A pilot open-label trial of individualized repetitive transcranial magnetic stimulation for patients with auditory verbal hallucinations

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Lay Summary

The large majority of patients with schizophrenia (Sz) experience auditory verbal hallucinations (AVH) as a core feature of their disorder. Treatment-resistant auditory verbal hallucinations (AVH) affect a third of patients with schizophrenia and can cause increased aggression, distress, suicide, and social dysfunction. The current standard of care is antipsychotic medication which can cause metabolic syndrome, sedation, orthostatic hypotension, extrapyramidal symptoms, and tardive dyskinesia among other adverse effects. Transcranial magnetic stimulation (TMS) emits a rapidly changing magnetic field over the scalp which induces current flow in underling brain tissue, either enhancing or disrupting function depending on the frequency of stimulation. It is generally well tolerated and repetitive TMS (rTMS) is currently FDA approved for treatment of depression. rTMS carries potential as an alternative treatment for schizophrenia patients with AVH who either do not respond to or do not tolerate medication. Inhibitory (1-Hz) standard TMS approaches, which use scalp-based targeting of speech perception areas such as left temperoparietal junction (TPJ) have yielded mixed results in reducing AVH, possibly due to variability of underlying brain anatomy between individual subjects. The influence of anatomical variability could be eliminated by individually positioning the TMS coil according to each patient's structural brain MRI. The proposed pilot project will investigate the clinical efficacy of open-label individualized MRI-guided TMS applied to the left TPJ in ten patients with schizophrenia or schizoaffective disorder. If the results of the pilot study show promising reductions in AVH, it will set up the foundation for a larger sham-controlled clinical trial.

Background, Significance, and Rationale

A significant presenting symptom for approximately 70% of schizophrenia (Sz) patients is the experience of auditory verbal hallucinations (AVH), which are the only Sz symptom independently correlated with "patient distress" (Takeuchi et al., 2016). Moreover, chronic AVH are a strong predictor of suicide (Birchwood et.al, 2000, Howes et al., 2014), low socioeconomic status, and poor social function (Howes et al., 2014). The only approved medications for AVH in Sz are antipsychotics, which fail in ~30% of individuals (Hasan et.al, 2012, Kane et.al, 1998). Transcranial magnetic stimulation (TMS) offers an alternative and safe approach for Sz patients suffering from AVH who either do not respond to medication or cannot tolerate medication side effects.

Transcranial magnetic stimulation (TMS) is a noninvasive method by which a rapidly changing magnetic field can be used to focally influence brain activity. TMS has been shown to be effective in both disrupting and facilitating ongoing cognitive processing. With TMS, a magnetic coil is positioned over a particular scalp region. A TMS device emits brief pulses of current through a stimulating coil held over and near the scalp. The current flow lasts less than a millisecond, and it produces a rapidly changing magnetic field around the coil. This magnetic field in turn induces current flow in cortical tissue near the surface of the head, stimulating neurons in a focal region, generating a brief modulation of neural activity (Luber et al., 2007). The magnetic field exponentially decreases in strength with distance as it passes unobstructed

through the skull, effectively depolarizing neurons up to two centimeters into the brain. The effects are not entirely local, as the depolarized neurons transmit their activity transsynaptically to connected subcortical and transcortical regions within functional networks. The actual neurobiological effects depend on the intensity of the magnetic field, the coil shape and its orientation, and the geometry of the underlying cortex in relation to the field. The neural effects of TMS also depend on the frequency of stimulation when applied repetitively in a pulse train (rTMS). While rTMS is FDA approved for the treatment of depression, it is also proposed as a novel treatment for schizophrenia patients with treatment-resistant AVH when applied using inhibitory frequencies over left language-receptive areas. rTMS is generally well tolerated and safe but see "Risks and inconveniences" section for a detailed discussion of potential adverse effects. Current studies of 1-Hz (inhibitory) rTMS targeting speech perception areas such as left TPJ/Wernicke's area have yielded mixed results in reducing AVH. However, most of these studies use scalp-based targeting approaches that don't account for individual variability in underlying brain anatomy (Briend et al. 2020, Schiz Res. https://doi.org/10.1016/j.schres.2020.09.001). Here we propose to pilot an individualized MR-guided rTMS approach of a left TPJ target to establish feasibility and potential efficacy using an open-label design in ten participants with schizophrenia or schizoaffective disorders with persistent AVH. In addition to assessing pre/post treatment changes in AVH severity and characteristics using established clinical scales, we will also assess pre/post changes in etiologically-relevant fMRI and neurophysiological (EEG) biomarkers.

Specific Aims and Hypotheses

Specific Aim 1: To evaluate the efficacy of individualized MR-guided inhibitory rTMS in reducing AVH symptoms in Sz. We hypothesize that TMS targeting an area of left TPJ involved in receptive language processing will reduce AVH severity.

Specific Aim 2: To evaluate the utility of etiologically relevant MRI tasks and EEG biomarkers in tracking treatment response. We hypothesize that pre/post treatment changes in AVH severity will correlate with normalization of previously established deficits in MRI and EEG measures associated with AVH.

Description of Subject Population

Population: Adults with schizophrenia and schizoaffective disorder
Number of completers required to accomplish study aims: 10
Projected number of subjects who will be enrolled to obtain required number of completers: 12
Age range of subject population: 22-55

Gender, Racial and Ethnic Breakdown

Based on prior studies of schizophrenia at NYSPI/Columbia:

60% male; 40% female
1/3 Hispanic; 2/3 non-Hispanic
50% Caucasian; 30% African-American; 10% Asian-American; 10% Mixed Race or Other

We will not exclude any subjects based on gender or ethnicity/race. Females of childbearing potential will be permitted to participate as long as they remain on adequate birth control. The proportions of ethnic groups in our study population reflect the demographics of schizophrenia patients within our catchment areas, and a significant proportion of Hispanic and African-American subjects are included in our studies. Prior trials conducted by our group have consistently obtained a demographic mix that is representative of schizophrenia within the New York City and Rockland County populations, particularly our neighborhood of Washington Heights, which has a large percentage of African American and Hispanic residents.

The demographics of schizophrenia in the United States are ~ 1% of the population of each ethnicity, with the exception of more men (ratio 1.4:1) and a 2 to 3 fold increased rate in African Americans (Regier et al, Acta Psychiatr Scand 1993, Bresnahan et al, Int. J. Epidemiol, 2007). The literature supports that the demographics of schizophrenia in any specific area, such as New York City in general, and Washington Heights specifically should reflect the demographics of the area (Reiger 1993). For example, Washington Heights (the neighborhood in which the New York State Psychiatric Institute is located) has a large percentage of Hispanic people with schizophrenia because of the relatively large number of Hispanic people in Washington Heights.

