**NORTHWELL HEALTH**

**THE ZUCKER HILLSIDE HOSPITAL**

***DEPARTMENT OF PSYCHIATRIC NEUROSCIENCE***

# Consent for Participation in a Research Study

**Title of Study**: Therapeutic Response and Neurobiological Prediction Markers in Auditory Verbal Hallucinations
**Principal Investigator**: Philipp Homan, MD, PhD
**Sponsor**: BioMEND

## Introduction

You are being asked to join a research study. The purpose of a research study is to answer specific questions.

This consent form will explain:

- the purpose of the study
- what you will be asked to do
- the potential risks and benefits

It will also explain that you do not have to be in this study to receive medical care. You should ask questions before you decide if you want to participate. You can also ask questions at any time during the study.

## Why is this research study being done?

The purpose of this research study is to examine the effects of repetitive transcranial magnetic stimulation (rTMS) for treating auditory verbal hallucinations (hearing voices). rTMS is an FDA-approved treatment for depression. It is also being used as an open-label treatment for patients suffering from voice hearing. To date there is not sufficient evidence for the efficacy of rTMS for the treatment of voice hearing in schizophrenia. This is the first study to use a shortened protocol (only 4 sessions on 1 days) to test the efficacy of rTMS in reducing the voice hearing.

In this study, rTMS involves placing an electromagnetic coil against the left side of the head. The advantage of rTMS as compared to conventional antipsychotic medication is that this treatment has very few side effects compared to medication.

We will be looking at changes in severity of the auditory verbal hallucinations (AVH) by comparing the severity of AVH after rTMS with severity before rTMS Therefore, participants are randomly assigned to either the group that receives real rTMS or the group that receives the placebo rTMS.

Also, we will be assessing cognitive functioning, such as memory and attention using paper and pencil questionnaires to assess whether rTMS has an effect on cognitive performance. In addition, we will be using functional magnetic resonance imaging (fMRI) to see how your brain works and if rTMS changes how your brain is working.

You are being asked to participate in this study because you are a patient who reports psychotic symptoms including "hearing voices."

**How many people will take part in this study?**
This research study hopes to enroll at least 40 participants who are "hearing voices".

**How long will you be in this study?**
If you choose to take part in this study, the study procedures will last for 1 to 4 days. On the first day, you will be screened to determine if you are eligible to complete the study. The screening day includes questions about your psychiatric and medical history and an assessment if your current diagnosis and symptoms. On the screening day, we will determine if you are eligible to participate. If you are eligible, you will be asked to continue in the study. If the study team determines that you are not eligible, your participation in the study will be terminated.

If you are asked to continue in the study, the study procedures include (1) a baseline assessment, which may occur on the same day as the screening, or on the first business day following the screening visit; (2) a treatment visit, which will occur the day after your baseline assessment; and (3) a follow-up assessment, which will occur the day after your treatment visit.

**What will happen in this research study?** For an overview see Table 1.

<u>Screening visit</u>
If you were hospitalized through LIJ Emergency Department, during your routine clinical blood draw, approximately half teaspoon (2-3mls) of blood was drawn to for potential use in this research study. We have not done anything with the blood yet and are now asking for your consent to participate in this study and use your blood for research. If you agree to participate in this study, this blood will be used to identify antipsychotic levels; otherwise we will throw it out. Otherwise, if this blood sample was not obtained in the LIJ Emergency Department (either because it was not logistically possible, or because you were referred to the study from a different clinical setting) we will obtain the blood sample after you sign the consent. To determine whether or not you are eligible for participation in the study, you will be asked to participate in an interview that will take approximately 90 minutes at The Zucker Hillside Hospital or at North Shore University Hospital. This is called a 'Screening Day.' During this interview, we will explore any history of psychiatric illness, medication or illicit substance use, and will administer a brief paper and pencil questionnaire to assess cognitive functions. We can

only include patients who are currently not taking any antipsychotic medication, which also refers to the last two weeks before the start of the study. However, should there be any clinical necessity, your treating physician will modify your medication according to the best clinical practice. In the case that this includes treating you with an antipsychotic medication, you will not be eligible to stay in the study. You may continue taking other medication such as antidepressants or medication to help with anxiety.

