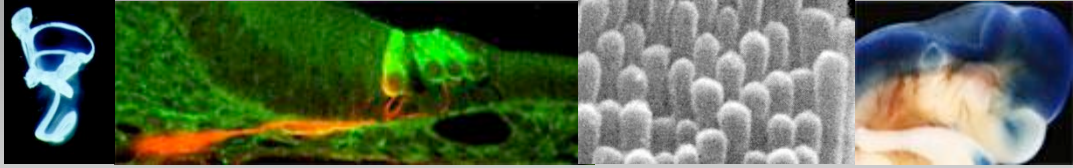


The 9th Annual Eastern Auditory Retreat



Date:

Friday, June 11, 2010

Time:

8:30 am - 6:00 pm

Location:

*Schapiro Center for Engineering and Physical Science Research (CEPSR) building
Columbia University's main campus, New York, NY 10016*

Keynote Lecture:

“From transduction to spiking in the vestibular inner ear”



Ruth Anne Eatock, Ph.D.

*Departments of Otology and Laryngology and Neurobiology
Harvard Medical School
Eaton-Peabody Laboratories, Massachusetts Eye and Ear Infirmary*

Eastern Auditory Retreat, June 11, 2010, Columbia University

	Time	Event	
	8:30 - 9:30	Continental breakfast and Registration	
	9:40 -	Opening of 9 th Annual EAR meeting by Elizabeth S. Olson, Ph. D.	
	9:40 - 9:50	Greeting by Lanny Garth Close, M.D., Chairman of OTO/HNS Department	
No.	Time	Speaker	Title
Development and Regeneration: E. Bryan Crenshaw (Moderator)			
1	9:50 - 10:05	A. Saliu	The development of hearing in rats: Contributions of middle- and inner-ear maturation
2	10:05 - 10:20	Sabrina W. Yum	Dominant and trans-dominant effects of Connexin26 mutants associated with human hearing loss
3	10:20-10:35	Jin Liang	Digital gene expression identifies the Stat3/Socs3 pathway as a key regulator of supporting cell division and hair cell regeneration in the zebrafish inner ear
	10:35-10:50	Discussion	
Hair cells: Joseph Santos-Sacchi (Moderator)			
4	10:50 - 11:05	Felicia L. Smith	Cochlear hair cell micro-isolates regulate the soma size of spiral ganglion neurons
5	11:05 - 11:20	Adria C. LeBoeuf	Ion- and ionic-strength-dependent cohesion in the electrostatic glycocalyx of the hair bundle
6	11:20 - 11:35	Lei Song	Effect of chloride and membrane holding potential on OHCs: simultaneous measures of electromotility and nonlinear capacitance
	11:35-11:50	Discussion	
	11:50 - 1:30	Lunch, group photo and poster viewing	
Neural Processing: Sarah Woolley (Moderator)			
7	1:30-1:45	Louisa J. Steinberg	Enhanced spectrotemporal and envelope coding in the intensity pathway of the barn owl
8	1:45-2:00	David M. Schneider	Extra-classical receptive fields predict stimulus-dependent auditory tuning
9	2:00-2:15	Michaël C. C. Slama	Effects of reverberation on the neural coding of amplitude modulation: Dynamic aspects
	2:15 - 2:30	Discussion	
Cochlear Implants and Emissions: Wei Dong (Moderator)			
10	2:30 - 2:45	Jian Zhang	Friction study on robotic insertions of outer-wall electrode arrays in cochlear implant surgery
11	2:45-3:00	Vanessa M. Cervantes	Development of hydrodynamic fluid-assisted injection method for cochlear implantation in gerbil
12	3:00-3:15	Simon Henin	Changes in distortion product otoacoustic emission (DPOAE) phase during contralateral acoustic stimulation
13	3:15-3:30	Christopher Bergevin	Effects of size upon stimulus-frequency otoacoustic emission delays: A survey into the tiger ear
	3:30- 3:45	Discussion	
	3:45 - 4:10	Coffee break	
Keynote: Ruth Anne Eatock			
14	4:15 - 5:15	Ruth Anne Eatock	From transduction to spiking in the vestibular inner ear
	5:15 - 6:00	More poster viewing, farewells	

The development of hearing in rats: Contributions of middle- and inner-ear maturation

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The onset of auditory function in humans takes place in utero, at around the 6th month of fetal life (Ruben, 1995. Int J Pediatr Otorhinolaryngol S199-204). In contrast, hearing development in altricial species such as rats occurs postnatally, enabling the investigation of developmental and neurological bases of auditory maturation outside the uterine environment.

