End of Summer Talks 2016

September 28, 2016
Meltzer Auditorium
Massachusetts Eye and Ear
4:05 pm  
Welcome and Introduction

4:15 pm  
**Sara Beach**  
*Neural basis of speech error detection and correction in aphasia*  
Advisor: Swathi Kiran, PhD - Aphasia Research Lab, Boston University

Recent neuroimaging evidence suggests that the human auditory system constantly monitors its own speech, making use of acoustic mismatches between predicted and realized speech in order to correct that speech online. We investigated these processes in aphasia, a communication disorder caused by damage to language-related brain regions. Persons with aphasia (PWA) took part in two experiments designed to examine their error detection and correction abilities. In Experiment 1, PWA spoke aloud 200 tokens each of the words eat, Ed, and add, forming a distribution of each individual’s more prototypical and less prototypical utterances. Analysis of the vowels’ first and second formant trajectories revealed that (1) overall, PWA had more variable speech production, measured at syllable onset, than healthy speakers; (2) PWA’s less prototypical utterances became more prototypical over the course of the syllable; (3) the more acoustically variable the syllable onset, the more the formants were corrected. These results suggest that PWA can make use of feedback to correct their speech online. In Experiment 2, we examined the neural basis of this ability using magnetoencephalography, during which PWA spoke aloud the same three words and listened to a recording of that speech in alternating blocks. In healthy speakers, suppression of early auditory cortical responses during speaking versus listening demonstrates a match between predicted and realized speech, while reduced suppression indicates a mismatch. We use this suppression index to examine how less prototypical utterances are corrected by PWA, given the anatomical and functional sequelae of left-hemisphere stroke. Results will contribute to an understanding of audio-motor feedback and may suggest opportunities to leverage intact feedback systems for individualized speech therapies for PWA.

**Keywords:** aphasia, speech, magnetoencephalography

4:30 pm  
**Meenakshi Asokan**  
*In-vivo calcium imaging to study the response of descending projections from the cortex*  
Advisor: Daniel Polley, PhD - Neural Plasticity Research Lab, Massachusetts Eye and Ear

*Background:* The auditory system is characterized by both ascending and descending projections. Despite the higher density of the feedback projections, very little is known about their role in processing of the sensory signals and the plasticity following sensory loss. The Cortico-Collicular (CCol) axons originating from layer V pyramidal neurons and terminating within the Inferior Colliculus (IC) are one of the main feedback projections. In mice, CCol axons form a dense plexus on the dorsal cap of the IC, between the cerebral cortex and cerebellum providing easy optical accessibility. Hence, we use calcium imaging to indirectly probe the sound-evoked spiking activity in CCol axons.

*Methods:* CBA/CaJ mice aged 4-6 weeks injected with a viral vector to induce expression of genetically encoded calcium sensitive fluorescent protein (GCaMP6s) in the neurons of the auditory cortex. After 3-8 weeks of incubation, a metal head-plate was implanted for head fixation, a circular craniotomy 3mm in diameter was performed over the IC, and covered with a glass coverslip that was secured in place with the surrounding skull to create a chronic cranial window. Post recovery and habituation, wide-field imaging was performed on head-fixed awake mice. Pure tones (8KHz and 32KHz) and noise burst that varied randomly in level (20-80dB SPL in steps of 10dB) were presented in free-field for a 50msec duration with an inter-trial interval of 2sec, and images were acquired using a 4X objective at a rate of 10Hz.

*Results:* Spiking activity was indirectly inferred from GCaMP6 fluorescence in CCol axons due to the close link between electrical excitation, calcium influx mediated by voltage dependent calcium channels and the change in fluorescence associated with calcium binding to GCaMP6s. The fractional fluorescence change (dF/F) relative to the baseline fluorescence after averaging over all pixels in a Region-of-interest (ROI) corresponding to the IC revealed strong acoustically driven responses from the CCol axons. Temporal information about the population spiking activity was recovered using "temporal de-convolution" of the broadened activa-
tion owing to the relatively slow dynamics of GCaMP6s. The fluorescence measurements for different SPLs revealed the CCol axon population to possess a combination of monotonic and non-monotonic "rate-level" functions for different sound stimuli.

