

PART B STUDY DESCRIPTION

TITLE OF PROTOCOL	Behavioral impact and neural correlates of network-based brain stimulation in schizophrenia
Principal Investigator	Roscoe Brady, MD, PhD

B1. PURPOSE OF PROTOCOL

The primary aims of this study are to investigate the behavioral effects of applying targeted transcranial magnetic stimulation (TMS) to a node of the brain network subserving attention in schizophrenia and schizoaffective disorder and to correlate these effects to changes in brain network connectivity.

Assumptions:

- Cerebral activity can be investigated through the correlated activity of cortical nodes that constitute functional brain networks
- Behavior can be correlated to the strength of correlated activity between and within nodes of these cortical networks
- TMS to targeted nodes leads to changes in patterns of activity in these cortical networks

Hypothesis:

TMS to a node of the attention network in schizophrenia or schizoaffective disorder will influence network connectivity leading to measurable and predictable effects on attention.

Aim 1: We will test if network connectivity reflects cognitive performance using an independent sample of individuals with schizophrenia or schizoaffective disorder (n=50). Hypothesis 1A: Network connectivity will predict attentional performance in schizophrenia and schizoaffective disorder. Hypothesis 1B: The magnitude of attentional performance improvement after TMS is also explained by change in network connectivity in schizophrenia and schizoaffective disorder.

Exploratory Aim: As an exploratory aim, we will test if TMS affects patterns of cigarette craving and if changes in cigarette craving are correlated to changes in functional connectivity. We hypothesize that craving will decrease following iTBS administration. We hypothesize that a decrease in cigarette craving will correlate with changes in brain network functional connectivity.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Overview:

- 1) Cigarette Use in Schizophrenia is Related to Cortical Networks
- 2) Functional connectivity as a measure of neural function
- 3) TMS effects on behavior and attention
- 4) TMS effects on cortical networks
- 5) Significance of the study

1) Cigarette Use in Schizophrenia is Related to Cortical Networks

Psychotic disorders such as schizophrenia are disabling, lifelong illnesses that afflict over three million people in the US. The life expectancy of individuals with schizophrenia is ~25 years less than the general population [1, 2]. Tobacco use is the top preventable cause of early mortality in schizophrenia [3]. The prevalence of smoking in schizophrenia is over 60% [4]. It is unknown why nicotine dependence is so prevalent in schizophrenia, and we do not treat nicotine dependence in schizophrenia differently than in the general population [5].

There is a significant gap in our understanding of nicotine dependence in psychotic disorders and how this diagnosis affects its treatment. Most neuroimaging studies of nicotine dependence are hypothesis-driven study designs focusing on reward circuitry. Studies of nicotine dependence in a psychotic population have typically used the same experimental design. This approach may be missing important circuits involved in nicotine dependence *specific* to psychotic disorders.

We used an agnostic, data-driven approach to investigate this problem. We observed that **individual variation in the severity of nicotine use is linked to individual variation in default mode network (DMN) organization**. We determined this relationship between network organization and nicotine use was ***specific to schizophrenia and schizoaffective disorder*** and not observed in a control smoker population, a novel finding (Figure 1).

Traditional imaging studies yield results which are correlational and do not test associations between findings. We therefore sought to test the **causality** of nicotine-network interactions. In an independent cohort [6] we observed that **acute nicotine administration reverses DMN**

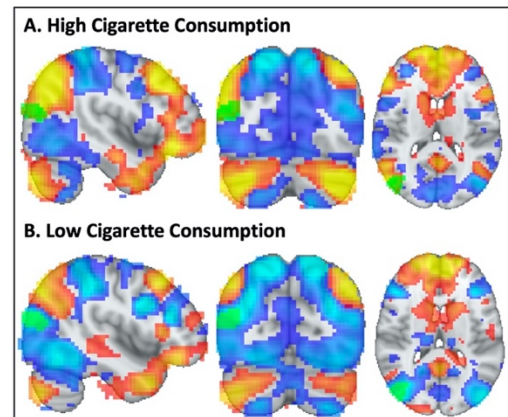


Figure 1. The spatial organization of the right parietal node (green) of the 'Default Mode Network' (DMN) (red) is strongly linked to cigarette use. Displayed here is the DMN (red) in two individuals with (A) high (40 cig/day) and (B) low (5 cig/day) cigarette use. In individuals with high cigarette use, the DMN (red) extends into this region (green), while in individuals with low cigarette use, the DMN is external to this region. While these two individuals are extremes, DMN topography in the green region varies linearly with cigarette use in the full sample. This link between network topography and cigarette use was not observed in control smokers.

hyperconnectivity in schizophrenia in a dose-dependent relationship (Figure 2). This is consistent with a model in which nicotine may correct schizophrenia-specific pathology.

Our central hypothesis is this: Brain circuits most relevant to nicotine dependence in schizophrenia are distinct from pathways identified in a non-schizophrenia population. DMN

disruption in schizophrenia is a well-replicated observation. Based on our data, we hypothesize that individual variation in the magnitude of this network disruption gives rise to: a) variation in the severity of network disorganization and b) variation in severity of nicotine use (Figure 1). Further, we propose that the DMN mediates the relationship between nicotine use and cognition in schizophrenia. DMN hyperconnectivity is linked to poor attentional performance [7] and, in healthy controls, nicotine can both reduce DMN connectivity *and* improve attention [8]. We propose that DMN connectivity mediates the relationship between nicotine use and attentional performance and that disruption of this network in schizophrenia drives the need for nicotine to correct network pathology (and cognition). This model can be empirically tested: If the effect of nicotine on cognition is truly mediated by these networks, then 1) modulation of network connectivity should affect attentional performance and 2) the degree of network modulation should explain performance change irrespective of the method used to manipulate network connectivity.

To test the **reproducibility** of our results, we will analyze multiple cohorts of participants with validated measures of nicotine dependence, clinical characterization, and brain imaging. To test the **rigor** of our scientific model, we will determine if modulating these networks using a different (non-nicotine) intervention (Transcranial Magnetic Stimulation, TMS) can replicate nicotine's effects on cognitive performance.

In this study, we will use transcranial magnetic stimulation (TMS) neuromodulation to target previously identified network pathophysiology unique to nicotine dependence in psychotic disorders. We here test a model that integrates brain network pathophysiology and cognition to 1) explain the prevalence of nicotine use in schizophrenia and 2) identify a target for engagement in future clinical trials in schizophrenia and schizoaffective disorder.

2) Functional connectivity as a measure of neural function

The human brain has evolved to perform different behaviors under different sets of conditions and as such must flexibly combine the functional processing capabilities of disparate neuroanatomical regions. Collections of structurally interconnected brain areas must interact dynamically to process a large and ever-changing set of inputs in the ultimate attempt to generate an appropriate behavioral output. Functional networks can therefore be defined as the collection of interconnected brain areas that interact to perform these circumscribed functions [9].

