Interactions of Fronto-Parietal High Frequency Repetitive Transcranial Magnetic Stimulation on Anterior Cingulate Cortex Activation in Schizophrenia

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1.0 Background and Rationale

Schizophrenia is a chronic and disabling illness that is associated with impairments in independent living as well as social and vocational functioning[1]. Schizophrenia also represents an important societal burden; only 10% of individuals maintain employment, translating into annual lost wages of nearly $15 billion[2,3]. Cognitive dysfunction is a core facet of schizophrenia, contributing to profound social and vocational difficulties[4-6]. Cognitive control (CC) is an important mental process that is reliably impaired in schizophrenia[7-9].

CC facilitates flexible, goal-directed behavior through real time adjustments in perceptual selection, response biasing, and on-line maintenance of contextual information[10,11]. CC deficits in schizophrenia are associated with poor treatment compliance, social and occupational dysfunction and decreased quality of life[7-9]. There are no effective treatments for CC impairment, due in large part to a **gap in knowledge** regarding the neural mechanisms of cognitive dysfunction in schizophrenia. In light of the significant functional disability and poor outcomes associated with impairment in CC there is a critical need for more effective therapeutic options for this important illness domain.

Recently research has suggested that CC is subserved by a functionally related neural circuit, referred to as the cognitive control network (CCN), that includes the left dorsolateral prefrontal cortex (LDLPFC), the left superior parietal cortex (LSPC), and the anterior cingulate cortex (ACC)[10,12-14]. The ACC is a key node within the CCN and is believed to act as a network hub that strongly affects processing and connection efficiency[15]. Though previous work has demonstrated that disruption within the CCN, particularly decreased activity in the ACC, is associated with deficits in CC functioning[12,16-18], a clear understanding of the impact of ACC dysconnectivity remains elusive. There is a critical need to identify investigational techniques that clarify the neural underpinnings of CC impairment in schizophrenia, such as ACC dysfunction, and contribute to the development of effective treatments for this important cognitive deficit in schizophrenia.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that received FDA clearance for use in treatment resistant major depressive disorder in 2008 and has become commonly used in clinical practice[19]. rTMS utilizes the application of a repetitively pulsed magnetic field over the scalp to induce an electric field within a discrete area of the cerebral cortex. This electric field results in altered ion flow across the neuronal cellular membrane and ultimately changes in neuronal polarization. rTMS modulates cortical activation depending on the stimulation parameters used[20,21]. Physiological studies have provided evidence that high-frequency (HF) rTMS produces an increase in local cortical excitability[20-24]. Studies have also demonstrated that rTMS may increase functional connectivity between separate but related cortical structures, utilizing high frequency stimulation[25-28]. Thus, rTMS allows investigators to manipulate focal brain activity in a target region and distal function in associated circuitry[25]. The ability to affect activity downstream from the point of stimulation is important, as this enables investigators to modulate structures not directly accessible to rTMS, such as the ACC.

Work by our group and others have shown that rTMS is a viable option for investigating cognitive dysfunction in schizophrenia[26,28-30]. We recently completed a pilot-study investigating the effects of HF rTMS, compared to sham stimulation, on cognitive dysfunction in an early phase psychosis (EPP) population. This study administered bilateral, sequential, double-blinded sham stimulation or HF (20 Hz) rTMS targeting the DLPFCs in twenty subjects with EPP. Ten

sessions of rTMS or sham were administered over the course of two-weeks. Our pilot-study demonstrated not only a beneficial effect of rTMS on cognition but also that the intervention is safe and well tolerated in subjects with EPP. There were no serious adverse events during the course of this study and there were no significant differences in adverse events between the rTMS and sham group.

