Informed Consent Form

Accelerated Transcranial Magnetic Stimulation for People With Schizophrenia Treated With Clozapine

NCT06003036

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UPMC LIFE CHANGING MEDICINE

CONSENT TO ACT AS A SUBJECT IN A CLINICAL STUDY

TITLE: Accelerated Neuromodulation of Prefrontal Circuitry during Clozapine Treatment

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Sponsor: National Institute of Mental Health

KEY INFORMATION:

- Treatment options for treatment-resistant schizophrenia (TRS) consist largely of clozapine and psychosocial interventions, like therapy, that can be effective, however there are cognitive and functional impairments that remain and limit daily life.
- In this study, we are using transcranial magnetic stimulation (TMS) to examine whether it can enhance cognition and connectivity in the brain to work alongside clozapine as an effective supplement to standard treatment for TRS.
    - There is no change to your medication regimen in this study, and all medical treatment will continue to be determined by your treatment team.
    - Risks of the study are minimal and are addressed in more detail below.
    - Participation is voluntary and we appreciate all the help we can get for this study.
    - We do compensate individuals for their time and help.

Why is this research being done?
The purpose of this research study is to use intermittent Theta Burst Stimulation (iTBS) to determine whether neurocognition and connectivity in the prefrontal cortex can be modulated in

schizophrenia to increase effectiveness of treatment. We know that clozapine is effective in treatment-resistant schizophrenia (TRS), however we have limited treatment strategies for cognitive deficits of TRS, specifically working memory. We know that certain areas of the brain are involved in cognition, but we want to find out how changing function in these areas influences brain function and memory. Eventually, the findings of this study might be useful in influencing treatment strategies.

What will happen in the study?
We are asking 30 adults (ages 18-65) with a diagnosis of schizophrenia and a treatment regimen of clozapine to participate in our research study. We will first need to determine your eligibility for this study.

The screening process will include:

- Questions checking for certain types of metal in your body because you cannot participate in the MRI if those metals cannot be removed.
- Completing a TMS safety screening.

If you are eligible to participate, then you will be asked to complete the following assessments:

- VISIT 1:
    - Baseline clinical evaluations to assess symptoms and diagnosis, a cognitive (thinking) test, demographic and medical history; the visit will include completion of surveys about your mood, your social interactions, and other questions about your life experience with your diagnosis of schizophrenia. These surveys will be repeated in follow-up visits. Some of them will be completed on an electronic device provided by the study team.
    - one 30-minute MRI session to determine where to place the TBS on your scalp,
    - finding your "motor threshold" to determine the intensity of the stimulation for visits 2 and 3.

- VISIT 2:
    - The TBS or Sham procedure,
    - a 30-minute MRI immediately following TBS completion,
    - clinical evaluations within a few days of TBS completion to assess changes in symptoms, which may be done in person at our offices or on your own device via a link sent to you.

- VISIT 3:
    - The TBS or sham procedure,
    - a 30-minute MRI immediately following TBS completion, and
    - clinical evaluations within a few days of TBS completion to assess changes in symptoms, which may be done in person at our offices or on your own device via a link sent to you.

The Baseline assessments will take approximately 4 hours to complete. Visits 2 and 3 will each take approximately 6 hours to complete, with clinical evaluations occurring within the week following TBS either remotely or within our research offices.

The Theta Burst Stimulation (TBS) procedure will include 5 rounds of:

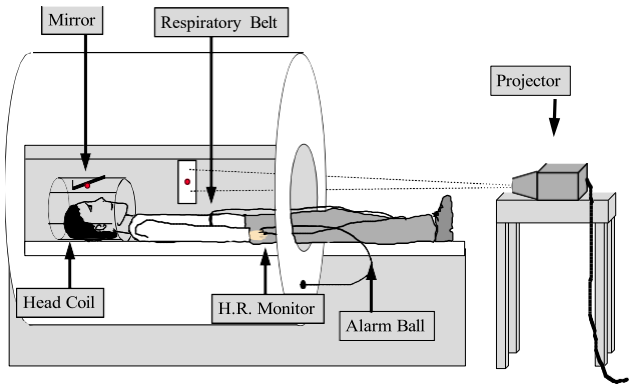
- 10 minutes active stimulation
- 50 minutes of rest

This study itself does not involve any new treatment. You will continue the treatment activities that are available to other patients. You will have routine clinical care, as all other patients have, including regular blood tests and other work-up tests. **The information that is collected in this research study will not be used to change the treatment you receive from your treating psychiatrist.**

fMRI Scan

The fMRI scan consists of you lying down on a table, which then slides into the scanner to take pictures of your brain while you are experiencing and doing different things. The pictures that the scan creates show the parts of the brain that are active and how they coordinate their activity. While the scanner is working, you will hear noises, like knocking or beeping sounds. We provide you with earplugs to reduce the noise level in the scanner. fMRI is a painless procedure that does not use radiation, but uses radio waves, a large magnet, and a computer to create images.

