Cortical Inhibition as a Biomarker of Response in a Comparison of Bilateral Versus Unilateral Accelerated Theta Burst Stimulation for Suicidal Ideation in Treatment-Resistant Depression (COMBAT-SI)

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University of California, San Diego
Consent to Act as a Research Subject

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Introduction

Dr. C.R. Weissman, Dr. Z.J. Daskalakis, Dr. I. Hadas, and Dr. L.G. Appelbaum are conducting this research and asking for your consent to participate. This section provides a summary of important information. The rest of the form provides additional details.

- Research is voluntary- whether or not you join is your decision. You can discuss your decision with others (such as family and friends).
- You can say yes but change your mind later.
- If you say no, we will not hold your decision against you.
- Your decision will not affect your relationship between you and UC San Diego or any other benefits you may be entitled to.
- You can say no even if the person inviting you is your healthcare team.
- Please ask questions or mention concerns before, during, or after the research.

The purpose of this study is to determine the effects of bilateral accelerated theta burst stimulation (aTBS), a form of repetitive transcranial magnetic stimulation (rTMS), on suicidal ideation and suicide prevention in patients struggling with difficult-to-treat depression. Participation in this study may not directly benefit you but may result in new knowledge to help other patients in the general field of psychiatry. This is a single-site trial, and we aim to enroll 76 participants at UCSD. Please take the time to decide, and be sure to ask any questions you may have. You will undergo an initial consultation with a psychiatrist to see if you are eligible for the study. Appropriate psychiatric care will be provided to you whether you continue with the study or not. Your participation will last approximately 6 months.

The most common side effects of aTBS include headaches, scalp discomfort at the site of stimulation, tingling, spasms or twitching of facial muscles, and lightheadedness.

The most serious adverse effect during aTBS is a generalized seizure. The risk of seizure is comparable to that of antidepressant treatment and occurs in less than 0.1 to 0.5 percent of patients when safety guidelines are followed.

Alternatives to this study can include medications, talk therapy, electroconvulsive therapy, and traditional rTMS. Below is additional, detailed information about this research. Please feel free to ask questions before signing this consent.

Why have you been asked to participate, how were you selected, and what is the approximate number of participants in the study?

You have been asked to participate in this study because you have been diagnosed with major depressive disorder (MDD). We aim to enroll 76 participants in this study. Repetitive transcranial magnetic stimulation (rTMS) changes the electrical brain activity in major depressive disorder (MDD). While known to be effective for MDD, it is unclear how effective rTMS is as a treatment to treat suicidal thoughts and prevent suicide overall. An "accelerated" form of rTMS will also be used, consisting of 5 days with 10 sessions per day. This is instead of the standard 4 weeks of treatment with once per day. This study will look at a state-of-the-art rTMS protocol in an attempt to treat suicidality in the context of MDD. It will determine a brain-activity signature that could help select the best rTMS treatment plan for an individual patient. This may also help researchers better understand the physiological mechanisms (things that happen in your brain) behind suicidality, which would help develop even better treatments in the future.

What will happen to you in this study? Which procedures are standard of care, and which are experimental?

In addition to the information at the beginning of this form, here are some additional details about what will happen to you if you agree to be in this study:

You may be randomized to two treatment courses where the stimulation will be applied to your head, called the dorsal lateral prefrontal cortex (DLPFC). You will either receive active bilateral aTBS on both sides of your head or unilateral left aTBS treatment with a sham or "fake" right-side stimulation. Sham treatments are methods used in medical trials to help researchers determine the effectiveness of a drug or treatment. This means that if you are assigned to the unilateral aTBS treatment group, no stimulation will be created on your right side, but you will receive active treatment at the left DLPFC. There is no sham component to the bilateral aTBS treatment. Therefore, everyone in the study will receive a form of active treatment. Your chance of being assigned to each group is 1 in 2 or 50 percent. Neither you nor the researcher(s) can choose the group to which you will be assigned.

We will also administer clinical assessments during all your visits except for the MRI. These assessments will include self-report questionnaires and clinical rater-administered questionnaires. These questionnaires will assess your mood (MADRS, HRSD-17, PHQ9, GAD-7, WHODAS 2.0, The DSM-5 Level 1 Cross-Cutting Symptom Measure, and BHS), suicidal ideation (INQ, SSI, CSSRS-Lifetime), and medical history (MINI).