We measured auditory brainstem responses (ABR) in Wistar rat pups between ages P13 and P15. We found a marked difference in the response to 70 dB SPL broadband clicks (1 to 50 kHz). The peak amplitude of wave I changed from a magnitude of 0 nV at P13 (5 of 5 pups did not display detectable responses), to 454.03 ± 81.55 nV on P14 (only including 6 of 12 pups that displayed detectable responses), and 497.20 ± 199.5 nV on P15 (for 4 of 4 pups that displayed detectable responses).

The observed rapid change in auditory responses could be due to the maturation of peripheral structures, probably by overcoming a conductive hearing loss. Therefore, clearing of soft tissue from middle ear airway passages and the ossification of inner ear ossicles could play important roles in determining the onset of hearing in this species.

Using 3D high-resolution microCT, we are assessing the presence of air in the middle ear passages and the degree of ossification in middle ear structures. Preliminary results using this imaging approach show marked differences between P8 and P21 samples. Altogether, these data suggest that the maturation of peripheral structures plays a key role during the development of hearing. Our proposed course of study may provide clues that would help further the understanding of auditory development in rats, humans and other vertebrates.

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Dominant and trans-dominant effects of Connexin26 mutants associated with human hearing loss

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Dominant mutations in *GJB2*, the gene encoding the human gap junction protein connexin26 (Cx26), cause hearing loss. We investigated whether dominant Cx26 mutants interact directly with wild type Cx26 or Cx30. HeLa cells stably expressing nine dominant Cx26 mutants, six associated with non-syndromic hearing loss (W44C, W44S, R143Q, D179N, R184Q and C202F) and three associated with hearing loss and palmoplantar keratoderma (G59A, R75Q and R75W), individually or together with Cx26V5 or Cx30, were analyzed by immunocytochemistry, co-immunoprecipitation, and functional assays (scrape-loading and/or

fluorescence recovery after photobleaching). When expressed alone, all mutants formed gap junction plaques, but with impaired intercellular dye transfer. When expressed with Cx26V5 or Cx30, all mutants co-localized and co-immunoprecipitated with Cx26V5 or Cx30, indicating that they interact physically, likely by forming admixed heteromeric/heterotypic channels. Furthermore, all nine mutants inhibited the transfer of calcein in cells stably expressing Cx26 and 8/9 Cx26 mutants inhibited the transfer of neurobiotin or calcein when co-expressed with Cx30, indicating that these Cx26 mutants have dominant effects on Cx26 and variable trans-dominant effects on Cx30; these effects may contribute to the pathogenesis of hearing loss.

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Digital gene expression identifies the Stat3/Socs3 pathway as a key regulator of supporting cell division and hair cell regeneration in the Zebrafish inner ear

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Sensory hair cells of the inner ear are the mechanotransductive units in the neuroepithelia. In mammals, lost hair cells are not replaced, resulting in various permanent deficiencies in vestibuloauditory sensation. In contrast, zebrafish can replace lost hair cells with new ones throughout adulthood. Our ultimate goal is to understand the molecular mechanism of the inner ear hair cell regeneration in adult vertebrates. As an initial step, we defined the genetic programs used for hair cell regeneration in zebrafish using emerging techniques for gene expression profiling.

We modified a previous noise-exposure protocol, which enabled us to induce consistent hair cell loss in the saccular epithelium of the adult zebrafish and characterize the subsequent regeneration process. We determined the inner ear gene expression profiles at different time points during the regeneration, focusing particularly on those genes with significant changes in expression at the various time points compared to control. Here we used Digital Gene Expression (DGE), to generate the gene expression profiles in an in-depth and high-throughput manner. Our analysis of the profiling data suggested new candidate genes as well as candidate pathways (stat3/socs3 pathways) involved in hair cell regeneration.

