Harvard University’s Speech & Hearing Bioscience & Technology

Presents the 2020 SHBT End-of-Summer Talks

September 24, 2020 7:00-9:40pm
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Schedule

7:00 – Opening Remarks

7:10 - Lightning Talks

7:30 - 8:10 – Session 1
8:10 - 8:15 – Break

8:15 - 8:55 – Session 2
8:55 - 9:00 – Break

9:00 - 9:40 – Session 3
Overview

Session 1

Investigating tools for protection against cochlear damage from acoustic trauma, Taylor Copeland

Inter-examiner differences in the prosodic realization of read sentences during language assessment, Ayelet M. Kershenbaum

Detecting vocal fold paralysis from acoustic samples using explainable machine learning, Daniel M. Low

The Multiple Demand System in Bilinguals, Saima Bashir Malik-Moraleda

Exploring dendritic mechanisms of learning in the auditory cortex, Wisam Reid

Session 2

Modeling Outer Hair Cell Electromotility, Gabriel Alberts

Using Naturalistic Imaging to Map Audiovisual Integration, Jefferey S. Mentch

Distributional reinforcement learning as a parsimonious explanation to behavioral optimistic biases in inferences made from reward feedback after lesions to the LHB, Sandra Romero

A Diffusion Tractography Investigation of the Shared and Distinct White Matter Tracts that Underlie Language and Theory of Mind, Leo Zekelman

Session 3

Automatic Segmentation of Hair Cells from Confocal Z Stacks, Christopher Buswinka

Long-Range Projecting Inhibitory Neurons in Primary Auditory Cortex, Christine Junhui Liu

Musical Training is Associated with Better Reading and Differences in Resting State Functional Connectivity in Adults, Steven Meisler

Influence of Linguistic Prediction on Speech Perception in Autism Spectrum Disorder, Amanda M. O’Brien
Please join us in welcoming our new cohort …

Charles Hem
   Rochester Institute of Technology, BS in Biomedical Engineering 2020

Corey Loeb
   Wellesley College, BA in Biology 2016
   Boston University, MEd Curriculum and Teaching Secondary Science 2018

Victoria Sanchez
   U of Massachusetts, BS in Biology and Psychology 2018

Yanming Zhu
   Fudan University, Clinical Medicine program (B. Med.) 2020

Ginnie Hu
   National Yang-Ming University, BS in Biomedical Engineering 2015
   National Taiwan University, MS in Biomedical Engineering 2017

Rahul Brito
   University of Washington, BS in Bioengineering 2013

Evan Hale
   Northeastern University, BS in Behavioral Neuroscience 2018

Jacob Antony Alappatt
   SRM Institute of Science and Technology, Bachelors in Biotechnology 2015

Ian Griffith
   University of California-Berkeley, BA in Cognitive Science 2018

David Sorensen
   Brigham Young University, BS in Neuroscience 2016
   Brigham Young University, MS in Neuroscience 2018

… and in congratulating our 2019 graduates!

Ariel Yeh
Advisor: Dr. David Liu
Dissertation: In Vivo Delivery and Therapeutic Applications of Base Editors
# Schedule with Zoom Links

## Opening Remarks & Lightning Talks (7:00 –7:30)

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## Session 1 (7:30-8:10pm)

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<td>Sandra Romero</td>
<td>Leo Zekelman</td>
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Abstracts

Session 1

Investigating tools for protection against cochlear damage from acoustic trauma

Taylor Copeland with Lisa Goodrich

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Sensorineural hearing loss (SNHL) was traditionally thought to arise after the death of cochlear hair cells (HCs). However, moderate levels of noise exposure lead to the acute destruction of synapses between HCs and spiral ganglion neurons (SGNs), without damaging HCs themselves. Over the course of years, SGN processes degenerate, followed by eventual death of the cell body. Moderate exposures may result in temporary threshold shifts, which recover within a few weeks despite enduring cochlear damage. Patients with cochlear synaptopathy experience subtle symptoms such as difficulty hearing speech in noisy environments. Thus, it is important to identify therapeutic targets for the preservation of synapses to prevent progressive degeneration of SGNs and SNHL.