To identify the critical nodes involved in these different functional networks, much of the work in the field of functional neuroimaging has used the fMRI blood-oxygen-level-dependent (BOLD) signal as a marker of cerebral perfusion, which in turn is known to reflect cerebral activity[9]. fMRI BOLD activation patterns have revealed network nodes that are involved in such cognitive functions as attention [10] working memory [11], language [12], and others.

In the resting state--while a subject is asked simply to look straight without performing a specific task in the MRI- analyses of the time-course of BOLD activation have revealed that activity patterns of several of these cerebral nodes exhibit coordinated fluctuations. As such, the activity patterns

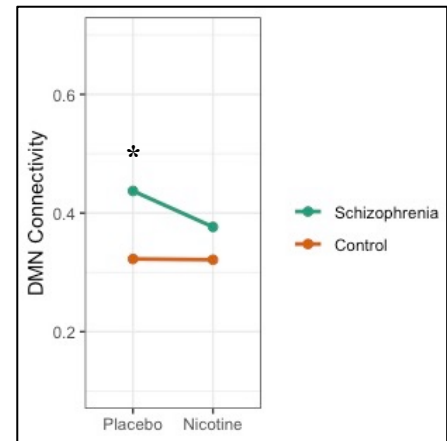


Figure 2. Subjects with SZ have significantly higher DMN connectivity compared to controls in the placebo condition but not with nicotine administration. * $p < .05$

between particular nodes appear to be highly correlated in time while others seem relatively independent of one another. Taken together, these coordinated nodes can be thought of as a coupled functional network.

Interestingly, the degree to which these nodes appear correlated depends on task demands. In certain conditions, nodes will be highly correlated while, in others, these very same nodes appear rather independent. This degree of functional coupling within and between nodes of specific functional networks is therefore thought to reflect a change in distributed processing that is essential in mediating a change in cognitive functioning.

In the domain of attention in particular, several groups have shown a correlation between the strength of connectivity in specific networks and performance on tests that rely on this specific domain. Examples include functional connectivity analyses in healthy controls [13] attention deficit hyperactivity disorder [14], neglect [15], and Parkinson's disease [16]. Studies such as these have reliably demonstrated a correlation between measures of attention and the connectivity patterns of several key networks including the default mode network, the salience network (SN), the dorsal attention network (DAN) and the ventral attention network (VAN).

Using this paradigm, complex cognitive functions such as attention can now be understood and investigated by monitoring the dynamic coupling and uncoupling of nodes within these pre-defined networks.

3) TMS effects on behavior and attention

TMS, (Transcranial Magnetic Stimulation) is a non-invasive, easily transportable, and relatively inexpensive procedure that utilizes magnetic fields to create electric currents in discrete brain regions [17]. TMS is based on Faraday's principle of electromagnetic induction and features application of rapidly changing magnetic field pulses to the scalp via a copper wire coil connected to a magnetic stimulator. These brief pulsed magnetic fields painlessly pass through the skull and create electric currents in discrete brain regions of sufficient magnitude to depolarize neurons. Applied in single pulses (single-pulse TMS) appropriately delivered in time and space, the currents induced in the brain can be of sufficient magnitude to depolarize a population of neurons. When applied to the motor cortex, this depolarization results in a series of descending (direct and indirect) corticospinal waves that can sum-up at the spinal segmental level, depolarize alpha motor neurons and lead to the contraction of contralateral muscles. This can be measured, for example, as motor evoked potentials (MEPs) using electromyography (EMG). Applied to any cortical region, TMS evokes a local field potential that can be recorded with EEG, or other brain imaging techniques, and reveals a measure of cortical reactivity to TMS. TMS intensity can be parametrically varied in its intensity thus allowing the establishment of a dose-response curve and providing insights into cortical excitability.

Trains of repeated TMS pulses (rTMS) at various stimulation frequencies and patterns can induce a lasting modification of activity in the targeted brain region which can outlast the effects of the stimulation itself. Such lasting changes presumably represent alterations in plasticity mechanisms. Therefore, TMS can be used with multiple pulses to facilitate activity in a region of the brain or suppress activity in a region of the brain. In this study, we will plan to use a specific form of rTMS called theta burst stimulation (TBS).

TBS

TBS was designed to mimic traditional paradigms of LTP and LTD induction in *ex vivo* models [18]. TBS consists of 3 pulses at 50 Hz repeated at 200 ms intervals. When applied intermittently (iTBS) cortical excitability can be enhanced, while application in a continuous fashion (cTBS) results in suppression of excitability. These effects of TBS are more prominent and longer lasting than those induced by conventional trains of rTMS.

TMS has been shown to be effective in modulating behavior and has been approved for the treatment of medically refractory depression by the FDA and for suppression of treatment-refractory auditory hallucinations in schizophrenia by the National Institutes of Mental Health (NIMH). Several studies using rTMS have demonstrated a measurable beneficial effect on spatial neglect [19]. Several other studies have demonstrated a change in cognitive functioning as secondary outcomes as measured by tasks of working memory, executive functioning and attention [20]. However, few studies have attempted to modulate non-spatial attention using TMS. One such effort, a study by Bloch et al. in 2010 [21], demonstrated an improvement in attention score following a single session of rTMS in patients with ADHD.

4) TMS effects on cortical networks

Previous studies by our group and others have demonstrated the ability of transcranial magnetic stimulation (TMS) to change patterns of activity in cortical networks of the human brain [22-24]. In addition, we have also previously demonstrated the ability to both increase and decrease connectivity within a specific network (e.g. default mode network, DMN) by neuroanatomically targeted TMS stimulation [24]. To effectively modulate attention, TMS stimulation will be delivered to the parietal node of the DMN, a network key to attentional performance.

5) Significance of the study

This study seeks to provide evidence that targeted stimulation of a brain network leads to both altered network activity and a concomitant functional change in attention in individuals with schizophrenia and schizoaffective disorder. This study will test a model that integrates brain network pathophysiology and cognition to 1) explain the prevalence of nicotine use in schizophrenia and 2) identify a target for engagement in schizophrenia. This study seeks to establish a neuroscientific framework to guide future treatment-oriented studies aimed at improving attention and nicotine use in individuals with schizophrenia and schizoaffective disorder.

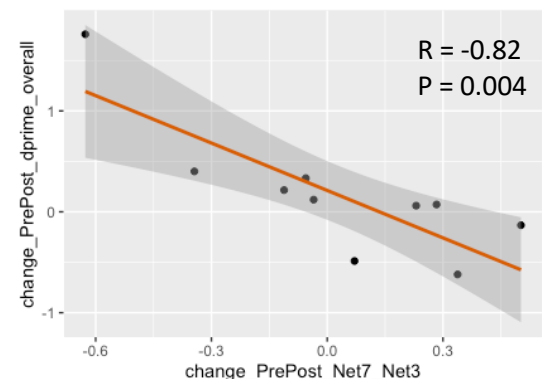


Figure 3. There was a strong negative correlation between change in DAN-DMN anticorrelation and change in attentional performance on the gradCPT following a TMS intervention in healthy controls.

