Protocol Title: Sound and Music for Mild Cognitive Impairment

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PI: Junxin Li, PhD

Junxin.li@jhu.edu

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1. Abstract

Alzheimer's disease and related dementia (ADRD) seriously affect health and quality of life of 5.8 million older Americans. There are limited treatment options for AD and its associated progressive loss of cognition. One promising treatment possibility is auditory gamma stimulation, but much remains unknown. Emerging studies in humans found that 40 Hz sound induce neural gamma oscillation and enhanced cognitive function in older adults with and without AD. Our group has created 40 Hz music intervention by combining the selected music with 40 Hz sound and harmonizing the intensity (decibel) of 40Hz sound with the volume waveform of the selected music. This randomized controlled crossover study is to test the feasibility and preliminary efficacy of 4-week 40 Hz music intervention (A), 40 Hz sound (B) and preferred music (C) on cognitive function in 30 community-dwelling older adults with mild cognitive impairment (MCI). The participants will be randomized to three groups with different sequences of exposure to three conditions (Group 1 A-B-C; Group 2 B-C-A; Group 3. C-A-B). Participants will be instructed to listen to the assigned sequence of conditions, with each condition for one hour each day, five days a week for four weeks. There will be a 10-14 days wash-out break between each condition. Findings from this study will provide fundamental evidence for future development, selection, evaluation, and implementation of music/sound interventions for cognitive health in older adults with MCI.

2. Objectives

3.

Primary objective 1: Evaluate the feasibility of study and the three conditions: A (40 Hz music), B (preferred music), and C (preferred music 40Hz sound) in older adults with MCI.

Primary objective 2: Determine the preliminary efficacy of *A* for four weeks on cognitive function, compared with *B* and *C*.

4. Background

Alzheimer's disease (AD) sriously affects health and quality of life of 5.8 million older Americans. There are limited treatment options for AD and its associated progressive loss of cognition. Target treatments for individuals with mild cognitive impairment (MCI) are essential to slow the cognitive decline and prevent or delay the onset of AD. One promising treatment possibility is auditory gamma stimulation, but much remains unknown. It has been shown that individuals with AD and MCI have abnormal neural activity including reductions in gamma-band oscillations (30–90 Hz). This aberrant gamma activity disrupts neural circuits that involve higher cognition and accelerates AD pathology. Further, gamma oscillations have been positively associated with multiple cognitive functions including attention and memory in humans, suggesting that entrainment of gamma oscillation (modulating neural activities by synchronizing brainwave frequency with stimuli) may reduce AD pathology and improve cognition in both humans and mice. For example, animal studies found that daily auditory stimulation at 40Hz (trains of tones repeating at 40 Hz) for one or two weeks (1 or 2 hours/session per day) decreased amyloid-beta (Aβ) and tau load in the auditory cortex and hippocampus, restored gamma-band oscillations and frontal-parietal connectivity, and improved hippocampal dependent recognition and spatial memory in mouse models of AD. Emerging studies in humans found that 40 Hz sound entrained gamma oscillations and enhanced cognitive function after 12 or more sessions (35 minutes to one hour each session) in older adults with AD. These promising cognitive benefits of 40 Hz sound stimulation need to be validated. In addition, 40 Hz sounds are typically perceived as rough to humans, making it challenging to evaluate clinical benefit. Our group has created a 40 Hz music intervention by underlaying the selected music with 40 Hz sound and harmonizing the intensity (decibel) of 40Hz sound with the volume

waveform of the selected music. This 40 Hz music keeps 40 Hz sound audible, may produce similar gamma entrainment, and is likely more aesthetically pleasing, allowing an evaluation of the long-term use of 40Hz stimulation on cognitive function. We will compare this 40 Hz music intervention to both 40 Hz sound and music alone in a clinical cohort of older adults with MCI for the first time.

5. Study Procedures

Overview of Study design

This is a pilot feasibility study. We will use a randomized controlled crossover design to test the feasibility and preliminary efficacy of 40Hz music (Condition A) intervention, 40 Hz sound intervention (Condition B), and preferred music (Condition C) on cognitive function in 30 community-dwelling older adults with MCI. The participants will be randomized to three groups (n=10 in each group) with different sequences of exposure to three conditions. In each condition, participants will be instructed to listen to the assigned condition for one hour each day for 4 weeks. There will be a 10-14-day wash-out between each condition. Cognitive function, possible covariates including sleep, anxiety, depression will be collected at baseline and the end of each condition using validated measures. Qualitative semi-structured interviews will be conducted after completing each condition to understand participant's experience, preference, and acceptability of the three conditions. (Figure 1).

