5-11-2018

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by

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A Thesis

Submitted to the Faculty of Graduate studies

through the Department of Biological Sciences

in Partial Fulfillment of the Requirments for

the Degree of Master of Science at the

University of Windsor

Windsor, Ontario, Canada

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Abstract

The ability to detect novel sounds in a natural environment has behavioral significance. For instance, novel sounds are important for predation, predator avoidance as well as inter- and intraspecific communications. One of the methods used to study novelty detection is to record neural responses to oddball paradigm. An oddball paradigm is a train of acoustic stimuli in which an oddball sound (Odd) is occasional and randomly interleaved in an otherwise repetitively presented qualitatively different standard sound (Std). Neurons sensitive to novel sounds exist in auditory structures including the auditory midbrain. This study investigated whether neurons in the auditory midbrain use directional cues in the detection of novel sounds. Two free-field speakers were used to present an oddball paradigm. Meanwhile, action potential discharges were recorded from single neurons in the rat's auditory midbrain. In reference to the frontal midline of an animal, the two sounds were either co-localized in front of the ear contralateral to the recording site, or spatially separated such that one sound was presented at the contralateral ear while the other sound was presented at a different location in the frontal azimuth. It was found that many IC neurons generated stronger responses to Odd than Std. Neurons with transient firing patterns increased their responses to Odd presented at the contralateral ear when Std in the same sequence of an oddball paradigm was presented at a location that was ipsilateral to the side of recording. In contrast, neurons with sustained firing typically did not change their response to the Odd sound at the contralateral ear regardless of the position of Std in the frontal azimuth. These findings suggest that transient neurons use directional cues to detect novel sounds under natural hearing conditions. The results provide insights into neuronal mechanisms underlying both auditory novelty detection and spatial hearing.

Acknowledgements

I am exceedingly grateful to my supervisor, Dr. Huiming Zhang, for affording me the opportunity to train in his lab. Dr. Zhang not only provided me with the training I needed as a young scientist, but also with a fatherly shoulder to lean on at tough times. I am forever indebted to him. I would like to extend my sincere gratitude to my committee members, Dr. Barbara Zielinksi and Dr. Christopher Abeare. Their insights were indispensable for my thesis. To the present and past Zhang Lab members, your support in the course of my thesis was humbling. My special thanks to Sarah Tran, Anam Asim, Arpana Balachandar, and Himani Dhar for helping with data analysis and data export. To the ever-reliable technician, Bob Hodge, words cannot express how indebted I am to you. I will never forget how you worked tirelessly with Dr. Zhang to recover my lost data files. Moreover, the mysterious projector glitch on the day of my defense was a nervy one but you stood with me to the very end. Thank you. My sincere thank you to Nancy Barkley, Melissa Gabrieau, and Linda Sterling. Your support was extremely invaluable. Finally, I would like to express my sincere gratitude to my family and friends especially Michael Ajang Garang, David Panchol Alier, Mayom Thon Jok, Lodai Natemo, Arop Deng Jok. Nathaniel Athian Deng, Chol Duot Gak, and Akech Ayor Bol. This project would have been very difficult without their support.

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List of Abbreviations

CN –Cochlear Nucleus

VCN –Ventral Cochlear Nucleus

DCN –Dorsal Cochlear Nucleus

SOC –Superior Olivary Complex

LSO –Lateral Superior Olive

MSO –Medial Superior Olive

MNTB –Medial Nucleus of the Trapezoid Body

SPO –Superior Paraolivary nucleus

PO –Periolivary nuclei

NLL –Nuclei of Lateral Lemniscus

DNLL –Dorsal Nucleus of Lateral Lemniscus

VNLL –Ventral Nucleus of Lateral Lemniscus

IC –Inferior Colliculus

CNIC –Central Nucleus of the Inferior Colliculus

ECIC –External Cortex of the Inferior Colliculus

DCIC –Dorsal Cortex of the Inferior Colliculus

GABA –Gama-aminobutyric acid

MGN –Medial Geniculate Nucleus

MGV –Medial Geniculate Ventral nucleus

MGD –Medial Geniculate Dorsal nucleus

MGM –Medial Geniculate Medial nucleus

AC –Auditory Cortex

AAF –Anterior Auditory Fields

PAF –Posterior Auditory Fields

VAF –Ventral Auditory Fields

SRAF –Suprarhinal Auditory Fields

SSA –Stimulus-Specific Adaptation

MMN - Mismatch Negativity

ITD –Interaural Time Difference

ILD –Interaural Level Difference

1. Introduction

A natural acoustic environment consists of sounds that differ in frequency, temporal characteristics, and spatial location. While some sounds occur occasionally, others are repetitive. Repetitive sounds provide an acoustic background (Clifford et al., 2007) that can be used as a reference in the detection of changes in existing acoustic stimuli (Escera and Malmierca, 2014; Jääskeläinen et al., 2007; Malmierca et al., 2014; Nelken, 2014) as well as prediction of the occurrence of subsequent acoustic events (Henry and Herrmann, 2014). Sounds that occur occassinally (i.e., novel sounds) are crucially important for predation, predator avoidance, inter- and intraspecific communications, and many other behavioural needs of animals (Casseday and Covey, 1996; Malmierca, 2003). Thus, the ability to detect the occurrence of a novel sound is an important function of the auditory system.

1.1. The Auditory System Overview

The sense of hearing is dependent on the auditory system. A sound as a form of mechanical vibration is the sensory modality that activates the auditory pathway. In mammals, hearing is dependent on both the peripheral and the central auditory systems.

In the peripheral auditory system, sound waves are transmitted from the outer to the middle ear then to the inner ear for sensory transduction (Figure 1). The cochlear is the sensory organ in the inner ear that transduces sounds into electrical neural signals. Hair cells are the receptor cells responsible for the auditory sensory transduction. Electrical signals generated by hair cells are transmitted to the central auditory nervous system via the cochlear nerve (also known as auditory nerve) (Figure 1).

Electrical neural signals received by the central nervous system are processed by a number of neural structures. The cochlear nucleus (CN), superior olivary complex (SOC), nucleus of the

lateral lemniscus (NLL), inferior colliculus (IC), medial geniculate nucleus (MGN), and auditory cortex (AC) are the most important structures for auditory signal processing. These auditory structures are connected with each other to form ascending and descending central auditory pathways.

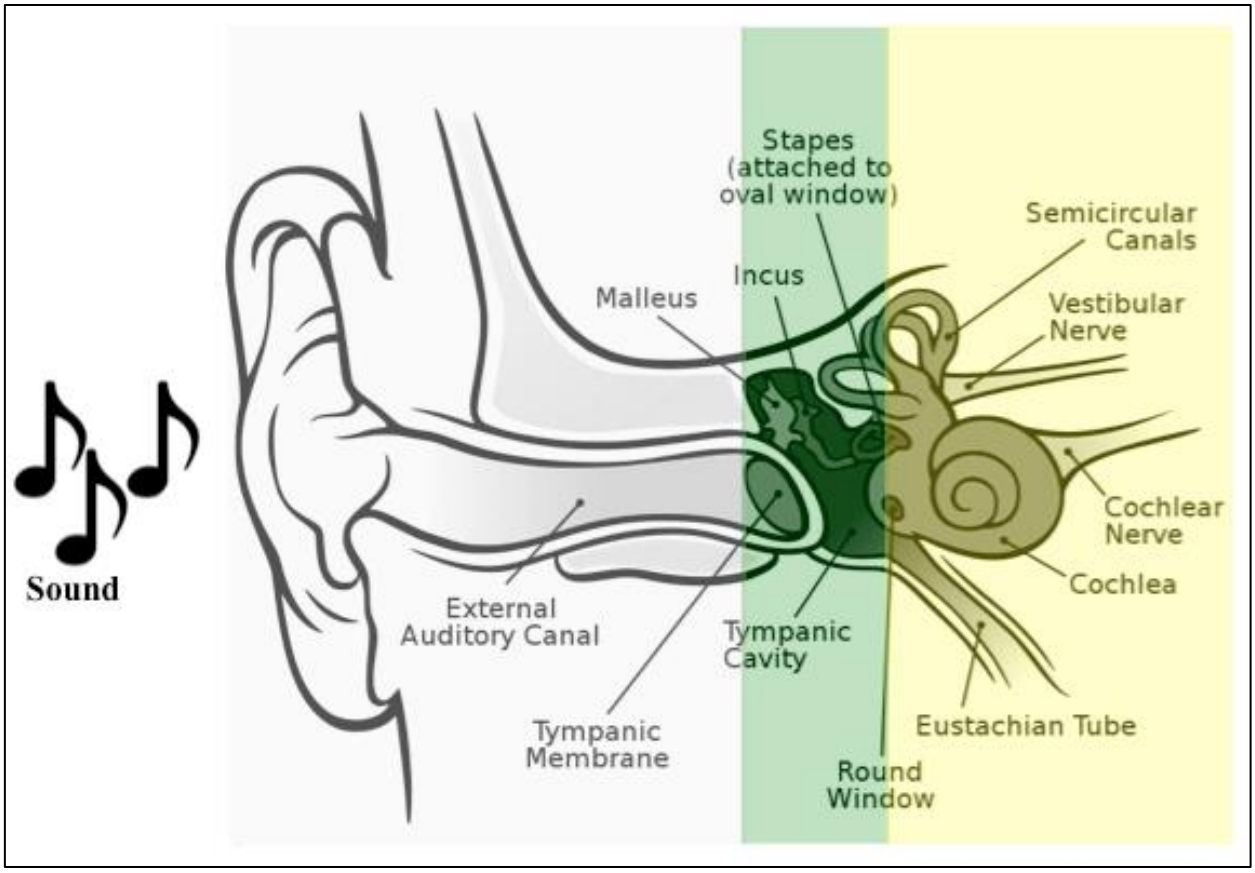
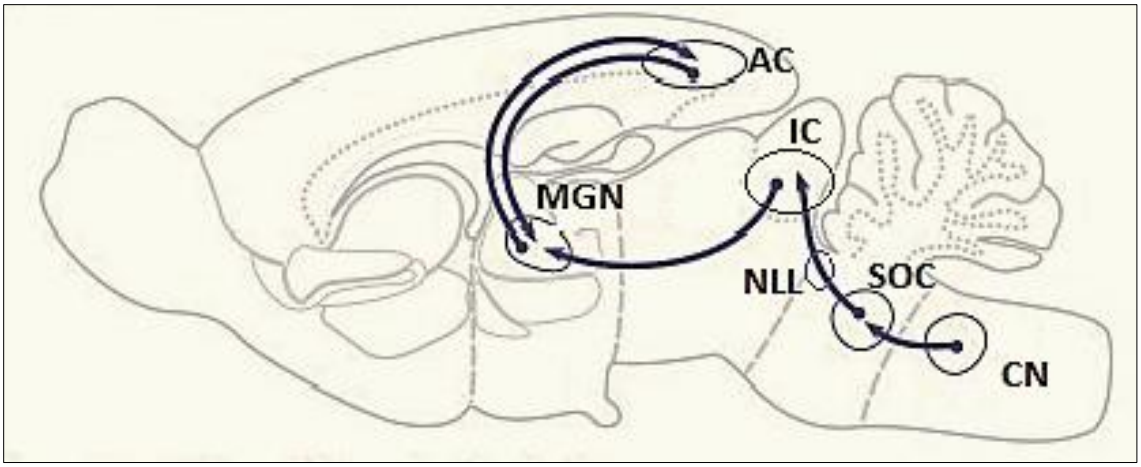


Figure 1. A diagram showing the peripheral auditory system. *Grey shade*: outer ear; *green shade*: middle ear; *yellow shade*: inner ear. Adapted from Chittka and Brockmann (2005).

1.1.1. Ascending Central Auditory Pathway

Ascending central auditory pathways transmit acoustic information obtained from the peripheral auditory system to forebrain auditory structures including the AC (Figure 2). Within these pathways, many neurons are driven by signals originating from both ears. These neurons are said to be binaurally driven or simply binaural. Conversely, other neurons are driven by signals originating from a single ear. These are said to be monaural.



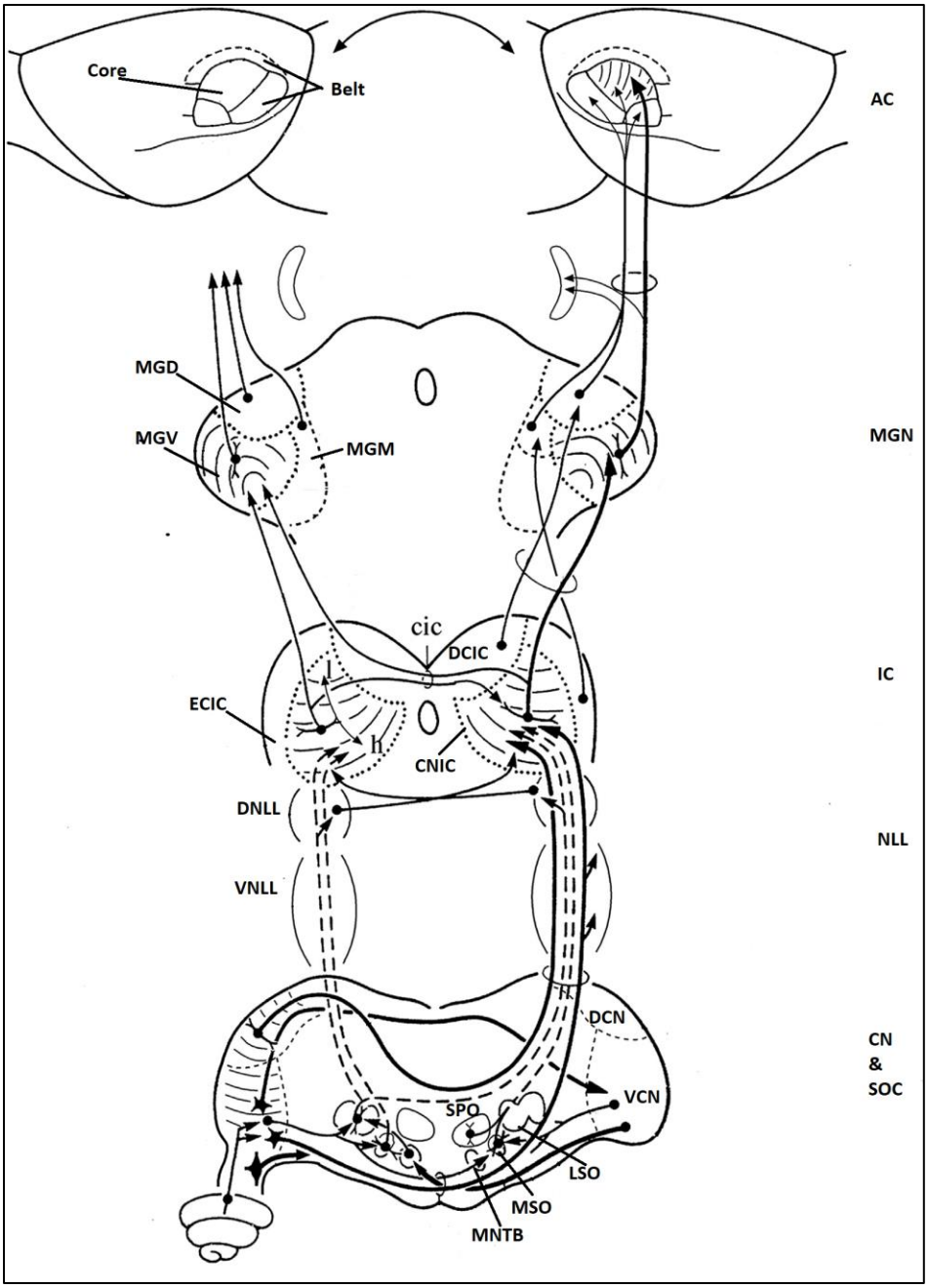


Figure 2. The ascending auditory pathway. Top panel: rodent brain showing major auditory structures (Adapted from Mueller, 2012). Bottom panel: neural connections at each level of auditory processing (adapted from Malmierca, 2015).

1.1.1.1.The Cochlear Nucleus (CN)

The CN is a monoaural brainstem structure and is the target of inputs from the inner ear on the ipsilateral side (i.e., the same side as the CN) (Ryugo and Parks, 2003; Figure 2). The CN and the hair cells in the inner ear are connected by the auditory nerve fibers. The CN is the first auditory processing nucleus in the CNS and consists of two major subdivisions, that is, the ventral cochlear nucleus (VCN) and dorsal cochlear nucleus (DCN) (Figure 2; Harrison and Feldman, 1969; Malmierca, 2015).

The VCN has a number of different types of cells including octopus, globular bushy, spherical bushy, small, and multipolar neurons (Brawer et al., 1974; Merchán et al., 1988; Osen, 1969; Saldaña et al., 1987). These cells are important for encoding and processing temporal information (Young and Davis, 2002; Young et al., 1988) and pitch (Oertel, 1999) of sounds. They are also important for processing frequency contents of behaviorally relevant complex sounds (Malmierca, 2015). Furthermore, they are important for the acoustic startle reflex (Sinex et al., 2001). Neurons in the VCN exhibit tonotopy (Friauf and Ostwald, 1988), that is, they are topographically arranged based on their responses to different sound frequencies. For instance, neurons that respond preferably to low frequency sounds are located in the ventral region of the VCN while neurons that respond preferably to high frequency sounds are located in dorsal region of VCN (Friauf, 1992).

The DCN is composed of pyramidal neurons, giant projecting neurons, and glycinergic interneurons (Rubio, 2004). Like the VCN, the DCN is tonotopically organized with the tonotopic axis running from ventral to dorsal for low and high frequencies respectively (Friauf, 1992). The DCN is mainly involved in coordination of head and/or ears orientation with sound

localization cues (Malmierca, 2015; Young and Davis, 2002). This feature is essential for precise localization of sounds emanating from different sources or moving sounds.

1.1.1.2.The Superior Olivary Complex (SOC)

The SOC is a brainstem structure, which comprises of lateral superior olive (LSO), medial superior olive (MSO), medial nucleus of the trapezoid body (MNTB), superior paraolivary nucleus (SPO), and periolivary nuclei (PO) (Figure 2).

The LSO consists of principal cells as well as other less abundant types of neurons (Rietzel and Friauf, 1998). Neurons in the LSO are tonotopically organized, with those sensitive to high frequencies and low frequencies being located in medial and lateral regions, respectively (Friauf, 1992). Neurons in the LSO are binaural. They receive excitatory inputs from ipsilateral CN and inhibitory inputs from the contralateral CN (Wu and Kelly, 1991; Wu and Kelly, 1992; Wu and Kelly, 1992). This pattern of neural innervation enables neurons in the SOC to encode interaural intensity difference (i.e., the difference in sound intensity between the two ears), which is critical for the localization of high-frequency sounds (Malmierca, 2015; Tollin, 2003; Wu and Kelly, 1992).

The MNTB is located in the most medial region of SOC. It consists of principal and non-principal neurons. While principal neurons resemble the globular busy cells of the CN in morphology and physiological characteristics (Banks and Smith, 1992; Sommer et al., 1993), non-principal cells are elongated and multipolar in shape (Banks and Smith, 1992; Morest, 1998). The MNTB is a primary target of monaural excitatory inputs from contralateral VCN (Brodal, 1981; Paxinos, 2014). Neurons in this structure are also topographically organized (Banks and Smith, 1992; Friauf, 1992; Tolnai et al., 2008). A wealth of experimental evidence about the neurochemistry and neurophysiology of MNTB suggests that the structure is involved

in encoding sound duration (Tolnai et al., 2008) and allows neurons in the LSO to localize high frequency sounds using interaural intensity difference (Banks and Smith 1992; Kopp-Scheinpflug et al., 2008; Sommer et al., 1993).

The MSO sits lateral to the MNTB and medial to the LSO. MSO neurons include principal and non-principal cells. All the cells in the MSO respond only to low frequency sounds (Guinan et al., 1972; Smith, 1995). Principal cells are tonotopically organized with those sensitive to the lowest frequencies of sounds located in the dorsal region and those sensitive to relatively high frequencies located in ventral regions (Golberg and Brown, 1969; Guinan et al., 1972). The MSO receives excitatory inputs from both the ipsilateral and the contralateral CN (Malmierca, 2003; Friauf and Ostwald, 1988). Integration of these inputs enables neurons in this structure to process information related to the interaural-time/phase difference (i.e., the time/phase difference between the two ears generated by a sound) and to localize sounds with low frequencies (Joris et al., 1998; Malmierca, 2015). In addition to excitatory inputs, the MSO also receives inhibitory inputs from MNTB (Smith, 1995).

The SPO is a prominent SOC nucleus, especially in rodents (Schofield, 1995; Schofield and Cant, 1991). It is composed of multipolar neuron population (Kulesza and Berrebi, 2000). These neurons use the gamma-aminobutyric acid (GABA) as a neurotransmitter in their synaptic interaction with other neurons. In many species, the SPO receives inputs from both contralateral and ipsilateral VCN (Friauf and Ostwald, 1988; Saldaña et al., 2009; Schofield, 1995) as well as inhibitory inputs from MNTB (Banks and Smith, 1992; Sommer et al., 1993). In rats, however, SPO neurons are only excited by stimulation of the contralateral ear (Behrend et al., 2002). The SPO encodes temporal features of complex sounds as well as stimulus features across wide frequency ranges (Dehmel et al., 2002; Felix et al., 2011; Kulesza et al., 2003).

The PO is the region surrounding the SOC. It is comprised of morphologically and physiologically diverse types of cells (Adams, 1983; Faye-Lund, 1986; Osen et al., 1984). The PO receives excitatory inputs from both contralateral and ipsilateral VCN (Warr, 1969) as well as inhibitory inputs from ipsilateral MNTB (Spangler et al., 1985; Thompson and Schofield, 2000). Until now, the precise role of PO in hearing is still unclear. Available evidence from neuroanatomical (Kulesza, 2008; Schofield and Cant, 1991) and neurochemical (Helfert et al., 1989; Osen and Roth, 1969; Vetter et al., 1991) studies suggest that this structure has multiple complex functions in auditory processing.

1.1.1.3.Nuclei of Lateral Lemniscus (NLL)

The NLL represents the highest brainstem auditory processing center in mammals. The nucleus has two unique subdivisions with distinct neurochemical and physiological characteristics (Covey and Casseday, 1991; Malmierca et al., 1998). These subdivisions are the dorsal nucleus of lateral lemniscus (DNLL) and the ventral nucleus of lateral lemniscus (VNLL).

The DNLL comprises of at least four types of neurons (Bajo et al., 1993; Wu and Kelly, 1995) with similar physiological properties (Wu and Kelly, 1995; Wu and Kelly, 1996). Although neuroanatomical studies suggest that neurons in the DNLL are tonotopically organized (Friauf, 1992; Kelly et al., 2009), electrophysiological recordings have been unable to find evidence supporting such a suggestion (Bajo et al., 1998; Kelly et al., 1998). The DNLL is a binaural nucleus, which receives inputs from various structures including the contralateral VCN, contralateral DNLL, ipsilateral MSO, ipsilateral SPO, ipsilateral VNLL, and both ipsilateral and contralateral LSO (Malmierca, 2003). The convergence of binaural inputs suggests that this structure is imporant for processing acoustic cues important for sound localization (Ito et al., 1996; Kelly et al., 1996; Malmierca, 2003).

The VNLL is located between SOC and DNLL, and consists of various types of neurons (Malmierca et al., 1998; Merchán and Berbel, 1996; Zhao and Wu, 2001). There is no clear evidence showing the existence of a tonotopic organization in the structure (Nayagam et al., 2006). The VNLL was previously thought to be monoaural with majority of its afferent inputs driven by contralateral VCN and ipsilateral MNTB (Friauf and Ostwald, 1988; Kelly et al., 2009). However, recent neurophysiological data suggest that the VNLL also analyzes binaural acoustic cues (Nayagam et al., 2005, 2006; Zhang and Kelly, 2006). Characteristics of physiological responses of VNLL neurons indicate that these neurons are well suited for processing temporal features of a sound (Nayagam et al., 2005, 2006). The VNLL is also sensitive to biologically meaningful components of a sound such as amplitude and/or frequency modulation. These characteristics make the structure ideal for encoding vocalizations and speech-like communications (Merchán et al., 1997).