B3. DESCRIPTION OF RESEARCH PROTOCOL**A. Study Design – Overview, Methods, Procedures****Primary Aims**

This is an investigational pilot study of the effect of TMS on attention in smokers with schizophrenia or schizoaffective disorder (Figure 4).

The principal aims of this investigation are:

- 1- to investigate the behavioral effects of applying targeted transcranial magnetic stimulation (TMS) to nodes of the brain networks subserving attention and
- 2- to correlate these effects to changes in brain network connectivity in schizophrenia and schizoaffective disorder.

Prospective subjects who meet inclusion and exclusion criteria will be entered into the study. We will study up to 50 subjects.

Participants will undergo an initial screening session to complete informed consent and undergo baseline assessments of psychiatric symptoms and tobacco use. These assessments include reporter-based measures (Positive And Negative Syndrome Scale (PANSS), auditory hallucination rating scale (AHRs), and Calgary Depression Scale for Schizophrenia (CDSS), Fagerstrom Test for Nicotine Dependence (FTND), Alcohol Use Scale/Drug Use Scale (AUS/DUS), Tiffany Questionnaire of Smoking Urges (QSU), and Wisconsin Smoking Withdrawal Scale (WSWS). Participants will then undergo an MRI scan that includes structural and resting state functional magnetic resonance imaging (rsfMRI). These rsfMRI images will be used to isolate individual resting-state networks for targeting of rTMS modulation. Participants will then undergo three separate sessions of rTMS with an MRI scan before and after each session. During these MRI scans, participants will perform a measure of attention. Participants will receive each of the following rTMS sessions:

A) intermittent theta-burst frequency rTMS (iTBS) targeted to the parietal node of the default mode network.

B) continuous theta-burst frequency rTMS (cTBS) targeted to the parietal node of the default mode network

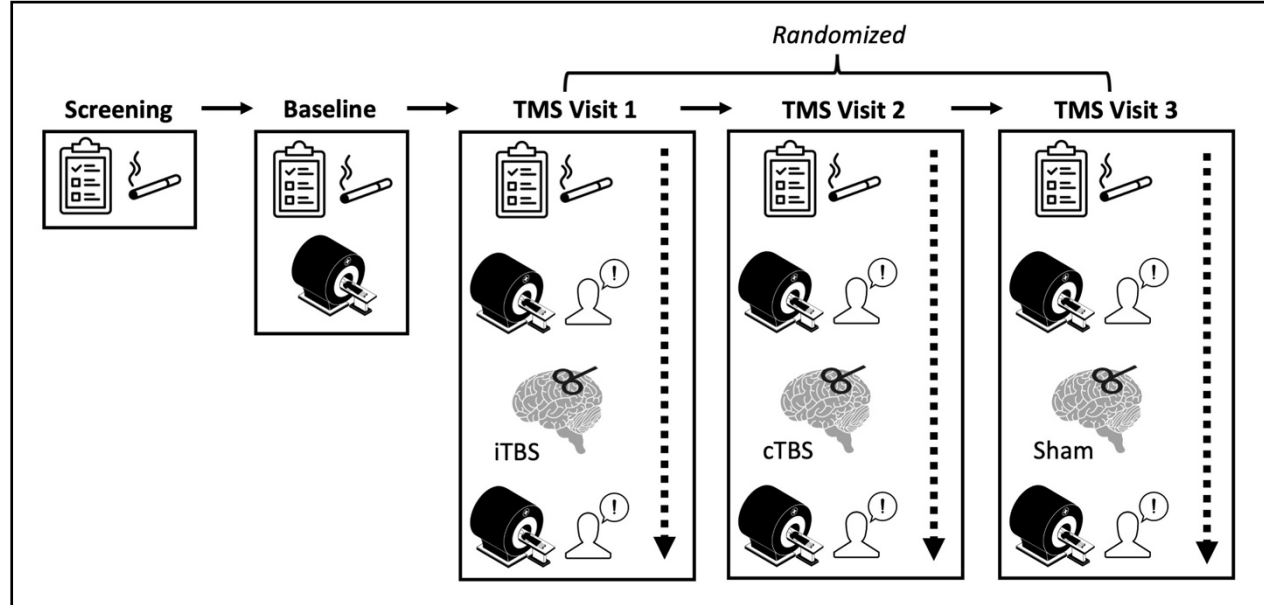
C) sham rTMS

The order of rTMS sessions will be randomized. Participants will be blinded to the rTMS session they are receiving.

Our primary endpoint will be to correlate within-subject difference in functional connectivity to within-subject difference on the measures of attention. We will regress the within-subject difference (pre- vs post rTMS) in attentional performance against within-subject differences in resting state functional connectivity pre- versus post-rTMS.

The structure of this trial is similar to the protocol previously approved by CCI (2011-P-00373/1). In that protocol participants with schizophrenia underwent similar assessments, imaging, and multiple sessions of TMS followed by the same assessments and imaging. This protocol differs primarily in the specific clinical assessments performed before and after TMS.

Figure 4. Study Visit Diagram



Study Visits and Assessments:

Screening/consenting and baseline visit:

Subjects will be prescreened over the phone and invited in if they appear eligible and continue to be interested in the study. Informed consent will be obtained prior to any study procedures. Participants will be offered the option to complete the informed consent using Starleaf secure video conferencing. Prior to Baseline MRI Visit #1 Informed Consent will be obtained and the following screening and baseline procedures will be completed:

- Review informed consent
- Assessment of Capacity Form
- Subject demographics: This includes information on age, race, ethnicity, and gender
- Medical history and medication review
- The participants will sign an authorization form that allows us to contact their psychiatric provider in order to confirm their diagnosis
- Inclusion and exclusion criteria review
- DSM-V diagnosis will be ascertained using the SCID [26].
- TMS safety screening
- MRI safety screening
- Expired Air Carbon Monoxide (CO)
- Nicotine Use Questionnaire
- Recent Substance Use Questionnaire
- Sample collection:
 - Urine toxicology. Participants will supply a urine sample for urine toxicology testing.
 - Pregnancy test: All participants who are able to become pregnant will provide another urine sample for a pregnancy test. If the participant is pregnant they will no longer be able to participate in the study.