**Conclusion:** We implemented a chronic imaging approach to isolate population activity from a select population of descending corticofugal neurons and track changes in their sound-evoked activity before and after hearing loss. The findings from in-vivo calcium imaging of the CCol axons in awake mice suggests that there is a robust acoustically driven response that originates from the cortex and spreads down through the descending projections to provide feedback to IC. This feedback circuit could potentially play a role in facilitating the plasticity of processing the sensory signals after sensory loss by spreading the effects of the cortical amplifier to subcortical centers and modulating their response.

**Keywords:** calcium imaging, cortico-collicular axons, plasticity

**4:45 pm**

**Olivia Murton**

*Impact of congestive heart failure on voice and speech production: A pilot study*

Advisors: Robert Hillman, PhD, CCC-SLP and Daryush Mehta, PhD - MGH Voice Center

Congestive heart failure (CHF) is a chronic condition in which patients are stable but may deteriorate into episodes of decompensation, which is acute and life-threatening. Current methods of identifying imminent decompensation (e.g. weight monitoring) have limited reliability and only reflect changes that occur shortly before the onset of symptoms. The goal of this pilot study was to determine whether voice and speech changes during hospitalizations for acute decompensated heart failure are correlated with conventional measures of volume status such as weight. We hypothesized that (1) vocal fold edema would reduce F0 and increase acoustic perturbation in the voice and (2) pulmonary edema would increase the frequency of breaths during continuous speech.

Ten CHF patients (8M/2F, mean age 70±13 years) who were hospitalized for acute decompensation were enrolled. Weights were recorded daily, and plasma NT-proBNP levels and patient-rated visual analog scales of dyspnea and global symptoms were assessed at admission and discharge. A daily speech recording protocol of sustained vowels, reading passages, and spontaneous speech was also performed. The most acoustically stable 1-second section of each vowel was analyzed for measures of acoustic perturbation and instability. The read passages were transcribed and the locations of breaths were identified automatically to yield measures of respiratory stress.

During their hospitalizations, weight decreased in all patients (mean weight loss 8.5 ± 5kg). Eight of the ten patients showed improvement in pitch standard deviation, jitter, and CPP standard deviation. CPP improved in 6/10 patients. Respiratory stress measures also showed improvement, with the number of phonemes per phrase increasing in 7/10 patients. These results point to some potential relationships between voice and cardiac status. Goals for future work include comparing these audio-based results to those derived from the neck-mounted accelerometer, and examining day-to-day changes in weight and voice during the hospital stays.

**Keywords:** voice and speech production, speech breathing, congestive heart failure

**5:00 pm**

**Salwa Masud**

*The effect of superior canal dehiscence on wideband acoustic immittance in fresh human cadaveric specimens*

Advisor: Hideko Heidi Nakajima, MD, PhD - Middle-ear Mechanics Lab, Massachusetts Eye and Ear

Superior canal dehiscence (SCD) is a hole in the bony wall of the superior semicircular canal, which can cause auditory and/or vestibular symptoms such as hyperacusis, aural fullness, autophony, and pressure- and sound-induced vertigo. Currently in the clinic, diagnosis of SCD involves assessment of symptoms, directed oto-logic exam, CT scan, vestibular evoked myogenic potential (VEMP) testing and an audiogram. Lower VEMP thresholds and conductive hearing loss (due to supersensitivity to bone-conducted acoustic stimuli and increased air-conduction thresholds) at low frequencies are common indicators of a possible SCD, but is not always present in all SCD patients. Mechanically speaking, a decreased sensitivity to air-conducted sounds may be due to the "third window" hypothesis in which an SCD shunts the oval-window volume velocity (in response to sound stimuli) away from the cochlea. Here, we test the effect of SCD on wideband acoustic immittance (WAI) and extract the reflectance (R) (which is the ratio be-
tween the reflected sound from the tympanic membrane and the forward sound stimulus). WAI is a potential non-invasive, cost-effective diagnostic tool that can be used to distinguish various middle-ear pathologies. In a controlled soundproof chamber, we measured WAI in five fresh human cadaveric temporal bones before and after surgically drilling a hole in the superior semicircular canal. The dehiscence was then patched with dental impression material to reverse SCD-induced changes in WAI. In all five experiments, there was a decrease in power reflectance (\( PR = |R|^2 \)) due to SCD between 300 Hz and 800 Hz, and an increase in PR between 800 Hz and 1500 Hz. Consistent SCD-induced changes across all five experiments show great promise in using WAI as a non-invasive diagnostic tool to detect SCD, and in developing phenomenological models to better understand the auditory and vestibular symptoms associated with SCD.