One such target is Bcl-w, an anti-apoptotic gene expressed in SGNs that has been shown to protect sensory axons and synapses from degeneration. Bcl-w’s protective effects likely result from a special region (BH4 domain), which binds IP3 receptors in axons, reducing calcium release within the axon. Bcl-w BH4 mimetics may protect SGNs from degeneration and prevent cochlear synaptopathy after acoustic injury. Before testing protective effects of Bcl-w BH4 mimetics in adult mice, we first wanted to determine whether these mimetics can penetrate SGN cell bodies. Cochlea from neonatal mice were dissociated and cultured with fluorescently labeled Bcl-w peptides to inform concentrations necessary for future functional hearing assays. In conjunction, we are validating Netring1Cre;Ai14 mice as a tool for selective targeting of high and medium threshold SGN subtypes, which are thought to have enhanced vulnerability to damage by acoustic overexposure.

Inter-examiner differences in the prosodic realization of read sentences during language assessment

Ayelet M. Kershenbaum with Stefanie Shattuck-Hufnagel
Background: Standardized sentence repetition tasks are widely used in clinical assessment to efficiently gain information about the examinee’s language processing across domains. While these tasks are often controlled in terms of lexical content and syntactic complexity, they are read aloud in real-time by the examiner, and thus can vary in their prosodic realization. Specifically, examiners may differ in the manner and/or degree to which they use prosody to mark prominent words or intrasentential phrases, which could impact the examinee’s ability to process and reproduce the material. This preliminary study therefore sought to investigate these potential inter-examiner prosodic differences.

Methods: Audio recordings of trained examiners administering a standardized sentence repetition task were annotated using the Tones and Break Indices (ToBI) labeling system based on a combination of perceptual listening and visualization of the speech spectrogram and F0 contours. Inter-individual differences in proportion of pitch accent and break labels were examined, as well as quantitative measures of sentence duration, number and duration of intrasentential pauses, and speaking rate.

Results: Analysis revealed significant inter-individual differences in proportion of L* (low) versus H* (high) pitch accents and intrasentential boundary types (3 versus 4 breaks), as well as in sentence duration.

Discussion/Conclusion: These preliminary results indicate that even highly experienced examiners differ in their prosodic realization of standardized sentences in ways that may impact listener processing. Future work should substantiate these results with a larger corpus, and importantly determine whether such prosodic differences impact the sentence reproduction accuracy of typical and clinical examinees
complex models perform detection is important to increase trust among clinicians and help further characterize UVFP scientifically.

**Methods:** 77 patients with confirmed UVFP and 77 controls with normal voices matched in age and sex were included. Two tasks were used to elicit voice samples: reading The Rainbow Passage (222 samples, mean length: 6.8s ± 5.4s) and sustaining phonation of the vowel /a/ (228 samples, mean length: 4.0s ± 1.0s). 88 eGeMAPS features were extracted using OpenSmile. Redundant features were removed to avoid multicollinearity which distorts feature importance interpretation. Machine learning models with increasing complexity were included. Training and testing was performed by bootstrapping across 50 splits. SHAP was used to identify important features.

**Results:** The highest median AUROC was 0.87 with similar performances across models and tasks. The most important features included intensity measures, mean MFCC1, mean F1 amplitude and frequency, and shimmer variability depending on model and task.

**Conclusion:** Using the largest dataset studying UVFP to date, we achieve high performance while discovering which features are important across models. We further demonstrate that different types of models (from linear to nonlinear) trained on data from different tasks (reading or sustaining a vowel) will use different features or weigh them differently and still achieve similar performance. Therefore, future studies should temper claims about feature importance related to detecting a given disorder when only explaining a single model trained on a single data-eliciting task.

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**The Multiple Demand System in Bilinguals**

Saima Bashir Malik-Moraleda with Ev Fedorenko

[Link to Zoom meeting]