The following evaluations will be done as baseline assessments:

Administered by Staff

- The MATRICS (Measurement and Treatment Research in Cognition in SZ) Consensus cognitive battery
- Positive and Negative Syndrome Scale (PANSS)
- Auditory hallucinations rating scale (AHRS)
- Calgary Depression Scale for Schizophrenia (CDSS)
- Fagerstrom Test for Nicotine Dependence (FTND)
- Alcohol Use Scale/Drug Use Scale (AUS/DUS)
- Recent Substance Use Questionnaire

Completed by Participant

- Tiffany Questionnaire of Smoking Urges (QSU)
- Wisconsin Smoking Withdrawal Scale (WSWS)

Baseline MRI visit #1

Subjects will have MR imaging at the Center for Brain Science (CBS) at Harvard University. We will use a Siemens 3T Prisma scanner utilizing a modified version of the HCP Lifespan Prisma protocol [27]. In brief, this sequence collects structural MRI and over twenty minutes of resting state functional MRI.

This MRI scan is used for research purposes only and the scans will be reviewed first by study staff. There is a potential for incidental finding with the MRI imaging in this study. If an incidental finding is noted on a participant's MRI, the PI (Dr. Brady) or a covering neurologist in the Berenson-Allen Center will review the scan. The neurologist will determine if the finding is in need of clinical follow-up. If this is the case, the neurologist will speak with the participant about the finding, will provide a letter describing the findings and need for follow-up and will be available to speak with the participant's provider if the participant agrees and give permission to do so.

For completing the consenting/baseline visit, including the first MRI scan, participants will be compensated with \$100. Participants will be paid for each study visit they attend. The study staff will arrange transportation to and from study visits.

Participant Randomization

Participants will receive 3 sessions of rTMS: iTBS, cTBS, and sham rTMS. The order of sessions will be randomly determined. Participants will be blinded to the rTMS session they are receiving. The Magpro coil (cool B65 A/P, Magventure A/S, Denmark) can deliver active and passive stimulation. The coil has one orientation to administer active TMS and one orientation that is 'sham' i.e. delivers no TMS stimulation. This renders real vs sham status invisible to the participant. After each TMS session, participants will be asked what type of stimulation they believe they received.

TMS visits (#1-3):

Each TMS visit will follow a similar procedure for all experiments, differing only in the type of rTMS (or sham) being applied. These visits will take place at the Harvard Center for Brain Science (CBS). Each visit will consist of one TMS session with MRI before and after.

For participants who are able to become pregnant: if it has been > 30 days since their last negative pregnancy test, the participant will be scheduled for a repeat pregnancy test before the TMS visit occurs.

The order of each session will go as follows:

- Cognitive Testing: Animal Fluency, Trails, BACS Symbol Coding
- Questionnaires: Recent Substance Use, QSU, WSWs, Craving VAS, Anxiety VAS
- Review of potential effects of TMS (to rule out any pre-existing problems, i.e. headache)
- MRI
- TMS stimulation
- Questionnaires & Cognitive Testing: Craving VAS, Anxiety VAS, BACS Symbol Coding
- MRI
- TMS acute side effects questionnaire
- *All subjects will be required to wear earplugs for the duration of the TMS stimulation and in the MRI scanner*

Participants will have motor threshold determination at the first TMS visit. Single pulse and repetitive stimulation will be performed with a MagPro stimulator (MagVenture) equipped with a biphasic figure-of-eight coil. To obtain an active motor threshold, single pulses will be used in the following manner: Electromyographic activity (EMG) will be recorded using surface electrodes attached to the skin to measure motor evoked potentials (MEP) during the motor threshold assessment. The TMS coil will be placed on the scalp. TMS pulses are applied over the hand area of the left motor cortex and individually localized for each participant based on the optimal position for eliciting a MEP. Neuronavigation will be used to record the motor 'hot-spot.' Resting and active motor threshold (RMT; AMT) will be obtained by following recommendations from the International Federation of Clinical Neurophysiology.

Participants will receive 1 of 3 types of rTMS at each TMS visit: iTBS, cTBS, and sham rTMS. Intermittent theta burst stimulation (iTBS) consisting of 2 s trains of 3 pulses at 50 Hz, repeated at 5 Hz, every 10s for a total of 600 pulses [18], will be applied to the parietal node of the default mode network. In previous work, we have demonstrated this stimulation parameter effectively modulated functional connectivity in schizophrenia [28]. Continuous theta burst stimulation (cTBS), which is generally viewed as inhibitory, will be applied to the parietal node of the default mode network at 3 pulses at 50 Hz repeated at 5 Hz (every 200ms) continuously for a total of 600 pulses [18]. Stimulation will be applied to the parietal lobe at 100% of AMT, consistent with previously published data and safety guidelines for cortical stimulation [29-32].

The participants will be compensated \$100 after completing each TMS visit #1 and TMS visit #2 and \$200 after completing TMS visit #3. Participants will be paid for each study visit they attend. The study staff will arrange transportation to and from study visits.

Test Descriptions:

The Positive and Negative Syndrome Scale (PANSS):

PANSS is a 30-item rating instrument evaluating the presence/absence and severity of positive, negative and general psychopathology of schizophrenia [33]. The scale was developed from the Brief Psychiatric Rating Scale (BPRS) and the Psychopathology Rating Scale. All 30 items are rated on a 7-point scale (1=absent; 7=extreme).

Auditory hallucinations rating scale (AHRs)

The AHRS is a seven-item questionnaire designed to measure the frequency and intensity of auditory hallucinations [34].

Calgary Depression Scale for Schizophrenia (CDSS)

The Calgary Depression Scale for Schizophrenia was developed to assess symptoms of depression in schizophrenia [35].

Fagerstrom Test for Nicotine Dependence (FTND)

This questionnaire assesses participant severity of nicotine dependence [36].

Tiffany Questionnaire of Smoking Urges – Brief (QSU)

This 10-item questionnaire assesses cigarette craving [37].

Wisconsin Smoking Withdrawal Scale (WSWS)

This questionnaire assesses participants for symptoms of nicotine withdrawal [38].

Alcohol Use Scale/Drug Use Scale (AUS/DUS)

This questionnaire assesses participants for frequency and severity of current substance use [39].

Nicotine Use Questionnaire

This questionnaire asks participants about their current and lifetime nicotine use.

Recent Substance Use Questionnaire

This questionnaire asks participants about cigarette and substance use in the past 24 hours.

Craving Visual Analog Scale (Craving VAS)

This 0-10 scale asks participants to rate their current level of craving for a cigarette.

Anxiety Visual Analog Scale (Anxiety VAS)

This 0-10 scale asks participants to rate their current level of anxiety.

Measurement And Treatment Research to Improve Cognition in Schizophrenia:

The MATRICS battery is used to provide a relatively brief evaluation of key cognitive domains relevant to schizophrenia and related disorders. It is used as a measure of cognitive change in repeated testing applications [40, 41]. Selected measures (Animal Fluency, Trails, BACS Symbol Coding) will also be assessed at the TMS visits.

TMS Acute Effects Questionnaire

This questionnaire assesses participants for both common as well as rarer side effects of TMS including change in mood.

