Accelerated Intermittent Theta-Burst Stimulation for Depressive Symptoms

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FOR QUESTIONS ABOUT THE STUDY, CONTACT: Dr Nolan Williams, 401 Quarry Road, Palo Alto, CA, 94304. (650) 498-9111

Are you participating in any other research studies?_____Yes_____No

PURPOSE OF RESEARCH

We are doing this research study to find out if an accelerated form of intermittent theta burst stimulation (iTBS) is effective in treating depressive symptoms. iTBS is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with depression that have not benefited from medication. This FDA treatment involves stimulating the left front area of the head with an electromagnet that produces a magnetic field delivered in short bursts. These bursts are focused on an area of the brain that is thought to be involved in causing depression. As the magnet rapidly turns on and off, the electrical currents in the brain tend to synchronize with the magnet. iTBS has been shown to help some patients with depression. Usually treatment lasts 6 weeks but we are trialing a stimulation course which lasts only 5 days.

You are being invited to participate in this research study because you are currently experiencing a depressive episode and have tried at least one antidepressant in the past that has not helped your depression.

This research study is looking for 200 people with depressive symptoms. Stanford University expects to enroll all 200 research participants.
If you decide to terminate your participation in this study, you should notify Dr. Nolan Williams at 650-498-9190.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take 1 week of active participation by each participant. If improvements in your mood are not found after initial study participation, you may be offered the opportunity to be enrolled for a second week (in which a different brain area will be targeted).

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Each brain stimulation session will be 10 minutes long with a 50-minute break between each session. The stimulation sessions will be delivered hourly for 10 hours for each of the 5 days (50 hours per week). Sessions will start at either 8:00 AM, 8:15 AM, 8:30 AM or 8:45 AM. Sessions will be at the same time past the hour, every hour for 10 hours.

PROCEDURES

If you choose to participate, the Protocol Director and his research study staff will ask you to sign this consent form before doing any study procedures.

Baseline

The baseline session will happen the day before you start the aiTBS course. During the baseline session:

- Your motor threshold will be measured; this is the degree of stimulation required to produce a thumb or toe twitch. Motor threshold measurements tell us what level of stimulation your brain requires.
- You will complete neurocognitive tasks on an iPad
- If you agree to contribute stool, blood and salvia samples, these will be collected at baseline and after the aiTBS course in order to identify potential biomarkers of treatment response. These samples will not be saved for future research.
- We will ask you questions about your mood
- You will complete questionnaires about your mood, sleep and quality of life.
- We will measure your heart rate at baseline and at the end of each stimulation day
- If you are involved in the sleep study, the night before the stimulation course begins, brain recordings will be made overnight whilst you sleep. More details can be found below.

Sleep Study Procedures:

If you choose to participate, the program director, Dr. Ruth O'Hara and her research study staff will contact you to schedule a study day for an overnight sleep recording.

1) In the evening around 7-8 pm, our research assistant will visit your bedside at Stanford Hospital to set up the sleep study device.

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2) You will be asked to wear a customized cap with a plastic connection to probes placed on its the surface.
3) Polysomnography electrodes (small metal probes with vinyl coated wires connected to device) will be applied to the plastic connector on the cap. Polysomnography is a noninvasive device.
4) Additional information, including oxygen saturation, pulse rate, motion, and position during sleep may be obtained through wearable device or bed with built in sensor.
5) During this process, the skin of your scalp will be prepped with cleaning cream, and conducting gel will be applied through the connector on the cap. You will feel something is cold gel scratching on the scalp, but it should not cause pain.
6) Other probes of PSG measuring eye movement and muscle activity include, 2 Electrooculogram electrodes (small stickers with metal probe) that will be applied around the eyes, 3 electromyogram electrodes (small stickers with metal probe) that will be applied to the chin, and pulse oximeter on fingers.
7) Other probes of PSG measuring heart beat, 2 Electrocardiogram electrodes (small stickers with metal probe), will be placed on the upper chest.
8) Other probes of PSG measuring breathing, Nasal pressure transducer and oral/nasal thermistor, will be placed by hooking up the loop of the tube to your ears.
9) Other probes of pulse oximeter will be placed on your fingers and more information (motion, temperature or sound) may be corrected from the sensors installed in the bed if the study is done in sleep lab.
10) You will be asked to go to bed at your regular bed bedtime and sleep on the bed whenever you feel ready to sleep.
11) In the morning, you will be asked to wake up at your usual wake-up time and all electrodes will be disconnected. Instructions will be given regarding how to disconnect it safely.

