HRP-503B – BIOMEDICAL RESEARCH PROTOCOL (2017-1)

Protocol Title: Neurocomputational Models of Auditory Hallucinations

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** *State the scientific aim(s) of the study, or the hypotheses to be tested.*

Hallucinations are percepts without stimulus. 70% of patients with schizophrenia suffer distressing auditory hallucinations. Their mere presence increases the risk of suicide (1-3). Most reach remission with D_2 dopamine receptor blocking drugs after 1 year of adherence. However, 30% of patients have intractable hallucinations, and 50% are non-adherent to their medications, commonly because of unfavorable side-effects – those intractable and non-adherent patients continue to suffer. There is a clear need for a mechanistic understanding of hallucinations as a prelude to rational treatment design. This proposal outlines the initial steps towards the development of an interventional biomarker for clinical hallucinations, grounded in computational neuroscience.

Computational psychiatry involves harnessing the power of computational neuroscience to address the clinical needs of those suffering from serious mental illnesses. There has been much discussion of the promise of the approach. There have been few studies thus far and they have largely involved correlative methods like functional neuroimaging. We propose to address this shortcoming by causally manipulating the neural loci of computational model parameters in-person in patients with psychosis using transcranial magnetic stimulation (TMS), tracking the impact of this manipulation on behavioral performance and model parameters. With such a causal intervention, the veracity of the model's explanation of hallucinations will be either validated or disconfirmed. If validated, the model can be further developed as a biomarker for predicting the hallucination onset, guiding, developing or tracking the effects of treatments for hallucinations. If disconfirmed, the model ought to be discarded and other alternatives should be pursued.

Rather than relying wholly upon sensory inputs, perception blends inputs with prior beliefs(4, 5). Our preliminary data show hallucinations involve an over-weighting of priors – relying too much on previous experiences rather than current sensory inputs, which we measure using a ***Conditioned Hallucinations*** task. Participants experience repeated pairings of visual and auditory stimuli and subsequently perceive the auditory stimulus when none is presented (*a conditioned hallucination*). We administered the task to participants with psychosis both with (P+H+) and without (P+H-) hallucinations, otherwise healthy voice-hearers (P-H+), and healthy controls (P-H-). Conditioned hallucinations were significantly more frequent in those who hallucinate (P+H+, P-H+). We employed a computational approach that yields quantitative estimates of participant-specific reliance on priors: The Hierarchical Gaussian Filter (HGF). Prior weighting – leaning more heavily on experiences earlier in the task - was increased in people with clinical and non-clinical *hallucinations* (P+H+ and P-H+; *'prior over-weighting'*) corresponding to **insula** responses measured with functional neuroimaging during conditioned hallucination events. In contrast, people with *psychosis* (P+H+ and P+H-, with and without hallucinations) exhibited deficits in updating their beliefs about audio-visual associations *('decreased updating 'being able to change decisions in light*

of the changing association between the light and the tone), associated with a dearth of activity in the **cerebellum**. In sum, there are two correlates of conditioned hallucinations in clinical voice hearers (P+H+): (1) **insula** mediated *prior over-weighting*, and (2) *Decreased updating* via a dearth of **cerebellar** engagement. We will test the importance of each correlate to the genesis of conditioned hallucinations with a specific aim:

Aim 1: To interrogate prior-overweighting with sham-controlled inhibitory TMS to the insula. We will recruit 30 clinical voice hearers (P+H+). They will complete two parallel forms of the conditioned hallucinations task (with different visual and auditory stimuli) on two occasions, separated by a week. TMS and sham will be delivered in a randomized counterbalanced order. **Hypothesis***: Inhibiting* the **insula** will decrease *prior over-weighting.* If this computational perturbation is responsible for conditioned hallucinations, then ameliorating it with TMS that decreases **insula** engagement will decrease conditioned hallucination responses. Furthermore, the prior weighting parameter will be reduced following active TMS compared with sham.

Aim 2: To interrogate poor belief-updating with sham-controlled excitatory TMS to the cerebellum. We will recruit a further 70 clinical voice hearers. Again, they will complete parallel forms of the conditioned hallucinations task on two occasions, separated by a week. They will receive excitatory TMS over the cerebellum (and sham on the other occasion, in a randomized counterbalanced order). **Hypotheses:** *Exciting* the **cerebellum** will increase *belief-updating*. If poor *belief-updating* contributes to conditioned hallucinations, increasing **cerebellum** engagement should decrease conditioned hallucinations and alter the *belief-updating* model parameter compared with sham TMS.

We propose hypothetico-deductive tests of the computationally derived predictions from our preliminary work. Disconfirming the model would militate against its further development. Validating the model will provide grounds for developing novel interventions that address *prior-overweighting* and/or *belief-updating* in those who suffer from intractable hallucinations and who are at risk of poor outcomes including suicide.

2. Probable Duration of Project: *State the expected duration of the project, including all follow-up and data analysis activities.*

   2 years for data acquisition and analysis (year1: aim 1, year 2: aim 2),
   1 year for publication and application for R01 level funding
   We anticipate completing data collection by July 2022

3. Background: *Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.*

Auditory verbal hallucinations (AVH) are among the most distressing and disabling aspects of psychotic illness. They increase the risk of suicide(1-3), and are only 70% likely to respond to antipsychotics. A deeper understanding of the mechanisms underlying hallucinations and how they might relate to psychotic illness is required for the identification of psychosis-specific biomarkers and AVH-specific treatments. Computational modeling of perceptual processes offers one approach to identifying aspects of information processing that might be specific to hallucinations and others that might be specific to psychosis. Our recent work has provided such a computational understanding (6). ***Here we propose to directly test this understanding (6, 7) using a causal intervention; the modulation of neural activity and thereby mental function using transcranial magnetic stimulation (TMS).***

Perception is not simply the passive reception of inputs (8). We actively infer the causes of our sensations (9). These inferences are influenced by our prior experiences (10). Priors and inputs are combined according to Bayes' rule (11). Prediction errors, the mismatch between priors and inputs, contribute to belief updating (12).

Hallucinations (percepts without external stimulus) may arise when strong priors cause a percept in the absence of input (13). We recently tested this theory by engendering new priors about auditory stimuli in human observers using Pavlovian conditioning. Even in healthy individuals, the repeated co-occurrence of visual and auditory stimuli can induce auditory hallucinations (14). We examined this effect with functional imaging. We used computational modeling to infer the strength of participants' perceptual beliefs;

We propose two specific aims, each addressing a particular aspect of our previous work on strong priors, using a sham-controlled TMS intervention prior to behavioral testing with our conditioned hallucinations task. Aim 1 will address the role of the insula in conditioned hallucinations. Our preliminary work suggests that the insula is hyper-engaged during conditioned hallucinations and as such, we propose to use 1 Hz inhibitory TMS to decrease insula engagement and curtail the belief that tones are predicted by visual stimuli in the task. Aim 2 will address the role of the cerebellum in psychosis. Our preliminary work suggests that the cerebellum is hypo-engaged during conditioned hallucinations in patients with psychosis. We propose to use theta-burst TMS over cerebellum to increase its activity and encourage belief updating.

The dependent variables will be conditioned hallucinations as well as computational model parameters [which capture participants' task beliefs and their tendency to weight their priors over oncoming sensory evidence (**Fig. 2)].**