B. Statistical Considerations

Sample Size Justification:

Participants: We will study up to 50 participants with a DSM-V diagnosis of schizophrenia or schizoaffective disorder who smoke cigarettes. Based on preliminary data, we anticipate attrition over the course of the study due to participant drop-out and fMRI data QC to result in 32 participants with both high quality imaging data and symptom assessments pre- and post rTMS. These 32 participants will each receive 3 sessions of TMS, resulting in 32 participants per arm (iTBS, cTBS, sham).

a) Power Analysis: This is a pilot study of TMS applied to the default mode network in schizophrenia and schizoaffective disorder, and there is no existing data in this population to calculate power and sample size. The purpose of this experiment is to generate power calculations for future experiments. An analysis of previous data in healthy controls identified a strong and highly significant correlation between changes in functional connectivity and attentional performance on the gradCPT after a TMS intervention ($p = .004$, $r = -0.82$, Figure 3). With an $\alpha = .05$, a sample size of 9 participants is required to have an 80% likelihood of observing a significant effect. These correlations will be performed across all participants (iTBS, cTBS, sham rTMS). In additional previous work, 9 healthy control participants were sufficient to identify a neurophysiological effect of rTMS on connectivity [24]. We also observed significant changes in connectivity to a different brain network in a pilot sample of 11 individuals with schizophrenia who received rTMS [42]. In this study, we will enroll up to 50 participants, ensuring that we will be adequately powered to detect differences in network connectivity.

Data Analysis:

General Analysis Plan:

Imaging: All data will be pre-processed and analyzed using standard published techniques, which utilize a combination of tools including DPABI [43] and SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>). Functional and structural images will be co-registered. Structural images were then normalized and segmented into gray, white and CSF partitions using the DARTEL technique [44]. A Friston 24-parameter model [45] is used to regress out head motion effects from the realigned data. The CSF and white matter signals as well as the linear trend are also regressed as nuisance covariates. After realigning and co-registration, framewise displacement (FD) is calculated for all resting state volumes [46]. All volumes with a FD greater than 0.5mm are regressed out as nuisance covariates. After nuisance covariate regression, the resultant data is band pass filtered to select low frequency (.01-.08Hz) signals. Filtered data are normalized by DARTEL into MNI space and then smoothed by a Gaussian kernel of 8mm^3 full-width at half maximum (FWHM). While the combination of GSR with volume editing effectively removes motion effects, there remain concerns about the effect of GSR to distort group differences [47-49]. We therefore will process the resting state data twice, once as above and a second time with global signal regression.

The time course of BOLD signal in voxels in the parietal node of the DMN and from the entire default mode network will be extracted [50]. We will calculate Pearson correlation coefficients between the parietal node of the DMN and the entire DMN. These values will be transformed to Fisher's z scores to generate measures of functional connectivity.

Behavioral: Typical attentional task measures such as reaction time and d' will be obtained before and after stimulation in each subject. Data will be analyzed with repeated-measures ANOVA using the R statistical software, comparing the interaction between the main effects of time (before and after stimulation) and main effect of experimental stimulation condition (<http://www.r-project.org/>). **TMS-MRI:** Seed-based resting state functional connectivity will be analyzed using standard software procedures [51]. An average default mode network functional connectivity measure will be obtained by calculating an average correlation of default mode network voxels over time. This measure will be normalized with a variance-stabilizing transformation (Fisher's transformation). A repeated-measures two-factor ANOVA will be used to assess the main effect of time (before and after stimulation) and stimulation condition, and the interaction between the two, to demonstrate a TMS effect upon MRI-observed physiology.

Data Analyses

Aim 1: We will test if network connectivity reflects cognitive performance using an independent sample of individuals with schizophrenia or schizoaffective disorder (n=50). Hypothesis 1A: Network connectivity will predict attentional performance in schizophrenia and schizoaffective disorder. Hypothesis 1B: The magnitude of attentional performance improvement after TMS is also explained by change in network connectivity in schizophrenia and schizoaffective disorder.

Our primary behavioral outcomes are the within-subject differences in measures of attentional performance between the pre-rTMS assessment and the post-rTMS assessment. These measures include:

Rater-independent measures: change in d prime and reaction time on the gradCPT, a measure of attentional performance

We will regress the within-subject difference in these outcomes against the within-subject differences in resting-state functional connectivity pre- versus post-rTMS. Given our preliminary rTMS data, our primary analysis will examine changes in functional connectivity between the parietal node of the default mode network and the entire default mode network. We will correlate changes in functional connectivity pre-versus post-rTMS to changes in the measures of attentional performance described above.

Our primary hypothesis is that network connectivity will predict attentional performance in schizophrenia and schizoaffective disorder and that the magnitude of attentional performance improvement after TMS will be explained by the observed change in network connectivity.

As a secondary analysis, we will explore which factors explain individual variance in rTMS-induced connectivity change. In our preliminary data connectivity change and symptom change are tightly linked but there is significant individual variation in the degree of connectivity change (and thereby variation in symptom change). We believe that variance in response may be a product of multiple factors, including: age, duration of illness, medication dosage (chlorpromazine equivalents), and sex. We will conduct an ANCOVA among participants who received active rTMS to determine the degree to which these factors explain individual variance in rTMS induced change in functional connectivity.

As an exploratory analysis, we will identify brain networks related to cigarette use and craving. We will also investigate if rTMS affects cigarette craving.

Dr. Mark Halko (McLean) will serve as a consultant for the design and analysis of this study but will not have access to any protected health information.

C. Subject Selection**Inclusion Criteria:**

- Age between 18-65 years
- At pre-visit screening (see attached phone screening questionnaire): Subjects must report that they have been given a diagnosis of schizophrenia or schizoaffective disorder by a mental health professional
- Current smoker (expired air CO of 5ppm or higher)
- Must be able to read, speak and understand English
- Must be judged by study staff to be capable of completing the study procedures
- Diagnosis of either schizophrenia or schizoaffective disorder according to DSM-V criteria and confirmed by SCID[26]
- Participants will be in stable outpatient treatment with no recent (within the past 30 days) hospitalizations or changes in their medication regimens.

