Theta-burst stimulation modulates criticality, working memory and subjective effort

Informed Consent Form

Protocol Number*: 2106003016

National Clinical Trial (NCT) Identified Number: <Number, once assigned by CT.gov>

Principal Investigator*: Andrew Westbrook, PhD
Sponsor: Brown University

21 October 2022

BROWN UNIVERSITY
CONSENT FOR RESEARCH PARTICIPATION

Criticality and Working Memory

[Version 4, October 21, 2022]
Informed Consent

KEY INFORMATION:
You are invited to take part in a Brown University research study. Your participation is voluntary.

- PURPOSE: The purpose of the study is to examine your performance on a series of computerized tasks as it relates to working memory, cognitive control, and decision-making.
- PROCEDURES: You will be asked to complete computerized tasks. You may be asked to complete these tasks while wearing a stretchy cap with electrodes attached if undergoing electroencephalography (EEG). You might also receive a type of brain stimulation called transcranial magnetic stimulation (TMS) while you do the task wearing the EEG cap. Before doing any TMS, you will be asked to have images of your brain taken using magnetic resonance imaging (MRI). You will be asked to stay as still as possible during the MRI and EEG, and may be asked to focus your attention during the task. We may also record your pupil dilation and / or your heart rate while you perform these tasks. You may also be asked to complete brief surveys. There may be certain aspects of the study session which will not be fully disclosed until after your participation is complete. Upon completion of the study session, you will be given a full debriefing describing all research procedures and contact information by the experimenter. Any questions you may have will also be addressed.
- TIME INVOLVED: A single EEG session should last approximately 3 hours. Participants doing TMS and EEG will complete three sessions. The first session (MRI) will be approximately 2 hours. The second and third (TMS + EEG) sessions will be approximately 3.5 hours each. When we schedule your appointments, we will let you know which types of sessions you're taking part in, and how long the sessions will last
- COMPENSATION: If you are participating in an EEG session, you will be paid $15/hr of your participation. If you are participating the MRI session, and the TMS+ EEG sessions, you will be paid $20/hr. If you are participating in the subject pool, you will not be paid per hour, but will receive 1 participation credit for each hour of the study. In all sessions, you may receive bonus compensation in the form of monetary rewards based on your choices on the computerized tasks amounting to $4 +/- bonus compensation.
- RISKS: The main risks from EEG include minor skin irritation and discomfort from sitting still. Main risks from TMS include twitching or contracting of muscles and nerves in the head and face, head and/or neck pain, hearing damage, and seizure. TMS can also electrically affect or heat up metal objects in close proximity, and may also briefly alter your memory and your ability to pay attention. Risks of MRI are detailed in the Brown University MRI Research Facility Informed Consent Addendum
- BENEFITS: There are no direct benefits to you from participating in this research study.

Researchers:

This study is being performed by Dr. Andrew Westbrook and his research team.

What is this study about?

The purpose of this project is to study your performance on a series of computerized tasks that investigate learning, working memory, and decision-making. To do so, we may use electroencephalography (EEG), magnetic resonance imaging (MRI), pupillometry or an electrocardiogram (ECG) to monitor your heart rate. You might also receive a type of brain stimulation called transcranial magnetic stimulation (TMS).

All of these techniques are commonly used clinical and research tools.

- Magnetic Resonance Imaging (MRI) uses a strong magnet to take pictures of the body.
- EEG is used to record brain electrical signals from sensors placed on the scalp, in some cases, using a water-soluble gel.
- TMS is a procedure in which magnetic fields outside of the head are used to stimulate electrical activity in certain parts of the brain, causing it to be either more or less active. This is referred to as "non-invasive" stimulation because the device used to create the magnetic fields is completely outside of the head.
- Pupillometry monitors pupil dilation with a camera that catches infrared light reflected from your eyes.
- ECG is used to measure heart rate from two sensors placed on your chest just below your collar bone and another placed near the bottom of your rib cage.

