Official Study Title: Transcranial Magnetic stimulation and Cognitive training for treatment of cognitive decline in adults with schizophrenia: A Pilot Randomized Trial

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Principal investigators: Ginger Nicol, MD
Rita Haddad, MD

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Study Rationale

Background:

A primary concern in long-term Schizophrenia treatment is the toll that sustained cognitive deficits have on functional capacity to work and live as a productive member of society[1]. Since the advent of antipsychotic medications, Schizophrenia treatment has improved significantly with respect to positive symptom control. However, there are limited resources for improving cognitive symptoms in Schizophrenia, which remain disabling for most with the diagnosis. Cognitive remediation and cognitive training programs have shown promise in improving these symptoms[2]. Specifically, adults with Schizophrenia show significant improvements in cognition after participating in 2 weeks of computer based cognitive training[3]. Functional capacity has also been shown to improve with longer periods of computer-based cognitive training[2]. However, the effects of cognitive training alone may be most effective in the short-term. Longer term effectiveness of cognitive training has yet to be shown.

There has been emergent interest in using neuromodulation for treatment of cognitive decline in people with various illnesses including children with ADHD[4], adults with schizophrenia[5] and older adults with late life depression[6]. There is promising evidence for the use of repetitive transcranial magnetic stimulation (rTMS). High frequency (20Hz) rTMS on the bilateral dorsolateral prefrontal cortex (DLPFC) has been shown to improve working memory in patients with schizophrenia[7-8].

Rationale:

Schizophrenia affects approximately 1.1% of U.S adults per year and is among the most disabling psychiatric illnesses, due primarily to poor functioning related to cognitive dysfunction[1]. Negative (e.g. flattened affect, limited speech output, lack of motivation) and cognitive symptoms (e.g. poor executive functioning, attention and working memory) are by far the leading cause of social, occupational and educational disability and functional impairment in patients with schizophrenia[9].

Cognitive training programs have been shown to improve cognition and functional capacity in adults with schizophrenia[2-3]. High frequency rTMS has been shown to improve working memory in adults with schizophrenia[7]. Here, we hypothesize

that rTMS combined with computerized cognitive training, will result in a larger and more generalized cognitive benefit, compared to cognitive training alone, and improvement in functional capacity. Here, we propose to test rTMS, in combination with a computerized cognitive training program, to remediate cognitive dysfunction in Schizophrenia, in a pilot randomized clinical trial.

The rationale for a combined intervention is based on data suggesting that rTMS induces neuroplasticity[7]. By improving neuroplasticity and working memory, rTMS could significantly improve effects of cognitive training in patients with schizophrenia. Also, combination treatment was tested in patients with depression and results were promising. At the same time, cognitive training programs are automated and therefore offer a feasible and scalable combination with neuromodulation treatment.

Hypothesis:

Hypothesis 1: high frequency rTMS will boost the cognitive benefits of computerized cognitive training in adults with schizophrenia

H1 will test the hypothesis that participants will have an acute improvement in neuropsychological executive functioning, as measured by the Screen for Cognitive Impairment in Psychiatry (SCIP).

Hypothesis 2: rTMS combined with cognitive training will improve everyday functioning.

H2 will test improvement in daily functioning as measured by the Canadian Objective Assessment of Life Skills (COALS) and the WHO Disability Assessment Schedule (WHODAS).

Primary Aim/Objective:

Test the efficacy of rTMS for acutely improving neuropsychological functioning in 30 participants aged 18 to 65 with schizophrenia or schizoaffective disorder, who will receive computerized cognitive training and will also be randomized 1:1 to rTMS or placebo.

Secondary Objective:

To test the efficacy of rTMS for improving daily functioning and self efficacy in 30 participants aged 18 to 65 with schizophrenia or schizoaffective disorder, who will receive computerized cognitive training and will also be randomized 1:1 to rTMS or placebo.

Primary Endpoint:
Our primary outcome measure will be the Screen for Cognitive Impairment in Psychiatry (SCIP). The SCIP will be carried out at baseline and at the end of the 2 weeks.
Secondary end point:
As a secondary outcome, we will assess participant function using the Canadian Objective Assessment of Life Skills (COALS) and the WHO Disability Assessment Schedule (WHODAS).