Exclusion Criteria:

- DSM-V intellectual disability
- Substance use disorder within the past three months
- Any history of a progressive or genetic neurologic disorder (e.g. Parkinson's disease, multiple sclerosis, tuberous sclerosis, Alzheimer's Disease) or acquired neurological disease (e.g. stroke, traumatic brain injury, tumor), including intracranial lesions
- History of head trauma resulting in any loss of consciousness (>15 minutes) or neurological sequelae
- Current history of poorly controlled headaches including chronic medication for migraine prevention
- History of fainting spells of unknown or undetermined etiology that might constitute seizures
- History of seizures, diagnosis of epilepsy, or immediate (1st degree relative) family history epilepsy with the exception of a single seizure of benign etiology (e.g. febrile seizures) in the judgment of a board-certified neurologist
- Chronic (particularly) uncontrolled medical conditions that may cause a medical emergency in case of a provoked seizure (cardiac malformation, cardiac dysrhythmia, asthma, etc.)
- Any metal in the brain or skull (excluding dental fillings) or elsewhere in the body unless cleared by the responsible covering MD (e.g. MRI compatible joint replacement)
- Any devices such as pacemaker, medication pump, nerve stimulator, TENS unit, ventriculo-peritoneal shunt unless cleared by the responsible covering MD
- All female participants of child-bearing age will be required to have a pregnancy test; any participant who is pregnant will not be enrolled in the study
- Medications will be reviewed by the responsible covering physician and a decision about inclusion will be made based on the participant's past medical history, drug dose, history of recent medication changes or duration of treatment, and use of CNS active drugs. The published TMS guidelines review of medications to be considered with rTMS will be taken into consideration given their described effects on cortical excitability measures.
- Any changes in medications or hospitalizations within the past 30 days.

- Subjects who, in the investigator's opinion, might not be suitable for the study or would be unable to tolerate the study visit

These exclusion criteria strictly follow all recommended guidelines as endorsed by the International Federation of Clinical Neurophysiology and the International Society for Transcranial Stimulation[29].

B4. POSSIBLE BENEFITS

As with any study focusing on basic research, the subjects will derive no direct benefit. This study could contribute to the overall understanding of the neural impact of TMS on the cognitive domain of attention in individuals with schizophrenia or schizoaffective disorder.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

General:

Subjects with schizophrenia and schizoaffective disorder may experience paranoia or fear at the idea of receiving TMS or during the protocol, or they may have difficulty sitting still for the duration of the protocol. The investigator (Dr. Brady, a psychiatrist) will be available to provide reassurance and answer questions regarding TMS at any time. Subjects will be offered breaks regularly during the protocol. In addition, subjects will be counseled that they may discontinue the protocol or request breaks at any point. Subjects may become paranoid about technology. Subjects experiencing elevated distress or paranoia will be advised to discontinue, and the investigator will be available to provide counseling and assessment and/or enlist further resources as necessary. As an additional objective termination criterion: Participants are assessed for mood at all study visits on PANSS, CDSS, or the TMS acute effects questionnaire. As described below, answers on these questionnaires can trigger assessment by physician study staff to assess for suicidality. Any participant who endorses suicidal planning or intent on this assessment will both be terminated from the study and managed clinically to ensure safety (as detailed below).

MRI:

Although there are no known general risks associated with MRI scans, it is associated with risks for individual participants who have contraindications to MRI scanning, including those with metal implants in their body (e.g. pacemaker, aneurysm clips, metal screws and plates for orthopedic purposes, hearing implants, certain kinds of tattoos, sheetmetal workers with lodged metal fragments in the eyes).

This study uses a MRI scanner whose magnetic field strength is standard for clinical scans (3 Tesla). Most people experience no ill effects from 3T scans, but some do report claustrophobia, dizziness, mild nausea, headaches, a metallic taste in their mouth, back tingling, double vision, or sensation of flashing lights. These symptoms, if present, disappear shortly after leaving the scanner.

Participants who have contraindications to MRI scanning, including those with metal implants in their body will be screened carefully and excluded from the study. This screening includes a questionnaire and an interview by an individual trained in MRI safety. All participants will be asked to remove jewelry, belts and other metal-containing objects and will be provided with scrubs to wear for the MRI. Participants will also be screened with a handheld metal-detection wand prior to the study to ensure no unidentified metal objects remain on their body.

As the effects of MRI on the fetus are not well-characterized, we have decided that in order to be eligible females of child-bearing age will have gravid status confirmed by both interview and urine pregnancy test.

During the scan, the examiner can see and hear the participants and will ask them to report any problems so the scan can be stopped. A magnetic resonance scan may be uncomfortable due to claustrophobia, lying still, or loud sounds. Participants expressing serious concern about these will not be included in the study. The examiner will stop the scan if the participant expresses discomfort.

The MRI scanning environment may be difficult for some participants to tolerate. However, our group has extensive experience imaging clinical populations and we take a series of measures to increase participant comfort during scans. First, we allow the participant to lie in the scanner for several minutes in advance, to allow them to acclimate to the enclosed space and dispel any fears. Second, a temperature and pressure sensitive foam pillow is used to help stabilize head position, thereby reducing fatigue and motion artifact. Third, participants are fitted with earplugs to reduce ambient noise. The proposed studies do not require participants to be in the scanner for more than 60 minutes at a time. Our group also has experience guiding participants through completion of tasks while in the scanner.

Questionnaires and behavioral tasks: The questionnaires and tasks employed as part of the proposed protocol may cause some subjects to feel frustrated, bored or upset. It might also cause them to feel dysphoric as it may remind them of their clinical symptoms. Similarly, if patients feel they performed poorly on the tasks this has the potential to adversely affect their mood or exacerbate their depression symptoms.

Our staff has expertise with this type of testing in a range of patient populations and ample experience with discussing processes and results of these sorts of tests with patients. Testing sessions will be appropriately set up and monitored to prevent distress and staff will be available to speak with any patients who experience distress.

Social risks to participants in this experiment are extremely unlikely. The identity of participants will be protected and any personal information relating to the participants will be safely guarded. The probability of social harm to the participants resulting from participation in this experiment is extremely low.

TMS:

TMS has been used in a growing number of laboratories worldwide since 1984. A series of adverse events have been identified since then and have been thoroughly reviewed for the development of recommended safety guidelines and precautions for the use of TMS, first at a consensus conference at the NIH in June 1996, and most recently in 2018, in Siena (Italy), in a meeting of an international panel of TMS experts (The Safety of TMS Consensus Group), published in 2021 [52]. We will carefully follow these updated safety guidelines in the present study.

More Common adverse effects:

Headaches and/or Neck Pain:

Up to 20%-40% of subjects undergoing TMS experience headaches or neck pain, which are believed to be due to muscle tension. All prior cases of headaches induced by TMS have promptly resolved with a single dose of acetaminophen (Tylenol®), or aspirin[53]. In some cases TMS may cause twitching or discomfort on the same side of stimulation. Subjects will be positioned to minimize twitching and discomfort.

Rare adverse effects:

Hearing:

TMS produces a loud clicking sound when a current is passed through the stimulation coil. This loud click can result in ringing in the ear and temporary shifts in the ability to determine the pitch and loudness of sounds, if no protection is used. In order to prevent this possible side effect, participants will wear earplugs or noise cancelling earphones that block the noise of the TMS. Animal and human studies have shown that earplugs can effectively prevent the risk of hearing disturbance due to TMS. The forms of TMS that we will use in this study have never caused hearing problems.

