Audiological management of children with unilateral hearing loss

Study Protocol and Statistical Analysis Plan

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Study Protocol

The study procedures fall under three aims: Aim 1 will evaluate the effects of auditory experience on behavioral measures of spatial hearing, including processing spatial cues, localization, and speech recognition in noise. Aim 2 will evaluate the effects of auditory experience on neural measure of spatial hearing, language, and cognition. Aim 3 will collect longitudinal measures of speech, language, academic achievement and cognition across three visits that are one year apart. Speech, language, academic achievement and cognition will be tested longitudinally. Auditory and neuroimaging visits will occur one time.

We will collect data from 80 children with mild to severe unilateral hearing loss between 6-16 years of age. Children with normal hearing in the same age range are included to serve as a local normative sample across all three aims. Following recruitment, all portions of the study will be fully explained to the participant and parent during the consent process, but before starting each visit, study staff will again review the key points with each participant/parent to ensure understanding. Participant's parents will complete an intake questionnaire that includes the child's general characteristics, hearing history, and device use (if any). Parents will also complete the HEARQL questionnaire, a hearing related quality of life questionnaire that has been validated for children.

Auditory Visits: Children will complete a battery of listening tasks that assess hearing sensitivity, speech recognition, and spatial hearing. Children with unilateral hearing loss who use air- or bone-conduction hearing aids will also receive electroacoustic hearing aid verification using a probe microphone system. Behavioral audiometry will be completed using conventional audiometric approaches with air conduction thresholds from 250 - 8000 Hz and bone conduction thresholds from 500 - 4000 Hz. Masking will be used as needed to isolate responses from each ear. Tympanometry or wideband acoustic immittance will be completed on each ear to assess middle ear function. Distortion Product Otoacoustic emissions will be measured using an insert earphone for each ear to assess outer hair cell function. All of these auditory tests are standard clinical assessments that will be conducted by a research audiologist. Experimental auditory measures will be completed at the same visit or a separate visit based on the preference of the participant and their family to minimize fatigue. Each participant will listen to speech, pure tone or noise stimuli presented via a speaker or headphones at a level where the signal is audible, but not uncomfortably loud. The experiments will assess processing of inter-aural level and timing differences (ILD and ITD), localization of sounds, and speech recognition in background noise where the target speech and noise are co-located (same speaker) or spatially separated. The participant will indicate their response by pressing a button (detection tasks), verbally responding (speech

recognition), or pointing/indicating the direction of the response (localization) using a mouse or computer interface. Participants will be given breaks between tasks to minimize fatigue.

Speech and Language Visits: Children will complete standardized measures of speech and language development using subtests from the Comprehensive Assessment of Spoken Language, Test of Integrated Language and Literacy Skills (TILLS) and the Children's Test of Phonological Processing (CTOPP). Language measures will be collected at three two-hour visits that are at least one year apart during the study.

Neuroimaging Visits: Approximately 40 of the children with unilateral hearing loss and 40 age-matched peers with normal hearing will undergo magnetic resonance imaging (MRI) and magnetoencephalography (MEG) at the Institute for Human Neuroscience at Boys Town National Research Hospital. Most participants will complete one or more set of MEG experiments and one or more sets of MRI experiments spread across at least two visits, and potentially more or less depending on the participants' fatigue or preference. Each MEG session will last approximately 60-90 minutes (total scan time), whereas each MRI session will last approximately 60 minutes (total scan time). Ideally, all appointments would be scheduled within a four-week period, but MEG and MRI scheduling may preclude this in some participants. We will then schedule the earliest available time. Of note, some older youth may elect to do one long MEG and MRI appointment to cut down on the number of visits. In this case, a break interval with a minimum of one hour after the MEG appointment will be offered before the MRI appointment begins. Alternatively, some younger participants might opt to split their MEG visits into two shorter intervals of 30-45 minutes each, as needed.

MEG session(s) : Participant will be escorted to the digitization suite next to the MEG suites by the MEG technician for MEG coil placement and further prepping prior to the study. These coils are simply small discs that are attached to the skin surface to allow for the head location to be calculated throughout the MEG recording session. After the coils are placed, they will be led into the magnetically shielded room, which houses the MEG system, and will be positioned into the acquisition chair by the MEG technician. Once positioned, the MEG technician will ensure that the participant is comfortable, go over the instructions specific to the task that the participant is about to complete, and remind the participant to remain still during recording. The MEG technician will then close the door to the magnetically-shielded room, walk to the acquisition workstation and test the intercom system by asking the participant a question (e.g., Can you hear me?). The MEG technician will then tell the participant we are ready to begin and remind them to stay very still. MEG data will then be acquired by the technician as the subject completes each task. Once a task is complete, the participant will then be informed via intercom that they can relax. After a few-minute break,

the participant will be told to get ready to begin again, and the process of recording will be repeated. Each recording will last from 5-20 minutes depending on the task, and between 3-10 tasks will be completed within a given MEG session. Once the session has been completed, the MEG technician will inform the subject they are finished, and they will enter the room to lead them out into the MEG suite. Once outside the magnetically shielded room, the MEG technician will remove the MEG coils from the participant and allow them to use the private bathroom with cleansing station to touch up their makeup and/or fix their hair. The cognitive tasks used in the MEG portion of the study may involve visual, somatosensory, and/or auditory stimulation (varies by task) and will be no more stressful or stimulating than watching public television. Some tasks require participants to perform a cognitive test such as memorizing stimuli, completing patterns, selectively pay attention to one or more stimuli, recall, listen to, and/or respond to words, etc.; finger or hand movements; or remain still and rest and/or receive passive somatosensory, visual, or auditory stimulation. The only risk involved is that the participant may be bored by the cognitive task.

