolam or have started to abuse ketamine or midazolam; if so, we will offer you a referral to an appropriate treatment facility.

You should know that unexpected, potentially harmful effects occasionally occur with administration of any type of drug and cannot be predicted with certainty. If serious side-effects occur, the study will be stopped.

You should know that there is the potential for people to abuse ketamine. It is unclear whether exposure to ketamine in the laboratory can result in ketamine use or abuse. Thus, if you are concerned about this possibility, you should not participate in this study. Also, if at any point after completing this study you become aware of a desire to use or abuse ketamine, you should contact us immediately. We will refer you to an appropriate treatment facility if necessary. In our experience doing research with ketamine, the risk that you may go on to abuse ketamine after laboratory exposure to ketamine is extremely small.

While you are receiving the study drug (ketamine or midazolam placebo) through the intravenous tube, you may notice that the study drug influences your thought processes, making you feel detached from your surroundings and reducing your concentration. It may also make you feel like you are in a dream, with colors or sounds seeming brighter or duller than usual. Your body may also feel different, for example you may feel that you are floating. You may also notice having blurred vision, and you may feel mildly sedated. If any of these feelings make you uncomfortable you can stop the procedure at any time. Other behavioral effects of the study drug can include decreased pain, increased anxiety, feeling high, confusion, and hallucinations (hearing or seeing things that are not really there). Other effects of study drug administration that you may experience include sweating, increased blood pressure, increased heart rate, rash, nausea or vomiting. Nausea is one of the most common side effects of the drug. The risks of vomiting are minimized by asking you to refrain from eating anything on the morning of the test session. There is a possibility that you may experience a PTSD reaction that is more intense than you have experienced in the past while receiving the study drug. These are potential effects from the study drug administration that you may or may not experience. At any time, you can tell the study staff that you want to stop the study and you will be taken out of the MRI scanner. Generally, noticeable effects are gone within 30-60 minutes of completing the

study drug administration. Some people have reported mildly decreased concentration or a "hangover" on the day after study drug administration.

You will be evaluated by a clinical member of the research staff prior to discharge from the study to ensure that all clinically significant ketamine or midazolam effects have resolved and that it is safe for you to leave the testing site. You will be allowed to leave the testing site using only an alternate transportation as you will not be allowed to drive. Prior to testing, arrangements should be made for transportation for you back home to avoid difficulties driving with any sleepiness. Although there are no long-term effects of ketamine or midazolam, individuals with a history of psychiatric problems are more likely to have an unpleasant experience or lingering effects. In healthy individuals, the most common after-effect appears to be vivid dreams.

Risks Associated with Blood Drawing:

We may need to draw additional blood for the routine laboratory testing. Having an intravenous (IV) line placed is a very safe procedure. There is a slight chance that multiple needle-sticks will be necessary to make sure the IV is placed correctly. You might feel a small amount of pain when the IV is placed but it does not last very long. A bruise or a minor infection might develop where the IV is placed. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Inflammation or swelling from infections can also be treated with a warm towel, and if necessary, antibiotics can be given to you. Risks associated with blood loss are minimal. Less than 200 cc (about 13 and a half tablespoons) will be drawn. This amount of blood is less than half of a 500 cc (1 pint) blood donation.

Risks Associated with Prolonged Exposure Therapy:

During your psychological treatment you will discuss, with a trained therapist, your traumatic memories associated with your psychiatric condition. It is expected that some psychological distress will be associated with this treatment but is expected that as treatment progress you will develop new psychological tools that will enhance your ability to better cope with these memories and other symptoms associated with PTSD.

Uncommon:

Risks associated with MR studies:

Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of different parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

You will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

There are some risks with an MR study for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this study because the strong magnets in the MR scanner might harm you. Another risk is the possibility of metal objects being pulled into the

magnet and hitting you. To lower this risk all people involved with the study must remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

We want you to read and answer very carefully the questions on the MR Safety Questionnaire related to your personal safety. Take a moment now to be sure that you have read the MR Safety Questionnaire and be sure to tell us any information you think might be important.

This MR study is for research purposes only and is not in any way a complete health care imaging examination . The scans performed in this study are not designed to find abnormalities. The principal investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a health care evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the principal investigator or consulting physician will contact you, inform you of the finding, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie only with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a health care MR exam and for that reason, they will not routinely be made available for health care purposes.