**Keywords:** superior canal dehiscence, power reflectance

**5:15 pm**

**Kameron Clayton**

*Possible roles of subcortical processing in informational masking*

Advisor: Bertrand Delgutte, PhD - Eaton-Peabody Laboratories, Massachusetts Eye and Ear

A central problem in auditory neuroscience is how the brain detects target sound sources in the midst of competing sound sources. Perceptual studies have shown that as the density of sinusoidal components in a masker tone complex increases, detection thresholds for a target tone first increase as the number of components grows, plateau between 10 and 100 components, and then gradually decrease as the number of components exceeds about one hundred. This pattern of masking is thought reflect informational masking, the confusability or uncertainty associated with sources within an auditory scene. For small numbers of masker components, the target tone is highly confusable with the masker tones. However, as the number of components becomes large, the masking complex is perceived as noise, thereby reducing confusability between target and masker.

To test whether subcortical mechanisms such as cochlear suppression and wide-band inhibition contribute to informational masking, we studied how the spectral density of sinusoidal components in a multi-tone masker complex impacts the detection of a target tone by neurons at two stages of the auditory system, the auditory nerve and the inferior colliculus. The stimuli consisted of two intervals; a masker tone complex with randomly selected frequency components was present in both intervals, while a target tone at the neuron’s CF was presented simultaneously with the masker in the first interval. The spectral density of the random masker components was systematically varied. Neural masked thresholds were determined by comparing firing rates between the two intervals using signal detection theory as the target tone level was varied. Simulations with an auditory nerve model (Zilany et al., JASA 135(1):283) revealed that model fibers displayed a non-monotonic pattern of masking as spectral density increased, with a sharp decrease in thresholds when the number of masker components was greater than 10. Ongoing work tests whether this non-monotonicity is due to cochlear nonlinearities by eliminating two-tone suppression in the auditory nerve model. Single-unit recordings from the inferior colliculus of unanesthetized rabbits revealed diverse patterns of dependence of masking on spectral density among neurons. Among the small sample of neurons studied so far, some showed a non-monotonic pattern of masking as spectral density was increased, qualitatively consistent with the psychophysical data. Our results suggest that neural processing at subcortical levels of the auditory system may contribute to the dependence of psychophysical thresholds on spectral density of the masker.

**Keywords:** neurophysiology, auditory scene analysis, coding

**5:30 pm**

**Dana Boebinger**

*Cortical sensitivity to temporal structure in speech and music*

Advisor: Josh McDermott, PhD - MIT

To examine the timescale of cortical sensitivity to acoustic speech structure, a previous study (Overath, McDermott, Zarate, and Poeppel, 2015) generated "sound quilts" by dividing a sound source into segments of various lengths and then rearranging them so that the transitions resemble those from the original sound source. The resulting stimuli disrupt natural acoustic structure at long time scales while preserving it at short time scales. Functional magnetic resonance imaging (fMRI) revealed speech-selective regions in non-primary auditory cortex whose response increased as the segment
length increased, up until a plateau at 500 ms. This result suggests that these speech-selective non-primary regions are sensitive to acoustic structure up to about half a second. It is natural to wonder whether a similar timescale can be identified for music analysis. Another recent study identified speech- and music-selective brain regions concentrated in distinct areas of non-primary auditory cortex (Norman-Haignere, Kanwisher, and McDermott, 2015), making it possible to conduct analogous experiments with music. In the current experiment, we created sound quilts from both speech and music in order to investigate whether the time scale of neuronal sensitivity is similar across domains.