Because we will be recruiting **a portion of the participants** from the study (protocol # 7114) within our division, we have used composite demographics from SZ patients in the study (which are representative of schizophrenia patients within the New York City and Rockland County areas) for the breakdown above.

Description of subject population
Subjects will be patients diagnosed with Schizophrenia or Schizoaffective Disorder, who suffer from AVH. Inclusion/exclusion criteria were based on previous studies.

Suicide Risk Management Plan

The rater who will be conducting C-SSRS has a master's degree in clinical psychology and has many years of experience working with vulnerable clinical patients. The rater has been administering C- SSRS under other protocols for the past two years. The C-SSRS will be conducted every week of the four-week study. In addition, the study PI (MD/PhD) will conduct a rigorous assessment with participants prior to the start of treatment, including asking if they have suicidal thoughts and plans, which will be recorded on the evaluation note form in the redcap. After the screening session, the study PI and the rater will go through the inclusion/exclusion criteria together to determine the patient's eligibility. On each day of the 10-day treatment, a covering MD will ask a series of questions about the patient's symptoms, mood, suicidal thoughts and medication use before starting the session. These will be recorded in the progress note form on the redcap after each day of treatment. All research members involved in the study have completed all necessary CITI training courses to ensure the safety and welfare of participants.

The rater will gather lifetime history of suicidality as well as any recent suicidal ideation and

behavior. The Suicidal Ideation section of C-SSRS contains 5 questions, which are 5 types of ideation of increasing severity. The Suicidal Behavior section will help us understand each type of suicidal behavior the patient has had or recently had. If a patient endorses items 4 or 5 of the Suicidal Ideation section, or they had suicidal behavior within the past 6 months as indicated in the Suicidal Behavior Section, they will be determined to be at risk of suicide. The study PI will be informed immediately and then he will communicate directly with the patient to further determine the patient's suicide risk level. During this time a more detailed and thorough medical assessment will be completed and other safety strategies will be initiated. If the patient already has a qualified mental health provider, that provider will be informed immediately of the situation and asked to meet with the patient as soon as possible for clinical management. If the patient doesn't already have a qualified mental health provider or that provider cannot meet with them in a time frame that the study PI thinks is safe, we will initiate the referral process to help locate and contact a qualified mental health provider who can offer an appointment within a safe time frame. A referral list will be developed for those who are at intermediate and low acute risk. The referral resources included in the list will vary based on the individual patient's situation (e.g., insurance status) and the availability of mental health providers to see patients. We will continue to be responsible for the patient's safety until we confirm with the provider that the patient will be seen in a timely manner and is now a patient of the provider. This active referral process and confirmation of follow-up will be documented in REDCap. In extreme circumstances, if a patient is judged to meet the criteria as an "immediate danger to self," he/she will be asked to come to the ER. The study PI will speak with the responsible ER physician to provide all relevant information and request follow-up on disposition. In the event of emergent imminent risk in which the participant is unable to get to an emergency room on their own, the covering MD may call upon community resources such as 911. In individual cases where the study PI doesn't believe that the patient 's presentation warrants active referral, a referral list with names and telephone nu e rationale for this will be documented in REDCap.

Recruitment Procedures

Recruitment of adults with schizophrenia or schizoaffective disorder from the study "Study of Early Cortical Processing in Schizophrenia"(Protocol #7114) within the Division of Experimental Therapeutics at NYSPI.

Potential participants will also be recruited through flyers and online advertisements posted on Craigslist, Facebook, and RecruitMe**.**

Research staff from the "Study of Early Cortical Processing in Schizophrenia" (Protocol #7114) will tell adult patients with schizophrenia or schizoaffective disorder about the study and ask if they would like to meet with investigators or research staff of this "A pilot open-label trial of individualized repetitive transcranial magnetic stimulation for patients with auditory verbal hallucinations" to learn more about the study and have any questions answered. For patients who express willingness to be contacted, the investigators and/or coordinators of the "Study of Early Cortical Processing in Schizophrenia" (Protocol #7114) will pass contact information along to appropriate research staff of the present protocol. A member of our research staff will send a targeted recruitment email and/or call the participants who express interest. Patients will also be recruited through flyers, Craigslist and online postings to recruitment websites.

Inclusion/Exclusion Criteria

Our criteria for the subject population are based on previously approved protocols of HD-tDCS on schizophrenia and schizoaffective patients led by Dr. Michael Avissar (IRB # 7882), previous trials on TMS in treating AVH (Auditory Verbal Hallucinations) in patients with schizophrenia (Hoffman et al., 2005; Thomas et al., 2019), and the FDA guidance on TMS (https://www.fda.gov/medical-devices/guidance-d-radiation-emitting-products/repetitive-transcranial-magnetic-stimulation-rtms-systems-class-ii-special-controls-guidance).

Inclusion

Criterion	**Method of Ascertainment**
1. Age between 22-55	Self-report
2. DSM-V diagnosis of schizophrenia or schizoaffective disorder	Structured Clinical Interview for DSM-5
3. Capacity and willingness to provide informed consent	Independent assessment of capacity
4. Mean AHRS item score of greater or equal to 2.	Auditory Hallucinations Rating Scale (AHRS)
5. If female and not infertile, must agree to use one of the following forms of contraception for the duration of study participation: systemic hormonal treatment, an IUD which was implanted at least 2 months prior to screening, or "double-barrier" contraception. Women of child bearing potential must have a negative pregnancy test at screening.	Self-report, urine pregnancy test
6. Right handed	Edinburgh Handedness Inventory
7. Normal hearing	Mean audiometry ≤25 dB above age corrected norms
8. Taking an antipsychotic medication at a stable dose for at least 4 weeks. All oral and depot antipsychotics are allowable.	Self report