Syncope:

Syncope can occur due to anxiety and psycho-physical discomfort during testing and treatment. This is reported less than seizure activity, but the true number may be higher due to under reporting. Subjects will be monitored for feeling any signs or symptoms of a pending syncopal event (i.e. feeling “dizzy, lightheaded, or going to pass out”). TMS will immediately be stopped and the subject will be assisted.

Seizures:

Subjects may have a seizure caused by TMS. If a seizure occurs, it will occur during the TMS application itself, not after. Repetitive TMS can induce a seizure even in the absence of pre-existing brain lesions, epilepsy, or other seizure risk factors, both in patients and healthy subjects. From the several thousands of studies that have used TMS to date, a total of 16 cases have been reported, of which 9 cases occurred after the 1998 safety guidelines. Based on the available data, the reported risk of seizures is less than 1 in 1000 for repetitive TMS. For the theta-burst rTMS stimulation protocol used in the study, the risks appear to be negligible. There is only one reported instance of a possible seizure triggered by theta-burst rTMS. Further, this event occurred with intensities higher than will be used in the current study. Nevertheless, this is a very concerning complication and to make the subjects' risk as small as possible, the investigators will follow precautions that are recommended by the International Society for Transcranial Stimulation and mentioned in the 2021 updated safety guidelines of The Safety of TMS Consensus Group [52]. Subjects will be carefully observed throughout the study by an investigator who has undergone specific training on how to identify and respond to a seizure. Additionally, a licensed neurologist will be available to evaluate participants if needed.

However, a seizure could occur. If a seizure occurs, the subject will receive prompt evaluation by a physician. In addition, in the event of a seizure, subjects will receive appropriate medical examination and follow-up at the Cognitive Neurology Unit and the Division of Epilepsy and Clinical Neurophysiology at the Beth Israel Deaconess Medical Center.

Memory:

TMS could induce short-term changes in memory, attention, and other cognitive and mental functions. This is a theoretical risk, as none of the safety studies conducted has found such side effects.

Mood:

Acute psychiatric effects have been described in patients receiving rTMS. Although single cases suggest a causal relationship between rTMS and mania, the overall rate (13 cases) across 53 randomized controlled studies in depression appears to be low (0.84% mania for active rTMS vs. 0.73% for sham rTMS) and even below natural switch rates in patients with bipolar disorders receiving mood stabilizers (2.3-3.45%). Similarly, cases of rTMS induced psychotic symptoms, anxiety, agitation, suicidal ideation, and insomnia, have been reported. Of note, as of 2017, multiple trials of transcranial magnetic stimulation have safely been performed in schizophrenia and schizoaffective disorder. A meta-analysis of TMS studies for treatment of hallucinations in schizophrenia did not find worsening of psychiatric condition as a possible risk of TMS [54]. Symptoms and suicidal ideation have never been described in normal subjects during or after rTMS.

In all the above cases the psychiatric side effects induced by TMS were transient, with a spontaneous resolution after TMS cessation or promptly controlled by pharmacological treatment. Nevertheless, patients who undergo rTMS will be informed about the unlikely possibility of developing such acute side effects. Should worsening occur, the contingency plan described under "Data Safety and Monitoring Plan" will be utilized to ensure participant safety.

Dental Pain:

The possibility of dental pain during rTMS has been reported. This potential adverse effect of TMS would occur during the application of the stimulation itself. Should such discomfort occur, we encourage the participant to alert the study investigator. The stimulation session will be immediately terminated, and the participant will be encouraged to seek a dental evaluation. This is a very rare occurrence, but it may point to the presence of a cavity that may require care. This adverse effect should not lead to any lasting problems or complications.

Blood pressure changes: In a study done by Demirtas-Tatlidede et al., blood pressure was monitored throughout a 5 day treatment protocol with increases and decreases noted equally throughout the 5 day treatment. Changes were asymptomatic and transient in nature [55].

Pregnancy:

There is no evidence of teratogenic affects at the level of magnetic field that is applied during TMS. Additionally, based upon modeling, the reduction in magnetic field from the head to the abdomen demonstrates that there is not any meaningful exposure of electromagnetic field or risk of induction of any current in a fetus. The electromagnetic field is only engaged by the TMS operator when the stimulation is being applied. Therefore, when the machine is not being activated, the magnetic field is not present. The rare risk of a maternal generalized seizure induced by TMS is of potential harm to a fetus. The overall risk of a generalized seizure induced by TMS is thought to be less than 1:1000 to 1:10,000. Furthermore, a seizure has never been induced by TMS in a pregnant woman and indeed pregnancy reduces the risk of seizures due to hormonal effects on brain cortical excitability. Thus, the true risk is quite small. Nevertheless, if a subject is a woman and capable of becoming pregnant, a pregnancy test will be done to verify that she is not pregnant.

Finally, even though TMS has been used in several laboratories worldwide since 1984, there could be some unforeseen complications.

General Safety Plan:

Steps to mitigate risks of TMS are detailed above including the use of hearing protection, assessing patients for pain or discomfort, and positioning during stimulation. In addition, participants will receive TMS sessions only when the PI or another licensed physician member of the study staff is available on campus for emergencies. To expand on the safety plan for seizures: all TMS sessions will be conducted by properly accredited and trained research staff, who (1) have been trained in the safe and efficient administration of TMS (through a course offered at the Berenson-Allen Center for Non-Invasive Brain Stimulation at BIDMC) and (2) are certified in basic life support and in the recognition and treatment of convulsions, syncope and other medical/neurological emergencies. There will be a medically responsible physician for the study who will assess all participants prior to entry into the study. The Center for Brain Science at Harvard University uses emergency medical services (911), which will be immediately notified in the event of an emergency. We will also monitor patients in detail during and after delivery of TMS, using an approach drawn directly from the guidelines endorsed by the International Federation for Clinical Neurophysiology.

Data and Safety Monitoring Plan:

All subjects will be monitored throughout the study for any adverse reactions in relation to the TMS using the Adverse Reaction Form for TMS. Adverse reactions will be reviewed daily prior to TMS and then following TMS.

Our experience using rTMS in participants with schizophrenia and schizoaffective disorder has demonstrated its safety in this population [55]. That said, there is a risk of symptomatic worsening either as a rare consequence of the study or as a part of the course of the disease being studied. If there is an indication that the subject is potentially suicidal based on study assessments (a response of >1 on question #8 “Suicide” on the Calgary Depression Scale or a score of 4 on the PANSS question G6 “Depression”), the PI or, on rare occasions, a covering psychiatrist will be alerted to make an assessment of the subject. If indicated, the subject’s treating psychiatrist will be contacted. If the PI or covering psychiatrist find any evidence that the subject is in immediate danger or the condition is an emergency, the subject will be transferred to the Emergency Department at Beth Israel Deaconess Medical Center. This assessment of urgent / emergent situations and the procedures to mitigate risk of harm are a part of the PI’s routine practice in supervising an outpatient training clinic at BIDMC.