In addition, we confirmed that pharmacological activation of stat3/socs3a pathway in larval fish accelerated HC regeneration in the lateral line neuromasts, without over-production of hair cells. Our results as well as previous publications suggest that stat signaling is a fundamental initiating mechanism of tissue regeneration of various tissues in different animals. Transient up-regulation stat3 expression without disrupting the normal negative feedback of socs3 may help achieve the desirable regenerative effect of accelerating the wound healing in many tissues without undesired over-production of cells, making stat3 a potential therapeutic target for injury treatment in a wide variety of tissues.

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Cochlear hair cell micro-isolates regulate the soma size of spiral ganglion neurons

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Specific features of spiral ganglion neuron morphology, such as soma area and branching patterns, vary with cochlear location, yet little is known about how the size and shape of these neurons is established. Therefore, this study is designed to determine the factors that regulate the soma area of spiral ganglion neurons.

We initially determined that neurons isolated from the basal cochlear region have a larger soma area ($303 \pm 9 \mu\text{m}^2$, $n=12$) than their apical counterparts ($265 \pm 6 \mu\text{m}^2$, $n=12$) *in vitro*. This difference was enhanced when spiral ganglion neurons are co-cultured with hair cell micro-isolates. Basal neurons paired with basal hair cell micro-isolates were larger ($351 \pm 24 \mu\text{m}^2$, $n=5$) while apical neurons co-cultured with apical hair cell micro-isolates were smaller ($221 \pm 5 \mu\text{m}^2$, $n=4$) than the soma areas observed in neuronal cultures. By mixing and matching hair cell micro-isolates with spiral ganglion neurons isolated from different cochlear regions we noted that cochlear tissues could alter soma area. For example, when basal neurons were paired to apical micro-isolates neuron size was significantly reduced ($206 \pm 7 \mu\text{m}^2$, $n=5$; $p<0.01$). Correspondingly, apical neurons paired with basal micro-isolates showed an enlarged soma area ($361 \pm 27 \mu\text{m}^2$, $n=5$; $p<0.01$). In both cases anti-neurotrophin function blocking antibodies significantly reduced the effects of altering the cochlear location of the hair cell micro-isolates.

Because cochlear hair cells can secrete both brain derived neurotrophic factor and neurotrophin-3 in differing amounts (Flores-Oterero et al., J Neurosci. 2007), we will next determine whether neurotrophins on their own or in combination with other factors can influence neuronal size. Our goal is to understand the regulatory mechanisms that control morphology and to determine how these features contribute to the initial stages of auditory processing. Supported by NIH NIDCD R01 DC-01856.

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Ion- and ionic-strength-dependent cohesion in the electrostatic glycocalyx of the hair bundle

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To enable us to hear frequencies up to 20 kHz, mechanosensitive hair bundles of our inner ears must oscillate and amplify at those frequencies while overcoming viscous drag and internal friction. How can such movements be accomplished for a lifetime without harming cellular structures and causing hearing loss?

For *accurate* sensory transduction to occur, mechanotransduction channels at the tips of stereocilia must open in unison when the bundle is deflected. For *efficient* sensory transduction, dissipative friction must be minimized between stereociliary tips as they slide against one another during stimulation. Two mechanisms might allow the bundle to function within these constraints. Stereocilia might exhibit sliding adhesion with low level frictional dissipation, or they might form elastic connections flexible enough to allow the requisite shear but that conserve the energy of the movement. Both of these mechanisms could be mediated by the charged sugars of the glycocalyx, the layer of glycoproteins and glycolipids decorating the stereociliary membrane. If stereocilia are coated with negatively charged sugars, they should repel each other owing to electrostatic forces. In the presence of multivalent cations, they might instead exhibit adhesion. Depending on the relative strength of these forces, stereocilia might exhibit either low-friction sliding adhesion or stiffer elastic connections between the apposing sugar-coated surfaces.