You are invited to be in this study because you are a healthy, right-handed adult (18-45 years old) with no pre-existing conditions or medications that could put you at increased risk for seizure or other complications.

What will I be asked to do?

Before you consent to participating in this study, it is important you understand what this research study will involve. Please take the time to carefully read the following information. Ask the experimenter at any time if there is anything that is not clear or if you would like more information. Your participation is voluntary, and you may withdraw at any point.

In this study, you may be asked to participate in a single EEG session or you may be asked to participate in three sessions in which you will be asked to take part in a MRI session, and two different EEG plus TMS sessions. All sessions will take place on different days.

☐ Use of Electroencephalography EEG:

In all of the sessions involving EEG, you will complete one or more computerized tasks in which you will make decisions in response to images or text on the computer screen. For computerized tasks, you may be asked to respond within a certain amount of time. You may experience stress or pressure for being timed. You will be given the opportunity to take a break between tasks.

If you are asked to participate in an EEG session, you will do a computerized task while we record electrical signals from your brain using EEG sensors placed on your scalp.

- Electroencephalography (EEG) is a non-invasive method of measuring brain activity which means there are no injections, drugs or radioactive tracers used. The EEG procedure requires putting on an "electrode cap," which looks similar

to a swimmers cap. The electrodes do not deliver electrical shocks, but instead will measure brain activity. Your hair and face may get wet while you are wearing the cap. Conductive paste is applied to each sensor and your scalp may be rubbed gently with an instrument similar to a Q-tip to ensure there is good contact between your scalp and the electrode.

- The EEG paste is similar to the consistency of hair gel and can be washed out with water. Due to COVID-19 restrictions, we are unable to offer the option to wash your hair in the lab after the experiment, and will request that you do so at home.

_____ EEG recordings will be done separately from MRI

☐ Use of Magnetic Resonance Imaging (MRI):

If you are asked to participate in three sessions, you will have an MRI in your first session.

- To capture images of the structure of your brain, we use Magnetic Resonance Imaging (MRI). This is a non-invasive method of imaging, which means there are no injections, drugs or radioactive tracers used while a person is in the scanner. The brain images collected so that we will have a map to help guide the orientation of TMS in a subsequent session.
- Before MRI, you will need to fill out a questionnaire about your health and handedness. You will be screened for "MR Safety" by answering questions about surgeries you had, and any medical devices or metal you may have on or in your body.
- The MRI session will last 1 hour which includes up to 30 minutes of screening, set-up, and training outside of the scanner and up to 20 minutes of physically being in the MRI scanning.

☐ Use of Transcranial Magnetic Stimulation (TMS):

During the second and third sessions, you will do a computerized task while we record electrical signals from your brain using EEG sensors. We may also apply transcranial magnetic stimulation (TMS) before or after you complete tasks. TMS is a way of stimulating the brain, without injections, drugs or surgical procedures of any kind.

- During the course of the experiment, we may apply TMS using a hand-held device. The TMS feels like a light tapping sensation and will make a loud noise. We will require you to wear earplugs (which we will provide) and/or headphones playing white noise during the experiment in order to protect you from this noise. You might feel muscles in your scalp and/or face tense up temporarily during the experiment, or head/neck pain following the experiment.

How TMS works: TMS works by passing an electric current through a "TMS coil" that is held against your head. A TMS coil looks like a wand with either a circle or a figure 8 at the end of it. Inside the coil are loops of wire. When the electric current goes through the coil, it creates a magnetic field that can safely go through your skull and your brain to briefly affect the way the cells in your brain work for a short time (1 second to 1 hour depending on the kind of TMS – described in detail below). The effects can be minor, such as a brief twitch, or you may not notice them.

TMS coils are not always "on," so even if the coils are on your head, the experimenter needs to start the equipment. The procedures used in this study are described in detail below. You may or may not receive the actual TMS.

Eligibility: Before the TMS procedure, you will be interviewed to see if you are eligible to participate in the study. The interview questions that determine your eligibility are chosen for both scientific and safety reasons. The interview will include some personal questions, such as questions about your health history, and any drugs or medications you might be taking. All your answers to our questions will be protected, as described in the "Confidentiality" section.