Important points for sleep study:

- No invasive procedure will happen.
- No specimen will be collected.

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Stimulation (Days 1-5)
You will be randomly assigned to receive stimulation to either a brain area called the left dorsolateral prefrontal (DLPFC) or the anterior cingulate cortex (ACC). Both of these areas are thought to be involved in the regulation of mood and have shown to display atypical activity in people with depressive symptoms or suicidal thoughts.

During stimulation sessions you will:

- Receive 10 iTBS sessions. Each session takes 10 minutes to complete with a 50-minute break between sessions.
- Complete some questionnaires about the way you have been feeling
- Have your heart rate variability measured once per day.
- If you take part in the EEG portion of the study, EEG recordings will be made before, during and after the first and last stimulation sessions to measure brain activity.

If you are involved in the sleep study, the night after the first and last day of stimulation, electrodes will be used to record brain activity overnight (in the same way as the night before stimulation).

If your mood improves significantly before the 5 days of brain stimulation sessions are complete, resulting in you being well enough to be discharged from hospital, you may be discharged from hospital before the end of the full 5 day course. This will be left to your clinician's discretion.

Alternatively, if you have not responded to the first course of aiTBS, you may be offered stimulation at the alternative stimulation site (DLPFC or ACC).

Immediate Post-Stimulation (Day 6-7)

- Complete some questionnaires about the way you have been feeling
- Perform some tasks measuring neurocognitive ability on an iPad
- Saliva samples will be collected.
- You will also complete online questionnaires about your mood, sleep and quality of life.

If you are still in hospital the night after the stimulation course and you are participating in the sleep portion of the study, you will undergo the same sleep recordings as you did at baseline.

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After discharge you will go to the Open Medicine Institute in Mountain View to have Blood and stool samples collected. The blood draw will be the same amount as a standard blood test.

Women of Childbearing Potential
If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking part in the study. The study doctor may ask for your permission to collect information about the outcome of your pregnancy and the condition of your newborn.

Tissue Sampling for Genetic Testing

As part of the analysis on your samples, the investigators (may/will) do genetic testing. Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research may include looking at information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual and family medical histories, reactions to medications and responses to treatment. Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks

can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

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PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Continue to take your medications as instructed by your physician.
- Arrive at the time specified for each of your study procedures.
- Keep your study appointments. If it is necessary to miss an appointment, please let the research staff know so they can reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Nolan Williams at 650-498-9190. At that time, your care will be transferred back to your primary psychiatrist for further assessment and treatment.

If you decide to stop taking part in the study for any reason, we will ask you to have a consultation with the study clinician which will take about 30 minutes.

During this consultation, the study clinician will:

- Ask you questions about your mood and well-being
- Complete some questionnaires about the way you have been feeling
- Review your medications

The Protocol Director may also withdraw you from the study and the study experimental treatment may be stopped without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

You will be asked about several things, which are potential risks to your health when getting TMS Therapy. These include:

- A history of a neurological disorder, including brain tumors, seizures, stroke, abnormalities in the blood vessels in your brain, dementia, Parkinson's disease, Huntington's chorea or multiple sclerosis,
- Anything which could increase your risk of having a seizure, including a history of a head trauma with a loss of consciousness for more than 5 minutes
- The presence in your body of cardiac pacemakers, implanted medication pumps of any sort, or a history of bad heart disease,
- The presence of any metal objects in or near your head which cannot be safely removed for the duration of this study.

During the TMS treatments, you may experience buzzing, tapping, or painful feelings at the treatment site during the stimulations. These are usually mild to moderate in strength and may become more bearable after the first day of treatment. Not all subjects experience these effects with TMS treatment.

Traditional FDA approved TMS has a low risk of seizure (1:30,000). The type of stimulation utilized in this study has never caused a seizure and we believe that there is little to no risk of seizure with aiTBS.

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Because the aiTBS device emits a loud noise, and there is a risk of temporary hearing loss, you will wear protective ear plugs during treatment.

The blood draws may cause slight discomfort at the puncture site. Some individuals may feel light headed or faint when having blood tests. Please let the staff member performing the blood draw know if you have felt this way before when receiving injections or blood tests or if you feel this way at any point during the blood tests so they can make you as comfortable as possible and prevent a faint from occurring.

