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Abstracts from Purdue University

Sunday

PS 280
Neural Envelope Coding in Middle-aged Humans with Normal Audiograms

Homeira Kafi; Alexandra Mai; Kelsey Dougherty; Anna Hagedorn; Hari Bharadwaj
Purdue University

Emerging evidence from animal models and human postmortem temporal bones suggests that cochlear synaptopathy is a primary form of age-related hearing damage. Hypothetically, cochlear synaptopathy can contribute to degraded coding of temporal information, particularly envelopes, in the ascending auditory pathway. Here, we used electroencephalography- based envelope-following responses (EFRs) to test this hypothesis in a cohort of listeners with a wide age range (18 – 60 years old) but with audiograms in the "normal" range (better than 25 dB HL up to 8 kHz). EFRs were measured in response to a broadband mixture composed of three carrier bands centered at 2, 4 and 8 kHz respectively with each band modulated at a different amplitude modulation rate. This design was based on previous work showing that separable, place-specific responses may be elicited from different cochlear sections with such stimuli. Despite audiograms being in the normal range for all subjects and accounting for residual audiometric variations across subjects using a linear model, significant age-by-frequency and age- by-modulation depth interactions were observed in the EFR magnitude (greater decline in EFR with age for shallower modulation and for higher frequency carriers), a result that is consistent with cochlear synaptopathy. In a separate study with the same cohort of subjects, auditory brainstem response wave I amplitudes and wideband middle-ear reflexes we simultaneous attenuated further corroborating this interpretation. One alternate interpretation for the EFR changes with age is that the central auditory system may be exhibiting age- related changes either independently or in response to peripheral de-afferentation. Overall, these results suggest that age-related peripheral de-afferentation may be a significant contributor to the common observation that supra-threshold temporal processing degrades with age even before symptoms of classic presbycusis are manifested. Finally, the use of the multiband stimulus to elicit place-specific EFRs as done in this study may help explain some of the inconsistencies in the previous literature exploring age effects on envelope coding.

PS 283

Blockade of Corticothalamic Projections Alters Coding in Medial Geniculate Body to Less Salient Modulated Stimuli

Srinivasa Prasad Kommajosyula[1]; Edward Bartlett[2]; Rui Cai[3]; Donald Caspary[3]
[1]Southern Illinois Univ. School of Medicine; [2]Purdue University; [3]Southern Illinois University School of Medicine

Background

To disambiguate speech in cluttered acoustic environments, additional cognitive resources are engaged and top-down cortical projections sharpen the ascending auditory message. The medial geniculate body (MGB) receives extensive corticothalamic projections. These are implicated in shaping MGB neural activity, which subsequently changes cortical representation. Here we posit that decreasing the salience of a SAM stimulus would increase neural jitter and mimic decreased inhibition in aged animals resulting in increased preference coding to predictable stimuli. We also hypothesize that diminishing cognitive resources with general anesthesia or selective optogenetic blockade of corticothalamic projections would impede preference coding noticed in MGB units.

Methods

Fischer Brown Norway rats of age (4-6mos) were used. Tetrode microdrives were implanted in MGB (awake group). In the awake optogenetic group, ArchT was injected into the primary auditory cortex, targeting layer 5/6, to selectively block corticothalamic tracts in animals implanted in MGB with tetrodes including an optical probe. Tungsten electrodes were used in the anesthetized group. Single-unit activity and/or local field potential (LFP) were recorded from the MGB of all groups. Salient and less salient SAM stimuli were generated and delivered as in Kommajosyula et al., (2019). Changes in single-unit response properties were compared across groups.

Results

Single-units (66 in the awake group; 28 in the anesthetized group; 31 in the awake optogenetic group) were recorded from rat MGB. In recordings from awake MGB units, as the salience of the SAM stimulus decreased, significant increases in MGB neuronal responses to predictable stimuli were observed. In contrast to adaptation, less salient stimuli result in increased responses to predictable/repeating stimuli. This switch toward predictable response preference was reduced by optogenetic blockade of corticothalamic inputs to MGB and was absent in anesthetized rats. These changes support our hypothesis that top-down processes alter sensitivity to repeating stimuli at MGB.