Exclusion

Criterion	**Method of Ascertainment**
1. Substance use disorder (excluding	SCID and self report

nicotine) within last 90 days, or positive toxicology screen for any substance of abuse	
2. Pregnancy	Urine pregnancy test at screening
3. Participation in study of investigational medication/device within 4 weeks	Self report
4. History of seizure, epilepsy and neurologic conditions with structural cerebral damage, including stroke, multiple sclerosis, traumatic brain injury, Alzheimer's and other neurodegenerative diseases, meningoencephalitis or intracerebral abscess, parenchymal or leptomeningeal cancers, dementia, developmental disability, cerebrovascular disease, increased intracranial pressure, or central nervous system (CNS) tumors, brain surgery, head injury with loss of consciousness >1 hour or clear cognitive sequelae, intracranial metal implants, known structural brain lesion	Physician evaluation/Medical history/TASS
5. Subjects with devices that may be affected by TMS (pacemaker, cardioverter defibrillator, medication pump, intracardiac line, cochlear implant, implanted brain stimulator/neurostimulator)	Physician evaluation/Medical history/TASS
6. Subjects with suicidal ideation with intent or plan (indicated by affirmative answers to items 4 or 5 of the Suicidal Ideation section of the baseline C-SSRS) in the 6 months prior to screening or subjects who represent a significant risk of suicide in the opinion of the investigator	Columbia Suicide Severity Rating Scale (CSSRS)
7. Frequent and persistent migraines	Physician evaluation/Medical history
8. Clinically significant skin disease	Physician evaluation/Medical history
9. Presence of unstable medical disorders, including those that are previously undiagnosed, untreated, inadequately treated, or active to an extent which might make participation hazardous. For	Physician exam with vital signs/Medical history

example, hypertension, previous stroke, brain lesions, or heart disease.	
10. History of prior clinically significant, adverse response to neurostimulation	Self report/TASS
11. Current treatment with ototoxic medications (amino- glycosides, cisplatin)	Self report
12. MRI incompatible implants	Physician evaluation/Medical history/NYSPI MRI safety metal screening questionnaire
13. Claustrophobia	NYSPI MRI safety metal screening questionnaire

Consent Procedures

The screen is straightforward and some patients will be referred from the approved study (protocol #7114), such that diagnosis has already been established, and inclusion/exclusion criteria will have been reviewed. However, when potential participants are told about the study, they will also be told of the eligibility criteria for the study. They can review whether they believe they meet these criteria (without our asking them for Personal Health Information) and if so, and if interested in participation, they can provide written informed consent. Eligibility criteria will be more rigorously assessed after provision of written informed consent (i.e. using the SCID and the MRI questionnaire, and urine test for women of childbearing age).
Consent procedures will be conducted by MDs only. During the consent process, an MD will discuss alternative treatments for hallucinations with potential participants and with their permission, the MD will attempt to reach out to their psychiatrist or equivalent provider to discuss clinical suitability of enrolling in the study. All individuals involved in screening and consent procedures have undergone HIPAA and CITI training and are familiar with study procedures of this protocol.

The risks of travel for in-person visits during covid-19 will be discussed during the consent discussion. We will ask participants to exercise caution when traveling in public and follow public health guidelines, such as wearing masks in public and avoiding crowds. It is important for them to stay informed about public health recommendations and guidelines regarding COVID-19, such as those issued by the Centers for Disease Control (CDC.gov) and local government guidelines and directives.

To minimize face to face interaction, we plan on conducting the bulk of the consent process, including a thorough explanation of the study and subject questions over the phone or on WebEx on site with the investigator and subject in separate rooms. This will allow for minimizing the face to contact to the actual physical signature when the consent is done in person. When the study MD is not onsite, we will utilize REDCap for consent, with an e-signature or use a digital signature on the PDF consent prior to printing for the patient. In all cases, the subject will be provided ample time to review the consent prior to signing.

The consent discussion process will include discussion of the technology HIPAA-compliant platforms to be used. If the subject is on site at NYSPI, the subject will be in a private office when consented, which meets the requirements for the subject to have adequate wifi or privacy for the consent process.

Study MDs obtaining informed consent will fully disclose and explain the risks and benefits of the study procedures to the participant, as well as answer any questions about the study and the material presented in the informed consent form that he/she may have. The consent form describes the nature of the procedures and time requirements, potential risks, the confidentiality of information, and the rights of research subjects, including their right to withdraw from the research at any time without loss of benefits to which they are otherwise entitled. Alternatives to study participation will be discussed, and the voluntary nature of participation in the study will be emphasized. This consent discussion will be documented in a consent note placed in the subject's chart.

Independent Assessment of Capacity

An independent MD, PhD, or licensed professional will assess capacity to provide informed consent. If a patient has difficulty understanding any study elements during the consent process, the procedures will be explained by a member of the research team. If there is still doubt about the subject's understanding of the key elements of the study and ability to provide informed consent, the subject will not be enrolled in the
study.

Study Procedures

We will recruit participants from NYSPl # 7114 (Study of Early Cortical Processing in Schizophrenia)**.** In order to better understand the burden to participants who enroll in both protocol #7114 and the current protocol, we are summarizing the study procedures in # 7114: After providing informed consent, participants undergo a 2 hours phone screen (such as the SCID) to confirm diagnosis and assess comorbidity. Participants then partake in a 9-hour in person behavioral session (across two visits) that involves IQ tests, neurophysiological evaluation, collection of speech samples, and behavioral tests such as basic sensory, emotion recognition and reading tasks. Participants then undergo EEG sessions (8 hours), which can be done across 1-2 visits as best accommodates participants' schedules. There are also 2 hours of MRI acquisition. Before going into the MRI scanner, all participants are screened using the NYSPI MRI safety questionnaire re metal implants. Women have urine pregnancy tests. #7114 is a cross-sectional study of deficits in early cortical or basic sensory processing, across stages of schizophrenia and related psychotic disorders and autism spectrum disorder (ASD). Participants in the protocol #7114 include patients (schizophrenia, recent-onset psychosis, clinical high risk and autism spectrum disorder) and for comparison, healthy volunteers similar in demographics. We will only recruit schizophrenia patients from the protocol #7114.

The total participation period for each subject in this pilot study is 4 weeks, starting at week 0 and ending at week 3.

Procedure Table:

Week	0	1	2	3
Activity	Consent, screening, audiometry, pre-treatment baseline assessments: AHRS (audiotaped), PSYRATS, SAPS, PANSS, CAPS, EEG tasks, fMRI	**C-SSRS (weekly);** CGI-S and CGI-I (daily; before treatment session); **SAFTEE (daily; before treatment session)** 5-day 1x/day treatment (5 sessions)	**C-SSRS (weekly);** CGI-S and CGI-I (daily; before treatment session); **SAFTEE (daily; before treatment session)** 5-day 1x/day treatment (5 sessions)	**C-SSRS** Audiometry, post-treatment assessments: AHRS (audiotaped), PSYRATS, SAPS, PANSS, CAPS, EEG tasks, fMRI

Screening/Informed Consent:
Informed consent will be obtained before any study procedures are initiated. After providing informed consent, subjects will undergo medical screening (medical history, physical examination, vital signs, urine pregnancy test for women of childbearing potential, psychiatric screening (i.e. Structured Clinical Interview for DSM 5 (SCID) (Dunn et al., 2002), Auditory Hallucination Rating Scale (AHRS) (Hoffman et.al, 2003), Columbia Suicide Severity Scale (C-SSRS) (Posner et al., 2007), Transcranial Magnetic Stimulation Adult Safety Screen (TASS) (Keel et.al., 2001) and audiometry to confirm eligibility. Screening procedures (except for physical exam) may be conducted by an RA trained by the Principal Investigator; consent procedures must be conducted by an MD. A study MD (Michael Avissar, MD/PhD or Daniel Javitt, MD/PhD) will be available to answer questions, if a subject wishes to speak to a doctor about the risks/benefits of TMS.

