**VICTR Research Proposal:**

**Impact of Auditory Access on Sleep Quality of Individuals who use Cochlear Implants**

**A) Specific Aims and Hypothesis**

***Specific Aim 1****:* Do **sleep patterns** of individuals with severe-to-profound bilateral hearing loss using cochlear implants (CIs) change when they have auditory access during sleep?

***H1****:*  We anticipate that sleeping patterns will change when additional auditory access is introduced to the participant during sleep. Because most CI users remove their device(s) prior to sleep, we expect that participants will initially have more difficulty falling asleep, which might result in less sleep, especially during the first week of the study that sound is accessible (Week 2). This will be reflected in the sleep logs and actigraphy data, particularly in analyses involving the total sleep time and sleep onset latencies data. We might see normal sleep behaviors return during Week 4, when the CI is in place but turned off.

***Specific Aim 2****:* Does increased auditory access during sleep affect **sleep quality** (i.e., movements and awakenings) for individuals with severe-to-profound bilateral hearing loss using CIs?

***H2****:*  Most CI users remove their device(s) while sleeping, resulting in a silent environment. We expect that sleep quality will change as a result of the additional auditory access during sleep. We predict that participants will report more disruptive sleep via the PROMIS Sleep Disturbance questionnaire, which is filled out weekly. Changes in sleep quality will also be reflected in the actigraphy data, particularly in analyses of sleep efficiency and number of awakenings.

***Specific Aim 3****:* Does increased auditory access during sleep in individuals with severe-to-profound bilateral hearing loss using CIs affect **next day functioning** (i.e., does auditory access impact restorative function)?

***H3****:*  Sleep has restorative processes necessary for physical, emotional, and cognitive functioning. When sleep is disrupted, it can negatively affect an individual’s ability to function the next day and impose additional stress on the brain and body. Because we predict that increased auditory access during sleep will produce more disruptive sleep, we expect to see a negative change in the individual’s next day functioning. This will be reflected in two different measures during the weeks the individual is sleeping with the CI in place and turned on: (1) higher ratings on the PROMIS Fatigue scale and (2) increased cortisol levels.

**B) Background and Significance**

Continuous advances in hearing technologies have provided auditory access for children and adults with hearing loss. Existing technology, such as hearing aids and CIs, allow individuals with all degrees of hearing loss an opportunity to hear (Zeng, 2004). Typically, these auditory devices are worn during waking hours only, so users are still experiencing periods of auditory deprivation when these devices are turned off and removed during sleep, the current recommendation given to users by most audiologists. Based on the recommended amount of sleep by the National Sleep Foundation, this would deprive adults 7-9 hours (Hirshkowitz et al., 2015) of auditory access each day. It is unknown how impactful this auditory deprivation is and whether increasing access to sound during sleep would be beneficial or detrimental to the individual.

Sleep has physiological restorative properties important for social and emotional functioning (Goldstein & Walker, 2014). Sleep is also important for increased cognitive functioning by supporting memory encoding, enhancing long-term memory, and improving working memory (Diekelmann & Born, 2010; Kopasz et al., 2010; Walker, 2009; Walker & Stickgold, 2004; Walker & Stickgold, 2014). Additional research is needed, as we still do not know if CI users are receiving the full benefit of the device if it is only worn during waking hours. This is an especially relevant question with the potential for the development of fully-implantable devices happening in the near future that would increase auditory access to levels closer to that of a normal-hearing system for these individuals.

We propose that the restorative function of sleep is particularly important for individuals with significant amounts of hearing loss who often experience listening fatigue, and any disturbances in quality of sleep will have a greater negative impact on individuals with hearing loss when compared to individuals with normal hearing. We expect this information to inform development of fully-implantable hearing devices and assist individuals with hearing loss in making decisions about choosing such devices. Additionally, information gained from extending this pilot study will inform our research questions for a more in-depth follow-up study that will examine the impact of nightly auditory deprivation on cognitive functioning of individuals who are deaf.

