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Neural Processing of Target Distance by Echolocating Bats: Functional Roles of the Auditory Midbrain

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Abstract

Using their biological sonar, bats estimate distance to avoid obstacles and capture moving prey. The primary distance cue is the delay between the bat's emitted echolocation pulse and the return of an echo. The mustached bat's auditory midbrain (inferior colliculus, IC) is crucial to the analysis of pulse-echo delay. IC neurons are selective for certain delays between frequency modulated (FM) elements of the pulse and echo. One role of the IC is to create these “delay-tuned”, “FM-FM” response properties through a series of spectro-temporal integrative interactions. A second major role of the midbrain is to project target distance information to many parts of the brain. Pathways through auditory thalamus undergo radical reorganization to create highly ordered maps of pulse-echo delay in auditory cortex, likely contributing to perceptual features of target distance analysis. FM-FM neurons in IC also project strongly to pre-motor centers including the pretectum and the pontine nuclei. These pathways may contribute to rapid adjustments in flight, body position, and sonar vocalizations that occur as a bat closes in on a target.

Keywords

combination sensitivity; combination-sensitive; echolocation; FM-FM; delay-tuned; mustached bat; sonar; *Pteronotus parnellii*

I. INTRODUCTION

The extraordinary ability of bats to analyze echoes from self-generated sounds allows them to orient through complex environments in complete darkness. In the case of aerial-hawking insectivorous bats, information obtained from echoes is also used to capture flying prey. A key piece of information obtained from echoes is the distance to a target, used by bats to create percepts that allow them to judge the distance and relative velocity of single targets (Simmons 1971,1973; Simmons et al., 1979; Wenstrup and Suthers, 1984) and to distinguish and track multiple elements of a complex environment (Moss and Surlykke, 2010; Surlykke

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et al., 2009). Bats also use this information to adaptively adjust motor control of flight, body position, and sonar vocalizations (Chiu et al., 2009; Moss and Surlykke, 2001, 2010). For example, as an insectivorous bat searches for prey, it emits a sonar signal with long duration and narrow bandwidth that is well suited for target detection. As the bat begins to track and approach potential prey, it increases the repetition rate, decreases the duration, and progressively modifies the amount of frequency modulation (FM) in its sonar signals (Griffin, 1986; Jones and Holdereid, 2007; Kalko and Schnitzler, 1993; Schnitzler and Kalko, 1998; Simmons et al., 1979; Surlykke and Moss, 2000). These active adjustments in the sonar signal that occur as the bat closes in on its prey create an optimal signal for localizing the position of the prey item in three dimensions (Jones and Holdereid, 2007; Moss and Schnitzler, 1995; Simmons and Stein, 1980). It is likely that multiple brain circuits process and represent distance information within echoes to form the basis for these distance-based percepts and behaviors.

To determine target distance, echolocating bats use the time delay between their emitted sonar signal and the returning echo (Simmons 1971, 1973; Simmons et al., 1979). Downward FM sweeps, used in most bat echolocation signals, provide for very good estimates of pulse-echo delays (Simmons and Stein, 1980). These time delays are encoded within the central auditory system of echolocating bats by specialized neurons that respond only to a limited range of pulse-echo delays (Feng et al., 1978; O'Neill and Suga, 1979). These so-called delay-tuned neurons are sensitive to delays between the FM sweep in the emitted pulse and the returning FM sweep in the echoes. Populations of delay-tuned neurons presumably contribute to the bat's analysis of the distance to objects.

Delay-tuned neurons occur in auditory systems of many bat species (*Pteronotus parnellii*, O'Neill and Suga 1979, Suga et al., 1979; *Myotis lucifugus*, Sullivan 1982a,b; *Eptesicus fuscus*, Dear et al., 1993; Feng et al., 1978), *Rhinolophus rouxi*, Schuller et al., 1988, 1991; *Carollia perspicillata*, Hagemann et al., 2010). In most of these species, the delay-tuned neurons respond to the same FM harmonic in the emitted pulse and the returning echo (Dear et al., 1993, Feng et al., 1978; Hagemann et al., 2010; Sullivan 1982a). In the mustached bat (*Pteronotus parnellii*) however, delay-tuned neurons respond to different FM harmonics in the pulse and echo. The mustached bat emits a four-harmonic echolocation pulse that contains a long (20-30 ms) constant frequency (CF) portion followed by a short (2-3 ms) FM sweep (Henson et al., 1987; Novick and Vaisnys, 1964) (Fig. 1A). Delay-tuned neurons in this bat respond specifically to the delay between the FM component of the first harmonic (FM₁, 29-24 kHz) in the emitted pulse and one of the higher harmonic FM components (FM₂, 59-48 kHz; FM₃, 89-72 kHz; FM₄, 119-96 kHz) in the returning echo (O'Neill and Suga, 1982; Olsen and Suga, 1991b) (Fig. 1B,C). Collectively, the physiological response properties of these so-called FM-FM neurons and their underlying neural mechanisms have been well studied in the mustached bat, providing a good understanding of how the auditory system of bats has evolved so they can accurately and quickly determine the distance to a target. In this review we describe the neural mechanisms for target distance analyses in the mustached bat.

In particular, we focus on the functional role of the auditory midbrain in processing target distance information, as delay-tuned, FM-FM response properties emerge here (Marsh et al., 2006; Nataraj and Wenstrup, 2005; Portfors and Wenstrup 2001b). Moreover, the mustached bat's inferior colliculus (IC, the main auditory midbrain nucleus) projects to multiple brain regions that may contribute to both perception of the distance of sonar targets and coordination of motor responses that depend on target distance (Frisina et al., 1989; Wenstrup and Grose, 1995; Wenstrup et al., 1994).