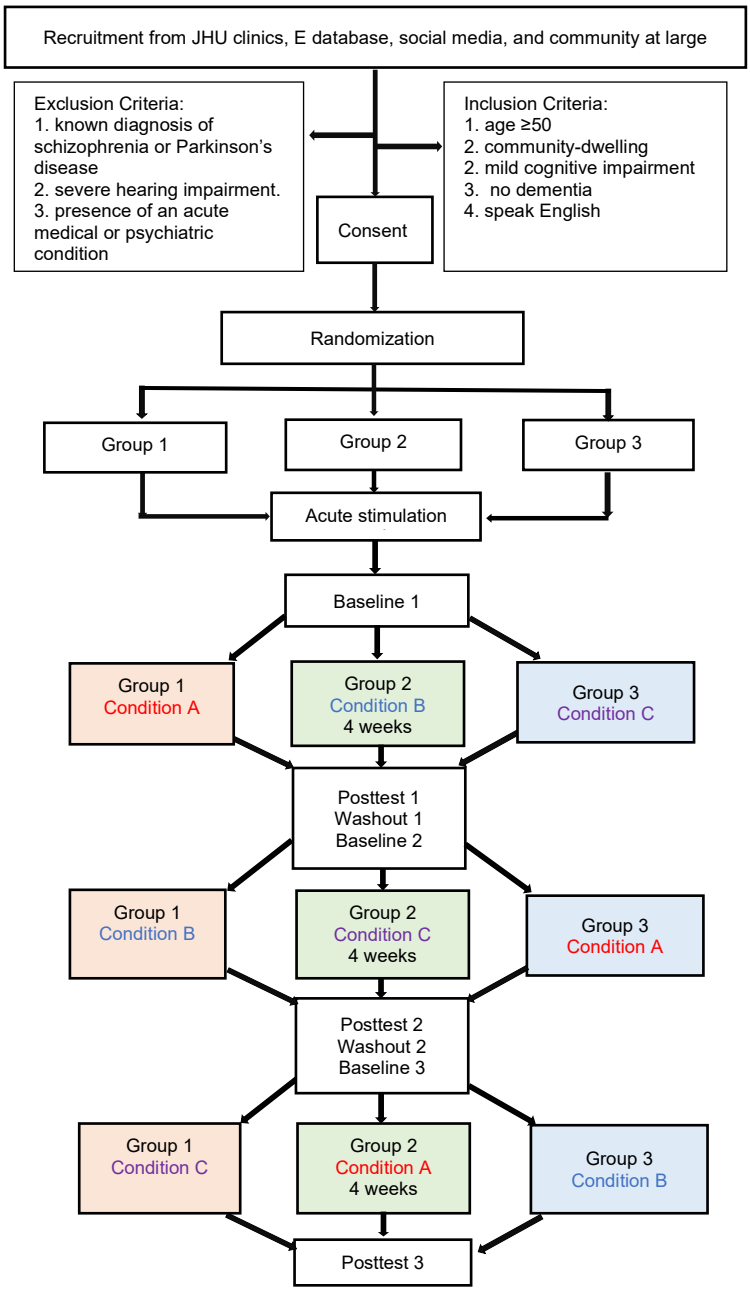

Figure 1: Proposed Study Procedure Chart

Recruitment: We aim to enroll 30 eligible older adults with MCI. The sample will be recruited from multiple sources including community recruitment, geriatric primary care and memory clinics affiliated with the Johns Hopkins University Health System, online recruitment. We will build upon successful recruitment strategies of the Johns Hopkins Center for Injury Research and Policy as well as the Center for Innovative Care in Aging which involves developing targeted study flyers, sending mailings by agencies and medical practices serving older adults, and working with community based advisory groups. The study flyers will be posted near the front desk and examine rooms of clinics, and the activity rooms in senior community centers; In addition, the study team will do presentations at the community center to inform residents of the research opportunity. Interested older adults will contact the research team or leave their contact information (name and phone number) and give

oral permissions that the research team can reach them by phone or onsite. Interested older adults may be contacted on site or through a phone call by the research team. During initial contact with the older adults, the research assistant will describe the study, address any questions or concerns the participant may have. The research team will pre-screen interested older adults to determine eligibility (age, cognitive function, sedentary lifestyle, and poor sleep). If the participant verbally agrees to come in, the research team will schedule a meeting with the potential participant to complete the informed consent. Also, older adults who have participated in prior studies and expressed interest in being contacted for future research will also be invited to participate. In addition, we will be utilizing social media to promote recruitment efforts for this study. We will post the study flyer along with a Qualtrics survey on social media. We will be working collaboratively with the Institute for Clinical and Translational Research (ICTR) to have the study flyer posted on the ICTR JHU Studies Page. Network recruitment strategies will be used, and we will encourage participants to pass the study information on to family and friends. The research team will provide a participant referral incentive of $25 for participants who refer others for enrollment in our research project.

