**PROTOCOL TITLE:**
Cerebellar transcranial magnetic stimulation (cTMS) in psychotic disorders: effect on time perception, executive function, and mood and psychotic symptoms

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## I. BACKGROUND AND SIGNIFICANCE:

Psychotic disorders, such as schizophrenia (SZ), schizoaffective disorder (SZA), and bipolar disorder (BP) with psychotic features, are severe and disabling illnesses that exact a tremendous toll on patients, families, and society[1-3]. These disorders are characterized by varying combinations of affective symptoms, hallucinations, delusions, thought disorder, disorganized behavior, negative symptoms (a decrease or absence of thoughts, feelings, or actions), and cognitive deficits (present in both SZ[4, 5] and BP[6-8]) that impair individuals' ability to function. These wide-ranging symptoms appear at the outset to be highly heterogeneous in nature. It is unclear how some of these symptoms are related to one another, and this is reflected in the way we treat psychotic disorders. The majority of existing pharmacological agents are limited in that they improve some but not all of these diverse symptoms (e.g., antipsychotic medications reduce positive symptoms such as hallucinations and delusions, but are relatively ineffective in treating negative or cognitive symptoms). In addition, such treatments are associated with significant side effects. There is an urgent need to develop new and effective treatments. For this purpose, understanding disease pathophysiology is critical. In this proposal, we focus on the role of the cerebellum in psychotic disorders. A growing body of evidence suggests that the cerebellum plays a key role in organizing cognitive and emotional processing and that abnormalities in this brain region may be implicated in psychotic disorders. Based on this evidence, we propose a proof-of-concept study of cerebellar stimulation and inhibition using transcranial magnetic stimulation (TMS). While this is not a definitive clinical trial, the sham-controlled double-crossover design of this study will provide valuable information about the focus on cerebellum as a potential treatment target in psychotic disorders and may pave the way for the development of this approach as a treatment intervention.

A major challenge is to determine whether a unitary pathophysiological model can cohesively explain the heterogeneous symptoms of SZ and other psychotic disorders, and what that model might be. According to Andreasen's "cognitive dysmetria" hypothesis, the many diverse symptoms of SZ reflect "dysmetria," or incoordination, of mental activity and may have in common misconnections within

cortico-cerebellar-thalamic-cortical circuits (CCTCC)[9, 10]. Independently, Schmahmann proposed a "dysmetria of thought" model, in which neuropsychiatric conditions, including psychosis, may result from impairments in the ability to properly "detect, prevent, and correct mismatches" between intended and perceived outcomes for mental processes, mediated by the cerebellum[11, 12]. Such impairments produce a cerebellar cognitive affective syndrome, characterized by deficits in executive function, spatial cognition, affective and behavioral regulation, and language processing[13]. At the center of both Andreasen's and Schmahmann's models is the idea of a dysfunctional cerebellum.

The cerebellum was traditionally thought to be involved exclusively in the planning and execution of motor activities. This classical view held that the cerebellum received inputs from widespread cortical areas, but projected solely to primary motor cortex; i.e., information from frontal, parietal, temporal, and occipital cortices was believed to be integrated entirely for motor control [14]. However, it is now well recognized that the cerebellum is extensively connected to higher-level association cortices, and that it contributes to non-motor as well as motor functions [14-17]. Viral trans-neuronal tracer studies, for example, have demonstrated that the cerebellum projects to the prefrontal[18] and parietal cortices[19]. Histological and electrophysiological studies in animals have also shown that the cerebellar vermis and fastigial nuclei project to several temporal areas important in learning and memory, including hippocampus and amygdala[20-22]. In fact, the cerebellum is a complex structure comprised of multiple parallel loops organized into modular subregions responsible for many distinct functions[23-25]. For example, the anterior lobe, consisting of lobules I-V, and lobule VIII, modulates primarily sensorimotor processes, the posterior lobules VI, VII, and VIIB modulate cognitive functions, and the posterior vermis regulates affect[26].

There is substantial evidence of cerebellar abnormalities in SZ. Postmortem studies report atrophy[27], reduced Purkinje cell size[28], and reduced Purkinje cell linear density (number of Purkinje cells per unit line length of Purkinje cell layer)[29] in the cerebellar vermis of patients with SZ. Postmortem studies have also documented reduced expression of cerebellar synaptic proteins (i.e., synaptophysin and complexin II)[30] and markedly altered expression of cerebellar serotonin 5-HT(2A) receptors[31] in SZ, suggesting dysfunction of neural circuits and neurotransmission in the cerebellum of patients with SZ. Structural MRI studies in SZ report decreased volumes of the vermis[32-39], cerebellar hemispheres[40] (especially posterior lobes[33, 41]), and total cerebellum[42-44]. (Findings are inconsistent, however, with some groups reporting no volumetric differences in cerebellar structures[45-50] or greater vermal volumes[51-53] in SZ.) Functional MRI (fMRI) studies also reveal abnormalities of the cerebellum in SZ. According to a recent quantitative review[54], of 234 fMRI SZ reporting abnormal activity in cerebellar regions, more than 80% were studies of cognitive, emotional, or executive processes in SZ. In this review, almost two-thirds of group comparisons showed hypoactivation of cerebellar regions in SZ, with the majority of hypoactivation foci in the medial aspects of the anterior lobe and lateral cerebellar hemispheres (lobules IV-V)[54]. Resting state fMRI studies have pointed to cerebellar dysconnectivity in SZ[55-61]. Most recently, our group found SZ patients to have decreased cerebro-cerebellar functional connectivity in higher level association networks (ventral attention, salience, control, and default mode networks) and increased cerebro-cerebellar connectivity in somatomotor and default mode networks relative to healthy individuals.

Cerebellar abnormalities are also implicated in BP. Though discrepancies exist[62], the literature points to reduced cerebellar and vermal volume[63, 64] in BP, with vermal lobules and VIII-X[65, 66] and VIII-X[67], in particular, reported to be smaller in patients with multiple affective episodes compared to first-episode mania patients and healthy individuals. Neuroimaging studies have reported a trend for lower cerebellar blood volume in BP compared to SZ and healthy individuals[68], and lower N-acetylaspartate levels in the cerebellar vermis in both BP and SZ[69].

While a unified theory of cerebellar function has yet to be been firmly established, there is growing evidence for the role of the cerebellum in a common timing function for diverse tasks[70-73]. Keele and Ivry conceptualized the cerebellum as an ''internal clock'' that performs temporal computations in both the motor and non-motor domains, hypothesizing that the cerebellum's highly regular cellular organization allows it to produce precise temporal delays[70]. While the cerebellum is not the sole regulator of timing functions, the [74]. Indeed, cerebellar lesion studies have found that patients with cerebellar

damage-- but not those with Parkinson's disease, cortical damage, or peripheral neuropathy-- are impaired at perceptual timing tasks that require maintaining a simple rhythm or discriminating between small differences in the duration of two intervals[75]. Precise computation of timing is critical for sensorimotor prediction[76, 77] and coordination of tasks. Given the involvement of the cerebellum in higher order functions, it is plausible that the timing functions of the cerebellum might also extend to cognitive and emotional domains.

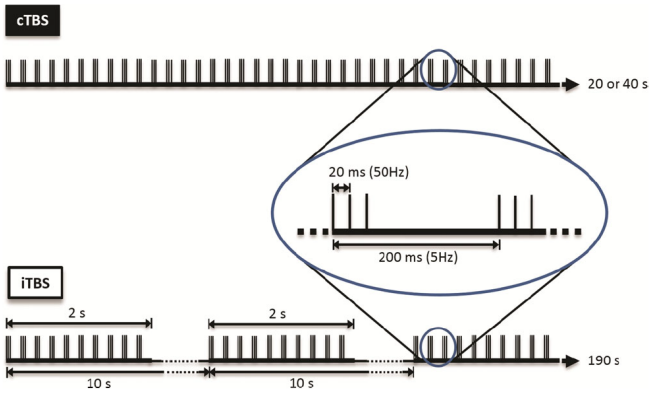
Studies have shown that patients with SZ (see review[78]) and BP[79] have impairments in time perception. There is no consensus on the tendency of the impairment, with patients demonstrating both overestimation and underestimation of time intervals in a variety of time estimation tasks. However, increased variability of time estimation has been observed in patients compared to healthy controls[80]. Such evidence has led researchers to suggest that such timing abnormalities might be intrinsically associated with these psychiatric disorders or even be part of the pathogenesis of other hallmark symptoms, such as hallucinations and delusions. For instance, Waters[81] proposed that in SZ patients with auditory hallucinations, a common set of disruptions in neural circuitry may underlie both timing perception abnormalities and dysfunctions of other internal processes that are linked to hallucinations. Similarly, it has been suggested that that the cerebellum may play a role as an "emotional pacemaker"[82].It is possible that the various symptoms in psychotic disorders-- e.g., affective symptoms, hallucinations, delusions, thought disorder, disorganized behavior, negative symptoms, and executive dysfunction-- are mediated by timing abnormalities.

