ST. MICHAEL'S
UNITY HEALTH TORONTO

Letter of Information and Consent to Participate in a Research Study

Before agreeing to take part in this research study, it is important that you read the information in this research consent form. It includes details we think you need to know in order to decide if you wish to take part in the study. If you have any questions, ask a study doctor or study staff.

Study Title:		**Deciphering Metacognition and Treatment Response in Depression with a Novel Digital Paradigm (Auditory MMN EEG)**
REB Study Number:		22-084
Study Team	**Principal Investigator:**	Venkat Bhat, MD MSc FRCPC DABPN Director, Interventional Psychiatry Program, St. Michael's Hospital, Unity Health Toronto 416-360-4000 ext. 76404 (24-hour contact)
	Co-Investigator:	Karim Ladha, MD, MSc, FRCPC St. Michael's Hospital and the University of Toronto 416-360-4000, Ext.49308
	Research Staff:	Walter Sim, BSc, CCRP® Study Coordinator, Interventional Psychiatry Program, St. Michael's Hospital 647-676-2317 (Monday to Friday, 9:00 am to 5:00 pm) Walter.Sim@unityhealth.to
Study Funding:		New Frontiers in Research Fund – Government of Canada

Conflict of Interest Statement:

The researchers have received funding for this study from the Government of Canada through the New Frontiers in Research Fund but receive no direct or personal benefit from any study activities. The principal investigator, co-investigators, and research staff do not have any conflicts of interest, financial or otherwise, related to this study or its outcome.

Introduction

You are being asked to consider participating in this research study because you have been diagnosed with depression and are receiving ketamine treatment clinically as administered by your clinician. Please read this Consent Form carefully and ask your primary doctor and study team as many questions as you would like before deciding whether to participate in this research study. This

Consent Form should inform you of what this research is about and what your participation will involve. If you would like more details about any information that is included or not included here, please ask the research team.

All research is voluntary – you do not have to participate, and you can withdraw at any time. Before agreeing to take part in this study, it is important that you read the information in this research Consent Form. It includes details we think you need to know in order to decide if you wish to take part in this study. If you have any questions, ask a study team member. You should be aware that it is possible that the St. Michael's Hospital study investigator(s) will also be your treating doctor(s).

Please take your time in making your decision. Deciding not to take part or deciding to leave the study later will not result in any penalty or affect your current or future health care.

If you choose to participate in this study, you will need to sign this Letter of Information and Consent form. You should not sign this form until you are sure you understand the information. You may also wish to discuss the study with others, such as a family member or a close friend.

Background and Purpose of the Study

The purpose of this study is to assess how brain function and biological signals change in response to ketamine treatment that is given to patients with treatment-resistant depression (TRD). This data will be used to develop a mathematical model to represent the underlying biological and physiological activities that occur in response to ketamine treatment. This model will be developed using:

1. Electroencephalography (EEG) to measure the brain's response following short-term and repeated ketamine intervention. During the EEG, the auditory mismatch negativity (MMN) task, which consists of listening to a series of alternating tones, will be done.
2. Electrocardiography (ECG) will be collected during the EEG and MMN task to assess physiological and emotional states and provide additional data.

The study activities are explained in further detail below within the "Research Tests and Procedures" section

This model may:

1. Provide us with a better understanding of the changes in the brain following repeated, short-term ketamine treatments,
2. Allow us to develop a computerized model linked to the brain activity changes following repeated, short-term ketamine treatments , and
3. Allow us to make treatment predictions that are specific to individuals.

At this time, the main purpose is to complete the study with 30 participants at St. Michael's Hospital (also known as a pilot study) to learn whether it will be possible to plan for a larger study in the future.

Study Design and Duration

Study Design

This study is a prospective, observational study. Observational studies are a type of research where researchers gather information on your health outcomes based on 'observations' (such as lab tests, questionnaires, etc.). In this study, additional data will be collected to better understand your response to the clinical treatment. The care that you receive for your condition will not be changed if you decide to participate in this study. All research activities will be in addition to usual care.

Study Duration

Overall, this study will run for about one year. Your involvement in the research study will last for about 2 weeks.

Participant Population and Study Enrolment

This study will include 30 participants aged 18-65 with a diagnosis of treatment-resistant depression (TRD). Patients with a major depressive disorder who have not seen improvement in their MDD symptoms in response to at least two antidepressant treatments will be considered treatment-resistant. Participants will be recruited from the outpatient Interventional Psychiatry Program at St. Michael's Hospital.

The clinical team at the Interventional Psychiatry Program will need to review your medical records prior to the consent process. This will be done in order to determine whether this study may be suitable for you before directing you to the study team.