II. ANALYSIS OF TARGET DISTANCE BY FM-FM NEURONS

The key features of FM-FM neurons are that they respond to the combination of an emitted sonar pulse and a returning echo and are tuned to appropriate time intervals between the pulse and echo (Fig. 1B). The specialized response of FM-FM neurons depends on both spectral and temporal tuning properties of these neurons. From a broader perspective, FM-FM neurons form a special class of combination-sensitive neurons that respond to combinations of elements in vocal signals and occur in auditory systems of many vertebrates (Fuzessery and Feng, 1983; Margoliash and Fortune, 1992; Rauschecker et al., 1995; Suga et al., 1978).

A. Spectral tuning permits distinct responses to pulse and echo

FM-FM neurons in all bats are responsive to the combination of a bat's emitted pulse and returning echo with particular time delays. What differs among bats is the relationship between the spectra of the pulse and echo that activate the delay-tuned response. In bats that primarily use FM signals in their echolocation calls, FM-FM neurons respond to similar spectral elements in calls and echoes (Dear et al., 1993; Feng et al., 1978; Hagemann et al., 2010; Sullivan 1982a). These neurons apparently distinguish the pulse and echo by their relative intensities. Thus, FM-FM neurons in these bats are responsive to the combination of a more intense FM sweep corresponding to the emitted pulse, followed by a less intense FM sweep corresponding to the returning echo.

In bats that emit sonar signals with combinations of long constant frequency (CF) elements and FM sweeps, FM-FM neurons display very different frequency tuning to the emitted pulse and returning echo. These bats, in the genera *Pteronotus* and *Rhinolophus*, utilize FM-FM neurons that are activated by the combination of the fundamental (or first) harmonic of the FM sweep in the emitted pulse in combination with a higher harmonic FM sweep in the returning echo (Fig. 1; O'Neill and Suga, 1979; Olsen and Suga, 1991b; Schuller et al., 1991). The use of different harmonics to mark the emitted pulse and returning echo may be based on the harmonic structure of these calls, which feature a suppressed first harmonic. Because the FM₁ sweep has a relatively low intensity in the emitted sound, it will be even less intense in the returning echo and most likely below the bat's hearing threshold. It thus serves as a reliable marker for the emitted pulse but not the returning echo (Kawasaki et al., 1988).

Although the term "FM-FM" suggests that these neurons respond only to FM sweeps, many such neurons respond well to brief tonal signals within the frequency ranges of FM signals (Mittmann and Wenstrup, 1995; Olsen and Suga, 1991b; Taniguchi et al., 1986). In the mustached bat's IC, combinations of brief tone bursts at frequencies within the related FM sweeps are effective stimuli (Mittmann and Wenstrup, 1995; Portfors and Wenstrup, 1999). Figure 2 shows spectral and temporal features of an FM-FM neuron's response in the IC. When stimulated with tonal stimuli, this neuron showed a weak response to its best excitatory frequency (BF) near 83 kHz, which falls within the frequency range of the FM₃ component of the sonar signal. The neuron did not respond at any sound level to a 27 kHz tone burst (within the FM₁ frequency range), but was strongly facilitated when the 27 kHz tone preceded the 83 kHz tone by 2 ms, its "best delay". The FM-FM neuron responded poorly when the delay was lengthened to 8 ms (Fig. 2A). The delay function in Figure 2B shows that facilitating interactions (see Fig. 2 legend for definition) occurred at delays of 0-4 ms. The facilitation tuning curves (Fig. 2C) reveal the spectral properties of facilitation. In general, for responses near a neuron's BF, the tuning curve for facilitation closely matches the tuning curve based on excitatory responses to single tonal stimuli. However, facilitatory tuning curves centered on the FM₁ frequency band show substantially greater sensitivity than do the corresponding tuning curves obtained in response to single tonal stimuli

(Portfors and Wenstrup, 1999). Moreover, the threshold for facilitation by the FM₁ signal is significantly elevated compared to the higher harmonic FM signal (Portfors and Wenstrup, 1999). As a result, the delay-tuned responses of FM-FM neurons will only be activated by echolocation signals with significant energy in the emitted FM₁ component.

Due to their tuning to distinct spectral elements within vocal signals, FM-FM neurons in the mustached bat are unusual among IC neurons. Typically, IC neurons display a single excitatory frequency-tuning curve, with other excitatory or inhibitory influences either tuned near the neuron's best excitatory frequency or tuned very broadly (Ehret and Schreiner, 2005). In contrast, mustached bat FM-FM neurons have their main excitatory response tuned to the higher harmonic FM signal, with a second response tuned to frequencies one to three octaves lower, in the range of the FM₁ (24-29 kHz). This requires that these high frequency-tuned neurons receive one or more separate inputs tuned to frequencies within the FM₁ harmonic (Wenstrup et al., 1999). This feature of FM-FM neurons in the mustached bat provides a model system for the study of frequency integrative mechanisms within the auditory midbrain.

While response to spectral combinations of different FM harmonics is thought to be unique to bats that use long-CF/FM echolocation signals, preliminary evidence suggests that *Pteronotus quadridens*, an “FM bat” closely related to the mustached bat (*Pteronotus parnellii*), also utilizes FM₁ and higher FM spectral combinations in cortical delay-tuned neurons. This suggests that lineage as well as sonar signal structure play roles in determining whether delay-tuned neurons are tuned to similar spectra in the emitted signal and echo (Hechavarría-Cueria et al., 2010).

B. Delay sensitivity in FM-FM neurons of the mustached bat's IC

FM-FM neurons in the mustached bat's IC show a variety of pulse-echo delay functions, revealing facilitatory and/or inhibitory effects of the FM₁ signal (Fig. 3) (Mittmann and Wenstrup, 1995; Nataraj and Wenstrup, 2005, 2006; Portfors and Wenstrup, 1999). These delay functions and their underlying neural interactions dictate how a neuron responds to sonar targets at different distances.

