Neural Mechanisms for Call Processing in the Auditory Cortex of Mustached Bats: Frequency Modulated Sounds and their Lateralization

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Neural Mechanisms for Call Processing in the Primary Auditory Cortex of Mustached Bats:
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Abstract

Speech processing is lateralized to the left hemisphere of the human brain, with some variation between sexes. Single unit electrophysiological recordings in the Doppler-shifted constant frequency processing (DSCF) sub-region of the mustached bat primary auditory cortex (A1) has revealed a left hemispheric advantage for processing species-specific (or conspecific) calls that at least superficially resembles the hemispheric specialization observed in humans. The hemispheric specialization for speech in humans has been related to an advantage of the left auditory cortex for processing information with a high temporal resolution, and, thus, the discovery of a similar mechanism in mustached bats would further demonstrate the similarity between lateralization for communication sounds in humans and bats. The first half of the research described herein is focused on the processing of frequency modulations (FMs) within the DSCF area, which comprises 30-50% of A1 in the bat. The second half is focused on observed hemispheric differences in the FM selectivity of DSCF neurons, specifically the peak response latency and magnitude elicited by FMs of varying slope and bandwidth. Results presented here demonstrate that not only are DSCF neurons responsive to FMs but also the left DSCF area responds more quickly and robustly to steep, broad-band FMs than do right DSCF neurons. Processing of relatively steep FMs requires finer temporal resolution than processing of relatively shallow FMs. Further, on average, hemispheric differences appear to be greater in male as opposed to female bats, reflecting a pattern
previously observed in humans. Since the conspecific calls of bats are largely composed of FMs that widely vary in instantaneous modulation slope, this left hemispheric advantage for processing steep FMs can be considered a mechanism for the previously observed left hemispheric advantage for processing calls.
This dissertation is dedicated to the memory of Glenelle Dolores Clark Washington for over 30 years of contributions to science and for her love and support.
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CHAPTER I:

GENERAL INTRODUCTION
Part I: Specific Aims

Speech processing is lateralized to the left hemisphere of the human brain (Galaburda, 1995; Geschwind and Levitsky, 1968; Sperry, 1962), though sex may influence the extent of this lateralization (McGlone, 1977). Indications of a similar lateralization for processing communication sounds have been observed in the brains of bats, mice, and macaques (Heffner and Heffner, 1984; Ehret, 1987; Hauser and Andersson, 1994). In the mustached bat (Pteronotus parnellii), single neuron recordings from the Doppler-shifted constant frequency processing (DSCF) area indicate that processing of the bat’s richly varied communication sounds (or calls) is lateralized to the left hemisphere (Kanwal et al, 1994; Kanwal and Suga, 1995). However, virtually nothing is known about the neural mechanisms and circuitry underlying this asymmetry. Two important questions define the specific aims of this proposal. These will test the central hypothesis stated below.

Hemispheric inequalities in FM selectivity produce an asymmetry in the call response properties of A1 neurons.

Aim 1: Are DSCF neurons responsive to and selective for linear FMs?

Chapter III: Neurons within the Primary Auditory Cortex Extract Multiple Parameters Of Frequency Modulations within Social Calls

Neurons in the central (DSCF) region of the primary auditory cortex (A1) respond not only to constant frequencies (CFs) but also respond to broad-band, frequency modulated species specific vocalizations (or calls). DSCF neurons have two excitatory response areas that are flanked by inhibitory frequency response areas (Kanwal et al, 1999). How a call interacts with an A1 neuron’s excitatory and inhibitory response areas determines whether the call will elicit a response from that neuron. Inhibitory response areas may influence excitatory response areas in such a way as to sharpen a neuron’s frequency tuning. These inhibitory “side bands” may also have a differential effect on temporal response properties of DSCF neurons. Here, I measured the relative response magnitudes, thresholds, and selectivity to frequency modulated sweeps (FMs) in DSCF neurons, bilaterally, for each animal. I was thus able to determine whether DSCF neurons have a preferred sweep speed (FM slope), sweep direction (positive or negative FM slope), bandwidth (difference in the initial and terminal frequency), and range (values of the initial and terminal frequencies of an FM that are proportional to its central frequency). I hypothesize that individual DSCF neurons have a preference for FM slope, direction, bandwidth, and range that underlies their selectivity for species-specific calls.

Aim 2: Do differences in FM response properties between left and right DSCF neurons underlie hemispheric lateralization for call processing?

Chapter IV: Neural Mechanisms for Hemispheric Lateralization for Call Processing in the Primary Auditory Cortex of the Mustached Bat

Left DSCF neurons respond more to species-specific calls than do right DSCF neurons (Kanwal and Suga, 1995). The lateralization of human speech processing to the left auditory cortex has been related to an advantage of the left auditory cortex for processing rapid formant transitions, a type of FM signal (Belin et al, 1998; Robin et al, 1990; Tallal et al, 1993). In humans, this lateralization is less pronounced in females than in males (Landsell, 1962; McGlone, 1977; Shapleske et al 1999). If the left hemispheric specialization for calls in the DSCF area is an evolutionary homologue to the lateralization observed in the human auditory cortex, then an advantage for processing relatively rapid (or steep) FMs would be expected in left DSCF neurons. Here, I compared the peak response magnitudes of left and right DSCF neurons elicited by the presentations of a series of FMs with 14 different slopes (0.04-4.0 kHz/ms) and 18 different bandwidths (0.66-7.88 kHz). I hypothesize that left DSCF neurons have a greater capacity to respond to FMs with steeper slopes and broader bandwidths than do right DSCF neurons and that this difference could be sexually dimorphic.
Part II: BACKGROUND AND SIGNIFICANCE

STUDIES OF SPECIES-SPECIFIC VOCALIZATIONS

The survival of communities of social animals depends on the auditory systems of conspecifics, which are capable of detection, discrimination, recognition, and interpretation of vocalizations (Kanwal, 1999). Recognizing and discriminating between species-specific communication sounds, hereafter referred to as "calls", are thus major functions of the auditory system that facilitate social interactions. The acoustic structures of naturally occurring sounds such as calls are often comprised of multiple harmonics, frequency modulations (FMs), and amplitude modulations (AMs). The power spectrum, amplitude, and temporal pattern for a type of call may vary with the emitter, behavioral context, and relative location of the receiver (Gould, 1983; Ohlemiller et al, 1994; Snowdon, 1982). It remains unclear how the auditory system can recognize a particular type of conspecific call, despite spectral variations caused by differences in speaker identity and affective state.

Calls, like all natural sounds, are composed of one or more of the fundamental three basic acoustic patterns (BAPs): constant frequencies (CFs or tones), frequency modulations (FMs), and noise bands (NBs). A CF is a single frequency and as such has a bandwidth ($\Delta f = f_{\text{terminal}} - f_{\text{initial}}$) that is equal to zero. CFs do not change in spectral composition over time and are thus not spectrally dynamic sounds. An NB is composed of a distribution of simultaneous spectral energies. The definition of NBs does not necessitate that these sounds change in spectral composition over time. FMs are defined as changes in spectral composition as a function of time. In their simplest, linear form, complete descriptions of FMs require knowledge of FM bandwidths, FM slopes ($\Delta f/\Delta t$, where $\Delta t = t_{\text{terminal}} - t_{\text{initial}}$ and $\Delta f = f_{[t_{\text{terminal}}]} - f_{[t_{\text{initial}}]}$), FM center frequencies (here, the midpoint between $f_{\text{terminal}}$ and $f_{\text{initial}}$), and FM amplitudes. Linear FM slopes can be either positive (upward) or negative (downward), and this direction of modulation has traditionally been considered a fifth descriptor (Erulkar, 1965).

Studies of the spectral composition of calls reveal that the majority of bat (Kanwal et al. 1994; Ma et al. 2006), bird (Margoliash 1983; Marler and Pickert 1984), frog (Fuzessery and Feng 1983), monkey (DiMattina and Wang 2006; Hauser 1991), rat (Boinski and Mitchell 1995; Brudzynski 2005), and whale (Payne and McVay 1971) calls contain FMs. Likewise, a type of FM called a formant transition is an
integral component of human speech sounds (Liberman et al. 1967). Until recently, however, much of our understanding regarding the response profiles of auditory neurons was based on excitatory tuning to CFs. CFs have been useful for addressing psychoacoustical and neurophysiological questions such as the frequency mapping of the auditory cortex (Imig et al. 1977; Merzenich et al. 1975; Reale and Imig 1980; Woolsey and Walzl 1942). The cochleotopic organization of the primary auditory cortex (AI) was elucidated by these classical studies (see Fig 1A). CFs have also been used to study of the perception of pitch (Fishman et al. 2000; Zatorre et al. 1994). Despite their beneficial uses in these classical auditory studies, CFs, by definition, do not capture the spectral dynamics within calls and would therefore be inadequate to predict neural responses to calls. This inadequacy became apparent in some of the earliest studies of call processing in which the excitatory frequency tuning of nearly 50% of auditory cortex neurons in squirrel monkeys could not predict whether they would or would not respond to conspecific calls (Newman and Wollberg 1973; Winter and Funkenstein 1973).

More recent studies have focused on the neural representations of FMs in AI and have used a variety of different FM classes, including linear (Heil et al. 1992a; b; Heil and Scheich 1992; Nelken and Versnel 2000), logarithmic (Mendelson et al. 1993; Zhang et al. 2003) and sinusoidal FMs (Liang et al. 2002; Suga et al. 1983a). These studies mapped representations of FMs in AI by determining the FM direction (Fig 1B) and FM rate (Fig 1C) that elicited peak responses from multi-unit clusters and, in some cases, from single units. In ferrets and cats, FM slope was systematically organized within A1 along the isofrequency axis for both linear and logarithmic FMs whereas the distribution of FM direction is dependent upon the experimental paradigm and animal model (Heil et al. 1992b; Mendelson et al. 1993; Nelken and Versnel 2000). The A1 neurons of cats are often selective for multiple linear FMs that vary in slope between 1-10 kHz/s, and the majority of these neurons have a downward preference (Heil et al. 1992a). Although these studies clearly demonstrate the existence of FM maps in AI, they also demonstrate that these FM maps depend on the class of FMs, the species under study, and even the individuals tested.

STUDIES OF ECHOLOCATION IN MUSTACHED BATS

Behaviorally relevant stimuli have been previously used to study the functional organization of the
Figure 1. Multiple Representations of Acoustic Signals in the Primary Auditory Cortex (AI). Topographic maps derived from the AI of 3 different squirrel monkeys (*Saimiri sciureus*) are shown in the columns labeled Animal 1-3. The left hemispheres of Animals 1 and 3 and the right hemisphere of Animal 2 are presented. Two-dimensional non-parametric local linear regression (LOESS) has been applied to each of these topographic maps in order to make spatially coherent aggregates and gradients more easily identifiable. (A) A cochleotopic map of neuronal tuning to frequencies ranging from 0.5-16 kHz. The color bar on the right shows how particular colors correspond to the preferred frequencies of multi-unit clusters. (B) A map of neuronal selectivity for frequency modulation (FM) direction. Selectivity has been determined using direction selectivity index (DSI) values (see Chapter II: General Methodology). The color bar on the right shows how particular colors correspond to DSI values of multi-unit clusters. (C) A map of neuronal preference for FM rate. The color bar on the right shows how particular colors correspond to the preferred FM rate of multi-unit clusters. Note that FM rate is used here to describe any change in frequency as a function of time. When an FM rate is described for a linear FM, it is called an FM slope and uses some unit multiple of Hz/sec (such as kHz/ms). The study from which these data are derived used logarithmic FMs and thus the units of octaves/sec are more appropriate. (Adapted from Godey et al, 2005 with the spoken permission of Craig Atencio, PhD).
auditory cortex of the mustached bat (*Pteronotus parnellii*) as it relates to echolocation (Suga 1978).

During echolocation, mustached bats emit sounds that are composed of a fundamental tone and downward FM (DFM) and the three harmonics thereof. These four signals (fundamental + 3 harmonics) are labeled $H_1$–$H_4$, where the fundamental and each harmonic are composed of a CF ($CF_1$–$CF_4$) component and a DFM ($FM_1$–$FM_4$) component (Fig 2). While in flight, a bat hears both its emitted and echoed pulses. When the bat hears the returning echo pulse, the echo pulse has been Doppler-shifted upward in frequency relative to the bat’s emitted pulse. At this time, there is the possibility of temporal overlap between the emitted and echo pulses. The auditory periphery of the mustached bat has thus evolved an enhanced sensitivity to the echo-$CF_2$ (between 57-59 kHz in *Pteronotus parnellii rubiginosus*; see Xiao and Suga, 2002) and is relatively insensitive to the emitted $CF_2$, minimizing masking of the echo pulse by the emitted pulse.

From the cochlea, echolocation signals are transduced and processed by multiple nuclei, via the mammalian central auditory pathway (Fig 3), en route to the auditory cortex. The auditory cortex of the mustached bat contains neurons that are responsive to combinations of the components of the emitted $H_1$ and echo $H_2$–$H_4$ such that combinations of particular components elicit a greater response (e.g., a greater number of action potentials, or higher peak response magnitude) than the sum of the responses to each component presented alone (Suga et al 1978; Suga et al 1983b). This concept is called facilitation and neurons that are facilitated by combined components of more complex sounds are referred to as “combination-sensitive” neurons. The CF|CF area is a portion of the non-primary auditory cortex of the mustached bat that is functionally organized into columns such that each column is tuned to a particular combination of frequencies (Fig 4). CF|CF neurons of these CF combinations, and are thus have spectral combination-sensitivity. These neurons are thus sensitive to the magnitude of Doppler-shift between the pulse and echo, which enables them to process relative velocity (Suga et al 1978; Suga et al 1983b).
Figure 2. Salient Features of Mustached Bat Echolocation Signals. Illustrations of spectrograms (horizontal axis: time [ms]; vertical axis: frequency [kHz]; intensity axis: amplitude [dB-SPL]) of (A) complete echolocation signals and (B-D) features of those same echolocation signals that facilitate the responses of combination-sensitive neurons in the mustached bat auditory cortex. Solid lines represent the emitted pulse and the non-vertical hatched lines represent the upward, Doppler-shifted echo pulse. Upward vertical lines appended to a gray box labeled “delay $\Delta t$" represent the onset of an inter-stimulus-interval (or delay) and downward vertical lines represent the offset of such a delay. (A) $H_1$-$H_4$ represent the fundamental + 3 harmonics of the complete echolocation signal and $CF_1$-$CF_4$ and $FM_1$-$FM_4$, respectively, represent their CF and FM components. Note that the $H_2$ has a greater amplitude (as shown by the greater line width) than either the $H_1$, $H_3$, or $H_4$. The translucent gray bar shows potential overlap between the emitted and echo pulses. (B) Stimuli that facilitate $CF|CF$ neurons. The first box shows stimuli that would facilitate responses from the most common type of $CF|CF$ neuron, a $CF_1|CF_2$ type (Suga et al 1983b). The second box shows stimuli that would facilitate responses from another type of $CF|CF$ neuron, a $CF_1|CF_3$ type. Note that the CF pairs that facilitate $CF|CF$ neurons are simultaneously presented, thus having no delays. Independent of harmonic preference, $CF|CF$ neurons can be responsive to either emitted CF pairs, like the first box, or echo CF pairs, like the second. (C) Stimuli that facilitate $FM|FM$ neurons. The first box shows stimuli that would facilitate responses from the most common type of $FM|FM$ neuron, an $FM_1$-$FM_3$ type. The second box shows stimuli that would facilitate responses to a less common type of $FM|FM$ neuron, an $FM_1$-$FM_3$ type. Note that each of these neurons, regardless of harmonic preference, is selective for a unique delay between the emitted and echo FM. (D) Stimuli that facilitate $DSCF$ neurons. The first box shows that the echo $CF_2$ and emitted $FM_1$ are facilitatory stimuli for a $DSCF$ neuron provided that an appropriate delay exists between them. The second box shows that simultaneous pairing of a CF in the $FM_1$ range (or $BF_{low}$) and a CF in the echo $CF_2$ range (or $BF_{high}$) will also facilitate a $DSCF$ neuron. Facilitation elicited by these stimuli is similar (Fitzpatrick et al 1993; Kanwal et al 1999). Note that the echo $CF_2$ has been lowered in this example relative to its position in previous examples.
Another portion of the non-primary auditory cortex that is tuned to combinations of pulse echo pairs is the FM-FM area (Fig 4). The FM-FM area contains neurons that are responsive to pairs of DFMs (e.g., pulse FM$_1$ and echo FM$_2$ or echo FM$_3$) and are selective for particular time intervals (or delays) between those DFMs. FM-FM neurons are facilitated by the temporal integration of the FM signals, and thus, FM-FM neurons have temporal combination-sensitivity. This tuning to echo delays in the FM-FM area enables FM-FM neurons to process target range (Suga et al 1978; Suga et al 1983b).

Likewise, the AI of the mustached bat also contains a set of combination-sensitive neurons. An expanded representation of a single frequency band corresponding to the Doppler-shifted echo CF$_2$ exists within the cochleotopic axis (Fig 4). The functional area containing this overrepresentation is called the Doppler-shifted constant frequency (DSCF) processing area and occupies between 30-50% of the mustached bat’s AI (Suga et al. 1983b). The CF that best elicits a response from a DSCF neuron in the echo-CF$_2$ frequency range is referred to as that neuron’s BF$_{high}$. Neurons within the DSCF area not only respond to their BF$_{high}$, but pairing the BF$_{high}$ of each neuron with the FM$_1$ also results in a facilitated response. Facilitation elicited by combining the BF$_{high}$ and the FM$_1$ is temporal in DSCF neurons such that particular delays between the two stimuli elicit greater responses than do others (Fitzpatrick et al 1993). In addition, DSCF neurons possess spectral combination sensitivity such that combining (without delay) the BF$_{high}$ with the single CF that best elicits neural responses in the FM$_1$ frequency range (or the BF$_{low}$) also facilitates these neurons (Kanwal et al. 1999).