Transcranial magnetic stimulation (TMS) is a noninvasive and well-tolerated method of neuromodulation in which magnetic fields applied over the surface of the skull generate electrical currents to stimulate or inhibit targeted brain regions[83]. TMS has a well-established safety profile and it is able modulate brain activity without surgery, anesthesia or the generation of a convulsion[84]. Single and paired-pulse TMS protocols have been used since the mid-1980s to study human neurophysiology, with a focus on the motor system, cortical excitability and neuroplasticity[85]. Diagnostic applications have been FDA-approved for years, allowing the use of these protocols by clinical neurophysiologist for the assessment of pathologies affecting the pyramidal tract (i.e. motor conduction studies)[86]. Repetitive TMS (rTMS) refers to the application of multiple pulses of TMS, repeated over the course of a given session, with frequencies commonly varying between 1Hz and 50Hz[83]. Repetitive TMS has been used extensively in systems and cognitive neuroscience research, given its capacity to modulate (both up- and down-regulating) brain regions and networks. Importantly, the safe and well-tolerated yet interventional nature of TMS has allowed the establishment of causal relationships between brain activity and mental states in humans in vivo (e.g.,[87]), something that other observational noninvasive neuroscience tools (e.g., neuroimaging) are unable to do (these are limited to establishing correlations). Repetitive TMS (rTMS) has been suggested to induce changes in neural activity at the systems level, which may contribute to its therapeutic effects. In the motor cortex, high frequency rTMS (hf-rTMS) has been shown to increase cortical excitability, while low frequency rTMS (lf-rTMS) has been shown to decrease excitability[88]. Clinically, rTMS has been FDA approved for therapeutic indications and since 2008 it is used for the treatment of major depressive disorders[89, 90]. Of primary relevance to this study, TMS has been safely administered to the cerebellum in wide-ranging studies focusing on saccadic eye movements[91-93], spinocerebellar degeneration[94], visual motion processing[95], timing tasks[96, 97], ataxia[98, 99], motor learning[100], Parkinson's disease[101, 102], and SZ[103].

Theta burst stimulation (TBS) is a very efficient rTMS protocol that uses high frequency rTMS burst with lower stimulus intensity, smaller number of pulses and much shorter train duration, yet capable of facilitating longer-lasting post stimulation effects compared with traditional rTMS[104, 105]. TBS was developed in 2004, based on the physiologic pattern of neuronal firing found in the hippocampus of animal[104]. The basic element of TBS contains a three-pulse burst at 50 Hz given every 200 milliseconds (i.e. at 5 Hz). By using this basic pattern, two major TBS paradigms were developed: continuous theta burst stimulation (cTBS, inhibitory) and intermittent theta burst stimulation (iTBS, excitatory), as shown in **Figure 1**. The stimulus intensity required for TBS (80% of active motor threshold –AMT) is lower than that for traditional rTMS protocols, which use 100 to 120% of the resting motor threshold (RMT). Of

note, not only the percentage is less, but the AMT is also of lower intensity than the RMT. Consecutive sessions of TBS have been safely administered in SZ[103, 106-108] and in BP[109-112].

**Figure 1: Continuous and Intermittent TBS protocols (from Chung et al., 2015)**




In this study, we will administer TBS to the cerebellum in psychosis patients (schizophrenia, schizoaffective disorder, and psychotic bipolar disorder) to investigate with causal explanatory power the role of the cerebellum in time perception abnormalities, executive dysfunction, and mood and psychotic symptoms, which are prevalent in these disorders. We will determine whether modulating (exciting or inhibiting) the cerebellum with TBS leads to changes in (1) time perception (measured by the interval discrimination and repetitive finger tapping tasks) (2) executive function (measured by the N-back, flanker task and multi-source interference tasks), and (3) mood and psychotic symptoms (measured by visual analogue scales). Finally, we will test the hypothesis that time-perception abnormalities mediate, at least partially, the myriad clinical manifestations (i.e., cognitive, mood, and psychotic symptoms) in these disorders. Testing the hypothesis that the cerebellum contributes to the diverse symptoms in psychotic disorders, possibly through a common impairment in time perception, will provide insights that will enable development of more effective therapies that treat the full syndromes, rather than select symptoms.

## II. SPECIFIC AIMS:

The cerebellum plays a major role in information processing but it has not been considered a treatment target for studies of major mental illness. The goal of this study is to investigate the impact of modulating cerebellar activity on mood and psychotic symptoms in patients as well as the closely related domains of executive function and time perception. We will study up to 100 healthy subjects and up to 100 psychosis patients (i.e., schizophrenia, schizoaffective disorder, and psychotic bipolar disorder). In sham-controlled crossover design, we will present validated cognitive paradigms and clinical measures to subjects before and after TMS. We hypothesize that abnormally reduced activity in the cerebellum contributes to the abnormalities in patients and therefore cerebellar stimulation will normalize outcome measures. The circuitry of the cerebellum is complex and the main projection neurons in this brain region (Purkinje cells) are inhibitory. Therefore, we will test the specificity of our hypothesis by including an "inhibition" TMS condition which we hypothesize will worsen the outcome measures. The specific aims are to:

**Aim 1:** Investigate the role of the cerebellum in abnormalities of time perception, cognition, and mood and psychotic symptoms by evaluating these functions before and immediately after excitatory, inhibitory, or sham TMS applied to the cerebellum in patients with psychosis and in healthy control participants. Participants will undergo three study visits, one for each of the three TMS conditions. At each study visit, we will measure the following before and after TMS:

a) **Time perception**: We will measure time perception using a time perception task. *Hypothesis:* Compared with healthy control participants, patients with psychotic disorders will have impaired timing perception (i.e., higher number of errors and/or greater inter-trial variability in the task) both at baseline and after sham TMS. We predict that the abnormalities in patients will further worsen after inhibitory TMS, and improve after excitatory TMS.

b) **Executive Function:** We will measure executive function using a behavioral task. *Hypothesis:* Compared with healthy control participants, patients with psychotic disorders will have executive dysfunction, as measured by a higher number of errors and longer reaction times on both tasks, both at baseline and after sham TMS. We predict that these deficits in patients will become more exaggerated after inhibitory TMS, and improve after excitatory TMS.

c) **Symptoms:** We will measure mood and psychotic (e.g., hallucinations, delusions) symptoms with visual analogue scales (VAS). *Hypothesis:* Symptom ratings will improve in the period immediately after excitatory TMS, and worsen in the period immediately after inhibitory TMS, and show no significant change after sham TMS.

**Aim 2:** Investigate the relationship between time perception and (a) executive function and (b) symptomatology in patients with psychotic disorders. Hypothesis: We hypothesize that performance on the time perception task will correlate with performance on a working memory task as well as with mood and psychotic symptoms.

## III. SUBJECT SELECTION:

We will recruit participants from the following two groups:

1. **Patients with psychotic disorders** – patients diagnosed with schizophrenia (SZ), schizoaffective disorder (SZA), or psychotic bipolar disorder (BP).
2. **Healthy controls (HC)**—individuals with no psychiatric illness.

We will enroll up to 100 participants for each of the two protocols (Protocol A and Protocol B, which are identical except that they involve different time perception and executive tasks that participants must complete before and after the cerebellar TMS. Specifically, the tasks in Protocol A are the interval discrimination ask, flanker task and the N-back working task, while those in Protocol B are the repetitive finger tapping task and the Multi-Source Interference Task, or MSIT). Participants may elect to participate in both Protocol A and Protocol B, should they wish to do so. Participation in the second protocol will be entirely optional.