Evaluation and motor threshold assessment

Clinical and medical screening includes a physical exam and history, vital signs, review of inclusion and exclusion criteria, and urine pregnancy test (for women). Participants will then have an assessment of resting motor threshold (RMT; 1 minutes). This procedure is described, in detail, below. This session will last about 1 hour.

EEG sessions:

EEG tasks related to AVH will be compared pre/post treatment. There are ~5 hours of EEG recording, which will be done across 2 visits at baseline and post treatment. Each EEG session is expected to last 2.5 hours (1 hour of setup + 1.5 hours of tasks). EEG will be acquired on a 64-channel, active-electrode Brainvision system, digitized at 500 Hz. RAs with EEG data collection experience will conduct this session. All tasks involve listening to sounds via headphones or speakers and some tasks require behavioral responses via button presses or mouse clicks. In some cases subjects are also instructed to view a fixation cross on a monitor or perform a basic visual task while listening to sounds.

MRI (structural MRI, task-related and resting-state functional MRI):

There are ~4 hours of MRI acquisition, which will be done across 2 visits at baseline and post treatment. Each MRI session will include anatomical scans, resting-state fMRI, and an auditory fMRI task. The participant will be placed in a supine position on the table. A head-holder will be used to decrease head movement during the scan. Participants will be given a squeeze ball which

they can squeezed if they don't feel well or if there is any problem during scanning. The participants will wear earplugs or headphones to reduce the noise of the MRI . Before going into the MRI scanner, all participants will be screened using the NYSPI MRI safety questionnaire re metal implants. Women will have urine pregnancy tests.

Audiometry:

The audiometry test is performed in a quiet room. Participants will wear headphones connected to a device that sends a series of sounds of different volumes and frequencies to one ear at a time. Participants will be asked to respond by pressing a button on the joy stick each time they hear a sound.

Standard audiometry will be performed before and after the full treatment at week 0 and week 3 to assess for any changes in hearing thresholds. This is a precautionary measure given the theoretical risk of hearing loss from the noise-inducing damage, as the magnet generates a series of sound clicks during operation. Participants and providers will wear earplugs during operation of the TMS device.

Assessments:

Clinical assessments include Auditory Hallucination Rating Scale (AHRS), the Psychotic Symptom Rating Scales (PSYRATS)**,** the Scale for the Assessment of Positive Symptoms (SAPS), the Positive and Negative Symptoms Scale (PANSS) and the Cardiff Anomalous Perceptions Scale (CAPS). These clinical assessments involve answering questions about psychiatric symptoms. The total assessment time will take up to 1 hour 40 minutes. There will be baseline (week 0) and post-treatment (week 3) assessments. These assessments will be conducted by RAs who have completed training for each measure used. The Clinical Global Impression Scale (CGI-S and CGI-I) will be completed by Dr. Avissar or other clinically trained personnel before each treatment session to quantify and track participant progress and treatment response over time, based on the above measures and general clinical impressions. AHRS assessment will be audiotaped. The second clinical rater will listen to an audiotaped session, blind to subject identity and session number. **I**n addition, Dr. Avissar or other clinically trained personnel will ask participants questions using the Systematic Assessment for Treatment of Emergent Events (SAFTEE), and this will be done once on each treatment day. The Columbia Suicide Severity Rating Scale (C-SSRS) will be conducted by a qualified clinician (e.g., physician, licensed clinical psychologist, psychiatric nurse practitioner, licensed clinical social worker, or other qualified mental health clinicians).
Participants will be administered the C-SSRS weekly to ensure that they meet the study safety/eligibility requirements. The study PI will be informed and will assess the participant for suicidality and safety. The PI will contact the participant’s primary mental health provider to inform them of patient’s current level of suicidality. If the PI determines that the participant is an immediate risk/danger to themselves or others, or feels that an emergency evaluation is clinically indicated, the patient will be referred the emergency room at CUMC/NYP-Columbia.

TMS Sessions:

All procedures will be administered in the TMS core of the NYSPI. The rTMS will be delivered by the PI, a study physician, or by research staff trained in the delivery of rTMS and approved by our local IRB. Stimulation will be delivered using a Magstim TMS device, including the Magstim Super Rapid2 Plus1 stimulator, and Magstim figure-8 coil (Magstim Active D70 AirFilm air-cooled figure-8 coil). Participants will initially undergo an assessment of resting motor threshold (RMT; 15 minutes, see below). The precise positioning and orientation of the coil will be tailored to the individual's MRI scan and monitored and adjusted in real-time using a state-of-the-art, gold-standard Neuronavigation system (Brainsight) at each session. The Brainsight system offers real-time three-dimensional display of cortical localization as the TMS coil is moved across the scalp. Optimization of target locations for TMS stimulation will be identified using Brainsight by applying an overlay of structural MRI and the previously identified TPJ target region. All subjects will be instructed to wear earplugs to protect hearing during each rTMS session and will be monitored by research staff throughout the entirety of each rTMS session. Dr. Michael Avissar, Dr. Daniel Javitt, Yadi Chen and other core approved providers will be delivering the TMS. They will receive the TMS training TMS Core of the NYSPI. Training on the use of the neuronavigation equipment is also provided.

The staff members who will administer the rTMS will be required to meet all of the following:

- Practical demonstration of ability to perform several determinations of the resting motor threshold, under supervision of a trained investigator or TMS consultant experienced in rTMS.
- Performing at least the first two rTMS study sessions under the supervision of a trained investigator or rTMS consultant experienced in rTMS.
- Working knowledge of the principles and practices of rTMS and the rTMS device being used in the study, including common side-effects and how to recognize them. Knowledge will be based on completed tutorial sessions with the investigators or rTMS consultant experienced in rTMS.
- Knowledge of how to contact the covering physician available in the building.
- Certification in basic adult life support (e.g. Cardiopulmonary Resuscitation (CPR).
- Knowledge of seizure first aid, the location of the emergency equipment and medication, how to engage the emergency response system.
- Bachelor's degree or higher.