Although the spectral combination sensitivity that is observed in the CF|CF and DSCF areas has the behavioral function of velocity calculation, its physiological functionality is similar to the communication-related spectral combination sensitivity that was subsequently observed for calls in the lateral belt of the rhesus macaque (Rauschecker and Tian 2000). Likewise, the physiological functionality of the range-calculating FM-FM area is similar to the communication related temporal combination sensitivity that was subsequently observed in the auditory forebrains of songbirds (Margoliash 1983). The knowledge that similar mechanisms underlie both echolocation in mustached bats and call processing in other mammals underscores that the echolocation specialized neurons of the CF|CF, FM-FM, and DSCF areas are also capable of processing conspecific social calls of mustached bats. The work of Kanwal
and colleagues demonstrated these echolocation regions are multi-functional such that they process both the echolocation and the conspecific communication signals of mustached bats (Esser, 1997; Kanwal 1999; 2006). The following section discusses Kanwal and colleagues’ classification of mustached bat calls, determination of their behavioral relevance, and studies of how bat calls are processed by the combination-sensitive neurons in the mustached bat auditory cortex.

AUDITORY CORTICAL NEURON RESPONSES TO CONSPECIFIC BAT CALLS

Kanwal et al (1994) used multi-dimensional scaling to classify and describe mustached bat calls using BAPs. Examples of common mustached bat calls and their descriptive nomenclature are the long quasi-CF (QCFI), true-CF (TCF), bent-upward FM (bUFM), fixed-sinusoidal FM (fSFM), and rectangular broad-band noise burst (rBNB). Unlike the repeating, stereotypic call sequences of frogs and song birds, mustached bats emit a variety of simple syllabic calls (e.g. fSFM) and calls that are composed of a combination of simple syllables (e.g., fSFM → bUFM). These composite calls reveal a phonetic-like syntax in their communication. For instance, if bats were to independently combine simple syllables to create composites, their call repertoire would include 342 different disyllabic composites. However, mustached bats emit less than 15 such composites. Mustached bats not only form composites in a non-random fashion, but also the order of simple syllables within a composite is important and is not shuffled during natural vocalizations. Further, only 11 of the 19 simple call syllables identified are used to construct composites (Kanwal et al 1994). Although communication amongst mustached bats may lack the verbal and linguistic complexity of human language, bat communication is syntactically similar to human speech and surpasses the complexity of calls in nonhuman primates. Among mammals, only the calls of dolphins and whales appear to be equally or more complex than that of different species of bats (Marler and Pickert 1984; Payne and McVay 1971; Wilkinson et al 1998).

Detailed analyses of mustached bat social behaviors and the calls emitted therein have elucidated the behavioral relevance of some calls (Clement et al 2006). The rBNB and fSFM call syllables, for example, are often emitted during aggressive interactions, whereas the QCFI call syllable is commonly emitted during the appeasement of an aggressor. The bUFM and TCF call syllables have been associated with fear. The pRFM (paraboloid rippled-FM) and sRFM (stretched rippled-FM) are
associated with defiance and warnings and could be used to maintain the “personal space” between animals in a colony.

The complexity of mustached bat calls is a consequence of their multiple modulations of frequency and amplitude as well as their harmonic structures. Despite the complexity of calls, it is shown here that portions of the bat auditory cortex are capable of temporally and spectrally integrating multiple acoustic components of the echolocation signal. The social calls of mustached bats are behaviorally relevant stimuli and are not as stereotypic as their echolocation signals. Variations in the acoustic structure of a single call, both within a single animal’s vocalizations and amongst the vocalizations of different animals, are a hallmark of audiovocal communication in virtually all species, including humans.

Both temporal and spectral integration (in the form of combination-sensitivity) contribute to the processing of species-specific calls in mustached bat auditory cortical neurons. FM-FM neurons are temporally combination-sensitive to composite calls (Esser et al 1997; Kanwal 1999; Ohlemiller et al 1994). Responses of FM-FM neurons are significantly diminished if the delay between the simple syllabic components within composites is greater than the naturally occurring inter-syllable-interval. Furthermore, the reversal of syllable order in a composite call also significantly diminishes FM-FM neuron responses to that composite, as does the complete reversal of a composite call. FM-FM neurons may also be considered to be spectrally as well as temporally combination-sensitive; FM-FM neurons require both a specific combination of spectral bands that overlap with the spectrally broad excitatory FM$_1$-FM$_n$ bands as well as the correct time structure of syllables to respond to a composite call.

In contrast, the call-elicited responses of the DSCF neurons studied to date primarily display spectral combination-sensitivity (Kanwal 1999). When call components that fall within the two excitatory response areas of DSCF neurons are extracted from the complete call and presented together, DSCF neurons show clear facilitation with a response that is at least 20% greater than the sum of the responses to each component alone. Combinations of bandpass-filtered call components often elicit a larger response magnitude than the complete natural call due to the lack of spectral energy in the
Figure 3. Central Auditory System of an Echolocating Bat. Both cochlear nuclei (CN) receive input from the ipsilateral ear via cranial nerve VIII (or the auditory nerve). Nuclei in the monaural pathway are symbolized by rectangles and nuclei in the binaural pathway are symbolized by triangles. **Monaural Pathway to IC:** The CN projects directly to the contralateral inferior colliculus (IC). The CN also projects to the contralateral nuclei of the lateral lemniscus (LL). These nuclei include the multi-polar cell region of the ventral nucleus (VLLm), the columnar region of the ventral nucleus (VLLc), and the intermediate nucleus (INLL). Each of these LL regions projects to the IC. Thus the IC receives direct and indirect monaural inputs from the contralateral ear. **Binaural Pathway to IC:** The CN bilaterally projects to the superior olivary complex (SOC), which in turn bilaterally projects to the dorsal nucleus of the LL and the IC. The DLL bilaterally projects to the IC as well. **IC to AC:** The IC projects to the medial geniculate body (MGB) of the thalamus, and the MGB projects in turn to the auditory cortex (AC). The AC sends descending contralateral and ipsilateral projects back to the IC.
Figure 4. Functional Organization of the Mustached Bat Auditory Cortex. Lateral view of the mustached bat’s brain showing the organization of functionally defined subdivisions of the auditory cortex. (a), A1-anterior; (b) A1-posterior; (c) DSCF area; (d) CF|CF area; (e) DIF area; (f) FM-FM area; (g) dorsal fringe (DF) area; (h) ventral fringe (VF) area; (i) dorsomedial (DM) area; (j) tiny enclosed (TE) area; (k) H1-H4 area; (l) ventroanterior (VA) area; and (m) ventroposterior (VP) area. The known call-responsive areas of DSCF, Ala, Alp, CF|CF, and FM-FM are labeled (adapted from Suga et al, 1984).
components is rare in the DSCF area, despite their tuning to the delay between the CF$_2$ and FM$_1$ (inhibitory response areas. As for the involvement of temporal integration, delay tuning to call see Fitzpatrick et al 1993). Selective, high magnitude responses to calls in the DSCF area thus appear to be based on spectral facilitation alone.

Certain aspects of the mechanism of call processing in the mustached bat auditory cortex remain elusive. For example, the DSCF area has been defined as a region that is specialized for processing CFs (Suga et al 1978), yet the majority of neurons neurons in this region are also responsive to CFs and broadband, often frequency modulated, calls (Kanwal and Suga 1995; Kanwal 1999; Kanwal and Rauschecker 2007). The mean width of excitatory frequency tuning in the echo-CF$_2$ range of a DSCF neuron is 1.35 kHz ($\pm 0.18$ s.d.) when CFs are presented in isolation. When CFs in the echo-CF$_2$ range are paired with the BF$_{low}$, the mean resultant excitatory (or facilitatory) frequency tuning width of the echo-CF$_2$ range is 1.71 kHz ($\pm 0.25$ s.d.). The excitatory echo-CF$_2$ range (which includes the BF$_{high}$) of a DSCF neuron is always flanked by broad inhibitory side-bands (Kanwal et al 1999). Depending on the amplitude at which a call is presented, a 10 kHz FM call harmonic that is centered at BF$_{high}$ would be expected to inhibit DSCF neuron responses to a greater extent than it would elicit them. Nevertheless, it is common for DSCF neurons to be excited (or even facilitated) by such multi-harmonic, broad-band FM calls (Kanwal 1999).

Another elusive aspect of call processing in the DSCF area is the observation by Kanwal and Suga (1995) that left hemispheric DSCF neurons are more responsive to calls than right DSCF neurons. This study of DSCF neurons showed that neurons in both hemispheres were facilitated by simultaneous CF pairs in the echo-CF$_2$ and FM$_1$ ranges. However, compared to ~50% of left DSCF neurons, less than 20% of right DSCF neurons showed an equivalent or greater response to the best call than to pairings of the BF$_{low}$ and BF$_{high}$. Understanding the neural substrates of this hemispheric asymmetry is crucial for determining if this asymmetry is in any way related to the left hemispheric lateralization of speech perception that is observed in the human brain (Geschwind and Levitsky, 1968; Sperry, 1962; Galaburda, 1995).

Although the DSCF area has been defined as a spectrally combination-sensitive, CF-specialized processing region, it is also a sub-region of the mustached bat AI. If the mustached bat AI has the
same functional organization as AI in other mammalian species, then the CF-specialization of the DSCF area would not necessarily negate the existence of representations of FM rate (or slope) and direction. If DSCF neurons had a preference for slope, direction, or other FM parameters, these preferences could be substrates for the call selectivity observed in the responses of these neurons. Demonstrating the existence and elucidating the mechanisms of FM parametric preferences in DSCF neurons would not only potentially aid in the understanding of neural substrates for call processing but might also explain the asymmetric representation of calls in the left DSCF area.

The aim of the research outlined in the subsequent chapters is to demonstrate how the FM selectivity of AI neurons contributes both to the neuronal selectivity of calls and to the general communication related phenomenon of hemispheric lateralization for calls. These research questions were addressed using single neuron, in-vivo electrophysiological data obtained from the DSCF areas of awake mustached bats. It must be noted that, although this dissertation refers to numerous studies of FM representations in AI, topographic mapping of FM representations in the DSCF area was never a goal of the studies summarized in this dissertation.

**Part III: Specific Research Questions and Hypotheses**

The fact that a multidimensional cortical representation of communication sounds is integrated within the cortical representation of echolocation signals in the mustached bat (Kanwal 2006) raises a number of questions about multiple representations within sensory cortex. Based on studies of AI in other species, the cortical representation of calls could be manifest in a distributed representation of FM slope and direction that is integrated into the iso-frequency axis. Though these representations are known to exist in AI, there have been only a few efforts to show that call responsive portions of auditory cortex are also selective for FMs (Tian and Rauschecker 1995; 2004; Wang et al 1995; 2003). Rarely have studies actually compared single neuron responses to calls and synthesized FMs in order to determine the extent to which FM preference underlies call selectivity.

My choice of animal model as well as the choice to restrict all studies outlined here to the DSCF area had multiple rationales. Mustached bats were selected as the animal model, because the auditory system of the mustached bat has been studied in finer detail than the auditory systems of most
mammalian species. There were three reasons for restricting these studies to the DSCF sub-region of AI. First, with few exceptions, most studies of FM representations in the auditory cortex have been restricted to AI. Second, the DSCF area is the largest portion of AI, is combination-sensitive, and is also call selective (Kanwal 1999); other portions of AI, such as posterior-AI (or Alp), are neither combination-sensitive nor call selective (Medvedev and Kanwal 2004). Third, there is an asymmetric representation for calls in the left DSCF area, but whether or not a similar asymmetry exists in the FM-FM or CF|CF processing areas is unknown and could be time prohibitive to satisfactorily establish. A prudent approach to an investigation of the neural substrates of hemispheric asymmetry for call processing would be to restrict this investigation to a region of the auditory cortex that has been shown to be asymmetric.

The chapters of this dissertation are organized in the following ways. Chapter II of this dissertation covers the stimulus paradigms, general electrophysiological methodology, and methods of analysis that were used in each study described in the subsequent chapters. Chapter III examines the FM response characteristics of DSCF neurons resulting from changes in FM slope, bandwidth, center frequency, and direction, and further relates this “FM tuning” to call responsiveness and call selectivity. Chapter III directly addresses the question: Are DSCF neurons responsive to and selective for linear FMs? Chapter IV examines whether left and right DSCF neurons differ in their responses to FMs. The results in Chapter IV are aimed at answering the question: Do differences in FM response properties between left and right DSCF neurons underlie hemispheric lateralization for call processing? Chapter IV ends with a discussion of the results of the lateralization study in the context of theories on the neural-acoustic substrates of call and speech perception with an emphasis on hemispheric asymmetry.
CHAPTER II:

GENERAL METHODOLOGY
All procedures and analyses used in the subsequent studies described in this volume are explained in this chapter. However, animal acquisition and maintenance, and data recording procedures were similar to those previously described (Kanwal et al. 1999; Medvedev and Kanwal 2004) and are only briefly described below. Stimulation presentation and data analysis procedures unique to these experiments are described in greater detail.

**Surgery and recording of neural activity**

Wild-caught Trinidadian mustached bats (*Pteronotus parnellii rubiginosus*) were transported to and housed in the Research Resource Facility at Georgetown University. Under isoflurane/air mixture (medical grade, Anaquest) anesthesia, a skin incision was made along the midline of the head, and a 2-mm-diameter metal post was glued (cyanoacrylic, Loctite 411) immediately caudal to the intersection of the sagittal and coronal sutures. Bats were allowed to recover for > 3 days before the first recording session.

Each bat was restrained during electrophysiological recordings by clamping the metal post, and the body was suspended in a Styrofoam mold by elastic bands in a heated (31°C), sound-proof, and echo-attenuated chamber (IAC 400A). A video camera was used to monitor the bat during recording procedures. The electrophysiological activity of single neurons was recorded using custom-made, sharpened, vinyl-coated tungsten-microelectrodes with tip diameters of ~10 µm and impedances of >1 MΩ. Electrodes were inserted into the cortex perpendicular to the skull to a depth of 300-650 µm through a 50 µm hole. A second tungsten-microelectrode (<1 MΩ impedance) was inserted through the dura mater in a non-auditory area and acted as a reference for differential recordings. Electrical signals acquired by the recording electrode were amplified by an AC preamplifier and band-pass filtered between 300 Hz – 3000 Hz. All methods and procedures used in this study were approved by the Georgetown University Animal Care and Use Committee.
Experimental design and data acquisition

To test neural responses, three types of stimuli were used: CFs, linear FMs, and conspecific, simple syllabic social calls. CF stimuli were generated using custom-made function generators, whereas FMs were digitally synthesized. Frequency-shifted variants of pre-recorded social calls (Clement et al. 2006) were presented using SIGNAL software (SIGNAL 3.0, Engineering Design, Inc.) running on a personal computer (Pentium, Intel, Inc.) with an A/D-D/A board (DT2821G). All manipulations of social calls and FMs (including filtrations and deletions) were performed using SIGNAL software. All CFs were 30 ms in duration. FMs ranged in duration between 0.5 to 200 ms. The duration of social calls ranged from 4 to 89 ms. CFs were presented from two condenser speakers that were flat (±6 dB SPL) between 20-120 kHz. FMs and social calls were delivered via a leaf-tweeter speaker that was flat (±3 dB SPL) between 5 and 100 kHz. All stimuli had a 10 ms onset delay relative to the acquisition of data on each trial. CF and FM stimuli were presented at a rate of 4 per second. Social calls and related stimuli, such as filtered “call fragments,” were presented at a rate of 2 per second. The initial and terminal 0.5 ms of all CF and FM stimuli were tapered in amplitude.

Subsequent examples of experimental stimuli are presented here as amplitude envelopes (volts) and spectrograms (kHz). Amplitude envelopes are presented in volts, because all experimental stimuli were electronically synthesized. Certain components of the amplitude envelopes and spectrograms shown below are colored in black and others are colored in white. Amplitude envelope and spectrogram elements that are colored in black were constructed from actual stimuli generated by SIGNAL 3.0, and amplitude envelope and spectrogram elements illustrated by white bars represent CF stimuli synthesized by function generators. In most cases, amplitude envelopes and spectrograms are shown relative to a time axis of between 50-100 ms in order to make them compatible for juxtaposition with peri-stimulus time histograms (see below). The 0.5 ms tapering at the beginning and end of all CF, and FM stimuli are thus not readily apparent from amplitude envelopes and spectrograms presented here.

Call selectivity and responsiveness were determined using methods previously described (Ohlemiller et al. 1994). Briefly, social calls were classified by basic acoustic parameters (or BAPs, which are CFs, FMs, and NBs) using a multidimensional scaling procedure (Kanwal et al. 1994). Digital techniques were used to decompose the social calls into frequency and amplitude components and were then
Figure 5. Experimental Design and FM Stimuli. (A) Flow chart depicting the experimental design to determine the parameters for the best FM stimulus at each recording location. Each FM array was composed of 15 stimuli: a no-stimulus control, 13 or 14 FMs, and (when the array had only 13 FMs) a CF in the BF<sub>high</sub> range. Each FM-array was repeated 100 times. Per every 10 repetitions, the stimulus level of each FM was attenuated by 10 dB SPL over a total range of 91 to -9 dB SPL. (B) Spectrograms of 5 upward FMs (S1-S5) with equal bandwidths (10 kHz) and center frequencies (60 kHz) but different durations and thus different slopes. Actual FM slope array contained 14 FMs. (C) Spectrograms of 5 upward FMs (B1-B5) with equal slopes (1 kHz/ms) and center frequencies (60 kHz) but different durations and thus different bandwidths. The actual FM bandwidth array contained 13 FMs. (D) Spectrograms of 5 upward FMs (R1-R5) with equal slopes (2 kHz/ms), bandwidths (10 kHz), and durations (5 ms), but different center frequencies and thus different frequency ranges. The actual FM range array contained 13 FMs. All spectrograms were generated by the same SIGNAL script that generated the FM arrays used in this study.
reconstituted with a new fundamental frequency. Six frequency variants (3 that varied from 1-3 standard deviations (s.d.) above and another 3 that varied from 1-3 s.d. below the mean fundamental) were generated for each of the 14 calls presented in this study. By changing the harmonic structure in this approximately natural and commensurate manner, this method imitates the natural spectral and temporal variations of social calls that may be indicative of affective changes or may signify an emitter's identity.