Although no induced-mania has been reported following iTBS, a small number of cases of TMS-induced mania have been reported for other TMS protocols. Staff members will monitor your symptoms carefully and it is important that you let members of the research team aware if you experience a noticeable decrease in the amount of sleep you require and increased energy. If you exhibit signs of hypomania/mania we will not administer further stimulation sessions.

The application and removal of EEG electrodes can cause some irritation. If you are involved in the sleep study, the quality of your sleep might be lower than normal because you are concerned about dislodging the electrodes. As a result, you may feel less rested in the morning, and your cognitive performance may be perceptibly diminished on the following day.

Protection Against Risk

It is unlikely, but possible that your depression may worsen or may not improve. Some of the questionnaires and interviews in this study may provoke feelings of frustration, fatigue, sadness or anxiety. You have the right to refuse to answer any question that makes you feel uncomfortable. Information you provide will remain anonymous and will be used only for the purposes of the research study. However, it is possible that, based on information gained from this study, the researchers may be required to report information (e.g., information relating to suicide, physical or sexual abuse or other conditions reflecting imminent risk) to the appropriate authorities.
The responses to questions concerning illegal drug use could be self-incriminating and harmful to you if they became known outside the study. As explained in the confidentiality statement of the consent, we do not intend to disclose this information.

There may be other risks associated with participating in this study that are unknown.

We will keep your study data as confidential as possible, with the exception of certain information that we must report for legal or ethical reasons, such as

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suspected child abuse or neglect, suspected elder or dependent abuse or neglect, or intent to harm yourself or others.

POTENTIAL BENEFITS

You may or may not benefit from taking part in this study. It is possible that your depression symptoms will improve and you may begin to feel better while you are taking part in this study. However, if you find the study intervention to be helpful you will not be able to continue to receive it upon completion of the study. The study aiTBS is investigational and not approved by the FDA for the treatment of depression.

The study may also benefit other people with depressive symptoms by furthering our understanding of the antidepressant effectiveness and safety of aiTBS.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

You do not need to take part in this study to be treated for depression. There are other treatments available for your depression. These include a variety of antidepressant medications such as fluoxetine (Prozac), paroxetine (Paxil), bupropion (Wellbutrin), and psychotherapies (talk therapies), such as cognitive behavioral therapy (CBT). These treatment options also include Electroconvulsive therapy (ECT) and traditional Transcranial Magnetic Stimulation (TMS) once out of the hospital.

Talk with the study doctor if you have questions about any of these treatments or procedures.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

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ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.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 Web site at any time.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

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Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to determine if to find out if a new form of transcranial magnetic stimulation (TMS) is effective in treating Major Depressive Disorder (MDD). The information gathered in this study will be submitted to the FDA.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study including receiving any research-related treatment.
Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health

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information in this study, you must write to: (Dr. Nolan Williams Department of Psychiatry, 401 Quarry Road Stanford, CA 94305).

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to name, address, telephone number, date of birth, race/ethnicity, gender, information about general health (current mood states, family history, general medical conditions, medications, therapy, alcohol and substance use), mental health history, physical examinations, results of tests for pregnancy and drug use, response to the
study device, side effects experienced, (blood, stool and salvia) and the results of any tests
done during the
study.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- ☐ The Protocol Director (Nolan Williams).
- ☐ The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- ☐ Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- ☐ The Office for Human Research Protections in the U.S. Department of Health and Human Services
- ☐ The Food and Drug Administration (FDA)

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- ☐ Our collaborators at the Open Medicine Institute and Brainsway TMS device vendor

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on February 28, 2050.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

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FINANCIAL CONSIDERATIONS

Payment

You will not be paid to participate in this research study.

Costs

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Sponsor

Stanford is providing financial support and/or material for this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Nolan

Williams, MD (650) 498-9190. You should also contact him at any time if you feel you have been hurt by being a part of this study.

The purpose of this research study is to obtain data or information on the safety and effectiveness of (insert name of drug, device, etc.); the results will be provided to the sponsor, the Food and Drug Administration, collaborators The Open Medicine Institute and Brainsway and other federal and regulatory agencies as required.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

If you cannot reach the Protocol Director, please contact Romina Nejad at (650) 497-3933.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;

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- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes_____No

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

☐ Please tick this checkbox if you agree to take part in the sleep study portion of the experiment.

☐ Please tick this checkbox if you agree to take part in the heart rate variability part of the study.

☐ Please tick this checkbox if you agree to take part in the EEG part of the study.

☐ Please tick this checkbox if you agree to have stool and salvia samples taken.

_____ _____
Signature of Adult Participant Date

_____
Printed Name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Conent