Conclusions

Here we tested the hypothesis that less salient temporal stimuli engage corticothalamic projections to switch preference coding in MGB neuronal responses. This switch was not observed in rats with selective optogenetic blockade of corticothalamic projections or in recordings from anesthetized rat MGB. These data support the contention from human studies and our previous rat studies (Cai et al., 2016) of increased use of top-down information to help disambiguate communication-like sounds in cluttered acoustic environments and the elderly.

PS 330

Improved Neural Responses in Cochlear Implants Using a Physiologically Based Stimulation Strategy: Preliminary Results

Andres F. Llico; Thomas M. Talavage
Purdue University

Introduction

Cochlear implants (CI) are implantable devices capable of partially restoring hearing loss by electrically stimulating the auditory nerve to mimic normal-hearing conditions. Resulting speech perception varies among CI users, depending mostly on their deafness and surrounding noise conditions. Current electrical-stimulation strategies are often developed following phenomenologically based approaches instead of being derived from known physiological functions of the auditory system. The framework developed in this study seeks to provide an optimized electrical-stimulation strategy by maximizing the similarity between simulated neural patterns elicited in the auditory nerve by acoustic and electrical means. Preliminary results show increased correlation and reduced mean square error between acoustic and electric stimulation when the proposed optimized strategy is used instead of a commonly used CI strategy that stimulates electrodes based on spectral energy content.

Materials and Methods

A 100-ms segment of t e utterance 'had' spoken by a male speaker was used as input to a computational model of normal hearing (NH) (Zilany et al., 2014) and a CI pulse generator followed by an electrical-stimulation model of the auditory nerve (Bruce et al., 1999), yielding two neural activity patterns (NAPs) for each speech sample. NAPs are compared using an objective function to maximize the correlation between them and select the electrical sequence that best matches the output from the normal hearing model. An implementation of the advanced combination encoder (ACE) strategy (Seligman & McDermott, 1995) was used as a reference to evaluate performance of the proposed optimized strategy through cross correlation and mean square error metrics.

Results and Discussion

Cross correlation and mean square error metrics were computed between the output NAP for normal-hearing and each of the output NAPs for the proposed and ACE strategies. Preliminary results yielded a 1.7% increase in cross-correlation and a 2.4% reduction in mean square error, both in favor of the proposed optimized strategy over the ACE strategy.

Conclusion

Preliminary results suggest that optimized CI stimulation patterns may provide neural responses more similar to NH than a commonly used CI strategy. This is supported by previous work in which this framework led to increased speech perception in background noise conditions, as well as provided more consistent performance in quiet conditions. (Llico et al., BMES 2017) Further research is necessary to evaluate alternative objective functions that could better represent in NAPs perceptual differences.

PS 379

Expression of Semaphorins and Their Receptors in Developing Chicken Auditory Ganglion and Cochlear Nucleus

Xiaoyu Wang[1]; M. Katie Scott[2]; Donna Fekete[2]; Yuan Wang[1]
[1]Florida State University; [2]Purdue University

Auditory ganglion (AG) neurons connect the ear to the brain via auditory nerve fibers (ANFs). Molecular mechanisms that guide the development of ANF projections within the cochlear nucleus are not fully understood. We have recently found that AG neurons express a high level of fragile X mental retardation protein (FMRP), a mRNA binding protein that regulates local translation of its targets in dendrites and axons. In chickens (*Gallus gallus*), ANFs reach and start terminating on neurons in the nucleus magnocellularis (NM), the avian analogue of the mammalian anteroventral cochlear nucleus, at embryonic day 8 to 10 (E8-10). Genetically knocking down FMRP expression in a subset of AG neurons at E8 results in abnormal projection of their axons away from their normal target in NM. In mammalian brains, a number of Semaphorins (Sema) and their receptors are predicted FMRP targets and FMRP regulates Sema-induced axonal protein translation of cultured hippocampal neurons. We hypothesize that FMRP interacts with Sema signals in developing ANF axons and that this interaction plays a substantial role in mediating connections at the first synaptic station in the ascending auditory pathway.