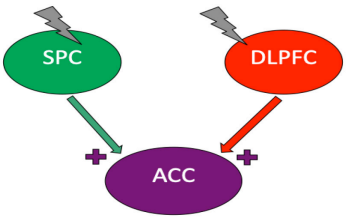
In spite of existing work studying rTMS as a treatment modality in schizophrenia, there are no studies that have examined the effects of rTMS targeting superficial CCN structures (LDLPFC and LSPC) on ACC activity or CCN connectivity in schizophrenia. It is also important to note that the vast majority of studies using rTMS in schizophrenia have examined chronic populations where confounds associated with prolonged duration of illness may be present. EPP is a desirable population to study because these individuals tend to have fewer psychiatric and physical comorbidities and less antipsychotic drug exposure, all of which are factors that may confound investigations of new treatment interventions for this illness. In light of the significant unmet medical need associated with schizophrenia and the grave clinical effect of disrupted CC in the illness, rTMS modulating the ACC, and potentially CCN circuitry, represents an unexplored and novel potential treatment option.

The **goal of this project** is to utilize HF (20 Hz) rTMS, in conjunction with functional magnetic resonance imaging (fMRI), to provide evidence that rTMS targeting superficial CCN structures (LDLPFC and LSPC) modulates: 1) activation in the ACC during in-scanner CC task performance and 2) functional connectivity between the CCN structures during in-scanner CC task performance. This study will provide vital preliminary data on target engagement informing future clinical trials seeking to investigate rTMS as a novel treatment for CC impairment in schizophrenia. This study will also seek to refine the understanding of the brain circuitry that mediates the potential pro-CC effects of rTMS through the use of fMRI at baseline and following the course of rTMS administration.

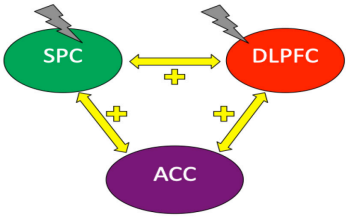
2.0 Specific Aims and Hypothesis

The **first primary aim** is to define the impact of HF (20 Hz) rTMS targeting the LDLPFC and LSPC on ACC activation in individuals with schizophrenia during in-scanner CC task performance. We predict that HF rTMS targeting the LDLPFC and LSPC will result in increased functional activation in the ACC during performance of an in-scanner CC task. The **second primary aim** of this study is to define the impact of HF rTMS targeting the LDLPFC and LSPC on CCN functional connectivity (FC). We hypothesize that HF rTMS of the LDLPFC and LSPC will result in increased FC between the LDLPFC, LSPC, and ACC during performance of an in-scanner CC task. An **exploratory aim** of this study is to determine the effects of HF rTMS targeting the LDLPFC and LSPC on CC performance. We will examine if HF rTMS targeting the LDLPFC and LSPC is associated with improved performance during on in-scanner CC task.

Primary Aim 1 Prediction

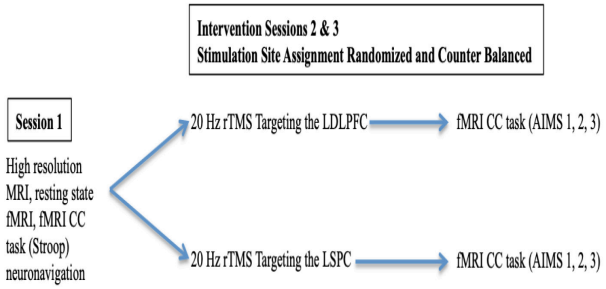


Primary Aim 2 Prediction



3.0 Study Design

Fig 1. Study Outline



This will be a single site pilot study. 20 subjects with EPP, defined as medical record documentation of the onset of clinically significant psychotic symptoms within the past 10 years, will be enrolled. Prior to randomization subjects will undergo fMRI during CC task (Stroop Color-Word paradigm) and resting-state paradigms. This baseline scan will also include a high-resolution structural sequence for neuronavigation purposes. Then, on two separate days, each occurring one-week apart, subjects will receive one session of excitatory (20 Hz) rTMS targeting the LDLPFC and one session targeting the LSPC. The order of stimulation sites will be randomized and counter-balanced. Immediately following each session, subjects will undergo repeat fMRI during CC and RS paradigms. We will also examine the effect of rTMS on CC performance.

rTMS Set up and Administration
rTMS will be delivered using the Magventure MagPro X100 Magnetic Stimulator (Magventure Inc., Alpharetta, Georgia). Motor threshold (MT) will be determined using single pulse stimulation over the left primary motor cortex, assessed as the lowest intensity producing five visible movements of the right abductor pollicis brevis out of ten stimulations.

