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

Protocol Title: Song-making In a Group (SING). HIC# 2000026376

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INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

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

   The overarching aim of the proposed work is to align a promising treatment lead – Musical Intervention (MI) – with a promising mechanistic account of psychosis – Predictive Processing. The R66 phase will investigate the impact of group musical intervention on predictive processing metrics of hallucinations and social dysfunction. Armed with a mechanistic understanding of musical intervention for psychosis, we will be well placed, in the R33 phase, to optimize its administration (Is active participation more effective than passive listening? Does creation of new music help more than performing others' creations?). By tracking the interrelation between symptom mechanisms and MI, we can use those metrics to prospectively assign patients to particular MI.

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

   5 years (2 years R61 phase, 3 years R33 Phase)

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. Despite statistical dissociation of positive and negative psychotic symptoms[4], AVH form and foment in the context of social isolation[5]. Furthermore, these social challenges do not respond to current pharmacotherapies, which may even iatrogenically worsen them, leading to challenges with adherence. *There is a need for improved treatments, for both AVH and social difficulties, with a favorable side effect profile*. Musical intervention (MI) is one such candidate. According to some small qualitative and quantitative studies, MI improves hallucinations and negative symptoms and it is remarkably well tolerated. However, we do not know how musical interventions lead to symptomatic recovery in psychosis. ***The overarching aim of the proposed work is to align a promising treatment lead – MI – with a promising mechanistic account of psychosis – Predictive Processing***. The R66 phase will investigate the impact of group musical intervention on predictive processing metrics of hallucinations and social dysfunction. Armed with a mechanistic understanding of musical intervention for psychosis, we will be well placed, in the R33 phase, to optimize its administration (Is active participation more effective than passive listening? Does creation of new music help more than performing others' creations?). ***By tracking the interrelation between symptom mechanisms and MI, we can use those metrics to prospectively assign patients to particular MI.***

Go/No Go Decisions: Do metrics of hallucinations and social processing change with musical intervention?

Music and Psychosis: MIs mollify the salient features of auditory verbal hallucinations – like their duration [6] with improvements lasting years into follow-up in some cases[7]. Meta-analysis of 19 studies showed MI to be effective for negative and cognitive symptoms of psychosis (d = 0.71), particularly for popular music over classical[8]. There were no significant differences between groups that passively listened versus those that produced music, nor between music selected by therapist or patient, they all helped[8]. However, the dependent variables were subjective ratings scales that often failed to capture both AVH and negative symptoms in the same participants[8].

There is a real need for objective measures of hallucinations and negative symptoms, which we feel our recent computational psychiatry work provides (see below). ***We propose to employ these metrics in a new, appropriately powered study of MI. We will compare active and passive engagement, with music that participants do and don't feel ownership for. It is these factors – ownership and activity - which we believe – based on our preliminary data (see below) – are the active ingredients of MI.***

Mechanisms of Psychosis: Computational modeling of perceptual and decision-making processes offers one approach to identifying objective metrics of processes relevant to AVH and social challenges. Our recent work has provided such a computational understanding of AVH[9]. Perception is not simply the passive reception of inputs[10]. We actively infer the causes of our sensations[11]. These inferences are influenced by our prior experiences[12]. Priors and inputs are combined according to Bayes' rule[13]. Prediction errors, the mismatch between priors and inputs, contribute to belief updating[14]. Hallucinations (percepts without external stimulus) may arise when strong priors cause a percept in the absence of customary input[15]. 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[16]. We examined this effect with functional imaging. We used computational modeling to infer the strength of participants' perceptual beliefs about stimuli, associations between stimuli, and the volatility of those associations[17]. 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[18]. 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, engendering a belief in audio-visual association. This belief was then tested with increasingly frequent sub-threshold and target-absent trials. *Conditioned hallucinations* occurred when subjects reported tones that were not presented, conditional upon the visual stimulus.

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. To understand these results in the context of our formal model of perception, we employed a three-tiered Hierarchical Gaussian Filter (HGF)[19,20], which uses participant responses and the task structure to model estimate perceptual beliefs across three levels of abstraction. The first level of the model (X_1) represents whether the subject 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 participants resulted in two findings critical to the present proposal:

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'*** $p<0.001$[9]). 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'***[9]. Furthermore, there was a significant negative correlation between change sensitivity and illness burden[9] and a significant positive correlation between prior weighting and hallucination severity score[9]. For the first time, we have an objective, laboratory-based measure of AVH, with component processes relevant to different features of hallucinations. ***We propose to examine whether and how those AVH components change with the experience of MI.***

Social Learning in Mental Illness: Distrust and relational turbulence are core features of social problems in serious mental illness[21,22]. These features can be modeled experimentally to interrogate their mechanistic basis. To assay social behavior, our research subjects play computer-based tasks with a partner (or confederate). We

record behavior and calculate trial-by-trial learning about partner trustworthiness[23,24], which varies over time (social volatility). Computational models can describe the details of how learning combines prior beliefs with new social experience during this task[25-29]. For example, we can measure how quickly subjects learn about trustworthiness. We expect learning rates to be slow early in the task when social volatility is low, and faster when social volatility is higher; players should change quickly to keep up. In our first paper describing this approach, recently published in *Biological Psychiatry*[25], we found that both control subjects significantly increase their learning rates when social volatility is high but people with social challenges do not. ***We hypothesize that MI will reduce social learning deficits in people with serious mental illnesses.***