Risks Associated with Psychiatric Evaluation and Clinical Assessments:

The major disadvantages of these tests are the time it takes to complete them, and the fact that the researchers may ask personal questions about sad and traumatic events from your past, which may feel unpleasant at times. We have asked these questions many times in the past for other studies without difficulty or side effects, so we believe you will probably find them acceptable, however, you do not have to answer any questions that you do not want to answer.

Risks Associated with the Portable physiotracking device:

If you experience discomfort or skin irritation while wearing the portable physiotracker, please notify a member of the research team. You may discontinue using the device.

General:

As in any other psychiatric treatment, in rare cases, if you will experience sever suicidal ideations that will be associate with a plan to harm your self or homicidal ideation that would involved a specific target, we may admit you to the hospital.

Restrictions: As a reminder, you will be advised not to drive or operate heavy machinery for at least 24 hours after completing the infusion. You will be asked to refrain from nicotine, and alcohol use for one day prior to each MRI session.

WOMEN PLEASE NOTE: You should not participate in this study if you are pregnant, might become pregnant during the period of this study, or are breast-feeding. Your blood will be drawn for a blood pregnancy test as part of the routine battery of laboratory tests. If your test result is positive, you will not be included in this study. Before entering this study, we will discuss with you in detail the need to avoid becoming pregnant during the whole time that you are in this study and what precautions you plan to take. If you change your mind about becoming pregnant or your method of avoiding pregnancy, we will ask you to notify us immediately.

How will I know about new risks or important information about the study?
We will tell you if we learn any new information that could change your mind about taking part in this study.

How can the study possibly benefit me?

This research may not have benefits to you directly. Ketamine may or may not help in reducing the severity of PTSD symptoms. Prolonged exposure (PE) therapy is a widely-used and effective form of psychotherapy. Although individuals vary in their response to ketamine and to PE, combining these treatments may have a positive effect on your PTSD symptoms. It should be noted, however, that this procedure is experimental and there is no guarantee of improvement. You will receive a thorough medical and psychiatric evaluation at no cost to you.

How can the study possibly benefit other people?

The benefits to science and other people may include a better understanding of effective treatment options for those with PTSD.

Are there any costs to participation?

You will not have to pay for taking part in this study. The only costs include transportation and your time coming to the study visits.

Will I be paid for participation?

You will be paid for taking part in this study. Please note that you will only receive compensation for the procedures in which you participate.

Screening Clinic (Visit 0) …….	$50.00 for psychological assessment; $50.00 for medical assessment
Visit 2 (first MRI)..……	$100.00
Visit 7 (second MRI)……..…	$150.00
Visit 8 (one month follow-up)..……	$400.00 ($350 MRI; $50 assessment)
Visit 9 (3-month follow-up)……	$150.00 ($100 MRI; $50 assessment)
Total ……	$900.00

You are responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments.

You will receive payment for the screening procedures from the VA Screening protocol. You will receive payments for Visits 2 – 9 via a Bank of America pre-paid debit card. **Please note that**

your name, address, and telephone number will be shared with Bank of America for ePayments. After your first payment milestone (your **second** study visit) you will receive a card in the mail which you will need to activate over the phone, any subsequent milestones payments will automatically add additional funds to your card. At the discretion of the Principal Investigator, cash reimbursement may be offered to subjects for whom receiving the debit card presents a significant hardship. If you are unable to receive the debit card, please discuss this with the PI.

At the principal investigator's discretion, further payment may be made by the National Center for PTSD or by Yale Department of Psychiatry for reasonable travel, parking, lodging, or transportation costs. Please discuss with the PI prior to assuming costs. Arrangements can be made for transportation to and from the study facilities. If commuting to the study facilities from home is impractical, hotel accommodations in the New Haven area can be made available at the discretion of the principal investigator. If too much time passes between your screening visit and first scan, it may be necessary for you to repeat the psychological interview, medical evaluation, or both. You will be paid $50 for completing a repeat psychological screening session, and $50 for completing a repeat medical evaluation. If you come to the scan session but are unable to take part in the scheduled scans due to MRI downtime or scheduling error, a $50 show-up fee will be offered.