**C) Preliminary Studies/ Progress Report**

Our auditory research lab has conducted a pilot study (N=6) that found adult CI users reported increased fatigue and more disturbed sleep in addition to having increased salivary cortisol levels upon awakening after sleeping with their CIs turned on compared to when they slept with their CIs turned off (Soman & Tharpe, 2014). In a smaller subgroup (n=2), we collected actigraphy data in addition to the other measures and found increased sleep onset latencies and reduced sleep efficiency (proportion of time the participant is asleep out of the total time in bed) during weeks when they slept with their CIs turned on compared to when they slept with their CIs turned off.

The PI is a postdoctoral fellow in the Pediatric Auditory Development Lab, headed by Dr. Anne Marie Tharpe. This research study has been developed and conducted under the guidance of experienced faculty in the departments of Hearing and Speech Sciences and Pediatrics (Drs. Anne Marie Tharpe, Beth Malow, and Alexandra Key). The key members of the research team are experts in their fields of research and will collaborate to collect, analyze, and interpret data from this pilot study. Dr. Anne Marie Tharpe has conducted research related to hearing loss in children and adults for the past 30+ years. Dr. Beth Malow has conducted research related to quality of sleep in children with and without disabilities, and Dr. Key has expertise in electrophysiologic techniques for measuring brain responses to sound.

**D) Research Design and Methods**

**Research Design.** We propose to collect behavioral and physiological data from 18- to -35-year-old adults with CIs (n=10). The data collection component of this study will take 5-weeks per participant (participants can be run concurrently). During this study, each participant will experience two conditions: a) experimental condition – participants will continue to wear at least one cochlear implant during sleep, and b) control condition – participants will remove their cochlear implant(s) before going to sleep. The following is a breakdown of the five weeks: Week 0 (participant baseline-control), adults with CIs will sleep as they normally do (with the CI off); Week 1 (study baseline-control), adults with CIs will sleep with their CIs in place but turned off to acclimate them to the physical experience of the device during sleep; Weeks 2 and 3 (experimental), adults with CIs will sleep with their CIs in place and turned on giving them access to sounds during sleep; Week 4 (recovery-control), adults with CIs will again sleep with their CIs in place and turned off.

**Inclusionary/Exclusionary Criteria.** Inclusionary criteria include the following: bilateral severe-to-profound hearing loss (unaided pure tone average >75 db) and use of unilateral or bilateral cochlear implants. Exclusionary criteria include: diagnosis of sleep disorders as determined by documentation of sleep history.

**Methods.** A combination of qualitative and quantitative measures will be used to document the impact of continuous auditory access on sleep quality and next day functioning (see Schedule of Study Events at end of section). All measures in this study are routinely used in clinical and diagnostic settings and are non-invasive. The following procedures will be implemented as per standard of care:

1. Eligibility Measures
   1. Documentation of sleep history via face-to-face interview
   2. Documentation of daily sleep habits via RedCap survey
2. Experimental Measures (additional information on behavioral scales and physiological measures is provided afer)
   1. Collection of saliva samples for analysis of salivary cortisol
   2. Use of actigraphy watches to document movement during sleep
   3. Administration of scales of fatigue and sleep quality via RedCap survey.

**Behavioral Scales**. Participants will be asked to fill out questionnaires to provide additional information concerning their sleep history (structured sleep history questionnaire),

sleep schedule (sleep diary), perceived levels of fatigue (PROMIS Fatigue Scale; Reeve et al, 2007), and sleep quality (PROMIS Sleep Disturbance Scale; Reeve et al., 2007). The structured sleep history questionnaire will be completed once at the beginning of the study and it will provide us information about the participant’s typical sleeping behaviors, consumption of substances that might impact sleep (e.g., caffeine or alcohol), levels of physical activity, etc. The PROMIS Fatigue Scale and the PROMIS Sleep Disturbance Scale will be completed weekly. The sleep diary will be completed daily by the participant. The questions reflected in the diary will help to verify that the individual wore his or her implant(s) while sleeping, that it stayed on during the night, and if/when the actigraphy watch was worn. It will also ask about the sleeping environment (e.g., noise levels, lighting, and location) and any potential factors that might have affected the participant’s sleep from the previous night.