TMS procedures

Resting motor threshold determination

The increasing popularity of TMS indicates the necessity for safe and effective application of brain stimulation. This means that an appropriate level of induced electric current should be used within a target region. Over-stimulation increases the risk of known adverse effects (Rossi et al., 2009) and reduces the focality of the induced excitation (Thielscher and Kammer, 2004), while under-stimulation may reduce the efficacy of treatment (Mosimann et al., 2002). Motor threshold (MT) is the standard in the field for determining the intensity of the TMS for each individual, as recommended by safety guidelines, to maximize stimulation efficiency while minimizing risk of seizure. MT is defined as the minimum TMS intensity, applied to the scalp zone overlying motor cortex, sufficient to produce an overt motor response in the contralateral hand muscle (Kozel et al., McConnell et al., 2001, Stokes et al., 2007). The participant will be seated in a chair, and the

resting motor threshold (RMT) will be determined by applying TMS over the motor cortex to elicit a twitch in the contralateral (right) hand muscle starting with 40% of the machine output. The coil will be adjusted until each pulse results in isolated movement of the right thumb (abductor pollicis brevis), and adjusted for the lowest intensity that reliably produced thumb or hand movement. The RMT will be defined as the lowest output that produces thumb movement 50% of the time.

Repetitive transcranial magnetic stimulation (rTMS)

Transcranial Magnetic Stimulation (TMS) is a noninvasive tool for the study of the human brain that has been approved by the FDA for use in depression and is being investigated as a potential therapeutic agent in other areas of psychiatry and neurology. Contrary to single-pulse TMS, rTMS is able to change and modulate cortical activity that can last beyond the stimulation period, as a potential method for the treatment of neuropsychiatric conditions such as AVHs. We will deliver rTMS at a low frequency (1 Hz) to produce inhibitory effects that may be required to reduce the severity of AVHs. In our protocol, all participants will receive a 20-min once-daily rTMS sessions over a period of 2 weeks (weekends off), and therefore accrue a total of 10 rTMS stimulation sessions. The rTMS parameters that will be used are a frequency of 1 Hz (1 pulse per second) at an intensity of 90% of the motor threshold (MT). Therefore, we will deliver 1200 continuous pulses per session/day which adds up to 12,000 pulses in total for the whole treatment. These parameters are well within established safety guidelines. Although the goal is to deliver 10 sessions over 10 days of rTMS treatment, the treatment will still be considered complete if the participant misses at most two days of treatment over the two week period.

Localization of brain regions for stimulation

Localization of brain regions is done by establishing skull landmarks for each individual and matching these against an MRI of each participant's brain using Brainsight's camera/computer system for coregistration of each participant to his or her MRI. Each individual subject’s structural MRI with overlay of the left TPJ target will be used to localize placement of the rTMS coil with frameless stereotaxy (Brainsight, Rouge Research, Inc., Montreal, Canada).

Criteria for Early Discontinuation

Subjects with a Clinical Global Impression-I (CGI-I) worsening of 2 or greater for two consecutive days, or a Clinical Global Impression-S (CGI-S) of 6 or 7 will trigger a clinical evaluation as to whether the patient should be discontinued. This will be documented in the clinical chart. Subjects who are unable to cooperate with study procedures (e.g., TMS, EEG, MRI) will be discontinued from the study.

Blood and other Biological Samples

Urine samples will be collected for purposes of pregnancy testing. Approximately 30 mL will be collected, tested, and immediately discarded. Test results will be documented and kept on file under the subject number (no identifying information will be used in the documentation).

Clinical Treatment Alternatives

Standard-of-care treatment for persistent auditory hallucinations consists of use of antipsychotic medications. Cognitive behavioral therapy for voices is sometimes used as adjunctive treatment for coping with AVH.

Risks/Discomforts/Inconveniences

Risks Associated with COVID-19:
Going out in public and traveling involves some risk of infection with COVID-19. There is risk of COVID-19 infection during in-office visits and during travel for research purposes.

Risks Associated with Medical Screening:
Medical screening can be associated with minor psychological distress (answering emotionally difficult screening questions). Study personnel are trained at monitoring patient comfort and providing reassurance in the advent of psychological discomforts. Being informed of clinically significant findings may also cause psychological distress. Dr. Avissar (PI), who is a licensed physician (NY State) and certified by ABPN in Psychiatry will discuss any such results with subjects to minimize distress and provide referral. Dr. Javitt (collaborator), who is also licensed and board certified, will serve as a back-up in cases when Dr. Avissar is unavailable.

Risks Associated with Clinical Assessments:
Distress can be experienced from thoughts or discussion about psychiatric symptoms. Some subjects may experience distress or anxiety related to participating in these procedures, and they will be encouraged to report any concerns. A psychiatrist will be available to assist the subject if needed, and subjects will be removed from the protocol if their distress of anxiety becomes intolerable. Also, each study participant will be provided with a 24-hour emergency contact number. Risks of an audiotaped AHRS assessment include boredom and fatigue, as well as risks to confidentiality and the protection of personal health and identifying information.

Risks Associated with TMS:
The pulses at TMS session per day will be 1200, as described in Study Procedures. This number is far below what is considered safe. For example, Anderson et.al. (2006) describe safely administering 12,960 pulses per day to 63 healthy young men (ages 18-45) without adverse effect. To date, no clear guidelines exist regarding the maximal number of pulses to be delivered per session. No studies since 2007 investigating inhibitory rTMS for treatment of AVH deliver more than 1200 pulses per session to our knowledge (Tranulis et al., 2008; Freitas et al., 2009; Slotema et al., 2010; Demeulemeester et al., 2012; Otani et al., 2015; He et al., 2017; Slotema et al., 2012; Slotema et al., 2014; Zhang et al., 2013). In the above mentioned studies, only mild side effects such as transient headache and scalp discomfort were reported. No significant adverse event was observed.

TMS safety was reviewed at meetings in 2008 and 2018 promoted and supported by the International Federation of Clinical Neurophysiology (IFCN), The report of these meetings (Rossi et al., 2009; Rossi et al., 2020) addressed the safety and ethics of TMS administration,

including subject-based risk, and questions about how, where, and by whom TMS should be delivered. Since the introduction and development of standard international safety guidelines, TMS is generally considered a safe treatment method.