Combining Quantitative and Qualitative Approaches: Quantitative and qualitative approaches may be differently appropriate for different study phases (exploration versus hypothesis testing). They also have fundamentally different conceptions of the scientific process (removed, objective versus engaged, subjective). We believe that these approaches are not fundamentally incompatible, rather, they can be mutually informative and enriching. For example, the move toward peer support and engagement in mental health research has highlighted the shortcomings of the patrician expert-by-education-led approach to AVH research. In brief, clinical trials often employ tools to assess AVH severity which conflate salient features of AVH into single metrics, and thus do not distinguish which features change with treatment. Clinical trials have also assumed that the goal of AVH treatment is the eradication of voices by decreasing their frequency. Peer-led advocacy groups like The Hearing Voices Network (HVN)**,** comprised of experts-by-experience, suggest instead that some voices can be positive and supportive, that even the negative voices carry important meaning and that the goal of treatment should be tailored toward the individual and honor that meaning. We have argued that whilst HVN and computational psychiatry may appear strange bedfellows, their shared focus on plurality of explanation (across levels of analysis) and focus on AVH phenomenology suggest a powerful and mutually beneficial collaboration is possible[30]. ***The proposed work, aligning quantitative computational work with qualitative analyses of AVH changes, social engagement and self-representation, will ensure that we capture the ways in which MI changes AVH and social challenges in ways that are meaningful to service users, whilst grounding those changes in the mechanistic model-based understanding of AVH that computational psychiatry provides.***

Music & Predictive Processing: According to the predictive processing framework, backward predictions are passed down cortical hierarchies to resolve prediction errors at lower levels. Unresolved prediction errors can ascend the hierarchy to evince better predictions, based on their relative precision (inverse variance). This computational motif subsumes sensorimotor, autonomic, and memory systems. And prediction errors serve as imperatives to act within these systems (engaging in actions and homeostatic regulation that minimizes them across systems). Music affords competing predictions and then dispels uncertainty by confirming a particular prediction. Generating music is quintessentially enactive. Music perception is likewise. As with language, we predict music based on how we might generate it ourselves[31]. We feel the drive to move our bodies to the beat to establish appropriate auditory predictions. Predictive processing implies the existence of a hierarchical generative model of precision that spans modalities. Attending to external music attenuates interoceptive and proprioceptive predictions of the sort we would encounter when generating music ourselves[31]. In this way, music perception is more akin to language processing. Above we suggested, based on our preliminary data, that hallucinations and social dysfunction involve imbalances in the relative precisions of perceptual, proprioceptive and social priors and prediction errors. ***Music impacts hierarchies of dynamic precision, particularly when it is self-produced. In so doing, we hypothesize it will impact the pathophysiological mechanisms underlying AVH and social deficits.***

Song-making in a Group (SING): Preliminary qualitative interviews and ethnographic observations who frequented our MI program's drop-in site and participated in music-making and performance activities included

twenty-one people, approximately 60% of whom reported currently receiving or having received mental health services. Analysis of the in-depth interviews and ethnographic field notes revealed four major characteristics of the musical intervention space and music making experience: 1) the importance of a nonclinical therapeutic and sober environment; 2) opportunities for social engagement and integration; 3) opportunities for identity (re)invention; and 4) an outlet for artistic and musical expression. For this proposal, we have adapted that MI to facilitate the examination of predictive coding relevant mechanisms. We term this adapted intervention **SING – Song-Making In a Group**. In a one-hour session, 5 individuals work together with a trained facilitator to experience and/or produce music. We propose to manipulate the SING group tasks to identify the impact of certain activities on AVH and social processing.

Our SING Team is unique, uniting people with lived experience of psychosis, quantitative and qualitative researchers, clinician scientists, and musicologists. This unity is made possible by the **Connecticut Mental Health Center**, a state mental health facility whose tripartite goals are treatment, education and research and whose unique partnership with Yale University is embodied in the two research centers connected by this application; the *Yale Program for Recovery and Community Health* and the *Clinical Neuroscience Research Unit in the Abraham Ribicoff Research Facilities*. Together these units have the real and virtual infrastructures, staff and experience to make the proposed work a success. We make this claim confidently, because the key players already collaborate, and the interventional musicologists are already active and successful in the Connecticut Mental Health Center.

A Mechanistic Trial of SING: According to NOT-MH-18-004 from the NIMH, a mechanistic study is designed to understand a biological or behavioral process, the pathophysiology of a disease, or the mechanism of action of an intervention. Our proposed R33 study, which will be indicated should we demonstrate that MI alters conditioned hallucination behavioral processes or social learning metrics, fits this definition. We note that this is not an efficacy trial. We do not aim to assess the impact of MI on the severity of symptoms. Rather, we aim to evaluate the relationship between computational symptom mechanisms and aspects of MI, namely passive or active engagement as well as co-production of music over which participants feel ownership (versus don't). Aligned with the NIMH notice, our goal is to address basic questions of MI as well as predictive processing as a concept in biology, behavior, and pathophysiology that will provide insight into understanding mental health and mental disorders, namely auditory verbal hallucinations and social deficits. Again, per NOT-MH-18-004, for this proposal we do not seek to establish safety, clinical efficacy, effectiveness, clinical management, and/or implementation of MI. This will be the topic of future work should we proceed from R61, after we prosecute our R33. That future work will be informed by and optimized based on our R33 data, if they are gathered.