In one category of FM-FM neurons, the FM₁ signal evokes only facilitating effects in the pulse-echo delay function (Fig. 2, 3A). These neurons typically respond somewhat to BF signals within one of the higher harmonic FM bands and show very little response to frequencies within the FM₁ band, when these signals are presented separately. In response to the signal combinations, the neurons have peaked delay functions that reveal facilitatory interactions at some delays, but no inhibitory effect of the FM₁ signal is observed. FM-FM neurons in this category have best delays of facilitation that are “short”, usually less than 6 ms (Fig. 3D, *FM-FM Neurons*). Neurons tuned to these delays respond best to sonar targets at distances less than 1 meter from the bat. (Note that positive delays indicate that the higher harmonic FM signal occurs *after* the FM₁ signal).

FM-FM neurons in a second category show both facilitatory and inhibitory effects of the FM₁ signal. Typically, these neurons respond to the higher harmonic FM signal alone, but this response is inhibited by an FM₁ signal that occurs simultaneously (Fig. 3B). In nearly all of these neurons, the best delay of inhibition occurs at 0 ms delay (Fig. 3E, *Neurons w/ Inhibition and Facilitation*). At longer delays between the emitted FM₁ signal and the subsequent higher harmonic echo-FM signal, (8-14 ms in the Fig. 3B example), there is strong facilitation. In nearly all of these FM-FM neurons, the best delays of facilitation are “long”, usually 5 ms or greater (Fig. 3D, *FM-FM Neurons*) (Nataraj and Wenstrup, 2005; Olsen and Suga, 1991b; Portfors and Wenstrup, 1999), corresponding to target distances greater than one meter. Functionally, these neurons do not discharge in response to

the FM-FM combination in the emitted multi-harmonic signal, because the elements occur simultaneously, favoring inhibition. After a bat detects a target, and begins to approach, these neurons will discharge strongly at distances for which pulse-echo delays evoke facilitation. As the bat continues to approach a target, closing the distance to within one meter, these neurons respond poorly because these pulse-echo delays favor inhibition over excitation.

A third category of FM-FM neuron in the mustached bat IC shows delay-sensitive inhibition by the FM₁ signal, but no facilitatory influence (Fig. 3C). These neurons display an excitatory discharge in response to a higher harmonic FM signal, but are inhibited by a simultaneous FM₁ signal (Fig. 3E, *Neurons w/Inhibition*) (Mittmann and Wenstrup, 1995; O'Neill, 1985; Portfors and Wenstrup, 1999). Functionally, they do not respond to an emitted pulse because the FM₁ component is sufficiently intense to activate inhibition simultaneous to the excitation evoked by the higher FM harmonics, just like the FM-FM neurons in the second category. At pulse-echo delays beyond a few ms, the inhibition activated by the emitted FM₁ has decayed. Further, the echo FM₁ is usually too faint to re-activate inhibition, allowing an excitatory discharge in response to the higher FM in the echo. As a result, these “echo-only” neurons respond to echoes at nearly all delays and target distances, and may perform a variety of analyses of echo features.

In the Jamaican mustached bat, Portfors and Wenstrup (1999) reported that about 50% of neurons with BF_s in frequency bands associated with higher FM harmonics displayed facilitated FM-FM responses, while about 25% of the same sample displayed inhibitory FM-FM responses without facilitation. Observations in the Trinidadian mustached bat suggest fewer facilitating FM-FM responses and more inhibitory FM-FM responses (Nataraj and Wenstrup, 2005, 2006). Whether these represent sub-species or methodological/sampling differences, both studies show that both facilitatory and inhibitory FM-FM response properties are abundant within the IC of mustached bats.

C. Delay tuning matches aspects of behavioral sensitivity

Echolocating bats that use high intensity sounds are able to detect small insects up to 5-10 meters away (Kick, 1982; Schnitzler and Kalko, 1998), although large targets are thought to be detected at greater distances (Holdereid and von Helversen, 2003; Surlykke and Kalko, 2008). Since each meter of target distance results in an echo delay of 5.8 ms, targets at 5 m are delayed by 29 ms. As a bat begins to inspect and approach a target of interest, the pulse-echo interval and signal duration shorten. Perhaps the greatest need for distance information occurs as the bat closes in on a target. Within the last few meters, bats produce signals at high rates as they precisely locate their targets and position their heads and bodies for capture (Surlykke et al., 2009). For mustached bats, the majority of FM-FM neurons are tuned to these pre-capture pulse-echo delays that correspond to distances of 2 meters (11.6 ms delay) or less, both in auditory cortex (Fitzpatrick et al., 2008a; O'Neill and Suga, 1982; Suga and Horikawa, 1986) and in the IC (Fig. 3D; Nataraj and Wenstrup, 2005; Portfors and Wenstrup, 1999, 2001a). This strongly suggests that a major function of FM-FM neurons is to perform distance-based analyses of sonar targets during the final stages of approach and capture. However, the IC distribution also shows that some neurons are tuned to best delays as long as 30 ms, indicating that delay-tuned neurons also function in the distance-based analysis of targets during detection and tracking/approach phases (Nataraj and Wenstrup, 2005). Overall, these results closely link delay-tuned neurons with the analysis of target distance.

The width, or sharpness, of delay tuning curves has implications for the precision of target distance analyses by bats. The width of delay tuning curves is typically measured at response rates 50% below the maximum at best delay (50% delay width). In the mustached

bat IC, FM-FM neurons show 50% delay widths ranging from <1.0 ms to nearly 20 ms (Fig. 3F; Portfors and Wenstrup, 1999; Nataraj and Wenstrup, 2005). Both narrow and broad tuning curves occur at short and long best delays, with only a weak trend for broader delay tuning in FM-FM neurons with longer best delays (Fig. 3F). There is no evidence among IC FM-FM neurons of a strong positive correlation between the best delay and the width of the delay tuning curves (Nataraj and Wenstrup, 2005; Portfors and Wenstrup, 1999; Yan and Suga, 1996a), as has been reported in some studies of the mustached bat auditory thalamus and cortex (Olsen and Suga, 1991b; Suga and Horikawa, 1986). Two other studies of auditory thalamic FM-FM neurons are consistent with the IC findings, showing a broad range of 50% delay widths in FM-FM neurons that are, at best, only weakly related to the best delays of these neurons (Wenstrup, 1999; Yan and Suga, 1996a). Further work is required to resolve these discrepancies.

