Title:	TMS Related Biomarker Assessments
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Study protocol

Background

Electrical neural oscillations of the brain can be measured at many levels, ranging from single cell to local field potentials in animals, to large-scale synchronized activities in the human scalp. New evidence suggests that there may be common underlying abnormalities in oscillatory activities that are associated with schizophrenia-related cognitive and functional impairments. There is currently no treatment for these electrical oscillation dysfunctions. Transcranial magnetic stimulation (TMS) provides a non-invasive means for altering brain electrical neural activity. TMS has been approved by FDA for the treatment of depression and many other mental disorders. It has been used in a wide range of clinical research, especially in neurology and psychiatry. The investigators aim to develop TMS paradigms that will modulate brain responses during basic sensory to more complex cognitive performance and determine the parameters in anatomic locations and TMS modalities that may effectively and safely modulate neural activities. If the current experiments successfully identified TMS methods/paradigms that improve neural oscillation and cognitive performances in schizophrenia patients, in the future (not part of the current protocol), the investigators can then develop specific TMS treatment that may correct abnormal brain function and improve cognition and clinical symptoms of schizophrenia.

The purpose of this research is to better understand how brain electric activities are changed during TMS. We will test the hypothesis that repetitive TMS pulses, such as theta-burst stimulations, and conventional low- and high-frequency stimulations (Huang et al 2005 Neuron; Williams et al 2018 Brain), will facilitate EEG neural oscillatory activities, cognitive behaviors, TMS-related responses, and fMRI brain circuitry measure improvement in schizophrenia patients.

Study Procedures

General TMS procedures: Motor threshold (MT): Motor threshold testing will start with around 50% intensity and an inter-stimulus interval (ISI) of about 0.2 Hz. The coil is moved in different directions and TMS intensity is gradually increased or decreased to find the site that most reliably elicits finger twitches. The intensity is then adjusted until about 5 of 10 consecutive pulses (100% MT) result in a finger twitch or finger muscular evoked potential (MEP). Motor evoked potential (MEP): MEP will be recorded from surface electrodes placed on one of the fingers. The minimal intensity required to elicit an EMG response of at least 50 uV with 50% probability in a fully relaxed muscle (Rossini et al., 1994) is the resting

motor threshold (RMT). We may mark the stimulation sites in the neural navigation system. During RMT tests, subjects are asked to keep their muscle relaxed. During active motor threshold (AMT) tests, subjects are instructed to make an isometric contraction between the thumb and index finger at certain percentage of maximum force before the TMS pulse. Subjects are instructed to relax, with head holding still or maintained by resting on chinrest. TMS will be administered using a Magstim or PowerMAG TMS machine. TMS single pulses are applied to the brain guided by the Brainsight (Rogue Research, Montreal, Canada) brain navigation system and the subject's anatomical MRI. The brain navigation system permits more precise TMS placement on the proposed anatomic regions. TMS will not exceed 120% magnetic field intensity relative to the patient's observed RMT. The TMS coils are fixed using a mechanical arm to keep the coil to scalp relationship constant throughout the experiment. Patient participants are required to give adequate responses on the Evaluation to Sign Consent (ESC) form prior to study entry to ensure that they understand the risks of the study and how to respond if they experience any distress or wish to withdraw from the study. A score of 10 or more out of the total possible score of 12 on ESC will meet the inclusion criteria.

MRI procedures: MRI will be done in a 3.0 Tesla magnet. During MRI, the subjects will perform resting and behavioral and cognitive tasks with visual and auditory presentations to be shown through a screen and head/ear phones. In some tasks the subject will be asked to simply rest, or to use a response pad. The specific tasks may include structural images for gray and white matter, resting scan, tasks that measure eye movement, motion perception and prediction, attention/working memory, learning and reversal learning tasks, finger tapping, and/or simple auditory and visual stimulus tasks. Each subject will perform only a subset of these tasks. Behavioral response, eye movement, basic physiological measures including breath, blood pressure, pulse, skin conductance can be recorded during imaging. Each subject will be inside the scanner for about 1 hour at different time of the rTMS treatment procedure. About four fMRI scans will be done in each sub-study. A repeat of scan is possible if other issues have led to incomplete or poor quality imaging data in previous scans. If a participant is not sure whether there are metal in their head or eye, for example past gunshot wound or involving in welding or metal drilling without eye protection, we may ask the participant to have a head x-ray of the head to make sure there is no metal in eyes or head before the MRI scan. The x-ray will involve a small amount of radiation, although the risk associated with a one-time x-ray is similar to any x-ray a doctor may prescribe during a clinic visit. They can refuse the x-ray and not participate in the MRI portion of the study. We may use some clinical assessments such as SCID done in other studies or previous clinical assessments if repeating them is not necessary. Similarly, data