4. Research Plan: *Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.*

   In the R61 phase, we will examine the impact of SING on computational behavioral metrics of (Aim 1) Conditioned Hallucinations, (Aim 2) Social Reinforcement Learning, (Aim 3) Language Use, in 50 participants with voice hearing in the context of a psychotic illness. Following a screening visit to determine eligibility, these computerized tasks will be administered behaviorally, and an interview will elicit speech, prior to and following the full SING intervention (in 10 groups of 5 participants, each facilitated by a trained musical interventionist, during the first two years of the project). If SING meaningfully alters these computational task parameters (decision criteria outlined below), we will proceed to the R33 phase, wherein we will recruit a further 200 voice hearing participants with similar diagnoses. These participants will complete the same

tasks deemed mechanistically relevant in the R61 phase, prior to and following randomization to four different conditions (facilitated by an interventionist musician) that will deconstruct the possible active ingredients of SING along two dimensions: Activity and Ownership: (a) SING (n=50, Activity + and Ownership +), participants produce and perform their own song; (b) Karaoke (n=50, Activity + and Ownership -), participants perform karaoke, singing along to others music; (c) Pop Music (n=50, Activity – and Ownership -), participants will listen to popular music chosen by the music interventionists; and (d) Curated Playlists (n=50, Activity -, Ownership +), participants will curate playlists of popular music and listen to them together. This deconstruction will provide insights into the predictive processing framework, as applied to hallucinations and music, specifically, whether changes at higher, a-modal, hierarchical levels, particularly sense of self and active inference, influence precision weighted perceptual and social inferences more so than inactive experiences or experiences that do not engage sense of self.

Participant recruitment and screening. The Connecticut Mental Health Center has specialty clinics for first episode and multi-episode patients that will serve as primary recruitment sites. People who pass an initial phone screen will be invited to an in-person screening which includes a review of medical history, the SCID[32], and Structured Interview for DSM Personality Disorders – Revised (SIDP-R)[33].
To ensure adequate variability in positive symptom severity and balance in the clinical groups (R33 Phase), we will review ratings of hallucinations, assessed using the BPRS[34], during the initial study visit. We aim to include participants with at least a score >3 on the hallucinations item.

Participants will be between the ages of 18-65. Exclusion of older subjects is based on concern for effects of aging on behavioral parameters. Subjects of any gender and any race/ethnicity will be recruited to ensure the recruited group closely approximates the racial/ethnic base-rates in New Haven.

Assessments and Questionnaires

Self-report measures. The Launay-Slade Hallucinations Scale provides a brief measure of hallucinatory experience. They need to have experienced hallucinations at least once a day. Subjects' distress associated with their experiences will also be assessed and used in our analyses, as we and others have found that it clinically relevant[35]. The Positive and Negative Affect Scale (PANAS[36]) will be used to provide an assessment of current affective state.

Standard Neuropsychological Measures. We will administer the Wechsler Test of Adult Reading (WTAR) [37] as a measure of premorbid intellectual ability, and the MATRICS[38] Battery to assess level of neuropsychological functioning. Correlations between these measures, task metrics and the effects of MI will reveal the degree to which the metrics we acquire (and how they change with MI) are mechanistically specific.

Experimental Procedures and Anticipated Results

SING Intervention (R61). A trained musician-facilitator will convene a series of four weekly two-hour sessions to which groups of five participants will be invited (total n=50 participants, or n=10 groups). The groups will be convened at the Connecticut Mental Health Center for convenience (though other locations may be employed). The facilitator provides keyboard, professional microphone, recording interface, headphones, guitar, computer and a Digital Audio Workstation (DAW) for recording. The first 10 minutes of group involve introductions to the other participants and facilitator as well as the goals of the session. Participants will be given paper and a pencil with which to brainstorm potential lyrics. The next 5 minutes involve body and vocal warm ups, listening to self and others. For the next 90 minutes, participants will work

together with the facilitator and independently to create their own original lyrics and melody. Each song will have at least one collaborative section (usually the chorus) where lyrics are written and performed together by the whole group. Participants also have the ability to write alone and perform sections by themselves. For the last 10 minutes, the group listens back to the entire song that they created. In the final 5 mins, the session is concluded, and the group disbands until the next session. Post-session, the facilitator notes level of contribution and any other significant points regarding individual participation and group coherence (these may be used to weight each participant's contributions to analyses of the intervention's impact on computational behavioral endpoints). Finally, we appreciate that it is crucial to provide continued opportunities for engagement with MI after the conclusion of the group, should the participants desire. In the final session, participants will be provided with information sheets on local studio opportunities, karaoke nights and other opportunities to produce, perform and experience music.

R61 Aim 1 Conditioned Hallucinations:

As in our preliminary data, we will present a visual stimulus as a predictor of tones presented at near-threshold intensities. Over the course of twelve 30-trial blocks, the stimulus pairings will change; early in training, louder tones (75% threshold) will be paired with the visual stimulus, and tone-absent trials will be rare. As the blocks proceed, the number of sub-threshold and tone-absent trials will increase while at-threshold trials will become relatively rare. We will assay the number of tone-absent trials in which participants report perceiving a tone (conditioned hallucination) and tone-absent trials in which they do not report perceiving a tone. We will use a custom-made three-tiered model of perceptual belief formation under uncertainty[19,20]. Trajectories can be calculated corresponding to the developing prior that tones are predicted by the visual stimulus for each participant. These can be compared pre- and post-SING to establish which processes differ and which change with SING.