Baseline Assessment

If during the screening day you are deemed eligible to continue in the study, you will complete a baseline assessment. This assessment may occur on the same day as the screening visit, or on the first business day following the screening visit. During the baseline assessment, you will undergo an MRI so we can examine how your brain is functioning.

The MRI will take place at North Shore University Hospital's MRI facility. The imaging procedures will include structural and functional magnetic resonance imaging (MRI). MRI machines use a strong magnet to make pictures of the inside of your body. During the scanning, you will lie on a long narrow couch for 55 minutes while the machine gathers data. You will not feel anything while the data is being collected. You will also hear loud noises that are from the MRI scanner.

Since the MRI scanner is a magnet, metal objects will be attracted to the scanner. It is very important that you tell the researcher about any metal objects, devices or implants that are in or on your body before you enter the scanner room. All metal objects must be removed before entering the magnet room. In some cases, having those devices may mean that you should not have an MRI scan.

Structural MRI takes pictures of your brain with the emphasis on measuring the structure of your brain, functional MRI measures brain activity, and ASL measures blood flow in the brain. During the functional MRI procedure, you will be asked to close your eyes, but do not fall asleep.

Treatment Visit

This is the day of the actual rTMS treatment. For this, you will have 4 appointments on this day at the Zucker Hillside Hospital.

rTMS uses a magnet to activate the brain. First developed in 1985, rTMS has been studied as a treatment for depression, psychosis, anxiety, and other disorders. The advantage of rTMS is that it can be targeted to a specific site in the brain. Scientists believe that focusing on a specific site in the brain reduces the chance for the types of side effects associated with other kinds of treatments.

In our study, we apply rTMS over the left side of the brain left (slightly above the ear) over a brain area that is thought to be hyperactive and thus contributes to the sensation of hearing voices. rTMS is thought to reduce this hyperactivation and in the process also the AVH.

*How is rTMS applied?*

An electromagnetic coil is held against the left side of the head (see Image 1). Then, short electromagnetic pulses are administered through the coil and cause small electrical currents that stimulate nerve cells in the targeted brain region. The magnetic field produced by rTMS is comparable with the strength of a magnetic resonance imaging (MRI) scan.

Since this is a clinical study in which we aim to test whether rTMS is good for the treatment of "hearing voices", the only way to assess this is by comparing the effects of real rTMS with placebo rTMS. Therefore, study participants will randomly be assigned to either the real or the placebo stimulation. Randomization is like a coin flip where you have a 50% chance of receiving the real treatment and a 50% chance of receiving the placebo treatment. You will not feel the difference between the real and the placebo treatment, because we will use the exact same device. This is done by the study coordinator and assures that the research assistants who perform the interview are unaware and thus unbiased as to which effect one could expect from the stimulation.

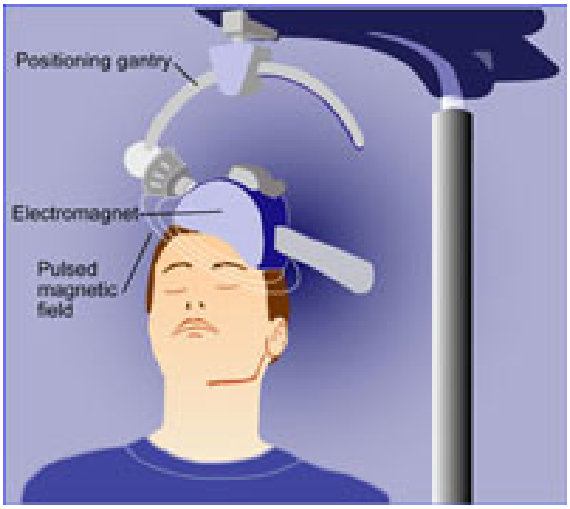

Image 1: Setup of rTMS stimulation
(soruce: https://www.nimh.nih.gov/health/topics/brain-stimulation-therapies/brain-stimulation-therapies.shtml)

Follow-up Assessment

This follow-up assessment will occur on the day following treatment and is the last day of the study. This assessment will include another MRI scan as well as an interview similar to the one on the Screening Day. Here, we will assess the severity of the hallucinations after the rTMS treatment as well as your cognitive functioning with the paper and pencil questionnaire.