1.1.1.4.The Inferior colliculus (IC)

The IC is a midbrain auditory structure. It integrates information from auditory brainstem and relays it to medial geniculate nucleus, and subsequently to the auditory cortex via ascending projections (Figure 2; Malmierca et al., 2003; Winer and Schreiner, 2005). Its strategic position makes it ideal for processing complex acoustic stimuli (Aguillon et al., 2013; Aitkin, 1986; Casseday and Covey, 1996). The IC is subdivided into three regions with distinct anatomical and physiological features. These subdivisions include central nucleus (CNIC), external cortex (ECIC), and dorsal cortex (DCIC) (Figure 3) (Faye-Lund and Osen, 1985; Loftus et al., 2008; Malmierca et al., 2011; Malmierca et al., 1993; Malmierca et al., 1995; Willard and Martin, 1983; Willard and Ryugo, 1983).

The rat CNIC is mainly composed of two cell types: the flat and the less flat neurons (Malmierca et al., 1993; Malmierca et al., 1995). These neurons are arranged in layers, leading to a laminar organization of the collicular subdivision (Faye-Lund and Osen, 1985; Loftus et al., 2008; Malmierca et al., 1991; Malmierca et al., 1995). Results from electrophysiological recordings have shown that this laminar organization serves as a structural basis of tonotopy in the CNIC (Hernández et al., 2005; Izquierdo et al., 2008; Malmierca et al., 2008).

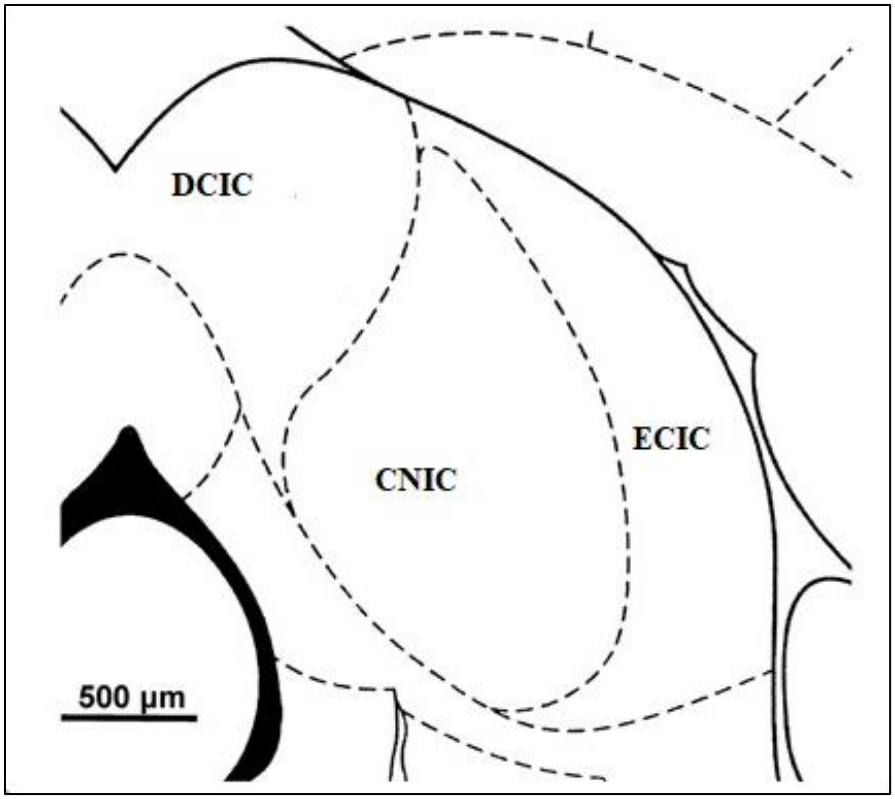


Figure 3. Subdivisions of the inferior colliculus. CNIC, central nucleus of the inferior colliculus; DCIC, dorsal cortex of the inferior colliculus; ECIC, external cortex of the inferior colliculus. Adapted from Ouda and Syka, 2012.

In the CNIC, neurons sensitive to low-frequencies are located in dorsolateral regions while those sensitive to high-frequencies are located in ventromedial regions (Kelly et al., 1991; Pierson and Snyder-Keller, 1994; Ryan et al., 1988). CNIC neurons typically display high frequency specificity as indicated by their narrow frequency tuning curves. Most of these neurons are excited by stimuli presented at the contralateral ear and inhibited by stimuli presented at the ipsilateral ear (Aitkin et al., 1975; Kelly et al., 1991).

The major inhibitory neurotransmitters in the CNIC are GABA and glycine as evident in the expression of their receptors (Burianova et al., 2009; Choy et al., 2015; Fredrich et al., 2009; Merchán et al., 2005; Ouda and Syka, 2012). The CNIC also express glutamate receptors (Altschuler et al., 2008; Ito et al., 2011), suggesting that glutamate is the major excitatory neurotransmitter. Intracellular current injections into the CNIC have revealed different firing patterns including onset, sustained-regular, pause-build, rebound-regular, rebound-adapting, and rebound transient (Peruzzi et al., 2000; Sivaramakrishnan and Oliver, 2001).

Major ascending inputs to the CNIC originate primarily from brainstem structures (Faye-Lund and Osen, 1985; Malmierca et al., 1993; Malmierca et al., 1995). It also receives excitatory descending projections from the auditory cortex (Saldana et al., 1996). The CNIC is thought to be important for processing essential characteristics (i.e. spectro-temporal) of a sound (Aitkin et al., 1994; Malmierca and Merchán, 2004; Jenkins and Masterson, 1982; Li et al., 1998).

The ECIC covers lateral, rostral, and ventral regions of the CNIC (Malmierca, 1991). The ECIC is composed of diverse types of cells including bitufted, pyramidal-like, chandelier (Malmierca, 1991; Malmierca et al., 2011) just to name a few. Unlike CNIC, ECIC does not exhibit a tonotopic organization. Neurons in the ECIC have very broad frequency tuning curves with poorly defined characteristic frequency (Aitkin et al., 1975; Binns et al., 1992). The ECIC

uses glutamate (Ohishi et al., 1993) and GABA as major neurotransmitters (Jamal et al., 2012). ECIC neurons respond typically to binaural stimulation (Aitkin et al., 1975) with various firing patterns including onset, pause, sustained, and adapting (Ahuja and Wu, 2007; Palombi and Caspary, 1996) The ECIC integrates information from multiple sensory inputs (Winer and Schreiner, 2005). For instance, it receives inputs from auditory cortex (Faye-Lund, 1985; Herbert et al., 1991; Huffman and Henson, 1990; Saldana et al., 1996) as well as non-auditory structures including substantia nigra (Coleman and Clerici, 1987; Olaźbal and Moore, 1989). It is believed that the ECIC is involved in conspecific vocal recognition (Aitkin et al., 1994).

The DCIC occupies the caudal and dorso-medial regions of the CNIC (Malmierca and Merchán, 2004). Neurons in this colliculuar subdivision are diverse and share some features with those CNIC and ECIC neurons bordering the DCIC (Malmierca et al., 2011). A distinct characteristic of DCIC neurons is the expression of nitric oxide synthase (Druga and Syka, 1993; Herbert et al., 1991), suggesting these neurons use nitric oxide as a neurotransmitter receptor. The majority of neurons in the DCIC typically have broad frequency tuning curves (Aitkin et al., 1994; Aitkin et al., 1975). Although its function is poorly understood, some studies suggest that the DCIC might be involved in re-directing attention to an acoustic source (Caird, 1991; Jane et al., 1965; Pérez González et al., 2005).

The IC also has commissural and intrinsic connections. While commissural projections connect the right and left IC, intrinsic connections link subdivisions within the IC on each side. Although the morphology of these fibers is yet to be described in details, studies have suggested that they might be axons of neurons projecting to other structures or axons of IC internerneurons sending inputs to the opposite IC (González-Hernández, 1991; Malmierca et al., 2009b; Saldãna and Merchán, 2005). Commissural inputs can be either excitatory or inhibitory (Malmierca et al.,

2003, 2005; Li et al., 1998, 1999), with GABA (Hernandez et al., 2006) and glutamate (Saint-Marie, 1996) as major neurotransmitters. Findings from Malmierca et al. (2003, 2005) suggest that commissural connections might serve to modulate spectro-temporal as well as binaural properties of IC neurons.

The IC is a common nexus for ascending inputs from brainstem structures and descending inputs from forebrain structures (Casseday et al., 2002; Pollak, 2012; Winer et al., 1995). These inputs can be excitatory and/or inhibitory, and are monoaurally or binaurally driven. Monoaural inputs to the IC originate primarily from the CN, the VNLL, and the MGN. CN efferent projections to the IC are mostly excitatory with stronger inputs to the contralateral IC (Malmierca, 2015; Pollak, 2012). The IC also receives inhibitory projections from ipsilateral VNLL (Riquelme et al., 2001). Inputs from MGN to the IC are primarily excitatory and ipsilateral (Ito et al., 2016; Malmierca, 2015).

Inputs from binaural auditory structures to the IC are from the LSO, MSO, SPO, PO, DNLL, MGN, and AC. Projections from the LSO to the IC are both excitatory and inhibitory (Pollak et al., 2002; Pollak, 2012). While excitatory inputs are driven by the contralateral ear, inhibitory inputs are mostly driven by the ipsilateral ear (Brodal, 1981; Kopp-Scheinpflug et al., 2008; Malmierca, 2015). Inputs from the MSO to the IC are mainly excitatory and ipsilateral (Malmierca, 2015). Projections from SPO project to the ipsilateral IC and are inhibitory (Malmierca, 2015; Pollak, 2012; Schofield, 1995). The DNLL sends inhibitory projections to both contralateral and ipsilateral IC (Grothe et al., 2010; Malmierca, 2015; Pollak et al., 2002; Pollak, 2012). Finally, the AC sends both ipsilateral and contralateral excitatory projections to the IC (Feliciano and Potashner, 1995; Malmierca, 2015). The IC also receives commissural projections (Saldaña and Merchán, 2005) from the opposite IC via the commissure of the IC.

1.1.1.5.The Medial Geniculate Nucleus (MGN)

The MGN represents the thalamic auditory processing center, which relays acoustic information from the auditory midbrain to the auditory cortex. It is subdivided into three subnuclei including ventral (MGV), dorsal (MGD), and medial (MGM) parts of the medial geniculate nucleus (Clerici and Coleman, 1990; Clerici et al., 1990; Winer et al., 1999a). The MGN receives afferent inputs predominantly from the ipsilateral IC (Winer, 1992; Winer et al., 1992). Compared with other 5 major auditory structures along the ascending auditory pathway, the MGN has the least number of GABAergic neurons (Winer and Larue, 1988).

The MGV mainly consists of tufted neurons (Bartlett and Smith, 1999; Clerici et al., 1990; Olucha-Bordonau et al., 2004; Winer et al., 1999a). It also has a small population of GABAergic interneurons (Clerici et al., 1990; Winer et al., 1999a; Winer and Larue, 1996). Tufted neurons have characteristic depolarizing sag potential (Hu, 1995) and exhibit narrow frequency tuning curves (Malmierca, 2015). Main afferent inputs to the MGV originate from ipsilateral IC (Ito et al., 2009, 2011; Ito and Oliver, 2010, 2012) with both inhibitory and excitatory effects (Peruzzi et al., 1997; Ito and Oliver 2012). The tufted neurons along with afferent fibres from the IC form fibrodendritic laminae (Clerici et al., 1990; Winer et al., 1999a), which serve as a structural basis of a tonotopic organization (Bordi and LeDoux, 1994). The laminae are characteristically arranged in a curved dorsovental axis inclined at 40˚ from vertical plane (Winer et al., 1999a). Evidence suggests that the MGV likely encode both interaural time and intensity differences (Malmierca, 2015). Moreover, it is involved in selective attention (Arcelli et al., 1997).

The MGD can be further divided into five subnuclei (Clerici et al., 1990; Clerici and Coleman, 1990; Winer et al., 1999a). The MGD receives inhibitory and excitatory ascending inputs from the ipsilateral IC (Bartlett and Smith, 1999) as well as nonauditory areas (Jones,

2012). Auditory functions of these subnuclei are less understood. These nuclei consist of two types of neurons including tufted and stellate neurons (Clerici et al., 1990; Bartlett and Smith, 1999; Winer et al., 1999a). Unlike the MGV, the MGD neurons are broadly tuned and respond to wide range of acoustic stimuli (Malmierca, 2015). Moreover, the MGD does not exhibit tonotopic organization (Storace et al., 2010). MGD neurons prefer complex acoustic stimuli to pure tones (Bordi and LeDoux, 1994) suggesting that they might be involved in discrimination of behaviourally relevant sounds.

The MGM is the smallest nucleus of the MGN (Malmierca, 2015), but has diverse types of neurons (Clerici et al., 1990; Winer et al., 1999b). Ascending inputs to this subdivision originate mainly from CN, SOC, VLL, and IC (Malmierca, 2002; Bajo et al., 1993; Vinuela et al., 2011). Besides auditory stimuli, MGM neuros also respond to somatosensory inputs and provide projections to the amygdala (Bordi and LeDoux, 1994; LeDoux et al., 1990). Thus, MGM is thought to process emotional significance of acoustic stimuli (LeDoux et al., 1984, 1986).

1.1.1.6.The Auditory Cortex (AC)

The AC is the highest processing center in the ascending auditory pathway. It is located in the temporal lobe of the cerebral cortex. In the rat, the AC is divided into *core area* (equivalanet to the primary auditory cortex or A1 in other species) and the surrounding *belt area* (equivalent to secondary and association auditory cortex in other species) (Paxinos and Watson, 2014).

The core area of the AC consists of six distinct layers based on cell types and density (Hefti and Smith, 2000; Malmierca and Ryugi, 2011; Storace et al., 2010, 2011; Winer et al., 1992). These are referred to as Layers I, II, III, IV, V, and VI (Games and Winer, 1988). While Layer I has very few neurons, Layer II is densely packed. Layer III is characterized by the presence of both pyramidal and non-pyramidal neurons with heterogeneous orientation of their dendritic

arbors. Layer IV has abundance of small stellate neurons and the density of neurons is slightly higher than that in Layer III. Layer V is the thickest layer and populated mainly by pyramidal cells especially in the upper regions. Layer VI has both non-pyramidal and pyramidal neurons. Neurons in the A1 have narrow frequency tuning curves and exhibit a tonotopic organization. Neurons sensitive to high and low frequency are at the dorsolateral and ventrocaudal regions, respectively (Doron et al., 2002; Polley et al., 2007; Pandya et al., 2007; Kilgard and Merzenich, 1998, 1999; Malmierca and Hackett, 2010). While pyramidal neurons in A1 are primarily gutamatergic, the presence of GABA receptors has been attributed to non-pyramidal neurons (Winer and Larue, 1989; Winer, 1992). The A1 receives inputs mainly from ipsilateral MGV (Clerici and Coleman, 1990; Winer et al., 1999b, Kimura et al., 2003; Storace et al., 2010, 2011, 2012; Jones, 2012; Winer and Lee, 2007).

The *belt area* is made up of anterior auditory fields (AAF), posterior auditory fields (PAF), ventral auditory fields (VAF), and suprarhinal auditory fields (SRAF) (Polley et al., 2007; Storace et al., 2010, 2011, 2012). Neurons in the *belt area* of the AC typically have broad frequency tuning curves and longer latencies of responses (Clerici and Coleman, 1990; Winer et al., 1999c, Kamura et al., 2003; Storace et al., 2010, 2011, 2012; Jones, 2012; Winer and Lee, 2007). Moreover, these neurons adapt slowly to tones and noise, and show no selectivity to direction of sound as well as rate of sound presentation (Pandya et al., 2008). Neurons in this area receive afferent inputs mainly from MGM and MGD (Arnault and Roger, 1990; Clerici and Coleman, 1990; Smith et al., 2010, 2012; Storace et al., 2010, 2011, 2012; Jones, 2007; 1990; Winer et al., 1999c, Kamura et al., 2003; Storace et al., 2010, 2011, 2012; Jones, 2012; Winer and Lee, 2007). Evidence obtained from human subjects with damaged AC (Cavinato et al.,

2012) and experimental animals with lesions (Heffner and Heffner, 1986) suggest that AC is the ultimate site of perception for auditory sensation.

1.1.2. Descending Auditory Pathway

Within the central auditory system, neurons in higher structures regulate neural processing in lower structures using descending pathways (Figure 4). Major descending projections include those from the AC (corticofugal pathway), the IC (colliculofugal pathway), and the superior olivary complex (olivocochlear pathway).

Descending projections from the primary AC terminate heavily in the MGV and MGD (Bartlett et al., 2000; Llano and Sherman, 2009) while most projections from the *belt area* or the secondary AC terminate predominantly in MGM (Arnault and Roger, 1990). The majority of these projections are excitatory (Bartlett et al., 2000; Potashner et al., 1988) although inhibitory projections are also found (Bartlett et al., 2000).

Projections from the AC to the CNIC originate primarily from the primary cortex (Saldaña et al., 1996) while projections to DCIC and ECIC originate primarily from secondary auditory cortex (Herbert et al., 1991). Efferent fibres from the AC to the IC are predominantly excitatory, although inhibitory projections are also found (Anderson and Malmierca, 2013; Games and Winer, 1988; Nwabueze-Ogbo et al., 2002; Saldaña et al., 1996). It is not completely understood whether these projections serve to modulate the activity of neurons in the IC or provide a major drive to excite these neurons. In addition to MGN and IC, the AC also sends direct projections to the SOC and CN in the auditory brainstem (Doucet et al., 2002; Saldaña et al., 1996; Weedman and Ryugo, 1996a, 1996b).

The colliculofugal pathway represents descending fibers that originate from the IC and terminate in brainstem auditory structures. Some of the descending fibres from the IC innervate

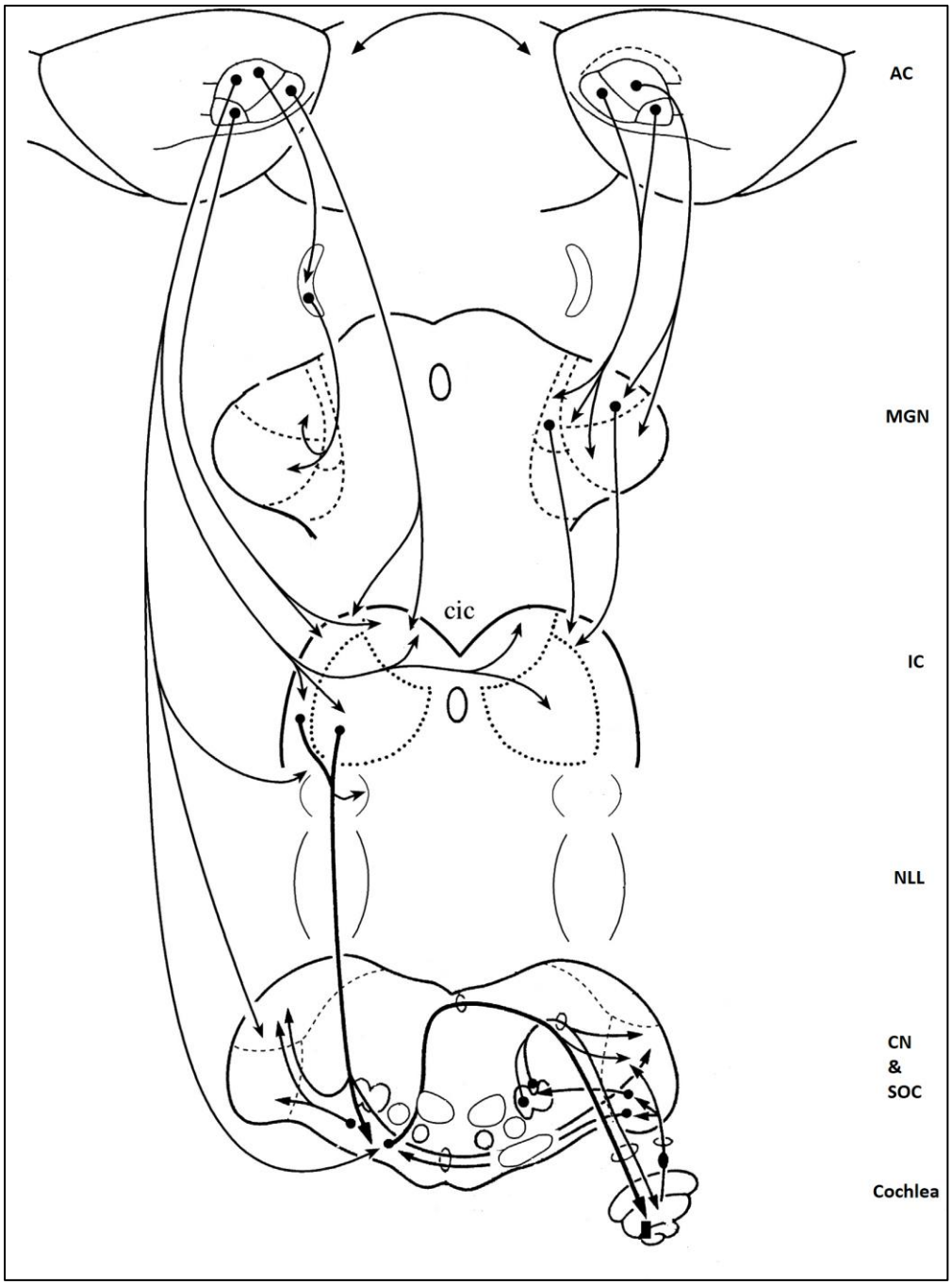


Figure 4. A diagram showing neural connections in the descending auditory pathway (See list of Abbreviations for names). Adapted and modified from Malmierca (2015).

the NLL (Malmierca and Ryugo, 2012). These fibers originate primarily from ECIC and CNIC (Brodal, 1981). Other fibers from the IC, especially those originate from the DCIC and ECIC, innervating those neurons in the PO that project to the cochlear (Caicedo and Herbert, 1993; Faye-Lund, 1986; Saldanã, 1993; Vetter et al., 1993). Findings from electrophysiological studies (Dolan and Nuttall, 1988; Rajan, 1990) suggest that these fibers modulate cochlear activity. There are also fibres from the ECIC and CNIC that project to the CN (Caicedo and Herbert, 1993; Faye-Lund, 1986; Saldanã, 1993; Vetter et al., 1993). The function of these projections is less understood.

The olivocochlear pathway consists of efferent fibres originating from the SOC that innervates the Organ of Corti in the cochlear (Rasmusen, 1946). These fibres innervate both outer and inner hair cells. Olivocochlear fibers innervating the outer hair cells originate bilaterally from medial region of the SOC (Horváth et al., 2000; Robertson et al., 1989; Warr et al., 1997; White and Warr, 1983) and are cholinergic (Osen et al., 1984; Vetter et al., 1991). Olivocochlear fibers that project to inner hair cells originate primarily from lateral SOC on the ipsilateral side (Horváth et al., 2000; Robertson et la., 1989; Warr et al., 1997; White and Warr, 1983). These projecting neurons in the lateral SOC are either GABAergic or cholinergic (Vetter et al., 1991).

Existing knowledge suggest that descending pathways plays an important role in the processing of behaviorally significant sounds.

1.2. The IC as a Major Auditory Integration Center

The IC is a target of convergent inputs from multiple brain areas (Ono and Ito, 2015). The convergence of inputs from different sources creates heterogeneity of neuronal ensembles that

can integrate information from different spectro-temporal domains (Pollak et al., 2002; Xie et al., 2005, 2007).

In the spectral domain, the IC is tonotopically organized into distinct frequency-response areas (Winer and Schreiner, 2005) especially in its CNIC (Kelly et al., 1991; Pierson and Snyder-Keller, 1994; Ryan et al., 1988). While majority of neurons in cortical regions of the IC process a wide range of frequencies (Aitkin et al., 1994, 1975; Binns et al., 1992), neurons in the CNIC typically respond to a relatively narrow range of frequencies (Aitkin et al., 1975). Studies with mustached bats (Mittmann and Wenstrup, 1995; Portfors and Wenstrup, 2002) and mice (Portfors and Felix, 2005) showed the existence of neurons in the IC that are tuned to multiple frequency bands. While majority of these neurons show facilitatory responses to combination of multiple frequencies (Mittmann and Wenstrup, 1995; Portfors and Felix, 2005; Portfors and Wenstrup, 2002), others are inhibited by the presence of a second sound (Mittmann and Wenstrup, 1995; Portfors and Felix, 2005).