collected here may be combined with data from other studies when appropriate. Data collected from this study may be combined with other related studies (e.g., brain imaging data collected from other protocols where combining data is stated) during data analyses. Subjects may not necessarily be excluded or withdrawn if they complete some but not all of the tests and assessments although we encourage them to complete all tasks.

EEG/ERP recording: subjects will be asked to wear a cap containing electrodes. Electrode paste will be used to facilitate the connection. Subjects may listen to sound stimulations by wearing a pair of headphones, hearing tubes, or through loudspeakers. Tests may include resting EEG, passive and active cognitive tasks. In resting EEG, subjects are asked to relax during brain wave recording. In brain wave recording during passive task: subjects may be asked to relax while sounds at different frequencies and durations are presented to elicit evoked potentials, which can be accompanied by visual presentations. No performance is required except to be alert. In brain wave recording for attention and memory tasks: subjects are asked to pay attention to auditory and visual stimuli while holding a response pad. They are trained and then perform the tasks by responding, remembering, or recalling certain items and ignoring the other items. These tasks are computerized auditory and visual stimuli and data are digitally recorded. Each test may last a few minutes to about half an hour; they are repetitive but with breaks between tasks to reduce subject fatigue. All recordings are stored in secure servers/computers using only a code.

TMS will be given in 2 sessions in 2 different days that are separated by one or more days. In one session you will receive active TMS. In another session you will receive sham TMS. The active or the sham TMS are delivered to one, two or three locations on your scalp. The TMS is given in about 4 minutes for each location. Therefore, in the active TMS day, you will receive 3 TMS administrations in three locations, one after another, for a total of about 12 minutes. In the sham TMS session, you may feel or hear similar TMS, but no actual TMS is stimulating your brain. TMS-evoked responses, brain waves, and MRI will be measured before and after each session to determine the TMS effects. It will take about 4 to 5 hours. It includes about 2 hours before and 2 hours after the TMS where we will perform clinical assessments, TMS-evoked responses, brain wave, and MRI assessments as described above. It also includes time to wear the electrode cap and remove the electrode cap and cleaning the hair after the experiment. About 30 participants will participate in this study.

Research Related Risks

General: There is a possibility of breaching of confidentiality. We plan to keep all your records confidential. Some of the procedures can cause boredom. In some of the interviews and questions we will be discussing and asking sensitive information (for example, feelings of sadness, unusual experience, alcohol use, mental illness in family members). You may feel embarrassed or distressed talking or giving out information. It is important to obtain accurate information from you to make the research valid and worthwhile. However, you can always stop and not participate without penalty. Our interviewers are experienced and should provide needed counseling.

TMS: TMS has been safely used in thousands of subjects at the US and throughout the world each year. Occasionally people may find the stimulations uncomfortable or even painful or causing headache, scalp or facial twitching or pain, or dental or muscle pain. If you find the procedure too uncomfortable you may discontinue it at any time. Headaches and pain usually go away promptly with over the counter pain medications. The magnetic pulse could heat up the scalp metal electrodes that could cause burning. The electrodes we use do not have metal that directly contacts the scalp. However, you should promptly inform the staff if you feel any increased heating. The skin stimulation sham electric pulses may cause skin discomfort, tingling, muscle twitching, headache or pain. As in real TMS, if you find the procedure too uncomfortable you may discontinue it at any time.

TMS can be loud and could cause temporary and, in one case, permanent decreases in hearing especially without hearing protection. You will be fitted with earplug or ear phones to wear during the study. This is to protect your hearing from the noise. You will sit in a position with minimal head motion. Sitting in a fixed position for a long time could be uncomfortable with possible body ache. There will be frequent breaks. You can ask for a break at any time.

Magnetic stimulation will not be performed in people who have pacemakers, implanted pumps or stimulators, or who have metal objects inside the eye or skull. Please inform the investigators if you have any of these conditions.

