Study Title: **Rhythm-based Intervention in Aphasia NCT**

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Center for Brain Health

The BrainHealth Imaging Center at the University of Texas at Dallas is located 2 miles away from the Center for Vital Longevity. All MRI imaging will be conducted here. The center occupies 4300 square feet of a UT Dallas building and includes a reception area and waiting room, equipment rooms, offices for technologists and other personnel, 3 computer-equipped laboratory testing rooms, a conference room, a changing room with lockers, storage rooms, and bathrooms. Two rooms are dedicated to two Siemens 3T Prisma scanners (scanner bays), which are separated by a central control room.

Callier Center

The Callier Richardson, which originally housed both clinical and research activities, recently underwent an expansion and a renovation, allocating a new 50,000-square-foot addition to clinical services and training and the original 20,000-square-foot building to foster high-quality research collaborations among multidisciplinary faculty. This updated laboratory space in Richardson not only has standard audiological equipment, including three 10 x 12 foot double-walled Industrial Accounts Company sound booths, but also has dedicated space for clinical evaluations, consenting participants, and completion of paperwork and online questionnaires.

Two Siemens 3T Prisma scanners that run Syngo MR E11C software that are separated by a central control room. Each scanner has a 60 cm bore and is capable of accommodating up to 204 connected coil elements and 64 RF channels, with two coil configurations available for imaging: a 20-channel (16 head, 4 neck) DirectConnect head/neck coil, and a 64-channel (40 head, 24 neck) DirectConnect/SlideConnect with opening for a 128-lead EEG. The maximum gradient amplitude is 80 mT/m, with a slew rate of 200 T/m/s, allowing for fast ramp times to strong gradients, both of which are vital to spatial and temporal resolution. Additionally, the Siemens Prisma scanners are capable of employing CAIPIRINHA for use in breath-hold experimental designs, and BLADE for rotational k-space sampling. These scanners feature TimTX/ZOOMit for parallel transmit capabilities and B1 shimming to reduce shading artifacts and improve image quality, iPAT² (integrated Parallel Acquisition Techniques) for simultaneous parallel imaging in 3D sequences in the phase encoding and 3D direction.

The visual stimulus presentation systems for both scanners utilize a custom-designed high-resolution, long-life triple LED laser light-source projector with a long-throw lens. Projectors are mounted outside of the scanner rooms to avoid RF noise. Stimuli are projected through a wave guide onto a rear projection screen mounted in the scanner bore. HDMI inputs and remote projector power controls are located near the scanner consoles. Windows 10 desktop PCs with dual-monitors are located at each of the scanner consoles. The computers have E-Prime 3, Presentation, and PsychoPy programs installed.

Delivery of auditory stimuli occurs through an in-ear headset using disposable bud-style canal tips that include passive acoustic noise reduction.

The control-room console unit is a 32-channel electronic interface with automatic gain adjustment and response-device identification and calibration. The interface synchronizes with the scanner via optical pulse triggering and provides complete USB, Serial and Parallel outputs. Button states and trigger inputs for up to 10 buttons are indicated by LEDs on the unit.

Participant responses are captured with non-magnetic, non-electronic response devices. The response devices utilize optical fiber cables to transmit signals to the interface unit located in the control room. Multiple device configurations are available including left and right hand-held button boxes and joysticks to accommodate many types of task-responses.

Two MR-compatible state-of the-art EyeLink 1000+ eyetracker systems (SR Research, Ottawa, Ontario, Canada) equipped with 2000Hz high-speed fiber-optic cameras are available.

Specific Aims

Every year, approximately 800,000 people have a stroke in the United States alone. Among these individuals, roughly 100,000 are diagnosed with aphasia—a disorder characterized by profound challenges in daily communication with their families and peers. Notably, many individuals with aphasia can sing despite their speech difficulties, an observation which led to the development of melodic-intonation therapy (MIT) in the 1970s. Although MIT has since been accepted as a viable aphasia therapy by the American Academy of Neurology, the underlying neurological mechanisms that enable speech recovery remain poorly understood. Here, we propose a highly interdisciplinary approach to study the neural mechanisms of language recovery in aphasia through a novel rhythm-based language intervention.