Recent *in situ* hybridization studies in the Fekete lab reveal that the class III Semaphorins and their receptors are expressed in the chicken inner ear including the AG, giving rise to the possibility that Sema pathways are employed in ANF pathfinding and targeting. In this study, we examined the spatiotemporal expression profiles of transcripts for Sema3D, Sema3F and their receptors plexin A1 (PlxnA1) and neuropilin (Nrp) in NM. At E8 and E10,*in situ* hybridization reveals robust expression of *PlxnA1*, but not *Nrp2*, in both AG and NM neurons. Notably,*Sema3D*is highly expressed by AG neurons at these ages, providing a potential ligand for activating PlxnA1 in NM. On the other hand, both *Sema3D* and*Sema3F* show modest expression in NM, which may potentially interact with PlxnA1 on ANF terminals. Although relative contributions of these potential bi-directional interactions are yet to be determined, one possible model is that presynaptic FMRP deficiency leads to increased Sema (or PlxnA1) in ANF axons, which prevents them from terminating on PlxnA1 (or Sema)-expressing NM neurons through a repulsive interaction, thus resulting in axonal misprojection. An alternative possibility is that FMRP does not regulate Sema-PlxnA1 binding so directly, but instead influences how axons respond to this binding by modulating protein pathways downstream of PlxnA1 activation. Our ongoing studies are investigating whether and how FMRP regulates expression and localization of *Sema3D* and*PlxnA1* in ANF axons and whether this regulation contributes to FMRP-mediated axonal targeting.

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PS 383

Patterning the Radial Axis of the Cochlea: Exploring the Role of Fgfs downstream of Wnt Signaling

Elizabeth R. Wehren; M. Katie Scott; Rachel M. Maibach; **Donna Fekete**
Purdue University

The hearing organs of amniotes are segregated into two functional compartments across the radial axis. In mammals, inner hair cells on the neural (medial) side connect to large, myelinated afferent fibers that convey auditory information to the brain, while outer hair cells on the abneural (lateral) side receive robust efferent input, display electromotility, and synapse with thin unmyelinated afferent fibers that convey pain sensation following damage to the sensory organ. Understanding how these neural-abneural specializations arise during development is an active area of investigation in both birds and mammals. Genetic or pharmacological perturbation of Notch, Wnt, Fgf or Bmp signaling prior to cell fate specification can alter the number and/or types of sensory cells across the radial axis. The current study explores whether and how Fgf signaling may function downstream of Wnt signaling to influence this radial axis patterning in the chicken embryo.

Previously our lab showed that retrovirus-mediated overexpression (OE) of Wnt9a in the developing basilar papilla enhances cell proliferation and disrupts radial patterning by embryonic day 6 (E6), which is 3 days after virus injection into the chick otocyst. Positional identities are altered at this time, as evidenced by a loss of abneural-side genes and an expansion of neural-side genes. Afferents respond by spreading across the entire radial axis, instead of remaining confined mostly to the neural side. By E18, Wnt9a-OE cochleas contain only tall hair cells with excess numbers of presynaptic puncta, while short hair cells are missing. RNAseq performed on E6 identifies *Fgf3* and *Fgf19* among the early genes upregulated in response to Wnt9a-OE. In the present study, in situ hybridization confirms their upregulation and further shows that this effect is spatially restricted within the cochlear duct to the prosensory domain; Wnt9a- infected cells in the non-sensory domains of the cochlea do not ectopically express these two *Fgf* transcripts.

We are focusing on Fgf19 because our lab previously showed that Fgf19 enhances neurite outgrowth when added to cultured E4 statoacoustic ganglia. This leads us to hypothesize that Fgf19-OE may phenocopy the Wnt9a-OE effect of excessive afferent projections. To test this idea, we have generated a retroviral vector that encodes both GFP and Fgf19 and we are injecting it into E3 chicken otocysts. We will examine cochlear innervation, hair cell phenotypes, cell proliferation and gene expression patterns to determine whether Fgf19 functions as a downstream effector of Wnt9a in any of these aspects of radial patterning.