Description of Research Activities

Research Tests and Procedures

This is an observational study that takes place in addition to standard care in patients who are undergoing clinical treatment with ketamine. Your participation in the study will not change the standard of care, including your current course of ketamine treatment.

We will collect various biomedical measurements three times during the study, before your clinical ketamine infusion at Visits 1, 2, and 4. The additional measurements will take approximately 30 minutes at each visit. The purpose of these measurements will be to assess how your brain function and biological signals change in response to ketamine treatment. You will be asked to listen to a series of alternating tones (MMN task) while seated. The EEG and ECG signals will be recorded while you are listening to the tones. The significance of collecting ECG is to provide additional biological markers to predict the response to ketamine treatment. Also, 10 to 15 minutes after each

infusion visit and in the follow-up visit will be considered for the administration of two clinical scales over the phone. If you feel uncomfortable, you may ask to pause the task or withdraw at any point.

The following biological measurements will be taken while you complete the auditory mismatch negativity (MMN) task as part of this study:

Electroencephalography (EEG):
The EEG measures brain activity through 32 electrodes placed on the scalp through an EEG cap. This cap has small metal disks that capture the electrical activity of your brain and will be placed on your head. This is a painless procedure that will give us a great deal of information about your brain activity at different points of the study.

Electrocardiography (ECG):
An ECG is a test that measures the electrical activity of your heart. An ECG is non-invasive and painless. During the ECG, a sensor (electrodes) with a wire attached will be placed on your wrist. No electricity is sent through your body. ECG collects information such as heart rate and heart rate variability.

Montgomery-Asberg Depression Rating Scale (MADRS):
MADRS is a 10-item clinical scale designed to measure depression severity and detects changes due to ketamine. MADRS assessments will track the speed at which you obtain antidepressant response and remission with each infusion.

Columbia-Suicide Severity Rating Scale (C-SSRS):
The C-SSRS is a clinical interview that utilizes a set of questions to help an interviewer get more complete information on events suggestive of suicidality.

Collecting Health Information from a Medical Record for Research Use

If you are eligible to participate in the study (diagnosed with MDD, referred to the program as a patient, and receiving ketamine per your standard of care), the clinical team will book the appointments for you to come to the hospital for the additional study procedures before your standard of care ketamine infusion.

If you agree to take part in this study, the study team will collect the following information from your medical record:

- Medical history
- Any medications or therapies that you are currently receiving or have received in the past.

We will also use the data that is collected through the General Anxiety Disorder 7-item (GAD-7) that will be collected as part of your standard of care.

Description of Study Visits

If you are interested in participating in this study, the clinical staff at the Interventional Psychiatry Program will direct you to the research coordinator over the phone or at a Zoom meeting. The research coordinator will provide further information about the study and answer any questions you might have. Once you have signed the consent form, the clinical staff will book an appointment for your first ketamine infusion, and an additional 30 minutes before infusions 1, 2, and 4 for the ECG and the auditory mismatch negativity (MMN) task. Also, 10 to 15 minutes after each infusion visit and in the follow-up visit will be considered for questionnaires and interviews. You will no longer be eligible to continue the study if you miss more than 1 infusion.

Infusion Visits 1, 2, and 4:

At the first, second, and fourth infusion visits, you will be asked to come in 30 minutes before your scheduled ketamine treatment to undergo the following study procedures: the MMN task and additional biomedical data collection including:

- Electroencephalogram (EEG)
- Electrocardiogram (ECG)

For these 3 visits, in addition to the administration of the GAD-7 questionnaire, as part of the standard of care, 10 to 15 minutes will be considered for the administration of MADRS and C-SSRS after the infusion, over the phone.

Infusion Visits 3:

At the third infusion visit, no additional biomedical data collection will be performed. You will not be required to come in 30 minutes before your scheduled ketamine treatment. For this visit, in addition to the administration of the GAD-7 questionnaire, as part of the standard of care, 10 to 15 minutes will be considered for the administration of MADRS and C-SSRS after the infusion, over the phone.

Please keep in mind that all visits may be shorter or longer in duration depending on individual circumstances. If you have further questions about the data collection that will take place, you may contact the study coordinator.

Participant Responsibilities

If you decide to take part in this study, it is important that you remember to:

- Ask your study team about anything that worries you.
- Tell study staff about any changes in your health.
- Tell study staff if you are considering any changes to your medications or doses.
- Tell study staff if you have changed any of your medications or doses.

- Tell your study team if you change your mind about being in this study.
- Tell your study team if you are considering enrolling in another study.

Potential Risks

Potential Risks of the Study Intervention

Risks associated with EEG and ECG data collection:

During the EEG and ECG data collection, there may be temporary mild physical discomfort (e.g., pressure or risk of skin irritation during the EEG cap preparation or ECG electrode attachment). There are no known risks associated with ECG or EEG data collection.