Our ultimate goal is to help clinicians and therapists optimize aphasia treatment by elucidating the neural basis underlying music-induced language recovery through multimodal neuroimaging and novel statistical analysis. In particular, **we will test a hypothesis that rhythm alone is sufficient to facilitate language recovery, without melody.** This prediction is based upon the theoretical and neuroscientific framework that demonstrates how language heavily relies on rhythm processes mediated by the bilateral sensorimotor network. To explore this hypothesis, we recently devised a novel framework for music-based language therapy that solely leverages rhythm to facilitate language production at the phrase or sentence level. Our therapy was used in a case study with a patient with chronic aphasia who had severely impaired speech fluency due to a large unilateral stroke in the left hemisphere. Following eight weeks of rhythm therapy, she exhibited remarkable improvement in speech production (i.e., from 1-2 spontaneous words to 16 sentences made from 42 words), and increased functional and structural connectivity within key regions of interest associated with the right sensorimotor network. While compelling, these preliminary data warrant further validation using proper active controls and a larger sample size, a goal to be achieved through the proposed research. We have since translated the rhythm therapy into a fun and engaging game termed "TheraBeat" that can be installed on a tablet PC or smartphone. In the proposed research, we will use TheraBeat as a home-based aphasia therapeutic intervention to minimize the burden of patient travel and increase accessibility to therapy. The proposed study will be accomplished by pursuing the following specific aims:

Aim 1. Determine the therapeutic role of rhythm in speech recovery for people with aphasia. Based on recent evidence garnered by our group as well as others, we expect that rhythm-based rehabilitation will enhance speech fluency in people with chronic aphasia, i.e., our target patients who are beyond six months after the onset of stroke. This hypothesis will be tested by directly comparing post-therapy outcomes of the treatment group, who will practice speech production daily through rhythmic activity, to an active control group who will receive conventional speech production therapy without the use of rhythmic activities.

Aim 2. Characterize the neural plasticity promoted by rhythm-based intervention. We hypothesize that daily participation in our new therapy program will promote neuroplasticity along the sensorimotor network, especially within the intact perilesional left or right fronto-striatal circuits that are known to play a key role in speech production and fluency. To determine structural neuroplasticity following the intervention, we will utilize patented myelin-based MRI in combination with diffusion tensor imaging (DTI). To explore functional neuroplasticity, we will use both resting-state fMRI and functional near-infrared spectroscopy (fNIRS). These structural and functional data will be analyzed via a novel statistical shape analysis that captures morphological changes, which cannot be detected by simple statistical approaches.

By using an innovative rhythm-based therapeutic intervention and cutting-edge neuroimaging techniques, we will address hitherto unknown questions regarding how and why music works as a therapeutic regimen for aphasia rehabilitation. With expertise in aphasia rehabilitation, neuroimaging, computer science, and data

analytics, our interdisciplinary research team is well poised to undertake this investigation. The proposed research will serve as a critical stepping stone toward understanding the therapeutic role of music in neurological disorders. Our results will lay the foundations for future studies on music-induced language recovery.

Inclusion of Women, Minorities, and Children

There will be no children enrolled, as the prevalence of stroke in children is much rarer than adults, and the rehabilitation paradigm has not been studied in children. Participants will not be excluded or specifically recruited based on gender or minority status. The sample will reflect the ethnic and racial diversity of Dallas and the surrounding area: 67.7% Caucasian, 30.6% White not Hispanic, 39.5% Hispanic, 6.2% Asian, 1.1% American Indian and Alaska Native, 23.1% African-American, 0.1% Pacific Islander, and 1.8% two or more races, according to the U.S. Census Bureau Data (2015) for Dallas County

Recruitment and Retention Plan

UTD has a large and growing clinical/medical facility including the Callier Richardson and UT Southwestern Medical Center through which we will recruit aphasic patients. In addition, we will recruit patients through Neuro Rehab of Dallas, Centre for Neuro Skills, Baylor Scott & White Institute for Rehabilitation Day Neuro Program, NeuroCare Outpatient Rehabilitation, Pate Rehab Dallas, Texas NeuroRehab Center, and social media (lab Facebook and website pages). Patients who are enrolled in our study will be incentivized for their participation. For example, participants will receive up to $200 for completing the daily video gaming therapy over the course of 8 weeks (a total of 40 sessions at $5 per session). Also, patients' participation for pre- post sessions will be compensated.