The existence of neurons sensitive to timing of acoustic stimulus (Koch and Grothe, 2003; Pollak, 2012) has been demonstrated in the IC. For instance, Zhang and Kelly (2009) found that a preceding ipsilateral sound presented a few milliseconds earlier can enhance or suppress an IC neuron's response to a contralaterally presented trailing sound. Similarly, a contralaterally presented preceding sound can enable an IC neuron to respond to a trailing ipsilaterally presented sound it was initially unresponsive to when presented alone (Burger and Pollak, 2001).

The convergence of inputs in the IC also creates neuronal populations that are sensitive to directional cues (Pollak, 2012). In the IC, majority of neurons are inhibited by ipsilateral stimulation and excited by contralateral stimulation (Pollak, 2012). The balance between excitatory and inhibitory inputs is a critical feature for signal processing in the central nervous

system (Burger and Pollak, 2001; Wehr and Zador, 2003; Sun et al., 2010), including the IC (Sivaramakrishnan et al., 2004; Xiong et al., 2013). In fact, sound localization, one of the IC's important functions (Kuwada et al., 1997) is in part attributed to the interaction of excitation and inhibition (Lauer et al., 2011; Li et al., 2010; Li and Pollak, 2013).

Put together, these findings suggest that IC neurons are capable of extracting spatiotemporal cues of an acoustic stimulus in the environment (Aitkin and Martin, 1987; Grothe et al., 1996).

1.3. Auditory Novelty Detection and Neural Sensitivity to Novel Sounds in the IC

1.3.1. Novel Sounds in the Acoustic Environment

Animals have the ability to effectively detect an occasionally occurring new acoustic stimulus rather than constant or regularly occurring stimuli. As occasionally occurring sounds are of crucial importance for behavioural needs of animals (Casseday and Covey, 1996; Malmierca, 2003), finding neural mechanisms responsible for the detection of such sounds are important for understand hearing.

1.3.2. Studying Auditory Neural Sensitivities in a Laboratory Setting

In the laboratory, neural processing of novel sounds is typically studied using oddball paradigms (Figure 5). An oddball paradigm is a train of acoustic stimuli constructed using two qualitatively different sounds. In the train of stimuli, the two sounds are presented in a random sequence, with one sound presented at a high probability (standard sound, or Std) and the other one presented at a low probability (oddball sound, or Odd).

Neural correlates of auditory novelty detection were studied in humans by recording cortical response to oddball paradigms. Compared with the response elicited by a standard sound, the response elicited by a novel sound has a mid to long latency component. This component is termed as mismatch negativity (MMN; Näätänen et al., 1978; Näätänen et al., 2007) and is

believed to reflect neural sensitivity to a novel sound (Näätänen et al., 2007; Näätänen and Alho, 1995). Recent studies suggest that multiple auditory structures contribute MMN (Escera and Malmierca, 2014; Grimm and Escera, 2012; Winkler et al., 2013). These structures include the AC, (Recasens et al., 2012), MGN (Cacciaglia et al., 2015; Grimm et al, 2011; Slabu et al., 2010), and IC (Cacciaglia et al., 2015; Slabu et al., 2012; Slabu et al., 2010).

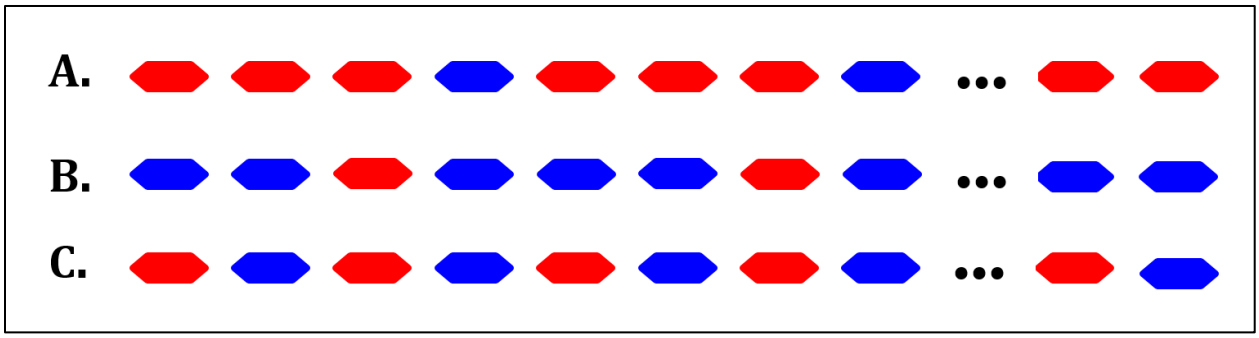


Figure 5. Figure of an oddball paradigm. A. *TL* (Blue) Odd, *TH* (red) Std; B. *TL* (Blue) Std, *TH* (red) Odd; C. *TL* (blue) equal probability, *TH* (red) equal probability.

Electrophysiological recordings from animal models have provided insights into neural correlates and mechanisms of auditory novelty detection at the level of single neurons. In these studies, the sensitivity of single neurons to a novel sound was termed as stimulus-specific adaptation (SSA) (Jääskeläinen et al., 2007; Ulanovsky et al., 2003). It has been found that auditory neurons reduce their responses to repetitive sound stimulation but restore their responses upon the presentation of a qualitatively different sound. Thus, the adaptation over repetitive presentation of a sound is specific for this specific sound but not generalized to other sounds in the environment. SSA resembles habituation and dishabituation of a behavioral response (Thompson and Spencer, 1966). It is believed that the SSA plays a significant role in filtering out sounds of less behavioral significance in the auditory scene while enhancing the

salience of sounds of behavioural significance in the scene (Nelken and Ulanovsky, 2007; Ulanovsky et al., 2004).

SSA has been widely studied in auditory structures including the AC (Antunes et al., 2010; Farley et al., 2010; Nieto-Diego and Malmierca, 2016; Szymanski et al., 2009; Taaseh et al., 2011; Ulanovsky et al., 2003; Von Der Behrens et al., 2009), MGN (Anderson et al., 2009; Antunes et al., 2010; Antunes and Malmierca, 2014; Duque et al., 2014), and IC (Anderson and Malmierca, 2013; Ayala and Malmierca, 2013, 2015; Ayala et al., 2012; Duque et al., 2012, 2016; Malmierca et al., 2009; Pérez-González et al., 2012; Zhao et al., 2011). It seems that SSA does not exist in lower brainstem structures such as the CN (Ayala et al., 2012; Nelken, 2014). Existing findings suggest that IC is the structure in the auditory pathway where SSA first emerges (Malmierca et al., 2009; Nelken, 2014). In the IC, SSA tended to be stronger in ECIC and DCIC (Duque et al., 2012; Malmierca et al., 2009) than in CNIC (Duque et al., 2012; Malmierca et al., 2009).

Previous studies on SSA were conducted by using oddball paradigms presented under a closed-field condition (i.e., from earphones) (e.g., Anderson et al., 2009; Antunes et al., 2010; Farley et al., 2010; Malmierca et al., 2009; Pérez-González et al., 2012; Ulanovsky et al., 2003; Von Der Behrens et al., 2009; Zhao et al., 2011). However, a natural acoustic environment presents a challenge to many animals as sounds can emanate from an array of sources. This can pose severe constraint to detection and perception of signals for receivers (Bronkhorst, 2000; Brumm and Slabbekoorn, 2005; Wiley, 2006, 2013). It is therefore important to study SSA in the presence of spatial cues.

A previous study investigated whether neurons displayed SSA for oddball paradigms containing spatial cues such as interaural time and intensity differences in barn owl. In this study,

a spatial cue was created using dichotic stimuli, that is, sounds presented from a pair of earphones that carry "virtual" spatial cues (Reches and Gutfreund, 2008). It found SSA in brain regions higher than the IC in hierarchy, but not in the IC. Although this study contributes to our understanding of the effect of spatial cues, it presents practical limits (Hartmann and Macaulay, 2014) in that it only artificially represents natural hearing conditions.

The co-existence of neurons sensitive to binaural cues, temporal sequence of sounds (Burger and Pollak, 2001; Zhang and Kelly, 2009), and novelty of sounds (Anderson and Malmierca, 2013; Ayala and Malmierca, 2013, 2015; Ayala et al., 2012; Duque et al., 2012, 2016; Malmierca et al., 2009; Pérez-González et al., 2012; Zhao et al., 2011) in the IC suggest that spatial cues can be used by IC neurons to detect a novel sound in an oddball paradigm. To verify this possibility, a recent study (Patel and Zhang, 2016) was conducted by presenting oddball paradigms from free-field speakers located in the azimuthal plane in front of the animal. Standard and oddball sounds of an oddball paradigm were either presented from one single speaker located directly in front of the animal (denoted as 0° azimuth) or with one sound from 0° azimuth and the other sound from another azimuthal location. Results indicated that spatial separation between oddball and standard sounds affects responses of IC neurons to both sounds. This study has provided important information about how the sensitivity of an IC neuron to a novel sound is dependent on the spatial relationship between standard and novel sounds. However, only limited speaker spatial arrangements were used in the study. A generalized conclusion about how neural detection of a novel sound is dependent on the spatial relationship between the novel sound and a regularly presented standard sound can be made only if more speaker arrangements are used in the research. From mechanistic point of view, it is important to find how neural detection of novel sounds is dependent on the excitatory-inhibitory interaction in

the midbrain auditory neurons. Previous studies have shown that an acoustic stimulus presented in the contralateral ear excites most neurons in the IC while ipsilateral stimulation inhibits them (Pollak et al., 2002; Pollak, 2012). Moreover, responses to a contralateral sound can be modulated by an ipsilateral sound (Zhang and Kelly, 2009). It is therefore important to examine whether a sound presented at the ear that exerts an inhibitory effect on an IC neuron (i.e., the ipsilateral ear) can affect the responses elicited by the stimulation of the ear that exerts an excitatory effect on an IC neuron (i.e., the contralateral ear). The present study was designed to address the above questions.

1.4. Objectives

The main objective of this study was to investigate whether spatial cues affect IC responses to the two sounds of an oddball paradigm. Specifically, I examined whether:

I. The position of one sound, presented at various locations in the frontal azimuth, affects single unit responses to the second sound presented at the contralateral ear.

II. The sound fixed at the contralateral ear affects responses to the second sound presented at various locations in the frontal azimuth.

III. And, to understand possible mechanisms underlying detection of novel sounds in a natural acoustic environment.

It was hypothesized that the effect of spatial cues on acoustic novelty detection (for instance, Patel and Zhang, 2016) is in part due to altered balance of excitation and inhibition between the two ears.

2. Materials and Methods

2.1. Subjects

Wistar albino rats (*Rattus norvegicus*) were used in the present study. Adult male rats weighing between 250-500g were obtained from Charles River Laboratories Inc. (St. Constant, Quebec, Canada) and housed in the University of Windsor Animal Care Facility for at least a week before experiment were conducted. The housing conditions were maintained at 25°C temperature, 40-60% humidity, and 55-60 dB SPL noise level with normal 12hr day/light cycle. The rodent food and water were available ad libitum. All procedures were approved by the University of Windsor Animal Care Committee, and carried out pursuant to the guidelines of the Canadian Council on Animal Care.

2.2. Surgical procedures

Surgical anesthesia was induced by a combined intramuscular injection of ketamine hydrochloride (60 mg/kg) and xylazine hydrochloride (10 mg/kg). The anesthesia was maintained throughout a surgery and subsequent neurophysiological recording session with supplemental injections of ketamine hydroxide (20 mg/kg) and xylazine hydrochloride (3.3 mg/kg) at an interval of 30-45 minutes or as necessary.

Once the animal was fully anesthetised, the fur was clipped from the head to expose the skin. A mid-sagittal incision was made in the scalp, followed by lateral retraction of periosteum to expose the cranium. Three bone screws were drilled into the cranium about the mid-sagittal suture just anterior to Bregma. A stainless steel headbar was cemented onto the cranium and the bone screws with dental acrylic. The headbar was used to keep the animal's head stably in a natural position.

A small craniotomy was made on the right side of the skull around the lambda suture just over the parietal and temporal lobes. The dura matter was removed to permit the placement of a recording electrode into the IC.

After surgery, the animal was transferred into a single-walled sound booth (Eckel Industries, Morrisburg, Ontario) for recording. Inside the booth, the head-bar was attached to a stereotaxic instrument (Kopf Instruments, Tujunga, California). The stereotaxic instrument and the micromanipulator used for holding a recording electrode were modified to minimize obstruction and reflection of acoustic stimuli. The body temperature of the animal was maintained at 37°C with a heating pad of a homeothermic system (Harvard Apparatus) throughout the experiment. The control unit of the homeothermic system was placed outside the recording booth to reduce electric and acoustic interferences.

2.3. Recording electrodes

A single-barrel glass micropipette with a tip diameter of 1.5-2.0μm was pulled using P-97 micropipette puller (Sutter Instruments) and ws used to record action potential discharges from single neurons. The micropipette recording-electrode was filled with either 2M NaCl, or 0.50 M CH_3COONa (sodium acetate) in 3% Chicago Sky Blue with the impedance ranging from 10 to 80 MΩ.

2.4. Acoustic stimulation

Sound waveforms were generated digitally and converted to analog signals using a System 3 signal processing system controlled by a desktop computer running OpenEx software (Tuck-Davis Technologies). The signals were amplified and fed into a pair of CF1 free-field speakers (each speaker 50 cm from the midpoint of the interaural line of the animal (See Figure 6). Each speaker was calibrated over 100 and 65,000 Hz at five azimuths locations using a model 4135 microphone and a model 2608 measuring amplifier (Brüel & Kjaer, Dorval, QC). The azimuths included the midline of the frontal field (denoted by 0°) and 45° and 90° on the ipsi- and contralateral of the recording site (denoted by i45°, i90°, c45°, and c90°) (Figure 6).

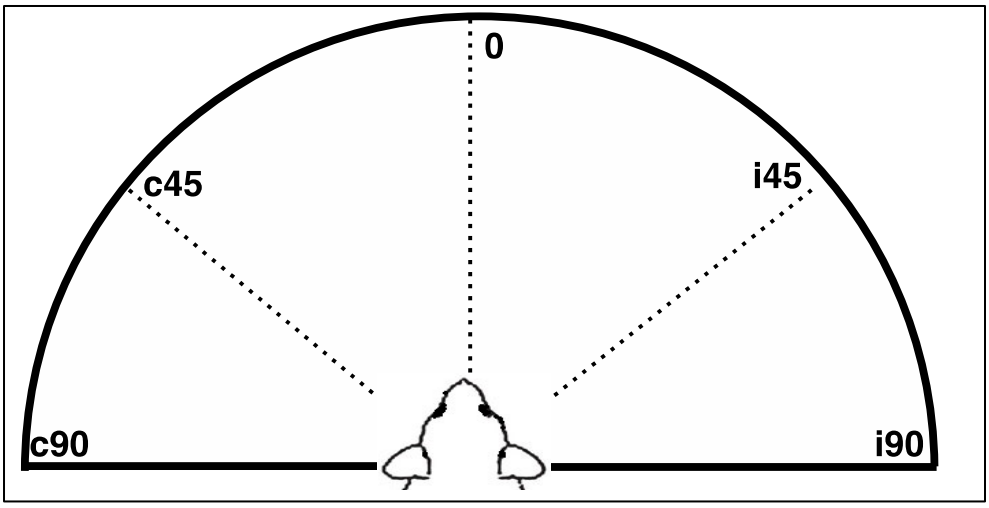


Figure 6. A diagram showing various spatial locations tested in the study in reference to the rat's head.

2.5. Search and characterization of neurons

A recording electrode was advanced into the IC using a model 2660 micropositioner (Kopf, Tujunga, California). In reference to the lambda, the electrode was placed at 0.00-0.40 mm rostral, 3.20-4.00 mm lateral, and 2.30-6.00 mm deep. The electrode was at an angle of 30° in reference to the midsagittal plane. While evoked action potentials were monitored audio-visually, Gaussian noise bursts at 60 dB SPL were presented at 4 /s from a loudspeaker at c90° azimuth to search for an auditory neuron. Evoked action potentials were amplified using a 2400A preamplifier (Dagan, Minneapolis, Minnesota). Action potentials generated by a single neuron were identified as spikes with identical waveforms (including amplitude) over the duration of an acoustic stimulus or, in rare instances (offset neurons), at the offset of an acoustic stimulus. Once a single neuron is isolated, a frequency-tuning curve was obtained by evaluating the threshold of sound-driven responses over a wide range of frequencies. The neuron's characteristic frequency (*CF*) was determined as the frequency at which the neuron displayed the

minimum threshold in response to tone-burst stimulation. The threshold at each frequency was defined as the first stimulus intensity at which a tone burst elicits sound-evoked action potentials. All tone bursts used in the search of a neuron had a fixed duration of 100ms (5ms rise/fall time, 90 plateau) and presented at the rate of 4/s. Once the CF of a neuron and the frequency-tuning curve of the neuron were determined, rate-level functions (RLFs) were obtained at the CF and two other frequencies (T_L, and T_H; *see* Section 2.6.). An RLF represented the strength of firing of a neuron in response to a tone burst over a wide range of stimulus levels (typically seven levels). The aximum level did not exceed 90 dB SPL. For obtaining an RLF, a tone burst was presented 20 times at each intensity. Tone bursts at different levels (e.g., 7 levels) were randomized and presented at a rate of 4 /s.

2.6. Recording of neural responses to oddball paradigms

After a neuron is characterized, responses of the neuron to oddball paradigms were recorded. An oddball paradigm was a train of acoustic stimuli created by using two-tone bursts with their frequency determined based on the *CF* of the neuron. The duration of each tone burst was 100 milliseconds. The frequencies of the two tone burst (named as T_L and T_H, respectively) were at f_L and $f_{H.}$ The centre frequency of f_L and f_H ((f_L x f_H) $^{1/2}$) was at the *CF* and the difference between the two frequencies ($\Delta f = (f_H - f_L)/(f_L \times f_H^{1/2})$) was at 0.10. Thus, the two frequencies, f_L and f_H, were at 0.951*CF* and 1.051*CF*, respectively. The train contained a total of 200 stimuli (i.e., presentations of T_L or T_H), with T_L and T_H presented at a random order but specific probabilities. The probabilities of T_L and T_H were either 90%-10% (oddball paradigm), 10%-90% (oddball paradigm), or 50%-50% (equal probability two-tone sequence) Figure 5. The sound presented at a high probability (90%) served as a standard sound (Std) and the sound presented at a low

probability (10%) served as a oddball sound (Odd). Within each train, tone bursts were presented at a fixed level at 10-20 dB SPL above the threshold at *CF* and at a constant rate of 4 /s.

In order to understand how two tone-bursts in an oddball paradigm affected each other in generating neural responses, two trains of stimuli were created by omitting one tone-burst (either T_L or T_H) from an oddball paradigm (Figure 7). A total of 6 such single tone-burst sequences, namely T_L as Std alone, T_L as Odd alone, T_H as Std alone, T_H as Odd alone, T_L at 50%, and T_L at 50% were generated.

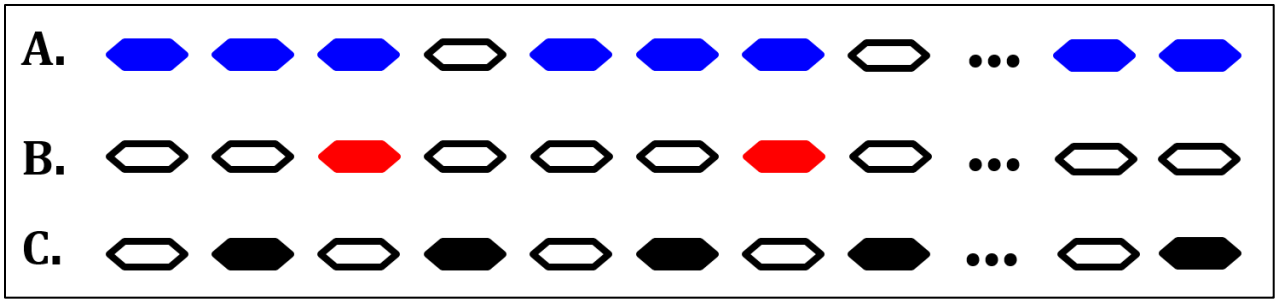


Figure 7. An oddball paradigm with one sound omitted (*open trapezia*). A. Odd omitted; B. Std omitted; C. equal probability sound omitted.

Responses to two oddball paradigms and an equal probability two-tone sequence were recorded when the two sounds of a train were presented from a single speaker located in front of the ear contralateral to the site of recording (c90°, Figure 8). In one of the oddball paradigms, T_H was presented as Std and T_L was presented as Odd (Figure 8A). In the other oddball paradigm, T_L was presented as Std and T_H was presented as Odd (Figure 8B). In the equal probability two-tone sequence, both T_L and T_H were presented at a 50% probability (Figure 8C). Responses to 6 single tone-burst sequences were also recoded when these sequences were presented at c90°.

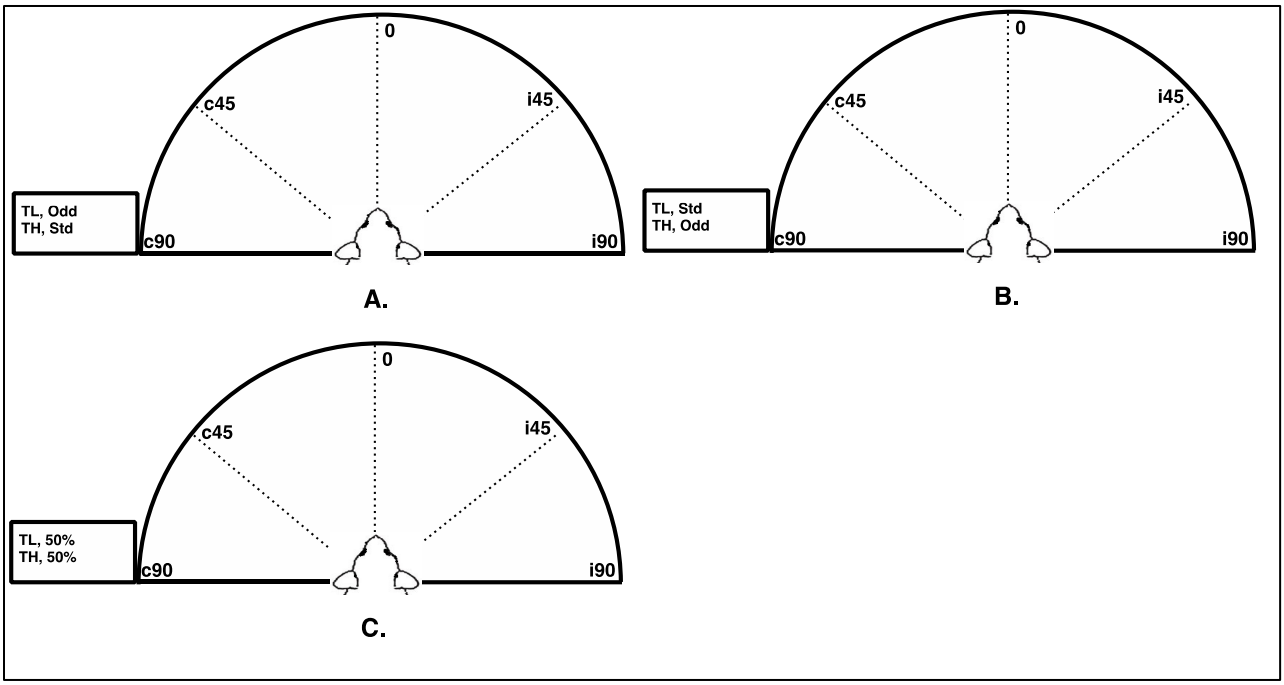


Figure 8. Oddball paradigm when two sounds are co-localized at the contralateral ear (c90°.). A: T_L Odd, T_H Std; B: T_L Std, T_H Odd; C: T_L 50%, T_H 50%.