When combined with the distribution of best delays, it appears that pulse-echo delays of 10 ms or less, corresponding to target distances of 1.7 m or less, are represented by a large number of neurons with best delays more or less evenly distributed throughout this range. On average, delay-tuning widths are about 6 ms, but range from <1 ms to 14 ms (Nataraj and Wenstrup, 2005; Portfors and Wenstrup, 1999). The large number of neurons tuned to these delays, and the sharpness of such tuning suggests a population code based on peak responses. Small changes in delay should substantially change population response rates. For this range of target distances, we believe that peak detection mechanisms are likely to underlie distance-based target analyses, rather than the edge detection mechanisms that are thought to analyze interaural level differences in bat and cats (Fuzessery and Pollak, 1985; Razak and Fuzessery 2002; Wenstrup et al., 1988; Wise and Irvine, 1985) and interaural time differences in small mammals (McAlpine 2005; McAlpine and Grothe, 2003).

At longer delays, there are significantly fewer neurons to cover a broader range of delays. On average, delay tuning widths are about 8-9 ms, but range from 3-19 ms. The population of neurons tuned in this range is smaller, but nonetheless uses both narrowly tuned and broadly tuned elements. The purpose of this is not clear, but we hypothesize that the variable width of delay tuning may be related to different resolutions required for target distance-related tasks. For instance, the distance resolution required to trigger an increase in sonar pulse repetition rate may be different from what is required for perception. This is consistent with observations that FM-FM neurons project in multiple pathways that are likely related to different components of echolocation behavior (see Section IV).

D. Other forms of combination-sensitive responses in IC

Although FM-FM neurons are a major type of combination-sensitive neuron in the mustached bat's IC, other types also occur. These other combination-sensitive neurons have distinctly different frequency and temporal tuning characteristics, and thus function differently in sonar and other acoustic behaviors. The most prominent type includes neurons tuned to frequencies of the second- or third-harmonic constant frequency (CF) component of doppler-shifted sonar echoes (CF₂, ~61 kHz; CF₃, ~91.5). These neurons display much sharper frequency tuning than FM-FM neurons (Portfors and Wenstrup, 1999). Their response to best frequency sounds is facilitated or inhibited by sounds tuned in the 23-30 kHz range of the first sonar harmonic, either to the CF₁ signal (CF/CF responses) or the FM₁ signal (FM/CF responses). The delay sensitivity for facilitation among these neurons is quite different from FM-FM neurons: nearly all are best facilitated by simultaneous low and high frequency sounds (Fig 3D; Nataraj and Wenstrup, 2005; Portfors and Wenstrup, 1999). In echolocation, CF/CF neurons may function in analyses of relative target velocity (Suga et al., 1983). Fitzpatrick and colleagues (1993) proposed that FM/CF neurons are involved in analyses at long echo-delays, but the predominance of this response type among the large populations of neurons tuned to CF₂ and CF₃ frequencies suggests a broader range of

functions, including those related to the analysis of social vocalizations (Washington and Kanwal, 2008).

Many combination-sensitive neurons found in the mustached bat's IC are activated by frequency combinations that do not occur in echolocation. For many, the best frequency of excitation is within one of the bands used in sonar signals, but low frequency facilitation is tuned to frequencies outside the sonar band, either above or below the first sonar harmonic. In nearly all of these neurons, the facilitation is strongest when the two signals occur simultaneously (Gans et al., 2009; Nataraj and Wenstrup, 2005; Portfors and Wenstrup, 2002). Many high-BF neurons, including those that show combination-sensitive facilitation, also display suppressive effects of frequencies below the first sonar harmonic. These suppressive effects appear to result from cochlear phenomena (Gans et al., 2009; Marsh et al., 2006; Peterson et al., 2009; Portfors and Wenstrup, 1999), but they may exert strong effects on a neuron's response to complex sounds, including social vocalizations and environmental sounds, that contain low frequency elements (Gans et al., 2009; Nataraj and Wenstrup; Portfors 2004). Other combination-sensitive neurons are facilitated by combinations of tones or noise in the frequency bands above and below the first sonar harmonic. Their facilitation is nearly always best when signals are presented simultaneously (Leroy and Wenstrup, 2000; Portfors and Wenstrup, 2002). These non-sonar combination-sensitive neurons likely participate in the analysis of social vocalizations because the frequency tuning characteristics of the neurons are consistent with the spectral content of many of the mustached bat's social vocalizations (Kanwal et al., 1994; Leroy and Wenstrup, 2000; Portfors and Wenstrup, 2002).

While most studies of combination sensitive neurons have focused on the mustached bat, there is some evidence that combination-sensitive neurons are also present in the IC of nonecholocating mammals. Portfors and Felix (2005) found both facilitatory and inhibitory combination-sensitive neurons in the IC of normal hearing mice. Almost 30% of the neural responses in the mouse IC showed combination sensitivity; 16% were facilitatory and 12% were inhibitory. These responses almost always occurred with simultaneous onset (i.e. 0 ms delay) of the two tones. Interestingly, the percentage of facilitatory neurons in mouse IC is similar to the percentage of facilitatory neurons found in non-sonar regions of the mustached bat IC (Portfors and Wenstrup, 2002). This suggests that combination-sensitive neurons are important for analyzing social vocalizations in both bats and mice. Moreover, the finding that combination-sensitive neurons exist in the IC of species as different as mice and bats suggests that common neural mechanisms exist among mammals for processing complex sounds. While studies in other non-echolocating mammals have found combination-sensitive neurons in auditory cortex (Brosch et al., 1999; Kadia and Wang, 2003; Sadagopan and Wang, 2009), it is possible that these species also have combination-sensitive neurons in the IC and the appropriate tests have not been conducted.