Pairs CFs in the range of the FM$_1$ and CF$_2$ were presented in order to identify DSCF neurons. Single DSCF neurons were identified as clusters of waveforms plotted across multiple dimensions from a sample of spontaneous and response activity (e.g., peak height versus peak time) using SciWorks software (Datawave Technologies, Inc). The frequencies were systematically increased and decreased at successively increasing amplitude levels to obtain the facilitatory response areas of single DSCF neurons. This procedure also provided the values for the BF$_{low}$ and BF$_{high}$ for each neuron. The lowest threshold was determined by decreasing the amplitude levels so that response activity was barely above the spontaneous level of activity. This threshold was determined by observing the response on an on-line dot raster plot of the responses. Final determination of the value of BF$_{high}$ and its best amplitude (BA) for facilitation was made with the simultaneous presentation of BF$_{low}$ at 10 dB SPL above threshold. Finally, a CF pair was presented with each CF at its BF and BA to obtain a peri-stimulus time histogram or PSTH. These histograms, calculated on-line by summation of spike trains over repeated trials, were used to measure the neuronal response that represents a stimulus-locked change in the peak response magnitude. This peak in the PSTH obtained in response to the reference stimulus was used to monitor the stability of the preparation when studying the response to various FMs.

FM stimuli were linear modulations of frequency in the BF$_{high}$ range (approximately 57-60 kHz). The procedure for studying FM response characteristics is shown in the form of a flow chart in Fig. 5. Variations in 3 parameters of FM stimuli were studied namely, FM slope (or rate of frequency change, in kHz/ms), FM bandwidth (or the difference between the highest and lowest frequencies included in the FM, in kHz), and the central frequency of the FM, in kHz. Our procedure involved fixing two FM parameters and systematically varying the third. Prior to varying the FM central frequency, the BF$_{high}$ of
the neuron under study served as the central frequency for each FM presented. Each set of FM stimuli (or FM-array) was presented 100 times and decreased in amplitude by 10 dB SPL every 10 repetitions. Experimenter input into a customized SIGNAL script for FM generation was used to generate the eighth (or median) FM in the array. Based on this input, the 6 FMs preceding the median had less parametric magnitude than the median (i.e., a shallower slope, smaller bandwidth, or lower central frequency) and the succeeding 6 FMs had greater parametric magnitude than the median (Washington and Kanwal 2004). An array of 15 stimuli was presented during each trial, with the first presentation acting as a no-stimulus control.

Stimuli in the FM-arrays were manipulated in the following ways. First, for the FM-slope array, we varied the slopes of 14 linear FMs between 0.04 and 4.0 kHz/ms for a constant bandwidth of 3.5 kHz that matched the mean width (varying from 0.2 to 5.4 kHz) of facilitatory tuning to BF\textsubscript{high} at its BA (see Kanwal et al, 1999). In later experiments, we expanded this bandwidth to 5.25 kHz. We determined the best FM slope for a given neuron by observing its peak response magnitudes in response to FMs in the FM-slope array (see below), and that slope was used for all FMs in the subsequent FM-bandwidth array. For the FM-bandwidth array, we equally and incrementally increased the bandwidths of 6 successive FMs above the median bandwidth (3.5 or 5.25 kHz), and likewise we incrementally decreased the bandwidths of 6 successive FMs below the median. This procedure thus generated 13 FMs in the FM-bandwidth array and established the best FM slope and bandwidth for the given neuron. The bandwidths in the FM-bandwidth array spanned a range of 1.31 - 7.88 kHz when the median FM was 5.25 kHz and 0.66 – 5.25 kHz when the median FM was 3.5 kHz. Finally, we incrementally increased the central frequencies of 6 successive FMs above the BF\textsubscript{high} and incrementally decreased the central frequencies of another 6 successive FMs below the BF\textsubscript{high} in steps equal to half of the “best bandwidth.”

The last stimulus in the FM bandwidth and central frequency arrays consisted of a 30 ms CF at the neuron’s BF\textsubscript{high}. An exception was made for the FM slope array such that the last stimulus was an FM with a slope of 4.0 kHz/ms and not the 30 ms CF. All stimuli within the arrays (the control, the FMs, and the BF\textsubscript{high}) were paired, at onset, with a 30 ms CF presented at the neuron’s BF\textsubscript{low}. This method ensured both facilitation of FM responses and provided a direct comparison between the FM responses, the BF\textsubscript{high} in the presence of BF\textsubscript{low}, and the BF\textsubscript{low} presented alone.
Peak response magnitudes from PSTHs (bin width = 10 ms) were used to determine which FM in an array was the “best FM.” The PSTHs obtained for each neuron provided a series of peak response magnitudes constituting a tuning curve. Since many of the tuning curves had multiple peaks and because we summed the responses across multiple amplitude levels, we refer to this curve as simply a “response curve,” for the FM-array. The response curve’s peak corresponded to the best FM in an array. These data provided an FM response curve and values for the slope, bandwidth and center-frequency parameters of prospectively the “best FM” for the neuron under study. Starting with this ‘best FM’, a second iteration of this series of tests for each parameter was sometimes performed to confirm the final parameters of the best FM. In this way, response peaks summed over all amplitudes tested for each parameter (ranging from -9 to 91 dB SPL) produced a response curve for the respective parameter of the FM.

Data generated by presenting FM-arrays also provided the BA of a neuron’s best FM in either the upward or downward modulation direction. After all of these procedures were completed for one modulation direction and if time permitted, the procedure was repeated for FMs in the opposite direction. More commonly, the best FM of a neuron was simply time-reversed to change its modulation direction and used to obtain a neuron’s response to the reversed best FM. The reversed FM was otherwise identical to the best FM in terms of slope, bandwidth and center-frequency. These data were used to calculate a neuron’s direction selectivity index (DSI) as described below.

The best CF, FM, and call stimuli were usually individually presented 200 times at either their best amplitudes (BA) of facilitation or 10 dB-SPL > threshold. Most calculations related to neural responses were determined using a 5 ms wide bin and were based on 200 repetitions of a single stimulus. The two exceptions were latency (1 ms bin width for improved temporal resolution) and response curves (10 ms bin width to consolidate tonic responses; 100 stimulus repetitions).

**Data analysis**

Peak response latencies were manually extracted from each PSTH by measuring the delay ($\Delta t = t_2 - t_1$) between the onset of the stimulus ($t_1$) and the 1 ms bin containing the neuron’s peak response to that stimulus ($t_2$). This calculation necessitates the omission of the 10 ms stimulus onset delay. If more than
one bin had the same response magnitude, the earliest of these bins would serve as \( t_2 \) in the latency calculation. Peak response latencies were measured only from PSTHs elicited by responses to 200 repetitions of a stimulus at BA or 10 dB-SPL > threshold. Unless otherwise stated, all peak response latencies reported here are for onset responses. For FMs shorter than the average peak response latencies to a CF, a distinction between onset and offset responses was not made.

We created mean response curves by first normalizing (to their own peak values) the individual response curves for each neuron and then averaging together only normalized curves that were elicited by the same FM array types (i.e., slope, bandwidth, or central frequency arrays). The values comprising each of the resultant mean curves were mean peak response magnitudes to each stimulus contained in the FM-arrays. Normalization ensured that, when averaged, both strongly and weakly responsive neurons would equally contribute to the resultant mean curves. In addition to generating mean response curves, we performed repeated-measures ANOVAs using Greenhouse-Geisser correction on the collection of individual FM slope, bandwidth, and central frequency response curves. Repeated-measures ANOVAs allowed us to determine whether variations across the FM (UFM or DFM) stimulus parameters of slope, bandwidth, or central frequency caused significant changes \((p < 0.05)\) in the peak response magnitudes of DSCF neurons. Note that all degrees of freedom are reported here in non-integer Greenhouse-Geisser corrected form.

We defined a neuron’s direction selectivity for FMs using the Direction Selectivity Index (DSI). DSI = \((R_{\text{UFM}} - R_{\text{DFM}})/(R_{\text{UFM}}+R_{\text{DFM}})\) where \( R_{\text{UFM}} \) is a neuron’s peak response magnitude to a UFM presented at its BA and \( R_{\text{DFM}} \) is the same neuron’s peak response magnitude to a DFM presented at its respective BA (Mendelson et al. 1993). Our criterion for direction selectivity was a 25% greater response magnitude in one FM direction (UFM or DFM) than in the other. This same criterion can also be restated as \(||\text{DSI}|| > 0.14\), where < -0.14 shows a preference for DFM and > 0.14 shows a preference for UFM.

In the interest of providing single values that can used to characterize some of the overall FM response characteristics for a single neuron, we adopted the use of a modified center of mass (COM) calculation. Specifically, this calculation consolidate into a single value a neuron’s preference for relatively steep or relatively shallow FM slopes and, though not so implemented in the present study,
could be likewise used to determine a neuron’s preference for relatively narrow or broad band FMs.

The COM calculations are primarily used in Chapter IV. The formula for the COM calculation is:

\[
\sum_{i=s}^{14} s(r_s), \text{ where } s \text{ is one of 14 slopes that linearly increases in value from 0.04-4.0 kHz/ms and } r_s \text{ is a DSCF neuron’s response to the FM with slope } s.
\]
CHAPTER III:

NEURONS WITHIN THE PRIMARY AUDITORY CORTEX EXTRACT MULTIPLE PARAMETERS OF FREQUENCY MODULATIONS WITHIN SOCIAL CALLS
Abstract

Neurons in the Doppler-Shifted Constant Frequency processing (DSCF) area in the primary auditory cortex of mustached bats, *Pteronotus pammelii*, are multifunctional, responding both to echolocation and communication sounds. Simultaneous presentation of a DSCF neuron's best low and high frequencies (*BF*$_{\text{low}}$ and *BF*$_{\text{high}}$, respectively) facilitates its response. *BF*$_{\text{low}}$ corresponds to a frequency in the frequency modulated (FM) component of the first harmonic in the echolocation pulse and *BF*$_{\text{high}}$ corresponds to the constant frequency (CF) component in the second harmonic of the echo. We systematically varied the slopes, bandwidths and central frequencies of FMs traversing the *BF*$_{\text{high}}$ region to arrive at the best FM for single DSCF neurons. We report that most DSCF neurons respond either equivalently or better to a linear FM than to the *BF*$_{\text{high}}$ (paired t-test; $p=0.08$) when either stimulus is paired with the *BF*$_{\text{low}}$. For linear FMs ranging in slope from 0.04-4.0 kHz/ms and in bandwidth from 0.88-7.88 kHz, the majority of DSCF neurons preferred upward (55%) to downward (21%) FMs. Central frequencies of the best FMs were typically close to but did not always match a neuron's *BF*$_{\text{high}}$. Neurons exhibited combination-sensitivity to “call fragments” (calls that were bandpass filtered in the *BF*$_{\text{high}}$ region) that were paired with their *BF*$_{\text{low}}$. There was also a close match between the modulation direction of a neuron's preferred FM and that of its preferred call fragment. These response properties demonstrate that DSCF neurons extract multiple parameters of FMs and are specialized for processing both FMs, for communication, and CFs, for echolocation.

Keywords: auditory system, communication, feature extraction, speech
Introduction

Naturally produced sounds are generally complex, containing multiple harmonics and many types of frequency modulations (FMs). Examples of complex sounds include the sounds used for echolocation and communication among conspecifics. Recognition and discrimination between communication sounds or “calls” is important for the survival of the members of a species. We have used complex sounds, including species-specific vocalizations, to gain a deeper understanding of the response properties of cortical neurons and the neural mechanisms underlying cortical processing. Much of our understanding regarding the response profiles of auditory neurons is based on excitatory tuning to constant frequencies (i.e., pure tones or CFs), a class of stimuli that have no spectral dynamics. CFs have been useful for addressing psychoacoustical and neurophysiological questions such as the cochleotopic mapping of the auditory cortex (Imig et al. 1977; Merzenich et al. 1975; Reale and Imig 1980; Woolsey and Walzl 1942) and the study of pitch perception (Fishman et al. 2000; Zatorre et al. 1994). How this critical task is accomplished by the auditory system within a fraction of a second remains unclear despite a vast amount of literature on auditory processing. One consistent weakness, from the viewpoint of understanding auditory communication, is the exclusive use of CFs as stimuli in the majority of these earlier studies. However, an increasing number of studies are using complex acoustic stimuli, such as FMs to study the responses of neurons at various levels of the auditory system, including the cortex (Atencio et al. 2007; Godey et al. 2005; Heil et al. 1992a; b; Heil and Scheich 1992; Liang et al. 2002; Mendelson et al. 1993; Nelken and Versnel 2000; Shamma et al. 1993; Suga et al. 1983a; Zhang et al. 2003). Here we report results of a detailed study of the response properties of neurons within the primary auditory cortex (A1) of the mustached bat, *Pteronotus parnellii*, using FM stimuli as well as simple syllabic calls and salient components of calls.

Studies of the spectral composition of calls reveal that the majority of bat (Clement et al. 2006; Kanwal et al. 1994; Ma et al. 2006), bird (Margoliash 1983; Marler and Pickert 1984), frog (Fuzessery and Feng 1983; Mudry and Capranica 1987), monkey (DiMattina and Wang 2006; Hauser 1991), rat (Boinski and Mitchell 1995; Brudzynski 2005), and whale (Payne and McVay 1971) communication calls
contain FMs. Likewise, formant transitions, which simulate FMs, are integral components of consonants in human speech sounds (Liberman et al. 1967). Conspecifics recognize a particular call type despite variations in its pitch and timbre. CFs alone do not capture the acoustic complexity within calls and may therefore be inadequate to predict neural responses to calls. Furthermore, any overlap of CF components between call types makes the representation of call types in the auditory cortex highly redundant.

Accordingly, earlier studies of excitatory frequency tuning of cortical neurons in squirrel monkeys failed to predict whether a neuron would or would not respond to conspecific calls (Newman and Wollberg 1973; Winter and Funkenstein 1973). One aspect of the acoustic structure of calls that may play an important role in determining their identity is the pattern of FMs that are predominant components of many social calls. In contrast to CFs and noise bursts (NBs) that are spectrally static over time, FMs are spectrally dynamic changes in the structure of a sound. They can be acoustically specified by their slope and bandwidth. For a given slope and bandwidth, FMs may be further characterized by their location on the frequency axis. For FMs of the same bandwidth, this range is a function of the value of an FM’s central frequency.

The auditory cortex of mustached bats has been studied in great detail to describe its functional organization and to elucidate the computational mechanisms involved in echolocation (Suga 1978). These early studies showed that the Doppler-shifted constant frequency processing (DSCF) area within the A1 of mustached bats contains an expanded representation of a narrow range of frequencies, which corresponds to the Doppler-shifted echo of the second harmonic of the CF component (CF$_2$) in the echolocation signal (Fig. 6). The best excitatory frequency of a DSCF neuron corresponding to the echo CF$_2$ (between 57-60 kHz) component is labeled as the BF$_{high}$ for that neuron (Kanwal et al. 1999; Xiao and Suga 2002). A pulse FM$_1$ paired with the BF$_{high}$ triggers a robust response in neurons within the DSCF area. This facilitated response is larger than the sum of the responses to each stimulus presented alone. A single FM$_1$ frequency (between 23-27 kHz), termed the BF$_{low}$, paired with the BF$_{high}$ is also sufficient to elicit a nonlinearly enhanced response from single DSCF neurons.

Our goal in this study was to test whether FM sounds sweeping through the BF$_{high}$ of a neuron can also trigger robust and facilitated responses when paired with its BF$_{low}$. If so, we were curious as to how
Figure 6. Echolocation and Communication Signals and Penetration Locations. (A) Schematized spectrogram of the mustached bat’s echolocation signal. H₁-H₄ refer to harmonics 1 through 4 of the echolocation pulse or echo. Note the constant frequency (CF) and frequency modulated (FM) components present in the pulse and echo. Shaded region shows the signal components (indicated by arrows) that trigger a facilitative response in the DSCF area. (B) Amplitude envelopes (above) and spectrograms (below) for two examples of social calls emitted by mustached bats that contain different patterns within them. (C) Lateral view of the mustached bat brain showing the location of the DSCF area (shown in gray) as defined based on its role in computing biosonar signals. Anatomical landmarks (blood vessels shown by thick lines) and tuning properties of neuronal responses were used to identify the DSCF area in each animal. Other areas, such as the Dorsomedial (DM) area, CF/CF area, a ventral FM-FM area and H₁-H₂ areas, are also shown (adapted from Suga 1984). Symbols in the DSCF area represent 55 penetrations from the left and right hemispheres of 8 animals.
these responses compared to the best CF pairs in the same neuron. We also wanted to know the shape of the response areas obtained to these FMs traversing the BF<sub>high</sub>, and the distribution of best FMs in an unbiased sample of DSCF neurons. Finally, we wanted to know whether the FM response characteristics of a DSCF neuron can predict its call selectivity, including its response to a whole call and/or appropriate spectro-temporally filtered “call fragments.” We performed neurophysiological recordings from single neurons in the DSCF area of awake mustached bats and examined the characteristics of their responses to FMs. We determined the best FM (i.e., the FM that elicited the maximum response) for each DSCF neuron by systematically varying several FM parameters – namely slope, bandwidth, central frequency, and modulation direction – while also pairing each manipulated FM with the neuron’s BF<sub>low</sub> in order to elicit a facilitated response. Variations in each FM parameter were presented over a range of amplitudes (-9 to 91 dB SPL).
Methods

See Chapter II.

Results

*Representation of CF versus FM sweeps*

Extracellular single unit recordings were obtained from 227 DSCF neurons in 10 bats (6 males and 4 females). Peak response magnitudes were measured from PSTHs obtained in response to 200 presentations of either the BF$_{high}$ or the best FM stimulus paired with the neuron’s BF$_{low}$. A comparison of PSTHs obtained for neural responses to BF$_{high}$ with each neuron’s best FMs presented at BA allowed us to classify DSCF neurons into three types (Fig. 7). CF neurons responded best to CFs (Fig. 7A), FM neurons responded best to either a DFM or a UFM stimulus (Figs. 7B and 7C), and bimodal neurons responded almost equally well to both CF and FM stimuli (Fig. 7D). Peak response magnitudes were unaffected by stimulus duration as relatively short FM stimuli produce peaks that are equal to or larger than longer duration CFs (Figs. 7C and 7D). We did not find evidence of duration tuning in the responses of DSCF neurons. DSCF neurons responded in a stimulus-locked manner with the response being mostly triggered by stimulus onset, though some offset responses for CF and/or FM stimuli were observed. The predominant response lasted for less than 30 ms, although tonic responses lasting for either the duration of the stimulus and/or up to 100 ms were also sometimes observed.