Seizures

Rossi and his colleagues (2020) provided an update on TMS/rTMS-induced seizures, which remains the most severe adverse event of this technique, although by now it is certain that such a risk is very low. The published papers up to February 2020 were searched for reports of seizures and 41 were identified (Chou et al., 2020). Of 41, 28 case reports were of seizures occurring in subjects who have neurological or psychiatric conditions. There were 19 with high frequency rTMS and 1 with low frequency. Even though several cases of seizures induced by TMS or rTMS have been reported to date, most of them happened prior to the definition of safety limits. Moreover, some of these cases may not have been seizures at all, and may have been respectively pseudoseizure (normal EEG and neurological exam) and convulsive syncope. Considering the large number of participants who have undergone TMS/rTMS since 1998 and the small number of seizures, we can assert that the chance of having a seizure during TMS/rTMS is extremely low.

According to Rossi et al. (2020), single/paired and low frequency stimulation accounted for 16 TMS induced seizures in over 200,000 sessions (16/200,000) across high and low-risk participants, while repetitive and high frequency stimulation accounted for 8 seizures (8/200,000). Evidently, high frequency rTMS delivered within the 2009 published guidelines to participants was less likely to cause seizures than low frequency and single/paired–pulse TMS. Moreover, low frequency rTMS seems even less likely to have seizures as a side effect than high frequency rTMS possibily because of its inhibitory effects. This study uses low frequency TMS is defined as TMS given at 1 Hz or below. TMS at this frequency has been repeatedly shown to be of minimal risk.

Heating

TMS can produce currents in skin electrodes (and jewelry, glasses, and watches) and implants that can heat them. Metallic brain implants could heat up as well. Heating of brain tissue over 43 degree Celsius can result in irreversible damage (Matsumi et al., 1994). However, the observed heating risk in rTMS subjects is extremely low overall. No significant heating was detected in ex vivo studies with rTMS applied over implantable electrodes (Phielipp et al., 2017; Shimojima et al., 2010). Moreover, rTMS applied over vascular stents placed in gelled saline found temperature increase less than 1 degree Celsius that is considered safe (Varnerin et al., 2017). In conclusion, the rTMS induced heating is estimated to be very small and this should not pose any safety risk. Exclusion criteria include having any implants whatsoever, and individuals must remove all jewelry and watches during study procedures.

Induced voltages

Likewise, wires, electronic devices, and brain implants (i.e. VNS devices, cochlear implants, aneurysm clips, skull plates, stimulation electrodes) can have a voltage induced by a magnetic pulse. While TMS has been safely done with individuals with these devices, to err on the side of

caution, exclusion criteria for this study include having any implants whatsoever, and as mentioned, individuals must remove all jewelry and watches during study procedures.

Exposure to magnetic fields
According to Rossi et al., 2009, adverse events from magnetic field exposure have not occurred even in situations where patients have received cumulative doses of 72,000 pulses, 156,000 pulses, and even 420,000 pulses. Also, chronic exposure to electromagnetic fields appears safe at levels even greater than what is possible with TMS (Rossi et al., 2009). In the current protocol, participants receive 1,200 pulses each day for 10 treatment days, for a total of 12,000 pulses, far below the cumulative doses listed above.

Hearing
Per Rossi et al., 2009, "rapid mechanical deformation of the TMS stimulating coil when it is energized produces an intense, broadband acoustic artifact that may exceed 140 dB of sound pressure", which they note exceeds recommended OSHA safety levels for the auditory system. After exposure to TMS, a small proportion of adult humans have experienced transient increases in auditory thresholds, and a permanent threshold shift was observed in one person who did not wear ear plugs, and who was being stimulated with a rather loud "H-coil". Most studies in which hearing protection was used reported no change in hearing after TMS (Rossi et al., 2009). While not applicable here in this study of adults, a pediatric study showed that 18 children who had TMS without hearing protection had no change in hearing. Given the risk of increasing auditory threshold in adults with TMS, especially when hearing protection is not utilized, all participants will wear earplugs or headsets during TMS procedures. Audiometry is conducted at baseline and post-treatment. Any change in hearing will prompt a referral to a specialist and reporting as an adverse event.

Local pain, headache, discomfort
Headache is the most common side effect of TMS. This headache is typically of a muscle-tension type. It usually develops during or immediately after the stimulation and may last for minutes to hours following the end of the stimulation. It is typically limited to the day of stimulation, and usually responds promptly to single doses of over the counter pain medications. TMS can also stimulate scalp muscles and produce a twitch in the scalp or upper face that can be uncomfortable for some, painful for others. Neck pain can occur related to head immobilization, and trigeminal stimulation can also lead to a sense of discomfort. Scalp pain may also occur. Migraine has not been reported with TMS. Pain, headache and discomfort, while uncomfortable, do not indicate any problems with safety, and are easily managed with over-the-counter analgesics.

According to Rossi et al., 2009, in therapeutic TMS, 28% of patients experience headache and 39% experience pain or discomfort (vs. 16% and 15% respectively with sham TMS). In prior clinical studies at NYSPI of daily therapeutic TMS for up to 10 days in depressed patients, the frequency of headache with active TMS did not differ from sham (also ~28%). In clinical trials, <2% of patients discontinue TMS because of pain.

In the majority of cases, any pain related to TMS rapidly vanishes with the cessation of TMS, though headaches may occasionally persist, such that an oral analgesic is indicated.

Cognitive changes
In general, the effects of TMS on cognition are relatively low, in both healthy and patient populations. Fitzgerald et al. (2005) reported the effects of low frequency rTMS in patients with treatment-resistant auditory hallucinations, without significant deterioration in any cognitive test. Per Rossi et al., 2020, to date no reliable evidence has indicated longer lasting side effects of TMS on cognition.

Acute psychiatric changes
In general, psychiatric adverse events induced by rTMS were transient and relatively minor in severity, occurring at a rate between 1 and 5% (Rossi et al., 2020). Per Najib & Horvath (2014), acute mania occurrence during rTMS over the left prefrontal cortex in patients with uni- and bipolar depression has been documented. But the prevalence of this emergence seems to be below natural change rates of bipolar patients taking mood stabilizers. Although cases of rTMS induced psychotic symptoms, agitation, anxiety, insomnia and suicidal ideation have been reported in psychiatric patient populations, it is still unknown if such side effects occur at a higher rate than during the natural course of each disease state (Rossi et al., 2020).

Endocrine effects, effects on immune system
None, per Rossi et al., 2009

Autonomic function
TMS can induce a short lasting increase in heart rate and blood pressure, and can briefly alter cerebral hemodynamics, which is of import in individuals with medical illnesses such as acute stroke. Therefore, all participants will be screened for medical illness and also have vital signs obtained.