All fMRI scans will take place at the Magnetic Resonance Research Center (MRRC) at UPMC Presbyterian Hospital. During the scan you can talk to the study staff, and you can hear them talk to you. If you want to leave the MRI machine or if you have difficulties, you can tell study staff and they will help you. You will be given a squeeze bulb to hold in your hand to squeeze if you want to leave the MRI machine. You will be asked to leave any metal objects in a locker in the waiting room of the MRI center. You will also be asked to remove any articles of clothing with metal inserts or clasps before entering the magnet room and to fill out a standard MRI safety questionnaire. It is important in these studies that you remain still while in the scanner; movement in the head, arms and legs can make the brain pictures blurry. Please ask the researcher if you are unsure about these instructions.



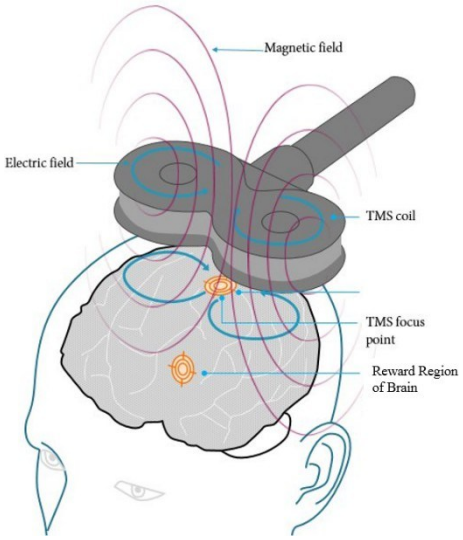
You will also complete a working memory computer task while in the scanner. You will see images on the screen and use a glove on your hand to press buttons in response to those images. This task assesses your ability to temporarily hold information for making decisions.

You will not be informed of the results of the brain imaging scans because the purpose of these MRI recordings is for research and this type of scan can't be used to get clinical information such as neurological health. However, if there is something unusual on the scans that requires further clinical evaluation (as judged by a radiologist) we will tell you this information and offer an appropriate referral to a medical facility.

Intermittent Theta Burst Stimulation (iTBS) and Motor Threshold

Theta Burst Stimulation (TBS) describes the type of brain stimulation that we are using. You may also see or hear the term TMS (Transcranial Magnetic Stimulation). Theta Burst Stimulation (TBS) is just a shorter version of TMS.

TBS is a technique to briefly stimulate a region of your brain with a magnetic field that passes through the scalp and the skull safely. We will use the MRI brain images to guide the TBS so that the stimulation is in the right place for our study.



In preparation for your TBS sessions, we will find your "motor threshold". The motor threshold is the lowest stimulation intensity needed to make your thumb twitch. The TMS coil will be positioned over the region of your brain that controls movement, and we will stimulate that region to cause a muscle twitch in your thumb and record that level of stimulation. Once we find your motor threshold, we are prepared for the TMS session.

We will ask you to complete 5 sessions of TBS at each visit, separated by one month. Each time you get TBS, it will last approximately 10 minutes, with 50-minute breaks in between sessions. In one of your visits, you will hear and feel a similar sensation around your head, but you will be getting a simulation of pulses, so nothing will be happening to stimulate your brain. To prevent any differences caused by personal expectations, we will not tell you which condition of TBS you will receive on which visit.

The study staff will be available to talk to you before you start the procedure and will give you a chance to see the device that will be used and to ask any questions that you have before beginning the TBS process. The staff will also be standing by while you are receiving TBS and you should tell the research team if anything is uncomfortable. You can also choose to stop the procedure at any time.

Risks

- ***Interviews/Questionnaires:*** Some of the questions we will ask you are personal. You may feel tired, upset, stressed or embarrassment about some of the questions or procedures. If this happens, you should tell one of the study personnel and he/she can stop the session. Depending on how you feel, you may then decide to (1) take a rest period; (2) reschedule the interview; or (3) not finish the interview. You may review the questions before deciding whether to join the study. Also, you do not have to answer any questions that may upset you. All interviews will be completed by highly trained staff. Some risks associated with neuropsychological testing include frustration with the testing, performance anxiety, and fatigue. Please let the research team if these occur and we will stop the assessment.

- ***Collection and storage of private health information:*** This carries a risk of a breach of confidentiality: Because we are collecting identifiable information from you, there is a rare risk that the information could become accessible to people other than those in this research study. Breaches in confidentiality are rare. To minimize these risks, all paper records related to your involvement in this research study will be stored in a locked file cabinet and all electronic

records are stored in a password-protected database with special permission to files that include identifying information. You will also be assigned a case number and it is this number, along with your initials (for proper identification by the research team), that is used on research assessments.

- ***MRI:*** 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 loud sounds, so we will ask you to wear protective earplugs during scanning. On rare occasions, some subjects may experience one or more of the following: momentary dizziness, nausea, tingling sensations and/or muscle twitches. Please tell the investigator over the intercom if any of these sensations occur.

  We are doing the MRI in this study to answer research questions, not to give you medical care. If at the time of the scan, the MRI technologist detects a potential incidental finding, a radiologist reviews the scan to assess its clinical significance. If the radiologist thinks there might be a problem or 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. This MRI is not the same as one that your own doctor would order. It may or may not show problems that would be found on a standard MRI.