High Frequency rTMS
High frequency rTMS, or rTMS greater than 5 Hz, leads to faciliatory effects on brain excitability[20-24,31]. Previous studies have demonstrated that administration of as little as a single train or a small number of trains are able to produce an immediate increase in cortical excitability[24]. Additionally, earlier investigations have utilized high frequency rTMS in schizophrenia populations, demonstrating that the treatment is safe, well-tolerated and capable of altering cognitive performance[30,32]. Our group has employed 20 Hz rTMS at 110% of motor threshold in a stimulation protocol in-line with the current proposal to improve cognitive function in an EPP cohort[30]. High Frequency rTMS Protocol*:* Subjects will receive two sessions of HF rTMS, targeting the LDLPFC and LSPC, within the following stimulation parameters: 20 Hz, at 120% of MT, 60 trains (1.0 second per train), 20 pulses per train, inter-train interval of 20 seconds, for a total of 1200 pulses over 21 minutes. This stimulation protocol is within safety limits for rTMS[21,33,34].

Neuronavigation
Brainsight software (Rogue Research, Montreal Canada) will be used to reliably target the LDLPFC and LSPC for stimulation. First, the subject's individual anatomy will be registered stereotactically using the acquired structural MPRAGE brain image and fiduciary points on the scalp visible with a Polaris vicar camera (Brainsight software). We will use the centers of mass of the LDPLFC and LSPC (derived via Freesurfer parcellation; Destrieux Atlas[35]; left/right combined) to identify the specific coordinates for stimulation. Stimulation sites will be marked on a swim cap worn by the subjects at each stimulation session, consistent with prior TMS studies[25].

Electrical field modeling
The processed structural image will be used to generate E-fields based on realistic conductor head models using SimNIBS (2.1 or latest version). SimNIBS includes volume conductor

modeling (following FreeSurfer segmentation), TMS coil specific magnetic dipole estimations, and finite element modeling of the electric field at each tetrahedral element of the subject's head mesh. In anticipation of actual TMS sessions with each patient, we will find the optimal TMS positioning to most strongly influence the LDLPFC and LSPC, which will be the target for neuronavigated rTMS delivery.

rTMS administration monitoring
All subjects will be instructed to wear earplugs during each rTMS session and will be monitored by medically trained research staff throughout the entirety of each rTMS session.

Duration of Treatment
Subjects will complete two stimulation sessions over two weeks, with one session occurring each week. Previous work has demonstrated that a single session of rTMS is sufficient to modulate target site functional activation as well as functional connectivity between the stimulation target and associated circuitry[25].

Sample Size
We plan to enroll 20 subjects and anticipate a 20% drop out rate, yielding 16 completers. This is consistent with our previous clinical trial efforts, including a study of adjunct rTMS in an EPP cohort[30,36]. For all planned analyses, a total of 16 subjects in a counter-balanced design will result in 0.8 power to detect an assumed stimulation effect at medium effect size 0.6; using an alpha level of 0.05 and conservatively assumed a within-subject correlation of 0.5. As no CCN rTMS pilot data was available, this standardized effect size of 0.6 is considered a conservative estimate to detect significant results.

Clinical Research Site
The IU Psychotic Disorders Program (IUPDP), which is directed by Dr. Alan Breier and is part of the IU Department of Psychiatry, is located in Indianapolis, Indiana. IUPDP research personnel will manage the day-to-day activities of conducting the trial, including subject recruitment, consenting and screening subjects, conducting study visits, and performing assessments. The IUPDP has 2 research psychiatrists, a fully dedicated study manager, a fully dedicated study coordinator, one dedicated subject recruiter, one dedicated research technician, and two raters (1 PhD, 1 Masters level) who have been trained and have extensive experience in conducting the assessments and cognitive tests used as outcome measures.