Following TMS, a study team member will administer the TMS Acute Side Effects Questionnaire. If a subject expresses a worsening in mood, the PI or covering psychiatrist will be alerted to assess the subject. That psychiatrist will determine if the subject is in need of a psychiatric evaluation. The rTMS sessions will be discontinued if the psychiatrist evaluates this side effect to be a worsening related to rTMS application and the patient’s treating psychiatrist will be contacted if clinically indicated. If they find any evidence that the subject is in immediate danger or the condition is an emergency, we will transfer him/her to the Emergency Department at Beth Israel Deaconess Medical Center.

All applicable local regulatory requirements related to the reporting of serious adverse events to regulatory authorities and the IRB will be followed during this study. Serious adverse events will be promptly reported to the IRB, the Clinical Research Center, and the FDA as per their policies.

B6. RECRUITMENT AND CONSENT PROCEDURES**Recruitment**

Patients who are over the age of 18, and who have been diagnosed with schizophrenia or schizoaffective disorder will be enrolled. There is a lack of data showing that repeated sessions of rTMS are safe on children, for this reason children and teens under the age of 18 will be excluded. The same rationale applies to the exclusion based on race, gender, or ethnic background. If, as the study progresses, we find that a representative population is not being entered into the study with respect to gender and race, recruitment methods will be reviewed. Patients will be recruited from Beth Israel Deaconess Medical Center and the Massachusetts Mental Health Center.

The PI, upon finding a possible participant from BIDMC, will contact their providers who will speak to them about the study. After being referred by their provider, prospective participants can contact our study staff. Prospective participants will also be recruited through the use of flyers and brochures. People receiving services at MMHC may contact study staff directly to obtain information about the study. At no time will any study staff contact MMHC patients before they have agreed to be contacted. During the screening procedures, the participant will be asked to sign a medical release in order for study staff to confirm their diagnosis with providers, describe the study to providers, and to answer any provider questions about the study. We will also recruit existing volunteers who have previously participated in studies at our center and have provided permission to be recontacted for future research opportunities.

Study staff may request to reach out to a participant's current mental health provider to confirm a diagnosis. This will only occur with written consent from the participant in the form of a signed authorization form.

Consent

Once pre-screening has occurred, subjects will be consented on location to assure privacy. The investigator or a trained member of the study staff will begin by discussing the study purpose, requirements, procedures, possible benefits, potential risks, and alternatives. If the subject remains interested in participating, he/she will be given an informed consent document and allowed to review the information with no time restriction. Only when the subject declares that they are comfortable with all aspects will the subject be allowed to offer consent. The informed consent form will be signed by the subject and a member of the study staff.

Because people who are recruited for this investigation display symptoms of psychosis, we will use the attached Assessment of Capacity form to assess ability to consent to participation. This form has been used in previous studies with schizophrenia and schizoaffective disorder at our center. The form prompts the investigator to assure that the subject is voluntarily choosing to participate in the study, has a factual understanding of the study, has an appreciation of the significance of the facts about research participation and is able to reason about his or her participation.

Subject Protection

Patients with schizophrenia or schizoaffective disorder may be considered a vulnerable population. The multi-step consent process involving both a phone screening questionnaire, and in-person visit provide safeguards and opportunities for subjects to understand the study and choose whether or not to partake. Subjects will be questioned to confirm their understanding of the protocol and possible risks or adverse side effects of transcranial magnetic stimulation, thus helping ensure that subjects with incomplete understanding do not unwittingly consent to the study. Finally, we will also complete a one-page Assessment of Capacity form to provide informed consent (attached), as described above.

We will assure subjects both on the informed consent form and in person that refusal to partake in

the study or drop-out from the study at any point has no impact on continued services from the Department of Mental Health, their current clinic, or Beth Israel Deaconess Medical Center. Clinical interviews will be performed by the PI, a psychiatrist who will be able to reassure subjects or if necessary, provide counseling if they are distressed. Subjects will be forewarned throughout the pre-screening and screening process that the protocol involves sitting in a chair for up to six hours, and that they may take breaks at any time. Breaks will be offered to subjects regularly, though they may decline to take them.

Again, if during the consent process or any study visit, study staff notice the subject expressing suicidality, homicidality, appearing agitated or distressed, or if they score a response of >1 on question #8 "Suicide" on the Calgary Depression Scale or a score of 4 on the PANSS question G6 "Depression", they will be instructed to pause the protocol and immediately contact the investigator (Dr. Brady, a trained psychiatrist), who will perform a safety assessment, contacting outpatient providers or emergency services as deemed necessary.

B7. STUDY LOCATION

Privacy

Subjects will be seen in a private lab space at the Harvard University Center for Brain Science or in a private room at Beth Israel Deaconess Medical Center or the Massachusetts Mental Health Center, for all consent, all screening activities, assessments, and TMS treatments, assuring privacy during all of the evaluations.

Physical Setting

The evaluations, interviews, and the behavioral testing will occur at the Harvard University Center for Brain Science, in the Clinical Research Center or Berenson-Allen Center at Beth Israel Deaconess Medical Center, or the Massachusetts Mental Health Center. MRI and TMS sessions will be conducted in Harvard University Center for Brain Science, where there is a TMS Laboratory fully equipped with all the needed equipment for this research.

B8. DATA SECURITY

To safeguard confidentiality and the privacy of protected health information, each study subject will be assigned a unique code number. A separate file linking the patient's name with study number and identifiers will be kept in a password-protected data file, accessible only by the study investigators. All study forms will be kept in secure locked file cabinets. The study investigators will assume full responsibility to maintain the confidentiality of all data. All study results will be presented only as statistical aggregates that will neither identify nor permit identification of individual subjects. All data will be collected using a secure REDCap database.

All paper information obtained in this study will be kept in a research office under lock and key at Beth-Israel Deaconess Medical Center. Research participants will be identified with a six digit code. All databases related to the study will be stored on a password protected computer network accessible only from a laboratory kept under lock and key. Only study staff will have access to this information. Identifying data will not be shared with researchers outside of Beth-Israel Deaconess Medical Center.

A secure Database will be implemented in REDCap for behavioral data, and in XNAT for MRI data. Data will be database freed of all personal identifiers. A unique code number will be assigned to each participant allowing linking between REDCap and XNAT databases. The Harvard Catalyst resources in Bio-informatics and BIDMC's Electronic Data Capture Core will be instrumental in establishing and maintaining a secure database and repository of all the data collected. Deidentified data will be shared with Dr. Heather Ward at Vanderbilt University.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Please explain whether you will be able to thank subjects and provide research results and, if so, how this will be accomplished. If you do not think this is feasible, appropriate or applicable to this research, please specify why.

Participants will be informed that any public results will be made available to them if they wish.

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