Table 1.: Chart of study visits

| Procedures | Screening Visit | Three consecutive days | | |
|---|---|---|---|---|
| | | Baseline Assessment | Treatment Day | Follow-up Assessment |
| Blood sample | Yes | No | No | No |
| rTMS | None | None | Any weekday, 4 session/day | None |
| MRI | None | 1st at baseline | None | 2nd after rTMS |
| Questionnaires | Yes | Yes | Yes | Yes |
| Compensation | $20 | $50 | $0 | $50 |

**What are the risks of the research study? What could go wrong?**

Blood-Drawing

This will only be done if a blood sample was not already collected in the emergency room. There are no major risks of having blood drawn. It can be uncomfortable and can sometimes cause a bruise. In rare cases, it can cause fainting. Only trained staff will draw your blood.

Repetitive transcranial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation (TMS) is a generally safe and well-tolerated brain stimulation treatment.

During the rTMS stimulation, tickling of the area under the coil can occur. In the case that this tickling should increase to the point of scalp pain or face muscle pain, the coil will be adjusted which usually alleviates the pain. Apart from this, the most common side effect is headache or pain. Both are transient and respond well to a combination of acetaminophen and ibuprofen. Both will be administered if required.

The most significant safety concern with rTMS is a seizure. Yet, this is highly unlikely to occur with the very low stimulation frequency (1 Hertz) applied in this study. As a safety precaution, however, we will exclude patients with seizure disorders or a history of epilepsy from this study. Also, patients with implanted metal in the skull or brain will be excluded as a precaution.

Magnetic Resonance Imaging (MRI) Studies

The magnetic resonance imaging (MRI) machine is a powerful magnet. This magnet may cause any metal in your body to move. If you know of any metal in your body, you will need to tell the researcher right away. Otherwise, there are no known risks of MRI. Some people with

claustrophobia (fear of closed spaces) may find the MRI scanner too confining. In that case, you can ask to be removed from the scanner and this will be done immediately. The MRI scanner makes a loud sound. We may ask you to wear protective earplugs during scanning.

If the scan reveals a condition that could affect your health, you will be referred for the proper follow-up care to your primary care physician or another specialist.

**For Female Participants**: Although there are no known risks from MRI scans associated with pregnancy, we will not scan someone who is pregnant.

Interviews/Questionnaires

Some of the questions we will ask you are personal. You may feel embarrassed or stressed. You may ask to see the questions before deciding whether or not to take part in this study.

Some of these questions may seem very personal or embarrassing. They may upset you. You may skip any question that you do not want to answer. If the questions make you very upset, we will help you to find a counselor.

**What are the benefits of this research study?**

The possible benefits you may experience from the procedures described in this study include a free of charge rTMS treatment for the auditory verbal hallucinations you are suffering from. Yet, there is also an rTMS placebo condition, so you might not benefit directly from this study. However, information we learn about the rTMS procedure and psychotic episodes with auditory verbal hallucinations may help patients in the future.

**If you do not want to take part in this research study, what are your other choices?**

The small amount of blood collected during your emergency department visit will be thrown out. If you do not join this study, you have other choices for treatment. Talk to your doctor about your choices. Your other choices may include:

- Another research treatment
- Standard treatment with medication including antipsychotic drugs
- No treatment

**Are there any costs for being in this research study?**

This research study is funded by an internal fund. You will not have any added costs from being in this study. All study related visits, procedures and medications will be given to you at no cost. Neither you nor your insurance company will be billed for your participation in this research.

**Will you receive any payments for participating in this research study?**

You will be paid $ 120 in total for your time and travel expenses for being in this study. If you do not complete the entire study, you will be paid for the number of visits that you have completed. Payment will be made at the end of the study or when you end your participation.