Treatment Course: this consists of a clinical screening visit, a baseline MRI and neurophysiology visit, 5 consecutive days of TMS sessions for 1 week, a post-treatment neurophysiology visit, and a consult with our study psychiatrist 4 weeks post-treatment to monitor your health. We also plan to follow up on overall health with clinical assessments at months 1, 3, and 6 post-treatment. These procedures are experimental.

rTMS, and specifically theta burst stimulation (TBS; a high-intensity version of rTMS that takes less time than traditional rTMS protocols but uses the same machines) is an FDA-approved treatment that is effective for MDD; it is not experimental. There is not yet a specific indication by the FDA for any form of rTMS as a treatment for suicidal ideation or suicide prevention, though. Additionally, there is not yet a specific indication by the FDA for any form of accelerated TBS. If you agree to be in this study, you will go through several experimental procedures: an accelerated TBS protocol for treating MDD and suicidality and brain activity assessments that try to identify patterns associated with suicidality, depression, and symptom improvement.

TBS: your brain will be non-invasively (i.e., over the scalp surface) stimulated by magnetic pulses. For this procedure, you sit on a chair and will be asked to wear earplugs. An rTMS coil will be positioned over the right for bilateral and unilateral treatments. Then, the left front part of your scalp is on top of your head, and a repetitive stimulation is delivered. The entire treatment procedure day will take approximately 10 hours. Treatment will be administered for 10 minutes, with approximately 50-minute breaks. You will be awake and communicate with a trained rTMS technician throughout the procedure.

Magnetic Resonance Imaging (MRI) Scan: an MRI uses electromagnetic radio waves in a strong magnetic field to take clear pictures of your brain. These pictures will help us identify the precise location of the rTMS stimulation on your head. You will be asked to lie still on a table in the MRI machine for 30-40 minutes during the scan. One MRI scan will be completed in this study at the beginning of your TMS treatment week.

Transcranial magnetic stimulation concurrent with electroencephalography (TMSEEG) neurophysiological assessments: your brain will be non-invasively (i.e., over the scalp surface) stimulated by magnetic pulses while being recorded for electrical

brain activity. For this procedure, you sit on a chair and will be asked to wear earplugs. You will be fitted to wear an EEG cap. A TMS coil will be positioned over the EEG cap in different locations, and stimulation will be initiated. This procedure is not a treatment but an accompanying test. You will undergo this test twice, once at the beginning and once at the end of the treatment phase of the study.

Study Visits and Procedures:

Procedures	Screening Visit 1	Baseline		rTMS Treatment	1 wk	2 wk	3 wk	1 mo	3 mo	6 mo
		Visit 2	Visit 3							
Informed Consent	x									
TMS Treatment				x						
MRI		x								
TMS-EEG			x		x					
Clinical Assessments	x		x	x	x	x	x	x	x	x

Visit 1 – Screening Visit– This visit will involve your initial enrollment into the study and can be done in person or virtually via IRB-approved platforms (UCSD Health Zoom, etc). This visit will first consist of reviewing and signing the consent form. If done virtually, informed consent signatures will be obtained online via UCSD DocuSign. After consenting, you will complete forms and clinical questionnaires (MADRS, SSI, HAMD-17, C-SSRS, PHQ-9, BHS, INQ, and the DSM-5 Level 1 Cross-Cutting Symptom Measure with a research coordinator. These questionnaires will assess your behavior and emotions. Participants of child-bearing potential will be asked to attest that they are not pregnant at the screening visit and the MRI visit to rule out pregnancy. This is documented on the Transcranial Magnetic Stimulation Adult Safety Screen (TASS) safety form. Participants will also be asked questions about the current method of birth control to ensure they have an adequate method to prevent pregnancy throughout the trial. Additionally, during this visit and/or on the first day of treatment, you may complete a bilateral resting motor threshold (RMT). This procedure consists of placing a TMS coil on your head near your motor cortex and sending magnetic pulses with a TMS coil to

determine the minimum intensity that evokes a motor response in your abductor pollicis brevis (APB) muscle on your thumb. This procedure is not meant to have any therapeutic effect and is done to determine treatment dosing. This visit will take 3-4 hours.

Below are sections for virtual consent only:

California law provides specific rights when you are asked to provide electronic consent:

- You have the right to obtain a copy of the consent document in a non-electronic format.
- You have the right to provide consent in a non-electronic format.
- If you change your mind about electronic consent, you have the right to request that it be withdrawn. You can then provide consent in a non-electronic format; however, a copy of your electronic consent will be maintained for regulatory purposes. Please contact the study team if you wish to withdraw your electronic consent.

This agreement for electronic consent applies only to your consent to participate in this research study.

Individuals of Childbearing Potential:

If you are a woman who can 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 breastfeeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breastfeeding during this study, you or your child may be exposed to an unknown risk.