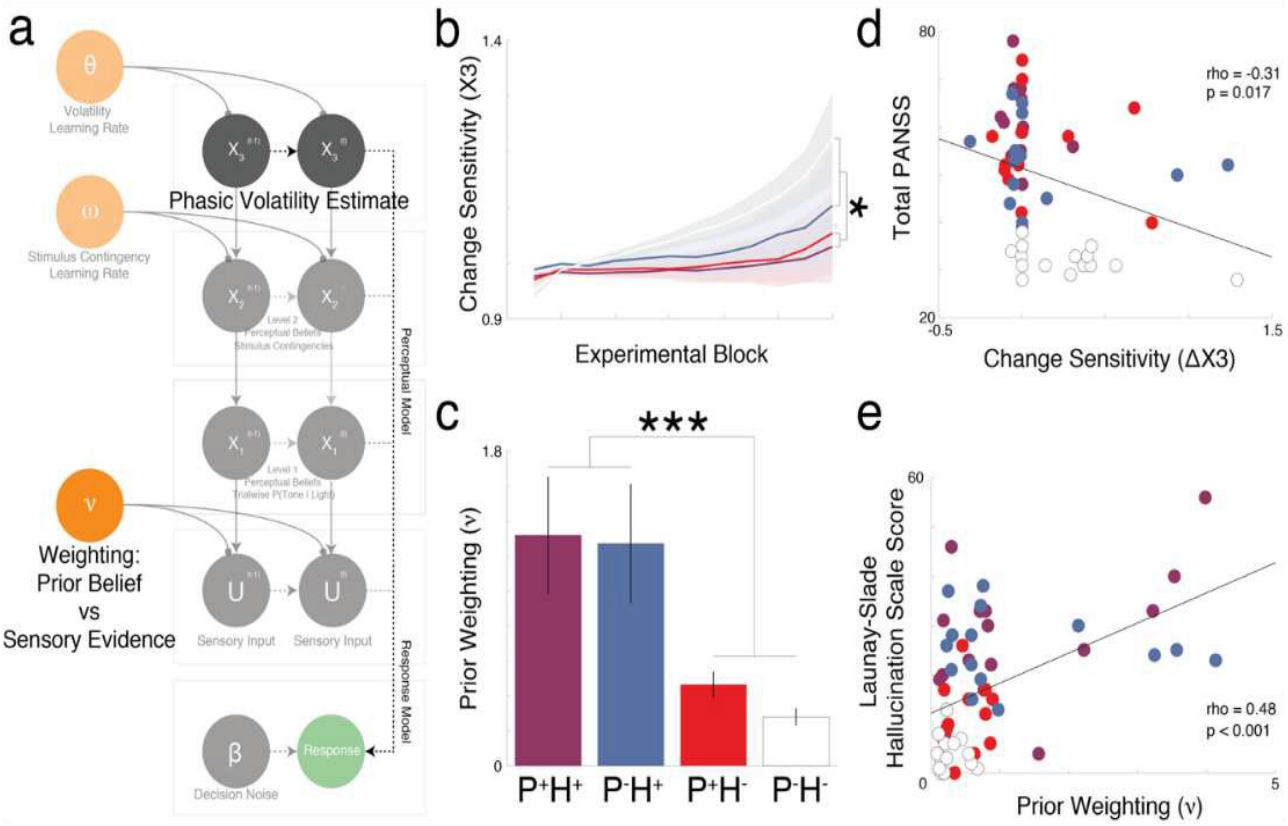

Figure 2. Hierarchical Gaussian Filter Analysis. a. A perceptual model is constructed, consisting of a perceptual model in which sensory input and three levels of perceptual belief are combined and fed into a response model, which determines participant responses. Of interest for this proposal are parameter ν, signifying the relative weights with which perceptual beliefs are combined with sensory input, and parameter X3, signifying how much the belief that the light predicts the tone changes over the course of the experiment. This model was fit to individual behavioral data from each participant, and when inverted was capable of re-creating individual behavioral performance (data not shown). **b.** The change in X3 ("change sensitivity") is significantly lower in those with psychosis compared to those without. **c.** By contrast, "Prior weighting," or the relative weighting of prior belief and sensory evidence, is significantly higher in those who have hallucinations compared to those without. **d-e.** Both of these measures correlate with symptom scores in the form of PANSS total score (**d**) and Launay-Slade Hallucination Scale-Revised Score (**e**). Error bars and shading represent 1 SEM. *, $p < 0.05$; ***, $p<0.001$.

Importantly, our model captured how priors are combined with sensory evidence, allowing us to directly test the strong prior hypothesis. First, we determined individual thresholds for detection and psychometric curves (16). Next, participants worked to detect a 1-kHz tone occurring concurrently with presentation of a checkerboard visual stimulus. At the start of conditioning, the tone was presented frequently at threshold (**Fig. 1a, left**), engendering a belief in audio-visual association. This belief was then tested (**Fig. 1a, right**) with increasingly frequent sub-threshold and target-absent trials. *Conditioned hallucinations* occurred when participants reported tones that were not presented, conditional upon the visual stimulus. We recruited four groups of participants (**Fig. 1b**): people with a diagnosed psychotic illness who heard voices (P+H+, n=15); those with similar who did not hear voices (P+H-, n=14); an active control group who heard daily voices, but did not have a diagnosed illness(17) (P-H+, n=15; they attributed their experiences metaphysically (18)); and finally, controls without diagnosis or voices (P-H-, n=15).

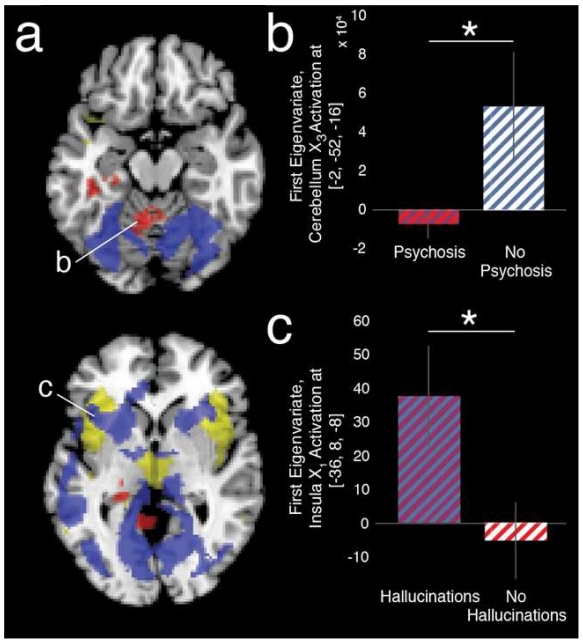

Figure 3. HGF imaging results. ***(a)*** *HGF trajectories for X_1 (blue) and X_3 (red) regressed onto BOLD time courses for the conditioned hallucinations task, superimposed on conditioned hallucinations network (yellow). Regions with activity covarying with X_3 included cerebellum and parahippocampal gyrus (top); activity in anterior insula and superior temporal sulcus (STS) tracked with X_1 perceptual belief trajectories (bottom).* ***(b and c)*** *Parameter estimates of X_1 (**b**) and X_3 (**c**) fits extracted from regions highlighted in* ***a.*** *Activity in cerebellum (**b**) differentiated those with psychosis from those without, whereas activity in insula (**c**) and STS (not shown) differentiated hallucinators from non-hallucinators.*

After learning the association between the visual and auditory stimuli, all groups reported hearing tones that had not been presented (***conditioned hallucinations***), although the H+ groups did so significantly more frequently (**Fig 1c**). Conditioned hallucinations activated a network of regions previously identified during symptom-capture based approaches to auditory hallucinations (e.g., bilateral anterior insula, association auditory cortex, inferior frontal gyrus, temporo-parietal junction, and thalamus) (19).

To understand these results in the context of our formal model of perception, we employed a three-tiered Hierarchical Gaussian Filter (HGF)(20, 21), which uses participant responses and the task structure to model estimate perceptual beliefs across three levels of abstraction (**Fig. 2a**). The first level of the model (X_1) represents whether the participant believes that a tone was present or not on each trial. The second level (X_2) is their belief that visual cues predict tones. The third level (X_3) is the change in belief about the contingency between visual and auditory stimuli (i.e., volatility of X_2).

HGF modeling of conditioned hallucinations in our four groups (P+H+, P-H+, P+H-, P-H-) resulted in two findings critical to the present proposal:

1) Those with **hallucinations** demonstrate higher degrees of perceptual belief on the first two layers (**X_1 and X_2**) and an over-reliance on prior beliefs (***'prior over-weighting'*** p<0.001. **Figure. 2c** (6));

2) Those with **psychosis**, regardless of whether they hallucinate or not, are **less likely to detect changes in the statistical structure of the task (X_3)** compared to non-psychotic participants (***'change insensitivity'***, p<0.05 **Fig. 2b**(6)). Furthermore, there was a significant negative correlation between change sensitivity and illness burden (**Figure. 2d** (6)) and a significant positive correlation between prior weighting and hallucination severity score (**Figure. 2e** (6)). Finally, we combined model parameters with the imaging data: the hierarchical levels of

representation were mediated by different brain circuits and those circuits dissociated voice hearers from those who did not hear voices (X_1/Insula), and patients with psychosis from people without psychosis (regardless of voice status, X_3/cerebellum; **Figure. 3**, this effect was also significant in the hippocampus). Patients were less able to update a belief about task volatility than high APS participants. This updating correlated with responses in the hippocampus and cerebellum (22, 23). *Our preliminary results bode well for the computational dissection of hallucination mediating neural circuits using TMS that we propose. Namely to decrease insula (**Aim 1**) and increase cerebellar activity (**Aim 2**) and track the effects on conditioned hallucinations and model parameters.*

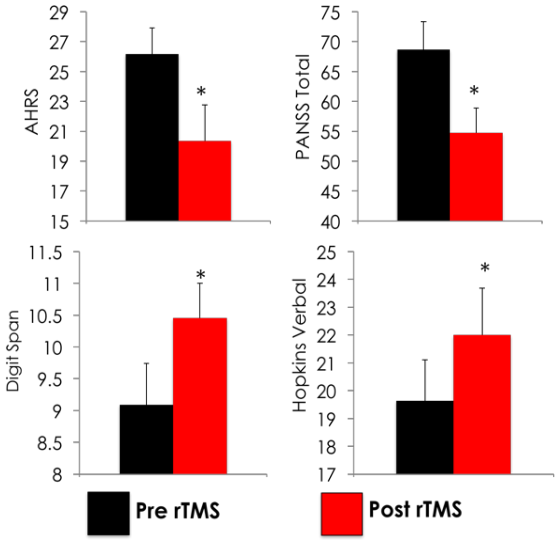

Figure 4. Symptom and cognitive effects of rTMS. 4 weeks of daily TMS significantly reduced hallucinations and symptoms more generally. Furthermore, TMS significantly improved cognition

Transcranial magnetic stimulation (TMS) is a focal, non-invasive form of brain stimulation that can depolarize or hyperpolarize superficial cortical neurons in the human brain(24). Hoffman and colleagues published the first double-blind crossover study showing that 1 Hz inhibitory stimulation of the left temporo-parietal junction (TPJ) reduced auditory verbal hallucinations (AVH, voice hearing) (25). We have delivered bilateral inhibitory 1Hz TMS over the superior temporal gyrus (960 pulses daily, 5 days a week for 4 weeks) to patients (n=15) with intractable AVH. TMS significantly improved hallucinations as well as verbal cognitive function (**Figure. 4**).

Furthermore, these improvements were associated with increases in functional connectivity between the STG and insula as well as global connectivity increases in the cerebellum. Taken together, our behavioral, imaging, computational, TMS and clinical data suggest that decreasing insula activity and increasing cerebellar activity may contribute to the therapeutic response to TMS.