The two-year study period consists of pilot phase, phase I, and phase II.

Activities during pilot phase (Y1Q1-Y1Q2)

- Establishing patient recruitment system
- Conducting a pilot clinical trial with 1 patient per group (treatment / active control).
- Constructing pipelines for both behavioral and neuroimaging data
- Modifying the study if needed including revising the Therapy app design, etc.

Activities during phase I (Y1Q3 – Y2Q1)

- Enrolling the first batch of 12 patients (6 per group)
- Conducting a clinical trial
- Revising pipelines for both behavioral and neuroimaging data
- Modifying the study if needed including revising the Therapy app design, etc.
- Progress report

Activities during the phase II (Y2Q2 – Y2Q4)

- Enrolling the second batch of 12 patients (6 per each group)
- Conducting another clinical trial
- Revising pipelines for both behavioral and neuroimaging data
- Conference presentation and manuscript write-up for publication
- Progress report

PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

a) Human Subjects Involvement, Characteristics, and Design

- This research will include 26 adults with chronic aphasia (>6 months post-stroke). To be included in the study, the patient's limb motor function, at least on the left side, should remain relatively intact. Also, participants should be able to name at least a few items. All participants must not suffer from any other type of neurological disease. We will use a pre-post design comparing rhythm therapy to non-rhythm therapy for aphasia with various behavioral assessments, an fMRI, and an fNIRS device.

- The primary site for administrative and data analysis work for this study will be The School of Behavioral and Brain Sciences at The University of Texas at Dallas, the home department of the Principal Investigator for this work (Yune Lee).

- Enrollment of subjects and data collection will occur in the Speech, Language, and Music Lab (SLAM Lab) by research staff, grad students, and undergraduate research assistants. All study staff who have recruitment and data collection roles will be required to complete their IRB training, CITI (Collaborative Institutional Training Initiative) training, and COI (Conflict of Interest).

- All participants will be adults from ages 19-90 in the local Dallas area. Therefore, UT at Dallas will be the IRB of record for this study. UTD will confirm that all study staff have met the requirements for human subject research as required by the institution. The PI for this study, Yune Lee, will serve as the PI of record for this IRB, which is currently in place for the proposed R21 research.

b) Study Procedures, Materials, and Potential Risks

- The proposed research involves a mixed design with pre- post- testing for treatment and an active control group. Primary study procedures include a rhythm gaming therapy that will be administered over 8 weeks of the rehabilitation period. Prior to the start of the study, participants will respond to a series of behavioral assessments. They will also be given a consent form to read and sign if they choose to participate in our study. Following the completion of all study activities, participants and caregivers will be given a debriefing of the study. Clinicians and speech language pathologists will administer these therapy sessions.

- The following private identifiable information will be collected for the

purposes of the proposed research study: (1) name of participant (2) email address or home address (if patient desires follow-up study information from study staff at the conclusion of this study). All data will be collected specifically for the

proposed project. An identification number assigned to each adult at the start of the study will be used on all research materials in lieu of other identifying information whenever possible; this number also will be used for data entry and in all phases of data analysis and data reporting. Hard copies of paperwork, computer files, and neuroimaging data will be stored in a secure research lab to which only key project personnel have access. Patients will be informed in writing on the consent form that all images and identifiable records will be kept for an indefinite amount of time, but that they may withdraw their authorization at any time by notifying the Principal Investigator for this study.

- This proposed investigation poses minimal risks to participants. No known and/or perceived stressors are associated with questionnaire or task completion, but unforeseen risks may be possible. Information collected as part of this study will not be entered into any one participant's respective patient medical record. Furthermore, as all data are collected, they will contain specific participant identifiers known only to the research team. In addition, careful precaution will be taken for the protection of subjects' well-being as well as related sensitive material. Personally identifying information will be anonymized directly following collection. The only key linking personal information to the subject's identity will be kept in a locked file in the lab of the PI and will only be accessible to key personnel. Any additional personally identifying information not pertinent to the research will be shredded immediately (envelopes, labels, etc.).