If the total payment you receive from Northwell Health, during this year, is equal to $600 or more, the payment is required to be reported to the IRS. Although this study does not pay $600, if you participate in other Northwell Health studies, it is possible your payment could end up totaling $600. If this occurs, the payment you receive on this study will be reported to the IRS. In this case, you will be issued a 1099 form and be required to provide your social security number at that time for reporting purposes. You will also be responsible for reporting this income while filing your tax return.

**What happens if you are injured while participating in this study?**
If you are hurt from being in the study, you will receive medical care and treatment as needed from Northwell Health. However, you will be responsible for the costs of such medical treatment, directly or through your medical insurance or other forms of medical coverage. No money will be given to you.

**What are your rights as a research participant?**
Your participation in this project is voluntary. The quality of your medical care will be the same, whether you join, refuse to join, or decide to leave the study.

If you do not join the study you will not be penalized or lose benefits to which you are entitled. If you join the study you may withdraw at any time without prejudice to your future care at Northwell Health. Follow-up examinations may be needed to assure your well-being.

**Could you be taken off the study before it is over?**
It is also possible that your participation in this study may end without your consent. This decision may be made by a researcher, study sponsor or the Institutional Review Board (IRB- the committee that oversees research at this institution).

Reasons for withdrawal may include:

- failure to follow instructions,
- failure to show up for study visits,
- it is not in your best interest to continue on this study, or
- the study is stopped.

If you withdraw from this study or if you are withdrawn from the study, any data (or samples) already collected will continue to be used. However, no new data will be collected.

**What happens if new information is learned?**
You will be told of any new findings that may change your decision to continue to participate. Your consent to continue to take part in this study may be obtained again.

**What will happen with the information we collect as part of this research study?**

Any study information about you will be kept private and will only be given out with your permission. If the results of this study are published, your name will not be used. Your research records will be private to the extent allowed by law. In order to make sure the research is done properly, the Human Research Protection Program (the group of people that oversees research at this institution) may need access to information about your participation in this study.

**What information will be collected and used for this study?**
If you agree to be in this study, we will collect health information that identifies you. We may collect the results of interviews and MRI scans. We may also collect information from your medical record. We will only collect information that is needed for the research. This information has been described in this consent form. If you sign this consent form, you are giving us permission to collect, use and share your health information. This permission is called authorization. If you do not want to provide authorization, then you cannot participate in this research study.

**Who else will see your information?**
Study records that identify you will be kept private. You will not be identified in study records or publications disclosed outside Northwell Health, except as detailed below.

Investigators will share information collected from this research study with:

- study sponsor and/or its agents,
- other researchers,
- accrediting agencies,
- data safety monitoring board,
- clinical staff not involved in the study who may be involved in participant's treatment, billing,
- health insurers or payers

The following reviewers may access your study and medical records to make sure that this study is being done properly:

- Representatives from Federal and state government oversight agencies, such as the Department of Health and Human Services and the Food and Drug Administration,
- Representatives from Northwell Health's Human Research Protection Program (a group of people that oversee research at this institution)

We will do our best to protect the privacy of your records but it is possible that once information is shared with people listed on this form, it may be released to others. If this happens, your information may no longer be protected by the federal law.

In the future, we may publish results of this study in scientific journals and may present it at scientific meetings. If we do, we will not identify you.

If the researchers learn about potential serious harm to you or someone else or other public health concerns, it will be shared with the appropriate authorities.

**Will you be able to access your records?**
If your research records are used for decisions related to your clinical care, then you have the right to review this information and request changes. This is limited to information about your treatment, and does not include information related to procedures or tests that are for research purposes only. You may access this information only after the study analysis is complete. You have the right to know who has and who will see your records. To request this information, please call the Human Research Protection Program at 516-465-1910.

**How long will your health information be kept?**
There is no limit on the length of time we will keep your information for this research because it may be analyzed for many years. We will keep it as long as it is useful, unless you decide you no longer want to take part or we close the study. You are allowing access to this information indefinitely.

