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Auditory Neurons in the Dorsal Cortex of the Inferior Colliculus: Responses to Contralateral Tone Bursts and Modulations by the Auditory Cortex

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AUDITORY NEURONS IN THE DORSAL CORTEX OF THE INFERIOR COLLICULUS: RESPONSES TO CONTRALATERAL TONE BURSTS AND MODULATIONS BY THE AUDITORY CORTEX

by

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Author's Declaration of Originality

I hereby certify that I am the sole author of this thesis and that no part of this thesis has been published or submitted for publication. While I played a major role in the execution of the project described in this thesis, the research could not have been done without the advising from my supervisor Huiming Zhang. His advising was critical for the development of key scientific ideas, design of experiments and analysis, as well as interpretation of data.

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ABSTRACT

The inferior colliculus plays a key role in auditory processing. In the current study I used the albino rat, *Rattus norvegicus,* as an animal model to investigate auditory responses in single neurons in the dorsomedial subdivision of the inferior colliculus (ICd).

My results reveal that ICd neurons exhibit various temporal firing patterns and long and variable first spike latencies. These neurons displayed a variety of frequency-tuning curves. Both monotonic and non-monotonic rate-level functions were present in these neurons. ICd neurons displayed stimulus-specific adaptation by reducing the strength of firing during repetitive tone burst stimulation but restored their responses when the quality of sound was changed. Functional decortication changed the strength of firing in ICd neurons, suggesting these neurons were controlled by the auditory cortex. My results suggest that the ICd may provide a gating mechanism that helps the auditory system to selectively process novel sounds in the acoustic environment.

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LIST OF ABBREVIATIONS

AAF – Anterior Auditory Field

AC – Auditory Cortex

AI – Primary Auditory Cortex

AII – Secondary Auditory Cortex

AM – Amplitude Modulated

AMPA - α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate

AN – Auditory Nerve

AP – Action Potential

AVCN – Anteroventral Cochlear Nucleus

BW – Bandwidth

CAS – Central Auditory System

CF – Characteristic Frequency

CN – Cochlear Nucleus

DCN – Dorsal Cochlear Nucleus

FTC – Frequency Tuning Curve

GABA – γ-Aminobutyric acid

IC – Inferior Colliculus

ICc – Central Nucleus of Inferior Colliculus

ICd – Dorsal Nucleus of Inferior Colliculus

ICx – External Nucleus of Inferior Colliculus

LSO – Lateral Superior Olive

MGB – Medial Geniculate Body

MSO – Medial Superior Olive

MT – Minimum Threshold

NLL – Nucleus of the Lateral Lemniscus

NMDA – N-methyl-D-aspartic acid

NMDAR – N-methyl-D-aspartic acid Receptor

NTB – Nucleus of the Trapezoid Body

PAF – Posterior Auditory Field

PSTH – Post-Stimulus Time Histogram

PVCN – Posteroventral Cochlear Nucleus

RLF – Rate-Level Function

SOC – Superior Olivary Complex

SPL – Sound Pressure Level

SSA – Stimulus-Specific Adaptation

SSA_A – Stimulus-Specific Adaption Index based on areas under iso-intensity curves

SSA_P – Stimulus-Specific Adaptation Index based on peaks of iso-intensity curves

Te1 – Temporal Area 1

Te2 – Temporal Area 2

Te3 – Temporal Area 3

VCN – Ventral Cochlear Nucleus

1 INTRODUCTION

1.1 The Central Auditory System: an Overview

Hearing is one of the most crucial sensory abilities in many mammalian species and permits species-specific communication. Hearing depends on both the peripheral and the central auditory system. The peripheral auditory system includes the outer, middle and inner ears. The outer ear is stimulated by pressure waves i.e. acoustic signals. These signals enter the outer ear and travel through the middle ear toward the cochlea. At the level of the cochlea these acoustic signals are transduced into electrical signals. The electrical signals are then processed at several structures in the central auditory system (CAS) (Figure 1). Acoustic information processed in the auditory system includes spectral, temporal and spatial characteristics of sounds (Fay, Popper and Webster, 1992).

The CAS is organized in a hierarchical manner. Auditory information is carried by action potentials through the ascending pathway commencing at the auditory nerve (AN) also known as the 8^{th} cranial nerve. The AN is in fact considered a part of the peripheral auditory system, thus the first center of processing in the CAS is cochlear nucleus (CN). From here auditory neural signals travel through the ascending pathway and are further processed at the superior olivary complex (SOC), the nucleus of lateral lemniscus (NLL), the inferior colliculus (IC), the medial geniculate body (MGB) and finally the auditory cortex (AC). The AC controls neural processing in subcortical structures using corticofugal descending projections.

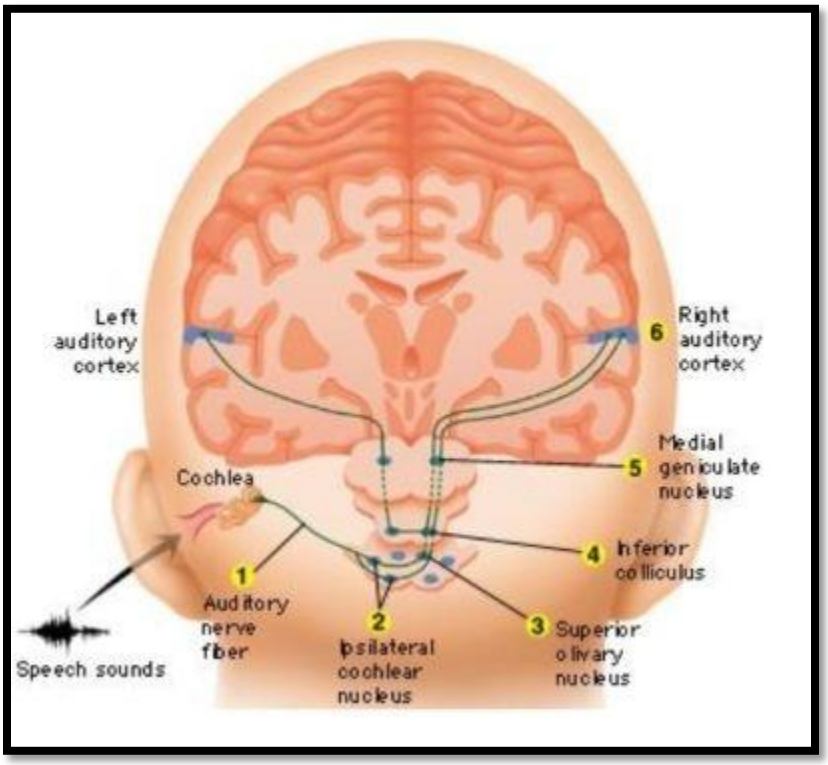


Fig.1. The human central auditory system. A representation of all levels of auditory processing in the ascending pathway including: 1) Auditory nerve fiber; 2) the cochlear nucleus (CN); 3) the Superior Olivary Complex (SOC); 4) the Inferior Colliculus (IC); 5) the Medial Geniculate Body (MGB); and 6) the Auditory Cortex. The green lines represent projections to each center of processing. The oscillogram shows the place of entry for the sound stimulus.

Benett Coleman & Co., 2009

The CN is the first relay station of the CAS. It receives inputs from the 8th cranial nerve, the auditory nerve. The cochlear nucleus is subdivided into ventral and dorsal divisions (VCN and DCN, respectively). The ventral division can be further subdivided into the anterior ventral cochlear nucleus (AVCN), and the posterior ventral cochlear nucleus (PVCN). Each division of the CN receives ascending input from the auditory nerve. Studies of the CN suggest that its functional importance arises from the fact that this structure receives inputs from the auditory nerve that preserves the topography of frequencies established in the cochlea (Osen, 1970). All three subdivisions of the CN contain this tonotopic organization, with low frequencies represented ventro-laterally and high frequencies represented dorso-medially within each subdivision (Sando, 1965). The CN is involved in the generation of basic response patterns and emergence of parallel pathways. Lastly, the CN receives an array of descending projections that arrive from higher order auditory structures providing feedback and aid in the overall complexity of auditory processing (Adams and Mugnaini, 1987; Kand and Conlee, 1982).

The SOC is found ventral and medial to the CN, in the caudal portion of the pons (Noback, 1985). The SOC is divided into multiple subnuclei including the lateral superior olivary nucleus (LSO), the medial superior olivary nucleus (MSO), the nucleus of the trapezoid body (NTB) and the lateral and medial periolivary nuclei. The SOC maintains the tonotopic organization seen in the CN. The most extensively studied subdivisions of this structure are the LSO and MSO. In the LSO, lower frequencies are represented laterally and higher frequencies are represented medially following the s-shaped contour of the nucleus (Tsuchitani and Boudreau, 1966). Research focusing on the SOC has illustrated that it is responsible for construction of binaural pathways and establishment of time lines. The SOC is a complex relay station in the auditory pathway. It is the first place where ipsilateral and contralateral inputs are

combined and information related to sound location is processed. Sound localization is determined mainly by interaural time and intensity differences reflected in inputs to the SOC (Masterton, Thompson, Bechtold, and Robards, 1975; Boudreau and Tsuchitani, 1970).

The lateral lemniscus is the primary auditory pathway in the brainstem and contains both ascending and descending fibers. The ascending portion extends bilaterally from the CN to the IC in the midbrain and contains both crossed and uncrossed fibers of the CN and SOC (Goldberg and Moore, 1967). The NLL is made of neurons scattered in the lateral lemniscus. This nucleus consists of three subnuclei, the dorsal, intermediate and ventral portions as well as axons in which they lie along the lateral surface of the brain stem, near the transition from the pons to the midbrain. The dorsal nuclei of the lateral lemniscus from either side of the brainstem are interconnected by a fiber tract called the commissure of Probst (Kudo, 1981). Most neurons of the dorsal segment of the NLL can be activated binaurally. However, most neurons from the ventral segment can be activated only by contralateral stimulation. Overall, the NLL adds further branches of segregated processing streams and additional diversity and complexity to the expression and role of functional stream segregation and information integration

The inferior colliculus (IC) is a midbrain structure and is known as the hub of the mammalian CAS (Winer and Schreiner, 2005). Based on previous research regarding the function and structure of the IC as well as the pattern of projections to the IC it is suggested that this structure can be divided into multiple subdivisions including the central nucleus (ICc), the dorsal cortex (ICd) and the external nucleus (ICx) (Faye-Lund and Osen, 1985). Among the three subdivisions of the IC, the ICc has been studied much more thoroughly than the ICd and ICX. Neurons in the ICc are well characterized neuroanatomically, neurophysiologically and neuropharmacologically. There is abundant knowledge about the role of ICc neurons in the

processing of temporal, spectral and directional response characteristics (Winer and Schreiner, 2005). In contrast, far less is known about the function of ICd and the ICx (see section 1.3).

The mammalian auditory thalamus, also known as the medial geniculate body (MGB), consists of an oval mass and exists bilaterally extending from the midbrain to the forebrain. The MGB provides auditory information to cortical and limbic systems for further processing. The MGB contains ventral, dorsal as well as medial divisions (Morest, 1964). Neurons in the ventral division respond primarily to acoustic stimuli, whereas the dorsal and medial divisions contain neurons that respond to both somatosensory and acoustic stimulation (Pickles, 1988). Research focusing on the ventral division of MGB has revealed that this division transmits specific auditory information to the primary auditory cortex (Winer, 1984). Studies involving the dorsal division illustrate that this part of the structure projects to association areas of the AC (Faye-Lund, 1985; Saldana, Feliciano and Mugniani, 1996). The dorsal division may also be involved in maintaining and directing auditory attention (Winer, 1984). Lastly, medial division studies have depicted this part of the MGB as an area of course tonotopic organization or gradient (Rouiller, Rodgrigues-Dagaeff, Simm, de Ribaupierre Y, Villa, and de Ribaupierre F, 1989). This structure may also function as a multisensory arousal center (Winer, 1984).

Lastly, the auditory cortex (AC) is found at the top of the hierarchical auditory ladder. The acoustic information encoded in neural signals is transmitted from the ear to the AC via the aforementioned CAS structures through the ascending auditory pathway. Several regions of the AC have been identified, including the primary AC (AI), the secondary AC (AII) and the association cortex. As in brain stem structures, the AC also possesses distinct tonotopic organization. The tonotopic organization exists in the AI of the AC with low frequencies represented rostrolaterally and high frequencies represented caudomedially (Merzenich and

Brugge, 1973). Response properties of cells in the AC are complex, showing binaural interactions and dependence on temporal combinations of tones. The structure and function of the AC will be further discussed in section 1.2. Overall, the AC is the interface between hearing and higher order communication and cognitive networks (Brodal 1981; Edelman, Gall and Cowan 1988; Popper and Fay 1992; and Fay et al. 1992). Although the AC is the highest structure in auditory signal processing, the information processing does not end here (Winer, 2006). The AC also possesses neurons that provide feedback projections to lower structures. These corticofugal projections control auditory neural processing in lower structures (Winer, 2006) (see also section 1.4).

The descending auditory system starts at the AC and projects to the MGB and the midbrain regions, including the IC. Based on both anatomical and physiological studies a loop system appears to exist between the AC and these structures. Fibers also descend from the AC to neurons in the brainstem (Winer, 2006).

The function of descending pathways has been studied to a lesser degree than that of the ascending system. Anatomical studies using anterograde and retrograde tracers have illustrated that corticofugal projections to the IC influence the way in which specific sets of IC neurons process acoustic signals (Bajo and Moore, 2005; Syka and Popelar, 1984; Suga et al., 2000; Sun et al., 1996; Yan and Suga 1996; Yan and Ehret, 2002). For the purpose of the current study the main focus of descending projections is the corticocollicular pathway. Neurophysiological studies have suggested that projections from the AC may modulate the processing of sounds in the IC through the activation of local inhibitory neural circuits (Malmierca and Merchan, 2004).

1.2 The Structure and Function of the Auditory Cortex

The AC is found at the top of the hierarchy in the central auditory system. The AC is essential for discrimination and localization of sounds, recognition of species specific vocalizations, embedding of acoustical cues into the behavioural context and auditory learning and memory. In many mammalian species including humans, it is subdivided into the primary auditory cortex (AI), secondary auditory cortex (AII), and association cortex. In rats, the AC can be subdivided into temporal cortex area 1, 2 3 (Te1, Te2 and Te3) (Figure 2) (Malmierca and Merchan, 2004). Te1 is equivalent to AI, whereas a clear equivalent of Te2 and Te3 is undefined (Herbert et al., 1991). AI receives its main input from the ventral division of the MGB. Research has shown that neurons in the AI are organized topographically based on frequency (Malmierca & Merchan, 2004). The AC is made up of six layers, with each layer having specific cell types and cell packing density. Layer I of the auditory cortex has few neurons but is rich in neuropil clusters. Approximately 90% of the neurons in this layer are GABAergic, or activated by the GABA neurotransmitter (Winer and Larue, 1989). The majority of layer I neurons synapse with apical dendrites of other layer I neurons (Winer, 1992). Layer II contains both pyramidal and non-pyramidal neurons (Malmierca and Merchan, 2004). Neurons in layer II form connections mostly with adjacent non-primary auditory field neurons. They also form local interlaminar connections with neurons in layers II and III (Winer, 1992). Layer III is made up of three types of pyramidal cells that are identified based on their variance in size (Malmierca and Merchan, 2004). This layer is comprised of complex intrinsic and extrinsic neural connections, including interactions with neurons in the medial geniculate body (MGB) and ipsilateral and contralateral auditory cortices (Winer, 1984). Layer IV is known as the internal granule cell layer and is made up of almost completely non-pyramidal cells (Malmierca and Merchan, 2004). Layer IV has

connections with thalamic and local cortical neurons and also receives inputs from the commissural system (Winer, 1992). Layer V is known as the internal pyramidal cell layer. Layer V of the AC is made up of both pyramidal and non-pyramidal neurons (Malmierca and Merchan, 2004). This layer forms neural connections with neurons in the ipsilateral non-primary auditory cortex, the contralateral AI, the MGB, the inferior colliculus (IC) and some brain stem structures (Winer, 1992). Researchers have also illustrated that layer V receives input from commissural and corticocortical axons, and that some of these may be GABAergic projections (Peterson, Prieto and Winer, 1990). Anatomical studies have shown that layer V is the source of abundant descending projections to the IC (Winer and Schreiner, 2005). Layer VI is made up of horizontal and pyramidal cells and receives input from axons arising in the medial division of the MGB. Layer VI is a source of descending projections to the MGB as well as the IC (Winer and Schreiner, 2005; Schofield, 2009). The AC is very diverse in its neuronal population and thus is physiologically complex.

From a physiologist's point of view auditory cortical subdivisions can be distinguished based upon response properties of single neurons such as characteristic frequency, spectral bandwidth, and latency to the first spike, binauralities, and sensitivity to amplitude and frequency modulation (Budinger, 2005). AI is tonotopically organized, as indicated by topographic locations of neurons sharply tuned to single frequencies (Clarey, Barone and Imig, 1992). Studies investigating the tonotopic organization of the associative cortex suggest that neuron responsiveness in this area is poor and is not as well organized by frequency as AI (Schreiner and Cynader, 1984).

Research focusing on temporal processing of AC neurons has demonstrated that similar to auditory brainstem structures, the AC can respond in various ways to the onset, sustained

presentation and offset of acoustic stimuli. Abeles and Goldstein (1972) studied single unit responses of AI neurons in cats and found four types of responses to a 100 ms tone burst. One type of neurons recorded generated sustained responses for the duration of the stimulus, although a noticeable decrease in the firing rate was present during the tone. Other types of responses included onset type in which a neuron responded only to the beginning of the stimulus presentation, and offset type in which a neuron responded only after the tone was terminated. The fourth type of response found was neurons that responded to both the onset and the offset of the tone.

AC neurons are especially responsive to sound with rapid changes in temporal, spectral and directional content. Neural responses to these transients are often timed with great precision. For many AC neurons, the jitter in transient response timing can be compared to that seen in the CN and may even be superior to the timing seen in CN neurons (Masterton, 1993; Heil and Irvine, 1997). These observations suggest that preservation of information about the timing of transient stimulus events is an important function of the AC.

The response of AC neurons to amplitude modulated (AM) sounds have been studied in various species, using both awake and anaesthetized preparations, and employing a variety of periodic sounds, including tones, noise and clicks (Eggermont, 1994; Schreiner and Urbas, 1988; Muller-Preuss, 1986). In most cases, neurons in the AC responded poorly to stimulus periodicities above 10 to 30 Hz. This ability to follow rhythmic amplitude change is far more effective than that seen in the CN. In this case, the temporal responses of CAS neurons appear to fall progressively along the ascending pathway. Thus periodic responses of AC cells are subordinate to those of MGB and IC neurons (Eggermont 1994; Batra, Kuwada and Stanford, 1989). Reasons for the poor responses to periodic sound amplitude changes in AC neurons are

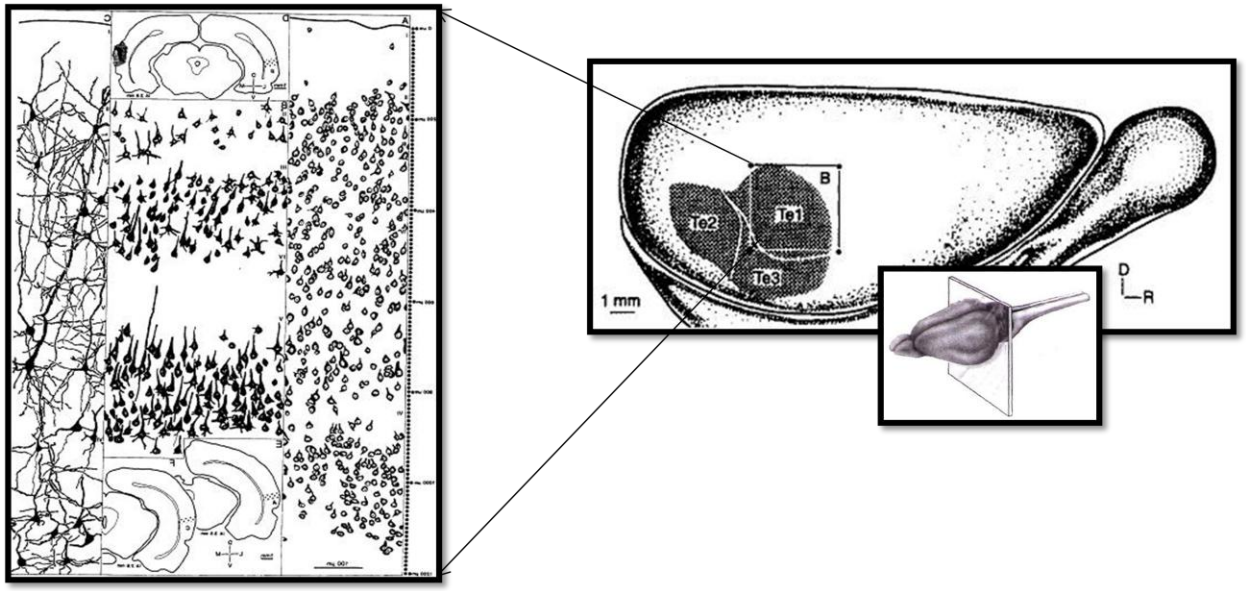
not well known, but one possibility is the development of inhibitory responses after onset (Eggermont, 1991) which would serve to prolong minimal inter-response intervals.

Timing of synaptic events within the AC plays a critical role in sound localization. Studies have shown that many neurons in the AI are sensitive to interaural phase and intensity differences (Benson and Teas, 1976). In a sound field, AC neurons fired more action potentials to sound stimuli from a contralateral earphone than from an ipsilateral one (Evans, 1968).

