APAN 2016 Program

Keynote address

Prof. Timothy D. Griffiths
Newcastle University, U.K.

Sound effects: Notes from the clinic

I will consider clinical aspects of auditory cognition, the brain mechanisms for understanding the acoustic world. Specifically I will consider how auditory cognition allows adjustment to peripheral hearing loss, and how an understanding of central auditory mechanisms informs us about disorders of perception, memory and emotion.

Young Investigator Award

Dr. Maria Geffen
University of Pennsylvania

Cortical circuits supporting dynamic auditory processing

Hearing perception relies on our ability to tell apart the spectral content of different sounds, and to learn to use this difference to distinguish behaviorally relevant (such as dangerous and safe) sounds.A number of recent studies, conducted in both human patients and animal models, suggest an important role for the auditory cortex in frequency discrimination and emotional auditory learning, challenging the “classical” view, which postulated that the auditory cortex was not important for frequency discrimination. Recently, we demonstrated that the auditory cortex regulates frequency discrimination acuity following emotional learning (Aizenberg and Geffen, Nature Neuroscience, 2013). However, the neuronal circuits that underlie this modulation remain unknown. In the auditory cortex, the excitatory neurons serve the dominant function in transmitting information about the sensory world within and across brain areas, whereas inhibitory interneurons carry a range of modulatory functions, shaping the way information is represented and processed.

I will discuss the results of two of our recent studies that elucidate the function of specific inhibitory neuronal population in sound encoding and perception. In the first study, we found that the most common class of interneurons, parvalbumin-positive (PVs), modulate frequency selectivity of excitatory neurons in the auditory cortex, and regulate frequency discrimination acuity and specificity of discriminative auditory emotional learning (Aizenberg et al., PLoS Biology, 2015). Photoactivation of PVs improved the ability of the mouse to detect a shift in tone frequency, whereas photosuppression of PVs impaired the performance. Furthermore, photosuppression of PVs during discriminative auditory fear conditioning increased generalization of conditioned response across tone frequencies, whereas PV photoactivation preserved normal specificity of learning. Our results demonstrate that cortical inhibition can

improve or impair acuity of innate and learned auditory behaviors that rely on frequency discrimination.

In a second study, we found that PVs and another class of interneurons, somatostatin-positive interneurons (SOMs), regulate adaptation in responses of cortical neurons to frequent sounds, in a complementary manner (Natan et al., eLife, 2015). Reliably detecting unexpected sounds is important for environmental awareness and survival. By selectively reducing responses to frequently, but not rarely, occurring sounds, auditory cortical neurons are thought to enhance the brain's ability to detect unexpected events through stimulus-specific adaptation (SSA). We found that PVs amplify SSA by providing non-specific inhibition. In contrast, SOMs selectively reduced excitatory responses to frequent tones. A mutually coupled excitatory-inhibitory network model revealed the distinct mechanisms by which cortical inhibitory neurons enhance sensitivity to unexpected sounds.

These results expand our understanding of how specific cortical circuits contribute to auditory perception in everyday acoustic environments. We will conclude by presenting more recent data on identifying the function of interneurons in context-dependent modulation of auditory behavior.

APAN 2016 Speaker Abstracts

L5 corticocollicular and L6 corticothalamic neurons support a parallel and complementary analysis of auditory stimulus features

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Neurons in layers (L) 5 and 6 of the auditory cortex (ACtx) give rise to a massive subcortical projection that innervates all levels of the central auditory pathway as well as non-auditory areas including the amygdala, striatum, and basal ganglia. L5 and L6 neurons feature distinct morphology, connection patterns, intrinsic membrane properties and synaptic properties, yet little is known about how these differences relate to sensory selectivity in vivo. Here, we focused on two distinct ACtx L5 and L6 projection neurons; L5 corticocollicular neurons (L5CCol), and L6 corticothalamic neurons (L6CT).

We developed a dual-channel antidromic optogenetic “phototagging” strategy to isolate single L5CCol and L6CT units from extracellular recordings in awake, head-fixed mice. We injected two adeno-associated viral constructs (AAV) into ACtx of Ntsr1-Cre transgenic mice, in which cre recombinase is expressed only in L6CT neurons. One cre-dependent AAV encoded Chrimson (a red-shifted channelrhodopsin) and a second non-specific AAV encoded hChR2. One optic fiber was then implanted near the surface of the inferior colliculus and a second near the medial geniculate body. By evoking antidromic spikes from L5CCol neurons with blue light and L6CT neurons with red light, we could simultaneously isolate and characterize both types of projection neurons with a single multi-channel recording probe in ACtx.