- There are no known significant risks associated with MRI at this time since the magnetic fields, at the strengths used, are known to be without harm. There are conservative Federal guidelines for radio frequency magnetic field exposure and our examinations fall within those guidelines. We feel these are safe levels and less hazardous than a comparable x-ray computed tomography examination (CT scan). Exceptions include if a person has a cardiac pacemaker or a certain type of metallic clip in their body (i.e., an aneurysm clip in the brain); if a person has worked with metal or had a piece of metal removed from the eye(s); or if a person has shrapnel, bullets, or buckshot in their body. As metallic objects may experience a strong attraction to the magnet, it is very important that the subject notify the researcher of any metal objects, devices or implants that are in or on his/her body before entering the magnet room. This includes biomedical devices such as pacemakers and aneurysm clips, prostheses, and other metallic objects embedded in the body such as bullets, buckshot, shrapnel, and any metal fragments from working around metal. All other metallic objects must also be removed from the subject prior to entering the magnet room or approaching the magnet to prevent them from becoming a projectile or being pulled by the magnet. This includes keys, jewelry, pocketknives, money clips, paper clips, safety pins, hairpins, and barrettes. In addition, objects such as watches, credit cards, and hearing aids could be

damaged in the presence of the magnetic field. A locker will be provided for the subject to secure all his/her items and valuables.

- NIRS is a non-invasive portable neuroimaging device that allows for measurement of brain activity by projecting near infrared light onto the scalp and recording the levels of light absorption and reflection. These measurements allow us to indirectly study the neuronal activities while participants perform a particular task. There are no known risks associated with NIRS.

2. Adequacy of Protection against Risks

a. Informed Consent and Assent

- The PI (Yune Lee), research staff, graduate students, and undergraduate research assistants for this study have recruited adults to participate in this study. Adults must be between the ages of 19-90, with chronic aphasia (>6 months post-stroke). Experienced grad students will train all researchers who will be responsible for obtaining informed consent and assent for this study, and each of these people will be directly observed at least one time by the main researcher before being allowed to seek consent/assent without assistance. The institution involved in this work follows all applicable federal regulations concerning the protection of human subjects for recruitment and consent of subjects in this project.

- Consent: Upon acceptance for adults who meet the inclusion criteria for this study, the researchers will communicate further instructions via email to the patient. During this time, participants will have the opportunity to ask any questions or express concerns about their enrollment and participation. If agreeable to participate, study staff will review the consent/assent forms in detail with them. They will include information to ensure that the patients understand that they have the right to withdraw themselves at any time, as well as the right to refuse to have their results used at the end of the study. As participation in this study is fully voluntary, refusal to participate or later withdrawal of consent or assent does not change any of the benefits given to the patient during study completion. The patient would still be eligible to participate in future studies with the lab. Copies of signed consent forms will be kept in a secure, locked drawer that only key personnel have access to.

b. Protections against Risk

- All project personnel will be trained extensively on project protocols as well as the protection of human subjects. All project staff must complete confidentiality agreements, conflict of interest disclosures, and human subjects trainings. Issues concerning human subjects' protection will be

addressed by the PI, who will be immediately accessible via office or mobile phone.

- Protections against Breaches of Confidentiality: Participants will be assigned a unique identification number that is separated from the master list ofenrolled participant names. This identification number will be used in all instances of data entry and/or archiving. The master list will be kept in a locked file accessible only to research staff who have been adequately trained in the importance of confidentiality and have a need for access to this information. Behavioral assessments, fMRI, and fNIRS data will be given identification numbers and not participants' names. All data will be reported as aggregates and never identified by participants' names. Consent forms/assent forms, background questionnaires, and subject payment receipts will be the only paperwork that includes participants' names.