Screening and Consent: Potential participants will first undergo a phone screening to elicit health history and receive detailed information about the study, then be scheduled for a meeting to complete writing consent, HIPAA authorization, and MCI diagnosis determination. A research personnel will meet with the potential participant at the research team office, clinic office or the participant's home per the participant's preference. During the meeting, we will start the consent process with the participant first. The research personnel will provide verbal and written description of the study in detail, allow the potential participant as much time as needed to read and ask questions, and then complete the informed consent. The consent form may be mailed or emailed to the participant before the meeting. After obtaining consent, we will assess participant's cognitive function to confirm the participant's eligibility for mild cognitive impairment using Montreal Cognitive Assessment, Activities of Daily Living, and Functional Activities Questionnaire (see details in Inclusion Criteria).

Study randomization and blinding: Before enrollment, a randomization schedule in REDCap will be created using a random number generator. After baseline data collection, eligible participants will be randomized to three groups (n=10 in each group) with different sequences of exposure to three conditions. The study is a single-blind study. The data collector for outcome assessments will be blinded for participant's exposed condition.

Study duration: The total duration of the study participation will be around 18-20 weeks including 4 weeks of each condition, 10-14 days washout, and 1 week of data collection.

Number of study visits: There will be six data collection visits at the participant's home or at the School of Nursing based on the participant's preference. The 3 baseline data collections will take about 40 minutes. The 3 posttest data collections will take about 60 minutes.

Delivery of Music/Sound Interventions. Within 1 week of baseline data collection, participants will start their assigned sequence of study activity at their home. Participants will listen to the three music/sound conditions: A (40Hz music), B (Preferred Music), and C (40 Hz Sound) with their group assigned sequence (Group 1 A-B-C; Group 2 B-C-A; Group 3. C-A-B). The research team will provide a MP3 player and headphones for each participant to listen to the assigned music/sound during the study. The research team will set up the "listening station" at home with the participant before any assigned activity. Participants will sit on a comfortable chair in front of a table while listening to music/sound. The speaker will be placed on the table. Participants can move hands, stretch arms at the sitting or standing position or they can move around the table

and then sit down if they feel sleepy during the session. The volume of sound/music will be adjusted to the participant's comfortable level, which will be used throughout the assigned listening condition (around 67-80 dB). Participants can listen to sound/music anytime between morning and at least 3 hours before bedtime. Mid-morning (9am-12pm) is the recommended time for the session as the tendency for sleep increases during the afternoon. In each condition, participants will be instructed to listen to the assigned condition for an hour 5 days a week for 4 weeks. The music interventionist or a research assistant will be present for the first two sessions of each condition to assist the participant set up the speaker and adjust volume etc. There will be a 10-14-day wash-out break between each condition. The sound/music list and the volume of sound/music will be updated based on the participant's exposed condition.

Condition A. personalized 40 Hz music: The 40Hz music playlist (15 to 20 pieces of 40Hz music) for each participant will be created using the same list of personal preferred music (See detail in C. Preferred music). The 40 Hz music pieces will be generated by mixing selected music and 40 Hz sound using Adobe Audition (Build 14.2.0.34). The volume of the 40Hz soundtrack will be adjusted to match the decibel level of the music playback. The harmonization of volume between 40Hz sound and the music playback is to make 40 Hz sound audible when the music is loud and improve musicality and avoid abruptness of 40 Hz when the volume of music is low. The music interventionist will assist the 40 Hz music creation.

Condition B. 40 Hz sound: The 40Hz soundtrack is generated using Adobe Audition (Build 14.2.0.34) and consists of a sound clip and a silent interval. In generating the sound clip, the base frequency is set to 17000Hz with a modulation depth of 7000Hz and the modulation rate is set to 40Hz per second. The decibel amplitude is -10.3 dB, and the duration is 1millisecond (ms). The duration of the silent segment is 25 ms. The sound clip and the silent interval are mixed down to a single piece of 25 ms and then repeat 40 times per second.

Condition C. Preferred music: A personalized preferred music playlist with 15-20 pieces of music will be created. We ask the participant to complete the "Assessment of Personal Music Preference"[47], provide the names of their favorite music, and select preferred music pieces from our music library during baseline data collection. To maximize participant's enjoyment and potential musical effect, a personal playlist for each participant will be created using their identified/selected music pieces and individual genre of music by the music interventionist. The study music library will be expanded as we add more participant-suggested music.