*We propose to test whether these neural systems implement the specific computational model-derived behaviors highlighted by our recent work. We will decrease insula activity in patients with AVH and track the effects on conditioned hallucination behavior and model parameters (**Aim 1**). Furthermore, we will increase cerebellar responses in another independent sample of patients with AVH and track its effects on conditioned hallucination behavior and model parameters (**Aim 2**). In both cases, stimulation will be compared to a sham intervention.*

4. Research Plan:

Abbreviations –

Clinical Assessment Interview for Negative Symptoms (CAINS(26)); Complete blood count (CBC) Comprehensive Metabolic Panel (CMP); Electrocardiogram (EKG); Human chorionic gonadotropin (hCG) Launay–Slade Hallucination Scale (LSHS); Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS); Positive and Negative Syndrome Scale (PANSS); Peters Delusions Inventory (PDI); Structured Clinical Interview for DSM-5 (SCID-5); Urine Toxicology (Utox)

Measures		Pre-screen Phone Screen	Screen Visit 1	Active TMS Visit 2, 3, or 4	Sham TMS Visit 2, 3, or 4	Control TMS Visit 2, 3, or 4
Clinical Assessments	CAINS(26)		□			
	PANSS		□			
	SCID		□			
Physiology Analysis	CBC		□			
	CMP		□			
	EKG		□	□	□	□
	Hearing Assessment		□			
	Physical Examination		□			
	Utox		□			
	Urine HCG		□			
Self-report	Demographics		□			
	LSHS		□			
	Medical History		□			
	PDI		□			
	Phone Screening Questionnaire	□				
	TMS Safety Questionnaire		□	□	□	□
Neuro-	MATRICS Battery		□			

Overall Strategy: Voice hearing patient participants with a diagnosis of schizophrenia or schizoaffective disorder (confirmed by SCID-5 interview at screening) will undergo one screening interview/assessment (1 hour) and three TMS behavioral sessions during each of which participants will perform the Conditioned Hallucinations task (40 mins). On one they will receive active TMS (of insula, n=30, or cerebellum, n=70, see power calculations below). On the other two they will receive sham stimulations prior to task performance (stimulations will be delivered in a randomized counterbalanced order). Participants will be compensated $200 for participation ($50 per visit). All study visits will take place at the Connecticut Mental Health Center (CMHC).

Phone Screen - telephone screen that delivers study information and assesses broad eligibility via conversation (confirms that the person hears voices, that they are between 18 and 45, that they do not have a pacemaker or suffer from seizures)

Screening (at CMHC): Yale has specialty clinics for first episode and multi-episode patients that will serve as primary recruitment sources. Dr. Powers works closely with these clinics and will facilitate recruitment.

Participants will read the consent from and provide informed consent before any screening procedures commence.

Diagnosis will be established according to DSM-5 criteria using information from a SCID interview, review of medical records, and collateral informants**.** Participants will be between the ages of 18-45. Exclusion of older participants is based on concern for effects of aging on behavioral responses and TMS effects. Participants of both sexes and any race/ethnicity will be recruited to ensure the sample approximates the racial/ethnic base-rates in New Haven.

Self-report Measures:

- AVH – In order to recruit a sample enriched for AVH, all patient volunteers will need to report AVH at least once a day.

Clinical Assessment Measures:

- PANSS – We will use the Positive & Negative Syndrome Scale (PANSS) to confirm presence and severity of hallucinations (score of > 3 for inclusion).
- CAINS(26) – We will use the Clinical Assessment Interview for Negative Symptoms (CAINS (26)) to assess negative symptoms. The samples recruited for Aims 1 and 2 will be matched on these measures.
- LSHS – The LSHS will be administered, providing a brief measure of quasi-hallucinatory experience.
- PDI – The PDI will also be used to measure delusional ideation including measures of distress, preoccupations, and conviction associated with delusions.

A licensed clinician (Dr. Powers) will conduct or review the responses to the surveys and will be able to identify suicidality signs and take appropriate action as necessary.

As appropriate we will:

- Refer for immediate follow-up with a primary therapist (if engaged in treatment)
- Refer to a crisis line and provide the number (National Suicide Prevention Lifeline, 1-800-273-8255)
- Refer to a walk-in community mental health clinic accompanied by another adult
- Refer to an emergency room accompanied by another adult
- Refer to an emergency room and research staff contacts emergency services

Physiological Analysis:

- Blood Draw – We will have a CMHC phlebotomist perform a blood draw. We will draw no more than 30ml or about two tablespoons of blood. We will run routine lab work (CBC and CMP). Abnormal levels of sodium in the blood (hyponatremiais and hypernatremia) is related to increased seizure risk. Therefore, we will exclude individuals with sodium levels outside of normal parameters (135 – 145 milliequivalents per liter). Abnormal CBC can indicate overall health and identify underlying conditions, therefore, participants with abnormal CBC level will be excluded.
- Urine Screen – A urine hCG and utox test will be performed. We will also be excluding participants that have a positive pregnancy test (urine hCG) and/or positive utox results.
- EKG – A EKG will be performed in order to exclude individuals with abnormal results, potentially indicating cardiac conditions.

Standard Neuropsychological Measures:

- MATRICS Battery – We will administer the MATRICS Battery to assess level of neuropsychological functioning. The samples recruited for Aims 1 and 2 will be matched on these measures and individual scores will be used as covariates in our key within-participant comparisons of TMS versus sham.

Hearing Assessment:

- Hearing Test – During the screening assessment, all participants will also undergo a hearing testing. Participants meeting criteria for mild hearing loss or greater (> 25 dB loss in the frequencies tested) will be excluded.

General TMS Procedure (at CMHC):

- rMT – Before receiving magnetic stimulation, participants will undergo a test to decide the strength of the stimulation. This will be done by using the electromagnet to stimulate a part of the brain that controls finger movement while monitoring muscle contractions with recording electrodes (similar to the ones used for the EKG) placed on your right thumb and, index finger. The amount of magnetic stimulation needed to produce slight muscle contractions will guide us in determining the level of magnetic stimulation to the part of the brain that may produce voices.A Magstim Rapid^2 system (Magstim Ltd, Whitland, Wales) will be used to assess resting motor threshold (rMT) and to administer TMS. For rMT, single pulses will be administered with an intensity and location so their finger twitches (abductor pollicis brevis contracts) 50% of the time (27).
- EKG – An EKG will be performed before and after TMS to indicate if the cerebellum was stimulated.

Sham Stimulation (sham TMS): This procedure involves a TMS coil with a hidden aluminum plate inside which prevents the magnetic field from stimulating the participant's brain. An eSham system will mimic the scalp feel of TMS. This system has been previously employed successfully and safely (28). There is no compelling evidence to suggest that alternating current from a TENS units or similar device modulates cortical activity. Whilst TMS is safe and highly tolerable, all screening and TMS sessions will be supervised by Dr. Albert Powers, MD, PhD.

Behavioral Task: These experiments will require repeated performance of the Conditioned Hallucinations task and re-estimation of model parameters. The task is a simple video game wherein we first ascertain the participant's threshold for detection of a 1KHz tone in white noise (the tone loud enough that they detect it 50% of the time). We then infer their 75% and 25% detection thresholds from their behavioral choices. Next, we pair tones of those intensities with the presentation of a chequerboard stimulus, such that presentation of the tones Is conditional on the chequerboards. On each trial, the participants are asked to indicate whether they heard a tone and how confident they are in their choice. By arranging for the contingencies to change over time we can track how

participants learn (and un-learn) that visual stimuli predict tones. There is no deception here. However, having completed the three study visits, out of courtesy and interest we will debrief participants about the point of the experimental task and TMS manipulations. Sensory conditioning effects tend to be stable across time (29-31), lasting from months to years. Fortunately, multi-sensory learning rarely generalizes to novel stimulus pairs and tasks (32). Therefore, re-testing will make use of unique visual stimuli for each visit (matched for luminance, complexity, and contrast). Similarly, target auditory stimuli of different frequencies will be used. Preliminary data demonstrates the feasibility of this approach. **Figure 5** depicts data from one hallucinating participant, obtained 356 days following original data acquisition (blue) and five controls (white), obtained 28 days apart. Both the Conditioned Hallucinations effect and model parameters remain stable over time. Participants' thresholds for detection of a tone embedded in white noise will be determined using the maximum-likelihood-based QUEST(16) method. During conditioning, all target auditory stimuli will be accompanied by a visual checkerboard stimulus (colors: red, green randomized across participants and sessions) present for the duration of the auditory stimulus presentation. Over a series of four training blocks, participants will be presented first with stimuli presented at their individually-defined threshold for detection, and then increasingly with stimuli that are sub-threshold and absent. This is will foster learning of the association between visual cue and tone specific to the particular session.

Aim 1: To interrogate prior-overweighting with sham-controlled inhibitory TMS to the insula.
We will recruit 30 clinical voice hearers (P+H+). They will complete two parallel forms of the conditioned hallucinations task (with different visual and auditory stimuli) on two occasions, separated by a week approximately. On one occasion, participants will receive inhibitory TMS to the insula. The other, they will receive sham. All TMS will be delivered in a randomized counterbalanced order. **Hypothesis***: Inhibiting* the **insula** will decrease *prior over-weighting.* If this computational perturbation is responsible for conditioned hallucinations, then ameliorating it with TMS that <u>increases **insula**</u> engagement will <u>decrease</u> conditioned hallucination responses. Furthermore, in model-based analysis, the prior weighting parameter will be reduced following active insula TMS.