L5CCol neurons exhibited shorter response latencies and broader frequency tuning than L6CT neurons. Linear spectrotemporal receptive field (STRF) fits were able to explain a higher percentage of response variance in L5CCol neurons, indicating a higher degree of linearity in their responses when compared to L6CT units. Finally, we used a closed-loop evolutionary stimulus optimization strategy to identify the best stimulus for L5CCol and L6CT neurons across a 4-dimensional stimulus manifold. The evolutionary search strategy manipulated the modulation frequency, level, spectral bandwidth, and center frequency of noise tokens in real time based on spike feedback to identify an optimal stimulus. We found that L5CCol neurons featured a lower multi-dimensional sparseness index, indicating a reduced stimulus selectivity and a broader response distribution than L6CT neurons. These findings suggest a functional dichotomy in the form of stimulus-related modulation imposed by L5 and L6 neurons to subcortical targets. Future work will entail recording from these projection neurons

during task engagement to establish how these functional differences are adaptively used in service of goal-directed behavior.

GABAA and GABAB mediated inhibition display distinct critical periods in auditory cortex.

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Introduction

Sensory deprivation can induce profound changes to central processing during developmental critical periods (CPs). For example, loss of visual or auditory function during development commonly leads to reduced GABAA receptor-mediated inhibitory synaptic responses in cortex. However, the effect of hearing loss on GABAB receptor-mediated inhibition is not known. Here, we used a novel recombinant adeno-associated virus (rAAV) that restricts channelrhodopsin expression to telencephalic GABAergic interneurons, permitting us to optogenetically activate only inhibitory interneurons while recording from pyramidal cells. Using this approach, we investigated whether auditory cortex GABAA and GABAB receptor function was differentially altered by a period of developmental hearing loss.

Methods

Bilateral earplugs were inserted in gerbils (Meriones unguiculatus) on postnatal day 11, and were subsequently removed at successively later ages (P13, P17, or P18). On P48, auditory cortex was injected with rAAV-mDlx-ChR2-mCherry (50 nl). Adult thalamocortical brain slices were generated and whole-cell current clamp recordings were obtained from unlabeled L2/3 pyramidal cells. Inhibitory postsynaptic potentials (IPSPs) were evoked by stimulating with 1 ms pulses of blue light (470 nm).

Results

Light stimulation reliably evoked IPSPs that were composed of a short latency GABAA and a long latency GABAB receptor-mediated component. In a subset of experiments, each component was validated with selective antagonists to either GABAA (bicuculline) or GABAB (SCH-50911) receptors. When hearing loss was reversed at P13, both GABAA receptor amplitude components were normal in adulthood (p's > 0.1). When hearing loss was reversed at P17, GABAAergic IPSPs were smaller in adults (mean mV ± SEM: Ctrl – 9.4 ± 0.9 vs. EP11 to 17 – 6.0 ± 0.4, $p < 0.01$). In contrast, GABAB receptor amplitude was normal (mean mV ± SEM: Ctrl – 5.8 ± 0.9 vs. EP11 to 17 – 6.1 ± 0.5, $p > 0.1$). Finally, when hearing loss was reversed at P18, then both GABAA (mean mV ± SEM: Ctrl – 9.4 ± 0.9 vs. EP 11 to 23 – 3.9 ± 0.4, $p < .001$), and GABAB receptor-mediated IPSPs were significantly diminished (mean mV ± SEM: Ctrl – 5.8 ± 0.9 vs. EP 11 to 23 – 1.9 ± 0.2, $p < .001$).

Conclusion

Our results support the concept that a brief period of sensory deprivation during developmental CPs has a long-lasting effect on synaptic inhibition. However, the two major classes of GABAergic transmission display unique CPs. Specifically, the effect of hearing loss on GABABergic transmission requires a longer period of auditory deprivation.