Study Plan

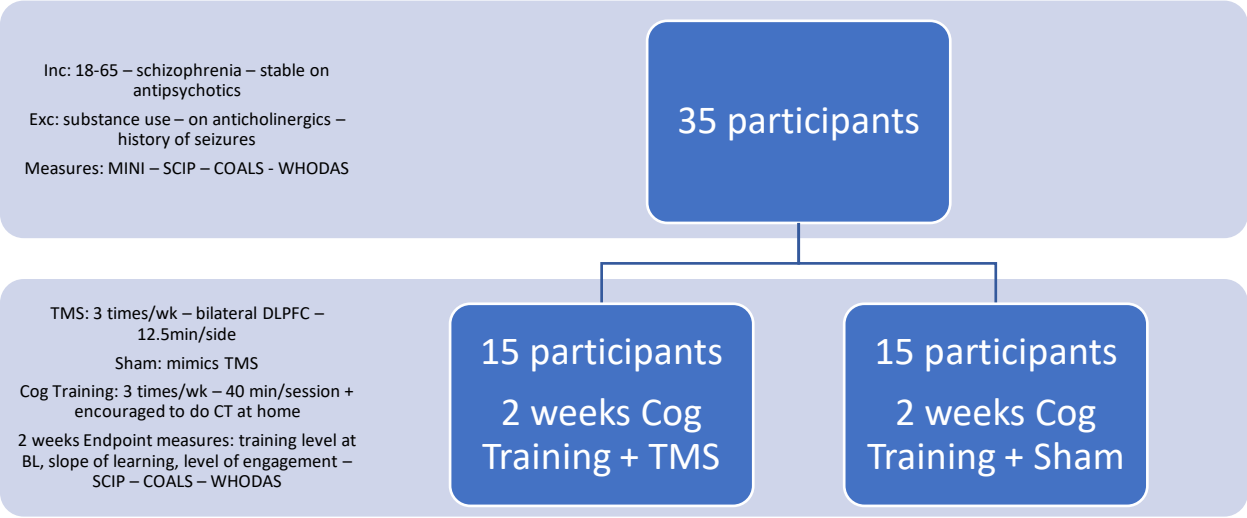
The key design features are:

(1) Parallel-group randomized, single-blinded controlled trial of rTMS vs placebo, 50:50 randomization.

(2) Randomize 30 adults aged 18-65 with schizophrenia or schizoaffective disorder. Initially up to 5 subjects will receive open label rTMS. Subsequent subjects will be randomized to receive either rTMS or placebo.

(3) All participants receive cognitive training using a well-validated program, “Scientific Brain Training Pro” (www.scientificbraintrainingpro.com). Prior to randomization, all participants receive a training session with research staff.

Study design and schedule of procedures



Description of the cognitive training program: Cognitive training techniques result in physiological adaptation of the brain as a result of neuroplasticity, leading to tissue growth and more efficient neurophysiological processing. These techniques increasingly rely on drill and practice computerized exercises, which include graded changes in difficulty level to adapt to the dynamic performance of the individual. That is, the participant's performance guides the task parameters and a trial-by-trial change in difficulty level is made to keep the activity challenging enough to stimulate neuroplasticity, but not so difficult that repeated failure produces discouragement and withdrawal. The training is feasible with older and even novice computer users; the participant logs into the activity online through a simple interface that only displays a request for username and password and the exercises appear automatically through a pre-selected order. Thus, participants click "play" or "exit", reducing the visual distractions and complexity that might be associated with computer use in general. There are 28 different cognitive exercises, each with 30 levels of difficulty. Training progresses from basic (i.e., processing speed, attention) to more complex (i.e., working memory, executive functions) cognitive functions. Difficulty levels change adaptively by increasing following consecutive trials of 80% success or better and decreasing following consecutive trials of 70% success or less. Feedback is provided after each trial and participants have access to visual displays of their progress on each task throughout their training period. A one-hour orientation and

training session is completed with participants following baseline assessment. This includes psychoeducation to the purpose of improving cognition, which is integrated into the participant's own profile of cognitive strengths and limitations and their self-defined goals for functioning. A manual is provided to participants with clear instructions, goals, and strategies for each of the exercises. The program has a moderated forum wherein participants share their cognitive strategies and how the tasks are relevant for everyday life skills.