Pregnancy
The effect of TMS on pregnancy and the unborn fetus are unknown and pregnant women are excluded from the study. Women of child bearing potential must use a medically acceptable birth control method during the study. All negative pregnancy tests have to have been obtained within the prior 5 days for women of childbearing potential to have any TMS procedures. Likewise, women who are breastfeeding cannot participate in the study.

Ineffective therapy
The efficacy of TMS on schizophrenia patients has not been established, though rTMS has been proposed as a promising treatment for people with schizophrenia, especially those who experience auditory hallucinations. In addition, there is no definitive answer to how long the effects of TMS treatment will last.

Risks associated with EEG:

Each EEG session length, including the application and removal of the electrode cap and any required breaks, will be approximately 2.5 hours. Based on our prior experience, we expect this session length to be tolerable for patients. Subjects may experience scalp itching/irritation due to the recording procedures. Otherwise

there are no explicit risks to the subject by participating in EEG. The EEG recording is performed with the patient in an enclosed, sound-proofed room, which may cause mild anxiety, but they are monitored with a closed-circuit camera, told to wave at the camera if they need to get the technician's attention, and the door is frequently opened between task blocks to check in. In our experience, these measures have been sufficient to mitigate any initial anxiety about the recording room.

Risks Associated with MRI:
Some participants may experience sensations during the MRI scan, which are caused by changes in the magnetic field that can stimulate nerves in the body. Subjects will be instructed to report any tingling, muscle twitching, or painful sensations (very rarely) that might occur during scanning.

Some participants may find it uncomfortable to remain still and may experience minor distress by the confined and noisy conditions in the MRI scanner (i.e. claustrophobia) - they can come immediately out of the MRI scanner if this develops. Of note, both the FDA and the NYSPI IRB have deemed MRI Scanning on the GE 3Tesla MRI Scanner at the New York State Psychiatric Institute to be classified as a non-significant risk.

For MRI, the long-term effects of being placed in a magnet of this strength (3 Tesla) are unknown, but there have been no reports of any long-term ill effects caused by magnets of the same or even higher strength, either here or elsewhere. However, although there are no known risks associated with pregnancy, pregnancy tests will be conducted before each MRI session, and subjects testing positive will be excluded from further participation.

Procedures in Place to Minimize Risk:

Informed Consent:
Written informed consent, approved by the NYSPI IRB will be obtained from each participant prior to entering the study. The informed consent document will explain in simple terms, before the patient is entered into the study, the risks and benefits to the patient. The informed consent document will contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, that the patient is free to withdraw from the study at any time, and that withdrawal from the study will not affect any aspect of the delivery of their current care. The nature of the procedures and the alternatives to study participation will be discussed with each subject prior to obtaining written informed consent. A multidisciplinary team including at least one psychiatrist not associated with the study will review the eligibility of the patients, with special attention to the ability of the patient to understand and evaluate the risks associated with the study (capacity evaluation). The evaluation of the psychiatrist not involved in the study is documented in the chart. Subjects will be informed that the information they provide will be kept confidential except within the research team and how that confidentiality will be assured. They will be told that their records are filed by a number, not by name, and that all records are kept in locked files accessible only to research personnel. Consent will be obtained

after a thorough explanation of the study and an opportunity for the participant to ask questions about the study. The consent form will be signed and dated by the subject and study personnel.

It will be the responsibility of the PI to ensure that an informed consent form is obtained from each participant and that the appropriate signatures and dates on the informed consent document are obtained prior to the performance of any protocol procedures and in accordance with current state and federal regulations.
The signed informed consent document will be retained with study records. Each participant will be given a copy of his or her signed informed consent.

Protections Against Risk:
As described above, subjects are safeguarded from undue risk by procedures to obtain informed consent, insure confidentiality, and minimize possible risks associated with the study. Described below are general safeguards that will be used to minimize risks. These include exclusion of subjects at highest risk, the monitoring of any side effects, and the termination of subjects from research participation if it is believed that such participation endangers their welfare.

1. Careful medical and psychiatric screening will identify patients whose risk for potential adverse effects would be elevated with study procedures. Such patients will be excluded from the study. As an example, an actively suicidal patient would be excluded from study participation and referred for appropriate treatment. In addition, pregnant subjects will be excluded.

2. Careful monitoring of patients during the assessment and study period will be performed. Psychiatrists in the inpatient units at NYSPI are available for clinical emergencies.

3. Patients who begin the study and experience adverse effects sufficient to require removal from the study will be referred for appropriate clinical care. The exact nature of "appropriate clinical care" will be determined by the judgment of clinicians familiar with the specific patient and may include medication, cognitive-behavioral therapy, or other modalities.

4. As in any type of research, patients' confidentiality must be carefully guarded and respected. All data with identifying information will be stored in locked file cabinets or password-protected computer files. Data being analyzed will be identified by subject codes and identifying information will be removed. The identity of patients will not be revealed in the presentation or publication of any results from the project. All individuals working on the project will be educated about the importance of strictly respecting patients' rights to confidentiality.

5. TMS: Routine safety procedures are in place to ensure only authorized personnel have access to the stimulation suite, which is locked and only accessible to study personnel. All TMS device settings are checked by two trained operators before initiation of any stimulation protocol to ensure correct stimulation duration and current intensity settings. Once set, parameters will not be changed during the stimulation protocol outside of aborting treatment in case of an adverse event. Subjects are encouraged to report discomfort or adverse events

and are informed that they may ask for stimulation to be aborted at any time. Furthermore, stimulation will be aborted for any concerning and/or unexpected adverse reaction at the discretion of the research physician. We will be monitoring the potential for adverse events in this study. All adverse events are documented in the treatment notes and reported. Data on the severity and duration of each adverse event will be collected, including information on any interventions performed to address the adverse event and whether the event was resolved.

One of the most common risks of rTMS is the possibility of having a headache after the sessions. To try to reduce the risk of headache we will assure participants' comfort before and during the procedures. If needed, participants can contact the study doctor to discuss their symptoms and receive over the counter pain medicines such as ibuprofen or acetaminophen.

To minimize risk of rTMS, individuals who have a history of seizures or have been diagnosed with epilepsy or current use of medications known to lower seizure threshold will be excluded from this research study. An MD will be present for the first three sessions in the building and immediately available during all rTMS sessions. In the event of a seizure, our staff will make sure that the participant is on the floor (cannot fall) and will clear the area of all objects. Most seizures will end spontaneously at 1 to 2 minutes. In the event that the seizure has not ended in two minutes, the hospital emergency team will be called and Lorazepam (which is stored in the room) will be administered IM (4mg). If seizures continue or recur after a ten to twelve minute observation period, an additional intravenous dose of 4 mg may be administered until the acute care medical team arrives. The New York State Psychiatric Institute has emergency response procedures for situations which would include a seizure. The emergency team has a "crash cart" that they bring to emergencies and is notified via building wide loud speaker and mobile phone. 911 would also be called and the subject would be transferred to the Emergency Department at New York Presbyterian, the hospital for the Columbia University Medical Center, which is within the same medical campus. Any seizure that may occur should not deny the participant of employability, motor vehicle licensure, of insurability. If desired, participants may receive a letter to state this.

