INDIANA UNIVERSITY INFORMED CONSENT STATEMENT AND AUTHORIZATION FOR RESEARCH

Frontal-Striatal Reward Circuit Neuromodulation and Alcohol Self-Administration

ABOUT THIS RESEARCH

You are invited to participate in a research study of the relationship between repetitive transcranial magnetic stimulation (rTMS), a brain stimulation technique that uses a magnet to temporarily change brain function, and alcohol related behavior. Scientists do research to answer important questions which might help change or improve the way we do things in the future.

This consent and Authorization form will give you information about this study to help you decide whether you want to participate. It is your choice whether or not you want to be in this research study.

You were selected as a possible subject because you are an alcohol consuming individual who has called our study line or participated in previous studies and expressed interest. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

The study is being conducted by Drs. Susan Conroy and Martin Plawecki of the Department of Psychiatry, Indiana University School of Medicine. It is funded by the National Institute on Alcohol Abuse and Alcoholism.

STUDY SUMMARY

The purpose of this study is to determine if repetitive transcranial magnetic stimulation (rTMS) affects your feelings and your alcohol drinking behavior, in both lab-based experiments and in your normal life. rTMS is a technique that uses a magnetic coil placed over the scalp to change brain function for a short period of time. Results from this study may help us better understand whether rTMS might change alcohol drinking. You will complete a screening visit (unless you already completed a screening visit as part of another related study), 2 rTMS and alcohol infusion sessions over 1-2 weeks, and a phone follow-up interview 4 weeks after the second experimental session. You will be enrolled in this study for about 1 month. While participating in the study, you might experience some risks, side effects, and/or discomforts, including risks and discomforts associated with rTMS, risks from the alcohol infusion, and other risks described later in this informed consent statement. There are no direct benefits to you for participating. There is no cost to you for participating in this study. You will be paid for participating in this study. Please read the rest of this document for more details.

Please review the rest of this document for more details about this study and the things you should know before deciding whether to participate in this study.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine if the study intervention, repetitive transcranial magnetic stimulation (rTMS), affects your feelings, your alcohol drinking behavior in a lab-based experiment, and your drinking behavior during the four weeks that follow the second treatment session. rTMS is a technique that uses a magnetic coil placed over the scalp to change brain function for a short period of time.

The rTMS study technique is considered investigational, meaning that this intervention is not approved by the Food and Drug Administration (FDA) to treat alcohol use disorders; however, this treatment is approved to treat other disorders, like depression. This study does not intend to be a treatment for alcohol use disorder, but instead is interested in examining the effects of rTMS on drinking behavior and feelings.

We are comparing the effects of rTMS and sham rTMS (a setup that looks and sounds like rTMS but does not produce a magnetic field), administered using the MagVenture MagPro TMS system, to determine if rTMS impacts your drinking behavior and feelings.

HOW MANY PEOPLE WILL TAKE PART?

You will be one of 30 participants taking part in this study.

WHAT WILL HAPPEN DURING THE STUDY?

Screening Procedures:

If you have already completed a related alcohol study interview or participation, and the information collected from that project was used to evaluate your eligibility to participate in this study, you will not have to repeat the interview. We may update a limited amount of the information you provided at that earlier interview.

If you have not completed a related study interview, you will:

- Participate in a physical exam done by an Indiana CTSI Clinical Research Center (CRC) nurse
- Provide about a teaspoon of blood drawn from a vein in your arm for testing liver function and genetic testing
- Provide a cup of urine for drug testing and, if female, pregnancy testing
- Complete various questionnaires and structured interviews regarding your alcohol use and your family's history of alcoholism.

Some or all of the interview, except those activities that require in-person screening such as the blood draw and urine sample testing, may be done on-line.

Experimental Procedures:

After your interview:

You will attend two scheduled sessions at the Neural Systems Lab (NSL) at University Hospital and the Neuroscience Research Center. You will go about your normal life, but not drink alcohol starting at 4pm the day before the testing sessions. You are able to eat anything and drink as much water or other non-alcoholic beverages as you want the day before and during your testing sessions.