- ***iTBS:*** The brain stimulation in this study comes with the risk of experiencing scalp discomfort and/or a mild headache during or immediately after the TBS procedure due to the activation of the scalp muscle near the device. There is also a less common risk with the TBS of a delayed onset headache (which can be helped with ibuprofen), and the very unlikely possibility of a seizure. Although considered rare, there are reports of seizures with iTBS/TMS in the published literature and it is unknown whether the risk is increased when someone is taking clozapine, a medication that is linked with seizures. There is also the rare chance that a hypomanic mood state could result from the TMS procedure. Lastly, there is also a possibility that a TBS session will produce worsening of depression symptoms (a rare side effect in TMS) however, we do not anticipate that anyone will experience long- lasting mood change from a single session.

You will not receive any direct benefit from participating in this research study. However, the research data obtained may provide information about treatment strategies for schizophrenia in the future. Your data used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

Your de-identified data and health information will be stored and may be shared with other researchers. The samples and information will be available for any research question, such as research to understand what causes certain diseases (for example heart disease, cancer, or psychiatric disorders), development of new scientific methods, or the study of where different groups of people may have come from.

If you agree to be in this study, we may also contact you in the future about the possibility of participating in future studies. If we contact you in the future about a study, you will be presented at that time with complete information about the study and you will then be given the opportunity to decide to either participate or not participate in the study.

We are also requesting your authorization or permission to review your medical records. Information from your medical record including your age, diagnosis, past psychiatric history, and ongoing psychiatric and behavioral assessments will be collected since this information is important for understanding how one might respond to antipsychotic treatment. This identifiable medical record information will be made available to members of the research team for an indefinite period. This authorization is valid for an indefinite period. However, you can always withdraw your authorization to allow the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing. If you do so, you will no longer be permitted to participate in this study. Any information obtained from you up to that point will continue to be used by the research team.

Any new information that comes to the attention of the investigators during the span of the research project and that may relate to your willingness to continue to participate will be provided to you. If any of the tests should reveal any abnormalities, you will be informed, and appropriate clinical follow-up referrals will be facilitated. If we learn that you or someone with whom you are involved is in danger or potential harm, we will need to inform, as required by Pennsylvania law, the appropriate agencies.

Are there any costs for being in this research study?
There is no cost to you for participating in the study. All study related visits and procedures will be provided at no cost to you, such as the MRIs. Costs related to your standard care will be billed as usual to you or your insurance company. Travel expenses to and from the UPMC facilities will be reimbursed, and you will be provided a meal pass when you come in for longer visits.
None of the procedures you complete for the purpose of this research study will be billed to you or your health insurance. Research funds will pay for all costs related to your participation. If you get a bill or believe your health insurance has been billed for something that is part of the study, please contact a member of the research team. You (or your insurance) will be responsible for any costs related to referrals for incidental findings found during the conduct of this study.

You will receive the following payments for participating in this research study:

Assessment	Baseline	Session 1	Session 2

Diagnostic Interview (SCID)	$25		
Cognition assessments	$25	$25	$25
Clinical Interviews	$20	$20	$20
MRI scan per hour	$38	$38	$38
Motor Threshold	$50		
iTBS/Sham		$75	$75
TOTAL	**$158.00**	**$158.00**	**$158.00**

If you complete the entire study, you will receive an additional $50.

In total, you can receive up to $524.00.

All compensation is taxable income to the participant regardless of the amount. If a participant receives $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 24% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 76% of the expected payment.

To protect your privacy and maintain the confidentiality of information we obtain from you, we will maintain all information about you in a secure location. Several procedures have been put into place to protect the privacy of your research data (see "Breach of Confidentiality" above). Only members of the research team, staff in the Office of Research Protections, and authorized representatives of the sponsor of this research study (the National Institute of Mental Health) may have access to your identifiable research data, including medical record information. Authorized representatives of UPMC or other affiliated health care providers may have knowledge of your identifying information based on services they provide to the research team. However, just as with the use of your medical information for health care purposes, we cannot absolutely guarantee its privacy. We will protect your privacy and the confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information obtained from your medical records once your personal information is disclosed to others outside UPMC or the University. Please note that text messages are not encrypted or secure during transmission and could be intercepted. **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.**

You may withdraw your permission for participation in this research study at any time. Your participation is completely voluntary and your decision whether to participate in all or part of this study, or to later withdraw from all or part of it, will not affect your current or future medical care at UPMC. Your research information and medical record information collected before you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

Your doctor may be involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested in both your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study

participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state, or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

You may be removed from the study if, at any time, we discover that you do not meet study eligibility, for serious non-compliance with the study protocol or if the study is not believed to be in your best interest. You may also be removed if you stop taking your antipsychotic medication.

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

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VOLUNTARY CONSENT:

All the above has been explained to me and all my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668).

By signing this form, I consent to participate in this research study and provide my authorization to share my medical records with the research team. A blank copy of this consent form will be given to me.

_____

Participant's Name (Print)

_____ _____

Participant's Signature Date

CERTIFICATION OF INFORMED CONSENT:

I certify that I have explained the nature and purpose of this research study to the above-named individual, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual has about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date