The most severe risk from TMS is seizure. The possibility that TMS used in this study will cause a seizure is very low. According to best current evidence, risk of seizures induced by

TMS is about <0.03%. A seizure has never resulted in permanent damage. Seizure, if induced by rTMS, occurs only during the application of stimulation. Beyond studies conducted specifically in patients with epilepsy, there has been no reported incidence of rTMS-associated seizure that had onset within hours or days after the stimulation procedure concluded. You will be carefully watched during each session. Staff is trained to promptly manage a seizure should one occur. Having a seizure could affect your future ability to drive, hold a job, or get insurance. Therefore, there may be financial risk with being in this study. Sleep deprivation, recent change in medication, alcohol consumption or too much caffeine intake may increase the risk of seizure. You might be at higher risk of having a seizure with TMS if you are taking clozapine. You will not be eligible for this study if you are taking >400mg clozapine daily. We will ask you to postpone the study if you had a recent change in certain medication, did not have a good night sleep, or consumed too many caffeinated drinks on the day of TMS or any alcohol within the 24 hours before TMS.

Other possible adverse events include fainting, nausea, changes in blood pressure and heart rate. If you feel you are not comfortable and weak, you should inform staff immediately, or you can stop at any time.

Another potential side effect from TMS treatment is changing of mood and occasionally other psychiatric symptoms such as increased psychosis, temporary changes in attention and memory. Heightened euphoria (mania) has happened to some people, most of whom had a history of mania or depression when they started TMS treatment.

The effects of TMS during pregnancy are unknown. If you are a female and are possibly pregnant (if you have child-bearing potential but are not taking contraceptives and missing menstrual period; or by your own report; or by positive a pregnancy test), you should not participate in this study. No one should enter the study that plans on fathering or conceiving a child between the times of study enrollment and completing the study. If you are female and are able to have children you must agree to use an approved birth control method. Acceptable birth control methods include the birth control pill, intrauterine device, or depot hormonal preparation (ring, injection implant). Correct use of a diaphragm, sponge with spermicide, or condom is also acceptable. We do not know if the experimental procedure affects fetal development.

MRI: The process itself is painless. There will be no x-rays or radioactivity in the MRI. However, you will be exposed to a high magnetic field. The magnetic field and radio waves used for MRI scans are considered too weak to do any damage to your body. However, nothing can be proven to be absolutely safe. There are potential side effects from the MRI scans. The first possible side effect is a mild backache from lying still for about one hour. You may experience claustrophobia, which is fear of small enclosed places. The MRI machine makes loud banging noises. You will be given earplugs or headphones that will lessen the sound. You may still experience some brief problems hearing soft sounds after the exam. Lying still for many hours may be a risk for the development of Deep Vein Thrombosis. This is blood clotting, usually in the legs, in persons with certain medical conditions. Persons with a history of thrombosis, family history of thrombosis, or medical conditions that may lead to an increased chance to develop blood clots cannot take part in this study. Please inform us immediately if you believe you should not take part for this reason.

Brain wave recording: A paste is used to attach the electrodes during brain wave testing, which may irritate the skin on the scalp or face. Irritation is mild and usually resolves quickly. We may ask you to not use hair products on the day of testing (or it has to be washed out prior to testing, which may be inconvenient). The electrode cap you wear can be tight and not comfortable, but it can be adjusted. The tasks can be quite long, boring, or even annoying. Some of the sounds can be loud and uncomfortable. We will give frequent breaks in-between. You can always ask for a break or re-schedule for another time to complete the study.

All safety measures to lessen any side effects will be taken. If you feel that you want to leave the study, you are free to do so at any time. If we feel that you should not continue, we will end the study. We may do this even if you do not want to end the study.

Because TMS is relatively new, its long-term effects are still unknown. We will monitor you at every visit. There may be risks in this study which are not yet known. You will be told of any new findings during the course of this study that may affect your participation. If you feel that you have an illness or symptoms related to your being in the study you should call us.

Statistical Analysis Plan

Demographics were compared using ANOVA or $\chi 2$ tests. We will examine the differences in performances of biomarkers in active TMS compared to sham TMS. We will explore effects of age, sex, baseline medication, cognition, smoking status, and functional measures on biomarkers, and significant findings will be included as covariates. Exploratory analyses were conducted comparing active TMS vs. sham at different time points using independent-sample t-test and comparing baseline vs. post-TMS measurements using paired-sample t-tests at $p<0.05$. Effect sizes were calculated for nominally significant measures using Cohen's d. All tests were two-tailed.