**Physiological Measures.** Salivary cortisol samples for determining cortisol concentration will be collected using a sampling protocol similar to that suggested by Stewart & Seeman (2000). Participants will be asked to provide samples of at least 1.00 ml of saliva four times a day -- immediately upon awakening, 30 minutes after awakening, 60 minutes after awakening, and 30 minutes prior to going to sleep. The samples will be collected on 15 days during the study duration (days 2, 3, 4, 9, 10, 11, 16, 17, 18, 23, 24, 25, 30, 31, and 32). To verify compliance, we will use MEMS caps and readers to store saliva. The MEMS caps will record the date and time the bottle is opened which allows us to monitor when the participant places the saliva collection into the tube. These samples will be analyzed by the Hormone Assay and Analytical Services Core in the Vanderbilt University School of Medicine. Participants will also wear actigraphy watches at least 3 hours before going to sleep every night and keep it on until one hour after awakening the next day to document movement during sleep. The actigraphy data will be analyzed by the Vanderbilt Sleep Research Core.

**Safety Monitoring.** Progress and safety will be monitored by completion of daily and weekly queries via RedCap. Participants will be given a calendar listing the various steps in the protocol and when those steps should be completed. Reminders to complete various steps in the protocol will be sent to the participant electronically through the RedCap system. Instructions required for completing the steps in the protocol (e.g., obtaining saliva samples) will be provided in writing at the beginning of the study and with each electronic reminder. Any participant concerns that are not easily resolved by the PI will be communicated to Dr. Tharpe, faculty advisor, immediately. She will determine whether the IRB needs to be notified prior to the time of continuing review.

**Data Collection**. Participants will be recruited, consented and compensated per IRB-approved procedures (IRB#131171). Each participant will be assigned a 3-letter code, consisting of the first letter of the first name and two letters from the last name. Only the PI and faculty advisor (Dr. Tharpe) will have access to the identification key. The PI will administer the eligibility measures and enter de-identified data into the REDCap database. Of the experimental measures, eligible participants will complete all questionnaires via REDCap. The PI will provide the actigraphy watches along with instructions for using the device. Participants will be asked to obtain saliva samples on their own. They will be provided with instructions for the procedure and materials that have been labeled with the participant’s unique three-letter code. Daily feedback from the participants will alert the PI to any discomfort felt by the participants. Specific feedback will be reported to the co-PIs. If an adverse event occurs during the experimental procedure or data maintenance and analysis, a report will be made to the IRB.

**Data Analysis and Interpretation**. All qualitative data obtained from questionnaires will be compiled and analyzed by the PI with support from members of the research team. The Hormone Assay and Analytical Services Core Lab at Vanderbilt University School of Medicine will analyze the cortisol samples. The Hormone Assay and Analytical Services Core Lab have experience in analyses of salivary cortisol and have been involved in federally-funded projects. Sleep durations (sleep and wake times) will be entered into the RedCap database and actigraphy data collected by the actigraph watches will be reviewed and analyzed by Dr. Beth Malow, manager of Vanderbilt Sleep Research Core, or a staff member of the core.