Task-Related Plasticity in the Inferior Colliculus of the Marmoset Monkey

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Recent evidence suggests that neurons in the inferior colliculus (IC) undergo receptive field changes during auditory behavior in carnivores (Slee and David, 2015. J Neurosci.). In this study, we tested for similar effects in the marmoset monkey, a primate species that uses vocalizations to communicate. Two marmosets were trained to detect a pure tone target embedded in a background of random spectral shape (RSS) distractor stimuli. The level of the target was manipulated to vary task difficulty. Both marmosets accurately performed this task over a 5-octave range of target frequencies (0.625-20 kHz). As the signal to noise ratio of the target was decreased, we found a significant decrease in hit rate and an increase in false alarm rate.

We measured the effects of task engagement by recording from single neurons in the IC. Neural responses to both targets and RSS distractors were compared between conditions when the marmoset performed the detection task or listened passively. The target frequency was presented near the best frequency (BF) of the neuron under study. Responses to the distractors were suppressed in about half of the neurons during task engagement relative to passive listening. The median global gain change (-14%) in these neurons was comparable to our previous study in the ferret (median=-20%). To measure local tuning changes, responses to the RSS distractor stimuli were also used to fit linear and nonlinear spectral weighting models. Spectral weights were tuned around BF for most neurons in the central nucleus of the IC. In about 1/3 of these neurons we found a significant decrease in the spectral weight at BF (target frequency) during task engagement. The median weight change (-25%) was also similar to previous measurements in the ferret (-32%).

Finally, we computed the discrimination index (d') between the distributions of neural responses to the target and distractor stimuli in both behavioral conditions. We found that while most IC neurons can discriminate between the task stimuli (d'>1), discrimination does not improve during task engagement. These results support a model with task-related plasticity in the IC as a prerequisite for the improved neural discrimination that has been reported in auditory cortex.

Functional organisation of the thalamo-cortical auditory system in awake ferrets using fast ultrasound imaging

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Large-scale functional imaging techniques are part of a fast growing field of neuroscience aiming at understanding whole brain activity. Functional Ultrasound Imaging (fUS) is a new method monitoring changes in blood flow with a high spatial (~100µm) resolution and sampling rate (500Hz) for a typical imaged section of 1cm wide and 2cm deep, providing a more detailed image than fMRI. We used this technique to study the functional organization of auditory circuit from the inferior colliculus (IC) to the cortex in the awake ferret. We characterized the tonotopic organization of several areas of the auditory cortex in three dimensions, including deep sulci which are cortical regions typically unaccessible to standard intrinsic and voltage sensitive imaging techniques. Using a linear classifier algorithm, we found that blood flow activity gave access to a precise representation of the information encoded in the auditory cortex. This information was mostly present in medium and deep layers, mirroring previous studies that showed more refined tonotopic organization in granular and infragranular layers. Taking advantage of the penetration depth of fUS, we functionally isolated several thalamic nuclei, including the lateral geniculate nucleus (LGN) and the medial geniculate body (MGB). We describe for the first time the 3D functional tonotopic organization of the ferret MGB, confirming previous anatomical studies, and of the IC. Finally, we studied the main projections from prefrontal cortex to parabelt auditory areas at the level of the whole auditory cortex, unravelling a possible functional pathway for top-down control of auditory processing. In summary, we show that fUS is a powerful tool to study the fine organization and connections of auditory brain structures with a great temporal precision and high spatial resolution.

Attenuation of responses to self-generated sounds in auditory cortical neurons

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Many of the sounds that we perceive are caused by our own actions, for example during speech or movement, and must be distinguished from sounds caused by external events. Studies using macroscopic measurements of brain activity in human subjects have consistently shown that responses to self-generated sounds are attenuated in amplitude. However, the underlying manifestation of this phenomenon at the cellular level is not well understood. In order to address this, we recorded the activity of neurons in the auditory cortex of mice in response to sounds that were generated by their own

behavior. We found that the responses of auditory cortical neurons to these self-generated sounds were consistently attenuated, in comparison to the same sounds generated independently of the animals' behavior. This effect was observed in both putative pyramidal neurons and interneurons and was stronger in lower layers of auditory cortex. Downstream of the auditory cortex, we found that responses of hippocampal neurons to self-generated sounds were almost entirely suppressed. Responses to self-generated optogenetic stimulation of thalamocortical terminals were also attenuated, suggesting a cortical contribution to this effect. Further analyses revealed that the attenuation of self-generated sounds was not simply due to the non-specific effects of movement or behavioral state on auditory responsiveness. However, the strength of attenuation depended on the degree to which self-generated sounds were expected to occur, in a cell-type specific manner. Taken together, these results reveal the cellular basis underlying attenuated responses to self-generated sounds and suggest that predictive processes contribute to this effect.