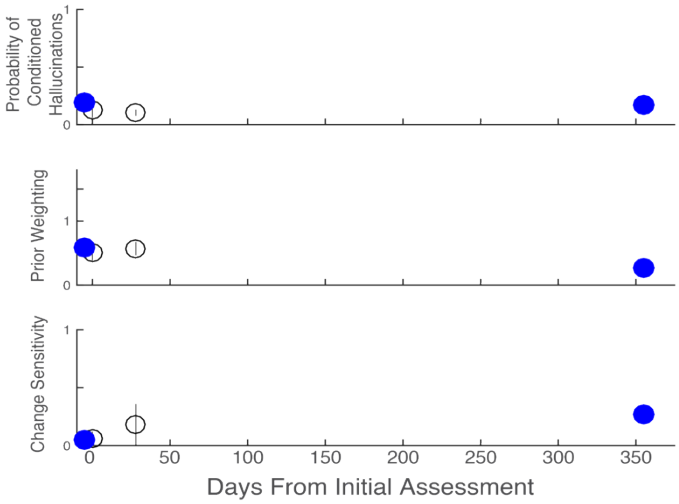

Figure 5. Preliminary Longitudinal Data.
Data from five P-H- participants (white) and one P-H+ participant (blue) modeled on data obtained at two-time points, separated by 28 and 355 days, respectively. The Conditioned Hallucinations effect and parameter estimates are stable. Data plotted on same vertical axes as **Figs. 1** and **2**. Error bars = 1 SEM.

These experiments will require repeated performance of the Conditioned Hallucinations task and re-estimation of model parameters. Sensory conditioning effects tend to be stable across time[39-41], lasting from months to years. Fortunately, multi-sensory learning rarely generalizes to novel stimulus pairs and tasks[42]. 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[18] 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. **We predict** that SING will reduce the number of conditioned hallucinations in people who hear voices. We expect that computational analyses will reveal: 1) that people who hear voices have stronger perceptual priors, and 2) that the strength of these priors will be decreased following SING experience.

R61 Aim 2 – Social Learning: Participants will play the social valuation task pre- and post-SING. As described above, this is a reinforcement learning task with distinct periods of high and low volatility. It is 120 trials long. For the first 40 trials, social volatility is low. For the remaining 80 trials, social volatility is high. The task also includes a non-social cue (green vs blue color) on each trial. Periods of volatility for the non-social cue are designed to be orthogonal to those for the social cue: this allows us to compare responses to both social and non-social cues. Participants will meet a gender-matched confederate for a brief interaction. Lab staff will review the task instructions with the subject and confederate together. The instructions include the information that the confederate's advice may be helpful or unhelpful because the confederate is responding to a separate reward scheme. The participant will complete a practice task to ensure that the instructions are clear. The participant will then watch the confederate complete a practice task. Having the participant watch the confederate practice helps to facilitate the fiction that the confederate is a real participant who needs to learn the task, and allows the participant to see the confederate make both helpful and unhelpful choices. We will use participant behavior to estimate prior expectations for volatility and prediction errors using the Hierarchical Gaussian Filter approach described above and previously employed with this task[26-28]. As above, parallel versions of the social valuation task with a different confederate and different card deck colors will be employed. **We predict** learning rates will be blunted under social volatility in people with AVH, and that this effect will normalize with SING

R61 Aim 3 - Qualitative Interviews: Participants will complete in-depth interviews both before and upon completion of SING. Interviews will focus on their previous experience with music, their experience of participating in the group intervention (post-intervention interview only), and their sense of self in three domains (narrative, embodied, intersubjective) related to the predictive processing theory of voices, psychosis and self.

Previous experience with music. Participants will be asked to describe their current and past relationship with music to both situate the interview within their life experiences and to gain a richer sense of how participating affected their sense of self at post-intervention.

The experience of the group. Asking for participants' experience of participating in the group will (1) help us refine the intervention for the R33 phase to ensure that it is aligned with the proposed targets, and (2) provide us with rich descriptions of the group experience, providing a foundation for exploring changes in sense of self in the post-intervention interview regarding self-experiences that are often difficult to articulate.

Sense of self. The interviews will focus on how people construct representations of self, other, and world and how these representations coincide with their ability to construe, predict, and understand others. Interviews will focus on three aspects of sense of self: (1) *Narrative self.* The ways in which people define themselves will be explored in terms of both identity and social roles (e.g., parent, friend, patient, etc.). Interview questions will elicit perceptions of agency, specifically the ways in which participants construct representations of self and other. (2) *Embodied self.* Interview questions will elicit embodied experience,

particularly the sensations, perceptions, and feelings associated with constructions of self and other. (3) *Intersubjective self.* Participants will explore the experience of interacting with others. Participants will be asked to describe how they perceive others, the ways in which they feel similar and different to others, and the feelings associated with interacting with others in order to deepen our understanding of the ways they construe others.

Qualitative Analysis: Grounded theory will be utilized to analyze interview data to develop an explanatory framework of how the intervention modifies participant's sense of self in relation to proposed targets[43-45]. Interview guides will be constructed in collaboration with stakeholders, including a co-investigator with lived experience of hearing voices (Bien), and piloted in a focus group of persons with 8-10 patients with SMI who hear voices who will not participate in the intervention. Interview guides and questions will be refined and targeted as themes emerge in the data collection phase. Due to: (1) scarcity of research on the topic, (2) uniquely personal yet often shared experiences of music hearing or making and of sense of self, shared sense of self, an extended inquiry is necessary and thus all R61 phase participants will be interviewed. A team of 4 qualitative researchers (Pavlo, Rowe, Bellamy, and Bien) will code interviews and develop a codebook[46,47]. Each transcript will be analyzed in succession and codes will be developed using a consensual approach[48]. The codebook will be refined as each transcript is coded, in line with the constant comparison method[44]. Once a coding structure has been developed, the code structure will be applied and verified by a review of transcripts by the research team[49]. The codebook developed for the pre-intervention interviews will be used to analyze the post-intervention interview to assess changes in self-experience.