Before beginning this research study, you will be asked to attest that you are not pregnant. 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 methods 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.

Visit 2 – Baseline Visit - You will be scheduled for a 1-hour MR imaging session at the UC San Diego Center for Functional MRI (9500 Gilman Drive, La Jolla, CA 92093, MC 0677). The MRI may not be appropriate if you have/had any metal-containing implant, such as cardiac pacemaker, heart valve replacement, venous umbrella or filter, aneurysm surgery, intracranial bypass, renal or aortic clips, joint replacements, shunts/stents, metal mesh/coil implants, metal mesh/coil implants, metal plates/pins/screws/wires or any other metal implants, neurostimulator, insulin pump, prosthetic devices such as middle ear eye joint or penile implants, I.U.D, permanent eyeliner or eyebrows, metal fragments in eyes, skin, or body, been employed as sheet-metal worker or welder, are pregnant or trying to get pregnant. Hearing aids must be removed as well. During the scanning session, you will be placed in a large donut-like machine called a magnetic resonance scanner. You must be able to lie still, flat on your back for 1 hour. Your head will be inside a helmet-like structure, and padding will be placed to cushion your head and reduce motion. While no one will be in the scanner room with you during the session, you will remain in direct verbal contact with the MRI technician via intercom and may squeeze a bulb placed in your hand, which will allow you to sound an alarm if you have any concerns or would like to stop.

Visit 3 – Baseline Visit – The visit will begin with the HRSD-17, SSI, GAD-7, WHODAS 2.0, and MADRS completed with the research coordinator. Our team will determine the stimulation level for TMS pulses as a component of the TMS-EEG measures. The researchers will move the intensity of the stimulation until it causes either your thumb or finger to twitch (when the coil is placed over the part of the brain controlling movement on the other side of the body), also called resting motor threshold (RMT). This calibration is done to ensure that sufficient stimulation intensity is used for each individual without excessive stimulation. The TMSEEG session will assess brain physiology by stimulating the brain using TMS simultaneous with EEG recordings. These sessions will take place at the Dove Canyon clinic and will take 3-4 hours. Like the MRI, TMS might not be appropriate if you have any magnetic-sensitive metal in your head. Objects that may have this kind of metal include:

- Aneurysm clips or coils
- Carotid or cerebral stents
- Implanted stimulators
- Electrodes to monitor your brain activity
- Ferromagnetic implants in your ears or eyes
- Bullet or shrapnel fragments
- Other metal devices or objects implanted in the head, such as implanted hearing aids
- Pellets, bullets, or metallic fragments

You should be aware that the magnetic fields generated by the stimulator may damage magnetic cards, watches, and some electrical devices. Please remove any such items before testing. A physician and research assistant will review this with you during your initial visit.

During the TMS-EEG session:

- You will be seated in a comfortable chair and wear an EEG cap and a neuronavigation head strap. A magnetic coil will be held on the surface of your scalp.
- When the magnetic stimulation is applied, you will feel a twitch or light tapping on the surface of your scalp. The stimulation is not painful and lasts a short time.
- You will also hear a clicking noise. We will provide you with earplugs for your comfort and protection.

There will also be a similar 2 to 3-hour TMS-EEG visit post-treatment. Clinical assessments will also be collected during this visit.

Treatment visits – You will arrive at the Dove Canyon site in the morning for 5 consecutive days, Monday through Friday. You will complete short screening clinical questionnaires with assistance from the research assistant and rTMS technician. You will also complete an active/placebo rating survey consisting of one question addressing whether you believe the right side is active or placebo (sham) at the end of the first session and the end of the last session. During treatment, you will sit in a comfortable chair, apply over-the-counter topical Lidocaine (4% strength) on your forehead, and wear earbuds to minimize hearing damage. Lidocaine reduces the sensation of TMS and makes the treatment more comfortable. An rTMS coil will be positioned over your scalp, and repetitive stimulation will be initiated for 10 minutes. It will be spaced out with a break approximately 50 minutes from each other, for at least 10 hours daily. After the stimulation session, you will rest in a designated room. Please note that you should bring lunch, snacks, or other items for entertainment, including technology (cell phones/tablets), during your treatment day. We will not provide meals. However, you are welcome to visit one of the local restaurants/grocery stores near our clinic. A study physician trained in rTMS treatment will be available onsite throughout your treatment course.

