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Protocol Title: An open-label extension study 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.

It is still unclear which brain regions are involved in the generation of hallucinations. Auditory verbal hallucinations (AVH) are thought to be associated with increased activity in brain regions involving speech perception, including the left temporo-parietal junction (TPJ) area, which suggest abnormal activation of normal auditory pathways. Low-frequency rTMS offers a non-invasive method for reversing hyperactivity of language regions involved in the emergence of AVH. In addition, a recent study on brain lesions (Kim et al., 2021) demonstrated that focal brain lesions connected to the right superior temporal sulcus (rSTS) play a causal role in the production of AVH. Thus, the rSTS is a promising therapeutic target for brain stimulation to reduce AVH. This is an open-label extension study to continue to evaluate the safety, tolerability and efficacy of rTMS in subjects with schizophrenia or schizoaffective disorder who previously completed the treatment study of #8116. Protocol #8116 investigates the clinical efficacy of open-label individualized MRI-guided TMS applied to the left TPJ in schizophrenia patients. Participating patients who have completed the 4-week project #8116 can be screened for eligibility for this extension study in which they will continue treatment/assessment. They will be divided into three groups (non-responders, partial responders, or full responders) based on a reduction in the Auditory Hallucination Rating Scale (AHRS) scores from the study #8116. Non-responders are defined as patients showing a reduction of AHRS less than 20% of the initial score. A partial response is defined as a reduction in a range of between 20% and 50% of the initial AHRS score. A complete response is defined as a reduction by at least 50% of the initial AHRS score. During this extension study, non-responders to protocol #8116 will be administered 10 days (10 sessions) of MRIguided 1 Hz rTMS delivered to the rSTS instead of the original target in TPJ. Partial responders will receive 10 additional low-frequency rTMS over the original left TPJ target. Like the protocol #8116, we will use the MRI-guided targeting approach during rTMS treatment sessions to achieve greater precision as it can account for individual differences in anatomy. Complete responders will instead be followed for sustainability of response. Their clinical ratings will be repeated at one week, two week, four week and eight week follow-ups. The combined outcome of protocol #8116 and the currently proposed protocol will help guide TMS targeting and the number of treatment sessions for a future larger randomized, double-blinded, shame-controlled clinical trial.

Background 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 in certain brain regions such as the left temporo-parietal junction area (TPJ) or the right superior temporal sulcus (rSTS). rTMS is generally well tolerated and safe but see "Risks and inconveniences" section for a detailed discussion of potential adverse effects.

The optimal neuroanatomical treatment targets remain unclear, though current neuroscience evidence suggests several brain areas may be involved in the generation and development of AVH. Neuroimaging studies have demonstrated that AVH are associated with increased neuronal activity in cerebral areas responsible for language perception such as the left TPJ (Strik & Dierks, 2008). And previous work on AVH indicated that inhibitory rTMS stimulation (≤1 Hz) can reduce excitability of cortical neurons in language–related areas (Kindler et al., 2013), and it has therefore been hypothesized that low frequency rTMS delivered to the left TPJ area would alleviate AVH in schizophrenia. However, many studies that delivered low-frequency rTMS in this area have yielded mixed results in reducing AVH (Marzouk et al., 2020). This may have been due to application of the targeting approach and variable stimulation parameters. In the opinion of most investigators, the left TPJ area is the most common target for AVH treatment using rTMS. In this extension study, partial responders will still continue to receive stimulation of the same brain region they did in the previous study, which is 20 minutes of stimulation with 1 Hz rTMS to the left TPJ. We also propose to use the right superior temporal sulcus (rSTS) as a secondary target for patients who fail to respond to the lowfrequency TMS over TPJ. Using a newly validated technique termed lesion network mapping, researchers (Kim et al., 2021) demonstrated that brain lesions that cause hallucinations were located in a single functionally connected brain network.

This network was defined by connectivity to the cerebellum and the right superior temporal sulcus (rSTS). The rSTS receives convergent somatosensory, auditory, and visual inputs and is thought to be a site of multimodal sensory integration. The researchers noted that patients with AVH have abnormal functional connectivity to this region. They therefore suggest that the rSTS may be the best TMS target for AVH (Kim et al., 2021).