Quantitative Analysis: We will analyze participant language use in transcribed quantitative interviews using LIWC[50]. We will focus initially on I, Biological and Negative Emotional Words to focus on the signals identified in our previous work[51,52] and to limit the number of statistical comparisons for which we need to correct with False Discovery Rate Correction[53]. These three categories will comprise one step of our Go/No Go Decision (see below). However, we will also perform exploratory analysis on the other categories of speech in spirit of discovery and knowledge expansion. **We predict** that SING will ameliorate the excessive use of I, Biological and Emotional words in people with psychosis and hallucinations.

5. Genetic Testing N/A ☒

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

A total of 250 (50 in R61, 200 in R33) voice hearing patients (aged 18-65 years) meeting diagnostic criteria for DSM-V psychotic disorder, hearing voices at least once a day, and PANSS P3 (Hallucinations item) greater than 3.

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?*

   A total of 250 (50 in R61, 200 in R33) voice hearing patients (aged 18-65 years) meeting diagnostic criteria for DSM-V psychotic disorder, hearing voices at least once a day, and PANSS P3 (Hallucinations item) greater than 3, will be recruited from the local community via advertisement, from databases of ongoing Clinical Neuroscience Research Unit projects, 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. Prior to study participation all patients will be evaluated for i) protocol eligibility; ii) interaction with the study team to determine participant's probability of completing the study; and iii) ability to cooperate with protocol procedures. The flow of all participants will be reviewed at weekly research meetings in consultation with the study team. 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) mental retardation (IQ<70); iv) Non-English speaking; v) no less than 2 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); vi) Co-morbid mood or anxiety diagnosis; viii) clinically/behaviorally unstable and unable to cooperate with SING procedures. ix) Unstable medical condition based on medical history, physical examination and routine laboratory work-up, including a urine drug screen for illicit substance use (results will remain confidential, they will not be retained, and they will only be used for eligibility determination).

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

   Eligibility will be determined initially by a telephone pre-screen and then confirmed with an in-person interview, by Dr. Corlett and his team.

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

    The risks from this study include 1) emotional distress, and 2) confidentiality.

    1) Emotional Distress: As music and the creation of music can be a personal and emotional experience, it is possible, though highly unlikely in our experience, that some participants could become upset and require mental health support. Trained clinicians and peer-support staff associated with this study will be available to meet with participants and take appropriate steps to support them.

    2) Confidentiality: All participant information will be kept confidential and only members of the Investigative team with appropriate IRB/HIC and HIPAA training will have access to the study data. Data will be maintained and secured in locked file cabinets or password protected electronic media. A numbering code will be used to assign a unique identifier to each participant.

11. Minimizing Risks: *Describe the manner in which the above-mentioned risks will be minimized.*

All participants will undergo a Structured Clinical Interview for DSM-V conducted by a research assistant and a psychiatric evaluation by Dr. Powers (MD, PhD). An outside informant specified by the participant will be contacted to confirm the history. At the end of the test day participants will be "debriefed" by research staff. Dr. Powers (MD PhD) will approve the discharge of participants from testing. We routinely conduct exit interviews to determine whether participants received sufficient information during the consent process and to determine if research staff needs to modify the study procedures to enhance the comfort of participants during testing. Participants will be provided a number to call to reach an on-call research psychiatrist (24 hours/day) should delayed unpleasant effects occur.

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.)*

    a. *What is the investigator's assessment of the overall risk level for subjects participating in this study?*

       We believe there is minimal risk associated with this protocol

    b. *If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?*

       N/A

    c. The principal investigator, Dr. Corlett, is responsible for monitoring the data, assuring protocol compliance, and conducting monthly safety reviews. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the participants and 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. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings and via email or telephone. The protocol's study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of serious adverse events within 5 days of the event becoming known to the principal investigator.

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

R61 Statistical Power: Aims 1-3: Since all participants will perform all studies in Aims 1-3 (Conditioned Hallucinations, Social Learning and Linguistic Markers), we powered our study based on our own preliminary data. Estimated effects for our proposed study of the impact of SING on conditioned hallucinations model parameters are based upon our own data in **Figure 2**. If SING can curtail these group differences – i.e. decrease hallucinating patient responses to the level of non-hallucinating controls, then we would predict the true difference in HGF model parameters pre- versus post-SING would be 0.01 arbitrary units and the within-patient standard deviation of the parameter estimates would be 0.02. We will analyze the model parameter specific to each Aim using paired sample's t-tests, leveraging the added power of within-participant designs. We estimate we will need at least 31 participants to have 80% power to detect a treatment difference at a two-sided 0.05 significance level[54]. We budgeted for 50 unique participants to allow for participant drop-out and the detection of smaller effects of SING on conditioned hallucination behavior, social learning and language use.