As could be inferred from the presence of tonotopic organization, the vast majority of AI neurons are narrowly tuned to stimulus frequency. Studies using tone burst stimuli illustrated, that the excitatory response areas of AI cells tend to have either V-shaped or a non V-shape. *(*Winer, 1984*)* The V-shaped tuning curve-type cells are the most common in AI, and comprise roughly 70 - 75% of all neurons sampled. These neurons tend to have monotonic spike rate-stimulus level function. The other cells with the non V-shape response areas are far less common. They comprise approximately 25 - 30% of AI neurons, and their firing rate-intensity profiles appear to be nonmonotonic, showing clear amplitude tuning. Researchers suggest that the response areas of the nonmonotonic type cells are likely shaped by lateral inhibition. Furthermore that this non-monotonic type of response seems to be more common in the AC than in the MGB (Young and Brownell, 1976; Winer, 1984; Shofner and Young, 1985).

In the primary auditory field, neurons with non-monotonic firing rate-intensity profiles are spatially segregated from the monotonic cell types (Eggermont, 1991). They are generally found in areas surrounding the center of AI. This is an interesting finding because anatomical studies have suggested that this area encompasses the greatest concentration of GABAergic neurons (Hendry & Jones, 1991).

Monotonic and non-monotonic rate level functions (RLF) have been thoroughly described in the AC of the cat, monkey, ferret, rat, and echolocating bat animal species (Brugge, Dubrovsky, Aitkin and Anderson, 1969; Phillips and Irvine 1981; Phillips and Irvine, 1982; Phillips and Orman, 1984; Phillips, Mendelson and Cynader, 1985; macaque monkey: Brugge and Merzenich, 1973; Pfingst, O'Connor and Miller, 1977; Pfingst and O'Connor, 1981; squirrel monkey: Funkenstein and Winter, 1973; ferret: Phillips, Judge and Kelly, 1988; rat Phillips and Kelly, 1989; mustached bat: Suga, 1977; Suga and Manabe, 1982). Non-monotonic cells that show greater than 50% reduction from discharge maximum in response to increasing intensity are less frequently encountered in the rat than in the cat AI (Phillips and Kelly, 1989). In the cat, there is a noticeable difference in the proportions of monotonic and nonmonotonic responses between the different fields of the AC. In AI (Phillips and Irvine, 1981) and in the anterior auditory filed (AAF) (Phillips and Irvine, 1982), the majority of cells exhibit monotonic type of RLF and the proportion of these cells appears similar in the two fields. In contrast, in the posterior auditory field (PAF) a far greater proportion of non monotonic cells exist as compared to AI (Phillips and Orman, 1984). This finding may reflect functional segregation as well as noticeable differences between tonotopic fields of the AC in the coding and processing of intensity information (Phillips and Orman, 1984).



Adapted from Malmierca and Merchan, 2004

Fig.2. The auditory cortex (AC). An illustration of the rat brain as seen from the lateral side of the head. The area shaded dark grey represents the rat's auditory cortex and is subdivided into Te1, Te2 and Te3. A frontal brain slice taken from the AC illustrates the 6 layers of complex cellular structure found within the AC.

1.3 The Structure and Function of the IC

The IC is an auditory processing center at the level of the midbrain. It is a dome shaped structure and is one of the largest auditory nuclei in the vertebrate brain. It is an essential synaptic terminus before ascending inputs reach the MGB (Aitkin and Phillips 1984). The IC receives inputs from almost all parts of the CN (Oliver 1984, 1987), from a large portion of the SOC (Glendenning, Baker, Hutson and Masterton, 1992), from both sides of NLL (Saint Marie, Shneiderman and Stanforth, 1997), and from all areas of the AC (Winer, Larue, Diehl and Hefti, 1998) Aside from the abundant array of extrinsic projections there are also many commissural (Aitkin and Phillips, 1984) and intrinsic projections (Oliver, Kuwada, Yin, Haverly and Henkely, 1991*).* The IC sends descending projections to almost all brain stem nuclei which project to it (Huffman and Henson, 1990), and ascending projections to both sides of the MGB (Andersen, Roth, Aitkin and Merzenich, 1980). Anatomical studies show that many interneurons exist in the IC, suggesting the presence of strong neuronal interconnections (Morest and Oliver, 1984). Almost all ascending or descending auditory pathways synapse in the IC (Winer and Schreiner, 2005). The IC thus represents a site of extreme convergence of information that has been processed in parallel in various brain stem nuclei.

There are three primary regions of the IC as mentioned previously (Rockel and Jones, 1973) (Figure 3). The subdivisions of the IC are made based on anatomical features such as neuropil and unique sets of cell types. The first of these is the ICc, the core of the IC that receives purely auditory inputs. This is a key auditory region of the midbrain, receiving projections arising from the lower brainstem. The ICc also sends projections to the MGB and is a major component in the classical (lemniscal) auditory pathway. The other two subdivisions of the IC are the ICx and ICd nuclei, collectively known as the pericentral nuclei. These two

regions are less well organized than the ICc. The ICx along with ICd surround the ICc like a belt, while the ICx is comprised of both auditory and somatosensory fibers (Popper and Fay, 1992). The ICx also includes fibers from the brachium (Geniec and Morest, 1971). Both the ICx and ICd nuclei contribute to the nonclassical (non-lemniscal) auditory pathway (Caird, 1991).

Three cell types make up most of neuron composition in the IC including disk shaped, simple and complex stellate (Oliver et al., 1991). From a physiology point of view the representations of high frequencies within the IC are presented in the ventral region, whereas the low frequencies are presented dorsally (Merzenich and Reid, 1974). Finally, when considering its neural connections as well as the IC's position spanning the auditory pathways, this structure has been referred to as an essential relay center, in transmitting auditory information to higher structures (Noback, 1985).

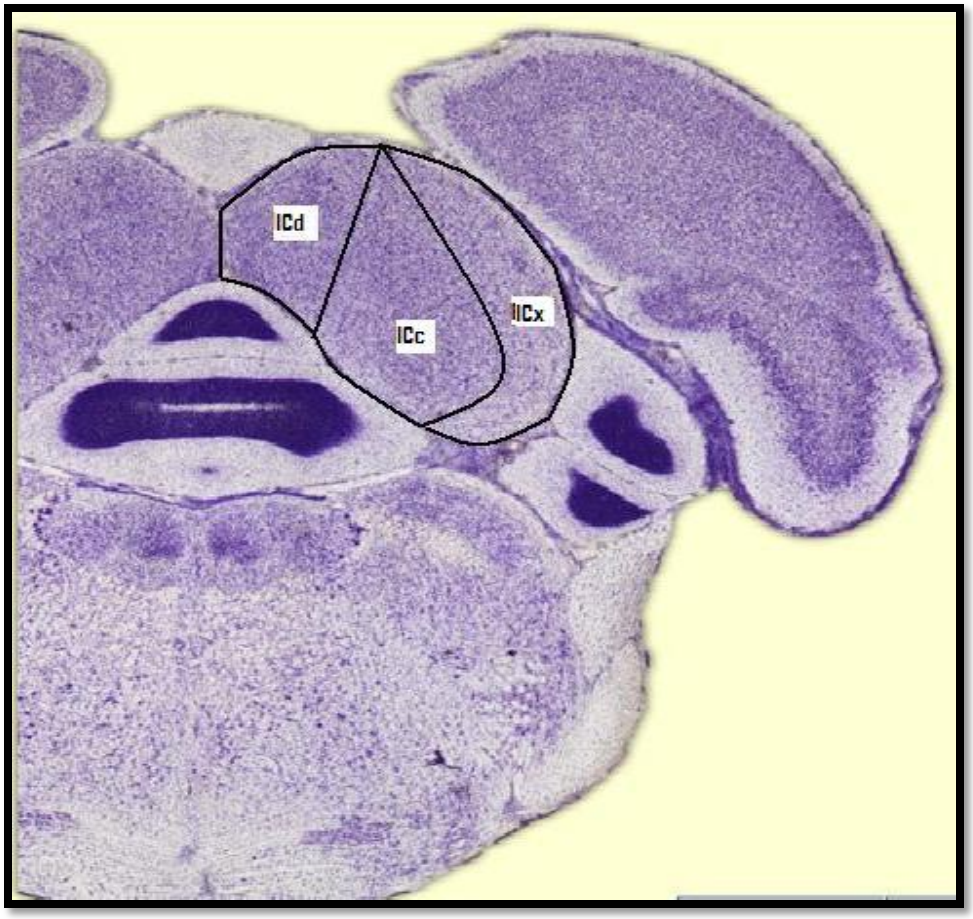


Fig.3. The inferior colliculus. A frontal section of the rat's brain showing the inferior colliculus (IC) (dome shaped structure) and its subdivisions. The IC subdivisions are outlined in black. Dorsal cortex of the inferior colliculus (ICd, top left); Central nucleus of the inferior colliculus (ICc, center); External cortex of inferior colliculus (ICx, top right). (Adapted from Paxinos and Watson, 2007).

1.3.1 The Central Nucleus of Inferior Colliculus (ICc)

The IC consists of several cytoarchitecturally distinct regions as mentioned previously, the most studied of which is the ICc. The ICc as mentioned previously is part of the classical ascending auditory system (Morest and Oliver, 1984; Oliver et al., 1991). The ICc is exclusively auditory (Aitken et al. 1994) and it is essential for normal hearing (Jenkins and Masterton, 1982). Anatomically the ICc is identified by its fibrodendritic lamina, which is comprised of disc-shaped neurons and the laminar plexus of afferent axons that terminate in it (Oliver, 2005). The ICc receives ascending input from ipsilateral and contralateral SOC, and ipsilateral and contralateral NLL. The ICc also receives excitatory input from anteroventral and dorsal CN. Neurons in a single lamina of the ICc are maximally sensitive to similar tonal frequencies. The ICc is a part of a tonotopically organized ascending auditory pathway to the thalamus, which continues to the AI. The ICc is essential for the processing of basic features of sounds (Winer and Schreiner, 2005).

Anatomical studies using large injections of tracers have illustrated that the proportion of labelled cells located in each source of ascending input to the IC is quite consistent both across studies and also across species (Bajo, Nodal, Bizley, Moore and King, 2007). However, when smaller injections are made, such as those made by iontophoretic pumps, of retrograde tracers into the ICc, the results are considerably more variable in terms of the proportions or even the presence of labelled cells in the different sources (Roth, Aitkin, Andersen and Merzenich, 1978; Brunso-Bechtold, Thompson and Masterton, 1981; Aitkin and Schuck, 1985; Maffi and Aitkin, 1987; Ross and Pollak, 1989; Wenstrup, Mittmann and Grose, 1999; cf. Oliver, Beckius and Shneiderman, 1995). Some studies showed that in some cases projections from the SOC dominated. In the most extreme example reported, after an injection of a tracer in the lateral IC,

98% of the labelled cells were located in the ipsilateral medial SOC (Aitkin and Shuck, 1985). In general, however, it is rare that so many labelled cells are located in only one source of input. Another comprehensive study carried out by Osen in 1972 examined the projections from the CN to the IC. She used degeneration methods in the cat, and demonstrated that both the dorsal and ventral CN project to the contralateral IC topographically and that the terminations from these two subdivisions appear to overlap throughout the ICc. Across species and studies, many different combinations of inputs have been seen, although some are more common than others.

Many of the functional properties of the IC have been previously described. As with brainstem auditory structures the IC encompasses a high degree of tonotopic organization (Merzenich and Reid, 1974) mostly observed in the ICc. Moreover, studies have shown that the IC contains a large number of neurons that yield extremely sharp tuning curves, suggesting a high level of frequency resolution (Aitkin, Webster, Veale and Crosby, 1975). The IC contains many time and spatially sensitive neurons and neurons sensitive to binaural stimulation (Benevento and Coleman, 1970). This sensitivity illustrated in IC neurons then suggests a role in sound localization (Musiek and Baran, 1986).

Previous research examining temporal response characteristics of ICc neurons revealed various types of response patterns which were obtained from post stimulus time histograms including onset response pattern where the neuron fired at the beginning of the stimulus presentation only; sustained response pattern, where the neuron fired action potentials throughout the duration of the stimulus presentation; pauser units had a precisely timed onset peak separated from a lower level of sustained activity by a short period of either a marked reduction or complete cessation of firing; chopper units had two or more clearly defined peaks near the stimulus onset (Syka, Popelar, Kvasnak and Astl, 2000).

Research has also shown that the rate intensity functions of ICc neurons with simple onset response to tone burst stimuli can range from monotonic or near monotonic to extremely nonmonotonic (Rees and Palmer, 1988; Syka et al., 2000). The ICc neurons showed a response pattern to tone bursts longer than 100 – 150 ms in which an onset response is separated by a brief pause from a sustained discharge that continues for the duration of the tone burst (Irvine, 1992). Rees and Palmer (1988) found a much higher proportion of monotonic rate intensity functions in the cat ICc when 50 ms tone bursts which would not usually elicit a sustained discharge components in most ICc neurons were used.

Research concerning the auditory midbrain revealed that neurons within the ICc have preferred elevation and a preferred horizontal location or azimuth for biologically pertinent sounds (Fay et al., 1992). Another important property of the ICc is its ability to process sounds within complex temporal patterns. Many neurons in the ICc respond only to frequency modulated sounds, and some respond only to sounds of specific durations (Fay et al., 1992).

1.3.2 The Dorsal Cortex of Inferior Colliculus (ICd)

The ICd occupies the dorsomedial and caudal regions of the IC. Anatomical studies show that ICd neurons tend to have un-oriented axons (Oliver et al., 1991). The ICd receives most of its projections from the cerebral cortex (Winer et al. 1998) and its role in hearing is unknown however, ICd neurons do receive abundant descending projections from the AC and their response has been proposed to be modulated by the AC (Fay et al., 1992). ICd receives its major projections bilaterally from the layer V of the AC (Bajo et al., 2007; Bajo and Moore, 2005) While most of these projections originate from the AI, some projections to the superficial part of the ICd originate from the area ventrocaudal to the AI. A recent study by Schofield in

2009 revealed that ICd along with ICx also receive projections from layer VI of the AC. In addition to the abundant projections from the AC, the ICd also receives some input from other structures including the MGB, the sagulum, the ipsilateral ICc and ICx, the contralateral IC, as well as lower auditory brainstem structures (Benson and Cant, 2008; Gonzalez-Hernandez, Meyer, Ferres-Torres, Castaneyra-Perdomo and del Mar Perez Degado, 1987; Malmierca, Rees, Le Beau and Bjaalie, 1995; Malmierca, Hernandez and Antunes, 2009; Saldaña and Merchán, 1992; Willard and Martin 1983; Winer, Chernock, Larue and Cheung, 2002). The fact that the major inputs to ICd are provided by descending projections from the auditory forebrain suggests that this midbrain structure plays a unique role in hearing.

Electrophysiological research has not been able to unravel any tonotopic organization in the ICd. Behavioural studies show that damage to the dorsal cortex affects attention and vigilance more severely than auditory discrimination behaviour (Jane, Masterton and Diamond, 1965). Some studies show that ICd neurons have broader tuning than ICc neurons (Aitkin, Tran and Syka, 1994). The functional significance of these projections is poorly understood.

ICd neurons were examined for their responses to various sounds (Aitkin et al., 1994; Malmierca et al., 2009; Pérez-González, Malmierca and Covey 2005; Syka et al., 2000) and these recordings revealed that neurons in the ICd display stimulus-specific adaptation (Aitkin et al., 1994; Malmierca et al., 2009; Pérez-González et al., 2005; Syka et al., 2000). These neurons generated strong firing in response to initial sweeps of repetitive stimulation but minimal or erratic firing thereafter. Responses of a neuron showing stimulus-specific adaptation could be restored by changes in the quality of stimulation (e.g., the frequency of a tone burst). Physiological research focusing on ICd neurons revealed that stimulation of the AC produced excitatory/inhibitory effects on ICd neurons; this observation supports previous findings that the

ICd receives abundant projections from the AC (Bledsoe, Shore and Guitton, 2003; Syka and Popelár, 1984). Although findings from these studies provided insight into the function of the ICd in auditory processing, these findings were based on small numbers of ICd neurons collected when electrodes were en route to the ICc. A better understanding of the function of the ICd is dependent on an examination of characteristics of auditory responses, including those of responses to tone bursts, using larger sample sizes.

1.3.3 The External Cortex of Inferior Colliculus (ICx)

The ICx is a multisensory integration center (Aitkin, Dickhaus, Schult and Zimmermann, 1978) and the target of considerable non-auditory inputs (Morest and Oliver, 1984). The ICx is composed of small, medium and large cell types, the most characteristic element being large multipolar neurons with coarse Nissl granules. The ICx lacks disc shaped cells (Winer and Schreiner, 2005). In the cat the ICx has a fibrous outer layer I and a small – celled layer II (Winer and Schreiner, 2005). Layer III has not been identified in the cat. However it is present in the rat and receives laminated input (Oliver, 2005). The main input of ICx comes from the ipsilateral ICc and the AC. The ICx does not show tonotopic organization in contrast to the ICc. ICx neurons respond with long latencies compared to those of ICc and they have very broad tuning curves (Binns, Grant, Washington and Keating, 1992). Researchers believe that the ICx is responsible for multisensory integration (Winer and Schreiner, 2005). One study suggested that the ICx may also be involved in auditory novelty detection (Covey, Malmierca and Perez-Gonzalez, 2005). The basis for this proposition is that ICx neuron habituate during repetitive acoustic stimuli by reducing neural response during repetitive stimuli.

1.4 Current Understanding of Corticocollicular Projections

The IC is a functionally diverse structure for auditory processing. It has the ability to process various characteristics of sounds due to the fact that it receives neural projections from all major auditory structures, including abundant descending projections from the AC. A great deal of research has been carried out focusing on the projections from the AC (Winer, 2006) (corticofugal system see Figure 4) and their involvement in the modulation of subcortical structures, nevertheless the functional significance of this system is poorly understood.

Anatomical studies have shown that there are abundant descending projections from the AC to the IC, and that these projections may be involved in the modulation of IC activity (Fay et al., 1992). Corticofugal projections to the IC arise from layer V of the auditory cortex. Projections to the IC neurons originating from layer V of the AC that provide excitatory input to the IC are pyramidal type and are mediated by glutamate as the neurotransmitter. Anatomical studies revealed that there are abundant corticocollicular projections terminating in the ICx and ICd, but substantially less projecting to the ICc.

Electrophysiological recordings demonstrated that manipulation of neural activity in the AC can modulate sensory processing in the IC (Yan and Suga, 1996; Zhang, Suga and Yan, 1997; Jen, Chen and Sun, 1998). Focal electrical stimulation of the auditory cortex can induce shifts in the frequency selectivity of neurons in the inferior colliculus (Yan and Suga, 1998; Zhou and Jen, 2000). Electrical stimulation has also illustrated a shift in threshold dynamic range, and spatial as well as temporal response properties (Suga and Ma, 2003; Yan and Ehret, 2002; Jen et al., 1998).

Whether response of IC neurons is enhanced or suppressed by cortical stimulation is dependent on whether the cortical area and the IC neuron are "matched" in terms of their response to sounds and their characteristic frequency (CF) (Yan and Suga, 1996). Corticofugal activity enhances the responses of IC neurons that are matched to AC neurons, while it suppresses the response of non-matched IC neurons (Yan and Suga, 1996). Within this proposal, corticofugal activity would help enhance and select responses to a particular auditory parameter.

Approximately half of the rat's IC cells responded to electrical pulses delivered to the cortex. Most of these cells had brief excitatory responses, and the excitatory responses preceded a longer lasting inhibition in some of these neurons. This inhibition suppressed spontaneous or sound evoked activity (Syka and Popelar, 1984).

One previous study showed that the descending projections from the AC to the IC are in fact excitatory (Feliciano and Potashner, 1995). While Syka and Popelar (1984) investigated the response of IC neurons during cortical stimulation, other researchers found that the inactivation of the AC produced facilitatory as well as inhibitory effect on the IC neurons (Zhang and Suga, 1997; Jen et al., 1998). The presence of the inhibitory effect drove researchers to propose that these IC neurons may be modulated by GABAergic interneurons found in the IC (Yan and Suga, 1996). If in fact the response is modulated by excitatory descending projections from the AC as well as GABAergic interneurons in the IC, this interaction is likely mediated by a feedback loop. This feedback loop likely involves excitatory descending projections from the AC as well as a local IC GABAergic interneuron that synapses with another IC neuron.

Although the role of these corticofugal pathways is not completely understood, it is clear from studies of different sensory modalities that cortical feedback can dynamically adjust the receptive fields and filtering properties of subcortical neurons (Suga, Xiao, Ma and Ji, 2002;

Alitto and Usrey, 2003; Winer and Schreiner, 2005). This in turn will influence the information that is sent to the cortex via ascending pathways. Thus, while being at the top of a hierarchy, the cortex makes a significant contribution to processing at lower levels of the brain.

While many studies investigated how ICx and ICc were modulated by neural projections from the cortex, corticofugal projections to the ICd are not well delineated and are poorly understood. Neurophysiological studies are required to elucidate the function of the abundant corticofugal projections to the ICd.

