

**RESPONSE LATENCY OF EXTERNAL AND CENTRAL NUCLEI
IN THE AWAKE MARMOSSET INFERIOR COLLICULUS**

by

Minmin Chen

A thesis submitted to Johns Hopkins University in conformity with the
requirements for the degree of Master of Science in Engineering

Baltimore, Maryland

February 2015

© 2015 Minmin Chen
All Rights Reserved

Abstract

The response latency of neurons has been used to represent properties of acoustic stimuli. However, the latency also indicates the characteristic of neurons themselves. The role of the inferior colliculus (IC) is unclear, especially the external nucleus (ICX). Latency studies may provide a clue as to how neurons process stimuli. Single unit recordings of responses to tones in the central nucleus of the IC (ICC) and ICX were utilized. The dependence of latencies on the units tuning properties, tone frequencies, and attenuations were analyzed. In particular, we computed a weighted average latency across frequencies at a variety of sound levels and the first spike latency at neuron's best frequency. Results showed that response latencies were shorter at higher sound levels in both the ICC and ICX. ICX neurons tend to have longer latencies than ICC neurons. Moreover, there was no discernable relationship between frequency selectivity and latency in ICX units.

Acknowledgement

I would like to express my special appreciation and thanks to my advisor Professor Dr. Eric Young for your guidance and support to my study and for your encouragement and patience to my research. I would also like to give a deep appreciation to my mentor Professor Dr. Brad May who offered me great patience, immense amount of time, and detailed instructions to my experiments and research.

In addition, a thank you to Phyllis Taylor, who helped order all needed materials for experiments, and to Roy Atkinson for your equipment maintenance. Thanks Dr. Troy Robin and Nishant Zachariah for shared data, and thanks Kevin Kostlan for participating in the discussions and helping with analysis. Furthermore, I would like to thank Dr. Tessa Ropp as well for your first demonstration of the animal experiment, Gail Larkin for your experience working with animals, and Qian Gao for help with the IT system.

Last but not least, I would like to thank my parents and my other family members for your endless love and support.

Table of Contents

ABSTRACT	II
ACKNOWLEDGEMENT	III
INTRODUCTION	1
A SOPHISTICATED SYSTEM.....	2
A PRINCIPLE HUB- THE INFERIOR COLLICULUS	5
TIME MATTERS- TEMPORAL CODE.....	8
MOTIVATION	12
METHODS	13
SUBJECTS.....	13
PROCEDURES	14
DATA ANALYSIS.....	15
<i>Response map</i>	16
<i>Best frequency</i>	17
<i>First spike latency</i>	17
<i>Spontaneous rate</i>	19
<i>Bandwidth of the tuning curve</i>	22
<i>Q values</i>	23
RESULTS.....	24
DISCUSSION AND CONCLUSION	47
REFERENCES	52
CURRICULUM VITAE	56

Introduction

Listening is not only a valuable skill but also an active sensing and perceiving process. In normal hearing, the auditory system has to process the surrounding sounds. Our ears (peripheral) and brain (central) constitute our auditory system, by which we are able to detect, identify, localize, and discriminate sounds. For example, we can hear music from a car radio while the car's engine is working. We can recognize the voice of a friend without seeing him/her. We can differentiate timbres of violin and cello in a symphony. We know our auditory system functions in challenging environments; we, nevertheless, know little about how the function is realized.

From a complex sound, how does our auditory system extract acoustic properties such as pitch, loudness, and location, encode them by neural activities, preserve them within firing patterns, carry them along the pathways, integrate them at higher central system, and finally decipher them to describe a complete 'auditory object' for our understanding? Although,

after years of studies, researchers mapped out most of the pathways, there are many questions to which we have no clear answers yet.

This chapter will briefly introduce the auditory system but particularly focus on the central system, the inferior colliculus and its temporal coding specifically.

A sophisticated system

The whole auditory system consists of the peripheral and central systems.

The peripheral system, which mainly transduces sounds, comprises the ear and auditory nerve fibers (ANFs), while the central system, which processes the sound information, includes the subcortical nuclei and the auditory cortices.

The first step of the peripheral processing occurs in the cochlea, representing sounds spectrotemporally. Each spatial location on the basilar membrane (BM) resonates most strongly to only one frequency (the *best frequency*) (Pickles, 2008: p41). These vibrations of the BM excite the ANFs by hyperpolarizing or depolarizing the hair cells. The base of the BM resonates most strongly at high frequencies and the apex at the low ones. This

tonotopy, a sequential mapping between space and the *log* of frequency, is maintained throughout the entire auditory system. (Pickles, 2008: p156).

The cochlear nucleus (CN), the initial step in the central auditory system, projects to bilateral superior olive complex (SOC). In the SOC, information from both ears meets at the first time. The ascending projections from the CN are split into two streams. The ventral stream begins in the ventral CN, travels through the trapezoid body, SOC to the inferior colliculus (IC), whereas dorsal stream travels through the dorsal stria to IC or along intermediate acoustic stria to lateral lemniscus and SOC (Pickles, 2008: p164). Two streams from there send to the medial geniculate body (MGB) and finally to the auditory cortex.

Although two streams may use the same auditory cues, the ventral stream is involved more in the azimuth localization by identifying the interaural delay and intensity differences in MSO and LSO respectively (Pickles, 2008: p167). However, the dorsal stream engages more in the elementary sound identification, such as sustained noise or spectral notches and the localization in the vertical plane. (Pickles, 2008: p161).

Acoustic features, like frequency spectrum, temporal variation, and localization, which are preliminarily analyzed by processing levels below IC in the central auditory system will be subsequently integrated at higher processing levels (usually IC, MGB, and cortex) to define an auditory object. IC as a convergence and relay center plays a crucial role in both ascending and descending pathways; MGB and auditory cortex are considered as a functional unit because of the reciprocal connectivity between them. The auditory cortex, as evident in numerous studies, conducts stimulus- processing in a more direct way than just the higher-level cognition. (Pickle, 2008: p234).

In addition to the ascending pathway, the auditory system includes a descending pathway that backtracks from the cortex to the cochlea. Its overall effect is considered to be an inhibitory modification, which may be for selective attention (Maison et al, 2001; Huffman, 1990) and hearing protection (Pickles, 2008: p239, p251; Lyon 1990).

A principle hub- the inferior Colliculus

The inferior colliculus, the rear pair of four dome-shaped lobes on the dorsal surface of the midbrain, is conventionally divided into three subdivisions: central nuclei (ICC), external nuclei (ICX), and dorsal nuclei (ICD) according to the morphology and architectures of the neurons (Pickles, 2008: p183).

The IC is a key hub on the ascending and descending auditory pathways. On the ascending pathway, it is the primary convergence stage of two streams. The ventral stream (VCN, MSO, and LSO) mainly terminates in the ventral and lateral ICC, while the dorsal stream projects to the entire ICC in a more diffuse manner (Zook, 1987). These projections to the IC are both excitatory and inhibitory. Excitatory projections are from the contralateral CN, LSO, IC, ipsilateral MSO, NLL, and INLL, while inhibitory inputs are received from the bilateral DNLL as well as the ipsilateral LSO (Winer & Schreiner, 2005: p282). Furthermore, information processed by the IC is sent to the MGB and the AC. Afferents from the ICC and the ICX send to the lateral ventral division of medial geniculate body (MGB) and ICX, respectively, yet projections from the ICD terminate in the dorsal division of MGB. On the descending pathway, the ICX and the ICD are the main targets of separate

descending inputs from the MGB, AC, and its internal synaptic connection (Huffman, 1990).

The IC is tonotopically organized: isofrequency laminae represent the (species dependent) frequency range. Best frequencies of the ICC isofrequency lamina increase from dorsal to ventral, but the tonotopy in the ICX and the ICD seem to be more diffuse and variable and are poorly understood. The ICX is where multisensory inputs connect. The ICD receives ascending inputs from the contralateral IC and descending inputs from the AC (Pickles 2008, p192). Neurons in the ICX and ICD are broadly tuned and easily adapted (Aitkin et al. 1975).

The ICC is constituted by disc shaped cells arranged in laminae, stellate cells cut across laminae, and input fibers from lateral lemniscus run parallel to the laminae. Among all three subdivisions of the IC, the ICC is the best studied. Based on contralateral responses to tones, neurons in the ICC are classified into three groups: type V, O, and I, in terms of their excitatory and inhibitory response areas to a range of frequencies at different sound levels (Ramachandran et al., 1999). The units were characterized as type V, I, and

O, based on the response maps and rate level functions. Neurons excited by monaural tones presented to either ear and that had little inhibition in the response map were classified as type-V. Neurons whose responses to contralateral BF tones were excitatory at low levels but turned inhibitory at high sound levels were classified as type-O. Neurons that were excited at all contralateral BF tone levels and displayed clear sideband inhibition were classified as type-I. The stimulus level was chosen to be near the center of the dynamic range of the neuron under study.

In addition, neurons in the ICC are also classified as EE, EI, and EO in terms of their contralateral and ipsilateral responses to the stimuli alone. Thus EE means excited by both ears, EI is inhibited by the ipsilateral and excited by the contralateral ear, and EO means excited by contralateral ear only.

Furthermore, a third letter behind a slash characterizes the binaural interaction to the stimulus. F, S, and O represent facilitation, suppression, and no interaction, respectively. For instance, EO/S indicates excitatory responses to the contralateral ear, no responses to the ipsilateral ear, and suppressed response to the contralateral ear when both ears are stimulated (Irvine, 1986).

Time matters- temporal code

Speech, music, and even natural sounds have temporally varying characteristics; therefore, temporal information is important. For example, temporal information contributes to the linguistic contrast in speech, denotes the difference and separates the source of the natural sound, play a role in the pitch perception (Moore, 1989: p172). Furthermore, studies indicate that changes in the amplitude and frequency rather than their absolute value bear more information in the sound (Rosen 1992; Shannon et al. 1995; Smith et al. 2002). Coherence of change among spectral components may help the auditory system to identify those components as originating from a single source. Low frequency modulations are important for speech perception and melody recognition, while higher frequency modulations contribute to pitch discrimination (Houtgast et al., 1973; Rosen, 1992).

For both tones and amplitude modulations, two strategies are commonly used by neurons to extract temporal information: *phase-lock* and *rate code*. The phase locking, which means neurons are apt to fire at a certain phase of the stimulating waveform, occurs frequently at low processing levels and at low tone/ modulation frequencies (Pickles, 2008: p82).

Neurons in the midbrain and above show much less phase locking to periodicity than neurons in the brainstem, and the phase locking of neural responses reduces significantly at high frequencies. For example, ANFs strongly phase lock to the tonic waveform at frequencies below 2kHz, weakly phase-lock up to 5kHz (Recio-Spinoso et al. 2005). IC neurons in the cat are rarely phase lock to frequencies above 300Hz (Langner et al. 1988).

Therefore, for amplitude modulation, neurons fire maximally to a particular envelope frequency but stochastically to a certain phase in a period instead to extract the temporal information of the stimuli (Langner 1983; Muller-Preuss et al. 1994). In addition to that, IC neurons integrate the temporal information extracted by parallel streams in the peripheral system to help recognize frequency, discriminate pitch and so forth. For high tonic frequencies, neurons code the periodicity by mean firing rate.

Latency (aka. reaction time) is a measure of time interval between stimulus onset and spike onset. Previous studies had been taken on rhesus macaques to investigate the factors that could affect latency. The latency of responses of single units to pure tones at their best frequencies were studied at different

levels of the central auditory system under two behavioral conditions, animal's performance and non-performance. Results shown task performance has significant effects on the latency. Comparing to nonperformance, the latency of evoked discharge was increased in CN and SOC; however, an increase in stimulus-evoked excitability caused by performance doesn't enhance the spontaneous rate in MGB and AC. Thus, a general enhancement of excitability in higher central auditory system cannot be attributed to the effects of performance (Ryan, 1984).

Similar experiments had been conducted in macaques' IC particularly to study the behavioral effect on single unit firing patterns. The study showed average initial latencies were increased in most IC units under behavioral task performance. However, different firing patterns were affected differently by the performance. Changes in initial latency rule out a stimulus-evoked, descending influence on the IC as a sole mediator of the effects of the performance. Above studies indicate that latency may be influenced by the attention.

At higher the auditory processing stage, the more complicated the firing patterns of neurons are more complicated. A big proportion of units in the ICC show onset, pauser, and sustained response types, and a small number of neurons are choppers (Pickles, 2008: p161). Various firing patterns indicate neurons' receiving from other projecting nuclei, different time of arrival of inputs and different superposition of excitation and inhibition. The effect of attention on the response latency of the unit may be confined to specific portion of the units' patterns as well (Tzounopoulos, 2009).