What are my choices if I decide not to take part in this study?

Instead of participating in this study, you have some other choices.
You could:

- Get treatment without being in a study. Veterans may inquire about PTSD treatment at West Haven V.A. clinics, and non-veterans may be eligible for treatment at the Connecticut Mental Health Center at 34 Park St, New Haven.
- Take part in another study.

How will you keep my data safe and private?

We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if you we learn that you are hurting a child or an older person.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and height, weight and age. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. All of the information collected in this study will be kept in locked files and/or password-protected data stored on computers. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for a maximum of

20 years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

We will also share information about you with other researchers for future research but we will not use your name or other identifiers. We will not ask you for any additional permission.

If you decide to take part in this research study, you will be required to give us information about your substance use. Any of your identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission, with the following exceptions: We will disclose to appropriate authorities reportable diseases, known or suspected abuse of a child or elderly person, or if you become a danger to yourself or others.

We have obtained a Certificate of Confidentiality (CoC) from the DHHS. The CoC will protect investigators from being forced, even under a court order or subpoena, to release research information that could identify you. This protection will not be in effect until we have obtained the CoC, which may take a few months.

Because the CoC is issued by the Department of Health and Human Services (or an agency within DHHS), staff from that and other DHHS agencies may review records that identify you only for audit or program evaluation. They cannot report anything that would harm you or other research subjects. The Certificate of Confidentiality is not an endorsement of this research by the Department of Health and Human Services, or by the National Institutes of Health.

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

What Information Will You Collect About Me in this Study?

The information we are asking to use and share is called “Protected Health Information.” It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this study.
- The entire research record and any medical records held by the VACHS and Yale New Haven Hospital

The following information:

- Records about phone calls made as part of this research
- Records about your study visits
- Laboratory, x-ray, and other test results
- Surveys and questionnaires

- The diagnosis and treatment of a mental health condition
- Use of illegal drugs
- Records about any study drug you received
- Data from MRI scans

How will you use and share my information?

We will use your information to conduct the study described in this consent form.
We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The National Institute of Mental Health, who provides funding for the study
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator, Ilan Harpaz-Rotem, PhD. and his research team.
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the drug product involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Empatica, manufacturer of the portable physiotracker

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider.)

Your urine will be screened for drugs, and you will be asked questions concerning drug use, and other sensitive issues.

Information collected from the portable physiotracker will be uploaded to the Empatica app. This information is does not contain any identifiers.

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

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality

protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, by deciding to take part in a single blinded treatment study and signing this permission form, you will not be allowed to look at or copy your study related information until after the research is completed.

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

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

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

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to Dr. Ilan Harpaz-Rotem, at VACHS/116B, 950 Campbell Avenue, West Haven, CT 06516.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to insure the integrity of the study and/or study oversight.

Who will pay for treatment if I am injured or become ill due to participation in the study?

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able. The study medical doctor, Dr. Shelley Amen, can be reached by telephone at (203) 974-7837. The Principal Investigator, Dr. Ilan Harpaz-Rotem, can be reached at (203)-937-4760.

Yale School of Medicine and the Connecticut Mental Health Center do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

What if I want to refuse or end participation before the study is over?

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

Withdrawing from the study will not harm your relationship with your own doctors or with the VA, Yale-New Haven Hospital, Yale School of Medicine or the Connecticut Mental Health Center.

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

The researchers may withdraw you from participating in the research if necessary. As this is a clinical trial, non-compliance with the treatment as was prescribed to you will result in terminating your participation in this study. In this case, if you interested in alternative treatments for your condition, we will offer you some contact information of other treatment for PTSD that might be available in the community.

What will happen with my data if I stop participating?

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to the principal investigator Ilan Harpaz-Rotem; Department of Psychiatry, 300 George St., #901, New Haven, CT 06511

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

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

Who should I contact if I have questions?

Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator Dr. Ilan Harpaz-Rotem at 203-937- 4760 or the study medical doctor Dr. Shelley Amen at (203) 974-7837.

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, (NCT05737693) 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.

Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

Participant Printed Name	Participant Signature	Date

Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date