Go/No Go Decision: We powered the R61 phase in order to detect complete resolution of conditioned hallucination metrics to the level of non-hallucinating control participants. But we propose a much larger sample of participants in order to be powered to detect smaller changes in conditioned hallucination metrics, social learning and language use. Given standard pharmacotherapies for hallucinations are associated with residual symptoms in 30-50% of participants[55], it would seem an unfairly high bar to demand complete normalization of a candidate behavioral metric in order for an effect on that metric to be meaningful and solicitous of follow-up investigation. In the clinical trials literature, Jacobson and Truax[56] determining clinical significance is often used. It is defined as two standard deviations or greater change in the direction of symptomatic improvement following treatment. We propose to adopt this standard for each metric examined in each of Aims 1-3. **If Conditioned Hallucination parameters, social learning rates or use of personal pronouns, biological words or negative emotional words change by two standard deviations or more from baseline pre-intervention, then those metrics will proceed to our R33 study. If no metrics meet that standard, we will not proceed with the R33.**

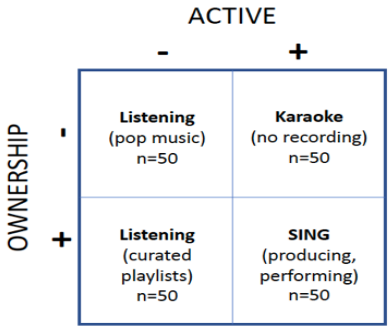

Figure 6. R33 Design

R33 Phase: Should we demonstrate a meaningful impact of SING on computational metrics of behavior, we will proceed to use those metrics in the R33 phase where we aim to deconstruct the active ingredients of SING along two key dimensions, Activity (whether engagement with the group is active or passive) and Ownership (creating some novel musical product, or not). Following screening, once participants have been deemed eligible, their behavior on the selected behavioral metrics will be assayed and they will be randomized to an intervention group. Performance on our computational metrics will be balanced across intervention groups prior to commencement of the four interventions (total n=200, n=50 per intervention, 10 groups of 5 participants per intervention):

(1) **Passive Listening without Ownership** (Activity - / Ownership -, n=50). The group will meet on four occasions, once a week for two hours. The trained facilitator, having procured a playlist of popular music, will spend 15 minutes introducing the session, reminding participants not to sing along and to just sit quietly listening to the music. Next, the facilitator will play music from the playlist through a high-quality speaker at 60-75 decibels for 90 minutes. In the final 15 minutes, the facilitator will summarize the session and dismiss the participants, sharing follow-up music opportunities at the end of the fourth and final session.

(2) **Passive Listening with Ownership** (Activity - / Ownership +, n=50). The trained facilitator will provide a computer and speaker with the ability to stream songs through many media outlets (i.e., Spotify, YouTube, Google). In the first fifteen minutes, the facilitator will introduce the session, participants are reminded not to sing along and to just sit quietly listening to the music. Next the participants will choose songs that they would like to hear. The list can be edited at any point. For the next 90 mins, the playlist will be played through a high-quality speaker at 60-75 decibels. In the final 15 minutes, the group will be concluded, and the participants will be dismissed. If it is the final session, they will be offered follow-up information about the musical opportunities.

(3) **Karaoke** (Activity +/ Ownership -, n=50). The trained facilitator will provide a microphone and speaker along with a karaoke playlist of music and a screen to view lyrics. In the first 10 minutes, participants will be encouraged to write down a list of songs that they would like to sing to. The list can be edited at any point. For 5 minutes, they will conduct body and vocal warm ups, listening to self and others. For 90 minutes, the facilitator will order the participants in turn and invite them to perform karaoke at 60-75 decibels. Each participant will be encouraged to participate. For the final 15 minutes, the session will be concluded, and if the final session, participants will be informed of local opportunities to engage further with music making and musical experiences.