Compared with standard scalp-based targeting approaches that have been used in most published studies, the proposed project will use individualized MRI-guided method that takes into account the inter-subject variability in brain anatomy. We expected that the rTMS treatment with individualized positioning based on each patient's structural brain MRI may show better clinical efficacy than the scalp-based targeting approach, and might thus represent a step toward tailored TMS interventions for AVH. Schizophrenia patients with AVH who have completed protocol #8116 (A pilot open-label trial of individualized repetitive transcranial magnetic stimulation for patients with auditory verbal hallucinations) will be recruited, and allocated to one of three arms based on their treatment responsiveness from protocol #8116 which included 10 low-frequency TMS treatment sessions using the TPJ target. Their treatment responsiveness is assessed by the Auditory Hallucination Rating Scale (AHRS) at pre- and post-TMS session. Non-responders, defined as those experiencing a reduction of AVH symptoms of less than 20% of initial AHRS score, will be offered 10 daily sessions of 1-Hz rTMS delivered to the rSTS region instead. Partial responders, defined as those experiencing a reduction in AHRS between 20 to 50%, will be offered 10 additional daily sessions of 1-Hz rTMS delivered to the same original left TPJ target used in protocol #8116. The two treatment groups will receive TMS to only one of these brain regions and not both. Full responders, defined as those experiencing at least a 50% reduction in AHRS, will be offered followup clinical assessments at 1,2,4, and 8 weeks to assess sustainability of their response. In addition, all participants in the treatment arms will be assessed post-treatment with the same neurophysiological (EEG) tasks used in protocol #8116.

Specific Aims and Hypotheses

After rTMS stimulation above the left TPJ area in pilot study #8116 for treatment of AVH, subjects will be identified as non-responders (reduction in AHRS score < 20%), partial responders (reduction in AHRS score >= 20 and < 50%) and full responders (reduction in AHRS >= 50%) based on their pre/post change in score on the Auditory Hallucination Assessment Scale (AHRS).

Specific Aim 1: To evaluate the efficacy of individualized MR-guided inhibitory rTMS in reducing AVH symptoms in Sz. We hypothesize that non-responders from protocol #8116 will show reduction in AHRS scores after a 10-day MRI-guided TMS treatment to an alternative target, rSTS. We also hypothesize that partial responders from protocol #8116 will show further reductions in AHRS with continued rTMS to the original left TPJ target.

Specific Aim 2: To evaluate sustainability of treatment response in full responders from protocol #8116. We hypothesize that maintained improvements in AVH will be observed in full-responders at 2 months follow-up.

Specific Aim 3: To evaluate the utility of etiologically relevant EEG biomarkers in tracking treatment response.

For non-responders and partial responders, we hypothesize that treatment changes in AVH severity will correlate with normalization of previously established deficits in EEG measures associated with AVH.

Description of Subject Population

Specify subject 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 from the study (protocol # 8116) 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 CSSRS under other protocols for the past two years. For the non and partial responders, C-SSRS will be conducted every week of the four-week study. For the complete responder, the C-SSRS will be administered at each visit during the 8-week trial. In addition, the study PI (MD/PhD) will conduct a rigorous assessment with non and partial responders 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.

Once a patient is 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 has been seen 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 a "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 warrant active referral, a referral list with names and telephone numbers of qualified providers be initiated. The rationale for this will be documented in REDCap.

Recruitment Procedures

Recruitment of adults with schizophrenia or schizoaffective disorder from the study ''A pilot open-label trial of individualized repetitive transcranial magnetic stimulation for patients with auditory verbal hallucinations"(Protocol #8116) within the Division of Experimental Therapeutics at NYSPI.
How and by whom will subjects be approached and/or recruited?
Research staff from the "A pilot open-label trial of individualized repetitive transcranial magnetic stimulation for patients with auditory verbal hallucinations" (Protocol #8116) will tell patients about the

extension study and ask if they would like to meet with investigators or research staff of this "An open-label extension trial of individualized repetitive transcranial magnetic stimulation in patients with auditory verbal hallucinations who completed protocol #8116" 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 Protocol #8116 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.
How will the study be advertised/publicized?
Subjects may also be recruited through advertisements in newspapers, flyers, and the Internet using advertisements approved by the NYSPI IRB.

Inclusion/Exclusion Criteria

Inclusion: non-responders and partial responders
1. Completion of the study #8116
2. Age between 22-55
3. DSM-V diagnosis of schizophrenia or schizoaffective disorder
4. A reduction of AHRS less than 50% of the initial score
5. Capacity and willingness to provide informed consent
6. 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.
7. Right handed
8. Normal hearing
9. Taking an antipsychotic medication at a stable dose for at least 4 weeks. All oral and depot antipsychotics are allowable
Exclusion: non-responders and partialresponders
1. Substance use disorder (excluding nicotine) within last 90 days, or positive toxicology screen for any substance of abuse
2. Pregnancy
3. Severe adverse events of TMS
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
5. Subjects with devices that may be affected by TMS (pacemaker, cardioverter defibrillator, medication pump, intracardiac line, cochlear implant, implanted brain stimulator/neurostimulator)
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 Columbia Suicide Severity Rating Scale (C-SSRS) screening or subjects who represent a significant risk of suicide in the opinion of the investigator
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 example, hypertension, previous stroke, brain lesions, or heart disease.
10. History of prior clinically significant, adverse response to neurostimulation
11. Current treatment with ototoxic medications (amino- glycosides, cisplatin)

Inclusion: complete responders
1. Completion of the study #8116
2. Age between 22-55
3. DSM-V diagnosis of schizophrenia or schizoaffective disorder
4. A reduction by at least 50% of the initial AHRS score
5. Taking an antipsychotic medication at a stable dose for at least 4 weeks. All oral and depot antipsychotics are allowable.