Procedures for the two sessions:

Orientation to laboratory: On testing days, you will:

- Arrive at the NSL at your scheduled visit time
- Receive a brief physical exam by Indiana (CTSI) Clinical Research Center (CRC) Nurses
- Provide a urine sample for testing for substances and pregnancy
- Complete a Breath Alcohol Meter test with zero breath alcohol concentration before a 550 calorie breakfast is served
- Provide a record of your drinking since the last time you were in the lab
- Answer questions about how you feel and whether any relevant information about you has changed since your last visit

Preparation for Testing:

- A catheter (a small tube) will be put in a vein at the elbow of one arm
- Study staff will then transport you to the Neuroscience Center for the rTMS treatment
    - You will receive rTMS and sham each once.
    - The order of the study and sham treatment will be randomized and double blinded.
        - Randomized means that the order will be determined purely by chance, like flipping a coin.
        - Double-blind means neither you, nor the research team, will know if you are receiving rTMS or sham.
    - Since you will receive both and the order will be randomized, you have an equal chance (1:1) of starting with rTMS or sham.

Immediately before you receive the rTMS or sham, you will be prompted to recall your most recent experience using alcohol through a series of questions. During both sessions, you will be instructed to imagine yourself in that experience.

During rTMS or sham administration, you will:

- Be seated comfortably in a well-lit room
- Be given ear plugs to protect your hearing, as the machine can be noisy
- Will have the coil, which administers the rTMS or sham, placed over your scalp and administered for about 16 minutes

- During rTMS or sham, it may feel like there is a finger tapping sensation under the area where the magnetic coil is placed
- The magnetic coil is held in place by a movable arm which is attached to a chair where you will sit
- The magnetic coil will rest gently on top of your head, but will not put pressure on your head (see Attachment A at the end of this consent for a picture)
- A trained member of the investigational team will be present during the rTMS or sham to ensure you are comfortable

This procedure will be repeated during each of the sessions. You are able to stop rTMS or sham administration at any point.

Upon completion of the rTMS treatment, you will be moved to the CRC in the Neuroscience Center and begin the alcohol infusion session.

Preparation for Infusion: You will:

- Be prompted for a bathroom break and the catheter in your arm will be connected to the infusion pumps via tubing
- Complete a set of baseline assessments, after which the infusion will begin
- Be unaware of your breath alcohol level and the rate of the infusion at all times
- Be allowed to speak with the technician at any time

We administer alcohol via your veins, or an infusion, using a ~6.0% (v/v) alcohol in half-normal saline (salt water) prepared by the IU Health research pharmacy. A model tailored to your characteristics (age, height, weight, gender) will be used to set the alcohol infusion. The safety limit will be set to 0.170 g/dL, more than twice the legal limit for driving of 0.080 g/dL and the software will prevent you from going beyond that limit.

You will be able to control how quickly alcohol goes into your body in 3 minute blocks, which will affect the rate/how quickly your breath alcohol concentration will change. You will do this by turning a dial with a computer display showing an indication of the past and upcoming blocks. We will monitor your breath alcohol concentration throughout. Towards the end of each block, you may complete a brief computer based questionnaire of how the alcohol makes you feel. After each block, you will specify the next rate of change in your breath alcohol concentration while the current breath alcohol concentration is maintained.

Except for bathroom breaks, you will:

- Remain in the room for the experiment; interaction with the technician will be limited to occasional breath alcohol samples and providing instructions. The infusion will lasts approximately 90 minutes and then you will be served a lunch.

- Remain in a room until study staff determines it is safe to transport you back to University Hospital.
- After returning to University Hospital, you will remain in an ICRC inpatient room until at least 7:00 pm or your BrAC falls below 0.035 g/dL, whichever occurs later, and it is safe for you to leave.

Four weeks after completion of the second rTMS/Alcohol session, you will be contacted and asked to complete an assessment of your drinking since the sessions.

You will be in this study for about four to six weeks.

You will not receive the results of any of these tests or procedures because they are being done only for research purposes.

WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?

While on the study, the risks are:
You may feel uncomfortable answering some of the assessment/questionnaires.

Drawing blood from your vein requires the insertion of a needle and can result in temporary soreness and bruising where the blood is drawn.