*Protocol A:*

n=50 patients with psychotic disorders
n=50 healthy controls

*Protocol B:*

n=50 patients with psychotic disorders
n=50 healthy controls

Thus, we will enroll between 100-200 participants in total. There may be overlap in the Protocol A and Protocol B participants. As previously stated, participants will be given the opportunity (optional) to participate in both Protocols A and B. (Thus, in the event that all participants complete both protocols, we will enroll only 100 total participants, i.e., 50 patients and 50 healthy controls).

This being the first study of its kind, it is difficult to do a formal power and sample size

analysis because we do not have a measure of effect size, but given previous similar studies and our usual rate of loss to follow up, we calculate we will need 50 participants per group for each protocol.

Our enrollment numbers take into account the likelihood of attrition. We will only be able to use data sets that are complete (i.e., data collected from sham, excitatory, and inhibitory TMS). However, we anticipate that a subset of enrolled participants will not be able to complete all three study visits within a protocol because of scheduling or other challenges. Though we aim to enroll up to 50 patients and 50 healthy controls per protocol, we expect that the number of participants on whom we have useable data will be smaller.

**Inclusion Criteria:**

*Patients*

- Men and women
- Ages 18-50 years
- Patients diagnosed with schizophrenia (SZ), schizoaffective disorder (SZA), or psychotic bipolar disorder (BP).
- On a stable psychiatric medication regimen for at least a month prior to and during study participation
- Have structural brain MRI data on file from previous participation in research within the McLean Hospital Schizophrenia and Bipolar Disorder Program
- Have clinical diagnostic data (Structured Clinical Interview for DSM-IV: SCID) on file from previous participation in research within the McLean Hospital Schizophrenia and Bipolar Disorder Program

*Healthy Controls:*

- Men and women
- Ages 18-50 years
- Without major psychiatric illness
- Have structural brain MRI data on file from previous participation in research within the McLean Hospital Schizophrenia and Bipolar Disorder Program

**Exclusion Criteria:**

*Patients*

- Any change in psychiatric medications within a month prior to and during study participation
- Legal or mental incompetency
- Intellectual disability
- Substance use disorder (abuse or dependence) with active use within the last 3 months
- Significant medical or neurological illness
- Prior neurosurgical procedure
- History of seizures
- History of ECT treatment or clinical TMS within the past three months
- History of participation in a *cerebellar* TMS study
- Implanted cardiac pacemakers
- Patients who have conductive, ferromagnetic or other magnetic-sensitive metals implanted in their head or neck, or are non-removable and within 30 cm of the treatment coil. These include:
    - Aneurysm clips or coils
    - Carotid or cerebral stents
    - Metallic devices implanted in the head (e.g. Implanted pacemaker, medication

pump, vagal stimulator, deep brain stimulator, TENS unit, or ventriculo-peritoneal shunt)
    - Magnetically active dental implants
    - Cochlear/otologic implants
    - CSF shunts
    - Ferromagnetic ocular implants
    - Pellets, bullets, fragments less than 30 cm from the coil
    - Facial tattoos with metallic ink, permanent makeup less than 30 cm from the coil
- Pregnant women

*Healthy Controls:*

- History of major psychiatric illness, including psychosis
- Has a first-degree relative with psychosis
- Active use of neuropsychoactive medications
- Legal or mental incompetency
- Intellectual disability
- Substance use disorder (abuse or dependence) with active use within the last 3 months
- Significant medical or neurological illness
- Prior neurosurgical procedure
- History of seizures
- History of ECT treatment or clinical TMS within the past three months
- History of participation in a *cerebellar* TMS study
- Implanted cardiac pacemakers
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    - Metallic devices implanted in the head (e.g. Implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, or ventriculo-peritoneal shunt)
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    - CSF shunts
    - Ferromagnetic ocular implants
    - Pellets, bullets, fragments less than 30 cm from the coil
    - Facial tattoos with metallic ink, permanent makeup less than 30 cm from the coil
- Pregnant women

**Source of subjects and recruitment methods**

For patients, we will preferentially, though not exclusively, recruit individuals who are already enrolled in one of two ongoing research studies in the McLean Hospital Schizophrenia and Bipolar Disorder Program:

- The **"Core Protocol"** (IRB Protocol #2014P000476, PI Dost Öngür, "Multimodal neuroimaging, genetic, metabolic, and clinical characterization of patients with schizophrenia, psychotic bipolar disorder, and related disorders"). This is a large, ongoing genotype-phenotype study of psychotic disorders. The pool of potential patients available for participation in the current proposal through this study is large. As of 11/2015, the

genotype-phenotype study has enrolled approximately 14000 patients with psychotic disorders (SZ, SZA, or psychotic BP), and MRI data are available for 285 of these patients.

- The **"First-Episode Protocol"** (IRB Protocol #2012P001796, PI Dost Öngür, "Longitudinal multimodal neuroimaging studies in patients with first episode psychosis"). This study seeks to characterize brain, genetic, and metabolic abnormalities in individuals with first episode psychosis, and includes a SCID assessment as well as collection of structural MRI data. As of 11/2015, the first-episode protocol has enrolled 55 patients.

The rationale for this recruitment strategy is three-fold: (1) Collecting many different types of data—with the goal to combine methods and technologies at multiple levels of analysis—within the same cohort of subjects may lead to greater understanding of the mechanisms underlying psychotic disorders. (2) Collection of clinical data can be more efficient and streamlined for subjects who have enrolled in the core and first episode protocols. Because individuals who have participated in these protocols have already undergone a SCID for diagnosis, we will not need to complete a new SCID for the purposes of this study. Instead, we will simply assess during the course of administering the scales that the core/first episode SCID diagnosis remains accurate (i.e., has not changed/evolved in the interim). (3) We will already have structural MRI scan data for these subjects from previous studies, which will be necessary for neuro-navigation to accurately identify and place the TMS coil over the target stimulation region of the cerebellum.

The IRB-approved consent form for the core/genotype-phenotype and first-episode studies asks participants whether they would like to be contacted about future studies. For individuals we recruit through these two other studies, we will contact only those who have explicitly indicated on the consent form their interest in being contacted about future studies. We will also make sure to contact only individuals who have provided such permission and for whom the "up to five years" period after signing the consent form has not expired. These individuals may or may not be receiving inpatient or outpatient care at McLean at the time of our recruitment efforts. Regardless of their treatment status at the time, these are individuals we will have identified through our research database (not through medical records or other clinical data sources). Therefore, we will make contact with these individuals directly through (IRB-approved) recruitment emails, recruitment letters, and/or by phone, rather than first contacting their treatment providers as we would for individuals we identify through outpatient or inpatient clinical services.

Though we will primarily recruit through the core/genotype-phenotype and first-episode protocols, these other studies will not be the exclusive source of our patient recruitment. We may also recruit patients we identify through medical records in the inpatient and outpatient services at McLean Hospital. In such instances, we will take special precautions, in accordance with the PHRC guidelines, to ensure that we respect patient privacy. In specific, we will not directly approach patients we identify through their private health information. Instead, we will first contact a member of the patient's treatment team, someone who is known to the patient and who has first-hand knowledge of the patient's medical history (e.g., attending physician for inpatients; therapist, prescriber, or case manager for outpatients). We will ask the patient's treatment provider if the particular patient in question is appropriate for the study. If the patient's treater indicates that the patient does seem appropriate, we will ask the treatment provider to briefly talk to the patient about the research and obtain the patient's verbal permission for study staff to contact the patient with more details. We may provide the treatment provider with IRB-approved recruitment materials, with the idea that written material may facilitate the discussion between the patient and treatment provider and thus help with the recruitment process.

Though we may make contact with and introduce the study to potential participants while they are hospitalized at McLean Hospital, we will not actually enroll any participants while they are inpatients. The main reason for this is that the TMS study procedures will take place at a different site, at the Massachusetts General Hospital Charlestown Navy Yard campus. Therefore, if there are

any hospitalized patients who express interest in the study, we will wait until after they are discharged to enroll them.

Patients that we recruit through clinical services at McLean Hospital rather than through our lab's core/genotype-phenotype and first-episode research studies are unlikely to have SCID diagnostic data or brain MRI data on file for TMS neuronavigation. We anticipate that such patients will constitute the minority of research participants, since we will preferentially recruit through the core/genotype-phenotype and first-episode protocols. In such cases, we will inform these patients that they are ineligible for this study. Should they be interested in hearing about other research studies that include MRI, independent from involvement in the current study, we will let the patients know about the core/genotype-phenotype and first-episode protocols. If they choose to enroll in either of these studies and indicate willingness to be contacted about future research studies, we will re-contact and re-screen them for participation in this study.