MRI session : Prior to entering the MRI, the participant will complete the MRI safety checklist. Once complete, an MRI technician will escort the participant into the room that houses the MRI scanner. This MRI protocol does not involve contrast agents or sedation of any kind, and earplugs will be provided to minimize the loud noise from the scanner. The technician will position the participant inside the magnet bore and ensure that they are comfortable. Once positioned, the participant will be asked to remain still and undergo a series of 6-12 minute MRI sequences (depending on the sequence), which may include one or more of the following: a structural MRI scan, resting-state or task-based fMRI sessions, diffusion-tensor imaging, or GABA spectroscopy. During the task-based fMRI sessions, participants may be asked to perform a cognitive task or remain still and passively be presented with auditory, visual, or tactile stimulation. Again, all sequences are completely noninvasive and do not involve contrast agents or sedation of any kind. There will be breaks of a few minutes between each MRI sequence collection. In total, MRI data collection will take about 40-60 minutes. After the MRI acquisition, the MRI tech will remove the participant from the MRI bed and lead them out of the room. At this time, the participant will be reminded to pick up any belongings they had removed prior to the MRI scan (e.g., keys, shoes, hats), and escorted to the waiting room to meet their parent and/or guardian.

Statistical Analysis Plan

Overall study design and power analyses. In each experiment, we will use linear mixed models with random intercepts for each subject to account for the correlation between repeated observations within subjects across conditions or over time. Each model may also include random slopes to account for individual variability across time, different variance parameters per level to account for heterogeneity, or different correlations between levels. Model selection criteria (e.g., Akaike or Bayesian Information Criteria) will be used to determine the best fitting covariance pattern to each model. Models will be organized within a path-analytic framework where variables serve as predictors, mediators of predictors, outcomes, or control variables. We will use empirical methods (model selection) and rational methods (scientific knowledge) for variable reduction prior to hypothesis testing to minimize collinearity between predictors. For each experiment, 1,000 datasets were simulated based on anticipated effect sizes from previous research to estimate statistical power and sample size (Lu et al. 2008). Power analyses reported for each experiment assume α=0.05 to achieve 80% power computed as the percentage of the 1,000 datasets that rejected the null hypothesis. For each experiment, the statistical power was calculated based on the smallest anticipated effect size from the previous literature or preliminary data. Simulation models for effect sizes and variance parameters are based on preliminary data, previous studies of children with normal hearing (CNH) and children with unilateral hearing loss (CUHL), and our experience recruiting large numbers of CNH and CUHL.

Our power analysis and target enrollment numbers are based on the assumptions that 1) participants will participate in multiple studies throughout the duration of the project and 2) that approximately 25% of participants will be lost to attrition from either not returning to participate or aging beyond the maximum age for inclusion in the study. Detailed power analysis based on simulation for each experiment is provided in the table below. Our total estimated enrollment for the study of 80 CUHL (ages 6-16 years) with mild to severe UHL provides a conservative estimate to detect the smallest effect size in the longitudinal mediation models in Aim 3 (n=62) with an additional 18 subjects to offset this anticipated attrition. Power analyses for experiments with CNH (n=80) are based providing a matched group of similar size and demographic characteristics as the group with UHL.

Estimated minimize sample size for each experiment based on linear mixed effects models simulation.			
Aim 1			
	Outcomes	Effect size	Estimated Sample size
Exp. 1A	Electroacoustic ILD/ITD distortion	ILD RMS ratio=2:1 ITD Cross-correlation <0.7	n=40 hearing aids
Exp. 1B	ILD and ITD thresholds	ILD group differences > 5 dB ITD group differences > 107µsec	CNH = 36 CUHL = 36
Exp. 1C	Localization accuracy and weights	Accuracy differences > 10º Weighting differences > 0.3	CNH = 50 CUHL = 50

Exp. 1D	Spatial release from masking	4 dB difference in SRM across groups or conditions	CNH = 30 CUHL =30
Aim 2			
Exp. 2A	Group differences in neural activation and effects of auditory dosage	Group differences > 10% accuracy in ILD/ITD detection	CNH = 40 CUHL = 40
Exp. 2B			
Exp. 2C			
Aim 3			
Exp. 3A	Language outcomes	Growth in standardized outcomes > 0.15/year with mediation effects.	CNH = 62 +18=80 CUHL=62+18 = 80
Exp. 3B	Academic outcomes		

We will attempt to minimize the likelihood of missing data by giving the participants breaks during experiments and breaking experiments up into multiple laboratory visits. The linear mixed models we are proposing for analysis in each experiment can accommodate for missing data. Patterns of missing data will be analyzed to determine if data are missing completely at random or if the pattern of missing data is related to any study-related variables of interest, including auditory or cognitive skills.