Rationale for all participants to receive cognitive training: numerous studies already have demonstrated the cognitive benefits of cognitive training for cognitive decline in adults with schizophrenia. This study would be the first to examine rTMS's benefits when given together with cognitive training. rTMS with cognitive training is expected to demonstrate greater cognitive benefits than has been shown in most of the existing studies with cognitive training alone.

Description of rTMS

We will use the rTMS device currently available at our institution for clinical and research applications. The stimulator is a MagPro R 30 magnetic stimulator manufactured by MagVenture A/S (Farum, Denmark) and FDA approved for treatment of major depressive disorder. Equipment components include: 1) R30 magnetic stimulator 2) coil cooler unit 3) dedicated C-B60 butterfly coil for Motor threshold assessments only 4) Treatment chair with neck rest and cloth cover, subjects will recline in this comfortable motorized recliner during intervention delivery 5) Head Stabilizer System (Airtight Pillow and Evacuation Pump).

The intervention will be delivered using:

- A Coil- cool B65 A/P butterfly coil. This coil functions as both active and sham coil. The coil has a symmetrical design, one side of the coil delivers active treatment and the other side delivers sham. Both sides of the coil are identical.

The Magpro R30 is a non-significant risk device because:

- It is not an implant
- It is not for use in supporting or sustaining human life
- It does not present a potential for serious risk to the health, safety or welfare of study

rTMS delivery:

High frequency (20Hz) bilateral DLPFC rTMS will be delivered at 90% resting motor threshold for 25 trains comprising 30 pulses per train, inter-train interval of 30s for a total of 750 pulses per hemisphere[7] and in accordance with published safety guidelines[10]. rTMS will be delivered over 12.5 mg per hemisphere. rTMS will be delivered 3 times per week, over 2 weeks.

Sham (placebo) delivery: To deliver sham, we will use the same B-65 A/P coil. Sham stimulation is ensured by an Internal shielding mechanism in the delivery coil, which reduces the magnetic field strength to < 5% of active field which is biologically inactive. The coil's symmetric design and identical clicking noises during both active and sham. The coil has a built-in position sensor to ensure that the correct (active or sham) side of the coil faces toward the subject's head. We will use synchronized gentle electrical stimulation to the scalp via pre-gelled surface stimulation electrodes to simulate scalp sensations on the sham delivery, which will mimic the active stimulation. Subject's assignment to the intervention will be defined by the Maglink software according to the randomization schedule.

Localization of the Dorso-lateral prefrontal cortex (DLPFC) for tTMS and placebo interventions: Subjects assigned to either rTMS or sham intervention will receive stimulation on the DLPFC. We will target the DLPFC because it is a key prefrontal cortex structure involved in orchestration of executive function[11].

Motor Threshold Determination: Each subject's Motor Threshold (MT) will be assessed using a dedicated C-B60 butterfly coil at the baseline session. MT is the lowest stimulation intensity required to induce a motor response of the Abductor Pollicis Brevis (APB)

muscle in the contralateral hand. MT will be measured via the visualization method, by observing movement of the contralateral thumb or adjacent fingers. We will “dose” rTMS at 90% of the resting MT.

The TMS device to be used in this study for delivery of the interventions is currently employed in clinical operations and is housed at the West Pavilion, suite 15340, Outpatient Psychiatric Clinic at 1 Barnes-Jewish Hospital Plaza. The equipment will remain in place once study is finished. Therefore, there is not need for maintaining device shipment and receipt records.