Healthy control participants will be recruited through community advertisements and through ongoing neuroimaging studies in our group. Potential healthy control participants will undergo a screening interview for eligibility by telephone. Similar to patient participants, potential healthy control subjects without MRI data on file will be ineligible to participate in the current study. Should they be interested in hearing about other research studies that include MRI, independent from involvement in this study, we will let them know about the core/genotype-phenotype and first-episode protocols that they may choose to participate in. If they choose to enroll in either of these studies and indicate willingness to be contacted about future research studies, we will re-contact and re-screen them for participation in this current study.

We will also recruit both patients and healthy control participants through a posting on the Partners Healthcare Clinical Trials website. The posting will use simple, layman language to describe the purpose of the study, inclusion and exclusion criteria, study procedures, and compensation details. It will allow potential subjects to contact the study staff, who will then conduct a screening interview for eligibility by telephone.

## IV. SUBJECT ENROLLMENT

### Screening for Eligibility

We will use a standardized form (see Healthy Control Phone Screen and Patient Phone Screen, attached) for eligibility screening. The form asks about history of participating in neuroimaging studies within the McLean Hospital Schizophrenia and Bipolar Disorder Program, age, medical and neurological illnesses, whether pregnant, psychiatric history, family history of psychiatric illness, substance use history, history of ECT or TMS treatments, history of participation in a cerebellar TMS study, and any conditions that would preclude TMS administration (e.g., metal implants near the head or neck). The screening interview will take approximately 10 minutes to complete.

- Inpatients: The research coordinator will regularly visit the Schizophrenia and Bipolar Disorder inpatient units in the McLean Hospital Psychotic Disorders Division, check patient medical records (e.g., admission notes, progress notes) and be in frequent contact with the treating psychiatrist on the units for referrals about potential subjects. The research coordinator will perform screening with potential subjects who are interested in participating in the study for inclusion and exclusion criteria.
- Outpatients: The research coordinator will be in contact with outpatient treaters within the Psychotic Disorders Division for referrals about potential subjects. The research coordinator will also refer to recruitment records of other ongoing imaging studies of our group to select potential subjects. Patients who are interested will undergo a screening interview for inclusion and exclusion criteria either in person or by telephone.
- Healthy controls: Potential participants will undergo a screening interview for eligibility by telephone.

Potential subjects will be informed that all information obtained during eligibility screening will remain confidential. Screening forms that are completed for individuals who end up not meeting eligibility criteria will be disposed of in the confidential waste bin, according to hospital guidelines.

The PI, Dr. Shinn, is a co-medical director of the On Track first episode psychosis clinic at McLean Hospital, and provides direct care to a small subset (n=5-10) of patients in the clinic. To ensure that patients who receive treatment from Dr. Shinn do not experience coercion to participate, Dr. Shinn will not approach her own patients about this research. This will be done by other research staff. Similarly, the consenting procedures will be performed by other research staff, i.e. the research assistant. Lastly, as we will do with all subjects, we will emphasize to patients under the care of the PI that participation in research is completely voluntary, and that declining to participate in research or withdrawing from the study after consenting will not affect clinical care in any way.

**Procedures of obtaining informed consent**

Informed consent will be obtained on all study participants. As already mentioned, for potential subjects who are inpatient hospitalized, we will wait until they are discharged from the unit to obtain informed consent, as patients may not enroll or participate in the current protocol as inpatients.

All subjects who meet eligibility criteria will be given a description of the study, and any questions they may have will be answered. Participants must be capable of understanding the nature of this study, its potential risks, discomforts, and benefits. Since all participants will be 18 or older, they will provide consent without parental or other guidance. We will obtain informed consent after the study purpose and procedures have been fully and clearly explained, and the potential participant has demonstrated an understanding of the protocol, willingness to participate, and capacity to consent.

As a means of assessing participants' understanding of what the study entails, we will conduct a one-on-one informed consent survey, which asks questions such as, "What illness is being studied in this project?" "Are there any risks to participating in this study?" and "Will you lose any of your benefits if you refuse to participate in this study?" If the participant is unable to answer the questions or demonstrates a lack of understanding, the investigator will review the details of the study again. The survey therefore serves to ensure that participants are actively engaged in the informed consent process. For each participant, we will re-administer the informed consent survey at the beginning of each visit, in order to ensure that the participant is capable of consent throughout the entire study. Participants who are unable to answer all 9 questions on the survey correctly even after additional information is provided will be excluded from the study.

We will acquire written informed consent for all participants using the IRB-approved consent form. All signed forms will be stored in a file cabinet in a locked office.

For individuals who wish to participate in the second protocol (e.g., Protocol B after completing Protocol A), we will take the necessary time to remind participants about the study procedures, risks, and benefits, and answer any questions they may have about the study. We will also re-evaluate whether participants continue to meet the eligibility criteria. However, because Protocols A and B are both part of this same IRB protocol, we will not maintain separate written informed consent forms for the two protocols.

**Treatment assignment, and randomization**

All subjects, including controls, will receive either cTBS (inhibitory), iTBS (excitatory), or sham TBS in each of the three visits. The order in which they receive a particular type of TMS will be randomized for each subject by the study staff prior to the first TMS administration. The investigators and the research coordinator will not be blinded to the randomized order, since all

assessments pre- and post-TMS require input solely from the subjects. However, subjects will be blinded as to which mode of TMS they receive at each study visit. Sham TMS will use the exact same procedure with a sham coil, which is designed to induce the same nonspecific sensory effects of TMS (auditory and somatosensory activation) without inducing the neuromodulatory magnetic fields. At the end of each study visit, subjects will be asked to speculate on which mode of TMS (inhibitory, excitatory, or sham) they received as well as the degree of certainty of their judgment so that we can assess the potential contributions of subjects' expectations on their task performance.

## V. STUDY PROCEDURES:

All subjects, including healthy controls, will undergo three visits at the MGH Laboratory for Neuropsychiatry and Neuromodulation in the Charlestown Navy Yard Campus, with at least 36 hours separating the visits.

The subject is free to withdraw from the study at any time simply by informing the investigators. Similarly, the investigators may decide to stop the study if the purposes of the study cannot be met (technical difficulties, new information on subject characteristics, etc.).

### Summary of Study Procedures

The first visit will include the following procedures (for the second and third visits, the clinical characterization step will be skipped):

*Patients:*

- Consenting procedures (15-20 minutes)
- Clinical characterization (1-2 hours)
    - Positive and Negative Syndrome Scale (PANSS)
    - Young Mania Rating Scale (YMRS)
    - Montgomery-Asberg Depression Rating Scale (MADRS)
    - North American Adult Reading Test (NAART)
    - Psychotic Symptom Rating Scale: PSYRATS-AH
    - The Behavior Rating Inventory of Executive Function – Adult Form (BRIEF-A)
    - Barratt Impulsiveness Scale (Version 11; BIS-11)
    - Fagerstrom Test for Nicotine Dependence
- Urine toxicology/pregnancy screen (5 minutes)
- Baseline/pre-TMS assessments (15-20 minutes)
    - Interval discrimination task for Protocol A (or repetitive finger-tapping task for Protocol B)
    - N-back working memory task for Protocol A (or multi-source interference task (MSIT) for Protocol B)
    - Flanker task for Protocol A
    - Visual analog scales (VAS) to assess mood and psychotic symptoms
- Transcranial Magnetic Stimulation (TMS) (15 minutes)
    - Excitatory, inhibitory, or sham (order randomized)
- Post-TMS assessments (15-20 minutes)
    - Interval discrimination task for Protocol A (or repetitive finger-tapping task for Protocol B)
    - N-back working memory task for Protocol A (or multi-source interference task (MSIT) for Protocol B)
    - Flanker task for Protocol A
    - Visual analog scales (VAS) to assess mood and psychotic symptoms