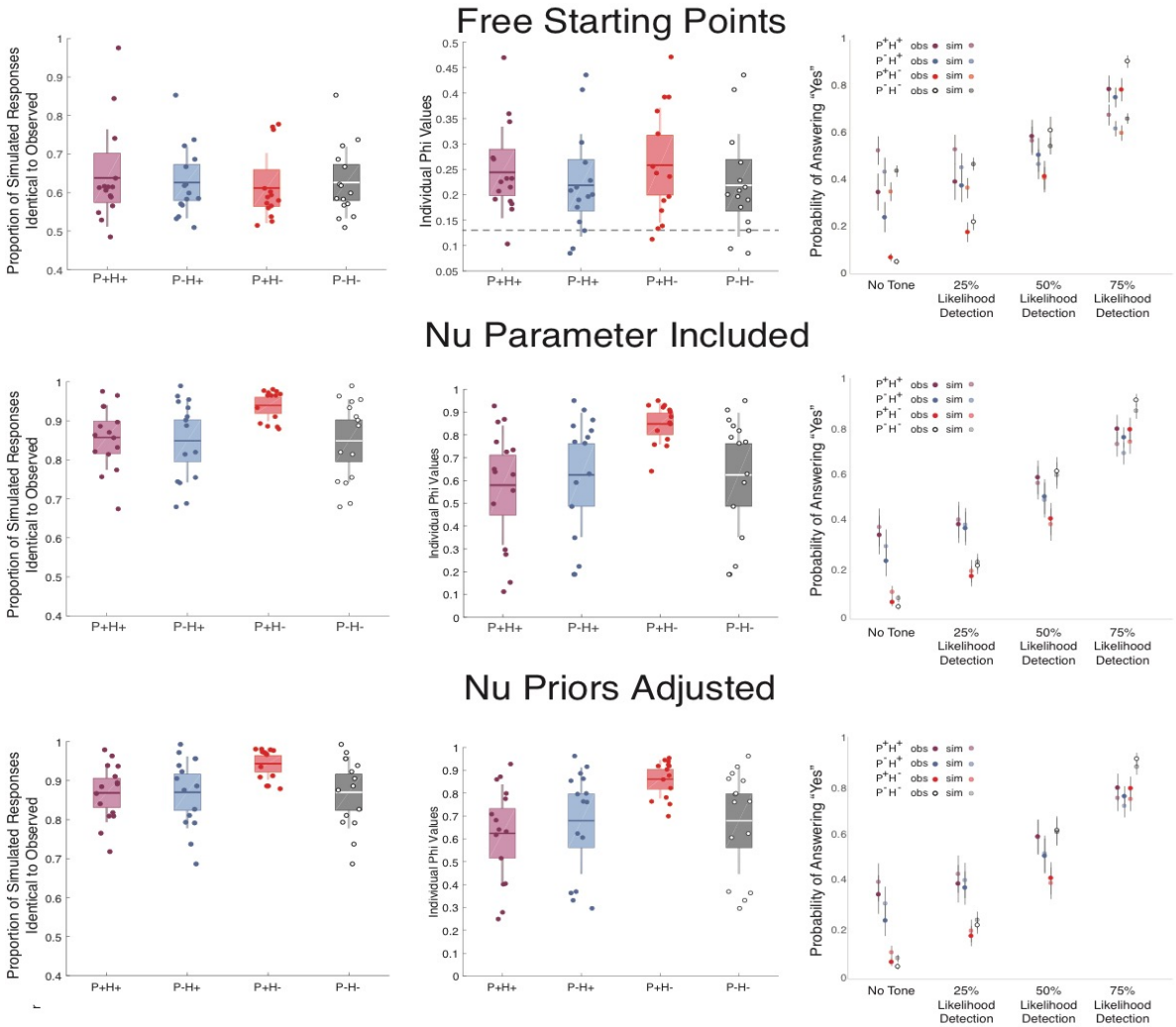

Figure 7. Behavioral simulation across three iterations of the HGF. 1) (top panel) standard HGF implementation; 2) (middle panel) adding Nu, which codes the weighting between sensory evidence and perceptual beliefs; 3) (bottom panel) allowing a more flexible influence of Nu on the overall model. Simulated responses were then compared with observed behavior, comparing the proportion of identical responses (left), individual phi coefficients (middle), and proportion of "yes" responses (right).

(4) **SING** (Activity +/ Ownership +, n=50). As in the R61, the trained facilitator will provide a keyboard, professional microphone, recording interface, headphones, guitar, computer and a Digital Audio Workstation (DAW) for recording. The first 10 minutes of group involve introductions to the other participants and facilitator as well as the goals of the session. Participants will be given paper and a pencil with which to brainstorm potential lyrics. The next 5 minutes involve body and vocal warm ups, listening to self and others. For the next 90 minutes, participants will work together with the facilitator and independently to create their own original lyrics and melody. Each song will have at least one collaborative section (usually the chorus) where lyrics are written and performed together by the whole group. Participants also can write alone and perform sections by themselves. For the last 10 minutes, the group listens back to the entire song that they created. In the final 5 mins, the session is concluded, and the group disbands until the next session. If it is the final session, information sheets on local studio opportunities, karaoke nights and other opportunities to produce, perform and experience music.

For all four intervention types, at the end of each session, the facilitator notes level of contribution and any other significant points regarding individual participation and group coherence (these may be used to weight each participant's contributions to analyses of the intervention's impact on computational behavioral endpoints

R33 Power to Detect Effects. Since all participants will perform all tasks; Conditioned Hallucinations, Social Learning and Linguistic Markers, we powered the R33 based on our own preliminary data (on the understanding that any and all of the tasks from the three R61 aims may or may not progress to the R33). Estimated effects for our proposed study of the impact of SING on conditioned hallucinations model parameters are based upon our own data in **Figure 2**. If SING can curtail these group differences – i.e. decrease hallucinating patient responses to the level of non-hallucinating controls, then we would predict the true difference in HGF model parameters pre- versus post-SING would be 0.01 arbitrary units and the within-patient standard deviation of the parameter estimates would be 0.02. We will analyze the model parameter specific to each of the four interventions in a 2x2 design (Activity vs Ownership) using Analysis of Variance, leveraging the added power of within-participants designs. We estimate we will need at least 31 participants to have 80% power to detect a treatment difference at a two-sided 0.05 significance level[54]. We budgeted for 50 unique participants per group to allow for participant drop-out and the detection of smaller effects of SING on conditioned hallucination behavior, social learning and language use.

Robustness and reproducibility (both phases). We have built in a replication study of the effects of SING on conditioned hallucinations, social learning and language use across our R61 and R33 studies (should those metrics satisfy our Go/No-Go criteria). We have chosen to focus on metrics with face and construct validity for psychosis, whose implication in the mechanisms of psychosis have been conceptually replicated across labs in different cities[57] and countries[58]. Our tasks, analysis code, and data will be made freely available via Yale's ModelDB site. We will optimize and manualize the SING and control interventions in order to prosecute the R61 and R33. Those manuals will be available open access also.

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

B. DRUGS/BIOLOGICS ☒N/A

C. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: *Give the number of subjects.*

   a. Targeted for enrollment at Yale for this protocol: R61, n = 50. R33, n = 200. Total n = 250.
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

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
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:
   a. *Describe how potential subjects will be identified.*

      Potential participants will self-identify in response to our recruitment materials. Potential participants may also be referred by the Specialized Treatment Early in Psychosis (STEP) program.

   b. *Describe how potential subjects are contacted.*

      Potential participants will contact us through call/text/email. If referred to us, we will contact potential participants through call/text/email. We will be contacting participants via our study email address (belieflab@yale.edu), our Yale study cellphone, or office phone.

   c. Who is recruiting potential subjects?