In order to more cleanly isolate neural circuitry involved in speech and music analysis, we used a recently developed voxel decomposition method that models voxel responses to a variety of natural sounds as a weighted sum of canonical response patterns to the sound set, or "components". Two of the resulting components show selectivity for music and speech. To investigate the timescales over which the associated neuronal processes integrate information, we parametrically varied the quilting segment length from 30 milliseconds to two seconds and measured the component responses. Our pilot data shows a clear effect of quilt segment length for the music and speech components, but a negligible effect for the other four components. Replicating the findings from Overath et al. (2015), the neural response to speech showed a plateau around 500 ms, even though participants' ratings of stimulus naturalness increase with quilt segment length up to 2 s. In contrast, the response to quilted music stimuli seems to continue to increase beyond 500 ms. This suggests that these regions could be integrating musical information over longer timescales.

**Keywords:** fMRI, speech perception, music perception

5:45 pm

**Wei Hsi (Ariel) Yeh**

*Develop a new gene therapy using base editor*

Advisor: David R. Liu, PhD - Department of Chemistry and Chemical Biology, Harvard University

My project focuses on developing a new therapy to rescue the impaired hearing functions by utilizing genome-editing technologies. Inherited mutation on transmembrane channel-like genes (TMC) results in profound deafness across all frequencies, yet no effective therapy exists currently. While Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology provides a new pave to rescuing the genetic hearing impairment, off-target editing raises the concern from the society. Therefore, we are working on "Base Editing" technology developed from our group, which enables safer and more efficient genome editing. Without reliance on double stranded breaks, base editor (BE3) utilized deactivated Cas9 fused with cytidine deaminases and uracil glycosylase inhibitor, demonstrating a direct, programmable, irreversible conversion of C→T. I am able to apply BE3 to modify single base pair of new targets with over 40% efficiency and largely reduce indels in vitro. Also, several in vivo delivery methods such as protein and viral delivery have been developed. In addition to rescuing inherited hearing impairment, I have focused on Wnt signaling pathways to regenerate the sensory cells that damage from noise exposure.

**Keywords:** genome engineering, gene therapy, hearing loss

6:00 pm

Break

6:20 pm

**Nicole Black**

*3D Printing of Biomimetic Anisotropic Tympanic Membrane Grafts from Biodegradable Polyurethane Elastomers*

Advisor: - Aaron Remenschneider, MPH, MD - Eaton-Peabody Laboratories, Massachusetts Eye and Ear

The tympanic membrane (TM) contains radial and circular collagen fibers that aid sound conduction. Current tympanoplasty and myringoplasty graft materials, including fascia and cartilage, lack this microarchitecture, resulting in isotropic remodeled tissues and variable hearing outcomes. Additionally, autologous tissues have unpredictable stiffness: 'too-soft’ results in retraction of grafts and ‘too-hard’ results in poor sound conduction. Three-dimensional (3D) filamentary extrusion printing can mimic the fiber arrangement of the native TM. A biodegradable poly(ester urethane urea) (PEUU) elastomer is 3D printed with micron-scale features. As the PEEU degrades it provides channels for the elongation of cells during remodeling, creating mechanically anisotropic tissue grafts. Various arrangements of 3D-printed PEEU fibers tune the sound induced motions of these new grafts. Biodegradable PEEU is synthesized with polycaprolactone diol, isophorone di-
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isocyanate and putrescine, and dissolved in acetone for printing. Filamentary extrusion printing with a 100 µm nozzle produces TM grafts with various circular, radial, and parallel fiber arrangements. Cast PEEU sheets and collagen sheets with random fiber arrangements serve as controls. The TM grafts are seeded with 250,000 green fluorescent protein-expressing human neonatal dermal fibroblasts and maintained in standard tissue culture conditions. Cellular ingrowth is determined by confocal laser microscopy. Laser holography and Doppler vibrometry (LDV) determines the acoustic responses of the grafts before and after 7 days in culture. Degradation studies on cast PEEU disks show a mass loss of 13.6 ± 2.1% after 5 days in PBS (n=8). 3D printed and control materials support fibroblast confluence after 7 days. Alignment of seeded fibroblasts along the print path is observed by confocal microscopy. LDV demonstrated the 30 circular / 30 radial grafts had a higher first resonant frequency than cast sheets and 30 circular only PEEU grafts. The peak velocity of PEEU grafts was higher than that of the collagen. Holography demonstrated frequency dependent surface motion patterns ranging from simple to complex that were more uniform in the PEEU grafts with organized fiber arrangements. Fibroblast remodeling tended to influence acoustic response of the grafts, observed by the increased first resonant frequency and the complexity of the surface motion patterns, suggesting increased anisotropy in the grafts with cellularization.