*Healthy Control Participants:*

- Consenting procedures (15-20 minutes)
- Clinical characterization (1-2 hours)
    - Structured Clinical Interview for DSM-IV-TR (SCID)
    - North American Adult Reading Test (NAART)
    - The Behavior Rating Inventory of Executive Function – Adult Form (BRIEF-A)
    - Barratt Impulsiveness Scale (Version 11; "BIS-11")
    - Fagerstrom Test for Nicotine Dependence
- Urine toxicology/pregnancy screen (5 minutes)
- Baseline/pre-TMS assessments (15-20 minutes)
    - Interval discrimination task for Protocol A (or repetitive finger-tapping task for Protocol B)
    - N-back working memory task for Protocol A (or multi-source interference task (MSIT) for Protocol B)
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    - Visual analog scales (VAS) to assess mood and psychotic symptoms
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- Visual analog scales (VAS) to assess mood and psychotic symptoms
    - Excitatory, inhibitory, or sham (order randomized)
- Post-TMS assessments (15-20 minutes)
    - Interval discrimination task for Protocol A (or repetitive finger-tapping task for Protocol B)
    - N-back working memory task for Protocol A (or multi-source interference task (MSIT) for Protocol B)
    - Flanker task for Protocol A
    - Visual analog scales (VAS) to assess mood and psychotic symptoms

**Clinical characterization**

For the purposes of clinical characterization, we will record demographic (i.e. age, sex, race/ethnicity, parental education, duration of illness, handedness) and medication information for all subjects during the first visit. For healthy control participants, we will administer the SCID, which assesses lifetime history of psychiatric symptoms and diagnoses, but not symptom severity, which can fluctuate over time. To capture the clinical presentation of patients at the time of the study, we will use the following clinical scales (included with this protocol): PANSS, YMRS, MADRS, PSYRATS-AH, BRIEF-A, BIS-11. Each of these scales will be used to capture the most severe symptoms in the previous month. The NAART, BRIEF-A, BIS-11, will be administered for all subjects. The clinical characterization step will not be repeated at study Visits 2 and 3 for either Protocol A or B.

As part of the clinical evaluation, we will also ask female participants about and record the first date of their last menstrual period (LMP). Clinical symptoms and cognitive functioning can vary according to the phase of the menstrual period. We will evaluate what phase of the menstrual cycle a female participant is in at the time of each study visit so that we can potentially control for any associated confounding effects.

Similarly, nicotine is well-documented to affect cognitive functioning, and is an important variable to control for. Therefore, we will administer a Fagerstrom Test for Nicotine Dependence in all research participants. For individuals who are smokers, we will record the time of the participant's last cigarette prior to each study visit.

For all subjects, during each and every visit, urine toxicology screens will be used to assess for current substance use, and urine pregnancy tests in women of child-bearing age to determine if she is

pregnant (and thus is ineligible to participate in the study).

**Scheduling of study visits**

As mentioned before, this will be a cross-over design, in which participants will undergo excitatory, inhibitory, and sham TBS over three study visits, separated by at least 36 hours. The order in which participants receive excitatory vs. inhibitory vs. sham TMS will be randomized.

The effects of a single session of rTMS are acute and reversible, and usually recede in less than an hour. Nonetheless, the study visits will be separated by at least 36 hours in order to provide more than ample time for the brain to return to homeostatic balance and ensure that there are no potential residual TMS effects from the previous study visit.

If scheduling permits, participants may be able to complete all three study visits in as short as one week. However, to accommodate scheduling flexibility for research participants, we will allow up to two months for participants to complete all three study visits within a single protocol.

Participants will participate in one of two protocols, Protocol A (**Figure 2**) or Protocol B (**Figure 3**). The two protocols are identical except that they involve different time perception and executive function tasks. Specifically, the tasks in Protocol A are the interval discrimination task, flanker task and the N-back working memory task, while those in Protocol B are the repetitive finger tapping task and the multi-source interference task (MSIT).

Should they choose to do so, participants may optionally return to participate in the protocol in which they have not already participated (e.g., Protocol B after completing Protocol A) at any time point that the study remains open to recruitment and the participant continues to meet eligibility criteria. Once a participant returns for Visit 1 of the second protocol, we will allow up to two months for participants to complete study Visits 2 and Visits 3 of the same protocol.

**Figure 2.** Protocol A

| Visit 1 | | Visit 2 | | Visit 3 |
|---|---|---|---|---|
| NAART*<br>PANSS<br>YMRS<br>MADRS<br>PSYRATS-AH<br>BRIEF-A*<br>BIS-11*<br>Fagerstrom* | | | | |
| Utox and upreg screens | | Utox and upreg screens | | Utox and upreg screens |
| Mood and psychotic symptoms (VAS) | **≥ 36 hours** | Mood and psychotic symptoms (VAS) | **≥ 36 hours** | Mood and psychotic symptoms (VAS) |
| Interval discrimination<br>N-back test<br>Flanker | | Interval discrimination<br>N-back test<br>Flanker | | Interval discrimination<br>N-back test<br>Flanker |
| **TMS - sham†** | | **TMS - excitatory†** | | **TMS - inhibitory†** |
| Mood and psychotic symptoms (VAS) | | Mood and psychotic symptoms (VAS) | | Mood and psychotic symptoms (VAS) |
| Interval discrimination<br>N-back test<br>Flanker | | Interval discrimination<br>N-back test<br>Flanker | | Interval discrimination<br>N-back test<br>Flanker |
| Compensation: $75 | | Compensation: $50 | | Compensation: $50<br>+ $25 completion bonus |

*Scale also administered to healthy control participants. †Order of TMS randomized

**Figure 3.** Protocol B

| Visit 4 | | Visit 5 | | Visit 6 |
|---|---|---|---|---|
| NAART*<br>PANSS<br>YMRS<br>MADRS<br>PSYRATS-AH<br>BRIEF-A*<br>BIS-11*<br>Fagerstrom* | | | | |
| Utox and upreg screens | **≥ 36 hours** | Utox and upreg screens | **≥ 36 hours** | Utox and upreg screens |
| Mood and psychotic symptoms (VAS) | | Mood and psychotic symptoms (VAS) | | Mood and psychotic symptoms (VAS) |
| Finger tapping task<br>MSIT | | Finger tapping task<br>MSIT | | Finger tapping task<br>MSIT |
| **TMS - sham†** | | **TMS - excitatory†** | | **TMS - inhibitory†** |
| Mood and psychotic symptoms (VAS) | | Mood and psychotic symptoms (VAS) | | Mood and psychotic symptoms (VAS) |
| Finger tapping task<br>MSIT | | Finger tapping task<br>MSIT | | Finger tapping task<br>MSIT |
| Compensation: $75 | | Compensation: $50 | | Compensation: $50<br>+ $25 completion bonus |

*Scale also administered to healthy control participants. †Order of TMS randomized

**Transcranial Magnetic Stimulation (TMS)**

TMS has a well-established safety profile and it is able modulate brain activity without surgery, anesthesia or the generation of a convulsion (Rossi et al., 2009). Since its development in the mid-1980s, it has become a widely used tool for neuroscience research and for clinical applications, both diagnostic and therapeutic (Camprodon, 2014). Repetitive TMS (rTMS) has been suggested to induce changes in neural activity at the systems level, which may contribute to its therapeutic effects. In the motor cortex, high frequency rTMS (hf-rTMS) has been shown to increase cortical excitability, while low frequency rTMS (lf-rTMS) has been shown to decrease excitability (Maeda et al., 2000).

We will use a MagVenture MagPro X100 with MagOption stimulator and two dynamic cooled butterfly coils: one real and one sham (MagVenture, Denmark) navigated with an infrared TMS Neuronavigation Research Premium system (Localite, Germany) to administer the TMS.

We will start by measuring the patient´s motor threshold (MT), which is a measure of cortical excitability used to standardize the intensity of stimulation across subjects. To do this, the TMS coil is placed over the primary motor cortex (M1). Single pulses are applied with an interpulse interval (IPI) of at least 5 seconds, to prevent additive neuromodulatory effects. When pulses are applied at suprathreshold intensities, a volley of activity travels through the pyramidal motor pathways and leads to the contraction of the contralateral target muscle (generally the Abductor Pollicis Brevis, Fist Dorsal Interosseus or Tibialis Anterior). The intensity of stimulation is sequentially reduced until we reach a point when fewer than 50% of the pulses (usually <3 out of 6) lead to a muscle contraction (identified by visual inspection or neurophysiological motor evoked potentials). The first TMS intensity that is unable to elicit a muscle contraction more than 3 out of 6 pulses is considered the motor threshold, and usually expressed as a percentage of the maximum stimulator output.