Procedure. The insula is a deep structure, compared to typical cortical targets for TMS (33). We have a double-cone coil that is optimized for targeting deeper structures (33). In prior work, inhibitory 1Hz TMS has been delivered to the insula using a double cone coil, with clinical efficacy for smoking cessation(34). We propose to use exactly this procedure; after defining RMT (see above), the coil is moved forward 6 cm anterior to the motor spot and aligned symmetrically (over the lateral prefrontal cortex) and trains of pulses will be delivered at 120% of the measured RMT We will deliver 600 continuous pulses at 1 Hz, which is designed to induce deactivation in the target region. The sham procedure (described above) will occur on a different day (separated by at least one week) but the number of pulses will be identical.

As an added control for non-specific effects, the pattern of stimulation to be applied in Aim 2 (excitatory 10Hz repetitive) will be applied to the insula (control TMS) on a third study visit.

The order of the three study visits will be randomized and counterbalanced across participants

Aim 2: To interrogate poor belief-updating with sham-controlled excitatory TMS to the cerebellum. We will recruit a further 70 clinical voice hearers (with a diagnosis of Schizophrenia or Schizoaffective disorder). Again, they will complete parallel forms of the conditioned hallucinations task on two occasions, separated by a week. They will receive excitatory TMS over the cerebellum (and sham on the other occasion, in a randomized counterbalanced order). **Hypotheses:** *Exciting* the **cerebellum** will increase *belief-updating*. If poor *belief-updating* contributes to conditioned hallucinations, <u>increasing **cerebellum**</u> engagement should <u>decrease</u> conditioned hallucinations and alter the *belief-updating* model parameter compared with sham TMS.

As an added control for non-specific effects, the pattern of stimulation to be applied in Aim 1 (inhibitory 1Hz rTMS) will be applied to the cerebellum (control TMS) on a third study visit.

The order of the three study visits will be randomized and counterbalanced across participants.

Procedure. The cerebellum is also a deep structure, compared to typical cortical targets for TMS, however, our double cone coil is able to penetrate it (35). The cerebellar vermis [-2, -52, -16] was correlated with belief updating and as such, we will target that region. Prior work has shown theta-burst stimulation of the vermis to be well tolerated in patients with schizophrenia. We will follow that published procedure(36). Using the BrainSight neuro-navigation system (Rogue Research, Quebec, Canada), loaded with an average T1 –weighted structural image from a human adult to permit targeting of the specific vermal co-ordinates. TBS will be applied at 100% of motor threshold with the standard iTBS burst pattern (3 pulses at 50-Hz repeated at a rate of 5-Hz; 20 trains of 10 bursts given with 8-s intervals; 600 pulses). Sham stimulation will be matched for number of pulses. Cerebellar TMS is a safe and tolerable procedure (37).

Analyses. Behavioral responses for each stimulation visit (active, sham, Aim 1, Aim 2) will be used to fit HGF model parameters, per the procedure that produced the data in **Figure 2**. Those parameters will be compared with paired samples t-tests comparing sham and active TMS (separately for each aim).

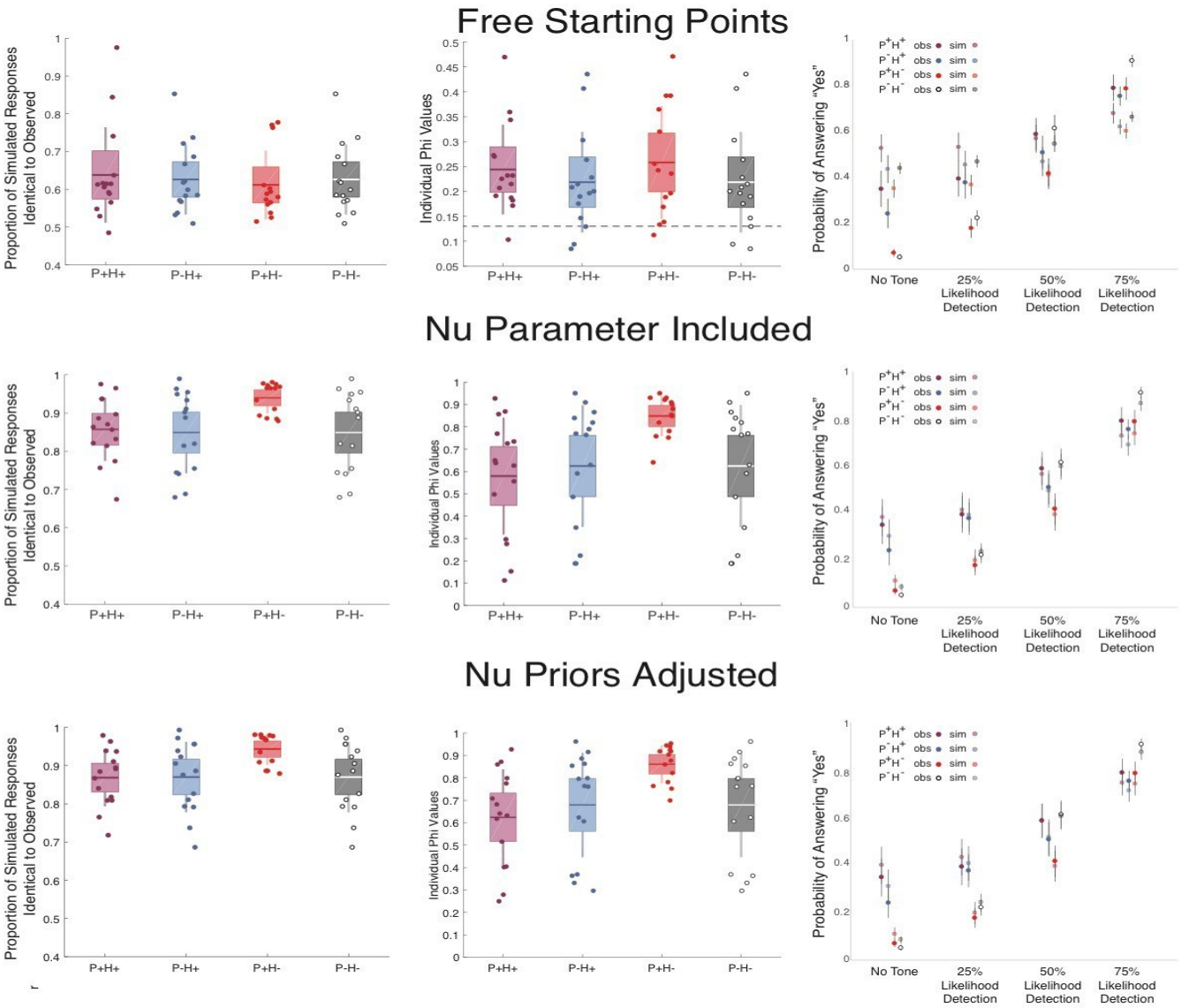

Figure 6. Behavioral simulation across three iterations of the HGF. 1) (top panel) standard HGF implementation; 2) (middle panel) adding Nu, which codes the weighting between sensory evidence and perceptual beliefs; 3) (bottom panel) allowing a more flexible influence of Nu on the overall model. Simulated responses were then compared with observed behavior, comparing the proportion of identical responses (left), individual phi coefficients (middle), and proportion of "yes" responses (right).

Power: Estimated effects for our proposed studies are based upon our own data in **Figure 2**. If TMS can curtail these group differences – i.e. decrease hallucinating patient responses to the level of non-hallucinating controls, then we would expect similar effect sizes in the present study. We will analyze the model parameter specific to each Aim using paired sample's t-tests, leveraging the added power of within-subject designs. For Aim 1, the effect of TMS on X_1 would be medium (Cohen's d = 0.6). We estimate we will need at least 24 participants to detect these differences with 80% power to detect a treatment difference at a two-sided 0.05 significance level(38). We budgeted for 30 unique participants to allow for participant drop-out. For Aim 2, the effect of TMS on X_3 would be small (Cohen's d = 0.36). We would need at least 63 participants to detect such a difference with a two-sided significance level of 0.05 and with 80% power(38).

We budgeted for 70 unique participants to allow for drop-out.

Potential Problems & Alternative Strategies:

Model propriety: We need to be certain that the model we are using is the best for our data, if we are to use it going forward. **Figure 6** shows the mean individual results of 10,000 simulations per participant for three models: 1) standard HGF implementation but including the ability for individual trajectories to vary freely in their starting points; 2) adding the parameter Nu, which allows for individual variability in the weighting between sensory evidence and perceptual beliefs; 3) adjusting the priors on Nu. Simulated responses were then compared to observed behavioral responses). The model we used and will continue to use in the proposed work was best. This was also supported by Bayesian Model Comparison (**Figure 7**).

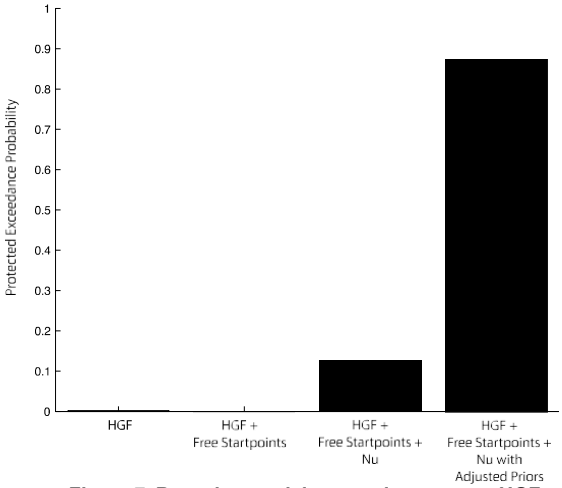

Figure 7. Bayesian model comparison across HGF iterations

TMS target engagement: In the absence of neuroimaging, it is difficult to confirm that we have engaged target regions. For each aim, we propose a brief test, post-TMS, as a positive control. The anterior insula regulates sympathetic and parasympathetic outflow and thus impacts heart rate variability (HRV)(39). For Aim 1, we propose to measure HRV before TMS administration and afterwards. Patients with psychosis who hallucinate have high HRV(40). If we engage the insula with TMS, HRV should decrease. For Aim 2, we are aiming to increase cerebellar function. Patients with psychosis tend also to have poor cerebellar motor control indexed by peg-board performance(41). Cerebellar TMS improves pegboard performance(42). We propose to measure motor ability before and after TMS administration to confirm that we have stimulated the cerebellum.