Exclusion: complete responders
1. Substance use disorder (excluding nicotine) within last 90 days, or positive toxicology screen for any substance of abuse
2. 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
3. Presence or positive history of unstable significant medical or neurological illness

Describe procedures used to obtain consent during the screening process
The screen is straightforward and patients will be referred from the approved study (protocol #8116), 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 Columbia Suicide Severity Scale (C-SSRS)). Consent procedures will conductedby MDs only. All individuals involved in screening and consent procedures have undergone HIPAA and CITI training and are familiar with study procedures of this protocol.

Describe Study Consent Procedures
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.

Study Procedures

This is an extension of the previous NYSPI study #8116 (A Pilot Open-label Trial of Individualized Repetitive Transcranial Magnetic Stimulation for Patients with Auditory Verbal Hallucinations). Participants who have completed the 4-week study #8116 will be screened and assessed for admission to this extension study. MRI is not included in the current study procedures since we will use their existing structural MRI scan that was used when they participated in protocol #8116. All study procedures of the current protocol will take place at the New York State Psychiatric Institute (NYSPI), Division of Experimental Therapeutics. Participants in the present protocol include non-responders, partial responders and complete responders. After providing informed consent, non-responders and partial responders will undergo a medical and safety screen to confirm eligibility and mitigate potential risks. They will then receive two weeks (10 sessions) of rTMS treatment, and then partake in clinical and EEG assessments post-treatment. Complete responders will undergo four follow-up clinical assessments at 1, 2, 4, and 8 weeks post-treatment.

The total participation period for non-responders and partial responders in this extension study is 4 weeks, starting at week 1 and ending at week 4; the total participation period for complete responders in this extension study is 2 months.

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.

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).

We will be using a secure web-based central electronic data capture system (i.e., REDCap) for data collection that require minimal infrastructure for end user (only internet connection). This electronic data capture system ensures the privacy and security of the data collected by meeting the Good Clinical Practice (GCP) guidelines and the following applicable Federal Regulations-Health Information Portability and Accountability Act (HIPAA), Federal Information Security Management Act (FISMA), and Food and Drug Administration (FDA) 21CFR Part 11. The REDCap project will be developed and maintained by Yadi Chen. Access to this database is limited to research approved personnel who have received training on handling human subjects' data and systems training. A qualified data management staff member will train research assistants on how to properly enter data into, review and resolve data queries in the electronic data capture system. Any and all videoconferencing sessions will be hosted via WebEx-secure, HIPAA-complaint video conferencing recommended by NYPSI. For participants with email access, reports related to their own health will be sent via encrypted email.

Assessment Instruments

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987): 45 min, performed by Dr. Avissar or a trained research assistant under Dr. Avissar’s supervision.
The Cardiff Anomalous Perception Scale (CAPS) (Bell et al., 2006): 20 min, performed by Dr. Avissar or a trained research assistant under Dr. Avissar’s superviseon.
The Auditory Hallucination Rating Scale (AHRS; Hoffman et al., 2005; Hoffman et al., 2003): 5 min, performed by Dr. Avissar or a trained research assistant under Dr. Avissar’s supervision.

Wong-Baker Faces Pain Rating Scale (WBFPRS, Wong-Baker, 1983): 1 min, performed by a trained research assistant.
Columbia Suicide Severity Scale (C-SSRS) (Posner et al., 2007): 10 min, performed by Dr. Avissar or other qualified clinicians.
The Clinical Global Impression Scale (CGI-S and CGI-I, Guy, 1976, 2000): 5 min, performed by Dr. Avissar or a trained research assistant under Dr. Avissar's supervision.
Systematic Assessment for Treatment of Emergent Events (SAFTEE): 5 min, performed by Dr. Avissar or a qualified staff under Dr. Avissar's supervision.
The Psychotic Symptom Rating Scales (PSYRATS; Haddock et al., 1999): 20 min, performed by Dr. Avissar or a trained research assistant under Dr. Avissar's supervision.
The Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984): 30 min, performed by Dr. Avissar or a trained research assistant.
Transcranial Magnetic Stimulation Adult Safety Screen (TASS): 20 min, performed by Dr. Avissar or a trained research assistant under Dr. Avissar's supervision.
TASS: Standard safety questionnaire to screen potential subjects for risk of adverse events during TMS; "A safety screening questionnaire for transcranial magnetic stimulation" JC Keel, MJ Smith, EM Wassermann - Clinical neurophysiology, 2001