Once the MT is determined, we will apply TBS to our main target: the ***cerebellar vermis***. In specific, we will target the posterior vermis (comprised of lobules VI-X), which is believed to subserve cognitive and affective functions (vs. the anterior vermis, comprised of lobules I-V, which is associated with somatomotor functions). From a practical standpoint, the posterior vermis (especially lobules VII-VIII) is also closer to the skull surface and thus will receive more direct TMS modulation (**Figure 4**). Using the Localite TMS neuronavigation system we will co-register the participant´s head to his or her MRI, and place the TMS coil over the scalp position that allows direct stimulation of the vermal lobules VII-VIII in the mid-sagittal plane.

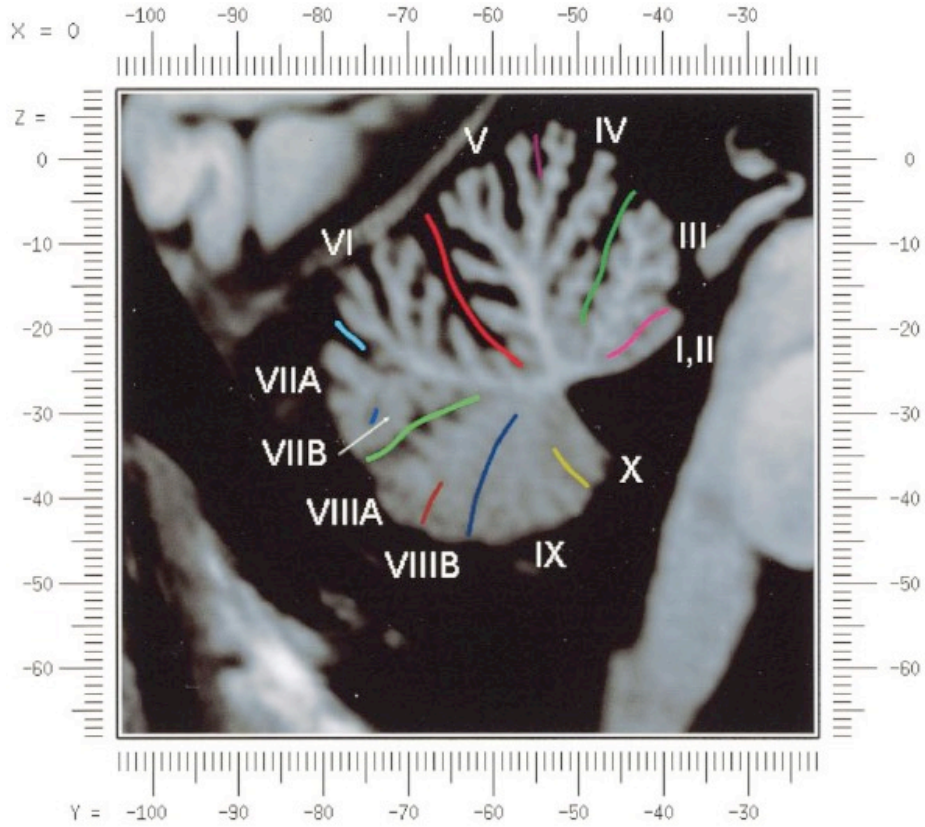


**Figure 4. Mid-sagittal view of the cerebellum.** We will apply theta-burst stimulation (TBS) to the posterior cerebellar vermis, directing the coil to lobules VII and VIII, which are closest to the skull surface. Figure from [113], pp. 241, figure 4.

At this point, the experimental session can begin. In a random order, patients will receive either cTBS (inhibitory), iTBS (excitatory) or sham TBS in each of the 3 sessions. Subjects will be blinded as to which mode of TMS they receive at each study visit. Sham TMS will use the exact same procedure with a sham coil, which is designed to induce the same nonspecific sensory effects of TMS (auditory and somatosensory activation) without inducing the neuromodulatory magnetic fields. At the end of each study visit, subjects will be asked to speculate on which mode of TMS (inhibitory, excitatory, or sham) they received as well as the degree of certainty of their judgment so that we can assess the potential contributions of subjects' expectations on their task performance.

**Visual Analogue Scales (VAS)**

A visual analogue scale (VAS) is a psychometric response scale, which easily and rapidly allows subjects to self-evaluate the intensity of subjective measures, such as mood and psychotic symptoms. Participants will complete visual analogue scales to indicate their current levels of

depression, anxiety, euphoria, auditory hallucinations, visual hallucinations, paranoia, referential thinking, and delusions of control before and after TMS using RedCap.

**Behavioral Tasks**

1. ***N-back task***: The n-back task engages working memory, a cognitive construct that falls under executive function. Deficits in working memory are observed across psychiatric diagnoses. In the n-back task, subjects are presented with a series of stimuli, such as words or numbers. The subjects are prompted to indicate whether the currently presented stimuli are the same as the stimuli presented n-stimuli previously. For instance, a 2-back task would ask the subjects to indicate whether the current stimuli was identical to that presented two previously. Outcome measures of interest include reaction time and accuracy.

2. ***Interval discrimination task (Papageorgioiu et al., 2013)*:** This experimental procedure requires subjects to perform time interval comparisons. In each trial, two tones separated by 1200 ms (the standard interval) are first presented, followed by a 1 s delay, and then a comparison pair of tones. For some trials, the time interval of the second pair is equal to the time interval of the first pair (E-condition). In another set of trials, the time interval of the second pair is longer than the standard interval (L-condition), while in the remaining trials, the time interval of the second pair is shorter than that of the first pair (S-condition). The order of the conditions in the trials will be ad hoc randomized and afterwards kept constant for all subjects. After each trial, subjects will be asked to identify whether the time interval of the subject was equal, longer, or shorter than that of the first pair of sounds. Each subject's performace will be evaluated through the overall percentage of correct responses (O), as well as the percentage of correct responses in the L, S, and E conditions.

3. ***Flanker task (Holmes at al., 2008):*** The flanker task is a measure of attention and inhibitory control. In the task, subjects must attend and respond to a certain stimulus that is surrounded ("flanked") by distracting stimuli. The stimuli are most commonly arrows. The flanking arrows can either have the same or opposing orientation as the central stimulus. Outcome measures of interest include accuracy and reaction time**.**

4. **Multi-Source Interference Task (MSIT):** the MSIT is a behavioral task that combines multiple dimensions of cognitive interference and decision-making, and other factors such as target detection, novelty detection, error detection, response selection, stimulus/response competition, and task difficulty. For the MSIT, subjects are given a button-press and instructed that the keypad buttons represent one, two, and three from left to right. They are told to use the index, middle, and ring fingers of the right hand to respond. They are instructed that sets of three numbers (1 and/or 2 and/or 3) and/or letters (x) would appear in the center of the screen every 1.75 s, and that one number would always be different from the other two (matching distractor) numbers or letters. Subjects are asked to report, via button-press, the identity of the number that was different from the other two items. Subjects are informed that each session will begin and end with fixation of a white dot for 30s, and that between these times there will be two trial types that would appear in alternating 42 s long blocks. In trials with numbers and letters (control trials), the target number will always match its position on the button-press (e.g. the number "1" will appear in the first [leftmost] position). In contrast, during the trials involving all numbers (interference trials), the target will never match its position. It will be emphasized that they are to "report what the target number is regardless of its position." Further, subjects are informed that in the numbers and letters (control) condition, the target number will always be large, while the numbers only (interference) condition the target number will sometimes be large and sometimes be small (in

actuality, unbeknownst to subjects, the number of large target trials and small target interference trials will be equal). For all trials, subjects are instructed to answer as quickly as possible but to make sure that they give the right answer.

5. ***Repetitive finger tapping task (Carroll et al., 2009):*** The repetitive finger tapping-task consists of two conditions: (1) tone-paced tapping, and (2) self-paced tapping. In both conditions, a press of the response button is used to calculate the inter-tap interval. Each trial begins with an auditory tone placed at 500 ms inter-tone intervals. In the tone-paced tapping condition, participants are instructed to tap the response button at the same rate as tone. After 12 taps, the tone is discontinued and participants are required to continue tapping at the same rate as the previously presented signal (self-paced tapping). Trials are terminated following 30 self-paced button presses. Error taps are defined as inter-tap intervals 250 ms above or below the 500 ms pacing interval during either the tone or self-paced portion of the trial. A total of 6 error-free trials, or a maximum of 12 trials, signal the completion of the task.