Repeated Measures: Although sensory conditioning experiments date back to the first half of the 20th century, there are few studies on these phenomena that include repeated measures. The ones that do suggest high test-retest reliability (43). The data in **Figure 5** suggest reliability of both the phenomenon and the computational model parameters we plan to test. Additionally, we will employ parallel stimulus sets.

Behavioral Variability: The model parameters of interest may be sensitive to inattention, level of arousal, and other task demands. The model assays this explicitly (ß, **Fig. 2a**).

Medication. While it might be ideal to recruit un-medicated patients, the representative positive symptom patient is medicated; therefore, studies of medicated patients are more generalizable. To address medication effects, we will convert current medications into equivalents and use these as covariates in our analyses.

5. Genetic Testing N/A ☒
   A. *Describe*
      i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
      ii. the plan for the collection of material or the conditions under which material will be received
      iii. the types of information about the donor/individual contributors that will be entered into a database
      iv. the methods to uphold confidentiality
   B. *What are the conditions or procedures for sharing of materials and/or distributing for future research projects?*

C. *Is widespread sharing of materials planned?*
D. *When and under what conditions will materials be stripped of all identifiers?*
E. *Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?*
    i. *How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?*
F. *Describe the provisions for protection of participant privacy*
G. *Describe the methods for the security of storage and sharing of materials*

6. Subject Population: *Provide a detailed description of the types of human subjects who will be recruited into this study.*

For aim 1 we will recruit 30 voice hearing patients (aged 18-45 years) meeting diagnostic criteria for DSM-V schizophrenia or schizophreniform disorder, hearing voices at least once a day, and PANSS P3 (Hallucinations item) greater than 3

For aim 2 we will recruit 70 voice hearing patients (aged 18-45 years) meeting diagnostic criteria for DSM-V schizophrenia or schizophreniform disorder, hearing voices at least once a day, and PANSS P3 (Hallucinations item) greater than 3

(Total n = 100 over the two studies, Aims 1 & 2).

7. Subject classification: *Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.*

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: *Is this research proposal designed to enroll children who are wards of the state as potential subjects?*
Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: *What are the criteria used to determine subject inclusion or exclusion?*
Prior to study participation all patients will be evaluated for i) protocol eligibility; ii) ability to give informed consent; iii) interaction with the study team to determine participant's probability of completing the study; and iv) ability to cooperate with protocol procedures. The flow of all participants will be reviewed at weekly research meetings in consultation with the study team.

Inclusion Criteria:
i) Age 18 - 45 years old;
ii) are voice hearing patients;
iii) meet diagnostic criteria for DSM-V schizophrenia or schizophreniform disorder;
iv) report hearing voices at least once a day;

v) score > 3 on PANSS P3 (hallucinations item).

Exclusion Criteria:

i) DSM-IV substance abuse or dependence (past six months);
ii) clinically significant medical conditions, head injury with neurological symptoms or unconsciousness;
iii) developmental disability (IQ<70);
iv) Non-English speaking;
v) contraindications for TMS including a history of seizures, metallic implants of any kind and pacemakers, pregnancy;
vi) no less than 6 weeks of stable doses of psychotropic medications (to avoid transient effects of medication regiment change; medication type and dose will be carefully recorded and used as a covariate in all analyses);
vii) co-morbid mood or anxiety diagnosis;
viii) clinically/behaviorally unstable and unable to cooperate with TMS procedures;
ix) unstable medical condition based on EKG, medical history, physical examination, and routine laboratory work-up;
x) personal history of stroke or immediate family history of seizures;
xi) facial tattoos (with could react with TMS and heat up).

9. *How will **eligibility** be determined, and by whom?*

All participants will be provided information about the study in a process involving the research assistant and investigator prior to obtaining written informed consent. Participants are also "tested" on their knowledge about the study prior to study participation. Overall eligibility will be determined by the PI – Dr. Corlett and the study MD – Dr. Powers.

10. Risks: *Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.*

Risks: The risks from this study (both Aims) involve 1) TMS procedures 2) a blood draw and 3) confidentiality.

1) *Transcranial Magnetic Stimulation (TMS)*. There are some risks with TMS for certain people.
   a. **Seizures**: The latest safety guidelines for TMS will be followed for all experiments. Despite these precautions, there is a very small chance that a participant could have a seizure associated with TMS. Approximately 25 seizures have been reported in the literature since 1980, the majority of which occurred in patients with identifiable seizure risk factors (multiple sclerosis, stroke, traumatic brain injury, medications that lower seizure threshold, personal or family history of seizures, etc.). Moreover, most reported seizures (15/25) occurred in patients receiving motor cortex stimulation (44).
   Based on the population we are recruiting from, we anticipate that many of our participants will be taking antipsychotics. Antipsychotics can lower the epileptogenic threshold and seizures are a serious potential adverse effect. However, there has been no interaction found between TMS and antipsychotics, suggesting that they have independent mechanisms.
   We also expect that some of our participants will being taking multiple medications for their condition(s). Polypharmacy has been categorized as a potential risk factor of seizures.

   b. **Mild Adverse Events:** Headache, scalp discomfort at the site of stimulation and nausea are among the most commonly reported mild adverse events (MAE) associated with TMS. Although precise data are lacking, studies report a 5% incidence of MAEs across TMS sessions with the majority of symptoms

(78%) occurring after the stimulation session ends. Some of these MAEs occurred in patients receiving placebo stimulation. Moreover, studies have shown that MAEs are more likely to occur during initial TMS sessions than later TMS sessions, suggesting adaptation and a potential role for initial expectations or anxieties about treatment (45). Studies have shown that scalp discomfort during TMS diminishes with time (46). The headaches associated with TMS are temporary and manageable with common over-the-counter pain remedies.

c. **Hearing Loss:** The TMS coil generates a high-energy click that may cause hearing damage. Humans exposed to TMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours.

d. **TMS & Pregnancy:** This protocol will exclude pregnant women. The risks of using TMS with pregnant women are currently unknown but studies are ongoing.

e. **Sham Stimulation Risks:** There is a risk of discomfort with the eSham system. This discomfort should not exceed the discomfort associated with real TMS and machine setting can be adjusted to modulate the experience. TENS units are readily available to the general public and are considered low risk devices by the FDA. There is no compelling evidence that TENS units or similar alternating current devices can directly influence cerebral cortex activity without modulating a superficial nerve.

2) *Blood Draw.*
   a. **Mild Adverse Events:** Bruising or soreness at the site where blood is drawn may be a result.

3) *Confidentiality.*
   a. **Breach:** Due to our procedures (outlined in Section IV), a breach in confidentiality is extremely unlikely, but still possible.

11. Minimizing Risks: *Describe the manner in which the above-mentioned risks will be minimized.*
    a. **Seizures**: Patients with a lifetime history of seizures will be excluded

    b. **Mild Adverse Events:** Participants will be clearly instructed that there is a risk of mild adverse events like headache and physical discomfort. These effects will be assessed pre- and post- stimulation and participants will be reminded that they can withdraw their participation at any point. In the study without further consequences

    c. **Hearing Loss:** Hearing will be measured at screening, as well as pre- and post-stimulation. People with a change in auditory thresholds greater than 10dB following stimulation will be discontinued. Pascual-Leone et al. (1993) was the only study that found temporary hearing loss in 3 of 9 patients when stimulating the motor cortical areas that resolved in two of the three patients within thirty minutes. The third patient had an abnormal pre-stimulation audiogram and the changes were reversed in four hours (47). To date, we have encountered no evidence of hearing impairments induced by rTMS – including patients with schizophrenia receiving stimulation at a Wernicke's site.

    d. **TMS & Pregnancy:** Urine pregnancy tests will be conducted at screening and prior to stimulation in female participants. Pregnancy will be an exclusion criterion for these studies.

12. Data and Safety Monitoring Plan: *Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)*

According to NIMH guidelines, TMS entails greater than minimal risk (https://www.nimh.nih.gov/funding/clinical-research/nimh-guidance-on-risk-based-monitoring.shtml). The risks detailed include discomfort at the stimulation site, headaches, light headedness and seizure (though this is extremely uncommon). Unanticipated Problems Involving Risks to Participants or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Participants or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies.

Independent Safety Monitor:

The Independent Safety Monitor (ISM) is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study.

The ISM, Dr. Rachel Katz, has been selected based on her relevant expertise in psychiatry and experience working with TMS. Her participation is for the duration of the study. She will be able to readily access participant records. She has no direct involvement in the conduct of the study. Dr. Katz does not have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making.

Data & Safety Monitoring Plan Aim 1:

Dr. Corlett (PI) will review safety data with Dr. Powers (study MD), after every test day, during weekly research team meetings, and will suspend or modify the study (with IRB approval) if indicated. The ISM and the IRB will be duly informed if there are any reasons to warrant "holding" the study. A review of the study will be submitted to the IRB annually.