- Protections against Discomfort during MRI and NIRS: If a participant expresses discomfort during this imaging portion, the researchers will ask questions to try to determine the nature of the problem. The lab has run numerous studies using these neuroimaging devices, and this has not previously been an issue. If a participant is particularly sensitive to the cap or head coil, the researchers will attempt to minimize discomfort and ask participants how they feel after adjustments before deciding to discontinue the session. If a participant expresses significant discomfort, they may refuse to participate in either of the imaging studies without penalty.

c. Vulnerable Subjects

- This research involves aphasia patients, who are a vulnerable population. The purpose of this study is to hopefully find a correlation between rhythm gaming therapy and aphasia symptoms. Thus, it is necessary to involve aphasia patients in this research.

3. Potential Benefits of the Proposed Research to Research Participants and Others

The risks associated with this study are very low compared to the anticipated benefits associated with this work. All subjects are guaranteed payment for their participation throughout the 10-week period. This study will help determine the usefulness and efficacy of rhythm gaming therapy, and will help future aphasia patients who may also benefit from such therapies.

4. Importance of the Knowledge to be Gained

This study contributes to a small yet critical body of research examining the ways in which aphasia patients can benefit from rhythm gaming therapy.

Data and Safety Monitoring

We will develop a data and safety monitoring plan that describes the procedures for the proposed study, including a description of how often and to whom serious and unexpected adverse events will be reported. The plan will help ensure the safety of all participants. Any activity resulting in significant participant distress, discomfort, or injury will be immediately reported to the Principal Investigator. Dr.
Lee is an experienced research scientist who will take appropriate action in such cases, including recommending medical treatment, providing community service referral information, and/or suspending participation in the project.

Measurement and Reporting of Adverse Events.

Data on adverse events will be reported weekly to the Principal Investigator and recorded on an adverse event form. We will use the participant's study ID on the reports in order to be able to track longitudinal adverse event data collected over two or more points in time. We do not anticipate any adverse events and if they do occur, they should be mild in nature. Reports of serious adverse events will result in immediate action. Summary reports of adverse events, and any subsequent IRB actions will be routinely provided to NIH Office of Research Administration. In addition, Dr. Lee will provide a summary of the Data and Safety Management report to the IRB and NIH as part of the annual progress report. The DSM report will include information on the participants' demographic characteristics, recruitment, treatment, retention, Adverse Effects (AEs) and Serious Adverse Events (SAEs), and any significant changes to research procedures that affect the safety of human subjects.

Stopping Rules

We believe this study is of minimal risk and the main results will be decreased aphasia symptoms due to the rhythm gaming therapy. The most likely need for stopping is failure to deliver the intervention as planned or any new information that becomes available on a given subject after the start of the study.
There may be other unexpected events that occur.

External Review for Protection of Human Subjects and Data Integrity

The Data and Safety Monitoring Plan will provide guidance regarding the study activities and help us effectively monitor and evaluate study activities as they relate to participant safety. This plan will undergo monitoring and periodic review of research activities and data to ensure participant safety and scientific validity and integrity of the data by IRB committee.

Internal Oversight for Protection of Human Subjects and Data Integrity

The Principal Investigator, Dr. Lee, has significant expertise and experience in working with aphasia patients. He will provide oversight and carefully monitor all research activities. Dr. Lee will train staff in the IRB approved plan for ensuring the comfort and safety of participants and integrity of the data in the proposed project.

Power analyses and sample size considerations

The anticipated effect size (Cohen's d) was drawn from a similar neuroimaging study examining therapy-induced structural changes in MRI with post-stroke patients (Gauthier Lynne V. et al., 2008). This study yielded the effect size of 2.34 and 1.02 for the treatment and active control group respectively. With the smaller effect size of 1.02, we computed a power analysis via 'pwr' function implemented in R (version 3.5). A minimum of 10 subjects was suggested to ensure 80% power at α=0.05. Although it is difficult to know if the effect size from other study would best reflect the effect size obtained by our study, we surmise that the two-digit number (n=10) per group is reasonably sufficient for the current exploratory work during the 2 years of R21 phase.

Reference

Gauthier Lynne V., Taub Edward, Perkins Christi, Ortmann Magdalene, Mark Victor W., & Uswatte Gitendra. (2008). Remodeling the Brain. *Stroke*, *39*(5), 1520–1525.