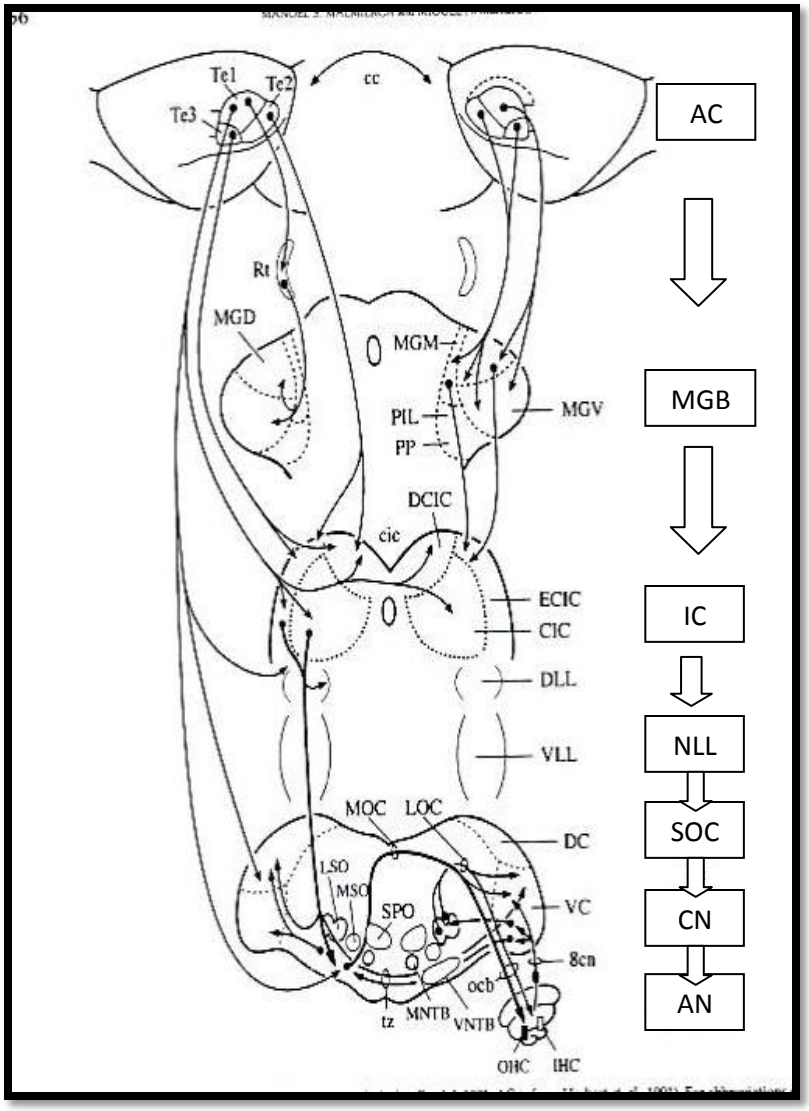


Fig. 4. Descending auditory projections. Arrows represent the direction of input to subcortical structures from the subdivisions of the AC. Te1, Te2 and Te3 represent the temporal areas 1, 2 & 3, the three subdivisions of the rat AC. MG represents the medial geniculate body. IC represents the inferior colliculus. NLL represents the nucleus of lateral lemniscus. CNC represents the cochlear nucleus. The SOC represents the superior olivary complex. The cochlea is part of the peripheral auditory system.

Adapted from Malmierca and Merchan, 2004

1.4.1 Possible Function of Corticofugal Projections in Novelty Detection

The descending projections terminating in the IC are of particular interest due to their profuse distribution in ICd and ICx. Perez - Gonzalez et al. (2005) demonstrated that neurons within the ICx habituated to repetitive stimuli, but recovered when a novel sound was presented (Figure 5). Zhang and Kelly, (2005) investigated neural responses in the ICd and found that neuron in this subdivision of the IC also display stimulus specific adaptation (SSA) to repetitive sound stimulation. Abundant corticocollicular projections as well as the ability of neurons in the ICd and ICx to exhibit SSA to repetitive stimuli suggests that neurons in the ICd and ICx are important for detecting novel sounds in the acoustic environment and this ability may be related to corticofugal projections.

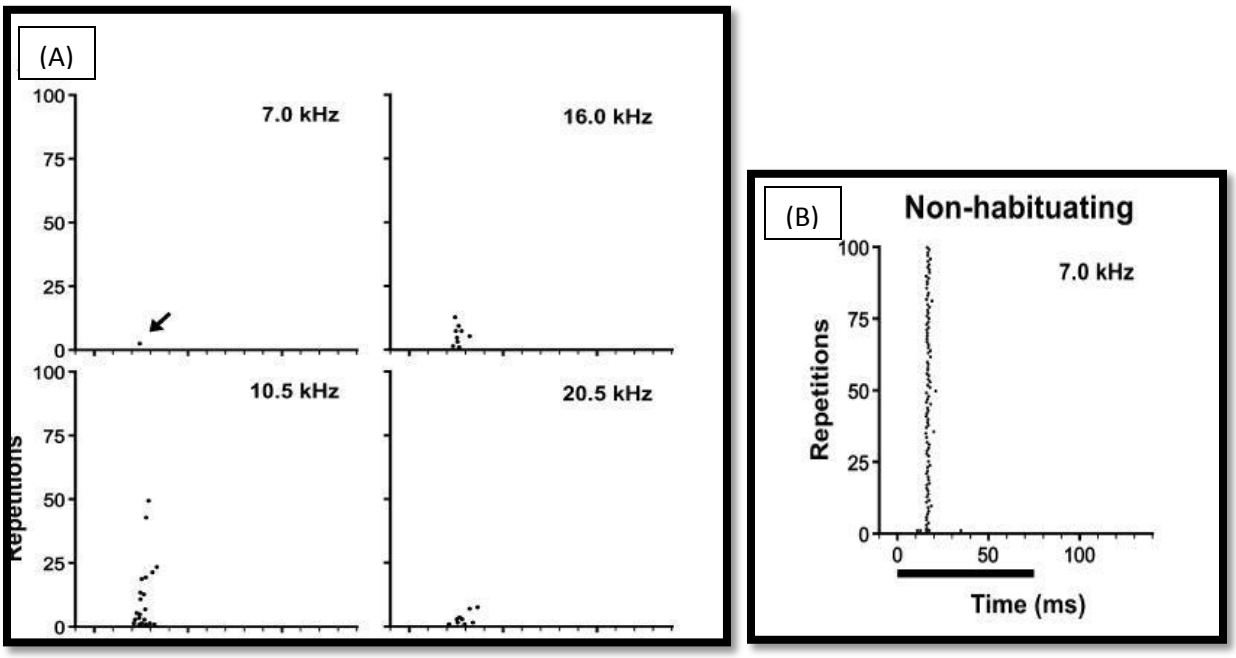


Fig. 5. Responses of two neurons in the ICx to repetitive tone burst presentations. (A) Responses of a neuron showing stimulus-specific adaptation. Responses were collected when tone bursts were presented four different sound frequencies including, 7, 10.5, 16 and 20.5 kHz. Each dot represents an action potential. This neuron displayed different levels of adaptation as seen by the reduction of action potentials. Y-axis represents the order of repetitions of the stimulus. (B) Response of a non-adapting neuron. This neuron fires an action potential at the onset of a 7 kHz tone burst in response to each of the 100 stimulus presentations. X- Axis is in ms. Black bar represents duration of the stimulus.

Adapted from Perez-Gonzalez et al, 2005

1.5 Objectives and Significance

In order to better understand the role of ICd neurons in auditory processing, I sought to investigate the neurophysiological responses of neurons in the albino rat ICd to various types of stimulus paradigms. This study also employed a new reversible inactivation approach to study the role and function of corticocollicular projections in auditory processing.

Although there have been few studies that have provided suggestions regarding functions of ICd neurons in auditory processing, these studies were based on small numbers of ICd neurons collected when electrodes were en route to the ICc. A better understanding of the function of the ICd is dependent on an examination of characteristics of auditory responses, including those of responses to tone bursts, using larger sample sizes. The current study was therefore dedicated to the characterization of basic temporal and spectral responses in ICd neurons.

There were three main objectives for this study:

1. To examine basic response characteristics of neurons in the ICd.

I wanted to use various stimulus paradigms (see sound stimulation section in Materials & Methods and Figure 6) to study the temporal and spectral characteristics of neurons in the ICd. Anatomical data has shown that ICd receives major projections from layer V of the AC and an array of commissural connections. In contrast the major inputs to the ICc are from brain stem structures. Thus, I expected to see more complex response patterns and longer 1st spike latencies as in ICd than ICc neurons.

The data obtained in the present study may serve beneficial for future studies focusing on the ICd, and may be used as a blueprint by researchers attempting to further dissect the mechanisms and function of neurons in the ICd.

2. To examine stimulus specific adaptation in ICd neurons.

Although stimulus specific adaptation has been studied to some degree in ICc and ICx neurons (Perez – Gonzalez et al., 2005), far less is known regarding the presence and function of this phenomenon in ICd neurons. I expect to find an abundance of neurons in the ICd that reduce their strengths of responses during repetitive tone burst stimulation but enhance their strengths of responses when a novel sound is introduced.

The data presented in this study combined with that obtained in other studies focusing on the ICc and ICx may serve as the foundation for future research in this field and may contribute to the understanding of SSA, its mechanism and its potential involvement in central auditory processing disorders.

3. To examine how the auditory cortex controls responses to sound in ICd neurons.

To determine the function of corticofugal projections in ICd neurons, I used a reversible inactivation technique (Horel, Lomber, and Payne, 1999) (Figure 7). This technique allowed me to inactivate cortical activity during the presentation of each stimulus paradigm and thus study how the auditory cortex controls neurons in the ICd. I expected that cooling the AC would change responses in ICd neurons.

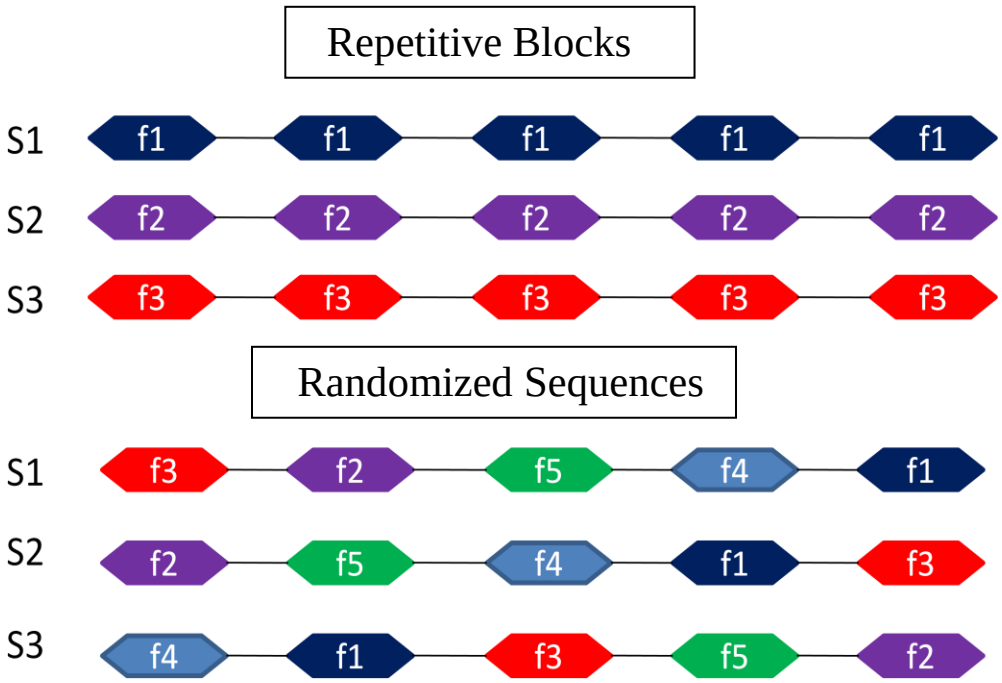


Fig. 6. Two stimulus paradigms. The above two stimulus sequences were used for the stimulation of ICd neurons. Each color represents a different frequency and Sn represents the sequence number. A repetitive block was comprised of 20 tone bursts with one fixed frequency. Multiple blocks were presented at ascending frequency values. A randomized sequence was made up of a pre-set number of tone bursts with different frequencies. Within a sequence, each frequency was used only once. A total of 20 sequences were generated at different randomized orders of frequencies.

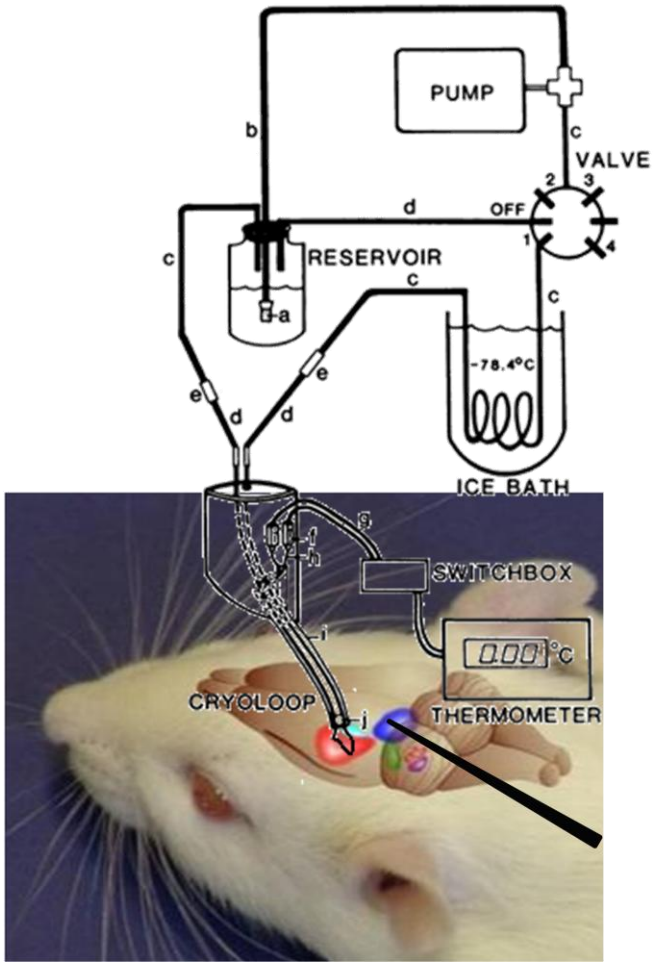


Fig. 7. An illustration of a cooling system. This system uses chilled methanol to cool the surface of the AC. (j) is attached to a cryoloop made up of hypodermic stainless steel tubing that is placed on the surface of the cortex. A microthermocouple is attached to the cryoloop and allows for the measurement of AC surface temperature by the thermometer.

Adapted from Horel et al. 1999

The present study is the first to investigate the role of descending projections in the central auditory system using a reversible inactivation technique. Though the data collected is preliminary, this technique serves extremely efficient and useful for the investigation of descending projections and their role in SSA. This technique may serve valuable in future investigations of descending projections, due to the fact that its effects are reversible and the recovery time is quite brief.

2 MATERIALS & METHODS

2.1 Animal Preparation

Experiments were conducted on 36 male adult Wistar albino rats (*Rattus norvegicus*) (250-450 g) obtained from Charles River Canada Inc., St. Constant, Quebec. Surgical anaesthesia was induced initially by combined injection of ketamine hydrochloride (75 mg/kg, i.m.) and xylazine hydrochloride (10 mg/kg, i.m). Supplemental injections of ketamine hydrochloride (25 mg/kg, i.m.) and xylazine hydrochloride (3.3 mg/kg, i.m) were made as needed throughout the course of an experiment to maintain a state of areflexia.

A midline incision was made in the scalp, the skin and muscles were retracted laterally and a small craniotomy was made over the left side of the parietal lobe as well as over the left temporal lobe to permit insertion of an electrode into the ICd as well as to permit surface cooling of the AC respectively. Small bone screws were placed in the skull and fixed to a stainless steel rod with dental acrylic. The rod was attached to a stereotaxic instrument (Kopf Instruments, Tujunga, California) to hold the head firmly in place while leaving the external ear canals free for insertion of earphone drivers. Recordings were made with the rats inside a single-wall sound-attenuated booth (Eckel Industries, Morrisburg, Ontario).

All procedures were approved by the University of Windsor Animal Care Committee and were in accordance with the guidelines of the Canadian Council on Animal Care.

2.2 Cooling Technique

The cooling technique was first instituted by Horel et. al. (1999) and is a reversible inactivation technique required to decrease neural activity of neurons for study of neurophysiology. This method utilizes chilled methanol pumped through plastic tubing attached to a stainless steel cryoloop placed on the brain surface (see Figure 7). The cryoloop was fashioned from 23 gauge stainless steel hypodermic tubing (Horel et al., 1999) and was shaped to conform to the shape of the AC. Attached in between the separations of the loop was a microthermocouple that permitted the measurement of the temperature of cortical activity before, during and after cooling.

Preceding the craniotomy over the AC, the dura mater was removed and the cryoloop was placed in contact with the cortical surface. Respiration rate was visually monitored, and atropine sulphate (0.08ml/kg, I.m.) was administered every 4 hours to reduce bronchial secretions. Internal body temperature was also monitored and maintained at approximately 37˚C for the duration of the experiment using a Homeothermic Blanket Control unit (Harvard Apparatus).

2.3 Sound Stimulation

Acoustic waveforms were generated digitally using a system 3 real-time signal processing system (Tucker-Davis Technologies (TDT), Alachua, Florida) including two RX6 multifunction processors and one SA1 power amplifier that was controlled by a desktop computer running OpenEx software. Sounds were generated using a pair of TDT CF1 closed-field speakers with each one connected to a piece of tygon tubing that is inserted into the rat's external meatus.

Sounds used in the present study included monaural noise bursts and tone bursts. These sounds had a100 ms duration and 10 ms rise/fall times. Monaural noise bursts and tone bursts presented to the ear contralateral to the recording site were used as search stimuli. Tone-bursts presented to the contralateral ear were used in the examination of a single neuron's temporal and spectral response characteristics. Contralateral tone bursts were also used to form two types of trains respectively named repetitive blocks and randomized sequences (see "*Recording procedure*" for more details) in the study of stimulus-specific adaptation (SSA) of an auditory neuron.

The sound-generating system was calibrated over a frequency range of 1 – 20 kHz using a condenser microphone (ACO Pacific 7017). The acoustic response of the closed-field speakers was adjusted to provide a constant sound pressure over the range from 100 Hz to 12 kHz.

2.4 Recording electrodes and neural signal acquisition

A single barrel glass micropipette was used to record action potentials from single neurons in the ICd. The tip of the pipette was 1.5-2.0 μm in diameter. The electrode was filled with 3 M potassium chloride. The electrode was driven by a model 2660 micropositioner (Kopf, Tujunga, California) into the ICd.

Neural activity registered by a micropipette was amplified by a 2400A preamplifier (Dagan, Minneapolis, Minnesota) and monitored audio-visually. Neural responses were digitized and sampled using the TDT system 3 real-time signal processing system. The occurrence times of spikes were recorded with a resolution of 40 μsec, stored on a computer, and processed later with standard database and graphics software.

2.5 Recording Procedure

Auditory responses were recorded from single neurons in the ICd on the left side of the brain. The ICd was approached with the electrode and the micromanipulator in a plane perpendicular to the horizontal plane and 45° relative to the mid-sagittal plane. The electrode was pitched backward and toward the mid-sagittal plane with a 45° angle relative to a horizontal plane. With reference to the lambda, the electrode was moved caudally by 0.7-1.1 mm and along the axis perpendicular to the electrode within the electrode/micromanipulator plane by 3.2-3.6 mm. The electrode was lowered into the brain to a depth between 2.7 mm to 5.5 mm while responses to noise bursts or tone bursts presented to the right ear were monitored.

Single unit activity was recognized as spikes with constant waveform and amplitude. A discrimination window was used to isolate spikes from background activity. A threshold bar was also used to discriminate between responses to auditory stimuli versus spontaneous activity. After an auditory neuron had been identified, monaural tone bursts were presented to the right ear at various frequencies and intensities to determine the neuron's frequency-tuning curve and the characteristic frequency (CF, the frequency at which a neuron showed the lowest threshold). A threshold was defined as the lowest stimulus level at which a neuron generated acoustically driven spikes in at least 2 consecutive trials of 10 tone burst presentations with similar temporal firing patterns.

Monaural tone bursts at the neuron's CF and at various sound-pressure levels were then used to determine a rate-level function and the temporal firing pattern of the neuron. Sounds were presented 20 times at a rate of once per second to generate summed neural responses for

examining spectral and temporal characteristics of responses to tone bursts as well as for generating rate-level functions.

For neurons in the ICd, two types of tone burst trains were used to examine stimulus-specific adaptation (see Figure 6). The first type was named as repetitive blocks and was constructed by using a chosen number (typically 7) of blocks, each of which consisted of 20 repetitive presentations of a tone burst. Tone bursts in different blocks had different frequencies but identical temporal characteristics including a fixed duration of 100 ms and rise/fall times of 10 ms The set of frequencies used in the train of blocks covered the frequency response area of a neuron and included the CF of the neuron. There were equal numbers of frequencies higher and lower than the CF. Logarithmic differences between two consecutive frequencies were equal. Tone burst blocks in the train were presented at an ascending sequence of frequencies. The second tone burst train was named as randomized sequences and was constructed by using 20 tone burst sequences, each of which consisted of the same set of tone bursts as used in the train of repetitive blocks. These tone bursts were presented at different randomized orders in different sequences. For both trains, the inter-stimulus interval between any two consecutive tone bursts was 1 sec. Tone bursts were presented at a level of 10 dB above the threshold at the neuron's CF. Responses to the two trains of tone bursts were compared and the degree of stimulus specific adaptation was studied.

2.6 Data Analysis

For each ICd neuron, I used a dot-raster histogram and a post-stimulus time histogram (PSTH) to display the temporal characteristics of firing elicited by a contralaterally-presented tone burst. A dot raster histogram illustrates the timing of action potentials generated by each sweep of tone bursts. Each dot on the histogram represents an action potential (see Figure 8 for example). A PSTH illustrates the temporal change in the firing strength of a neuron over the duration of the stimulus. These histograms were created by using responses evoked by 20 presentations of the sound. Temporal characteristics of neurons were also examined by calculating the average first spike latency and the standard deviation of the first spike latencies of responses to the 20 tone-burst presentations.

Frequency tuning curves were generated to display the threshold of response to a tone burst at each frequency. The characteristic frequency of a neuron, i.e. the frequency at which the neuron displayed minimum threshold, was noted by using the frequency-tuning curve.