PS 515

The Effect of Broadband Elicitor Duration on Transient-Evoked Otoacoustic Emissions and a Behavioral Measure of Gain Reduction

William B. Salloom[1]; Kristen Wade[1]; Hari Bharadwaj[2]; Elizabeth A. Strickland[1]
[1]Purdue University; [2]Speech, Language, & Hearing Sciences, and Weldon School of Biomedical Engineering, Purdue University

Background

Physiological and psychoacoustic studies of the medial olivocochlear reflex (MOCR) in humans have often relied on long elicitors (> 100 ms). This is largely due to previous research using otoacoustic emissions (OAEs) that found MOCR time constants in the 100's of milliseconds when elicited by broadband noise. However, Roverud & Strickland (2014), using a psychoacoustic measure of gain reduction, found differential effects of duration for on- and off-frequency tonal elicitors. For the on-frequency elicitor, thresholds increased with increasing on-frequency duration up to about 50 msec, and then plateaued. In contrast, thresholds with off-frequency elicitors continued to increase with elicitor duration. These results are consistent with cochlear gain reduction, possibly by the MOCR, in which the on-frequency elicitor is affected by gain reduction at the signal frequency place, but the off-frequency elicitor is not. The effect of the duration of broadband noise elicitors on similar psychoacoustic tasks is currently unknown. Additionally, the relationship between gain reduction measured psychoacoustically and physiologically with OAEs in the same subjects as a function of elicitor duration are unknown. This study measured the effects of ipsilateral broadband noise elicitor duration on transient-evoked OAEs (TEOAEs) and psychoacoustic gain reduction estimated from a forward-masking paradigm.

Methods

The effects of an ipsilateral pink broadband noise precursor (0.2 - 10 kHz) on TEOAEs and behavioral thresholds were measured as a function of precursor duration in normal-hearing humans. For all experiments, the precursor was fixed at a level below MEMR threshold (50-60 dB SPL). TEOAEs were measured to estimate MOCR strength (magnitude and phase) at precursor durations of 50, 100, 200, and 400 msec. For the same subjects, a psychoacoustic forward-masking paradigm was used to measure the effects of precursor duration (50, 65, 100, 200, 400, and 800 msec) on masking by on- and off-frequency maskers at a 4 kHz signal frequency. Gain reduction is indicated by a relatively larger shift for the off-frequency masked threshold than for the on- frequency one.

Results/conclusions

The effects of the precursor on TEOAEs and behavioral thresholds will be compared as a function of precursor duration. The goal is to determine how duration of a broadband MOCR elicitor affects cochlear gain physiologically and perceptually, and if there is a relationship between these measures.

Acknowledgements

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Monday

PS 730

Attentional Modulation of the Neural Representation of Speech: Spectral Profile and Individual Differences

Vibha Viswanathan[1]; Hari Bharadwaj[2]; Barbara Shinn- Cunningham[3]
[1]Weldon School of Biomedical Engineering, Purdue University; [2]Speech, Language, & Hearing Sciences, and Weldon School of Biomedical Engineering, Purdue University; [3]Carnegie Mellon Neuroscience Institute, Carnegie Mellon University

The ability to selectively attend to speech in the presence of other competing talkers is critical for everyday communication; yet the neural mechanisms facilitating this process are poorly understood. Here, we use electroencephalography (EEG) to study how a mixture of speech streams is represented in the brain as subjects attend to one of two sound streams. To characterize the speech-EEG relationships and how they are modulated by attention, we estimate the statistical association between each canonical EEG frequency band (delta, theta, alpha, beta, low-gamma, and high-gamma) and the envelope of each of ten different frequency bands in the input speech. Consistent with previous literature, we find that low-frequency (delta and theta) bands show greater speech-EEG coherence when the speech stream is attended compared to when it is ignored. We also find that the envelope of the gamma band shows a similar attention effect, a result that has previously been reported only in invasive recordings. This is consistent with the theory that neural dynamics in the gamma range are important for attention-dependent routing of information in cortical circuits. In addition, we also find that the greatest attention-dependent increases in speech-EEG coherence are seen in the mid-frequency acoustic bands (0.5—3 kHz) of input speech and the temporal-parietal EEG sensors. Finally, we find individual differences in: (1) the specific set of speech-EEG associations that are the strongest, (2) the overall magnitude of the attentional enhancement of speech-EEG coherence, and (3) the EEG and speech features (i.e., the specific channels and bands) that are most informative about attentional focus. This suggests that for applications such as BCIs that aim to decode auditory attention from EEG, individual-specific customization of features might be necessary to obtain optimal performance.