Visit 1 week after treatment – A post-treatment TMS-EEG session for brain physiology assessment at Dove Canyon Clinic. This visit will be identical to visit 3 and will occur about 1 week after the end of your treatment. Additionally, you will be asked to complete clinical questionnaires. This visit will take 3 to 4 hours.

Visits 2 weeks – 6 months after treatment –2 weeks, 3 weeks, 1 month, 3 months, and 6 months after treatment, you will complete a 1-hour clinical assessment. These visits can be made in person at the Dove Canyon Clinic or remotely via IRB-approved platforms

(UCSD Health Zoom, etc.). During this assessment, you will answer clinical questionnaires. During the 1-month post-treatment follow-up visit, you will have a scheduled follow-up visit with the study physician in addition to the clinical assessments. During this psychiatrist consult, the physician will assess your mood and well-being.

Throughout the study, the study psychiatrist will monitor you, and you can request to meet with the research psychiatrist at any time to assess your mood and well-being. Generally, an MD follow-up will be scheduled one week after treatment and after the study conclusion, but additional MD follow-ups can be scheduled if needed.

How much time will each study procedure take?

If you agree to be in this study, the following will happen:

- Once you have consented, we will conduct the screening visit, asking questions about your mental health history and family background. We will also ask questions to determine your eligibility for study procedures. These questions will last approximately 1 hour, with the entire visit lasting 3-4 hours.
- The MRI scan is an integral part of this trial. We will schedule you for a one-hour functional MRI scan at the UCSD Center before your aTBS treatment.
- On a separate pre-treatment day, we will conduct a 2 to 3-hour electroencephalography (EEG) measurement simultaneous with TMS to assess the brain's response evoked by TMS. For the EEG measurement, you will sit on a chair and wear a cap to collect information about electrical signals produced by different parts of your brain. This is the pre-treatment TMS-EEG visit. There will also be a similar TMS-EEG visit conducted post-treatment, i.e., at 1 to 2 weeks after the treatment was initiated.
- Treatment Course -The treatment will consist of 5 consecutive days, approximately 10 hours each day, with 10 sessions per day. Each treatment session will take 10 minutes, followed by approximately 50-minute intervals. Additional time will be collected to complete the symptom screening scales beforehand.

What risks are associated with this study?

Participation in this study may involve some added risks or discomforts. In addition to the risks described at the beginning of this form,

The main risks associated with this study are related to the rTMS treatment protocol itself. rTMS has a strong, well-documented safety record and has been used to treat many thousands of patients with depression. Please see below for more details. There is also a potential risk of worsening mood and suicidality, as with all antidepressant treatments, which could trigger an inpatient admission. Your health will be followed closely by our study team. If it is determined that your symptoms are worsening, including the

immediate threat of self-harm, you will be taken to the nearest emergency room. If at any point you feel unsafe, please go to your nearest emergency room or contact the national suicide hotline at (800)-273-8255. The risk for worsening mood or suicidality is not necessarily greater than if you were to decide not to participate in the study.

Specific risks and side effects may include:

EEG device: possible risk of discomfort or skin irritation/ reactions due to scalp contact with devices.

Neuronavigation head strap: discomfort caused by pressure applied to the strap on the head.

rTMS Device: rTMS is generally safe and well-tolerated with little difference in side effects and risks between actual stimulation versus sham (placebo) rTMS. The most serious adverse effect during rTMS is a generalized seizure. The risk of seizure is comparable to that of antidepressant treatment and occurs in less than 0.1 to 0.5 percent of patients when safety guidelines are followed. Seizures that do occur are documented as being self-limited and not leading to chronic illness.
There is no evidence of rTMS increasing the chances of severe psychological disorders, but there is a theoretical risk of this happening.
Other adverse effects:

- Hearing loss: Preventable with the use of foam earplugs
- Fainting
- Headaches or neck stiffness
- Unpleasant clicking noise

If you experience any of the above or other symptoms, tell the research staff.

- MRI and TMS should not be administered to anyone who has magnetic-sensitive metal in their head or magnetic-sensitive metal within 12 inches of the TMS coil that cannot be removed. Failure to follow this restriction could result in serious injury or death. Objects that may have this kind of metal include:

    - Aneurysm clips or coils
    - Carotid or cerebral stents
    - Implanted stimulators
    - Electrodes to monitor your brain activity
    - Ferromagnetic implants in your ears or eyes

- Bullet or shrapnel fragments

Other metal devices or objects implanted in the head

- Pellets, bullets, or metallic fragments

You should be aware that the magnetic fields generated in an MRI and by the TMS may damage magnetic cards, watches, and electrical devices. Please remove any such items before testing. If you have any of the above metals in your body, you should not participate in this study.