For Women: It is unknown if TMS is safe during pregnancy. If you are, or you think you might be, pregnant, you cannot take part in this study.

Location of TMS: The TMS coil will be put on your head. Before the formal study begins, a member of the research team will show you the place(s) we will put the coil. Example places are on your forehead above your eye, above your temple, or on the back of your head.

TMS Research Procedures: The TMS procedure(s) pre-marked with an "X" in the box next to its title will be used in this study. We may continue to record the activity of your muscles for all the protocols listed below with an "X." All TMS procedures will last approximately 45 minutes out of the full 3.5-hour session. This includes time necessary to identify motor thresholds and two trains of theta-burst stimulation with a 5-15 minute break in between each train. These stimulation protocols are described below.

☐ *Motor Threshold*
We will find your motor threshold (which is your baseline). This TMS procedure is used to customize the strength of stimulation specifically for you and your brain.

You will be asked to sit comfortably in the chair in the TMS testing room. Your muscle may twitch or move without you telling it to move (involuntarily) from this test. TMS feels like tapping on your head. Muscles on your eyes, head, or neck may also twitch, if the coils are on the side of your head near those muscles.

Finding your motor threshold will take about 25 minutes.

When finding your baseline, there will be occasional short, single pulses of TMS (lasting a fraction of a second) delivered through the coils while you complete the task(s). You will get no more than 1 pulse per second, and most pulses will have at least 1 second in between them.

☐ *Offline Theta-burst Stimulation*
You will be comfortably sitting up or reclining in the TMS chair and we will slowly stimulate your brain in one place with 50 pulses per second, in sets of 3 pulses at a time; sets will happen 5 times every second. This stimulation will last no longer than 6 minutes maximum.

TMS feels like tapping on your head. Muscles on your eyes, head, or neck may also twitch, if the coils are on the side of your head near those muscles. After the stimulation, you will be asked to do a task and then there will be a break.

This kind of TMS might change the way your brain works for up to 1 hour after the TMS ended, and you will stay in the lab during this time. If you finish the task before 1 hour has gone by, we will ask you to stay in the lab until 1 hour has passed.

Pupil dilation
While completing behavioral tasks, your pupil dilation may be monitored using an eye tracker. The eye tracker measures pupil dilation based on the size of an infrared light that reflects off your pupil as you are looking at stimuli on a computer screen. There will be a head and chin rest used to stabilize your head during this procedure.

Heart rate
If we record your heart rate, we will attach three electrodes – two to your chest just below your collar bone and a third near the bottom of your rib cage. The electrodes do not deliver electrical shocks, but instead will measure muscle contractions.

Today we are asking for your consent to participate in the following (please initial):

MRI _____

EEG without TMS _____

EEG with TMS _____

Pupillometry _____

Heart Rate (ECG) _____

You may also be asked to complete questionnaires. The questionnaires may measure traits associated with mental/psychiatric conditions; however, the questionnaires will not be used as diagnostic tools. You will not be given the results of any of the questionnaires.

It should be understood that there may be certain aspects of the study session which will not be fully disclosed until after your participation is complete. Upon completion of the study session, you will be given a full debriefing describing all research procedures and contact information by the experimenter. Any questions you may have will also be addressed.

How long will I be in this study?
Approximately 2-3.5 hours of time will be needed to complete each study session. If you are asked to complete three sessions, your study participation will be approximately 9 hours over three sessions/days.

Are there any risks to me?
The possibility of a breach of confidentiality with regard any data collected from you during your participation (including EEG recordings, questionnaire responses, or your performance on the computer tasks) is extremely minimal. To protect your confidentiality, any data we receive from you will only be labeled with a subject identification number and not your name or any other demographic information. Furthermore, any identifying information, such as your name, will be deleted permanently from files at the completion of data collection for the study.