6. COVID-19: (1) All in-person procedures will be done in accordance to standard NYC and NYS DOH COVID precautions for healthcare workers interacting with patients, which currently include wearing a mask, PPE and eye protection at all times for staff members; (2) The components of the TMS device will be wiped down and disinfected before and after each session; (3) We have also minimized in office visits to lessen this risk. We may also be able to arrange alternative transportation for subjects to avoid the subway and the bus; (4) We will keep subjects informed about current public health recommendations, such as federal and local government guidelines and directives.

Audiotaping

Audiotapes will be converted into computer files that adheres to HIPAA regulations, which will be stored on a secure room at NYSPI for up to five years, and then will be erased.

EEG

These studies entail the recording of EEG from the scalp employing standard sensors and amplification methods. These procedures are well standardized and there are few known risks. These are principally due to equipment malfunction. The recording equipment used in these studies meet the current design criteria for subject safety, including isolation from potential electrical hazards.

MRI

There are no significant risks associated with MRI and fMRI. It is possible that some participants might experience minor distress from the confined and noisy conditions in the scanner. This possibility will be minimized by the use of earplugs, and experienced technicians will monitor all participants for any signs of distress. In the event that a participant becomes anxious during a scan, the study will be halted. Participants will be able to communicate with the investigators at all times using the intercom system should they wish to request that the study be terminated or if they have concerns or questions during the procedure. The participant is in full view of the operator at all times. Participants cannot have an MRI if they have any metallic implants or metal on their person, of if they are pregnant.

The probability of an incidental finding that might lead to the diagnosis of an unknown abnormality is greater than zero. All participants will be alerted to this possibility during the consent process. In that event, participants or their designated physician will be provided copies of their anatomical scans and advised to seek further evaluation if they have concerns.

Measures taken to minimize risks and discomforts related to MRI include: a) a questionnaire used for screening for metallic devices, implants, and other contraindications to scanning; b) exclusion for pregnancy using a pregnancy test prior to scanning; c) exclusion of those unlikely to tolerate the sense of confinement during scanning; d) providing adequate medical, safety monitoring and observation during scanning as appropriate; e) reducing scanning time to that necessary to accomplish the scientific aims of the study; f) enhancing the subjects' physical and emotional comfort during the scan (i.e. ear plugs or headphones for the loud noise produced by the scanner).

All precautions and protections are given to the participant to ensure that they are as safe and as comfortable as possible. For participants' comfort within the scanner, they lie on a padded table with a pillow to rest their heads on. A blanket is also provided to keep participants warm during the procedure. If the participant appears nervous or anxious, a trained member of the research staff remains with them inside the scanning suite for the duration of the scan. The participant is given a button box to terminate the scan at any time. If he/she pushes the button, he/she will be removed from the scanner immediately. Participants may end the MRI scans at any time.

Methods to Protect Confidentiality

All data (written and electronic) will be coded by number. Personal identifying information will be stored in an electronically secure database at NYSPI. A master list matching subjects with codes will be kept under lock and key, separate from any research records or the computer

database, with access restricted to research staff, to the extent permitted by law. Only staff directly involved in this project will have access to the master list linking subject names to code numbers. All paper records will be kept in a locked office. Computerized data including MRI data will be kept on encrypted computers that are password protected. Any files that contain identifying information will be kept electronically in folders on a computer that is password protected.

In the informed consent form, subjects are told that the information they provide and all findings of testing will be kept strictly confidential, with access limited to the research staff, and possibly state or federal regulatory personnel. All staff members involved in this project are required to receive training in the protection of human subjects. This includes both Good Clinical Practices at Columbia University (entitled Health Sciences: Protection of Human Research Participants [GCP] for Patient-Oriented Clinical Investigators) and the Collaborative Institutional Training Initiative (CITI) at NYSPI.

For remote visits, we will use HIPAA-compliant videoconferencing, phone and web-based platforms.

De-identified data may also be shared with other investigators at NYSPI for the purposes of substitution in the case of failure of data collection. For instance, if the subject participates in another MRI protocol at NYSPI, and during those sessions the investigators fail to collect all of the needed anatomical and functional MRI sequences, we may share our data with them if we have collected the same types of MRI sequences for our protocol. The inverse may happen as well; we may receive data from another NYSPI protocol if because of a technical failure we are unable to collect all of the necessary MRI sequences.

Direct Benefits to Subjects

Participants may not experience any direct benefits from their involvement in this study.

The proposed project is a clinical trial of TMS for treatment of AVH and an experimental intervention. Therefore, we do not consider AVH treatment a definite benefit of participation. Nevertheless, participants are informed of the purpose of the trial and may in fact experience a reduction in AVH.

MRI findings and clinical assessments are unlikely to be of direct benefit to participants, but subjects will be informed of any clinically significant findings from the MRI and clinical assessments.

Compensation and/or Reimbursement

Subjects will be compensated as follows:

- Pre-treatment session (screening, clinical assessment, EEG and MRI): $185
- Treatment day: $100
- Post-treatment session (clinical assessment, EEG and MRI): $160

In this study, each subject will undergo 1 pre-treatment session, 1 post-treatment session and 10 treatment days. Total compensation for all sessions is $1345.

Statistical Analysis Plan

We will use a repeated measures t-test to analyze changes in the Auditory Hallucination Rating Scale (AHRS). This involves comparing scores before and after TMS treatment in participants who completed all study procedures. The goal of this analysis is to determine if there are improvements in symptoms of auditory verbal hallucination. Additionally, similar analyses will be performed for secondary outcome measures such as PANSS, investigating if there is a significant decrease in PANSS P3 scores for participants after the TMS treatment sessions.

Furthermore, the study will explore potential associations between the intensity of TMS treatment and the extent of AHRS improvement. This will involve conducting Pearson's correlation analysis to assess whether higher treatment intensity is linked to a more favorable treatment response.

The study also aims to assess the utility of EEG biomarkers that are relevant to the condition's etiology in tracking treatment response. Specifically, changes in EEG biomarkers related to hallucinations will be examined. Moreover, the investigation will extend to evaluating functional connectivity using fMRI.

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