Other risks in this study include the following:

- You may experience worsening mental health symptoms during or after this study. The research staff will periodically ask you questions to assess your current mood. You can always decide to withdraw from the study.

Personal identifiers will be removed from the information collected as part of the research. After such removal, the data could be used for future research studies or distributed to another investigator for future research studies and research sponsors without your additional informed consent. Because this is a research study, there may also be some unknown risks that are currently unforeseeable.

This clinical trial will be described at 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.

You will not receive any results of this study; however, if new information relevant to your health or safety becomes available, you will be informed promptly.

What are the alternatives to participating in this study?

In addition to the alternatives to participation listed at the beginning of this form, other alternatives are not to participate. Your decision to participate in this study will not affect your eligibility to receive standard-of-care through the Interventional Psychiatry clinic, which may include electroconvulsive therapy, ketamine, or other forms of treatment.

What benefits can be reasonably expected?

In addition to the benefits listed at the beginning of this form, the investigators may also learn more about MDD and suicidality. These procedures may or may not directly benefit you. However, repeat sessions may allow you to experience a positive change in mental health.

What happens if you change your mind about participating?

You may refuse to participate or stop your participation at any time without penalty and without jeopardizing your continuing medical care at this institution. If you decide that you no longer wish to continue in this study, you will be requested to:
• Let the researchers know immediately that you wish to withdraw from the research.
• Return to the research center for tests that may be needed for your safety.
• Discuss your future medical care, if any, with the researchers and/or your Doctor.

If you choose to withdraw from the treatment portion of the study or cannot finish all of the scheduled treatment appointments due to unforeseen circumstances, you may still agree to participate in the remaining clinical assessments as scheduled.

Throughout your participation in this study, you may continue your regular appointments with your original treating physician.

You will be informed if any important new information is found during this study that may affect your decision to continue.

Can you be withdrawn from the study without your consent?
You may be withdrawn from the study for the following reasons:

- A study physician believes that it is in your best interest not to continue with the study.
- You begin to pose a serious threat to your own life or to another person's life - You feel unmanageable pain/discomfort at any point throughout the study.
- You no longer wish to participate in the remainder of the study.
- You may also be withdrawn from the study if you do not follow the instructions given to you by the study personnel.
- It is determined that your treatment stimulation intensity is above a pre-established limit for inclusion (65% Machine Stimulator Output (MSO)).
- You may also be withdrawn from the study if you do not follow the instructions given to you by the study personnel.

Will you be compensated for participating in this study?
In compensation for your time and travel, you may receive a maximum of $60, depending on your level of participation: you will receive $20 for each MRI session and $20 for each time you participate in the TMS-EEG session. All compensation will be provided at the end of the study in the form of e-gift cards to retailers (e.g., Amazon).

Are there any costs associated with participating in this study?

The TMS treatments will be supplied at no cost while you take part in this study. It is possible that the TMS treatments may not continue to be provided while you are in the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

What if you are injured as a direct result of being in this study?
If you are injured directly due to participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide you with any other form of compensation if you are injured. You may call the UCSD Office of IRB Administration (OIA) at 858-246-4777 for more information about this, to inquire about your rights as a research subject, or to report research-related problems.

What about your confidentiality?
Research records will be kept confidential to the extent allowed by law.
Under California law, the only exceptions to this privacy rule are: 1) if you express suicidal thoughts or plans, the confidentiality may need to be broken to help you; 2) We may need to report information about known or reasonably suspected incidents of abuse or neglect of a child, dependent adult or elder including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may report such information to the appropriate authorities.

De-identifying all measurements and individual test results and treating them confidentially will minimize privacy risks. Written informed consent/assent and minimum identifying information collected from participants will be stored in secure, HIPAA-compliant electronic locations from the securely stored de-identified study data so that individuals cannot be easily connected to the study results. The UCSD Institutional Review Board may review research records.

Who can you call if you have questions?
This study has been explained to you, and your questions have been answered. You may reach Dr. Cory R. Weissman at (858) 207-0938 if you have other questions or research-related problems.
You may call the UCSD Office of IRB Administration (OIA)at 858-246-4777 to inquire about your rights as a research subject or to report research-related problems.

Your Signature and Consent

I have received a copy of this consent document and a copy of the "Experimental Participant's Bill of Rights" to keep. I agree to participate in the research described in this form.

Printed Name of Participant

Signature of Participant Date

Printed Name of Person Obtaining Consent

Signature of Person Obtaining Consent Date

**If oral consent or waiver of documented consent is requested, no signature line is needed