**Participant selection.** Up to 10 adults with hearing loss will be consented through IRB-approved procedures.

**Schedule of Study Events**

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| Procedure/Activity | Frequency |
| Participants will complete a medical and demographic questionnaire via REDCAP or in person with the PI to determine eligibility for participation (See Attachment 1) | Once before the study begins |
| Participants will meet with the PI and complete the structured sleep history to determine eligibility for participation. (See Attachment 2) | Once before the study begins |
| Monitoring of movement through actigraphy watch | Daily from 3 hours before going to bed until one hour after waking up the next morning |
| Participants will wear cochlear implants during sleep | Every night on day 15 to day 28 |
| Participants will complete sleep diary via RedCap. (See Attachment 3) | Daily |
| Participants will complete PROMIS Fatigue scale via RedCap. (See Attachment 4) | Weekly on Day 7, 14, 21, 28 and 35 |
| Participants will complete PROMIS Sleep Quality scale via RedCap. (See Attachment 5) | Weekly on Day 7, 14, 21, 28 and 35 |
| Participants will extract at least 1.00ml of saliva on their own using saliva collection materials kit provided by the investigator. | Four times a day on Day 2, 3, 4, 9, 10, 11, 16, 16, 17, 18, 23, 24, 25, 30, 31 and 32.  Saliva 1– immediately upon awakening  Saliva 2 – 30 minutes after awakening  Saliva 3- 60 minutes after awakening  Saliva 4 – 30 minutes prior to sleeping at night. |

**E) Sample Size Justification and Statistical Analysis Plan**

We propose to extend our pilot study to examine the feasibility of applying standard techniques used to diagnose and monitor sleep-related issues to a novel population of adults with hearing loss who use cochlear implants. Such a study has never been conducted before. Consequently, data to conduct a power analysis are not available. We propose to conduct this study with a convenience sample of at least five participants. Data obtained from this pilot study will inform the sample size and statistical analyses plan for future studies.

The following qualitative and quantitative data on sleep quality of participants in this study will be collected:

1. Wrist actigraphy data to measure movement during sleep
2. Salivary cortisol to measure changes in cortisol levels during experimental and  control conditions
3. Sleep quality scale ratings to obtain participants’ perspective on their quality of sleep
4. Fatigue scale ratings to obtain participants’ perspective on level of fatigue and next-day  functioning
5. Daily sleep diary records to document any changes in sleep habits or environment

The primary focus will be to analyze the impact of the independent variable, presence or absence of auditory access during sleep, on two dependent variables, a) sleep quality and b) fatigue. Dr. Beth Malow and members of the sleep core will analyze the actigraphy data to identify the following constructs for every day that the actigraphy watch is used:

* Total Sleep Time (TST), sum of all sleep epochs between sleep onset and end
* Sleep Efficiency (SE), ratio of time slept vs. time spent in bed
* Sleep Onset Latency (SOL), time required to fall asleep after first trying to fall asleep
* Wake Time After Sleep Onset (WASO), sum of all awake times during sleep onset to  sleep end

Within subject differences across conditions will be analyzed. Correlational analyses will be conducted on the subjective measures of sleep quality (i.e., responses on the sleep quality questionnaire and daily sleep diary) and objective measures of sleep quality (i.e., SOL and WASO from the actigraphy). Similar analyses have been conducted in previous studies evaluating sleep quality (Bagai et al., 2013; Malow et al., 2012).

The second dependent variable – fatigue and next day functioning will be analyzed using salivary cortisol samples and responses on the fatigue scale. Cortisol levels provide an indication of stress level in the individual during the time of sample collection. The highest levels of cortisol occur in the morning, reduce throughout the day and are lowest at night. The staff in the Hormone Assay and Analytical Services Core Lab at Vanderbilt University School of Medicine will analyze the cortisol samples to identify the amount of cortisol present in the participants’ saliva at time of sample collection. Within subject differences in cortisol levels across time (i.e., morning sample vs. night sample) and conditions (i.e., during weeks with and without cochlear implant usage at night) will be analyzed.  The fatigue scale and next day functioning scale will provide data on the participants’ perceived stress level over the course of the study. Within subject differences in fatigue and next day functioning as reported by the participants will be analyzed. Correlation analyses will be used to compare cortisol levels and responses of the fatigue scale.  Additionally, using these preliminary data, we will identify factors that might mediate quality of sleep and next day functioning in individuals with hearing loss who use cochlear implants.

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