The bilingual experience may posit special cognitive demands on speakers, likely impacting their general-domain executive functions both behaviorally (Bialystok & Craik, 2014) and in the brain (Costa & Sebastián-Gallés, 2014). Using large samples of bilinguals and monolinguals (n=78 in each group), matched by age, gender and fluid intelligence, we test four claims from the prior literature about executive function processing in the bilingual brain: 1) bilinguals exhibit stronger responses to executive function tasks in the domain-general multiple demand (MD) system than monolinguals (Rodríguez-Pujadas et al, 2013); 2) MD brain areas are more active in bilinguals than in monolinguals during language processing (Abutalebi & Green, 2008); 3) language areas
show greater engagement during executive tasks (Garbin, et al, 2010); and 4) language processing and executive functions are less spatially segregated in bilinguals than in monolinguals (Abutalebi & Green, 2008). Each participant performed a sentence comprehension task (Fedorenko et al., 2010) and an executive (spatial working memory) task while undergoing fMRI. In line with the first two claims, the bilinguals’ MD system exhibited stronger responses than that of the monolinguals during the working memory task and during sentence comprehension. However, contrary to the third and fourth claims, the language system was similarly selective for language over executive functions in the two groups and showed similarly small amounts of overlap between the two networks. In tandem, these results suggest that bilingualism may affect the functional architecture of the executive MD system, but not the language system’s selectiveness. Some of the prior contradictory results in the literature may be due to the failure to clearly separate the language and the MD networks in the left frontal lobe (e.g., Fedorenko & Blank, 2020).

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**Exploring dendritic mechanisms of learning in the auditory cortex**

**Wisam Reid** with Anne Takesian

https://harvard.zoom.us/j/93212224028?pwd=YlRDREtSdVRNMTRnbmdTS0xBY1liQT09
Phone: +13126266799,,93212224028#, Password: 774910

Historically, neuroscience has guided seminal work in artificial neural network (ANN) theory. This research aims to answer two neurobiological questions that will provide insight into the subcellular mechanisms of learning to propel advances in ANNs: (1) How do differences in activity across the subcellular compartments of cortical neurons contribute to sensory plasticity and learning? (2) What are the cortical circuit mechanisms that contribute to these differences in subcellular activity? Recent experimental and theoretical work suggests that a predictive coding 2+ scheme may drive the subcellular recruitment of calcium (Ca2+) activity in cortical pyramidal neurons (PNs) during learning. We hypothesize that unexpected reinforcement during auditory 2+ association learning will lead to an increase or decrease in Ca2+ activity within the apical dendrites of neurons tuned to reinforced or unreinforced stimuli, respectively. Here, we present our simulations demonstrating efficient learning in a multi-layered ANN using local dendritic voltage to drive synaptic plasticity. Our parallel experiments are testing this hypothesis in mice engaged in auditory learning tasks that rely on the activity of two neural populations within the primary auditory cortex: (1) a set of projection neurons to striatum (PNs→STR) and (2) neuron-derived neurotrophic factor-expressing inhibitory interneurons (NDNF-INs) that target PNs→STR apical dendrites. We will combine viral, genetic, and optical strategies to target 2+
subcellular domains of these neurons for Ca2+ imaging and optogenetic perturbation. Beyond advancing our understanding of the active role of dendrites in learning, this work could inform novel ways to design neural implant technologies to efficiently encode and decode learned sensory information.

Session 2

Modeling Outer Hair Cell Electromotility

Gabriel Alberts with Sunil Puria

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The tuning of the cochlea is due in large part to the motility of outer hair cells (OHCs). Current cochlear models that account for this active process do so indirectly by relating forces within the organ of Corti. Here we performed a preliminary investigation into the direct modeling of OHC electromotility using finite-element methods in COMSOL Multiphysics. A 2D model was constructed of one OHC with two stereocilia and a tip link between them. By implementing structural mechanics, electrostatics, and beam physics coupled by piezoelectricity and solid-beam connections, we successfully produced phase-shifted OHC compressions and elongations from prescribed sinusoidal tip link displacements. The model, which requires relatively little computation power to solve, is a promising first step on the path to a finite-element model of the active cochlea with motile OHCs placed within the larger framework of the organ of Corti.

Using Naturalistic Imaging to Map Audiovisual Integration

Jefferey S. Mentch with Satrajit Ghosh

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Historically, many fundamental insights about the processes underlying cognition stem from highly controlled experiments using classical parametric tasks. While this approach has been revealing, in everyday life, we perceive dynamic, multisensory information in complex
real-world environments. Recently, naturalistic stimuli such as rich audiovisual movies have gained momentum in fields like neuroimaging as a more ecologically valid means of studying cognition, more closely approximating real-life scenarios.

In this project we use naturalistic movie viewing (fMRI data to 1) investigate audiovisual speech integration using a GLM, 2) lay the groundwork for data-driven approaches for parcellating the brain into auditory and speech regions, and 3) move towards a data-driven method of domain-general cortical parcellation. Here we will present methods and data towards aim 1, including an experiment where 18 participants viewed the TV show *Merlin* during fMRI acquisition (Zadbood et al., 2017).