Iso-intensity curves were generated for the study of the spectral response characteristics of ICd neurons. The iso-intensity curves were generated by using responses obtained over a wide range of frequencies at the same intensity. The total number of action potentials elicited by 20 sweeps of a tone burst was obtained at each frequency. The iso-intensity curve generated for each neuron allowed me to examine supra-threshold responses of neurons. The frequency at which the neuron fired at with the maximum response, also known as best frequency (BF), was noted by using the iso-intensity curve.

Finally, to further investigate the basic response characteristics of ICd neurons I used a rate-level function (RLF). This type of plot was generated using one fixed frequency (the CF)

and a wide range of intensities. A RLF gives an indication of a neurons preference for a specific intensity. RLFs were classified into two categories. A monotonic RLF shows that a neuron exhibits an increase in response with increase in intensity to a saturated level of response. A non-monotonic RLF shows a neurons ability to favour a narrow range of intensities. A neuron exhibiting this type of response displays an increase in intensity to a peak, and a further increase in intensity causes a decrease in response.

Previous research focusing on ICd and ICx neurons, demonstrated that these neurons exhibit adaptation to repetitive blocks of stimulation. Once all ICd neurons were obtained, an adaptation index (AI) was calculated using the response of a neuron to repetitive blocks of stimulation over the course of 20 sweeps:

AI = (# of AP (first 10) - # of AP (last 10))/ (# of AP (first 10) + # of AP (last 10))

The adaptation index was generated using the number of action potentials of a response for the first 10 sweeps versus the last 10 sweeps of stimulation. The formula resulted in an AI between -1 and +1, with the positive numbers indicating adaptation to repetitive blocks of stimulation and negative numbers indicating sensitization over the course of the 20 sweeps of stimulation.

Responses to trains of repetitive blocks and randomized blocks were used to study stimulus-specific adaptation in ICd neurons. For this purpose, two iso-intensity curves were constructed respectively using responses elicited by a train of repetitive blocks and a train of randomized sequences. For randomized sequences the responses to tone bursts at the same frequency were summed. Cumulative responses at all frequencies were used to create an iso-intensity curve.

To examine an ICd neuron's ability to detect novel stimuli, I used two stimulus-specific adaptation indices. I used the peak response index SSA_P to investigate the difference between peak responses of neurons to repetitive versus randomized stimulation.

$$\mathbf{SSA_P = (P_{Rand} - P_{Rep})/ (P_{Rand} + P_{Rep})}$$

Where P_{Rand} is the peak response of the iso-intensity curve obtained by using randomized sequences. P_{Rep} is the peak response of the iso-intensity curve obtained by using repetitive blocks.

An index was also calculated for each neuron using the area under the iso-intensity curve (SSA_A).

$$\mathbf{SSA_A = (A_{Rand} - A_{Rep})/ (A_{Rand} + A_{Rep})}$$

Where A_{Rand} is the area below the iso-intensity curve obtained by using randomized sequences. A_{Rep} is the area below the iso-intensity curve obtained by using repetitive blocks.

For both SSA indices, an arbitrary criterion was used to classify neurons that I recorded. Those neurons with an SSA index smaller than 0.2 were categorized as non – SSA neurons. Neurons with an SSA index above 0.2 were classified as SSA neurons. Equal responses to randomized blocks and repetitive blocks result in an SSA index value of 0.

3 RESULTS

Thirty six rats were used for the present study. In these rats, 36 of all the neurons recorded from, were used for analysis of basic response characteristics to contralaterally presented tone bursts in the ICd. In all these neurons, I examined stimulus-specific adaptation by comparing responses to trains of repetitive sequences with those to randomized blocks. In 12 out of 36 neurons, I also investigated how corticofugal projections control the responses of ICd neurons by reversibly inactivating neurons in the AC.

3.1 Spontaneous activity

The level of spontaneous activity was typically low for ICd neurons. Fifteen of the 36 ICd neurons did not display any spontaneous firing. Thirty one of the 36 ICd neurons had spontaneous firing rates lower than 1.5 spikes/sec; inclusive of neurons with no spontaneous activity. The median of spontaneous firing rate for the entire sample of ICd neurons was 0.2 spikes/sec, while the mean was 1.1 spikes/sec. The level of spontaneous firing in ICd neurons was similar to that in ICc neurons (Syka et al., 2000).

3.2 Responses of ICd neurons to tone bursts

In response to a contralateral tone burst with a100 ms duration and 10 ms rise/fall times, a neuron in the ICd generated one or multiple action potentials. For all neurons that I recorded except one, these action potentials occurred either at the onset (19 of 36 neurons) or over the entire duration (16 of 36 neurons) of the tone burst. One of the 36 ICd neurons generated action potentials immediately after the offset of the tone burst in addition to those fired at the onset of the sound. Figure 8 displays the response of an ICd neuron to repetitive tone burst presentation.

Tone bursts were presented at the neurons CF (1.5 kHz) and 10 dB above its threshold at CF (73 dB SPL). Figure 8A is a dot-raster histogram showing the occurrence times of action potentials generated by the neuron. It is noted that in response to each tone burst presentations, the neuron generated action potentials after a short time delay (i.e., the latency) and firing sustained the duration of the tone burst. Across 20 presentations of tone bursts, variations were observed in the time delay before the first action potential was generated. Figure 8B is a post-stimulus time histogram (PSTH) based on action potentials generated during the 20 tone burst presentations. This figure shows the overall temporal distribution of action potentials over the duration of the tone burst. This ICd neuron generated relatively stronger transient firing with a primary-like firing pattern, at the onset of the sound. The firing strength was reduced to a sustained level afterwards. This temporal change in firing strength is typical for neurons with "primary-like" firing pattern (See section 3.3).

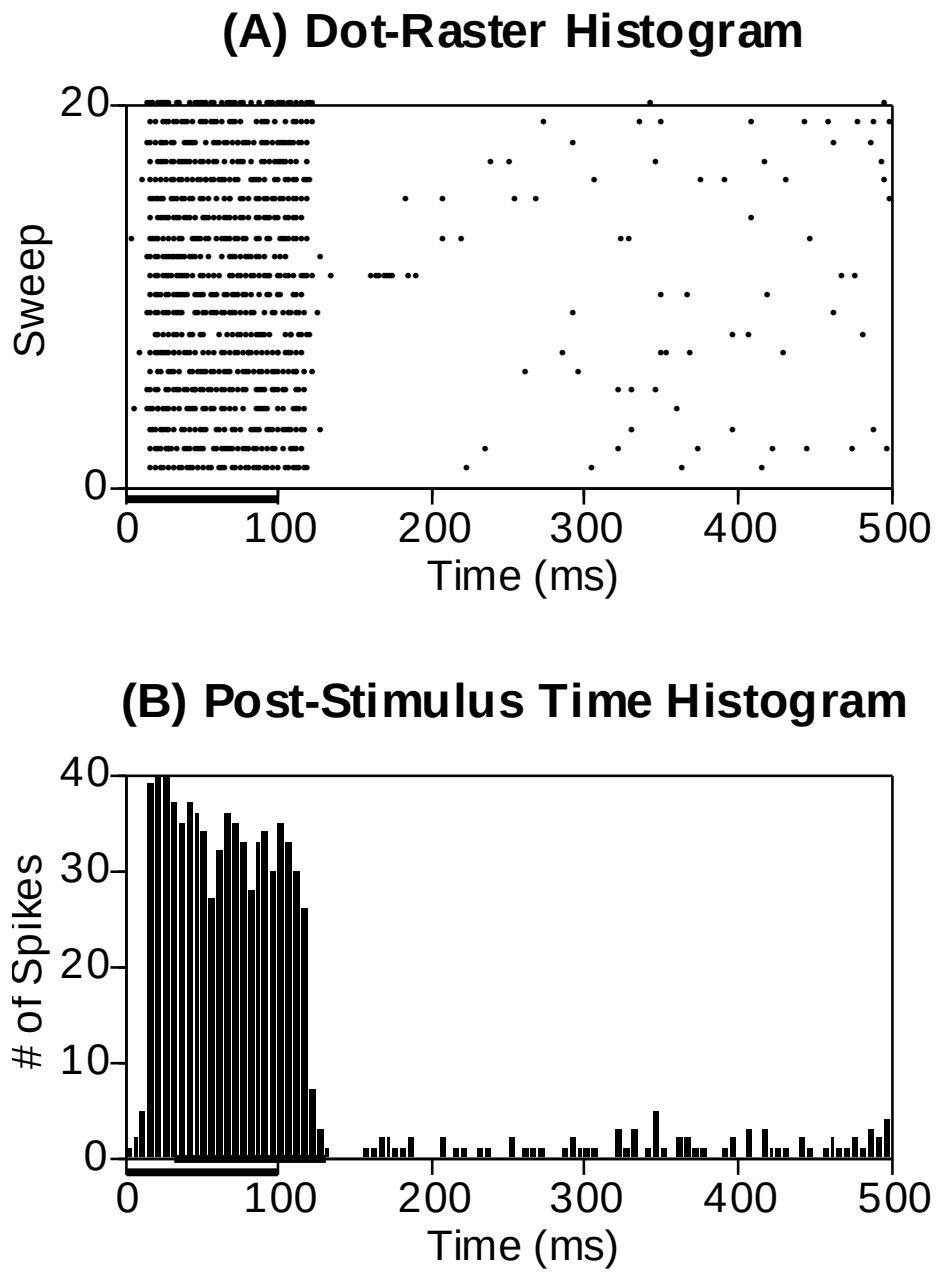


Fig. 8. Dot raster and Post stimulus time histogram. The above illustration is an example of a dot raster histogram (A) and a post stimulus time histogram (PSTH) (B). The dot raster histogram illustrates action potentials generated by a neuron in response to each of the 20 presentations of tone bursts (black dots). Each dot indicates one action potential with the abscissa representing the occurrence time of the action potential. The black bar on the x-axis represents the duration of the stimulus. The PSTH illustrates cumulative numbers of spikes generated by the same neuron as in A over 20 presentations of tone bursts. Bin width for generating the histogram was 5 ms. The horizontal bar underneath the figure shows the duration of a tone burst presentation.

3.3 Temporal firing patterns in response to monaural tone bursts

For each ICd neuron studied, I examined the PSTHs for the response elicited by a 100 ms tone burst presented at a neuron's CF and 10 dB above its MT. The PSTHs displayed by ICd neurons were categorized into three different types including onset, sustained, and on-off (Figure 9). Neurons with onset responses had a brief period of firing at the onset of a tone burst with no additional sound-driven action potentials for the duration of the stimulus. These responses fell into three subcategories: phasic, in which only one or two action potentials occurred after the onset of a tone burst; phasic burst, in which several action potentials were evoked after the onset of the tone burst; and fast adapting, in which strong transient action potentials at the onset of the stimulus presentation were followed by a reduced response that sustained for more than 50 ms but not the total 100 ms duration. Neurons with sustained responses had a discharge of spikes both at the onset and for the remainder of the tone burst. These responses fell into three subcategories: primary-like, in which a neuron fired in a continuous fashion throughout the entire duration of the stimulus; pauser, in which continuous late firing was separated from transient early firing by a brief pause; and build-up response, in which a neuron generated a continuous increase in firing till the end of the stimulus only after an initial silent period of at least 20 ms. Finally, neurons classified as the on-off type fired action potentials at the onset of the stimulus as well as immediately after the offset of the stimulus. The numbers of ICd neurons showing different temporal firing patterns are illustrated in Figure 9.

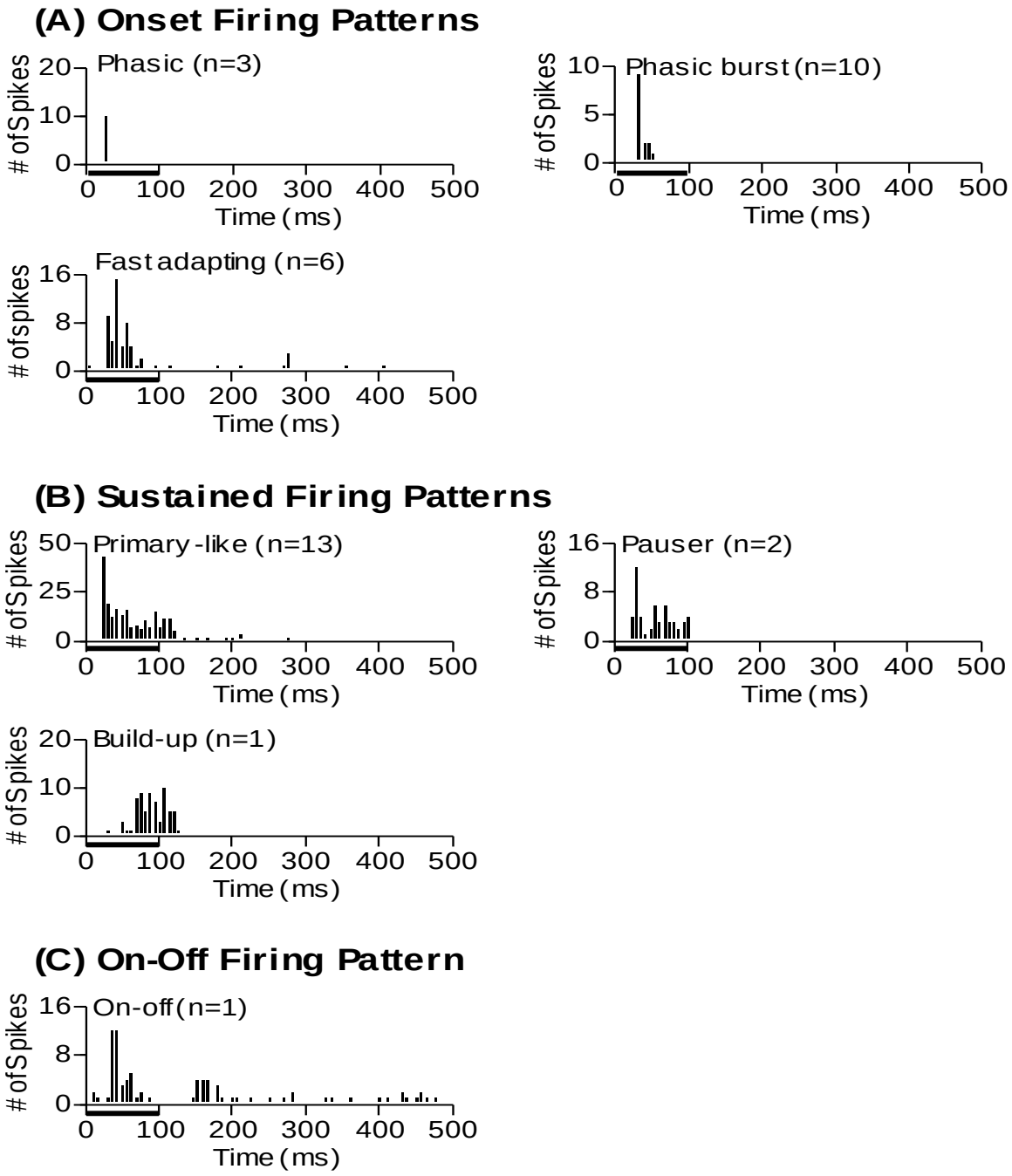


Fig. 9. A, B and C represent the major categories of temporal firing patterns displayed by ICd neurons. Responses are shown as post stimulus time histograms (PSTHs) representing the total number of spikes in 5 ms time bins, during and after presentation of a 100 ms tone burst. Spike numbers are based on a 20 tone presentations. Duration of stimulus presentation is indicated by the black horizontal bar below the x-axis of each histogram.

As an important temporal response characteristic, the time of occurrence of the first spike was analyzed in each ICd neuron (Figure 10). This figure illustrates the mean first-spike latency of responses elicited by 20 presentations of a contralateral tone burst at a neuron's CF and 10 dB above its MT. Mean first spike latency was measured in ms and plotted as a bar graph in Figure 10A. A comparison of the mean first spike latencies between onset and sustained neurons is indicated in Figure 10B.

Overall, for the total number of ICd neurons examined the first spike latencies ranged from 15.0 to 74.1 ms (A). Neurons in ICd show a wide range of mean first spike latencies even when they have similar CFs. Thus, no significant correlation was found between the mean first-spike latency and the CF of the neuron. For the subset of onset neurons (B), the first-spike latencies ranged from 25.5 to 51.5 ms (mean=33.7; median=32.3). For sustained neurons (B), the mean first spike latencies ranged from 15.0 to 74.1 ms (mean=42.6; median=42.4). The distributions of first spike latencies for these two groups of neurons were statistically different (Kolmogorov-Smirnov test, $p<0.05$).

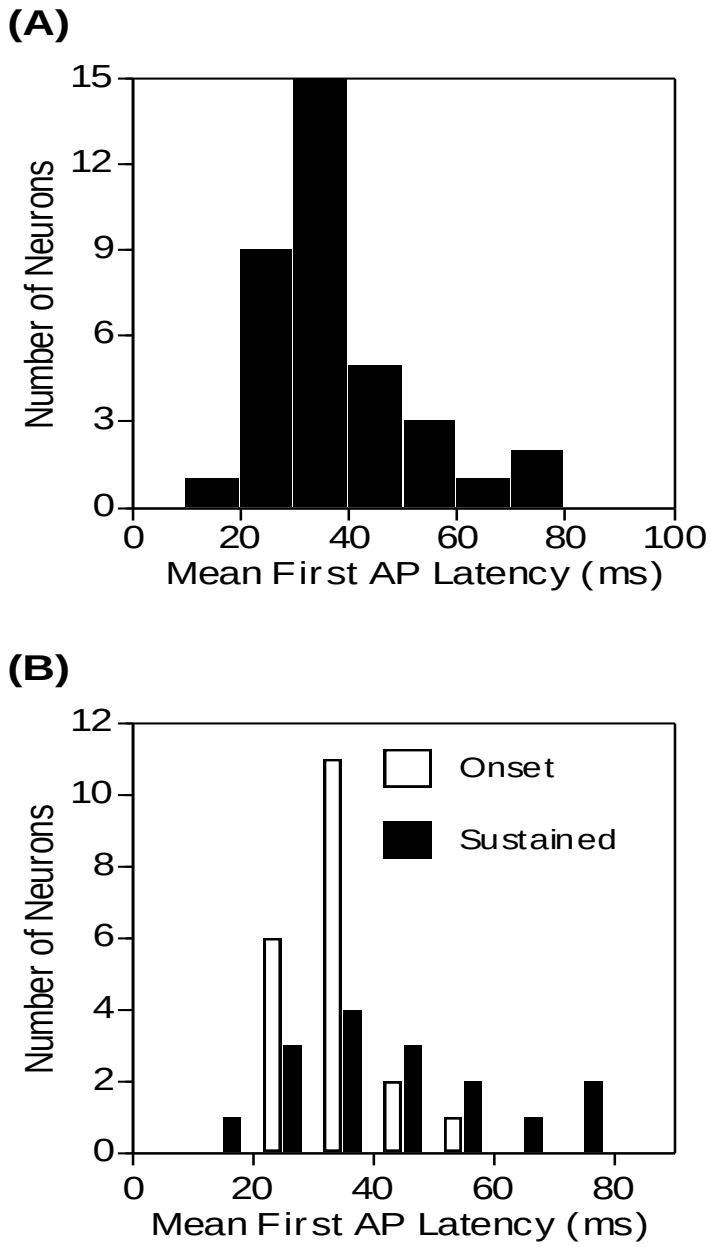


Fig. 10. Mean first spike latencies in ICd neurons. The mean first spike latency of all ICd neurons is illustrated in A. The abscissa represents the mean first spike latency of ICd neurons in ms. The range of first spike latencies in all ICd neurons varied from 15.0 - 74.1 ms. Most neurons responded with a latency in a range between 30 and 40 ms. Onset neurons shown here as white bars (B), displayed a narrower range of first spike latencies varying from 25.5 - 51.5 ms. Sustained neurons shown as black bars (B), exhibited a broader first spike latency range from 15.0 - 74.1 ms. The values obtained here are based on responses elicited by 20 presentations of a tone burst at CF and 10 dB above threshold.

The occurrence time of the first spike varied from one presentation of a tone burst to the next. The magnitude of this jitter in the first spike latency was examined by calculating the standard deviation of the latencies of the first spikes elicited by 20 presentations of a tone burst at a neuron's CF and 10 dB above its MT (Figure 11). The overall magnitudes of jitter ranged from 0.6 to 28.5 ms in the total of 36 ICd neurons with a mean of 7.9 and a median of 6.3 (Figure 11A). Most ICd neurons responded with a relatively small jitter of less than 5.0 ms.

For 19 neurons with onset responses, magnitudes of jitter were within a range from 0.6 to 14.7 ms with a mean of 6.0 ms and a median of 5.3 ms. For 16 neurons with sustained responses, magnitudes of jitter ranged from 1.1 to 28.5 ms with a mean of 9.9 ms and a median of 7.0 ms (Figure 11B). On average, neurons with onset and sustained responses however, showed no statistical difference in jitter of the first spike latency (Kolmogorov-Smirnov Test, $p=0.583$).