You may read below for more details corresponding to each study procedure type:

Behavioral Tasks
The tasks involved may require some mental effort, and you may therefore experience some fatigue. For these kinds of tasks, you will receive ample time for reset periods and/or stretch breaks.

Eye-Tracking
You may experience some discomfort from a head and chin rest, but you may take breaks during the experiment to alleviate this discomfort.

Electromyography (EMG) and Electroencephalography (EEG)
There are minimal risks associated with the use of the EEG and EMG in this study. There is a small possibility that you may experience some tenderness or reddening of the skin where the electrodes are placed, as your head will be mildly scraped. This feels similar to scratching your head with your hand. You may also feel slight irritation from the gel solution, but the irritation commonly dissipates soon afterwards. The electrode cap may feel tight on your head.

Researchers will wear latex-free gloves and have received extensive procedural training to minimize the possibility of the reddening of skin while preparing participants for recording. All equipment in direct contact with you will be chemically sterilized with an FDA-approved solvent immediately after each use.

Magnetic Resonance Imaging (MRI)
There may be some discomfort from being in the MRI scanner because you will be asked to lie down and be very still for a long time. The research team will try to make you as comfortable as possible before the imaging begins. If you feel claustrophobic or anxiety, let the researcher know immediately. MRI scanning risks and discomforts are discussed in further detail in the MRI addendum to this consent form.

Transcranial Magnetic Stimulation (TMS)

- TMS carries a small risk of inducing a seizure. This is rare. The stimulation parameters used have been chosen based on safety norms that minimize this risk. In addition, you will be screened for risk factors related to seizure, such as epilepsy, history of prior seizure or convulsions, or a family history of seizures/epilepsy. A seizure may be thought of as a convulsion where a person's body shakes. Many seizures are not like this. Some have very mild symptoms. Experiencing a seizure caused by TMS does not mean that you will have another seizure. The researcher is trained to manage the room and call for medical help in the unlikely event of a seizure.
- It is possible that you could faint during TMS. This does not happen often, but can happen if you are anxious, nervous, or have not eaten. You should immediately tell the research staff if you feel dizzy or lightheaded.

If you have the above symptoms, the TMS study procedure will be stopped. You will be monitored until you are feeling better.

- When current is passed through the TMS coil, it moves within its casing producing a loud "click." It is possible that you could experience a temporary ringing in your ears. You will wear earplugs during the TMS to reduce the noise

to prevent the risk of hearing problems.

We will ask you to let us know immediately if your ear plugs loosen or fall out.

- The sensation of TMS is a tapping on the head at the site of stimulation. Depending on the site of stimulation, there can also be twitching in nearby muscles around the head, eyes and neck. The immediate effect of these sensations can range from mildly irritating to painful at high frequencies. Based on your feedback, we will adjust the stimulator output to a level that is not painful for you.
- Participants undergoing TMS sometimes experience headaches. The cause of headaches can relate to the procedure set-up (for example, neck tension) as much as the TMS stimulation itself. Headaches usually start after the session (about 20 mins. to 3 hours after TMS). If you feel a headache coming on, we will stop the session and allow you to cope with the headache in your preferred way.
- There is a risk of fatigue. We will give you regular breaks through the procedure.
- TMS for research is regulated by the FDA. Although TMS is an FDA regulated device, it is being used for research purposes and is considered an investigational device. There may be complications that are not yet known.

In order to minimize these risks, participants are in constant contact with an experimenter while seated in the recording room and while connected to the recording equipment. Experimenters will have received extensive procedural training to minimize risks.

Also, prior to the experiment, we will ask you to fill out a questionnaire that will allow us to make sure that (1) our study participant group is representative of the greater population, and (2) that TMS is safe for you. Some of the questions pertain to gender and ethnicity. These questions are included so that we can properly interpret our study results at the population level, and to ensure that we are assessing a fair and representative group from the greater population. Other questions pertain to overall health, mental health status, medications and pregnancy. These questions are for your safety, and your answers will be subsequently anonymized and protected- we will not share this information with anyone other than necessary lab personnel. You may refuse to answer or skip any questions we ask.