In comparing FM-FM neurons to other types of facilitated neurons, whether in the mustached bat or the mouse, the difference in delay sensitivity and the presence of early inhibition for FM-FM neurons with long best delays is striking. Other combination-sensitive neurons show a narrow distribution of best delays centered on 0 ms, while FM-FM neurons show a very broad distribution that includes neurons tuned to pulse-echo delays as large as 30 ms (Fig. 3D). These characteristic features strongly suggest that FM-FM neurons participate in the analysis of target distance. Nonetheless, target distance analyses may not be the only function of FM-FM neurons. In both the IC and auditory cortex, some FM-FM neurons respond to combinations of elements found in social vocalizations (Esser et al., 1997; Holmstrom et al., 2007; Ohlemiller et al., 1996). Thus, these neurons may change their role in perception based on behavioral context. During orienting and foraging, FM-FM neurons are actively engaged in providing target distance information to the bat, whereas

during social interactions, FM-FM neurons may be involved in discriminating among social vocalizations with different meanings.

III. INTEGRATIVE MECHANISMS UNDERLYING COLLICULAR FM-FM RESPONSES

An in-depth discussion of the mechanisms of facilitatory and inhibitory interactions that contribute to FM-FM responses is beyond the scope of this review. Here we summarize major findings that demonstrate that facilitatory and inhibitory elements of FM-FM responses originate at different levels of the mustached bat's auditory brainstem and midbrain.

Inhibitory FM-FM interactions, which occur separately from or in combination with facilitated responses, originate in the nuclei of the lateral lemniscus, principally the ventral and intermediate nuclei (VNLL and INLL, respectively). Evidence is based on both single unit recording and micro-iontophoretic experiments. Inhibitory FM-FM interactions do not occur in the cochlear nucleus (Marsh et al., 2006), but many occur in the VNLL and INLL (Peterson et al., 2009; Portfors and Wenstrup, 2001b). Moreover, the inhibitory FM-FM responses in INLL neurons can be eliminated through blockade of glycine receptors with strychnine, supporting an origin within INLL (Peterson et al., 2009). We have proposed that these INLL neurons send excitatory, glutamatergic projections to IC neurons that in turn inherit the inhibitory FM-FM response (Peterson et al., 2009; Yavuzoglu et al., 2010). For some FM-FM responses in IC, FM₁ inhibition may be enhanced through interactions within IC (Nataraj and Wenstrup, 2006; Peterson et al., 2008).

Facilitatory FM-FM interactions, like other facilitatory combination-sensitive interactions, arise in IC. There are very few or no such responses in cochlear and lateral lemniscal nuclei (Marsh et al., 2006; Portfors and Wenstrup, 2001b). Moreover, facilitatory responses of FM-FM and other combination-sensitive neurons are completely eliminated through blockade of glycine receptors in IC neurons (Nataraj and Wenstrup, 2005; Sanchez et al., 2008; Wenstrup and Leroy, 2001), while GABA-A receptors do not appear to play a significant role (Nataraj and Wenstrup, 2005; Sanchez et al., 2008). These results initially suggested that the lower frequency signal (e.g., FM₁ signal) activates a glycinergic inhibition and rebound that facilitates the glutamatergic excitation evoked by a higher FM harmonic. Surprisingly, however, Sanchez and colleagues (2008) showed that the facilitation resulting from the combination of FM₁ and delayed higher harmonic FM sounds is entirely dependent on glycinergic inputs to the FM-FM neuron (Fig. 4A-C). Glutamatergic inputs play no role in the facilitating response, although they convey an excitatory response to the higher harmonic FM responses alone. Further, the glutamate-mediated response to the higher frequency signal may be inhibited by simultaneous FM₁ signal inputs. These glutamatergic inputs may originate in the INLL neurons that display combination-sensitive inhibition. Thus, there is a striking paradox in the mechanisms underlying the delay-sensitive responses of FM-FM neurons in the mustached bat's IC, illustrated in Figure 4D: delay-tuned facilitation in IC neurons is based on the *inhibitory* neurotransmitter glycine while delay-tuned inhibition in these IC neurons depends on an *excitatory* input from INLL neurons (Peterson et al., 2008, 2009; Sanchez et al., 2008).

IV. HIERARCHICAL CHANGES IN FM-FM RESPONSES IN THE ASCENDING AUDITORY SYSTEM

A. Transformations in the response properties of FM-FM neurons

Delay-tuned FM-FM neurons are found in the auditory cortex (O'Neill and Suga, 1979, 1982; Suga and O'Neill, 1979), medial geniculate body (Olsen and Suga, 1991b; Wenstrup, 1999) and inferior colliculus (Mittmann and Wenstrup, 1995; Portfors and Wenstrup, 1999; Yan and Suga, 1996a) of mustached bats. There is strong evidence that hetero-harmonic sensitivity, range of best facilitatory delays (Fig. 5A), and early inhibition are features of FM-FM neurons that undergo little modification between IC and MGB (Portfors and Wenstrup, 1999, 2004; Wenstrup, 1999). In other features, particularly in the sharpness of delay tuning and the strength of facilitation, there are differing views. Yan and Suga (1996a) described sharper delay tuning curves in MGB compared to IC, but Portfors and Wenstrup reported no difference (Figure 5B, Portfors and Wenstrup, 1999, 2004; Wenstrup, 1999). Yan and Suga (1996a) reported that the strength of facilitation increased among FM-FM neurons in MGB. Portfors and Wenstrup (2004), on the other hand, found no change in the average strength of FM-FM facilitation, but observed more neurons in MGB with nearly 100% facilitation (Fig. 5C). A change consistent across both sets of studies is that there is a greater likelihood that FM-FM neurons in MGB will not respond to separate FM₁ or higher harmonic FM signals, but will only respond to the appropriate combination of signals. Further work may clarify these transformations, but the overall impression is that physiological response properties of FM-FM neurons in MGB are similar to those in IC. In general, this is consistent with comparisons of other response properties between the IC and MGB in mammals (Wenstrup, 2005).