To test how a spatial separation between T_L and T_H in an oddball paradigm affected the responses to the two sounds, the two sounds were presented from two speakers. One of the two speakers was located at a fixed location at c90°, while the other speaker was located at either c45°, 0°, i45°, or i90° (Figure 9). Four oddball paradigms and two equal probability two-tone sequences were presented at each angle of separation between the two speakers. In these 6 trains of stimuli, for instance, the sound at c90° was T_L as Std (Figure 9A), T_L as Odd (Figure 9B), T_L at 50% probability (Figure 9C). Similare trains were presented for T_H. Responses to 6 single tone-burst sequences were recorded when these sequences were presented at each of the non-c90° azimuths. Responses to oddball paradigms with T_L and T_H spatially separated were compared with responses to oddball paradigms with T_L and T_H colocalized to evaluate how a spatial separation affected response to an oddball paradigms. Furthermore, these responses were also

compared with responses to equal probability tone-tone sequences as well as responses to single tone-burst sequences to evaluate how two spatially separated tone bursts in an oddball paradigm interact with each other in generate responses.

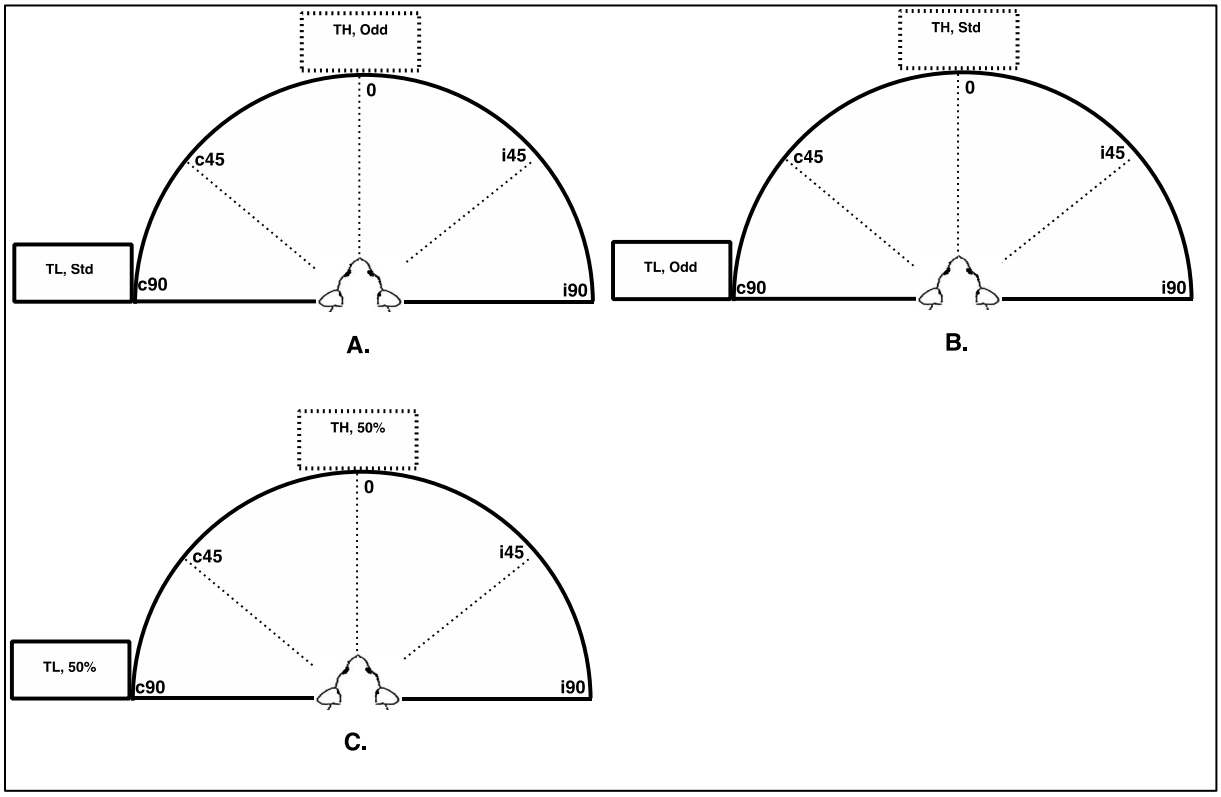


Figure 9. Example Oddball paradigm containing spatial cues when one sound was at the contralateral ear while the other sound was directly in front of the animal. Dotted rectangles represent sound at a location other than contralateral ear.

3. Data analysis

Action potentials elicited by a tone burst (either presented alone or in an oddball paradigm) were plotted in a dot-raster histogram and a peri-stimulus histogram (PSTH). The temporal pattern of firing of a neuron was evaluated by using these histograms.

In response to a single tone burst, neurons recorded in the present study displayed onset, fast adapting, pauser, primary-like, and offset/on-off patterns of firing, respectively. An onset pattern was defined as action potential discharges over a period shorter than 20 ms at the onset of a tone burst, while a fast adapting pattern was defined as discharges at the onset of a sound that last longer than 20 ms but shorter than the duration of the sound. A primary-like pattern had strong firing at the onset of the sound followed by reduced firing over the rest of the tone burst without an interruption, while a pauser pattern had the two parts of firing separated by a brief pause. A build-up/late pattern had firing initiated after a long silent period and ended at the offset of the sound. An offset pattern was characterized by transient action potential discharges at the offset of a tone burst, while an on-off pattern was classified as bursts of spiking at both the onset and offset of a sound. Neurons with sustained firing component in their firing patterns such as primary-like, pauser, build-up etc were grouped as sustained neurons. Other types such as onset, offset, fast adapting etc were grouped as transient neurons. Except for neurons showing offset/on-off firing patterns, the mean number of action potentials elicited by a tone burst was calculated over a period of 130 ms starting from the onset of stimulation.

The sensitivity of a neuron to Odd vs. Std was evaluated when T_L and T_H were colocalized at c90°. Two frequency-specific SSA indices, $I_{SSA}(T_L)$ *and* $I_{SSA}(T_H)$, and one general SSA index, gI_{SSA}, were calculated for this purpose (Duque et al., 2016; Malmierca et al., 2009; Ulanovsky et al., 2003, 2004):

$$I_{SSA}(T_{L.}) = \frac{T_L(Odd.) - T_L(Std.)}{T_L(Odd..) + T_L(Std.)}$$

$$I_{SSA}(T_{H.}) = \frac{T_H(Odd.) - T_H(Std.)}{T_H(Odd.) + T_H(Std.)}$$

$$gI_{SSA} = \frac{T_L(Odd.) + T_H(Odd.) - T_L(Std.) - T_H(Std.)}{T_L(Odd.) + T_H(Odd.) + T_L(Std.) + T_H(Std.)}$$

where $R_{Odd}(T_L)$, $R_{Std}(T_L)$, $R_{Odd}(T_H)$, and $R_{Std}(T_H)$ are strengths of responses (as measured by the number of spikes per sound presentation) to T_L as Odd, T_L as Std, T_H as Odd, and T_H as Std, respectively, when T_L and T_H were colocalized at c90°. The values of $\boldsymbol{I}_{SSA}(T_L)$, $\boldsymbol{I}_{SSA}(T_H)$, and $g\boldsymbol{I}_{SSA}$ range from -1 to +1 with positive indicating stronger sensitivity to Odd, and negative indicating stronger sensitivity to Std. To asses whether special separation affects deviant and standard sounds differently, we calculated NdRs separately for deviant and standard responses:

$$NdR_{Odd.} = \frac{R_b(Odd.) - R_a(Odd.)}{R_a(Odd.) + R_b(Odd.)}$$

$$NdR_{Std.} = \frac{R_b(Std) - R_a(Std)}{R_a(Std) + R_b(Std)}$$

where R_α(Odd) and R_β(Std) represents sums of oddball and standard responses to co-localized condition and separated conditions respectively. Similar NdRs were also calculated using co-localized sound and a sound presented at a different location to assess how a sound at the contralateral ear affects responses to sound presented at another location in the azimuth. All statistical tests were significant at a fixed $p < 0.05$ unless otherwise stated.

4. Results

Sound driven responses were recorded from 88 well-isolated single units in the IC. From 66 neurons (75%), data was obtained for all the five spatial locations tested. For the other 22

neurons (25%), only three spatial locations (c90°, 0°, and c45°) were tested with all the acoustic paradigms used in this study (See Methods).

4.1. Classification of IC neurons based on single tone bursts presented at c90°.

Basic features of neurons were studied by presenting *CF*, f_L and f_H singly at 7 different intensities that included the intensity at which the oddball paradigm was presented (or oddball intensity). The order of intensities at each frequency was completely random. Presentation of one tone burst (that is frequency at a given intensity) was repeated 20 times, making a total of 140 stimuli at each frequency-intensity combination.

Peristimulus histogram (PSTH) of responses at oddball intensity was used to classify the neuron's firing pattern. Based on this approach, five major neuronal firing patterns were identified. This included onset, primary like, pauser, fast adapting, and offset neurons (Figure 10A). The frequency tuning curves and the rate level functions of these example neurons are presented in figure 10B and figure 10C respectively. These neurons were grouped into transient and sustained neurons (See Methods) for further analysis.

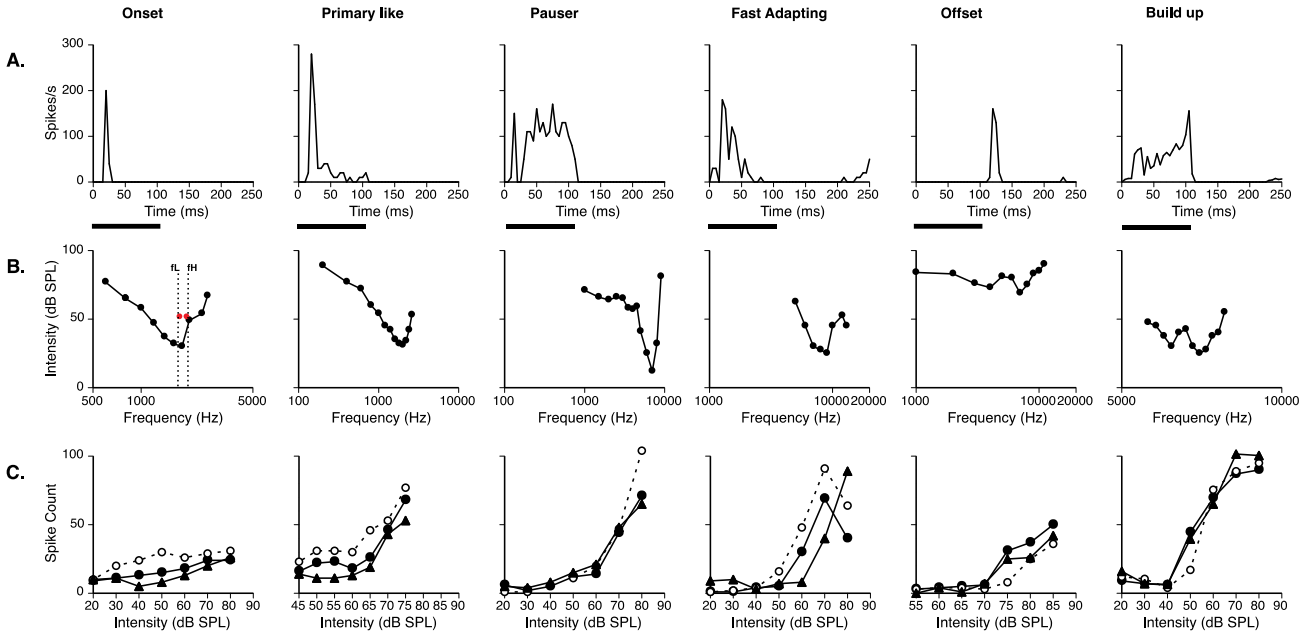


Figure 10. Classification of IC neurons. A. PSTHs of six single units showing different patterns. B. Frequency tuning curves of single units. The two red dots indicate the position of fL and fH with respect to CF (lowest data point). C. Rate level functions at CF (*filled circles*), fL (*open circles*), and fH (*Triangles*).

4.2. Directional dependence of IC responses to single tone bursts

The same stimulus condition used to classify neurons (See section 4.1.) was also presented at off-c90 locations (c45°, 0°, i45° and i90°) in order to study how responses of IC neurons depend on spatial location. Responses associated with f_L and f_H were collected at each spatial location and used to create directional response curves. Figure 11A shows an example IC neuron that responded strongly to a contralateral sound but reduce the strength of responses when the same sound was presented at an ipsilateral position. A near complete or complete suppression of ipsilateral responses was commonly observed in transient neurons (Figure 11B). Conversely, sustained neurons typically showed ipsilateral reduction in response but rarely exhibited complete suppression (Figure 11C).

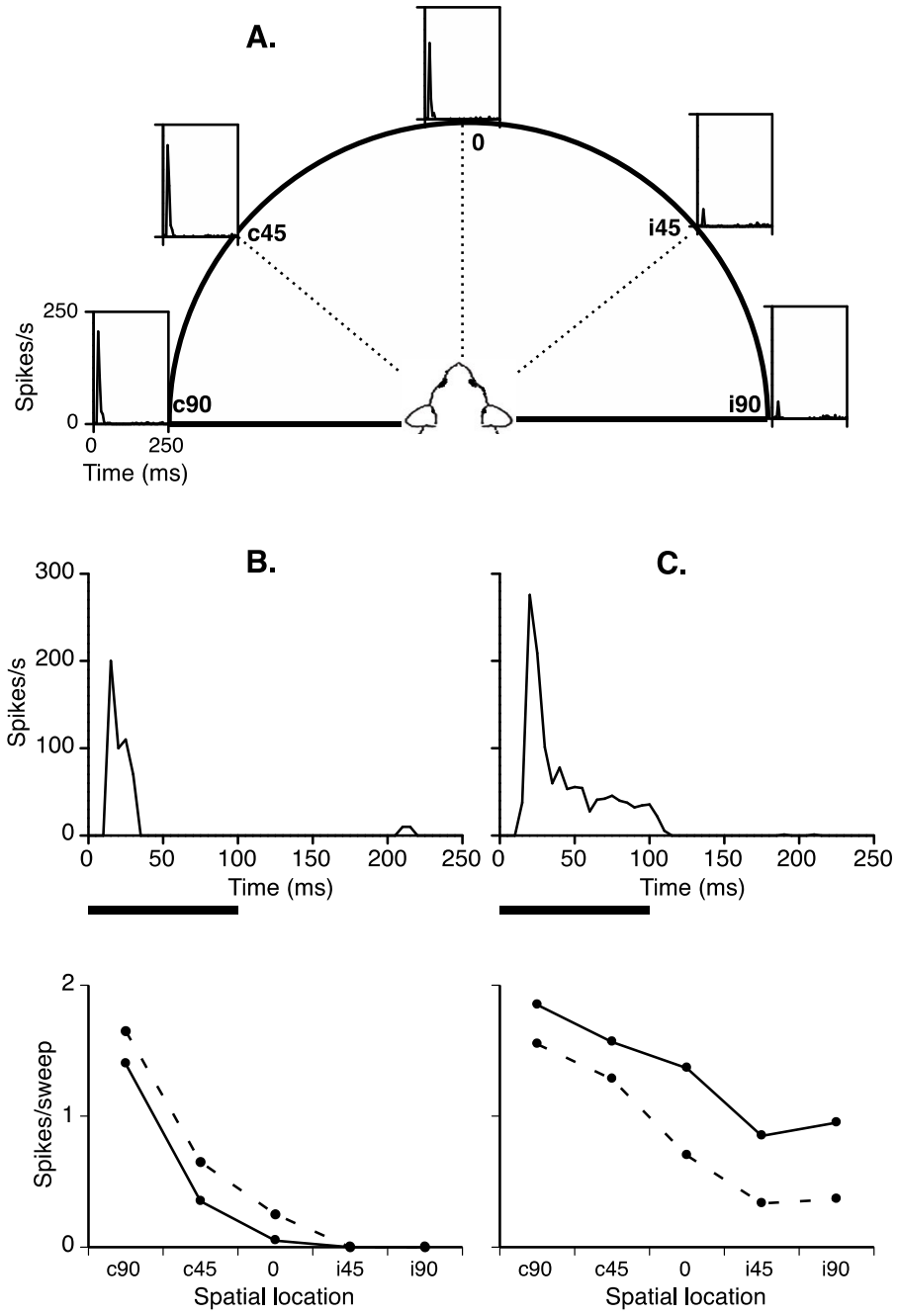


Figure 11. Directional dependence of responses in the IC. A. PSTHs showing strength of responses to single tone bursts at each spatial loction in the frontal azimuth. B and C represents PSTHs (top panels) and responses to tone bursts at variouns spatial locations (bottom panel) for

a transient and a sustained single unit respectively. Thick lines: responses to TL. Dashed lines: responses to TH. Horizontal bars indicate stimulus duration

Next, NdRs were computed for responses at each spatial location using responses at the contralateral ear. Population analysis of these results revealed that IC neurons generally reduced their responses to an off-c90 sound especially at ipsilateral locations (Figure 12). Transient neurons (Figure 12A) showed significantly stronger reduction in responses at i45° (Mann-Witney test, U = 758.0, p = 0.004) and i90° (Mann-Witney test, U = 742.0, p = 0.007) than sustained neurons (Figure 12B).

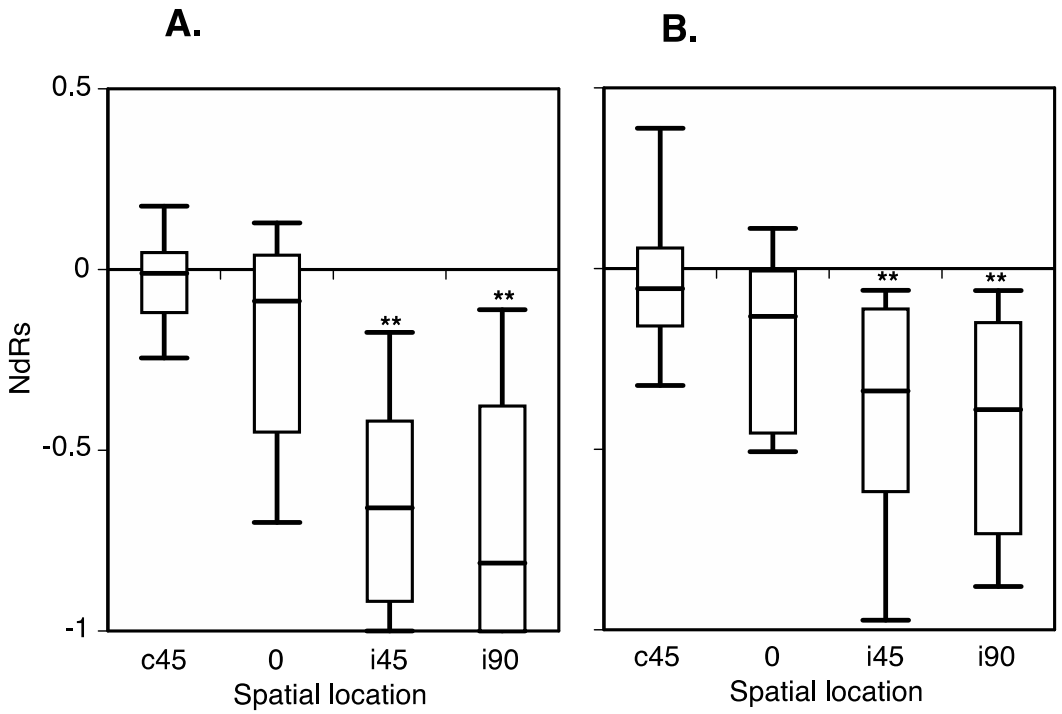


Figure 12. Distribution of directional dependent responses in the IC. A. Responses of transient neurons to single tone bursts. B. Responses of sustained neurons to single tone bursts. Thick boxes: responses to TL; Dashed boxes: responses to TH. Horizontal lines: population medians.

4.3. Responses to oddball paradigms with two composing tone bursts co-localized at c90°

Responses to oddball paradigms were first recorded when the two sounds of an oddball paradigm were presented from a free-field speaker located in front of the contralateral (c90°) ear. Figure 13 illustrates a typical IC single unit that showed significantly stronger responses to oddball than to standard sound regardless of the tone frequency.

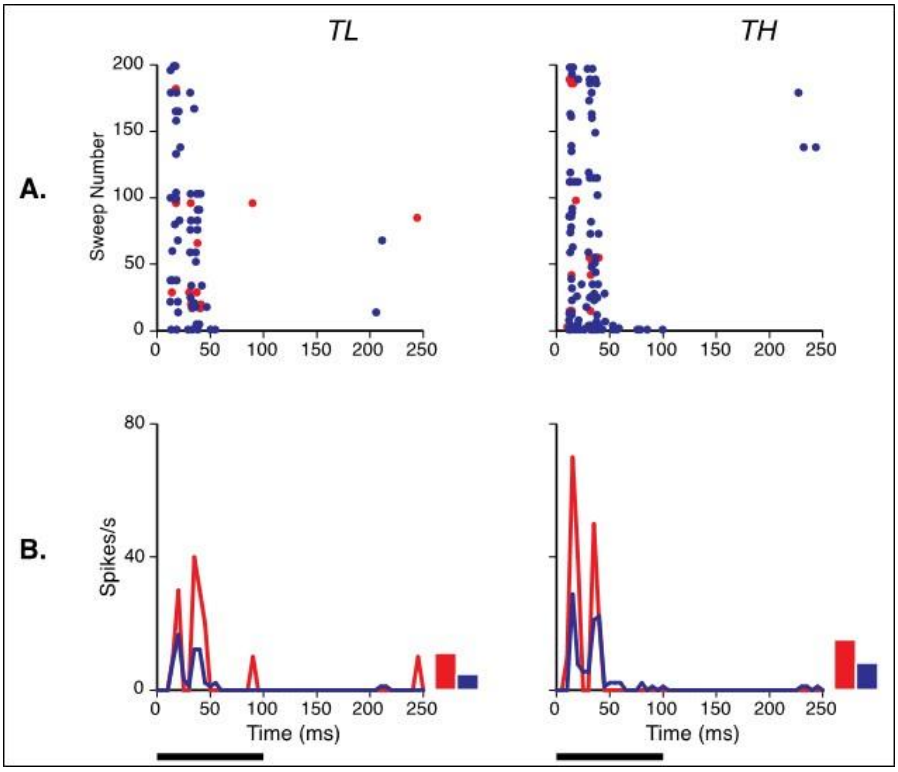


Figure 13. An IC single unit showing stronger responses to Odd than Std sound. A. Dot raster plots indicating action potentials. B. PSTHs showing the rate of firing. Vertical bars: number of action potentials per sweep. Horizontal lines: duration of stimulation. Red: responses to Odd; blue: responses to Std.

SSA indices were computed for each individual neuron as described in Methods section. Figure 14 shows distributions of SSA indices of all the 88 IC single-units based on responses to oddball paradigms when the two composing tone bursts of a paradigm were co-localized at c90°. There were more neurons showing positive than negative SSA indices as evaluated by responses to T_L (i.e., $I_{SSA}(T_L)$), responses to T_H (i.e., $I_{SSA}(T_H)$), and both responses to T_L and T_H (i.e., gI_{SSA}).

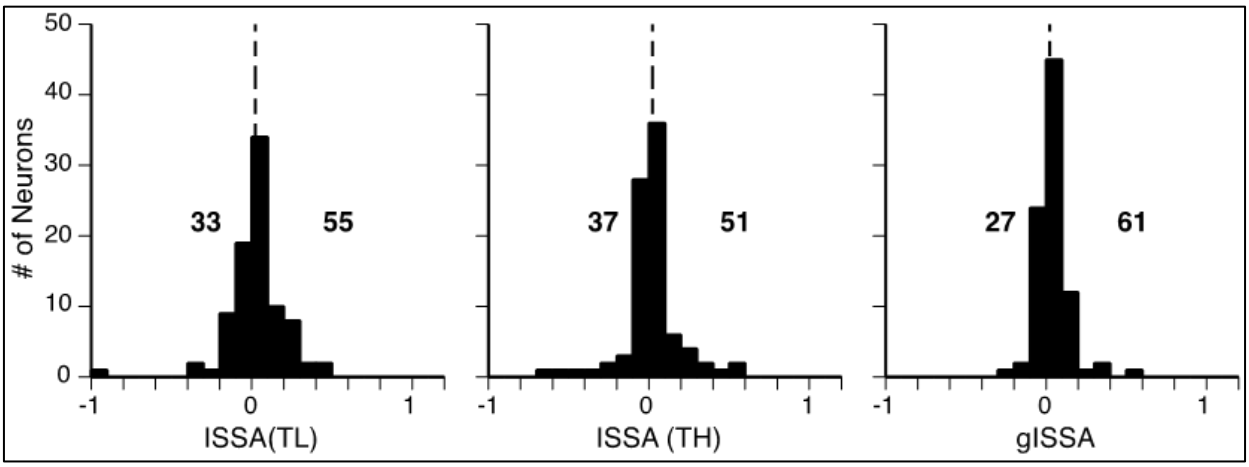


Figure 14. Distribution of SSA indices obtained from oddball paradigm colocalized at c90°. Dashed line represents zero SSA index. Numbers represent neurons showing positive or negative SSA indices.