Schedule of assessments:

	Weeks in the study		
	-1	0	2
Outcome measures			
Hypothesis 1: SCIP		X	X
Hypothesis 2: COALS - WHODAS		X	X
Baseline assessments:			
Mini International Neuropsychiatric Interview (MINI) to confirm the diagnosis	X		
Medical history, medication, substance use to confirm eligibility	X		
Motor threshold	X		

Schedule and Description of Study Assessments

Baseline Diagnostic Evaluation and Screening Methods:

General Principals: Prior to conducting any of the planned experimental conditions, all subjects will be screened for the presence of listed exclusions and a careful assessment

of diagnoses. In order to accomplish this end, subjects will undergo a Mini International Neuropsychiatric Interview (MINI).

Medical Examination and History: Subjects will be screened with a detailed history and physical examination and history of any major medical or psychiatric disorders.

Motor Threshold determination: Each subject's Motor Threshold (MT) will be assessed using a dedicated C-B60 butterfly coil at the baseline session. MT is the lowest stimulation intensity required to induce a motor response of the Abductor Pollicis Brevis (APB) muscle in the contralateral hand. MT will be measured via the visualization method, by observing movement of the contralateral thumb or adjacent fingers. We will "dose" rTMS at 90% of the resting MT.

Outcome measures:

Screening for Cognitive Impairment is Psychiatry (SCIP)[12]: This is a brief assessment tool designed for bedside evaluation of key features of cognitive impairment common is psychiatric illnesses including immediate and delayed verbal learning, working memory, verbal fluency, and psychomotor speed.

Canadian Objective Assessment of Life Skills (COALS)[13]: This is a brief assessment that captures functional outcome variance by assessing procedural knowledge routine and executive operations.

WHO Disability Assessment (WHODAS)[14]: This is a self report assessment measuring disability and functional impairment. It had good reliability, validity and sensitivity to change.

Rationale for study length: the two-week duration allows for a rapid test of rTMS benefits in the setting of co-administered cognitive training. Two weeks was chosen because it is sufficient to demonstrate cognitive improvement with cognitive training and to expect neuroplasticity and working memory improvement with rTMS. This duration will also be beneficial in achieving high compliance with visits and adherence to intervention.

Adherence monitoring to the cognitive training program and the rTMS: participants will have their entire intervention (rTMS/Sham and cognitive training) on site. Compliance with appointments will be monitored by research staff. Adherence to cognitive training will

be monitored by directly supervised by research staff. Research staff will provide motivational feedback to participants to reinforce or increase adherence

Blinding measures taken to minimize bias: Subjects receive blinded study intervention (rTMS versus sham). Investigators will not be blinded.

Inclusion criteria: (1) Med and women age 18 to 65; (2) diagnosis of schizophrenia or schizoaffective disorder

Exclusion criteria: (1) substance use disorder per DSM5 criteria in the past 6 months; (2) use of psychotropic medication affecting cognition (like anticholinergic medications), per PI discretion; (3) contraindications for TMS including the presence of metallic objects within 30 cm of the TMS coil, intracranial implants (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed; presence of intracardiac lines, defibrillators or a cardiac pacemaker and unable to assess safety; presence of implanted electronic devices that control physiologic functions and unable to assess safety; (4) have a personal history of a primary seizure disorder or a seizure associated with an intracranial lesion; (5) History of severe head trauma or neurological disorders that substantially increase seizure risk, per PI discretion

Safety and Adverse Events

Interventions and precautions to minimize subject's risk during TMS intervention:

• Treating personnel is trained to act as first line responder, and has had cardiopulmonary resuscitation (CPR) training, in case of a seizure event.
• Intervention will be delivered in a suite equipped with necessary materials to assist the subject in case of a seizure (oxygen, pulsoxymetry monitor, etc.). The suite is located in house Barnes-Jewish hospital and the emergency response team at Barnes-Jewish hospital is readily available to assist. The TMS attendant will call the emergency response team in case of a seizure or other event deemed an emergency.
• The TMS suite has a written protocol to handle a seizure occurrence

• Subjects with increased risk of seizure or history of head trauma that may increase seizure won't be eligible for intervention.
• Cognitive function is monitored throughout the intervention.
• Side effects of the intervention will be monitored by the study physician during sessions.
• Hearing will be protected by the use of earplugs during intervention sessions