Many features of the cortical responses of FM-FM neurons are similar to those in the IC and MGB. There are no dramatic differences in the basic frequency and temporal tuning features of FM-FM neurons. Quantitative comparisons that may highlight additional processing of target distance information in auditory cortex are not straightforward; many of the IC experiments focused on mechanisms and relation to tone-based response properties, while the cortical experiments typically emphasized responses to sonar elements or full sonar signals. The general impression is that cortical FM-FM neurons may be more likely to respond to FM-FM combinations than to separate elements, to display preferences for FM sweeps rather than to tonal stimuli (Taniguchi et al., 1986), and to respond to more than one FM harmonic in the echo (Misawa and Suga, 2001). Cortical FM-FM neurons are also more likely to show longer term changes in delay tuning as the result of conditioning or other experience (Suga et al., 2002; Xiao and Suga, 2004; Yan and Suga, 1996b).

B. Transformations in the organization of the tecto-thalamo-cortical projection

In contrast to physiological response properties, there are major changes in the organization of FM-FM neurons from IC to auditory cortex (Fig. 6). The transformation in FM-FM representations with hierarchical processing appears to be due in large part to the special features of the tecto-thalamic projection (Frisina et al., 1989; Wenstrup and Grose, 1995; Wenstrup et al., 1994). In addition to ascending projections to auditory thalamus, IC neurons in the FM frequency bands target several other areas (Fig. 7).

FM-FM neurons in IC are distributed within the framework of the tonotopic organization of the central nucleus of IC (Frisina et al., 1989; Zook et al., 1985). FM₁-FM₂ neurons, for example, are located within the 48-59 kHz tonotopic representation according to their best excitatory frequency. In similar fashion, delay-tuned neurons with best frequencies in the FM₃ and FM₄ frequency bands are located within the appropriate 72-89 kHz and 96-119 kHz frequency bands, respectively. Within these bands, there is no organization of neurons

according to their delay tuning or to the type of FM-FM response (facilitation and/or inhibition) (Fig. 6A; Portfors and Wenstrup, 2001a, 2004).

The organization of FM-FM neurons in MGB differs substantially (Fig. 6B; Portfors and Wenstrup, 2004; Wenstrup, 1999). Within the main part of the tonotopically organized ventral division of MGB, there are few neurons with best frequencies in the higher harmonic FM ranges, including singly tuned, facilitated FM-FM, or inhibited FM-FM responses. Instead, the vast majority of FM-FM neurons are located in the rostral half of the MGB (Olsen and Suga, 1991b; Wenstrup, 1999), a region that has alternately been considered to be the dorsal division (Olsen and Suga, 1991a,b), rostral pole of the dorsal division (Wenstrup et al., 1994; Wenstrup, 2005; Winer and Wenstrup, 1994a,b), or a non-tonotopic extension of the ventral division (Pearson et al., 2007). Whatever its affiliation, this region is dominated by FM-FM neurons and shows a complex organization. There is no single tonotopic organization of frequencies, as best frequencies may increase or decrease along any dimension, but FM-FM neurons associated with each harmonic are segregated in two areas. Each representation contains at least a crude map of best delay, where shorter best delays are located more medially and longer best delays are located more laterally (Fig. 6B). Further, one of the representations appears to have a broader distribution of best delays than the other (Wenstrup, 1999).

The transformation in organization of FM-FM responses can be related to the special features of the tecto-thalamic projection from the IC frequency bands associated with each of the higher FM harmonics of the sonar signal. While other frequency bands in IC project to the tonotopically organized ventral division in the caudal MGB (Wenstrup and Grose, 1995; Wenstrup et al., 1994), there are very few labeled terminals in this region after tracer deposits in the FM₂, FM₃, or FM₄ representations of IC (Frisina et al., 1989; Wenstrup and Grose, 1995; Wenstrup et al., 1994). Instead, there is heavy labeling in the rostral half of MGB, where terminal zones from FM₂ projections are located adjacent to FM₃ projections, which are in turn adjacent to FM₄ projections. The tecto-thalamic projection effectively segregates FM-FM neurons from other auditory responsive neurons, organizes each harmonic into adjacent clusters, creates multiple representations of each harmonic, and, based on physiological results, creates at least a crude map of best delay (Portfors and Wenstrup, 2001a, 2004; Wenstrup, 1999, 2005). This reorganization is unprecedented in studies of auditory tecto-thalamic projections in mammals (Wenstrup, 2005).