The peak response magnitude of 12% (28/227) of neurons was roughly equal for both CF and FM stimuli (±10% of the best CF normalized response). Forty-six percent (105/227) of neurons responded better to FMs than to CF stimuli and 41% (94/227) responded better to CFs compared to the best FM stimulus. Thus, a slight majority of neurons in the DSCF area preferred FMs to CF stimuli. Fig. 8A is a scatter-plot of the peak response to UFMs and to DFM$s$ plotted against each neuron’s BF$_{high}$. A log scale is used for each axis to minimize the disparity due to the large differences in the peak firing-rate among DSCF neurons. As seen in the plot, each BF$_{high}$ corresponds to several different response
Figure 7. Peri-stimulus Time Histograms (PSTHs) Depicting 4 types of DSCF Neurons. Each row (A-D) represents a different neuron type. CF neurons (A) responded best to CFs (30 ms duration), FM types (B and C) responded best to either a UFM or a DFM and bimodal type (D) responded well to both an FM and a CF stimulus. Each FM stimulus was presented at its best amplitude (BA) of facilitation as well as at its best slope and bandwidth. Stimulus parameters are listed in the upper right corner of each PSTH graph. Dashed lines represent stimulus onset (10 ms) and the black bars at the bottom of each graph represent stimulus duration. The horizontal axis is time in milliseconds (ms) and the vertical axis is the number of spikes per 200 trials (spikes/200 trials) in a 5 ms-wide bin. The first and last 0.5 ms of all FMs in this study and their paired BF low were tapered.
values for the best FM or vice-versa. Also, each raster sitting on the horizontal axis represents a neuron that was highly selective for CFs and each raster sitting on the vertical axis represent a neuron that was highly selective for FMs. Approximately 25% of the neurons responded to UFMs with a peak that was within 25% of the peak response to DFMs. A similar number responded only slightly better to DFMs. These neurons were labeled as “bi-directional” and are plotted as gray circles in the scatter plot in Fig. 8A. Other neurons showed a clear preference for either a DFM or a UFM with up to ten-fold greater response magnitudes. The mean peak response to FM stimuli, however, was not significantly ($p = 0.08$; paired t-test) different from that to CFs (Fig. 8B).

**Directional Preference**

Over the total population of DSCF neurons, 75% (171/227) exhibited a preference for either the upward or downward direction of FM. Fifty-five percent (124/227) preferred UFMs, 21% (47/227) preferred DFM, and 25% (56/227) were bidirectional. Of the 105 neurons that preferred FMs over CFs, 63% (66/105) preferred UFMs, 23% (24/105) preferred DFM, and 14% (15/105) were bidirectional. The mean peak response to UFMs was also significantly (paired t-test, $p < 0.01$) better for UFMs compared to DFM (Fig. 8C). The distribution of DSI values for all neurons is shown as a density plot in Fig 9. Forty-seven percent of the DSCF neurons sampled (107/227) responded with a 50% greater peak response magnitude to FMs in their preferred direction than to FMs in the non-preferred direction.

**Distribution of FM slopes, bandwidths and frequency ranges**

The distribution of the best FM slopes across all neurons tested is shown as a density histogram in Fig 10A. Across all slopes tested for the full sample of DSCF neurons, best FM slopes were within the range of 0.04-4.0 kHz/ms. For both UFMs and DFM, DSCF neurons showed a general preference for the shallower FM slopes along the range of 0.04 and 4.0 kHz/ms. For both UFMs and DFM, a slope of 0.34 kHz/ms was nearly as likely to be the best slope of a neuron as 0.04 kHz/ms, the most shallow slope tested. Only a small proportion of neurons exhibited best slopes matching the slope of FM$_2$ component of the echolocation pulse (indicated by the vertical dashed line). Across all bandwidths
Figure 8. Preference for CFs, UFM, and DFMs. (A) Scatter plot for peak response magnitudes (spikes/200 trials in 5 ms bin) of 227 DSCF neurons to DFM (crosses), and UFM (black triangles) stimuli plotted against of their peak responses to constant frequencies (CFs). Bidirectional responses are plotted as filled (gray) circles. Bidirectionality was estimated by computing a direction selectivity index (DSI > 0.14 criterion), for each response. Axes use a logarithmic scale to more easily display the distribution of rasters. (B) Bar plot showing a pair-wise comparison of the peak response magnitudes elicited by each neuron's best FM, regardless of direction, and its peak response magnitude to its best CF response (paired t-test; p = 0.08). (C) Bar graph showing the peak response magnitudes elicited by UFM versus DFM stimuli. The majority of neurons responded significantly more to UFM than to DFMs (paired t – test p < 0.01).
Figure 9. Density Histogram of the DSI Values of 227 DSCF Neurons. The left-most vertical axis shows the number of neurons represented by each bar and the right-most vertical axis shows the percentage of the population represented by each bar. DSI values ranging from 1 to -1 are shown on the horizontal axis.
tested, the mean best bandwidth was 5.35 kHz (± 2.49 s.d.) for UFMs and was 5.60 kHz (± 2.36 s.d.) for DFM (Fig. 10B). These preferred FM bandwidths are in contrast to the 1.35 kHz (± 0.18 s.d.) excitatory frequency tuning (or the excitatory tuning to the BF<sub>high</sub> alone) and the 1.71 kHz (± 0.25 s.d.) facilitatory frequency tuning (or the excitatory tuning to the BF<sub>high</sub> when paired with BF<sub>low</sub>) width of DSCF neurons (Kanwal et al, 1999). Across all neurons, the preferred frequency range for the FM with the best slope and bandwidth is designated by its central frequency. Since the best bandwidth was not the same for all neurons, the frequency range (x-axis) of this plot is best plotted as the number of steps (halves of best FM bandwidth) by which the central frequency of an FM was offset from a neuron’s BF<sub>high</sub> (Fig. 10C). The distribution of FM slopes in the DSCF area was skewed heavily towards shallow slopes for both DFM and UFM. The distribution of best FM bandwidths was relatively flat and the distribution of the best FM frequency range was the closest to a normal distribution.

Response curves for FM parameters

FM Slope

The top panel in Fig. 11 shows three DSCF neurons with different patterns of response curves when presented with an array of systematically increasing slopes. Responses to FM slopes across all stimulus amplitudes are summed for each slope (Fig. 11), as they are for the FM bandwidth (Fig. 12), and FM range examples (Fig. 13) as well. Peak responses in these response curves show a tuning to increasingly steep slopes from left to right. The top row of PSTHs in Figs. 11A to 11C shows responses to shallower slopes than those in the bottom row. The FMs that elicited the responses from the neurons in the top row differed from those in the bottom row only by slope and duration, slope being a function of the latter.

FM Bandwidth

The patterns of response curves elicited by different bandwidths of FMs were more heterogeneous than those obtained for FM slopes. Neurons exhibited a variety of response patterns based on peak response magnitudes summed across stimulus amplitudes ranging from 91 to -9 dB SPL (Figs. 12A to 12D). Two basic patterns were observed: response curves were either relatively flat (Figs 12A and
12C) or showed one or more sharp peaks in response to particular bandwidths (Figs 12B and 12D) within the range tested. Monotonically increasing response functions at the two extremes, such as those obtained for changes in slope, were not observed with respect to increasingly narrowband or broadband stimuli. PSTH plots show the response patterns of neurons for encircled values of the FM bandwidth on the response curve together with amplitude envelopes and spectrograms corresponding to each FM.

**FM Range (or Central Frequency)**

Similar to the previous two examples, Fig. 13 shows examples of response curves to changes in the range or location on the frequency axis of the FM being tested. Zero on the x-axis indicates the central frequency of the FM in the middle of the FM array. This corresponds to a neuron’s BF and is different for each neuron. Each step or interval in this shift always equaled half the best bandwidth of the neuron. For both UFM and DFM, the response curves exhibit Gaussian tuning with the peak centered at or close to 0. PSTH plots show response patterns of spiking in 5 ms bins for each neuron. The PSTHs shown in Fig. 13A and 13B responded better to DFM than to UFM presented at their best FM range. In Fig. 13C and 13D the neuron’s response to CFs (not shown) as well as to UFM was better than that to DFM.

**Population response functions**

The mean response curves of a total of 227 DSCF neurons to UFM and DFM of varying slope, bandwidth, and central frequency are illustrated in Fig. 14A, 14B, and 14C, respectively. For all three manipulations of the stimulus, FM response curves of single neurons were normalized to their peak responses and relative response magnitudes for each were averaged together to obtain a mean response curve. The mean best slope for DFM was 0.829 kHz/ms (± 1.05 s.d.) and for UFM was 0.803 kHz/ms (± 1.28 s.d.). However, many of these neurons responded best to FMs at different modulation slopes as seen in Fig. 11. The large value for the standard deviation of the mean best DFM and UFM underscores the variability in the FM slope tuning of DSCF neuron. Some neurons responded best to the maximum slope (4 kHz/ms) routinely presented in our study. In a few cases, when tested,
Figure 10. Density Histogram of Best FM Parameters. (A) Density histograms of the best UFM (bars upward hatching) and DFM (bars with downward hatching) slopes of the 116 DSCF neurons. The left-most vertical axis shows the percentage of the population represented by each bar for DFMs and the right-most vertical axis shows this same information for UFMs. The central vertical axis, which shows the actual number of neurons per bar, applies to both UFMs and DFM plots. The horizontal axis is an integer scale of FM slopes (kHz/ms). The left side of the horizontal integer scale, which measures the slopes of DFMs, is the reverse of the right side, which measures the slopes of UFMs. A dashed line in the DFM plot shows where the echolocation FM would be located on the slope scale. (B) Density histogram of the best UFM (n = 162) and DFM (n=97) bandwidths of DSCF neurons. (C) Density histogram of the best UFM (n=124) and DFM (n=109) center frequencies for DSCF neurons. Dashed lines represent FMs centered on the neuron’s BF$_{high}$. 
neurons responded better to even steeper slopes (8 kHz/ms) in both the upward and downward directions, indicating that a saturation of response magnitudes was not always achieved. Repeated-measures ANOVAs revealed a significant effect ($p < 0.01$) of FM slope on DSCF neuron peak response magnitude. Thus, across 116 neurons, at least one of the 14 FM slopes elicited a change in peak response magnitude that significantly differed from the response magnitude changes elicited by other FMs. This result was significant whether or not the FMs presented were UFMs ($F[13, 868.30] = 23.97$, $p < 0.01$), DFMs ($F[13, 708.86] = 21.84$, $p < 0.01$), or FMs in the best direction for each neuron ($F[13, 708.05] = 31.52$, $p < 0.01$).

To determine whether relatively shallow ($\leq 1.87$ kHz/ms) or steep ($\geq 2.17$ kHz/ms) slopes had a greater effect on peak response magnitude, we ran separate repeated-measures ANOVAs on the responses to shallow and steep slopes. Shallow slopes had a significant effect on peak response magnitude for UFMs ($F[6, 690] = 20.16$, $p < 0.01$), DFMs ($F[3.14, 360.82] = 27.06$, $p < 0.01$), and best direction ($F[6, 708] = 28.13$, $p < 0.01$). Steep slopes, however, were significant for DFMs ($F[5.44, 626.21] = 2.292$, $p < 0.05$) but not for either UFMs ($F[6, 690] = 0.48$, $p = 0.83$) or for best direction ($F[5.48, 646.25] = 0.56$, $p = 0.75$).

Based on a minimum threshold of 60% of peak response for local maxima and a maximum threshold of 80% of peak response for local minima, 48% of neurons in our sample showed multi-peaked response curves to FM slopes within the range of 0.04-4.0 kHz/ms. Neurons with multi-peaked FM slope response curves had a mean of 3 peaks within the range of 0.04-4.0 kHz/ms ($\pm 0.92$ s.d.). When compared with the directional preference data, these slope data show that 98% of the neurons thus far observed in DSCF respond to linear FMs that do not resemble the FM$_2$, the stereotyped 4 kHz/ms DFM in the second harmonic of the echolocation pulse.

Repeated-measures ANOVAs showed that the significance of the effect of FM bandwidth on DSCF neuron responses depended on the range of bandwidths presented. When bandwidths ranged between 7.87-1.31 kHz, FM bandwidth had a significant effect on DSCF neuron peak response magnitude.
Figure 11. FM Slope Preference in 3 DSCF Neurons. Top panel: Line plots to show the response curves of 3 DSCF neurons to the slope of an FM. Neurons show tuning (peak response) to steeper slopes from left to right. Lower panels: Amplitude envelopes (top), spectrograms (middle) and PSTH (bottom), for two data points (encircled) on the response curve. FM duration is shown by solid rectangle in the oscillogram and as a solid line in the spectrogram (SIGNAL software, Engineering Design), and CF duration at BFlow by unfilled rectangle and bar in the spectrogram. Each row shows a neuron’s response to a relatively shallow (top row) and steep (bottom row) slope. FM direction and stimulus parameters are indicated at the top of each panel. PSTHs (bin width = 5 ms) are based on 200 repetitions of the stimulus.
magnitude when FMs were modulated in the best direction for each neuron ($F[7.18, 452.27] = 2.94, p < 0.01$), as well as when the FMs were all upward ($F[7.02, 407.24] = 2.68, p < 0.01$) or downward ($F[6.48, 213.94] = 2.33, p < 0.05$). When bandwidths ranged between 5.25-0.88 kHz, FM bandwidth had a less significant effect on firing if the FMs were modulated in the best direction for each neuron ($F[8.58, 1227.07] = 2.17, p < 0.05$). Further, UFMs ($F[8.66, 883.05] = 1.80, p = 0.07$) and DFMs ($F[7.79, 452] = 1.29, p = 0.247$) with bandwidths between 5.25-0.88 kHz had no significant effects on peak response magnitude.

To determine whether relatively broadband (>5.25 kHz) or narrowband (< 4.59 kHz) FMs had a greater effect on peak response magnitude, we ran separate repeated-measures ANOVAs on the neural responses to broadband and narrow FMs in the 7.87-1.31 kHz range. Although DSCF neurons robustly respond to broadband FMs, changes in broad FM bandwidth did not significantly affect the peak response magnitudes of DSCF neurons regardless of whether the FMs were UFMs ($F[3.53, 204.45] = 0.51, p = 0.71$), DFMs ($F[3.32, 109.64] = 0.78, p = 0.52$), or modulated in the best direction for each neuron ($F[3.49, 219.81] = 0.45, p = 0.75$). Narrowband FMs, however, showed a significant effect on response magnitude whether they were UFMs ($F[4.07, 236.26] = 4.89, p < 0.01$), DFMs ($F[3.81, 125.67] = 4.38, p < 0.01$), or modulated in the best direction for each neuron ($F[4.12, 259.34] = 5.25, p < 0.01$).

Though response curves to FM bandwidth varied between neurons, for both UFMs and DFMs, the population of DSCF neurons we tested responded with equal if not slightly greater magnitude to FMs with the broadest bandwidths than to those with the narrowest bandwidths. For instance, when the FM bandwidth array was shifted from a range of 0.88 and 5.25 kHz to a range of 1.31 to 7.88 kHz, the bandwidth preference increased such that the broadest bandwidths (> 3.94 kHz) were again preferred over the narrowest bandwidths (< 3.28 kHz). This result demonstrates that, despite their narrowband excitatory frequency tuning, DSCF neurons are capable of responding to relatively broadband FM signals over narrowband FM signals.
Figure 12. FM Bandwidth Preference in 4 DSCF Neurons. Top panel: Line plots to show the response curves of 4 DSCF neurons to the bandwidth of an FM. Neurons show tuning (peak response) to increasing bandwidths from left to right. Lower panels: Amplitude envelopes (top), spectrograms (middle) and PSTH (bottom), for two data points (encircled) on the response curve. The FM is shown as a black rectangle in the amplitude envelope and as a black line in the spectrogram, and the CF at BFlow is shown as a white rectangle in the amplitude envelope and a white line in the spectrogram. Each row shows a neuron’s response to a narrow (top row) and wide (bottom row) bandwidth. FM direction and stimulus parameters are indicated at the top of each panel. PSTHs (bin width = 5 ms) are based on 200 repetitions of the stimulus.
Averaging response curves elicited by shifting the central frequency in the best FM in a step-wise fashion towards lower and higher frequencies resulted in normally distributed mean response curves. For nearly all individual neurons (79.0% of UFMs and 80.7% of DFMs) as well as the average for the whole population, this manipulation yielded a Gaussian ("bell") shaped distribution for both directions of frequency modulation (Fig. 10C). In 46.8% of cases for DFMs and 29.8% of cases for UFMs, the best central frequency of the FM corresponded to the BF_{high} of the neuron under study. Repeated-measures ANOVAs revealed that FM range (or central frequency) had a more significant effect \((p < 0.01)\) on DSCF neuron peak response magnitude than either FM bandwidth or slope. Results were highly significant whether the FMs were upward \((F[7.72, 950.60] = 37.13, p < 0.01)\), downward \((F[7.44, 810.50] = 42.66, p < 0.01)\), or modulated in the best direction for each neuron \((F[7.92, 942.97] = 50.67, p < 0.01)\).