4.0 Study Population (Inclusion/Exclusion Criteria)

Inclusion criteria:

1. Between 18 and 40 years of age
2. Within 10 years of illness onset as defined by entry into treatment for psychotic symptoms
3. Able to give informed consent
4. Willing and able to adhere to the study schedule
5. Structured Clinical Interview for DSM-5 (SCID-5-RV) diagnosis of schizophrenia
6. Clinical stability defined by:
    a. Subjects must not have experienced an exacerbation of their illness within 4 weeks prior to randomization, leading to an intensification of psychiatric care in the opinion of the investigator. Examples of intensification of care include, but are not limited to: inpatient hospitalization, day/partial hospitalization, outpatient crisis management, or psychiatric treatment in an emergency room AND

b. Antipsychotic treatment stability for at least 4 weeks prior to randomization (no change in antipsychotic dosing or addition of new antipsychotic medication)

Exclusion criteria:

1. Lifetime history of a seizure, excluding febrile seizures and those induced by substance withdrawal
2. First degree relative with idiopathic epilepsy or other seizure disorder
3. History of significant neurological illness
4. History of head trauma as defined by a loss of consciousness or a post-concussive syndrome
5. Pregnant or breast feeding
6. Known IQ < 70 based on subject report
7. Current acute, serious, or unstable medical conditions
8. Metallic objects planted in or near the head, including implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, ventriculoperitoneal shunt, or cochlear implants
9. Contraindications to MRI or otherwise unable to tolerate MRI procedures
10. History of electroconvulsive therapy
11. Subjects taking clozapine
12. Subjects who have participated in a clinical trial with any pharmacological treatment intervention for which they received study-related medication in the 4 weeks prior to randomization
13. Subjects considered a high risk for suicidal acts – active suicidal ideation as determined by clinical interview OR any suicide attempt in 90 days prior to screening
14. Current DSM-5 diagnosis of alcohol or drug use disorder (excluding nicotine or caffeine)
15. Subjects who require concomitant treatment with prohibited medication, as specified in Attachment 2

5.0 Subject Recruitment

Subjects will be recruited through referring community mental health centers, treatment providers, the IUPDP registry, and self-referrals through advertisement and word-of-mouth.

6.0 Clinical Assessments and Procedures

The following assessments will be administered according to the Study Procedures Table (Attachment 1). All assessments will be completed by study personnel trained to administer the instruments and will be based on interviews with the subject or questionnaires completed by the subject.

Columbia Suicide Severity Rating Scale (C-SSRS)
The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The definition of behavioral suicidal events used in this scale is based on those used in the Columbia Suicide History Form[41]. During the baseline assessment, questions are in relation to lifetime experiences and all subsequent questioning is in relation to the last assessment.

The Positive and Negative Syndrome Scale (PANSS)
The PANSS is the primary assessment instrument for psychopathology. The PANSS contains 30 items that assess symptoms of psychotic disorders including positive, negative and general psychopathology. The PANSS was chosen because of its widespread use in clinical studies of psychosis, and its demonstrated reliability in assessing psychopathology across diverse patient populations[42].

Diagnostic Interview
The Structured Clinical Interview for DSM-5 (SCID-5-RV) will be used to confirm the diagnosis of a psychotic disorder and/or rule out other diagnoses. The SCID-5-RV is a semi-structured interview designed to evaluate DSM-5 Axis I diagnoses[37].

Clinical Global Impressions Severity Scale (CGI-S)
The CGI-S is used for repeated evaluations of global psychopathology[43]. The CGI-S scale is widely used in schizophrenia research and is a single 7-point Likert scale rating severity of psychopathology on a scale of 1 (normal, not ill) to 7 (very severely ill).

Clinical Global Impressions Severity Improvement Scale (CGI-I)
The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point Likert scale, ranging from very much improved (1) to very much worse (7)[43].

Abnormal Involuntary Movement Scale (AIMS)
The AIMS is a 12-item scale designed to record the occurrence of dyskinetic movements[44]. Items 1 to 10 are rated on a 5-point scale, with 0 being no dyskinetic movements and 4 being severe dyskinetic movements. Items 11 and 12 are yes/no questions regarding the dental condition of a subject.