Adverse events will be graded in severity as follows:

0 No adverse event or within normal limits
1 Mild adverse event
2 Moderate adverse event
3 Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
4 Life-threatening or disabling adverse event
5 Fatal adverse event

Adverse events > level 3 will be reported to the IRB immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB. Other adverse events will be reported to the IRB within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB in a timely manner, using the following predefined causal relationships:

i. Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention
ii. Probable: Adverse event(s) will likely be related to investigational agent(s)

iii. Possible: Adverse event(s) may be related to investigational agent(s)
iv. Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)
v. Unrelated: Adverse event(s) will clearly not be related to the investigational agents(s)

Data & Safety Monitoring Plan Aim 2:
Dr. Corlett (PI) will review safety data with Dr. Powers (study MD), after every test day, during weekly research team meetings, and will suspend or modify the study (with IRB approval) if indicated. The ISM and the IRB will be duly informed if there are any reasons to warrant "holding" the study. A review of the study will be submitted to the IRB annually.

Adverse events will be graded in severity as follows:

0 No adverse event or within normal limits
1 Mild adverse event
2 Moderate adverse event
3 Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
4 Life-threatening or disabling adverse event
5 Fatal adverse event

Adverse events > level 3 will be reported to the IRB immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB. Other adverse events will be reported to the IRB within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB in a timely manner, using the following predefined causal relationships:

i. Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention
ii. Probable: Adverse event(s) will likely be related to investigational agent(s)
iii. Possible: Adverse event(s) may be related to investigational agent(s)
iv. Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)
v. Unrelated: Adverse event(s) will clearly not be related to the investigational agents(s)

13. Statistical Considerations: *Describe the statistical analyses that support the study design.*

Statistical Analysis Plan – Aim 1

Our experiment is concerned with whether inhibitory TMS to the insula weakens strong perceptual beliefs. Our preliminary data suggest a relationship between X_1 (participant perceptual beliefs estimated from the hierarchical Gaussian Filter analysis) and activity in the anterior insula cortex. We are proposing to compare the effects inhibitory TMS over the anterior insula immediately prior to task performance with the effects of a sham intervention in a within-subject crossover design.

The magnitudes of X_1 parameter estimates following insula TMS and sham will be compared using analysis of variance.

In our preliminary data, Hallucinating participants with psychosis had significantly stronger perceptual beliefs than non-hallucinators (X_1). This was a medium-sized effect (Cohen's d = 0.6)

If TMS can curtail these group differences – i.e. decrease hallucinating patient belief strength to the level of non-hallucinating controls, then we would predict a similar effect size.

We estimate we will need at least 24 participants to detect such a difference with a two-sided significance level of 0.05 and with 80% power (38).

We budgeted for 30 unique participants to allow for participant drop-out.

Statistical Design & Power – Aim 2

Our experiment is concerned with whether TMS to the cerebellum facilitates belief updating. Our preliminary data suggest a relationship between X_3 (participant beliefs about task volatility from the hierarchical Gaussian Filter analysis) and activity in the anterior insula cortex. We are proposing to compare the effects of excitatory TMS over the cerebellum immediately prior to task performance with the effects of a sham intervention in a within-subject crossover design.

The magnitudes of X_3 parameter estimates following cerebellar TMS and sham will be compared using analysis of variance.

In our preliminary data, Hallucinating participants with psychosis had significantly weaker perceptual belief updating than non-hallucinators (X_3). This was a small effect (Cohen's d = 0.36)

If TMS can curtail these group differences – i.e. increase hallucinating patient belief updating to the level of non-hallucinating controls, then we would predict a similar effect size.

We estimate we will need at least 63 participants to detect such a difference with a two-sided significance level of 0.05 and with 80% power (38).

We budgeted for 70 unique participants to allow for participant drop-out.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒ N/A

1. *Name of the radiotracer:*

2. *Is the radiotracer FDA approved?* ☐ YES ☐ NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. *Check one:* ☐ IND# or ☐ RDRC oversight (RDRC approval will be required prior to use)

4. Background Information: *Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this radiotracer is being administered to humans, include relevant data on animal models.*

5. Source: *Identify the source of the radiotracer to be used.*

6. **Storage, Preparation and Use:** *Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.*

B. DRUGS/BIOLOGICS ☒ N/A

1. *If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (and delete the inapplicable categories):*

Exempt Category 1 – The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☐
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☐
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☐
7. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☐
8. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☐

Exempt Category 2 *(all items i, ii, and iii must be checked to grant a category 2 exemption)*

☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

- ☐ Blood grouping serum
- ☐ Reagent red blood cells
- ☐ Anti-human globulin

☐ ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐ iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. Background Information: *Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.*

3. Source: *Identify the source of the drug or biologic to be used.*
   Is the drug provided free of charge to subjects? ☐ YES ☐ NO
   If yes, by whom?

4. Storage, Preparation and Use: *Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.*

Check applicable Investigational Drug Service utilized:

☐ YNHH IDS	☐ CMHC Pharmacy	☐ West Haven VA
☐ PET Center	☐ None	☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation*.

1. Use of Placebo: ☐ Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) *Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.*
b) *State the maximum total length of time a participant may receive placebo while on the study.*
c) *Address the greatest potential harm that may come to a participant as a result of receiving placebo.*
d) *Describe the procedures that are in place to safeguard participants receiving placebo.*

2. Continuation of Drug Therapy After Study Closure ☐ Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ **Yes –** If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☐ **NO –** If no, explain why this is acceptable.

B. DEVICES ☐ N/A

1. *Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)?* ☐ Yes ☒ No

<u>If Yes, please be aware of the following requirements</u>:

A YNHH New Product/Trial Request Form must be completed via EPIC: Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested

including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request;

AND

Your request must be reviewed and approved in writing by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. Background Information: *Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.*

MAGSTIM SUPER RAPID REPETITIVE MAGNETIC STIMULATION SYSTEM.
The FDA has approved this device for research purposes and does not require an IDE for moderate risk studies.

Information about TMS, including prior human use, known risks and other factors influencing risk are discussed in the prior section of this document. Additionally, information about sham stimulation has also been discussed elsewhere. The PI and Co-PI have nearly a decade of experience employing TMS for clinical and research purposes. An IDE has never been required for any of the TMS research protocols with which the PI and Co-PI have been involved.

Figure-of-eight transcranial magnetic stimulation (TMS) is a focal, non-invasive form of brain stimulation that can depolarize or hyperpolarize superficial cortical neurons in the human brain ((24); Figure 1). TMS typically involves positioning an electromagnetic coil on the scalp. This coil uses electrical current to create powerful (approximately 1.5 T) yet transient (approximately microseconds) magnetic fields that enter the brain unimpeded by electrical resistors such as skin, muscle and skull. In accordance with theories of electromagnetism developed by James Clerk Maxwell, Michael Faraday and others in the 19th century (48, 49), pulsing magnetic fields induce electric current in neuronal membranes. Thus, electrical energy in the TMS coil is transformed into magnetic energy that traverses the skull. This magnetic energy is converted back into electrical energy in the brain (50).

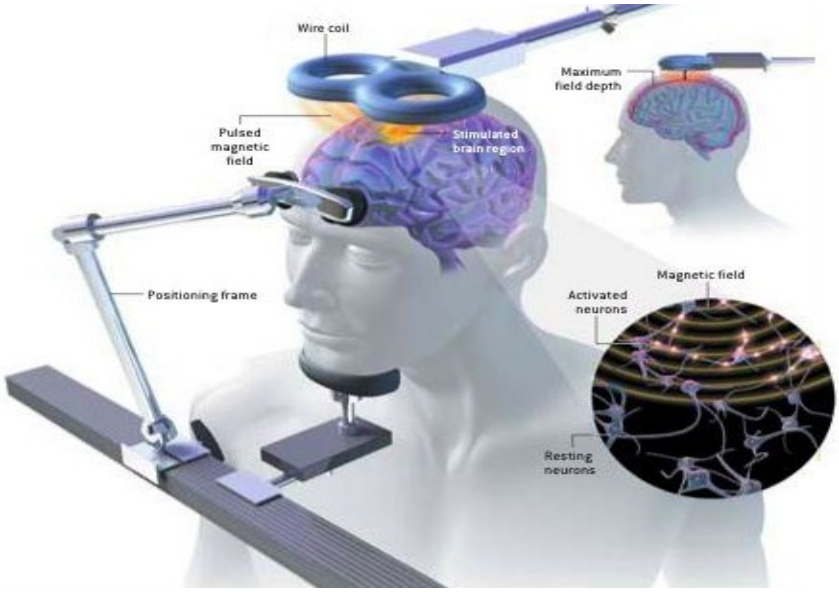

FIGURE 1: A diagram of how TMS is used to depolarize or hyperpolarize superficial cortical neurons (adapted from (George 2003)).

Although its immediate effects are superficial and focal, TMS may also modulate cortical and subcortical structures synaptically connected to the region being stimulated. Successive trains of pulses, known as repetitive TMS (rTMS), may enhance the local and distributed effects of single-pulse TMS. These staccato magnetic fields have the capacity to induce neurophysiological changes that persist after the stimulation paradigm ends (51, 52). It is for this reason that TMS can be used as an investigational tool as well as a therapeutic tool for depression (53-56), migraine and potentially other neuropsychiatric disorders.

Under 21 CFR 812.3(m), a significant risk device means an investigational device that:

(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant;
(2) Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a participant;
(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a participant; or
(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

To make this determination, it seems that the risks to health are key.

(1) We can dismiss because the device is not an implant.
(2) We can dismiss because the aim of the study is investigational medicine, NOT supporting or sustaining human life.
(3) We can dismiss again, because the aim is an investigational study on an experimental task paradigm, the aim is NOT diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health.
(4) To answer, we listed have already listed the risks of, but to summarize again:

Based on prior work using this device in this and other populations and substantial clinical experience with this population, and with psychosis (delusions and hallucinations) in particular, the device and its intended use in this protocol does *not* present a serious risk to the health, safety or welfare of patients with psychosis.