To tease apart dissipative and elastic components of stereociliary cohesion, we rubbed individual isolated stereocilia together under different ionic conditions while making quantitative force measurements using a flexible glass fiber and photomicrometer. In physiological solutions, rubbing stereociliary tips together dissipated little energy while the attachments formed between apposing surfaces appeared stiff and elastic. Stiffness decreased and energy dissipation increased in low-ionic-strength solutions and in physiological solutions with high multivalent ion concentrations. These experiments suggest the hair bundle's glycocalyx and its surrounding medium have been optimized evolutionarily to conserve energy.

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Effect of chloride and membrane holding potential on OHCs: simultaneous measures of electromotility and nonlinear capacitance

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Mammalian outer hair cell (OHC) electro-motility is believed to arise from conformational changes of the membrane protein prestin. Under whole cell patch clamp, the conformation of prestin is monitored by its signature voltage-dependent nonlinear capacitance (NLC). A number of factors influence NLC and shift prestin's voltage response profile. Both intracellular Cl and membrane holding potential (pre-pulse effect) alter NLC, shifting its voltage at peak capacitance (V_h) in the hyperpolarizing or depolarizing direction.

In this study, we combine patch clamp and video imaging to record simultaneously OHC electromotility and NLC. As expected, we find that at 140 mM intracellular Cl concentration, there is an excellent match between V_h of NLC and motility. When intracellular Cl concentration is changed to more physiological levels, 10 or 1 mM, there is a disparity between each V_h . The V_h of motility is more hyperpolarized than that of NLC. We find that the rate and direction of voltage stimulation, as well as turgor pressure, can influence the magnitude of this disparity. These data suggest that intracellular Cl modulates the coupling between prestin's conformational change and the whole cell response.

Enhanced spectrotemporal and envelope coding in the intensity pathway of the Barn Owl

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Owls principally use two variables to determine sound source location: interaural time difference (ITD), which indicates the azimuth coordinate and interaural level difference (ILD), which cues the vertical coordinate. These variables are processed in two parallel pathways in the brainstem, which converge on the inferior colliculus (IC), where they give rise to space-specific neurons in the external nucleus of the inferior colliculus (ICx). Neurons in nuclei of the auditory brainstem preceding the lateral shell of the core of the inferior colliculus (ICcl) are narrowly tuned to frequency. As neurons' space specificity emerges, their frequency tuning expands and their spectrotemporal receptive fields (STRFs) become more complex. The STRFs of neurons in the ascending ITD pathway preceding ICcl have been shown to be simple and highly separable in frequency and time. However, STRFs in the intensity pathway have not been characterized and may contribute to IC neurons' spectrotemporal complexity. We have thus recorded neurons in nucleus angularis (NA) and the pars posterior of the lateral lemniscus (LLDp), two nuclei belonging exclusively to the ILD pathway. In these neurons we found highly separable STRFs comparable in spectral and temporal width to those found in the ITD pathway. However, the predictive power of STRFs of NA neurons is greater than those of NM neurons.

We also measured the reproducibility and temporal precision of the neural response to the stimulus envelope in both pathways. We found that neurons of the early ILD pathway exhibit greater reproducibility, while neurons of the late ILD pathway display greater temporal precision in their response compared to neurons belonging to the ITD pathway. This is surprising, as neurons in the early ITD pathway are able to phase lock to frequencies up to 9 kHz. Thus, although neurons of the ILD pathway lack the temporal accuracy to sustain phase locking, they are able to more precisely encode envelope timing. Our model shows that at the level of the cochlear nuclei this difference in envelope coding can be accounted for by a suppressive subfield found in NA neurons' STRFs.

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Extra-classical receptive fields predict stimulus-dependent auditory tuning

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The receptive fields of many sensory neurons adapt to the statistical properties of complex stimuli such as natural sounds and natural visual scenes, a phenomenon called stimulus-dependent tuning. For example, the range of sound frequencies to which auditory neurons are receptive changes during the processing of communication vocalizations compared to synthetic noise. Changes in frequency bandwidth during the processing of different sound classes are