Risks and Discomforts Associated with rTMS:

In a clinical trial of rTMS in 323 adult patients utilizing the MagVenture MagPro TMS system, adverse events commonly observed more frequently with rTMS than sham and occurring at a rate of ≥ 10% (10 or more people out of 100 people) include:
-Headache
-Nausea

In a clinical trial of rTMS in 204 adult patients utilizing the MagVenture MagPro TMS system, adverse events commonly observed more frequently with rTMS than sham and occurring at a rate of ≤ 10% but ≥ 1% (between 1 to 10 people out of 100) are:

-Headache	-Dizziness
-Nausea	-Fatigue (excessive tiredness)
-Insomnia (being unable to sleep)	-Anxiety or agitation
-Back or neck pain	-Abnormal sensations

Seizure Risk: Generalized seizures have been reported with the use of TMS in the clinical trial literature, though they are rare. The estimated risk of seizure under ordinary clinical use is approximately 1 in 30,000 treatments (0.003% of treatments) or 1 in 1000 patients (0.1% of patients). Nevertheless, TMS should be used with caution in patients who have a history of seizures.

- Having a seizure includes a potential effect on your future employability, insurability, and ability to drive. Should you experience a seizure that is related to magnetic stimulation, your doctor will provide you with a letter stating that the seizure was produced under experimental conditions and that there is no reason to expect another occurrence.

Risks to Women: Women who are pregnant should not participate in this study. There may be unknown risks to an embryo, fetus, or unborn child. If you are a woman and you could possibly become pregnant during this study, you will be given urine pregnancy tests throughout the study. While taking part in this study, you should use an adequate form of birth control, such as oral contraceptives ("the pill"), long-acting contraceptive injections (Depo-Provera), intrauterine device (IUD), or barrier methods (e.g., condom or diaphragm) plus spermicidal. If you have had tubal ligation ("tubes tied"), that is also an acceptable form of contraceptive. We ask that you inform the study doctor immediately if you have a reason to suspect pregnancy, if circumstances have changed and there is now a risk of becoming pregnant, or if you have stopped using the approved form of birth control.

Risks associated with the alcohol infusion:
There is a risk of physical discomfort that goes with inserting a small tube into a vein on the inside of one of your elbows, along with a possibility of bruising or infection that goes with having that tube in place.

There is a possibility that the tube could be misplaced or slip out of your vein while the alcohol is being infused, leading to infusion of alcohol in the tissues surrounding that vein and short-term discomfort.

There is a possibility that the rapid infusion of alcohol in your vein could cause irritation to the inside of your vein and lead to a burning sensation for a few minutes each time you "order" more alcohol.

However much or little alcohol you choose to self-administer, you must stay at the Indiana CTSI Clinical Research Center (CRC) until at least 7 pm on the day of testing, but you may have to stay longer if your breath alcohol concentration has not gone down to 0.035 g/dL yet.

If you are a smoker, you may experience nicotine withdrawal because smoking is not permitted at the CRC.

If you choose to administer a lot more alcohol than you typically enjoy, there is a possibility that you may become intoxicated or get a headache or become nauseated (sick to your stomach) or even vomit. In addition, any time you are exposed to alcohol, you will have the urge to urinate more often than usual for a few hours.

While on the study, there is a risk of loss of confidentiality of your data.

THE FOLLOWING WILL BE USED TO MINIMIZE THE RISKS LISTED ABOVE:
You may choose to not answer questions that make you feel uncomfortable.

A trained member of the study team will administer rTMS or sham and will be present during the entire session to check on discomfort or other side effects.

The tube will be inserted into your arm by skilled nurses who use techniques designed to minimize discomfort and the possibility of infection and the chances that the tube will slip out of your vein.

The concentration of alcohol in the liquid infused into your vein is kept at 6% to reduce the possibility of an unpleasant sensation.

If you request it, you will be offered nicotine gum or a nicotine patch if you experience nicotine withdrawal or at the beginning of a session if you prefer.

During the infusion session, we will be measuring your breath alcohol concentration to make sure that the concentration does not get too high, and we will be asking you questions about intoxicating effects, and remind you that you should be seeking only pleasant effects of alcohol self-administration.

We will keep your records in a secure location and limit the access to those records to the people who are conducting and analyzing the results of this study, unless required by federal regulations to provide those records to other people for review or you give us written permission to share those records with others. The results of urine drug and pregnancy tests will only be used for the purpose of determining study eligibility and will not be shared with outside entities.

WHO WILL PAY FOR MY TREATMENT IF I AM INJURED?
If you are injured as a result of participating in this study, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. No money or funds are set aside to pay for these types of injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled by signing this Informed Consent form.

WHAT ARE THE BENEFITS OF TAKING PART IN THE STUDY?
We don't think you will have any personal benefits from taking part in this study, but we hope to learn things that will help other people in the future.