Dr. Hoffman and Dr. Corlett have previously studied patients with schizophrenia who suffer from intractable hallucinations (perceiving sounds/voices that are not present). Inhibitory 1Hz rTMS is employed over left prefrontal cortex or temporoparietal cortex. Dr. Hoffman does not operate under an IDE. No adverse events have been reported in Dr. Hoffman's studies in approximately 200 stimulation sessions. Many of these data are published, for example (57).

The patient population (patients with psychotic illness) and stimulation parameters (1hz rTMS) are almost identical to the proposed study.

Here are the key differences: we will be targeting different brain regions (insula and cerebellum) and we will be using theta-burst stimulation on the cerebellum

The safety of rTMS has been carefully considered in a number of review articles (47, 58, 59) One of these articles has reported clear-cut safety guidelines that consider the frequency, strength and number of pulses of stimulation (59). These Guidelines include:

(1) ethical requirements regarding informed consent patient disclosing all known and potential risks of rTMS and the judgment that the potential benefit of rTMS outweighs the risk;
(2) stimulation parameters (those we propose fall within this guidelines);
(3) physiological monitoring by continuously monitor the EMG from hand muscles contralateral to the stimulation site for elicited MEPs when areas other than the M1 are stimulated;
(4) careful monitoring of cognition and symptomatology to observe contraindications to rTMS including metal in cranium, intracardiac lines, or increased intracranial pressure (relative contraindications are pregnancy, childhood, heart disease, cardiac pacemaker, or a family history of epilepsy). Like other studies of rTMS conducted at Yale, the present protocol will adhere to these guidelines. Adhering to these guidelines significantly mitigates the potential risks associated with TMS.

I perceive three further risks associated with study participation. I perceive each to be minimal. The first is the risk of seizure induction. The second risk is temporary hearing loss. The third risk is discomfort at the stimulation site. I will detail how we plan to minimize each risk. I do not believe that these five issues, taken together, represent a significant risk to the health, safety or welfare of the participants who are recruited and randomized to this study.

1. **Risk of Seizure:** The most significant risk of rTMS highlighted by safety studies is that of seizures. Practically all cases of seizures induced by rTMS have occurred in patients with a prior history of seizure or in which rTMS is administered at much higher frequencies (10 Hz) with stimulation trains separated by short inter-train durations (59). One seizure has been reported for a female patient on psychotropic medication while stimulated at lower frequency (3 Hz) with motor threshold of 90% (ibid). However, the rate of stimulation for this patient was three times that which we will use in our study.

   Rate of stimulation appears to correlate directly with risk of seizure induction. Seizures have been intentionally induced by rTMS in patients with epilepsy although, paradoxically, seizure induction using this method has often been unsuccessful (59). Seizures have also been induced in patients with stroke and other disorders involving the central nervous system following single pulse TMS (59). These patients presumably have a lower seizure threshold.

Of note is a report suggesting that one hertz rTMS, when administered at 110% motor threshold to motor cortex, produced spread of cortical activation -- a possible early sign of seizure risk -- when the number of pulses administered exceeds fifty (Pascual-Leone et al., 1993).

Anderson et al. (2006) examined the tolerability and safety of high doses of rTMS in sleep deprivation of young healthy males by exposing the young men to 12,960 magnetic pulses a day for up to 3 days in one week (60). Despite the intense treatment regimen, Anderson et al. failed to produce significant side effects and concluded; "doses of up to 12,960 pulses per day appear safe and tolerable in healthy young men (60).

We are proposing a single TMS administration that is 11,000 pulses less then what was used in Anderson study (60). We will remain conservative, however, regarding seizure risk. Our strategy for minimizing risk of seizure induced by rTMS is twofold:

- We will screen out all patients who have had a previous seizure.
- Motor threshold will be established at the beginning of each session and the maximum stimulation strength will be 110% of motor threshold, which remains well within published safety guidelines (59).

The risks are no higher for theta burst stimulation, please see www.ncbi.nlm.nih.gov/pmc/articles/PMC3260517/ (37).

There have been two cases of theta-burst stimulation induced seizure when targeting the insula cortex:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6364800/

We do not want to deliver a stimulation associated with seizure risk to the insula. We do want to activate the insula (as a control). The 10Hz protocol is sufficient to activate the insula, and serve as a control, and there is no evidence that it induces seizures. We propose to stimulate the insula with 10Hz rTMS which is safe and well tolerated.

We use theta burst stimulation to the cerebellum in aim 2. Theta burst stimulation has been delivered to the cerebellum without seizure side effects (and with clinical benefit to patients with Schizophrenia):

https://www.sciencedirect.com/science/article/pii/S0987705312002675

2. **Temporary Hearing Loss**: Hearing damage that may result from the loud sound (approximately 140 dB) produced by rTMS stimulation. To date, we have encountered no evidence of hearing impairments induced by rTMS – including patients receiving stimulation at a Wernicke's site. Pascual-Leone et al. (1993) was the only study that found temporary hearing loss in 3 of 9 patients when stimulating the motor cortical areas that resolved in two of the three patients within thirty minutes (47). The third patient had an abnormal pre-stimulation audiogram and the changes were reversed in four hours. To date, we have encountered no evidence of hearing impairments induced by rTMS – including patients with schizophrenia receiving stimulation at a Wernicke's site. Pascual-Leone et al. (1993) was the only study that found temporary hearing loss in 3 of 9 patients when stimulating the motor cortical areas that resolved in two of the three patients within thirty minutes (47). The third patient had an abnormal pre-stimulation audiogram and the changes were reversed in four hours.

   We will mitigate this risk by placing earplugs in the outer ear canal and sound protection headphones over the ears themselves to avoid hearing damage that may result from the loud sound (approximately 140 dB) produced by rTMS stimulation.

The risks are no higher for theta burst stimulation, please see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3260517/ (37).

3. **Discomfort:** For most patients rTMS produces a knocking sensation and varying degrees of scalp contraction. In about 20% of patients' actual discomfort is experienced at the stimulation site. We have administered rTMS to approximately 90 hallucinating patients and in no case has the patient requested to terminate the procedure due to physical symptoms. In small number of cases (three) discomfort caused us to reduce stimulation strength. This was done in increments of 10% to determine the tolerable limit of stimulation strength. During the rTMS session the patient will be constantly monitored by the research team member administering the rTMS to ensure that the patient is not experiencing significant discomfort or adverse reactions to rTMS.

   The risks are no higher for theta burst stimulation, please see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3260517/ (37).

In summary – we do not expect significant risk for the health, safety and welfare of participants randomized to our planned study. Whilst there are risks, those risks are mitigated by screening out individuals at highest risk and carefully monitoring those participants who are randomized. Any deterioration in health, safety and welfare of a participant will result in immediate termination of their participation.

Specific Stimulation Protocols Compared to FDA and other Published Guidelines:

Aim 1: Insula
rTMS will be administered either at 1Hz (active) or 10Hz (control). Both are within FDA guidelines and have been deemed safe and tolerable in the literature.

1Hz – Inhibitory – TMS will consist of 600 total pulses at 120% of resting motor threshold

10 HZ – excitatory – TMS will consist of 6 trains of 10 second trains at 10 Hz (at 80% of resting motor threshold), with an intertrain interval of 50 seconds. Total 600 pulses, per this protocol:

https://core.ac.uk/download/pdf/37500095.pdf

These stimulus intensities were safe and well tolerated, with no evidence of seizure:

https://www.sciencedirect.com/science/article/pii/S0006322314003874

Aim 2. Cerebellum

TBS will be applied at 100% of motor threshold with the standard iTBS burst pattern (3 pulses at 50-Hz repeated at a rate of 5-Hz; 20 trains of 10 bursts given with 8-s intervals; Total 600 pulses).

TMS control stimulation, on a separate visit will be rTMS at 1Hz for 600 pulses (as in Aim 1).

It is not possible to compare to Table 2 in the FDA Class II Special Controls Guidance Document.

The document only addresses rTMS, not theta-burst stimulation.

For theta-bust, I will refer to:

Oberman, L., Edwards, D., Eldaief, M., & Pascual-Leone, A. (2011). Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. *Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society*, *28*(1), 67–74. doi:10.1097/WNP.0b013e318205135f (37)

"*Researchers who employ TBS highlight that these paradigms use less pulses and shorter duration of stimulation than typical rTMS paradigms. One implication is that TBS may be safer than other frequently used rTMS trains. However, it cannot be ignored that TBS protocols employ very high frequency stimulation. It is currently unknown whether frequency, duration, or total number of pulses is a better predictor for risk of adverse events, including the risk of seizure. Current guidelines on safety of TMS (Rossi et al., 2009) do not include recommendations for the maximum duration or intensity of stimulation when applying patterned trains of stimulation such as TBS*."