Magnetic Resonance Imaging (MRI) Procedures
Subjects will practice tasks on a personal computer during Visit 1 and prior to the scan at subsequent visits. Subjects will complete all pre-MRI procedures (e.g., completion of MRI screening form) before stimulation sessions to minimize the time in-between the stimulation session and MRI. We intend to conduct post-stimulation scans within fifteen minutes of completing a stimulation session. Siebner et al. (2009) noted in a consensus paper on combining transcranial stimulation with neuroimaging that protocols applying prolonged trains of rTMS can induce changes in neuronal excitability that may last for more than one hour post-TMS[45]. We believe that an interval of 15 minutes between rTMS session and fMRI will capture changes in excitability.

MRI will be performed at the IU Center for Neuroimaging using an integrated 45-minute exam, including structural and fMRI. Scans will be completed on a research-dedicated Siemens MAGNETOM Prisma 3T scanner. Subjects will undergo a high-resolution 3D magnetization prepared rapid gradient echo (MPRAGE) scan for individual anatomical reference. An MRI-compatible response box will be utilized for tasks, recording reaction time and accuracy. fMRI will employ a computerized version of the Stroop Color-Word task. A task-free resting state fMRI scan will also be acquired to measure functional connectivity between CCN structures.

Stroop Color-Word Task

Subjects will perform an in-scanner computerized version of the Stroop Color-Word task. This and similar paradigms have been shown by our group and others to elicit reliable ACC activation during task performance[46]. In this task, stimuli consist of three words: “Red”, “Green”, or “Yellow”, displayed in the corresponding color. Trials are either “congruent” (word matches ink color), “incongruent,” where the word and the color of the word differ in incongruent colors, or “nonwords,” which are “XXX”, “XXXX”, or “XXXXX”. The Stroop Color-Word task requires participants to press one of three buttons to identify the ink color of a presented word (red, green, or yellow; randomly assigned). Subjects are instructed to indicate the color but ignore the word and to respond as quickly and accurately as possible via button press. There are multiple iterations of this task available, mitigating potential practice effects. Participants will practice examples of the CC task on a personal computer during Session 1 and prior to the scan at subsequent visits.

Emotional Stroop Color-Word Task

Subjects will also perform an Emotional Stroop Color-Word task during the scan. This task is identical to the standard Stroop Color-Word, except emotional words (e.g., poor, sick, hurt) and neutral words (e.g., note, run, spin) are used instead of congruent and incongruent words. Subjects are again instructed to indicate the ink color of the word via button-press. This task will be practiced prior to each scan as well.

Positioning and motion

Subjects are instructed to remain still during scanning and deformable foam cushioning is used to stabilize the head. Real time image reconstruction and processing are used for quality assurance at the time of scanning. For fMRI, minor subvoxel-level translation or rotation is adjusted during post-processing. Noise: Noise-attenuating headphones and ear stopples provide excellent noise reduction and permit adequate auditory perception.

Functional Imaging Stimulation and Physiological Monitoring Procedures

A comprehensive physiological monitoring system will be used with synchronized digital recording including pulse oximeter, respiratory belt, HR and BP measures, which will be available for analysis in relation to BOLD fMRI time series.

7.0 Safety Assessments

Vital Signs

A seated blood pressure and pulse will be assessed at study visits per Study Procedures Table (Attachment 1).

Medical History

The subject’s lifetime medical history will be taken during the screening period. Medical history includes previous and current diseases.

Physical Examination

A physical examination including a neurological examination will be conducted as outlined in the Study Procedures Table.

8.0 Laboratory Assessments

A urine pregnancy test will be conducted in all female subjects, and a urine drug screen will be conducted in all subjects, as outlined in the Study Procedures Table.

9.0 Concomitant Medication

See Attachment 2.

10.0 Adverse Events

Adverse events (AEs), especially those for which the relationship to study treatment is not "unrelated," will be followed up until they have returned to baseline status or stabilized at the discretion of the PI. If after the follow-up period, return to baseline or stabilization cannot be established an explanation will be recorded in the source documentation.