Peak response latency to FM versus CF stimuli

Peak response latencies were measured for 188 DSCF neurons in response to their best CFs and FMs presented 200 times at BA. Latency analyses were restricted to those neurons that had clear, robust, measurable responses when measured with a 1 ms bin size. Based on the aforementioned criteria (see Methods: Data Analysis), onset latencies accounted for 98% (184/188) of responses to CFs, 93% (175/188) of responses to DFMs, and 96% (181/188) of responses to UFMs. The scatter-plots in Figs. 15A and 15B show the peak response latencies for onset responses elicited by the best UFMs and DFMs of DSCF neurons, respectively, plotted against the peak response latencies for onset responses elicited by their best CFs. Responses to UFMs and DFMs had significantly longer latencies than responses to CFs \((p < 0.01, \text{paired t-test})\), but UFMs and DFMs did not significantly differ from one another \((p = 0.93, \text{paired t-test})\). The relatively long peak response latencies elicited by FM stimuli could be a function of overall FM duration. To determine whether response latency is a function of the central frequency as opposed to the FM as a whole, we repeated 100 trials for each value of the slope of an FM within a response curve similar to the ones shown in Fig. 11. We examined the initial and peak
Figure 13. FM Central Frequency Preference in 4 DSCF Neurons. Top panel: Line plots to show the response curves of 2 DSCF neurons to a step-wise shift of the central frequency of an FM in the upward and downward direction from both neuron’s BF_high. Neurons show tuning (peak response) to higher frequencies from left to right. Lower panels: Amplitude envelopes (top), spectrograms (middle) and PSTH (bottom), for two data points (encircled) on the response curve. FM duration is shown by solid rectangle in the oscillogram and as a solid line in the spectrogram (SIGNAL software, Engineering Design), and CF duration at BF_low by unfilled rectangle and bar in the spectrogram. Each row shows a neuron’s response to a low (top row) and high (bottom row) central frequency or FM range. FM direction and stimulus parameters are indicated at the top of each panel. PSTHs (bin width = 5 ms) are based on 200 repetitions of the stimulus.
response latencies in several neurons within each set of PSTHs in order to determine whether latency was dependent on changes in FM slope. Fig. 16A shows changes in a neuron’s response latency to an FM as a function of its central frequency as the steepness of the FM’s slope was increased from 0.08-0.22 kHz/ms. Such an increase in slope magnitude would bring the central frequency closer to the FM’s onset, and, if the neuron were responsive only to the BF (which was synonymous with the central frequency during FM slope array presentations) would cause a decrease in latency. This neuron, like the majority of neurons in our sample, showed no significant change in latency as the FM slope was either increased or decreased. Neurons with multi-peaked FM slope response curves, also showed a similar lack of effect on response latency (Fig. 16B). For this second exemplar neuron, not only did the latency remain largely unchanged with increasing slopes, but also two slopes that differed by an order of magnitude gave similarly robust responses. Other slopes, however, did not elicit responses from this neuron.

Responses to calls versus FMs

Neurons that are tuned to the Doppler-shifted CF$_2$ component of the echolocation pulse (Fitzpatrick et al. 1993; Kanwal et al. 1999; Manabe et al. 1978; Suga 1978; Suga and Manabe 1982) are also responsive to and selective for calls (Kanwal 2006; Kanwal 1999; Kanwal and Rauschecker 2007). The purpose of this section is to show the responses of specific DSCF neurons to calls and/or call-related stimuli. The individual examples are meant to relate the FM response characteristics detailed above to actual DSCF neuron call processing capabilities.

Role of combination-sensitivity

DSCF neurons respond to calls by non-linearly integrating the spectral energy of call harmonics that enter their BF$_{low}$ and BF$_{high}$ ranges (Kanwal 2006; Kanwal 1999; Kanwal and Rauschecker 2007). Figs17A-J show how combination sensitivity affects the responses of two DSCF neurons to CFs and calls. The top row (Figs 17A-E) shows the responses of a neuron that had a BF$_{low}$. The top row (Figs
Figure 14. Average Response Curves Elicited by Parametrically Changing FMs. (A) Average response curves of 116 DSCF neurons in response to arrays of 14 UFMs (solid) and DFMs (dashed) ranging in slope from 0.04-4.0 kHz/ms. The horizontal axis is slope (kHz/ms). Each response is based on 100 stimulus trials (bin width = 10 ms) for each of 14 FMs at several different intensities ranging from 91 to -9 dB SPL. Response curves were normalized to their absolute maxima prior to averaging. Since FMs were attenuated 10 dB SPL per every 10 trials, these cumulative individual and average response curves inevitably obscure amplitude information. (B) Average response curves of 162 DSCF neurons in response to arrays of UFMs and 97 DSCF neurons in response to DFMs ranging in bandwidth between 0.88 and 7.88 kHz. These average response curves resulted from the interleaving of FM bandwidth response functions elicited by two different FM arrays, one of which ranged from 0.88-5.25 kHz and another that ranged from 1.31-7.88 kHz. All other aspects of this representation are the same as those in “A”. (C) Average response curves of 124 DSCF neurons to UFMs (solid) and 109 neurons to DFMs (dashed) that vary in central frequency by 6 (from -3 to 3) times their bandwidths in steps of ½.
Figure 15. Peak Response Latencies of DSCF Neurons (A) Scatter-diagram of peak response latencies of UFMs versus CFs. (B) Scatter-diagram of peak response latencies of DFM versus CFs. (C) Bar plots showing comparisons of neuron peak response latencies to CFs, DFM, and UFM. All latencies shown here either responded prior to stimulus offset or did not exceed the mean peak response latency for CFs.
17A-E) shows the responses of a neuron that had a BF$_{\text{low}}$ of 25.25 kHz, a BF$_{\text{high}}$ of 59.22 kHz, and responded selectively to the single humped FM (sHFM) call. Similarly, the bottom row (Figs 17F-J) shows the responses of a different neuron that had a BF$_{\text{low}}$ of 23.72 kHz, a BF$_{\text{high}}$ of 59.24 kHz, and responded selectively to the stretched rippled FM (sRFM) call. We band-pass filtered the best calls of these neurons such that the only remaining frequencies were a 5 kHz band centered on the BF$_{\text{high}}$. In both cases, the remaining “call fragments” contained one or more FMs. Both neurons responded to 200 simultaneous presentations of their BF$_{\text{low}}$ and frequency modulated call fragments with greater peak response magnitudes than they did to simultaneous presentations of their BF$_{\text{low}}$ and BF$_{\text{high}}$ or even to their best calls. Like their best CF pairs, responses to call fragments were facilitated by simultaneous presentation of the BF$_{\text{low}}$ such that the response to both was greater than the sum of the response of each component presented alone.

**Direction selectivity**

When the best calls of DSCF neurons were band-pass filtered around the BF$_{\text{high}}$, the resultant FM components (or “call fragments”) elicited responses from DSCF neurons. When call fragments were paired with the BF$_{\text{low}}$, those responses often exceeded their responses to their paired BF$_{\text{low}}$ and BF$_{\text{high}}$ (Fig 18E). Figs 18A and 18D, respectively, show a DSCF neuron’s response to its best call, the bent upward FM (bUFM), and to its BF$_{\text{low}}$ alone. A band-pass filtered, quasi-linear fragment of the bUFM that was centered on the neuron’s BF$_{\text{high}}$ elicited a response that is ~60% less than the peak response magnitude elicited by the complete bUFM call (Fig 18C). The addition of the BF$_{\text{low}}$ more than doubles the neuron’s response to the bUFM fragment (Fig 18B). DSCF neuron responses to their best calls depended on spectral summation of the call elements that entered their BF$_{\text{low}}$ and BF$_{\text{high}}$ excitatory response areas, but responses to calls were more dependent on FM direction. When the same bUFM fragment was reversed (and as such became a DFM), it elicited no response from the neuron in Fig 18. The neuron was unresponsive to the reversed bUFM whether or not the bUFM fragment was presented alone (Fig 18G) or paired with the BF$_{\text{low}}$ (Fig 18F). Likewise, reversal of a complete bUFM call abolished (Fig 19E) or elicited (Fig 19F) responses depending on the DSCF neuron under study.
Figure 16. PSTHs of Two DSCF Neurons Elicited by a Series of FMs with Increasing Slopes. (A) Four PSTHs were elicited by an array of shallow FMs and represent responses to 100 presentations at 10 different intensities. Above each PSTH is an illustration of the FM that elicited it. The white circle in the center of the UFM represents its central frequency (here, 59.48 kHz) and the dashed line that drops from the central frequency illustrates the time (ms) that the central frequency occurred relative to the peak response. (B) Four PSTHs elicited by an array of FMs from another DSCF neuron. Note that the slopes of these UFMs increase more rapidly than those in “A.”
Bidirectional and sinusoidal FMs

We extended the use of linear FMs to predict DSCF neuron responses to calls to a neuron that preferred the sHFM call, the same neuron shown in Figs. 17A-E. The amplitude and spectrogram of the sHFM call fragment are shown above the PSTH. The neuron, with a DSI of -0.35, preferred a linear DFM to a linear UFM (Figs. 20B and 20C) and was responsive to multiple DFM slopes. The slope of this neuron’s best FM was 8 kHz/ms, but the neuron also responded to 1.16 kHz/ms. When the stimuli were paired with the BF\textsubscript{low}, this neuron’s responses to the sHFM call fragment and the 1.16 kHz/ms DFM surpassed its response to the complete sHFM call.

We compared one neuron’s responses to its best DFM and best UFM to its response to the sRFM, one of the two best calls for this neuron (Fig 21). PSTHs show that the peak response magnitude to the neuron’s best DFM is lower than that of the best UFM (DSI = 0.45). The accompanying raster diagrams show that the DFM not only elicits fewer spikes than the UFM but the responses to the DFM are less stimulus locked than those to the UFM (Fig 21A and 21B). This same UFM selective neuron displayed similar stimulus locked responses to at least 3 phases of the sRFM sinusoid (Fig 21C). Based on its response latency and direction selectivity, these 3 stimulus locked responses indicate the neuron’s excitation by the UFM components of the sRFM and, possibly, its inhibition by the DFM components. Note that the best FM slope for this neuron (0.4 kHz/ms) was similar to the slope of the bUFM call component that enters the BF\textsubscript{high} range of DSCF neurons (~0.63 kHz/ms). This neuron responded to the bUFM with an equal peak response latency and magnitude as to its best UFM and the sRFM (data not shown). On the far right, we show the responses of second neuron to the sRFM call. It should be noted that the neuron shown responding to phases of the sRFM on the far right is the same UFM selective neuron as in Fig. 18.
Discussion

At least 5 parameters of an FM signal (slope, bandwidth, central frequency, amplitude, and direction) have been described as important determinants for neural responses in the central auditory system (Erulkar et al. 1968). The question of how FM parameters may be represented along the ascending auditory pathway and within the neocortex cannot be easily answered without thoroughly understanding the systematic changes in neural response pattern that accompany changes in FM parameters. Studying the neural responses of changes along each individual FM parameter, however, is time consuming and is best done in awake animals for studies at the cortical level. Mustached bats provided an excellent model for conducting these studies.

Most studies of FMs use either linear or logarithmic FMs. One major rationale for the use of logarithmic FMs (that they more closely conform to cochleotopic organization and thus ensure more equivalent acoustic stimulation across audible frequencies than do linear FMs) is negated by the fact that the echo CF range represents only a narrow band of frequencies that are audible to the mustached bat. Further, we opted not to use of logarithmic FMs due to our interest in call processing, because mustached bat calls do not contain logarithmic FMs (Kanwal et al. 1994). Linear FMs, on the other hand, can simulate instantaneous rates of frequency change, and, potentially, the information-bearing elements within mustached bat calls.

**Representation of FMs in the Mustached Bat A1**

Our data demonstrate that, although DSCF neurons respond well to the Doppler-shifted echo CF frequencies (Fitzpatrick et al. 1993; Kanwal et al. 1999; Suga 1978), they may also respond equally well to and, in some cases prefer, linear FMs traversing the excitatory and inhibitory response areas in the echo CF range. Slope, bandwidth, central frequency, and modulation direction appeared to be the four key parameters dictating neural responses to FMs in the DSCF area. Neither FM slope (n=116) nor bandwidth (n= 162) response profiles produced “bell shaped” Gaussian curves for single unit activity averaged over the sample. Neural responses to FM slopes within a 0.04-4.0 kHz/ms range, on average, yielded curves that monotonically decreased with increasing FM slope. However, over half
(55%) of DSCF neurons studied preferred FM slopes > 0.04 kHz/ms. Furthermore, nearly half (48%) of the neurons preferred multiple FM slopes on the range of 0.04-4.0 kHz/ms. Considering that DSCF neurons are largely selective for shallow UFMs, the 4 kHz/ms (12 kHz per 3 ms) downward echolocation FM would seem almost perfectly orchestrated to avoid stimulating DSCF neurons.

DSCF neuron responses to FMs ranging in bandwidth between 1.3-7.9 kHz, on average, responded to relatively broad bandwidths. The narrow-band excitatory frequency region of the BF is flanked by inhibitory side-bands (Kanwal et al. 1999). This arrangement, by itself, suggests that DSCF neurons should prefer FMs that have relatively narrow bandwidths that span only the width of excitatory frequency tuning of a neuron. The observed preference for FMs > 5 kHz could be explained, however, by non-linear interactions resulting from stimulation of excitatory and inhibitory frequencies with certain temporal delays. These interactions between the excitatory and inhibitory frequency response areas could lead to post-inhibitory rebound that would expand the effective facilitatory response area of a neuron. However, more detailed studies, perhaps at the intracellular level, would be needed to confirm or deny the involvement of post-inhibitory rebound as a mechanism for FM processing in the DSCF area.

“Bell shaped” Gaussian response curves were observed for the majority of DSCF neurons in response to changes in FM central frequency. These normal distributions were almost always obtained for both directions of modulation. Further, our results indicate that for less than half of cases in the downward modulation direction and for less than a third of cases in the upward direction was the best central frequency for an FM the neuron’s best frequency (or the BF, in the case of DSCF neurons). In the anterior auditory field (AAF) and posterior auditory field (PAF) of the cat, it was determined that a neuron’s BF is not necessarily the instantaneous frequency that elicits its response to a linear FM (Tian and Rauschecker 1994; 1998).

Gaussian-like response distributions that are elicited by changes along multiple FM parameters have proven elusive in several animal models and at different levels of the auditory system (Gordon and O'Neill 2000; 1998; Heil et al. 1992a; Mendelson et al. 1993; Nelken and Versnel 2000; Poon et al. 1991; Shamma et al. 1993). Likewise, variations in two of our parameters (slope and bandwidth) did not yield Gaussian-like response curves from DSCF neurons. Most notably, one study of linear FM
response characteristics in the rat inferior colliculus (IC) used a procedure very similar to that in the present study to independently examine IC neuron responses to variations in FM slope, bandwidth, and amplitude (Poon et al. 1991). Gaussian distributions along all 3 parameters were obtained for only 11% of neurons in the rat IC.

One study that yielded different results from the present study reported both a downward directional preference and Gaussian-like response curves to FM slopes in the pallid bat A1 (Razak and Fuzessery 2006). The differences between FM response properties in the mustached and pallid bat A1 may result from species differences, since the pallid bat does not emit a CF signal that can be used to calculate target velocity (Razak and Fuzessery 2002). Therefore, data obtained in the pallid bat high-frequency FM sweep-selective area cannot be directly compared to data obtained in the DSCF area, and may be more comparable to data obtained in the mustached bat FM-FM area.

Responses to FMs in other species.

FM responses at cortical levels

There have been many studies on the neural representations of FMs in A1 that have focused on a variety of different FM classes, including linear (Heil et al. 1992a; b; Heil and Scheich 1992; Nelken and Versnel 2000), logarithmic (Mendelson et al. 1993; Zhang et al. 2003) and sinusoidal FMs (Liang et al. 2002; Suga et al. 1983a). These studies mapped representations of FMs in the primary auditory cortex (A1) by determining the FM rate (or slope) and FM direction that elicited peak responses from multi-unit clusters and, in some cases, from single units. When logarithmic FMs were used in the cat, a significant minority (~45%) of multi-unit clusters showed a direction preference. Over 50% of those direction preferring clusters preferred DFM (Mendelson et al. 1993). When linear FMs were used instead, 66% of those direction preferring clusters preferred DFM (Heil et al. 1992a; b). Only 5% of the multi-unit clusters showed no direction preference. Studies in the ferret that used logarithmic FMs demonstrated that same studies in the cat and ferret A1 found that FM slope preferences were independent of FM class and reported that the A1 of both species contained consistent topographic representations of FM slope along the iso-frequency axis (Heil et al. 1992a; b; Mendelson et al. 1993; Nelken and Versnel 2000; Shamma et al. 1993). In cats, where a 5.5 - 35 kHz bandwidth was used to assess slope
Figure 17. The Role of Combination-sensitivity in Call Processing. A-E represent stimuli and responses of one DSCF neuron, and F-J represent stimuli and responses from a second DSCF neuron. Top panels are amplitude envelopes (top: volts) and spectrograms (bottom: kHz) for sounds presented to awake mustached bats. Bottom panels are PSTHs (bin-width = 5 ms) representing the sum of neural responses to 200 repetitions of the sound in the corresponding top panel. The amplitude envelope and spectrogram of the BF\textsubscript{low} are shown in white and all other stimuli are shown in black. (A) Top panel: the BF\textsubscript{low} (23.72 kHz) of a single DSCF neuron presented at 91 dB-SPL. Bottom panel: the neuron’s response to the BF\textsubscript{low}. (B) Top panel: the best call (sHFM) of the neuron, presented at 91 dB-SPL (BA). Bottom panel: the neuron’s response to the sHFM call. (C) Top panel: band-pass filtered sHFM call “fragment” with a 5 kHz bandwidth (61.74 – 56.74 kHz) presented at 91 dB-SPL. The sHFM call fragment is predominantly downward and centered on the BF\textsubscript{high} (59.24 kHz). Bottom panel: response of the neuron to the sHFM call fragment. (D) Top panel: the sHFM call fragment paired with BF\textsubscript{low}. Bottom panel: response of the neuron to the sHFM call fragment paired with BF\textsubscript{low}. (E) Top panel: the BF\textsubscript{high} paired with the BF\textsubscript{low}, presented at BA (respectively 41 and 91 dB-SPL). (F) Top panel: the BF\textsubscript{low} (25.25 kHz) of the second DSCF neuron presented at 91 dB-SPL. Bottom panel: the second neuron’s response to the BF\textsubscript{low}. (G) Top panel: the best call (sRFM) of the second neuron, presented at 91 dB-SPL (BA). Bottom panel: the second neuron’s response to the sRFM call. (H) Top panel: band-pass filtered sRFM call “fragment” with a 5 kHz bandwidth (61.72 – 56.72 kHz) presented at 91 dB-SPL. The sRFM call fragment is a series of curvilinear FMs that is centered on the BF\textsubscript{high} (59.22 kHz). Bottom panel: response of the neuron to the sRFM call fragment. (I) Top panel: the sRFM call fragment paired with BF\textsubscript{low}. Bottom panel: response of the neuron to the sRFM call fragment paired with BF\textsubscript{low}. (J) Top panel: the BF\textsubscript{high} paired with the BF\textsubscript{low}, presented at BA (respectively 61 and 91 dB-SPL).
preference, FMs responded both monotonically (62%) and non-monotonically (38%) to increasing the magnitude of linear FM slopes (Heil et al. 1992a). Only 21% of the total sample in that study responded to variations in linear FM slopes with a normal distribution. A topographic organization of FM slope preference was also observed in the non-primary auditory cortex of the cat (Tian and Rauschecker 1994; 1998) and rhesus macaque (Tian and Rauschecker 2004).