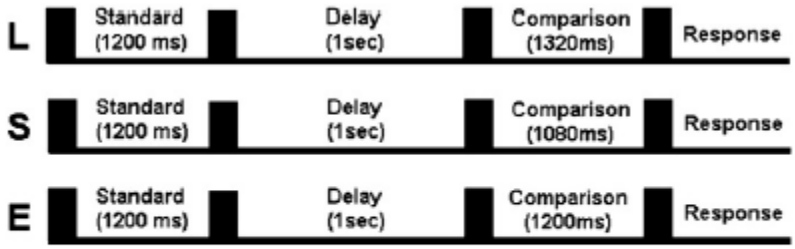


**Fig. 2.** Diagram of interval discrimination task. The black bars represent the 50 ms standard tones that establish the intervals of the standard and the comparison time intervals.

**Compensation**

Subjects will be compensated by check for up to $200 for completion of a protocol (Protocol A or B). The breakdown of compensation is as follows:

| | |
|---|---|
| • 1st Visit (Clinical evaluation, TMS, and pre- and post-TMS assessments) | $ 75 |
| • 2nd Visit (TMS and pre- and post-TMS assessments) | $ 50 |
| • 3rd Visit (TMS and pre- and post-TMS assessments) | $ 50 |
| • Protocol completion bonus | $ 25 |
| TOTAL | $ 200 |

Because data from all three visits (sham, excitatory, and inhibitory TMS) are necessary to interpret the results with causal explanatory power, participants will be paid a completion bonus for completing all three visits.

If the subject does not complete the entire study he/she will be compensated for the procedures listed above that were completed. Subjects are informed that it may take up to 4-6 weeks for them to receive their payment.

Should they choose to do so, subjects may participate in both Protocol A and Protocol B. Subjects will be additionally compensated by check for up to $200 for completion of the second protocol (e.g., Protocol B after completing Protocol A). The breakdown of compensation for Protocol B is as follows:

| | |
|---|---|
| • 4th Visit (Clinical evaluation, TMS and pre- and post-TMS assessments) | $ 75 |
| • 5th Visit (TMS and pre- and post-TMS assessments) | $ 50 |

- 6th Visit (TMS and pre- and post-TMS assessments) $ 50
- Protocol completion bonus $ 25

TOTAL $ 200

## VI. BIOSTATISTICAL ANALYSIS:

### A. Data variables being collected for the study (Data collection sheet)

We will collect the following data variables for this study:

**Demographic information:**

- Age
- Gender
- Race
- Ethnicity
- Handedness
- Education level
- Parental education level
- Clinical diagnosis
- Age at onset of illness
- Medications
- Past medical history
- Smoking habits
- Substance use/abuse history
- For female participants: first day of last menstrual period
- Results from urine screening for pregnancy and drug use

**Scores from clinical scales:**

- SCID (both patients and healthy controls)
- NAART (both patients and healthy controls)
- PANSS (patients only)
- YMRS (patients only)
- MADRS (patients only)
- PSYRATS (patients only)
- BRIEF-A (both patients and healthy controls)
- BIS-11 (both patients and healthy controls)
- Fagerstrom Test for Nicotine Dependence

**Scores from subject-completed surveys and tasks:**

- Visual Analogue Scales scores on mood and psychosis symptoms
- Interval discrimination task accuracy (Protocol A)
- N-back working memory task accuracy and reaction time (Protocol A)
- Flanker (Protocol A)
- Repetitive finger-tapping task accuracy (Protocol B)
- MSIT accuracy and reaction time (Protocol B)

### B. Study endpoints

As this study is not a clinical trial, there is no particular outcome measure that will be indicative of a study endpoint. We will end the study when we meet our recruitment goals. In the event that we encounter any major adverse events, we will consult with the IRB to discuss whether the study needs to be terminated.

**C. Statistical analysis**

We will test for group differences in demographic and clinical variables using SPSS, using $\chi^2$ and t-tests for ANOVA as appropriate. We will first measure the change (Δ) in each of the pre- and post-TMS assessments at each study visit: i.e. accuracy in time interval discrimination task, accuracy and reaction time (RT) in N-back working memory task, executive function in Flanker task accuracy and RT in repetitive finger tapping task, and accuracy and RT in MSIT. We will then run two-way ANOVA for each outcome measure, with diagnosis (patients vs. healthy controls) and the TMS type (excitatory, inhibitory, or sham) as independent variables. These models will include as covariates sex, age, handedness, medication load, and symptom severities (derived from the clinical scales scores: NAART, PANSS, YMRS, MADRS, PSYRATS, BRIEF-A, BIS-11, and the Fagerstrom Test).

**D. Power analysis (e.g. sample size, evaluable subjects)**

This is a pilot study. This being the first study of its kind, it is difficult to do a formal power and sample size analysis because we do not have a measure of effect size, but given previous similar studies and our usual rate of loss to follow up, we estimate we will need 50 participants per group for each protocol. Of primary interest to the study is the change (Δ) in outcome measures within the psychosis group. With 50 subjects in the psychosis group, we will have 80% power to detect an effect size of 0.35, which is a moderate effect.

## VII. RISKS AND DISCOMFORTS:

**Common risks of TMS procedure**

Subject may feel twitching of the scalp muscles during stimulation and/or local discomfort (tapping sensation) under the coil. It is possible that the subject may feel a headache after the TMS measurement that is generally caused by keeping the head in the same position for a lengthy period of time and/or by stimulation of the scalp muscles and nerves by the TMS pulses. TMS may also induce nausea in some patients[114]. The headache or nausea, if present, is typically mild, disappears soon and can be treated by mild over-the-counter analgesics.

Although there are no reports suggesting increased risk for TMS during pregnancy, pregnant women are excluded from this study due to insufficient knowledge of the effects of the strong magnetic fields on the fetus.

Subjects are thoroughly screened by a research assistant prior to their enrollment in the study to ensure subject safety. Subjects are carefully assessed before, during, and after TMS administration by study staff to ensure that they suffer no adverse reactions.

**Uncommon risks of TMS procedure**

Repetitive TMS at high frequencies has the rare potential to induce a seizure even in healthy individuals (~ 8 reported cases worldwide since the invention of TMS in 1985, 1 with cTBS), but the risk for seizure can be effectively managed by using appropriate subject selection criteria and by keeping the TMS parameters within the safety parameters of the international safety consensus (Rossi et al., 2009).

Compared with traditional low or high frequency TMS protocols, theta burst stimulation (TBS) uses less pulses (600 vs. 1200-1800), lower intensity (80% of AMT vs. 120% RMT) and shorter duration (40-190 seconds vs. 20-30 minutes). With such low intensity, subjects receiving TBS seldom complain of any unpleasant sensation that is seen in the other rTMS stimulation protocols, and TBS has been considered safer than other TMS protocols. Nevertheless, one should consider that theta burst stimulation uses higher frequencies, even if in a patterned manner. One single case has been reported of a seizure using TBS, but with a stimulation intensity of 100% of the RMT (higher than the currently used 80% of the AMT). Oberman and colleagues published a recent review and meta analysis of the safety of TBS, and concluded that the "general risk of adverse events during TBS is comparable to or less than other high frequency rTMS protocol (Oberman et

al., 2011).

The TMS parameters used in this study will not result in long-term changes. Continuous TBS at an intensity of 80% AMT over the primary motor area produces significant inhibition of Motor Evoked Potential size lasting for 20 or 60 minutes depending on whether the stimulation is given for 20 seconds (300 pulses) or 40 seconds (600 pulses) (Huang et al., 2009).

To protect the subjects from the risk of a seizure, this study strictly adheres to the international safety consensus by using only TMS parameters that have never induced seizures in healthy subjects and by excluding subjects at increased risk for seizures (Rossi et al., 2009). In the unlikely event that a seizure occurred, the seizure would stop as soon as the TMS was stopped, and the MGH TMS clinical service safety plan would be activated, including transfer of the subject with an ambulance to MGH ER for a medical check-up. No one has ever developed epilepsy as a consequence of TMS. There are no known or foreseeable long-term risks associated with TMS.

Subjects are thoroughly screened by a research assistant prior to their enrollment in the study to ensure subject safety. Subjects are carefully assessed before, during, and after TMS administration by study staff to ensure that they suffer no adverse reactions.