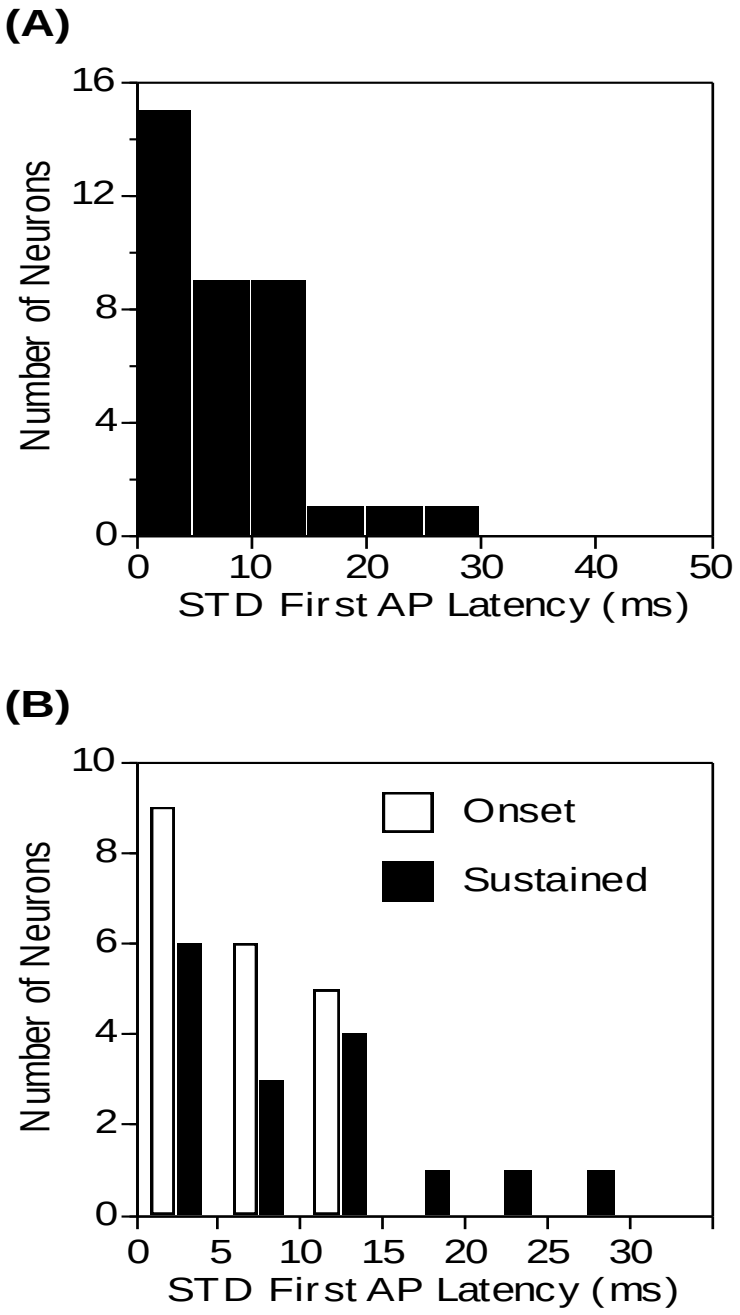


Fig.11. Representation of the degree of jitter in first spike latency in ICd neurons. The range of jitter in ICd neurons varies from 0.6 – 28.5 ms (A). Mean: 7.9 ms, Median: 5.7 ms. Onset neurons illustrated by unfilled bars, sustained neurons displayed by black bars (B). Most onset neurons display a short jitter at approximately 1.0 ms with a mean of 6.0 ms. Majority of sustained neurons exhibit a jitter at 2.5msec with a mean of 9.9 ms, Komogorov-Smmirnov Test: p=0.583. Jitter is expressed as the standard deviation (STD) of first spike latencies of responses to 20 tone burst presentations for each ICd cell.

3.4 Frequency-tuning characteristics

For each neuron, I determined a characteristic frequency (CF) (i.e. the frequency at which a neuron showed lowest threshold for responses to tone bursts). The CFs were distributed from 1 to 11 kHz. For each neuron, I also examined minimum threshold (MT) to the tone bursts. The MT ranged from 0 to 73 dB SPL. The CFs and thresholds at CF are plotted in figure 12 together with the rat's behaviorally determined auditory sensitivity curve (Kelly and Masterton, 1977). The abscissa and ordinate of each data point represent the CF and MT from an individual ICd neuron. The CFs and MTs of ICd neurons fall into the area defined by the rat's behaviorally determined audiogram.

Frequency-tuning curves were determined in 36 ICd neurons. These frequency tuning curves included V/U -shaped (n=27), multi-peaked tuning curves, including W-shaped (n=8) and other complex shapes (n=1). Examples of different types of FTCs are illustrated in Figure 13.

ICd neurons display a variety of FTCs all of which exhibit differences in sharpness of tuning. Sharpness of tuning was reflected as quality factor at 10dB above the MT.

$$\mathbf{Q_{10} = CF/BW_{10}}$$

In which Q_{10} stands for quality factor at 10dB above minimum threshold. CF stands for the center frequency of a neuron and BW_{10} stands for the bandwidth of a frequency tuning curve at 10dB above minimum threshold. Overall, ICd neurons exhibited a broad range of Q_{10} values from 0 – 11 with a mean of 3.78 kHz and a median of 3.03 (Fig. 14). Many neurons displayed Q_{10} values of approximately 2. According to the data obtained, ICd neurons have no particular distribution patterns in reference to the sharpness of tuning. Neurons with similar CFs could show either broad tuning (small Q_{10} values) or narrow tuning curves (large Q_{10} value).

An iso-intensity curve was generated by recording responses to tone bursts at a wide range of frequency with a fixed intensity (usually 10 dB above MT). Figure 15 is an example of an iso-intensity curve from one ICd neuron (A). At 10dB above MT, this neuron generated the strongest response when the frequency of a tone burst was 2.2 kHz. The FTC of the same neuron was generated and displayed a V-shaped curve (B). The FTC indicates that the CF was 3.5 kHz and the MT is 52 dB SPL. For this neuron, the best frequency for generating the strongest response was different from the CF. The BF is the best response of the neuron at a particular frequency, while CF is the best response at the lowest possible threshold. For many neurons in my study, the best frequency and the characteristic frequency were in fact the same.

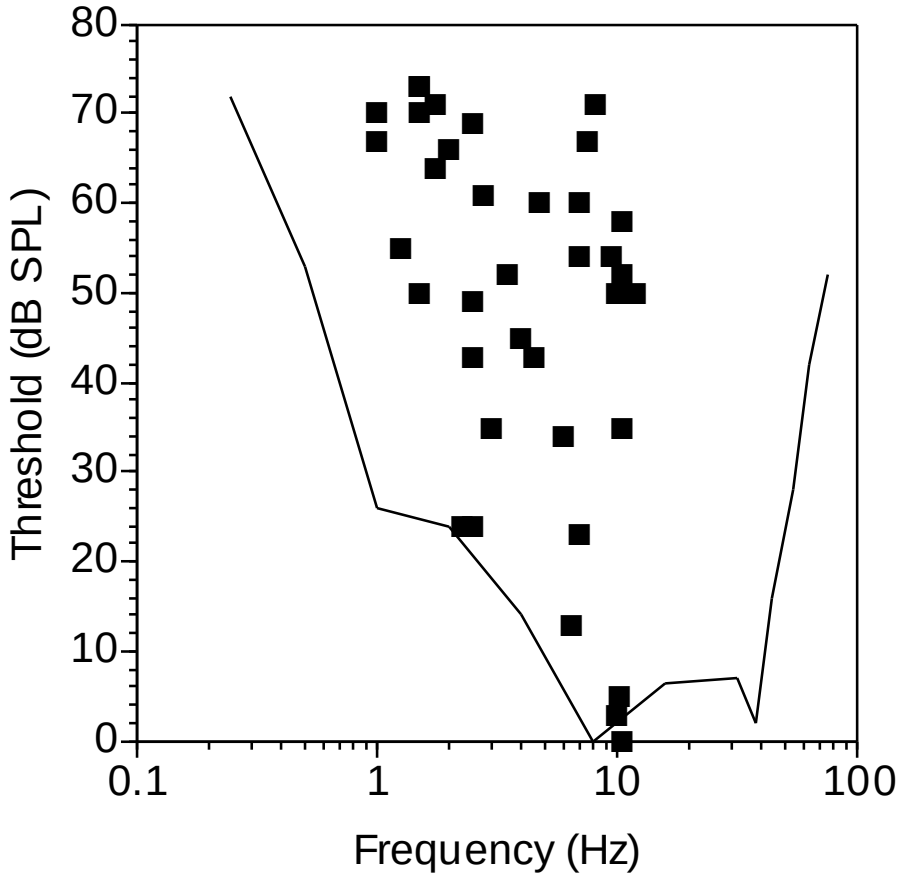


Fig. 12. Excitatory thresholds at characteristic frequency (CF) for ICd neurons plotted together with the rat's behavioral audiogram illustrated by the solid line. Each filled square represents results from one individual neuron. At each sound frequency there was a wide range of thresholds for different neurons.

Kelly and Masterton, 1977

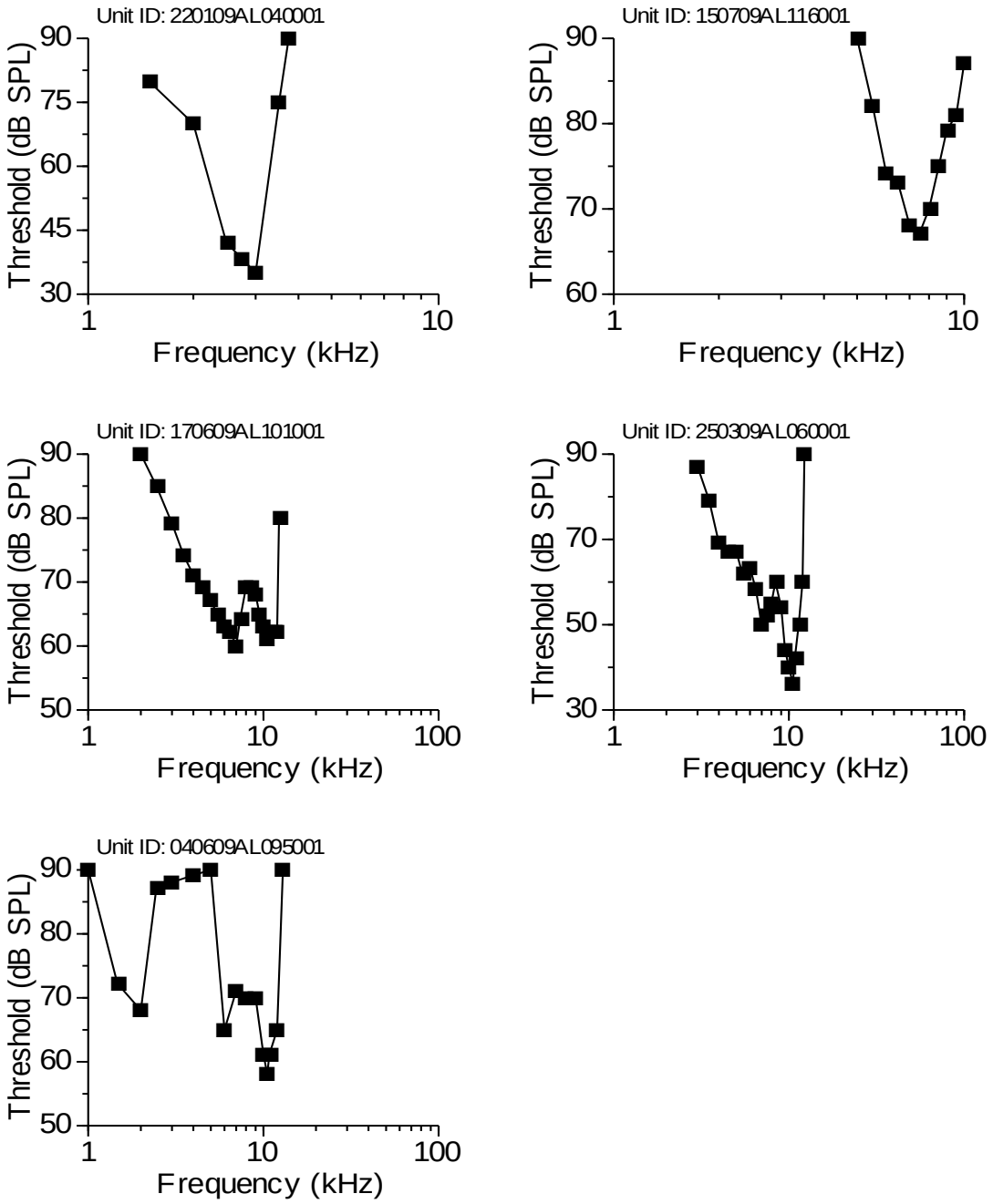


Fig. 13. Frequency tuning curves of representative neurons in the ICd. Tuning curve examples found in ICd neurons included V/U-shaped, W-shaped and complex. The top left panel illustrates a V-shaped neuron. The top right panel is a V/U-shaped neuron with a CF close to 10 kHz and an FTC that is more symmetrical than that seen on the top left side. Also seen above, in the middle left panel is a W-shaped FTC, with two peaks at approximately similar thresholds, while on the right hand side a different W-shaped FTC has peaks at different thresholds. On the bottom left hand panel, this neuron displays a complex FTC with multiple peaks and all at different thresholds. FTCs generated from 5 different ICd neurons.

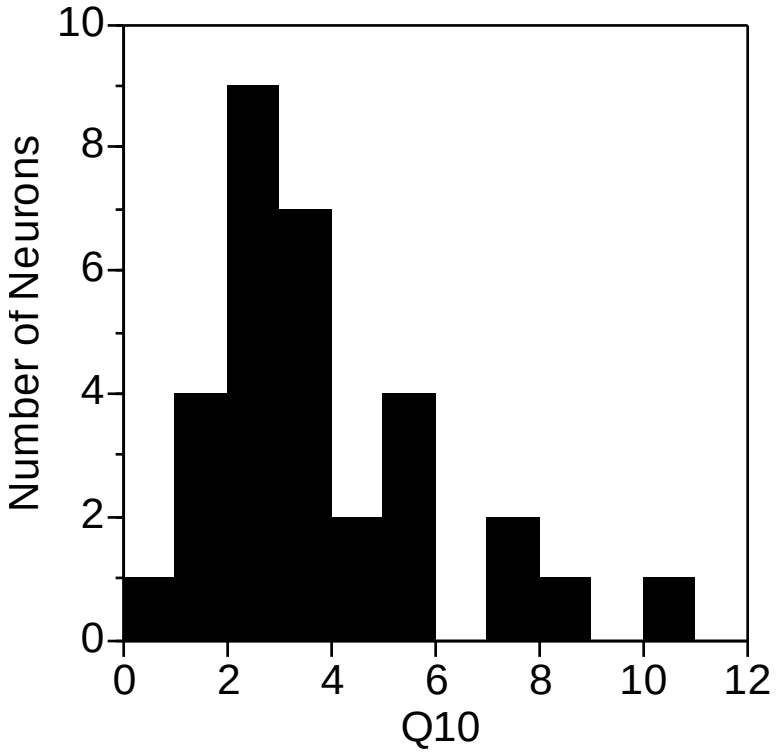


Fig. 14. Bar graph illustrating Q10 values derived from ICd neuron responses. Q10 is a measure of the neuron's CF in proportion to the tuning curve bandwidth 10dB above MT. Most ICd neurons display a Q10 value of approximately 2.0. The range of Q10 values varies from 0 to 11. Overall, the majority of ICd neurons exhibit Q10 values under 6.

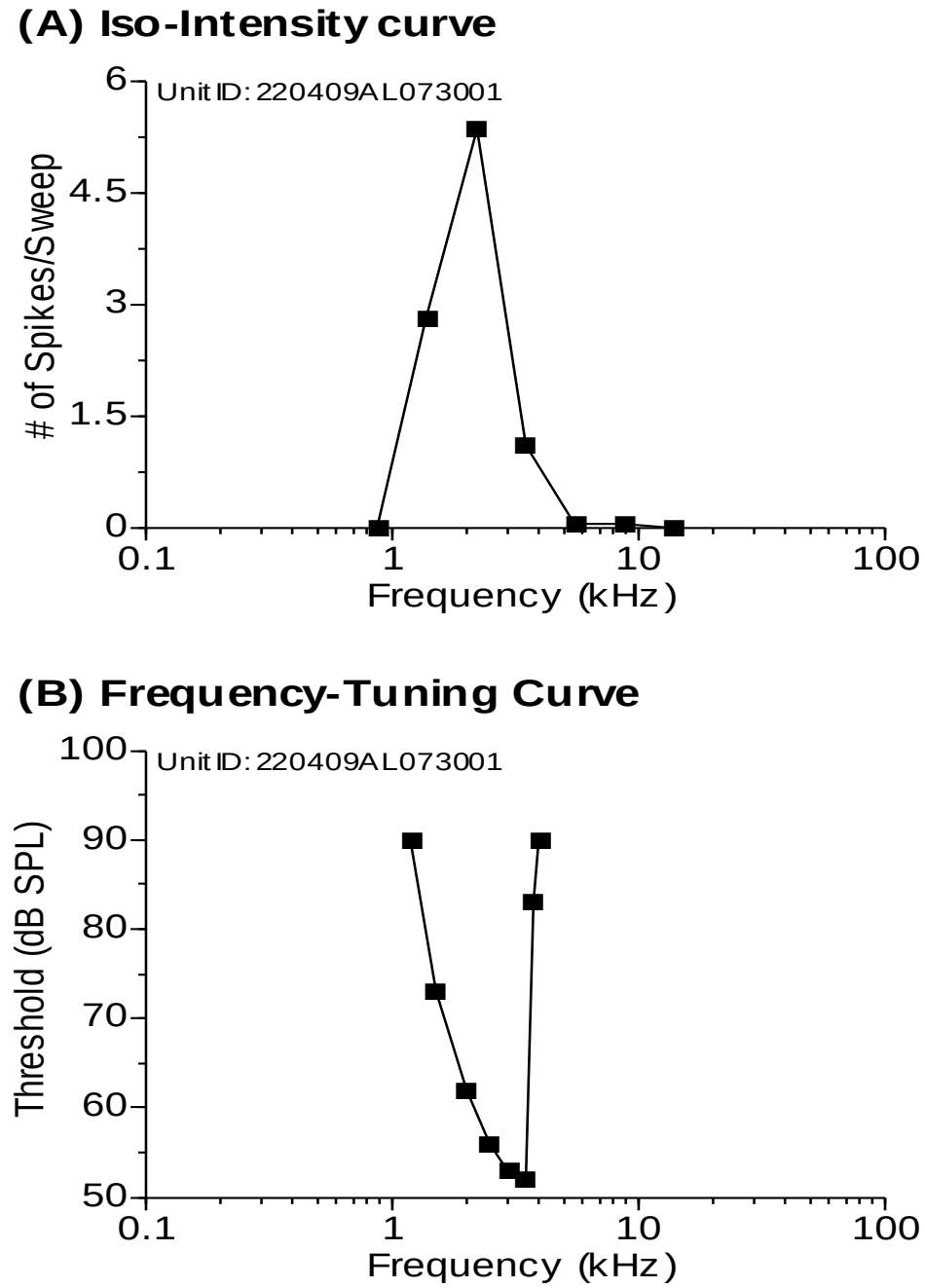


Fig. 15. Illustrated in figure A is an iso-intensity curve of a representative neuron in the ICd obtained at 10 dB above MT. This neuron has a best frequency (BF) at which it fired most APs of 2.2 kHz. Below 1 kHz this neuron did not respond. At frequencies above its BF the neuron drastically decreases its response. A frequency tuning curve of the same neuron is displayed in B here exhibiting a V-shaped FTC. The CF of this neuron is different than its BF. The CF for this neuron is 3.5 kHz and displays a narrow tuning curve.

3.5 Level dependence of responses to monaural tone bursts

The firing rate of an ICd neuron was dependent on stimulus intensity. At 10 dB above MT at the neurons CF, ICd neurons displayed firing strengths between 0.35 and 31.55 spikes/sweep (Figure 16). The majority of neurons exhibited low firing rates of approximately 2 spikes/sweep. However, some neurons also displayed firing rates above 8 spikes/sweep, with a few displaying extremely high firing rates of approximately 30 spikes/sweep. Overall, based on the data obtained, ICd neurons tend to exhibit low firing rates.

For 9 of 14 ICd neurons, an increase in sound-pressure level resulted in a monotonic increase in firing strength. Two representative neurons displaying monotonic rate level functions are illustrated in Figure 17A. On the left panel the ICd neuron displayed a dynamic range of approximately 60 to 80 dB SPL the firing saturated at around 3 spikes/sweep when stimulus intensity was above 80dB SPL. The ICd neuron on the right panel however, showed a dynamic range of approximately 67 – 90 dB SPL. For this neuron the strength of firing saturated at a rate of around 4 spikes/sweep when stimulus intensity was above 90dB SPL.

The remaining 5 ICd neurons displayed non-monotonic rate-level functions (Figure 17B). This example illustrates an ICd neuron whose firing rate increased with intensity when the intensity was below 45dB SPL. A peak firing rate of approximately 3 spikes/sweep was reached at an intensity of approximately 45 dB SPL. The firing rate decreased when the intensity was above 45 dB SPL and appeared to continue a steady decrease at approximately 55 dB SPL.