In short, studies across different species have some to disparate conclusions. In ferrets and cats, FM slope was systematically organized within A1 along the isofrequency axis for both linear and logarithmic FMs. The distribution of FM direction therefore appears to be dependent upon the experimental paradigm and animal model (Heil et al. 1992b; Mendelson et al. 1993; Nelken and Versnel 2000). Neurons in the A1 of cats are often selective for multiple linear FMs that vary in slope between 1-10 kHz/s, and the majority of these neurons have a downward preference (Heil et al. 1992a).

**FM responses at sub cortical levels**

We elected to study FM processing in the mustached bat A1, because auditory information from regions such as the auditory nerve, cochlear nucleus (CN), inferior colliculus (IC), and medial geniculate body of the thalamus (MGB) is integrated at the level of the cortex. Subcortical regions in a number of mammalian species, including bats, show a preference for FMs of a particular direction and slope, and this direction preference is species dependent. In the auditory nerves of cats, 60% of neurons are insensitive to FM sweep direction except at slopes > 5 kHz/ms (Sinex and Geisler 1981).

Neurophysiological studies of the CN of cats, however, have demonstrated that 72% of neurons in this region have a DFM preference that is dependent on FM slopes (Britt and Starr 1976). Sixty-one percent of rat IC neurons are selective for direction, slope, and bandwidth (Poon et al. 1991). Neurons in the MGB of the cat also display a directional preference for DFM with relatively steep slopes (Purser and Whitfield 1972).

**Neural mechanisms underlying FM responses**

**Direction preference**

Directional preference has been seen in DSCF neuron responses to calls in present study and in previously published work (Kanwal 2006). The directional preference for an FM does not correlate with
Figure 18. FM Directional Preference and Combination-sensitivity in Call Processing. Top panels are amplitude envelopes (top: volts) and spectrograms (bottom: kHz) for sounds presented to awake mustached bats. Bottom panels are PSTHs (bin-width = 5 ms) representing neural responses to 200 repetitions (2/s) of the sound in the corresponding top panel. All responses shown here originate from the same DSCF neuron. The amplitude envelope and spectrogram of the BF<sub>low</sub> are shown in white and all components of the call are shown in black. (A) Top panel: the best call of the neuron, the bUFM. Bottom panel: the neuron’s response to the bUFM call. Asterisk (*) denotes that this axis range differs from the adjacent axis in “E.” Note that this panel contains the unit number. (B) Top panel: band-pass filtered bUFM call fragment paired with the BF<sub>low</sub> (25.60 kHz) respectively presented. The call fragment is quasi-linear (slope = ~0.63 kHz), centered on the BF<sub>high</sub> (59.19 kHz), and has a 5 kHz bandwidth (61.69 – 56.69 kHz). Bottom panel: response of the neuron to the call fragment and BF<sub>low</sub>. (C) Top panel: band-pass filtered bUFM call fragment alone. Call fragment is parametrically identical to its description in “B.” Bottom panel: response of the neuron to the call fragment. (D) Top panel: the BF<sub>low</sub> presented alone. Bottom panel: the neuron’s response to the BF<sub>low</sub>. (E) Top panel: the BF<sub>low</sub> paired with the BF<sub>high</sub>. Bottom: response of the neuron to the BF<sub>low</sub> and BF<sub>high</sub>. (F) Top panel: reversed band-pass filtered bUFM call fragment paired with the BF<sub>low</sub>. All stimulus parameters are the same as in “B” except for call fragment direction. Bottom panel: response to the reversed call fragment and BF<sub>low</sub>. (G) Top panel: reversed band-pass filtered bUFM call fragment alone. All stimulus parameters are the same as in “C” except for call fragment direction. (H) Top panel: the BF<sub>high</sub> presented alone. Bottom panel: the neuron’s response to the BF<sub>high</sub>. All stimuli presented at BA.
the central frequency of its preferred FM in the DSCF area. In the mustached bat DSCF neurons, asymmetric inhibitory response areas flank the excitatory response area at BF_{high} (Kanwal et al. 1999). Thus, an excitatory response area alone may give no indication of a neuron’s preference for a DFM or a UFM. It has been suggested that direction selectivity for an FM is less a function of excitatory frequency tuning than a result of asymmetries in inhibitory side bands (Gordon and O’Neill 1998; Razak and Fuzessery 2006; Suga 1965). Detailed in-vivo intracellular studies of the rat A1 have provided additional evidence for this proposed substrate of direction preference (Zhang et al. 2003). Studies in the cat and ferret A1 also showed that CF and FM direction preference were not related to each other (Heil et al. 1992a; Mendelson et al. 1993; Nelken and Versnel 2000).

DSCF neurons have been considered to be sensitive to SFM type of stimuli (Suga et al. 1983a). This sensitivity is considered as a basis of detecting wing beats of an insect for target detection and pursuit using echolocation. Our results suggest that the responses to SFM stimuli, in fact, depend on the selectivity for a particular FM direction as seen in Fig. 14. Thus, a large response to an SFM may emerge from the presence of successive upward and/or downward FMs (depending on the neuron’s DSI) within an SFM. Temporal summation of these responses to successive FMs may also occur because of temporal interactions between two or more FMs within an SFM.

**Slope and duration**

Two neural mechanisms have been shown to underlie preference for FM slope. One mechanism depends on high or low frequency inhibition that arrives later than the initial excitation caused by the FM’s onset (Razak and Fuzessery 2006). A second mechanism depends on duration tuning for component CFs (Fuzessery et al. 2006; Gordon and O’Neill 1998). Although experiments in both the mustached and pallid bats confirm the presence of both slope preference mechanisms in the IC, experiments in the pallid bat confirm only the presence of the former mechanism in A1. The present study is the first to investigate the responses of A1 neurons in the mustached bat to FMs presented in their primary excitatory frequency band. Although we did not explore slope preference mechanisms per se, the fact that DSCF neurons are mostly onset neurons is evidence against duration tuning to
component CFs (Kanwal et al. 1999). Although the pallid bat does not echolocate using a CF signal (Razak and Fuzessery 2002), the mechanisms of FM slope preference in that mammalian species could give insight into the mechanisms of FM slope preference in the A1 of mustached bats and other mammals. Future studies in the mustached bat or another species of CF-FM bat, such as Rhinolophus rouxi, may also show how similar the FM slope tuning mechanisms are between FM and CF-FM bats, and between other mammals as well.

**Correlating FM selectivity with call responses**

There have been relatively few studies of auditory cortical processing of FMs that directly link FM selectivity with selectivity for natural, social calls. Systematic studies of FM processing include the AAF, PAF, and Al in cats (Heil et al. 1992a; b; Mendelson et al. 1993; Tian and Rauschecker 1994; 1998) and were also used as stimuli, but focused only on a highly restricted call set (specifically, sinusoidal FM “twitter” calls). Studies in the lateral belt of the rhesus macaque (Tian and Rauschecker 2004) did not directly compare the responses of neurons to synthetic FMs with calls despite the fact that recordings were made in a call-responsive sub-region (anterior-lateral belt). In our study, many DSCF neurons were presented with 7 frequency variants of 14 different call types as well as their best FMs in order to relate call responses with their component FMs. Much of the knowledge of call selectivity (Hurley and Pollak 2005; Klug et al. 2002; Pillat and Schuller 1998; Portfors 2004) and FM selectivity (Casseday et al. 1997; Gordon and O'Neill 2000; 1998; Suga 1968) in the inferior colliculus (IC) has emerged from neurophysiological studies of various bat species. To our knowledge no study of auditory processing in the IC has directly compared selectivity for calls to selectivity for FMs in the same neurons, but results of bat IC studies do predict many of the FM and call response characteristics of DSCF neurons. Like the DSCF area, the mustached bat IC contains neurons that are combination-sensitive to spectral elements of calls and echolocation signals (Portfors 2004). Neurons in the mustached bat IC are also predominantly UFM selective and are responsive to multiple FM slopes of up to 12 kHz/ms. Almost no FM responsive IC neurons in the mustached bat are unresponsive to CFs (O'Neill 1985). In the Mexican-free tailed bat, IC neurons responded selectively only to some calls that crossed their excitatory response regions but not to other calls that did the same (Klug et al. 2002). Removal of
Figure 19. Directional Preference Observed in a Complete Social Call. (A) Amplitude envelope (top: volts/ms) and spectrogram (bottom: kHz/ms) of a bUFM call presented at 91 dB-SPL. (B) Amplitude envelope and spectrogram of a reversed bUFM call presented at 91 dB-SPL. (C) PSTH (bin width = 5 ms) of responses from a single DSCF neuron that were elicited by presentations of a bUFM call. (D) PSTH of responses from the same neuron in "C" that were elicited by presentations of a reversed bUFM call. (E) PSTH of responses from another single DSCF neuron that were elicited by presentations of a bUFM call. (F) PSTH of responses from the same neuron in "E" that were elicited by presentations of a reversed bUFM. All PSTHs here resulted from 200 repetitions of a single call.
GABA-ergic and glycinergic inhibition in these same IC neurons in the Mexican-free tailed bat resulted in neural responses to most calls that crossed their excitatory response regions. Similar effects have been shown for FMs in the IC of the big brown bat (Lu et al. 1998). Thus, inhibition shapes both frequency tuning and slope selectivity in the IC, much as it does in the AI of the pallid bat (Razak and Fuzessery 2006) and, presumably, the mustached bat. IC (or auditory midbrain) neuron responses to calls and FMs in other species such as cats (McAnally and Calford 1989), rats (Lee et al. 2002; Poon et al. 1991), and songbirds (Woolley and Casseday 2005) similarly reflect cortical (or auditory forebrain) responses to calls and FMs.

An underlying reason that call processing is not often integrated into FM studies may be that it is difficult to make assumptions about key auditory features without prior knowledge of the animal’s species-specific vocalizations. This integration becomes especially difficult when studying species that do not regularly emit highly stereotyped vocalizations, as bats do for echolocation, in addition to their communication sounds (Young 1998). The technique of reverse correlation, in which a neuron’s responses to random noise enables an auditory neuron to define its own ideal feature set has recently enabled studies of stimulus preference in auditory neurons to be performed without a priori knowledge of the acoustic structure of calls (deCharms et al. 1998; Fritz et al. 2003). Reverse correlation estimates the optimal response of the neuron as a function of frequency and time (a spectro-temporal receptive field, or STRF) and can be used to determine which calls may ideally or maximally drive a given neuron. This approach, however, assumes the absence of nonlinear interactions (combination-sensitivity) between stimulus components in both the time and spectral domains. Since calls can be considered as multi-dimensional acoustic objects (Nelken et al. 2003), systematic variations in call parameters can result in unpredictable interactions in the frequency, time, and amplitude domains. These interactions are difficult to study because it is virtually impossible to independently alter only one parameter without influencing others. Given the propensity of nonlinearity within the cortex of mustached bats and the previous work on DSCF neurons (narrowband excitatory frequency tuning near 58.5 kHz, etc.), our studies did not require the generation STRFs or the use of reverse correlation to determine the best FM for a neuron.
Figure 20. Linear FMs Predict Call Responses. Top panels are amplitude envelopes (top: volts) and spectrograms (bottom: kHz) for sounds presented to awake mustached bats. Bottom panels are PSTHs (bin-width = 5 ms) representing neural responses to 200 repetitions of the sound in the corresponding top panel. Amplitude envelopes and spectrograms of this neuron’s BF_{low} are shown in white, and stimuli in the BF_{high} range and/or complete calls are shown in black. All responses shown here originate from the same DSCF neuron. (A) Top panel: sHFM call fragment presented at 91 dB-SPL, centered on the BF_{high} (59.24 kHz) and paired with the neuron’s BF_{low} (23.72 kHz). Bottom panel: neural responses to the paired sHFM call fragment and the BF_{low}. (B) Top panel: a DFM (slope = 0.50 kHz/ms) presented at 91 dB-SPL, centered on the BF_{high}, and paired with the neuron’s BF_{low}. Bottom panel: neural responses to the paired DFM and BF_{low} from a single DSCF neuron. (C) Top panel: a UFM (slope = 1.16 kHz/ms, bandwidth = 5 kHz) presented at 91 dB-SPL, centered on the BF_{high}, and paired with the neuron’s BF_{low}. Bottom panel: neural responses to the paired UFM and BF_{low} from the same neuron as in “A.”
Despite their narrow band excitatory and facilitatory tuning, previous studies indicate that DSCF neurons respond well to many calls that contain FMs (Kanwal 2006; Kanwal 1999). Our results suggest that the ability of DSCF neurons to respond to species-specific calls may emerge from their tuning to linear FMs. These FMs likely constitute some of the acoustic features that make one call distinct from another. The neural mechanisms related to combination-sensitivity, tuning to FM slopes, bandwidth and central frequency as well as directionality appear to underlie the observed call selectivity, although the response to its best FM alone cannot be used to predict a neuron’s overall call selectivity. We therefore propose that a tuning to or selectivity for a specific set of FM parameters plays a critical role in the extraction of key acoustic features that distinguish one call from another. Additional experiments, however, are needed to completely define the multidimensional stimulus space of a DSCF neuron to fully explain its selectivity to calls.

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Figure 21. Linear FM Preference as an Explanation for Responses to SFMs. A-C represent stimuli and responses of one DSCF neuron and D represents the responses of a second DSCF neuron. Top panels are amplitude envelopes (top: volts) and spectrograms (bottom: kHz) for sounds presented to awake mustached bats. Middle panels are peri-stimulus raster plots of neural responses to 200 repetitions of the sound in the corresponding top panel. Bottom panels are PSTHs of neural responses in 5 ms-wide bins. The amplitude envelope and spectrogram of the BFlow are shown in white and all other stimuli are shown in black. (A) Top panel: BFlow and best DFM for the neuron. DFM was delivered at 61 dB-SPL and had a 1.75 kHz bandwidth, a slope of 0.402 kHz/ms, and a central frequency of 59.48 kHz. Middle panel: responses of the neuron to the DFM on a per trial basis. Bottom panel: sum of the neuron’s responses to the DFM. (B) Top panel: BFlow and best UFM for the neuron. UFM was parametrically identical to the DFM in “A.” Middle panel: responses of the neuron to the UFM on a per trial basis. Bottom panel: sum of the neuron’s responses to the UFM. (C) Top panel: the sRFM call. Middle panel: responses of the neuron to the sRFM call on a per trial basis. Bottom panel: sum of the neuron’s responses to the sRFM call. (D) Top panel: the sRFM call. Middle panel: responses of a second neuron to the sRFM on a per trial basis. Bottom panel: sum of the neuron’s responses. Note that this neuron (3_2_07c2) is the same neuron as in Fig. 15.
CHAPTER IV:

NEURAL MECHANISMS FOR HEMISPHERIC LATERALIZATION FOR CALL PROCESSING IN THE PRIMARY AUDITORY CORTEX OF THE MUSTACHED BAT: FREQUENCY MODULATIONS AND TEMPORAL DOMAIN PROCESSING
ABSTRACT

Human speech sound processing is lateralized to the left hemisphere of the human brain, and the extent of this laterality may be sex-dependent. Behavioral and neuroimaging experiments on normal and brain lesioned patients revealed a possible neural mechanism underlying this asymmetry, specifically that the left primary auditory cortex (A1) has an advantage over the right for processing rapid formant transitions, a type of frequency modulated (FM) signal. This mechanism has not been tested at the single neuron level. Mustached bats, *Pteronotus parnellii*, produce a rich variety of calls, and neurons in the left Doppler-shifted constant frequency processing (DSCF) sub-region of the bat’s A1 respond better to calls than do right DSCF neurons. We postulated that differences in FM tuning underlie left hemispheric preference for communication sounds. To test this hypothesis, we recorded single DSCF neuron responses to a series of 14 linear FMs in 6 awake male bats. All FM stimuli were optimized in terms of bandwidth and center frequency to obtain the best FM for each neuron under study, and FMs ranged in slope from 0.04 to 4.0 kHz/ms. Although both right and left DSCF neurons exhibit multiple shapes of response areas when systematically presented with increasing FM slopes, over 50% (13/25) of right DSCF neurons have monotonic-descending tuning to the most shallow slope (0.04 kHz/ms) as opposed to 26% (5/19) of left DSCF neurons. Based on a 70% of peak response criterion, almost 50% (9/19) of left DSCF neurons showed tuning to more than one FM slope, as opposed to 16% (4/25) of right DSCF neurons. Total, 91% of right DSCF neurons preferred FMs with slopes of <500 Hz/ms whereas 47% of left DSCF neurons preferred this same FM slope range. Left DSCF neurons also have shorter latencies for FMs and CFs than do right DSCF neurons. Further, there was a left hemispheric preference for FMs > 5 kHz. Results suggest that the animal’s sex influences this asymmetry such that female bats showed less lateralization for CF and FM latency (n = 4), FM slope (n = 1), and FM bandwidth (n = 3) than do males. Our results suggest that hemispheric differences in tuning to FM slopes and bandwidths may underlie the left-lateralized representation of social calls.
INTRODUCTION

Speech perception and processing is lateralized to the left hemisphere of the human brain (Geschwind and Galaburda 1985; Geschwind and Levitsky 1968; Sperry 1982). This hemispheric specialization has been related to an advantage of the left auditory cortex for processing information with a high temporal precision (Efron 1963; Hammond 1982; Lackner and Teuber 1973). Support for this assertion comes from psychoacoustic, neuropsychological, and functional neuroimaging studies on humans that revealed that formant transitions, a type of frequency modulated signal from which consonant speech sounds are comprised, are selectively processed in the left auditory cortex of the human brain and may even suppress the right auditory cortex (Belin et al. 1998; Merzenich et al. 1996; Schwartz and Tallal 1980; Tallal and Piercy 1973; Zatorre and Belin 2001). Single neuron investigations of the mechanisms of hemispheric lateralization for language, however, are not ethically possible in healthy humans. Although a right ear advantage for processing speech is an indicator of left hemispheric lateralization for language in humans (Kimura 1963), evidence of a right ear advantage for communication sounds (or “calls”) in macaques and rodents (Ehret 1987; Hauser and Andersson 1994; Heffner and Heffner 1984; Poremba et al. 2004; Wetzel et al. 2008) has not led to single neuron analyses of hemispheric lateralization for call processing in these species.