correlated with a neuron's ability to accurately encode each sound class, suggesting that bandwidth plays a functional role in the differential processing of statistically different sounds. However, the physiological mechanism(s) responsible for this type of stimulus-dependent tuning remain unknown. We show that stimulus-dependent frequency tuning in the songbird auditory midbrain is predicted by the presence, valence and laterality of excitatory and inhibitory extra-classical receptive fields, which were revealed by recording responses to tones. Stimuli that fell within the extra-classical receptive field modulated responses to stimuli within the classical receptive field, but did not produce a response when presented alone. Neurons with wider frequency bandwidths during song processing exhibited extra-classical excitatory tuning, a mechanism that has not been previously described. Neurons that did not change their tuning during the processing of song and noise had either no extra-classical tuning or inhibitory extra-classical tuning, traditionally described as inhibitory sidebands. We show through simulations that extra-classical tuning can explain stimulus-dependent receptive fields measured from responses to different complex sound classes, providing support for the conclusion that extra-classical receptive fields provide a physiological mechanism for stimulus-dependent frequency tuning.

Effects of reverberation on the neural coding of amplitude modulation: Dynamic aspects

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Speech reception depends critically on temporal modulations in the amplitude envelope of the speech signal. These modulations are substantially attenuated by reverberation encountered in everyday acoustic environments. To assess the effect of reverberation on the neural coding of amplitude envelope, we recorded from single units in the inferior colliculus of unanesthetized rabbit, using sinusoidally amplitude-modulated broadband noise stimuli presented in simulated anechoic and reverberant environments. The modulation frequency was typically varied from 4 to 256 Hz.

Phase locking to modulation frequency was consistently weaker in the reverberant condition than in the anechoic condition, indicating that reverberation degrades temporal coding. However, phase locking was on average better for reverberant stimuli than for anechoic stimuli whose modulation depth was matched to the average modulation depth of the reverberant stimulus. This suggests that envelope frequency representation is more robust for realistic, dynamic reverberant stimuli, than for static, anechoic stimuli, when controlling for average modulation depth. We tested the hypothesis that this dynamic coding advantage results from firing rate adaptation boosting the early response when reverberant energy is lowest. Consistent with the hypothesis, we found a positive correlation across neurons between the dynamic coding advantage and the amount of adaptation.

In some neurons, phase locking to each modulation cycle of a reverberant stimulus sharply degraded during the first 100 ms of the stimulus before stabilizing, paralleling the evolution of modulation depth in the stimulus as reverberant energy builds up. However, in other neurons, phase locking was stable or even slowly increased over time, despite the decrease in stimulus modulation depth. This observation suggests that the nonlinear transformation from

stimulus modulation depth to neural phase locking is not static, and may depend dynamically on preceding stimulation history.

Overall, our results point to an important role of dynamic neural processes for robust stimulus coding in reverberation.

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Friction study on robotic insertions of outer-wall electrode arrays in cochlear implant surgery

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Robotic assistance to cochlear implant surgery aims to achieve atraumatic insertions of electrode arrays with improved electrode positioning and force control during insertion process. From preliminary research, the authors have discovered that the insertion friction forces depend on insertion speeds for outer-wall electrode arrays. This presentation shows this relationship and models the electrode insertion friction forces as a function of its insertion speeds. Robotic insertions of out-wall electrode arrays into plastic scala tympani models and *in vitro* tests on cadaver cochlear bones have been conducted and compared under different conditions. A 6 Degrees-of-Freedom (DoF) Force and Torque (F/T) sensor is used to quantify the insertion forces in three directions. Up-lifting forces caused by electrode insertions are analyzed and presented. Experimental results show that with increased insertion speeds, insertion forces decrease by 31.8% on plastic models and decrease by up to 33.3% on cadaver cochlear bones when 100% glycerin is used as lubricants. Statistical models of insertion forces with safe bounds have been generated for both plastic models and cadaver cochlear bones. Electrode array critical buckling forces are analyzed and preferred insertion speeds for outer-wall electrode arrays are recommended.