Targeted optogenetic stimulation in the auditory pathway enables access to the tonotopic axis

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The auditory brainstem implant(ABI) restores hearing sensations to individuals who are deaf and cannot benefit from a cochlear implant(CI) due to anatomical constraints. ABI outcomes are inferior to CI. ABI performances may be limited by electrical stimulation, indiscriminately stimulating all cells of CN: excitatory and inhibitory. We explore whether optical stimulation might provide targeted activation of certain populations of auditory neurons in the CN. We perform narrow optical activation of the CN for 5 unique transgenic lines and study the activated response areas in the inferior colliculus(IC) compared to electrical stimulation.

Surgical exposure of the CN is performed acutely in 6 mouse lines: Bhlhb5, Parvalbumin, Atoh1, Nestin and Vglut2 and CBA. Light stimulation is delivered by a collimated diode laser. Electrical stimulation is performed with a custom made 8-channel device. Multiunit activity is recorded from the IC using a single-shank 16 site

recording probe. Auditory brainstem responses (ABR) are measured. Post-experiment histology is performed confirming opsin expression in the CN.

Histology shows specific patterns of expression for each transgenic line. Optical stimulation of the DCN enables controlled evoked neural activity across the tonotopic axis of the IC but electrical stimulation does not. Light stimulation elicits excitatory and inhibitory responses. Optically evoked ABRs (oABRs) depend on the type of cells stimulated in the CN as well as stimulation site on the CN.

Our experiments reveal that optical stimulation enables higher control of evoked activity with respect to stimulation location compared to electrical stimulation. Evoked responses depend on the type of neuronal population stimulated.This suggests that the selection of a promoter or transcription factor for targeting cell-specific opsin expression is essential for an optically-based ABI.

Neural entrainment during beat perception and its relation to psychophysical performance

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The ability to pick up on regularities in environmental stimuli is apparent in infancy and supports language learning, movement coordination, and parsing auditory scenes into “objects”. Here, we were interested in the seemingly unique sensitivity humans show to temporal regularities in rhythm: they spontaneously feel a “beat” in rhythmic sequences. In particular, we examined how synchronization of neural oscillations with auditory rhythms might give rise to beat perception, and in turn how entrained neural oscillations might affect psychophysical performance. In the current electroencephalography (EEG) study, participants detected near-threshold targets (changes in spectral bandwidth) embedded in long (~19-s) simple or complex auditory rhythms. Simple rhythms were composed of intervals related by integer ratios (1:2:3:4), and had a regular grouping that resulted in standard and target events always being present at “on-beat” locations given a duple meter. Simple rhythms thus induced a relatively strong sense of a beat. Complex rhythms were also composed of intervals related by integer ratios, but were grouped irregularly and thus did not induce a strong beat percept. We compared spectral power at beat-related frequencies (1.25, 2.5, and 5 Hz, where 5-Hz was the base inter-tone interval) for simple and complex rhythms. We observed significantly stronger spectral power at 1.25 Hz for simple compared to complex rhythms in particular for individuals that were “good beat perceivers” as determined by a behavioral measure of beat-tapping variability. This result indicates stronger subharmonic entrainment for rhythms that gave rise to a strong sense of beat. We did not observe power differences between rhythm types at 2.5 or 5 Hz. We also examined power-envelope fluctuations in the beta (13–30 Hz) frequency band, which have been previously linked to temporal prediction of events comprising isochronous sequences.

Beta power fluctuations at 5 Hz (the base inter-tone interval) were stronger for simple than for complex rhythms, suggesting that temporal prediction of upcoming events is sharpened in the presence of a strong beat percept. We found that targets were better detected when beta power increased in anticipation of a target, but that this effect was similar for simple and for complex rhythms. That is, although beta fluctuations were stronger in the presence of a beat, high beta power was universally beneficial for psychophysical performance. The results provide the first link between electrophysiological correlates of beat perception and the psychophysical consequences of beat perception.