Motivation

In comparison with units in the ICC, the understanding of ICX and ICD units is limited. What roles are they playing in temporal information coding?

The response latency is one aspect of the electrophysiological properties of non-ICC units in IC, and maybe acoustic information is imbedded in it.

Previous studies showed attention increases the average latency of units in nuclei in the central auditory system except for the AC (Ryan, 1977). Are there any other factors that alter the latency, and what is the difference in the average and first spike latency between ICC and non-ICC units. Will neuron's firing pattern or physical locations affect their latencies? Is there any relationship between the latency and the frequency selectivity?

These questions provide many perspectives to study the non-ICC units. This experiment is designed to tentatively answer some of above questions for knowing better about the function of non-ICC unit in acoustic single processing.

Methods

This experiment used single-unit extracellular recording technique to study neurons in the IC. Neuronal activities in response to pure tones were recorded, analyzed, and compared between ICX and ICC to tell the differences in the latency, frequency selectivity, and their relationship. Data were recorded by Troy Rubin and Nishant Zachariah but analyzed separately. This method chapter provides a brief description of surgical procedure, recording procedure, and a detailed data analysis. All protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at the Johns Hopkins University and were consistent with the guidelines issued by the National Institutes of Health.

Subjects

Two young adult male marmosets (about three-year old) were used in the electrophysiological test. Animals were trained to be able to sit quietly 3 hours for recording.

Procedures

Experiments were performed in a soundproof chamber (IAC Acoustics) with free-field sound presentation. The movement of the marmoset was restricted by a fixed head cap and a cylinder chair. A 1mm craniotomy was drilled through the skull to place the electrode into the IC. Once the craniotomy was made, the path was regularly sterilized and cleaned. At the end of use of a craniotomy, it would be sealed completely.

A Tungsten microelectrode (A-M System, $5M\Omega$) held by a Kopf hydraulic Microdrive was progressively inserted into the IC dorsoventrally from the skull through its non-auditory cortex and thalamus. The electric signal was amplified 10,000-30,000 times using an AM systems amplifier (model 1800, AM Systems) and bandpass filtered between 400Hz to 5Hz using a Krohn Hite filter (model 3202). Individual neurons were isolated with the Schmitt trigger and sent to the computer for analysis. Spike times were digitized and recorded using a National Instruments digital interface board (model PCI6602). All data are based on clear signal neuron recordings. The best frequencies (BFs) of neurons were determined manually.

Typically, electrode entry into the auditory area was recognized by the onset of ‘multi-unit-hash’ in response to the white noise. The hash in the ICX and ICD was often tuned poorly, adapted rapidly, or exhibited marked offset responses. Neurons in the central nucleus of inferior colliculus (ICC), nevertheless, were usually sharply tuned with short latencies (Merzenich and Reid, 1974; Aitkin et al., 1975). The location of electrode was beyond the IC, when the background hash disappeared.

Sometime, the hash would give way to an isolated neuron before the electrode went beyond the IC. A sequence of pure tone stimuli 180 in length plus 10ms linear rise/fall edges, followed by an 800 ms silent interval was used to characterize the best frequency of the unit.

Data Analysis

Data were analyzed for individual units and for an overall summary.

MATLAB code was used for analysis and visualization.

Response map

The response map of a neuron was constructed by using its neuronal responses to sequences of tone bursts varying in frequency (frequency sweeps) at several intensities of stimuli. An example of response map of ICX unit associated with its best frequency is shown in Figure 1.

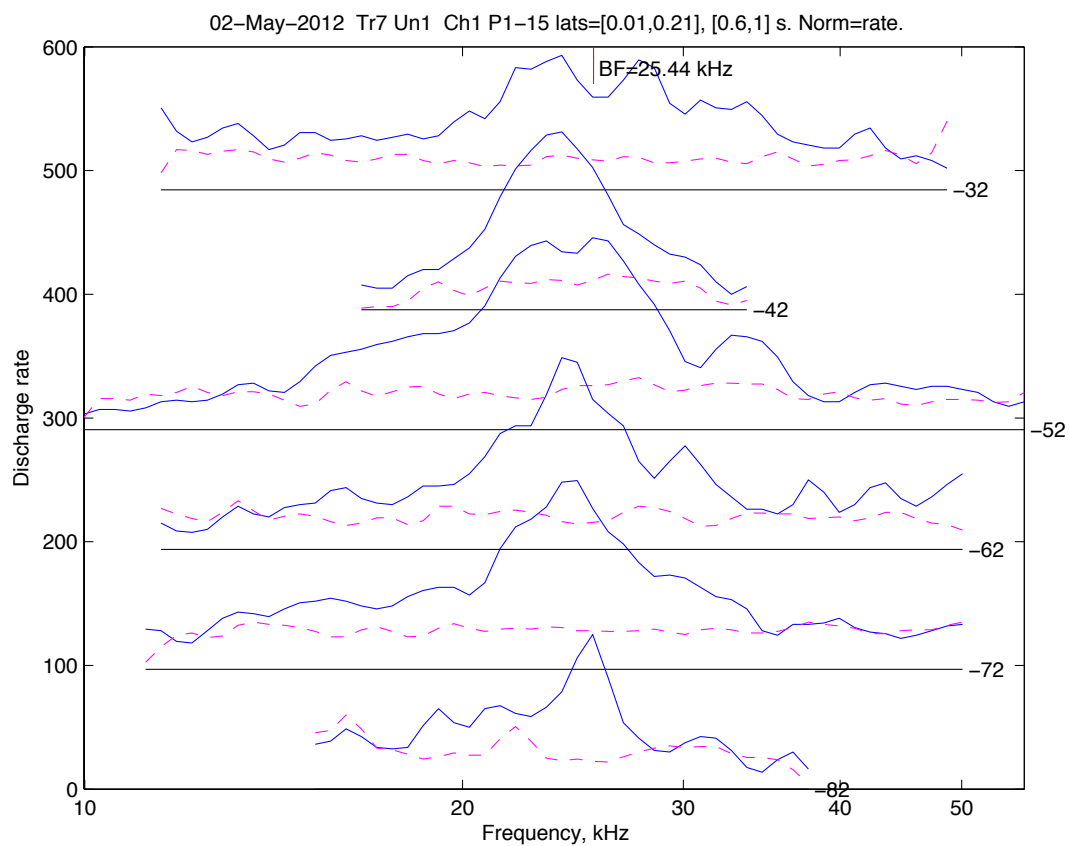


Figure 1. A representative response map of an ICX unit with its best frequency at 25.44kHz. The blue lines show responses during the stimulus; the magenta dashed lines show spontaneous rates.

Best frequency

The best frequency (BF) is the frequency that elicited the most robust excitatory response of a neuron at the threshold intensity of the stimuli. In the experiment, it was determined manually according to neuron's response map. An example of the best frequency is also shown in the Figure 1.

First spike latency

The first spike latency is the response onset delay of a neuron to one stimulus. It varies at different stimulus frequencies and intensities. The first spike latency used in data analysis was selected manually at the best frequency of the neuron. An example of identifying the first spike latency of ICX unit is illustrated in the Figure 2.

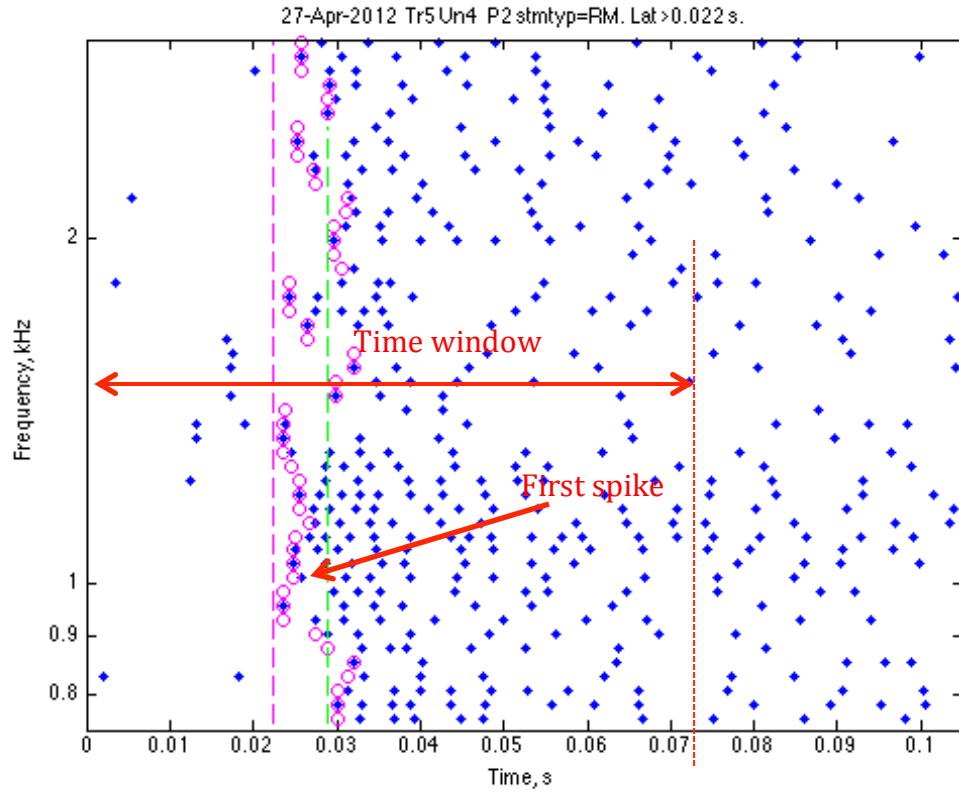


Figure 2. An illustration of identifying the first spike latencies of a representative ICX unit at its best frequency in the experiment. The green dashed line in the plot is drawn at the calculated weighted latency. Pink circle indicates the latency calculated by Poisson Chase model. The blue dot pointed by the red arrow indicates the real first spike of the unit. In this study, the first spike latencies were all real first spike latencies, which were manually selected at neuron's best frequency. The best frequency of this unit is 1.05kHz.

Spontaneous rate

The spontaneous rate is the firing rate of the neuron itself when no external stimulus is presented. In this experiment, it was calculated as the average firing rate over the second half of each stimulus presentation “line” over all lines.

Weighted latency

The weighted latency was calculated by taking a weighted average of the latencies in each bin:

$$\text{the weighted latency} = \frac{\sum w_i \cdot l_i}{\sum w_i}$$

Where w_i (the weight) is the total number of spikes counted within a square area. The width of the bin and the length of the time window define the width and length of this square, respectively. One bin is three frequency-adjacent stimuli presentation ‘lines’ (shown in Figure 3), and the time window is 0.07s by default.

Where l_i is the latency of the first spike or Poisson Chase method selected spike in each bin.

There were two strategies to calculate the latency used in above equation: the first spike latency and a modified Poisson Chase method. The first spike latency was used if the expected value of the number of spontaneous spikes in the bin in the time window was less than two; otherwise, the Poisson Chase method was used. The first spike latency is applicable in cases where spontaneous rate is low since for those units it is unlikely that the first spike of each bin will be a “spont” spike. However, the Poisson Chase method, which selects the first spike for which the firing rate underwent a statistically significant increase above spont (we used $p < 0.01$), doesn’t work for units with a low overall firing rate since it takes several spikes to achieve the necessary p-value. Thus it was only used when necessary (in units with high spontaneous rates). Combining these two methods gave the analysis a more robust estimator of the latency. Figure 3 illustrates an example of the calculation of the weighted latency for an ICX unit.

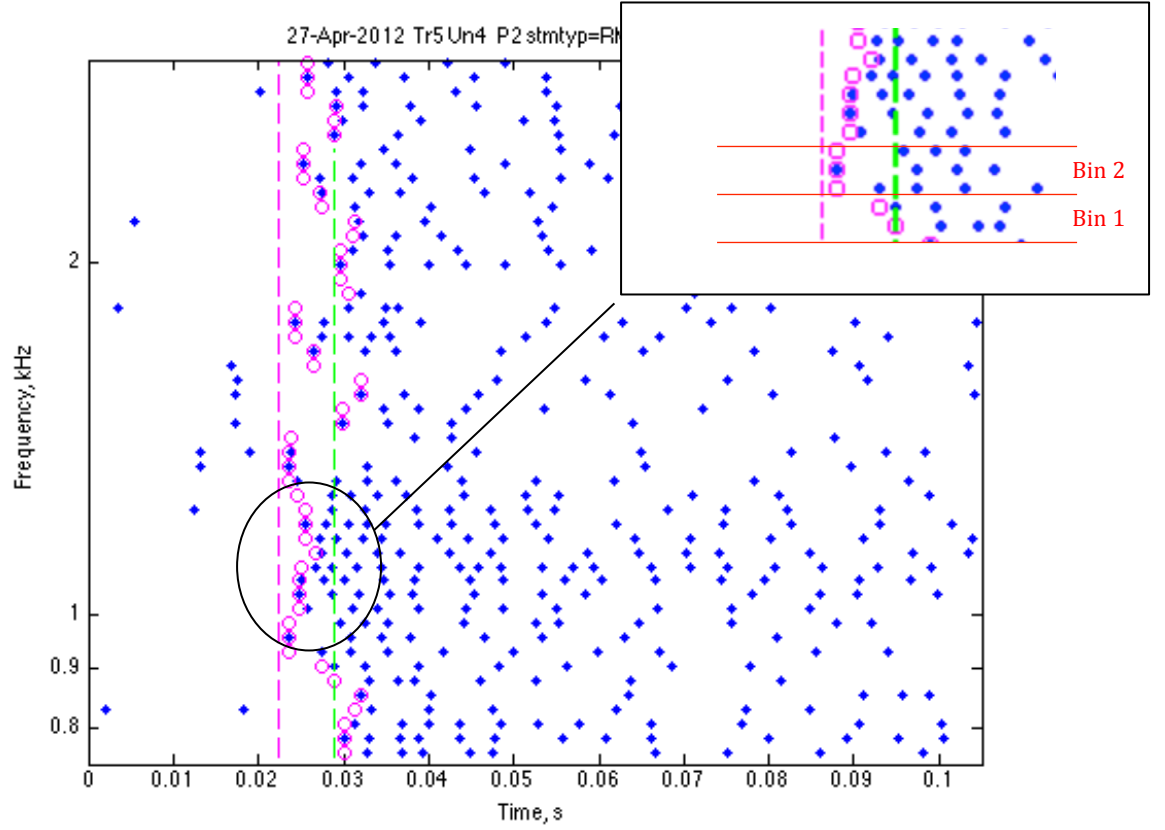


Figure 3. An illustration of calculating the weighted latency for a representative ICX unit. w_1 is the weight of the spike in the bin 1. It was the total number of spikes in bin 1 in 0.07s time window. w_2, w_3, \dots, w_i can be counted in the same manner. The value of l_i is calculated by Poisson Chase method (first purple circle in bin i) due to the number of spontaneous spikes on average per bin for this neuron is greater than two. Weighted latency of this unit is calculated by substituting the value of w_i and l_i in above equation. In this plot, the weighted latency is indicated by the green dashed line, and it is value is 0.029s.

Bandwidth of the tuning curve

The bandwidth of the tuning curve reflects the frequency selectivity of a neuron at its best frequency (bf). It was calculated based on the shape of the response curve at frequencies around the bf .

First, the driven rate was defined at each frequency by below equation:

$$R_{driven} = R - R_{spont}$$

The bandwidth of the tuning curve was defined as the difference between the low and high “90 % edges” of the receptive field:

$$BW = f_{hi} - f_{lo}$$

$$f_{hi} \ni \frac{\sum_{i=ind(f_{lo})}^{ind(b_f)} (R_{driven}(i))}{\sum_{i=1}^{ind(b_f)} (R_{driven}(i))} = 0.9$$

$$f_{lo} \ni \frac{\sum_{i=ind(b_f)}^{ind(f_{hi})} (R_{driven}(i))}{\sum_{i=ind(b_f)}^n (R_{driven}(i))} = 0.9$$

Where n is the number of lines in the response map and $\text{ind}(f)$ maps frequencies to the line in the response map that corresponds to a sound at frequency f . In practice, the value of 0.9 cannot always be achieved exactly so we selected the values of f_{lo} and f_{hi} and make it as close to 0.9 as possible but not above 0.9. Since the logs of the frequencies are equispaced in the response map, the sums in the above equation are discretization of integrals over $d(\log(f))$.

Q values

Q value is a measure that describes the width of tuning of a neuron at a variety of sound levels above its bf in order to standardize the comparison of the frequency selectivity of neurons with different bf . In this study Q_{40} was used to evaluate the tuning quality of neurons.

$$Q_{40} = \frac{BF}{BW}$$

Where BW is evaluated at 40 dB above the threshold.

Results

A total of 46 neurons in the ICX and 21 neurons in the ICC were recorded from two marmosets. The weighted latency and Q value of each neuron was calculated by aforementioned method at each recording intensity level of the stimuli. The first spike latency of each neuron was manually selected at its best frequency. Units in the ICC were classified into three types (I, V, O) according to their response maps, but units in the ICX were not classified in terms of their response maps. Response maps of three representative ICC neurons for each type are shown below.

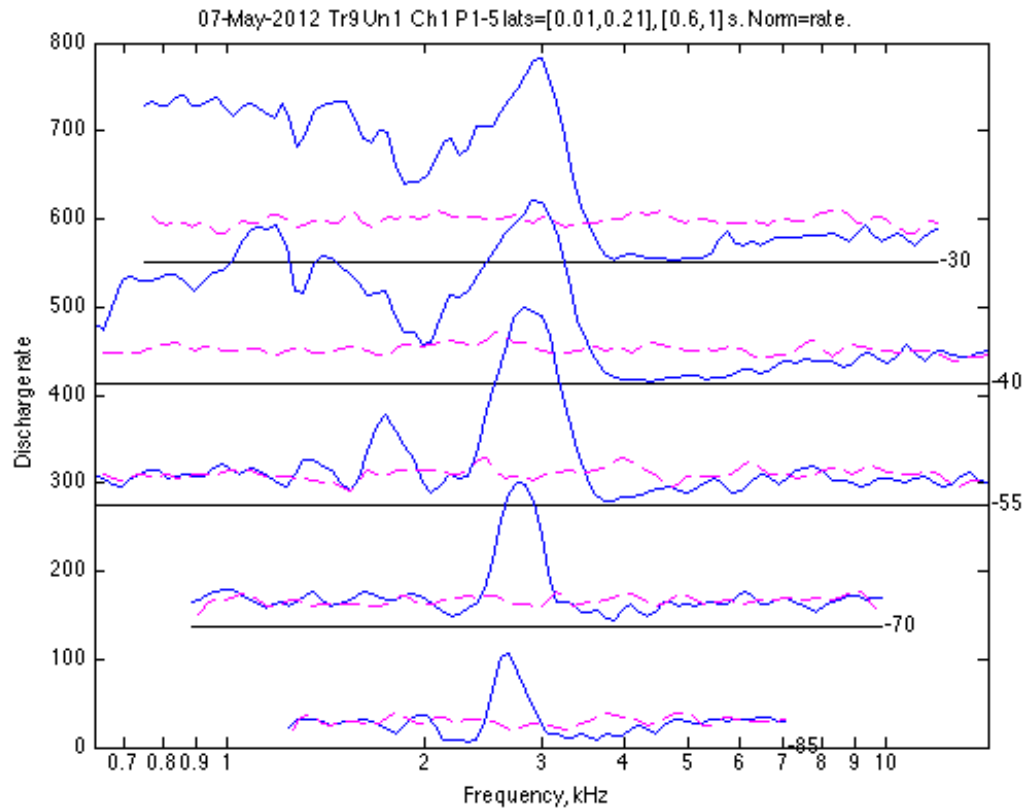


Figure 4. Response map of a representative type-I ICC unit. The blue lines show responses during the stimulus; the magenta dashed lines show spontaneous rates. As this figure shown, the frequency range of excitatory areas at five different sound levels is remained similar, and sideband inhibitions are clearly shown. Thus, this response map is a typical type-I unit.

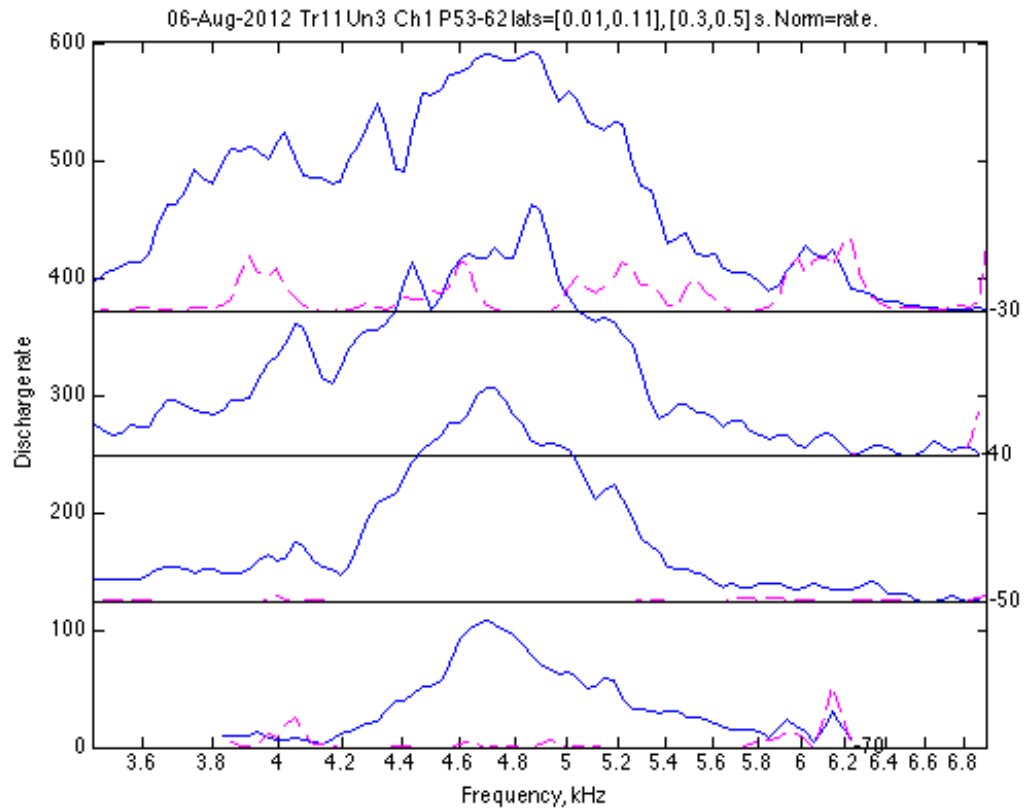


Figure 5. Response map of a representative type-V ICC unit. The blue lines show responses during the stimulus; the magenta dashed lines show spontaneous rates. As this figure shown, the frequency ranges of excitatory areas become broader as sound level increases, and no sideband inhibitions are shown at each sound levels. Thus, this response map is a typical type-V unit.

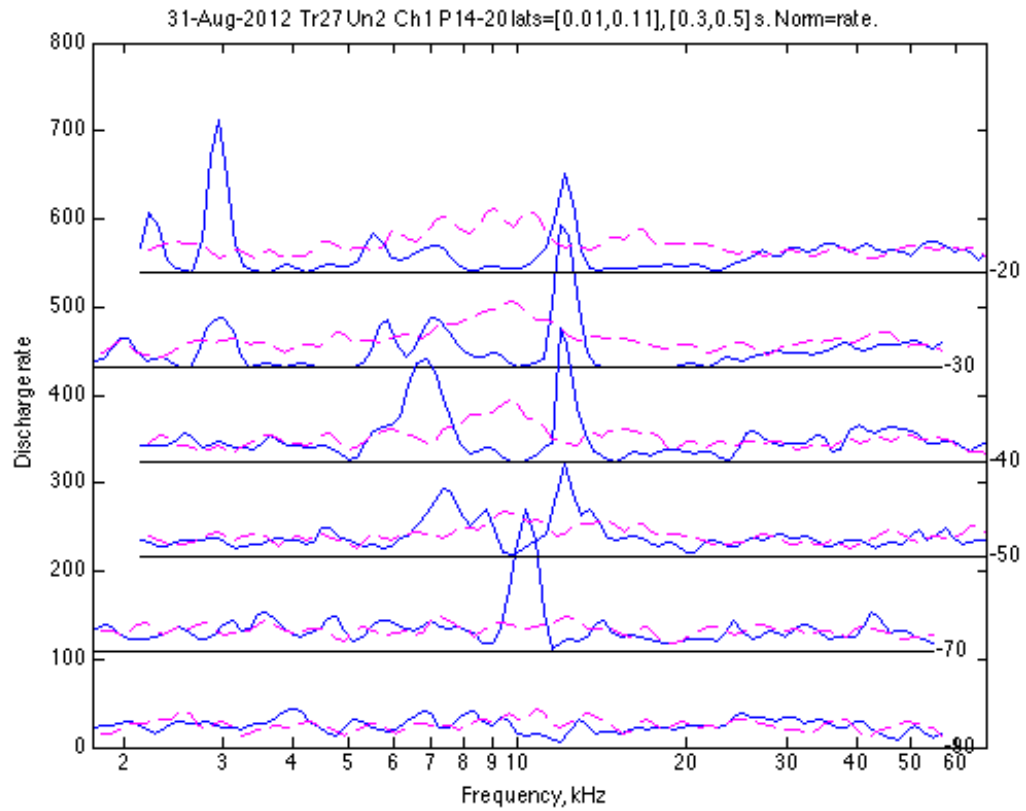


Figure 6. Response map of a representative type-O ICC unit. The blue lines show responses during the stimulus; the magenta dashed lines show spontaneous rates. The excitatory response area shown at 70dB attenuation was not seen at either higher or lower sound levels. Thus, this response map is a typical type-O unit.

The characteristics of response maps of ICX units recorded in this experiment did not fall into obvious subclass so were not otherwise classified. For sample ICX response are shown below. Often these neurons are quite broadly tuned.

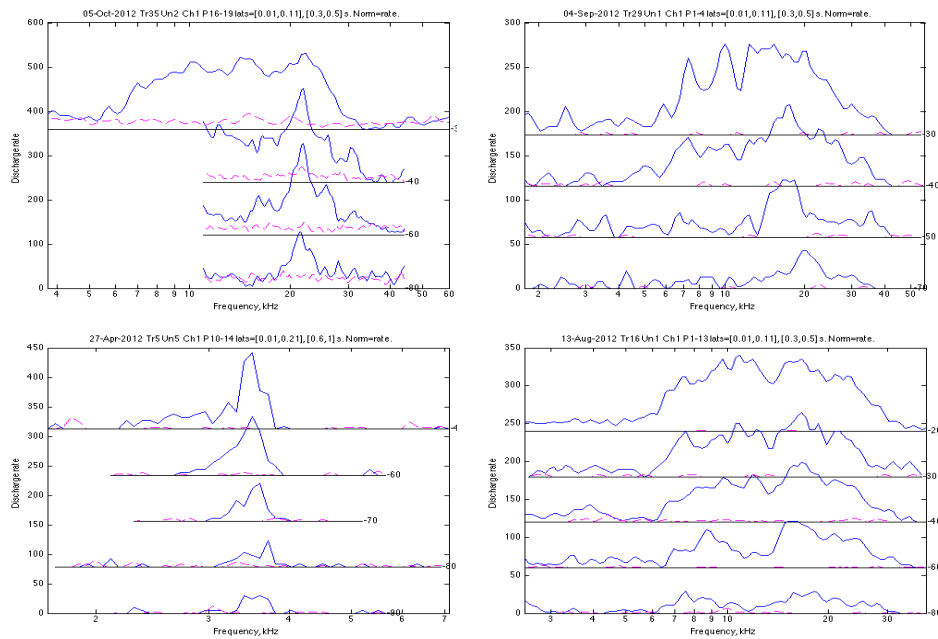


Figure 7. Response maps of four representative ICX units. The blue lines show responses during the stimulus; the magenta dashed lines show spontaneous rates.

In order to investigate the role of response delay in encoding the sound level, the relationship between the response latency of a neuron and the intensity of stimuli was analyzed. For ICC units, the relationship was compared

between and within neuron types, whereas, for ICX units, neuron type was not considered as a factor. Both the weighted latency and the first spike latency were analyzed.

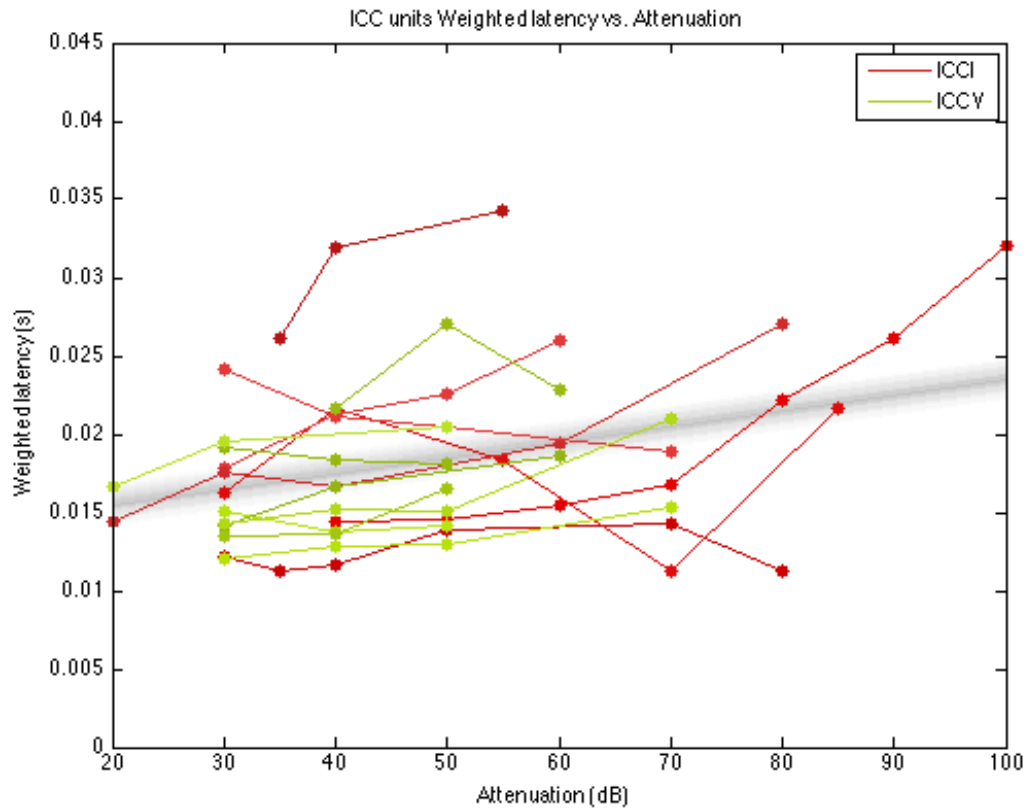


Figure 11. Relationship between the weighted latency (taken at best frequency of the corresponding neuron) and the sound level of ICC units. On the X-axis, from the left to the right, the sound level decreases. The grey line is the regression line of which R^2 is 0.0971 and the p value is less than 0.05.

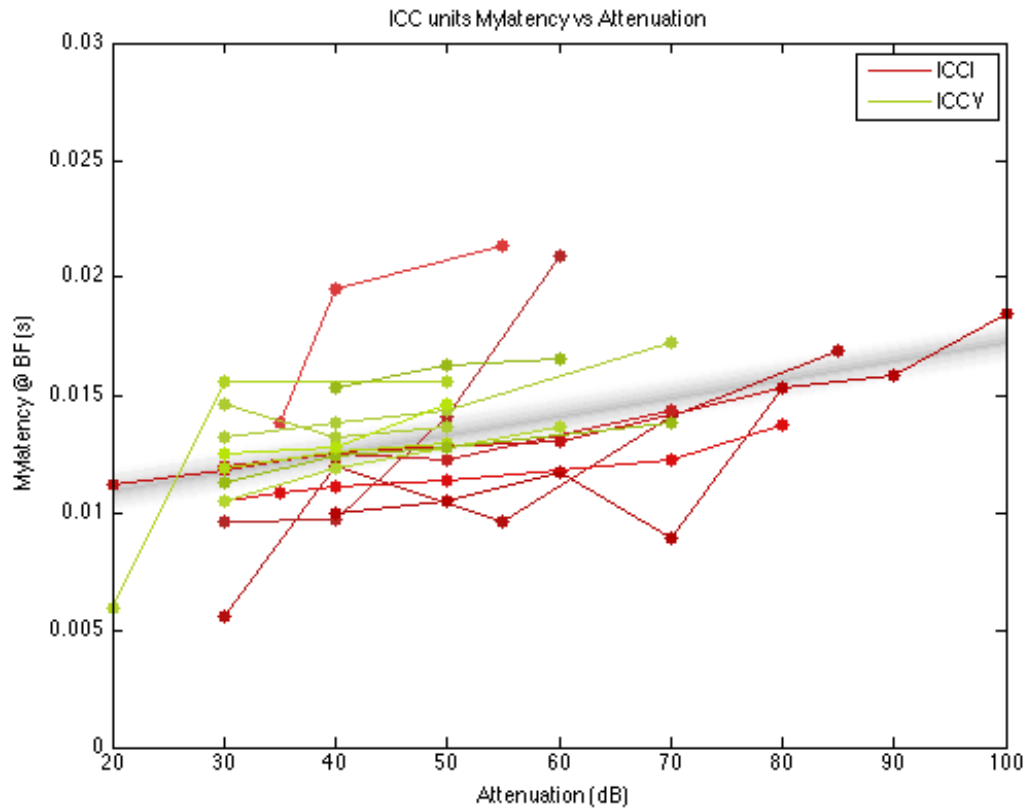


Figure 12. Relationship between the first spike latency (taken at best frequency of the corresponding neuron) and the sound level of ICC units. On the X-axis, from the left to the right, the sound level decreases. The grey line in is the regression line of which R^2 is 0.219 and the p value is less than 0.05.

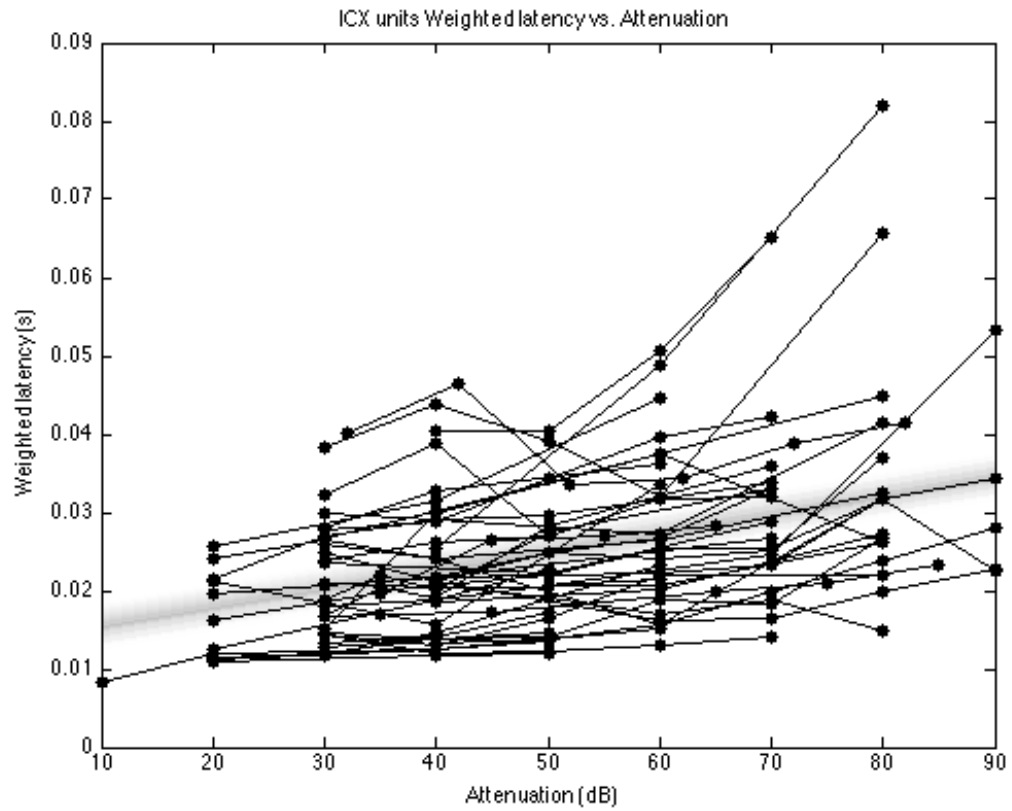


Figure 13. Relationship between the weighted latency (taken at best frequency of the corresponding neuron) and the sound level of ICX units. On the X-axis, from the left to the right, the sound level decreases. The grey line is the regression line of which R^2 is 0.1611 and the p value is less than 0.05.

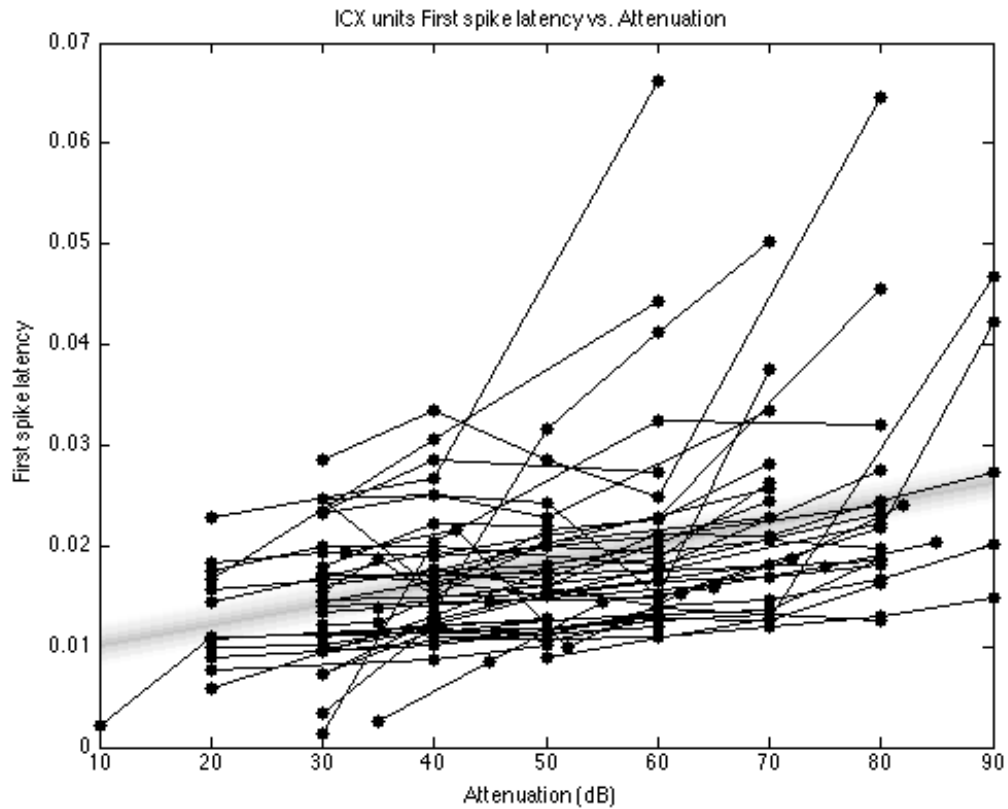


Figure 14. Relationship between the weighted latency (taken at best frequencies of the corresponding neuron) and the sound level of ICX units. On the X-axis, from the left to the right, the sound level decreases. The grey line is the regression line of which R^2 is 0.1611 and the p value is less than 0.05.

The p values of the regression lines in Figure 11-14 are all less than 0.05, which means the trend shown by the regression lines is statistically significant. Although the range of first spike latency is shorter than that of the weighted latency, for both ICC and ICX units, increase in the sound level

shortens the response latency of neurons, including both the weighted latency and the first spike latency.

In Figures 11- 14, both the relationships between latency, including the weighted latency and the first spike latency, and the intensity of stimulus in ICC and ICX units were analyzed across units with different best frequencies. In order to identify the influence of the value of the best frequency to the response latency in above analyses, the relationship between the best frequency and the response latency within ICC and ICX neuron groups at low, medium, and high sound levels (20dB, 40dB, and 50dB above the threshold) were analyzed separately as shown below.

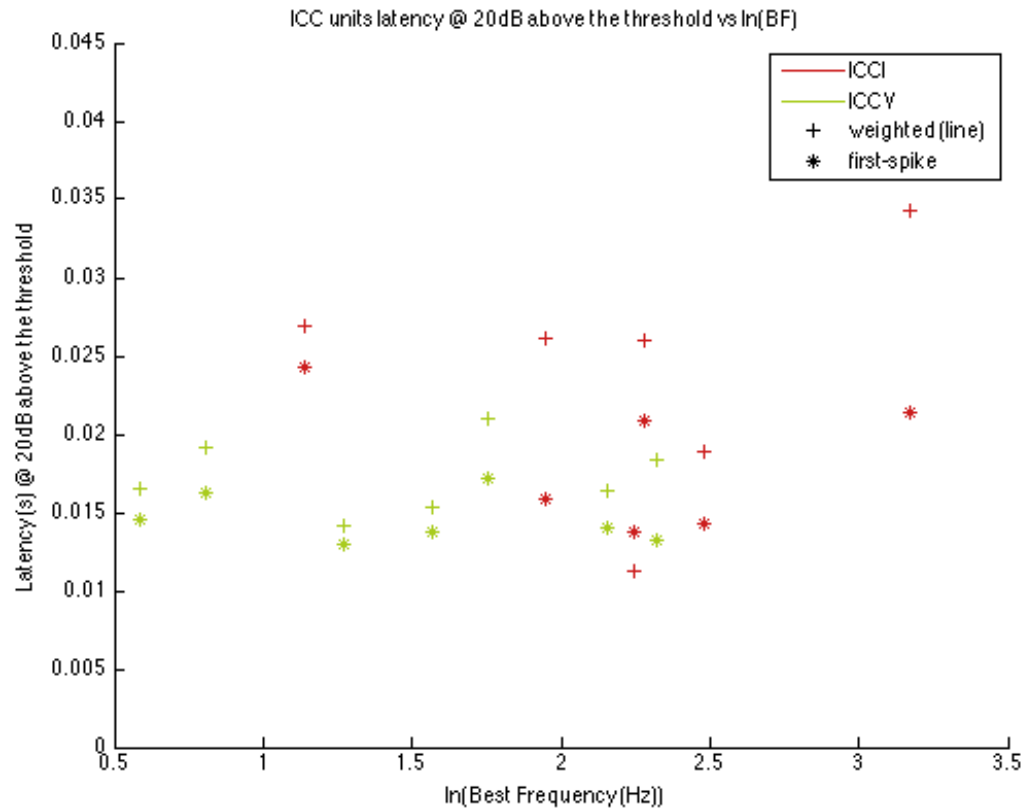


Figure 15. The influence of the best frequency to both the weighted and the first spike latency of ICC neurons at low sound level (20dB above the threshold of corresponding neuron). Each dot represents one ICC neuron.

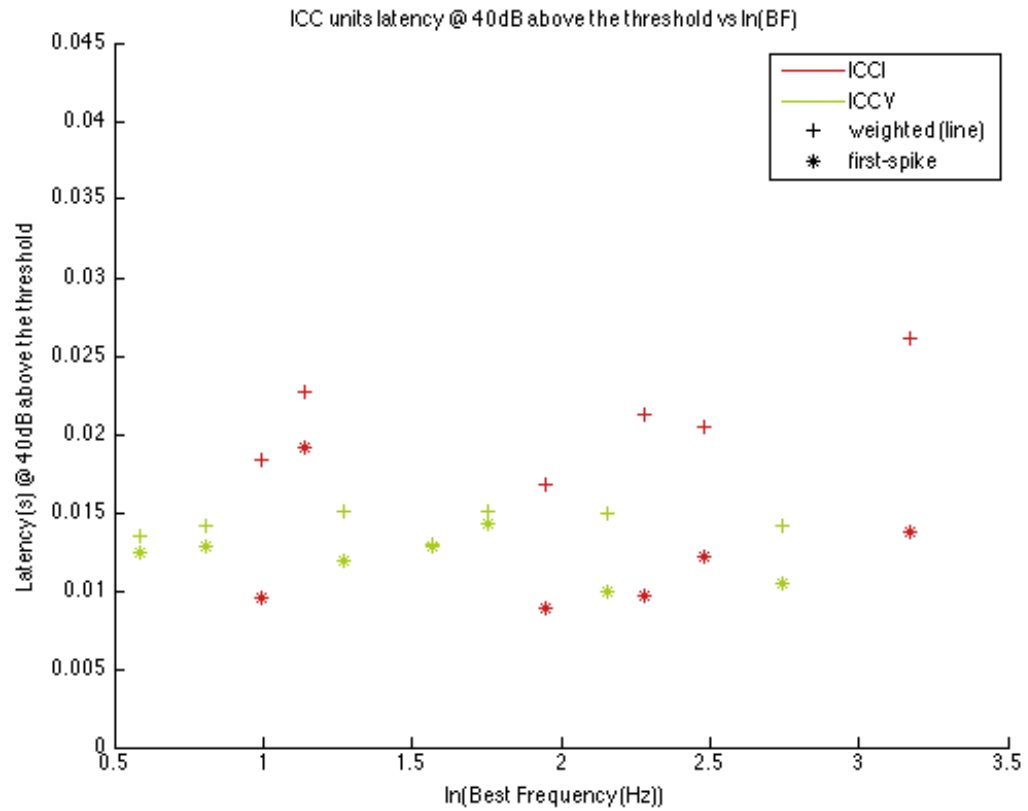


Figure 16. The influence of the best frequency to both the weighted and the first spike latency of ICC neurons at medium sound level (40dB above the threshold of corresponding neuron). Each dot represents one ICC neuron.

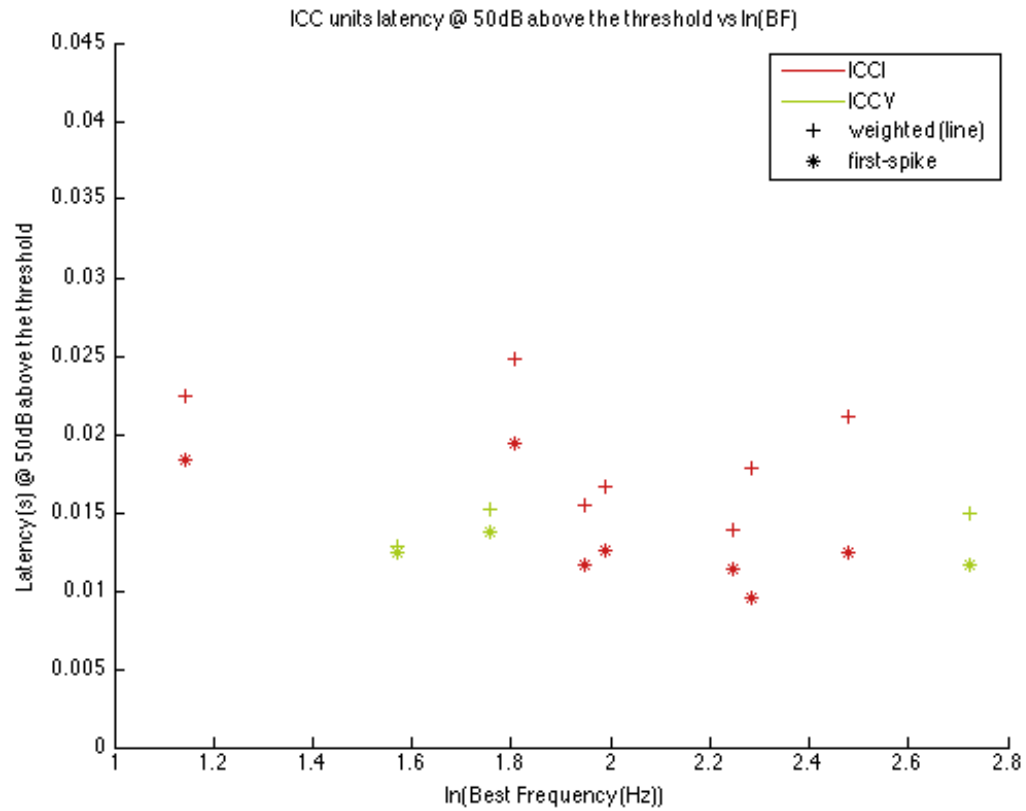


Figure 17. The influence of the best frequency to both the weighted and the first spike latency of ICC neurons at high sound level (50dB above the threshold of corresponding neuron). Each dot represents one ICC neuron.

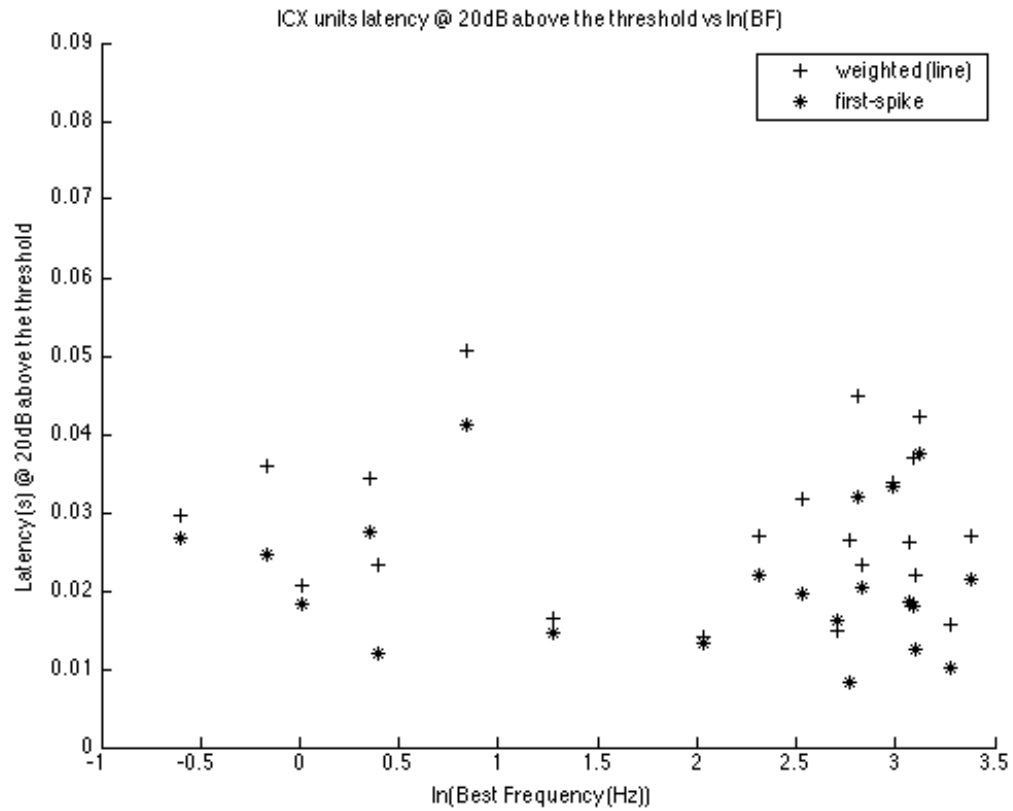


Figure 18. The influence of the best frequency to both the weighted and the first spike latency of ICX neurons at low sound level (20dB above the threshold of corresponding neuron). Each dot represents one ICX neuron.

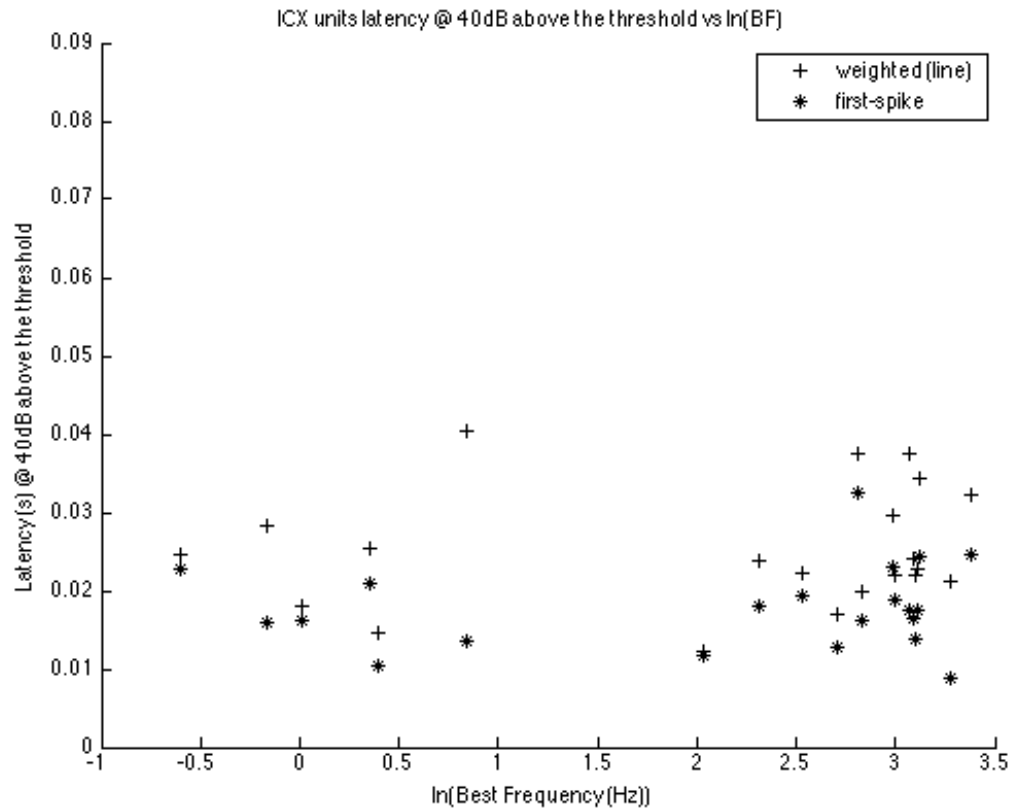


Figure 19. The influence of the best frequency to both the weighted and the first spike latency of ICX neurons at medium sound level (40dB above the threshold of corresponding neuron). Each dot represents one ICX neuron.

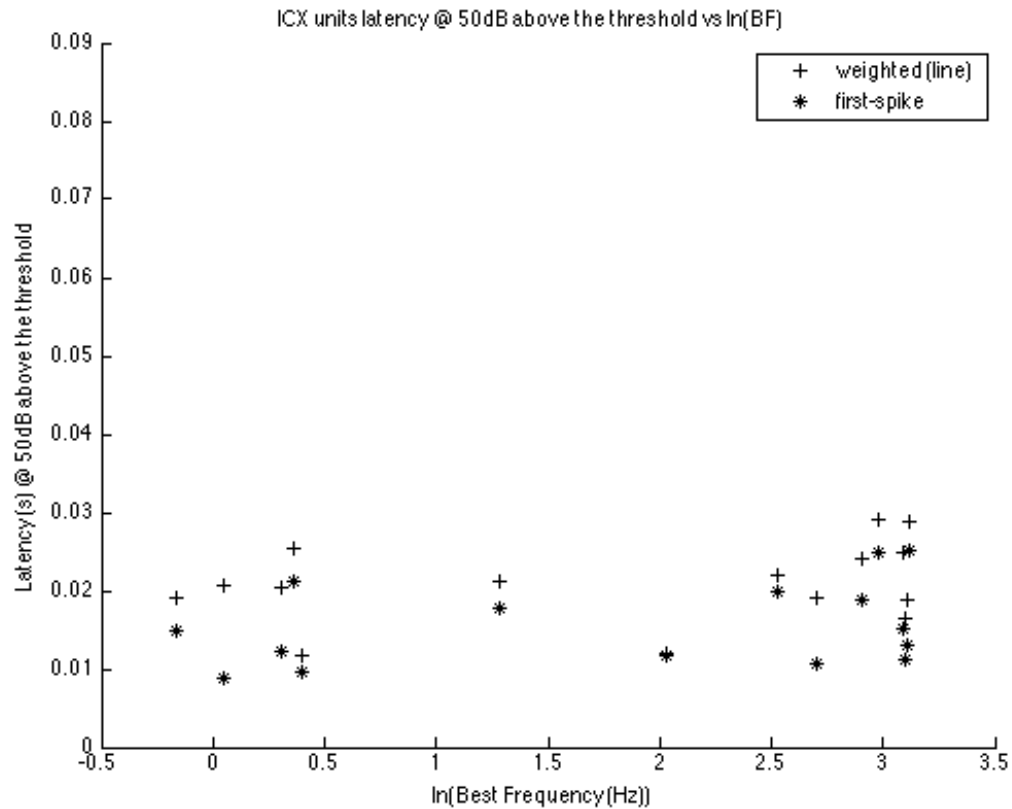


Figure 20. The influence of the best frequency to both the weighted and the first spike latency of ICX neurons at high sound level (50dB above the threshold of corresponding neuron). Each dot represents one ICX neuron.

According to Figure 15-20, the correlation between best frequency and latency is not significant at low, medium, and high sound levels, which means there is no significant trend in the relationship between best frequency and latency of a neuron. The influence of differences in best frequency to the latency can be ignored. Therefore, neurons with difference best frequencies can be grouped together in analysis.

All studies completed by far are within either ICC or ICX group, so is there any differences between two neuron groups in terms of their response latencies? The weighted latency and the first spike latency at three sound levels, 20dB, 40dB, and 50 dB above the threshold, are compared between ICC and ICX neurons. In that the histograms of weighted latency and first spike latency at all three sound levels are identical, only histograms of weighted latency are shown below.

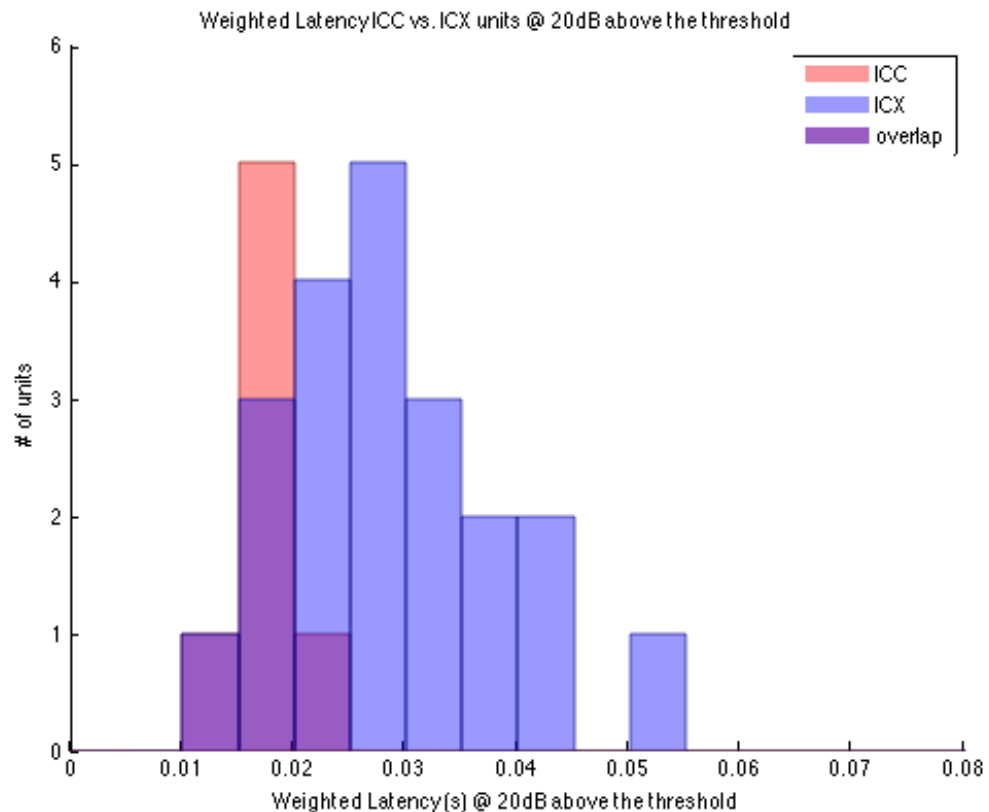


Figure 20. The comparison of weighted latencies of ICC and ICX neurons at low sound level (20dB above the threshold of corresponding neuron).

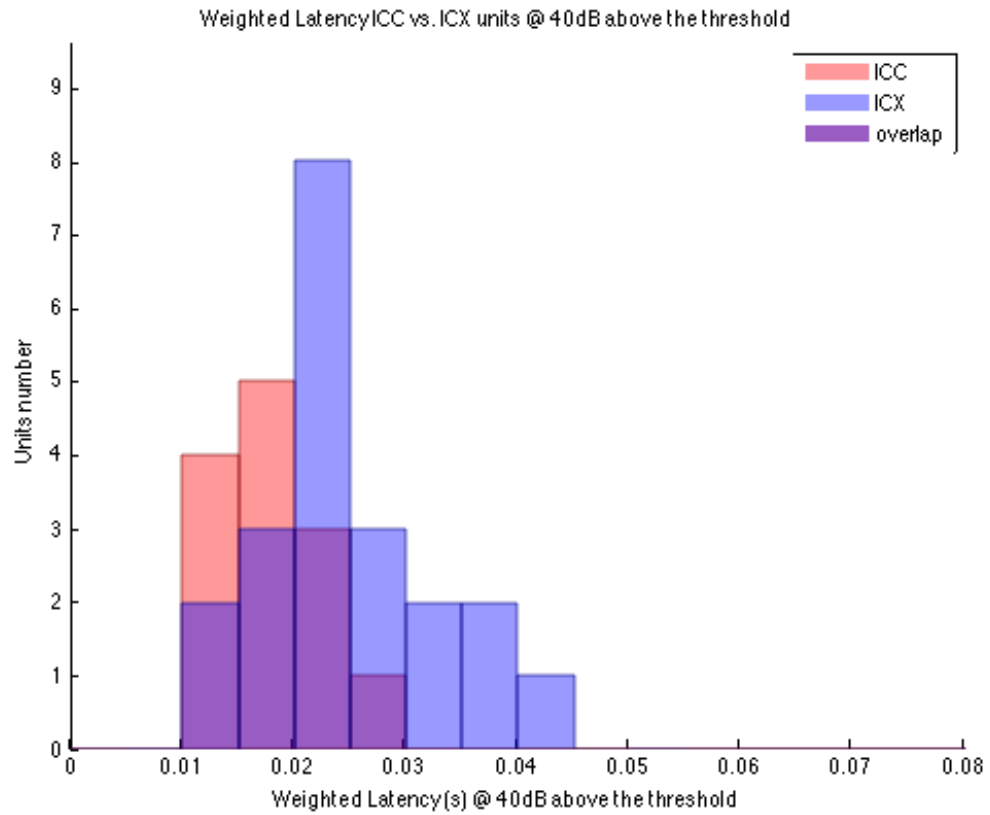


Figure 21. The comparison of weighted latencies of ICC and ICX neurons at low sound level (40dB above the threshold of corresponding neuron).

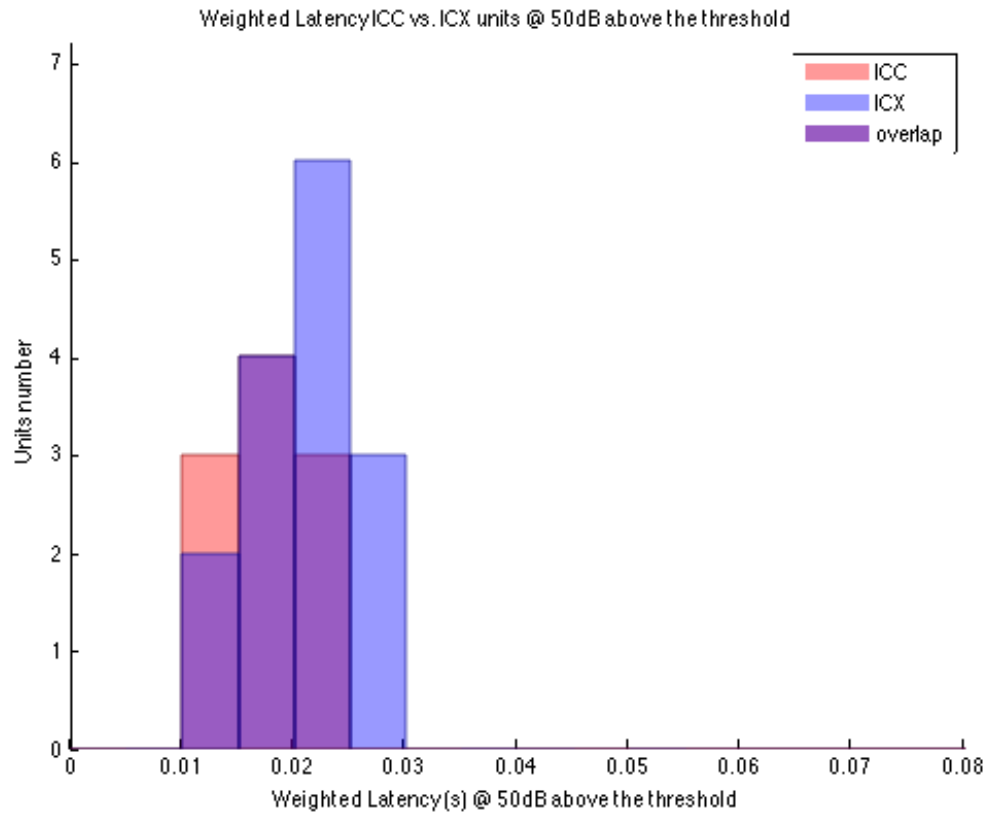


Figure 22. The comparison of weighted latencies of ICC and ICX neurons at low sound level (50dB above the threshold of corresponding neuron).

In comparisons of response latency between two neuron groups, ICX neurons have longer response latency than that of ICC neurons. Moreover, ICX neurons have broader range of response latency than that of ICC neurons across different sound levels. As sound level increases, reductions in the range of response latency of ICX neurons are much larger than that of ICC neurons. Also, the inversely proportional relationship between latencies

and sound levels can also be observed Figure 20-22. In addition to sound level and best frequency, other factor may affect latency such as the frequency selectivity was studied.

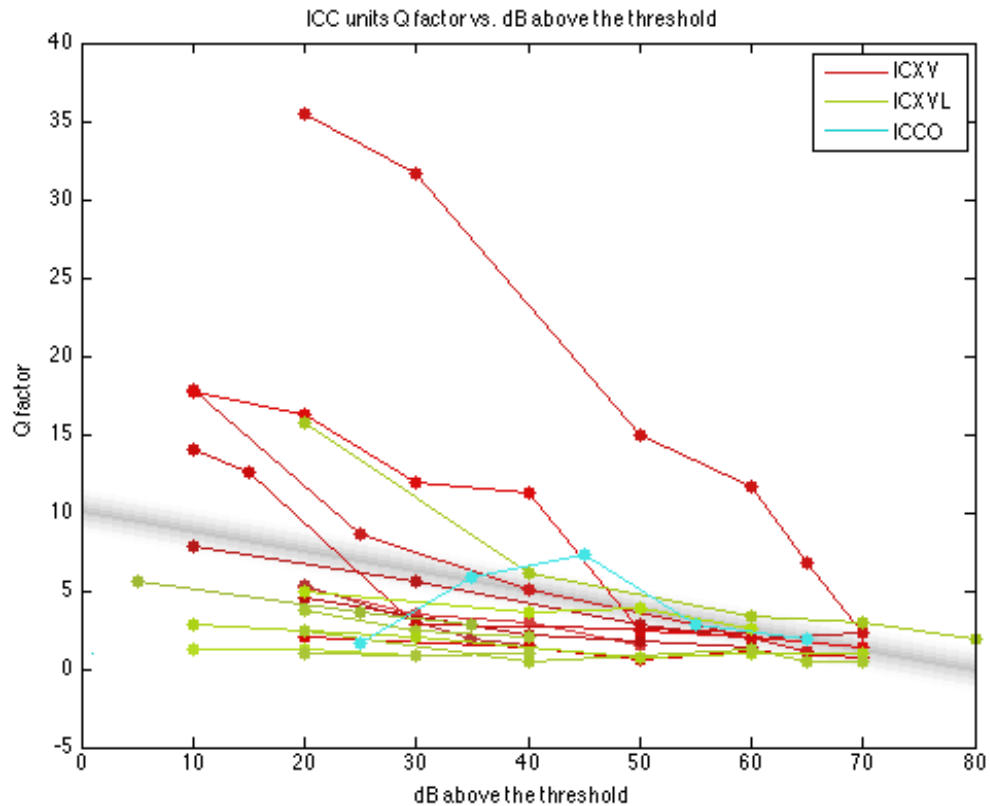


Figure 23. The relationship between Q factor and dB above the threshold of ICC units.

The grey line is regression line of which p value is less than 0.05.

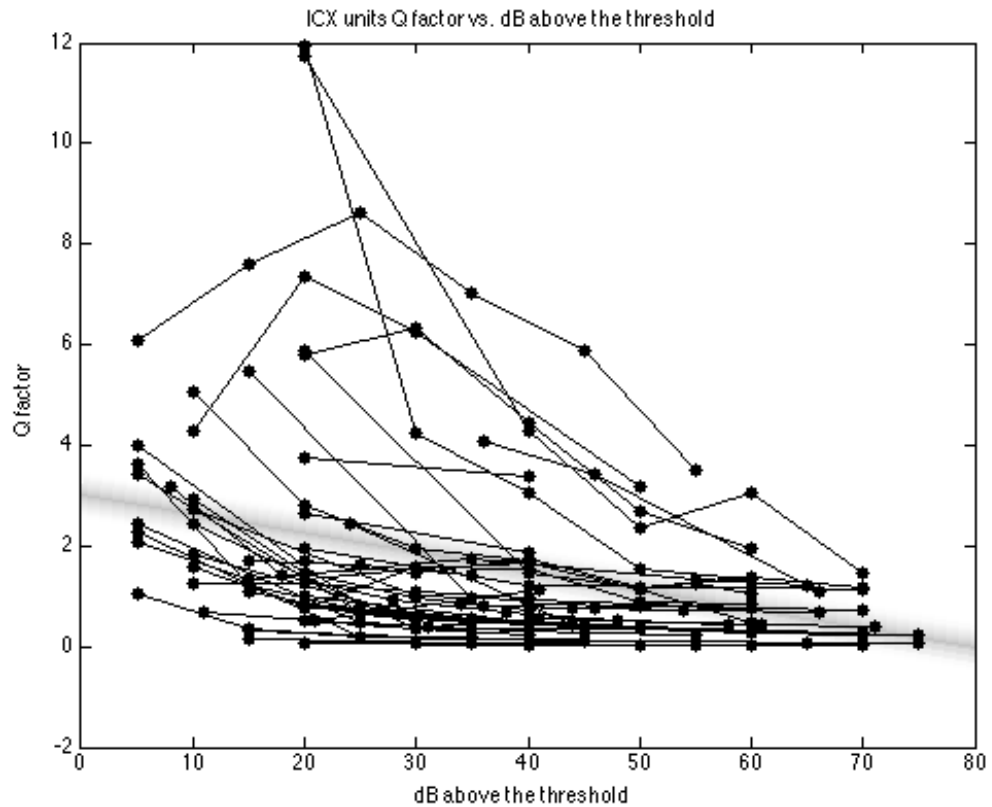


Figure 24. The relationship between Q factor and dB above the threshold of ICX units.

The grey line is regression line of which p value is less than 0.05.

Comparing to the ICX neurons, ICC neurons are more sharply tuned. The Q values of ICC neurons are overall greater than that of ICX neurons. However, according to the results of the study shown in Figure 25 and 26, there is no significant correlation between the weighted latency and the frequency selectivity in either ICC or ICX units.

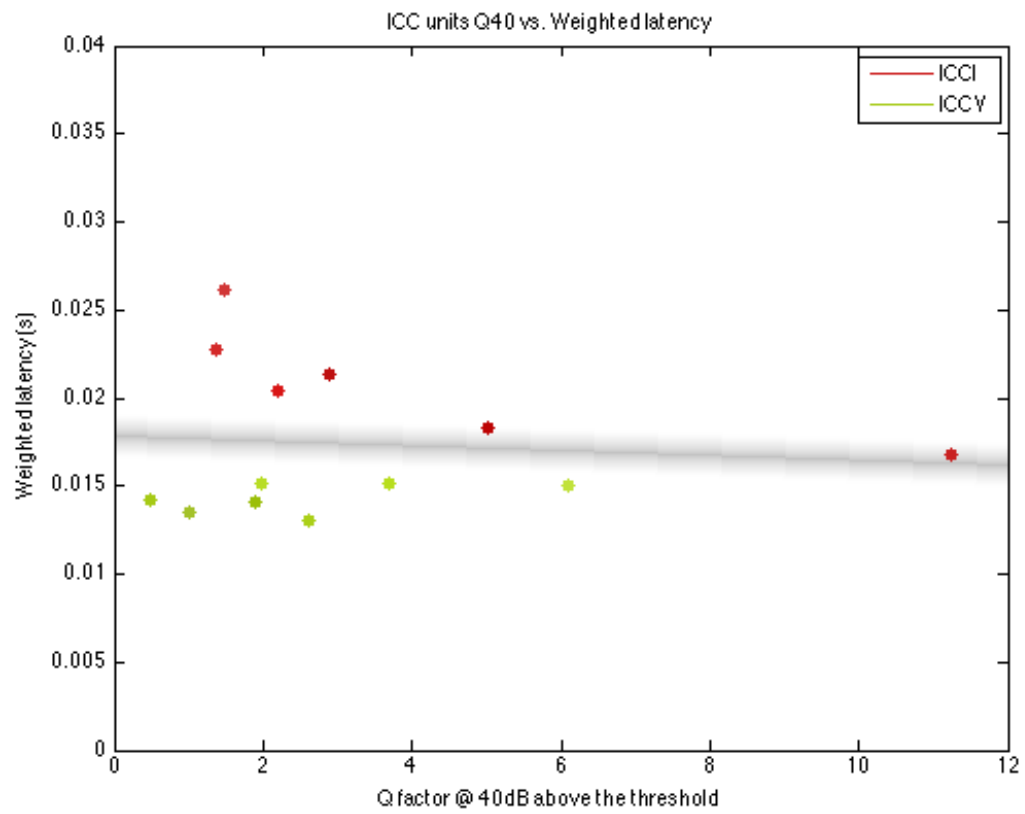


Figure 25. The relationship between Q_{40} and dB above the threshold of ICC units. The grey line is the regression line of which the p value is 0.7625.

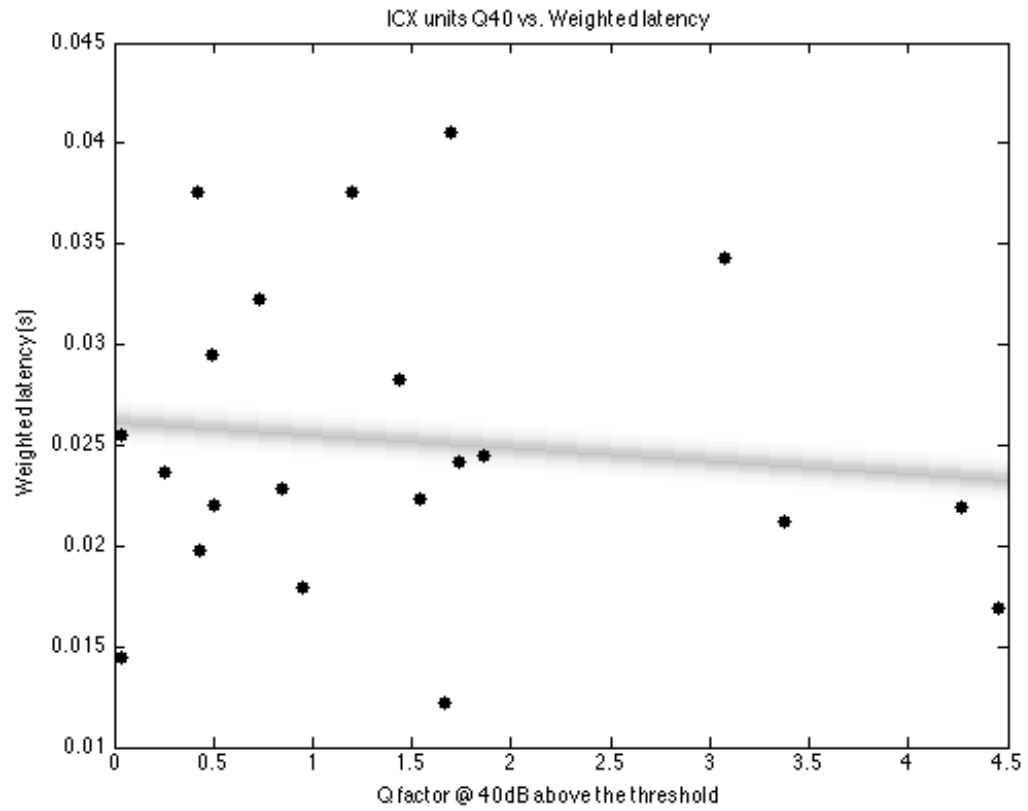


Figure 26. The relationship between Q_{40} and dB above the threshold of ICC units. The grey line is the regression line of which the p value is 0.6391.

Discussion and Conclusion

Is a weighted latency or a first spike latency (un-weighted) more reliable to be used in the study? Although both were used, theoretically the former should be a more reliable measurement because it adjusts for stimulus salience. However, the first spike latency is more robust in analyzing strongly adapting neurons, in that it is less affected by changes in total number of spikes. The first spike latency is completely immune (within a given line) since adaptation will not happen before the first neuronal spike.

For calculating the weighted latency, either the Poisson Chase modified latency or the first spike latency can be used, depending on the driven and spontaneous rate of a neuron. The Poisson Chase method detects an increase in firing rate above the spontaneous rate. The spontaneous rate allows us to calculate the expected number of spikes in a time interval $[0, t]$ for any t in the absence of stimulus. If the actual number of spikes in the interval $[0, t]$ is significantly greater ($p < 0.01$) than t that is equal or larger than the unit's latency, the Poisson Chase method selects the lowest value of t for which this is true. The Chase method will tend to overestimate the "true" latency τ because it takes several extra spikes in order to achieve $p < 0.01$. For low

discharge rate units, the overshoot, $t-\tau$, will be larger because statistical analysis gets less powerful within small sample sizes. On the other hand, the first spike latency is better for lower discharge rate units because it is less likely that there will be a spontaneous spike in $[0 \tau]$. Moreover, it is very difficult for either method to estimate the latency for units with a high spontaneous rate and a low driven rate (small increase above spontaneous). However, these units would be missed in the searching process because for them it is hard to notice any response to sound at all. Thus, using the Chase method for higher rate units and the first spike latency for lower rate units gave us reliable estimates for all units in our dataset.

Possible influential factors to the response latency of a neuron are the intensity of stimulus, best frequency of a neuron, and the Q value. First of all, the response latency (both first-spike and weighted) decreases with increasing intensity of stimulus. This is expected because a louder sound is generally a stronger stimulus to the neuron. Second, the best frequency of a neuron is not statistically significantly correlated to its response latency. Low frequencies take longer to get to the apex of the cochlea; however, this effect may be corrected when the time information gets to the IC. Third, no

correlation was found between the Q_{40} value and the latency. Higher Q_{40} values would be expected to have higher latencies because the filter needs more cycles of the sound wave to occur before it is maximally driven. The latency values were calculated over the entire receptive range of frequencies, which was (relatively) larger for lower Q_{40} units. However, the effect of this on latency is not clear but it may be cancelling out the number-of-cycles effect. Furthermore, non-linearities in neural processing could weaken this effect as well.

While comparing the response latency between the ICC and ICX neurons at low, medium, and high sound levels, the following tendencies were observed. First of all, most ICC neurons fell into the latency range of 0.01 to 0.25s, whereas the range of latencies for the ICX neurons was broader, from 0.01 to 0.055s. Second, the spread of latencies of ICC neurons remains similar across three sound levels (20dB, 40dB, and 50dB above the threshold) despite the overall trend of decreasing latency with loud sound levels. In contrast, the spread of latency of ICX neurons *broadens* as sound level increases. Third, the overall latency of ICX neurons is longer than that of ICC neurons, seen across all sound levels.

In order to understand the above observations, potential mechanisms should be discussed from the perspectives of neuronal projects and physiological functions of ICC and ICX neurons.

The ICX has a role in multisensory integration. In addition to receiving projections from contralateral CN and ICC, it receives a somatosensory input from the dorsal columns nuclei, spinal cord and sensory trigeminal nuclei (Pickles, 2008: p192). It also receives descending inputs from auditory and somatosensory cortices. Since experimental animals used in this study were awake marmosets, instead of anesthetized animals that are common in the literature, the animal should respond to tactile stimuli as well. In contrary, ICC only participates in primary auditory pathways. An ICX neuron may receive, integrate, and process information from both auditory and somatosensory inputs, while an ICC neuron only relays and processes auditory information. The extra time it takes to integrate these stimuli may account for the longer latency of some ICX neurons.

As shown in Figure 20-22, some of ICX neurons have as short latencies as ICC neurons. Individual neurons in the ICX may play different roles in the

function of the ICX, so some of the neurons would be used in long-latency integrative pathways while others would be directly excited via the lower brainstem auditory pathway and have ICC-like latencies.

Additionally, the response latencies referred in this thesis were all recorded in response to tone stimuli. ICC and ICX units may have different latencies in response to complex sounds.

The reason of less change in the range of response latency of ICC neurons across sound levels could be that the latencies of ICC neurons have already short at low sound level (20dB above the threshold). Even if the intensity of stimulus increases, there is not much room for the latency to further shorten. At least 2ms is the minimal latency of a neuron since this is the time a sound wave takes to travel through the air and the cochlea.

References

Aitkin LM and Moore DR (1975) Inferior colliculus. II. Development of tuning characteristics and tonotopic organization in central nucleus of the neonatal cat. *Journal of neurophysiology*. 38(5): 1208-1216

Houtgast T and Steenkeken JHM (1973) The modulation transfer function in room acoustics as a predictor of speech intelligibility. *Acta Acustica united with Acustica*. 28 (1): 66-73

Huffman RF and Henson OW Jr. (1990) The descending auditory pathway and acousticomotor system: connections with the inferior colliculus. *Brain Research Review*, 15: 295-323

Irvine, DRF (1986) The auditory brainstem: A review of the structure and function of auditory brainstem processing mechanisms, ed. by Ottoson D, *Progress in Sensory Physiology*, Vol. 7. Springer-Verlag, Berlin, 1-279

Langner G and Schreiner CE (1988) Periodicity coding in the inferior colliculus of the cat. I. Neuronal mechanisms. *Journal of neurophysiology*. 60 (6): 1799-1822

Langer G (1983) Evidence for neuronal periodicity detection in the auditory system of the guinea fowl: implication for pitch analysis in the time domain. *Experimental Brain Research*, 52: 333-355

Lyon RF (1990) *The Mechanics and Biophysics of Hearing*, ed. by P. Dallos et al., Springer-Verlag, New York, 395-402

Maison SF, Micheyl C, and Collet L (2001) Influence of focused auditory attention on cochlear activity in humans. *Psychophysiology*, 38 (01): 35-40

Moore BCJ (1989) *An introduction to the psychology of hearing*, Third Edition. Waltham, MA: Academic Press

Muller-Preuss P, Flachskamm C, and Bieser A (1994) Neural encoding of amplitude modulation within the auditory midbrain of squirrel monkeys. *Hear Research* 80: 197-208

Pickles JO (2008) *An Introduction to the Physiology of Hearing*, Third Edition. Waltham, MA: Academic Press.

Ramachandran R, Davis KA, and May BJ (1999) Single unit responses in the inferior colliculus of decerebrate cats I. classification based on frequency response maps. *Journal of neurophysiology*, 82: 152-163

Recio-Spinoso A, Temchin AN, Dijk P et al. (2005) Wiener-Kernel analysis of responses to noise of chinchilla auditory-nerve fibers. *Journal of Neurophysiology*, 93: 3615-3634

Rosen S (1992) Temporal information in speech: acoustic, auditory and linguistic aspects. *Philosophical Transactions Royal Society*, 336 (1278): 367-373

Ryan AF, Miller JM, et al. (1984) Effects of reaction time performance on single-unit activity in the central auditory pathway of the rhesus macaque. *Journal of Neuroscience*, 4 (1): 298-308

Shannon, RV, Zeng F-G, Kamath, V, et al (1995) Speech recognition with primarily temporal cues. *Science*, 270 (5234): 303-304.

Smith ZM, Delgutte B, and Oxenham AJ (2002) Chimaeric sounds reveal dichotomies in auditory perception. *Nature*, 416: 87-90 Houtgast and Steeneken

Tzounopoulos T and Kraus N (2009) Learning to encode timing: mechanisms of Plasticity in the Auditory Brainstem. *Neuron*, 62 (4): 463-469

Winer JA and Schreiner CE (2005) The auditory cortex, Springer Science & Business Media, New York

Zook JM and Casseday JH (1987) Convergence of ascending pathways at the inferior colliculus of the mustache bat, *pteropus pumilus*. The journal of comparative neurology, 261:347-361

Curriculum Vitae

Education

- M.S.E 2015 Biomedical Engineering (Neuroengineering)
Johns Hopkins University
Supervisor: Dr. Eric Young
- M.S.E 2012 Biomedical Engineering (Nanomedicine)
Peking Union Medical College, Tsinghua University
Supervisor: Professor Cunxian Song
- B.S 2009 Material Science and Engineering
Tianjin University of Science and Technology

Research Experience

Johns Hopkins University Center for Hearing and Balance Baltimore, MD

Research Assistant Sep. 2013-Present

- Project: Study of response latency of external and central nuclei in the Inferior Colliculus
- Perform brain surgery and record single neuron activities on animals for studying electrophysiological properties of neurons in the auditory pathway
- Analyze electrophysiological data of neurons in response to different stimuli to investigate the mechanisms of sound processing

Department of BME & Engineering for Professionals Baltimore, MD

Lab Teaching Assistant Sep. 2013-Aug. 2014

- Assisted teaching lab courses: Biomedical System I & II, Biomedical Engineering Practice and Innovation
- Assisted professors with the Biomedical Engineering Practice and Innovation course design
- Collaborated with other TAs to prepare labs; guided students during the lab sessions
- Answered students' questions; graded and commented their pre/post lab reports and exams

Wilmer Eye Institute, Johns Hopkins Medical Institution Baltimore, MD

Research Trainee Jan. 2011-Feb. 2012

- Project: Mucus-Penetrating nanocrystals for improved cancer treatments
- Optimized reaction conditions; formulated mucus-penetrating nanocrystals
- Characterized chemical properties; estimated coating effectiveness of nanocrystals

Center for Biomaterial and Drug Delivery, PUMC, THU Beijing, China

Research Assistant Sep. 2010-Jul. 2012

- Project: Novel drug carrier–PLGA-4/-8-PEG branched polymeric nanoparticles
- Synthesized the star-shaped PLGA-PEG block polymer; formulated drug-loaded particles
- Conducted cell studies to evaluate the chemical and physical properties of synthesized particles