Data collection: Data will be collected before and after each condition. In total, the study includes 3 baseline and 3 posttest data collections. Data collection will take place at the participant's home or in a private room at the School of Nursing, a private room at Wald Community Nursing Center, or JHU clinical research unit per the participant's preference. Demographic and other information, and music preference will be collected at 1st baseline data collection. Cognitive function, sweat neurology biomarkers, survey on sleep, anxiety, depression data will be collected at each baseline and posttest data collection. Semi-structured interview data will be collected at each posttest data collection. The interview conversations will be audio recorded and field notes will be taken by a research team member during the interview. We estimate each interview will last about 20 minutes. The participant will be asked to answer open-ended questions about the participant's experience with the study interventions. The voice recordings will be sent to Production Transcripts for transcription (https://www.productiontranscripts.com/).

Measures:

Primary outcome 1: Episodic Memory will be measured using "One Card Learning" (visual)and International Shopping List, and Delayed Recall"(verbal) using Cogstate Alzheimer's Battery

(CAB). A composite episodic memory score will be calculated by taking the average of the standardized scores across the three tests

Primary outcome 2: Global cognition will be measured using Cogstate Alzheimer's Battery (CAB), a set of rapid, reliable and highly sensitive computerized cognitive tests across a comprehensive list of cognitive domains in people with MCI and Alzheimer's disease.CAB has shown good acceptability, efficiency, and stability for the repeated assessment of cognitive function for neuro-epidemiological studies in older adults with MCI and AD. Sub-domains of global cognition in CAB are secondary cognitive outcomes of the study, which include 1) Episodic memory; 2) Executive function will be measured using Modified Groton Maze Learning Test; 3) Attention will be measured using the Identification Test; 4) Working memory will be measured using One Back Test; 5) Processing speed will be measured using "Detection Test"; calculated by following the Cogstate data analysis guidelines. Global cognition will be a composite score of these assessments calculated by following the Cogstate data analysis guidelines.

Feasibility and Acceptability measures: *(1) Study level:* the research team will track the recruitment process from each source, data completeness, and adherence of each study condition, and rate and reasons for participant withdrawal. *(2) Participant level:* We will send a Redcap survey link to each participant daily to collect data on intervention adherence and safety of the prior session (time, duration, volume of sound, any adverse events). Qualitative individual interview data will be collected after the participant completes each condition and used to understand the participant's perceptions and experience with the sound/music conditions, the possibility for long-term use of the conditions, how to build a sound intervention to their routine (best to remember to do it).

Sleep: Actiwatch 2 (Phillips, MA) will be used to measure participant's sleep for 3 days. A sleep diary will be filled out during days of wearing actiwatch. Sleep Profiler (EEG sleep monitor) will be used to monitor sleep for two nights at each data collection. The participants could assess their sleep at home with instructions. Both Actiwatch 2 and Sleep profiler are FDA 510(K) cleared medical devices. Sleep profiler will be used for automatic detection of sleep stages as FDA indications. Pittsburgh Sleep Quality Index and Insomnia Sleep Index will be used to measure subjective sleep quality. Depression will be measured using the 15-item Geriatric Depression Scale (GDS), which has been validated in older adults with different levels of cognitive function. Anxiety will be measured using the short form Geriatric Anxiety Inventory (GAI). It has been commonly used to assess anxiety symptoms in older adults and validated in people with cognitive impairment. We will notify the participant's primary care provider if participants endorse significant levels of anxiety or depression (e.g. GAI>26 or GDS>12). Pain will be measured using the Promis Pain measures.

Demographic and Other information including age, sex, race, education, lifestyle (tobacco and alcohol use, BMI), number of self-reported medical conditions, and medication use, will be collected via questionnaires at baseline. Baseline musical sophistication will be assessed using Goldsmiths Musical Sophistication Index.

6. Inclusion/Exclusion Criteria

Inclusion criteria: 1) age 50 and older; 2) community-dwelling; 3) MCI: The MCI clinical diagnosis will be determined using the 2018 diagnostic criteria: a. 18 ≤Montreal Cognitive Assessment (MoCA) score≤25; b. Memory impairment; c. Preserved Function (Activities of Daily Living (ADLs=6) and Functional Activity Questionnaire (FAQ < 6).

Exclusion Criteria:1) known diagnosis of schizophrenia or Parkinson's disease; 2) severe hearing impairment (Hearing Handicap Inventory≥26); 3) presence of an acute medical or psychiatric condition which would interfere with the subject's ability to follow the study protocol realistically.