Direct comparisons were made between T_L and T_H to assess whether their responses were dependent on spectral attribute of the sound. It was found that there was no significant difference in response to the two tones when presented either as Odd (Mann-Witney test, U = 3714.5, p = 0.641) or as Std (Mann-Witney test, U = 3841.0, p = 0.927) (Figure 15). Similarly, comparison between $I_{SSA}(T_L)$ and $I_{SSA}(T_H)$ showed that there was no dignificant difference between the two indices (Mann-Witney test, U = 3632.5, p = 0.0.479) (Figure 15).These results indicated that responses elicited by T_L and T_H were similar to each other as long as they were presetned at the

same probability. For this reason, results based on responses elicited by T_L and T_H when presetend at the same probability (i.e Odd or Std), and under similar conditions (e.g. same spatial location), were grouped together throughout the rest of the thesis. Due to the same reason, a general stimulus-specific adaptation index (gI_{SSA}) rather than the two frequency-specific stimulus-specific indices (i.e., $I_{SSA}(T_L)$ and $I_{SSA}(T_H)$) was used to evaluate the degree of stimulus-specific adaptation.

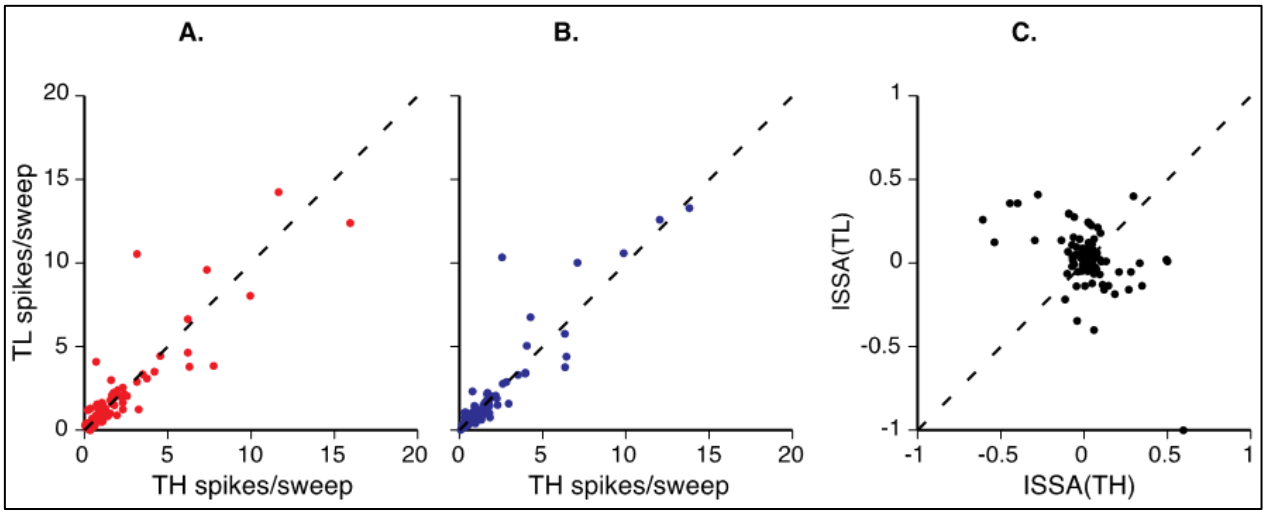


Figure 15. Scatter plots comparing population responses to TL and TH. A. Responses to Odd. B. Responses to TH. C. Stimulus-specific indices.

4.4. Responses to equal probability two tone-burst sequences with two composing tone bursts co-localized at c90°

In order to ascertain whether the strength neuronal responses to T_L and T_H were dependent on probability, the two tone bursts were presented at equal probability (or equiprobable) in a sequence. Figure 16 illustrates and example IC single unit's responses to T_L and T_H relative to Odd and Std responses. Responses to an equiprobable sound were intermediate in comparison to neuronal responses to Odd and Std (Figure 16A and 16B)

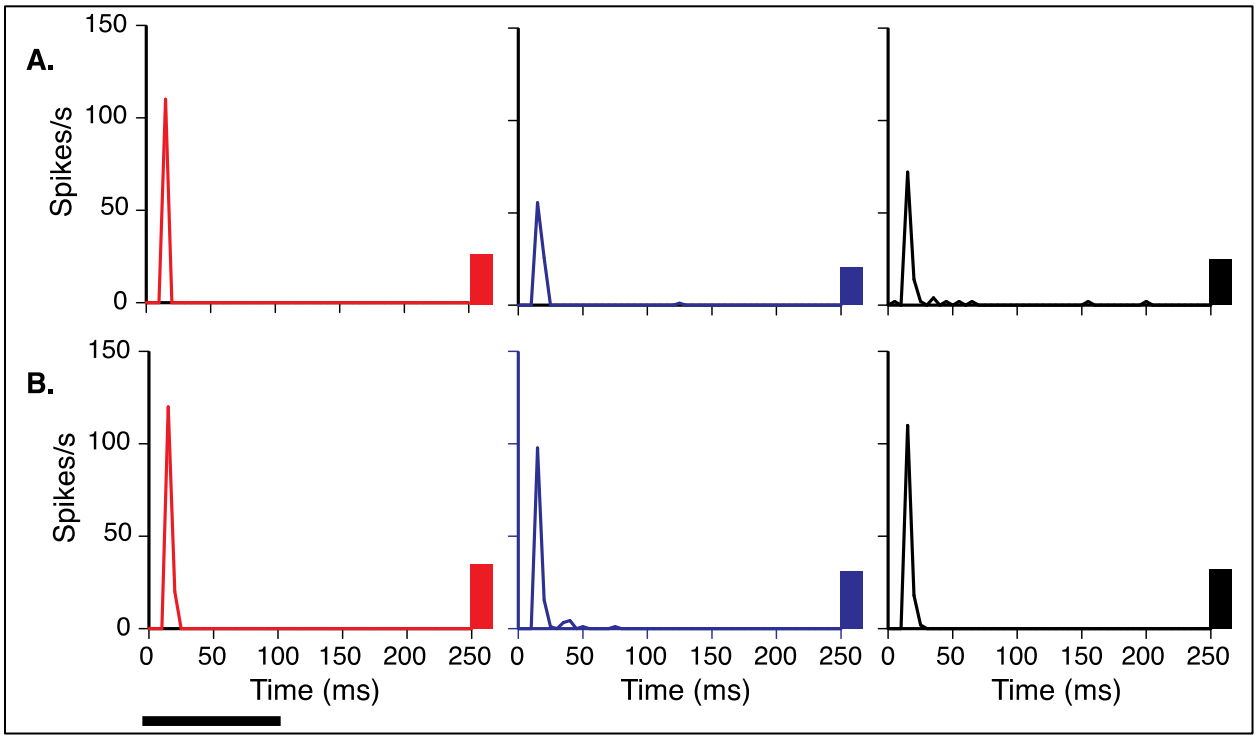


Figure 16. An example single unit showing responses to odball paradigms with equiprobable tone bursts (black) alongside responses to Odd (red) and Std (blue). A. Responses to TL. B. Responses to TH. Lines: PSTHs showing the rate of firing. Vertical bars: number of action potentials per sweep. Horizontal line: stimulus duration.

Figure 17 shows direct comparison of responses to equiprobable T_L and T_H. There was no difference in neuronal responses to the two tone bursts (Mann-Witney test, U = 3811.5, p = 0.858).

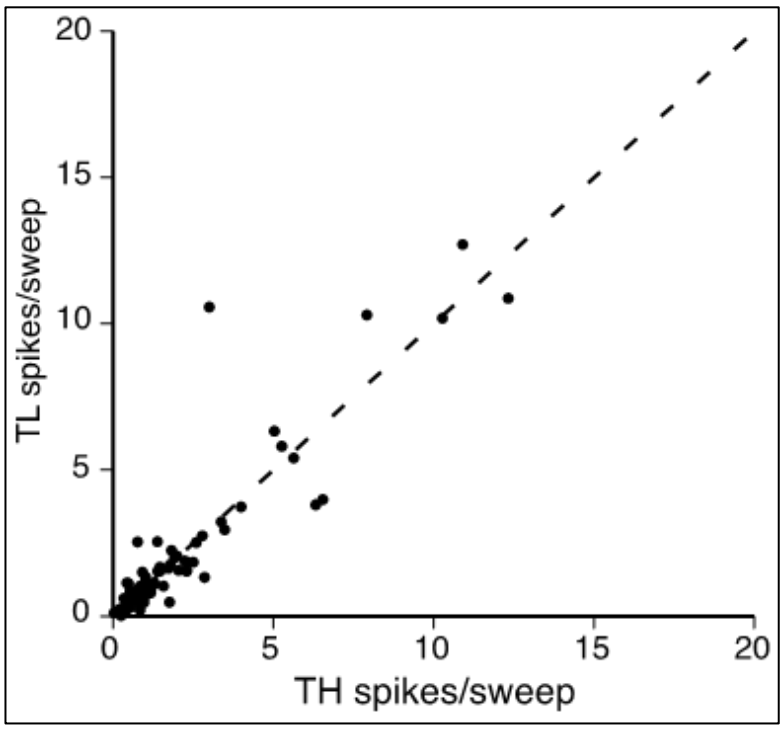


Figure 17. Scatter plot comparing population responses to equiprobable *TL* and *TH.*

4.5. Responses to an oddball paradigm with two composing tone bursts spatially separated:

The response elicited by the tone burst at a fixed location at c90°

After studying responses to oddball paradigms co-localized at *c90°*, it was important to investigate dependence of responses on other natural acoustic contexts. Spatial cues provide an important control in studying how the strength of responses depends on probability. In order to address this, oddball paradigms were presented with one tone burst at c90° while the other tone burst was spatially separated. First, Odd tone bursts were presented at c90° with corresponding Std tone bursts at a different location. Figure 18 provides example responses of an IC single unit to Odd tone bursts. The neuron's response to Odd was enhanced when Std was spatially separated (Figure 18A and 18B).

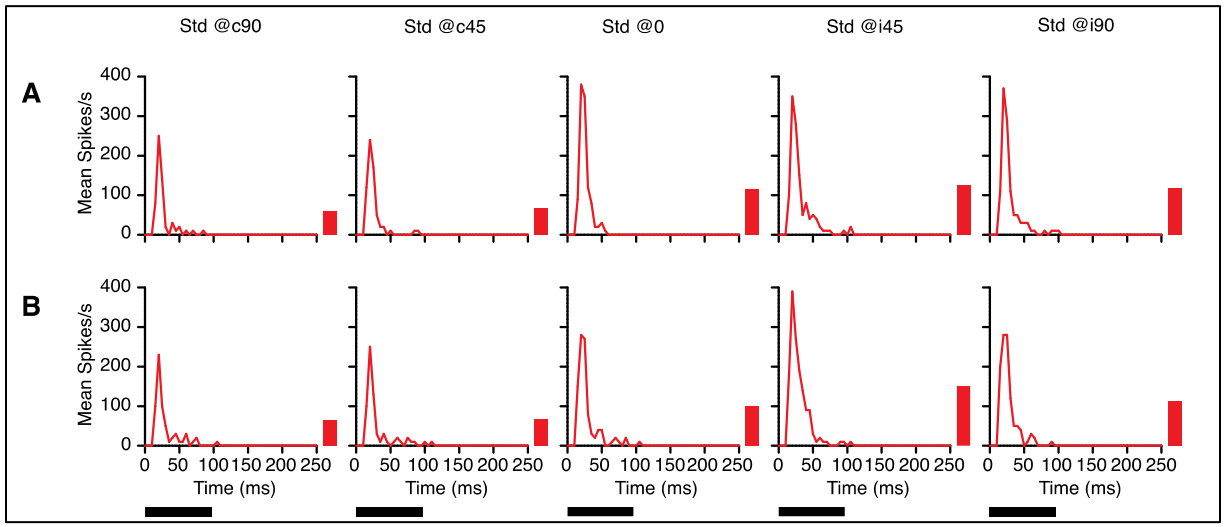


Figure 18. Single unit responses to Odd tone burst presented at a fixed c90° location when the position of Std in the same sequence was varied. A. Responses to *TL*. B. Responses to *TH*. Line plots: firing rate; Vertical bars: number of spikes per sweep; horizontal lines: stimulus duration.

In the reverse sequence, Std tone bursts were presented at c90° while corresponding Odd tone burst were presented at another location. Responses of the same neuron (in Figure 18) to Std are provided in figure 19. The neuron showed no apparent alteration in its response to Std regardless of the spatial location of Odd tone bursts (Figure 19A and 19B).

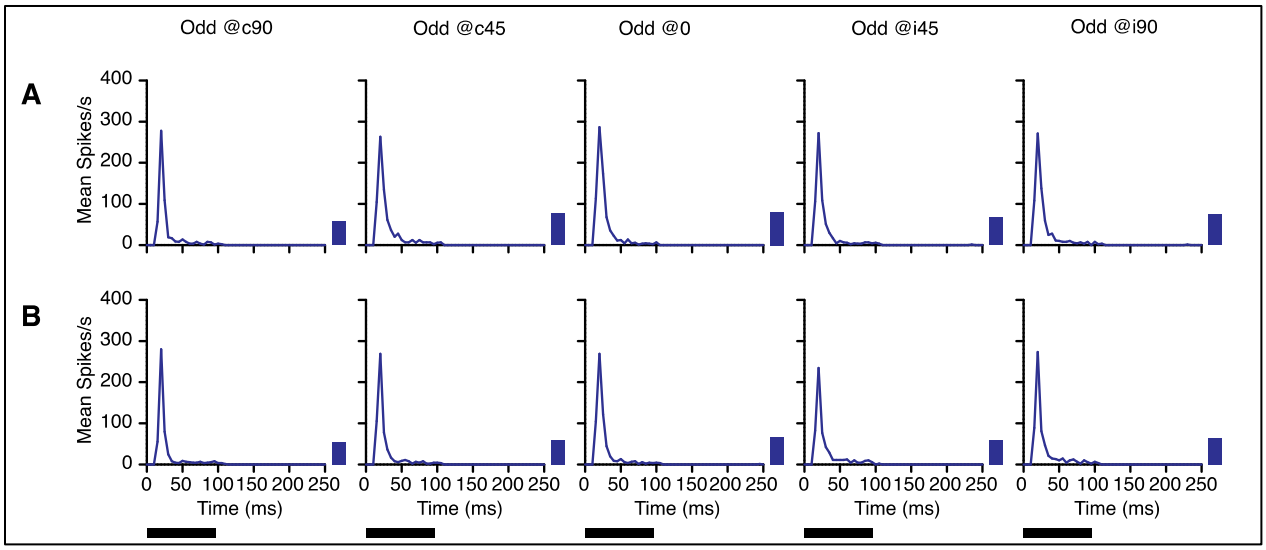


Figure 19. Single unit responses to Std tone burst presented at a fixed c90° location when the position of Odd in the same sequence was varied. A. Responses to TL. B. Responses to TH. Line plots: firing rate; Vertical bars: number of spikes per sweep; horizontal lines: stimulus duration.

An NdR value (see "Methods") was used to quantitatively evaluate a change of response to the sound at c90° caused by a spatial separation such that NdR at c90° was always zero. Since this data violates the two way ANOVA assumptions of normal distribution and homogeneity of variance, one sample Wilcoxon Signed rank test was used to evaluate if the median of NdRs at each angle of spatial location was different from zero.

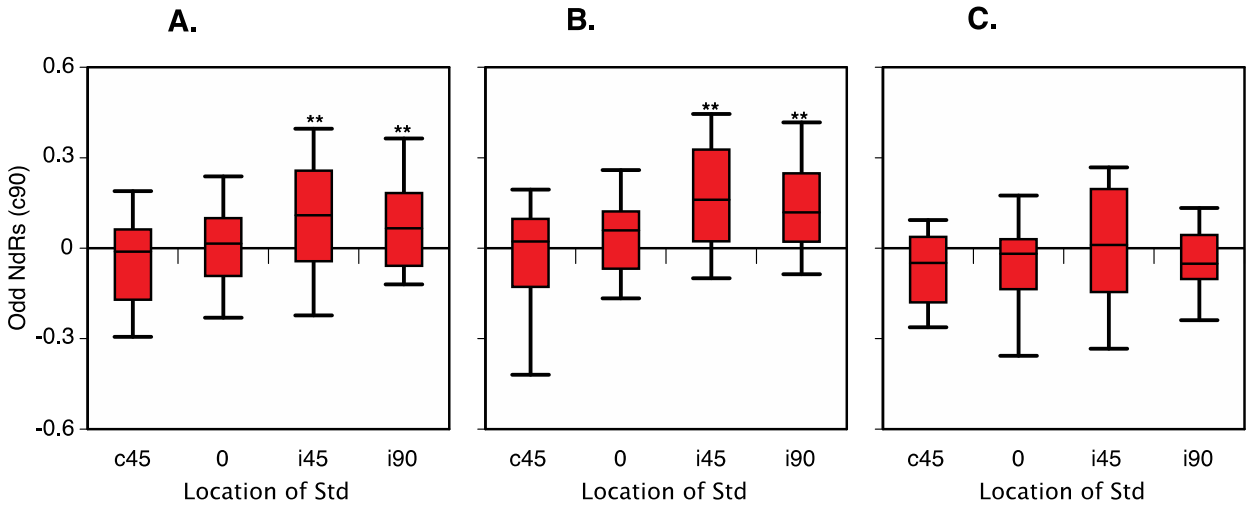


Figure 20. Distribution of Odd NdRs when the Std spatial position was varied. A. Population NdRs. B. NdRs of transient neurons. C. NdRs of sustained neurons. ** Indicates significant median NdRs (p = 0.0001, Wilcoxon Signed rank test).

Population of 66 neurons revealed that responses to Odd were enhanced when Std was relocated from c90° to an ipsilateral location (Figure 20A). The median of NdR values was significantly positive when standard sound was at i45° (p = 0.001) and i90° (p = 0.004). Further

analysis was conducted for the two groups of neurons with transient and sustained firing patterns. The effect of spatial separation on the response to Odd at c90° was dependent on the pattern of firing of neurons. For neurons with transient firing (n =40), median of Odd NdRs was enhanced when Std was at i45° (p = 0.0001) and i90° (p = 0.0001) (Figure 20B). For neurons with sustained firing (n =25), medians of Odd NdRs were not different from zero regardless of the position of standard in the azimuth (Figure 20C).

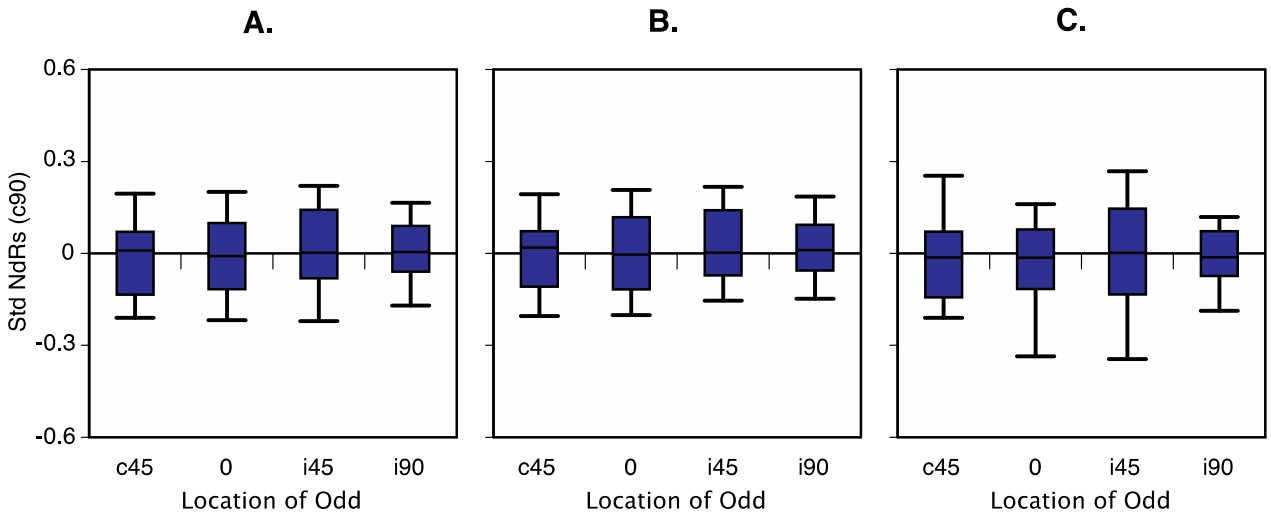


Figure 21. Distribution of Std NdRs when the Odd spatial position was varied. A. Population NdRs. B. NdRs of transient neurons. C. NdRs of sustained neurons.

Responses to Std at c90° were not affected by spatial position of Odd tone bursts in the azimuth (Figure 21). At any given angle of separation, the median of Std NdR values was not different from zero for the entire population of 66 neurons (Figure 21A). Similar findings were observed in neurons showing transient firing (Figure 21B) and sustained firing (Figure 21C).

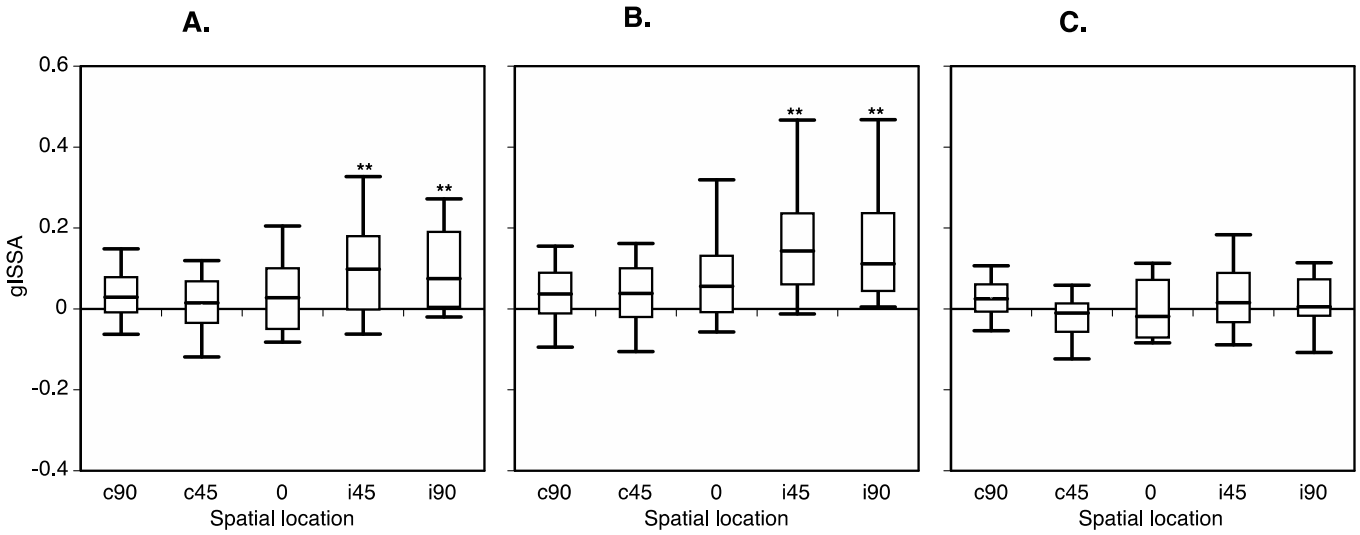


Figure 22. Comparison between distributions of gI_{SSAs} containing spatial cues and those without (c90°). A. Population distribution. B. Transient neurons. C. Sustained neurons. Horizontal lines in box plots: group medians. **Significant gI_{SSA} medians relative to gI_{SSA} at c90° (p = 0.0001, Wilcoxon Signed rank test.