WILL I BE PAID FOR PARTICIPATION?
You will receive payment for taking part in this study. You will receive $25.00 for completing the screening interview, unless you already received compensation for an interview with another alcohol

related study. If you complete the online portion of the interview and are withdrawn before completing the in-person portion of the interview, you will be compensated $15. If there is a significant delay between the online and in-person portion of the interview, you may request compensation with $15 in electronic gift card, or mailed a check or gift card. Upon discharge from the CRC, for the infusions you will receive $125.00 for completing the first session and $175.00 for completing the second session. If you complete the follow-up interview 30 days after your second session, you will be compensated $25. If you fail to complete a testing session or withdraw early, you will be paid $15/hour for the time spent participating on that day. You will be paid $15/hour for any time you have to stay past the discharge time in 20 minute increments.

If it is likely you will receive $600 or more in one calendar year from Indiana University, you will need to complete a form giving us your Social Security number (SSN) or tax identification number (TIN). You will receive a 1099 tax form the following year from Indiana University and may need to report this payment as income on your federal and state tax returns. You are responsible for paying any local, state, or federal taxes. If you have questions about how this impacts your tax return, please contact a tax professional. If you do not have an SSN or TIN, the Internal Revenue Service (IRS) requires Indiana University to deduct 30% from your research payment to pay required taxes on your behalf.

WILL IT COST ME ANYTHING TO PARTICIPATE?

There is no cost to you for taking part in this study.

HOW WILL MY INFORMATION AND SPECIMENS BE USED?

The study team will collect information about you from your medical records. This information, some of which may identify you, may be used for research-related purposes. This may include making sure you meet the criteria to be in the study, gathering information about your medical history to include in the research data, reviewing results of your medical tests for safety purposes, checking your health information in the future to help answer our research questions or to inspect and/or copy your research records for quality assurance and data analysis. This permission is for health care provided to you. The personal health information that will be used for research purposes may include some or all of your health records. This includes, but is not limited to: information provided by you directly to the Research Team, hospital records and reports; admission histories, and physicals; X-ray films and reports; operative reports; laboratory reports; treatment and test results; immunizations; allergy reports; prescriptions; consultations; clinic notes; and any other medical or dental records needed by the Research Team.

The information released and used for this research will include:

- Radiology records
- Medical history / treatment
- Medications
- Radiology films (like X-rays or CT scans)

- Laboratory / diagnostic tests
- EEG reports
- Psychological testing
- Diagnostic imaging reports

If you agree to participate, you authorize the following to disclose your medical record information:

- Indiana University Health
- IUMG – Primary Care Physicians
- Eskenazi Health
- Indiana Network for Patient Care (INPC)

The following individuals and organizations may receive or use your identifiable health information:

- The researchers and research staff conducting the study
- The Institutional Review Boards (IRB) or its designees that review this study
- Indiana University
    - The Indiana Clinical Research Center (ICRC)
- US or foreign governments or agencies as required by law
- Data safety monitoring boards and others authorized to monitor the conduct of the study
- State or Federal agencies with research oversight responsibilities, including but not limited to:
    - Office for Human Research Protections (OHRP)
    - National Institutes of Health (NIH)
    - The United States Food and Drug Administration (FDA)

Information or specimens collected for this study may be used for other research studies or shared with other researchers for future research. If this happens, information which could identify you, such as your name and other identifiers, will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. 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.

HOW WILL MY INFORMATION BE PROTECTED?

Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. No information which could identify you will be shared in publications about this study. Your personal information may be shared outside the research study if required by law and/or to individuals or organizations that oversee the conduct of research studies and these individuals or organizations may not be held to the same legal privacy standards as are doctors and hospitals. Your identity and participation in this study will become part of databases maintained by the Indiana University School of Medicine and the Indiana CTSI Clinical Research Center.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use any information, documents, or specimens that could identify you in any legal action or lawsuit unless you say it is okay.

However, the Certificate does not apply to some types of sharing. The Certificate does not stop reporting required by federal, state, or local laws, such as reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate does not stop a government agency who is funding research from checking records or evaluating programs. The Certificate also does not prevent your information from being used for other research when allowed by federal regulations. The Certificate also does not stop sharing of information required by the Food and Drug Administration (FDA).

Researchers may release information about you when you say it is okay. For example, you may still give them permission to release information to insurers, medical providers, or others not connected with the research.