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Development of new hydrodynamic fluid-assisted injection method for cochlear implantation in gerbil

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Current trends in cochlear implantation research are moving towards preservation of residual hearing and are largely focused on reducing surgically-induced trauma and inflammation, as well as promoting cell growth. We are developing a new surgical technique for

cochlear implantation in gerbils (*Meriones unguiculatus*) that utilizes a hydrodynamic fluid-assisted injection method to deliver a silicone implant to the scala tympani (ST). The goals of this technique are to (1) achieve deep electrode insertions, (2) induce no trauma to intracochlear structures, and (3) preserve natural hearing. This technique could provide an alternate surgical technique for human cochlear implantation, and also be a useful animal model for implant-mediated drug delivery. METHODS: Silicone implants were injected into cochleae by loading them into a syringe filled with ~1% hyaluronic acid (HA) and injecting both the implant and HA into the ST via the round window. A scala vestibuli cochleostomy was made to serve as an exit port for the displaced perilymph and injected HA. Trauma was determined by histological examination, and hearing status in *in vivo* implantations was determined through compound action potential measurements. RESULTS: In postmortem studies, implantations of up to 2 full turns were achieved with no trauma to intracochlear structures. In the three *in vivo* studies performed, 1.5-turn insertions were achieved, but thus far no hearing preservation has been seen. Injection of 1.0% HA only into the cochlea also resulted in a global hearing loss. CONCLUSION: Deep atraumatic insertions of silicone implants are possible with the hydrodynamic-assisted injection method, however hearing preservation has yet to be seen. The hearing loss may be due to dampening of basilar membrane movement by the presence of the HA or implant within the ST, contamination of the middle ear with HA causing a conductive hearing loss, or disruption of the endocochlear potential. The effects of HA concentration and speed of injection on insertion depth, and the effects of HA in the middle ear have yet to be determined.

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Changes in distortion product otoacoustic emission (DPOAE) phase during contralateral acoustic stimulation

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Efferent activation evoked by contralateral acoustic stimulation (CAS) produces both suppression and enhancement of distortion product otoacoustic emission (DPOAE) level. When phase was ignored, DPOAE levels with and without CAS did not significantly differ. The level enhancement occurred near fine-structure minima because the frequency of the DPOAE fine structure consistently shifted upwards during CAS. Larger frequency shifts were observed at increased CAS levels. Using vector subtraction (which takes into account both level and phase) to estimate the changes in the unseparated DPOAE provides consistent evidence of DPOAE suppression. Including phase information provide a more sensitive, valid and consistent estimates of CAS function when we know where we are in the fine structure. It should also provide a more sensitive tool for evaluating efferent function even if one does not know where in the fine structure one is collecting data (such as the typical DPOAE measures at octave frequencies). Separation of the two DPOAE components responsible for the fine-structure revealed that the frequency shift stemmed from differential phase modulation with CAS stimulation: The reflection component exhibited increasing phase lags as function of frequency while the generator component phase was nearly invariant. Efferent innervation is expected to

modify cochlear gain of the reflection component, leading to wider filters and thus shorter travel time,

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Effects of size upon stimulus-frequency otoacoustic emission delays: A survey into the tiger ear

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Stimulus-frequency otoacoustic emission (SFOAE) delays have been proposed as a means to objectively quantify the sharpness of peripheral auditory tuning. In light of observations that human SFOAE delays appear larger than any other species so far examined, there has been much debate with regard to how other sources of delay, such as those associated with basilar membrane length, could affect such estimates. In order to gain insight into how 'size' affects SFOAE delays, emissions were measured in a relatively large mammal: *Panthera tigris*. This particular choice of animal is notable in several aspects with regard to size. First, anatomical data indicate that tigers have a basilar membrane length similar to that of humans (roughly 38 mm and 33.5 mm respectively), allowing for a comparison of delays between two species with relatively long cochleae. Second, a direct comparison with the domestic cat (*Felis catus*) provides an opportunity to examine SFOAEs across two groups within the same taxonomic family, but differing in body mass by roughly one and a half orders of magnitude. Our results indicate that, for stimulus frequencies spanning more than 4 octaves from 0.7-13 kHz, tiger delays are significantly longer than those of domestic cat, but still significantly shorter than those of human.