PS 746

Graded control of neuromodulatory brain state using parametric stimulation of the Vagus Nerve

Zakir Mridha[1]; Jan Willem de Gee[1]; Yanchen Shi[1]; Rayan Alkashgari[2]; Justin Williams[2]; Aaron Suminski[2]; Matt Ward[3]; Wenhan Zhang[1]; **Matthew J. McGinley**[4] *[1]Baylor College of Medicine, Department of Neuroscience; [2]University of Wisconsin, Department of Bioengineering; [3]Purdue University, Department of Bioengineering; [4]Department of Neuroscience, Baylor College of Medicine*

The vagus nerve relays information about brain state to the body. Vagus nerve stimulation (VNS) is thought to 'back fire' neuromodulatory centers (such as LC), releasing neuromodulators throughout the brain. The neuromodulatory effects of VNS are thought to mediate its clinical benefits, in for example the treatment for refractory epilepsy, tinnitus, or depression. Furthermore, VNS enhances auditory learning in healthy individuals, which is thought to boost cortical plasticity via the same neuromodulators (Engineer et al., 2015). A major challenge in using VNS, for therapeutic purposes or auditory enhancement, is that there is no known readout of nerve engagement or its subsequent neuromodulatory impact. As a result, stimulation parameters are chosen and optimized, largely through trial-and-error and feedback from patients about symptoms and side effects. We have previously shown that pupil size tracks neuromodulatory brain state and its influence on auditory physiology and behavior (McGinley et al., 2015; Reimer et al., 2016).

Here, we developed a VNS preparation for awake, head- fixed mice and tested if pupil dilation is a biosensor of VNS-triggered cortical neuromodulation. We adapted an implanted cuff design from prior work in rats (Ward et al., 2015). Stimulation via our cuff is well-tolerated by mice for up to several months. We performed an extensive search across a VNS parameter space of 4 pulse widths (0.1-0.8 ms), 5 amplitudes (0.1-0.9 mA), and 3 rates (5- 20 Hz; 10 s trains), while monitoring pupil size and other eye movements. We found consistent pupil dilation that parametrically increased with increasing pulse width, amplitudes or rate. Experiments with promiximal (or proximal and distal) cut of the nerve confirm that the pupil dilation results from selective activation of the vagus nerve. Using two-photon imaging of neuromodulatory axons in auditory cortex, we observed that cortical neuromodulation was phasically boosted during VNS, and then decayed back to a stable baseline. We also found that care with grounding and current spread is necessary to avoid major off-target effects such as small phase-locked eye movements and further pupil dilation. Taken together, our results provide a foundation for carefully controlled VNS, and pupil dilation as its readout, for the enhancement of auditory learning and other applications requiring closed-loop, graded control of brain state.

References: McGinley et al. (2015), Neuron, 87. Reimer, McGinley, et. al. (2016), Nature communications, 7. Engineer et al. (2015), Brain Stimulation, 8. Ward et al. (2015), IEEE Trans Neural Syst Rehabil Eng, 23.

Tuesday

PS 821

A model with efferent gain control explains the time-varying responses of inferior colliculus neurons to amplitude-modulated stimuli

Afagh Farhadi[1]; Skyler G. Jennings[2]; Elizabeth A. Strickland[3]; Laurel H. Carney[1]
[1]University of Rochester; [2]University of Utah; [3]Purdue University

The medial olivocochlear (MOC) efferent system has been hypothesized to account for psychoacoustic phenomena, such as the effect of a precursor on detection and discrimination thresholds. However, a time-varying gain control efferent system that simulates ascending and descending neural pathways has not been implemented in previous models. The MOC efferent system receives excitatory projections from both the central nucleus of the inferior colliculus (ICC) and from the small cell-cap (SCC) in the anteroventral cochlear nucleus. High-spontaneous- rate (HSR) auditory-nerve (AN) fibers, which have saturated average rates at mid-to-high sound levels but have fluctuating instantaneous rate patterns that vary across frequency channels, initiate the ascending path to the ICC. Low- and medium-spontaneous-rate fibers, which encode sound level in their average rates, project to the SCC, which in turn projects to the MOC. In this work, phenomenological models of AN fibers and midbrain neurons included the two projections to the MOC, which controlled cochlear gain. The response rates of ICC neurons in awake rabbit to AM stimuli at several modulation depths change over a long time course (hundreds of msec). These responses were used to adjust the time constant of the efferent activity. The hypothesis tested in this modeling study was that a model with efferent control could explain the time course of the increase in discharge rate observed for IC cells with band- enhanced (BE) modulation transfer functions (MTF). In the proposed model, lower cochlear gain reduces inner- hair-cell saturation and thus increases fluctuations in responses of HSR ANs, leading to increased rates of BE IC cells and increased MOC activity. This process provides positive feedback that increases ICC rates over time in response to AM stimuli. Supporting the hypothesis, most IC BE cells had rates that increased over time in response to AM stimuli, especially for stimuli with lower modulation depths. BE ICC cells were the focus of this preliminary study because the increase in their rate over time cannot be confused with rate adaptation. The impact of modulation depth, modulation frequency and sound level on the time course of ICC responses was studied. This information was employed to adjust the parameters of the MOC efferent system in the proposed model for subcortical processing. This research has been supported by NIH-DC010813.

PS 893

Sensory Cells of Amniote Cochleas are susceptible to Zika Virus Infection

Vidhya Munnamalai[1]; Nabilah Sammudin[2]; Caryl Young[1]; Ankita Thawani[3]; Richard Kuhn[2]; Donna Fekete[4] *[1]The Jackson Laboratory; [2]Purdue; [3]Baylor College of Medicine; [4]Purdue University*

Congenital Zika Syndrome in humans is caused by vertical transmission of Zika virus (ZIKV) to the gestating fetus, often resulting in microcephaly and ventriculomegaly. Previous research has demonstrated that ZIKV preferentially infects neural progenitor cells and causes increased cell death and reduced proliferation of infected cells. More recently, it has been reported that ~6% of ZIKV-associated microcephalic newborns show diminished otoacoustic emissions and auditory brainstem responses, suggesting at least some pathogenesis may originate within the cochlea. This supposition is supported by our unpublished results from chicken embryos infected *in ovo*. ZIKV (~10^8 pfu/ml) is delivered into the fluid cavity of the otocyst at embryonic day (E)2 to 5. Antibody against double-stranded RNA is used to detect infection. Sensory and non-sensory otic epithelium, the statoacoustic ganglion, and periotic mesenchyme are infected 2-8 days post injection. Although infection of the auditory organ is seen at all time points, it is most robust following injections at later ages and/or at later stages of harvest (up to E13). These data suggest that there is a critical time window for ZIKV to infect (and perhaps spread) in the embryonic cochlea.

To further address the time course of susceptibility to ZIKV, we studied cultured mouse cochleas at either pre- or post-mitotic stages. Mouse cochleas are explanted on E12.5, E15.5 and postnatal day 2 (P2) and ZIKV (5-10 x 10^5 pfu) is added for the first 24 hours. Samples are analysed after 3-6 days in vitro. At all 3 ages, ZIKV infects hair cells, supporting cells and periotic mesenchyme. On E12.5, the prosensory domain is still proliferating, confirming that ZIKV infects sensory progenitors in the cochlea. By E15.5, the organ of Corti has exited the cell cycle, providing evidence that post- mitotic progenitors are also susceptible to infection. By P2, hair cell differentiation is underway and under damaging conditions the organ shows less plasticity to return to a proliferative state; nonetheless, the sensory cells can be infected. In fact, more hair cells were infected at P2 than at earlier ages. The inner hair cells were also found to be more susceptible to infection than outer hair cells. Finally, we performed virus neutralization experiments where cochlear cultures are preincubated with the ZIKV-117 antibody against the viral envelope protein for 6 hours and then ZIKV is added. Infection is completely blocked under these conditions. When the antibody is washed out prior to ZIKV infection, ZIKV infection prevailed.

PS 1001
Central Gain in the Human Auditory System: Investigations in "Normal Hearing" and in Tinnitus

Kelsey Dougherty; Alexandra Mai; Anna Hagedorn; Hari Bharadwaj
Purdue University

The nervous system is known to adapt in many ways to changes in the statistics of the inputs it receives. An example of such plasticity observed in animal models is that central auditory neurons tend to retain their driven firing rate outputs despite reductions in peripheral input due to hearing loss. This “central gain” has been demonstrated to occur even when the peripheral loss is not accompanied by audiometric threshold shifts, i.e., following noise-induced or age-related loss of afferent synapses and nerve terminals innervating the cochlea (cochlear synaptopathy) despite intact sensory hair cells. Down-regulation of inhibitory neurotransmission is thought to contribute to such plasticity. Pathological versions of such central gain are thought to underlie disorders such as tinnitus and hyperacusis.

Here, we studied two human cohorts that are at risk for peripheral deafferentation by virtue of above-average noise exposure or age. Consistent with cochlear synaptopathy, suprathreshold auditory brainstem response (ABR) wave I amplitudes and the middle-ear muscle reflex (MEMR) were simultaneously attenuated in both high-risk groups despite audiograms and otoacoustic emissions (OAEs) matched to young controls. For the same subjects, we then examined whether there was evidence of central gain accompanying the reduced auditory nerve responses. To this end, we designed an electroencephalogram (EEG)- based paradigm that concurrently elicits separable responses from different levels of the auditory pathway. We find that (i) for a moderate-high stimulus intensity, individual differences in response amplitudes that are as large as 20 dB at the auditory nerve level were reduced to less than 2 dB at the cortical level, (ii) individual differences in the rate of response amplitude growth as a function of stimulus intensity were progressively smaller as we ascend the auditory pathway from the nerve to the cortex, and (iii) a central gain metric defined as the size of the cortical response relative to the size of the auditory nerve response monotonically increased with age despite normal audiograms.

Together, these findings suggest that peripheral deafferentation and consequent central gain are ubiquitous in the human auditory system. To examine the behavioral consequences of reduced inhibition associated with this central gain, we measured individual comodulation masking release (CMR) which is thought to be mediated in part by inhibitory action. Finally, we applied the same battery of physiological measures in individuals with self-reported tinnitus. This presentation will describe these results and discuss the clinical implications.

Wednesday

PD 129

Degradation of Speech-In-Noise Coding in Auditory-Nerve Fibers Following Cochlear Hearing Loss: Insights from Spectro-Temporal and Information-Theoretic Approaches

Satyabrata Parida; Michael G. Heinz
Purdue University

Benefits of studying neural coding of speech include a better understanding of how the normal auditory system encodes speech, as well as how this neural representation is degraded following hearing impairment. Ultimately, this knowledge can serve as a guide to optimize clinical interventions prescribed to patients. To this end, we collected extra-axonal spike trains from single auditory-nerve fibers of normal-hearing and noise-exposed chinchillas. Responses were collected to a natural speech sentence in quiet as well as in noisy backgrounds, including spectrally-matched speech-shaped stationary and fluctuating noises, at perceptually important signal-to-noise ratios. Our approach focused on neurophysiological evaluations of two psychophysically inspired speech-coding hypotheses, namely the multiresolution envelope power spectrum model and the efficient-coding framework. We found that noise-exposed fibers had response envelopes to noisy-speech that were more like noise responses and less like speech responses than control fibers; this effect was particularly severe for fluctuating backgrounds. Thus, our data support the merit of temporal envelope coding as a neural basis for why hearing-impaired listeners show a lack of masking release in fluctuating backgrounds. As a proxy for channel capacity in the auditory nerve, we estimated the average Victor- Purpura distance between spike trains from pairs of neurons in response to speech for normal-hearing and noise-exposed animals; interneuron distance was significantly lower for the hearing-impaired fibers, suggesting a reduction in overall channel capacity of the auditory nerve. Response entropy was also estimated by first constructing probability density functions by binning spike trains across trials and then computing the cumulative f-divergence based distance between density functions of adjacent bins for individual neurons. We found significantly higher entropy for noise-exposed fibers, consistent with enhanced envelope coding in quiet; however, it will be important to estimate entropy in background noise to establish whether enhanced envelope coding is actually detrimental in the presence of competing maskers. Overall, our results highlight the importance of considering the deleterious effects of enhanced inherent noise-response fluctuations following cochlear hearing loss, in addition to degradations in speech-coding fidelity, for predicting speech intelligibility. In addition, our data support the importance of accounting for across-channel interactions in efforts to improve outcomes of hearing-aids and devising neurally based speech-intelligibility models, especially for individuals with hearing impairment.