WHAT WILL YOU DO WITH MY GENETIC INFORMATION?

We may use the specimens collected as a part of this study for whole genome sequencing, which involves mapping all of your DNA.

Your signature on this consent form gives us permission to study your DNA (genetic information that we get from your blood) at any time in the future in order to look for relationships between your genes and other variables. If you do not qualify to participate in this study, we may still look for relationships between your genes, your family history, and your behavioral, personality, and health information collected during the screening visit. Your DNA may also be studied to help detect any genetic influences that increase the risk of alcohol dependence.

The specimens collected in this study will be used for genetic studies which may include taking your DNA from the specimens. Every person's DNA is unique; therefore, it may be possible some day that someone could find out who you are just from knowing your DNA sequence.

The genetic information that comes from your participation in this study will never be identified with your name or social security number. In most cases the samples collected will need to be identified so that it can be linked to your study information; however, your identity will not be released to anyone outside the study. The blood and genetic information will be stored in secure, locked cabinets in the Neural Systems Lab research office or in a locked laboratory at the Indiana Alcohol Research Center. To minimize the risk of loss of confidentiality, the sample will be registered and processed by an experienced technician. No personal information will be recorded on the sample itself. Rather, the assigned subject number will be placed on the envelope or tube containing the sample. The subject number will be linked to your personal information. Personal information linked to your sample will be

maintained in protected files. These files will be secured by encryption using a secret code and by safety procedures that prevent unauthorized access to computers and files. The stored information will be available only to scientists in this study, or to other researchers who gain institutional review board approval to use this information in similar research. The investigators in this study plan to keep your blood sample and DNA indefinitely, and then use them later in analyses for this project.

The genetic information in this research is protected by the Genetic Information Nondiscrimination Act (GINA), a federal law that makes it illegal for health insurance companies, group health plans, and most employers with 15 or more employees to request the genetic information we get from this research and to discriminate against you based on your genetic information. This laws does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

WHO SHOULD I CALL WITH QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researchers, Drs. Conroy at (317) 963-6221 or Plawecki at (317) 948-6550.

After business hours or in the event of an emergency, you may reach Dr. Conroy or Plawecki by calling (317) 944-5000 and asking that one of them be contacted.

For questions about your rights as a research participant or to discuss problems, complaints or concerns about a research study, or to obtain information, or offer input, contact the IU Human Subjects Office at contact the IU Human Subjects Office at 800-696-2949 or irb@iu.edu.

WHAT IF I DO NOT PARTICIPATE OR CHANGE MY MIND?

After reviewing this form and having your questions answered, you may decide to sign this form and participate in the study. Or, you may choose not to participate in the study. This decision is up to you. If you choose not to participate in this study or change your mind after signing this document, it will not affect your usual medical care or treatment or relationship with Indiana University.

If you change your mind and decide to leave the study in the future, the study team will help you withdraw from the study safely. If you decide to withdraw, inform the study staff that you want to withdraw from the study.

If you choose to withdraw your authorization for use and disclosure of your protected health information, you must do so in writing by notifying IU Health University Hospital, 550 University Blvd, UH5505, Indianapolis, IN 46202. If you withdraw your authorization, you will not be able to continue in this study. However, even if you cancel this authorization, the research team, research sponsor(s), and/or the research organizations may still use information about you that was collected as part of the research project between the date you signed this document and the date you cancelled this

authorization. This is to protect the quality of the research results. Otherwise, this authorization remains valid until the research ends and required monitoring of the study has been completed.

Your participation may be terminated by Drs. Conroy or Plawecki without regard to your consent in the following circumstances: you do not cooperate with the study rules, you miss the scheduled infusion session, you show up for a session with a non-zero breath alcohol concentration, testing of your urine sample is positive for any drug of abuse that could impact your safety or study objectives, if (for women) testing of your urine sample indicates that you are pregnant, or if in the clinical judgement of the investigator it would not be safe and/or prudent for you to continue participating.

PARTICIPANT'S CONSENT AND AUTHORIZATION

In consideration of all of the above, I agree to participate in this research study. I will be given a copy of this document to keep for my records.

Participant's Printed Name	**Date**
Participant's Signature	
Participant's Address	

Printed Name of Person Obtaining Consent	**Date**
Signature of Person Obtaining Consent	

Attachment A: