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ABSTRACT

The soundscape of a natural environment can often contain multiple complex sounds, which are perceived binaurally, i.e., by both ears. Under such conditions, the perception of one sound can be affected by another sound. This study was conducted to find the neural basis of such a perceptual phenomenon. The rat is used as an animal model. Action potentials were recorded from individual neurons within the rat inferior colliculus in response to acoustic stimulation. The inferior colliculus is an auditory midbrain structure which receives converging inputs from many other structures along the auditory pathway. It plays a significant role in the integration of neural signals elicited by stimulation of both ears. Temporal and spatial characteristics of sounds affect responses of neurons in the IC to the sounds. It has been found that a priming tone can suppress the response to a testing tone when the two sounds occur closer together both temporally and spatially. This research was conducted to further investigate how responses of neurons to two sounds were dependent on the temporal and spatial relationship between the sounds. Further analysis was performed on a set of neurophysiological data collected by former graduate student, Sarah Tran by removing interfering signals. It was then determined how the responses to a pair of priming-testing sounds were dependent on the temporal and spatial relationships between the sounds. The programming language R was used for analysis. Reanalysis indicated that the response of IC neurons to a testing tone can be suppressed by a priming tone, and that this suppression is reduced when the priming and testing tones are separated temporally and spatially. This effect is especially large in neurons that have transient firing patterns. These results may help understand neural mechanisms responsible for the psychophysical phenomena of masking and spatial release from masking. Results can help to understand spatial hearing and hearing in a natural acoustic environment in general.

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The initial dataset used in this thesis was collected by Sarah Tran between 2018 & 2019, although changes have been made to the dataset as described for optimized analysis.

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LIST OF ABBREVIATIONS

0°.....0 degrees, with respect to the recording electrode

AC.....Auditory Cortex

ANOVA.....Analysis of Variance

AP.....Action Potential

c45°.....Contralateral 45 degrees, with respect to the recording electrode

c90°.....Contralateral 90 degrees, with respect to the recording electrode

CF.....Central Frequency

CN.....Cochlear Nucleus

CNIC.....Central Nucleus of the Inferior Colliculus

CNLL.....Central Nucleus of the Lateral Lemniscus

DCIC.....Dorsal Nucleus of the Inferior Colliculus

DCN.....Dorsal Cochlear Nucleus

DMGB.....Dorsal Nucleus of the Medial Geniculate Body

DNLL.....Dorsal Nucleus of the Lateral Lemniscus

ECIC.....External Nucleus of the Inferior Colliculus

F_H.....Frequency of the Tone Burst Higher than the Central Frequency

F_L.....Frequency of the Tone Burst Lower than the Central Frequency

FTC.....Frequency Tuning Curve

GABA.....γ-aminobutyric acid

$GABA_A$.....γ-aminobutyric acid A

$GABA_B$.....γ-aminobutyric acid B

i.m.....Intramuscular Injection

i45°.....Ipsilateral 45 degrees, with respect to the recording electrode

i90°.....Ipsilateral 90 degrees, with respect to the recording electrode

IC.....Inferior Colliculus

IHC.....Inner Hair Cell

ILD.....Interaural Level Difference

INLL.....Intermediate Nucleus of the Lateral Lemniscus

ISI.....Interstimulus Interval

ITD.....Interaural Time Difference

LL.....Lateral Lemniscus

LNTB.....Lateral Nucleus of the Trapezoid Body

LSO.....Lateral Superior Olive

MGN.....Medial Geniculate Nucleus

MMGB.....Medial Nucleus of the Medial Geniculate Body

MNTB.....Medial Nucleus of the Trapezoid Body

MSO.....Medial Superior Olive

MT.....Minimum Threshold

NMDA.....N-methyl-D-aspartic acid

NR.....Normalized Response

OHC.....Outer Hair Cell

PO.....Periolivary

PSTH.....Post-Stimulus Time Histogram/Peri-Stimulus Time Histogram

Rt.....Reticular Thalamic Nucleus

SOC.....Superior Olivary Complex

SPO.....Superior Paraolivary Complex

SPON.....Superior Periolivary Nucleus

Te1.....Temporal Area 1

Te2.....Temporal Area 2

Te3.....Temporal Area 3

VCA.....Anteroventral Nucleus

VCN.....Ventral Cochlear Nucleus

VCP.....Posteroventral Nucleus

VMGB.....Ventral Nucleus of the Medial Geniculate Body

VNLL.....Ventral Nucleus of the Lateral Lemniscus

VNTB.....Ventral Nucleus of the Trapezoid Body

1. INTRODUCTION

1.1. The Acoustic World

To navigate an environment, organisms must interpret and react to various stimuli, including sights, smells, textures, tastes, and sounds. Sound can be particularly important as it not only informs an organism about the outside world – its dangers, obstacles, and the necessities of life – but also allows for organisms to impart information to each other. Many organisms are able to communicate with each other at varying levels of complexity through the use of sound to warn, mate, locate each other, and fulfill their unique behavioural needs. Sounds are able to bypass many obstacles which would normally obstruct other senses and render them useless. Unlike sight, sound can be heard in the dark. Unlike touch and taste, sound can cover great distances. For this reason, many animals rely on sound for survival. However, with such great versatility, comes greater complexity. How is an animal able to sort out the sounds it encounters when there may be so many, of such varied and wide-ranging characteristics?

1.1.1. Complexities of the Acoustic World

Animals make use of frequencies, volume, timing, and other qualities of a sound to gather information about the source, location, and meaning of the sound, and produce behaviours as a response. They can do all of this in the presence of competing sound. Sorting through disparate sounds, each with its own complex temporal, spatial, and spectral characteristics can be vital to survival.

1.2. Hearing Phenomena that Involve Multiple Sounds

Hearing in a complex acoustic environment is frequently described as the "cocktail party effect". It has been found that in such an environment (e.g., a cocktail party), an individual is able to selectively attend to one conversation and make sense of "what" and "where" these conversation sounds are despite sonic interference (Cherry, 1953). In the presence of competing sounds, the perception of one sound may be influenced by another sound even when the two sounds do not share characteristics (Shinn-Cunningham et al., 2005). One example of this influence is called masking.

1.2.1. Psychoacoustic Phenomena Revealed by Human Psychoacoustical Studies

Situations wherein perception of one sound is affected by another is called "masking", a psychoacoustic phenomenon. Masking occurs when a sound (a "target sound") is made more difficult to perceive due to the presence of a second (a "masking sound" or "masker") sound (Deatherage & Evans, 1969; Mokri et al., 2015; Wallach et al., 1949). Three major types of masking are known to occur; "simultaneous", "forward", and "backward" masking, based on the temporal relationship between the sounds (Nelson et al., 2009; Salimi et al., 2017). Simultaneous masking occurs under conditions where sounds occur at the same time, over the same duration, leading the masking sound to alter responses to the target sound (Plack & Moore, 2010). In situations where a masker is followed consecutively by a target sound, the presence of the masker lessens response to the target, suppressing it. Such "forward masking" is particularly prevalent under conditions of low frequency (Jesteadt et al., 1982). Backwards masking occurs

when a target sound is followed by a masking sound, typically within a brief time-frame of 20 milliseconds (Plack & Moore, 2010).

The degree to which one sound can mask another is dependent on the temporal, spatial, and spectral characteristics of the masker relative to the target (Casseday & Covey, 1992; Chot et al., 2019, 2020; Deatherage & Evans, 1969; Oertel, 1999). Maskers, particularly those in forward masking conditions, which have a similar frequency or a low intensity relative to the target may cause stronger inhibition, where maskers of different frequencies, having a high intensity tend to have a weaker effect. Where there exists a small gap of time between the masker and target, there is a higher threshold required for the target to be detected, resulting in stronger masking (Plack & Moore, 2010). As this time gap increases, the degree of masking decreases until the target is no longer suppressed by the preceding masker. The range of a masking sound is around a few hundred milliseconds (Gulick et al., 1989; Plack & Moore, 2010). Something similar occurs under masker-target relationships of varied spatial separation. In forward suppression particularly, sounds which are colocalized, appearing to originate from the same area of space, show greater suppression of the target than sounds which are farther apart. This “spatial release from masking” is most noticeable when the sounds are occurring on opposite sides of the head(Gulick et al., 1989; Plack & Moore, 2010). When simultaneous masking is examined, the degree of masking shown by the response to the target sound is dependent on the duration of the masker, the delay between the onset of the masker and the target sound, and the frequency of the sounds involved (Fastl & Zwicker, 2007)

Masking appears to be dependent on neural mechanisms at work within the central auditory system. At low intensities, forward masking is shown to involve structures lower in the auditory pathway, such as the cochlear nucleus (Deatherage & Evans, 1969; Nelson et al., 2009). Responses under these conditions show the cochlear nucleus's characteristic narrow tuning. However, at high intensities forward masking involves structures such as the dorsal nucleus of the lateral lemniscus, and the superior paraolivary complex, showing broad-tuned inhibitory responses (Nelson et al., 2009). The processing involved in forward masking is most likely completed before reaching higher structures such as the medial geniculate nucleus and the thalamus (Nelson et al., 2009).

Some studies suggest that bottom-up and top-down factors influence spatial release from masking. Such bottom-up factors relate to the characteristics of a sound external to the auditory pathway, such as temporal and spatial relationships. They include; separation of the masker and target, interaural decorrelation, and increasing the energy ratio between masker and target. Top-down factors relate to the influence of auditory processing on responses to a sound which originate in the higher structures of the auditory pathway, and include spatial attention (Shinn-Cunningham et al., 2005). Initial spatial attention, that is, the initial region of space to which the listener hears the sound as well as anticipation of the sound's location have been known to influence auditory perception. This influence is known as the law of first wavefront. When one sound follows another with very little interval between them, typically between 1 and 5 milliseconds for simple clicks, and less than 40 milliseconds for speech, a subject perceives only

one auditory event (Cremer, 1948; Wallach et al., 1949). If the sounds occur at different locations, the sound will appear to come from only one direction, known as “localization dominance” (Wallach et al., 1949). The auditory processes which aid in resolving the conflict generated by processing two sounds in quick succession are known as the precedence effect.

1.2.2. Studies of Psychoacoustic Phenomena in Animal Models

Human studies of effects such as masking and the precedence effect often face issues in studying the underlying neural mechanisms which cause them. Due to ethical constraints human studies must minimally invasive, limiting the number of procedures which can be performed. The human brain cannot be recorded from within, and human studies must rely on non-invasive techniques such as electroencephalograms and magnetic resonance imaging (MRI). The spatial resolutions of these techniques make it impossible to pinpoint neurons that contribute to psychophysical phenomena. Muscle activity from the scalp may interfere with recordings, as well as background activity in other, unrelated brain structures. While loose correlations can be made based on the known location of certain structures, the information provided is rarely specific. Studies performed on animals which share the characteristics of the human auditory structure can be of great benefit to understanding the mechanisms involved.

Some animal models, in particular the rat, have auditory pathways that are homologous to that of humans. Rat studies often show the same or similar behavioural responses to masking and precedence effect-generating stimuli as those seen in humans, as detailed above. For example, many studies have used classical and operant conditioning to gauge the ability of animal models

such as rats to produce behaviours under masking conditions. Gourevitch, 1965 shows rats trained to press a bar after hearing a tone. When this tone was presented simultaneously alongside different levels of noise, the rat continued to press the bar after the tone could no longer be heard due to the effects of masking. This indicated that the masked threshold in rats increases with respect to the noise level of the environment, similarly to humans (Gourevitch, 1965). Another study, Hoeffding and Harrison, 1979, examined the precedence effect in rats. In this study, a rat was trained to press a lever in response to a click while another click was present (creating an artificial echo of the first click). When the delay between the first and second click was altered, a majority of the correct responses occurred when the delay between the two clicks was greater. This indicates that it is possible for one sound to affect the response to another based on their temporal relationship (Hoeffding & Harrison, 1979).

The ability to explore the underlying neural causes of such behaviours may reveal new information. Many of the auditory processing structures of the rat brain show unique activity in response to the spatial relationship between sounds. In particular, the inferior colliculus. These structures and their related activities shall be explained below.

1.3. The Mammalian Auditory System

Sounds are detected and processed by a group of anatomical structures that are collectively called the auditory system. The mammalian auditory system consists of the peripheral auditory system, i.e., structures that are responsible for the collection and transduction of sounds, and the central auditory system, neural structures within the skull that are responsible for the encoding

and processing of acoustic information (Rees & Palmer, 2010). The layout and characteristic activity of each structure greatly influences its role in auditory processing. This section primarily delineates the auditory system of the rat, as it is the model organism used in this study. Where rat studies are not available, studies from other animals have been used as indicated, information about the anatomical details of the rat auditory system are drawn primarily from Malmierca & Merchan, 2004, unless otherwise stated.

1.3.1. The Peripheral Auditory System

The peripheral auditory system comprises three major sections; the outer, middle, and inner ear. The outer ear structures are the pinna and the ear canal. The external cartilaginous pinna helps an animal to collect and amplify sounds in an environment, and funnel them towards the opening of the ear. Sound then travels through the ear canal where it reaches the tympanic membrane at the end. From there, sound passes into the middle ear.

The middle ear contains three bones, or "ossicles"; the malleus, the incus, and the stapes. These bones working together convert the sound from one medium, the outside air, to a new medium, the fluid of the inner ear. It is the stapes that interfaces with the inner ear. Vibrations caused by the sound are passed from the stapes onto the membrane of the oval window of the inner ear. The structure in the inner ear that is responsible for hearing is the cochlea, a coiled bone structure. Inside the hollow opening of the cochlea, called the cochlear duct, resides the organ of corti – a vital structure involved in hearing. The organ of corti is host to the hair cells which convert vibrations into electrical signals which can be used by the central nervous system. The two types

of hair cells found are the outer hair cells (OHC) and inner hair cells (IHC), both found resting on the basilar membrane. The primary function of OHCs is to amplify the vibrations passing through the cochlear duct, whereas IHCs are mainly responsible for conversion of vibrations into signals. Different sections of the basilar membrane respond maximally to different frequencies, thus each hair cell is sensitive to a specific frequency determined by its position on the basilar membrane (Pulkki and Karjalainen, 2015). Hair cells found closest to the middle ear (i.e., close to the oval window) are generally sensitive to high frequencies, while hair cells further from the middle ear (i.e., close to, or at the apex of the cochlea) are generally sensitive to low frequencies. This topographic organization is observed in all mammals including the rat. Electrical signals generated by the IHCs travel along the connected cranial nerve VIII, also called the vestibulocochlear nerve, until they reach the first structure of the central auditory system (Malmierca & Merchan, 2004; Rees & Palmer, 2010)

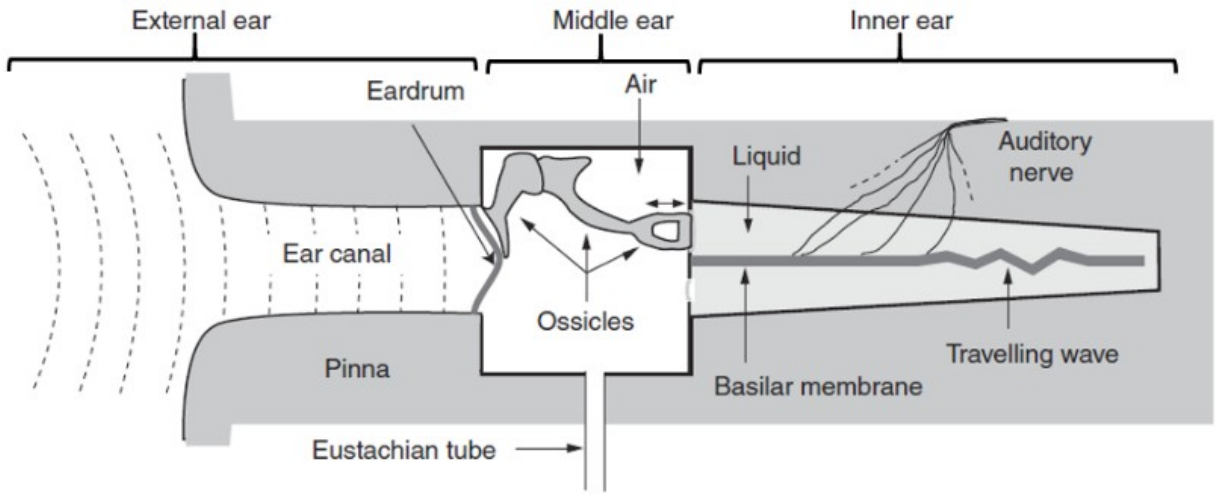
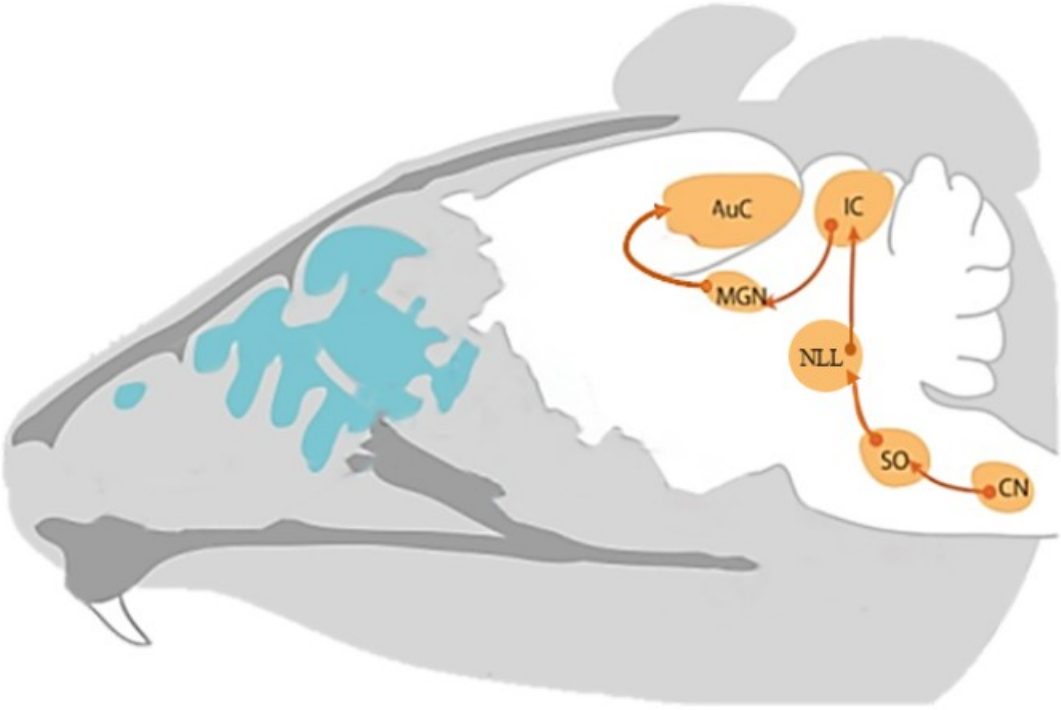


Figure 1. A diagram of an ear showing the external ear, the middle ear, and inner ear (modified from Pulkki and Karjalainen, 2015).

1.3.2. The Central Auditory System

After auditory sensory transduction, electrical signals elicited by sounds in the peripheral auditory system are sent to the central auditory system for further processing. The central auditory system is comprised of six major structures, which include the cochlear nucleus (CN), the superior olivary complex (SOC), the nucleus of the lateral lemniscus (NLL), the inferior colliculus (IC), the medial geniculate nucleus (MGN), and the auditory cortex (AC). This pathway is mirrored on both sides of the brain. Each structure projects to the others along the pathway in a variety of complex ways, their organization shown in Figure 2. Projections from lower auditory structures to higher auditory structures in the system (e.g., from the CN to the SOC) are known as “ascending projections”. Projections from a higher structure to a lower structure are known as “descending projections”. Projections may also occur between the same structure on opposite sides of the longitudinal fissure. These projections are known as “commissural” connections. Each structure within the central auditory system can also be divided into subnuclei. Projections which connect the subnuclei within a single structure are called “intrinsic” connections. (Malmierca & Merchan, 2004; Rees & Palmer, 2010). The SOC, NLL, and IC are known to receive inputs from structures on both the left and right sides of the pathway, being major centres of binaural inputs (Rees & Palmer, 2010; Pulkki and Karjalainen, 2015).

a.



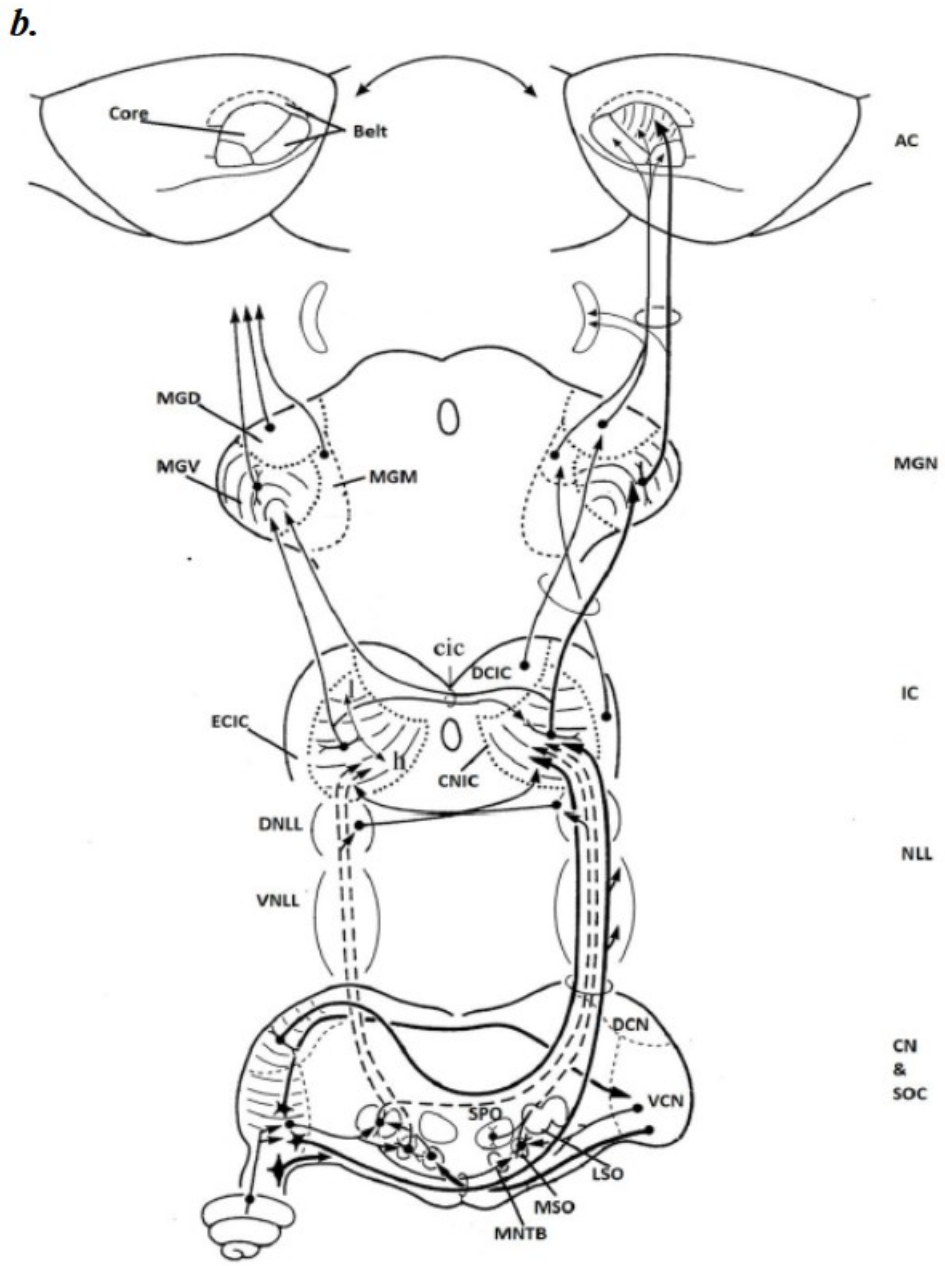


Figure 2. Schematic representation of the auditory pathways in a rodent. ***a.*** Major structures within the central auditory system (modified from Asaba et al., 2014). ***b.*** Major ascending projections within the central auditory system (adapted from Malmierca 2015).

1.3.2.1. The Cochlear Nucleus

The first relay stop in the ascending auditory pathway is the cochlear nucleus. The CN is found on the dorsolateral side of the brainstem. Synaptic inputs received by the structure, neuronal membrane properties, intrinsic fibre systems, and descending inputs all influence the ways the CN transforms and transmits signals to the next stop on the ascending pathway. The CN consists of two major subnuclei, referred to as the ventral nucleus (VCN), and dorsal nucleus (DCN). Fibres of ascending projections are from cranial nerve VIII, which originate from the IHCs of the cochlea. These fibres innervate all regions of the CN (Harrison and Feldman, 1970). Descending projections to the CN originate from the AC, IC, ventral nucleus of the lateral lemniscus (VNLL), and the SOC. Many of SOC projections are inhibitory. Only a few are excitatory. Projections to and from the CN tend to be tonotopically organized, meaning neurons within this structure are arranged according to the frequency to which they respond best, forming a gradient map of high and low frequency-responding neurons (Malmierca & Merchan, 2004).

1.3.2.1.1. The Ventral Cochlear Nuclei

The VCN is a flat structure which can be found ventrolaterally to the inferior peduncle. It can be further subdivided into the anteroventral nucleus (VCA) and the posteroventral nucleus (VCP) on the two sides of the cochlear nerve root. The VCN contains 5 types of neurons, i.e., spherical bushy, globular bushy, octopus, multipolar, and small cells (Osen, 1969). Spherical bushy cells are found in the rostral VCA. Globular bushy cells are found in both the caudal VCA and rostral VCP. Octopus cells are found in the caudal VCP. And multipolar and small cells are found throughout the VCN. Spherical and globular bushy cells show ‘primary-like’ responses to pure

tones (i.e, with strong firing over the initial period of stimulation and reduced firing throughout the rest of stimulation). They appear to specialize in the processing of temporal information carried by a sound (Oertel, 1997; 1999). Spherical bushy cells project bilaterally to the medial superior olive (MSO, a subdivision of the SOC, see 1.3.2.2.) and to the ipsilateral lateral superior olive (LSO, a subdivision of the SOC, see 1.3.2.2.), while globular bushy cells project to the contralateral medial nucleus of the trapezoid body (MNTB, a subdivision of the SOC, see 1.3.2.2.). Octopus cells display a single onset spike response to tone bursts. They receive little inhibitory influence and project bilaterally to the superior paraolivary complex (SPO, a subdivision of the SOC, see 1.3.2.2.), and the contralateral ventral nucleus of the lateral lemniscus (VNLL). Multipolar cells can generally be subdivided into two types: T-stellate and D-stellate. T-stellate cells generate a "chopper" firing pattern in response to tone bursts, and project to the periolivary region of the SOC, the NLL, and the central nucleus of the inferior colliculus (CNIC, a subdivision of the IC, see 1.3.2.4.). They provide information about the frequency and level of a sound. S-stellate cells display an "on-chop" response to pure tones, and project to the contralateral CNIC, and the ipsilateral VCN and DCN. Small cells project to the IC, the bilateral MSO, ipsilateral LSO, and the MGN. They provide information on stimulus intensity. (Malmierca & Merchan, 2004).

1.3.2.1.2. The Dorsal Cochlear Nuclei

The Dorsal Cochlear Nucleus consists of 3 layers and a central nucleus, and contains large numbers of inhibitory interneurons (Osen et al., 1990). Pyramidal cells found in the layers of the DCN project to the contralateral IC (Malmierca et al., 1999a,b), and the MGN (Malmierca et al.,

2002). It is tonotopically organized. The tuberculoventral system reciprocally interconnects the DCN and VCN. Frequency-specific inhibitory interneurons within the tuberculoventral system begin in the DCN and terminate in the VCN, while frequency-specific excitatory T-stellate cells begin in the VCN and terminate in the DCN. Wide-frequency D-stellate cells compose inhibitory inputs across both the DCN and VCN. The "pauser" and "built-up" responses seen from pyramidal cells are influenced by the inhibitory interneurons of the tuberculoventral system. It is believed that the DCN may participate in sound localization. (Malmierca & Merchan, 2004).

1.3.2.2. The Superior Olivary Complex

The subnuclei of the superior olivary complex are known as; the lateral superior olive (LSO), the medial superior olive (MSO), the medial nucleus of the trapezoid body (MNTB), which is surrounded by the periolivary region (PO). There is another region, the superior paraolivary nucleus (SPON) which is also present in rats ((Harrison and Feldman, 1970). The SPON is located dorsomedially, and projects to the ipsilateral IC. The LSO, which is more developed in rats, plays a role in the processing of a large range of high frequencies, and is thought to be involved in the localization of high frequency sounds. The MSO, which in contrast receives inputs that are activated by lower frequency sounds, is underused in the rat. This is likely due to the natural hearing range of the rat being skewed towards higher frequencies (Malmierca & Merchan, 2004).

1.3.2.2.1. The Medial Superior Olive

The MSO is located between the LSO and the MNTB. It is a tonotopically organized structure, in which most of the neurons are devoted to the processing low frequency sounds. In many animals that have good low frequency hearing, such as the cat, the MSO is important for localizing low frequency sound using interaural-time differences (ITDs), i.e., the difference in time between the left and the right ear when a sound reaches the two ears. For small animals (e.g., the rat), the difference is very small and barely perceptible. This information is therefore of little use, and the MSO is usually underdeveloped in these animals (Covey et al., 1991). In these animals, the MSO may contribute to the suppression of echoes. The principal cells of the MSO are multipolar rather than bipolar, with a small population of nonprincipal cells present. Both types of cells send excitatory projections to the ipsilateral CNIC and the ipsilateral dorsal nucleus of the lateral lemniscus (DNLL a subdivision of the NLL, see section 1.3.2.3.3.). The MSO receives excitatory inputs from spherical bushy cells in the VCA, bilaterally, as well as inhibitory inputs from the ipsilateral MNTB and LNTB. Ipsilateral inputs terminate in the MSO's lateral region, while contralateral inputs terminate in the medial region (Malmierca & Merchan, 2004).

1.3.2.2.2. The Lateral Superior Olive

The LSO is an S-shaped structure, which consists of a collection of bipolar neurons that are organized tonotopically. It is thought to be involved in the detection of interaural-level differences (ILDs), i.e., the difference in intensity between the left and the right ear when a sound reaches the two ears. As this difference is associated with the azimuthal location of a sound, the LSO is believed to be important for sound localization. In the LSO, lower frequency

sounds are processed by neurons on the lateral side, while higher frequency sounds are processed by neurons on the medial side. There are 7 types of neurons in the LSO, namely bipolar and multipolar (the most populous), small multipolar, banana-like, bushy, unipolar, and marginal cells. The LSO receives projections from both sides of the VCA. Specifically, ipsilateral projections are from spherical bushy cells, while contralateral projections are from globular bushy cells (indirectly through the MNTB). These inputs reach the LSO simultaneously. The LSO is excited by ipsilateral stimulation, and inhibited by contralateral stimulation. The LSO projects bilaterally to the IC and the DNLL. Projections from the LSO to structures on the ipsilateral side are inhibitory, while projections from the LSO to structures on the contralateral side are excitatory (Malmierca & Merchan, 2004).

1.3.2.2.3. The Superior Periolivary Nuclei

The SPON is found dorsal to the MNTB. It is tonotopically organized and contains several cell types. This structure receives inhibitory inputs from the ipsilateral MNTB, and excitatory inputs from the contralateral VCA and VCP, as well as ipsilateral VCP. In response to a sound, many neurons in the SPON fire action potentials at the offset of the sound. Neurons in the SPON send inhibitory projections to the ipsilateral IC. These projections may enable a sound to suppress the response of IC neurons to a subsequent sound. As well, this structure is thought to encode temporal features of sounds and contribute to sound duration discrimination (Malmierca & Merchan, 2004).

1.3.2.2.4. Other Subnuclei in the Superior Olive

In rodents, there is another well-developed structure within the SOC known as the medial nucleus of the trapezoid body (MNTB). The principal cells in this structure resemble globular bushy cells in the VCA. While not identical, responses of these neurons resemble those of neurons in the VCA as well. Nevertheless, these responses lack a sharp onset. The MNTB receives excitatory input from globular bushy cells in the contralateral VCA. It then converts inputs into inhibitory signals, and relays them to the LSO. Its principal cells generally project to the ipsilateral LSO, MSO, SPON, VNTB (see the following paragraph), and LNTB (see the following paragraph), while non-principal cells project to the ipsilateral ventral nucleus of the lateral lemniscus (VNLL, a subdivision of the NLL, see section 1.3.2.3.1.). The MTNB causes general inhibition of the SOC in response to contralateral stimuli.

The other periolivary nuclei found in the SOC include; the ventral nucleus of the trapezoid body (VNTB), the lateral nucleus of the trapezoid body (LNTB), as well as the dorsal, dorsolateral, ventrolateral, anterolateral, ventromedial, rostral, caudal, and posteroventral periolivary nuclei (collectively, the PO). These PO regions mainly receive input from the T-stellate and octopus cells of the VC, with the lateral PO regions receiving ipsilateral stimulation, and the medial receiving bilateral inputs. Medially situated areas of the PO project to the ipsilateral IC, while lateral and ventral areas project bilaterally to the IC. Bilateral projections are also sent to the CN and cochlea.

The LNTB is located ventral to the MNTB. It receives bilateral projections from the VCA. These projections tend to arise from bushy, small, and multipolar cells. It sends bilateral inhibitory projections to the IC, LSO, MSO, and CN. The VNTB is found ventral to the MTNB, and receives projections from the IC, as well as projections from the globular bushy, octopus, and multipolar cells of the contralateral VC, multipolar cells of the ipsilateral VCP, and bilateral projections from the VCA. This makes it a major convergence point for CN and IC inputs. It projects bilaterally to OHCs in the cochlea, as well as to the contralateral DCN and LSO, and the ipsilateral IC, DCN, VCN, and LL (Malmierca & Merchan, 2004).

1.3.2.3. The Nucleus of the Lateral Lemniscus

The nucleus of the lateral lemniscus is a region of auditory neurons found dorsolaterally in the pons. This region functions as relay stop for information travelling from the SOC to the CNIC. It can be roughly divided into three subnuclei. The dorsal nucleus of the lateral lemniscus (DNLL) is well defined, while the intermediate nucleus of the lateral lemniscus (INLL), and the ventral nucleus of the lateral lemniscus (VNLL) have less consistent boundaries and are often grouped together. These subnuclei are thought to comprise two functional systems within the LL, the DNLL aids in binaural processing, while the INLL and VNLL are monaural, and thought to be involved in the processing of temporally precise information (Malmierca & Merchan, 2004).

1.3.2.3.1. The Ventral Nucleus of the Lateral Lemniscus

The VNLL is organized into tonotopic laminae. It displays very little, if any, spontaneous activity, suggesting its role in the processing of temporally precise information (Malmierca et al.,

1999a,b). There are two types of neurons in the VNLL: bushy, and stellate. The bushy cells typically display an “onset” firing pattern, while the stellate cells display three types of firing patterns. The VNLL receives projections from the contralateral VCN and ipsilateral MNTB, with excitatory contralateral inputs being more populous. It is thought that octopus neurons showing “primary-like” and “chopper” firing patterns provide important temporal information for neurons in the VNLL to process. The dorsal region of the VNLL receives projections from the MNTB. Additionally, the entire VNLL receives inputs from stellate and globular bushy cells of the VCN. Some projections to the VNLL originate from the ipsilateral PO region. Neurons in the VNLL inherit response properties from neurons in source structures through projections that the VNLL receives. As a result, most neurons in the VNLL respond monauraly to contralateral stimuli. The VNLL is a major source of inhibition to the IC (Malmierca & Merchan, 2004).

1.3.2.3.2. The Intermediate Nuclei of the Lateral Lemniscus

The INLL is often grouped together with the VNLL and shares many of its characteristics, such as a lack of spontaneous activity, and reception of inputs from the contralateral VCN and ipsilateral MNTB. It is primarily excited by contralateral stimulation, and sends inhibitory projections to the ipsilateral CNIC, the dorsal cortex of the inferior colliculus (DCIC, a subdivision of the IC, see section 1.3.2.4.2.), and parts of the MGN (Malmierca & Merchan, 2004).

1.3.2.3.3. The Dorsal Nuclei of the Lateral Lemniscus

In rats, the DNLL appears as an "onion-like" structure, composed of many concentric tonotopically organized rings. It is involved in binaural processing and sound localization, receiving input from both ears. There is no consensus about the number of cell types contained within the DNLL. Some studies suggest that there are two, but others suggest that there are four, or even five distinct types based on morphology. However, each type of neuron shows sustained firing in response to stimulation. Projections to the DNLL arise in the contralateral VCA, ipsilateral MSO, SPON, VNLL, and bilaterally from the LSO and INLL. Contralateral stimulation excites the DNLL, while ipsilateral stimulation inhibits it. The DNLL is a convergence point for olivary projections, cementing its role in binaural processing and usefulness in sound localization. The majority of DNLL neurons use inhibitory neurotransmitters (i.e., GABA and glycine), while some neurons are excitatory and glutamatergic. Projections from the DNLL are sent to the IC of both sides. The DNLL also makes use of the commissural fibres of the commissure of Probst to send and receive input from the contralateral DNLL (Ito et al., 1996, Kelly et al., 1996, Malmierca & Merchan, 2004).

1.3.2.4. The Inferior Colliculus

The IC is the major structure of interest for this study. This structure is a major relay centre for the auditory system, and a site of binaural processing. The IC receives inputs from all the other structures in the auditory pathway. It also receives inputs from some nonauditory structures. The IC can be subdivided into the central nucleus of the inferior colliculus (CNIC), dorsal cortex of

the inferior colliculus (DCIC), and external cortex of the inferior colliculus (ECIC) (Malmierca & Merchan, 2004).

1.3.2.4.1. The Central Nucleus of the Inferior Colliculus

The CNIC is the most prominent area of the IC, it consists of layers of laminae which form the basis for the structure's tonotopic organization (Malmierca & Merchan, 2004).

1.3.2.4.1.1. Cytoarchitecture of the CNIC

Within the rat CNIC, there are two types of cells; "flat" and "less-flat" cells. Flat cells are thinner, and more densely packed than less-flat cells. Flat cells are also oriented nearly parallel to each other, often forming layers of laminae one or two cells 50 μm thick. The interlaminar compartments contain less-flat cells. These compartments are much thicker than the laminae, at about 100 μm. In the low frequency areas of the CNIC (i.e., the dorsolateral region of the CNIC), cell bodies are smaller and densely packed. In contrast, cell bodies in high frequency areas (i.e., the ventromedial region of the CNIC), cell bodies are larger and more loosely packed, which is a likely reason for the greater distinction between laminae seen in high frequency areas. The dorsal region of the CNIC is thinner (7-12 μm) than the ventral region (9-20 μm). Neurons in the dorsal region have less myelination, while neurons in the ventral region have greater myelination . The laminae of the CNIC are known to be tonotopically organized, each individual layer differs by ~0.3 octaves in their best frequencies, as well as possibly being organized by temporal response (Malmierca & Merchan, 2004).

1.3.2.4.1.2. Projections To and From the CNIC

As a major auditory processing centre, the CNIC receives inputs from many areas of the left and right auditory pathways, allowing the response to one sound affect the response to another. Inputs to the IC tend to be inhibitory if they are activated by stimulation of the ipsilateral ear, and excitatory if they are activated by stimulation of the contralateral ear. Inhibition tends to play a larger role in binaural interactions. Ascending projections from lower auditory structures originate from both sides of the DNLL and LSO, the ipsilateral VNLL, MNTB, and MSO, and the contralateral VCA, VCP, and DCN. Most of these projections terminate on the ventral area of the CNIC. Descending projections to the CNIC arise from both sides of the AC, and the ipsilateral MGN. Most of these projections terminate in the dorsal region of the CNIC. The CNIC sends projections to the MGN ipsilaterally, which innervate the AC. Excitatory inputs to the CNIC are glutamatergic and arise primarily from the contralateral CN and LSO, and the ipsilateral MSO. Inhibitory inputs include GABAergic projections from both the left and right DNLL, and ipsilateral SPON. Of the projections ascending from the CNIC, these projections are most likely glutamatergic and GABAergic, with the GABAergic cells inhibiting thalamocortical MGN neurons (Malmierca & Merchan, 2004).

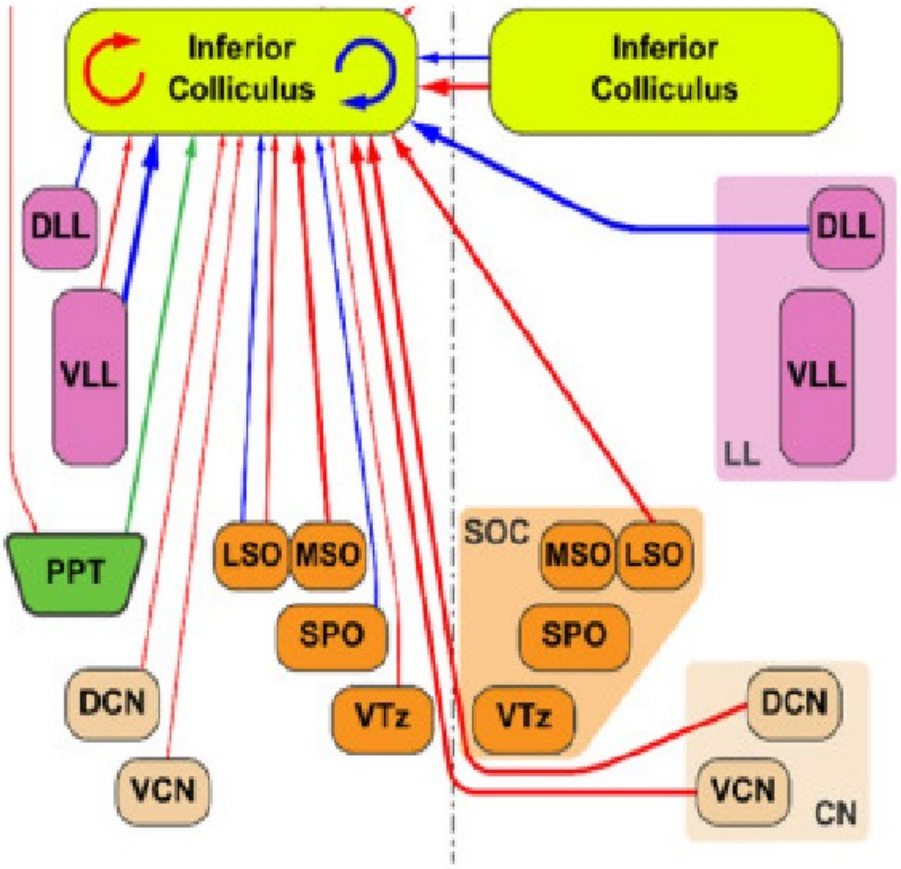


Figure 3. Schematic diagram of the excitatory (red) and inhibitory (blue) projections to the inferior colliculus. The thickness of the lines indicates strength of projection. The vertical dashed line indicates the midline. DLL, VLL: dorsal and ventral nucleus of the lateral lemniscus (LL); SOC: superior olivary complex; LSO, MSO: lateral and medial superior olive, respectively; Vtz, ventral nucleus of the trapezoid body; SPO: superior periolivary nucleus; DCN, VCN: dorsal and ventral subdivisions of the cochlear nucleus (CN). Modified from (Malmierca, 2003).

1.3.2.4.2. The Dorsal Nucleus of the Inferior Colliculus

The DCIC is found dorsomedially and caudally to the CNIC, and is made of 3 layers in rats. The first layer, the most superficial, is the thinnest and contains small flat neurons. It is continuous with the ECIC (see the next subsection). The second and third layers are progressively thicker, containing a mixture of small and medium neurons. Large multipolar "transitional" cells can be found at layer 3's border with the CNIC. The DCIC receives inputs from the AC bilaterally, and the sagulum. Some minor inputs also arise from the CNIC. These projections are tonotopically organized. Projections originating in the DCIC are sent to the dorsal MGN. It is possible that the DCIC has a role to play in language and the processing of new sounds (Malmierca & Merchan, 2004).

1.3.2.4.3. The External Nucleus of the Inferior Colliculus

The ECIC covers the CNIC ventrally, laterally, and rostrally. Like the DCIC, this structure has 3 layers. The first layer is continuous with the first layer of the DCIC, the second layer comprises small and medium neurons, often in dense clusters. The largest part of the ECIC, the third layer, contains neurons of three distinct types: bi-tufted, pyramidal-like, and chandelier (Malmierca, 1991). They are differentiated by the types of Ca^{2+} currents which are activated at low, mid, and high voltage levels, respectively. Neurons of the ECIC show greater excitability than those in the other structures of the IC. Inputs to the ECIC originate from the ipsilateral MGN, the cerebral cortex area rostral to the ipsilateral AC, and several other nonauditory structures. The ECIC sends projections to the ipsilateral MGN, these projections overlap with projections to the MGN from other IC regions. The ECIC also sends projections to nonauditory regions such as the

sagulum, suggesting its role in language, the processing of new sounds, and the integration of multisensory information (Malmierca & Merchan, 2004).

1.3.2.5. The Medial Geniculate Body

The thalamus is involved in many physiological processes, of which auditory processing is only one. The MGN is the primary region of the thalamus involved in hearing, and the last relay station in the ascending auditory pathway before the AC. There are no intrinsic or commissural projections within this structure. It can be divided into three main regions: the ventral, dorsal, and medial (Malmierca & Merchan, 2004).

1.3.2.5.1. The Ventral Nucleus of the MGN

The ventral nucleus of the medial geniculate body (VMGB) is the main region of the MGN involved in auditory processing, it is often divided into 3 subnuclei: the ventral nucleus, the ovoid nucleus, and the marginal zone. Each subnuclei has a distinct pattern of lamina, the ventral nucleus having long, slightly curved laminae, and the ovoid nucleus having shorter, more coiled laminae. Main inputs to the VMGB include the ipsilateral CNIC, and some from the contralateral CNIC. Interneurons provide inhibition of the structure. High frequency inputs are sent to the medial area of the VMGB, while low frequency inputs are received laterally. Contralateral stimulation excites the VMGB, while ipsilateral stimulation either excites or inhibits. The primary type of neuron found here is the “tufted” variety. Many “tufted” neurons receive converging excitatory and inhibitory inputs and send glutamatergic outputs. The lack of GABAergic inhibition in the VMGB may be related to the rat’s need to process similar,

uncomplicated sounds in this part of the auditory pathway (Winer & Laure, 1996). Frequency, intensity, and binaural auditory information from the ipsilateral IC is passed on by the VMGB to the AC, to which it is reciprocally connected. Projections from the VMGB are sent to the Reticular thalamic nucleus (Rt), and layers III and IV of Te1 (Malmierca & Merchan, 2004).

1.3.2.5.2. The Dorsal Nucleus of the MGN

The dorsal nucleus of the MGN (DMGB) is located dorsally to the VMGB. It can be divided into 5 subnuclei: the dorsal superficial, dorsal, deep dorsal, suprageniculate, and the ventrolateral. The role of the DMBG in hearing is unclear. A few inputs to this structure arise from the DCIC and the ECIC, the Rt, as well as the nonprimary cortices of the AC. It contains tufted cells similar to those in the VMBG, as well as radiate and stellate cells. The 5 subnuclei are characterized by the different density and concentration of each of these cell types. The DMGB projects to Te2 and 3 of the AC, and some nonauditory structures (Malmierca & Merchan, 2004).

1.3.2.5.3. The Medial Nucleus of the Medial Geniculate Body

The medial nucleus of the MGN (MMGB) is the MGN's smallest region. It contains many types of neurons, all of which make up the 200mu-wide, flat, curved nucleus. The MMGB receives many inputs, which may enlighten us as to its function. Inputs arrive from the ipsilateral ECIC, CNIC, superior colliculus, SOC, VNLL, vestibular nuclei, PO region, and other somatosensory areas, as well as descending inputs from the Rt, Te1, and Te3. The structure projects to all areas of the AC, most of which are concentrated in the Te2, Te3, and nonauditory regions such as the

somatosensory cortex, and amygdala. It may be involved in visual and nociceptive functions (Malmierca & Merchan, 2004).

1.3.2.6. The Auditory Cortex

The Auditory cortex (AC) is the highest, and final structure in the ascending auditory pathway. It is a part of the temporal cortex, found in the lateral sulcus in the fissure of Sylvius. It is tonotopically organized, and is a major site of termination for ascending fibres from the MGN. There are several proposed maps of the AC in rats, the lack of distinct features in each region makes it hard to define. According to current descriptions, there are three major areas: the primary cortex, composed of temporal area 1 (Te1), and the secondary cortex composed of temporal area 2 & 3 (Te2 & Te3). Te1 is found in the centre of structure, wrapped by Te2, which is in turn wrapped by Te3 (Malmierca & Merchan, 2004).

1.3.2.6.1. The Primary Auditory Cortex: Temporal Area 1

The Te1 is defined primarily by its inputs, which mainly derive from the VMBG. The structure also receives some weak projections from the DMBG and MMBG. It consists of 6 layers, each defined by the types and densities of cells present. Neurons in the Te1 are either pyramidal which are glutamatergic, or non-pyramidal which are mostly GABAergic. Among the 6 layers, layer I contains the least number of cells. Most cells in this layer are non-pyramidal. Layer II contains both pyramidal and non-pyramidal cells, which appear small in the superficial part and become larger in the deep part. Layer III also contains both cell types, with non-pyramidal cells resembling tufted, stellate, and multipolar cells. Most VMBG neurons terminate on layer IV

tonotopically, many of the cells within the structure are small, and densely myelinated. Both layers V and VI contain pyramidal and non-pyramidal cells, the non-pyramidal cells resembling multipolar and bipolar neurons. Within layer VI there is a third type of cell known as the horizontal type. The excitatory pyramidal cells found in layers V and VI of Te1 send descending projections to the MMGB and CNIC, projections to the CNIC are tonotopically organized (Saldana et al., 1996). There exist some projections to other IC subnuclei, but they are sparse and unevenly distributed.

There exist some differences in the Te1 between the two sides of the brain. The left Te1 is believed to play a role in processing sequential differences in sound, as found in speech. As for the right Te1, its role lies in processing the tonality of sound, as in music. However, both the right and left Te1 have some role in identifying the pitch and intensity of sounds (Malmierca & Merchan, 2004).

1.3.2.6.2. The Secondary Auditory Cortices: Temporal Area 2 & 3

The Te2 and Te3 form the “belt” and “parabelt” regions of the AC, respectively. The Te2 subnuclei receives projections from the Te1. Cells are less densely packed and do not have much myelination. Projections to this region originate in the DMBG and MMGB. As to the Te3 region, it is provided with inputs from Te2 and the DMGB. Inputs from the Te1 to the Te3 are nonexistent. Both the Te2 and Te3 project to several higher nonauditory regions, such as the amygdala, and the frontal, parietal, and temporal lobes (Malmierca & Merchan, 2004). The Te2 in particular sends major projections to the DCIC and ECIC (Herbert et al., 1991)

1.4. Neurophysiology and Function of the IC

1.4.1. Function of the IC

The inferior colliculus is a major sound processing centre. It is capable of processing temporal, spectral, and spatial auditory information. Damage to this structure in human subjects often results in difficulties recognizing sound patterns, sound locations, and words under competing interference from other sounds (Champoux et al., 2007; Johkura et al., 1998). Depending on the extent of damage, it may cause central hearing loss as well (Hoistad & Hain, 2003). These impacts indicate an important role played by the IC in speech processing. It is also implicated in the control of defensive reactions to sounds, such as auditory-conditioned fear responses (Brandao et al., 1993; Goff & Wine, 1997; Heldt & Falls, 2003, Malmierca & Merchan, 2004).

1.4.2. Neurophysiological Characteristics of IC Neurons

1.4.2.1. Temporal Firing Patterns of IC Neurons

Neurons within the IC display several patterns of firing in response to tone burst stimulation. Four of which are particularly important: the onset, pauser, primary-like, and bursting/chopping patterns. Onset, pauser, and primary-like patterns in the IC are similar to other patterns described in auditory structures lower in the pathway. Onset firing is characterized by a single, or multiple short bursts of APs at the sound's onset. Onset patterns are also described as being "transient" (Moore & Irvine, 1980; Chot et al., 2019). Pauser firing have a short activity burst at the beginning of stimulation, a pause, then continual activity less than the initial burst until stimulation offset (Chot et al., 2019; Moore & Irvine, 1980). Primary-like firing patterns begin with strong initial activity which steadily declines until stimulus offset. Bursting/chopper firing

begins at stimulus onset, and shows multiple bursts of APs separated by pauses until stimulus offset. Pauser, primary-like, and bursting/chopper patterns are described as “sustained” patterns (Chot et al., 2019, 2020; Moore & Irvine, 1980), Other patterns have also been described in the IC to a lesser extent. Such patterns include; buildup/late firing patterns, which begin firing after a long pause at the stimulus onset and continues until offset, and fast-adapting firing characterized by a strong onset response which decreases in strength and discontinues before stimulus offset (Malmierca & Merchan, 2004).

1.4.2.2. Frequency Sensitivities of IC Neurons

Each neuron within the IC has a spectral range of the frequencies which it responds to, among these frequencies is the characteristic frequency (CF) to which the neuron is most sensitive. A frequency tuning curve (FTC) can be used to graph the spectral range of a neuron, created by plotting the lowest level of stimulation required to generate an AP at that frequency against the frequency of the sound. At the CF, a neuron displays lowest threshold for generating APs. FTCs can show many shapes. V-shaped FTCs are the most common in studies run on the bat IC, an example of this shape is shown in figure 4 (Casseday & Covey, 1992).

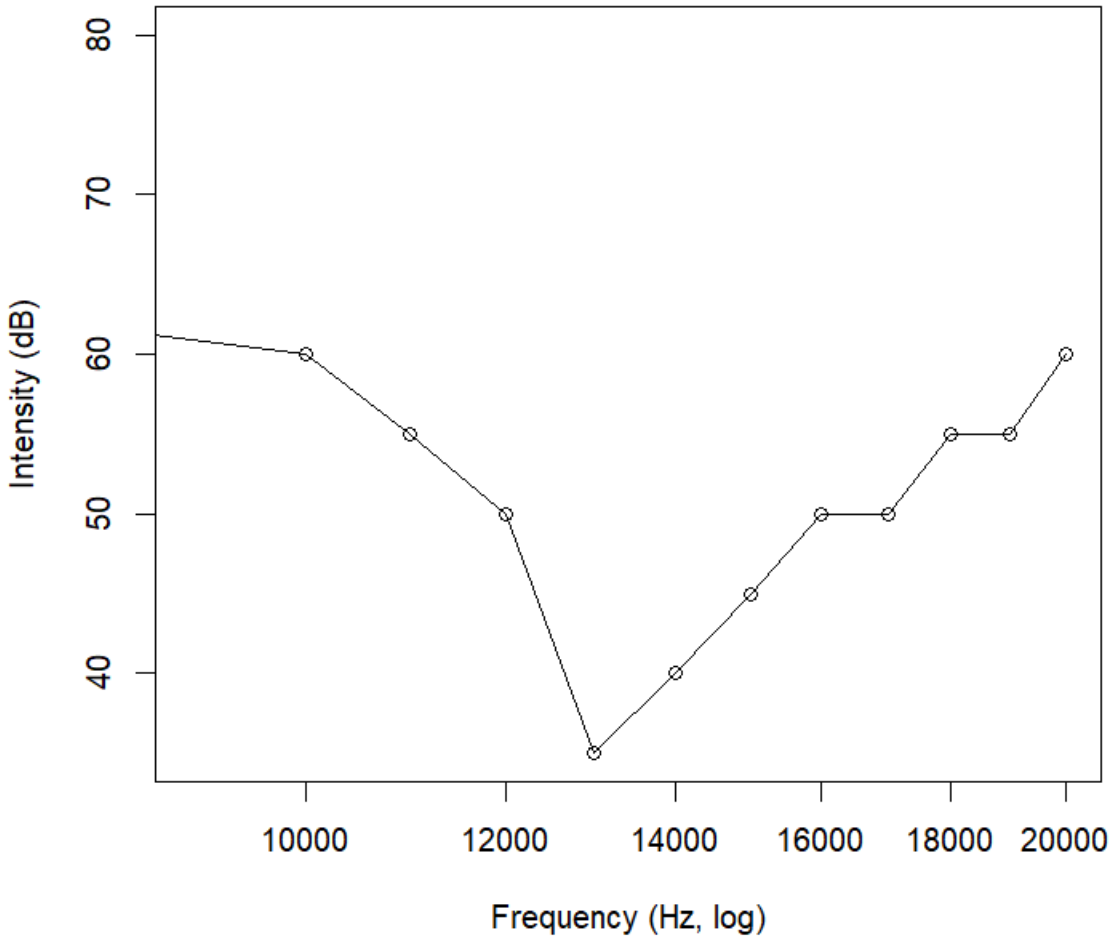


Figure 4. Example FTC. An example of an FTC obtained from the neuron ST20190730_5. The CF for this particular neuron is 13,000 Hz, while the minimum threshold of intensity is 35 dB.

The FTC of an IC neuron is primarily determined by the excitatory inputs received by the neuron, although it's also shaped by inhibitory inputs. Side-band inhibition occurs when sounds of a frequency outside of the neuron's spectral range cause inhibition of the neuron in response to a sound at CF. A two-tone stimulus paradigm can be used to evaluate side-band inhibition. To do

such an evaluation, a “probe tone” is presented at a neuron’s CF at 10dB above the threshold at CF. A “test tone” at a frequency outside the neuron’s spectral range is presented simultaneously to change the rate of action potential firing elicited by the “probe tone”. A reduction in action potential firing indicates side-band inhibition. By changing the frequency and intensity of the test tone, one is able to find the frequency and intensity range of the test tone’s effect. The range of frequencies over which the test tone is able to cause inhibition is called the “inhibitory side-band”, as a result excitatory FTCs are often flanked by inhibitory side-bands of low and high frequencies (Grecova et al., 2009; Casseday & Covey, 1994).

Two-tone suppression is more noticeable at stimuli of low intensities. Several studies indicate that side-band inhibition is mediated by GABAa and glycine in several species, as application of agonists such as bicuculline and strychnine result in a change in the shape of IC neuron FTCs (Zhang et al., 1999; LeBeau et al., 1996).

1.4.2.3. Sensitivities of IC Neurons to Binaural Cues

1.4.2.3.1. Directional Dependence of Responses of IC Neurons to Sounds

The strength of an IC neuron’s response to a stimulus is dependent on the direction from which the stimulus originates. Studies of directional dependence often rely on free-field stimulation, in which sounds are presented to the subject through a set of loudspeakers placed in different location, to better simulate the natural environment of the model animal. Such studies have shown that neurons of the IC which are sensitive to frequencies between 0.5 and 4kHz are often the most sensitive to directional cues (Leiman & Hafter, 1972). Those which are most sensitive

to sounds presented at the midsagittal plane are thought to help guide movement of the head, ears, and eyes towards a sound source. Despite this, IC neurons are not known to be topographically organized by their sensitivity to location.

In studies of the cat IC, it has been found that the size of the receptive field of a neuron is related to the neuron's CF (Semple et al., 1983). Neurons having a low CF are receptive to sounds in all directions, while those having a high CF have smaller fields which favour the contralateral side. This may be due to the influence of the contralateral pinna on the receptive fields of neurons, as cats are able to aim their ears in different directions, rather than processes occurring within the auditory pathway. Studies of the frog IC reveal a directional dependence in the frequency tuning of their neurons. FTC graphs appear to narrow when a sound is presented ipsilateral to the recorded IC neuron, rather than contralateral to it (Gooler et al., 1996, Shinn-Cunningham et al., 2005). It is thought that this directional dependence is reliant on GABAergic inputs, at application of bicuculline to the studied area results in a reduction of the effect direction has on the neurons' response (Zhang et al., 1999). Some animals have an internal auditory space map within their IC, as is the case with owls. Damage to this area is found to impact head turns and sound localization (Wagner, 1993).

1.4.2.3.2. Sensitivities of IC Neurons to Interaural Level and Time Differences

Sound in an environment has to travel before reaching an organism. Depending on the location where a sound is presented in reference to the head, the sound can reach the organism's two ears at two different times, and with two different intensities. The differences in time and level

between the two ears when the sound is received by the ears are called the interaural time difference (ITD) and the interaural level difference (ILD). These differences are major cues used in the localization of sound. Dichotic stimuli, namely two independently controlled stimuli presented separately at the two ears, can be used to mimic sounds from different spatial locations to study how directional information of a sound is processed by neurons.

Studies of this nature show that neurons sensitive to low frequencies in the IC tend to have more responsibility for the processing of ITDs. Rats, being relatively small animals, have correspondingly small heads, the distance between their two ears is negligible. Therefore, the ITD between the left and right ears is a less reliable cue than the ILD between the two ears. While some rat IC neurons are still capable of detecting ITDs, ILDs present the main cue for spatial location in the rat IC. Those neurons which can detect ITDs are excited by both ipsilateral and contralateral stimulation, simultaneous stimulation of both ears tends to enhance responses in these neurons (Chot et al., 2020). Sound pressure level is often higher, and therefore louder, at the ear closest to the sound, rather than the ear farthest away. Dichotic studies show that neurons sensitive to ILDs tend to be more sensitive to high frequency sounds, as well (Davis et al., 1999). IC neurons tend to be excited by contralateral stimulation and inhibited by ipsilateral stimulation (Gooler et al., 1996; Wenstrup et al., 1988; Zhang & Kelly, 2010).

As the IC is a major binaural processing centre, receiving inputs from both the right and left auditory pathways, the LSO, MSO, and DNLL of both sides, as well as the opposite IC are involved in ILD and ITD processing (Koch & Grothe, 2003; Oertel, 1999). Studies making use

of dichotic stimuli observed that IC neurons having onset response patterns were less sensitive to ILDs. Additionally, those neurons which are ILD-sensitive tend to have varying inhibitory thresholds. (Moore & Irvine, 1980; Wenstrup et al., 1988). Some IC neurons require an ipsilateral sound to be of a certain level of intensity in order to have an effect on the contralateral response, while others can be suppressed at ipsilateral sounds of even 15dB less than the contralateral sound. It is thought that ILD-responsive neurons have a narrow range of intensities at which suppression is activated (Wenstrup et al., 1988), although the sensitivity of these neurons to ILDs can change.

Often, neurons in the IC show different degrees of binaural interaction during the late and early periods of their response. For many neurons, binaural inhibition is stronger during the late rather than the early period of stimulation. This phenomenon may be partly due to time courses of neurotransmission between inputs and IC neurons.

1.4.2.4. Responses of Neurons in the IC to Two or More Sounds

Integration of a large number of inputs from both the left and the right auditory pathway enables the IC to process multiple complex sounds with different sound qualities occurring at different time and locations. Oftentimes, different sounds affect one another in generating responses. Several studies have been performed to examine the interaction between two or more sounds under various conditions of timing, location, frequency, and intensity. Studies performed previously in the Zhang lab examined how responses to two recurring sounds were dependent on frequency difference, temporal and spatial relationships between the sounds, and sound

"novelty". A train of stimuli made of two tone bursts at different frequencies were used to elicit APs in the IC. Stimuli in the train were presented at a constant rate, with the rate of presentation (which reflects one aspect of the timing of sounds) being controlled by an experimenter. These sounds were presented either at equal probabilities to simulate two independently occurring sounds (Chot et al., 2019), or at different probabilities to mimic a "novel sound" (i.e., a low probability sound) interlaced with a "standard sound" (i.e., a high probability sound) (Chot et al., 2020). These studies found that relocating one sound from the contralateral ear to another location reduced the response to the sound. Meanwhile, it enhanced neural responses to the other sound, which had a fixed location at the contralateral ear. This was especially true when the sound with a fixed location was of low probability. The enhancement was moderate when the two sounds had equal probabilities and was lessened when the sound with a fixed location was of higher probability. These results suggest that a stronger suppressive aftereffect was generated when both sounds were colocalized at the contralateral ear (Chot et al., 2020). The effect of spatial separation on neural responses to the two sounds was particularly significant in neurons with transient firing.

Some studies were conducted using a pair of sounds. In some IC neurons, it was found that stimulation of the ipsilateral ear can generate an "inhibitory aftereffect" to suppress the response to a subsequent contralaterally presented stimulus (Zhang & Kelly, 2009). In other neurons, stimulation of the ipsilateral ear can generate an "excitatory aftereffect" to enhance the response to a subsequent contralaterally presented stimulus. The aftereffect generated by a sound is also evaluated in populations of neurons by recording local-field potentials in the IC. Results indicate

that under stimulation by two sounds that are presented in a fee-acoustic field, a leading sound can also generate a suppressive aftereffect to influence the response to a trailing sound. Temporal and spatial separations between the two sounds could reduce the suppressive effect produced by the leading sound (Asim et al., 2020).

1.5. Potential Mechanisms that Can Contribute to the Inhibitory Aftereffect by a Priming Sound in the IC

There are many possible mechanisms that can lead to the suppressive aftereffect observed in IC neurons. One major factor is the influence of inputs on neurons in the structure. Most of the IC's neurons are inhibited by inputs originating ipsilateral to the IC, and excited by inputs originating contralateral to the IC. Among these inhibitory ipsilateral inputs are those which arise from the DNLL (Li & Kelly, 1992; Burger & Pollak, 2001). However, the DNLL alone is not capable of producing the degree of suppression observed in the IC. Many contralateral inputs have a suppressive effect as well, such as those associated with the SPON (Saldana & Berrebi, 2000). The SPON sends inhibitory projections to the IC at the offset of a sound after it is initially excited by contralateral pathways. It is thought possible that this offset inhibition may contribute to the suppressive aftereffect in the IC, as changing the location of the priming sound to the ipsilateral ear reduces the suppressive aftereffect (Salimi et al., 2017).

Another mechanism that may contribute to the suppressive aftereffect in the IC is adaptation. Many types of firing patterns have been observed in the IC in response to a sound. A neuron can show different strengths of firing over the early and late periods of stimulation. It is possible that

the change is due to reduced availability of local neurotransmitters. Such reduction can lead to adaptation of a postsynaptic neuron.

Pharmacological manipulation experiments have shown that suppression in the IC is largely dependent on local $GABA_A$ and glycine-mediated inhibition. In some studies, presenting the priming sound of a priming-testing pair contralaterally results in very strong inhibition at the IC level, however, upon changing the location of the priming sound to the ipsilateral ear, suppression of the testing sound is reduced and the IC regains full strength of firing. Changing the location of the sound reduces the amount of excitation occurring, as well as the level of the neurons' adaptation. This leads to less suppression of the following sound. Adaptation may be combined with the inheritance of suppressive inputs, as neurons in lower structures such as the LSO and SPON may become adapted to stimulation, and cease sending signals to the IC, rather than IC neurons themselves adapting to continuous stimulation.

1.6. Hypothesis and the Data Set Obtained Previously in the Laboratory

Based on existing results, it was hypothesized that a sound could suppress the response to another sound in individual IC neurons. Such an effect could be particularly strong when the two sounds were colocalized at the contralateral ear, and would be reduced when the two sounds were separated spatially and temporally. A temporal separation could be caused by making the sound that would generate a suppressive effect (i.e., a priming sound) lead the other sound (i.e., a testing sound) by an interval of a few milliseconds. A spatial separation could be caused by relocation of the priming sound to a different horizontal position.

Neurophysiological experiments were carried out by a previous student, Sarah Tran, in the Zhang laboratory to verify the above hypothesis. A glass micropipette electrode was used to record action potential firing extracellularly from individual IC neurons. The firing was elicited by pairs of priming-testing sounds. It is well understood that action potentials generated by a well isolated neuron should have similar waveforms (including amplitudes), and that such waveforms should not change over time. However, a careful examination revealed that the many neurons in the obtained dataset had large variations in waveform during a single recording trial, and across recording trials. Such variations made it necessary to further analyze the data set before a reliable scientific conclusion could be reached.

It is well established that action potential waveforms recorded extracellularly are different from those recorded intracellularly owing to a difference in the location of the recording electrode (outside vs. inside a neuron's cell membrane). The electrical signals recorded extracellularly by an electrode can be dependent on the number of neurons nearby the electrode, the spatial relationship between the recording electrode and individual neurons, and changes in the condition of neurons. A recording electrode located farther from a neuron will receive a weaker signal, while a recording electrode located nearer to a neuron will receive a stronger signal. During a prolonged period of recording, changes in the location of a recording electrode in relation to the brain can happen due to the physical characteristics of the brain. Such changes can affect the neural activity recorded by the electrode.

Sometimes, such changes can even lead to damage of a neuron that is being recorded, causing K+ ions to leak out of the neuron, and Na+ ions to leak in. Such leakages could affect both the rate of action potential firing and the amplitude of action potentials. Preliminary examination revealed that data previously obtained by Sarah Tran included those from neurons that experienced "rundown" (deterioration of condition and change of electrical activities). Some recordings were affected by electrical interference form the environment. Such factors could greatly affect scientific conclusions. Thus, reanalysis was required to identify which recordings were of high quality and which recordings were to be eliminated from further analysis. This reanalysis can ensure that a reliable scientific conclusion was obtained.

1.7. Specific Objectives of This Thesis

The primary goal of this thesis is to reanalyze a data set previously obtained by former graduate student Sarah Tran concerning the effects of spatial and temporal separation between two sounds on responses of individual IC neurons to the sounds. Reanalysis will focus on the isolation of single neurons' APs based on the shapes of their waveforms.

2. MATERIALS AND METHODS

2.1. Data Collection Methods

2.1.1. Experimental Subjects and Preparatory Procedures

This experiment was performed using 150-750 g adult male Wistar albino rats sourced from Charles River Canada Inc. (St. Constant, QC). Prior to experimentation, the animals were housed in the University of Windsor's central animal care facility, and quarantined for 5 days before an

experiment. Rats were kept in an environment maintaining a 25 °C temperature, 40-60% humidity, a 55-60 dB noise level, and 12 hour day/night cycles with food and water available at all times.

Animals were subjected to a clap test upon arrival in the lab, with reaction to the clapping sound indicating normal hearing and no major auditory deficiencies. Anaesthesia was administered initially using intramuscular injection of ketamine hydrochloride (60mg/kg), and xylazine hydrochloride (10mg/kg). Supplementary injections of ketamine hydrochloride and xylazine hydrochloride were provided to maintain anaesthesia every 40-60 minutes at 20mg/kg and 3.3 mg/kg doses, respectively. Intramuscular injection of atropine at a 3.3 mg/kg done was used to treat any breathing issues during the experiment. Proper anaesthesia was confirmed using toe and tail pinch tests.

A midline incision was made in the scalp. The scalp and muscle were retracted, and a headbar was cemented onto the skull using three bone screws fixed to the skull. The headbar helped keep head position constant throughout the experiment. A craniotomy with a diameter of about 3 mm was performed 4 mm laterally and 0.4 mm rostrally in reference to the lambda point. Once the surface of the brain was exposed, the dura and pia maters were removed.
The rat was placed in a model CL-15ALP auditory chamber (Eckel industries, Morrisburg, ON). A single barrel glass micropipette (tip diameter ~1.5mu) loaded with 3% chicago sky blue dye in 0.5M sodium acetate (impedance ~1Mohm) was lowered through the craniotomy into the IC (depth 2200-6000 μm from the surface of the brain) using a model 650 micropositioner (Kopf Instruments, Tujunga, CA). The micropositioner was mounted onto a model 900 stereotaxic

instrument (Kopf Instruments, Tujunga, CA). The electrode was aligned along the coronal plane, at a 30° angle in reference to the midsagittal plane. Experimental procedures were approved by the University of Windsor animal care committee in accordance with the guidelines of the Canadian Council on Animal Care.

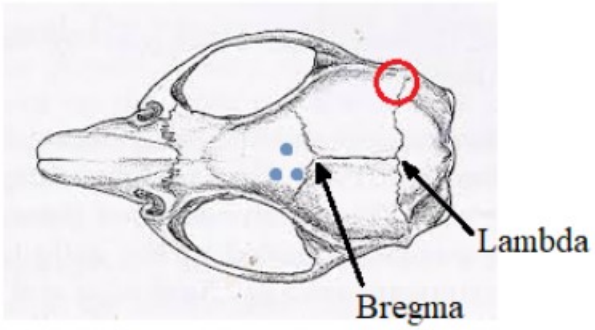


Figure 5. Schematic diagram showing the location of a craniotomy. The red circle indicates the location of the craniotomy. The three dots next to the bregma indicate the location of the three bone screws.

2.1.2. Acoustic Stimulation

Sounds were generated using a system 3 real-time signal processing system (TDT; Alachua, FL), controlled by the OpenEx software (TDT, Alachua, FL) running on a PC computer. Two model FF1 free-field speakers (TDT, Alachua, FL) were mounted within an acoustic chamber. The speakers were 50cm from the midpoint of a rat's interaural line. Instruments within the recording chamber were placed so as to minimize acoustic interference.

Each speaker was calibrated with the SigCalRP61 software (TDT, Alachua, FL) and an ACO pacific condenser microphone (Belmont, CA) within a frequency range between 0.1 and 40 kHz. Calibration was conducted when the speakers were at each of the 5 azimuths used in the present

study. They included directly in front of the contralateral ear (c90°), directly in front of the ipsilateral ear (i90°), the front midline (0°), at a 45 degree angle from the contralateral ear (c45°), and at a 45 degree angle from the ipsilateral ear (i45°) (Fig. 6).

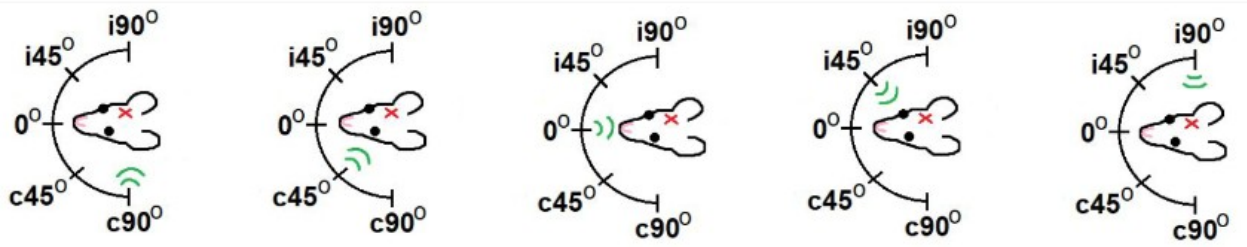


Figure 6. Schematic diagrams showing locations where a sound (green) will be presented. A cross symbol indicates the location of recording.

2.1.3. Neurophysiological Recording

A recording electrode was inserted into the brain tissue while Gaussian noise bursts were presented from a speaker at the contralateral ear. These noise bursts were presented at 60 dB SPL at a rate at 4 /sec. Neural signals collected by the recording electrode were amplified by 1,000 times using a 2400A Dagan preamp (Minneapolis, MN) and sampled at 24.4 kHz using the System 3 Real-time Signal Processing System. The signals were band-pass filtered (lower cut-off at 30 Hz and high cut-off at 30 kHz. The signals were monitored audio-visually.

Upon isolation of a neuron, tone bursts of various frequencies and intensities were presented to determine the frequency tuning curve (FTC, a response threshold vs. sound frequency relationship) of the neuron. The neuron's characteristic frequency (CF, the frequency at which

the neuron displayed the lowest threshold) and the minimum threshold (MT, the threshold at the CF) were determined. The threshold was set at the lowest intensity that was required to generate APs over at least 5 of 20 tone burst presentations.

A pair of priming and testing tone bursts were generated based on the CF and the MT of the neuron. The frequency of the testing tone was set at the CF, while the frequency of the priming tone was either above or below the CF (named as f_L and f_H, respectively). The centre frequency of f_L and f_H was at CF (i.e., $\sqrt{f_L \times f_H}$=CF), while the difference between f_L and f_H was 10% of the CF (i.e., $\frac{f_H - f_L}{\sqrt{f_H \times f_L}} = 0.1$). Priming and testing tone bursts were presented with the same intensity, between 10 and 30 dB above the MT. The two sounds both had a total duration of 100ms (5 ms rise/fall, 90 ms plateau).

Priming-testing tone bursts were presented either simultaneously, or with the priming sound leading the testing sound. The testing sound was presented at a fixed location at the c90° azimuth. The priming sound was either colocalized with the testing sound at c90°, or separated from the testing sound (i.e., at one of the four non-c90° azimuths). At each angle of spatial separation, priming-testing tone bursts were presented at various inter-stimulus intervals (ISIs, 0, 25, 50, 75, 100, 150, 200, 250, 500, 750, and 1000 ms). The delay between the offset of a testing sound and the onset of the following priming sound was 1000 ms. Under each of the 55 conditions of temporo-spatial separation, a pair of priming-testing sounds were presented 20 times. Neural activities recorded over the 20 presentations of sound pairs were averaged. Neural responses to a priming sound presented alone at each of the 5 azimuths and the response to a testing sound presented alone at c90° were also recorded. These responses were used as

references in the evaluation of how the priming and testing sounds affected each other in generating responses.

2.2. Data Analysis

The major focus of the present thesis was to reanalyze data obtained by a previous graduate student, Sarah Tran, by isolating action potentials generated by only single auditory neurons.

2.2.1. Isolation of Action Potential Firing Generated by Single Neurons

Neurophysiological signals recorded from the IC were sorted using the OpenSorter application of the OpenEx software package (TDT, Alachua, FL) to isolate action potentials generated by single neurons (see Section 2.1.3. for the protocol of recording from a neuron).

Despite intending to obtain signals from a single IC neuron, many traces of recordings contained signals not originating in the neuron of interest. These unwanted signals include APs generated by other neurons, and interference signals of origins other than neurons (see Fig. 7 for example, white traces are unwanted signals). For many recording sessions, waveforms changed their amplitudes over the duration of a session. Signals obtained in each recording session were sorted, so that APs generated by a single neuron (with consistent amplitude and waveforms) were isolated from other interfering signals.

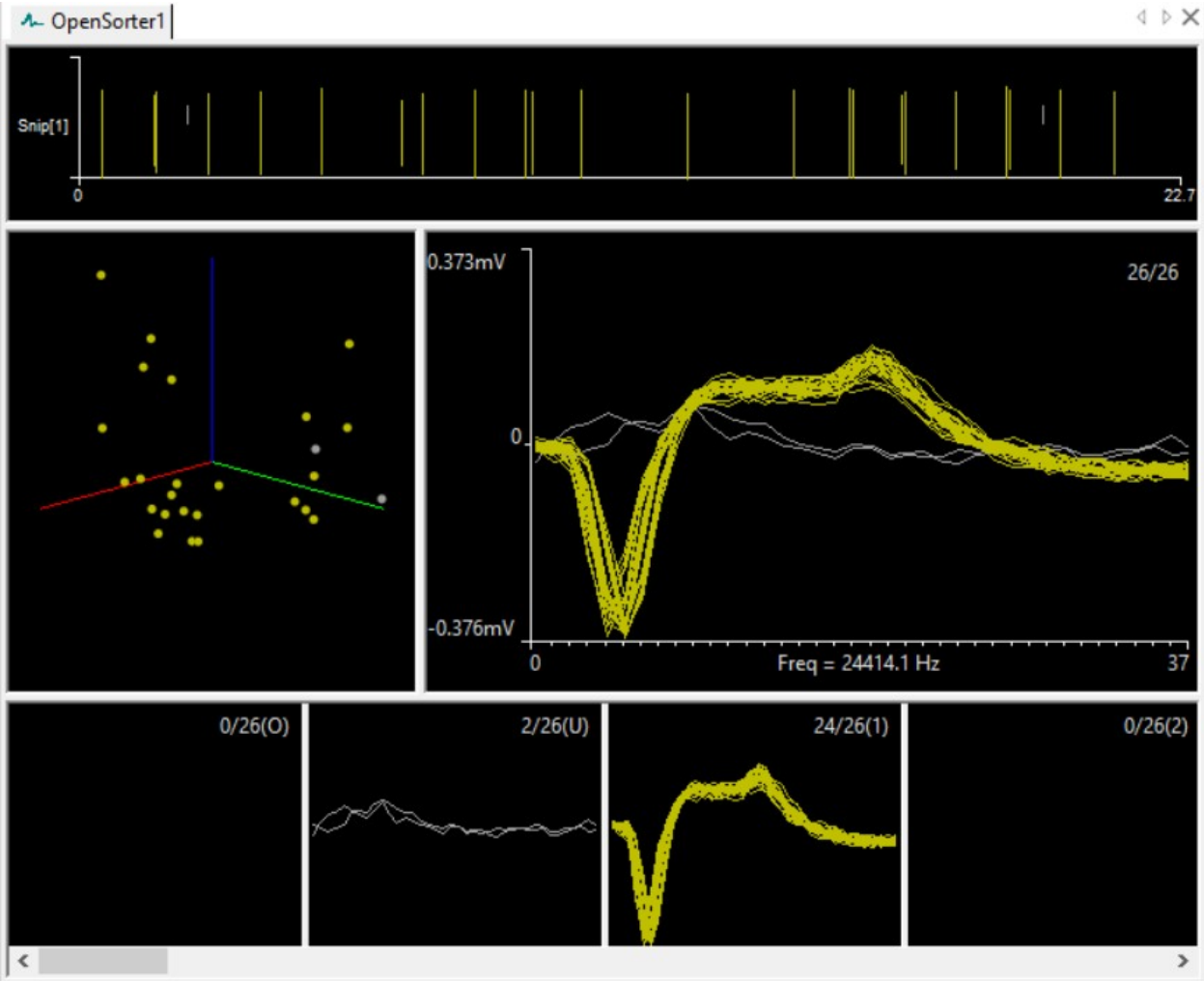


Figure 7. An example of a neuron sorted with OpenSorter. This example is taken from neuron ST20181224_1. Waveforms that will be included in the analysis are shown in yellow, while waveforms that will be discarded are shown in grey.

Within each recording trial, only spiking waveforms that displayed the largest amplitudes and consistent shapes were considered APs generated by a neuron near the recording electrode, which was the neuron of interest (yellow traces in Fig. 7). These waveforms were retained in this analysis. All other waveforms (white traces in Fig. 7) were sorted out. Across different trials of

recording, any change of 50% or greater in the amplitude of AP from the neurons of interest (Re: amplitude of AP generated at the beginning of a recording session) was considered to indicate a change in the condition of the recorded neuron. For data collected over the entire session of recording, those from the first trial showing such a change and those from subsequent recording trials were removed from further analysis.

A manual spike sorting method was used in this thesis's sorting process. Such a method uses a "detection threshold" and various spiking selection tools to include/exclude waveforms (Fig. 8).

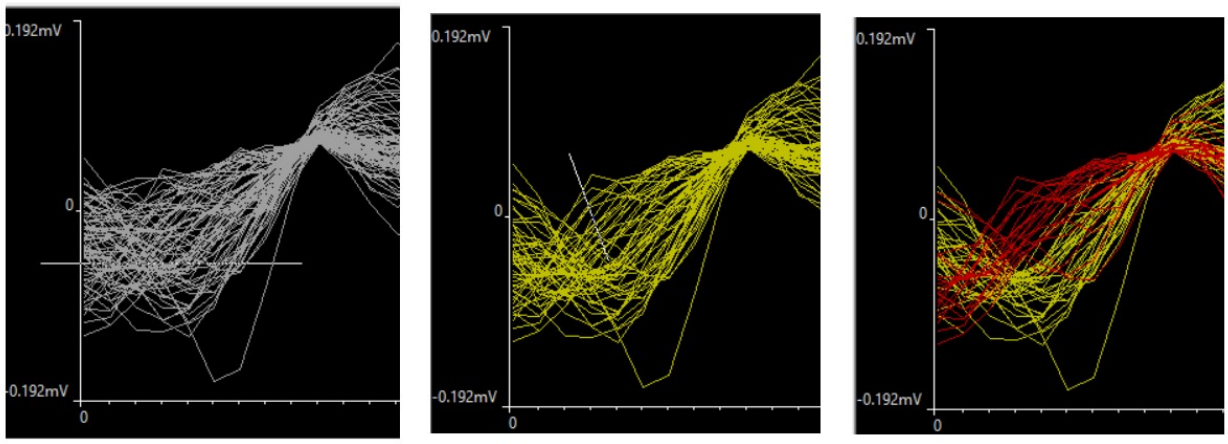


Figure 8. Demonstration of the OpenSorter Snip tool used to isolate AP waveforms. This example shows the process of establishing a detection threshold, then removing nonconforming AP waveforms on a recording taken from neuron ST20181224_1.

2.2.2. Analysis of Results from Individual Neurons and the Entire Group

After sorting of spike waveforms using OpenSorter, data were exported into a CSV file using OpenBrowser (TDT, Alachua, FL). CSV files obtained from each neuron under different conditions of stimulation were further analyzed using the programming language "R" (The R Foundation).

Under each condition of stimulation (lone priming sound, lone testing sound, or paired priming and testing sounds), APs collected over 20 trials were used to create a post-stimulus time histogram (PSTH, see Figs. 10, 12, and 15 for examples). A 5-ms bin width was used to make these PSTHs. The strength of firing of a neuron elicited by a sound (either a lone priming or a testing sound, or a priming or a testing sound that did not temporally overlap with another sound) was evaluated using all the APs collected over a 150 ms period starting from the onset of the sound. The strength of firing elicited by a pair of simultaneously presented priming-testing sounds was evaluated using all the APs collected over a 150 ms period starting from the onset of the sound.

Responses elicited by a lone priming sound at various azimuths were compared with the response elicited by the sound presented at c90° to evaluate the directional dependence of the response to the sound.

$$NR_{Priming} = N_{Priming}(\theta) / N_{Priming}(c90°)$$

Where $NR_{Priming}$ is a normalized response, while $N_{Priming}$ (θ) and $N_{Priming}$ (c90°) are the numbers of APs elicited by the priming sound at a non-c90° azimuth θ and c90°, respectively.

Responses elicited by a pair of simultaneously presented priming-testing sounds at various angles of separation were compared with the response elicited by the two sounds presented simultaneously and colocalized at c90° to evaluate the separation dependence of the response to the sounds.

$$NR_{Paired} = N_{Paired}(\theta) / N_{Paired}(c90°)$$

Where NR_{Paired} is a normalized response, while $N_{Paired}(\theta)$ and $N_{Paired}(c90°)$ are the numbers of APs elicited by the two sound when they were separated by an angle at θ and when they were colocalized at c90°, respectively.

Responses elicited by a pair of temporally non-overlapping priming-testing sounds (regardless of the spatial relationship between the two sounds were compared with the responses elicited by the two sounds presented alone at c90° to evaluate how temporospatial separation between the two sounds affected the responses to the sounds.

$$NR_{Priming}(\theta, dT) = N_{Priming, paired}(\theta, dT) / N_{Priming}(c90°)$$

$$NR_{Testing} = N_{Testing, paired}(\theta, dT) / N_{Testing}(c90°)$$

Where $NR_{Priming}$ (θ, dT) and $NR_{Testing}$ (θ, dT) are normalized responses to a priming and a testing sound, respectively, when the priming sound was presented at the θ azimuth and the ISI between the two sounds was at dT. $N_{Priming, paired}$ (θ, dT) and $N_{Testing, paired}$ (θ, dT) are the numbers of APs elicited by the priming and testing sounds in a pair, respectively, when the priming sound was presented at the θ azimuth and the ISI between the two sounds was at dT. $N_{Priming, Single}$ (c90°) and

$N_{Testing, single}$ (c90°) are the numbers of APs elicited by lone priming and testing sounds at c90°, respectively.

PSTHs, and graphical representations showing the dependence of sound-elicited responses on the azimuth of a sound, or temporal/spatial separations between the priming and testing sounds were further analyzed using R.

"R" is an open source programming language designed for statistical analysis and graphical representation of data. This software suite was also used to analyze group results to find values such as the mean and the standard error of the mean of a data set. It was also used to obtain lines of regression and results of statistics analysis (including ANOVA tests).

3. RESULTS

Responses elicited by single tone bursts and paired priming-testing tone bursts recorded from 49 neurons in the IC were analyzed.

3.1. Basic Characteristics

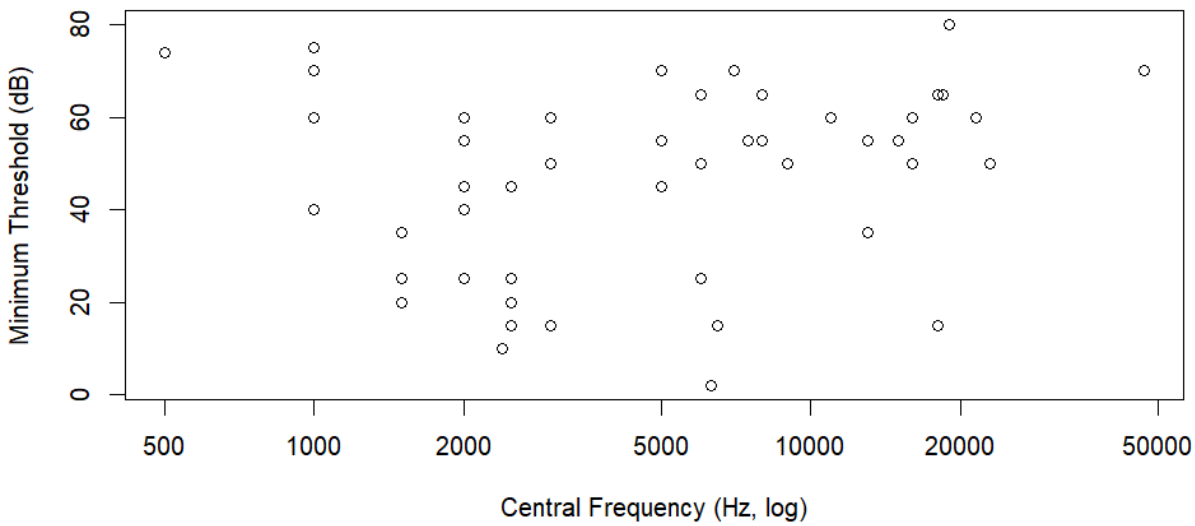


Figure 9. The distribution of Central Frequencies for each neuron observed for this study. Scatter plot depicting the rate of firing recorded in each neuron observed in the present study alongside their minimum intensity thresholds.

As shown in Figure 9, CFs of recorded neurons ranged between 500 and 50000 Hz. The minimum thresholds (MT, the threshold at CF) were between 5 and 80 dB. The distribution of CFs and MTs were above and within the rat's audiogram.

Neurons analyzed in the present study displayed four major patterns of firing. These included onset (n=9), fast-adapting (n=5), primary-like (n=18), and pauser (n=5) patterns. Figure 10 shows PSTHs of four representative neurons. As evident in the figure, neurons with an onset pattern (top panel) displayed strong firing over a brief period (<20 ms) at the onset of sound stimulation. These neurons ceased firing over the remaining duration of stimulation. Neurons

with fast-adapting patterns (second panel) generated strong firing at the onset of a sound, with the rate of firing gradually declining over a period longer than 20 ms. The rate of firing reached 0 before stimulation offset. Primary-like neurons (third panel) displayed strong initial firing at the onset of sound stimulation. The rate of firing gradually declined before it maintained a sustained level over the duration of stimulation. A pauser neuron (bottom panel) displayed stronger initial firing and weaker late firing, which was separated by a brief cessation of firing or 'pause'. Generally, the first two firing patterns (i.e., onset and fast-adapting) were considered to be "transient" types, while the last two firing patterns (i.e., primary-like and pauser) were considered to be "sustained" types.

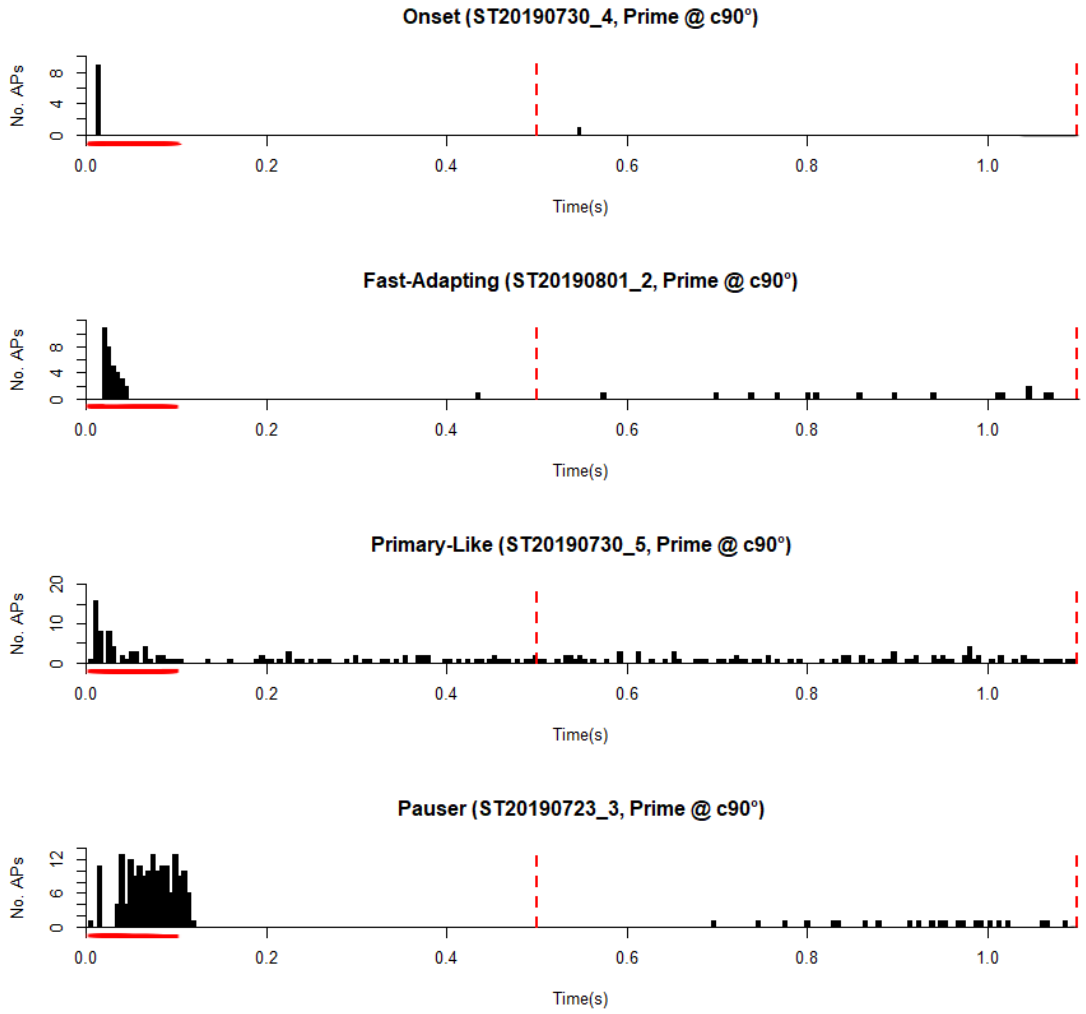


Figure 10. Example PSTHs showing 4 typical firing patterns displayed by neurons in this study. Recordings are from the neurons ST20190703_4, ST20190801_2, ST20190730_5, and ST20190723_3 respectively. Responses were elicited by a lone priming sound at the c90° azimuth. The red horizontal bars along the X-axes of each plot represent the duration of stimulation. Dashed vertical bars at 0.5 & 1.1s represent the time window during which responses are considered "spontaneous firing".

Many neurons generated spontaneous firing in the absence of acoustic stimulation. In the present study, the rate of spontaneous firing was evaluated using APs recorded over a time window beginning at 400 ms after testing sound offset to 1000 ms after testing sound offset. This time window is indicated by the two vertical dashed red lines in figure 10. As shown in Figure 11, the majority of neurons (44 of 49) analyzed in the present study generated spontaneous firing at a rate lower than 8 spikes/sec. Only 2 of 49 neurons fired at a rate higher than 20 spikes/sec. The mean rate of spontaneous firing was 3.6 spikes/sec.

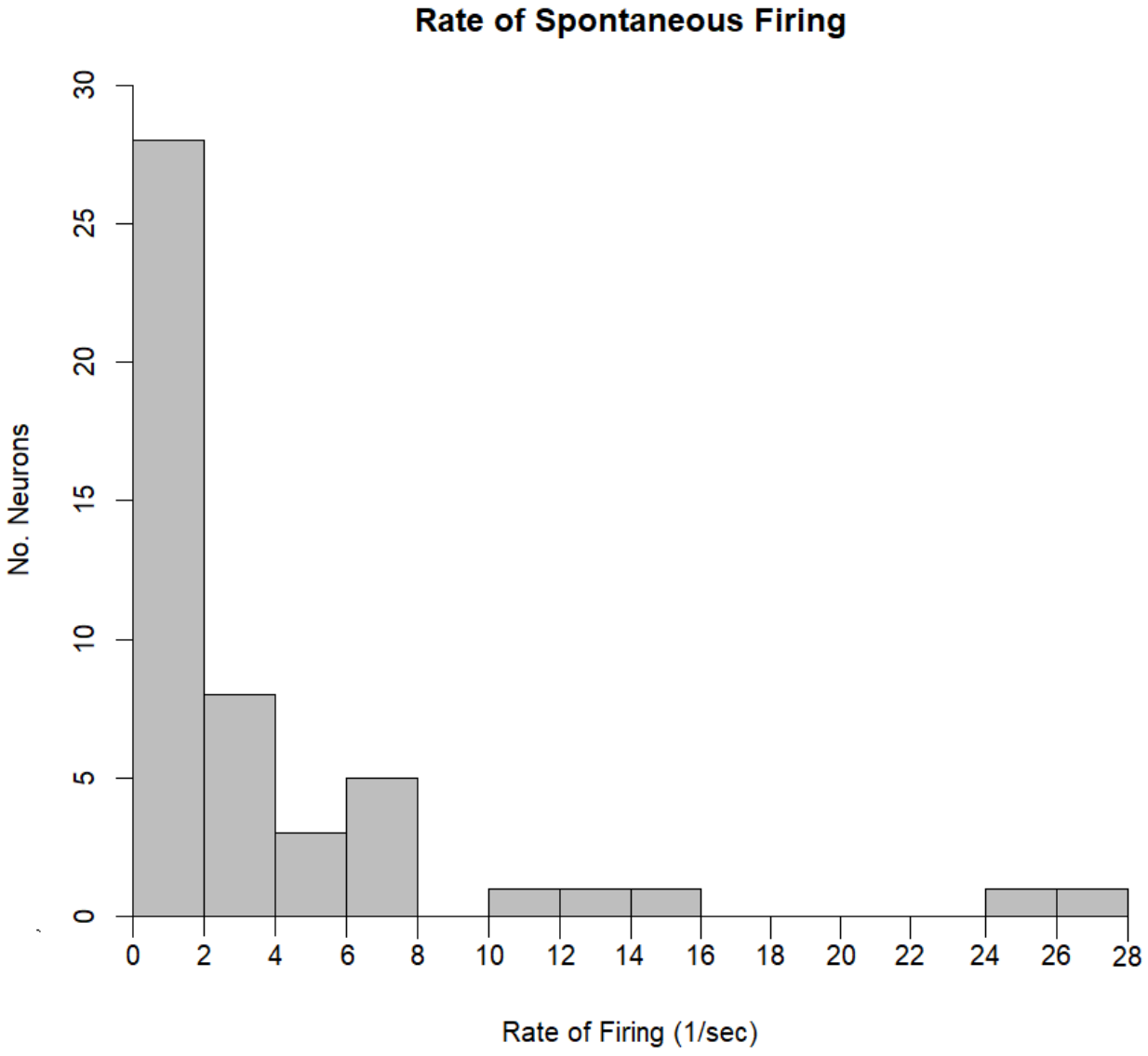


Figure 11. The distribution of spontaneous firing rates within the group of neurons analyzed in this study. "Spontaneous firing" was evaluated within the time window from 0.4 to 1.0 s after offset of stimulation (indicated by 2 vertical red dashed lines in Fig. 10).

3.2. Directional Dependence of Response to a Single Tone Burst

For each neuron observed in this study, the response to a priming sound was recorded when presented at each of 5 azimuths to evaluate the dependence of the response on the direction of the sound.

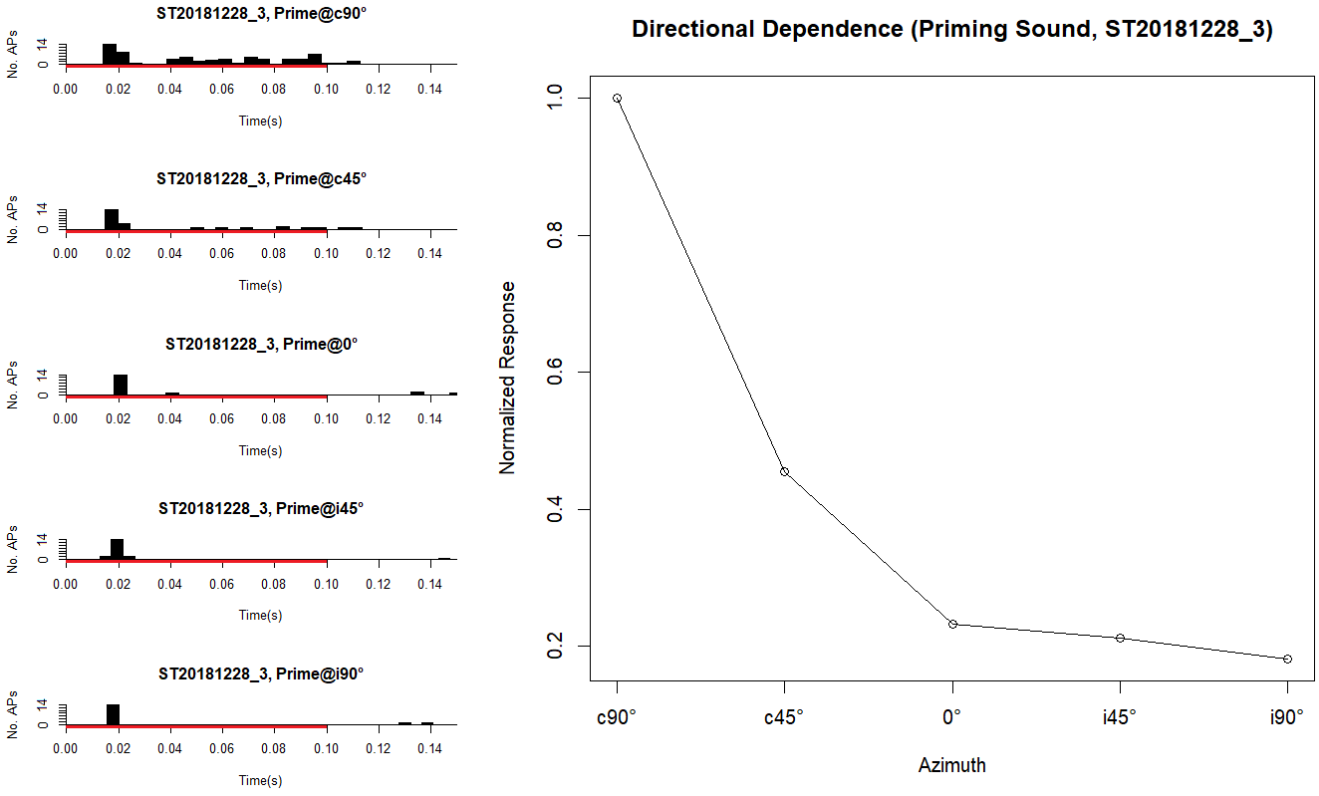


Figure 12. PSTHs and the directional-dependence curve of an example neuron. Recordings were obtained from the ST20181228_3 neuron, and were elicited by a lone priming tone at each

of the 5 azimuths. The red bar along the X-axes of the histograms indicates the duration of stimulation. Responses were normalized against the response to a lone priming tone at c90° for the directional-dependence curve.

Shown in Figure 12 are results from a representative neuron. This neuron generated a pauser firing pattern with a large onset component when a priming sound was presented at the c90° azimuth. The early (onset) firing decreased and late firing disappeared when the sound was relocated from this azimuth. Thus, the overall strength of firing was lower when the sound was at an ipsilateral, rather than contralateral azimuth. The response to the sound at c90° was used as a reference to normalize responses obtained at other azimuths. Resulting normalized responses were used to create a directional dependence curve. This curve indicates that the level of firing gradually decreased as the sound was moved away from the contralateral ear. The shape of the curve displayed by this neuron was classified as a "contra-pass" type.

In addition to neurons showing "contra-pass" directional dependence curves (Figures 12 and 13a), neurons also showed "front-pass" (Figure 13b), "front-suppress" (Figure 13c), and other (Figure 13d) curve types. Generally, a neuron with a "contra-pass" curve (19 of 36 in the present study) generated the strongest firing when a sound was presented at the c90° azimuth. The firing gradually reduced when the sound was moved away from this azimuth, with the maximum reduction being larger than 50%. A neuron with a "front-pass" curve (7 of 36 in the present study) generated stronger firing when a sound was at one of the three frontal azimuths (c45°, 0°, and i45°). The maximum rate of firing was at least 50% larger than those at c90° and i90°. A neuron with a "front-suppress" curve (3 of 36 in the present study) generated the weakest response when a sound was presented at one of the three frontal azimuths (c45°, 0°, and i45°) oriented towards the midline of the head, in comparison to those elicited by sounds at c90° and

i90°. Directional dependence curves having shapes not corresponding to any of the above three categories were classified as “other” (7 of 36 in the present study).

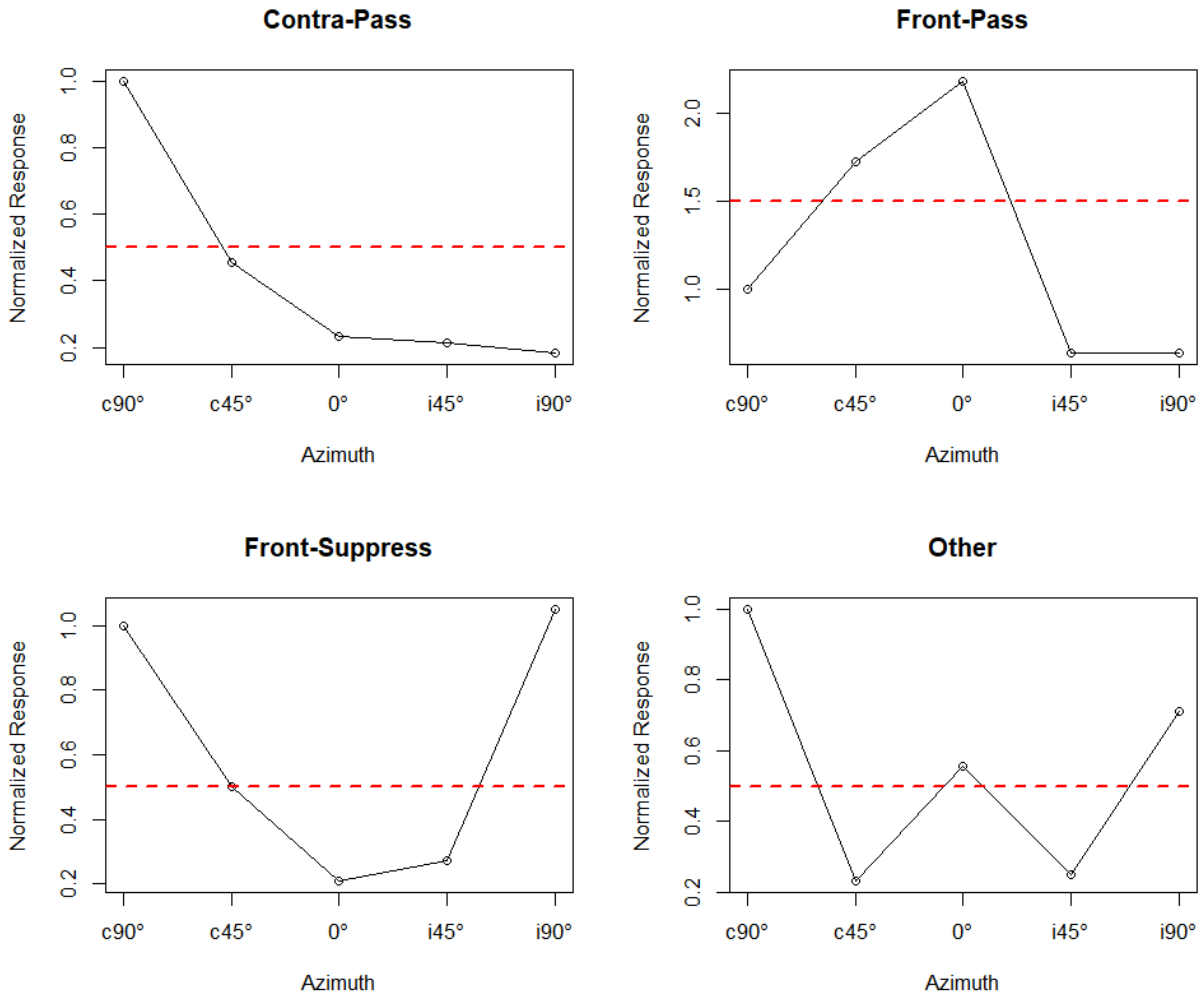


Figure 13. Example directional-dependence curves displayed by neurons analyzed in the present study. Results were obtained from the ST20181218_3 (13a), ST20190528_2 (13b), ST20190723_3 (13c), and ST20190118_3 (13d) neurons (left-right, top-bottom), respectively. Each curve was created by using responses to a lone priming tone presented at five different

azimuths. A dashed red line indicates 50% decrease or increase (compared to the response elicited by the sound at c90°), which is used as a threshold level of change in response.

Despite a diversity in shape of directional dependence curves, neurons analyzed in the present study displayed weaker firing when a priming sound was at i90° than when at c90° (Figure 14). However, the change was not statistically significant (ANOVA test, $F = 1.5$, $p = 0.2$)

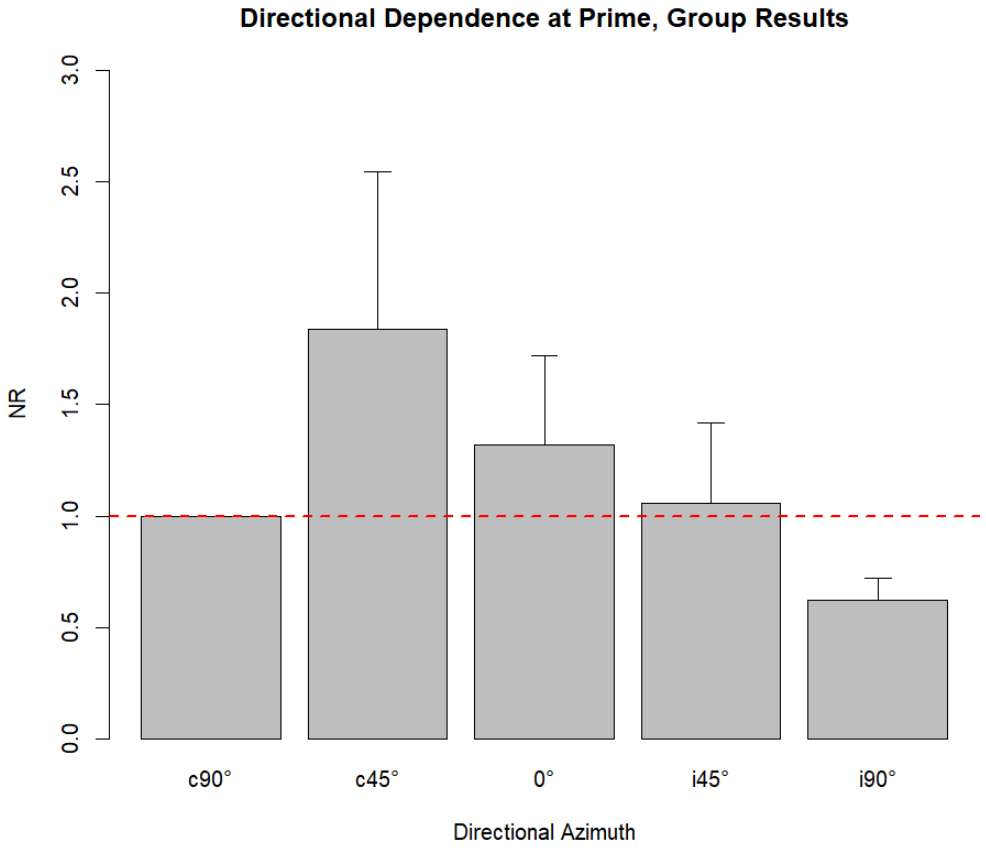


Figure 14. Group results showing the mean normalized response at each of the 5 azimuths. Responses were elicited by a lone priming sound at each of the indicated azimuths over a 0 –

150ms time window from onset of sound stimulation. The red dashed horizontal bar represents the normalized response to a priming tone at c90°.

3.3. Responses of IC Neurons to a Pair of Simultaneously Presented Priming-Testing Sounds

A pair of priming-testing sounds were used to evaluate whether the response to a testing sound presented at c90° was affected by a simultaneously presented priming sound, and whether the effect was dependent on the direction of the priming sound. Figure 15 shows results from an example neuron. This neuron generated its strongest response when a priming and a testing sound were colocalized at c90°. When the priming sound was moved away from c90°, response to the sounds decreased. The response trended slightly upwards when the priming sound was moved further away from the contralateral ear.

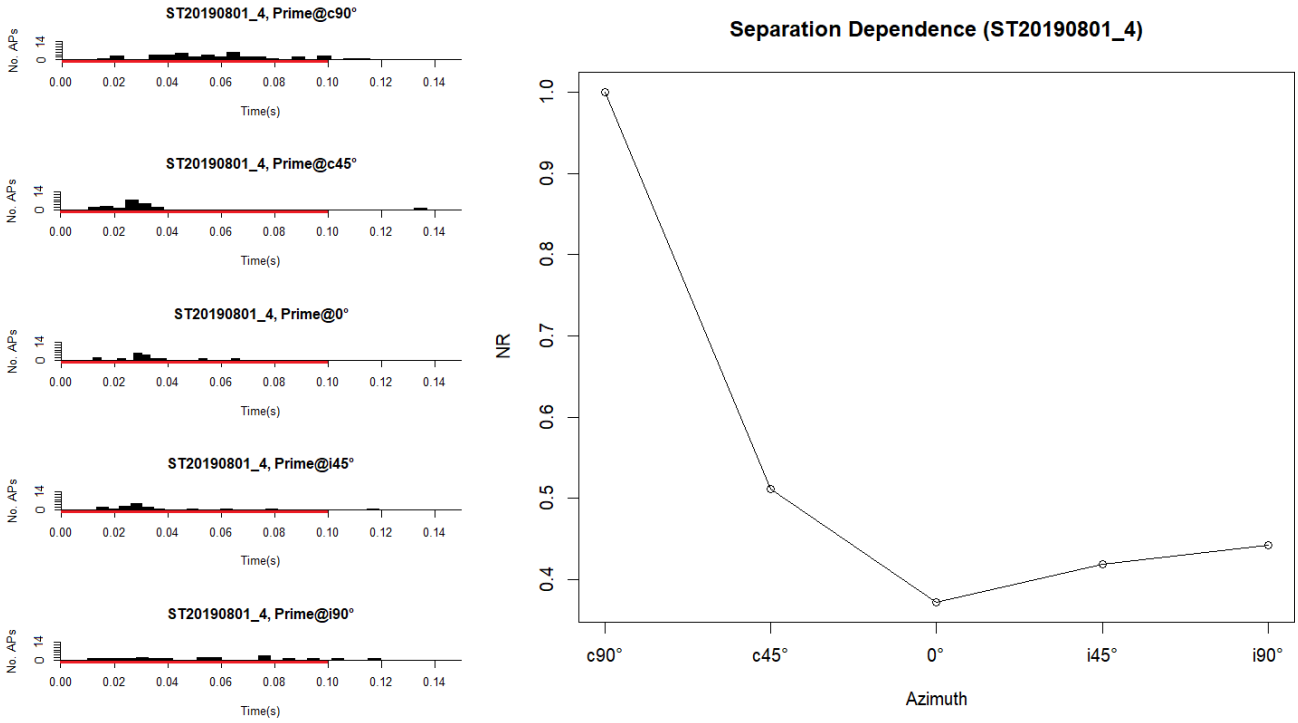


Figure 15. Example PSTHs and a separation-dependence curve showing that moving a priming sound away from a simultaneously presented testing sound that had a fixed location at c90° affected the response to the two sounds. Recordings were from neuron ST20190801_4. The red bar along the X-axes of the histograms represents the duration of stimulation. Responses were normalized against the response to simultaneously presented priming and testing tones colocalized at c90° for the separation-dependence curve.

Some neurons displayed other types of spatial separation-dependent changes when they were stimulated by a pair of simultaneously presented priming-testing tone bursts. Shown in Figure 16 is another example. For this example, response strength increases as the priming and testing sounds become further separated.

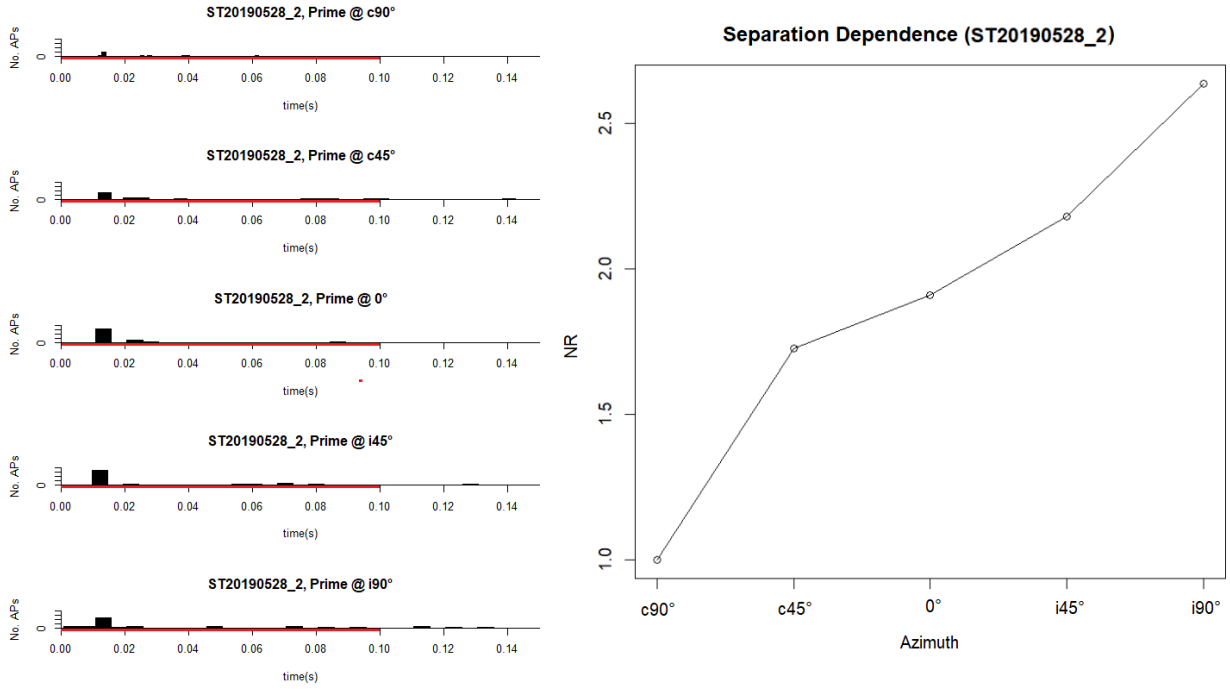


Figure 16. Example PSTHs and a separation-dependence curve showing that moving a priming sound away from a simultaneously presented testing sound that had a fixed location at c90° affected the response to the two sounds. Recordings were from neuron ST20190528_2. The red bar along the X-axes of the histograms represents the duration of stimulation. Responses were normalized against the response to simultaneously presented priming and testing tones colocalized at c90° for the separation-dependence curve.

The effect of spatial separation on the response to a pair of priming-testing sounds was evaluated in each of the 49 neurons analyzed in the present study. Group results indicate that responses were generally strongest at the c45° azimuth, decreasing as the priming tone was moved towards the i90° azimuth. The effect of spatial separation on the response to a simultaneously presented

priming-testing sound pair was statistically insignificant (one-way ANOVA test, F = 0.8, p = 0.52).

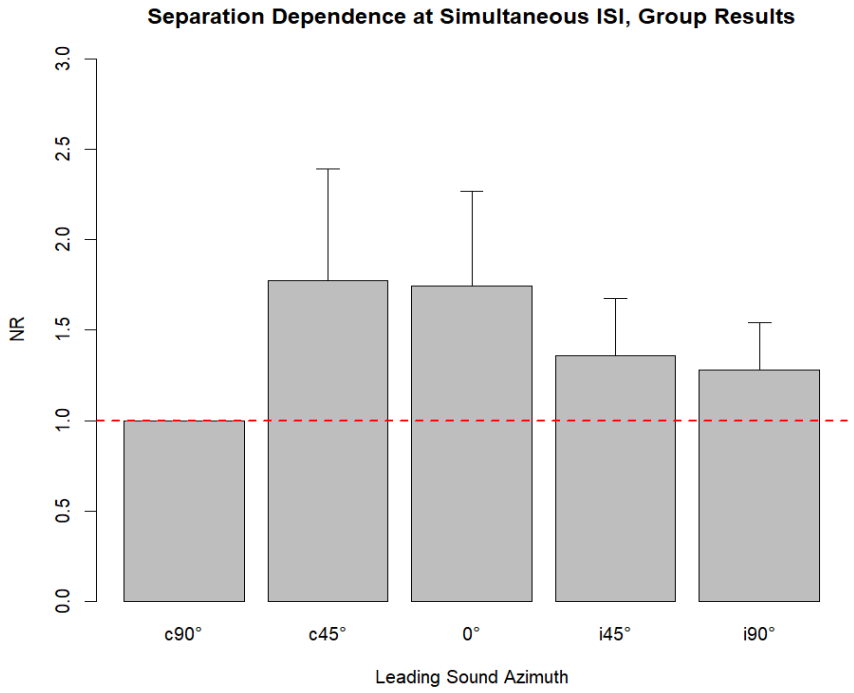


Figure 17. Group results showing the mean normalized response at each of the 5 angles of separation between a priming and a testing sound. Results were collected from responses to simultaneously presented priming and testing tones, with the testing tone fixed at c90° while the priming tone at each of the five azimuths. The red dashed horizontal bar represents the normalized response to simultaneous priming and testing tones at c90°.

The effect of spatial separation on the response to a pair of priming-testing sounds was evaluated in the subgroup of 19 neurons that displayed transient firing (Figure 18). Results indicate that among this group of neurons, firing is strongest when the priming tone is located at the 0°

azimuth, and lowest at the i45° azimuth. The change caused by spatial separation was statistically insignificant (one-way ANOVA test, $F = 0.87$, $p = 0.49$).

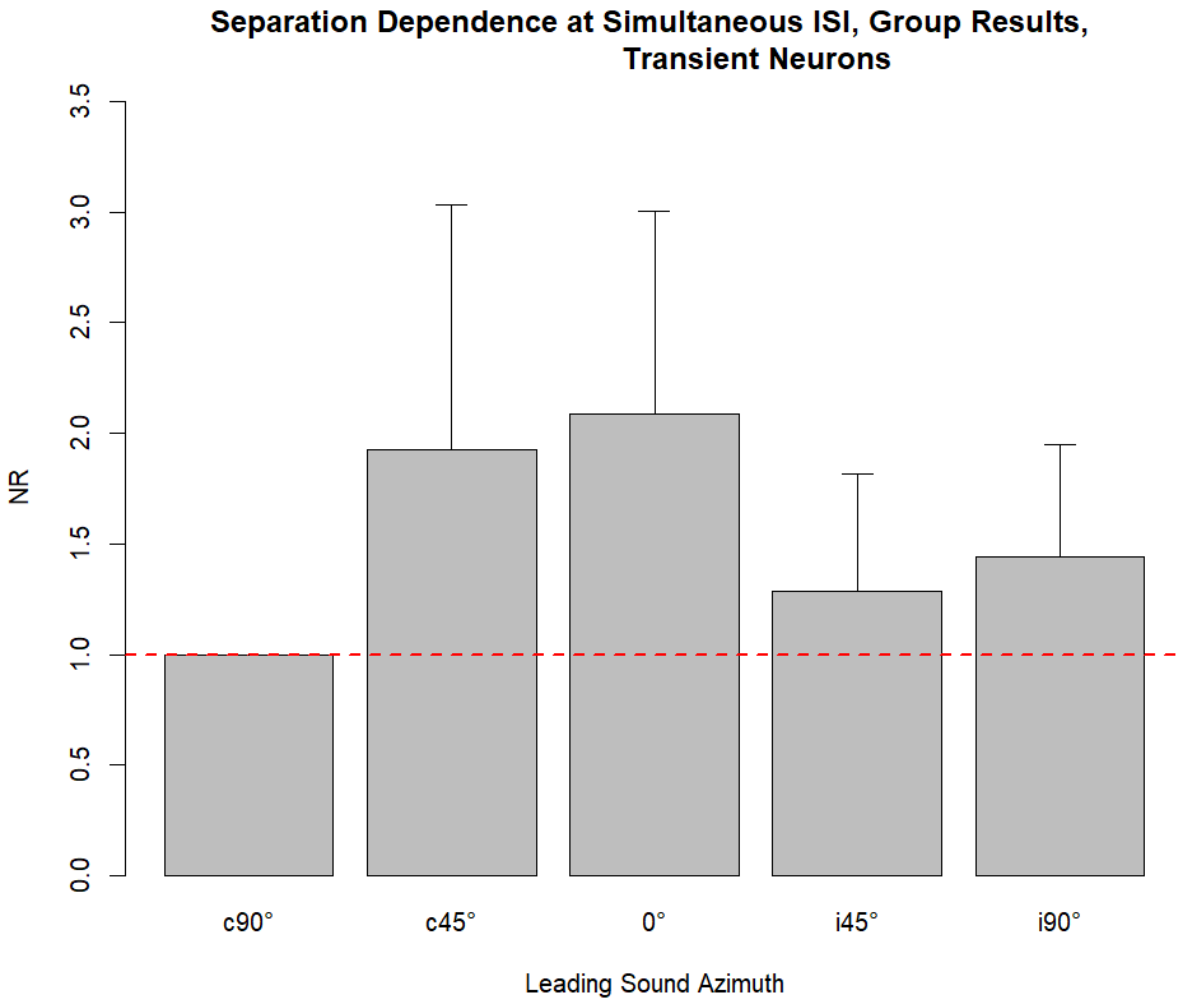


Figure 18. Group results showing how the response to simultaneously presented priming and testing sounds was dependent on angle of separation between the sounds in a group of neurons with transient firing. A testing tone was at a fixed location at c90°, while a priming tone was either colocalized at c90° or presented at a non-c90° azimuth. The red dashed

horizontal bar represents the normalized response to simultaneous priming and testing tones at c90°.

Relocating a priming sound from c90° to another azimuth when presented simultaneously with a testing sound fixed at c90° changed the response elicited by the pair of sounds (Figures 15 & 17). Relocating the same priming sound presented alone from c90° to a specific azimuth also changed the response elicited by the sound (Figures 12 & 13). These two changes were compared within individual neurons at each azimuth (Figure 19). Results indicate that the two changes were correlated with each other at all azimuths. Meaning, when the relocation of a lone priming sound from c90° to another azimuth caused a large reduction in response to the sound, the relocation of the same sound presented in a priming-testing sound pair also caused a large reduction of the response to the sound pair. When relocation of a lone priming sound from c90° to an azimuth caused a large enhancement of the response to the sound, relocation of the same sound presented in a priming-testing sound pair also caused a large enhancement of the response to the sound pair.

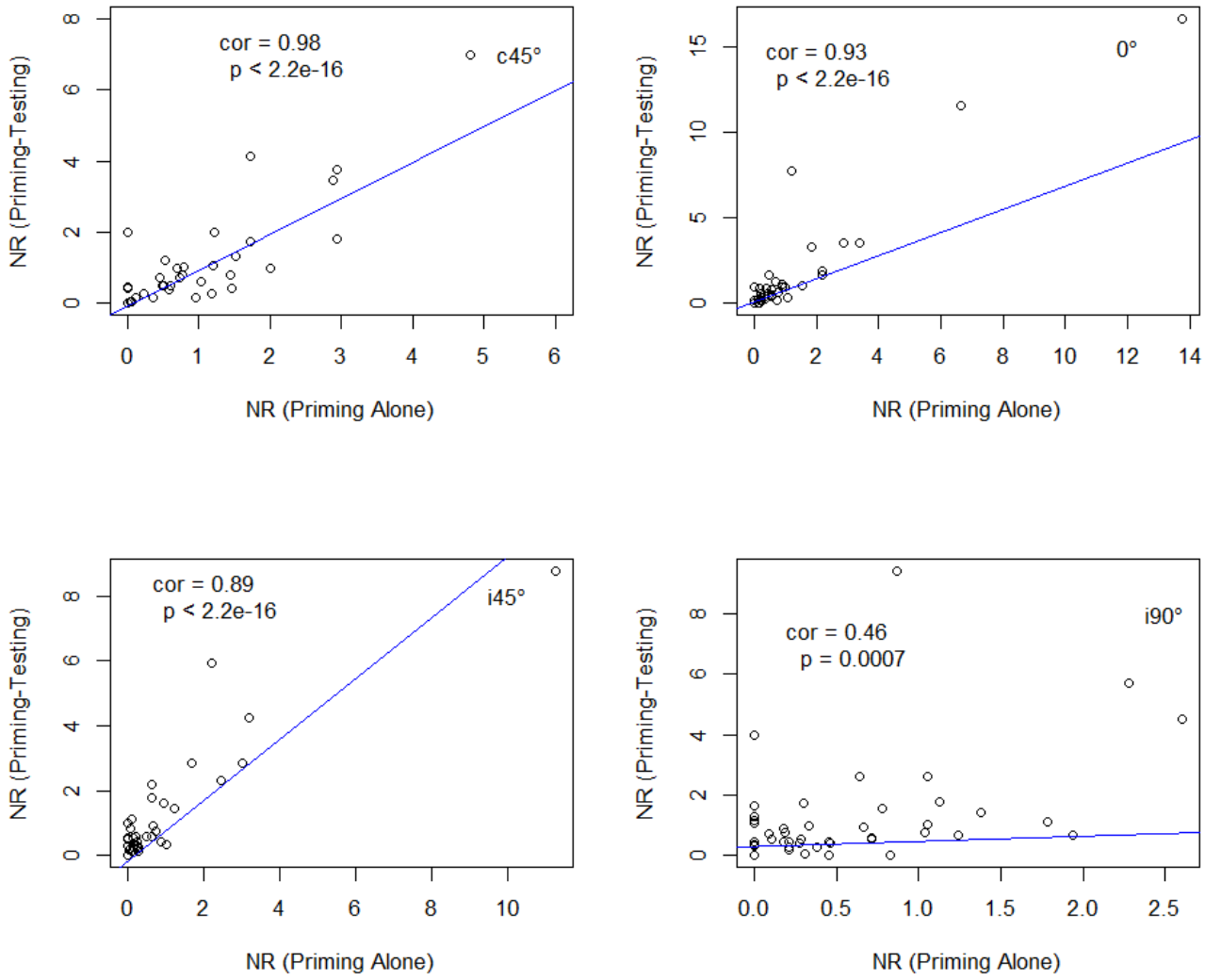


Figure 19. A comparison between the normalized response to a lone priming tone vs. the normalized response to simultaneous priming and testing tones in individual neurons.

Results from neurons showing all firing patterns are included in the comparison. Responses were obtained when the priming sound was at four individual azimuths [c45° (top left), 0° (top right), i45° (bottom left), and i90° (bottom right)]. A regression line of all data points is shown in each panel: y = 1.01x – 0.08 in top left, y = 0.68x + 0.06 in top right, y = 0.94x – 0.19 in bottom left, y

= 0.17x + 0.31in bottom right. NR (Priming Alone) is a normalized response to a priming sound (Re: response to a priming tone at c90°), while NR (Priming-Testing) is a normalized response to a pair of priming-testing sounds (compared to response to priming and testing sounds presented simultaneously at at c90°).

Responses to priming tones alone and paired priming-testing tones were compared in the group of neurons showing transient firing (Fig. 20). Results mirror those from all neurons included in this study (Fig. 19), indicating that the two changes were correlated with each other at all azimuths. When the relocation of a lone priming sound from c90° to another azimuth caused a large reduction in response to the sound, the relocation of the same sound presented in a priming-testing sound pair also caused a large reduction of the response to the sound pair. When relocation of a lone priming sound from c90° to an azimuth caused a large enhancement of the response to the sound, relocation of the same sound presented in a priming-testing sound pair also caused a large enhancement of the response to the sound pair in transient neurons.

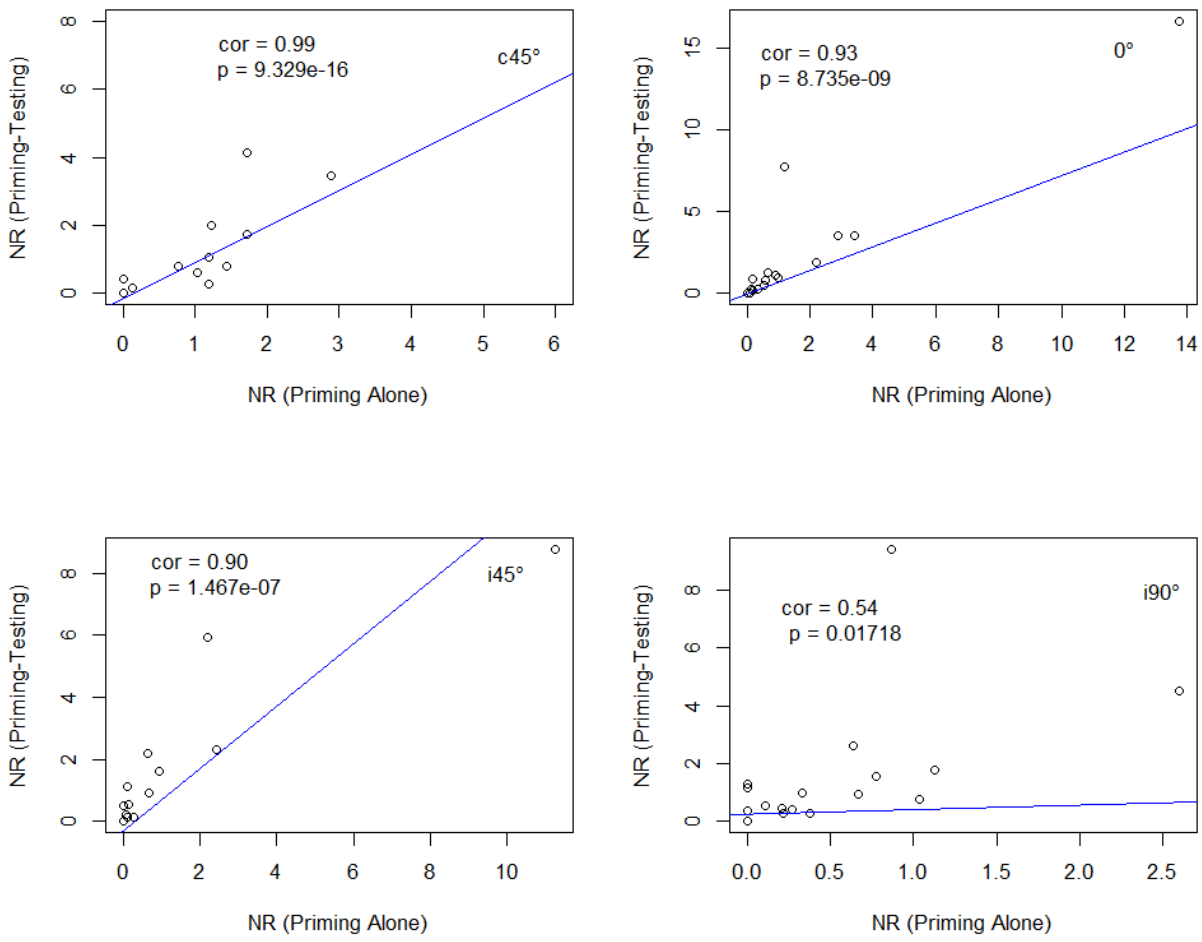


Figure 20. A comparison between the normalized response to a lone priming tone and the normalized response to simultaneous priming and testing tones in individual neurons. Results are from all the neurons showing transient firing patterns. Responses were obtained when the priming sound was at four individual azimuths [c45° (top left), 0° (top right), i45° (bottom left), and i90° (bottom right)]. A regression line of all data points is shown in each panel: y = 1.1x – 0.13 in top left panel, y = 0.73x – 0.05 in top right panel, y = 1x – 0.31 in bottom left panel, y = 0.15x + 0.26 in bottom right panel. NR (Priming Alone) is a normalized response to a priming tone (compared to response to a priming tone at c90°), while NR (Priming-Testing) is a

normalized response to simultaneous priming and testing tones (Re: response to priming and testing sounds presented simultaneously at c90°).

3.4. Responses of IC Neurons to a Pair of Sounds Colocalized at c90°: Dependence on Temporal Separation

To understand how the response to a sound was affected by a preceding sound, a pair of priming-testing sounds were presented at c90° with the priming sound leading the testing sound by various inter-stimulus intervals (ISIs). Shown in Figure 21 are results from an example neuron. For this neuron, the response to a priming sound was not affected by temporal separation between priming and testing sounds. In contrast, the response to a testing sound was lower when the two sounds were separated by a small ISI. Response was heightened when the ISI became larger. At the 1000ms ISI, the strength of response to the testing sound was almost identical to the strength of response elicited by the sound presented alone. Responses to priming and testing sounds presented in a pair were normalized against those elicited by the two sounds presented alone, respectively. Results were used to create two ISI-dependence curves for responses to the two sounds. These curves show that the response to a priming sound was independent of ISI, while the response to a testing sound was dependent on ISI. The suppression of response to a testing sound by a priming sound was reduced when the temporal separation between the two sounds increased.

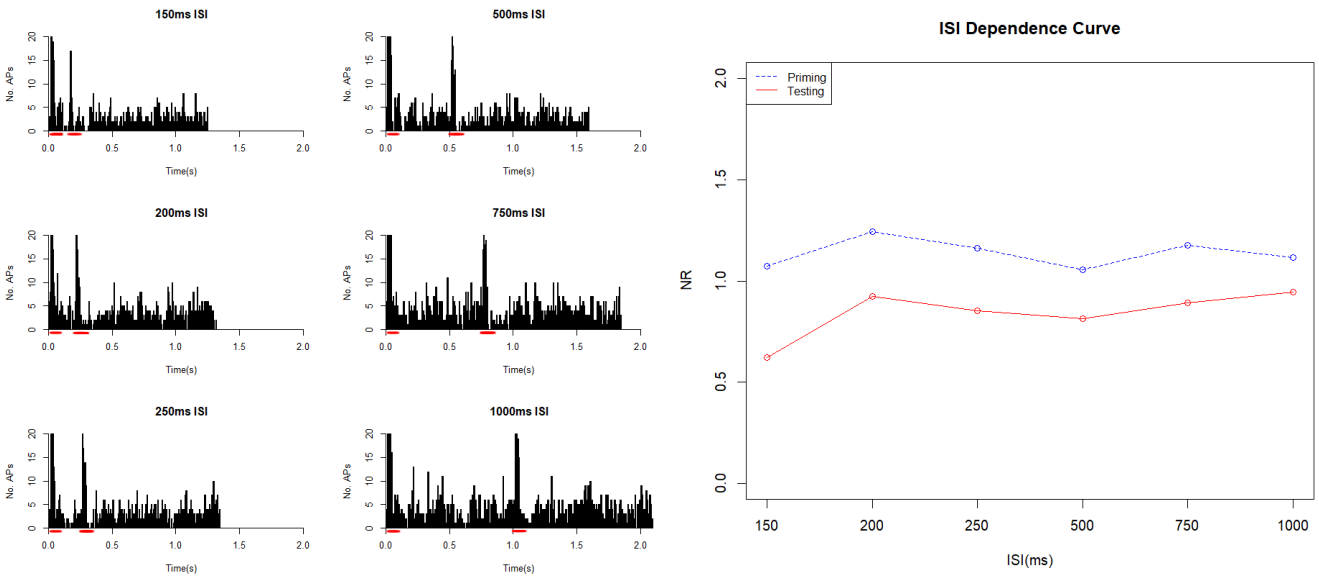


Figure 21. Example PSTHs and ISI-dependence curve. Recordings are from neuron ST20190725_3. The testing tone and the priming tone were colocalized at c90°. The red bars along the X-axes of each histogram represent duration of priming (leading) and testing (trailing) sounds. To create an ISI-dependence curve, responses to the testing tone were normalized against the response to a testing tone alone at c90°. Responses to the priming tone were normalized against the response to a priming tone alone at c90°.

Results for the entire group of neurons examined in this study show that responses to a priming sound were not affected by a testing sound, while the response to a testing sound was affected by a priming sound in a temporal separation-dependent manner (Fig. 22). The normalized response to a testing sound was slightly above 0.5 at the 150 ms ISI. It approached 1 at the 1000ms ISI. The change caused by temporal separation was statistically significant (one-way ANOVA test, $F = 11.68$, $p = 0.007$) for the response to a testing tone, and insignificant (one-way ANOVA test, $F = 0.68$, $p = 0.41$) for the response to a priming tone.

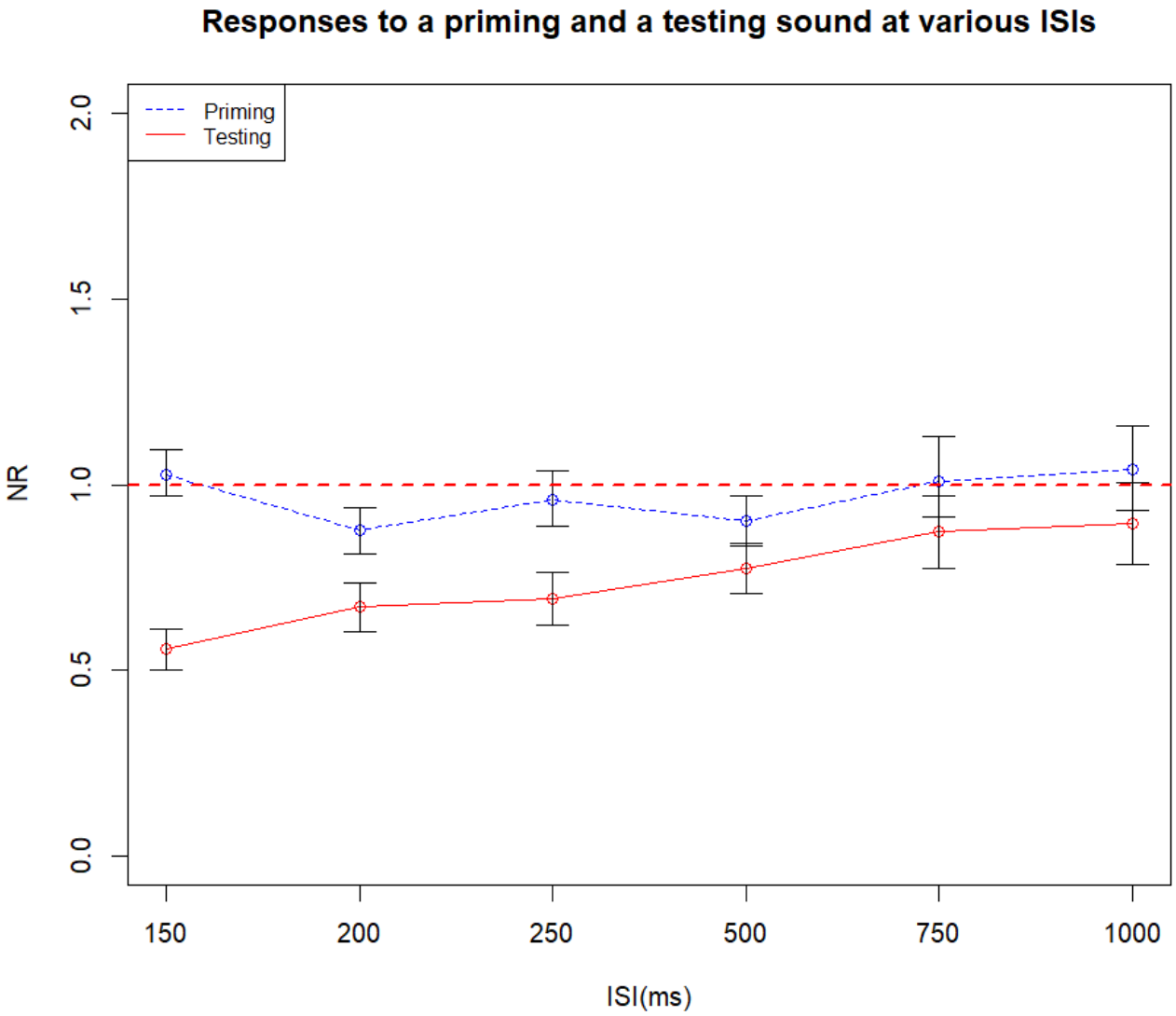


Figure 22. Group results showing the mean normalized response at 6 ISIs. Responses to a priming and a testing tone were obtained when the sounds were colocalized at c90° but temporally separated by various ISIs. Responses here were gathered from a 150ms time window starting from the onset of a priming or testing sound. The red dashed horizontal bar represents the expected normalized response for priming and testing tones at c90°.

3.5. Responses of IC Neurons to a Pair of Temporally Separated Priming-Testing Sounds: Dependence on Spatial Separation

To understand whether the response to a trailing testing sound was affected by a leading priming sound in a spatial separation-dependent manner, the two sounds were presented at various combinations of ISIs and spatial separations. A spatial separation was created by presenting a testing sound at a fixed location at c90° and a priming sound at one of the 4 azimuths (c45°, 0°, i45°, and i90°). Shown in Figure 23 are results from one representative neuron obtained at a single ISI at 150ms but different angles of spatial separation. The results indicate that the response to a leading priming sound was reduced when the sound was relocated from c90° to c45° and was completely suppressed when the sound was relocated to 0° or an ipsilateral azimuth (Fig. 23). In contrast, the response to a trailing testing sound was increased when the priming sound was at an ipsilateral azimuth (Fig. 23). The opposite changes of the responses to a leading priming and a trailing testing sound displayed by this neuron contrasted with the results obtained when a priming and a testing sound were presented simultaneously.

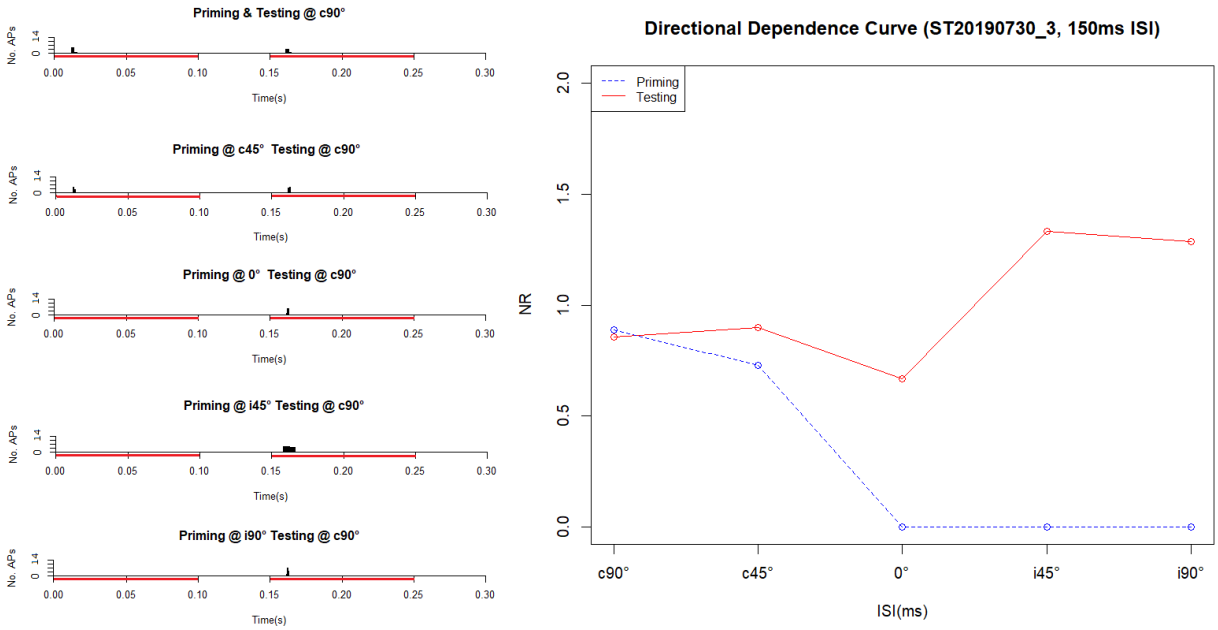


Figure 23. Example PSTHs and separation-dependence curve for responses to a leading priming sound and a trailing testing sound that were separated by an ISI at 150 ms. Recordings were from neuron ST20190730_3. A testing tone was at a fixed location at c90°, while the priming tone was either colocalized at c90° or at another azimuth. The red bars along the X-axes of each histogram represent duration of priming and testing sounds. To create a separation-dependence curve, responses to a priming tone were normalized against the response to the sound at c90°, and responses to a testing tone were normalized against the response to the sound at c90°.

Not all neurons displayed the same changes upon relocation of a leading priming sound from c90° to another angle. Shown in Figure 24 are results from another neuron obtained at the ISI at 150 ms.

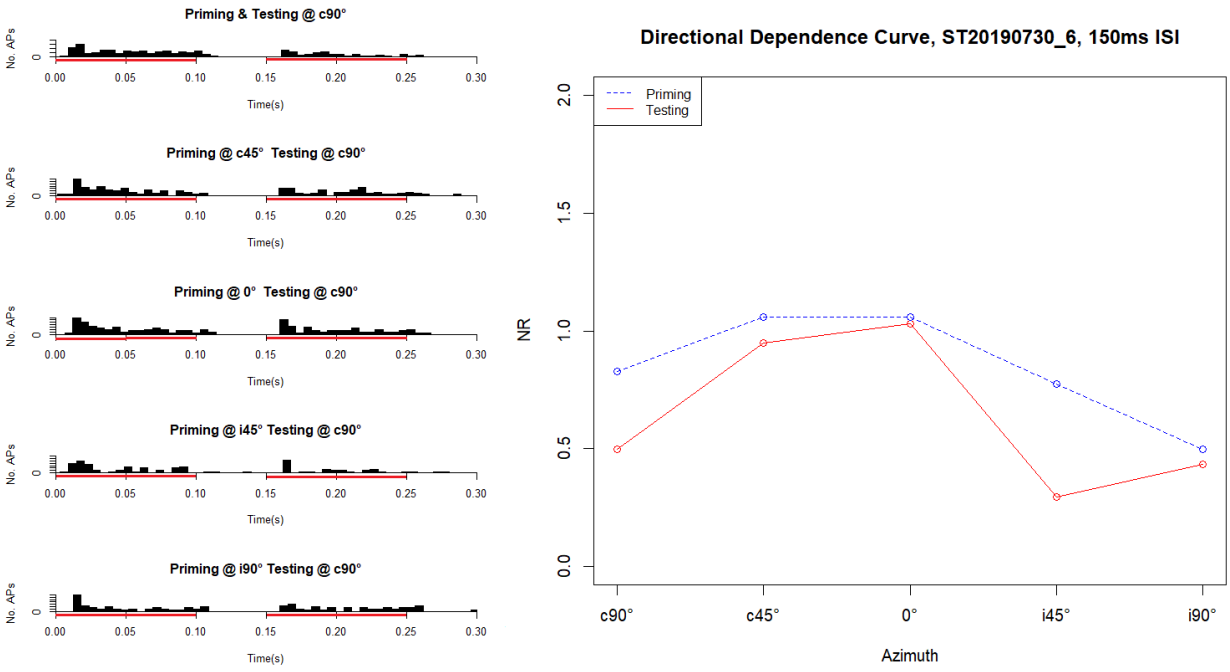


Figure 24. Example PSTHs and separation-dependence curve for responses to a leading priming sound and a trailing testing sound that were separated by an ISI at 150 ms. Recordings were from neuron ST20190730_6. A testing tone was at a fixed location at c90°, while a priming tone was either colocalized at c90° or at another azimuth. The red bars along the X-axes of each histogram represent duration of a priming and a testing sound. To create a separation-dependence curve, responses to a priming tone were normalized against the response to the sound at c90°, while responses to a testing tone were normalized against the response to the sound at c90°.

Spatial separation-dependent changes of responses to a leading priming sound and a trailing testing sound that had a 150-ms ISI were analyzed in all neurons. Mean changes of responses to the two sounds were obtained to generate two separation-dependence curves (Fig. 25). These curves suggest that the neurons analyzed in the present study as a group did not show large

changes of the responses to a leading priming sound and a trailing testing sound. Such relatively small effects were likely due to diverse effects of spatial separation on individual neurons.

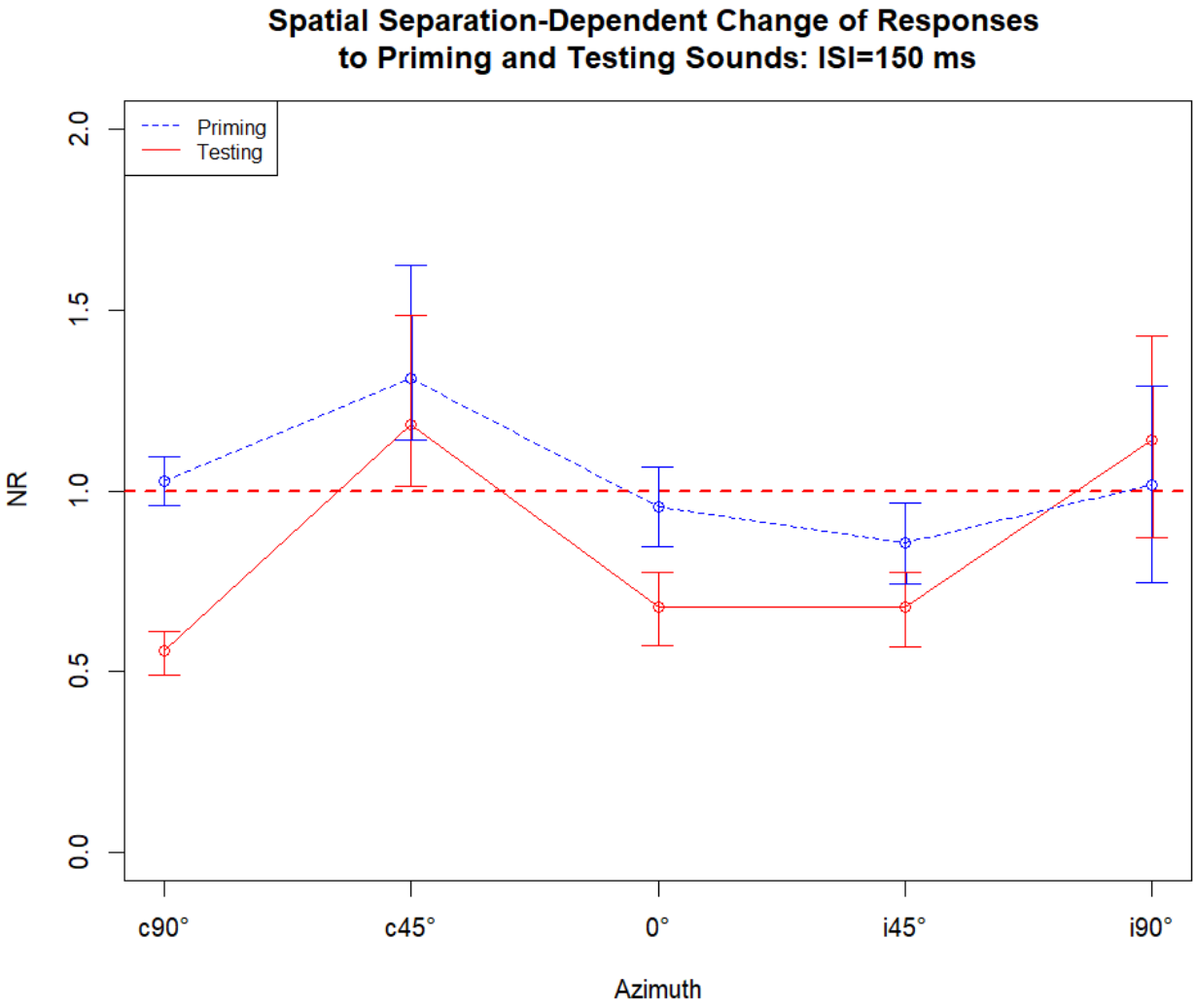


Figure 25. Group results showing the dependence of responses to a leading priming sound and a trailing testing sound on the angle of separation. Results were collected when a testing tone was at a fixed location at c90° while a priming tone was either colocalized at c90° or at another azimuth. The priming and testing tones were temporally separated by an ISI at 150ms. Responses were gathered from a 150-ms time window starting from the onset of a priming or a

testing sound. The red dashed horizontal bar represents the expected normalized response for priming and testing tones at c90°.

At the 150 ms ISI, the change of response to a leading priming sound and the change of response to a trailing testing sound caused by relocation of the priming sound to a specific azimuth was compared in each neuron. Results from all neurons at each angle of separation were used to create a scatter plot as shown in Figure 26. These results suggest that there was no strong correlation between the two changes, except at the 0° azimuth.

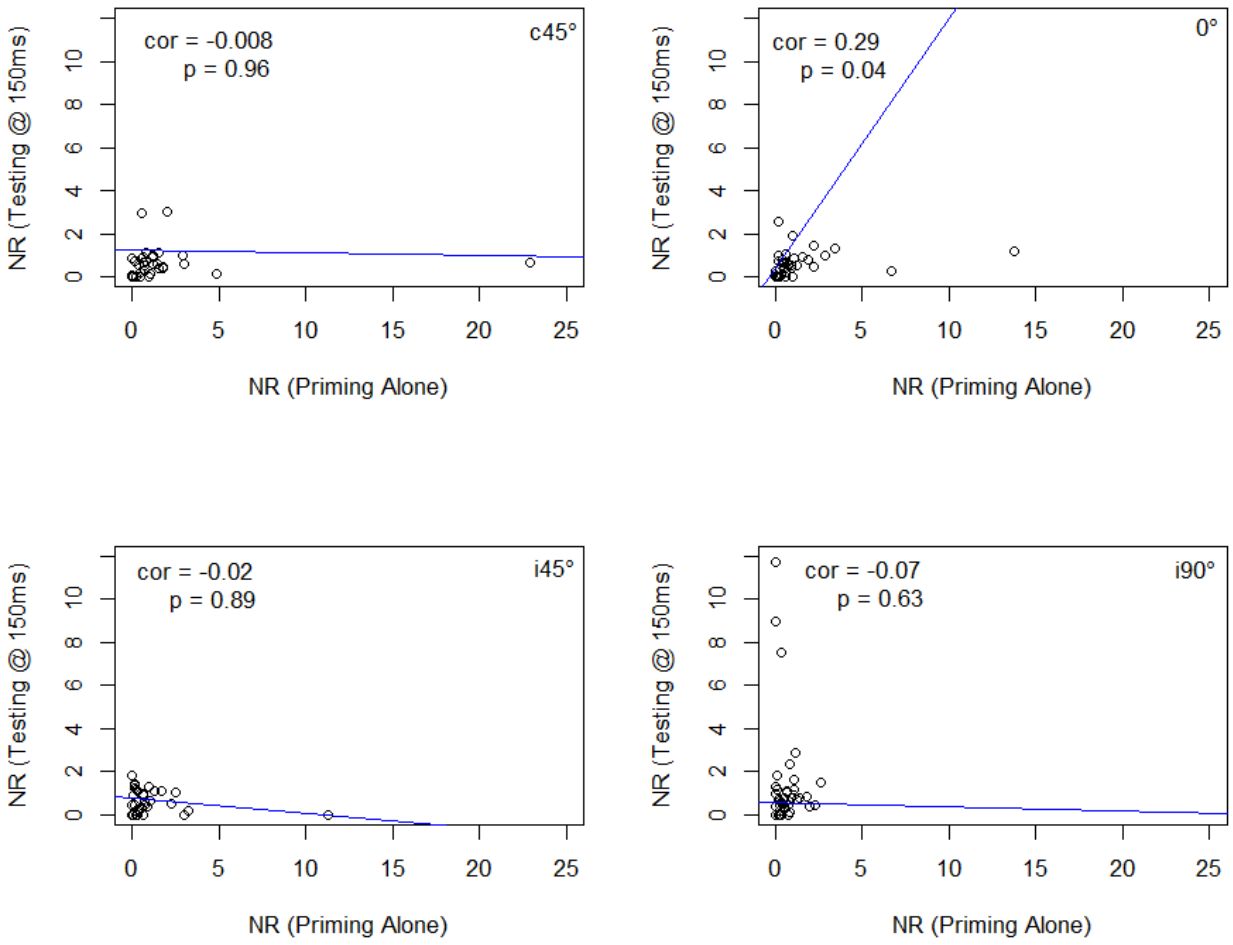


Figure 26. A comparison between a change of the normalized response to a lone priming tone vs. a change of the normalized response to a testing sound when the testing sound trailed the priming tone by 150 ms in individual neurons analyzed in this study. The top left, top right, bottom left, and bottom right panels show results obtained when a priming sound was at c45°, 0°, i45°, and i90°, respectively. A regression line of all data points is shown in each panel: y = - 0.01x + 1.26 in the top left panel, y = 1.16x + 0.46 in the top right panel, y = - 0.07x + 0.73 in the bottom left panel, y = - 0.02x + 0.54 in the bottom right panel. NR (Priming Alone) is a normalized response to a priming tone (relative to response to a priming tone at at c90°, and NR (Testing @ 150ms) is a normalized response to a testing tone at c90°.

3.5.1. Results from Transient Neurons in Response to Spatial Separation

Spatial separation-dependent changes of responses to a leading priming sound and a trailing testing sound with the ISI at 150 ms were analyzed in transient neurons. Mean changes of responses to the two sounds were obtained to generate two separation-dependent curves (Fig. 27). These curves suggest that the response to a priming tone remained relatively unaffected by relocation, while the response to a testing tone was increased by the relocation of the priming tone. The response was suppressed by 50% when the priming sound was at c90°. Such a suppression was released when the priming sound was moved to i90°.

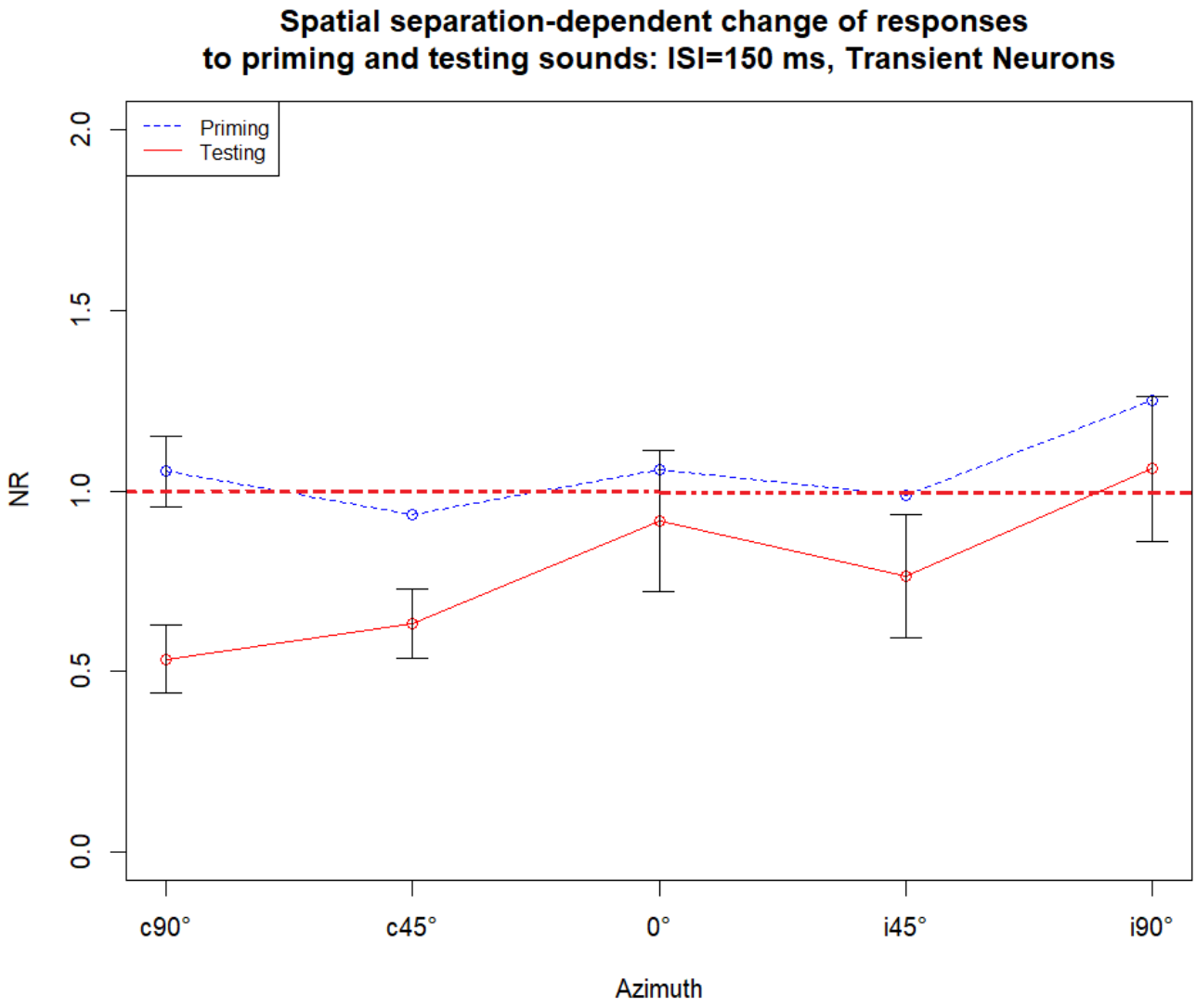


Figure 27. Group results showing the dependence of responses to a leading priming sound and a trailing testing sound on the angle of separation. Results were collected when a testing tone was at a fixed location at c90°, while a priming tone was either colocalized at c90° or at another azimuth. Results were obtained from neurons that had transient firing patterns. The priming and testing tone were temporally separated by 150ms. Responses here were gathered from a 150 ms time window starting from the onset of a priming or a testing sound. The red

dashed horizontal bar represents the expected normalized response for priming and testing tones at c90°.

At the 150 ms ISI, the change of response to a leading priming sound alone and the change of response to a trailing testing sound when paired with a priming sound at a specific azimuth was compared in each neuron. Results from all neurons at each angle of separation were used to create the scatter plots shown in Figure 28. These results suggest a strong correlation between the two changes at the c45°, 0°, and i45° azimuths. There is less of a strong correlation between the strength of the two responses at the i90° azimuth.

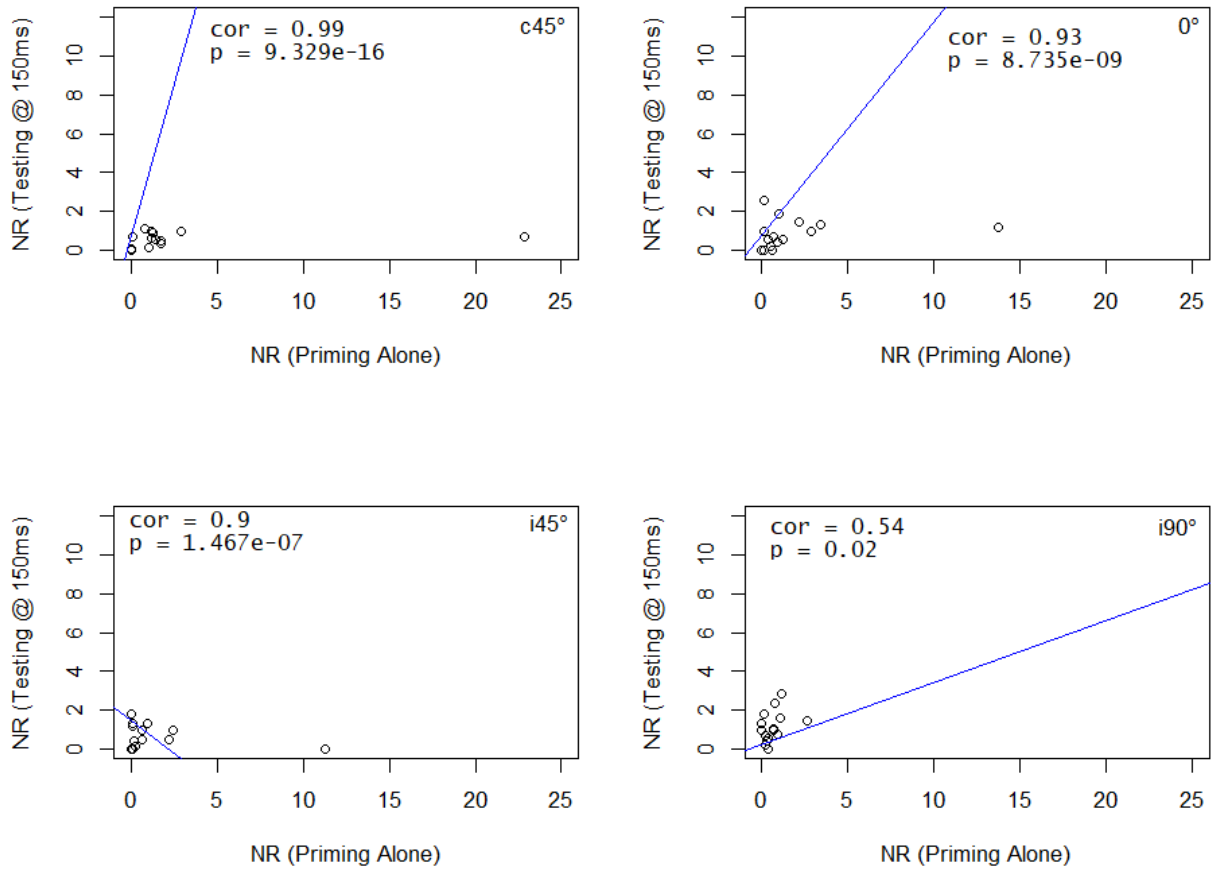


Figure 28. A comparison between a change of the normalized response to a lone priming tone vs. a change of the normalized response to a testing tone when the testing sounds trailed the priming tone by 150 ms ISI in neurons with transient firing. The top left, top right, bottom left, and bottom right panels show results obtained when a priming sound was at c45°, 0°, i45°, and i90°, respectively. A regression line of all data points is shown in each panel: y = 3.13x + 0.73 in the top left panel, y = 1.1x + 0.84 in the top right panel, y = -0.68x + 1.48 in the bottom left panel, y = 0.32x + 0.25 in the bottom right panel. NR (Priming Alone) is a normalized response to a priming tone (relative to response to a priming tone at c90°). NR (Testing @ 150ms) is a normalized response to a testing tone (relative to response to a priming tone at c90°).

3.6. Time Course of an Effect Generated by a Priming Sound: Dependence on Spatial Separation

To understand how the response to a sound was affected by a preceding sound, a pair of priming and testing sounds was presented with various temporal and spatial separations. Specifically, the priming sound preceded a testing sound with various inter-stimulus intervals (ISIs). While the testing sound was always presented at a fixed location at c90°, a priming sound was either at c90° (i.e., colocalized with the testing sound) or a non-c90° azimuth (i.e., separated from the testing sound). Figure 29 provides results from an example neuron. For this neuron, the response to a priming sound was not affected by temporal separation between priming and testing sounds. In contrast, the response to a testing sound was lower when the two sounds were separated by a small ISI. Response was heightened when the ISI became larger. At the 1000ms ISI, the strength of response to the testing sound was almost identical to the strength of response elicited by the sound presented alone. Responses to priming and testing sounds were normalized against those elicited by the two sounds presented alone, respectively. Results were used to create two ISI-dependence curves for responses to the two sounds at each of 5 azimuths. These curves show that the response to a priming sound was independent of ISI at c90°, began to decrease at lower ISIs at c45° and 0°, appeared to be enhanced at i45°, and was decreased at larger ISIs at i90°. The response to a testing sound was dependent on ISI and the location of the priming sound. The suppression of response to a testing sound by a priming sound was reduced when the temporal separation between the two sounds increased at c90°, c45°, and 0°, and matched the firing strength of the priming tone at i90°. Response to a testing tone increased generally when the priming tone was relocated to c45°, and 0° in comparison to the strength of response at c90°.

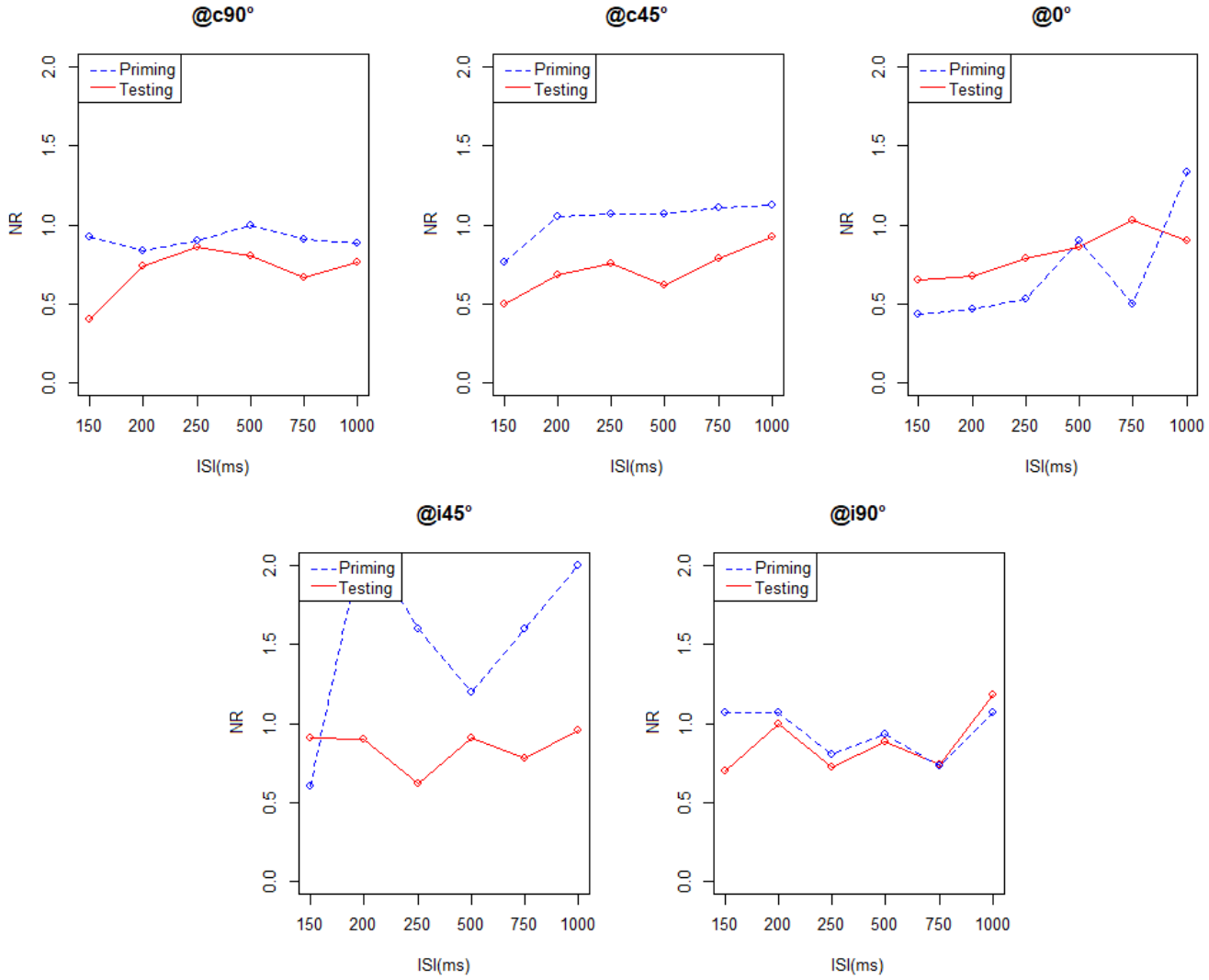


Figure 29. ISI-dependence curves obtained from an example neuron. The curves were obtained when a priming sound was at each of 5 azimuths while a testing tone was at a fixed location at c90°. Recordings are from neuron ST20190620_2. To create a directional-dependence curve, responses to a priming tone were normalized against the response to the sound presented alone at c90°. Responses to a testing tones were normalized against the response to the sound presented alone at c90°.

Group results obtained at each of the five angles of separation indicate that the response to a testing sound was lower when the ISI between the sound and a priming sound was small (150ms, 200ms). The response became greater when the ISI was larger (750ms, 1000ms).

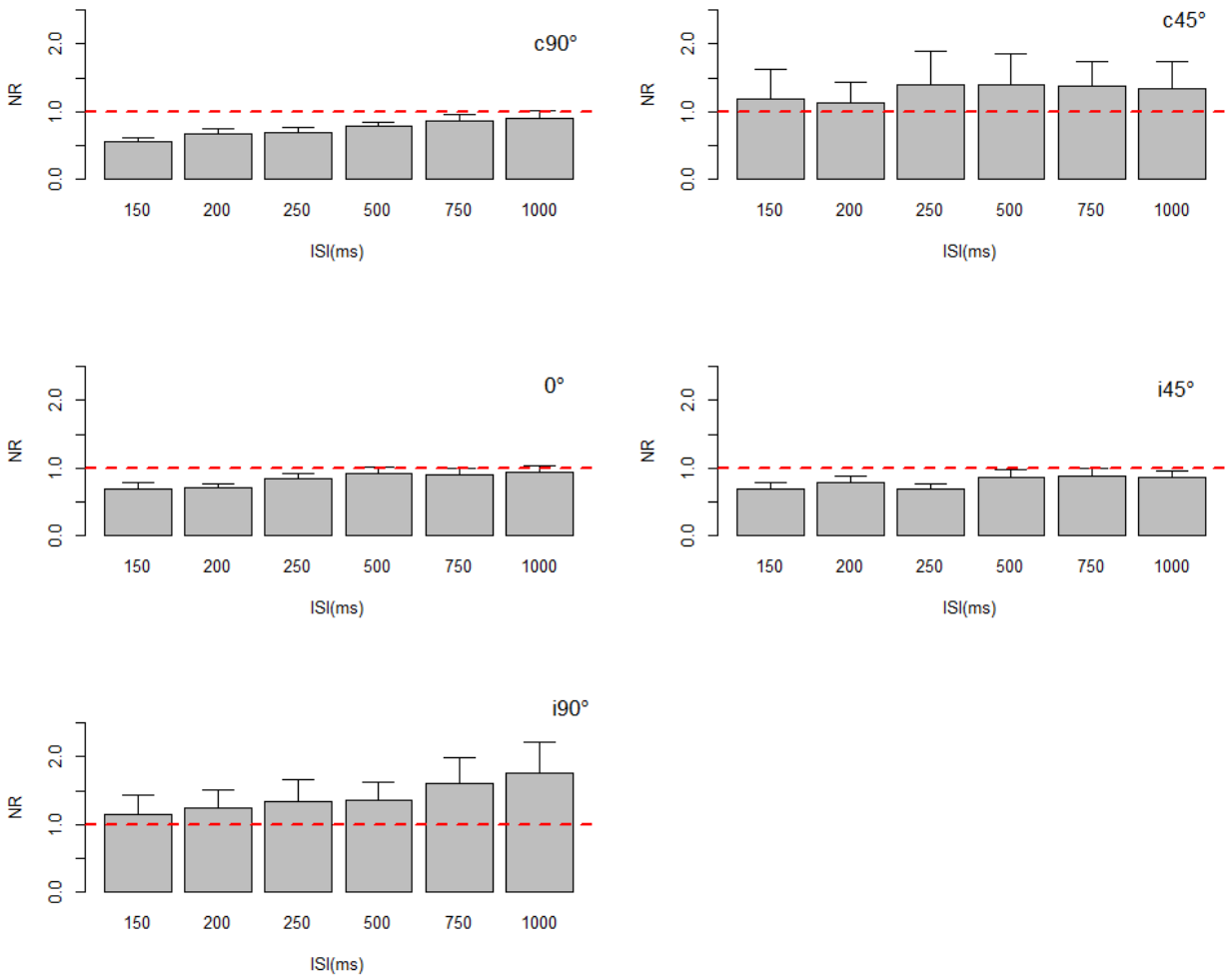


Figure 30. Group results showing the mean normalized response to a testing tone when it was preceded by a priming tone presented at various azimuths with various ISIs. The testing tone had a fixed location at c90°. Responses were obtained over a 0 – 150ms time

window starting from the onset of a testing sound. The red dashed horizontal bar represents the normalized response to simultaneous testing tones at c90°.

3.7. Summary of Results

The response to a testing sound was weaker when the sound and a priming sound were colocalized at the contralateral ear, and stronger when the priming sound was at the ipsilateral ear. The response to a testing sound was weaker when the testing sound was preceded by a priming sound by a smaller ISI. The response became stronger when the two sounds were separated by a larger ISI.

4. DISCUSSION

The suppressive effect produced by priming sound on the response to a testing sound corresponded to the psychoacoustical phenomenon of masking. Specifically, the suppressive effect observed when the priming and testing sounds were presented simultaneously corresponded to the phenomenon of simultaneous masking, while the effect observed when the two sounds were presented with a time interval corresponded to the phenomenon of forward masking. The dependence of the degree of suppression of the response to a testing sound on the time interval between the sound and a priming sound reflected the time dependence of the degree of forward masking. The dependence of the degree of suppression of response to a pair of simultaneously presented priming-testing sounds on the degree of suppression between the sounds reflected spatial release from masking.

4.1. Results and their Corresponding Practical Implications

4.1.1. Spatial Dependence

Responses to lone priming tones (Section 3.2.) show that when a sound was moved from a position at the contralateral ear (c90°) to one at the ipsilateral ear (i90°), response to the tone is reduced. This “contra-pass” pattern is the most common pattern observed in the present study (19/36 neurons, fig. 12). Other patterns such as “front-pass” and “front-suppress” were also seen, but in smaller proportions. Many neurons showing contra-pass curve patterns had transient firing patterns. These neurons may likely be important for the phenomenon of masking. Many neurons with front-pass directional dependence curves had sustained or other firing patterns. It is possible that these neurons are less involved in masking.

Sustained firing neurons generally show stronger firing over the duration of a stimulus due to relatively strong excitatory inputs. Such inputs can counteract the inhibitory inputs. At the c45°and 0° azimuths, stronger stimulation of the contralateral ear led to stronger excitatory inputs received by IC neurons, which surpassed inhibitory inputs caused by stimulation of the ipsilateral ear (Fig. 13). When a sound was from a ipsilateral hemifield, increased stimulation of the ipsilateral ear and heightened inhibitory inputs received by IC neurons can reduce the firing generated by IC neurons.

It is unknown how a “front-suppression” pattern was generated. One possibility is the involvement of commissural fibres connecting the two sides of the IC. Finally, neurons classified as having “other” patterns of firing may be unrelated to the mechanisms of masking and

suppression of interest in this study. More research is needed to accurately determine their role in auditory perception.

4.1.2. Interactions Under Temporally and Spatially Separated Sound Pairs

Results collected from priming and testing tones presented at various temporal separation conditions show greater suppression of the testing tone by the priming tone when the sounds are separated by a smaller ISI (150 – 250ms). In comparison, suppression becomes weaker when the ISI becomes larger (500 – 1000ms). This is shown by the relative strength of firing in response to a testing tone when paired with a priming tone, as can be seen in Figs. 21 & 22. Such a temporal dependence is a likely contributor to temporal release from masking. The observed temporal dependence is perhaps due to adaptation of IC neurons as they respond to stimuli. Other studies performed in this lab previously (Asim et al., 2023) and the initial results obtained by Sarah Tran, support that these observed results correspond to a reduction in masking. These results agree with studies indicating that the range for a masking sound's effect is within a few hundred milliseconds (Gulick et al., 1989; Plack & Moore 2010). Although, slight differences among each study suggest that the range of forward suppression depends on the duration, intensity, and character of sound presented.

Results collected from simultaneously presented priming and testing tones indicate greater suppression when both sounds are colocalized at the c90° azimuth, and a weakening of suppression when the sounds are separated by a greater angle. This is indicated by the relative strength of responses to the testing tone seen in Figs. 15 & 17. This effect corresponds with the

phenomenon of spatial release from masking. This supports other studies performed in this lab researching spatial release from masking. Chot et al., 2019, 2020 also showed the unmasking seen here as a result of spatial separation, which is more pronounced in neurons with transient firing patterns. The resulting increase in response to a testing tone when the sounds are no longer colocalized likely originates in the binaural pathways which provide IC neurons with inputs. However, in almost all of the group results produced from the neurons observed here, responses at the c45° were stronger than those at any other azimuth. This may be in part due to the relatively small number of neurons involved in mean calculations, causing results to appear more exaggerated than they would be under ideal conditions. It is also possible that these heightened responses correspond to some heretofore unknown phenomenon. One may speculate that this is related to commissural inputs which have been mentioned in relation to neurons showing front-suppress firing patterns (Section 4.1.1.)

4.1.3. Mixed Temporal and Spatial Conditions

In all cases shown in this thesis, a priming tone reduced responses to a testing tone when the sounds were located closer together temporally and spatially. When presented with a larger ISI and a larger spatial distance between the priming and testing tones, less suppression of the testing tone was apparent. Figure 30 shows a gradual increase in response as the priming tone is moved towards the i90° azimuth in each of the 5 graphs, and a gradual increase in testing tone response as the ISI increases in each graph individually, excepting results from the c45° azimuth (see section 4.1.2.). This is consistent with the known characteristics of forward masking (Gulick et al., 1989). The mixed interactions appearing in this study may correlate to the varied responses

shown by sustained and transient firing neurons. Transient firing neurons may be useful in identifying spatial and temporal cues, while sustained neurons may respond primarily to temporal changes. The overlapping functions of sustained and transient neurons in response to temporal changes may help to explain why the gradual reduction in suppression as ISI between priming and testing tones is increased is more uniform than the reduction in suppression as the sounds are spatially separated.

4.2. Possible Underlying Mechanisms

4.2.1. Adaptation

Of the potential causes of masking and suppression, one worth considering is adaptation of those neurons involved in response to sound (Deatherage & Evans, 1969; Smith 1977). Neural adaptation occurs after repeated activation of a neuron, following which the neuron becomes "depleted", and is unable to respond to further stimulation of the same kind. After an action potential, there is a period of time during which the neuron must regain the balance of ions on either side of the membrane which allow the neuron to fire. The rate at which this repolarization occurs may have an effect on a neuron's ability to respond to rapidly occurring stimuli. Different types of neurons have different repolarizing channel characteristics. Neurons showing an onset pattern tend to have low K+ thresholds, requiring less potassium to activate the channels involved in firing, allowing faster repolarization and detection of sound (Peruzzi et al., 2000).

Relocation of one sound may alleviate demands on a neuron, as a sound presented at another azimuth would activate a different pathway through the auditory system, uninvolved with

neurons that had been depleted. This would explain the lessened effect of suppression as the priming tone was relocated in this study. Additionally, because stimulation of the contralateral ear results in the strongest degree of response, it can also be considered the site of greatest suppression considering adaptation, as the strongest-firing neurons had become depleted when responding to further stimulation – which may explain the results seen here (Litovsky & Yin, 1998). By relocating the location of the sound, suppression would be reduced. Temporal separation of the two stimuli would also lessen suppression, as a greater ISI would provide a neuron with more time to recover from previous stimulation. Sustained firing neurons may also help explain why suppression is reduced under certain circumstances. Due to their continual firing, sustained neurons may overload neurons in the IC, causing a period of suppression as observed. This correlates with the similar level of response to priming and testing tones at low ISIs irrespective of azimuthal location (Fig. 29).

The lack of complete suppression during periods of overlap between priming and testing sounds, with complete suppression occurring after stimulus offset, indicate that adaptation alone is not enough to explain the full extent of suppression within the IC. Adaptation likely combines with other elements such as binaural interaction, and the inherent characteristics of IC neurons to produce the full scope of suppressive activity (Plack & Moore 2010).

4.2.2. Binaural Interactions

The IC is a major way-station for neural signals prompted by auditory stimulation on their way through the auditory pathway to the AC. It receives many inputs from structures both above and

below it in the pathway. These inputs originate binaurally, from the ears both contralateral and ipsilateral to it. It is these inputs which may contribute to the masking phenomena seen here. Inputs which interface directly with the IC, such as those originating in the contralateral CN, may have a shorter course of action when compared with inputs from the ipsilateral pathways which travel through several other auditory structures before reaching the IC in an indirect route. This would cause excitation to occur faster than inhibition. As a result, inhibitory inputs to the IC would just begin to become active, and continue to be active as the excitatory signals from the next sound are beginning, if the ISI between the two is small enough.

Contralateral inputs to the IC tend to provide excitatory inputs, while ipsilateral inputs to the IC tend to cause inhibition. By relocating the sound from the contralateral to the ipsilateral side of the head, this would be expected to cause a reduction in excitation, and/or an increase in inhibition. However, inputs to the IC often follow convoluted pathways through the auditory system, interacting with other auditory nuclei in the process. One such example is the LSO's excitation of the contralateral IC. Ipsilateral stimulation causes the MNTB to inhibit the LSO, as well as causing the contralateral DNLL and ipsilateral LSO to inhibit the IC. This results in a mixed inhibitory-excitatory aftereffect on response to a testing tone by an ipsilateral priming tone in the IC (Chot et al., 2019, 2000; Zhang & Kelly, 2009), which could create the long-lasting binaural interaction seen here. These inputs to the LSO are found to rely on glycine as a neurotransmitter (Asim et al., 2023).

The results of this study indicate that the inhibitory aftereffect produced on a response to a testing tone is lessened when the priming tone is presented ipsilaterally in comparison to both testing and priming tones colocalized at the contralateral ear. This phenomena is more prominent in transient neurons. Under conditions of overlap, such as seen in the simultaneously-presented tone results of this study, response to a testing tone increases when the priming tone is located at the ipsilateral azimuths. Projections to the IC which utilize GABA as a neurotransmitter tend to originate from the opposite ear.

GABAergic projections to the IC from the DNLL (Gai 2016), have been considered as a potential source of suppression in ISIs under 5ms. However, Li & Kelly 1992 found that blocking the DNLL does not completely eliminate binaural responses in the IC, a finding which was confirmed by Asim et al., 2023. A study performed by Asim et al., 2023 suggested that application of $GABA_A$ antagonists to the IC did not appear to have an effect on suppression when tones were presented at the ipsilateral ear. Similar effects were found when Glycine antagonists were applied. Therefore, other contributors are likely involved in masking phenomena.

Inputs from the SPON may play a particularly important role in generating a suppressive aftereffect in IC neurons. The structure sends long-lasting inhibitory contralateral projections to the IC. These projections have an offset firing pattern, becoming activated after stimulation offset. The SPON itself can be influenced by the timing and strength of excitatory-inhibitory projections from other structures in the pathway, such as the VCN. Particularly, the octopus cells

of the VCN which tend to have sustained firing patterns. This pattern of firing may enable a stimulus to generate a strong suppressive aftereffect in IC neurons.

A source of ipsilateral projections to the IC originates in the VNLL, which is itself supplied by projections from the MNTB. These MNTB projections may contribute to inhibition within the IC. Neurons in the VNLL show a variety of firing patterns, and it is possible these patterns may be inherited by higher centres of auditory processing, as mirrored by the different firing patterns observed in the IC. Stellate neurons within the VNLL contain NMDA receptors, having a diverse range of time courses. These receptors may correspond with the difference in temporal influences within the IC (Sanchez et al., 2007) as well. In particular, the shorter time courses of NMDA receptors may be associated with sustained firing neurons. Therefore, if suppression of response to a sound occurs in an auditory structure which sends projections to the IC, that suppression will be shown by neurons in the IC when observed.

4.2.3 Characteristics of the IC

While it is believed that much of the suppressive aftereffect in the IC owes itself to activity originating in other auditory structures and the projections they send, neurons within the IC may play a role themselves. Previous publications such as Tollin 2003 suggest the influence of transient IC neurons on the auditory brain's ability to locate the origin of a sound. The most significant difference between the characteristics of sustained and transient neurons is the hyperpolarization of their currents, Koch & Grothe 2003 suggest that intrinsic onset firing

neurons, or transient neurons have larger hyperpolarized currents compared to those neurons showing sustained firing.

The hyperpolarization of currents within a neuron causes an increase in firing afterwards, known as rebound. Hyperpolarizing currents may originate ipsilaterally, resulting in a heightened response to a priming tone when presented at the ipsilateral azimuths, and less suppression of the testing tone. Additionally, GABA and glycinergic receptors present on IC neurons may have some effect on temporal inhibition originating in the IC (LeBeau et al., 1996, Asim et al., 2023). When exposed to GABA agonist and antagonist pharmacological substances, more dramatic excitation and suppression is observed in the IC in comparison to those substances targeting glycinergic receptors (Faingold et al., 1989). This suggests that GABA has some role in inhibiting binaural responses within the IC. Additionally, the application of strychnine can counteract the complex local circuits which utilize glycine as a neurotransmitter to generate responses in the IC (Asim et al., 2023), causing a slight change in suppression – which would correspond to the activity of local IC circuits and neurons. While it is suggested that the firing patterns observed in the IC may be intrinsic to IC neurons, this may be complicated by extracellular recording as used in this study. Neurotransmitter receptors, excitatory-inhibitory inputs, ion channels, and the activity of nearby neuron synapses may exert an influence on the observed results obtained from IC neurons.

4.3. New Implications of Reanalysis and Differences from Original Results

While the results presented here largely reaffirm the initial findings of Sarah Tran's thesis, the removal of potential interference from the results has produced some differences. One-way ANOVA tests of the results agree with initial findings that the differences between responses at various azimuths are not statistically significant, many of the statistical values produced in this study are closer to statistical significance than those determined initially.

Additionally, responses to simultaneously presented testing and priming sounds had not been analyzed in a previous study. As shown in correlational analysis, suppression of response under simultaneous priming and testing conditions were related to suppression at various azimuths of a lone priming tone. It is possible that the mechanism responsible for spatial separation is active in both circumstances, with this mechanism responsible for suppressing the priming tone under simultaneous presentation. The response to the testing tone may be suppressed as well, or response to the testing tone may be freed from suppression by some degree by the lack of response to a priming tone. As seen in Figures 17 & 18, some responses were enhanced by the removal of sustained neuron responses, while others were more suppressed. As stated in section 4.3.1., the characteristics of sustained neurons may contribute to responses seen at low ISIs, such as simultaneous presentation.

4.4. Technical Limitations and Sources of Error

While the general trends seen in this study indicate phenomena inherent to the auditory system and appear to support the results obtained by previous research efforts, several aspects of the

experiment and its procedures may have affected the obtained results. Potential sources of error introduced through the initial collection of this data by Sarah Tran have been outlined in section 1.7 & 1.8, and while a variety of measures have been taken to eliminate them from the present study, some may still be present. Great care had been taken to identify single neurons for this dataset, however the electrodes used in the recording procedure were capable of picking up signals over a large range. Interactions from nearby neurons may have effected recorded APs by adding to or subtracting from the amplitudes and waveforms of the neuron of interest. This is a result of recordings taken extracellularly, rather than intracellularly – within the neuron itself. Nearby synapses may have contributed to recordings.

In addition, the recording booth used was not entirely soundproof. Vibrations from sounds occurring external to the booth may have been detected by the animal in the chamber and produced unwanted APs, or may have been identified by the recording neuron itself. This may also have introduced error from the stimulation itself. Stimuli was aimed at each ear via the five azimuths outlined in this experiment, but soundwaves may have reflected from uncovered equipment within the recording booth and presented themselves to the test subject as originating from a location other than the original azimuth. The drug ketamine was used extensively in this experiment as an anaesthetic. Ketamine is known to be an antagonist for NMDA receptors within the brain (Popik et al., 2017), depressing the effects of the neurotransmitters glutamate and GABA. Both of these neurotransmitters are used extensively within both the excitatory and inhibitory pathways of the auditory system. Therefore, responses obtained under anaesthesia may appear more sluggish, delayed, or depressed than may occur under real-life circumstances.

Anaesthesia was also performed by hand. Thus, the level of anaesthesia may fluctuate over the duration of a recording session. Steps taken to rid the dataset of sources of outside interference, such as sorting may not have wholly removed low-quality APs. As sorting was done by hand, researchers may have missed some waveforms for either inclusion or exclusion due to the sheer number of waveforms needing to be sorted. These waveforms may have appeared too similar to high-quality waveforms and were overlooked for exclusion, or had been hidden by the bulk of waveforms in the dataset and were not removed.

4.5. Future Directions and Applications

Given the findings of this study, further research into the topic of suppression and masking in the IC may take the form of several possibilities. To uncover the underlying mechanisms responsible for suppression and masking, future studies may make use of techniques such as electrical stimulation, ablation, and pharmacological interactions to disrupt structures which input to the IC such as the LSO or SPON, and then observe the behaviour of IC neurons without these structures' inputs. This type of mechanistic study could further develop theories regarding the SPON's and LSO's influence on IC neurons. Additionally, further studies may make use of pharmacological agents which act as agonists and antagonists to the neurotransmitters seen in the IC. This would allow for the examination of the role IC neuron channels play in determining the patterns of response typical of the structure. Another option for exploring the phenomenon of masking further would be to examine the effects of altering the duration or frequency of the priming and testing tones on IC neurons. Scientific research drawing inspiration from papers such as this may seek to identify a ratio or formula relating to the suppressive aftereffect as seen

in the IC, or compare observed firing patterns with the morphology of cells producing them. The results found here may also be useful in analysis of responses to priming and testing tones which overlap.

The use of the programming language R in this thesis opens the possibility for future use in the Zhang lab. Its documented uses here are only a small fraction of the language's capacity for statistical analysis – showcasing only the most basic functions. Further, the creation of an "R phrasebank" provides pieces of R code with demonstrated applications which can be lifted and applied in many other circumstances, and to many other sets of data going forward. This phrasebank may serve as a jumping-off point for more projects utilizing the computing power of R, and greater efficiency in analysis overall.

The findings of this study may also one day pave the way for developments in the treatment of hearing problems and auditory processing disorders. Hearing issues are an extremely important area of medical research, and are likely to continue being so as the average age of the Canadian population rises. In addition, interest in the science of hearing has been renewed among the general public by recent science fiction media and speculative commercial products proposing technologies which interface with the brain. Studies such as this one play an integral role in the advancement of technologies which address deficiencies in the auditory pathway and neurological understanding in general.

5. CONCLUSION

The findings of this study contribute to a greater understanding of the mechanisms of hearing under natural conditions, by providing evidence for several psychoacoustic phenomena observed in the auditory system in various circumstances. This study suggests that the responses of IC neurons to a target sound are suppressed by the presence of a sound preceding it. It suggests that this observed suppression can be reduced by separation of the two sounds spatially and temporally. These results provide some insight into the use of spatial cues by the nervous system as it seeks to locate the sources of sound in an environment. In addition, this study adds to the growing set of evidence allowing researchers to speculate that the mechanism responsible for the occurrences seen here are caused by a balance between excitatory and inhibitory inputs to the Inferior Colliculus. Finally, the novel use of the R programming language in this study presents a more efficient means of data analysis than conventional methods formerly used in this lab. The proof-of-concept detailed within this thesis regarding R's application to studying IC masking and suppression may find new life in other projects going forward.

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