The authors thus conducted a literature review of all published studies of TBS. They state:

"*Of the subjects in the 67 protocols (n=1001, 776 healthy controls), the reported adverse events were*

1. *seizure in 1 healthy control subject during continuous TBS,*
2. *mild headache in 24 subjects (20 healthy controls, 2 patients with tinnitus, and 2 patients with Parkinson's Disease),*
3. *nonspecific discomfort in 5 patients with tinnitus,*
4. *mild discomfort due to cutaneous sensation and neck muscle contraction in 5 healthy control subjects, (5) worsening tinnitus in 3 tinnitus patients,*
5. *nausea in 1 patient with Parkinson's Disease,*
6. *light headedness or vagal responses in 11 healthy control subjects, and*
7. *unilateral eye pain and lacrimation in 1 healthy control subject (which ceased upon cessation of the treatment session).*

The one incident of seizure induced by TBS was described by Oberman and Pascual-Leone (2009) and occurred in a 33-year-old healthy man with no risk factors for epilepsy. The seizure occurred following approximately 50 trains (10 seconds) of TBS to the primary motor cortex at an intensity of 100% of resting motor threshold (RMT). Given this one incident of a seizure, the resulting crude risk per subject of seizure as a result of TBS is estimated as 0.1 % while the crude risk per subject of mild adverse events (encompassing the remainder of the reported events) is 5% overall and 4.8% for healthy controls"

They conclude:

"Based on our meta-analysis of the published literature, we find that both the reported symptoms and general risk of adverse events during TBS is comparable to or less than other high frequency rTMS protocols (see Rossi et al., 2009 for a review)"

They do recommend caution in administering TBS above motor threshold. However, we are planning to deliver stimulation at motor threshold.

We are also targeting cerebellum, not motor cortex. All seizures associated with any TMS (rTMS or TBS) have been a result of motor cortex stimulation.

Finally, we are using intermittent rather than continuous stimulation (the planned stimulation has 8 seconds between bursts) – the only seizure occurred with continuous stimulation.

This specific procedure was safe and well tolerated (with no seizures) in treatment refractory patients with schizophrenia:

Demirtas-Tatlidede, A., Freitas, C., Cromer, J. R., Safar, L., Ongur, D., Stone, W. S., ... & Pascual-Leone, A. (2010). Safety and proof of principle study of cerebellar vermal theta burst stimulation in refractory schizophrenia. *Schizophrenia Research*, *124*(1-3), 91-100. doi: 10.1016/j.schres.2010.08.015 (36)

There were mild adverse events (headache, discomfort), however there were also improvements in cognition.

This paper has been cited 76 times and studies adopting its stimulation parameters have been conducted in depression, obsessive-compulsive disorder, Tourette's disorder, nicotine and cocaine addiction, and pathological gambling. They were reviewed in Rachid (2018) (61) who concluded, that, in these patient studies of TBS: "*Studies have not reported major adverse effects with TBS, except for mild headaches, local painful sensations, dizziness, palpitations, and nausea.*"

There is evidence for seizure (2 cases) induced by TBS to insula:
https://www.ncbi.nlm.nih.gov/pubmed/29805097
We are not targeting Insula with TBS in either Aim 1 or Aim 2.

3. Source:
   a) Identify the source of the device to be used. MAGSTIM, Ltd. (Whitland, England)
   b) Is the device provided free of charge to subjects? ☒ Yes ☐ No

4. Investigational device accountability: *State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:*
   a) *Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):*
   b) *Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):*
   c) *Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:*
   d) *Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:*
   e) *Distributes the investigational device to subjects enrolled in the IRB-approved protocol:*

   Not applicable. Device is static and sessions are administered either at the CMHC TMS Suite.

   The device was installed and is serviced by MAGSTIM accredited employees.

Access to the device is limited to those with appropriate training and approval received. All those administering TMS treatment have attended a residential training course on how to use and maintain the device.

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol:
   30 subjects for aim 1, 70 subjects for aim 2, for a total of 100.

   b. If this is a multi-site study, give the total number of subjects targeted across all sites:
   No, Yale is the only site.

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☒ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☐ Other:		

*** Requests for medical records should be made through JDAT as described at**
medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:
   a. *Describe how potential subjects will be identified.*
   Potential participants will be recruited from the local community via advertisement, from databases of ongoing Clinical Neuroscience Research Unit projects (only those participants who have previously consented to be re-contacted by consenting during participation in prior protocols on which there are overlapping study team members), community outpatient facility contacts and among the patients being recruited under Dr. Vinod Srihari's existing STEP clinic protocol, patients attending the Psychosis Clinic at the Connecticut Mental Health Center, Program for Recovery and Community Health, and the Connecticut Hearing Voices Network. We will discuss with providers whether it is appropriate for a participant to take part. We will also add a research progress note to their chart.

   If they have a chart at CMHC, the research note will be added to their chart.

   If they do not have a chart at CMHC, a chart will be created.

   b. *Describe how potential subjects are contacted.*
   Potential participants will contact us, by responding – via telephone.

   c. *Who is recruiting potential subjects?*
   Dr. Corlett, Dr. Powers, and our Research Assistants will recruit potential participants.

4. **Assessment of Current Health Provider Relationship for HIPAA Consideration:**
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☐ Yes, some of the subjects
☒ No

If yes, describe the nature of this relationship.

5. Request for waiver of HIPAA authorization: *(When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)*

Choose one:

☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. *Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:*
ii. *If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: *Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.*
After a telephone screen to determine eligibility, potential participants will be invited in for a screening visit. First, they will read and sign a consent form, after having had the opportunity to discuss with the PI, MD and other research team members.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: *Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.*
Participants will be given a multiple-choice test on the contents of the consent form to ensure that they have comprehended the procedures and in particular the risks involved.

8. Non-English-Speaking Subjects: *Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.*
   Non-English-speaking participants will not be recruited to the study, given the cognitive tests involved

   As a limited alternative to the above requirement, will you use the short form for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?* YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. *If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.*

   ☐ **Not Requesting any consent waivers**

   ☒ **Requesting a waiver of signed consent:**

   ☒ **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

   We will present the study to potential participants by telephone, and we will assess their initial eligibility via this conversation (confirm that the person hears voices, that they are between 18 and 45, that they do not have a pacemaker or suffer from seizures). If they might qualify, we will invite them in to CMHC to consider consenting. If they consent to the study, we will proceed with the screening visit procedures.

   ☐ **Entire Study (**Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- *Would the signed consent form be the only record linking the subject and the research?* **YES ☐ NO ☐**
- *Does a breach of confidentiality constitute the principal risk to subjects?* **YES ☐ NO ☒**

OR

- *Does the research pose greater than minimal risk?* **YES ☐ NO☒**
- *Does the research include any activities that would require signed consent in a non-research context?* **YES ☐ NO ☒**

☐ **Requesting a waiver of consent:**

☐ **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ **Entire Study**

For a full waiver of consent, please address all of the following:

- *Does the research pose greater than minimal risk to subjects?*
  ☐ Yes – *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- *Will the waiver adversely affect subjects' rights and welfare?* **YES ☐ NO☐**
- *Why would the research be impracticable to conduct without the waiver?*
- *Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. *What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?*
   Demographics and information about medications and past medical history will be collected.

2. *How will the research data be collected, recorded and stored?*
   Data will consist of verbal, written, or computerized ratings of sensory stimuli, questionnaires, and computerized responses to mood, cognitive and various neuropsychological assessments. All data will be kept confidential. Participant information is maintained in computer files that are password protected, and data from individuals (computer files and hard copy versions) are identified only by code. Only the primary investigator and research staff, the Yale HIC, and the National Institute of Health, which sponsors the study, will have access to these files. The data will be archived in the same manner after the research is completed. Seven years after completion of the study the identifying data will be deleted by zeroing with software as in accordance with policies and procedures as determined by Yale University.

3. *How will the digital data be stored?*

☐ CD	☐ DVD	☐ Flash Drive
☐ Portable Hard Drive	☒ Secured Server	☒ Laptop Computer
☒ Desktop Computer	☐ Other: _____	

4. *What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?*

   A database with subject identifiers and means to link subject names and codes with research data will be stored on an encrypted password protected server in the BLAM Laboratory at the CMHC. Access to the database itself is password protected. Hardcopy PHI data will be locked in a cabinet. All other digital media (Laptop computers) only contain research data that are identified by a subject code.
   Identifying data will be retained for a period of seven years after publication.

   No other entities besides research staff and the investigator will have access to PHI or de-identified data, with the exception of presentations of data. These are typically reported as group averages. Where individual data are reported, individuals will not be identified except by code.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on URL its.yale.edu/egrc or email mailto:it.compliance@yale.edu.

   What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. Identifying data will be retained for a period of seven years after publication.
   The link between the study data and PHI will be broken by de-identifying after 7 years. De-identified data will be retained indefinitely.

5. *If appropriate, has a Certificate of Confidentiality been obtained?*
   N/A

SECTION V: POTENTIAL BENEFITS

Potential Benefits: *Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)*
There are few direct benefits to participants who elect to participate in the study. However, it is hoped that the information gained will help researchers learn how brain stimulation can be used to map and modulate neural circuitry implicated in healthy function and disease states.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC

1. Alternatives: *What other alternatives are available to the study subjects outside of the research?*
   The alternative is to not participate in the study.

2. Payments for Participation (Economic Considerations): *Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.*
   Participants will receive up to $200 for study participation ($50 for screening, $50 for visit 1, $50 for visit 2, $50 for visit 3).

3. Costs for Participation (Economic Considerations): *Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.*
   N/A

4. In Case of Injury: *This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).*
   a. *Will medical treatment be available if research-related injury occurs?*
   b. *Where and from whom may treatment be obtained?*
   c. *Are there any limits to the treatment being provided?*
   d. *Who will pay for this treatment?*
   e. *How will the medical treatment be accessed by subjects?*

   If a participant is injured as a result of participation in this study, care and treatment for those injuries will be provided. The patient or their insurance company will be charged for the cost of this treatment. There is no provision for financial compensation for injuries.

IMPORTANT REMINDERS

Will this study have a billable service? **Yes ☐ No ☒**

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology).
Notes:
1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored).

2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. *Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?*
Yes ☐ No ☐
b. *Will you be using any new equipment or equipment that you have not used in the past for this procedure?*
Yes ☐ No ☐
c. *Will a novel approach using existing equipment be applied?* Yes ☐ No ☐

If you answered “no” to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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