In conclusion, 3D printing with a novel biodegradable elastomer produced TM grafts with micron-scale anisotropic fiber arrangements that are remodeled by cellular ingrowth into anisotropic tissues. The anisotropy mimics the circular and radial fiber arrangements seen in native TMs and improves sound conduction in remodeled grafts.

Keywords: 3D printing, tympanic membrane, LDV, holography

6:35 pm

Hannah Goldberg
Noninvasive delivery of antibiotics across the tympanic membrane for treatment of acute otitis media
Advisor: Daniel Kohane, MD, PhD - Laboratory of Biomaterials and Drug Delivery, Boston Childrens Hospital and Harvard Medical School

In the United States, bacterial infection leading to otitis media is the most prevalent reason for children to be prescribed antibiotics. The current standard treatment option is an oral formulation that patients must take daily for up to ten days. This administration route proves challenging in regards to patient compliance with young children and promotes antibiotic resistant bacteria due to systemic circulation. This study has focused on the development of a novel drug delivery system, in the form of a hydrogel, that when applied directly to the tympanic membrane (TM) can deliver antibiotics into the middle ear. The gel is comprised of a pentablock copolymer poloxamer (P407-PBP) that exhibits strong reverse thermosensitive properties (fast-gelling at body temperature) and is mechanically stable on the TM. Chemical permeation enhancers (CPEs) have been incorporated within P407-PBP to assist in the flux of ciprofloxacin (a fluoroquinolone antibiotic) across the membrane. Results demonstrated complete eradication (100%) of non-typeable Haemophilus Influenzae in chinchilla models of otitis media compared to 1% Ciprofloxacin otic drops (62.5%) after seven days. Furthermore, the hydrogel has proven biocompatible and undetectable in plasma; thus, highlighting its local delivery and having considerable implications in avoiding the impact on the patient’s microbiome. This summer, my work has been focused on optimizing this therapeutic formulation and performing pharmacokinetic studies to understand the flux of ciprofloxacin and CPEs across the TM in both healthy and diseased chinchilla tympanic membranes.

Keywords: drug delivery, otitis media

6:50 pm

Justin Fleming
Neurophysiological correlates of enhanced speech perception following action audio game training
Advisor: Daniel Polley, PhD - Easton-Peabody Laboratories, Massachusetts Eye and Ear

Perceptual abilities can be enhanced via training on sensory tasks, but such improvements typically do not generalize to untrained tasks or stimuli. However, recent work using more engaging, closed-loop sensorimotor games has shown broad sensory benefits that generalize to real-world sensory situations. In particular, our lab has developed a suite of training games that require participants to track various dimensions of auditory signals (e.g. frequency modulation (FM) rate, signal-to-noise ratio (SNR), pitch) to complete in-game challenges. Behavioral results indicate that training with
these games does not change thresholds for detecting changes in low-level sensory features, but does impart generalized benefits for understanding spoken sentences or strings of digits in high levels of background noise. Importantly, subjects randomly assigned to a comparably challenging ‘placebo’ game did not exhibit any change in speech processing performance. This suggests that audiomotor game training may have enhanced participants’ abilities to sustain and direct their attention to dynamic auditory features, rather than low-level sensory perception.

The neurophysiological mechanisms that support these behavioral changes have yet to be identified. In the present study, electroencephalography (EEG) data will be collected from young healthy participants during both an AM rate discrimination task and a pitch discrimination task that requires participants to attend one set of auditory stimuli while ignoring another simultaneously presented stream. These stimuli are constructed such that the auditory cortex "onset responses" (the EEG N1 potential), cortical auditory steady-state responses (ASSR), and the brainstem envelope following responses (EFR) can be simultaneously obtained as subjects attend to target stimuli and ignore distractors. Participants will then complete 1-2 months of game training, during which psychophysical data will be collected to corroborate previous findings of improved sentence and digit-recognition in noise with training. Participants will then return for post-training EEG data collection, where they will perform the AM and pitch discrimination tasks again. Changes in N1, ASSR, and EFRs will then be assessed. If training results in substantial changes to behavioral and neural encoding, a subset of the participants will return for EEG testing one month after training concludes. This final session will determine if training results in persistent changes to auditory encoding abilities—an important issue in determining the clinical potential of audiomotor training approaches.