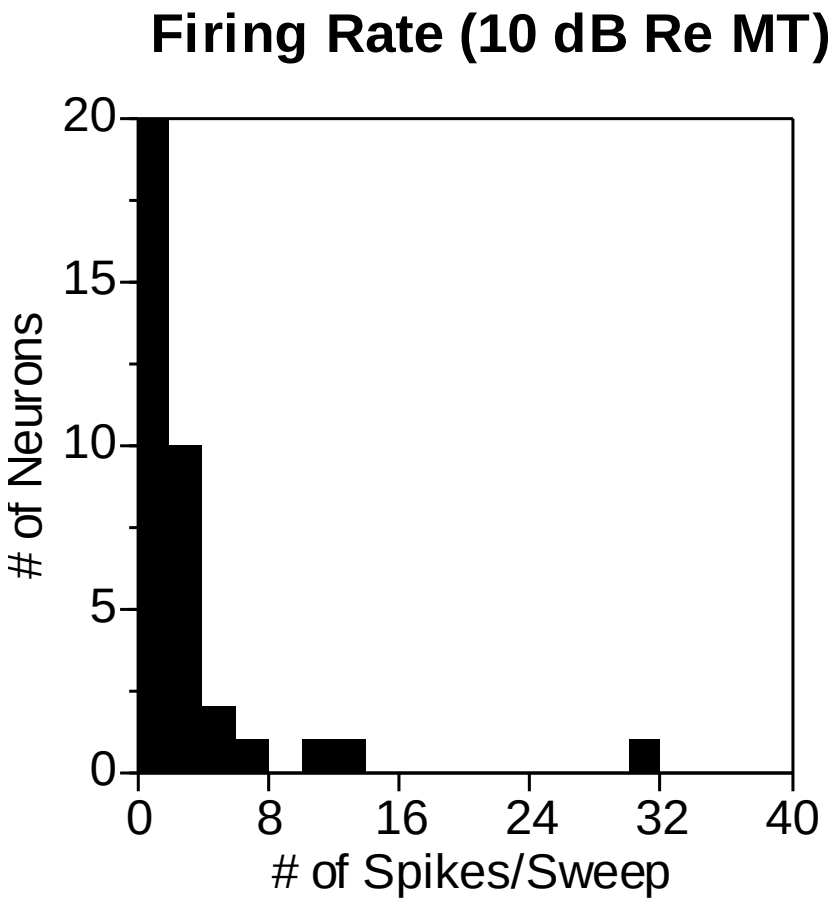


Fig. 16. Firing rates at CF and 10 dB above MT in ICd neurons. The majority of ICd neurons exhibit firing rates below 8 spikes/sweep, with most neurons displaying firing rates of 2 spikes/sweep. Only two neurons displayed higher firing rates of approximately 30 spikes/sweep. The mean firing rate for ICd neurons was 3.43 spikes/sweep. Median for firing rate of ICd neurons was 1.83 spikes/sweep.

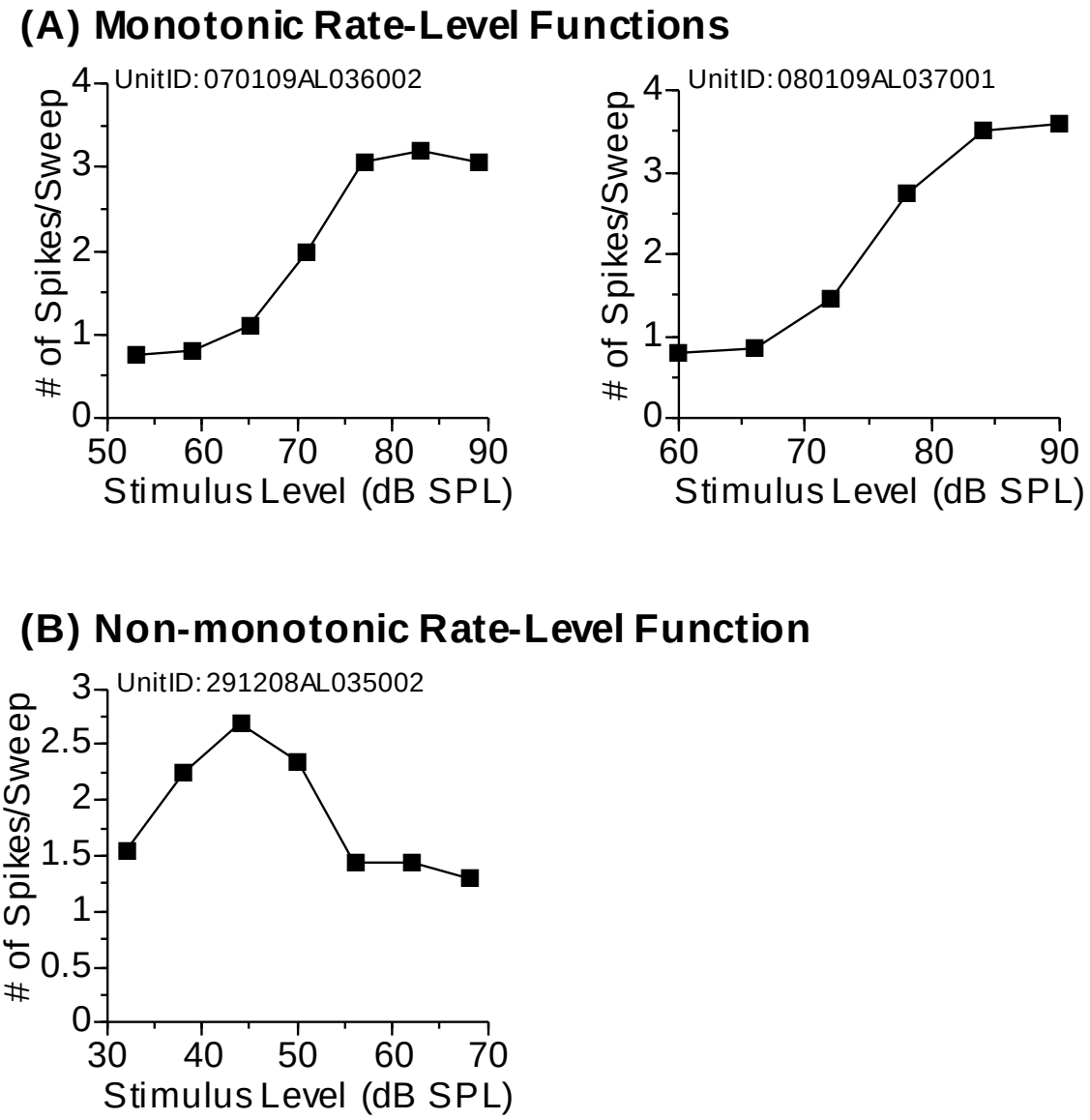


Fig. 17. Two representative neurons illustrated in (A) show a monotonic rate level function. The ICd neuron displayed in the top left panel exhibits a dynamic range of approximately 60 – 80 dB SPL with a peak firing rate of approximately 3 spikes/sweep. The neuron in the top right panel shows a dynamic range of approximately 67 – 90 dB SPL with a peak firing rate of approximately 4 spikes/sweep. Neuron illustrated in (B) shows a non-monotonic rate level function. This ICd neuron exhibits an increase in firing rate at an intensity of 30 dB SPL and a firing rate of 1.5 spikes/sweep reaching a peak firing rate of 3 spikes/sweep at an intensity of 45 dB SPL. After this the response decreases and remains steady at a rate of 1.5 spikes/sweep and an intensity of approximately 55 dB SPL. Responses were recorded at a neurons CF and a wide range of intensities.

3.6 Stimulus-specific adaptation

During repetitive tone burst stimulation, the number of action potentials generated by an ICd neuron was different from one sweep of stimulus presentation to the next. In some cases, this difference reflected a random variation in the firing strength of a neuron. For example, the neuron in the lower right panel of Figure 18 displayed a fast adapting temporal firing pattern. This neuron generated a different number of spikes across 20 presentations of tone bursts. However, no systematic increase or reduction was found during repetitive tone burst presentations. For other ICd neurons a reduction in the number of spikes was found during repetitive tone burst presentations. These neurons displayed strong firing in response to the first few repetitive tone bursts but weaker or erratic firing thereafter. For the two examples shown in top panels of Figure 18, the number of spikes elicited by the first 10 sweeps of a tone burst and that elicited by the last 10 sweeps were different. Strong firing was generated during the initial presentations of the tone burst. I used an adaptation index (AI) to describe quantitatively the degree of reduction in firing during repetitive stimulation. The AI was calculated using the areas below two iso-intensity curves:

AI = (# of AP (first 10) - # of AP (last 10))/ (# of AP (first 10) + # of AP (last 10))

For the neurons in the upper panels of Figure 18 the adaptation index was 0.625 and 0.429. For the neuron in the lower right panel, the adaptation index was close to 0. However, when looking at the bottom two neurons the difference between the first 10 sweeps vs. the last 10 sweeps was virtually identical, although a variation was observed among individual sweeps.

Figure 19 shows the distribution of adaptation indices for the entire population of 36 neurons. The range of AI values fell between -0.3 and 0.7. The majority of ICd neurons were

distributed toward positive values of at least 0.1 or higher and show adaptation to repetitive blocks of stimulation. Statistical analysis confirmed this trend (Binomial distribution, $p < 0.05$). This data suggests that ICd neurons show a reduction in response over 20 sweeps of tone burst stimulation.

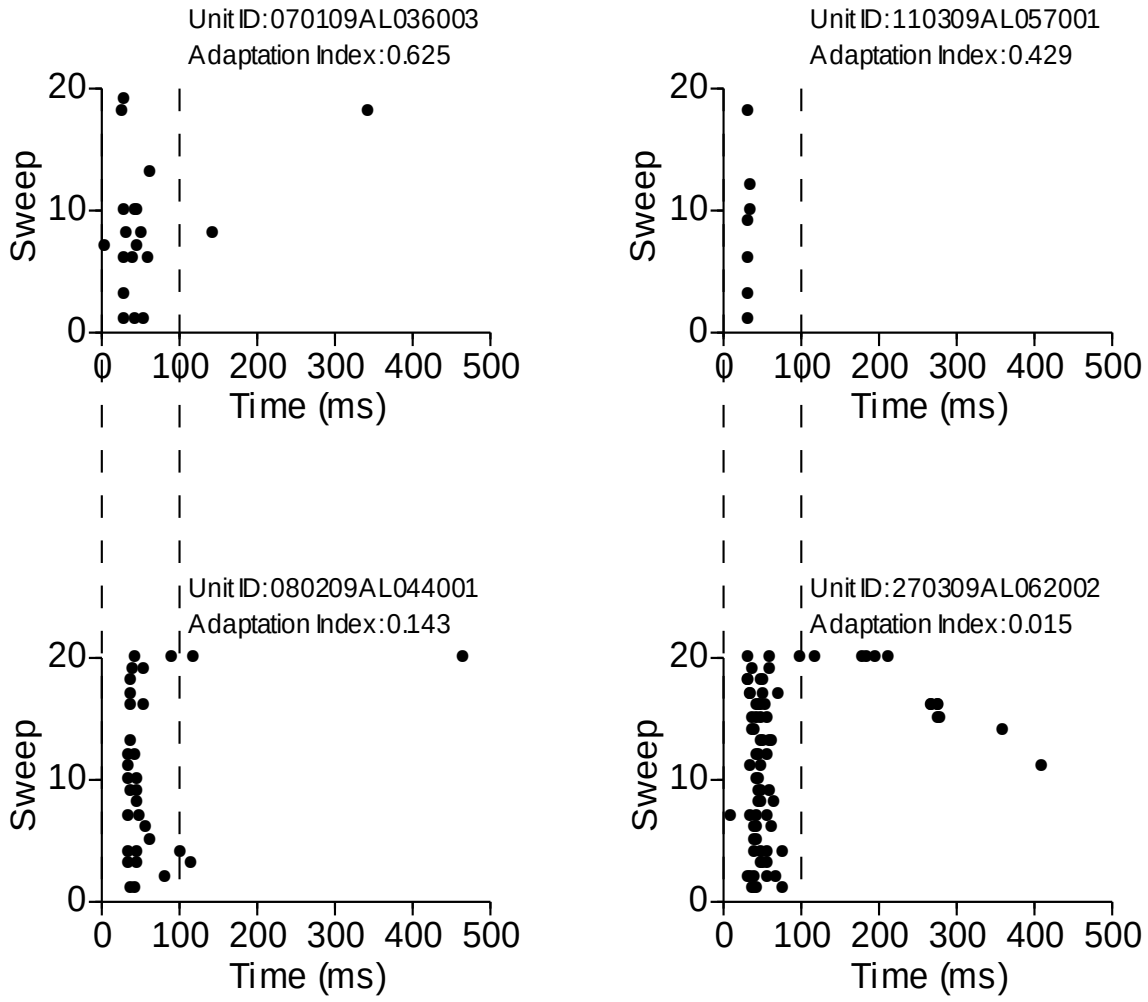


Fig. 18. Dot raster histograms for four representative ICd neurons. Each dot represents an action potential. The two neurons in the upper panels display apparent adaptation to repetitive blocks, while the two neurons in the lower panels display low degree of adaptation for the same stimulus paradigm. An adaptation index is stated below each unit ID. The dot raster histograms were generated using responses of neurons over 20 sweeps at a neurons CF and 10dB above MT. Vertical dashed lines represent the duration of a single tone burst sweep.

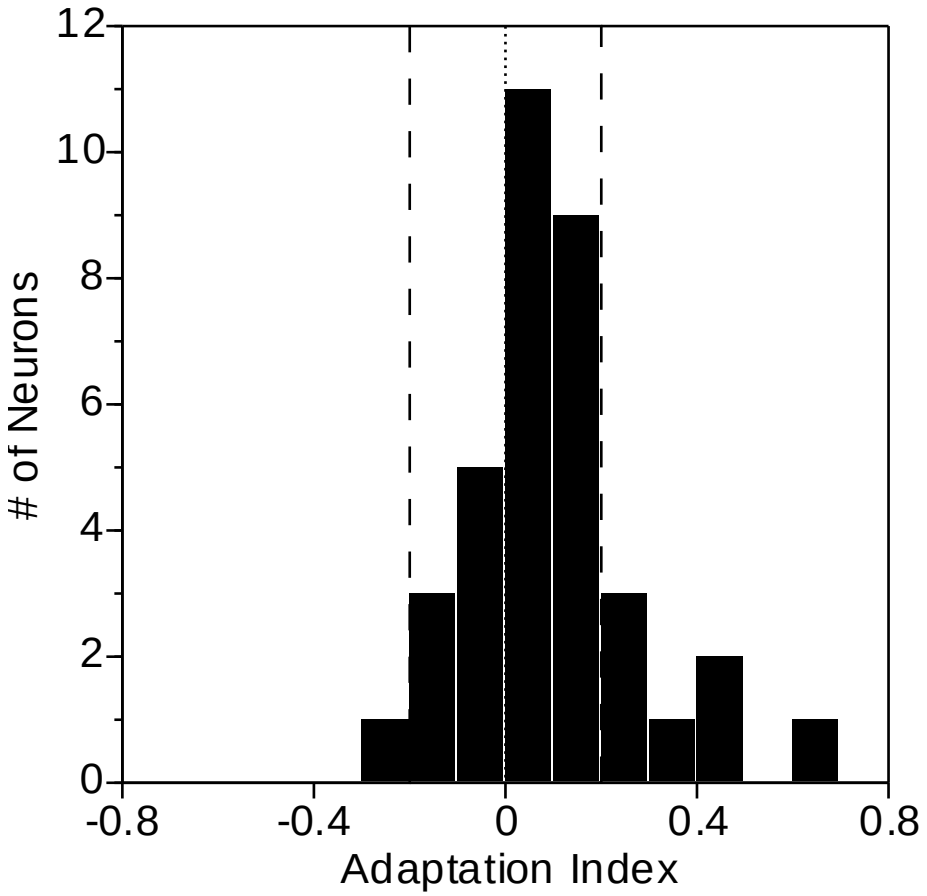


Fig. 19. Adaptation index (AI) values for units recorded in the ICd. The AI is based on the number of spikes for the first 10 vs. the last 10 sweeps of tone bursts, presented at a neuron's CF and 10 dB above MT. ICd neuron adaptation indices ranged from approximately -0.3 to 0.7. The majority of ICd neurons display indices above 0 (Binomial distribution ($p< 0.05$)). Dashed line represents the range of $-0.2 < AI < 0.2$.. The dotted line represents point 0.

In order to study whether the adaptation displayed by ICd neurons was a passive fatigue related adaptation or an active stimulus specific adaptation I recorded responses to randomized sequences as well as repetitive blocks. Two iso-intensity curves were compared for all ICd neurons. Figure 20 compares the responses to two types of stimuli in four neurons. For the two neurons in the lower panels the responses were very similar for both two stimulus conditions. These two neurons did not display stimulus specific adaptation. In contrast, for the two neurons in the upper panels of Figure 20, responses to randomized sequences were substantially higher than those to repetitive blocks. The fact that repetitive blocks elicited weaker responses while randomized sequences generated stronger responses suggest that these neurons display stimulus specific adaption.

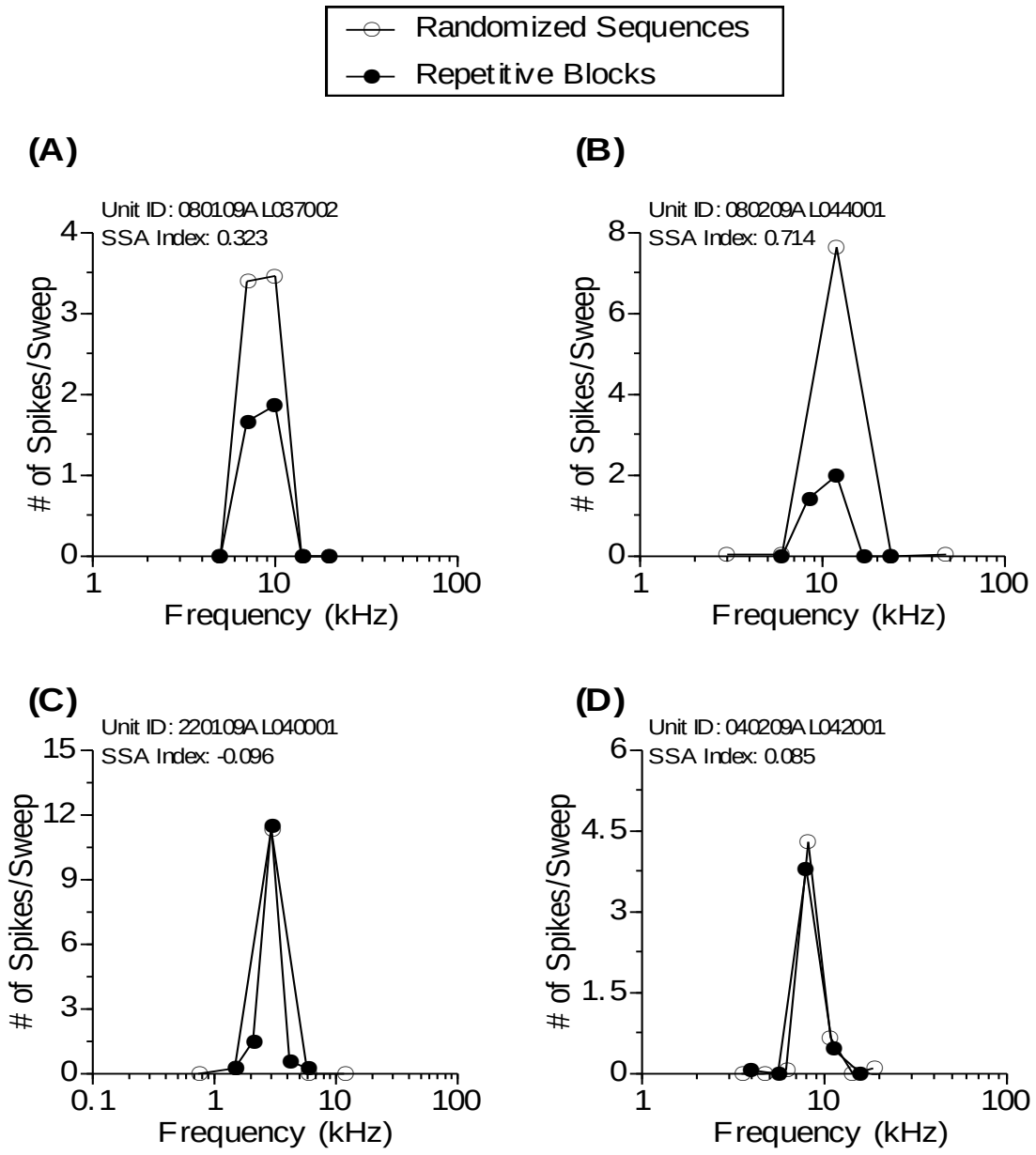


Fig. 20. Iso-intensity curves of four representative ICd neurons. Illustrations showing response of neurons to randomized versus repetitive sequences. White unfilled circles represent responses to randomized sequence, while the filled circles represent responses to repetitive sequences. Top two neurons displayed SSA with an adaptation index of above 0.2. B displays a drastic difference in spike count during randomized stimulation (approx. 8 spikes/sweep) vs. during repetitive stimulation (2 spikes/sweep). The lower two panels (C and D) did not display SSA, and spike numbers were almost identical between responses obtained using the two different stimulus paradigms.

Two indices were used to describe the degree of SSA quantitatively. The peak response index SSA_P was used to examine the difference between peak responses of neurons to repetitive versus randomized stimulation.

$$\mathbf{SSA_P = (P_{Rand} - P_{Rep})/ (P_{Rand} + P_{Rep})}$$

Where P_{Rand} is the peak response of the iso-intensity curve obtained by using randomized sequences. P_{Rep} is the peak response of the iso-intensity curve obtained by using repetitive blocks. The peak values obtained under the two stimulus conditions were compared in Figure 21A. Those neurons whose responses fall below the diagonal line are neurons that prefer randomized sequences, while those above the diagonal line prefer repetitive blocks of stimulation. SSA indices were generated for the peak responses for all ICd neurons and were illustrated in Figure 21B. The SSA indices were distributed toward positive values. This suggests that most ICd neurons prefer randomized sequences. Our data indicate that ICd neurons show stimulus-specific adaptation (Binomial distribution, $p<0.05$).

An index was also calculated for each neuron using the area under the iso-intensity curve (SSA_A).

$$\mathbf{SSA_A = (A_{Rand} - A_{Rep})/ (A_{Rand} + A_{Rep})}$$

Where A_{Rand} is the area below the iso-intensity curve obtained by using randomized sequences. A_{Rep} is the area below the iso-intensity curve obtained by using repetitive blocks. In Figure 22A group results exhibit that most ICd neurons favor randomized sequences and generate higher numbers of spikes as compared to repetitive blocks of stimulation. Figure 22B shows that the distribution of the SSA index of ICd neurons is skewed toward positive values. The overall range of indices varies from -0.4 to 0.7; although, the majority of the population is

made up of index values of above 0.1 (Binomial distribution, $p<0.05$). My data supports the fact that ICd neurons show stimulus-specific adaptation.