The organization of FM-FM neurons in auditory cortex shows similarities to that in the MGB, but further transformations occur. Here we focus on the two largest regions containing FM-FM neurons that have been identified in functional mapping studies (Fig. 6C; Fitzpatrick et al., 1998a; Suga and Horikawa, 1986; Suga et al., 1983). The so-called “FM-FM” region is the larger and better described. It contains, almost exclusively, FM-FM neurons tuned to the harmonic combinations FM₁-FM₂, FM₁-FM₃, or FM₁-FM₄. The harmonic combinations are segregated within cortical slabs (extending across all layers) so that the FM₁-FM₂ slab is located most ventrolaterally along the cortical surface. The adjacent FM₁-FM₄ slab is more dorsomedial, and the FM₁-FM₃ slab is the most dorsal and medial (Fig. 6C). Within each slab, FM-FM neurons are arranged based on their delay tuning, with short best delays represented more rostrally and longer best delays systematically represented more caudally. The second cortical area dominated by FM-FM neurons is termed the dorsal fringe (DF) area. The organization of the DF area is virtually identical to the FM-FM area. There are segregated slabs of FM-FM neurons tuned to each of the FM-FM combinations, and these are arranged in a similar ventral-to-dorsal sequence. Moreover, each FM-FM cortical slab, defined by echo harmonic sensitivity, contains a map of delay tuning from rostral (short best-delays) to caudal (longer best-delays). The main difference between the two areas is that the FM-FM area contains more neurons tuned to

longer best delays; few DF neurons are tuned to delays greater than 8 ms (Fitzpatrick et al., 1998a; Suga and Horikawa, 1986). These two cortical regions contain the vast majority of neurons tuned to the frequency bands associated with FM₂, FM₃, and FM₄ echolocation components, yet neither area contains a tonotopic organization characteristic of the ascending lemniscal system. Interestingly, the topographical relationship among the harmonic representations differs from MGB. In the cortical areas, the FM₄ representation is sandwiched between the FM₂ and FM₃ representations (Fig. 6B,C). Thus, further reorganization in the representation of the FM frequency bands occurs as a result of the thalamo-cortical projection.

In retrograde transport studies of the thalamo-cortical projection, Pearson and colleagues (2007) showed that the FM-FM and DF regions receive input from mostly separate portions of the rostral MGB. Thus, the DF region receives input from more medial parts of the rostral MGB, in accord with its representation of short pulse-echo delays, while the FM-FM region receives inputs from more lateral parts, in accord with its representation of longer delays. This work confirms that the MGB contains at least a crude organization of best delays and demonstrates that the separate FM-FM areas have origins in different parts of the rostral MGB. Overall, we conclude that the cortical organization of FM-FM responses is based primarily on the radical reorganization of the tecto-thalamic projection, and secondarily on the less striking but significant reorganization within the thalamo-cortical projection.

Do these areas play a role in target distance analyses in echolocation? The data are not definitive. However, operant conditioning experiments suggest that reversible inactivation of the FM-FM area diminishes some forms of temporal analysis (Riquimaroux et al., 1991). Further work that relates these areas to specific behavioral features of target distance analysis would improve our understanding of the functions of these areas.

C. Extrathalamic projections

Although the MGB is a major projection target of FM-FM neurons in the IC, some FM-FM neurons in IC project to other targets (Fig. 7). These extrathalamic projections suggest that information related to target distance is sent directly from IC to premotor areas. Here we focus on the two largest projections.

A major extrathalamic target of FM-FM neurons in IC is a region in the rostral brainstem that may be a part of the pretectum (Fig. 7, Frisina et al., 1989; Wenstrup and Grose, 1995; Wenstrup et al., 1994). IC neurons in each of the frequency representations associated with higher harmonic FM signals (FM₂₋₄) project strongly. In contrast, neurons in the FM₁ representation project only weakly and neurons associated with the CF frequency bands near 60 kHz and 90 kHz do not appear to project (Wenstrup and Grose, 1995; Wenstrup et al., 1994). Terminal labeling associated with higher harmonic FM projections is very dense, more so than their corresponding projections to MGB (Wenstrup et al., 1994). The near-exclusive projection from FM-sensitive regions in IC to this pretectal region suggests a premotor function associated with target distance analyses.

This pretectal area in the mustached bat may correspond to a region designated as the “intertectal nucleus” in the big brown bat, between the superior colliculus and MGB, that contains delay-tuned neurons (Dear and Suga, 1995). It is noteworthy that this intertectal nucleus contains a population of delay-tuned neurons tuned to pulse-echo intervals that are longer than those found in the ascending pathway to auditory cortex (Dear et al., 1993). These observations support the view that the extrathalamic pathways underlie different distance-related behaviors in bats.

A second major extrathalamic target of FM-FM neurons in IC is to the pontine nuclei (Frisina et al., 1989; Wenstrup et al., 1994). Each frequency band in IC associated with the sonar signal, including those tuned to FM frequency bands, projects to both the dorsolateral and lateral nuclei of the pons (Wenstrup et al., 1994). These nuclei in turn project to the contralateral cerebellum, where many neurons respond to tones and sonar signal elements in either the FM or CF frequency bands (Horikawa and Suga, 1986; Jen et al., 1982). Some cerebellar neurons display delay-tuned, FM-FM facilitation (Horikawa and Suga, 1986) with latencies that suggest they may inherit these response properties via the indirect input from FM-FM neurons in the IC. The function of FM-FM neurons in this circuit is not known, but they may contribute to a range of adaptive behaviors that depend on the distance between a bat and either its prey or an obstacle. These behaviors include changes in sonar pulse repetition rate and duration, as well as changes in flight and body positioning as a bat attempts to capture prey or avoid obstacles.

V. SUMMARY AND FUTURE DIRECTIONS

The work described here identifies several major contributions of the auditory midbrain to neural analyses of target distance information in the mustached bat. First, the auditory midbrain plays a critical role in the integration of information within different frequencies of the sonar signal to create selective responses to pulse-echo delay. Second, the projection of delay-tuned, FM-FM neurons in the auditory midbrain to the auditory thalamus dramatically reorganizes the representation of target distance information, setting the stage for separate and topographically organized representations of target distance in auditory cortex. Third, the projection of FM regions in the auditory midbrain to the pretectum and the pontine nuclei likely establishes the bases for adaptive changes in behaviors that occur during echolocation.