Keywords: plasticity, attention, speech

7:05 pm

Jessica Sagers

Audiometric correlates of primary auditory neuropathy: a temporal bone study
Advisor: Konstantina M. Stankovic, MD, PhD - Massachusetts Eye and Ear, Harvard Medical School

Previous work in our lab shows that the principal diagnostic tool of the clinical hearing research community, the audiogram, is not capable of indicating cell-type specific damage to the inner ear. Here, we compare medical and histopathological data from deceased human patients with age-appropriate hearing with data from primary auditory neuropathy patients, in whom cochlear hair cells are intact but spiral ganglion neurons are missing. We present a linear mixed model to correlate the degree of primary neuronal loss with audiometric thresholds and speech discrimination scores. Analysis of 51 ears from 34 patients shows that for every ten percent increase in neuronal loss, average thresholds across all patients drop by 2.85dB. Additionally, there is a weak correlation between increased neuronal loss and increased speech discrimination scores (R²=0.26). Histopathological study of the human inner ear continues to emphasize the need for non- or minimally invasive clinical tools capable of establishing cellular-level diagnoses.

Keywords: auditory neuropathy, spiral ganglion neurons, audiogram

7:20 pm

Malinda McPherson

Inharmonicity in music and speech: evidence for multiple pitch mechanisms
Advisor: Josh McDermott, PhD - Laboratory for Computational Audition, The Department of Brain and Cognitive Sciences, MIT

Pitch is generally defined as the percept corresponding to the fundamental frequency (F0) of a sound. However, many real-world tasks thought to rely on pitch could in principle be performed without computing the F0 of the sounds in question, and there is little evidence for the importance of F0-specific mechanisms. In order to investigate the extent to which pitch perception tasks depend on F0 extraction, we conducted a battery of pitch-related music and speech tasks, comparing performance for standard harmonic sounds with inharmonic sounds that lack a clear F0. The tasks included basic pitch discrimination, melodic contour discrimination, sour-note detection, probe-tone tonality ratings, interval recognition, interval discrimination, and familiar melody recognition (crowd-sourced through Amazon Mechanical Turk). Speech tasks, enabled by a modified version of the STRAIGHT speech analysis and synthesis method, included pitch contour discrimination, voice discrimination, and speaker recognition. Collectively,
these studies indicate that F0 is not necessary to extract a pitch contour in speech or music, but does appear to be necessary for accurate interval estimates, in addition to aiding speaker recognition. These findings suggest that there may be two or three distinct systems responsible for what has conventionally been couched as pitch perception: one which tracks shifts in fine spectral patterns and does not rely on F0, another that is dependent on F0 for determining precise interval relationships between musical notes, and another associated with voice qualities.

Keywords: pitch, inharmonic

7:35 pm
Stefan Raufer

Beam Models of the basilar membrane - facts and fantasy
Advisor: Hideko Heidi Nakajima, MD, PhD - Massachusetts Eye and Ear

The shape of the radial displacement of the basilar membrane is many times modeled as a simple beam model, meaning that it can be approximated by well-established equations used in structural analysis. Being able to measure the deformation of the beam when a pressure is applied, allows both, to determine properties of the material (such as the elasticity), and infer the stiffness of the structure. In auditory research, this information is used to describe properties of the basilar membrane.

A detailed description of the radial displacement profile is only available for some species (facts) and so it is believed, without experimental evidence, that the deflection of the human basilar membrane is similar to that of other species (fantasy). However, when examining the anatomy of the human inner ear, one cannot ignore the fact that the osseous spiral lamina, occupying 85% of the width of the border between scala tympani and the other two cochlear ducts in the base of the cochlea, might play a role in influencing or even dictating the motion of the human basilar membrane.

Experimental evidence will be presented that makes the assumption of a simple beam model for the human basilar membrane untenable.

Keywords: basilar membrane deflection, cochlear mechanics