Stimulus specific adaption was further analyzed for the two groups of neurons with onset and sustained responses. I found that most of the ICd neurons displaying SSA exhibited onset firing patterns. For the 14 neurons with an SSA_A larger then 0.2, 11 (or 79%) displayed onset responses. Only three of the 14 neurons (or 21%) displayed a sustained firing pattern. In contrast, the majority (67%) of non-SSA neurons displayed sustained firing patterns Only 33% of the non-SSA neurons displayed onset firing patterns (Figure 23).

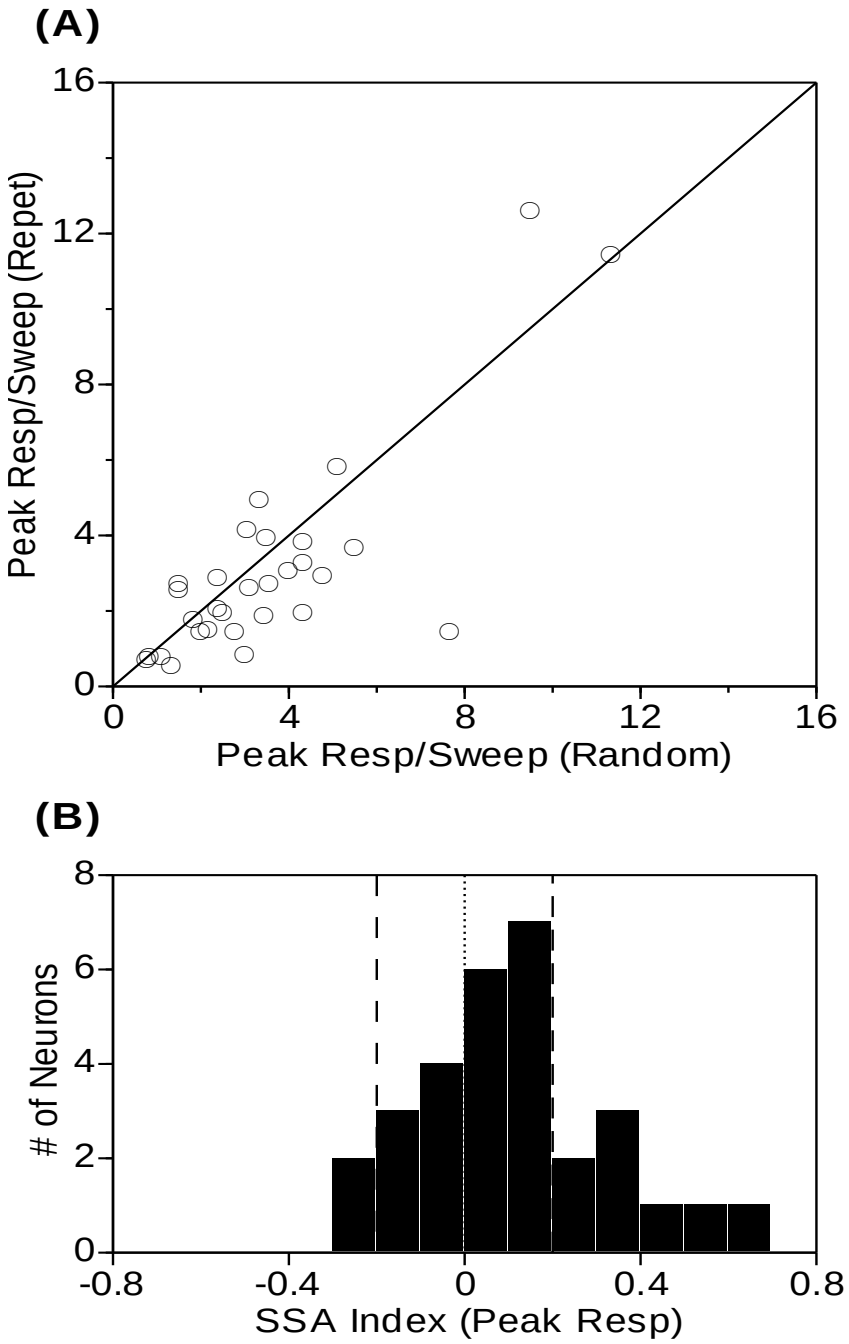


Fig. 21. Comparison of group results for peak responses evoked by repetitive blocks versus randomized sequences. Each open circle represents responses from a single ICd neuron (A). Most of the points fall below the curve and prefer randomized sequences. Illustration of SSA index for peak response of all ICd neurons (B). Overall distribution is skewed toward positive values (Binomial distribution, ($p<0.05$)). Peak response ranges from -0.3 to 0.7. Most neurons display index values above 0.1. Dashed line represents range of $-0.2 < SSA_P < 0.2$. Dotted line represents point 0.

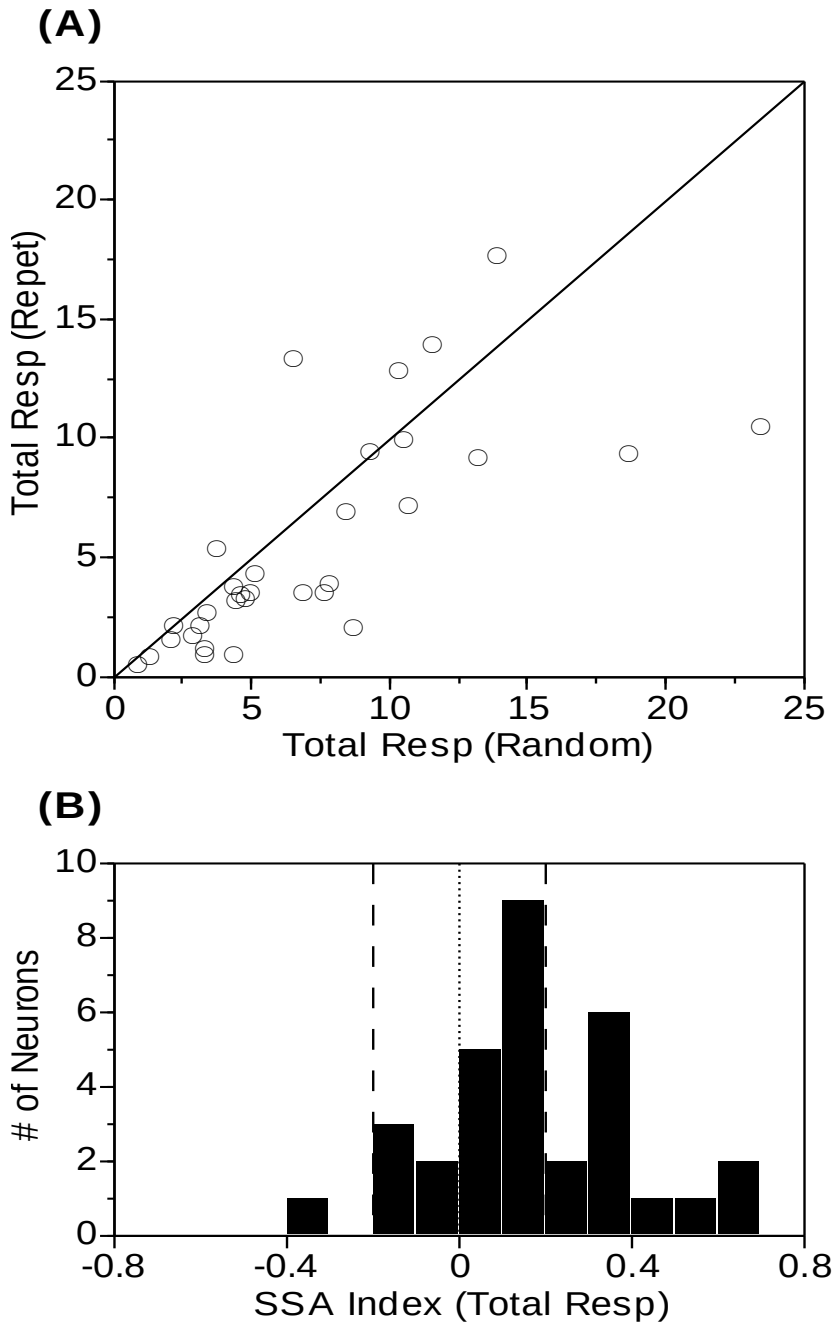


Fig. 22. Comparison between total responses under iso-intensity curve obtained using repetitive blocks and randomized sequences. Each unfilled circle represents responses from a single ICd neuron (A). Most data points are below the diagonal line, indicating stronger responses to randomized blocks than to repetitive blocks. In B, the total response index for SSA index based on total responses under iso-intensity curve in ICd neurons is illustrated. Index values range between -0.4 to 0.7. Majority of neurons display index values above 0.1 Most neurons display positive SSA index values (Binomial distribution, ($p<0.05$)). Dashed lines represent the range of $-0.2 < SSA_A < 0.2$. Dotted line represents point 0.

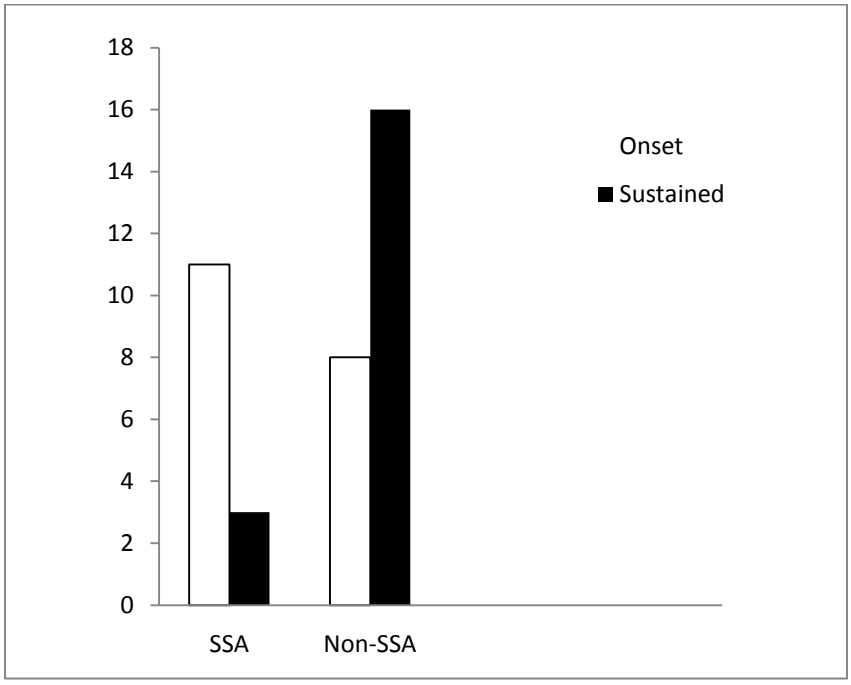


Fig. 23. An illustration showing that neurons with SSA vs. non-SSA have different temporal firing patterns. The two left columns represent the SSA neurons. The two right columns represent the non-SSA neurons. The white bars represent onset neurons. The black bars represent sustained neurons. The ordinate represents the number of neurons displaying the SSA vs. non-SSA.

3.7 Cortical modulation of ICd neurons

The effect of suppressing cortical neural activity on responses of ICd neurons was studied on a total of 12 ICd neurons. A reversible cooling method was used to inactivate AC neurons. The neuron in Figure 24 displays an increase in firing during cortical cooling. Dot raster histograms and PSTHs demonstrate the neurons change in spike number (Figure 24A). No change in temporal firing pattern was observed for this neuron between the three different treatment conditions. The iso-intensity curve shown in Figure 24B verifies the change in spike numbers for this representative ICd neuron.

The ICd neuron in Figure 25 demonstrated a decrease in response during cortical cooling. Figure 25A shows a change in spike numbers when cooling the AC. However, no recovery data was present to compare these results thus the observation is inconclusive. Figure 25B is an iso-intensity curve displaying the drastic reduction in spike numbers during the cooling condition. The filled squares in this example represent the neuron pre cooling while the filled circles illustrate the neurons response during cooling. Data regarding post cooling conditions for this neuron was not obtained.

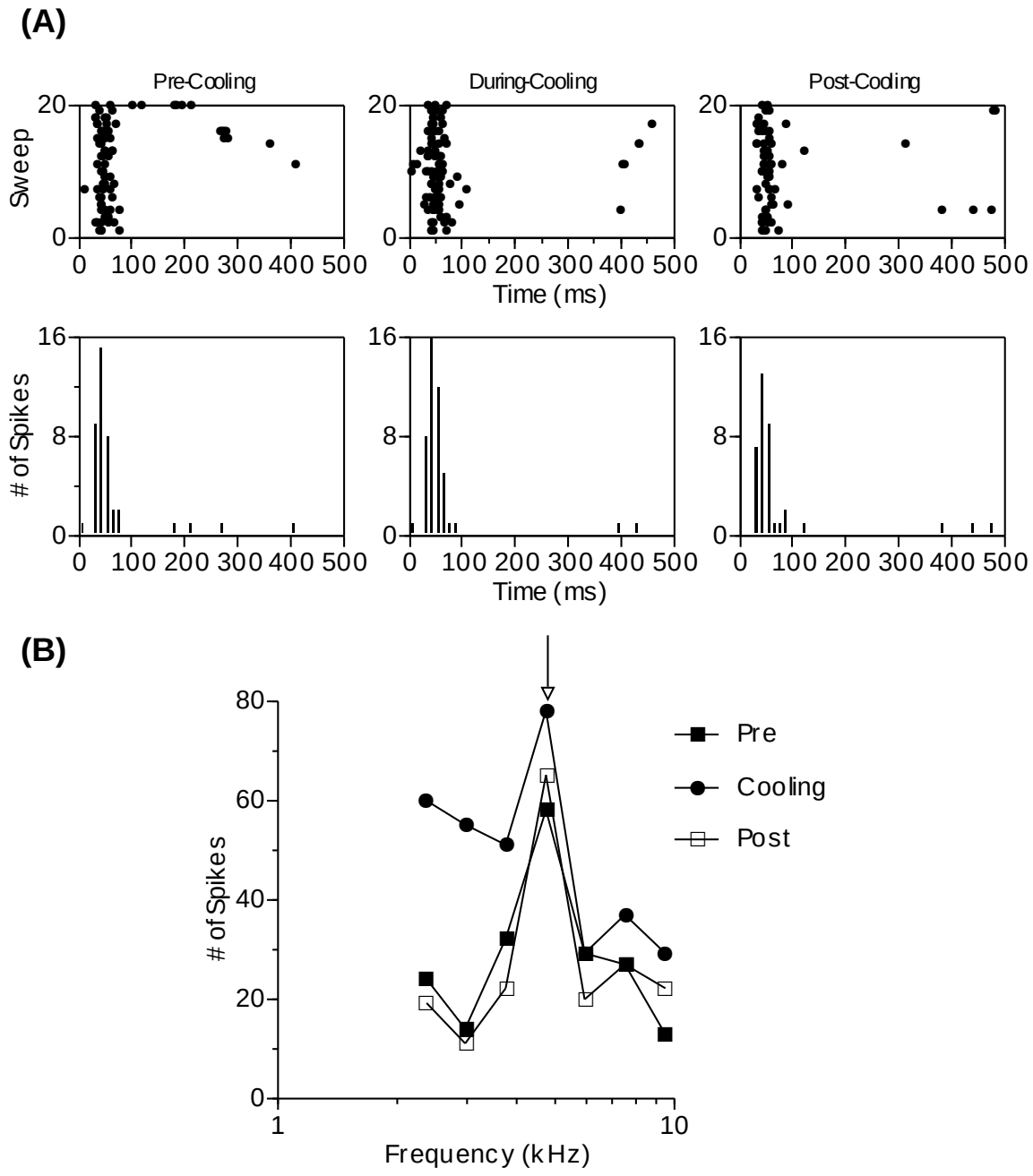


Figure 24. (A) An ICd neuron showing an increase in response during cortical cooling. Dot raster histograms and PSTHs of a representative ICd neuron pre-cooling, during cooling and post cooling. A change in spike numbers is evident during cooling when compared to the other two treatments (B). Iso-intensity curves of the same neuron obtained before, during and after cooling. The filled squares represent the neuron's response before cooling. The filled circles represent the neuron's response during cooling. The open square represents the neuron's response post cooling. Note the change in peak number of spikes during the cooling condition. The arrowhead in (B) indicates that the dot raster histograms and PSTHs were obtained at the best frequency of iso-intensity curves.

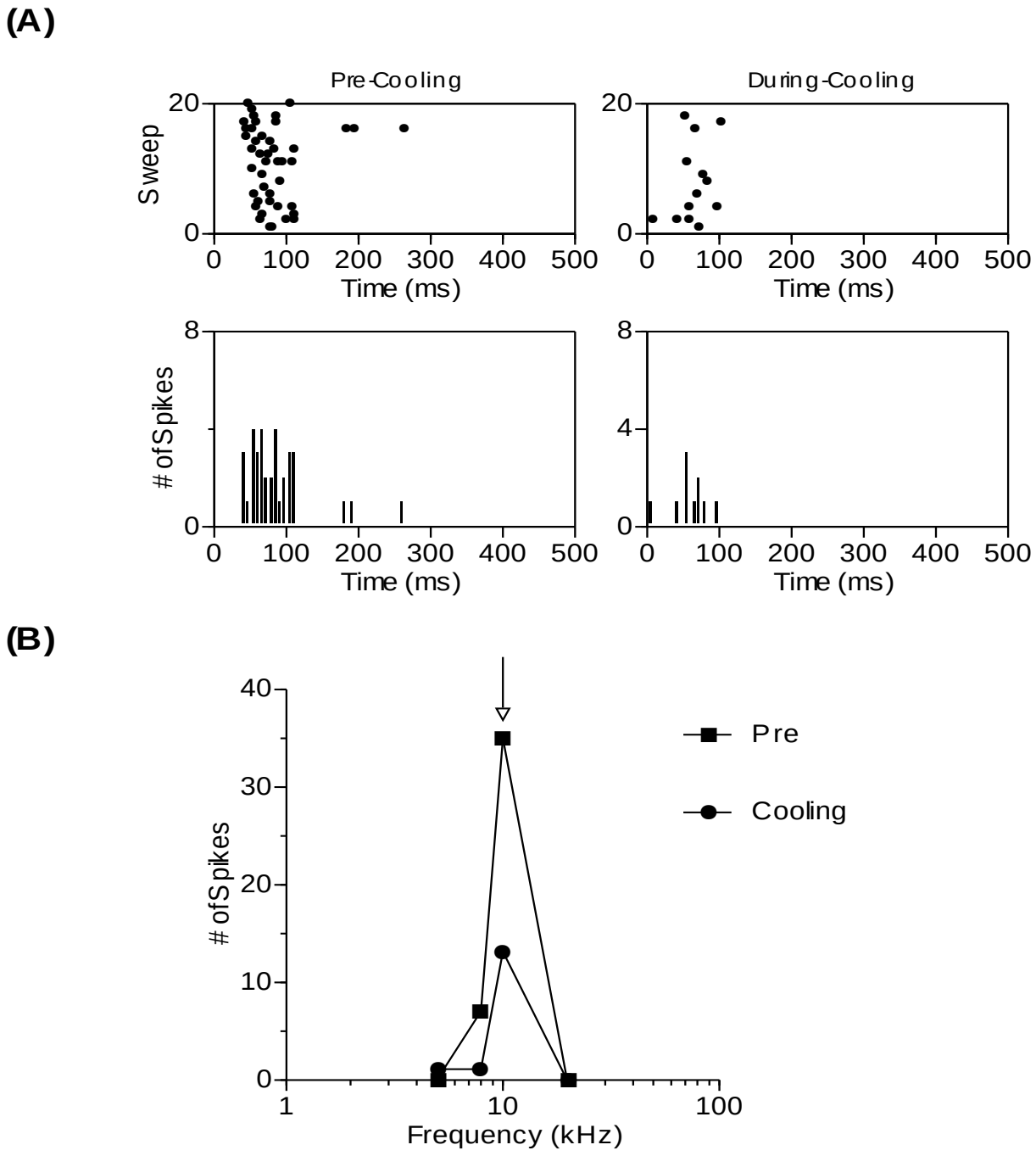


Figure 25. An ICd neuron showing a reduction in response during cooling conditions. Dot raster histogram and PSTH showing the change in spike numbers for pre and during cooling conditions (A). Iso-intensity curve portraying the change for each condition, filled squares representing the pre-cooling period of recording, while the filled circles represent the period of recording during cooling (B). No recovery data was collected for this neuron. Note drastic change in spike numbers during the cooling condition. Arrowhead in (B) indicating the plots were generated using the BF of this neuron.

3.8 Summary of Results

Objective 1 – Classification of ICd neurons

- 3 categories of neurons classified in ICd
    - Onset
        - Phasic
        - Phasic Burst
        - Fast Adapting
    - Sustained
        - Primary Like
        - Pauser
        - Late
    - On/Off
- ICd neurons demonstrate stimulus intensity sensitivity
    - Most neurons examined show monotonic RLFs

Objective 2 – Studying SSA in ICd neurons

- ICd neurons show SSA to repetitive tone burst stimuli
- ICd neurons almost always fire action potentials to a randomized tone burst stimulus

Objective 3 – Corticofugal modulation of ICd neurons, using a reversible inactivation method.

- Most neurons examined show increase in spike numbers during cooling conditions
- Few neurons show a reduction in response during cooling.
- Preliminary data, thus results are inconclusive.

4 DISCUSSION

4.1 Temporal Response Characteristics in ICd Neurons

Temporal firing patterns of auditory neurons in response to tone burst stimulation is an important reflection of the way in which auditory information is encoded and processed. Neurons in the rat's ICd exhibit a diversity of temporal firing patterns. Some of these firing patterns are similar to those reported for the central nucleus and the external cortex of the IC subdivisions. My results indicate that there are three major categories of firing patterns in the ICd of the rat. Over half of the neurons (53%) demonstrated onset firing including phasic, phasic burst, and fast adapting response patterns. Other neurons (44%) exhibited a sustained firing including primary like, pauser and late response patterns. A small number of neurons (3%) exhibited on/off type of response pattern.