While the unique response properties and organizational features of FM-FM neurons in the auditory midbrain, thalamus, and cortex strongly suggest roles in target distance processing, it must be recognized that this link is not conclusive. We believe that the next steps in understanding how these responses contribute to distance-based behaviors in echolocation will depend on the recognition that there are several regions of the brain that receive the distance-based analyses performed by the auditory midbrain, that these centers may perform different distance-based analyses, and that these analyses should be related to specific types of distance-based behaviors.

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Figure 1.

FM-FM neurons in the mustached bat respond to particular combinations of elements in the emitted sonar pulse and returning echo. A. Schematic sonogram of the multi-harmonic emitted sonar pulse and echo, including constant frequency (CF) and frequency modulation (FM) elements. *Black ovals* indicate elements required to activate the facilitated response shown in B and C. *Thickness of lines* indicates relative sound levels. B, C. Critical features of the FM-FM response of a thalamic neuron. This neuron respond best to the combination of an FM₁ element in the emitted pulse and FM₃ element in the returning echo (B), but only at echo delays of 2-4 ms (C). Adapted with permission from Olsen and Suga (1991b), J Neurophysiol, Am. Physiol. Soc.

Figure 2.

FM-FM neuron in the mustached bat's inferior colliculus. A. Peristimulus time histograms show that this neuron responded weakly to individual tone bursts in the FM₁ and FM₃ ranges, but was strongly facilitated by the combination when the signal in the FM₃ frequency range was delayed by 2 ms. The strength of the facilitation was quantified by an index value that compares the response to the combination with the response to the separate tonal elements (Dear and Suga, 1995). Facilitation index values range from 0.09 (20% facilitation, our threshold for facilitation) to 1.0 (maximum facilitation). This neuron has a facilitation index value of 0.75. B. The response is delay-tuned, with maximum response at the *best delay*. C. The facilitation is tuned to two frequency bands (*arrows at top*), one within the FM₁ sonar component and the other within the FM₃ sonar component. The *best frequency* (BF) of 83 kHz is based on responses to single tone bursts and is within the frequency band of the FM₃ component. Adapted with permission from Portfors and Wenstrup (1999), J. Neurophysiol., Am. Physiol. Soc.

Figure 3.

Variation in delay sensitivity among FM-FM neurons in the mustached bat's IC. A. Schematic delay function for FM-FM neuron with only facilitatory responses to combinations of tones in the FM₁ and higher harmonic FM frequency bands. The facilitation is tuned to short delays (3 ms best delay) between low-frequency and subsequent high-frequency signals. B. Delay function for FM-FM neuron with both facilitatory and inhibitory responses to combinations. The inhibitory interaction is strongest at 0 ms delay, while the facilitatory interaction is strongest at a longer delay (10 ms). C. Delay function for FM-FM neuron with only an inhibitory influence of signals in FM₁ frequency band. Inhibition is strongest at 0 ms delay. D. Best delays of facilitation for FM-FM neurons and other combination-sensitive neurons (including FM-CF, CF/CF, and non-sonar combinations) from the mustached bat's IC. The FM-FM neurons have distinctly different delay tuning. *Dashed vertical line* indicates approximate separation between facilitated FM-FM neurons without inhibition (having short best delays) and facilitated neurons with inhibition (having long best delays). Data from Leroy and Wenstrup, 2000; Nataraj and Wenstrup, 2005; and Portfors and Wenstrup, 1999. E. Best delays of inhibition for FM-FM neurons that show no facilitation (illustrated in C) and those that also show facilitation (illustrated in B). For both groups, inhibition is strongest at 0 ms delay. Mechanistic studies suggest that inhibition in both groups has a common origin (see Section III). Data from Nataraj and Wenstrup, 2005; Portfors and Wenstrup, 1999. F. Width of delay tuning (50% Delay Width) in FM-FM neurons from IC is weakly correlated with best delay. Data from Nataraj and Wenstrup, 2005; Portfors and Wenstrup, 1999.

Figure 4.

Mechanisms of facilitation and inhibition for FM-FM neurons. A-C. Responses of FM-FM neuron before and during pharmacological blockade of ionotropic glutamate receptors alone (iGluR Block) or in combination with glycine receptor blockade (+Gly Block). iGluR Block eliminates nearly all single tone responses (A,B), but facilitation in response to tone combinations persists (C). Addition of glycine receptor blocker eliminates facilitation (C). Facilitation is independent of glutamatergic inputs to IC neuron. Adapted with permission from Sanchez et al. (2008). D. Proposed origin of FM-FM and other combination-sensitive (CS) responses in IC neurons. Inhibitory interactions originate in nuclei of the lateral lemniscus (NLL) and depend on low-frequency tuned glycinergic inhibition. Inhibitory CS interactions in IC neurons inherit this response property from NLL neurons via glutamatergic synapses. Facilitation in IC neurons depends on low- and high-frequency tuned glycinergic inputs. Used with permission from Peterson et al., (2009); J. Neurophysiol., Am. Physiol. Soc.

Figure 5.

Comparison of physiological response features of FM-FM neurons in IC and MGB. FM-FM neurons in IC and MGB have similar best delays (A), 50% delay widths (B), and strengths of facilitation (C). Used with permission from Portfors and Wenstrup, 2004; © 2004 by the University of Chicago.

Figure 6.

Organization of FM-FM neurons in IC, MGB, and auditory cortex. A. In IC, each higher harmonic FM frequency band lies within the tonotopically organized IC. No organization of best delays is apparent, as illustrated for the FM₃ representation. B. In MGB, FM-FM neurons are segregated from other neurons in a rostral, non-tonotopic part. Neurons tuned to each of the harmonics are clustered, but there is no overall tonotopic organization. There is at least a crude representation of best delays. C. In “FM-FM” and “Dorsal Fringe” areas of auditory cortex, FM-FM neurons are clustered by harmonic sensitivity and organized along an axis of best delay. Used with permission from Portfors and Wenstrup (2001a); © from Elsevier.

Figure 7.
Outputs of IC regions containing FM-FM neurons.