You are free to stop at any point during the experiment, for any reason whatsoever. In the event of study-related injury, illness or distress, please contact the study PI, Andrew Westbrook at andrew.westbrook@brown.edu.

COVID-19 Countermeasures

Due to the coronavirus public health emergency, the U.S. government issued a Declaration under the Public Readiness and Emergency Preparedness (PREP) Act. This Declaration may apply to this study if it involves procedures or other actions that are related to or in response to coronavirus. If it applies, this Declaration limits your right to sue the researchers, healthcare providers, study sponsors, manufacturers, distributors, and potentially others that are involved with this study. However, the U.S.

government has a program that may provide compensation to you or your family if you experience serious physical injuries or death related to procedures or other actions taken in this study. To find out more about the 'Countermeasures Injury Compensation Program,' please visit https://www.hrsa.gov/cicp.

Will there be any costs to me?
Aside from your time, there are no costs for taking part in the study.

Are there any benefits to me?
There is not direct benefit to you for participating. However, you will be able to learn about the psychological concepts investigated in this study, the relevance of these concepts to everyday life, and how psychological research is conducted.

Will I be paid to participate in the study?
Monetary compensation will only be provided if you are not enrolled in the subject pool. If you are enrolled in the subject pool, you will be offered 1 credit per hour of participation.

- ☐ *If you are participating in the decision-making task, you will receive a $4.00 +/- bonus depending on the outcome of the game.*
- ☐ *If you are enrolled in the subject pool, you will earn 1 credit per hour of participation.*
- ☐ *You will be paid $15 per hour for EEG sessions without TMS.*
- ☐ *You will be paid $20 per hour for MRI sessions or EEG sessions with TMS. This may add up to approximately $160.00, if you complete all of the visits. If you leave the study early, or if we have to take you out of the study, you will only be paid for the visits you completed.*

If your performance on the computer tasks will affect your compensation, you will be notified prior to beginning and given the option of abstaining from participation.

Will my information be kept confidential?
All unique identifying information (e.g. your name) will be removed from electronic study data following data collection. Any electronic files containing participant information will be stored securely and password-protected. Physical participant information (i.e. paper questionnaires and signed consent forms) will be kept secured in a locked storage box inside a locked cabinet.

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.

Are there any alternatives to this study?
This study is for research purposes only. Since it is not intended as a clinical intervention or treatment, there are no 'clinical alternatives'. However, you do not have to participate in this study if you don't want to.

May I change my mind about participating?
Your participation in this study is voluntary and you may decide to stop the study at any time. Your student status does not depend on whether you choose to not participate or terminate participation in this study. Also, any new information discovered about the research will be provided to you. This information could affect your willingness to continue your participation.

Your current or future relationship with Brown University will not be affected in any way if you refuse to participate or decide to leave the study.

Clinical Trail
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 Web site at any time.

Who can I talk to if I have questions about this study?
If you have any questions or concerns about your participation in this study, you can contact the PI, Dr. Andrew Westbrook at andrew.westbrook@brown.edu.

Who can I talk to if I have questions about my rights as a participant?
If you have questions about your rights as a research participant, you can contact Brown University's Human Research Protection Program at 401-863-3050 or email them at IRB@Brown.edu.

CONSENT TO PARTICIPATE

1. I confirm that I have read and understand this information sheet and I have had the opportunity to ask questions.

2. I agree to take part in the above study.

_____

Participant Name

_____ _____

Participant's Signature Date

In some cases, we may be interested in re-contacting you for additional information or to participate in a follow-up experiment. If we do, your participation is completely optional and you would be compensated appropriately for your time. If you agree to be recontacted for future studies, please initial below to indicate this.

Please initial if you agree to be recontacted for future studies: _____

STATEMENT OF PERSON OBTAINING CONSENT

I certify that I have presented the above information to the participant and secured the participant's consent.

_____

Experimenter Name

_____ _____

Experimenter's Signature Date