Neurons in the auditory cortex of the mustached bat (Pteronotus parnellii) are responsive to both the animal’s echolocation signals and to social conspecific calls (Esser et al. 1997; Medvedev and Kanwal 2004). The tonotopic axis of the primary auditory cortex (A1) of this bat species, for instance, contains a large group of neurons that is tuned to the Doppler-shift compensated echo of the second constant frequency (tone or CF) component of the echolocation signal. This component is also called the echo-CF$_2$ and is approximately 58 kHz. The cortical area that contains “echo-CF$_2$ specialized” neurons is called the Doppler-shifted constant-frequency processing (DSCF) area, an over-representation of the echo-CF$_2$ that comprises 30-50% of the mustached bat’s A1 (Suga, 1978). Responses of DSCF neurons are also facilitated by pairing a ~25 kHz CF with the echo-CF$_2$ (Fitzpatrick et al., 1993; Kanwal et al., 1999) and are strongly influenced by the directions and slopes of linear frequency modulations (FMs) that contain the echo-CF$_2$. These amongst other neural filter properties enable DSCF neurons to
respond selectively to the social calls of conspecifics and to echolocation pulses (Kanwal et al. 1999; Washington and Kanwal 2008).

Here we present evidence that left DSCF neurons are able to respond to FMs with relatively steep slopes and broad bandwidths and that these FMs tend to suppress the responses of right hemispheric DSCF neurons. Furthermore, the sex of the animal is a strong determinant of this lateralization such that the responses of right DSCF neurons from female bats are less often suppressed by the steep and/or broadband FMs that suppress those of males. These properties may underlie an observed lateralization of social call processing to the mustached bat’s left DSCF area (Kanwal and Suga 1995).

METHODS

See Chapter II.

RESULTS

Lateralization of Peak Response Latency

The method for measuring peak response latencies was identical to that described in Chapter II. In short, peak response magnitudes were measured from PSTHs representing responses to 200 repetitions of a single stimulus presented at its best amplitude (BA). Peak response latencies were measured from a total of 184 DSCF neurons, 55% (101/184) of which originated from 6 male mustached bats and the other 45% (83/184) originated from 4 female bats. We measured responses of DSCF neurons to their best echo-CF$_2$ (or BF$_{\text{high}}$) as well as their responses to downward FMs (or DFM) and upward FMs (or UFM) presented in the echo-CF$_2$ range. All of the CF and FM stimuli presented in the echo-CF$_2$ range were paired with a 25 kHz CF (or BF$_{\text{low}}$) and both the BF$_{\text{low}}$ and BF$_{\text{high}}$ were 30 ms in duration.

Left DSCF neurons responded to pairings of their BF$_{\text{high}}$ and BF$_{\text{low}}$ with significantly shorter latencies than did right DSCF neurons (t-test, $p < 0.01$). Further, right DSCF neuron response latencies to both DFM and UFM were significantly longer than those of left DSCF neurons (t-test, $p < 0.01$). Left DSCF neurons that originated from male bats (72/101) had significantly shorter latencies to CFs (t-test, $p < 0.01$), DFM (t-test, $p < 0.05$), and UFM (t-test, $p < 0.05$) than did right DSCF neurons. In the 4 female
bats, left DSCF neuron (49/83) response latencies were similar to those of right DSCF neurons for CFs (t-test, $p = 0.85$), DFMs (t-test, $p = 0.08$), and UFMs (t-test, $p = 0.10$). Figs 22A-C show these differences in the form of bar plots.

**Lateralization of FM Slope Selectivity**

The responses of 123 DSCF neurons to FMs that varied in slope were recorded from the cortices of 5 mustached bats: 4 males (82/126) and 1 female (44/126). Responses were elicited by a series of 14 FMs (FM-arrays) that varied in slope between 0.04-4.0 kHz/ms, maintained a constant bandwidth of either 3.5 or 5.25 kHz, and were centered on the BF$_{high}$ of each neuron. As described in Chapter II, responses to FM arrays are represented in the form of response curves that represent responses to 100 stimuli at amplitudes ranging from -9 to 91 dB SPL. As we showed in Chapter III, such curves can be averaged to create mean response curves.

Of all FM slopes tested, 0.04 kHz/ms was the most common preferred slope for DSCF neurons in both hemispheres. In general, increasing the FM slope resulted in a decrease in DSCF neuron peak response magnitude ($F[6.12, 716.50] = 32.06$, $p < 0.01$). Differences in peak response magnitude were also observed between left and right DSCF neurons ($F[1, 117] = 6.15$, $p < 0.02$). The effects that the interacting factors of FM slope and hemisphere of origin had on the peak response magnitude of DSCF neurons were significant ($F[6.12, 716.50] = 2.61$, $p < 0.02$). The mean response curves for the left (67) and right (59) DSCF neurons presented FMs that varied in slope from 0.04-4.0 kHz/ms are shown in Fig 23.

In the 4 males, fifty-nine percent (48/82) of DSCF neurons were obtained from the left hemisphere and 41% (34/82) were obtained from the right hemisphere. Twenty-nine percent (14/48) of DSCF neurons in males preferred a slope of 0.04 kHz/ms, and another 27% (13/48) preferred the next shallowest slope, 0.34 kHz/ms (Fig. 24A). However, ninety-one percent of their right DSCF neurons responded best to FM slopes of 0.04 and 0.34 kHz/ms (Fig. 24B). Neurons that prefer FM slopes exceeding 0.95 kHz/ms represent over a quarter of left DSCF neurons but represent only 6% of right DSCF neurons. These significant differences in center of mass of responses between hemispheres (t-
Figure 22. Response Latencies for Left vs. Right and Male vs. Female DSCF Neurons. (A) Mean peak response latencies for 121 left and 63 right DSCF neurons from 6 male and 4 female bats in response to CF, UFM, and DFM stimuli. Responses all occurred at stimulus onset. FMs varied in duration from 0.5-200 ms, but CFs were always 30 ms. CFs were always delivered at and FMs were usually centered on the neuron’s BF_{high} (see Chapter III). All stimuli were paired with the neuron’s BF_{low}. (B) Mean peak response latencies for neurons from the 6 male bats. (C) Mean peak response latencies for neurons from the 4 female bats. Significance indicators: (*) \( p < 0.05 \) and (**) \( p < 0.01 \). “T” bars represent standard error of the mean.
test, \( p < 0.02 \) demonstrate that left DSCF neurons respond more to steep FMs than do right DSCF neurons. Based on the data from the 4 male bats alone, increases in FM slope resulted in a significant decrease in DSCF neuron peak response magnitude (\( F[5.58, 446.07] = 20.84, p < 0.01 \)). Significant differences in peak response magnitude in response to variations in FM slope were observed between left and right DSCF neurons (\( F[1, 80] = 17.21, p < 0.01 \)) and there was a significant interaction effect of between the factors of FM slope and hemisphere of origin (\( F[5.58, 446.07] = 3.01, p < 0.01 \)).

Further comparisons of the response profiles of the left and right DSCF neurons from the 4 male bats were made in order to determine the percentage of DSCF neurons that robustly responded to multiple slopes along the range of 0.04-4.0 kHz/ms. For a neuron to be defined as responsive to multiple slopes, it had to satisfy the following two conditions: (a) at least one FM slope (other than the slope eliciting the absolute peak response along the 0.04-4.0 kHz/ms range) had to elicit a “local peak” response from a DSCF neuron that was at least 60% of the peak response, and (b) at least one FM slope had to exist between the absolute peak and/or any local peaks such that it elicited a response from the same DSCF neuron that was both < 80% of the absolute peak and less than the local peak. Based on these criteria, fifty-five percent (45/82) of DSCF neurons in male bats responded to a single slope whereas 45% (37/82) responded to multiple slopes. Sixty-nine percent (31/45) of neurons that responded to a single FM slope originated in the right DSCF area and 31% (14/45) originated in the left DSCF area. Seventy-eight percent (29/37) of the neurons that responded to multiple FM slopes originated from the left DSCF area whereas 22% (8/37) originated from the right DSCF area. Increasing the local peak threshold level to 75% yielded similar disparities between hemispheres.

Though FM slope data obtained from the left and right DSCF areas of the female bat represents data from a single animal, these data are potentially telling in light of the latency data on 4 female bats (see above) and the bandwidth data on 3 female bats (see below). Forty-three percent (19/44) of the DSCF neurons obtained in the female bat were obtained from the left hemisphere and the remaining neurons 57% (25/44) were obtained from the right hemisphere. Like the 4 male bats, 0.04 kHz/ms was the most common preferred FM slope for both left and right DSCF neurons in the female bat. Similarly as in males, increases in FM slope resulted in a decrease in DSCF neuron peak response magnitude (\( F[5.30, 222.62] = 21.56, p < 0.01 \)). However, no differences in peak response magnitude were observed
between left and right DSCF neurons \( (F[1, 42] = 1.803, p = 0.187) \). There was still a significant interaction effect of FM slope and hemisphere of origin on the peak response magnitude of DSCF neurons in the female bat \( (F[5.30, 222.62] = 5.46, p < 0.01) \). Left DSCF neurons in the female bat responded more to FM slopes of 0.34 and 0.65 kHz/ms than did right DSCF neurons. However, FM slopes greater than 1.26 kHz/ms elicited greater mean responses from right DSCF neurons than from left DSCF neurons. Furthermore, based on the same criteria used to determine whether DSCF neurons responded to multiple FM slopes within the 0.04-4.0 kHz/ms range in male bats, 54\% (13/24) of neurons that responded to a single FM slope were right DSCF neurons in the female and so were 60\% (12/20) of neurons that responded to multiple slopes along the same range. The mean response curves of 4 males and the one female bat are respectively shown in Fig 25A and 25B.

When a singular value is needed to describe the response curve for each neuron, we calculate the center of mass (COM) for each neuron’s response curve. Fig 26 shows COM comparisons showed little difference when all the data from left and right DSCF neurons in the 4 male and 1 female were combined. However, left DSCF neuron responses to FMs along the 0.04-4.0 kHz/ms slope range had a significantly greater (t-test, \( p < 0.02 \)) mean COM \((1.70 \pm 0.39 \text{ s.d.})\) than did right DSCF neurons \((1.47 \pm 0.42 \text{ s.d.})\) in males (Fig 26B). Conversely, COM calculations for FM slope preference demonstrate that right DSCF neurons in the female bat preferred steeper slopes \((1.67 \pm 0.39 \text{ s.d.})\) than did left DSCF neurons \((1.33 \pm 0.33 \text{ s.d.})\) and significantly so (t-test, \( p < 0.01 \); see Fig 26C). The results of the COM calculations and the previously described latency calculations warrant separate comparisons of males and females. However, given that the slope variation experiments described in this section were performed on only one female bat, the data that are initially discussed are solely combined male/female data or just data on the 4 males.

**ASYMMETRY OF FM BANDWIDTH SELECTIVITY**

The responses of 127 left (blue) and 81 right (red) DSCF neurons to FMs that ranged in bandwidth from 0.88-7.88 kHz were recorded from the cortices of 9 bats: 6 males and 3 females. Although there was a significant effect of increasing FM bandwidth on peak response latency \( (F[11.45, 618.27] = 3.47, p < 0.01) \), there was no significant difference in FM bandwidth preference between left and right DSCF
neurons along the tested interval ($F[1, 54] = 0.0, p = 0.99$). In general, increasing the FM bandwidth resulted in no difference in DSCF neuron peak response magnitude in between hemispheres ($F[11.45, 618.27] = 0.91, p = 0.53$).

The responses of 74 left and 41 right DSCF neurons from the 6 male bats are summarized in Fig 27A. In male bats, there was neither a significant effect of increasing FM bandwidth on peak response magnitude ($F[8.65, 242.19] = 1.47, p = 0.16$) nor a significant difference in the peak response magnitudes of left and right DSCF neurons that was elicited by changes in FM bandwidth along the tested interval ($F[1, 28] = 2.18, p = 0.15$). However, the interaction of increased FM bandwidth and hemisphere of origin showed a strong effect on the peak response magnitudes of DSCF neurons in the male population ($F[8.65, 242.19] = 3.97, p < 0.01$).

It is worth noting that, when analyses were restricted only to the 4 male bats that were studied for FM slope preference above, the results for FM bandwidth were similar. Increasing FM bandwidth had no significant overall effects on the peak response magnitudes of DSCF neurons ($F[6.49, 90.69] = 1.23, p = 0.30$) and there were no significant changes in the peak response magnitudes of left and right DSCF neurons ($F[1, 14] = 0.427, p = 0.52$). Again, there was a significant interaction effect of increased FM bandwidth and hemisphere of origin in the male population ($F[6.48, 90.69] = 2.93, p = 0.01$). The responses of 53 left and 40 right DSCF neurons from the 3 female bats are summarized in Fig 27B. In female bats, there was a significant effect of increasing FM bandwidth on peak response magnitude ($F[9.44, 301.91] = 2.99, p < 0.01$) but there was no significant difference in the peak response magnitudes of left and right DSCF neurons that was elicited by changes in FM bandwidth along the tested interval ($F[1, 32] = 0.339, p = 0.57$). The factors of increased FM bandwidth and hemisphere of origin did not interact in such a way as to affect the peak response magnitudes of DSCF neurons in the female population ($F[9.44, 301.91] = 0.53, p = 0.86$).

DISCUSSION

Neurons in the DSCF area respond selectively not only to CFs but also to FMs and social calls (see Chapter III; Kanwal 2006). The present study demonstrates that some key aspects of DSCF neuron
Figure 23. Line Plot of Left versus Right DSCF neuron Slope Preference. Comparison of the response profiles of 67 left (blue) and 59 right (red) DSCF neurons to linear FMs in 5 mustached bats (4 males, 1 female). Curves are based on peak response magnitudes (number of spikes in a 10 ms bin using a 1-ms sliding window) of DSCF neurons in response to FM slope scans (linear increase of 0.04-4.0 kHz/ms). The curves above represent neural responses across multiple amplitudes and were selected from each neuron’s best modulation direction (upward or downward). Each DSCF neuron in the comparisons above was normalized to its own absolute maximum response to an FM over the range of 0.04-4.0 kHz/ms.

Figure 24. Pie Chart of Left versus Right DSCF Neuron Slope Preference. (A) Categorization and distribution of left DSCF neurons based on preferred slope on a range from 0.04-4.0 kHz/ms. (B) Categorization and distribution of right DSCF neurons based on preferred slope on a range from 0.04-4.0 kHz/ms. Since only one female bat was tested on the 0.04-4.0 kHz/ms paradigm, these data are based solely on the 4 male bats.
Figure 25. Line plots of FM Slope in Left versus Right DSCF Neurons in Male and Female bats. (A) Comparison of the response profiles of 48 left (blue) and 34 right (red) DSCF neurons to linear FMs in 4 male mustached bats. (B) Comparison of the response profiles of 19 left and 25 right DSCF neurons to linear FMs in one female mustached bat. All other aspects of these data are identical to those presented in Figure 3.
Figure 26. Center of Mass Calculations for FM slope. (A) Mean center of mass (COM) calculations for the response curves of 67 left and 59 right DSCF neurons that originated from 4 male and 1 female bat. Response curves are based on single neuron responses to 14 FMs varying in slope from 0.04 to 4.0 kHz/ms. FMs remained constant in bandwidth (3.5 or 5.25 kHz) and were varied in amplitude from -9 to 91 dB SPL. (B) Mean COM for the response curves of 48 left and 34 right DSCF neurons from the 4 male bats. (C) Mean COM for the response curves of 19 left and 25 right DSCF neurons from a single female bat. Significance indicators are the same as in Figure 22.
response characteristics are dependent on the neuron’s hemisphere of origin and the sex of the animal. Specifically, in males, left DSCF neurons respond with shorter latencies to CFs and FMs \((n = 6\) bats) and respond with greater peak response magnitudes to FMs with steeper slopes \((n = 4\) bats) and broader bandwidths \((n = 6\) bats) than do right DSCF neurons. In female bats, these data indicate that peak response latencies of DSCF neurons are similar for CFs and FMs \((n = 4\) bats) in the left and right hemisphere, and left and right DSCF neurons respond similarly to FMs with different bandwidths \((n = 3\) bats). Although data from one female bat warrants a cautious interpretation, these data also suggest that right DSCF neurons could potentially respond with greater peak response magnitudes to FMs with steeper slopes than do left DSCF neurons in female bats.

These data also demonstrate that right DSCF neurons in males are more likely to respond to a single, often shallow, FM slope than are the left DSCF neurons of males or DSCF neurons from either hemisphere in females. The most common preferred slope of DSCF neurons, 0.04 kHz/ms, is so shallow that a preference for it likely indicative of a preference for CFs. Since most neurons that responded only to a single slope responded overwhelmingly to 0.04 kHz/ms and were right hemispheric, one could presume that right DSCF neurons are more CF selective than are left DSCF neurons.

Responsiveness to and selectivity for steep FMs (>0.5 kHz/ms) is a major substrate for call responsiveness and selectivity in DSCF neurons (see Chapter III; Kanwal 2006). Taken together, observations from this study and previous studies of DSCF neurons would suggest that right DSCF neurons would be less call responsive than left DSCF neurons. Indeed, Kanwal and Suga (1995) showed that call responsive DSCF neurons primarily reside in the left hemisphere. Since the DSCF area comprises 30-50% of the mustached bat’s A1, we can safely say that there is a hemispheric lateralization for processing steep FMs and social calls in the left A1 of the mustached bat.