Please discuss any changes in your feelings or behaviour with the study doctor during your involvement in the study. You may stop your participation in this study at any time.

Risks Related to Study Questionnaires:

Self-report questionnaires contain questions regarding sensitive personal information. You may experience a negative reaction or feelings of distress when responding to some of the questions. You can skip questions that you do not wish to answer. If you have any questions or concerns while answering these questions, please talk to a study team member. Additionally, if this happens, you can pause or stop your participation in the questionnaire. You can also choose to withdraw from the study. The study team is available to discuss your concerns and/or to refer you to appropriate resources. You will be assured upon intake that only study personnel will see any rating form responses.

Potential Benefits

There may not be any direct benefits to you for participation in this study. There will be no difference in your clinical care if you choose to take part in the study or not. Your participation may allow the researchers to determine the effectiveness of the ketamine treatment.

Alternatives to Participation

This study is not researching ways to provide you with medical treatment, so the alternative to taking part in this study is to not take part in the study. Whether you choose to take part in this study or not, you will receive the same standard and level of care at Unity Health Toronto.

Privacy and Confidentiality of Your Personally Identifying Information and Study Data

This section describes how your personally identifying information and study data will be accessed, disclosed, and stored during this study. All persons involved in this study are committed to respecting your privacy. Other than the individuals or groups described in this section, no persons will have access to your personally identifying information without your consent, unless required by law.

Personally identifying information is any information that could be used to identify you; this includes your name, date of birth, email address and telephone number.

Study data is information that is generated by and/or collected for a study that has been stripped of personally identifying information.

Protecting Your Privacy

The study team will make every effort to keep your personally identifying information private and confidential in accordance with all applicable privacy legislation, including the Personal Health Information Protection Act (PHIPA) of Ontario.

Any information that is recorded for study purposes will be de-identified by using a unique study identification number instead of any of your personal identifiers. The principal investigator at St. Michael's Hospital is in control of the key that links your study number to you personally.

No personally identifying information will be allowed off site in any form, unless required by law or as described in this consent form.

Accessing and Collecting Information from Your Unity Health Toronto Medical Records

By signing this form, you are authorizing access to your medical records by the study team. The study team will also collect information from your medical record. The information that will be collected is described in the Research Activities section. The study team will use this information to conduct this study.

You are also authorizing access to your medical records by representatives of the Unity Health Toronto Research Ethics Board, the study sponsor, and by applicable government regulatory authorities (e.g. Health Canada, the US Food and Drug Administration (FDA), and/or regulatory agencies from other countries). Such access will only be used to verify the authenticity and accuracy of the information collected for this study, without violating your confidentiality, to the extent permitted by applicable laws and regulations.

Use of Email for Research

There are common risks of using email to communicate:

- Information travels electronically and is not secure in the way a phone call or regular mail would be.

- If someone sees these emails they may know that you are a participant in this study or see the health information included in the email and/or text.
- Emails may be read or saved by your internet or phone provider (i.e. Rogers, your workplace, "free internet" providers).
- Copies of an email may continue to exist, even after efforts to delete the email and/or text have been made.
- There is always a chance with any unencrypted email, however remote, that it could be intercepted or manipulated.

Do not use email for medical emergencies. If you require immediate help, call your clinic or care provider, or seek emergency services.

Personally Identifying Information Storage and Retention

All your personally-identifying information will be collected in a database. The data will be stored on a secure internal hospital server and will be password protected so that it is only accessible to authorized research personnel.

Your personally identifying information will be kept by the Principal Investigator and Unity Health Toronto for 5 years after study completion at St. Michael's Hospital in a highly secure and confidential manner, as per hospital requirements. After 5 years any documents with personally identifying information will be destroyed.

Study Data Storage and Retention

As a reminder, study data is information that is generated by or collected for a study that has been stripped of personally identifying information.

Study data will be securely stored at Unity Health Toronto. Study data may also be transferred outside of Unity Health Toronto and shared with others for purposes related to the conduct of this study.

Study data may be kept indefinitely and may be used for other research or analyses by the study investigators and the study sponsor.

Individual level study data may also be made available to scientific journals, their reviewers, other researchers inside or outside of Unity Health Toronto, or the public.

Study Results and Study Registration

Results

The results of this study may be presented at a scientific conference or published in a scientific journal. If you are interested in obtaining the results of this study, you can contact the study team. We estimate that the results of this study will be available in two years.

You will never be personally identified in any publication, report, or presentation that may come from this study.

Registration

A description of this trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

The registration number for this study is NCT05464264.

Potential Costs and Reimbursement

There are no anticipated costs to you for participation in this study.