11.0 Criteria for Repeat Assessments, Rescreening, and Discontinuation

Repeat Assessments
Screening assessments can be repeated within the screening window under the same screening number with the exception of eligibility criteria related rating scales/questionnaires. Subject diagnosis confirmation will not be repeated.

Rescreening
Subjects who screen fail may be rescreened one time, under the same screening number. If a subject is rescreened, all screening assessments (with the exception of the diagnosis confirmation) must be repeated and the stability criteria timelines must be met.

Discontinuation
Subjects will be discontinued under the following circumstances:

1. Subjects unwilling or unable to complete study assessments or procedures
2. Subjects who experience seizure occurrence at any point during study participation
3. Subjects who require a change in dose of antipsychotic medication or the addition of a new antipsychotic medication
4. Subjects experiencing an exacerbation of illness requiring an increased level of care or one judged to be clinically significant by the PI.

If subjects discontinue from the study, completion of discontinuation assessments will be at the discretion of the PI. A subject may withdrawn from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the PI for safety, behavioral, or administrative reasons.

12.0 Data Safety Monitoring Board

The Indiana University Adult Psychiatry Data Safety Monitoring Board (DSMB) will be responsible for data and safety monitoring. The DSMB is responsible for reviewing study procedures, adverse events, safety mailings (if applicable), enrollment, active subjects, and ongoing conduct of the research. The DSMB members can ask questions and make comments and/or recommendations. The IRB is notified of significant findings by way of the DSMB meeting

minutes at the time of continuing review. Due to the small sample size and single site design of this protocol, there is not sufficient justification for conducting interim analyses to examine trends. Data on the number of subjects enrolled and the number of adverse events will be reviewed by the DSMB every six months and more frequently if needed. The resultant report will be issued to the Indiana University IRB at least at the time of continuing review or more frequently by request. Any unanticipated events will be immediately directed to the PI who will follow the Indiana University IRB reporting procedures.

13.0 Statistical Considerations

Analyses

Power Analyses

In terms of the power to detect a significant effect of HF rTMS on CC neurocircuitry or performance, there are no known calculations with EPP patients. However, previous investigations, including our own, used similar stimulation designs when investigating the effects of rTMS on overall cognitive performance. These studies demonstrated statistically significant results with sample sizes consistent with the current proposal[32], and Cohen's effect sizes of d = 0.92 and 1.15, respectively[30,32]. Though these previous studies examined different cognitive constructs than the CC task in this current protocol, these studies do provide evidence that a similar stimulation design is sufficient to elicit a biologic response and assumedly appropriate for investigating the effects of rTMS on CC.

We believe that for the purpose of this pilot study, we can demonstrate significant results with a sample size of 16 (eight per group). This accounts for the effect size estimate derived from the literature, d = 1.1, and the estimation of power to detect an effect at .75, utilizing a one-sided independent test and significance levels of 0.05.

Statistical Analyses

Preliminary analyses will consist of descriptive statistics for all outcome variables, including summary statistics, graphical displays of distributions, and spaghetti plots of individual data over time to detect possible data errors. Demographic and clinical characteristics at baseline will be examined using parametric or nonparametric test statistics as appropriate. Any demographic variables that show significant differences will be added to the final models as covariates in order to ensure that the observed stimulation effects are not spurious or due to demographic confounds.

To minimize the potential for Type II error, all treatment comparisons will be evaluated based on a one-sided significance level of 0.05. To compare overall effect of stimulation over time for the two groups, a set of multivariate repeat measures analysis of variance (ANOVA) will be utilized, with stimulation as the between-group factor and time as the within-subject factor.

14.0 Data Management

Primary data will be collected via paper source documents, phone interviews, and direct data capture from clinical and symptom measurements. Data will be stored electronically in REDCap and paper source documents will be stored in a double locked and access controlled research records room. REDCap will be backed up automatically weekly. Imaging data will be stored in

separate electronic files and merged with primary data as needed. The imaging data will automatically be stripped of all PHI prior to uploading to the database. Quality assurance steps will include: 1) Quality control data checks after each visit, 2) Single data entry by study staff, and 3) Data verification procedures throughout the study to ensure proper transfer of data from paper source to REDCap.