Left hemispheric lateralization for social calls in the mustached bat A1 would seem to be an evolutionary homologue to the asymmetrical representation of speech discovered in the human brain’s left hemisphere by Broca and Wernicke and further elucidated by Geschwind (1979) and Sperry (1982). Subsequent neuropsychological experiments have provided insight into the neural mechanisms underlying hemispheric lateralization for speech (Belin et al 1998; Efron 1963; Schwartz and Tallal, 1980). These studies implicate a hemispheric difference in spectral and temporal processing of
communication sounds as the underlying basis of left hemispheric dominance for communication
sounds. Specifically, spectro-temporal transients, such as the rapid (< 100 ms) formant transitions that
comprise consonants, are more readily processed in the left auditory cortex than in the right.
Conversely, slower transients, such as those observed in music, tend to be processed by the more
spectrally refined right auditory cortex. By providing an acoustic basis for hemispheric lateralization
rather than a semantic or otherwise psychological basis, these studies provided a basis for comparing
hemispheric specialization for call processing in an animal with a similar phenomenon for speech in
humans. In Chapter V, we review in detail the research on hemispheric differences in spectral and
temporal resolution as well as the literature on sex differences related to hemispheric asymmetry for
communication sounds.
Figure 27. Line Plots of FM Bandwidth for Left and Right DSCF Neurons in Male and Female Bats. (A) Response curves for 74 left (blue) and 41 right (red) DSCF neurons to the variations of FM bandwidths of FMs in 6 male mustached bats. Curves represent the interleaved responses to the 22 FMs along both a 5.3-0.9 and a 7.9-1.3 kHz interval. (B) Response curves for 53 left and 40 right DSCF neurons to variations of FM bandwidths in 3 female mustached bats. Other aspects of this comparison are identical to those in “A.”
CHAPTER V:

GENERAL DISCUSSION
In this final chapter, I will focus on the interpretation and larger implications of my studies of FM processing in the DSCF area. I will first describe the extent to which each FM parameter influenced the firing of DSCF neurons and whether or not the DSCF area should be considered a CF or FM processing area. Second, I will discuss the literature on humans that led to the spectro-temporal hypothesis of hemispheric asymmetry for communication sound processing and directly relate it to my results in the mustached bat.

Part I: DSCF or DSFM?

If the data summarized in the preceding chapters have one conclusive result, it is that neurons in the Doppler-shifted constant frequency processing (DSCF) area process not only CFs but also process a wide variety of FMs. The fact that DSCF neurons respond to FMs inevitably instigates controversy as to whether the term “Doppler-shifted constant frequency” is a misnomer. The DSCF area, one could argue, is indeed a region that is composed of neurons that process a narrow range of frequencies, but, otherwise, the neurons contained within it respond to stimuli in a manner similar to A1 in most other mammalian species. That is to say that constant frequencies are just one type of stimulus to which A1 neurons respond (Heil et al, 1992a,b; Mendelson et al, 1993; Shamma et al, 1993), and DSCF neurons are no different in that regard.

However, the functional anatomical distinction of DSCF should be maintained for the following scientific reasons. First, DSCF can be considered to be distinct from the rest of A1 simply because it is a region that is composed of neurons that process a narrow range of frequencies (57-60 kHz, in P.p. rubiginosus). The ethological relevance of this frequency range for tracking target velocity provides an even greater scientific basis for making a distinction between the DSCF area and other regions of A1. The DSCF area also contains neurons that are highly susceptible to changes in a sound’s amplitude due to their having “closed” frequency tuning curves whereas A1p does not contain neurons with closed tuning curves (Medvedev and Kanwal 2004). Many of these neurons with closed tuning curves are located in the ventral portion of the DSCF area and are EE neurons. A1a and A1p contain only IE neurons (Liu and Suga 1997). DSCF neuron responses to calls are often abolished when the call is
reversed, presumably due to their directional preference (see Chapter III), but such reversals do not abolish call responses in A1p (Medvedev and Kanwal 2004). Thus, A1p neurons tend to respond to most calls that are present within their excitatory response region, whereas DSCF neurons are more selective.

Another claim that could be made is that the DSCF area should be renamed in order to account for its FM selectivity (perhaps the “Doppler-shifted CF and Call FM area”). Again, however, I would support the traditional nomenclature for one logistical reason. Though individual DSCF neurons may differ in their selectivity for FM direction and slope, DSCF neurons (for the most part) are tuned to a similar range of constant frequencies. If the DSCF area were redefined based on its responses to FMs, it would have to be broken down into multiple sub-regions based on FM slope, direction, and bandwidth. These sub-regions would likely super-impose, forming a complex set of maps like in Figure 1. Ultimately, these criteria would undoubtedly blur the lines between DSCF, A1a, and A1p, and could even merge DSCF with FM-FM and CF|CF. Although this may be advantageous from the point of view of mapping the communication sound representation in A1, the most salient feature unifying the functionality of 30-50% of neurons in the A1 of mustached bats is their tuning to frequencies between 57-60 kHz. For reasons aforementioned (sensitivity to changes in amplitude and directional, call selectivity, and the presence of EE neurons), DSCF differs from other portions of the auditory cortex to such an extent that it probably should not be considered as just another component of the mustached bat’s A1.

**Part II: Acoustic Basis of Left Hemispheric Dominance for Communication Sounds**

The data that I obtained from DSCF neuron responses to CFs and linear FMs revealed a left hemispheric advantage for processing rapid, broadband FM signals that may be related to shorter latency responses to acoustic stimuli in the left DSCF area. Based on measurements of latency in 6 males and 4 females, measurements of FM slope in 4 males and 1 female, and measurements of FM bandwidth in 6 males and 3 females, this asymmetry appears to depend on the sex of the animal. Here, I will discuss the acoustic basis for hemispheric lateralization for speech in humans and how its neural substrates are similar to those for hemispheric lateralization for calls in mustached bats.
Efron (1963) was the first paper to demonstrate that patients with damage to the left hemisphere had disruptions with sequence discriminations that coincided with aphasia. Efron inferred from the fact that aphasics comprehend relatively slow speech better than normal speech that aphasias are not disorders that are unique to language. Rather, Efron defined aphasias as global deficits in acoustic temporal analysis. Further, Efron showed that the left hemisphere has sharper temporal resolution than the right hemisphere. One implication of Efron’s result was that the asymmetrical representation of speech sounds in the human brain depended on acoustic, rather than semantic, stimulus characteristics.

Efron’s result was corroborated by subsequent neuropsychological studies in patients with and without aphasia. Combined visual and auditory perception of temporal order was impaired in patients with left hemispheric lesions but not in patients with right hemispheric lesions (Carmon and Nachshon 1971). Developmental aphasics and aphasics with focal left hemispheric damage were impaired in their ability to discriminate short-duration and/or rapidly changing acoustic stimuli, regardless of whether the stimuli were verbal or nonverbal (Tallal and Newcombe 1978; Tallal and Piercy 1973; 1975). Similar temporal deficits to those observed in developmental aphasics could be produced for non-verbal tasks in patients that had non-developmental aphasia that resulted from focal temporoparietal lesions in the left hemisphere (Robin et al. 1990). A right ear advantage for consonant-vowel syllable discrimination (an indicator that verbal information is processed in the left hemisphere [Kimura, 1963]) showed a dramatic reduction in healthy subjects when the rate of frequency change of the component formant transitions was synthetically extended in these syllables (Schwartz and Tallal 1980). These neuropsychological results were corroborated by a PET study that demonstrated that slower formant transitions (200 ms duration) elicited bilateral regional cerebral blood flow (rCBF) activation in the STG (BA 41, 42, and 22) whereas faster formant transitions (40 ms duration) resulted in a >50% reduction in significant rCBF in the right STG and a reduction of <25% in the left STG (Belin et al 1998).

Efron’s result has been expounded upon by a further elucidation of the right auditory cortex’s contribution to speech perception. Though the right hemisphere plays a major role in processing music (Berlin and McNeil 1976; Gordon 1970; Kallman and Corballis 1975; Milner 1962), this role could be indicative of a right-hemispheric specialization for processing spectral information rather than a uniquely musical specialization (Sidtis 1980). Patients who undergo right posterior temporal lobectomies
involving Heschl’s gyrus make more errors on a complex pitch perception task (signals that contained a missing fundamental) than did patients with anterior right temporal lobectomies, left posterior temporal lobectomies, or healthy subjects (Zatorre 1988). A study by Robin et al (1990), which demonstrated temporal but not spectral deficits in patients with left temporo-parietal lesions, also showed a double-dissociation such that patients with right temporo-parietal lesions were impaired in their ability to perform pitch matching and frequency discrimination tasks but showed no deficits in temporal analysis. Subjects with right temporal lobectomies are reported to have deficits in perceiving prosodic variations in their own speech as well as in the speech of others (Robin et al. 1990; Ross 1981). Of the acoustic correlates of prosody (fundamental frequency, duration, and intensity), impairments in the ability to process fundamental frequency cues seem to accompany right hemispheric lesions to a greater degree than do durational cues (Cooper 1981; Robin et al. 1990).

Taken together, results of left and right hemispheric lesion studies in humans have led to the formulation of the spectro-temporal hypothesis of hemispheric lateralization in humans. This hypothesis states that, as a mathematical consequence of classical Fourier-analysis, a relative trade-off exists between the temporal and spectral resolution of the auditory cortices of the two hemispheres. Although the existence of a perfectly reciprocal relationship between temporal and spectral resolution is highly unlikely in such a non-linear system as the human auditory cortex, hemispheric lateralization may reflect the auditory system’s adaptation to the presence of spectral and temporal features in the environment. Such an adaptation might involve the processing of rapidly changing information (high temporal resolution) setting an upper limit on frequency resolution in the auditory cortex, forcing the development of a largely temporally resolved left auditory cortex and a nearly reciprocal, spectrally resolved right auditory cortex. Such a spectro-temporal disparity has been observed in multiple functional neuroimaging studies of the human auditory cortex (Boemio et al. 2005; Schonwiesner et al. 2005; Zatorre and Belin 2001).

The issue of sex differences has been a major concern in the literature of hemispheric lateralization for speech processing since the 1960s and 1970s. It has been shown that lateralization for non-verbal functions exist in the right hemispheres of males but not females (Lansdell 1962). It has been further demonstrated that left hemispheric lesions depressed verbal IQ and right hemispheric lesions
depressed nonverbal IQ in males, but this same study also showed that there was no selective verbal or
performance deficits after unilateral brain injury in females (McGlone 1978). Further, after damage to
the right hemisphere, women but not men showed mildly depressed verbal intelligence relative to
normal controls (McGlone 1977). In another study, only right-handed males showed a consistent right
ear advantage for listening to numbers and a left ear advantage for listening to melodies; left handed
males and both left and right handed females showed no significant advantage for left or right ears for
either stimulus (Dawe and Corballis 1986). Anatomical analyses demonstrate that planum temporale, a
triangular area situated on the superior temporal gyrus, is larger in the left side the brain in normal male
subjects but is reduced in left handers and females (Shapleske et al. 1999). Further, inverse asymmetry
towards the right side was observed more frequently in women in one neuroanatomical study of 14
women and 13 men (Rademacher et al. 2001). It has also been demonstrated that sex differences in
the perception of temporal order exist such that women needed longer inter-stimulus-intervals than did
men to correctly indicate temporal order (Wittmann and Szelag 2003). It is worth noting that, as a whole,
hemispheric lateralization studies of speech and related spectro-temporal stimuli do not conclusively
show such sex differences (van Kesteren and Wiersinga-Post 2007) and some studies even show
greater left hemispheric lateralization in females (Obleser et al. 2001).

Ultimately, this review of the neural substrates of hemispheric lateralization for speech processing in
humans leads to a fundamental question: do the present data in the mustached bat reflect the
hemispheric specialization for speech in humans in so far as paralleling the underlying acoustic
mechanisms described above? Based on the review of human speech lateralization literature above,
the present data need to answer the following 3 questions: (a) Do neurons in the left DSCF area have
sharper temporal resolution than do right DSCF neurons? (b) Do right hemispheric DSCF neurons have
sharper spectral resolution than do left DSCF neurons? (c) Are there any indications of a sex difference
between the spectral and/or temporal resolution of DSCF neurons?

The present data answer the first question in the following ways. In the present study, left DSCF
neurons responded with significantly shorter latencies to CFs, UFM, and DFM than did right DSCF
neurons. This result would seem to suggest that, if a stimulus falls into a salient spectro-temporal
acoustic range, left DSCF neurons can more quickly respond to those stimuli than right DSCF neurons.
Further, a steeper reduction of peak response magnitude was observed in right DSCF neurons when FM slopes were increased from 0.04-4.0 kHz/ms than in left DSCF neurons. Conversely, left and right DSCF neurons similarly responded to FM slopes of ~0.04 kHz/ms. These results would seem to mirror those of Schwartz and Tallal (1980), where extending consonant-vowel formant transition rates eliminated the right ear advantage for processing these verbal stimuli, and Belin et al (1998), where slow formant transition rates (200-300 ms duration) elicited near equal rCBF activation in both auditory cortices but fast formant transition rates (25-50 ms duration) elicited a far greater reduction of rCBF activity in the right auditory cortex than in the left.

Since UFMs and DFMs varied in duration and since there were not enough neurons that responded consistently to one slope, including 0.04 kHz/ms, to generate an appropriate level of signal-to-noise, we could not determine whether or not duration alone could determine the magnitude of the response latency for FMs. However, all CFs in the present study had a constant duration of 30 ms, and left DSCF neurons still responded faster to CFs than did right DSCF neurons. Furthermore, regardless of whether or not duration or slope determines response latency, slope is a function of duration, and thus the magnitude of the response latency is a function of stimulus duration. Ultimately, when left and right DSCF neurons were presented with the same FM slope arrays, more left hemispheric DSCF neurons selected relatively short-duration FM stimuli than did right DSCF neurons and vice-versa for long-duration FM stimuli. Therefore, the first question concerning superior temporal resolution in left DSCF neurons can be affirmatively answered.

The answer to the second question, as to the spectral resolution of right DSCF neurons, is less straightforward on a number of grounds. First, none of our analyses has as yet demonstrated sharper spectral resolution in the right DSCF area, but this is a reflection more of the on-going nature of our data analysis and less with a clear lack of supporting data. An analysis of excitatory frequency tuning curves obtained for most neurons in our sample as well as an analysis of FM center frequency may eventually reveal sharper spectral resolution in right DSCF neurons. Second, regardless of whether or not these data reveal a respective double-dissociation for temporal and spectral resolution in the left and right DSCF areas, such a clear double-dissociation remains controversial even in the human literature on spectro-temporal differences. For instance, Zatorre and Belin (2001) demonstrated sharp temporal
resolution in the left human A1 relative to the right but the reciprocal sharp spectral resolution was not in the right A1, but rather resided in a more rostral lateral belt area. Boemio et al (2005) found that, bilaterally, A1 is highly sensitive to acoustic temporal structure but also found that the spectro-temporal differences lie in non-primary auditory areas. Schönwiesner et al (2005), on the other hand, showed a double-dissociation between the left and right A1 (amongst other adjacent regions) for temporal and spectral processing. We can suffice it to say that any result as to the spectral resolution of right DSCF neurons would only contribute to this debate.

Nevertheless, the FM bandwidth data could partially elucidate this issue. Sharp spectral resolution implies a relatively narrow effective excitatory frequency domain in right DSCF neurons. Kanwal et al (1999) demonstrated that excitatory frequency response area corresponding to the BF\textsubscript{high} is surrounded by inhibitory side-bands and Xiao and Suga (2002) demonstrated that these inhibitory side-bands are GABA-mediated. Thus, regardless of the distribution of best frequencies in right DSCF neurons, if most of these neurons show sharp spectral resolution, and if all the FMs that vary in bandwidth are centered on the best frequency (BF\textsubscript{high} in the case of DSCF neurons) of each neuron, one would expect to observe a decrease in the mean peak response curve as bandwidth increased. Indeed, this is what is observed in the mean response curve elicited by changes in FM bandwidth in right DSCF neurons of male bats. Again, however, measurements of the sharpness of frequency tuning as well as FM center frequency will more accurately address with question.

Lastly, the question of whether or not salient sex differences exist in our data in so far as hemispheric specialization for call processing and how similar those results are to sex differences observed in the human lateralization for speech may be addressed as follows. First, segregation of male and female DSCF neuron latency data revealed that males but not females had significant differences in their response latencies for CFs and FMs. Second, right DSCF neurons from female bats did not have the same preference for narrow bandwidths that right DSCF neurons from male bats had. Lastly, although the data originated from one bat, DSCF neuron responses to varying FM slopes displayed no hemispheric bias for multiple or single FM slope preference in the female bat. Further, preference for steep FM slopes was reversed such that right DSCF neurons processed steep slopes and left DSCF neurons were capable only of processing relatively shallow FM slopes. Taken together,
these data seem to suggest an overall lack of acoustic hemispheric specialization in the DSCF areas of female bats. These observations are not unlike those made in neuropsychological studies of humans that compared the effects of brain lesions on the verbal and non-verbal IQ of men and women, and found selective verbal or performance deficits after unilateral brain injury in men but not women.

In conclusion, Efron (1963) states that temporal processing is necessarily present to some extent in all animals, so why should it be so localized in humans alone? Where is it in “lower animals?” This statement belies the fact that once hemispheric lateralization was removed from a semantic context and placed in a more acoustic context, as Efron did in 1963, hemispheric lateralization for communication could escape the confines of the hominid brain and could take its place as a more generalized mechanism underlying the representation of sounds that are used for audiovocal communication amongst conspecifics. Recent studies of the auditory systems of rhesus macaques (Poremba et al 2004) and gerbils (Wetzel et al 2008) have joined a litany of previous studies in corroborating Efron’s prediction that hemispheric lateralization for communication sounds is not a phenomenon endemic only to the human brain (Ehret 1987; Hauser and Andersson 1994; Heffner and Heffner 1984).
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