4.1.1 Onset response patterns

Neurons with onset firing patterns may play a role in the detection of onset of sounds. One type of neuron with an onset response fired one or two action potentials at the onset of a tone burst and such a neuron was named as phasic type. Another type of neuron with onset response exhibited a few action potentials at the stimulus onset and was named phasic burst type. Another type displayed a response for a brief period of about 50 ms of a100 ms stimulus duration; this type of onset neuron was named as a fast adapting type. The differences observed in the firing pattern of onset neurons could be attributed to several factors. One important factor is the interplay between excitation and inhibition. An initial excitation followed by inhibition could lead to an onset firing pattern. Another possibility is that neurons showing onset responses

may be driven by inputs that had an onset discharge pattern. Yet another possibility is that the response pattern may be a consequence of the membrane properties of the ICd neurons (Sun and Wu, 2009; Sivaramakrishnan and Oliver, 2001; Syka et al., 2000).

Different neurons with onset responses may play different roles in processing complex stimuli. When presented with two successive tone bursts, onset neurons that mirror an onset temporal characteristic of an input or even those that acquire their response as a result of intrinsic membrane properties may respond well to both tone bursts even when the time between them is short. This is because neurons in lower auditory centers show little suppression to the lagging tone (Fitzpatrick, Kuwada, Batra and Trahiotis, 1995; Parham, Zhao and Kim, 1996). In contrast, onset neurons that reflect an inhibitory input would be expected to respond weakly to the second tone burst at short interstimulus intervals. Such a population of neurons with slow recovery times has been previously observed in IC neurons (Yin, 1994; Fitzpatrick et al., 1995).

It is important to study the response of neurons to paired tone burst stimuli. Paired tone bursts can generate neural responses exhibiting adaptation. Neurons can have strong responses to an initial sound presentation, but little or no firing thereafter. The degree of adaptation and the time for which it lasted depended on the stimulus parameters. Therefore, the study of responses to paired tone burst stimuli may provide insight into the neural mechanisms responsible for stimulus specific adaptations.

4.1.2 Sustained response patterns

The second category of temporal firing found in ICd neurons was the sustained firing pattern. The sustained firing pattern may provide information regarding the duration of the input

signal. Neurons with sustained responses had a discharge of spikes both at the onset and for the remaining of the stimulus duration. These responses fell into three subcategories: primary-like, in which a neuron fired in a continuous fashion throughout the entire duration of the stimulus; the majority of sustained type of neurons in the ICd exhibited this type of response. Pauser displayed continuous late firing which was separated from transient early firing by a brief pause. The brief pause within this type of response may be created by inhibitory input. Finally build-up: this was the type of response where the neuron generated a continuous increase in firing until the end of the stimulus, only after an initial silent period of at least 40 ms.

The sustained firing patterns observed in ICd are similar to those seen in other subdivisions of the IC. Sustained discharge pattern can be generated in a few possible ways. One theory is that the response type may be a consequence of the intrinsic membrane properties of a neuron. Sivaramakrishnan and Oliver (2001) examined intrinsic membrane properties of ICc neurons in brain slices preparations of the rat and suggested that sustained temporal firing pattern is determined by delayed rectifying 4-AP-sensitive K^+ currents that cause sustained firing during an excitatory stimulus.

Another possibility is that the response type can reflect the interplay of excitatory and inhibitory inputs. In the ICd, while excitatory inputs are likely mediated by glutamate, the inhibitory inputs are likely mediated by GABA and glycine. Both GABA and glycine neurotransmitters have been found to influence responses in ICd and ICc neurons (Oliver, Winder, Beckius and Saint Marie, 1994; Sun and Wu, 2009). Further experiments will be necessary to determine the extent to which each of these factors contributes to the sustained response of ICd neurons.

4.1.3 On/Off Response Patterns

On/Off temporal firing patterns exhibit action potentials at the onset as well as shortly after the end of the stimulus presentations. In the current study only 3% of neurons displayed this type of temporal firing pattern. The relatively low percentage of neurons showing On-off firing pattern could be attributed to the present study. The offset response displayed by ICd neurons may be due to an intrinsic mechanism such as rebound from inhibition, or a result from offset excitation via an ascending input (Casseday, Ehrlich and Covey, 1994). The idea that extrinsic offset excitation is absent in some cells is supported by intracellular recordings showing that the size of the inward current that is correlated with stimulus offset decreases as stimulus duration increases. That is, when inhibition has more time to decay before sound offset, the inward current at sound offset is smaller (Covey, Kauer and Casseday, 1996).

4.1.4 First spike latencies in ICd neurons

In the past, studies have illustrated latencies of higher structures to be generally longer and broader than those of lower CAS nuclei (Heil & Irvine, 1997). Research concerning higher CAS structures such as the AC has illustrated that the primary AC fibers have exhibited latencies with variable range however, the majority of neurons exhibited latencies of less than 20 ms (Phillips and Irvine, 1982). Previous studies examining the range of first spike latencies of IC neurons demonstrated that the range is very large and varies anywhere from 5 – 50 ms (Kitzes, Farley and Starr, 1978; Harrison and Palmer, 1984; Park and Pollak, 1993; Klug, Khan, Burger, Bauer, Hurley, Yang, Grothe, Halvorsen and Park, 2000; Fuzessery, Wenstrup, Hall and Leroy, 2003). A study by Syka et al., 2000, examined latency response in all subdivisions of the guinea

pig IC and revealed that a variation in first spike latency was observed more so in the ICd and ICx, which ranged anywhere from 6 to 70 ms. Whereas, in the ICc the latency values were uniformly distributed in individual frequency bands and were much shorter than those revealed by ICd and ICx neurons (Syka et al., 2000).

In agreement with results by Syka et al (2000), our research exhibited that ICd neurons exhibiting a wide range of first spike latencies anywhere from 15.0 – 74.1 ms. The fact that these two subdivisions receive mostly descending input is a plausible explanation for the observation of longer latencies. Neurons with onset and sustained types of temporal responses have different first spike latencies. Onset neurons displayed shorter first spike latencies with a mean of 33.8 ms, while sustained neurons displayed longer first spike latencies with a mean of 42.6 ms. These observations may be attributed to the pattern of connectivity of the different subdivisions of the IC. For example, ICd receives abundant input from the AC, and to a lesser extent some input from ICc. The difference in the first spike latencies suggest that neurons with onset firing patterns might receive major inputs from the ICc while those with sustained firing patterns might receive major inputs from the cortex.

Several other mechanisms may contribute to long response latencies in the ICd. One possibility is the involvement of NMDA receptors (NMDARs). Previous research has shown evidence of the NMDA receptors playing a role in temporal integration and alter timing of neural discharges (Binns, 1999; Kelly and Zhang, 2002). NMDARs have been shown to contribute to both onset responses as well as later responses in IC neurons acting independently of AMPA receptors (Sanchez, Gans and Wenstrup, 2007; Zhang and Kelly, 2001). As NMDARs have slower time courses for activation/deactivation, the involvement of these receptors may result in longer response latencies.

Another possible mechanism which may explain the relatively long first spike latencies in the IC is inhibition. A few studies have suggested that longer latencies are created in part by fast inhibitory inputs that precede excitation (Park and Pollak, 1993; Casseday and Covey, 1995; Covey et al., 1996). A study done by Park and Pollak in 1993 in the IC of the mustached bat, demonstrated that blocking inhibition can reduce response latencies up to 20 ms. It has also been suggested that the large changes exhibited in such a case are in part due to the conversion of response patterns in IC neurons from "off" to "on" discharges. In contrast, much more modest changes in response latencies (<4 ms) have been reported in other studies (Johnson, 1993; Casseday and Covey, 1995; Lu, Jen and Zheng, 1997; Fuzessery et al., 2003). The inhibitory neurotransmitters contributing to longer latency values in the ICd may include GABA. Research utilizing bicuculline, a $GABA_A$ antagonist revealed that application of this drug shortened latency in about half of the cells examined (Park and Pollak, 1993).

The long first spike latencies in the ICd may also be because of the fact that there are intrinsic connections within the IC (Saldaña and Merchán, 1992). In addition to intrinsic innervations, the ICd receives many descending projections from the AC (Diamond, Jones and Powel, 1969; Andersen, Roth, Aitkin and Merzenich, 1980; Druga and Syka 1984; Faye-Lund 1985; Syka, Popelar, Druga and Vlkova, 1988; Druga, Syka and Rajkowska, 1997). It is possible that long response latencies in the ICd are produced by long feedback loops running through corticotectal pathways. In addition, the inhibitory influences of descending fibers on IC neurons have been demonstrated in studies using electrical stimulation of the AC (Syka and Popelár, 1984; Torterolo, Zurita, Pedemonte and Velluti, 1998).

ICd neurons display relatively large magnitude in jitter. Jitter is the deviation in or displacement of some aspect of the first spike from one sweep to the next. This large variation in

jitter seen in ICd neurons may be due to the presence of spontaneous activity. A large magnitude in jitter suggests low temporal precision in these neurons. One study investigating the presence of jitter in the ICc revealed that these neurons have a much lower level and thus higher temporal precision as oppose to that seen in ICd neurons (Zhang, unpublished results). This finding suggests that the difference seen in the degree of jitter between the ICc and ICd may be due to the differences in input that they each receive. Neurons in ICd also showed differences among jitter of onset and sustained type of responses, though the difference between the two was not statistically significant.

4.1.5 Frequency tuning curves (FTCs)

The present study provides information regarding the various types of frequency tuning curves in ICd neurons of the albino rat. The neurons in the ICd of the rat exhibited a wide range of CFs and illustrated response thresholds covering most of the rat's audible range. The neuron's in ICd display at least four types of FTC curves including, V-shaped, U-shaped, W-shaped and complex (see Zhang & Kelly, 2006 for classifications).

One possible conclusion that can be drawn from our data is that FTC types in the ICd do not follow any particular trends, and a variety of shapes exist with a broad range of variability across the entire frequency range. This finding suggests that the commonly found V-shaped FTC discovered in responses of the auditory nerve may in some cases be maintained in higher auditory nuclei, but in many other cases it may be shaped to various degrees by combinations of excitatory and inhibitory inputs as suggested in previous studies (Yang, Pollak and Resler, 1992; LeBeau, Malmierca and Rees, 2001).

The FTC types that I found in ICd neurons of the rat are very similar to those previously described in the ICc of other mammals such as the guinea-pig (LeBeau et al., 2001), mouse (Egorova, Ehret, Vartanian and Esser, 2001), and cat (Ehret and Merzenich, 1988; Ramachandran, Davis and May, 1999) although the percentage of the various types differs across species (V-shaped: 69% in rat, 84% in guinea-pig, 66% in mouse, 12% in cat; non-V-shaped: 29% in rat, 16% in guinea-pig, 34% in mouse; 88% in cat). These differences may be explained, at least in part, by the fact that different authors used different classification methods. For example, all of my different classifications of FTCs were identified as such based on the Zhang and Kelly, 2006 classification method. These differences likely result in minor variations. Other factors such as anaesthetic may also affect results regarding frequency tuning characteristics. It has been ascertained that various anaesthetic regimens may reduce or even abolish the amount of inhibition in response areas (Evans and Nelson, 1973). The differences observed between studies may be attributed to the method in which the breadth of tuning was measured, and how the boundaries between FTCs classes were determined.

4.1.6 The Quality Factor of ICd neurons

The quality factor (Q10) at 10 dB above MT describes the neurons narrowness in tuning. The present study demonstrated that the ICd neurons had Q10 values in a wide range with a mean of 3.78. My results suggest that while some neurons in the ICd are broadly tuned, others are narrowly tuned to single frequency range. My results partially agree with those obtained by an early study indicating that neurons in the ICd were broadly tuned (Syka et al., 2000). Testing tuning width of ICd neurons at higher intensities such as 20 dB or 40 dB above MT may provide further information regarding the tuning of these neurons, as integration between excitation and

inhibition at higher stimulus levels can be influenced by additional mechanisms that are not activated at lower levels.

4. 1.7 Rate Level Functions of ICd neurons

Neurons in ICd display rate level functions (RLFs) similar to those seen in the other IC subdivisions. The present study illustrated that the majority of ICd neurons (64%) exhibited monotonic RLFs. These neurons display an increase in response with stimulus intensity and eventually reach a saturation point. The majority of the monotonic neurons found in the ICd were the onset firing pattern type. Non-monotonic RLFs were present in ICd neurons at a lesser extent (36%). Neurons with non-monotonic RLFs increased their response with stimulus intensity up to a specific sound pressure level. These neurons reduce the strength of firing at even higher stimulus intensities. Neurons with non-monotonic RLFs can have onset and sustained types of response patterns.

The percentage of neurons showing non-monotonic RLFs is different among different auditory structures and different subdivisions of the IC. A study by Rees and Palmer in 1988, examined RLFs in the ICc of guinea pigs using contralateral monaural stimulation and found that the percentage of non-monotonic RLFs in this subdivision was low at approximately 24%. In contrast, Semple and Kitzes in 1985 reported a larger proportion of units with non-monotonic RLFs in response to ipsilateral (41%) versus contralateral stimulation (28%). It seems possible that the number of non-monotonic RLFs during binaural or free-field stimulation would be higher than the number of such units during monaural contralateral stimulation. A study about the response characteristics of neurons in the three-subdivisions of the IC found that the number of non-monotonic RLFs was greater in the ICc (41%) than in the ICd (28%) or ICx (31%) in

response to white noise stimuli (Syka et al., 2000). Similar results were obtained by Palombi and Caspary in 1996 in young adult Fischer rats where the percentage of non-monotonic RLFs was higher (48.3%) in ICc neurons and to a lesser extent only 25.3% in ICx neurons. Studies carried out in the cat revealed similar proportions where they found 41% in the ICc neurons and 21–24% in the ICd or ICx, neurons (Aitkin et al., 1994).

It has been demonstrated previously that the number of spikes in response to sound depends on the excitatory/inhibitory interactions of individual neurons. It has been revealed in the ICc that iontophoretic application of GABA or glycine decreased the firing rate whereas the application of their antagonists, bicuculline and strychnine, increased the firing rate and selectively blocked the firing reduction at the high intensities observed during non-monotonic RLFs (Faingold, Hoffmann and Caspary, 1989; Faingold, Boersma-Anderson and Caspary, 1991; Le Beau et al., 1996; Fuzessery and Hall, 1996; Palombi and Caspary, 1996). It has yet to be determined whether the RLFs in the ICd are also shaped by local inhibitory neurotransmission.

The presence of non-monotonic RLFs may also be related to anaesthesia. Bock, Webster and Aitkin (1972) reported that in non-anaesthetized animals most of the units in the IC had monotonic RLFs. Non-monotonic RLFs have been commonly found in neurons in the auditory centers of unanesthetized animals (Aitkin and Prain, 1974; Brugge and Merzenich, 1973; Young and Brownell, 1976). These results seem to suggest that non-monotonicity in RLF is not necessarily dependent on anaesthesia. Further experiments are needed to determine the role of anesthesia in the creation of non-monotonic RLFs.

The results obtained in my study are consistent with previous investigations of RLFs in the other IC subdivisions (Semple and Kitzes, 1985; Rees and Palmer, 1988; Syka et al., 2000). The

majority of ICd neurons tested displayed monotonic RLFs, with non-monotonic RLFs existing at a much lesser degree. However, the presence of non-monotonic RLFs in the ICd may suggest that this structure is involved in encoding intensity.

4.2 Stimulus Specific Adaptation in ICd neurons

Stimulus specific adaptation (SSA) is likely an active mechanism used for detecting novel sounds. The structural and physiological basis of this phenomenon is yet to be determined. It is likely that in order for novelty response to occur, the nervous system must register and retain information about the history of stimulation. The duration of sensory memory ability in primates has been estimated to be in the order of few seconds (Javit, Steinschneider, Schroeder, Vaughan &Arezzo, 1994; Naatanen & Escera, 2000). Our observation that ICd units show SSA in response to repetitive stimuli presented at interstimulus intervals of one second is consistent with this time scale.

In the present study I found that ICd units appeared to show SSA to a repetitive stimulus pattern. Changes of acoustic parameters such as amplitude or frequency were sufficient to reactivate neurons showing SSA.

My results suggest that not only do neurons in the ICd possess relatively complex computational capacities than that seen in neurons at lower levels of auditory processing, but also that the response may be modulated by an interplay of inhibitory/excitatory projections. ICd is a region that in the rat receives dense innervation from the AC (Herbert, Aschoff and Ostwald, 1991; Saldana, Feliciano and Mugnaini, 1996). This pattern of connectivity raises the possibility that descending projections from cortical neurons synapsing with ICd neurons are specialized to respond to novel stimuli and may contribute to the responses of novelty detection in the IC. Thus, SSA could be inherited from neurons in the AC that provide inputs to the ICd. In this case, it is expected that ICd neurons have longer latencies than those in the AC. SSA could also be created locally in the ICd, in which case local inhibitory neural circuits are required.

Activation of local inhibitory interneurons could interact with excitatory inputs provided by corticofugal descending projections and reduce responses during repetitive tone burst presentations. Studies using electrical stimulation to activate the auditory cortex (Syka and Popelár, 1984) suggested that the IC activity could be modulated by a brief period of excitation due to glutamatergic projections (from the auditory cortex) followed by a long lasting inhibition produced presumably by local inhibitory interneurons. Pharmacological experiments are required to determine whether SSA displayed by neurons in the ICd is shaped by corticofugal projections through feedback loops within the IC or intrinsic properties of ICd neurons or other factors.

4.3 Corticofugal projections and their role in the modulation of ICd neurons

A reversible inactivation technique was used in the present study to inhibit the corticofugal input to neurons in ICd. I have shown that unilateral deactivation of the AC by cooling induces a change in spike numbers of ICd neurons during tone burst stimulation. Out of the twelve neurons obtained to date for this project, seven exhibited an increase in spike numbers during the cooling condition, while five neurons displayed a reduction in response. Most of the twelve neurons analyzed, did not exhibit strong adaptation responses before cooling, thus examining the role of descending projections in SSA neurons was really difficult.

The fact that a change in response was displayed by ICd neurons during the cooling condition can be attributed to the excitatory/inhibitory nature of corticofugal projections. An increase in response indicates the involvement of local inhibitory neural circuits within the IC controlling the response exhibited by ICd neurons (Figure 24). In contrast, the reduction in response would suggest that there is direct excitatory innervation of ICd neurons by the AC.

It has long been known that layer V of the AC sends abundant descending projections to both the ICx and ICd (Winer, 2002) Anatomical research has also suggested that the descending projections from the AC to the IC are in fact excitatory. Acoustic stimulation activates neurons in the AC. The AC then sends excitatory inputs to the ICd. Inhibitory interneurons within the ICd are excited by corticofugal projections and may provide input to other neurons within the ICd. Therefore it is likely that if the AC is cooled, some neurons in the ICd can increase their firing. In the small group of ICd neurons exhibiting a reduction in spike numbers, the likely input to these ICd neurons is a direct excitatory one from neurons in the AC. As the results in the present

study related to cortical cooling are quite preliminary this mechanism of corticofugal projections and their function in processing of sound stimuli in ICd neurons is still quite speculative.

5 CONCLUSIONS

This study represents a comprehensive analysis of responses of single neurons in the ICd of the albino rat. I have demonstrated that a variation of temporal firing patterns exists within this structure. Neurons have a broad range of first spike latencies and latency jitters. I also presented data illustrating ICd neurons display various FTC categories and tuning widths. These data may be utilized for further study of temporal and spectral characteristics when further dissecting the mechanism and functions of neurons in the ICd.

Another finding in the present study is the presence of SSA neurons in ICd. These neurons exhibited a decrease in response when utilizing repetitive blocks of stimulation. However, their response was recovered when some stimulus parameter was changed. The knowledge regarding this phenomenon in ICd neurons is quite scarce, thus the present study provides generous contribution to SSA and their tentative function in central auditory processing.

Corticofugal projections were also studied using a reversible inactivation technique. The use of this method for future study of neurons in ICd and their function in auditory processing may prove valuable. Furthermore, even though the data were quite preliminary and the data set was small, one possible conclusion was that a feedback loop exists between the AC and IC which may explain the changes seen in the majority of ICd neurons studied.

The data obtained in this study serve as a baseline for future investigations focusing on ICd neurons. This data may be used for comparative purposes in pathology-related studies such as age-related hearing loss, tinnitus, audiogenic seizures or other central auditory processing disorders.

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APPENDIX A: EQUIPMENT USED

2400A Preamplifier, Dagan, Minneapolis, Minnesota.

2660 Model Micropositioner, Kopf Instruments, Tujunga, California.

CF1 Closed field speakers, Tucker-Davis Technologies (TDT), Alachua, Florida.

Condenser microphone, ACO Pacific 7017, Belmont, California.

Homeothermic Blanket Control unit, Harvard Apparatus, Holliston, Massachusetts.

RX6 Processor, Tucker-Davis Technologies (TDT), Alachua, Florida.

SA1 Power Amplifier, Tucker-Davis Technologies (TDT), Alachua, Florida.

Stereotaxic Instrument: Kopf Instruments, Tujunga, California.

Single-wall sound-attenuated chamber ,Eckel Industries, Morrisburg, Ontario.

APPENDIX B: CHEMICALS USED

Atropine sulphate, 0.08ml/kg, injected intramuscularly (i.m).

Euthanyl, Pentobarbital Sodium, MW = 248.254 g/mol.

Ketamine hydrochloride, 75 mg/kg, (i.m).

Potassium Chloride, 3M, MW = 74.55g/mol.

Xylazine hydrochloride, 10 mg/kg, (i.m).

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