Numerous features can be labeled from such a rich movie stimulus and an initial challenge in dealing with the resulting large set of extracted features is a means of visualization and quality assessment. To that end, a feature visualization web-app was created. Next, brain data were analyzed with Neuroscout (de la Vega et al., 2019). Preliminary results suggest that when a character is both seen and heard during the film, a specific network of brain regions including the superior temporal sulcus (STS) are activated. Future work will explore this in greater detail, expanding to more datasets, encoding models, and clinical populations of interest.

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*Distributional reinforcement learning as a parsimonious explanation to behavioral optimistic biases in inferences made from reward feedback after lesions to the LHb*

Sandra Romero with Naoshige Uchida and Michale Fee

https://harvard.zoom.us/j/95192586341?pwd=OWNmhdQ3U014L2RvdHBPRzJYRDliUT09
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There is evidence that dopamine neurons (DANs) drive learning via the computation of reward prediction errors (RPEs). Recent work from AI and neuroscience (Dabney, 2020) has attested in favor of a distributional code for value, a framework termed as distributional reinforcement learning (DRL). Such code is reflected in asymmetric learning rates of single units for negative versus positive RPEs leading them to represent a set of expectiles of the distribution. The origin of this asymmetry may be determined by the lateral habenula (LHb), which has an inhibitory role in RPEs scaling, and is implicated in disorders such as depression. Here, we provide evidence that LHb dysfunctions could provide a mechanistic account of the systematic distortions in inferences made from positive or negative feedback, by potentially inducing biases in the asymmetric scaling of RPEs, in analogy to RL models of depression (Niv,2018).
Our previous study (Tian & Uchida, 2015) examined the effects of permanently lesioning the LHb in mice trained in a probabilistic Pavlovian task. The lesions preserved RPEs but led to behavioral ‘optimistic’ biases. Our hypothesis was that the preservation of average RPEs after lesions could be hiding a systematic bias in the distributional code, linked to the behavioral effects. We analyzed single unit DANs responses in lesion and control groups and categorized them into optimistic, neutral and pessimistic. The proportion of cells falling into the pessimistic cluster was lower in lesion group than in controls. We derived the distribution of expectiles finding that the lesion group presented a positive bias in the decoded value distribution. Finally, the distortions in the distribution found in the lesion group were reproduced when training a DRL model but with the addition of a constant subtractive bias that imposed a deficit in the single cell negative learning rates derived from the control group.

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**A Diffusion Tractography Investigation of the Shared and Distinct White Matter Tracts that Underlie Language and Theory of Mind**

**Leo Zekelman** with Alexandra Golby

https://harvard.zoom.us/j/92893742377?pwd=NVhJa3hJcXJKNW5DeEd5eGVySGM4QT09
Phone: +19294362866,,92893742377#, Password: 619146

Successful communication depends not only on the ability to understand words but also emotional states. Often described as components of language and theory of mind (ToM), these lifelong skills develop simultaneously during childhood, pointing to their shared roots. However, functional MRI research demonstrates that language and ToM are part of two functionally distinct networks that lateralize to opposite hemispheres. To further understand their distinction and interrelation, we examine how two foundational measures of language and ToM (i.e. TPVT and PERT, respectively) relate to diffusion MRI data collected from 965 healthy young adults in the Human Connectome Project. To consistently parcellate the white matter (WM), we apply a neuroanatomically curated WM atlas that leverages machine learning to identify the WM tracts in each participant’s brain (Zhang et al., 2018). The mean fractional anisotropy (FA) of 12 major WM association tracts is then calculated across both hemispheres separately. TPVT most strongly and significantly correlates with FA of the left ILF, PERT with FA of the right SLF III. The tract FA most strongly and significantly correlated with both assessments is the left AF. Our results bolster the understanding that ToM and language are not only functionally separate but are also supported by structurally separate WM tracts. Additionally, the results suggest that the
left AF may be a common tract to both ToM and language, perhaps pointing to the AF’s involvement in their synchronous but lateralized development.