7. Drugs/ Substances/ Devices

Sleep profiler and Actiwatch will be used to measure sleep

8. Study Statistics

Sample size and power: We will recruit 30-50 participants based on feasibility for recruitment and study cost estimation. With 10%-15% attrition, statistical power of 0.80, within-subject correlation (r) = 0.8, alpha of 0.05, we will be able to detect a moderate effect size (ES) of 0.5 for changes in cognitive outcomes overtime between conditions. If the ES turned out to be small, this study would provide precise ES for future efficacy trials.

Descriptive analysis will be performed to examine the underlying distributions of each outcomes measure. Distributional assumptions for the proposed statistical method will be verified and data transformation will be performed if required.

Aim 1 is to test the feasibility and acceptability of the three sound/music in older adults with MCI. Both qualitative and quantitative data will be used.

Qualitative data: we will code each transcript (naming segments of data with labels) and then use constant comparison (systematic comparisons of data with data, data with concepts, concepts with concepts, comparison within cases, and comparisons across cases). The interview guide may be revised if the findings suggest the need to include additional perspectives. We will file, index, and catalogue all data and use audit trails to trace the thinking and decision making by writing accurate and comprehensive notes and memos. Nvivo version 12 will be used to manage the interview data and field notes. Transcript of audio-recording with the filed notes will be analyzed using conventional content analysis to identify patterns, consistencies, and differences throughout the interviews.

Quantitative data: Descriptive analysis will be used to test recruitment, retention, adherence, and safety.

Aim 2 is to determine the preliminary efficacy of A for four weeks on cognitive function, compared with B and C. Linear mixed effect (LME) models will be used to examine the change in the outcome measures over time, with the post-pre difference score as the dependent variable. LME models allow the analysis of unbalanced data. The data is considered unbalanced when the study participants have varied number of observations and the observation times differ among the study participants. The model includes condition (treatment) as a fixed effect of primary interest, and controlled for sequence (as a fixed effect) to account for potential order effects due to the crossover design. Age and sex will be included as additional covariates. A random intercept for participant is specified to account for within-subject correlation across conditions.

Treatment of Missing Data. With the use of direct data entry, we expect to minimize missing data. We will obtain reasons for the study drop-outs so that we can assess the missing data mechanism. The pattern of missingness will be examined, and baseline responses compared between those with and without missing data. Variables related to missingness will be included in the analyses, which should yield valid inferences. We will use imputation to impute missing data

and then compare the results from with and without imputation. If the assumption of missing at random is reasonable, likelihood-based methods that ignore the response mechanism will be appropriate. If the probability of missingness depends on the unobserved data even after the observed data are conditioned (i.e., non-ignorable missingness), we will consider both selection models and pattern-mixture models to guide our chosen model. The effect of our assumptions on inferences regarding the missing mechanism will be assessed using sensitivity analyses.

9. Risks

Minimal risks to study participants are expected. Subjects may experience boredom or feel the sound/music is unpleasant during the sessions. The risk is minimized as we use participant preferred music and 40 Hz music to develop the personal playlist. We will stop the assigned sound/music exposure if the participant reports that they feel uncomfortable or cannot tolerate the condition. In addition, the participant may experience psychological reactions to completing the questionnaire data and cognitive tests. Since the questions are benign, the risk is minimal.

The risk of breaching study participant confidentiality will be minimized. We will setup a study database in REDCap, a direct data entry system (REDCap), for all subjective measures (e.g., demographics and questionnaires). Qualitative interview data will be audio-taped, transcribed, and de-identified to ensure accuracy and anonymity. All qualitative interview, EEG, sleep, and cognition data will be encrypted and stored in the study folder on JHdrive, the HIPAA-compliant cloud storage. All participants will be assigned unique study identifiers that will appear on all data collection instruments, documents, and files used in statistical analysis and manuscript preparation. Personal information is needed for tracking informed consent, which will be stored separately from other data and accessible only to select team members. Access to these files will be password protected, recordings will not contain respondent names or other personal identifying information.

Financial risks to the participants: There are no anticipated financial risks to the participants.

Any concerns about the study intervention and adverse events will be reported to the PI and discussed in the weekly team meeting. All research personnel will complete the Collaborative IRB Training Initiative (CITI) Basic Human Subjects Protection course and be certified prior to joining the research team. The PI will report any study related adverse events to JHM IRB.

10. Benefits

There are no direct benefits for the participants from the study. Participants may improve their cognitive function through their participation. In addition, the participants will receive reports of their sleep and cognitive assessment.