Confidentiality: Subject's confidentiality will be assured through a multi-layered approach, entirely compliant with HIPAA regulations. We will have the following formal mechanisms limiting access to information that can link data to individual participants. Data forms that include identifying information will be kept in locked cabinets. Only the unique ID number, assigned by the research assistant at the time of initial contact will represent participants during data entry, data transfer, or data analysis. Only members of the investigative group will have access to secured files or to master lists for participant code numbers and will be well informed regarding the protection of patients' rights to confidentiality. Identities of participants will not be revealed in the publication or presentation of any results from this project

Safety and Compliance Monitoring

At each intervention session, the intervention administrator will monitor subjects for safety and compliance with study procedures.

Compliance monitoring: All missed intervention days will be recorded in a log for each participant and reviewed by the PI.

Medical Monitoring

At each intervention session, the intervention administrator will monitor subjects' safety during study procedures. Subjects will also be provided with Dr. Rita Haddad's number for a 24-hour emergency contact number to cover subjects' concerns.

Data and Safety Monitoring Plan (DSMP) :

General considerations:

The PI will have primary responsibility for the monitoring of participants throughout their participation, both with respect to their safety and the integrity of the research data. Likewise, the PI will follow IRB adverse event reporting guidelines. All participants will be reviewed by the PIs at baseline; exclusion criteria will reduce the risk to participants. Participants will be carefully monitored during the study. Additionally, the study will have a 24-hour answering service with physician coverage.

The PIs will meet regularly for research meetings to focus on screening forms; inclusion/exclusion criteria; case report form review; adverse events and other Human Research Protection Office (HRPO) required monitoring and reporting activities. The PIs will record each subject screened for study inclusion and maintain records of reasons for subject exclusions.

Statistical analysis:

The PI and his research team will carry out all data analyses and publish findings from the study. Efficacy analyses will be: primary – neurocognitive changes; secondary – functional changes.

The rationale for the study design and its sample size of 30 is based on the feasibility for a pilot study.

Data management Plan

The PI and/or other designated research staff will be responsible for data collection, error resolution, data entry and protecting the integrity of the data.

Source Data: Source data includes information in original records or copies of clinical findings, observations, ratings, or other activities in a study necessary for the reconstruction and evaluation of the study.

Procedures: Source data received by the delegated individual responsible for data management should be reviewed for any missing data, incomplete fields or data outside the normal ranges in a timely manner. If any discrepancies are raised at this point, these must be clarified, and any queries recorded immediately. Any amendments made on the original data collection sheet will be documented, initialed and dated by the individual/s using a single line through method so as not to obscure the original data collected. No correction fluid should be used.

On completion of the above process, a delegated member of the research team will enter the data into REDCap (Research Electronic Data Capture data capture software developed by Vanderbilt University for clinical researchers). This web-based software allows researchers the ability to perform checks on the data during the entry process, as well as while the data is in the system. Additional benefits of REDCap are: Support of Multiple Data Types, Textbox Data Validation, Audit Trails / Data Logging, Data Quality Module, Double Data-Entry, Branching Logic to conditionally show/hide fields, Custom Reports, and Study Calendar tool.

REDCap includes data import and export tools. Exported data can be done so with the removal of identifying information, and to any of the following software packages: CSV/Microsoft Excel, SPSS, SAS, R, Stata.

Electronic records (computer files, electronic databases, etc.): All electronic records will be collected and maintained in compliance with Washington University approved policy and practice. The risks of breaching confidentiality will be strictly limited by the use of locked and restricted access to data, as well as the use of participant ID numbers rather than names in the data base. All sensitive electronic information is kept in password-protected files on a password-protected computer. All other data will be entered and secured in a WUSM database system.

Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.): The risks of breaching confidentiality will be strictly limited by the use of locked and restricted access to data, as well as the use of participant ID numbers rather than names in the data base. Medical records containing PHI and research records are kept in a locked cabinet behind two locks. No identifiers are included in any reports generated by this study.

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