      Dr. Phil Corlett and his team will recruit 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

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: We would like to talk to all potential participants by telephone prior to their screening visit (and their signing consent) to confirm eligibility, interest, and ability to commit to the study*.

      Participants will contact us or will be contacted for a phone screen prior to being invited in for the informed consent and in-person screening session.

   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: Since their first point if contact with the study will be telephone.*

      It would be impossible to provide signed consent prior to a telephone screen that allows us to discern whether to see someone in person for a screening session.

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 participants' independent decision-making.*

   After phone screen, eligible participants will be invited to come to the CMHC for consent. A member of the research team will describe the study to potential participants, provide those who are interested with a consent form to read, answer all questions, and then obtain oral and written consent before beginning any study. Participants who wish to take the form home to consider it further before providing consent will have the option to do so. They may call study staff later to arrange a follow-up visit if they wish to consent to the study and continue the full clinical characterization. Otherwise, this may be completed at time of consent.

   It is possible that some people with schizophrenia will have a conservator. They may wish to participate. In this case we will seek the person's assent and that of their conservator (by adding an optional conservator

signature on the document). We will also ensure that they understand the procedure and their relationships with the study team and their clinical team (that they are different). Since the conservator will need to sign the document too, this will ensure that there is an extended decision period for conserved persons. We will also arrange, with the person's assent, for Dr. Corlett or one of the study team members to speak with the conservator before the person is randomized to the study.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: *Indicate how the personnel obtaining consent will assess the potential participant's ability and capacity to consent to the research being proposed.* A member of study personnel will complete an in-person clinical assessment at intake. This assessment will include questions about the study procedures and possible risks to ensure the participant understands the study and is making an informed decision.

8. Non-English Speaking Subjects: *Explain provisions in place to ensure comprehension for research involving non-English speaking participants. If enrollment of these participants is anticipated, translated copies of all consent materials must be submitted for approval prior to use.*

   We will not recruit non-English speaking participants, they must be fluent in English to participate.

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)*

   ☐ 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 participants will be collected and used for the research?*

   Identifiers that will be collected include:

   i. Name
   ii. D.O.B. (age)
   iii. Sex and Gender
   iv. Telephone number
   v. Email address
   vi. Home address
   vii. Last four digits of SSN

   Health information that will be collected include:

   i. Mental health diagnoses (DSM IV Axis I and II disorders)
   ii. Physical health history
   iii. Current physical health information

2. *How will the research data be collected, recorded and stored?*

   All participants' physical study documents will be kept in a locked cabinet within a locked office so only members of the study team have access. To abide with sponsor (NIH) reporting guidelines, participants' full names, D.O.B., last four digits of social security number (SSN), and address will be documented (demographic forms). Consent forms and other identifying documents (e.g. demographic forms) will be kept separately, in a locked cabinet, from study documents to protect PHI. Other study documents containing health information will be coded with the participants ID numbers. The master list, connecting participant ID number to participant name, will be stored electronically on a secure server within an encrypted file.

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

☐ CD	☒ Portable Hard Drive	☒ Laptop Computer
☐ DVD	☒ Secured Server	☒ Desktop Computer
☐ Flash Drive	☐ 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 participant's participation in the study?*

   The information we collect will be de-identified at the earliest reasonable time after we receive it, meaning we will replace identifying information with a code that does not directly identify the participant. The PI will keep a link that connects identified participants to coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify an individual participant will remain confidential. Data and research materials will be stored in locked cabinets and in password-protected files on a computer. Computers will be encrypted. The research team will only give coded information to others to carry out this research study.

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 http://its.yale.edu/egrc or email it.compliance@yale.edu

5. *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.*

   The data and identifiers will remain in separate locked cabinets at the CMHC as described above. The link to your personal information will be kept for 10 years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

6. *If appropriate, has a Certificate of Confidentiality been obtained?*

   A Certificate of Confidentiality is automatically granted upon notice of award from NIH.

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.)*

Participants will receive a comprehensive psychological assessment during the course of this study, and feedback will be provided to participants about their mental health. If the participant chooses, they may request that this diagnostic information be provided to their clinician at CMHC or to other clinicians, at no charge to the patient, which may help to enhance the quality of care they receive. If the participant does not wish to have this information released to their clinician, it will of course be kept confidential. Participants who are not already in treatment a will be provided with referrals to mental health professionals as needed, which may help them to gain access to treatment that they would not otherwise receive. In terms of benefits to society, we hope that this study will increase our understanding of the processes through which music confers health benefits.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: *What other alternatives are available to the study subjects outside of the research?*

   The alternative is not to participate.

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 can be compensated $100 for each visit of the seven visits, for a total of $700.

   We can compensate up to $50 in transportation studyper visit as necessary to help people attend.

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.*

   There are no costs associated with participation in this research. The assessments included in this study will be provided to the participants at no cost. The CMHC, where the study will occur, is a short walk from areas where participants may receive medical care and is accessible by public transportation from areas throughout New Haven County.

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).*

   No injuries are anticipated from participation in this study. No special provisions for medical treatment are included with this study, although medical personnel from the study team will be available throughout all phases of the study. Participants will be able to access their usual providers and the emergency department should they require evaluation or treatment during the study. They and their insurers will be responsible for paying for this treatment.

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 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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