In agreement with the fact that a spatial separation between two sounds of an oddball paradigm increased strengths of responses to Odd presented at c90° but not responses to Std, it was hypothesized that spatial-dependent changes in response to Odd or Std can directly enhance the resulting gI_{SSA}. In order to link the two, gI_{SSA} values computed from co-localized sounds (without spatial cues) were compared with gI_{SSA} values obtained from sounds that contained spatial cues. A non-parametric Friedman test showed that there was a significant difference among gI_{SSA} values at various spatial locations, and from different types of neurons (χ^2 (14) = 55.692, p = 0001). Post hoc analysis was performed using Wilcoxon Signed rank tests with Bonferroni correction such that the new significant level was at $p < 0.003$. The results are summarised in figure 22. The population gI_{SSA} median was significantly greater when spatial separation was at i45° (Z = -3.561, p = 0.0001) and i90° (Figure 22A; Z = -3.517, p = 0.0001) than median of gI_{SSA} values obtained from sounds co-localized at c90°. Transient neurons also

showed significantly higher gI_{SSA} median at i45° (Z = -4.309, p = 0.0001), and i90° (Figure 22B; Z = -4.348, p = 0.0001). Although sustained neurons showed more positive gI_{SSA} means (Figure 22C) as the angle of separation shifted to the ipsilateral side, the median value was not different from gI_{SSA} median at co-localized location.

The contribution of Odd and Std sounds in enhancing gI_{SSA} in spatial context was further explored by directly comparing on-c90° gI_{SSA} values with oddball and standard NdRs at on-c90° in scatter plots. Figure 23A revealed that majority of population Odd NdRs fell with the top right quadrant as the spatial separation became more ipsilateral. However, this change was less apparent for Std NdRs (Figure 23B).

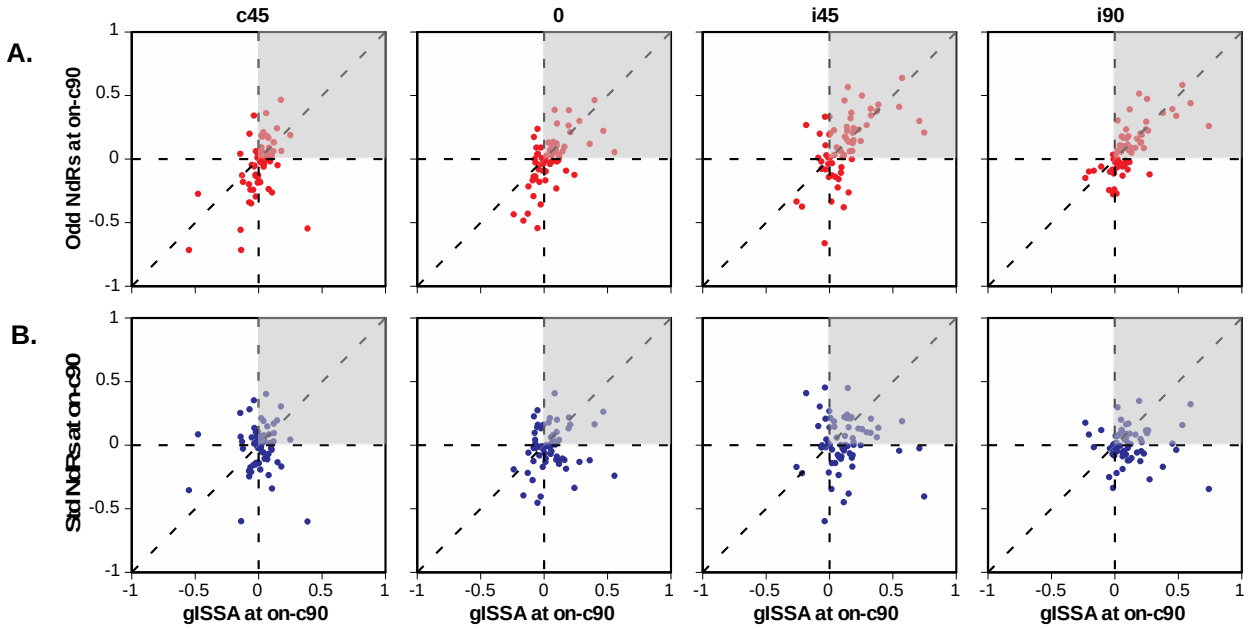


Figure 23. Scatter plots illustrating population dependence of gI_{SSA} on Odd and Std responses containing spatial cues. A. relationship between Odd NdRs and gI_{SSA}. B. Relationship between Std NdRs and gI_{SSA}. Shaded quadrants represent the region of correspondence between positive NdRs and positive gI_{SSA} values.

Statistical examination using Pearson correlation was conducted to further study the relationship between Odd, Std, and gI_{SSA} for the two populations of neurons. Results revealed that Odd NdRs for transient neurons had strong positive correlation with gI_{SSA} at c45° (r = 0.497, p = 0.001), 0° (r = 0.579, p = 0.0001), i45° (r = 0.593, p = 0.0001), and i90°(r = 0.641, p = 0.0001) (Figure 24A). Sustained neurons showed similar patterns 0° (r = 0.505, p = 0.01) and i90° (r = 0.620, p = 0.0001) (Figure 24B).

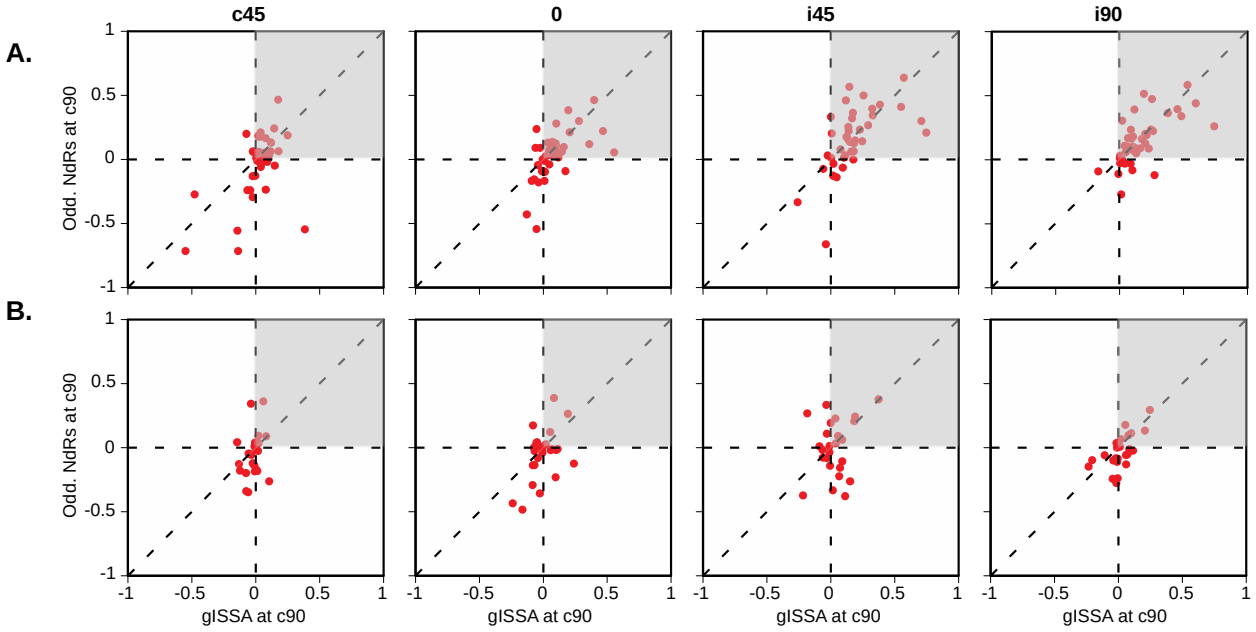


Figure 24. Scatter plots illustrating dependence of gI_{SSA} on Odd responses containing spatial cues. A. Transient neurons. B. Sustained neurons. Shaded quadrants represent the region of correspondence between positive NdRs and positive gI_{SSA} values.

There was no significant relationship between gI_{SSA} and Std NdRs for the two groups of neurons at any given spatial separation (Figure 25A and 25B).

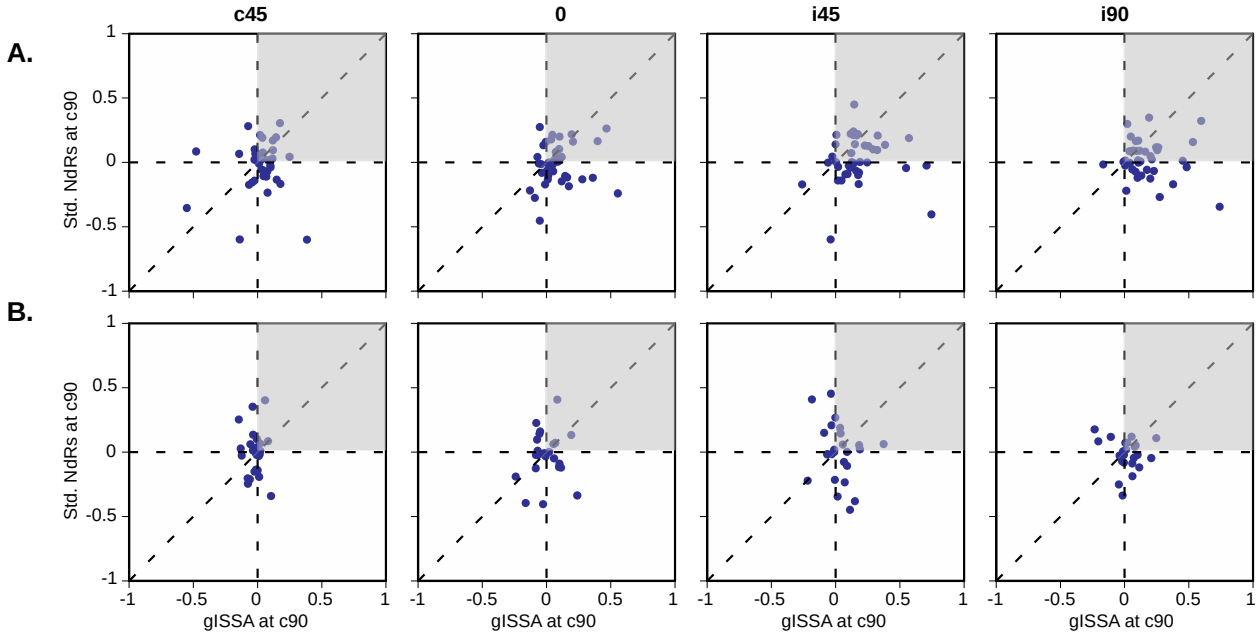


Figure 25. Scatter plots illustrating dependence of gI_{SSA} on Std responses containing spatial cues. A. Transient neurons. B. Sustained neurons. Shaded quadrants represent the region of correspondence between positive NdRs and positive gI_{SSA} values.

4.6. Responses to an oddball paradigm with two composing tone bursts spatially separated: The response elicited by the tone burst at an off-c90° azimuth

As the present results showed, IC neurons as a population reduced responses to off-c90 sound but not a complete suppression. It is therefore important to ask if the sound at c90° affects responses of the other sound presented at a different location in the same sequence of oddball paradigm. Figure 26 shows responses of an IC single unit to Odd and Std tone bursts presented at various locations in the azimuth when their corresponding Std and Odd was tone bursts were presented at c90°.

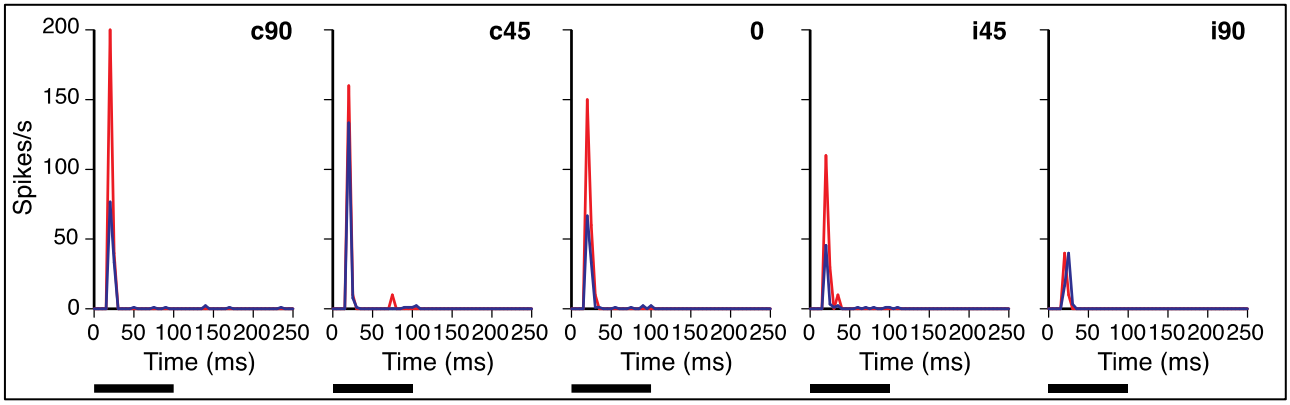


Figure 26. PSTHs showing responses of a single unit to an off-c90° tone bursts when the second sound in the oddball sequence was presented at c90° location. Red: responses to Odd; blue: responses to Std. Horizontal lines represent stimulus duration.

Most IC neurons reduced their responses to Odd tone bursts presented at off-c90° location when Std was fixed at c90° (Figure 27A). This reduction was significantly stronger in transient neurons (Figure 27B) at i45° (Mann-Witney test, U = 697.0, p = 0.008) and i90° (Mann-Witney test, U = 687.5, p = 0.011) than in sustained neurons (Figure 27C).

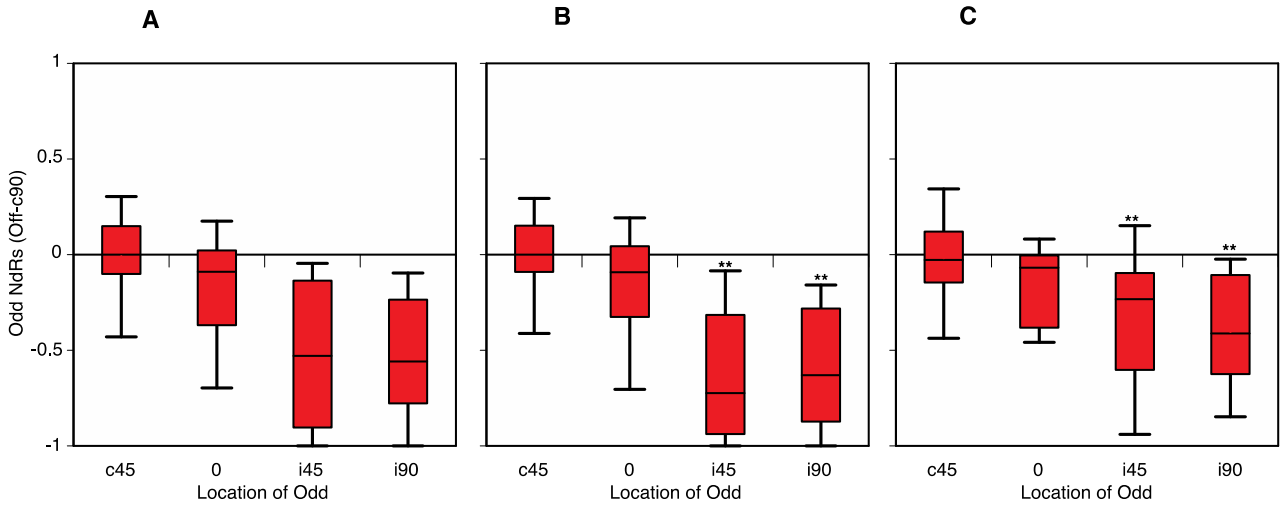


Figure 27. Distribution of Odd NdRs at off-c90° locations. A. Population NdRs. B. Transient neurons. C. Sustained neurons. Horizontal lines in the box plots represent the group median NdR. **Significantly stronger reduction in transient compared to sustained neurons (Mann-Witney test)

Similarly, most neurons showed off-c90° reduction in response to Std tone bursts when corresponding Odd tone bursts in the sequence were fixed at c90° (Figure 28A). Transient neurons (Figure 28B) showed significantly stronger reduction in response to off-c90° Std than sustained neurons (Figure 28C) at ipsilateral locations, i45° (Mann-Witney test, U = 762.0, p = 0.0001) and i90° (Mann-Witney test, U = 722.5, p = 0.003). It is important to note that reduction was stronger when the off-c90° sound was Std rather than Odd.

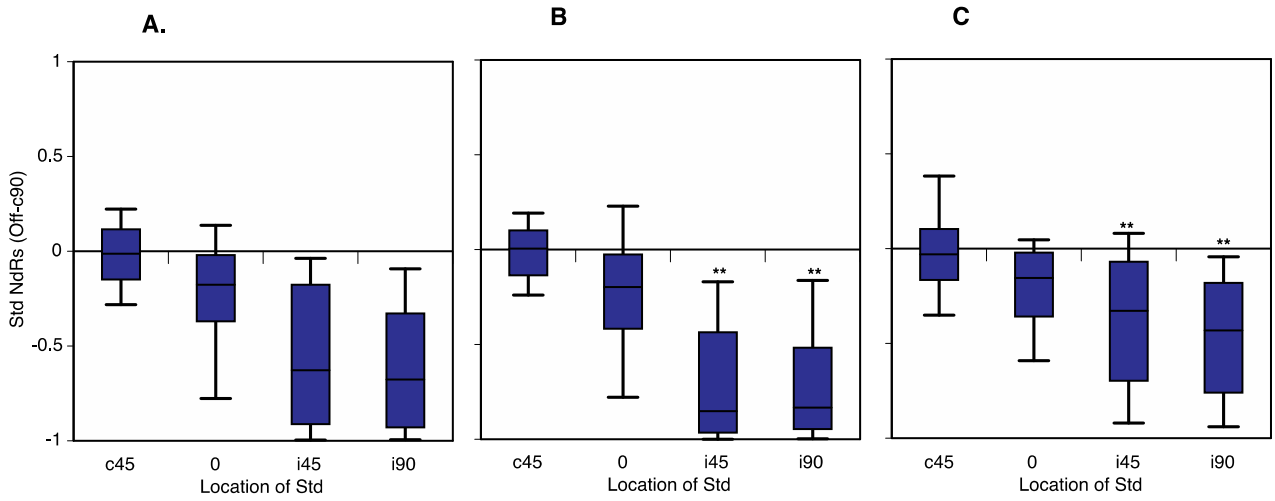


Figure 28. Distribution of Std NdRs at off-c90° locations. A. Population NdRs. B. Transient neurons. C. Sustained neurons. Horizontal lines in the box plots represent the group median NdR. **Significantly stronger reduction in transients compared to sustained neurons (Mann-Witney test)

Figure 29 represents population distribution of gI_{SSA} values obtained from off-c90° responses in comparison to gI_{SSA} values obtained from sounds co-localized at c90°. Most IC neurons generally showed lower gI_{SSA} values at off-c90° than at c90° (Figure 29A). Consistent with neuronal responses to Odd and Std, reduction in off-c90° gI_{SSA} values was more apparent in transient neurons (Figure 27B) than in sustained neurons (27C) especially at ipsilateral locations. For this reason, there was needless to run statistical tests for the difference in reduction.

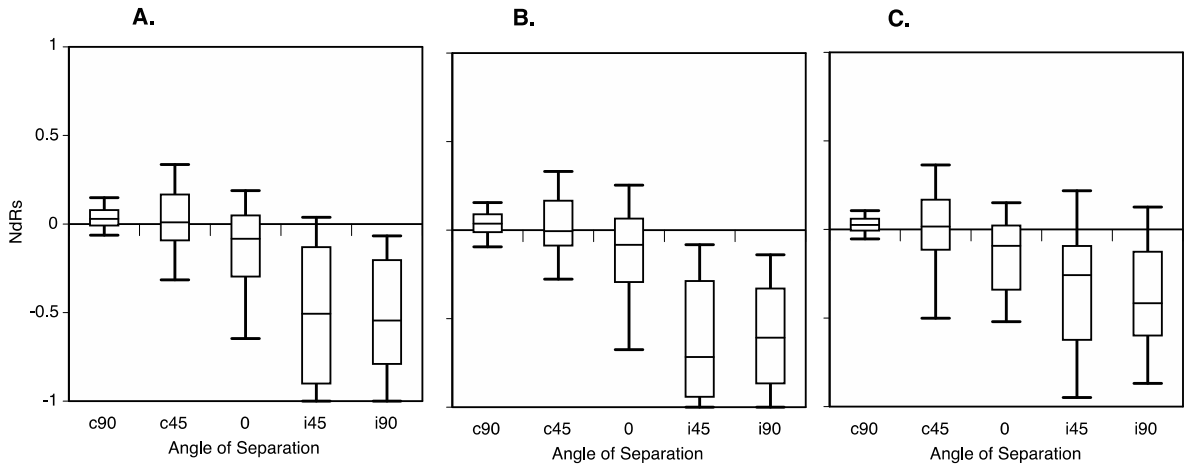


Figure 29. Box plots comparing distribution of off-c90° gI_{SSA} values to gI_{SSA} values obtained from sounds colocalized at c90°. A. Population distribution. B. Transient neurons. C. Sustained neurons. Horizontal lines in box plots indicate the group median gI_{SSA}.

4.7. Responses to an equal probability two-tone-burst sequence when they were spatially separated.

It has been demonstrated so far that spatial context affects neuronal sensitivity to oddball and standard sounds in the IC.

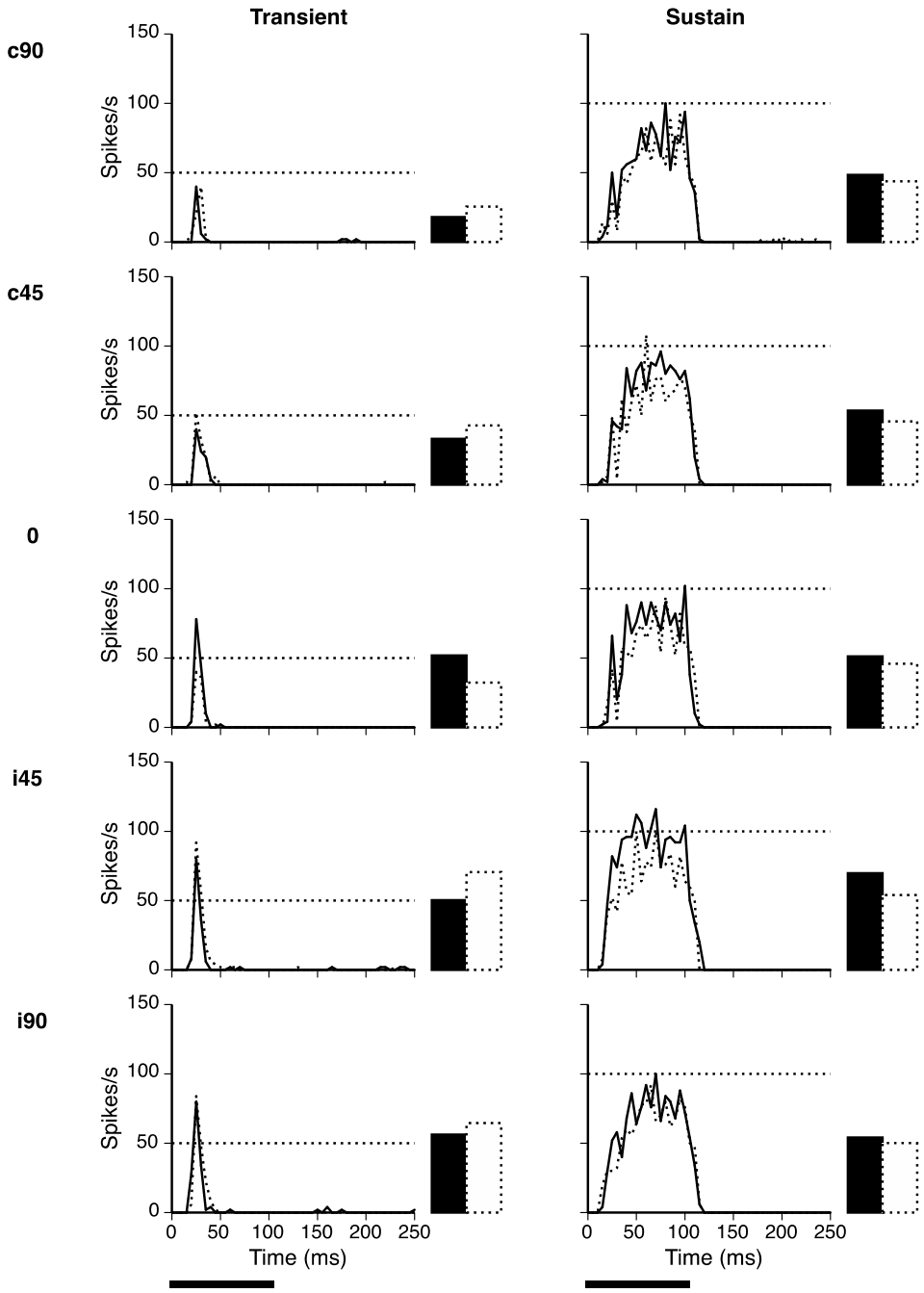


Figure 30. Responses of a transient and a sustained single unit to 50% sound presented at a fixed c90° location when the second sound in the sequence was varied at different spatial locations. PSTHs represent the neuron's firing rate. Vertical bars indicate number of action potentials per sweep. Thick plots: responses to TL; Dotted plots: responses to TH. Dotted horizontal line estimates relative magnitude of change in responses. Thick horizontal line indicates stimulus duration.