Session 3

**Automatic Segmentation of Hair Cells from Confocal Z Stacks**

Christopher Buswinka with Artur Indzhykulian

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Histopathological techniques can stain all 15,000 hair cells in a cochlea, however the cell by cell analysis of an entire cochlea is entirely limited by manpower. To gain access to this wealth of data, we have developed a histopathological analysis pipeline which leverages two deep learning algorithms which, in tandem, automatically detect and uniquely segment hair cells from a confocal z-stack. The pipeline employs u-net in three dimensions to segment instances of hair cells, and faster r-cnn in two dimensions to uniquely identify each cell. This pipeline can automatically and rapidly analyze histopathological data of the whole cochlea on a cell by cell basis, enabling new experiments that would previously be too labor intensive to perform.

**Long-Range Projecting Inhibitory Neurons in Primary Auditory Cortex**

Christine Junhui Liu with Anne Takesian

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Identifying neural targets that control central auditory plasticity will have far-reaching impact, offering potential ways to restructure neural circuitry. Emerging work from our lab and others has identified a group of GABAergic inhibitory neurons in superficial layers of the auditory cortex (ACtx) as a key hub for auditory plasticity. However, little is known about their anatomy.
or function within the cortical circuits. Previous studies have only focused on short-range, local outputs of these GABAergic neurons. Our preliminary results show that a subset of these GABAergic neurons send long-range projections to distant cortical and subcortical regions, which may gate sensory integration and feedback to earlier auditory centers. By combining transsynaptic tracing techniques and immunohistochemistry, we reveal that several subtypes of superficial GABAergic neurons expressing vasoactive intestinal peptide (VIP), neuron-derived neurotrophic factor (NDNF), neuropeptide Y (NPY), and somatostatin (SST) send long-range projections. Ongoing electrophysiological studies aim to evaluate the intrinsic and synaptic properties of these long-range projecting inhibitory neurons. These results will guide future in vivo studies to determine the effects of these neurons in promoting plasticity within auditory circuits. Together, the characterization of these long-range projecting GABAergic neurons offers a key first step to uncover mechanisms regulating auditory plasticity, providing potential novel therapeutic targets for recovery from peripheral hearing loss.

Musical Training is Associated with Better Reading and Differences in Resting State Functional Connectivity in Adults

Steven Meisler with John Gabrieli and Ola Ozernov-Palchik

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Musical training has been linked to better language and reading performance. This has been demonstrated in both correlational and interventional studies. Few studies to date, however, have examined the neural networks supporting these cognitive advantages. Here, we compared the performance of typical adults (mean age: 26 years) with (MUS, N=11, mean years of musical training: 7.65) and without (NMUS, N=25) musical training on multiple reading and language measures. We conducted a whole-brain ROI-to-ROI resting state functional connectivity (RsFc) analysis to compare intrinsic differences in networks supporting language and reading between MUS and NMUS. All results were thresholded at $p < 0.05$ FWE corrected. MUS performed significantly better than NMUS across language and reading measures ($p < 0.05$). This was associated with greater connectivity in ROIs in the default-mode network and some regions important for language, which both support reading. These findings provide some insights into the neural mechanisms underlying the increasingly well-documented positive effects of musical
training on language and reading skills. Future intervention studies measuring differences in skill and intrinsic connectivity are needed to delineate the causal nature of this relationship.

Influence of Linguistic Prediction on Speech Perception in Autism Spectrum Disorder

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Categorical speech perception allows listeners to ignore irrelevant variations in the speech signal and thus supports efficient speech processing. Within the context of a sentence, however, top-down predictions may shift categorical perception toward a predictable word. Relative to neurotypical adults, individuals with autism spectrum disorder (ASD) may demonstrate impairments in categorical perception at both the word and sentence level. These differences in speech perception may be due to increased attention to lower-level acoustic features at the expense of higher-level linguistic representations, and decreased use of top-down linguistic predictions. This study aims to understand the effect of linguistic prediction on categorical perception in individuals with and without ASD. An online paradigm was created to explore the role of top-down linguistic predictions on categorical perception of speech sounds and words that vary along a voice time continuum. Individuals with ASD and controls were asked to report perceived sounds, isolated words, and words within highly predictable sentences. Preliminary results from neurotypical controls show the expected categorical perception boundaries at the word level, with a shift in categorical boundary toward the predictable word in the predictable sentence condition. Online data collection has been approved for individuals with ASD and will begin this fall. To our knowledge, this is the first study to examine the effect of sentence-level linguistic prediction on categorical speech perception. The results will further elucidate speech processing mechanisms used in typical and atypical speech perception.