KEYNOTE ADDRESS:

From transduction to spiking in the vestibular inner ear

Ruth Anne Eatock, Jocelyn Songer, and Radha Kalluri

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Afferent signals from vestibular organs of the inner ear contribute to our sense of heading and orientation and drive powerful reflexes that compensate for head motions, allowing us to navigate our environment. The utricle and saccule - the linear accelerometers - are organized into striolar and extrastriolar zones, innervated by afferent fibers with markedly different morphology and physiology. In mammals, striolar afferents form calyceal synaptic endings

around one or more type I hair cells; some also make bouton endings on type II hair cells. They respond with greater adaptation to head motions and fire with irregular inter-spike intervals. Extrastriolar afferents form bouton synaptic endings; some also make simple calyces around single type I hair cells. They show less adaptation and have strikingly regular inter-spike intervals, which may afford an information advantage at low vestibular stimulus frequencies.

By studying the properties of ion channels in hair cells and afferent neurons, we hope to uncover mechanisms underlying the segregation of striolar and extrastriolar signals and gain insight into the significance of the zonal organization for vestibular processing. Some potentially important differences have emerged recently. Preliminary comparisons of transduction by striolar type I hair cells and extrastriolar type II hair cells in the rat saccule suggest that transducer adaptation may contribute to zonal differences in response dynamics. Immature hair cells express different voltage-gated Na channels in different zones, raising the possibility that electrical activity in the immature epithelia influences development of zones. Low-voltage-activated (LV) K channels, which are prominent on both sides of the type I-calyx synapse, have multiple possible roles. They affect the gain and speed of receptor potentials and the excitability of afferents. They may contribute to a significant non-quantal component of afferent transmission, and are potential targets for modulation by efferent transmitters. Recordings from isolated afferent neurons suggest that the LV channels of striolar afferents cause them to fire with irregular inter-spike intervals. Extrastriolar afferents lack such channels, and consequently fire at regular intervals.

Supported by an RO1 (RAE) and NRSA (RK) from NIDCD, and an NSBRI fellowship to JES from NASA.

POSTERS:

Effect of juvenile auditory training on adult perception

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A general theory of sensory development holds that early experience can influence central nervous system function, thereby shaping adult perceptual skills. However, support for this idea is based largely on the neural effects of *sensory deprivation* or *continuous exposure* to a limited sensory environment. A more cogent test of this theory would provide sensory training to juvenile animals and ask whether their perceptual skills were affected in adulthood. Here, we trained juvenile gerbils (P25-40) on an amplitude modulation (AM) detection task, and determined whether their performance in adulthood was better than naïvely trained adults (P70). Juvenile animals were trained on a conditioned avoidance task for a total of 10 days. The AM detection thresholds of naïve juveniles were poorer than those of naïve adults, suggesting that this percept is not yet mature. Furthermore, compared with adults, juveniles did not display a similar ability to improve over the course of repeated testing. When these juvenile-trained animals returned as adults, initial AM thresholds were obtained, followed by 10 days of additional testing. Adult animals trained as juveniles displayed similar initial thresholds as naïve Adults. However, asymptotic performance was significantly better in juvenile-trained adults as

compared to naïve adults (Juvenile trained: $15.4 \pm 0.7\%$ depth; Adult naïve: $22.5 \pm 1.4\%$). As a control, a group of animals trained in adulthood were re-tested after one month to determine whether the effect of training depends on age. AM thresholds did not improve in these adult animals. These results suggest that adult behavioral performance can be improved by early sensory training, even before perceptual skills are mature.

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Newborn cells in the auditory brainstem of rats during early postnatal development