However, these findings do not isolate the effect of probability from effect of spatial cues. In order to eliminate the probability effects, the oddball paradigms used in the previous sections was presented with the same spatial cues but with T_L and T_H occurring at 50% probability each. Figure 30 is an example of responses of a transient neuron and a sustained neuron to 50% sounds presented at c90° when the second sound in the sequence was presented at another location.

NdRs were computed for responses to a c90° 50% sound when the second sound in the same sequence was either co-localized c90° or presented at a different location in the frontal azimuth (See "Methods"). This approach resulted in zero NdRs when both sounds were co-localized at c90°. Due to this reason, one sample Wilcoxon Signed rank test to evaluate if the median of NdRs obtained from sounds containing spatial cues was different from zero i.e. median of NdRs without spatial cues. Populations analysis (n = 65) revealed that medians of NdRs containing spatial cues was significantly greater than zero when spatial separation was at i45° (Z = 1499.0, p = 0.005) and i90° (Z = 1423.0, p = 0.010) (Figure 31A). Transient neurons (n = 40) also showed enhanced values when spatial location was at i45° (Z = 630.0, p = 0.003) and i90° (Z = 664.0, p = 0.0001, Wilcoxon Signed rank test) (Figure 31B). For sustained neurons (n = 25), the location-dependent change in NdR values was not significantly different from zero regardless of the spatial position of the second sound (Figure 31C).

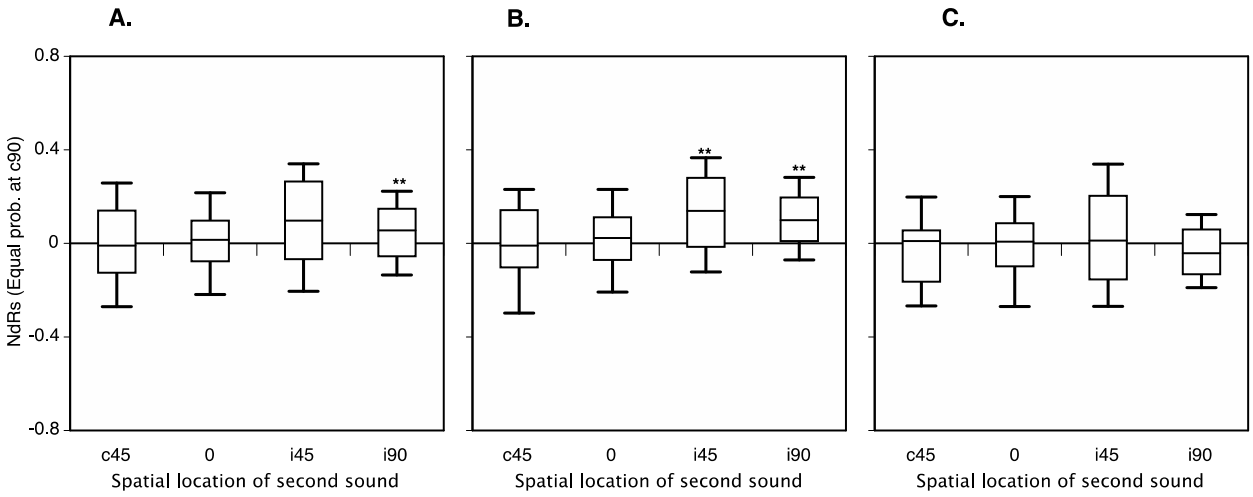


Figure 31. Distribution of 50% sound NdRs when the two composing sounds were presented at c90° while the corresponding second sounds in the sequence were presented at off-c90° locations. A. Population NdRs. B. Transient neurons. C. Sustained neurons. Horizontal line in box plots indicates the group median. **Significant median NdRs based on Wilcoxon Signed rank test.

Next, NdRs obtained from responses to 50% sound presented at off-c90° location when the second sound in the sequence occurred at c90° were examined. Figure 30 provides a summary of these findings. Most IC neurons showed NdR values lower than zero as the spatial location shifted toward the ipsilateral side (Figure 32A). Transient neurons (Figure 32B) showed stronger reduction in response at i45° (Mann-Witney test, U = 237.0, $p = 0.001$) and i90° (Mann-Witney test, U = 232.5, $p = 0.001$) than sustained neurons (Figure 32C).

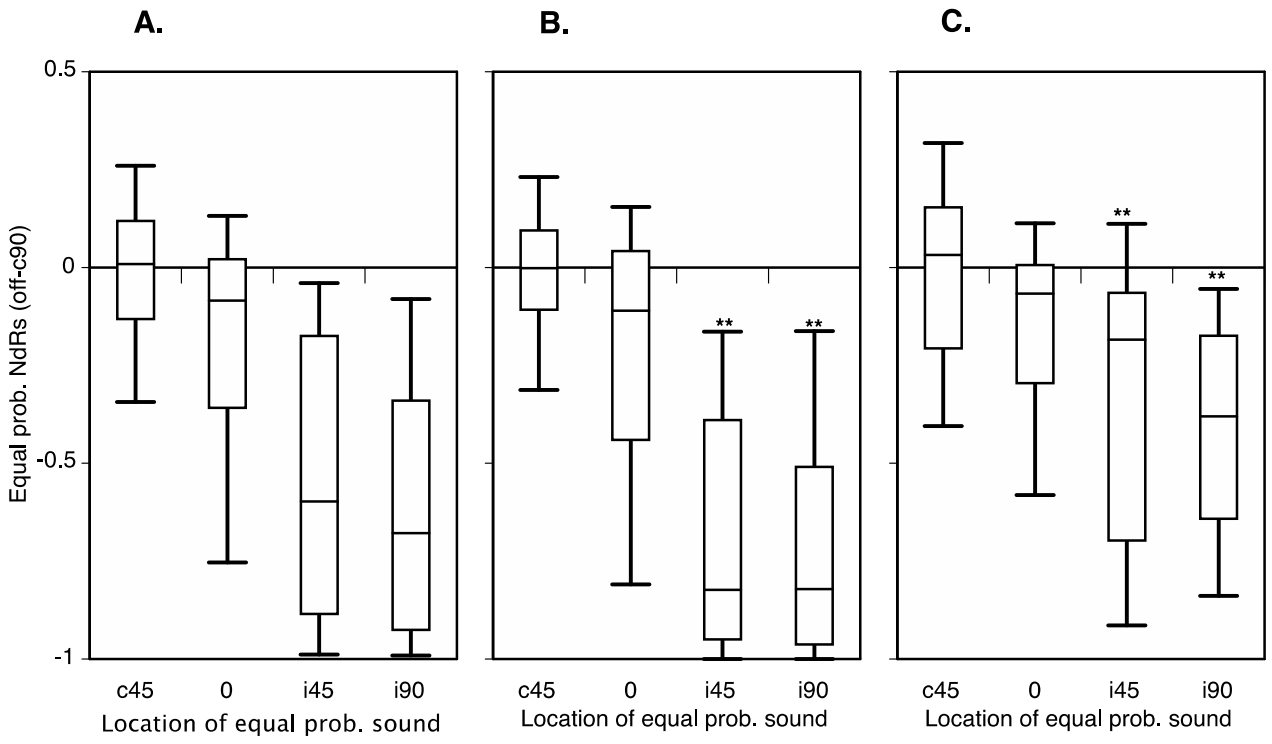


Figure 32. Distribution of 50% sound NdRs when the two composing sounds were presented at off-c90° locations while the corresponding second sounds in the sequence were fixed at c90°. A. Population NdRs. B. Transient neurons. C. Sustained neurons. Horizontal line in box plots indicates the group median. **Significantly stronger reduction in transients compared to sustained neurons (Mann-Witney test)

4.8. Responses to an oddball paradigm with only one sound presented in the sequence: c90° location.

In order to understand how the two composing sounds of an oddball paradigm interact with each other in generating auditory responses, responses to one sound were studied when the other sound was omitted from the oddball paradigm. Figure 33 compares responses of a single unit to the same sound of an oddball paradigm when the second sound in in the same sequence was omitted and when it was present at a fixed c90° location.

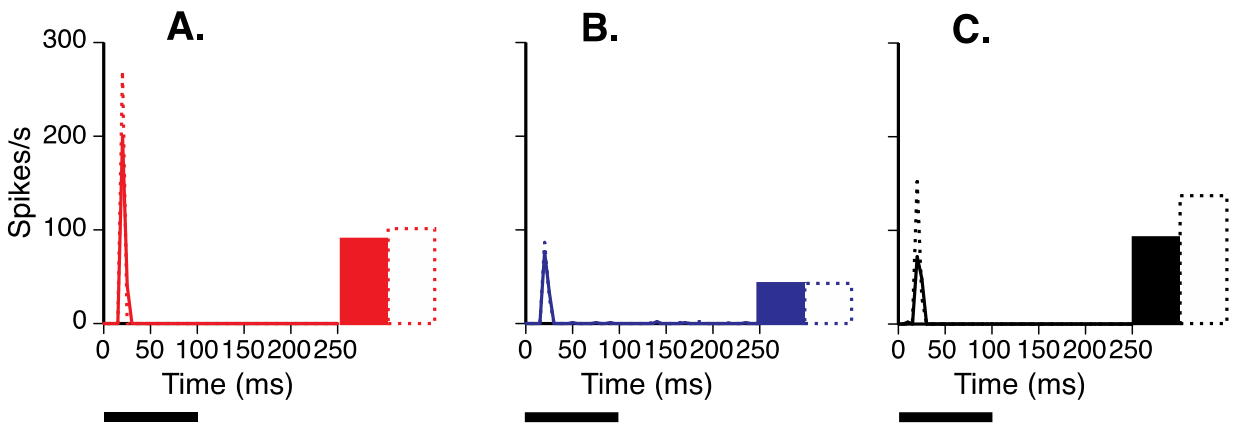


Figure 33. Responses of a single unit to the same sound when it was persented with another sound (thick plots) or when it was presented alone (Dotted plots). A. Responses to Odd. B. Responses to Std. C. respones to 50% probability. Vertical bars represent number of action potentials per sweep. Horizontal line indicates stimulus duration.

The two sets of responses were used to obtain NdRs such that NdRs for a sound presented in the presence of the second sound in the sequence had fixed zero values. Population analysis was conducted using Wilcoxon Signed rank test for 66 neurons. These findings are summarized in figure 34. Median of NdR values for the entire population was significantly larger than zero (Z = 1842.0, p = 0.0001) when Odd was presented in the absence of Std. The same findings were seen in two subgroups of neurons showing transient firing (Z = 759.0, p = 0.0001) and sustained firing Z = 240.0, p = 0.037).

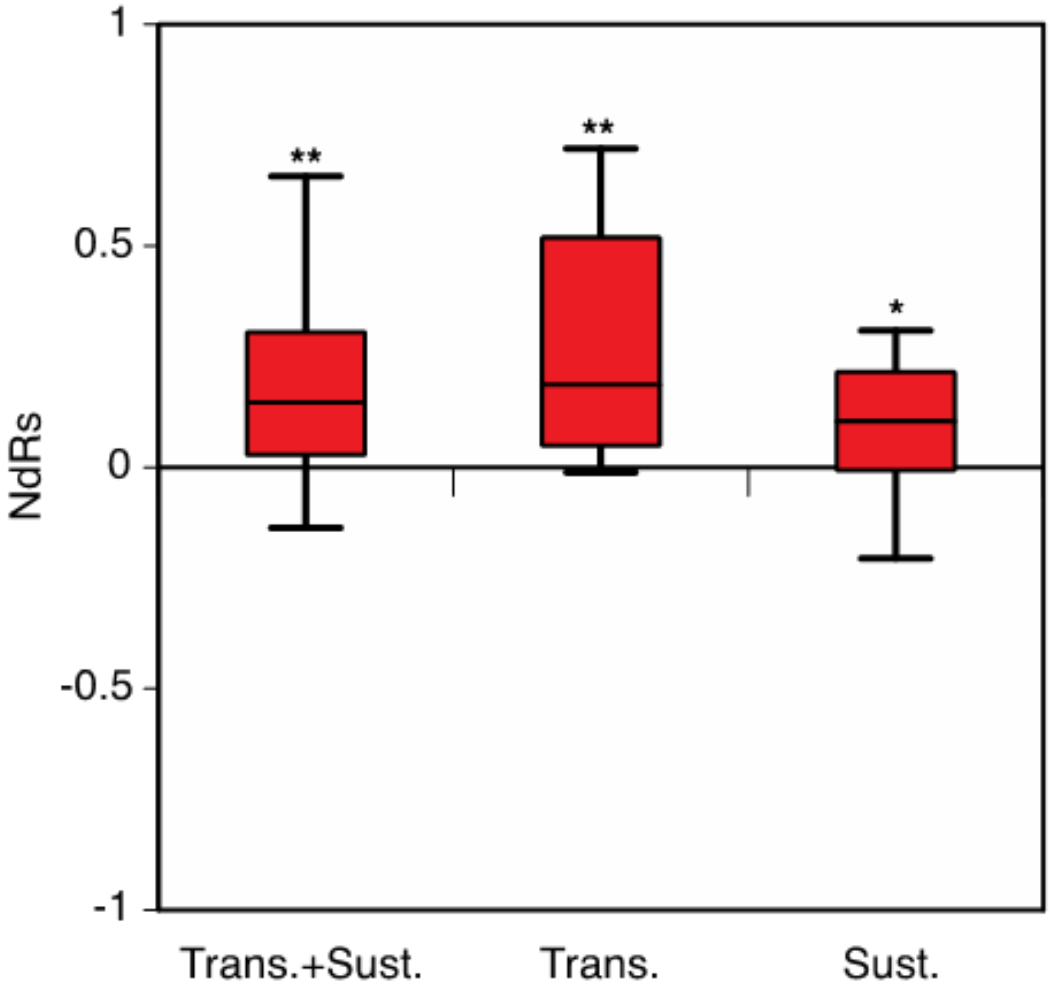


Figure 34. Box plots showing distribution of Odd NdRs when Std was omitted from the sequence. Horizontal line indicates group NdR median. **Significant NdR median at 0.005 p-value; * Significant NdR median at 0.05 p-value Significant NdR median at 0.005 p-value, Wilcoxon Signed rank test.

In contrast to responses obtained when Odd was presented alone at c90°, medians of NdRs obtained from responses to Std alone (Figure 35; when Odd in an oddball paradigm was omitted) were not significantly different from zero. This was true for the entire population of neurons as well as the two subgroups of neurons with different firing patterns (Figure 35).

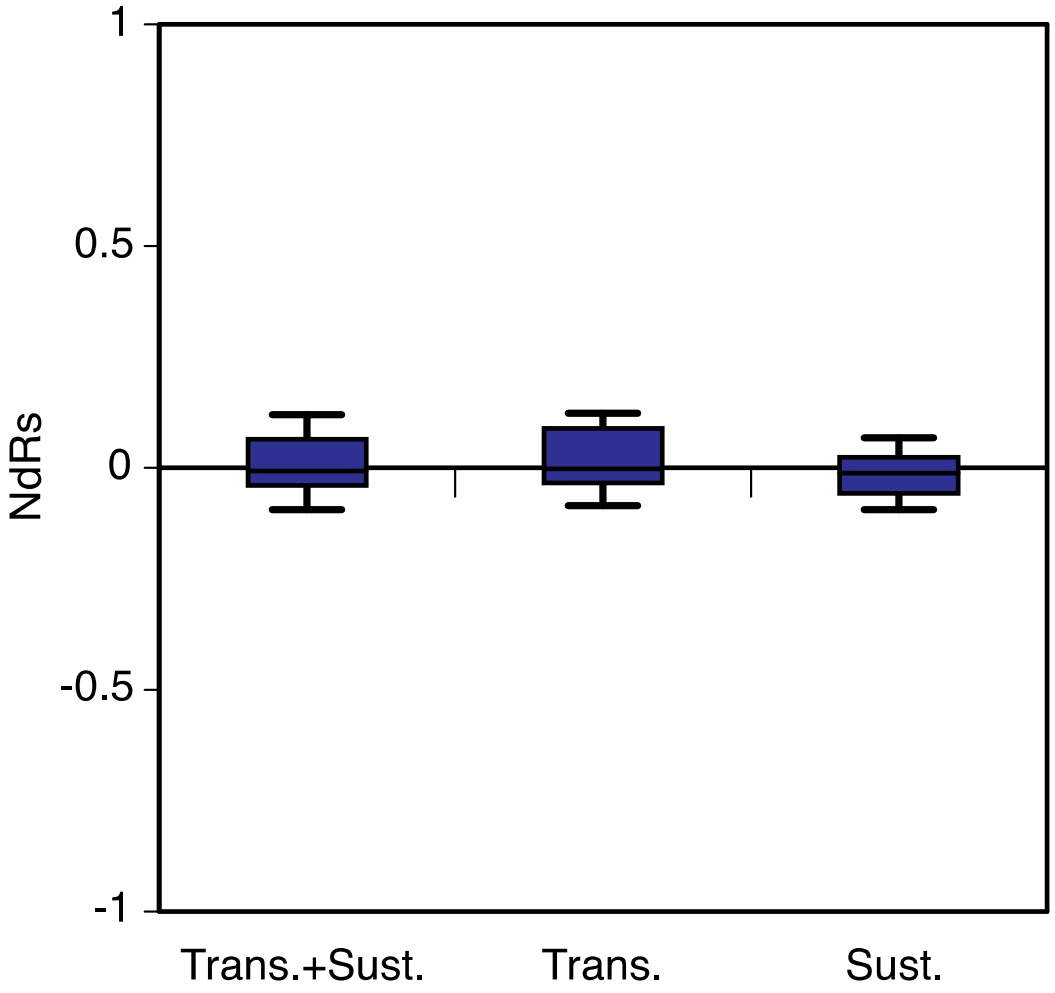


Figure 35. Box plots showing distribution of Std NdRs when Odd was omitted from the sequence. Horizontal line indicates group NdR median.

When 50% sound was presented alone, the results similar to when Odd was presented alone (Figure 33B and 33) were observed. As shown in figure 36, the population medians of NdRs in response to equiprobable sound presented alone were significantly greater than zero (Z = 1690.0, p = 0.0001). Similarly, NdRs median of transient neurons was also greater than zero (Z = 719.0, p = 0.001). Sustained neurons, however, showed completely contrasting findings (Z = 197.0, p = 0.179).

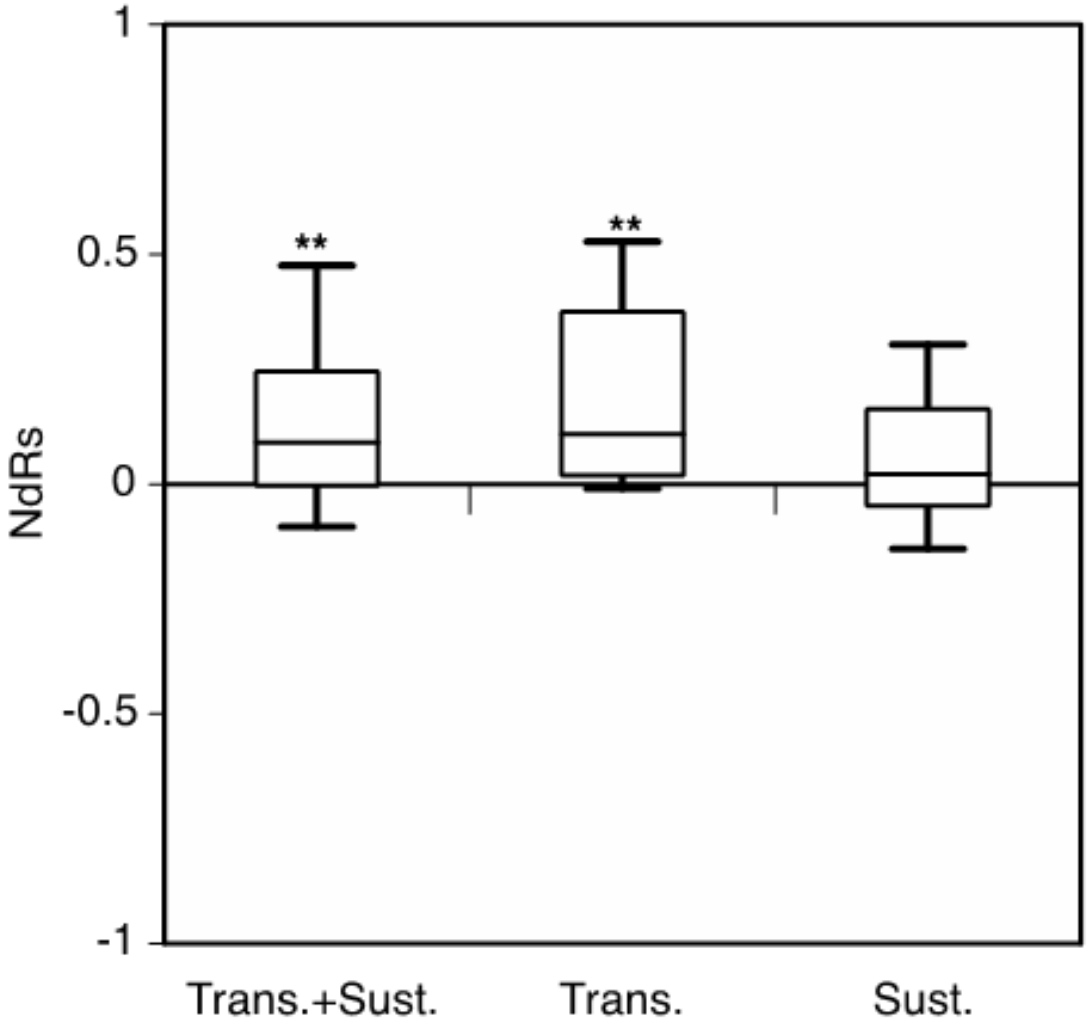


Figure 36. Box plots showing distribution of Odd NdRs when Std was omitted from the sequence. Horizontal line indicates group NdR median. **Significant NdR median based on Wilcoxon Signed rank test.

4.9. Responses to an oddball paradigm with only one sound presented in the sequence: 0ff-c90° locations.

Finally, it was important to study how the two tone bursts in an oddball paradigm interact to generate responses at off-c90° locations in the frontal azimuth. The same paradigm used in the previous section (when one sound was omitted) was presented at each off c90° location (c45°, 0°, i45°, and i90°). Figure 37 compares responses of a single unit to the same tone burst when it

was presented alone or with another sound in the sequence at various spatial locations, and at different probabilities. The neuron reduced the strength of responses to a sound presented with another sound at off-c90°. This reduction was alleviated when the same sound was presented alone as Odd or equiprobable, but not when it was alone as Std.