15.0 Privacy/Confidentiality Issues

Confidentiality will be protected by ensuring all research staff have been properly trained in confidentiality and human subject research procedures, coding all subject information when possible, and by securing subject files in a locked filing cabinet or on secured databases with access available only to the PI and research staff. Furthermore, data entered into a computer database will only use subject codes on secured computers that will be password protected with access available only to the PI and research staff. Any screening information obtained from potential research subjects who subsequently do not participate in the research study will be destroyed.

16.0 Record Retention

Paper copies of medical records and source documentation will be kept for seven years after the study is closed with the IRB. One year after study closure, the documents will be shipped to the Indiana University Department of Psychiatry long-term storage facility until destruction.

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ATTACHMENT 1: Study Procedures Table

Visit Number	1[c]	2	3	4[d]
Day[b]		0	7	21
Informed Consent	X			
Screening (Demographics, Inc/Exc, Medical & Psychiatric History of Self and Family)	X			
SCID[a]	X			
Physical Exam	X			
CGI-S	X			
CGI-I		X	X	
Vitals	X	X	X	
Urine Drug Screen	X			
Pregnancy Test	X	X	X	
Motor Threshold Determination	X			
MRI – Baseline	X			
Randomization (Order of Study Intervention)		X		
Neuro Navigation		X	X	
rTMS Administration (LDLPFC or LSPC)		X	X	
Post Stimulation MRI-CC Task		X	X	
PANSS	X			
AIMS	X	X	X	
C-SSRS	X	X	X	
Adverse Events	X	X	X	X
Concomitant Medication	X	X	X	X

[a]If subject received a SCID interview within 6 months of screening, it may not be repeated at the discretion of the PI

[b]Ideal time frame for administration will be on the same day of two consecutive weeks. A total of 2 sessions. Visit window deviations will be granted at the discretion of the PI and will not be a protocol violation.

[c]Visit window for Visit 1 is 0-30 days

[d]Visit 4 may occur by phone and ideally will occur 14 days after Visit 3. Visit window deviations will be granted at the discretion of the PI and will not be a protocol violation.

Attachment 2: Concomitant Medication Table

Medication	Allowed	Notes
Amitriptyline	No	
Amphetamines et., methylphenidate, dextroamphetamine)	No	
Antiemetics (eg., metoclopramide, domperidone, others with dopamine blocking properties)	No	
Antiepileptic mood stabilizers	Yes	Stable dose, no changes or additions
Antihistamines, nonsedating (eg., loratidine, fexofenadine, cetirizine)	Yes	
Antihistamines, sedating (eg., diphenhydramine, hydroxyzine, meclizine, benztropine)	Yes-Episodic Use Only	No use within 24 hours of cognitive assessments
Antipsychotic medications	Yes	Stable dose over four weeks prior to randomization, no changes or additions during duration of trial
Barbiturates	No	
Benzodiazepines	Yes-Episodic Use Only	No use within 24 hours of cognitive assessments
Chlorpromazine	No	
Bupriopion	No	
Clozapine	No	
Decongestants (eg., pseudophedrine)	Yes-episodic use only	No use within 24 hours of cognitive assessments
Doxepine	No	
Dicyclomine	No	
Herbal medications or Over the Counter Medications w/ primary CNS activity	No	
Lithium	Yes	
MAOIs	Yes	
Methadone	No	
Mirtazepine	Yes	Stable dose, no changes or additions
Muscle Relaxants	Yes-Episodic Use Only	No use within 24 hours of cognitive assessments
Nicotine Replacement	Yes	
Nortriptyline	No	
Opiates	No	
Benzodiazepine derivative sleep agents (eg., Zolpidem)	Yes-Episodic Use Only	No use within 24 hours of cognitive assessments
SNRIs	Yes	
SSRIs	Yes	
Tricyclic antidepressants	Yes	
Trazodone	Yes-Episodic Use Only	