**Psychosocial risks**

Answering questions about psychiatric history and symptoms during the psychiatric evaluation may cause anxiety or discomfort. However, patients will not be forced to answer any questions, will be given multiple opportunities to take breaks, and may completely withdraw from the study without any negative consequences. The risk of breach of confidentiality is present by extremely slight, given the precautions we take in de-identifying and protecting our data. The subject may feel mildly bored or frustrated while participating in the behavioral tasks, but he or she is free to stop at any time.

Though we anticipate no increase in risk of suicide or self-harm as a result of study procedures or participation, we are (a) studying psychiatric patients and (b) our study procedures involve asking participants about mood and psychosis symptoms at each of the study visits. Therefore, it is possible that in the course of study participation, participants may have and/or express suicidal ideation or intent. If a research staff has any concerns about participant suicidality during a study visit, the research team will follow the plan outlined below:

1. Study staff will page study PI (Dr. Ann Shinn), site-PI (Dr. Joan Camprodon), or covering clinician (to be designated if both Dr. Shinn or Dr. Camprodon cannot be available for a particular study visit). Study staff will discuss with the responsible PI/clinician the clinical details relating to the participant's safety/suicidality. The responsible PI/clinician will recommend a plan as is appropriate to the clinical situation.
2. If the responsible PI/clinician determines that the patient or clinical situation warrants further (i.e., a higher level of) evaluation, he/she will physically go to the location where study procedures are being conducted, evaluate the research participant in person, and act as the clinical situation warrants. If the responsible PI/clinician determines that the participant is at imminent risk of harm, the safety plan may include urgent transfer of the participant to the MGH Emergency Room via ambulance, contacting the participant's clinician, and/or other similar procedures."

We will follow a similar plan in the event that a research participant experiences any other psychiatric symptoms that are acutely or imminently concerning (not just suicidal thoughts or thoughts of self-harm), including but not limited to confusion, agitation, severe anxiety/panic, and paranoia or other psychotic symptoms.

**Informed Consent**

Participants must be capable of understanding the nature of this study, its potential risks, discomforts, and benefits. Since all participants will be 18 or older, they will provide consent

without parental or other guidance. The candidate will obtain informed consent after the study purpose and procedures have been fully and clearly explained, and the potential participant has demonstrated an understanding of the protocol, willingness to participate, and capacity to consent.

As a means of assessing participants' understanding of what the study entails, the candidate will conduct a one-on-one informed consent survey, which asks questions such as "What illness is being studied in this project?" "Are there any risks to participating in this study?" and "Will you lose any of your benefits if you refuse to participate in this study?" If the participant is unable to answer the questions or demonstrates a lack of understanding, the investigator will review the details of the study again. The survey therefore serves to ensure that participants are actively engaged in the informed consent process. For each participant, we will re-administer the informed consent survey at the beginning of each visit, in order to ensure that the participant is capable of consent throughout the entire study. Participants who are unable to answer all 9 questions on the survey correctly even after additional information is provided will be excluded from the study. This process is designed to enroll only participants who have the capacity to make informed decisions about participation in this research and to prevent undue influence on the subject to enroll in the study by their physician. Participants will be given a copy of the consent form, signed by them and the investigator.

**Confidentiality**

We will collect sensitive clinical and personal information from subjects, as well as measures related to brain function and structure. These data have personal meaning, and loss of privacy around them would result in substantial harm to all subjects, especially patients with psychotic disorders.

Thus, we will ensure that the data collected in this study remains protected and confidential. All information obtained in this study will be kept in a research office under lock and key at McLean Hospital. Research participants will be identified by code numbers only, and no description of individual patients will be included in any publication. All databases related to the study will be stored on a desktop computer belonging to the candidate in the research office. Only the PI and her designated assistant will have access to this information. If data are shared for purposes of analysis, they will be transmitted only in pooled form and subjects will be identified by code. If imaging data are shared, they will first be "scrubbed," or removed, of any personally identifying header information and transferred via the Partners Research Computing Secure File Transfer and Collaboration system (http://rc.partners.org/sFTP), which is secured via 256-bit SSL encryption, scans all files with anti-virus software, and is HIPAA compliant.

Subjects will be informed that all the information obtained in this study will be used for research investigational purposes only. The names of subjects will never be publicly disclosed at any time. Subjects will not be identifiable in any publication that may arise from this research. Subjects will receive a copy of the consent document to keep. Subjects will be informed that this research will be conducted and administered in compliance with all state and federal laws.

Subjects will be informed of their confidentiality rights in the informed consent form. To ensure that subjects' rights and safety are protected during the conduct of this research study, subjects consent to the inspection of medical records by specifically authorized monitors. Such monitoring may be performed by the Partners IRB, or by the FDA or other involved federal agency.

Any email communication with subjects will be done using encryption, i.e. using the "Send Secure" function in the Partners Healthcare email system. We will also discourage subjects from communicating about medical issues via non-secure email.

## VIII. POTENTIAL BENEFITS:

**Potential benefits to participating individuals and society**

Subjects are informed that there is no direct benefit to them from participating in this study. As mentioned in the section on Background and Significance, the potential benefits to society are increased understanding of mood and psychotic disorders, and the role that the cerebellum plays in them, specifically in the abnormalities of time perception, cognition, and mood and psychotic symptoms. The current research, which uses TMS as a tool to investigate with causal explanatory power the role of the cerebellum in psychotic disorders, may provide the basis for the development of TMS as a potential treatment tool in such disorders in the future.

## IX. MONITORING AND QUALITY ASSURANCE:

**Human Subjects Protections:**
See Section VI (Risks and Discomforts) for measures to protect research subjects from the risks associated with the informed consent process, confidentiality, psychiatric evaluations, and TMS procedures.

**Independent monitoring of source data**

Ann Shinn, the Principal Investigator (PI), will be responsible for monitoring the validity and integrity of the data, as well as adherence to the protocol. She will be present for the informed consent procedures, assessments, and TMS administration for the first several subjects and closely supervise the training of all study staff involved in carrying out this research. In addition, co-investigator Joan Camprodon, who is a physician, will be on-site at the MGH Laboratory for Neuropsychiatry and Neuromodulation in the Charlestown Navy Yard Campus, to monitor the correct and safe administration of TMS for each subject.

Standard operating procedures (SOP) will be written, routinely followed, and updated as necessary to ensure adherence to the IRB-approved protocol. Any time there is a change in study staff, the PI will again provide direct hands-on training in order to ensure that all procedures are conducted in adherence with the IRB-approved protocol and that the data collected are of high quality, validity, and integrity. Moreover, the PI will meet at least once a week with the study staff to review any issues and data quality. Finally, the PI will be responsible for subsequently signing all consent forms, thereby allowing her to monitor the informed consent process on a consistent basis. The research coordinator and PI will report any minor deviations from the protocol at each yearly continuing review. Major deviations will be reported within 5 working days of the incident's occurrence or detection.

**Safety monitoring (e.g. Data Safety Monitoring Board, etc.)**

The current research uses standard nonsignificant risk applications of TMS in the context of a physiological/cognitive study, not a therapeutic clinical trial; thus reporting of adverse events to the FDA is not applicable. Given the relatively low risk posed by the study we do not feel that monitoring by a DSMB is necessary.

**Outcomes monitoring**

All subjects' clinical data will be coded with research numbers that do not contain any identifying information. The code linking the research number to personal identifying information will be stored in a password-protected encrypted computer file on a locked computer in a locked office at McLean. Subject interview information is stored in locked file cabinets in locked rooms at McLean.

**Medical Follow-up and Referrals**

Participants who test positive on the urine pregnancy test conducted as a part of this research study will be informed of the positive test result and recommended to follow-up with their primary care

doctor or other physician. Participants who wish to speak with a medical doctor about the test results will be offered the opportunity to consult with the study PI.

**Reporting of Adverse Events**

As soon as the PI or a member of research staff learns of an adverse event, he/she will first consider the immediate safety of the patient. If the patient is not safe, either to him/herself or others, the member of the research staff/PI will take appropriate steps to acutely stabilize the patient. Members of the research staff will defer to the PI's judgment. If there is an adverse event without an imminent safety concern, then the person who learned of the adverse event will call the PI and/or other members of the research staff and decide the best course of action to deal with the event, guided by the principles of Human Subjects research. They will then submit an adverse event report to the IRB and regulatory officials using the Research Subject Report of Adverse Event form, according to the PHRC reporting guidelines, within 5 working days or 7 calendar days of the date they become aware of the problem.

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