**Can you change your mind?**
If you change your mind about being in the study, you may withdraw at any time. If you want us to stop collecting your health information, you need to send a letter to the researcher at the following address:

Dr. Philipp Homan
The Feinstein Institute for Medical Research
Hofstra Northwell School of Medicine
Dept. of Psychiatry Neuroscience
350 Community Drive
Manhasset, NY 11030

Your letter needs to say that you have changed your mind and do not want the researcher to collect and share your health information. You may also need to leave the research study if we cannot collect any more health information. We may still use the information we have already collected. We need to know what happens to everyone who starts a research study, not just those people who stay in it.

**Will information about this study be available to the public?**
A description of this clinical trial will be available on http://www.Clinical Trials.gov , as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

**Does the investigator of this study receive money if you take part?**
The investigators on this study receive money to conduct the study, but do not financially benefit from your participation. The money they receive is to pay them back for the costs of conducting the research study. Funding for this research study is provided by BioMEND, an internal fund. If

your doctor is an investigator for this study s/he is interested in both your healthcare and the conduct of this research. You do not have to take part in a research study conducted by your doctor.

**Who can answer your questions about this study?**
If you have any questions about the study, you may call the Principal Investigator, Dr. Philipp Homan, at (718) 470-8267 or the study's coordinator, Stephanie Winkelbeiner at (718) 470-4588. If you have questions about side effects or injury caused by research you should call Dr. Philipp Homan at (718) 470-8267. If you need emergency care, dial 911 or go to the nearest Emergency Room. If you have questions about your rights as a research participant, concerns about being in the study, or would like to offer input, you may contact the Office of the Institutional Review Board (the committee that oversees research at this institution) at (516) 465-1910.

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

**[Signature Page Follows]**

**NORTHWELL HEALTH**
**THE ZUCKER HILLSIDE HOSPTIAL**

**Participant Name:** _____ **Date:** _____

**Asssessor Name:** _____

**Assessor's Signature:** _____

## STUDY INFORMATION REVIEW VERSION FOR POTENTIAL SUBJECTS ONLY

**DIRECTIONS**: Below are questions that people frequently have about the study. Each question is followed by 2 answers. One answer is correct and the other answer is wrong (or false). Please put a check mark next to the correct answer.

**Example question**: *Where is the hospital located?*

✓ a) I am currently in New York.

OR

☐ b) I am currently in New Jersey.

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Question 1: *Do I have to be in the study to get treatment at the hospital?*

☐ a) To get treatment, I must be in the study.

OR

☐ b) To get treatment, I do not have to be in the study.

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Question 2: *If I start in the study, can I leave before it is over?*

☐ a) If I decide to be in the study, I must stay until it is over.

OR

☐ b) If I decide to be in the study, I can leave any time that I wish.

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Question 3: *How long does the study last?*

☐ a) If I want to, I may be in the study for up to 3 days.

OR

☐ b) If I want to, I may be in the study for up to 3 weeks.

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Question 4: *Does everybody in the study get the same amount of TMS sessions?*

☐ a) All participants will receive the same amount of TMS sessions.

OR

☐ b) The amount of TMS sessions will be changed depending on the individual participant.

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Question 5: *Can the TMS in the study make me feel tired?*

☐ a) TMS in the study may make me feel tired.

OR

☐ b) TMS in the study cannot make me feel tired.

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Question 6: *Can the MRI make me feel anxious?*

☐ a) Yes, the MRI can make me feel anxious.

OR

☐ b) No, the MRI will not make me feel anxious.

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Question 7: *Will I have to complete the neurocognitive and clinical assessments during the study?*

☐ a) Yes, I will complete the neurocognitive and clinical assessments during the study.

OR

☐ b) No, there are no assessments required in this study.

## Summation/Signature

You have read the above description of the research study. You have been told of the risks and benefits involved and all your questions have been answered to your satisfaction. A member of the research team will answer any future questions you may have. You voluntarily agree to join this study and know that you can withdraw from the study at any time without penalty. By signing this form, you have not given up any of your legal rights.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____ _____ _____
Witness's Printed Name Witness's Signature Date

**Investigator's Statement**
In addition to advising the above participant of other forms of treatment and therapy which are appropriate, I have offered an opportunity for further explanation of the risks and discomforts which are, or may be associated with this study and to answer any further questions relating to it.

_____ _____
**Investigator's signature** **Date**

_____
**Investigator's printed name**