You will be compensated up to $20 per in-person EEG visit to cover all travel expenses by public transit, but we are not able to provide compensation for additional expenses such as parking or food. You will receive a cheque at the end of your involvement in the study, and no receipts will need to be provided. If you withdraw from this study before completing it, you will receive compensation for the parts of the study that you have completed.

If a discovery is made or a commercial product or method is derived from this study, it will be the property of the study sponsor and you will not be entitled to any financial benefits resulting from it.

Compensation for Injury

If you experience side effects from the study procedures, you should inform the study team as soon as possible. If you have any other concerns about safety or unexplained symptoms, contact us immediately.

If you are injured because of your participation in this study, medical care will be provided to you in the same manner as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor release the study doctor(s), sponsor, or involved institution(s) from their legal and professional responsibilities.

Participation and Withdrawal

Participation in the Study

Your participation in this study is voluntary. If you choose not to participate, there will be no impact to the medical care received at, employment at, or other relationships with Unity Health Toronto now or in the future for you or your family.

Withdrawal from the Study

If you choose to take part in this study, you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the regular clinical care you or your family will receive at St. Michael's Hospital. If at any time you choose to withdraw from this study, please contact a member of the study team.

Your participation in the study may be stopped without your consent for the following reasons:

- If it is discovered that you do not meet the eligibility requirements.

The study may be terminated by the investigators at any time for any reason.

Continued Collection and Use of Your Data After Withdrawal

If you withdraw from the study, any data collected about you up to that time will still be used for analysis. No more data about you will be collected. We may be required to retain the personally identifying information and study data that we have already collected until after the end of this study (described in the Privacy and Confidentiality section).

New Information About this Study

We may make changes to this study as it progresses. We may also learn new things about the study that you may need to know. Some of the new information or changes might affect your decision to take part in the study. If so, you will be notified about the new or changed information in a timely manner and we will ask you if you consent to remain in the study. You may be asked to sign a new consent form at that time.

Research Ethics Board Contact

If you have any questions regarding your rights as a research participant, you may contact the Unity Health Toronto Research Ethics Board Office at 416-864-6060 ext. 42557 during business hours (9:00am to 5:00pm). The Unity Health Toronto Research Ethics Board is made up of a group of scientists, medical staff, and individuals from other backgrounds (including law and ethics) as well as members from the community. The Board is established by Unity Health Toronto to review studies for their scientific and ethical merit. The Board pays special attention to the potential risks and benefits to the research participant, as well as the potential benefit to society.

Unity Health Toronto is a health network that includes Providence Healthcare, St. Joseph's Health Centre, and St. Michael's Hospital.

Study Contacts

If at any time during this study you have questions about the study or the research activities, or if you suffer a research-related injury, you should contact the Principal Investigator. That person is:

Venkat Bhat, MD MSc FRCPC DABPN
St. Michael's Hospital
24-Hour Contact/Pager: 416-360-4000 ext. 76404

(You will be asked to leave your phone number to be called).

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Signature Page(s): Documentation of Informed Consent
Study Title: Deciphering Metacognition and Treatment Response in Depression with a Novel Digital Paradigm (Auditory MMN EEG)

Participant Statement of Consent

By signing this consent form, I acknowledge that:

- This research study has been explained to me, and my questions have been answered to my satisfaction.
- I have been informed of the alternatives to participation in this study.
- I know that I have the right not to participate and the right to withdraw from this study without affecting the medical care received at, employment at, or other relationship with Unity Health now or in the future for me or my family.
- The potential risks and benefits (if any) of participating in this study have been explained to me.
- I have been told that I have not waived my legal rights nor released the study investigator, study sponsor, or involved institutions from their legal and professional responsibilities.
- I know that I may ask, now or in the future, any questions I have about this study.
- I have been told that information about me and my participation in this study will be kept confidential and that no personally identifying information will be disclosed without my permission unless required by law.
- I have been given sufficient time to read the information in this consent form.
- I will be given a signed and dated copy of this consent form

I consent to participate in this study.

Participant name (print)	Participant signature	Date	Time

I have explained to the above-named participant the nature and purpose, the potential benefits, and possible risks of participation in this study. All questions that have been raised about this study have been answered.

Name of person obtaining consent (print)	Position/Title of person obtaining consent (print)	Signature of person obtaining consent	Date	Time

Complete the following section only if the participant has verbally consented:

- The informed consent form was accurately explained to, and apparently understood by, the participant, and
- Informed consent was freely given by the participant

☐ The consent form was read to the participant and consent was received verbally via _____ (telephone, Zoom healthcare, etc.). The person signing below attests that the study as set out in this form was accurately explained to the participant, and any questions have been answered. The participant will be mailed or emailed a copy of the consent form for their records.

Signature of person conducting the consent discussion	Printed name and role	Date