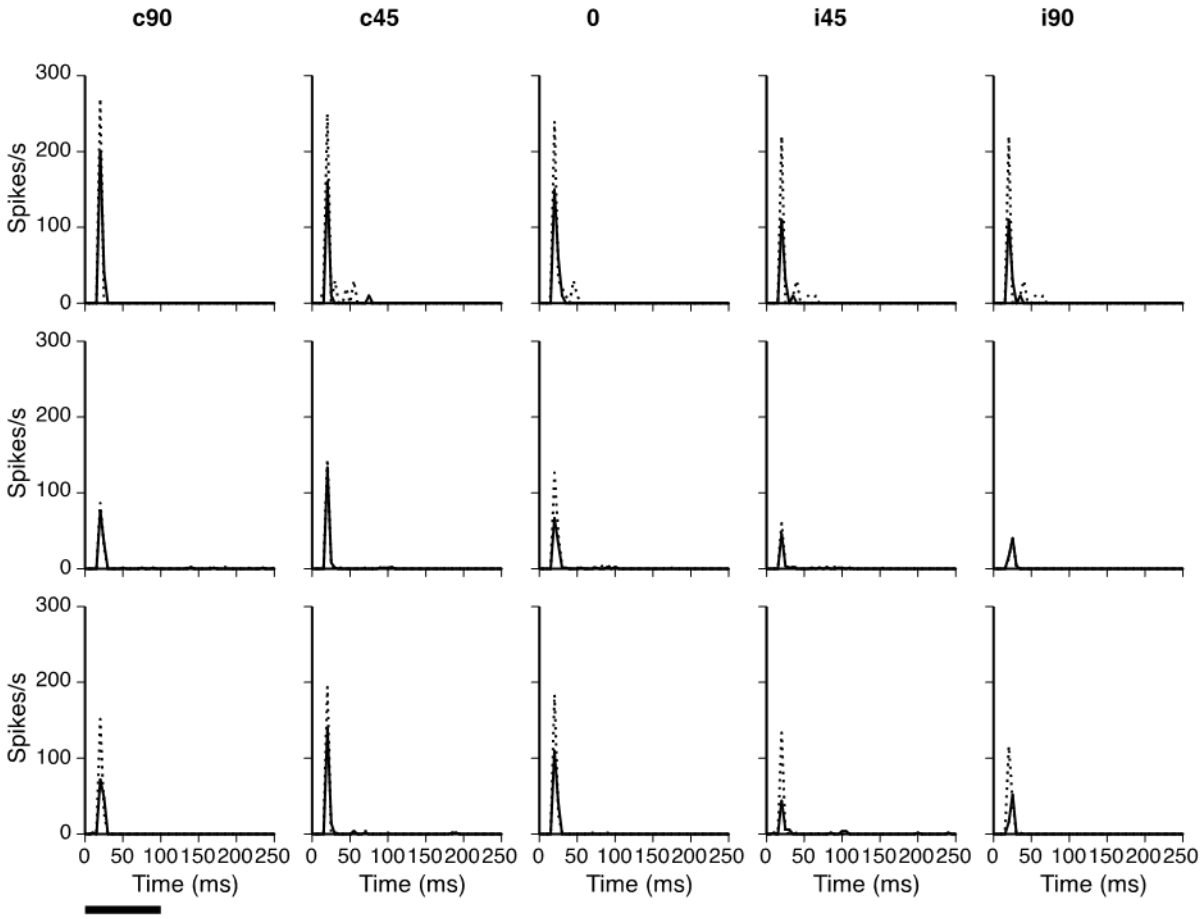


Figure 37. PSTHs showing responses of a single unit to the same sound presented at various spatial locations either alone (dashed lines) or with another sound (thick lines). Top panel: Odd responses; middle panel: Std responses; bottom panel: 50% sound responses. Horizontal line indicates stimulus duration.

In a group of 26 neurons, NdRs were calculated for responses to a single sound as a function of response to a sound co-localized at c90° with another sound. This approach resulted in a non-zero NdR at c90°. Wilcoxon Signed rank tests were used to compare medians of single sound NdRs and medians of co-localized sound NdRs (i.e. zero NdRs). Due to the small sample, statistical tests were conducted only for population results. When Odd was presented alone, the population median NdR of all the 26 neurons was only significantly less than zero at i45° (Figure 38A; Z = 59, p = 0.003) and i90° (Z = 59, p = 0.003). Both transients (Figure 38B; n = 6) and sustained neurons (Figure 38C; n = 17) also exhibited reduction only at the two ipsilateral locations. The reduction looked stronger in transient neurons than sustained.

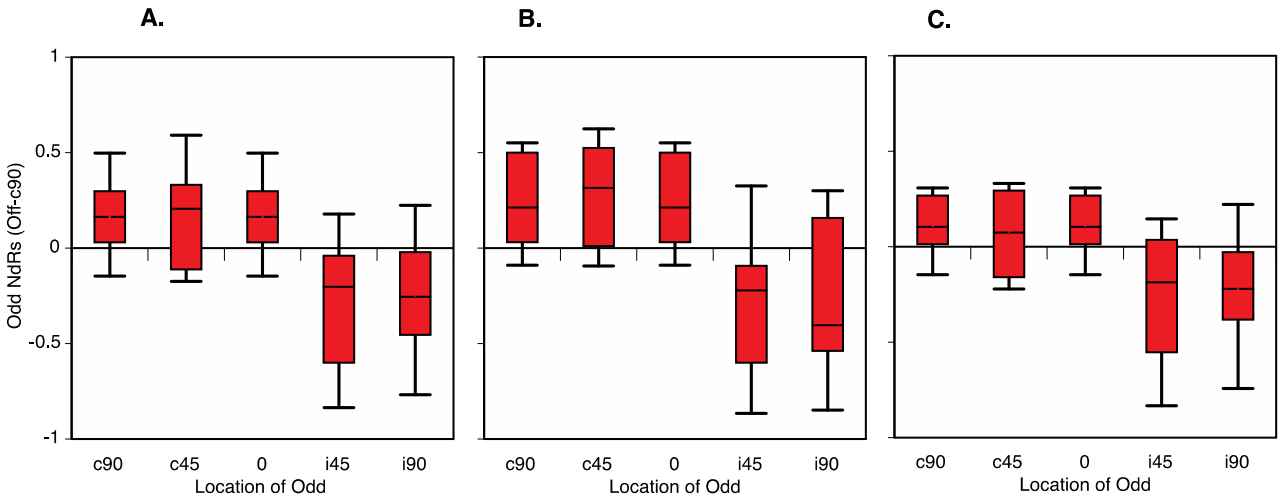


Figure 38. Distribution of Odd NdRs obtained from single sound presented at various spatial locations. A. Population NdRs. B. Transtient neurons. C. Sustained neurons. Horizontal lines indicate group median. No statistical tests were conducted for B and C.

Contrary to the above findings, the population Std NdRs were not different from zero at c90° and c45° but significantly plummeted below zero at 0° (Z = 55, p = 0.002), i45° (Z = 1, p = 0.0001) and i90° (Z = 0, p = 0.0001) (Figure 39A). Similar trend was observed for transient and

sustained neurons (Figure 39C and 39C) except that the reduction was more pronounced in transient neurons.

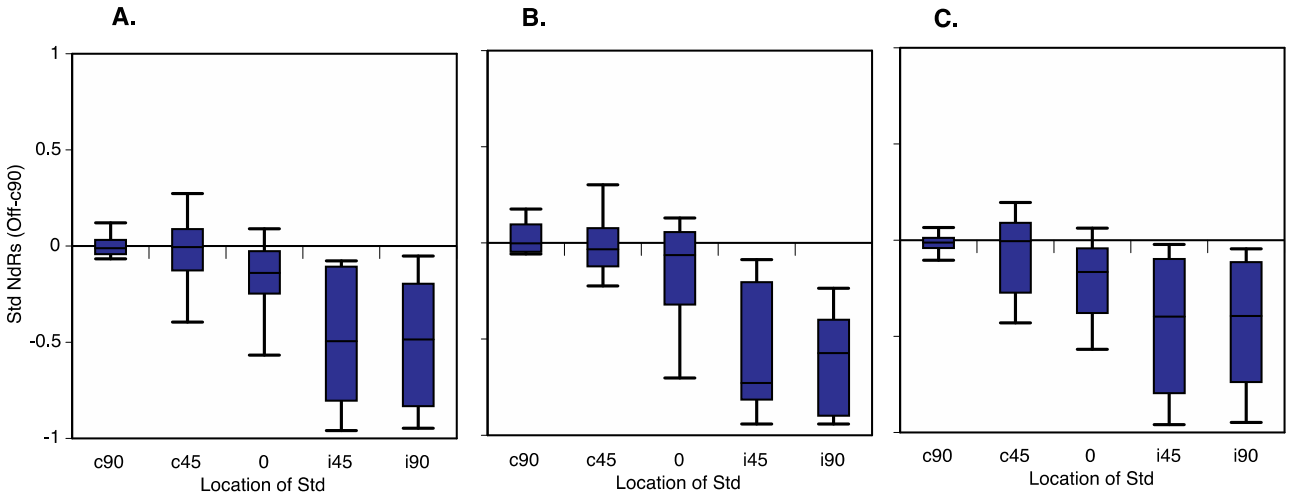


Figure 39. Distribution of Std NdRs obtained from single sound presented at various spatial locations. A. Population NdRs. B. Transtient neurons. C. Sustained neurons. Horizontal lines indicate group median. Note: No statistical tests were conducted for B and C.

When 50% sound was presented alone, the population results were similar to when Odd was presented alone. That is, the NdRs began to fall significantly below zero at i45° (Figure 40A; Z = 29, p = 0.0001) and i90° (Z = 37, p = 0.0001). Transient and sustained neurons showed similar trends (Figure 40B and 40C). However, the medians of NdRs at ipsilateral locations were much lower in transient neurons.

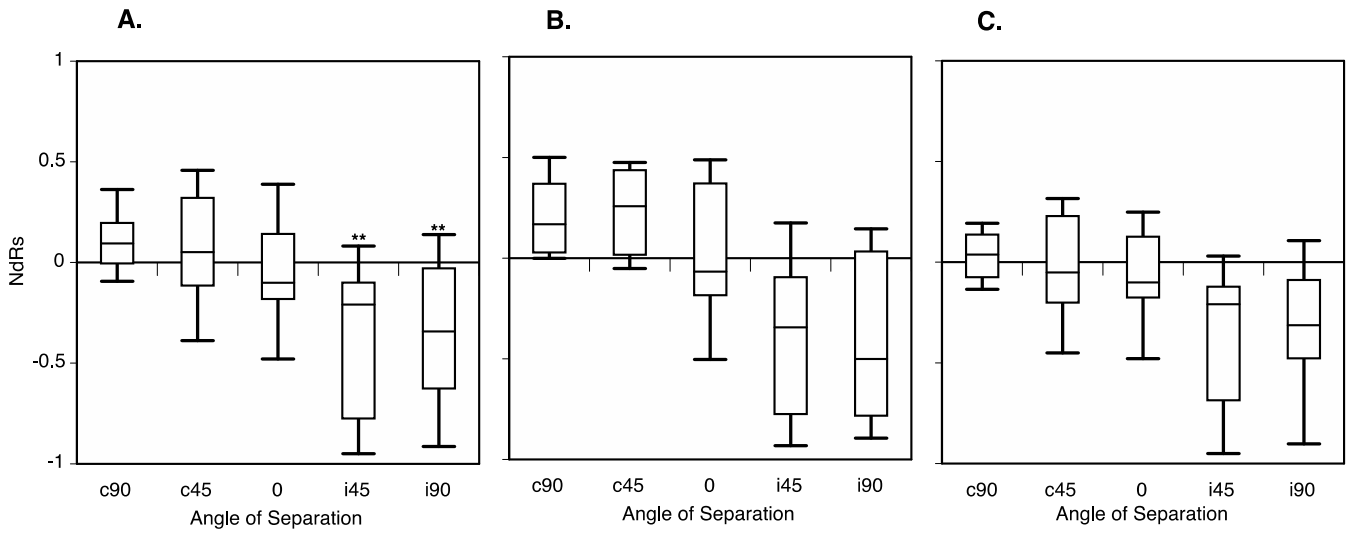


Figure 40. Distribution of 50% sound NdRs obtained from single sounds presented at various spatial locations. A. Population NdRs. B. Transtient neurons. C. Sustained neurons. Horizontal lines indicate group median. **Significant median NdRs (Wilcoxon Signed rank test). Note: No statistical tests were conducted for B and C.

In order to obtain a clear idea about how a sound at c90° affects neuronal responses to off-c90°, population median NdRs for responses to off-c90° sound when the corresponding sound in the sequence was omitted and when it was present at c90° were plotted for comparison. Median NdR values were lowest at ipsilateral locations when the second sound was presented at c90° in all categories compared (Odd, Std, and Equal probability) (Figure 41).

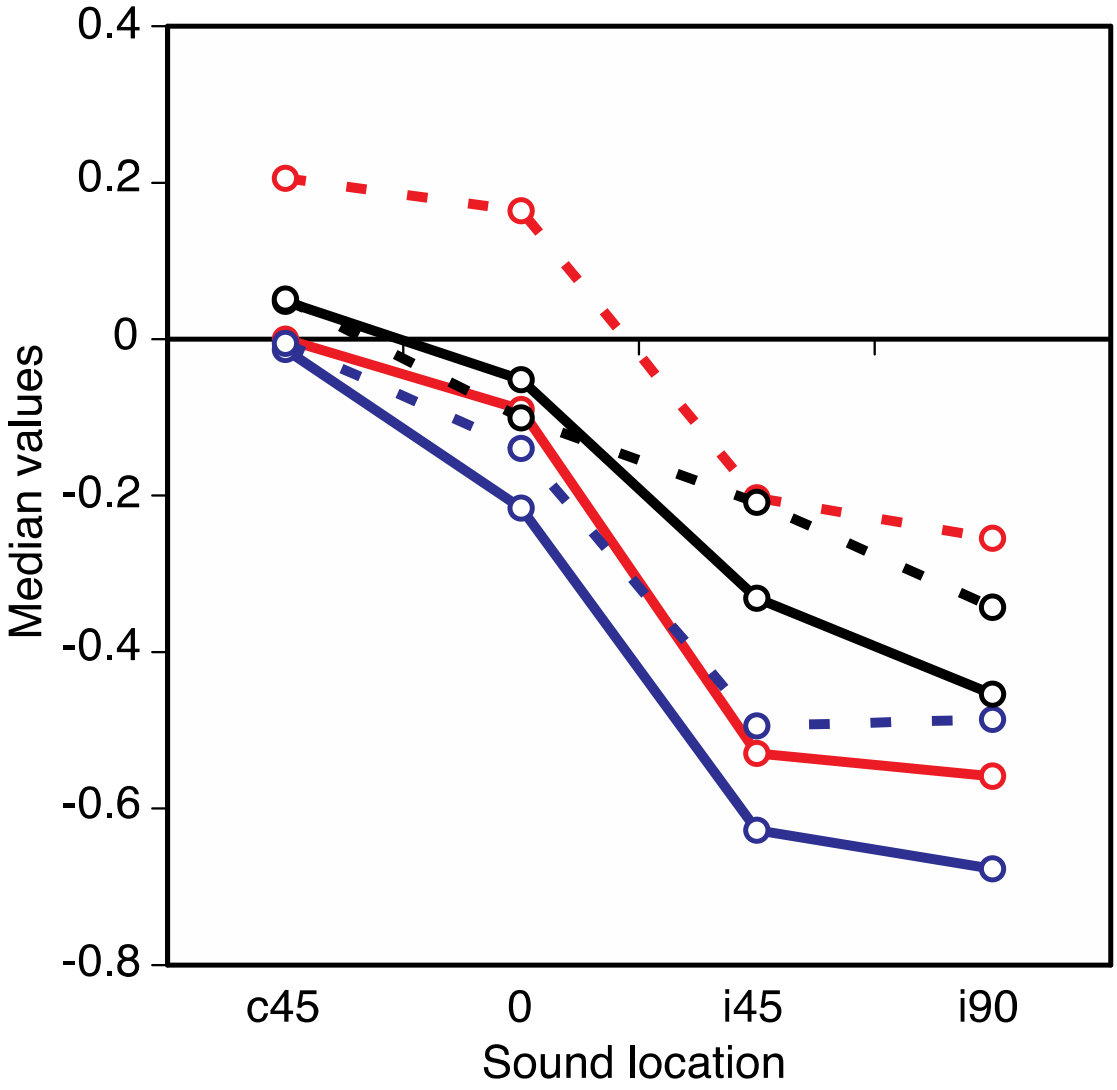


Figure 41. Line plots comparing median NdRs obtained when a sound was presented at off-c90° alone (dashed lines), and when it was presented at off-c90° while the second sound was presented at a fixed c90° location (think lines). Red; Odd, blue; Std, black; 50% sound.

5. Discussion

This study demonstrates that majority of IC neurons showed SSA under free-field conditions. Transient neurons, but not sustained neurons, enhanced responses to Odd presented at the contralateral ear especially when Std was presented at an ipsilateral location. In both types of neurons, the position of Odd in the frontal azimuth did not affect neuronal responses to Std presented at the contralateral ear. In the contrary, a sound presented at the contralateral ear reduced neuronal responses to a sound presented at another location in the frontal azimuth regardless of whether it was Odd or Std. This reduction was typically stronger for responses to Std and in transient neurons.

SSA has been studied in IC neurons using oddball paradigm presented through earphones (Anderson et al., 2009; Antunes et al., 2010; Farley et al., 2010; Malmierca et al., 2009; Pérez-González et al., 2012; Ulanovsky et al., 2003; Von Der Behrens et al., 2009; Zhao et al., 2011). The present study replicates these findings. Most IC neurons responded more strongly to Odd than Std in an oddball paradigm presented through a free-field speaker located at c90° in front of the contralateral ear. This was regardless of whether the tone was T_L or T_H.

5.1. SSA derived from sounds spatially separated sounds vs SSA derived from co-localized sounds

The SSA obtained from spatially separated sounds is stronger than SSA obtained from co-localized sounds. Previous studies have hardly investigated SSA under ecologically relevant listening conditions. A study in the barn owl used interaural time difference (ITD) and level difference (ILD) to investigate SSA (Reches and Gutfreund, 2008). This study differs substantially from the present findings. Apart from being conducted in a different species and under artificial stimulus conditions, it did not find spatially related SSA in the inferior colliculus.

A recent study investigated IC responses to sounds of an oddball paradigm that was presented through free-field speakers (Patel and Zhang, 2016). It was found that collicular neurons had better sensitivity to both Odd and Std when co-localized in front of the animal than when they are spatially separated. This study differs from the present study in both design (See "Methods) and findings. For instance, SSA in the present study was strongest for responses to sounds at the contralateral ear when the corresponding sounds of the oddball paradigms were presented at an ipsilateral location. This finding was unique to neurons with transiently firing patterns. Moreover the spatial-dependent increase in SSA in this neurons was directly attributable to enhanced responses to Odd rather than Std. These findings suggest that transient neurons are capable of processing acoustic stimuli containing complex cues such as spatial cues, and might be best suited for detecting novel stimuli in a natural environment. Sustained neurons, on the other hand, did not showed spatial-dependent increase or decrease in SSA and might serve to process basic acoustic features such as intensity and frequency.

5.2. Enhanced responses to Odd presented at the contralateral ear when Std is at an ipsilateral location.

Responses to Odd were strongly augmented when Std was relocated to an ipsilateral location in transient neurons. The same was not true for sustained neurons. In both populations, the position of Odd in the frontal azimuth did not alter responses to Std presented at the contralateral ear. It is thus important to account for the disparity in spatial-dependent sensitivity to Odd between the two neuronal populations.

A recent model proposed that adaptation of excitatory inputs in neurons with narrow frequency range shapes responses to Odd and Std in an oddball paradigm (Taaseh et al., 2011). Thus, replacing Std with silent gaps in an oddball paradigm sequence would reduce adaptation

and effectively enhance responses to Odd (Duque et al., 2016; Hershenhoren et al., 2014; Taaseh et al., 2011). The present results agree in part with previous findings. Omitting Std in an oddball paradigm sequence enhanced responses to Odd alone in both transient and sustained neurons. It is noteworthy that this enhancement was stronger in transient than sustained neurons. The adaptation model can explain why transient neurons enhanced responses to Odd upon the relocation of Std to an ipsilateral location. Nonetheless, it fails to address why sustained neurons did not alter responses to Odd regardless of the Std position in the azimuth. These findings suggest that a separate and/or complementary mechanism exists in the IC that might be responsible for disparity in responses to Odd between transients and sustained neurons. It was therefore important to examine differences between the two groups.

The most apparent difference between transient and sustained neurons in this study is their responses to directional stimuli. Most transient neurons exhibit stronger reduction in response to ipsilateral stimulation than transient neurons, suggesting that sustained neurons receive at least weak excitatory ipsilateral inputs. Thus it is plausible to speculate the balance of binaural excitation an inhibition could be one of the possible mechanisms responsible for the difference in sensitivity to Odd. A population of rebound neurons has been described previously in the rat IC (Sivaramakrishnan and Oliver, 2001). These neurons respond strongly to low threshold excitatory currents, which they would normally not respond to, only if it is preceded by prolonged inhibitory hyperpolarizing current. This phenomenon has been described as post-inhibitory rebound. This phenomenon is likely responsible for location-dependent sensitivity to Odd in transient neurons. For a neuron inhibited by ipsilateral location, Std sound would provide sufficient prolonged inhibition. Odd sound presented at the contralateral ear under such conditions would elicit rebound firing. Conversely, Odd presented at an ipsilateral location

would not provide prolonged inhibition sufficient enough to cause rebound in firing. Thus, responses to Std presented at the contralateral ear would undergo adaption. This model is consistent with enhanced responses to Odd in transient neurons, and no alteration in responses to Std in both populations.

5.3. Enhanced responses to equal probability sound presented at the contralateral ear when the second sound is at an ipsilateral location.

In order to isolate probability effects on responses to an oddball paradigm from effect of spatial separation, it is important to study the same composing sounds when presented at equal probability. This present results indicate that transient neurons enhanced responses to equal-probability sound at the contralateral ear when the other sound was either presented at an ipsilateral location or when it was omitted. Sustained neurons did not alter their responses regardless. These findings suggest that the enhancement observed in transient neurons in response to Odd is attributable to the spatial separation between the two sounds. Enhanced response to equal probability sound in transient neurons can be explained by rebound in firing. That is, equal probability sound at an ipsilateral location is likely sufficient enough to cause rebound firing in response to sound at the contralateral ear. The absence of change in response in sustained can be due to adaptation. This is likely due to alternating activation of both weak excitatory inputs at the ipsilateral location, and strong excitatory inputs at the contralateral ear. The fact that sustained neurons did not alter their responses when one sound was omitted supports the hypothesis that these neurons might be poorly tuned to subtle cues in a complex acoustic stimulus.

5.4. A sound of an oddball paradigm presented at the contralateral ear reduces neuronal responses to another sound presented at a different location in the azimuth.

A sound presented at the contralateral ear reduced neuronal responses to a second sound in the same sequence that was presented at a different location. Both IC neuronal populations generally reduced their responses to an off-c90° sound regardless of whether it was Odd, Std, or equal probability. This reduction was always greatest at ipsilateral locations. This is consistent with the fact that most IC neurons are inhibited by ipsilateral stimulation (Pollak et al., 2002; Pollak, 2012). However, the reduction was alleviated when one sound in the paradigm was omitted, suggesting that the contralaterally presented sound had an inhibitory effect. The amount of reduction was predictably dependent on neuron types. That is, transient neurons showed stronger ipsilateral reduction in response to Odd sound when Std was presented at the contralateral ear than sustained neurons. Similar pattern was observed for responses to Std when Odd was at the contralateral ear. Ipsilateral reduction in response was stronger for responses to Std rather than Odd in both neuronal types. The stronger reduction in response to ipsilateral Std can be explained by adaptation model especially in sustained neurons.

6. Conclusions and Future Directions

Collicular neurons use spatial cues to detect novel sounds in ecologically relevant acoustic scenes. Neurons with transient firing patterns are likely capable of extracting complex acoustic cues and, thus, are better tuned to novelty sensitivity. Spatial-dependent sensitivity to novel sounds, or lack thereof, can be accounted for by adaptation model and/or balance between binaural excitation and inhibition. This study not only provides insights into novelty detection, but also mechanisms underlying binaural hearing in natural acoustic environments.

Neurons used in this study were grouped according to whether the firing rate lasts the duration of stimulus. As a result, single units with distinct firing patterns were clumped in one group (See Methods). Moreover, rare neurons such as onset neurons were not included in the

analysis. In order to obtain a better idea about spatial processing, future studies should focus on collecting sufficient data on each individual single unit types.

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