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The medial nucleus of the trapezoid body (MNTB) in the rodent brainstem is a relay nucleus involved in sound localization. Because the MNTB has a relatively simple cellular composition we are investigating neuro-glial interactions during the period of circuit maturation and refinement. We previously showed that despite a steady increase in normal cell death, the total number of cells in the MNTB nearly doubles between birth and P15 (Rodriguez-Contreras et al., 2006). We hypothesized that the observed increase in MNTB size is a function of the number of glial cell precursors migrating into it, how they differentiate, and when they undergo cell death. To address this idea we first measured cell proliferation in the MNTB of prehearing (P8-11) and hearing (P17-19) rat pups. We injected the nucleoside analog 5-ethynyl-2'-deoxyuridine (EdU) followed by intracardiac perfusion and detection with a copper-catalyzed fluorescent hydrazide reaction. We found that the density of EdU labeled cells in the MNTB of prehearing rats was markedly higher (199 ± 14 cells/mm², n=3) when compared to that in hearing animals (62 ± 39 cells/mm², n=2). To determine the identity of EdU labeled cells we performed triple staining experiments using EdU labeling and immunohistochemistry for glial (S100 β) and neuronal (NeuN) cell markers. Our preliminary results show that proliferating cells in the MNTB can differentiate into S100 β + cells. Lastly, since cell proliferation occurs during a period of ongoing cell death, we explored the possibility that autophagy is enhanced in the MNTB of prehearing animals. Using the fluorescent probe Lyso-tracker red in acute brainstem slices, we observed a decrease in lysosome-like particles between prehearing (145 ± 62 particles/mm², n=6) and hearing (42 ± 32 particles/mm², n=4) rats. Altogether, these results provide evidence that cell proliferation, death and autophagy play concerted roles during the normal development of the auditory brainstem.

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Spatiotemporal receptive fields in the owl's map of auditory space

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Few studies have examined the space-time dynamics of auditory spatial receptive fields. Receptive field (RF) analysis using brief stimuli from randomized locations in space, also called white-noise analysis, has shown to be a powerful technique in studying temporal properties of RFs in the visual system. In previous applications of white-noise analysis to the auditory system, was used to study the auditory system, auditory space was studied in cortical regions using virtual-space stimuli. We studied auditory spatiotemporal RFs in the external nucleus of the inferior colliculus (ICx) of the barn owl (*Tyto alba*). RFs were measured in real-space using a hemispherical speaker array with 10-degree resolution in azimuth and elevation. Our paradigm more closely mirrors the use of white-noise analysis in visual systems because like the retina, and unlike the auditory cortex, a well-characterized topographical representation of auditory space exists in ICx. We observed that neurons exhibit sharper RFs when randomized, overlapping, noise bursts are played, a difference that is likely due to lateral inhibition from areas surrounding the center of the RF. First-order white noise analysis showed delayed inhibitory modulation during the response to noise bursts from the center of the RF. Neural response were most effectively inhibited when sound bursts from the surround were played 10-20ms preceding sound played from the center of the RF. In addition, inhibitory modulation showed a consistent asymmetry, being stronger from the ipsilateral side relative to the recording site. This finding may represent the basis of topographically represented movement-direction selectivity. White-noise analysis in ICx thus offers a unique window into spatial and temporal dynamics of auditory RF as well as local circuitry for representing space and motion in the auditory system.

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Subharmonic responses in the plateau region of gerbil auditory nerve tuning curves

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In the literature, an auditory nerve tuning curve obtained from single unit recording typically has a tail and a tip. Responses beyond the tip in the well supra-CF frequency region had never been documented. In a study designed to explore that region specifically, we found plateau responses in the supra-CF region of several auditory nerve tuning curves at very high sound pressure levels (~120dB SPL). (Huang&Olson, ARO 2009, poster #623) However, a complicating issue at high sound pressure levels is the generation of subharmonics, which are likely generated in the eardrum (Dallos & Linnell 1966 JASA 40(3):561-564). Indeed, we found subharmonics in a subset of ear canal pressure we measured in gerbils, and they might have contributed to the supra-CF responses.

Here we present auditory nerve tuning curves in which supra-CF neural responses were present while subharmonics were beneath the noise floor in the ear canal pressure. Thus these detections of supra-CF neural responses did not seem to suffer from subharmonic “contamination.” To probe this further, we delivered loud tones and compared ear canal pressure and intracochlear pressure at subharmonics frequencies, and the quantitative relationship between the two reinforced that subharmonics were probably not responsible for the supra-CF neural responses we measured.

It’s conceivable that this subharmonic finding has at least two clinical implications. First, eardrum produced subharmonics might occur with very high power hearing aids. This could pose a problem to patients with band limited or high frequency hearing loss, since subharmonics that are within their normal-hearing frequencies could be perceived to be “louder” than the fundamental. Second, we found that the eardrum (the putative source of the subharmonics) was a reasonably effective sound radiator. Thus hearing aids that drive the eardrum directly might produce feedback.

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